Cardiovascular disease in rheumatoid arthritis: risk factors, clinical presentation, treatment and prognosis

Ängla Mantel

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Cover; The painting 'La Ferme des Collettes' by Pierre-August Renoir (1841–1919), who suffered from rheumatoid arthritis and cardiovascular disease. Renoir experienced a stroke in 1910 and died from a fatal myocardial infarction in 1919.

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Cardiovascular disease in rheumatoid arthritis: risk factors, clinical presentation, treatment and prognosis

THESIS FOR DOCTORAL DEGREE (PhD)

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The possession of knowledge does not kill the sense of wonder and mystery.

There is always more mystery.

- Anaïs Nin

To Ivan, Dante & Noomi – My family, my everything
ABSTRACT

It is well known that patients with rheumatoid arthritis (RA) are at increased risk of developing or dying from cardiovascular disease (CVD). There are several important questions remaining regarding the association between RA and specific CVDs. In this work, we have identified gaps in the existing knowledge and translated them into the objectives of the four sub-studies included in this thesis, which all focus on clinical aspects of CVD in RA.

Several studies have assessed potential risk factors for CVD overall in RA, whereas no previous study has investigated the impact of RA-related factors on the risk of clinically significant acute coronary syndrome (ACS) in contemporary RA-patients. Existing results are thereby difficult to extrapolate into clinical praxis. Using a nested case-control design, we therefore aimed in Study I to investigate risk factors for ACS in new-onset RA. We found that laboratory measures of high inflammatory activity, clinical markers of high disease activity as well as poorer perceived health and a high number of sick days already during the first year following RA-onset were associated with an increased risk of ACS in RA. Seropositivity for the autoantibody rheumatoid factor (RF) was not associated with ACS, whereas antibodies towards citrullinated peptides (ACPAs) and in particular high positive levels of ACPAs was associated with an increased risk of ACS.

Thus, the increased risk of ACS in patients with RA seems to be, at least partly, driven by inflammatory activity. Inflammation is known to affect the extent and composition of atherosclerosis, why the clinical phenotype of ACS in RA might differ compared with non-RA patients. However, little is known about the actual clinical phenotype, its treatment, follow-up care and outcomes of ACS in RA. For this reason, we investigated clinical ACS characteristics, short- and long-term outcomes and the usage of gold standard secondary preventive drugs in 1,135 RA-patients with ACS compared to 3,184 non-RA patients with ACS in Studies II and III. Our results indicated that patients with RA suffer from more severe ACS compared with non-RA patients. Furthermore, patients with RA also suffer from an increased risk of developing recurrent events or dying after the ACS. Usage of secondary preventive drugs was not substantially different in patients with RA compared with non-RA patients, and did not seem to explain the impaired prognosis following ACS.

In the fourth and final study, we focused on assessing the relative risk (RR) of heart failure (HF) in RA, which, despite the known involvement of inflammation in the pathogenesis of HF, has only been assessed in a few studies. In Study IV, we estimated the relative risk (RR) of HF in RA both in the presence and absence of ischemic heart disease (IHD) in patients with new-onset RA and patients with established RA compared with non-RA patients. We also investigated the impact of RA-related inflammation on the risk of HF in patients with new-onset RA. We found that the risk of both ischemic and nonischemic HF was increased in RA. The risk increase, in particular for nonischemic HF, developed early after RA-onset and was associated with high inflammatory activity.

The results of the four studies emphasize the importance of early disease control in RA, suggest that RA comorbidity should be acknowledged when risk stratifying ACS patients and also point out the importance of observing and investigating clinical signs of HF in patients with RA.
LIST OF SCIENTIFIC PAPERS

I. Risk Factors for the Rapid Increase in Risk of Acute Coronary Events in Patients with New-Onset Rheumatoid Arthritis – A Nested Case-Control Study
   Ängla Mantel, Marie Holmqvist, Fredrik Nyberg, Göran Tornling, Thomas Frisell and Johan Askling
   *Arthritis & Rheumatology* 2015; 67: 2845-2854

II. Rheumatoid arthritis is associated with a more severe presentation of acute coronary syndrome and worse short-term outcome
   Ängla Mantel, Marie Holmqvist, Tomas Jernberg, Solveig Wållberg-Jonsson and Johan Askling
   *European Heart Journal* 2015; 36: 3413-3422

III. Long-term Outcomes and Secondary Prevention after Acute Coronary Events in Patients with Rheumatoid Arthritis
    Ängla Mantel, Marie Holmqvist, Thomas Jernberg, Solveig Wållberg-Jonsson and Johan Askling
    Accepted for publication in *Annals of the Rheumatic Diseases*

IV. Association Between Rheumatoid Arthritis and Risk and Risk of Ischemic and Nonischemic Heart Failure
    Ängla Mantel, Marie Holmqvist, Daniel C. Andersson, Lars H. Lund and Johan Askling
    *Journal of American College of Cardiology* 2017; 69: 1275-1285
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACPA</td>
<td>Antibodies towards citrullinated peptides</td>
</tr>
<tr>
<td>ACR</td>
<td>American college of rheumatology</td>
</tr>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical therapeutic code</td>
</tr>
<tr>
<td>CDR</td>
<td>Cause of death register</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DAG</td>
<td>Directed acyclic graph</td>
</tr>
<tr>
<td>DAS28</td>
<td>28 Joint count disease activity score*</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>DMARD</td>
<td>Disease-modifying antirheumatic drug</td>
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<tr>
<td>ECG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>EIRA</td>
<td>Epidemiological investigation of rheumatoid arthritis</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>EULAR</td>
<td>European league against rheumatism</td>
</tr>
<tr>
<td>GH</td>
<td>General health</td>
</tr>
<tr>
<td>HAQ</td>
<td>Health assessment questionnaire</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failure</td>
</tr>
<tr>
<td>IHD</td>
<td>Ischemic heart disease</td>
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<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>MTX</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>NBHW</td>
<td>National board of health and welfare</td>
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<tr>
<td>NPR</td>
<td>National patient register</td>
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<tr>
<td>NSAID</td>
<td>Non steroid anti-inflammatory drug</td>
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<tr>
<td>NSTEMI</td>
<td>Non-ST segment elevation myocardial infarction</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>PDR</td>
<td>Prescribed drug register</td>
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<tr>
<td>PIN</td>
<td>Personal identity number</td>
</tr>
<tr>
<td>PS</td>
<td>Propensity score</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SRQ</td>
<td>Swedish rheumatology register</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>TPR</td>
<td>Total population register</td>
</tr>
<tr>
<td>UA</td>
<td>Unstable angina</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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</table>

*A composite measurement used to assess disease activity in RA.*
1 INTRODUCTION

Rheumatoid arthritis (RA) is, according to the World Health Organization, one of the musculoskeletal conditions with the greatest impact on society. RA-onset typically occurs in middle-aged individuals in their most productive years. It is a chronic condition, often associated with pain and functional impairment, leading to substantial disability throughout life. In addition to the disability caused by the RA itself, patients with RA are also at increased risk of developing several other comorbid conditions adding to the already existing disease-related morbidity. Cardiovascular disease (CVD) is the most common comorbidity in RA. The increased risk of CVD was first observed several decades ago, and later studies have reported risk increases of magnitudes similar to what is observed in diabetes mellitus (DM) type 2. Patients with RA are at increased risk of most subtypes of CVDs, which accounts for a majority of the excess mortality and morbidity seen in RA. Importantly, the presence of traditional CV risk factors cannot fully explain the increased risk of CVD in RA, which has led to attempts to identify other risk factors involved in the pathogenesis of CVD in RA. Parallel to the increasing number of reports on the association between RA and CVD, the knowledge of the pathophysiology of specific CVDs, and in particular atherosclerosis, has progressed remarkably. The involvement of inflammatory activity in the development of atherosclerosis has been established and it has been demonstrated that inflammation affects the extent and composition of atherosclerotic lesions. Recently, an association between inflammation and heart failure (HF) has also been established. The RA-related inflammation might therefore be involved in the development of CVD in RA, which potentially also affects the characteristics and outcomes of CVD in RA.

Needless to say, studying the association between RA and CVD can have multiple approaches and perspectives, making it a difficult but primarily an interesting and rewarding task. All four studies included in this thesis use epidemiological methods to study the risk of, risk factors for, clinical characteristics of and outcomes following acute coronary syndrome (ACS) and/or HF. Apart from elucidating the specific associations studied aiming to find ways to identify, treat or prevent CVD in patients with RA in clinical practice, the results may hopefully also be useful for understanding CV pathophysiology.

Undoubtedly, trying to understand the aetiology of associations or diseases is a complicated task. Repeated investigations and translational research, combining several different research fields, is often required in order to confirm a hypothesis. The aim of this thesis is to highlight a few well-defined areas of the field, which can hopefully contribute a few of many pieces to the jigsaw puzzle.
2 BACKGROUND

2.1 RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease with predominant musculoskeletal manifestations. The key symptoms of RA are local inflammation of joints, tendons and bursae\textsuperscript{8, 9} and systemic inflammation leading to manifestations such as fatigue. RA is divided into two subgroups based on the presence of autoantibodies, including rheumatoid factor (RF) and autoantibodies against citrullinated peptides (ACPA).\textsuperscript{10}

2.1.1 Epidemiology

RA has a reported global prevalence of 0.24\%, and is ranked high among conditions contributing to global disability.\textsuperscript{11} In incidence and prevalence studies, the occurrence of RA typically varies between countries, ethnicities and racial groups.\textsuperscript{12} The reported prevalence of 0.5-1\% in northern Europe and North American\textsuperscript{13} is higher compared with, for example, southern European countries and low-income countries, where the incidence and prevalence is reported to be significantly lower.\textsuperscript{14} Despite some differences in RA-definition, methodological approach and the apparent difficulties in estimating disease occurrence in low-income countries, these observed variations are likely to be partly true. Naturally, this observation has led to assessments of the effects of potential environmental factors, such as diet, and genetic factors on the risk of RA.\textsuperscript{15}

In a large Swedish register-based study, approximately 60,000 individuals with RA were identified in 2008, corresponding to a prevalence of 0.77\%.\textsuperscript{16} The nationwide incidence in Sweden is approximately 40 per 100,000, twice as common in women and increases with age.\textsuperscript{17}

2.1.2 Risk factors and pathogenesis

Several genetic and environmental risk factors for RA have been identified to date. A family history of RA is a strong risk factor for developing RA with two to six times higher prevalence in individuals with first-degree relatives with RA.\textsuperscript{18} The heritability is stronger for seropositive compared to seronegative disease.\textsuperscript{19, 20} Genome-wide association studies have identified over a hundred genetic risk alleles that are associated with risk of RA.\textsuperscript{21} A majority of these alleles are located within the human leukocyte antigen (HLA) complex, a region on chromosome 6 with certain genes known to play a crucial role in the susceptibility and pathogenesis of several autoimmune diseases.\textsuperscript{22, 23} In particular, there are disease-associated alleles (termed shared epitope [SE]) in the \textit{HLA-DRB1} gene that have been associated with an increased risk of RA.\textsuperscript{24} Cigarette smoking seems to be the most important environmental risk factor for RA \textsuperscript{25-28} and is in particular associated with RF- and CCP-
positive RA\textsuperscript{29} in the presence of the SE-alleles,\textsuperscript{30} indicating an epigenetic contribution
to the RA pathogenesis via gene-environment interactions.\textsuperscript{30-32} Low socioeconomic
status,\textsuperscript{33} low educational level,\textsuperscript{34} physical workload\textsuperscript{35} and hormonal factors\textsuperscript{36-39} and
work-related exposure to silica-dust\textsuperscript{40} and textile dust\textsuperscript{41} have also been associated with
an increased risk of RA. Alcohol intake \textsuperscript{42-43} and a diet high in fish oil \textsuperscript{44} have been
proposed to decrease the risk of developing RA.

Despite the large amount of research in the field, the specific pathogenesis is not yet
completely understood. It is presumed that the interaction between environmental
factors, such as smoking, and genetic factors, such as the SE alleles,\textsuperscript{45} triggers
epigenetic modifications, i.e. citrullination and subsequent immunological response
leading to inflammation and hence corresponding symptoms and clinical signs. Many
immunological cells, pathways and mediators have been identified as central in the
pathogenesis of RA.\textsuperscript{8, 46} Briefly, antigen presenting cells are triggered to activate CD\textsubscript{4+}
T cells. The T-cells differentiate into specific subtypes of T-cells, which in turn activate
B-cells and stimulate macrophages and fibroblasts to secrete proinflammatory
mediators, such as tumour necrosis factor α (TNF-α) and different interleukins.\textsuperscript{47}
Certain B-cells produce ACPAs, which can be detected several years prior to RA-onset
and are a strong predictors for disease.\textsuperscript{48, 49} The autoantibodies can bind various
citrullinated self-proteins\textsuperscript{8} in different tissues which, except for the potential role in
the pathogenesis of RA, has also been suggested as being involved in the pathogenesis
of other diseases.\textsuperscript{50} Additionally, ACPAs are themselves pathogenic by activating
macrophages and immune complex formation, triggering the immune system. The
key clinical feature of joint swelling in RA is a consequence of synovial membrane
inflammation due to the immune activation. The inflammatory milieu within the
synovial compartment consists of a variety of immune cells and complex cytokine and
chemokine networks. Enhanced chondrocyte metabolism leads to destruction of the
cartilage. Aggravation of the inflammation can trigger osteoclast generation and
subsequent bony erosions.\textsuperscript{8, 47}

2.1.3 Symptoms, diagnosis and classification
The disease onset of RA can be acute or insidious and, as already described, the
common presenting symptoms are tender and swollen joints, and symptoms of
systemic inflammation, such as fatigue. The joints most frequently involved are the
wrists, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints.
Laboratory tests typically shows elevated concentrations of C-reactive protein (CRP)
and erythrocyte sedimentation rate (ESR).\textsuperscript{8, 47} There are no specific diagnostic criteria
for RA, but, after eliminating several potential differential diagnoses, the diagnosis can
be aided by classification criteria developed, and most recently updated in 2010, by the
American College of Rheumatology (ACR) and the European League against
Rheumatism (EULAR).51 The 2010 ACR/EULAR criteria aim to detect patients with RA early to identify those who would benefit from early disease-modifying therapy. Based on the number of the affected joints, presence of autoantibodies (RF and ACPAs), acute-phase reactants (CRP and ESR) and duration of symptoms, a score between 0 and 10 is yielded, where a score above 6 indicates definite RA (Figure 2.1). Patients not fulfilling the 2010 ACR/EULAR criteria, but with erosive disease (defined as a cortical break in at least three separate joints) are also classified as RA according to a more recent update.52 Importantly, the classification system also serves as a tool for identifying subgroups of RA patients, based on the presence or absence of RF and/or ACPAs. RA is, however, a heterogeneous disease with variability in clinical presentation and treatment response, which is why there are probably even further disease subgroups.53 Clinically, seropositive and seronegative RA (based on RF/ACPA status) are typically recognized as two distinct entities. Seropositive RA is associated with a more severe clinical prognosis.51, 54

<table>
<thead>
<tr>
<th>JOINT DISTRIBUTION (TENDER AND/OR SWOLLEN JOINTS)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>5</th>
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<tbody>
<tr>
<td>1 large joint</td>
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<td>2–10 large joints</td>
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<td>1–3 small§ joints</td>
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<td>4–10 small§ joints</td>
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<td>&gt;10 joints (at least 1 small)</td>
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<th>SEROLOGY</th>
<th>0</th>
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<tbody>
<tr>
<td>Negative RF AND negative ACPA</td>
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<tr>
<td>Low positive RF OR low positive ACPA</td>
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<td></td>
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<tr>
<td>High positive RF OR high positive ACPA</td>
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<tr>
<th>SYMPTOM DURATION</th>
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<tr>
<td>&lt; 6 Weeks</td>
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<tr>
<td>≥ 6 Weeks</td>
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<th>ACUTE PHASE REACTANTS</th>
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<td>Normal CRP AND normal ESR</td>
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<tr>
<td>Abnormal CRP OR abnormal ESR</td>
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| §Small joints = Metacarpophalangeal joints, Proximal interphalangeal joints, Metatarsophalangeal joints and Radiocarpal joints |
| RF, rheumatoid factor; ACPA, antibodies towards citrullinated peptides; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate |

Figure 2.1. The 2010 EULAR/ACS Classification criteria. ≥6 points indicates definite RA.
2.1.4 Disease assessment and treatment

Measurements of disease activity is important in the clinical evaluation of RA as well as in the research setting, and is typically evaluated using one of several existing composite measurements including clinical and laboratory parameters. The most commonly used measurement, the 28 joint count disease activity score (DAS28), was developed for this purpose, and is based on an algorithm including the tender and swollen joint count (of 28) assessed by the physician, ESR (or CRP) and general health (GH), i.e. assessed on a VAS scale. According to the DAS28, disease activity is classified into low, moderate or high. High disease activity is related to impaired functional capacity and the progression of joint damage. Based on DAS28, there are also remission criteria, used to evaluate treatment targets. The health assessment questionnaire disability index (HAQ DI) is the most commonly used instrument used to assess physical functioning in patients with RA.

There are several efficacious drugs available for the treatment of RA. The overarching principles in the EULAR recommendations for the management of RA (updated 2016) include i) that a rheumatologist should be responsible for the treatment, ii) that the treatment should be chosen based on disease activity and other patient factors such as comorbidities, and iii) that treatment decision-making should be shared between the rheumatologist and the patient. The two major classes of disease-modifying anti-rheumatic drugs (DMARDs) used to target the inflammatory activity are synthetics and biologics. Synthetic DMARDs are further divided into conventional or targeted synthetic DMARDs. Non-steroidal anti-inflammatory drugs (NSAIDs) are used to relieve symptoms, but do not have any effect on joint damage and are hence not disease-modifying. Treatment with glucocorticoids is also used, especially in early disease to relieve symptoms before the DMARD of choice has had any effect. According to the EULAR guidelines, DMARD treatment should be initiated in direct relation to the diagnosis. In the absence of contraindications, methotrexate (MTX), often in combination with glucocorticoids, is the first treatment choice. The aim of treatment is reaching sustained remission or low disease activity, and evaluation should be undertaken frequently. If there is no improvement after three months of treatment, changing to another type of DMARD should be considered. Which type of DMARD that is used depends on the presence of prognostic factors such as autoantibodies should be considered. Biological DMARDs are often used in patients with seropositive RA or high disease activity where monotherapy with MTX has failed. Different combination therapies exist depending on subsequent evaluations and treatment response. When the treatment target is reached, the aim is to sustain it over time and thereafter consider tapering off the drugs.
2.1.5 Morbidity and mortality

Patients with RA suffer from impaired quality of life as a consequence of the functional status related partly to RA, but importantly also influenced by the several comorbid conditions occurring more frequently in RA-subjects compared to non-RA subjects. Patients with RA suffer from increased mortality risk and have a shorter life expectancy compared with the general population. Despite the observed decreased mortality rates in RA over recent decades, mortality is still significantly increased compared with the general population. The most common comorbid condition is cardiovascular disease (CVD), which contributes to a majority of both excess morbidity and mortality in RA. RA is also associated with infectious diseases, diabetes mellitus (DM), renal diseases, certain malignancies and depression.

2.2 CARDIOVASCULAR DISEASE

CVD is a broad disease group affecting blood vessels and/or the heart, and is the leading cause of death globally. A majority of the various subtypes of CVD share some pathophysiological mechanisms and clinical features, but they also have their own unique hallmarks, making it important to distinguish between them. This thesis include studies of the association between RA and acute coronary syndrome (ACS) and heart failure (HF), which is why these conditions are described in detail in this section.

2.2.1 Ischemic heart disease

Ischemic heart disease is a consequence of coronary artery disease (CAD), which is characterized by atherosclerosis of the coronary arteries. IHD can be asymptomatic or symptomatic and present as chronic stable angina or in acute onset as acute coronary syndrome (ACS). ACS includes the diagnoses unstable angina pectoris (UA) and myocardial infarction (MI). The aetiology of ACS is not always CAD, but can also be coronary spasm.

2.2.1.1 Traditional risk factors

Identification of risk factors for CAD was initiated in 1948 in the Framingham heart study and subsequently many studies have replicated and extended these results. The traditional and currently well-known risk factors are divided into non-modifiable and modifiable or life-style related. Non-modifiable risk factors include age, male sex and hereditary factors. Major modifiable risk factors include hypertension, DM, smoking, physical inactivity, increased LDL-C and decreased HDL-L.
Atherosclerosis was previously considered a lipid storage disease, but the knowledge of the involvement of inflammation has progressed rapidly during the last decades. In fact, inflammatory activity is involved in all steps of the complex atherogenic pathway, which shares similarities with the pathophysiological mechanisms in RA. The development of atherosclerosis is initiated by endothelial dysfunction, which can be caused by several factors. For example, smoking, hypertension or hyperglycaemia triggers endothelial dysfunction by stimulating the expression of adhesion molecules for leucocytes in the endothelium. Leucocytes and lipids, carried by LDL-C particles, and macrophages can in this way infiltrate the intima. Fatty streaks, eventually starting to protrude into the arterial lumen, are formed as the macrophages ingest LDL-C particles and develop into foam cells. A fibrous cap is formed over the fatty streak as smooth muscle cells, from the tunica media migrate into the intima and start to release extracellular matrix molecules. At this stage, the damage is no longer reversible. Over time, the plaque continues to progress and develops into an advanced lesion characterized by a dense fibrous cap and underlying haemorrhage and apoptotic cells. The plaque growth will eventually lead to significant narrowing of the arterial lumen, which may cause ischemia (manifested as angina pectoris) during periods of physical or psychological stress. Pro-inflammatory cytokines can stimulate macrophages and other cell types to release matrix metalloproteinases (MMPs), which are enzymes capable of catabolizing macromolecules of the arterial extracellular matrix. This in turn may cause a plaque rupture leading to clinical significant thrombus formation, manifested as an ACS. The fibrous cap of ruptured plaques are generally thin, which has been proposed to be caused by the impaired collagen synthesis of smooth muscle cells as a consequence of inflammatory signals. Superficial erosion of the intima is another mechanism precipitating ACS in which a potential involvement of inflammation is not clear.

Since inflammation is involved in many steps of the atherogenic process and affecting both extent and composition of the atherosclerotic plaques, the potential use of various inflammatory biomarkers in predicting clinically significant CAD, such as ACS, has been researched. White blood cell (WBC) count, TNF-α, CRP and various cytokines are examples of biomarkers that have been associated with CV events. TNF-α and CRP predict CV events independent of each other and present traditional risk factors. Furthermore, TNF-α is associated with short-term risk of CV events. Since neither of these biomarkers are specific to atherosclerosis, but are also mediators in several other conditions, including RA, their role in clinical praxis remains to be determined. RF has been associated with an increased risk of CVD in the general population, but there is no clear role of its involvement in the pathogenesis of CVD.
Similarly ACPAs have also been associated with an increased risk of CVD in non-RA subjects.92

2.2.1.3 Acute coronary syndrome – symptoms and treatment

Acute coronary syndrome is stratified into acute ST-segment elevation MI (STEMI), unstable angina pectoris (UA) or non-ST segment elevation MI (NSTEMI) based on symptoms, electrocardiogram (ECG) and cardiac biomarkers. The pathophysiology of the different subtypes of ACS differs, as does the risk stratification and treatment, between them.93 Four pathophysiological processes contribute to the development of UA/NSTEMI, which is caused by a reduced oxygen supply to the myocardium and/or an increased myocardial oxygen demand: i) a rupture or erosion of non-occlusive thrombus, ii) coronary spasm, iii) rapid progression of atherosclerosis or restenosis following percutaneous coronary intervention (PCI) causing mechanical obstruction, and iv) increased oxygen demand or reduced oxygen supply caused by another condition, for example tachycardia or anaemia, causing UA. UA is diagnosed based on characteristic ischemic symptoms in the absence of evidence of myocardial necrosis (as measured by a cardiac biomarker). Symptoms of UA in combination with ECG-findings and elevated cardiac biomarkers define NSTEMI. STEMIIs are typically caused by a total thrombotic occlusion of a coronary artery. Usually, the thrombus has developed rapidly at the site of a vascular injury, and a collateral network has not had time to develop. Patients with STEMIIs typically present with a more intense, often radiating, pain compared to UA/NSTEMI, or even dyspnoea or syncope. Importantly, there are patients presenting with painless STEMIIs, which is more common in patients with diabetes and in the elderly. STEMI are characterised by elevated cardiac biomarkers and typical ECG-changes.

Primary PCI is the gold standard treatment for STEMI94 and intermediate or high risk UA/NSTEMIs, whereas low risk UA/NSTEMIs are usually treated conservative with anticoagulants.95 Several factors have been identified as important predictors for outcomes following ACS, and there are several tools that can be used to identify high risk patients. The Killip classification is a bedside assessment of risk based on clinical signs of HF in patients with ACS, which is convenient to use in clinical practice. Higher Killip class scores are associated with increased short- and long-term mortality following ACS. Inflammatory activity has been associated with adverse outcomes following ACS in the general population.96, 97 The gold standard of secondary preventive pharmacotherapies includes aspirin, P2Y12-inhibitors, beta-blocking agents, RAS-blocking agents and statins.98 Usage of these drugs is associated with an improvement in the long-term mortality and morbidity after ACS.
2.2.2 Heart failure

Heart failure is a complex clinical syndrome with a high prevalence especially in the elderly, and is associated with substantial morbidity.

Various conditions are capable of altering the structure of the left ventricle (LV) and in this way predisposing the development of HF which is classified into HF with reduced ejection fraction (EF) (HFREF) and HF with preserved EF (HFPEF). Some aetiologies overlap and may predispose both subtypes of HF, whereas others are more specific to either subtype. Coronary artery disease and hypertension are the most common risk factors for HF in western countries, and can lead to the development of both HFREF and HFPEF. In addition to the established risk factors for HF, the association between inflammation and HF has recently been recognized. Several proinflammatory biomarkers are elevated in HF, but it remains unclear whether the association between inflammation and HF reflects a causal effect between inflammation and HF.

Symptoms and clinical signs of HF include dyspnoea, decreased exercise tolerance, paroxysmal nocturnal dyspnoea, orthopnoea, pulmonary rales, oedema, abdominal pain, etc. The New York Heart association (NYHA) Classification for HF groups HF into levels of severity based on the level of physical activity. HF is diagnosed based on the typical symptoms in combination with laboratory biomarkers and echocardiography so as to determine the aetiology and subtype of HF.

Treating HF includes treatment of the underlying conditions as well as specific HF-treatment including diuretics, RAS-blocking agents and beta-blockers.

2.3 CARDIOVASCULAR DISEASE IN RHEUMATOID ARTHRITIS

2.3.1 The risk of CVD in RA

A meta-analysis of observational studies on the risk of CVD in RA found a pooled relative risk (RR) of 1.48 for CVD overall. RA has been associated with most subtypes of CVD and, of the various CVDs, IHD and in particular MI has been most extensively studied. The incidence and prevalence of IHD in RA is increased and in various cohort studies, RRs of IHD in RA between 1.5 and 3 have been reported. The risk of IHD seems to develop rather rapidly after RA-onset and is increased in both men and women. Furthermore, the risk of ACS has, despite improvements in RA treatment and disease control, remained constant over time.

In contrast to IHD, not many studies have addressed HF in RA. However, retrospective cohort-studies have indicated an increased life-time prevalence of HF in
RA, as well as a doubled RR of incident HF in RA and increased HF-related mortality.

RA has also been associated with an increased risk of cerebrovascular disease, venous thromboembolism, certain cardiac arrhythmias and peripheral arterial disease.

### 2.3.2 Risk factors for CVD in RA

As we have seen, the pathophysiological mechanisms of the inflammation characteristic for RA and the involvement of inflammation in the atherogenic process share many features. Inflammatory cells, such as macrophages, mast cells and T-cells are activated in both atherosclerosis and in RA. Furthermore, the production of TNF-α, various cytokines and leukocyte adhesion molecules are also similar. In addition to promoting the initiation and progression of atherosclerosis, inflammation promotes development of vulnerable plaques prone to rupture. The structure of atherosclerotic lesions in RA shows more signs of inflammation and instability compared to non-RA subjects.

The traditional CV risk factors influence the risk of CVD in RA, especially when potentiated by inflammatory activity. However, their presence cannot explain the overall risk increase of CVD in patients with RA. Given the similarities between RA-related inflammation and atherosclerotic disease, markers of the RA-related inflammation have been assessed as potential risk factors. Elevated levels of CRP and ESR have been associated with an increased risk of subclinical CVD, CVD and CVD-related mortality in RA. Other indications of severe RA disease, such as extra-articular manifestations and high disease activity have also been associated with an increased risk of CVD and CV-related mortality. Low functional status, measured using HAQ has also been associated with CVD and CV-related mortality.

Several studies have associated RF-positivity with an increased risk of clinically significant CVD in RA, whereas one study comparing two different cohorts from different time periods found an association with RF-positivity and CVD in the older cohort, but failed to replicate the association in the more recent cohort. There is no established exact role for RF in the development of CVD, why it remains unclear whether RF itself actually influences the risk of CVD or if RF-positivity reflects the higher disease activity and inflammatory activity in this subgroup of RA patients. ACPAs are newer autoantibodies used in the diagnosis and classification of RA and fewer studies have addressed their potential role as a RA-related risk factor for CVD. However, ACPA-positivity has been associated with an increased risk of CVD in the general population as well as an increased risk of IHD in RA. ACPA-positivity in RA
has also been associated with an increased risk of subclinical manifestations of CVD, such as structural myocardial abnormalities and more substantial atherosclerotic lesions. RA has also been associated with a higher degree of citrullination of the myocardial interstitium compared to non-RA subjects. No observational study has assessed the impact of fine-specific ACPA-titres and the risk of CVD. However, specific ACPAs have been associated with markers of endothelial dysfunction and overall atherosclerotic burden.

Various genetic markers have also been associated with the increased risk of CVD in RA. The HLA-DRB1*0404 and 2 alleles of HLA-DRB1*0104 have been associated with an increased risk of CVD and CV-related mortality in RA. Polymorphisms of several genes have also been associated with an increased risk of CVD in RA.

Treatment with MTX has been associated with a decreased risk of CVD in RA, whereas assessments of the impact of glucocorticoids on the CV risk has been inconclusive. It is unclear whether the association between MTX and reduced CV risk is caused by a direct effect on atherosclerotic lesions or reflects the reduction in RA-related inflammation.

These previously published studies of risk factors for CVD and CV-related mortality in RA are summarized in table 2.1. The vast majority of these studies have used CVD as a composite outcome including several subtypes of the disease.

A few additional studies have addressed potential risk factors for HF RA (summarized in table 2.2). In similarity with studies on CVD overall, high inflammatory activity measured using ESR or CRP, high DAS28, RF-positivity and other signs of severe RA have been associated with an increased risk of HF. None of the studies distinguish between different types of HF.
Table 2.1 Previously published studies of risk factors for cardiovascular disease and cardiovascular death in rheumatoid arthritis (not including papers with drugs as main exposure/s).

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>YEAR OF DIAGNOSIS</th>
<th>STUDY DESIGN</th>
<th>INCIDENT RA</th>
<th>DISEASE DURATION</th>
<th>MEAN/MEDIAN FOLLOW-UP</th>
<th>MEAN/ MEDIAN AGE AT STUDY ENTRY</th>
<th>OUTCOMES</th>
<th>RISK FACTORS</th>
<th>RELATIVE RISK (95% CI)</th>
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<td>5 (2-12) mo</td>
<td>N/A</td>
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<td>HLA-DRB1</td>
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<td>Gonzalez-Gay</td>
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<td>13 (10-16) yr</td>
<td>61 (51-70)</td>
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<td>55 (42-68)</td>
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<td>RF+</td>
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<td>DAS28 Baseline</td>
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<td>DAS28 AUC</td>
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<td>Innala</td>
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<td>5 yr</td>
<td>55 ± 14</td>
<td>CVD</td>
<td>DAS28 Baseline</td>
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<td>DAS28 AUC</td>
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<td>DAS28 AUC 6mo</td>
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<td>CVD</td>
<td>RF+</td>
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<td>DAS28 AUC 2 yrs</td>
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<td>Cohort</td>
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<td>4 (2-10) mo</td>
<td>10.3 (10.1-10.8) yr</td>
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<td>13 (8-21) yr</td>
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<td>11 ± 8yr</td>
<td>54 ± 15</td>
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<td>16 ± 12 yr</td>
<td>3yr</td>
<td>62 ± 13</td>
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<td>N/A</td>
<td>63 (56-70)</td>
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<td>IL-6-174G/C Polymorphism</td>
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<td>Panoulas146</td>
<td></td>
<td>Case-control</td>
<td>No</td>
<td>10 (4-18) yr</td>
<td>N/A</td>
<td>63 (56-70)</td>
<td>CVD</td>
<td>Lymphotoxin 252A&gt;G Polymorphism</td>
<td>OR 2.6 (1.1-5.9)</td>
</tr>
<tr>
<td>Palomino-morales149</td>
<td>1996-2006</td>
<td>Case-control</td>
<td>No</td>
<td>N/A</td>
<td>14 ± 9 yr</td>
<td>N/A</td>
<td>CVD</td>
<td>MTHFR A1298C Polymorphism</td>
<td>5 yr OR 1.5 (1.0-2.1)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>10 yr OR 1.6 (1.1-2.4)</td>
</tr>
<tr>
<td>Gonzalez139</td>
<td>1955-1995</td>
<td>Cohort</td>
<td>Yes</td>
<td>N/A</td>
<td>16 yrs</td>
<td>RF+ 57</td>
<td>CV Death</td>
<td>RF</td>
<td>RF+ SMR 1.4 (1.0-1.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RF- 60</td>
<td></td>
<td></td>
<td>RF- SMR 1.0 (0.7-1.4)</td>
</tr>
<tr>
<td>Turesson137</td>
<td>1939-2001</td>
<td>Cohort</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>CVD</td>
<td>ExRA</td>
<td>HR 3.8 (2.0-7.2)</td>
</tr>
<tr>
<td>Kapetanovic154</td>
<td>1985-1989</td>
<td>Cohort</td>
<td>Yes</td>
<td>11 ± 7 mo</td>
<td>N/A</td>
<td>51 ± 12</td>
<td>CVD</td>
<td>AUC CRP/ESR/DAS yr 1/1-2/0-2</td>
<td>No association</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DMARDs yr 1/1-2/0-2</td>
<td>No association</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GC yr</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>López-Longo140</td>
<td>1988-2003</td>
<td>Cohort</td>
<td>No</td>
<td>11 ± 8 yrs</td>
<td>N/A</td>
<td>52 ± 13</td>
<td>IHD</td>
<td>ACPA+</td>
<td>OR 2.6 (1.2-5.7)</td>
</tr>
</tbody>
</table>

*Inflammatory polyarthritis 8 At baseline/study recruitment 9HLA-DRB1*01|*04 compared to 0 or 1 SE allele *Symptom duration for inception cohort and disease duration for prevalent non-inception cohorts. **Time-dependent covariates
mo, months; yr, years; HR, Hazard ratio; OR, Odds ratio; SMR, standardized mortality ratio; CVD, cardiovascular disease; IHD, ischemic heart disease; PE, Pulmonary embolism; DVT, deep venous thrombosis; HT, hypertension; DAS28, Disease activity score; HAQ, Health assessment questionnaire; GC – Glucocorticoids; DMARD, disease modifying antirheumatic drug; ExRA, extra articular disease manifestations; RF+,Rheumatoid factor positivity; RF-, rheumatoid factor negativity
<table>
<thead>
<tr>
<th>Author/s</th>
<th>Country</th>
<th>Year of RA-diagnoses</th>
<th>Study Design</th>
<th>Study Size</th>
<th>Incident/Prevalent RA</th>
<th>Mean/Median age at study entry</th>
<th>Mean/Median FUP</th>
<th>Outcomes</th>
<th>Prevalence/Incidence rate</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolfe</td>
<td>USA</td>
<td>&lt;1999</td>
<td>Retrospective cohort-study NDBa</td>
<td>9093 RA 2470 OA</td>
<td>N/A</td>
<td>RA – 59.8 ± 13.0 OA – 66.0 ± 11.2</td>
<td>N/A</td>
<td>(self-reported)</td>
<td>Prevalence (/100 pts) RA 2.3(2.0-2.8) OA 1.6 (1.5-1.8)</td>
<td>OR 1.4 (1.3-1.6)</td>
</tr>
<tr>
<td>Myasoedova</td>
<td>USA</td>
<td>1980-2008</td>
<td>Population-based cohort-study REPb</td>
<td>795 RA</td>
<td>Incident</td>
<td>55.3 ± 15.5</td>
<td>9.7 ± 6.9 yrs</td>
<td>(Framingham)c Incident HF</td>
<td>N/A</td>
<td>RF+ HR 1.6 (1.0-2.5) Incident ESR ≥60 HR 1.6 (1.2-2.0) Repeat ESR ≥60 HR 2.1 (1.2-3.5) Severe ExRA HR 3.1 (1.9-5.1) RA &lt; 1 yr HR 2.0 (1.1-3.8) DAS28&gt;2.6</td>
</tr>
<tr>
<td>Schau</td>
<td>Germany</td>
<td>N/A</td>
<td>Prospective cross-sectional</td>
<td>157 RA 77 matched controls</td>
<td>N/A</td>
<td>RA 61 ± 13 Controls 59 ± 12</td>
<td>N/A</td>
<td>Prevalent HF</td>
<td>N/A</td>
<td>OR 3.4 (1.3-9.8) RA-duration &gt;10yrs OR 2.6 (1.2-5.8) CRP median &gt;10 OR 4.8 (1.1-21) ESR &gt;16 OR 5.4 (1.1-16)</td>
</tr>
<tr>
<td>Nicola</td>
<td>USA</td>
<td>1955-1995</td>
<td>Population-based retrospective cohort</td>
<td>575 RA 583 Non-RA</td>
<td>Incident</td>
<td>RA 57 ± 15 Non-RA 57 ± 15</td>
<td>Median (iqr) RA 12(7-20) yrs Non-RA 14 (8-23) yrs</td>
<td>Incident HF</td>
<td>IR (/100 pyrs) RA 1.99 Non-RA 1.16</td>
<td>All HR 2.0 (1.5-2.5) RF+ HR 2.5 (1.9-3.3) RF- HR 1.4 (1.0-2.0)</td>
</tr>
<tr>
<td>Nicola</td>
<td>USA</td>
<td>1955-1995</td>
<td>Population-based retrospective cohort</td>
<td>603 RA 603 non-RA</td>
<td>Incident</td>
<td>RA 58 ± 15 Non-RA 58 ± 15</td>
<td>Median RA 13 yrs (8842 pyrs) Non-RA 15 yrs (10101pyrs)</td>
<td>Incident HF</td>
<td>IR(/1000pyrs) RA 19 (16-22) Non-RA 12 (10-14)</td>
<td>Chf-related mortality RA HR 4.9 (3.8-6.1) Non-RA HR 4.3 (3.3-5.5)</td>
</tr>
<tr>
<td>Gabriel</td>
<td>USA</td>
<td>1965-1985</td>
<td>Population-based cohort</td>
<td>450 RA 450 controls</td>
<td>Prevalent</td>
<td>RA 64.1 Controls 67.5</td>
<td>N/A</td>
<td>HF</td>
<td>RA 17.3% Controls 12.0%</td>
<td>1.60 (1.12-2.27)</td>
</tr>
</tbody>
</table>

aNational data bank for rheumatic diseases. Enrolled patients receive survey at 6 month intervals. bRochester epidemiology project. cFramingham heart failure criteria: HF, Heart failure; RA, rheumatoid arthritis; OA, Osteoarthritis; OR, odds ratios; pts, patients; RF+, Rheumatoid factor positivity; HR, Hazard ratio; ExRA, Extraarticular RA; yrs, Years; PYRS, person-years; MI, Myocardial infarction
2.3.3 Clinical presentation

As the development of CVD in RA seems to be, at least partly, driven by factors other than the traditional CV risk factors and inflammatory activity has been linked to the severity of ACS and more extensive coronary atherosclerosis, patients with RA might hypothetically experience a different clinical phenotype of ACS compared to non-RA patients. Few studies have addressed the clinical presentation of ACS in RA and the existing scarce results are inconclusive. Nevertheless, patients with RA have been reported to present with atypical symptoms more often as well as experiencing silent MI, collapse or sudden cardiac death more frequently compared with non-RA patients. In contrast, no difference other markers of severity such as Killip class or NSTEMI vs. STEMI has been reported (summary of previous studies of clinical ACS-presentation in table 2.3).

RA has also been associated with a subtler presentation of HF and higher frequencies of HFREF compared with non-RA patients.

2.3.4 Outcomes

Inflammatory activity has been linked to adverse outcomes following ACS in the general population. Studies investigating short-term outcomes following ACS have reported both no differences as well as increased short-term mortality in RA compared to non-RA patients. An increased risk of long-term mortality and recurrent events in patients with RA with ACS compared to non-RA patients with ACS (summary of previous studies of outcomes following ACS in RA in table 2.3).

2.3.5 Follow-up care

Follow-up care after ACS aims to prevent further CV events, and consists of modification of risk factors using pharmacotherapies and other preventive measurements as discussed in the previous section. Few studies have assessed the usage of secondary preventive drugs in patients with RA following ACS. One case-control study has reported that the in-hospital usage of beta-blocking agents and lipid-lowering agents was lower among RA-patients compared to population controls, whereas another study of in-hospital treatments could not detect a difference. Lower rates of initiation and adherence to aspirin, beta-blocking agents and lipid-lowering agents were also observed in a nationwide Danish cohort-study.
Table 2.3 Previous studies assessing clinical ACS characteristics and outcomes following ACS in patients with RA.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Study size</th>
<th>Year of event</th>
<th>Outcome/s</th>
<th>Follow-up</th>
<th>Relative risk Case-fatality</th>
<th>Clinical characteristics outcomes</th>
<th>Difference/Relative risk clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maradit-Kremers</td>
<td>Cohort</td>
<td>603 RA-subjects and 603 comparators</td>
<td>Fup 2001</td>
<td>Incident CHD Information retrieved from medical records</td>
<td>RA: 14.7 yrs Non-RA: 16.8 yrs NOT ASSESSED</td>
<td>Unrecognized MI(^a) HR 2.20 (1.18-4.18)</td>
<td>PTCA HR 1.77 (0.92-3.41)</td>
<td>CABG HR 0.35 (0.16-0.78)</td>
</tr>
<tr>
<td>Douglas</td>
<td>-</td>
<td>40 RA-patients 40 Controls with incident ACS</td>
<td>1990-1999</td>
<td>Clinical presentation, All-cause mortality, CV-mortality and recurrent cardiac events. Collected from medical charts and death certificates.</td>
<td>31(^{st}) Dec 2001</td>
<td>RA 48% vs. controls 25% (p=0.036)</td>
<td>Chest pain RA 82% vs. controls 100 % (p=0.003)</td>
<td>Dyspnoea NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CV-Death RA 40% vs. controls 15% (p=0.012)</td>
<td>Dyspnoea NS</td>
<td>NS</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrent ACS RA 45% vs. controls 25% (p=0.011)</td>
<td>Collapse RA 18% vs. controls 3% (p=0.025)</td>
<td>Arrhythmia NS</td>
</tr>
<tr>
<td>Södergren</td>
<td>Cohort</td>
<td>35 RA-subjects and 105 matched controls with incident MI</td>
<td></td>
<td>All-cause mortality</td>
<td>24 h HR 1.26, p=0.58 28 days HR 1.43, p=0.27 5 yrs HR 1.56, p=0.11 10 yrs HR 1.67 (1.02-2.71)</td>
<td>Typical ECG-signs RA 17% vs. controls 34%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCoy</td>
<td>Cohort</td>
<td>77 RA-subjects and 154 matched controls with MI</td>
<td>1979-2009</td>
<td>All-cause mortality</td>
<td>FUP RA med 2.6yr Comp 2.7 yr</td>
<td>Killip class II-IV RA 36% vs. Comparators 35% (NS)</td>
<td>STEMI RA 21% vs. Comparators 28% (NS)</td>
<td>Revasc. Procedures OR 1.19 (0.63-2.23)</td>
</tr>
<tr>
<td>Authors</td>
<td>Study Design</td>
<td>Study size</td>
<td>Year of event</td>
<td>Outcome/s</td>
<td>Follow-up</td>
<td>Relative risk Case-fatality</td>
<td>Clinical characteristics outcomes</td>
<td>Difference/Relative risk clinical characteristics</td>
</tr>
<tr>
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</tr>
<tr>
<td>Van Doornum¹⁶¹</td>
<td>Cohort</td>
<td>359 RA</td>
<td>2001-2003</td>
<td>All-cause mortality after MI</td>
<td>30 Days</td>
<td>OR 2.3 (1.6-3.1) Adj.OR 1.8 (1.3-2.6)</td>
<td>CHF during hospitalisation</td>
<td>OR 1.6 (1.2-2.1) Adj.OR 1.2 (0.9-1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29924 comparators</td>
<td></td>
<td>CVD mortality after MI</td>
<td>30 Days</td>
<td>OR 2.3 (1.7-3.2) Adj.OR 1.9 (1.3-2.7)</td>
<td>PTCA</td>
<td>OR 0.4 (0.3-0.7)</td>
</tr>
<tr>
<td>Van Doornum¹⁶²</td>
<td>Cohort</td>
<td>90 RA patients</td>
<td>1995–2005</td>
<td>(medical chart review)</td>
<td>NOT ASSESSED</td>
<td></td>
<td>CABG</td>
<td>Insufficient sample size</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90 comparators</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ICU/CCU</td>
<td>OR 0.6 (0.5-0.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute reperfusion</td>
<td>OR 0.27 (0.1-0.6) Adj.OR 0.21 (0.1-0.6)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombolysis</td>
<td>OR 0.3 (0.1-0.8) Adj.OR 0.3 (0.1-1.0)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>PCI</td>
<td>OR 0.2 (0.1-0.5) Adj.OR 0.2 (0.1-0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PCA</td>
<td>OR 0.4 (0.2-0.9) Adj.OR 0.2-1.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CABG</td>
<td>OR 0.6 (0.2-1.5) Adj.OR 0.3 -1.7)</td>
</tr>
</tbody>
</table>

¹Unrecognised MI defined as presence of characteristic ECG-findings in non-acute setting

CHD, coronary heart disease; MI, Myocardial infarction; ACS, acute coronary syndrome; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting
3 RATIONALE FOR THE SPECIFIC SUB-STUDIES

3.1 STUDY I – RISK FACTORS FOR ACS IN RA

Firstly, most previous studies assessing potential risk factors for CVD in RA are based on older cohorts, making the results difficult to extrapolate to the contemporary RA-patient, with an in comparison more modern and different treatment regime. Secondly and importantly, the vast majority of these studies have used CVD as a composite outcome, in which several subtypes of and also different combinations of subtypes of CVD have been included. Composite outcomes, such as CVD, are commonly used, especially in cardiovascular research, in order to increase the event rate and in this way also increase the statistical efficiency. Limitations using composite end points and difficulties in interpreting the results have repeatedly been pointed out, and several aspects must be considered when interpreting the results from studies using a composite outcome. The validity of the composite outcome partly depends on the number of events across components. Furthermore, using a composite outcome requires an underlying assumption of a similar underlying biological mechanism behind the association between the exposure and the respective component. Hence, the existing results from studies of risk factors for CVD in RA are difficult to relate to specific CV events, such as ACS.

The previous reported differences in time-to-risk between different types of CVDs in RA indicate that the pathophysiologies behind the risk increases are in fact at least partly different. It is possible that some of the risk factors are shared but contribute to the risk increases via different routes. For example, the risk of IHD seems to increase rapidly after RA-onset, in contrast to the risk of cerebrovascular events, which develops later. Hypothetically, inflammation constitutes a risk factor for ACS by making existing atherosclerosis unstable or via other direct effects on the coagulation or coronary circulation. Long-term inflammation might instead lead to more extensive atherosclerosis and an increased risk of cerebrovascular events as a consequence.

In Study I, we aimed to assess potential risk factors for ACS in RA in order to identify clinically usable and easily accessible predictors of the ACS-risk in patients with RA.

3.2 STUDIES II AND III – CLINICAL CHARACTERISTICS AND OUTCOMES

The results from Study I indicated that high inflammatory activity and disease activity soon after RA-onset triggers an increased risk of ACS in patients with new-onset RA. These results are in line with previous reports, and inflammation has also been shown to potentiate the effect of traditional CV risk factors in patients with RA. Given that
the risk of ACS in RA seems to be driven partly by factors other than the traditional CV risk factors, one might question whether the clinical phenotype of ACS in RA differs compared with ACS in non-RA patients (driven by traditional CV risk factors). As described in the background, inflammation affects the characteristics of the atherosclerotic plaque. Specific inflammatory cells and mediators are known to impair the collagen synthesis, which leads to thinner fibrous caps covering the atherosclerotic lesion.\textsuperscript{169} Most severe and fatal MIs are typically caused by a ruptured thin cap.\textsuperscript{85} Systemic inflammation also promotes thrombus accumulation by increased thrombogenicity. In the general population, the degree of inflammatory activity has also been linked to adverse outcomes following ACS.\textsuperscript{96}

Based on the above a priori knowledge of the impact of inflammation on the ACS phenotype we hypothesized that patients with RA differ in their clinical presentation of ACS in comparison with non-RA patients with ACS. Importantly, a different clinical presentation and increased risk of adverse outcomes might motivate a different risk stratification of this group of patients. Only a few previous studies have assessed the clinical characteristics and outcomes after ACS in RA, and their results have been inconclusive. Furthermore, most of these studies have been based on a small number of RA-patients and controls leading to statistical imprecision and difficulties in interpreting the results. There have, however, been indications, such as an increased risk of sudden cardiac deaths,\textsuperscript{107} that patients with RA suffer from more severe events and impaired short- and long-term outcomes.\textsuperscript{105, 107, 156, 157, 161}

With the apparent gap in our knowledge of clinical presentation and prognosis after ACS in RA in mind, we aimed at comparing these parameters in RA-patients compared to non-RA patients with ACS in \textit{Study II} and \textit{Study III}.

An impaired outcome following ACS could, of course, have causes other than the clinical phenotype itself. As described in the background, usage of standard of care secondary preventive drugs is beneficial for, in particular the long-term prognosis following ACS. A difference in usage of secondary prevention between RA and non-RA patients with ACS could therefore potentially explain a difference in observed adverse long-term outcomes. As for studies on clinical characteristics and prognosis, few studies with conflicting results have assessed treatment following ACS in patients with RA. Two of these studies have assessed in-hospital treatment, and no information on usage thereafter, of various agents making the results difficult to extrapolate to long-term outcomes.\textsuperscript{163} One larger cohort-study has assessed initiation and adherence to gold standard secondary preventive drugs following ACS during a two time periods of 30 and 180 days following ACS. This study has, however, not taken the increased mortality rate among RA-patients into account in its design, which might lead to an underestimation of the drug usage among RA-patients due to a higher frequency of
Furthermore, none of the studies have assessed secondary preventive drug usage and mortality in the same study and have therefore not assessed mortality in groups with a known combination of drugs. In Study III, therefore, in addition to assessing long-term outcomes, we also investigated the usage of gold standard secondary preventive drugs following ACS in the RA patients compared to non-RA patients with ACS.

3.3 THE RELATIVE RISK OF HEART FAILURE IN RA

Heart failure is associated with substantial morbidity and mortality, and has several potential aetiologies. Hypertension and IHD are the most common causes of HF in high-income countries, and it is, therefore, no surprise that patients with RA, who are at increased risk of IHD also seem to suffer from an increased risk of HF. Inflammatory activity has been associated with HF, and it has been suggested that inflammation is not only a marker of disease, but rather a cause and is involved in the pathogenesis. In animal studies have shown that the inflammation in sepsis leads to myocardial depression. For example, several of the inflammatory cytokines, such as TNF-α, associated with myocardial depression are also involved in the pathogenesis of RA.

Firstly, only a small number of studies have addressed the association between RA and HF, but they have all indicated an increased incidence, prevalence and HF-related mortality in RA. Hypothetically, the increased incidence of HF in RA could, in addition to developing after IHD, also be driven by RA-related inflammation or other factors directly. Yet, no study has investigated the risk of HF in RA in the presence and absence of IHD separately, or the impact of clinical markers of inflammation and disease activity on different HF subtypes. Based on these grounds, in Study IV we assessed the RR of ischemic and non-ischemic HF overall and in time periods before and after RA-onset as well as the impact of RA-related inflammation and disease activity.
4 OBJECTIVES

4.1 OVERALL OBJECTIVES

The overall objective of this thesis was to expand existing knowledge of the association between RA and specific CVD-types, CVD outcomes and CVD management.

4.2 SPECIFIC OBJECTIVES

The following specific aims have been addressed within the four sub-studies of this thesis:

1. To identify risk factors for ACS in patients with new-onset RA Study I
2. To describe the clinical characteristics of, and short-term mortality after, ACS in patients with RA Study II
3. To assess the long-term recurrence and mortality following ACS in patients with RA, and to investigate whether usage of secondary preventive drugs differs in patients with RA compared to non-RA subjects Study III
4. To estimate the relative risk of ischemic and non-ischemic HF in RA and to assess the impact of RA disease activity on the HF risk Study IV

Figure 4.1 Overview objectives
5 METHODS

5.1 SETTING

The long tradition of collecting and compiling information on the inhabitants in Sweden, initiated as early as in the 17th century, has paved the way for the existing national demographic and healthcare registers with nearly complete coverage. In combination with the structure of the Swedish health care system, these comprehensive register sources provide an excellent setting for conducting epidemiological research. Nevertheless, regardless of the extensive nature of the register sources there are many sources of potential bias to consider in epidemiological research, some of which are discussed in this section and others in the discussion section.

Traditionally, Swedish health and welfare services have been tax-financed and have been considered a public responsibility, enabling equal access to all healthcare services. Maintaining the equity in the access to health care has been a growing reason for concern as health care gradually has moved toward an increased proportion of market-orientation. However, access to specialized care for chronic diseases such as RA and acute conditions such ACS, which is concentrated to hospital emergency, inpatient or outpatient care, still seems to remain equal and importantly enables identification of unselected population-based cohorts including patients with these conditions. Prescribed standard drugs are subsidized, and after reaching a fixed annual spending limit, all subsequent prescriptions are free of charge.

The Swedish personal identity number (PIN) was introduced in 1947, and since 1967 it has consisted of a six-digit birthdate followed by a four-digit identification number. The PIN, which is unique to the individual, is assigned by the Swedish tax agency to all inhabitants at birth or immigration if they are intending to stay for at least one year, and it can be used as an identifier in Swedish health care and other administrative areas. Immigrants with a shorter intended duration of stay will, if utilizing the Swedish social security system, instead be assigned a coordination number, and will not be included in national registers and thus not included in register-based studies such as the ones included in this thesis. In epidemiological research, the PIN can be used for linkage of different data sources.

5.2 DATA SOURCES

Except for the national health registers, quality of care registers to evaluate and improve the quality of care for specific diseases of interest, such as RA and CVD, have been developed. Using the PIN as a key, information from these different register
sources can be linked together when researchers perform register-based epidemiological research. Data used in the studies of this thesis was collected from several national registers, quality registers and medical charts

5.2.1 National registers

National demographic registers are kept by Statistics Sweden, and the national health registers are kept by the National Board of Health and Welfare (NBWH).

5.2.1.1 The total population register

The total population register (TPR) contains demographic information such as birth, death, sex, residential care, civil status and information on migrations, and since 1968 has been kept by Statistics Sweden.\textsuperscript{176} TPR was used to sample general population comparators in Studies II–IV.

5.2.1.2 The National Patient Register

The National Patient Register (NPR) has since 1964 contained information on in-hospital care with complete coverage since 1987. Since 2001, NPR has also contained an outpatient part that includes visits to non-primary care with increasing coverage in the last few years (87% of all visits were reported in 2013). NPR holds information on admission, discharge dates and type of hospital department involved.\textsuperscript{177} Discharge primary and contributory diagnoses are coded according to the contemporary Swedish version of the International Classification of Diseases (ICD) system. The ICD10 coding system has been in use since 1997. Validity of many diagnoses, especially those of chronic and severe diseases, has been proven to be high in the NPR.\textsuperscript{178} NPR is a resourceful tool when conducting register-based research, and is used for identifying study subjects and/or outcomes of interest in all of the studies included in this thesis.

5.2.1.3 The Cause of Death Register

Information on death and causes of deaths in Sweden has been kept in the Cause of Death Register (CDR) since 1961.\textsuperscript{179} The international version of the ICD-system is used to code the supposed cause of death. CDR is also used in all studies included in this thesis.

5.2.1.4 The Prescribed Drug Register

Information on dispensed prescribed pharmacotherapies has been collected from the Prescribed Drug Register (PDR) since July 2005. The PDR contains information on the prescribed drug in the form of an Anatomical Therapeutic Chemical (ATC) code, name, dosage, expenditure, administration-route as well as information on the prescriber and the patient\textsuperscript{174}. In Study I, PDR was used to identify certain exposures of interest, in Studies II and IV PDR was used to collect information on drug-status at
baseline that served as proxies for comorbidities of interest, and in Study III, where one of the outcomes was CV secondary preventive drug use, PDR was used to collect this information.

5.2.2 Quality of care registers

Both RA-specific and CVD-specific quality of care registers were used to obtain data used in the studies of this thesis.

5.2.2.1 Swedish Rheumatology Register

The Swedish Rheumatology Register (SRQ), initiated in 1995, includes patients with predominantly RA but also other rheumatic diseases diagnosed by rheumatologists. Initially, only patients with new-onset RA and patients on specific drugs were included, but the utility of the register has expanded over the years to include patients with established disease. SRQ contains information on disease duration, inflammatory activity and overall disease activity collected at pre-specified time points, and is used by rheumatologists to evaluate the disease-activity of their patients. SRQ includes over 15,000 patients with new-onset RA. In Study I, SRQ was used to collect information on inflammatory activity and disease activity, which was combined with information retrieved from medical charts of the study subjects. In Study IV, SRQ was used to identify one cohort of patients with new-onset RA and for the study subjects of this cohort also to extract information on inflammatory and disease activity.

5.2.2.2 RIKS-HIA

RIKS-HIA RIS-HIA started as a regional register at the beginning of the 1990s and was established as a national quality of care register for heart intensive care in 1995. RIKS-HIA is part of SWEDEHEART, which collects data for five separate registers aiming to support and improve the development of evidence-based therapies in acute and chronic coronary artery disease. Based on admissions to cardiac intensive care units, RIKS-HIA includes information on baseline characteristics, symptoms, in-hospital examinations, treatments, interventions, complications and discharge-status. Coverage has improved over the years and is generally higher in patients younger than 80 (92% in 2015) compared to patients older than 80 (75% in 2015) due to different inclusion criteria for patients above 80 depending on geographical region. In Study IV, where one of the outcomes was clinical ACS characteristics, data were collected from RIKS-HIA.
5.2.3 Other data sources

5.2.3.1 Epidemiological investigation of rheumatoid arthritis

The epidemiological investigation of rheumatoid arthritis (EIRA) is a population-based case-control study of incident RA. The cases enrolled constitute patients between 18 and 70 years of age diagnosed with new-onset RA by rheumatologists from clinics in central and southern Sweden. Questionnaires are used to collect information on health status, lifestyle related factors and environmental exposures. Blood samples are drawn for analysis of autoantibodies and DNA extraction. For each case, a control is sampled using the TPR and matched on sex, age and area of residency. As for all the cases, participating controls are asked to complete the questionnaire and provide a blood sample. In Study I, both cases and controls were sampled from the cases included in EIRA. Information on certain CV risk factors, as reported on the questionnaires, autoantibodies and selected genetic markers was also extracted from EIRA.

5.2.3.2 Medical charts

All health care personnel are by law obligated to document everything concerning the patients’ health status related to the health care visit or hospitalization in the patient’s medical record, which is individually linked to the patient via the PIN. The medical record should include relevant background information as well as diagnoses, assessments, laboratory measurements, examination findings, treatments, etc. Apart from being an important clinical instrument ensuring patient security and useful for health care evaluations, the medical chart is also a useful research tool and can be used to validate information from other register sources as well as providing detailed information on variables of interest. In Study I, medical charts for all study subjects were retrieved so as to validate the outcome as well as collect information on selected disease variables.

Figure 5.1 Overview of data sources included in the respective study.
5.3 STUDY POPULATIONS AND STUDY DESIGNS

5.3.1 Overview

The different aims of the four sub-studies required slightly different definitions of RA with/without ACS (the exposure) to suit the specific objective/s with the respective study.

Exposures, outcomes and other covariates of interest have all been collected from the various data sources described in the previous section. This register-based setting is very different from the clinical setting where the physician has direct access to the patient and thereby can confirm the different variables of interest direct. Although diagnoses and/or drugs registered in the national health registers readily can be used as proxies in register-based research, it is crucial using well-deliberated definitions to avoid introducing bias. The different definitions of RA used in the sub-studies are either based on inclusion in SRQ or EIRA (as reported by rheumatologist) or on validated diagnostic algorithms using the NPR. Incident RA is defined as new-onset RA, whereas prevalent RA is defined as established disease including patients with various disease durations. Outcomes (ACS, IHD and HF) have typically been captured using the NPR and/or CDR where most diagnoses have a high reported validity. See table 5.1 for detailed information on validity on respective exposure and outcome used in the different studies.

Table 5.1 Overview of validity of exposures and outcomes of the respective study.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DIAGNOSIS DEFINITION</th>
<th>REFERENCE</th>
<th>GOLD STANDARD</th>
<th>VALIDITY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY I</td>
<td>Incident RA in EIRA</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Patients are diagnosed and included by rheumatologists</td>
</tr>
<tr>
<td>STUDY II &amp; III</td>
<td>Prevalent RA in the national patient register</td>
<td>Waldenlind et al. 183</td>
<td>Medical charts</td>
<td>PPV = 90%</td>
<td>Fulfilment of 2010 ACR/EULAR classification criteria</td>
</tr>
<tr>
<td>STUDY IV</td>
<td>Prevalent RA the national patient register</td>
<td>Waldenlind et al. 183</td>
<td>Medical charts</td>
<td>PPV = 90%</td>
<td>Fulfilment of 2010 ACR/EULAR classification criteria</td>
</tr>
<tr>
<td>STUDY IV</td>
<td>Incident RA in the Swedish rheumatology register</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Patients are diagnosed and included by rheumatologists</td>
</tr>
</tbody>
</table>
### Table 5.1 Continued

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DIAGNOSIS DEFINITION</th>
<th>REFERENCE</th>
<th>GOLD STANDARD</th>
<th>VALIDITY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STUDY I, II and III</strong></td>
<td>ACS = Main diagnosis of ACS (MI or UAP)</td>
<td>Lintersjö et al. 184, Ljung et al. 185</td>
<td>Medical charts</td>
<td>PPV = &gt;95%</td>
<td></td>
</tr>
<tr>
<td><strong>STUDY IV</strong></td>
<td>HF overall = Main diagnosis of HF in</td>
<td>Ingelsson et al. 186</td>
<td>Medical charts</td>
<td>PPV = &gt;95%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ischemic HF = Main diagnosis of HF in patients with an antedating diagnosis of IHD or specific ICD-code indicating ischemic HF</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>The exact definition used has not been validated. However, HF\textsuperscript{186} and IHD\textsuperscript{184} have separately been reported to have high validity.</td>
</tr>
<tr>
<td></td>
<td>Nonischemic HF = Main diagnosis of HF in patients without an antedating diagnosis of IHD</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>The exact definition used has not been validated. However, HF\textsuperscript{186} and IHD\textsuperscript{184} have separately been reported to have high validity.</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; EIRA, epidemiological investigation of rheumatoid arthritis; HF, heart failure; PPV, positive predictive value; MI, myocardial infarction; NPR, national patient register; UAP, unstable angina pectoris

### 5.3.2 Study I

#### 5.3.2.1 Study design

Study I is a nested case-control study in which cases (subjects with RA and ACS) and controls (subjects with RA without ACS) were sampled among patients with incident RA included in the EIRA-study between 1996 and 2011.
5.3.2.2 Study population

Cases were defined as subjects with incident RA included in EIRA between 1996 and 2011 who, after the RA-diagnosis, developed an ACS during the follow-up. Between 1996 and Dec 31th 2009, ACS was defined as a registered diagnostic code for ACS and/or intervention for ACS and/or CDR during the follow-up. This initial definition of ACS was validated against medical records, and cases which did not fulfil the diagnostic criteria for ACS as defined by the Joint European Society of Cardiology/American College of cardiology Committee were excluded. Validation of ACS showed, consistent with previous validations, a high predictive value for ACS identified using diagnostic code in NPR and/or CDR, whereas most events captured using intervention codes could not be classified as ACS (and hence were excluded). Therefore, only diagnostic code for ACS was used when identifying study subjects during an extended period of follow-up between 2010 and 2012.

Controls were sampled from the same cohort of subjects with incident RA enrolled in EIRA between 1996 and 2011. Up to five unique controls, who did not develop ACS during the follow-up, were matched to each case using incidence density sampling (see box 5.1 for description of incidence density sampling) based on sex, year of RA-diagnosis and EIRA-centre.

Box 5.1 Incidence density sampling

Incidence density sampling is sometimes also referred to risk set sampling. The controls are selected from the entire at-risk source population at the time point as the case is identified (and are eligible to become a case during a later time point). The control serie provides an estimate of the proportion of the total person-time for exposed and unexposed in the source population.

The advantages with incidence density sampling are that the odds ratio estimates the rate ratio and that the estimate is not biased due to differential loss of follow-up.

5.3.2.3 Exposures of interest

Information on the exposures of interests (potential risk factors) was collected from several register sources in combination with information extracted from the medical charts. Table 5.2 provides an overview of these exposures and their respective data sources.
Table 5.2 Exposures and their respective data source, Study I.

<table>
<thead>
<tr>
<th>EXPOSURE</th>
<th>DATA SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV risk factors: BMI and Smoking at baseline</td>
<td>EIRA</td>
</tr>
<tr>
<td>CVD at baseline</td>
<td>EIRA, Medical charts, NPR</td>
</tr>
<tr>
<td>Disease activity during follow-up</td>
<td>Medical charts, SRQ</td>
</tr>
<tr>
<td>Autoantibodies, genetic markers</td>
<td>EIRA</td>
</tr>
<tr>
<td>RA Drugs</td>
<td>Medical charts, PDR</td>
</tr>
</tbody>
</table>

5.3.3 Study II and Study III

5.3.3.1 Study design

Studies II and III are cohort-studies based on the same cohort of prevalent RA patients with ACS and their matched general population comparators with ACS.

5.3.3.2 Study population

One cohort of prevalent (actively monitored) RA patients was identified each year between 2006 and 2009. Prevalent RA was defined as subjects above 18 years of age with i) at least two RA-diagnoses at in- or out-patient clinics, of which at least one of these visits at internal medicine or rheumatology clinic, or ii) listed in the SRQ. One of the visits had to occur in the years 2006, 2007, 2008 or 2009 to be defined as having actively monitored the disease in that particular year. Between 31,000 and 34,000 subjects were identified each year using this definition and matched with up to five general population comparators based on year of birth, sex, educational level and area of residency using the TPR. Among the comparators, all subjects with a RA-diagnosis prior to the matching-year were excluded.

Follow-up for identifying all subjects with ACS started the year following identification (i.e. the year in which the RA subjects were defined as having prevalent disease) between 2007 and 2010. All subjects with a diagnosis of ACS prior to start of follow-up were excluded. Subsequently, all subjects were followed via linkage with the NPR over one year so as to identify all subjects with a first ever hospitalization for ACS. ACS were defined as a main diagnosis of myocardial infarction or unstable angina.

A total of 1135 RA patients with incident ACS and 3184 general population comparators with incident ACS were identified between 2007 and 2010, and these made up the two study cohorts used for analysing outcomes of interest.

5.3.3.3 Follow-up and outcomes

Clinical characteristics
Among the subjects with incident ACS in the NPR, all subjects also registered with ACS in RIKS-HIA within a time interval of -10 to +10 days following NPR-registration were identified. Information on clinical characteristics for these subjects was retrieved from RIKS-HIA. In order to characterize the clinical event information on status at admission (symptoms, blood pressure, heart rate, Killip class, ECG registration and biomarkers), in-hospital treatments (reperfusion if diagnosed as STEMI and anticoagulants if diagnosed NSTEMI), in-hospital complications and diagnosis at discharge were compiled, analysed and presented in Study II.

Mortality

Following the ACS, all subjects were followed in the CDR to identify all deaths following the ACS. Short-term mortality was defined as mortality during the first week and the first month following the ACS (Study II). For these deaths, the proportion of a specific underlying cause of IHD, HF and/or arrhythmias were also analysed in a sensitivity analysis. Long-term mortality (Study III) was defined as mortality during a follow-up of one year and during a longer follow-up period ending 31 Dec 2011 (Mean 2.3 years).

Recurrence

As long-term mortality, recurrent ACS was analysed at one year and during the complete follow-up period ending 31th Dec 2011. Recurrent ACS was defined as an additional ACS-diagnosis in the NPR during follow-up starting at 30 days after the original ACS-date to avoid double-registrations from the same event.

Secondary preventive drugs

During the year following the ACS, usage of gold standard secondary preventive drugs (aspirin P2Y12-inhibitors, beta-blockers, RAS-blocking agents and statins) was analysed via linkage with the PDR. Initiation and subsequent usage of each drug was defined as the filled prescription of respective drug within four time periods (-7-90, 91-180, 181-270, 271-365 days) after the ACS.

5.3.4 Study IV

5.3.4.1 Study design

Study IV is a cohort study in which the relative risk of HF was assessed in two contemporary cohorts of RA patients compared to matched general population comparators.
5.3.4.2 Study population

Two separate cohorts of RA patients, one population-based cohort with subjects with prevalent disease and one cohort of subjects with incident disease, were identified. The NPR was used to identify the prevalent cohort using a similar algorithm as in Studies II and III. All subjects 18 years or older with at least two visits listing RA, of which at least one visit at internal medicine or rheumatology clinic, at inpatient or outpatient clinic between 2006 and 2012, were identified. The incident cohort was identified using the SRQ, where all patients with new-onset RA, defined as < 12 month with RA symptoms, between 1997 and 2012 were identified. Up to ten general population comparators were matched to each RA patient based on birth year and area of residency using the TPR.

5.3.4.3 Follow-up and outcomes

An index-date, serving as start of follow-up date, was assigned to all study subjects. For the prevalent RA patients, the index-date was set to the second visit listing RA and their corresponding general population comparator subjects received the same index-date. For the patients with incident RA and their matched comparators, the index-date was defined as the date of RA-diagnosis.

All subjects with a diagnosis of HF prior to the index-date were excluded. Study subjects were then followed in the NPR for the outcomes HF overall, ischemic HF and nonischemic HF. The different outcome definitions were based on ICD-coding and required slightly different exclusion-criteria, censorings during the follow-up and actual outcome-definition.

HF overall was defined as a first ever main diagnosis of HF during the follow-up. Ischemic HF was defined as i) a first ever main diagnosis of HF in subjects with a pre-existing diagnosis of IHD, or ii) a first ever main diagnosis specifically indicating ischemic HF. Subjects with incident HF without antedating IHD (nonischemic HF) during follow-up were censored. In contrast, nonischemic HF was defined as a first ever main diagnosis of HF in subjects free of pre-existing IHD. Subjects with IHD prior to the index-date were excluded, and subjects with incident IHD or incident ischemic HF during follow-up were censored. Follow-up ended at fulfilment of outcome definition, December 31th 2012, death, first migration from Sweden or the any of the outcome-specific censoring-criteria. The different outcome definitions are illustrated in Figure 5.2.
<table>
<thead>
<tr>
<th>EXCLUSION-CRITERIA</th>
<th>HF</th>
<th>HF</th>
<th>HF &amp; IHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Censorings during follow-up</td>
<td>Death Migration</td>
<td>Death Migration</td>
<td>Death Migration</td>
</tr>
<tr>
<td></td>
<td>Nonischemic HF</td>
<td></td>
<td>IHD Ischemic HF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>HF Overall</th>
<th>Ischemic HF</th>
<th>Nonischemic HF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>= First main diagnosis of HF</td>
<td>= First main diagnosis of HF in subjects with IHD or ischemic HF</td>
<td>= First main diagnosis of HF in subjects without IHD</td>
</tr>
</tbody>
</table>

**Figure 5.2** Illustration of the different outcome definitions heart failure overall, ischemic heart failure and nonischemic heart failure of *Study IV*. 
Figure 5.3 Illustration of the different study populations and specific outcomes in respective sub-study
5.4 STATISTICAL ANALYSES

5.4.1 Usage of statistics in epidemiological research

Naturally, the aim of most analytic epidemiological research is to assess the causal effect of one exposure (e.g. RA) on one outcome (e.g. HF y/n). Importantly though, statistical analyses used in epidemiology describe the relationship between the exposure and outcome, but do not necessarily imply a causal relationship between the two. Therefore, prior to describing the statistical models applied within the different studies of this thesis, the difference between association and causation and strategies for getting closer to estimating a true causal effect will be briefly discussed.

Estimating the true causal effect would require observation of counterfactual outcomes. This actually means that, apart from observing the outcome (e.g. HF y/n) corresponding to the factual exposure status (e.g. RA), we would also have to observe the outcome in the same study subjects in a scenario where they switch exposure status (to non-RA) under exactly the same time period. Needless to say, this is a completely unrealistic scenario, as we can only observe one outcome corresponding to the factual exposure status; all counterfactual outcomes are missing. In the epidemiological research setting, we try to overcome this issue by attempting to create exchangeability between the exposed (RA) and non-exposed (non-RA) groups. Using Study IV, where the RR of HF in RA, was assessed as an example, exchangeability would imply that the risk of HF would be exactly the same among the non-RA patients as among the RA-patients if they switched exposure-status to RA. The consequence of the risk being equal in all groups defined by exposure status is that the risk must be equal to the risk under exposure in the whole population. In an ideal randomized controlled trial (RCT) where all pre-exposure variables are equally distributed over exposure-levels, exchangeability is achieved by design. Hence, association is equal to causation in the ideal RCT.

Considering that RCTs often are impractical, unethical and unfeasible, we must instead rely on observational studies, such as the ones included in this thesis, in epidemiological research. Exposed and non-exposed groups included in observational studies are not exchangeable. The non-exchangeability is caused by selection bias or confounding. Selection bias arises when the association between exposure and outcome differs in the study population and the source population and is further discussed in the section on methodological considerations. Confounding occurs when the exposure and outcome share common causes (confounders), which distort the observed association. To identify and limit non-exchangeability, all causal and non-causal paths, linking the different variables (including all potential confounders) under study should be identified based on a priori subject matter knowledge about the
underlying biological mechanism before deciding on which analytical approach to take.\textsuperscript{192}

Directed acyclic graphs (DAGs) are a graphical approach to identifying and visualizing the causal relations between the different variables of interest.\textsuperscript{193}

\textbf{Figure 5.4.} Example of a directed acyclic graph (DAG). X represents the exposure, Y the outcome and the directed arrow between them the direct effect of X on Y. Alternative pathways exist via confounder U, mediator V and collider Z.

In Figure 5.4 a basic DAG is provided so as to illustrate the fundamental concepts of DAGs. Variables of interest are linked by arrows, stating a causal effect and also the direction of the effect, i.e. an arrow pointing from X to Y indicates that variable X affects Y. Consider the relationship (path) between X (exposure) and Y (outcome) is the association we are interested in estimating. To do so, all other variables linked to X and Y creating alternative pathways should be identified, and this is where the DAG is truly helpful. Confounders (U) are common causes of exposure and outcomes as previously described. Mediators (V) are factors in the causal pathway between the exposure and outcome. Colliders (Z) are factors that can arise from both exposure and outcome.

Prior to estimating the effect of X on Y, one has to decide which effect is of interest and all ‘back-door’ paths must be identified. Back-door paths are those other than the direct path connecting X and Y and these can be opened or closed. In Figure X, the back-door paths connecting X and Y via confounders U (X-U-Y) and mediators V (X-V-Y) are opened. In contrast, the back-door path via collider Z (X-Z-Y) is closed.\textsuperscript{193}
When aiming to assess the total effect, neither confounders nor mediators are accounted for in the analyses. Aiming to assess the direct effect only requires conditioning on both confounders and mediators in the statistical analysis. Importantly, conditioning on mediators is not uncomplicated as it can result in opening additional paths and thereby introduce bias. The closed back-door path via collider $Z$ should generally not be controlled for, since it results in an open path which could lead to biases.

5.4.2 Statistical concepts

Several factors affect the choice of statistical method, and typically there are a number of assumptions, which should be satisfied for the specific statistical method of choice to be valid. Firstly, there are different sets of tests depending on whether the comparison groups are paired (as, for example, in cross-over design or matched pairs) or independent. Secondly, the characteristics (categorical vs. continuous, distribution) of the data further affect the choice of statistical method.

**Logistic regression**

Logistic regression is used when the dependent variable is binary (ACS y/n), whereas the independent variables can be of any type (categorical or continuous). For instance, logistic regression is used to predict the binary outcome in the presence of a particular feature. Logistic regression produces Odds ratios (ORs) as effect estimates. In **unconditional logistic regression**, all cases are compared with all controls. In matched study-designs, **conditional logistic regression** is instead used to compare cases with their matched controls. When we are interested in the simultaneous relationship between the dependent variable and several independent variables, the logistic regression can be extended to **multiple regression**, containing several independent variables. Logistic regression models were used to some extent in all of the substudies included in this thesis. When it is necessary to adjust for a large number of potential confounders (which can lead to diminished power), a propensity score (PS) can be calculated based on the chosen variables and used for adjustment (see Box 5.2 for a more detailed explanation of propensity score).
**Box 5.2 Description of propensity score**

**Propensity Score**

A propensity score (PS) is defined as the probability (between 0 and 1) of belonging to a specific exposure-status (RA y/n) based in selected baseline covariates (confounders).\(^{194}\) The PS is commonly calculated using a logistic regression model and serves as a balancing score aiming to create exchangeability between exposed and non-exposed study groups.\(^{195}\) Several methods can use the PS to create balance between exposed and unexposed groups. The PS can be used for matching, stratification, inverse probability weighing and covariate adjustment. Adjusting for the PS as a covariate allows adjustment for a large number of covariates and minimizes loss of information.

**Time to event analysis – Cox proportional hazard regression**

Statistical methods used in time to event analyses must be able to deal with censored observations during follow-up, which typically arises when the study subject is lost to follow-up (e.g. emigrates) or is still alive and has not developed the outcome at the end of follow-up. There are also often competing risks, an event other than the outcome of interest that prevents the outcome of interest from occurring (e.g. IHD during follow-up in Study IV which prevent the outcome nonischemic HF), to take into account, by for example censoring. The Cox Proportional Hazard model, which is commonly used in time to event analysis, estimates the effect of specific exposures, which can be time-dependent, on the event of interest. Hazard ratios (HRs) are the effect estimate produced by Cox regression models and gives an estimate of the probability of the event occurring in a given time period when comparing two groups. Importantly, the assumption of proportional hazards, meaning that HR of the two compared groups should remain constant over time, must be satisfied for the Cox regression model to be considered a valid method. The proportional hazard assumption is tested by, for example, visually inspecting survival or cumulative incidence curves or by introducing an interaction term in the statistical model.

**5.4.3 Study I**

In Study I, the association between each exposure of interest (Table 5.2) and the outcome ACS in RA was assessed using conditional logistic regression models. For the disease activity exposures, for which there were several reported values during the
follow-up, area under the curve (AUC) measurements were calculated by taking the average of all reported values during the different time periods under study. For inclusion in the AUC-analysis, at least two reported values were required, and for inclusion in a follow-up period of two or three years at least one value each year was required. Only values up until the outcome were included. AUC values were assessed as overall means and also by further categorizing them into tertiles or into predefined threshold values (comparing high values with lowest/normal as a reference). Crude ORs were estimated using conditional logistic regression models, taking the individual-matching design into account and adjusted for a linear effect as well as a quadratic effect of age. To minimize the impact of other potential confounders and/or mediators, a multivariate logistic regression model of AUC measurements was further adjusted for smoking, high BMI, history of MI and sick leave during the first year following RA-onset. Furthermore, analyses were also stratified by history of ACS and/or CV risk factors.

5.4.4 Studies II & III

In Study II, clinical ACS characteristics were compared between RA- and non-RA patients with ACS, and the variables of interest included both dichotomous and continuous variables with different distributions. In Study III, filled prescriptions of gold standard secondary preventive drugs (dichotomous) were compared among the same study subjects. Differences in dichotomous variables and normally distributed continuous variables were assessed using logistic regression models adjusted for age and sex so as to obtain a two-tailed p-value. For ordinal or non-normally distributed continuous variables, the Mann-Whitney U test was used to obtain a two-tailed p-value. A p-value < 0.05 was considered significant.

The Kaplan-Meier method was used to analyse all-cause mortality in Studies II and III. The relative risk of all-cause and cause-specific death, and recurrent events among RA-patients compared to non-RA patients with ACS was analysed using Cox regression models. The models were stepwise adjusted to account for all known accessible confounders and/or mediators. The crude model was adjusted for age and sex. RA is, as described in the background section, associated with several comorbid conditions which in the present analysis could be considered mediators between RA and mortality/recurrence. The second model was, therefore, adjusted for a propensity score (PS) including age, sex and educational level as potential confounders in terms of comorbid conditions and/or pharmacotherapies (used as proxies for these conditions) up until 90 days prior to baseline. The results from Study II suggest that RA is associated with a more severe clinical ACS phenotype, why ACS type could also be considered a mediator (a more severe ACS is associated with poorer outcomes compared to milder ACS types) between RA and, in particular short-term, mortality.
Therefore, the third model was, in addition to the PS, also adjusted for ACS type. Finally, inadequate usage of secondary preventive drugs (as assessed in Study III) after ACS is known to be associated with poorer long-term outcomes. Different usage of these drugs in RA-patients compared to non-RA patients could, therefore, mediate an observed association between RA and long-term mortality/recurrence following ACS. Since filled prescriptions of secondary preventive drugs were assessed in study subjects alive during the entire time period under study, adjusting for filled prescriptions would introduce bias. Analyses of long-term mortality and recurrence were instead stratified into subgroups including subjects fulfilling a combination of at least three secondary preventive drugs during i) the first time period after ACS for one year analysis, and ii) at least two time periods for the complete follow-up period (Figure 5.5).

Figure 5.5. Directed acyclic graph illustrating the confounders and mediators adjusted and/or stratified for in analyses of Study II and Study III. Model 1 adjusted for demographics; Model 2 adjusted for demographics and comorbidities; Model 3 adjusted for demographics, comorbidities and ACS-type; Model 4 stratified on the number of filled prescriptions of secondary preventive drugs.

5.4.5 Study IV

In Study IV, where the RR of HF types was assessed, a logistic regression model adjusted for age and sex was used to estimate ORs as a measurement of the RR of HF prior to the start of follow-up among the incident RA patients compared with the controls. Cox regression models were used to calculate HRs as a measure of the association between RA and the different HF outcomes after the start of follow-up. Crude HRs were calculated with time since the index-date as time-scale and adjusted
for sex, age at the index-date and residential area. For analyses of the prevalent RA cohort with corresponding controls, the model was further adjusted for educational level and CV comorbidities and/or treatments at baseline (hypertension, IHD, diabetes type 1 or 2, chronic obstructive pulmonary disease, heart valve disease or surgery, atrial fibrillation, renal failure, alcohol-related conditions, usage of nitroglycerine, warfarin, acetylsalicylic acid, calcium antagonists, diuretic agents, RAS-blocking agents, beta-blockers, lipid-lowering agents, insulin and oral antidiabetic agents). Analyses were stratified on sex and RF-status at baseline, and among patients with new-onset RA and their comparators, analyses were stratified within time periods since RA-diagnosis to assess the impact of RA duration. The impact of RA disease characteristics on the short-term RR of HF was also assessed among the patients with new-onset RA. A series of sensitivity analyses were performed.

All analyses included in the studies of this thesis were carried out with SAS version 9.3.
6 ETHICAL CONSIDERATIONS

All researchers conducting medical research involving human study subjects are responsible for protecting the study subjects from the potential harm and discomfort their involvement might cause.

The Declaration of Helsinki, an international agreement developed by the World Medical Association, contains ethical guidelines for the protection of human subjects included in medical research and serves as an ethical compass for international researchers. According to these guidelines, a detailed research protocol including ethical considerations must be carefully evaluated and approved by a research committee prior to commencing the research. In Sweden, this process is regulated in the Act of Ethical Review and there is one central and six regional ethical review boards responsible for this process.

It is specified in the Act of Ethical Review that research without informed consent, but of course it applies to all medical research and should only be conducted if results could be beneficial for the study subject or for others with the same condition. The aim of the studies included in this thesis is that the result will contribute to increased knowledge about the association between RA and specific CVDs and their outcomes, which could partly be implemented into clinical routine care and thereby be beneficial for patients with RA.

Informed consent constitutes one of the foundations of the ethical principles concerning all medical research including human subjects. Generally speaking, with few exceptions, each potential study subject should, prior to forming an opinion on whether to give consent for study-participation, receive sufficient and structured information, adapted to be easily understood. Larger register-based studies, such as the ones included in this thesis, constitute one of the exceptions to informed consent. The data used has already been collected and it would not be possible to collect informed consent from the, usually, large number of study subjects included.

Study 1 included data partly collected from the medical charts of all of the study subjects. Informed consent was not collected from the study subjects prior to retrieving the medical records, but each head of clinic was informed and asked for permission. All study subjects were already included in the EIRA study and had upon inclusion in EIRA also given their consent to information being collected from their medical charts. We argued that requesting another informed consent from these study subjects might result in yet more privacy-intrusion, due to having to find out more information on each study subject and also by risking causing concern by informing them about the study aims. Thus, we assessed that the risk of causing the study subjects discomfort would overweight the potential benefit from informing them.
Data used in *Studies II–IV* included anonymized data from population-based health registers and quality of care registers, and informed consent was not requested.

Another key element of ethical considerations in medical research is prevention of violation of personal integrity, which is regulated in the Personal Data Act. The privacy of the study subjects must be protected and sensitive individual information should be handled with care in accordance with the act. The PIN from the data used in *Studies II–IV* had been replaced with an anonymous study participant number by the NBHW upon delivering of the data. In *Study I*, the PIN was replaced with an anonymous study participant number when collecting the data. All data used are stored in secure servers available only to researchers involved in the specific project through password-protected computers. Due to the format of the data used in all studies in combination with the storage and handling of the data, the risk of identifying specific individuals and violation of privacy was regarded as minor.

All studies included in this thesis were approved by the Ethical Review Board Stockholm, Sweden.
7 MAIN RESULTS

7.1 RISK FACTORS FOR ACUTE CORONARY SYNDROME IN NEW-ONSET RA (STUDY I)

The 138 cases and 624 matched controls included in Study I were followed for a median duration of 4.8 years (range 0.4–11). Half of the events occurred within the first five years following RA-onset. Of the traditional CV risk factors, smoking, BMI and a history and CVD was associated with ACS risk. Neither usage of corticosteroids nor DMARDs within the first 60 days following RA-diagnosis were associated with an increased ACS risk.

Measurements of high disease activity compared to lower were generally associated with an increased risk of ACS both during the first year and during the complete follow-up period (Figure 7.1). High disease activity measured using DAS28 was associated with a three-fold ACS-risk compared to low disease activity. Out of the DAS28-components, high ESR and high general health were associated with a three-fold and 2.5-fold ACS-risk during the first year of follow-up. Among other DAS28-components there was also an association or borderline significant association between high markers compared with lower.

Figure 7.1 Forrest plot of the relative risk of ACS for measurements of disease activity during the first year following RA-onset and the complete follow-up period. Highest tertile compared to lowest. Odds ratios with 95% confidence intervals. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GH, general health; TJC, Tender joint count; SJC, swollen joint count
ORs of DAS28, ESR and GH remained significantly increased after adjusting analyses of CV risk factors and history of MI and also in a subset of the population where subjects with a history of CVD were excluded.

Shared epitope, one or two alleles, was not associated with any increased ACS risk. Approximately two-thirds of both cases and controls were RF- and/or ACPA-positive. There was no association between RF-positivity and risk of ACS, whereas ACPA-positivity and in particular high positive ACPA was borderline significant associated with ACS-risk (Figure 7.2)

Figure 7.2 Forrest plot of the relative risk of ACS for autoantibodies. Odds ratios with 95% Confidence intervals. ACPA, Antibodies towards citrullinated peptides; RF, Rheumatoid factor.

Please see Paper I and corresponding Supplementary information for the complete results.

7.2 CLINICAL ACS CHARACTERISTICS (STUDY II)

A total of 743 (65%) of the RA patients with ACS and 2203 (69%) of the non-RA patients with ACS were included in RIKS-HIA and analysed regarding clinical ACS parameters. Of the subjects included in RIKS-HIA, RA patients and non-RA patients did not differ regarding presenting symptoms. However, during the same period in
which study subjects were identified in the NPR, another 243 (0.20%) of the RA patients vs. 785 (0.13%) of the non-RA subjects died from ACS or sudden cardiac death out of hospital (and were not registered in the NPR with incident ACS). In RIKS-HIA, RA patients showed several signs of experiencing a more severe ACS compared to the non-RA patients. The RA patients more often presented with STEMI, poorer Killip-class and had higher troponin-levels compared to non-RA patients. Out of the patients with STEMIs, RA patients more often received primary reperfusion treatment. The RA patients also suffered from higher frequencies of in-hospital complications, such as received treatment with IV diuretics and inotropic agents, going into cardiogenic shock and dying in-hospital, compared to non-RA patients (Table 7.1).

Table 7.1 Clinical presentation, in-hospital treatment and complications in RA patients and non-RA patients with ACS.

<table>
<thead>
<tr>
<th></th>
<th>RA patients (%)</th>
<th>Non-RA patients (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AT ADMISSION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBBB</td>
<td>4.8</td>
<td>5.6</td>
<td>0.44</td>
</tr>
<tr>
<td>ST-Elevation</td>
<td>35.3</td>
<td>30.5</td>
<td>0.001</td>
</tr>
<tr>
<td>ST-Depression</td>
<td>19.8</td>
<td>22.4</td>
<td>0.16</td>
</tr>
<tr>
<td>Killip-Class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>83.3</td>
<td>87.1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12.8</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Troponin, tertiles</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>1</td>
<td>27.5</td>
<td>35.3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>34.7</td>
<td>32.8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>37.8</td>
<td>31.8</td>
<td></td>
</tr>
<tr>
<td><strong>TREATMENT AMONG SUBJECTS WITH STEMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any reperfusion</td>
<td>74.1</td>
<td>66.2</td>
<td>0.01</td>
</tr>
<tr>
<td>PCI</td>
<td>62.3</td>
<td>54.4</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>IN-HOSPITAL COMPLICATIONS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment IV. Diuretics</td>
<td>25.3</td>
<td>20.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Treatment IV. Inotropic agent</td>
<td>4.6</td>
<td>2.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>3.6</td>
<td>2.2</td>
<td>0.04</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>6.1</td>
<td>4.1</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>DISCHARGE DIAGNOSIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>42.0</td>
<td>37.4</td>
<td>0.04</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>58.0</td>
<td>62.6</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Please see Paper II and corresponding Supplementary information for the complete results in clinical characteristics in ACS.
7.3 MORTALITY AND RECURRENCE AFTER ACS (STUDY II AND III)

Both short-term and long-term mortality as well as recurrence were increased among RA patients with ACS compared to the non-RA patients with ACS (Figure 7.3).

*Figure 7.3* Failure function of recurrent ACS (above) and overall Kaplan-Meier survival (below) in patients with RA and general population comparators with incident ACS between 2007 and 2010.

RA patients with ACS suffered an approximately 60% increased all-cause mortality risk within the first week as well as the first month following the ACS. A majority of all deaths among both RA- and non-RA patients were related to cardiac mortality, and
the risk of cause-specific mortality was similar to all-cause mortality. The mortality risk remained increased with 60% during a follow-up of 1 year and increased to 70% during the complete follow-up period. The risk of recurrent ACS was increased by approximately 30% both during a follow-up of 1 year and during the complete follow-up period. Adjusting analyses using the propensity score, based on all accessible confounders, only reduced the HRs slightly, but they all remained significantly increased (Figure 7.4).

Figure 7.4 The relative mortality and recurrence risk among RA-patients with ACS compared with non-RA patients with ACS during the different time periods.

Please see Papers II and III with corresponding Supplementary information for the complete results on mortality and recurrence.

7.4 SECONDARY PREVENTION (STUDY III)

Figure 7.5 shows the proportion of RA patients with ACS and non-RA patients with ACS filling prescriptions of each drug during the four consecutive time periods following ACS. When analysing prescription pattern after any type of ACS, patients with RA filled significantly fewer prescriptions for antiplatelets, statins and RAS-blocking agents during several of the time periods (figure 7.5).
**Figure 7.5** Proportions of dispensed prescriptions of secondary preventive drugs during 4 consecutive time periods following any ACS in patients with RA (solid line) and non-RA patients (dotted line).

After stratifying the result on type of ACS, based on ICD-codes registered in the NPR, a majority of observed differences disappeared. Among patients registered with transmural MI, there were virtually no remaining significant differences. (Figure 7.6) shows filled prescriptions of the different drugs in patients with transmural MI).
Figure 7.6 Proportions of dispensed prescriptions of secondary preventive drugs during 4 consecutive time periods following transmural infarction in patients with RA (solid line) and non-RA patients (dotted line).

Please see Paper II with corresponding Supplementary information for the full results on secondary prevention after ACS.

7.5 THE RELATIVE RISK OF HEART FAILURE IN RA (STUDY IV)

The relative risk of HF in prevalent RA

The prevalent RA patients had higher incidence rates of all HF subtypes compared to their matched general population comparators. The incidence rate of HF overall was 6 per 1,000 person-years among RA patients compared with 3 per 1,000 person-years among their comparators, corresponding to an approximately 70% increased risk of HF overall (Figure 7.7). Similarly, 3.5 and 2.7 per 1,000 person-years among prevalent RA patients developed nonischemic and ischemic HF respectively (compared to 1.9 and 1.4 per 1,000 person-years among comparators). The prevalent RA patients suffered an approximately 70% increased risk of nonischemic HF and a 90% increased risk of ischemic HF. Adjusting for confounders in term of pharmacotherapies and comorbidities at baseline only reduced HRs slightly (Figure 7.7).
Figure 7.7 Forrest plot of the relative risk of heart failure by subtype in subjects with prevalent RA compared with general population comparators. Hazard ratios with 95% CI.

The relative risk of HF by RA duration

A history of all subtypes of HF prior to RA-onset was equally common among the patients with new-onset RA compared to their general population comparators. Stratifying the RR of HF within time periods after RA-onset revealed an increased RR of all subtypes already in the first year following RA-onset. Within the first year following RA-onset, there was an approximately two-fold increased relative risk of nonischemic HF and a 1.5-fold increased relative risk of ischemic HF. The RR of Nonischemic HF seemed to decline over time after RA-onset whereas the RR of ischemic HF on the other hand increased (Figure 7.8).
**Figure 7.8** Forrest plot of the relative risk of heart failure in patients with RA compared with general population comparators in time-periods after RA-onset

**Risk factors for HF in RA**

High mean DAS28 and ESR during the first year following RA onset was associated with an increased risk for all subtypes of HF, but most pronounced for nonischemic HF. Similarly, high CRP and usage of corticosteroids within the last 3 months prior to the HF was associated with an increased risk of nonischemic HF, whereas there was no effect on ischemic HF (Table 5.4).
Table 7.2 The impact of various RA disease factors on the risk of incident heart failure within 1 year after RA-onset in patients with new-onset RA. Hazard ratios adjusted for age and sex.

<table>
<thead>
<tr>
<th></th>
<th>HF OVERALL</th>
<th>ISCHEMIC HF</th>
<th>NONISCHEMIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>All</td>
<td>1.75 (1.40-2.19)</td>
<td>1.49 (1.05-2.12)</td>
<td>2.04 (1.52-2.73)</td>
</tr>
<tr>
<td>Mean values:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR ≥ 40 vs. &lt;40</td>
<td>2.80 (1.78-4.42)</td>
<td>2.41 (1.15-5.08)</td>
<td>3.03 (1.69-2.73)</td>
</tr>
<tr>
<td>CRP ≥30 vs. &lt;30</td>
<td>1.72 (1.08-2.74)</td>
<td>0.90 (0.39-2.09)</td>
<td>2.40 (1.36-4.24)</td>
</tr>
<tr>
<td>GH ≥60 vs. &lt;60</td>
<td>1.95 (1.20-3.15)</td>
<td>1.56 (0.69-3.52)</td>
<td>2.45 (1.32-4.52)</td>
</tr>
<tr>
<td>DAS28 ≥5.2 vs &lt;5.1</td>
<td>2.93 (1.83-4.69)</td>
<td>2.68 (1.24-5.78)</td>
<td>3.35 (1.84-6.09)</td>
</tr>
<tr>
<td>HAQ ≥1.0 vs. &lt;1.0</td>
<td>2.09 (1.32-3.31)</td>
<td>2.59 (1.26-5.25)</td>
<td>1.70 (0.94-3.08)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>0.96 (0.53-1.74)</td>
<td>0.39 (0.15-1.02)</td>
<td>3.12 (1.30-7.44)</td>
</tr>
<tr>
<td>Biologic drugs</td>
<td>0.80 (0.32-2.03)</td>
<td>0.81 (0.19-3.55)</td>
<td>0.41 (0.12-1.42)</td>
</tr>
</tbody>
</table>

ESR, Erythrocyte sedimentation rate; CRP, c-reactive protein; GH, general health; DAS28, disease activity score; HAQ, health assessment questionnaire

Please see Paper IV with corresponding Supplementary information for the complete results on association between RA and HF.
8 DISCUSSION

8.1 METHODOLOGICAL CONSIDERATIONS

The aim of observational studies is, of course, to present accurate effect measurements of the association studied. Observational studies are, however, prone to include a certain set of weaknesses, which are important to be aware of when planning, conducting and interpreting the results. The validity of the study is categorized into internal validity and external validity. Internal validity involves factors related to the study populations’ representativeness. High internal validity implies that the observed association is similar to the actual association of the source population. External validity is also referred to as generalizability, and reflects whether the results can be transferred to populations other than the one under study. The precision (random error) refers to data variability due to chance. The accuracy of the study is determined by the validity in combination with the precision.

8.1.1 Internal validity

The internal validity is affected by systematic (or non-random) errors and random errors.

8.1.1.1 Systematic error

The classic systematic biases affecting the internal validity are categorized into selection bias, information bias and confounding. The impact of these biases is, in contrast to random error, not affected by sample size.

Selection bias

As the name implies, selection bias is occurs in the process of selecting the study population and is defined as a different association between exposure and outcome among the study population compared with the source population. For instance, sampling a study population from a specific hospital setting or register source, which tends to include or hospitalize subjects with severe disease, would lead to a study population including subjects with overall a more severe disease in comparison with the source population. Selection bias leads to under- or overestimation of the measurement of the true association and would, if there is an association between disease activity and the outcome, lead to an overestimation of the true effect, which in turn affects the internal validity of the study. Selection bias and confounding often overlap, and selection bias can sometimes be dealt with as confounding.

Using population-based cohorts, as in Studies II-IV, reduces the risk of introducing selection bias. In these studies, the NPR was used to identify cohorts of patients with prevalent (established) RA. In Study IV we included an additional study population of
patients with incident RA. The incident RA cohort was identified using the SRQ, which, as previously described, includes patients diagnosed and entered by rheumatologists. The entering of patients in such registers (and thereby their coverage) might be affected by the underlying health status of the patient as well as the disease characteristics. Patients with a poorer health status and a short expected survival time might not be included, which would lead to a healthier RA-population in SRQ compared with the source population. This might distort the comparison of the RA group to the population group.

In Study I the population was identified within the EIRA study where RA patients, similarly with SRQ, are included by rheumatologists from certain centres which could affect the internal validity of the study. The participation rate in EIRA is, however, high and previous investigation of non-participation demonstrated that non-participation among cases (which the study cohorts were sampled from) was associated with lower socioeconomic status. Since low socioeconomic status is associated with an increased risk of ACS, some degree of selection bias leading to an underestimation of the true effect is possible.

One specific type of selection bias referred to as informative censoring could pose a limitation in Study IV. Informative censoring occurs in cohort studies when there is a differential loss of follow-up or censoring between an exposed and non-exposed group. In the analysis in which we assessed the RR of nonischemic HF, we censored subjects who developed IHD during the follow-up period. Since RA is associated with an increased risk of IHD, a higher proportion of RA patients were presumably censored due to IHD during follow-up. Potentially, the subjects developing IHD are also at increased risk of developing nonischemic HF, which in would lead to an underestimation of the RR of non-ischemic HF among the RA patients.

Information bias

Inaccurate collection of study variables leads to biased information, which is referred to as misclassification. Misclassification is categorized into differential and non-differential. When misclassification is equal among exposed and unexposed, it is non-differential the measure of the association is typically not affected. In contrast, differential misclassification differs depending on exposure status. Recall bias refers to the differential misclassification caused by the tendency of exposed study subjects to report information differently compared with non-exposed study subjects. Surveillance bias refers to another specific type of differential misclassification, in which the outcome differs among exposed subjects due to more intense or frequent surveillance compared with non-exposed subjects.
In Study I some of the information on potential risk factors was collected from the questionnaires used in the EIRA study. The information was, however, collected before the outcome of Study I (ACS) and analyses pertained to baseline in the analyses, which minimizes the risk of recall bias. Both cases and controls in Study I were subjects with RA, which is why differential misclassification of the outcome by RA status is not an issue. Furthermore, the ACS-diagnoses were validated within the study.

In Study IV, the outcome was HF. The more intense and frequent health care contact among RA patients could potentially introduce a surveillance bias. We did, however, use main diagnosis only, which is known to have a high validity.

Other information included in the studies was collected from nationwide registers where it has been prospectively collected and with almost complete coverage, which prevents misclassification to occur.

Confounding

The concept of confounding was introduced in section 5.4.1. To repeat, confounding refers to the presence of common causes (confounders) of exposure and outcome, which might distort the observed association. Confounders should be identified based on a priori subject matter knowledge, which can be illustrated using DAGs as previously described. The issue with confounding can be overcome by restriction, matching, stratification or adjusting.

In Study I, age, sex and year of RA diagnosis were considered to be confounders. Cases and controls were matched based on sex and year of RA diagnosis, and analyses were adjusted for age. Confounding in Studies II and III is illustrated in the DAG in figure 5.5. Age, sex, educational level, CV risk factors and CVD are associated with ACS and also affect the outcome after ACS, why analyses were adjusted for these factors in a first and second step. Furthermore, the type or severity of ACS affects in mortality and recurrent events. Since the patients with RA suffered from more severe ACS compared to non-RA patients, we adjusted for ACS-type in a third step to assess the influence of the higher frequency of more severe ACS among RA-patients. In Study IV, we considered age, sex and area of residency confounders and matched the RA-subjects to general population comparators based on these factors. Additionally, we considered educational level and a number of CVDs and other diseases (or pharmacotherapies used as proxies for these diseases) confounders due to a known association with RA and HF and adjusted for these in a multivariate model.
8.1.1.2 Random error

Random error refers to the variability of the data due to by chance. The precision can be improved by increasing the sample size. To measure the variability of the data and to derive the measurements from the study population to the source population statistical methods are used. The \textit{P-value} is used for hypothesis testing and \textit{confidence intervals} are used for estimation of the data variability. If the p-value is less than or equal to the probability level $\alpha$, which almost always is arbitrarily set to 0.05 (the risk of incorrect rejection of null hypothesis is less than 5%), the null hypothesis is rejected (i.e. the result is statistically significant). In contrast, a p-value greater than $\alpha$ does not reject the null hypothesis (the result is not statistically significant). Importantly, statistical significance does not necessarily transfer into clinical significance, and the results should be interpreted in relation to other aspects such as a plausible biological hypothesis and presence of systematic errors. Confidence intervals are used to describe the statistical variation underlying the point estimate. The level of confidence is usually set to 95%, meaning that, if data collection and analysis were to be repeated a number of times, the interval would include the correct value 95% of the time. The P-value and confidence intervals, which are based on the same equation, are related. If the 95% CI include the null hypothesis value (1 if using relative risks), the p-value will not be greater than 0.05 and thus indicate non-statistical significance.

We used confidence intervals as an estimation of the precision around the point estimates in all studies. In some of the analyses in \textit{Study I} where the number of observations was smaller, the CIs are hence wider, which is why the result of these specific analyses should be interpreted with care. In the other studies, CIs were narrow (with a few exceptions) indicating that there was enough power to detect differences between exposed and non-exposed group. In \textit{Studies II} and \textit{III} we used \textit{p-values} to determine whether statistically significant differences in clinical ACS characteristics and usage of secondary preventive drugs.

8.1.2 External validity

External validity refers to the generalizability of the study, i.e. how well the study results can be applied to study settings and populations other than those included in the study. In \textit{Study II- IV} we included prevalent RA-cohorts based on the NPR. Selecting subjects fulfilling a definition for prevalent RA and thereby excluding subjects with incident RA, might affect the external validity. There are several potential differences in disease characteristics, such as treatment, level of or accumulated inflammatory activity, physical impairment etc. among prevalent compared with incident RA. Therefore, the results might not be readily transferred to patients with new-onset RA. In \textit{Study II}, RIKS-HIA was used to characterize the ACS
phenotype in a subset of the study population. Information in RIKS-HIA is based on admissions to coronary intensive care units. In some areas, inclusion in RIKS-HIA is not indicated in patients above 80 years of age, which is why many elderly RA and non-RA subjects were not included in this specific analysis. The coverage was similar for both RA- and non-RA patients, which is why the results were not biased in any direction, but the generalizability to RA patients with ACS above 80 may be limited. In Study I, we identified cases and controls from EIRA. EIRA has an upper age limit of 70, which limits the generalizability to older age groups.

All studies were based on a Swedish RA population and conducted in the Swedish health care system, which might to some degree affect the generalizability to other populations and settings.

8.2 FINDINGS AND IMPLICATIONS

In this thesis, results regarding potential risk factor for ACS, clinical ACS characteristics, prognosis and usage of secondary preventive drugs after ACS as well as risk of and risk factors for HF in RA have been reported.

8.2.1 Risk factors for ACS in RA

The main finding of Study I was an association between markers of high inflammatory activity and disease activity, in particular during the first year following RA-onset, and an increased risk of ACS. Out of the CV risk factors, high BMI, a medical history of MI and previous smoking were also associated with an increased risk of ACS. The impact of these factors could however not explain the increased risk of ACS caused by high inflammatory and disease activity. Rheumatoid factor-positivity was not associated with ACS-risk, whereas ACPA-positivity and in particular high levels of ACPA was associated with an increased risk of ACS. Treatment with DMARDs or corticosteroids was not associated with ACS-risk.

Similarly with our results, previous studies have reported an association between high inflammatory activity and disease activity and risk of CVD in RA. Since results based on studies using a composite CVD outcome can be difficult to translate into specific conditions and clinical practice, we instead focused on clinically significant ACS in our study. Additionally, we used a contemporary RA-cohort where we could access information exposures of interest from RA-onset.

The involvement of inflammation in the development of atherosclerosis is well established and inflammatory activity has been shown to affect the extent and composition of atherosclerotic lesions. In fact, the pathophysiology of atherosclerosis, which is currently considered a chronic inflammatory disease, share
many features with the pathophysiology of RA. The inflammatory process of both atherosclerosis and synovial inflammation is characterized by endothelial activation and subsequent expression of adhesion molecules followed by infiltration of various types of leukocytes and other immune cells. Many of these immunological responses in RA are also seen in patients with ACS. For example, specific subsets of CD4+ T-cells, described to be involved in the pathogenesis of RA, have also been detected in blood-samples from patients with ACS. The characteristics of this specific subset of T-cells have been observed to be similar in patients with RA and patients with ACS as an indication of a similar autoimmune response. Our results suggest that a high mean inflammatory activity soon after RA-onset is associated with an increased risk of ACS.

The development of atherosclerotic lesions occurs over several years. Since the high inflammatory activity seem to affect the development of ACS within a relatively short time-period, the risk increase might be caused by the destabilization of atherosclerotic plaques within the coronary arteries. It has been proposed that the T-cells contribute to destabilization of atherosclerotic plaques. Furthermore, data from post mortem and coronary CT angiography indicates that patients with RA have a higher frequency of vulnerable plaques.

ACPA-positivity and in particular high positive ACPA-levels was also associated with an increased ACS-risk in our study. ACPA has previously been associated with an increased risk of CVD in both the general population and an increased risk of IHD in patients with RA. In the later study, the association between ACPAs and IHD remained after adjusting for ESR, RF-positivity and treatments. There is not an established exact role for ACPAs in the pathogenesis of CVD in RA, but ACPAs have been associated with subclinical manifestations of CVD, such as more extensive atherosclerotic lesions, in RA. Furthermore, specific ACPAs have been associated with endothelial dysfunction and overall atherosclerotic burden.

In contrast to several previous reports, RF-positivity was not associated with an increased risk of ACS in our study. The specificity of RF is not as high as the specificity of ACPAs, which is the currently recommended biomarker to use in the evaluation of RA. Rheumatoid factor has been associated with an increased risk of CVD in the general population, but there is no established mechanism for this association. RF is also found in other autoimmune conditions, infectious diseases, in smokers, and healthy subjects, in particular among elderly individuals. Rheumatoid factor-positivity in RA is also associated with a more severe clinical prognosis. The observed association between RF and CVD in the general population might be caused by other factors related to RF and CVD (confounders). The previously described association between RF and CVD in RA could reflect the impact of severe disease related to RF-positivity rather than a direct association between RF and CVD. In fact, in one study
based on 2 cohorts of RA patients from different time periods, there was an association between RF and CVD in the older cohort, whereas no association could be detected in the more recent cohort. Perhaps, the more modern treatment regimes available for the patients of the more recent cohort effectively altered and improved the inflammatory and disease activity of these patients.

The rapid risk increase of ACS after RA-onset, the observed association between RA-related inflammation in relation to RA-onset and the risk of ACS and the impact of ACPAs on the ACS-risk in RA suggest that RA-related factors are indeed involved in the development of ACS. In support, usage of methotrexate has been associated with a decreased risk of CVD in RA. However, the exact mechanism of ACS-development in RA remains to be determined.

Our results underline the importance of a rapid clinical evaluation in patients with suspect RA to identify those with RA. Early treatment-initiation and lowering of inflammatory activity might decrease the risk of developing ACS. In addition, patients with a sustained high inflammatory and disease activity should be extra carefully monitored regarding risk factors and symptoms of CAD.

8.2.2 Clinical characteristics of ACS in RA

In Study II, we observed more severe ACS characteristics among the patients with established RA and ACS compared with the non-RA patients with ACS. In contrast, most previous studies investigating the clinical characteristics of ACS in RA have not observed any difference. The small number of study subjects included in these studies, have however affected the statistical precision and they did not have access to equally detailed information on the clinical event as we did in our study. Furthermore, the RA characteristics differ between studies, which might also lead to different results.

The RA-patients in our study more often suffered from STEMIIs, showed signs of more severe ACS and more often developed in-hospital complications. Of the patients with STEMIIs, the RA-patients were more often treated with primary reperfusion treatment and received primary PCI. These results indicates that the ACS phenotype differ in patients with RA compared with non-RA patients. Previous reports have observed an increased risk of sudden cardiac death in patients with RA, which support this observation. Inflammatory activity in non-RA patients has been associated with more severe ACS characteristics and a predisposition towards MI rather than UA.

Since the pathophysiological mechanism of STEMIIs and sudden cardiac death typically are caused by total or near total occlusion of a coronary artery caused by a thrombus this further supports the impact of RA-related factors on existing atherosclerotic lesions by making them unstable and prone to rupture. Inflammation
does not only affect the atherosclerotic lesion locally, but also affects the fluid phase of blood by promoting thrombus accumulation by increased thrombogenicity and impaired fibrinolysis.\textsuperscript{169} Moreover, inflammation has been associated with impaired development of coronary collateral circulation in chronic CAD,\textsuperscript{204} which could lead to larger infarct size due to insufficient blood supply at the time of occlusion.

The finding of a more severe ACS phenotype in patients with RA, emphasize the importance of recognizing this group of patients when assessing and identifying high risk ACS patients in clinical practice.

8.2.3 Outcomes after ACS in RA

In \textit{Study II}, we in addition to clinical ACS characteristics also assessed short-term mortality, which was significantly increased among RA patients compared with non-RA patients, which has also been reported in one previous study. In contrast, two other studies on short-term mortality after ACS in RA could not detect a difference. The increased mortality risk in our study remained after adjusting for a large number of potential confounders. Further adjusting for type of ACS decreased the short-term mortality risk, which supports the impact of the ACS severity, but could not fully explain the overall short-term survival. In \textit{Study III}, we extended the follow-up period and assessed long-term mortality and also risk of recurrent events. Similarly with short-term outcomes, the long-term mortality and recurrence risks were also increased among RA-patients compared with the non-RA patients. Consistent with our findings, a few previous studies have reported an impaired long-term prognosis after ACS in RA. Adjusting for comorbidities and ACS-type decreased the RRs slightly, but they remained significantly increased.

Since the more severe ACS-phenotype in RA does not explain the impaired mortality and recurrence, other factors are likely to be involved. Several inflammatory biomarkers, including hsCRP, have been associated with more severe outcomes following ACS in the general population.\textsuperscript{96} The mechanisms behind these observations are not understood, but the inflammatory effect on the atherosclerotic lesions and coagulation system has been proposed as an important factor. Furthermore, certain inflammatory cells have been shown to affect the electric conduction of the heart, which might predispose for arrhythmias, such as ventricular fibrillation, after ACS.\textsuperscript{205}

8.2.4 Follow-up care after ACS in RA

Suboptimal usage of secondary preventive drugs after ACS has been linked to adverse outcomes, such as mortality and recurrence, in the general population. The observed impaired long-term prognosis after ACS in patients, which could therefore potentially be explained by a suboptimal usage of these drugs in this patient group. Therefore, we
also, in addition to mortality and recurrence, aimed at assessing the usage of secondary preventive drugs in Study III. We found that, when conditioning our analyses on type of ACS, the usage of secondary preventive drugs was not consistently lower among the patients with RA compared to the non-RA patients. One previous study has reported on lower in-hospital initiation of certain secondary preventive drugs in patients with RA, whereas another study could not detect a difference. Since these studies only assessed in-hospital initiation of the drugs it is difficult comparing them with our results. In another large population-based study, a lower initiation and adherence of aspirin, beta-blockers and statins were observed in patients with RA and ACS compared with non-RA patients and ACS. The different results might be explained by variations in geographic region and clinical setting, but there were also major differences in study design and analytic approaches used. Importantly, we stratified the analyses by type of ACS and among patients with transmural infarction (which is likely to be translated into STEMI), there were virtually no differences in filled prescriptions of any drugs among RA-patients and non-RA patients. As the first study, we assessed long-term outcomes and usage of secondary preventive drugs in the same cohorts and also attempted to evaluate the impact of drug-usage on the impaired outcomes. We assessed mortality and recurrence in study subjects with a combination of at least three secondary preventive drugs and found that it was equally increased as in the main analyses which further supports that some other mechanism cause the impaired prognosis after ACS in patients with RA. There are obviously other types of secondary prevention, such as dietary recommendations, stress management and implementation of an adequate physical activity level, which we did not assess in this study.

8.2.5 Heart failure in RA

In Study IV, we reported an increased risk of HF regardless of the presence of IHD that could not be explained by CVDs or other conditions. There was no increased risk of HF prior to RA-onset, but it emerged rapidly after RA-onset and was associated with high inflammatory and disease activity. The early risk increase and the impact of high inflammatory activity was most pronounced for nonischemic HF. Since patients with RA more frequently develop IHD, the increased risk of ischemic HF is perhaps not surprising. However, the increased risk of nonischemic HF in our study is a novel finding. An association between inflammation and HF has been described as several studies have reported elevated inflammatory biomarkers in patients with HF. Whether there is a causal relationship between inflammation and HF is however not established. Our findings where the HF-risk developed first after RA-onset and was affected by high inflammatory activity, which was most pronounced for nonischemic HF do however support the hypothesis of a causal relationship between inflammation and HF onset or aggravation. There are several established effects of inflammatory
mediators on the myocardium. For example, various cytokines, such as TNF-\(\alpha\), which is also involved in the pathogenesis of RA, is associated with impaired myocardial contractility in septicaemia.\(^{170}\) Inflammation also leads to reduced cardiomyocyte contractility and induces hypertrophic and fibrotic response in the myocardium which could lead to development of HF.\(^{206}\)

Given the rapid increase of HF after RA-onset it is important to consider other potential risk factors, such as RA-related pharmacotherapies. In fact, we noted a strong association between usage of corticosteroids, which is common in the initial treatment of RA in Sweden, and the risk of nonischemic HF. Since it is the patients with high inflammatory and disease activity that are treated with corticosteroids, the observed association between corticosteroids and nonischemic HF might reflect inflammatory activity rather than the drug itself. However, the finding is a reason for concern. Treatment with the biologic drugs TNF-\(\alpha\) antagonists in patients with HF has previously been a concern due to the elevated levels of TNF-\(\alpha\) in individuals with HF. However, treatment with TNF-\(\alpha\) antagonists in patients with HF, but without overt autoimmune disease, has shown no beneficial or harmful effect in severe HF.\(^{207}\) Likewise, a study of RA-patients found no increased risk of HF among patients with TNF-\(\alpha\) antagonists compared to traditional DMARDs.\(^{208}\) Furthermore, it has been hypothesized that TNF-\(\alpha\) antagonists in RA can exert positive effects of cardiac function and disease biomarkers in HF.\(^{209,\ 210}\)

RF-positivity was associated with a greater risk of in particular ischemic HF in our study. Since RF-positivity is associated with high inflammatory and disease activity it is unclear whether RF per se is a risk factor or if the finding rather reflects the inflammation. RF correlates with the occurrence of ACPAs, which we did not have access to data on in this study. Citrullinated proteins in the myocardial interstitium, which is associated with interstitial fibrosis, have however been found to be increased in patients with RA.\(^{211}\) Moreover, a recent study found that citrullination can impair the contractility of cardiomyocytes by reducing the myofilament Ca\(^{2+}\) sensitivity.\(^{50}\) Hence, inflammatory mediated signals affecting the myocardium could be involved in the pathogenesis of HF in RA.
9 CONCLUSIONS

In this thesis, various clinical oriented research questions within the field of cardiovascular comorbidity in RA were explored. The results contribute to expanding the knowledge of CVD in RA, can be implemented in clinical practice, and may serve as point of departure for further investigations of the questions generated.

The specific conclusions of the four sub-studies are:

- Clinical markers of high inflammatory activity and high disease activity are associated with an increased risk of acute coronary syndrome in patients with incident RA (Study I).
- Early treatment with DMARDs in incident RA is not associated with an increased risk of acute coronary syndrome (Study I).
- Rheumatoid factor and/or ACPA positivity per se is not associated with an increased ACS-risk in incident RA, whereas high levels of ACPA seem to be associated with an increased risk (Study I).
- Patients with RA suffer from, in terms of subtype, more severe acute coronary events, receive more invasive in-hospital interventions and suffer from more complications compared to non-RA patients (Study II).
- Patients with RA suffer from impaired short- and long-term outcomes in terms of mortality and recurrent events, which cannot readily be explained by underlying comorbidity or type of ACS (Studies II and III).
- When taking ACS subtypes into account, the usage of secondary preventive drugs is largely similar among patients with RA and ACS when compared to non-RA patients and ACS, and cannot therefore explain the poorer outcomes following ACS (Study III).
- Patients with RA are at increased risk of HF both in the presence and absence of IHD (Study IV).
- The risk of non-ischemic HF seems to develop rapid after RA-onset, whereas the risk of ischemic HF appears to develop more slowly (Study IV).
- Clinical markers of high inflammatory activity are associated with the increased risk of both ischemic and non-ischemic HF, but are most pronounced for the increased risk of non-ischemic HF in incident RA (Study IV).
10 SUGGESTIONS FOR FUTURE RESEARCH

The findings of each sub-study included in this thesis have raised several new questions, which will constitute the objectives of future studies, some of which are already planned and initiated, of CVD in RA.

In Study I, the association between high inflammatory activity and disease activity and the risk of ACS in patients with incident RA was the main finding. Seropositivity for ACPAs was borderline significant associated with ACS, and there seemed to be an association between high ACPA-levels and ACS. Since ACPAs are a fairly novel group of autoantibodies, including several fine-specific subtypes, only a few studies have investigated their role in CV pathogenesis, which remains to be determined. Certain fine-specific ACPAs have, however, been associated with endothelial dysfunction and overall atherosclerotic burden, for example. Hence, investigating the potential association between fine-specific ACPAs and ACS in RA and in the general population and their potential usefulness as a clinical predictor of CV events would be of interest. Further exploration of the potential beneficial effect of other novel anti-inflammatory drugs could also confirm the results presented in the study.

In Study II, the patients with established RA suffered from more severe ACS and also a substantially increased risk of dying after these events compared with general population comparators. The increased short-term mortality risk remained after adjusting for type of ACS, indicating a different aetiology of the impaired short-term prognosis. Since the histopathological features of atherosclerosis are affected by inflammation, potentially the extent and composition of coronary artery atherosclerosis differ in patients with RA compared to non-RA patients, and this could explain the more severe ACS and also impaired short-term prognosis. Comparing angiographic patterns between the RA patients compared to the non-RA patients with ACS included in the study could further elucidate the findings and hopefully shed some new light on the observed differences in clinical ACS characteristics and outcomes.

In addition to the impaired short-term mortality, patients with RA are also at increased risk of long-term recurrence and mortality as presented in Study III. In the same study, usage of secondary preventive drugs was also assessed, but no apparent differences between RA and non-RA patients were identified and the usage of such drugs did not seem to explain the increased risk of developing additional acute coronary events or dying. Of course, these drugs are only one part of the secondary preventive strategies used following ACS. Other secondary preventive measurements include implementation of life-style-related implementations such as physical activity and dietary recommendations, which we did not have information on. We have
planned further investigation of such additional factors, which hopefully will provide further insights into the area.

In *Study IV* we showed that the risk of HF is increased in RA independently of concomitant IHD, and that the risk increase is driven partly by inflammatory activity. Despite the association between inflammation and heart failure, few studies have addressed the association between RA and HF. We plan to pursue the study of HF in RA with characterizing the clinical presentation and assessing outcomes.
Epidemiologi

Epidemiologi är ett forskningsfält där man kartlägger förekomsten av olika sjukdomar i en population samt studerar potentiella samband mellan olika exponeringar och sjukdomsförekomsten. I den här avhandlingen ingår 4 delstudier där vi använt registerbaserade källor, såsom nationella hälsoregister, och epidemiologisk metoder för att studera utvalda aspekter av sambandet mellan ledgångsreumatism och hjärtkärlsjukdom.

Ledgångsreumatism


Ledgångsreumatism och hjärt- kärlsjukdom

Det är sedan länge känt att patienter med ledgångsreumatism löper en ökad risk att drabbas av andra sjukdomar och även har en ökad dödlighet. Framför allt så löper patienter med ledgångsreumatism en ökad risk för att drabbas av och dö i hjärtkärlsjukdomar. I synnerhet har samsjukligheten med kranskärlssjukdom (kärlkramp eller hjärtinfarkt) blivit undersökt och risken att utveckla kranskärlssjukdom har visat sig vara påtagligt förhöjd vid ledgångsreumatism. Kranskärlssjukdom orsakas i sin tur av åderförkalkning, ateroskleros, av hjärtats kranskärl. Vid alltför utbredda förändringar eller om det plötsligt lossnar en bit av förändringarna (en så kallad propp) leder
åderförkalkningen till försämrat eller avstannat blodflöde vilket orsakar syrebrist i hjärtmuskulaturen. Detta yttrar sig antingen som kronisk kärlkram eller som en akut hjärtinfarkt, som kan ha olika symptom och svårighetsgrad beroende på lokalisation av stoppet och hur utbredd syredisten blir. Det har senaste tiden kunnat fastställas att inflammation är involverad i utvecklingen av åderförkalkning och även att inflammation bland annat påverkar hur stabila förändringarna blir, dvs. hur enkelt en propp kan lossna.

**Studie I – Riskfaktorer för akut kranskärlssjukdom vis ledgångsreumatism**

Det har visat sig att de traditionella riskfaktorerna för hjärtkärlsjukdom (rökning, fetma, diabetes, högt blodtryck och hypertoni) inte helt kan förklara riskökningen för hjärtkärlsjukdom bland patienter med ledgångsreumatism. Detta innebär att andra faktorer, åtminstone delvis, kan förklara utvecklingen av hjärtkärlsjukdom hos patienter med ledgångsreumatism. Då inflammatorisk aktivitet tycks vara en gemensam nämnare vid ledgångsreumatism och ateroskleros har olika markörer för inflammation utvärderats i flertalet studier som potentiella riskfaktorer för hjärtkärlsjukdom vid ledgångsreumatism och det har visat sig att hög inflammatorisk aktivitet är en riskfaktor för utvecklingen av hjärtkärlsjukdom både i vanliga befolkningen och hos patienter med ledgångsreumatism. Man har även funnit samband mellan olika ärftliga faktorer och autoantikroppar och risken att utveckla hjärtkärlsjukdom vid ledgångsreumatism.

De flesta av tidigare studier som undersökt olika riskfaktorer för hjärtkärlsjukdom vid ledgångsreumatism är delvis baserade på äldre populationer, vilket gör det svårt att veta vilken deras effekt är på mer nutida patient-underlag som behandlas på ett annat sätt. Dels är studierna även baserade på alla olika typer av hjärtkärlsjukdom (som förutom kranskärlssjukdom även kan innefatta bland annat stroke och hjärtsvikt), vilket gör det svårt att veta vilken effekt de har på respektive sjukdom. *I delstudie I undersökte vi därför olika potentiella riskfaktorer för akut kranskärlssjukdom vid ledgångsreumatism.* Vi genomförde en så kallad fall-kontroll studie baserad på 138 fall och 624 kontroller. Fallen utgjordes av patienter med ledgångsreumatism som utvecklat akut kranskärlssjukdom medan kontrollerna var patienter med ledgångsreumatism som inte utvecklat akut kranskärlssjukdom. Information om de olika riskfaktorerna insamlades från befintliga register-källor och medicinska journaler och jämfördes därefter mellan fall och kontroller. **Det visade sig bland annat att hög inflammatorisk aktivitet och sjukdomsaktivitet redan under första året efter insjuknande i ledgångsreumatism var associerat med risk för akut kranskärlssjukdom. Likaså var höga nivåer av en utav autoantikropparna associerat med risk för akut kranskärlssjukdom. Våra resultat understryker vikten av att ledgångsreumatism behandlas framgångsikt i tid för att**
förhindra utvecklingen av andra sjukdomstillstånd såsom akut kranskärllssjukdom.

**Studie II - Allvarlighetsgrad och prognos efter akut kranskärllssjukdom**


**Studie III – Förebyggande läkemedelsbehandling efter akut kranskärllssjukdom**

Efter en akut kranskärllshändelse behandlas patienter med en kombination av läkemedel som förebygger ett återinsjuknande. En sämre användning av dessa läkemedel hos patienter med ledgångsreumatism skulle eventuellt kunna förklara den sämre långtidsprognosen som vi såg i studie III. **I studie III så använde vi oss därför av läkemedelsregistret och tittade även på användningen av dessa läkemedel under ett år efter det akuta insjuknandet. Vi kunde inte se några större**
skillnader i användningen av förebyggande läkemedel mellan patienterna med ledgångsreumatism och de utan och kunde därmed inte heller förklara den försämrade prognosen med hjälp av detta.

**Studie IV – Hjärtsvikt vid ledgångsreumatism**

Hjärtsvikt är en annan typ av hjärtkärlsjukdom som innebär att hjärtats pumpförmåga är nedsatt till följd av påverkan på hjärtmuskulaturen. Högt blodtryck och kranskärlssjukdom är de vanligaste orsakerna till hjärtsvikt i västvärlden, men det finns många fler. Nyligen har man även funnit att det finns ett samband mellan inflammation och hjärtsvikt, men det är oklart om det är ett orsakssamband. Eftersom ledgångsreumatism är förknippat med kranskärlssjukdom är det inte förvånande att patienter med ledgångsreumatism även löper en ökad risk att drabbas av hjärtsvikt. Hjärtsvikt vid ledgångsreumatism har dock inte blivit undersökt i samma utsträckning som kranskärlssjukdom och det är oklart om ledgångsreumatism är förknippat med hjärtsvikt oberoende av kranskärlssjukdom. **Målet med studie IV var att utvärdera den relativa risken för hjärtsvikt vid ledgångsreumatism.** Vi utvärderade både risken för hjärtsvikt orsakad av kranskärlssjukdom och hjärtsvikt som inte orsakats av kranskärlssjukdom. Vidare så undersökte vi också hur bland annat inflammatorisk aktivitet påverkar risken att utveckla hjärtsvikt vid ledgångsreumatism. Vi fann att patienterna med ledgångsreumatism i vår studie löpte en ökad risk att drabbas av bågge typerna av hjärtsvikt. Riskökningen inträffade tidigt efter insjuknande i ledgångsreumatism. Vidare så var hög inflammatorisk aktivitet och andra mått på hög sjukdomsaktivitet associerat med utvecklingen av hjärtsvikt och mer uttalad för hjärtsvikt som inte orsakats av kranskärlssjukdom. Resultaten indikerar att inflammationen vid ledgångsreumatism driver utvecklingen av hjärtsvikt inte enbart via kranskärlssjukdom utan även via andra mekanismer. Resultaten manar även till att tecken på hjärtsvikt bör uppmärksammas hos patienter som nyligen insjuknat i ledgångsreumatism.
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