Atrial Fibrillation in the setting of Coronary Artery Disease

Risks and outcomes with different treatment options

GORAV BATRA
Abstract

Coronary artery disease (CAD) is the leading cause of mortality worldwide and atrial fibrillation (AF) is a prevalent arrhythmia associated with increased risk of mortality and morbidity. Despite improved outcome in both diseases, there is a need to further describe the prevalence, outcome and management of CAD in patients with concomitant AF.

AF was a common finding among patients with MI, with 16% having new-onset, paroxysmal or chronic AF. Patients post-MI with concomitant AF, regardless of subtype, were at increased risk of composite cardiovascular outcome of mortality, MI or ischemic stroke, including mortality and ischemic stroke alone. No major difference in outcome was observed between AF subtypes. At discharge, an oral anticoagulant was prescribed to 27% of the patients with MI and AF undergoing percutaneous coronary intervention (PCI). Aspirin or clopidogrel plus warfarin versus dual antiplatelet therapy with aspirin plus clopidogrel were associated with similar 0-90-day and lower 91-365-day risk of cardiovascular outcome, without increased risk of major bleeding events. Triple therapy with aspirin, clopidogrel plus warfarin versus dual antiplatelet therapy was associated with non-significant lower risk of cardiovascular outcome, but with increased risk of bleeding events. Treatment with renin-angiotensin system (RAS) inhibitors post-MI was associated with lower risk of all-cause and cardiovascular mortality in patients with and without congestive heart failure and/or AF. However, RAS inhibition in patients without AF was not associated with lower risk of new-onset AF. Approximately 1 in 3 patients undergoing isolated coronary artery bypass grafting (CABG) had pre- or postoperative AF. Patients with AF, regardless of subtype, were at higher risk of all-cause mortality, cardiovascular mortality and congestive heart failure. Furthermore, postoperative AF was associated with higher risk of recurrent AF.

In conclusion, AF was a common finding in the setting of MI and CABG. AF, irrespectively if in the setting of MI or CABG was associated with higher risk of ischemic events and mortality. Also, postoperative AF was associated with recurrent AF. Oral anticoagulants post-MI and PCI in patients with AF was underutilized, however, optimal antithrombotic therapy is still unknown. RAS inhibition post-MI seems beneficial, however, it was not associated with lower incidence of new-onset AF.

Keywords: atrial fibrillation, coronary artery disease, acute coronary syndrome, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, antithrombotic therapy, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, epidemiology

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To my beloved family
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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### Abbreviations

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<th>Description</th>
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<tr>
<td>ACEI</td>
<td>Angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin II receptor blockers</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical therapeutic chemical classification</td>
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<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoproteins</td>
</tr>
<tr>
<td>LV-EF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>Non-ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>RAS</td>
<td>Renin-angiotensin system</td>
</tr>
<tr>
<td>RIKS-HIA</td>
<td>Swedish register of information and knowledge about Swedish heart intensive care admissions</td>
</tr>
<tr>
<td>SCAAR</td>
<td>Swedish coronary angiography and angioplasty registry</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>SWEDHEART</td>
<td>Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies registry</td>
</tr>
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1. Introduction

Coronary artery disease (CAD) and its acute manifestation – acute coronary syndrome (ACS) – are common disorders and a leading cause of mortality and morbidity worldwide.\(^1,2\) However, during the last decades outcome after ACS has considerably improved due to new pharmacological and invasive treatment options.\(^3\) Despite improvements in outcome, there is a need for accurate and early identification of patients who are at a high risk of morbidity and mortality, and to tailor treatment based on the individual risk.

Atrial fibrillation (AF) is a prevalent arrhythmia affecting approximately 3% of the population, with the number predicted to rise with years to come due to aging population.\(^4\) The clinical importance of AF is due to the associated symptoms and the long-term outcomes in patients with the arrhythmia, including higher risk of mortality and morbidity, foremost due to the increased risk of ischemic stroke.\(^5\) AF frequently occurs in patients with CAD and is associated with poor outcome.\(^6\) Hence, there is ample room for improved understanding of AF as a risk factor in the setting of CAD, and a need to further improve treatment for patients with CAD and concomitant AF.
2. Background

2.1 Historical perspective

2.1.1 Coronary artery disease

Angina pectoris, the sensation of pain and tightness in the chest, is the characteristic symptom of CAD and has been described in several occasions throughout history. It is believed that Hippocrates, the father of empirical medicine, may have described angina pectoris in his work around the year 400 B.C.:

“Sharp pains, irradiating soon towards the clavicle and towards the back are fatal”

However, the first detailed account of angina pectoris is believed to be by Dr. William Heberden, a famous British physician who served King George III of the United Kingdom. In 1768, Dr. Heberden presented the term angina pectoris at the Royal College of Physicians in London:

“There is a disorder of the breast, marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, of which I do not recollect any mention among medical authors. The seat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris”

At the time, the pathogenesis of angina pectoris was still unknown. During the 19th century, pathologists started observing clots obstructing coronary arteries in postmortem examinations of patients with history of angina pectoris. Parallel to these discoveries, physiologists reported that occlusions in the coronary arteries might cause quivering of the heart and mortality. It was Dr. Ludvig Hektoen, an American pathologist, who first described the correlation between coronary thrombosis and myocardial infarction (MI) in 1879:

“While cardiac infarction may be caused by embolism, it is caused much more frequently by thrombosis, and thrombosis again is usually secondary to sclerotic changes in the coronaries”
Twenty-two years later, in 1901, the German physician Dr. Ludolf von Khrel may have been the first one to describe the association between symptoms, pathogenesis and MI.\(^\text{13}\)

In the early years and until mid-20th century, treatment for acute MI was based on total bedrest as proposed by the American physician Dr. James Herrick in 1912.\(^\text{14}\) This approach was golden standard of care until the 1960s, when a turn in the management of acute MI was seen due to several medical advances such as introduction of coronary care units, coronary artery revascularization, insights into risk factors and secondary prevention, and introduction of several potent drugs.\(^\text{15}\)

### 2.1.2 Atrial fibrillation

AF comes with several symptoms, among which irregular pulse and symptomatic palpations are the most characteristic. Perhaps, the earliest description of these symptoms and of AF are to be found in The Yellow Emperor’s Classic of Internal Medicine (Huang Ti Nei Ching Su Wen) from around 400-200 B.C.:

“When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades; when the pulse is slender (smaller than feeble, but still perceptible, thin like a silk thread), then the impulse of life is small.” \(^\text{16}\)

Moreover, it is believed that Hippocrates among his many discoveries might have stumbled upon symptoms characteristic of AF around 400 B.C.:

“…there was violent palpitations of the heart” \(^\text{7}\)

However, it was probably Dr. William Harvey, a British physician who first described fibrillation of the auricles in animals in 1628.\(^\text{17}\)

A milestone in the pathway for the discovery of AF was in 1902 when the Dutch physician Dr. Willem Einthoven invented the electrocardiograph (ECG).\(^\text{18}\) Four years later, in 1906, the first human ECG illustrating AF was published by Dr. Einthoven\(^\text{19}\) From that point onwards it only took three years until the correlation between irregular pulse and the ECG findings in AF was presented simultaneously by the British physician Dr. Thomas Lewis and the German physicians Dr. Carl Julius Rothberger and Dr. Heinrich Winterberg.\(^\text{20}\)
2.2 Symptomatology and classification

2.2.1 Coronary artery disease

Angina with chest pain, tightness in the chest and discomfort in one or both of the arms are classic textbook examples of symptoms patients with CAD, especially ACS, might experience. However, there is a wide array of symptoms that may be contributed to CAD, e.g. dyspnea, fatigue, dizziness, nausea, vomiting, excessive diaphoresis and psychosocial distress. Despite the excessive list of symptoms, some patients might not experience any symptoms at all.\(^{21}\)

The term CAD compromises several diseases that are characterized by a reduced blood supply to the heart muscle. Clinically, CAD is a collective term for stable angina pectoris and ACS. ACS refers to a spectrum of clinical manifestations due to reduced blood supply and/or increased demand from the heart and is further divided into unstable angina, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), see Table 1. For the diagnosis of MI, evidence of myocardial necrosis in an relevant clinical setting must be meet, as defined by the third universal definition of MI; dynamic changes of a cardiac biomarker plus characteristic symptoms of CAD or pathological ECG changes.\(^{21}\) Moreover, MI is further classified into five subtypes based on underlying pathological, clinical and prognostic characteristics and include; spontaneous MI, MI due to supply/demand imbalance, MI related to death were results from biomarkers are not available, MI related to percutaneous coronary intervention (PCI), stent thrombosis or coronary artery bypass grafting (CABG).\(^{21}\)

*Table 1. Clinical classification of coronary artery disease based on the third universal definition of myocardial infarction\(^{21}\)*

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Stable coronary artery disease</td>
<td>Episodes of reversible myocardial demand/supply mismatch which can be induced by exercise, other stress or occur spontaneously.</td>
</tr>
<tr>
<td>Unstable coronary artery disease</td>
<td>Often incomplete/subtotal occlusion of the coronary arteries with symptoms or ECG changes without ST-elevation, but without evidence of myocardial necrosis (no elevated biomarkers).</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>Often incomplete/subtotal occlusion of the coronary arteries with symptoms or ECG changes without ST-elevation, and with evidence of myocardial necrosis (elevated biomarkers)</td>
</tr>
<tr>
<td>STEMI</td>
<td>Often complete occlusion of a coronary artery with symptoms and ECG changes including ST-elevation, and with evidence of myocardial necrosis (elevated biomarkers).</td>
</tr>
</tbody>
</table>
2.2.2 Atrial fibrillation

AF is a common arrhythmia with a wide spectrum of symptoms. Approximately one third of patients have silent AF and are asymptomatic. However, many patients complain about symptoms including; chest palpations, chest tightness, irregular pulse, dyspnea, fatigue and psychosocial distress. In some instances, patients may even have symptom of severe hemodynamic instability. Moreover, studies have reported that the quality of life is poorer in patients with AF versus healthy controls.

AF is clinically classified into five categories: first diagnosed AF, paroxysmal AF, persistent AF, long-standing persistent AF and permanent AF. The categorization is based on several factors including; duration of disease, clinical presentation, medical management and therapeutic goals, see Table 2.

**Table 2. Classification of AF based on the European Society of Cardiology guidelines for the management of atrial fibrillation 2016**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>First diagnosed AF</td>
<td>New-onset AF in patients with no previous history of AF. This classification is irrespective of symptoms associated with AF and duration of the arrhythmia.</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>AF episodes that self-terminate within 7 days. If patients are treated with drugs or by direct current cardioversion within 7 days, the episodes are considered paroxysmal.</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>AF episodes that last longer than 7 days. If patients are treated with drugs or by direct current cardioversion after 7 days, the episodes are considered persistent.</td>
</tr>
<tr>
<td>Long-standing persistent AF</td>
<td>AF episodes that lasts for ≥ 1 year and when it is decided to adopt a rhythm control strategy for the patients.</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>AF that is accepted as permanent by the patient and by the physician. In these instances, rhythm control strategies are not implemented.</td>
</tr>
</tbody>
</table>

2.3 Epidemiology and implications

2.3.1 Coronary artery disease

CAD, also known as ischemic heart disease, is the leading cause of morbidity and mortality worldwide, foremost in men than women, according to reports from the Global Burden of Disease Study published in 2015 and 2016. In the same reports, the estimated number of deaths globally due to ischemic heart disease was 5.7 million in 1990 and 8.9 million in 2015, an 55% increase. However, when taking into account the differences in age structure of the populations being compared, the age-standardized mortality rate due to ischemic heart disease decreased by 20% between 1990 and 2015. Similarly, the global age-standardized annual incidence of acute MI decreased from 180 per 100,000 individuals in 1990 to 155 per 100,000 individuals in 2010. The largest decline in the incidence of acute MI during this period was observed...
in high-income developed regions, and in contrast, an increase in incidence was observed in developing and transitional countries.\textsuperscript{27} Moreover, epidemiologic data suggests that the proportional incidence of NSTEMI has increased over time, while the incidence of STEMI is decreasing.\textsuperscript{28} The decline in incidence of acute MI and mortality due to CAD is explained by the increased awareness of cardiovascular risk factors and due to advances in acute in-hospital management of the disease with coronary interventions and improved secondary prevention strategies that include potent medication.\textsuperscript{28-30} However, advances in diagnosis of acute MI, such as more sensitive cardiac biomarkers detecting smaller infarctions, could potentially diminish the future reduction in incidence of acute MI observed.\textsuperscript{30}

As previously mentioned, patients with acute MI are at increased risk of mortality, including short- and long-term mortality. Mortality rates in patients with acute MI is highest within the first week, and gradually declines. According to reports, the current rate of short-term mortality within a month following an acute MI is approximately 5\%, with higher mortality rates in the acute stages of STEMI than in NSTEMI.\textsuperscript{31} However, real-life data from the Swedish National Board of Health and Welfare suggests that the mortality rate within one month from an acute MI is 25\%, with 18\% of the patients dying the same day as the event, with a majority dying prior to hospital admission.\textsuperscript{32} In the same report, long-term mortality within one year from event was reported to be 34\%. Compared to short-term mortality, long-term mortality rates are similar among patients with NSTEMI and STEMI.\textsuperscript{33}

In addition to mortality, patients after acute MI are at considerable risk for recurrent MI, with the risk reported to vary between 5-7\% during the first year.\textsuperscript{34} Also, patients post-MI are at increased risk of left ventricular dysfunction and congestive heart failure (CHF).\textsuperscript{35}

2.3.2 Atrial fibrillation

AF is the most common sustained heart arrhythmia, with an increasing prevalence and incidence globally.\textsuperscript{36} It is estimated that approximately 33.5 million individuals suffered from AF in 2010.\textsuperscript{37} Probably an underestimation due to sparse data on prevalence of AF in Africa, Asia and South America,\textsuperscript{36} and due to the fact that AF can go undetected without symptoms in the general population.\textsuperscript{38} Moreover, epidemiologic data suggests that AF is more prevalent in men than in women, and that the prevalence of AF doubles with each decade of age after the age of 50 years, with the prevalence increasing from 0.1\% among individuals younger than 55 years to approximately 9\% among adults above 80 years.\textsuperscript{39-41} Thereof, it is projected that the number of patients with AF will rise during the coming decades, foremost due to aging population.\textsuperscript{4,39}
In AF, the inappropriate contraction of the atria leads to formation of blood clots, especially in the left atrial appendage. The lone impact of AF as a risk factor for stroke was established based on data from the Framingham study. In the study, it was showed that patients with AF had a more than fivefold increased risk of stroke. In addition to stroke, the Framingham study also concluded that patients with AF were at increased risk of mortality and CHF. Since then, further research has recognized AF as a risk factor for MI.

2.3.3 Coronary artery disease and atrial fibrillation

AF is a common finding in patients with CAD, with the prevalence reported to vary between 3% and 22% in patients with acute MI. Few studies have reported the distribution between different subtypes of AF in the setting of acute MI, with some studies reporting that a history of AF is more common than new-onset AF in patients with acute MI. In patients undergoing CABG, higher incidence rates of AF have been reported, with postoperative AF reported to occur in approximately one-third of patients undergoing CABG. However, few researchers have reported preoperative rates of AF, with a handful of studies showing that the prevalence might vary between 7-9%.

Studies analyzing the impact of AF as a prognostic factor following acute MI have reported conflicting findings. Nevertheless, two meta-analyses studying the independent association of AF in the setting of acute MI consistently show that AF is associated with increased risk of all-cause mortality, with one study showing a doubled risk of in-hospital mortality (odds ratio 2.00, 95% confidence interval [CI] 1.93 – 2.08) and another study showing an increased risk of long-term mortality (odds ratio 1.46, 95% CI 1.35 – 1.58). In addition, meta-analyses report that both pre-existing and new-onset AF in the setting of acute MI is independently associated with risk of all-cause mortality. Furthermore, AF in the setting of acute MI has in some studies been linked to other cardiovascular outcomes, including stroke, and recurrent MI. However, uncertainty still remains whether AF after MI should be regarded as an indicator of present cardiovascular condition or as an independent factor leading to unfavourable cardiovascular outcomes.
2.4 Pathophysiology

2.4.1 Coronary artery disease

CAD compromises several diseases that are characterized by a reduced blood supply to the heart muscle, most often due to atherosclerosis with or without thrombosis and vasospasm in the coronary arteries. Atherosclerosis is a lipid-driven immune-inflammatory condition that begins early in life and develops during several years resulting in the formation of atherosclerotic lesions. The lesions, called atheroma, are formed within the walls of the coronary arteries through numerous multifactorial steps and are focal thickenings of the arteries. Simplified, the coronary arteries comprise three layers; tunica intima, the innermost layer which consists of endothelial cells and an elastic membrane that forms the barrier between the artery lumen and the remaining layers; tunica media, which consists of smooth muscle cells; and tunica adventitia, which contains an external elastic membrane and connective tissue. During the early stages in the formation of an atheroma, excessive lipoproteins, particularly low-density lipoproteins (LDL), invade the coronary walls and gather beneath the endothelium forming what is known as fatty streaks. Within the fatty streaks, LDL particles start to oxidize and trigger endothelial cells to express leukocyte adhesive molecules and other chemo-attractants on its surface, which stimulates the entrance of monocytes into the atheroma. The monocytes within the atheroma start differentiating into macrophages and scavenge oxidized LDL particles, ultimately transforming the macrophages into foam cells. In addition to monocytes, T-cells are recruited and activated in the atheroma. Together, the foam cells and the T-cells produce cytokines, proteases and other inflammatory molecules which promote recruitment of additional macrophages and smooth muscle cells into the tunica intima causing the atheroma to grow. During this process, foam cells degrade releasing its content of cholesterol crystals forming a necrotic core within the atheroma. The increasing number of smooth muscle cells within the atheroma intensifies the synthesis of collagen, creating what is known as the fibrous cap, a layer which is located between the coronary artery lumen and the necrotic core of the atheroma.

Over time, some atheromas develop into vulnerable plaques that might rupture and form blood clots known as thrombus. These plaques often have characteristic findings which include lipid-rich necrotic cores and thin fibrous caps. However, the mechanism behind plaque rupture is poorly understood and in some instances plaque rupture is not necessary for thrombus formation and could occur through other mechanisms such as plaque erosion. MI occurs when an atheroma prevents blood to flow through the coronary arteries.
In some cases, this is due to coronary spasm, but in most cases due to thrombus formation on a ruptured plaque. When the innermost layer of a plaque is exposed to the lumen, e.g. by plaque rupture, platelets in the blood system come in contact with the thrombogenic core of the atheroma and start the process of thrombosis.

In the process of thrombosis, platelets play a central role. Platelets are normally recruited during instances of vascular injury, but also during the pathologic process of thrombosis. When the innermost core of an atheroma is exposed to the blood circulation, platelets are activated and involved in a three step process; adhesion, activation and aggregation. In the process of adhesion, activated platelets express receptors that cross-link with von Willebrand factor and fibrinogen, making it easy for platelets to bind to other platelets and to the ruptured plaque and the exposed collagen. Second, activated platelets release granules containing platelet agonists such as adenosine diphosphate, adenosine triphosphate, serotonin and thromboxane A2. Thromboxane A2 stimulates the thromboxane prostanoid receptors, which results in platelet shape change. Adenosine diphosphate in turn stimulates platelet activation through two different G-protein coupled receptors; P2Y1 and P2Y12. Activation of the P2Y1 receptor stimulates activation of the glycoprotein (GP) IIb/IIIa receptor resulting in calcium mobilization, platelet shape change and platelet aggregation. Activation of P2Y12 receptor instead stimulates additional platelet degranulation and is also involved in the activation of the GPIIb/IIIa receptor, again results in an elevated platelet aggregation.

If a plaque rupture or erosion leads to formation of a thrombus obstructing the local blood flow in a coronary artery, ischemia of the myocardium might follow. The size of ischemia depends of several factors including the myocardial area covered by the obstructed artery and collateral blood flow to the affected areas. If an ischemia is prolonged, death of myocardial cells might occur.

2.4.2 Atrial fibrillation

AF is a supraventricular arrhythmia were electrical activity within the atrium of the heart is uncoordinated and chaotic. In a healthy heart the sinus node, a group of cells located in the right atrium of the heart, initiate and regulate the normal heart rhythm called the sinus rhythm. In AF, other foci than the sinus node initiate the uncoordinated fibrillation of the atrium. Fortunately, the ventricular heart rate is slower and irregular in patients with the arrhythmia, this due to the electrical relay station located between the atrium and the ventricles.
Simplified, the pathophysiological mechanisms behind AF can be divided into; triggers for the onset of AF, and substrate for the continuation of the arrhythmia. A key arrhythmogenic trigger site for the initiation of AF has been described as the myocardial sleeves extending from the left atrium into the pulmonary veins. However, the ectopic activities of the myocardial sleeves are poorly understood and experimental evidence suggests that the activity could be due to re-entry, automaticity and triggered activity in the myocardial sleeves. Furthermore, it is believed that remodeling of the heart, such as structural remodeling due to connective tissue deposition and fibrosis, and ionic remodeling might initiate the arrhythmia. Nevertheless, isolation of the pulmonary veins using ablation techniques have shown to reduce the AF burden among symptomatic patients.

For the continuation of the arrhythmia, the mechanisms are complex and not fully understood. Nonetheless, it has been recognized that electrical and structural remodeling of the atria play a key role. Experimental theories suggest that intercellular calcium-handling abnormalities play an important role in both electrical and structural remodeling of the atria. Among several other possible mechanisms, it has been proposed that the renin–angiotensin system (RAS) might have an important role in the structural and electrical remodeling seen in patients with AF. The RAS is a major endocrine/paracrine system which is involved in the regulation of the cardiovascular system using angiotensin II as an important mediator. Angiotensin II in turn expresses its activity using two receptors; the angiotensin II type 1 receptor (AT₁) and the angiotensin II type 2 receptor (AT₂). Experimental evidence suggests that RAS might induce AF through several mechanisms including; increased atrial pressure, increased proinflammatory and profibrotic effects of angiotensin II, and through alteration of the electrical properties of the atrial tissue. Additionally, studies have shown that left ventricular dysfunction and abnormal ventricular pressures could provide a substrate for AF.

### 2.4.3 Coronary artery disease and atrial fibrillation

CAD and AF share several risk factors that might explain the coexistence of both diseases, with the most important risk factor being age. Higher age is associated with increased occurrence of AF, but also of CAD. In addition to age, several other atherosclerotic risk factors such as diabetes mellitus, CHF, dyslipidemia, hypertension and obesity are overrepresented among patients with CAD and AF.

Previous studies have shown that patients with AF are at an increased risk of future MI. In addition to above risk factors, systemic inflammation in patients with AF might promote MI. This is supported by the fact that higher levels of inflammatory biomarkers, such as interleukin 6, tumor necrosis factor α and C-reactive protein, are associated with increased risk of AF and
CAD. In addition to systemic inflammation, other possible causative mechanisms are AF induced systemic endothelial dysfunction, platelet activation and thrombin generation triggering CAD. Also, case reports of sporadic thromboembolic MI have been described in the literature among patients with AF.

As earlier noted, new-onset AF is a frequent finding among patients with MI, and AF in MI appears to be multifactorial. In patients post-MI, left ventricular dysfunction and CHF might be present. In such patients, ventricular dysfunction could trigger structural remodeling of the atria and alter the calcium-handling, increasing intercellular calcium levels, prompting electrical and structural remodeling. In addition, myocardial ischemia, especially in the atria, could promote the onset of AF due to conduction disturbances in the atria. Other experimental theories suggest that neurohormonal factor alterations during MI might be associated with onset of AF. Moreover, it is possible that MI associated myocardial damage leads to inflammation, which in turn could promote new-onset AF. In summary, there seems to be a bidirectional relationship between AF and MI, probably due to similar risk factors for their onset and common pathophysiologic processes driving both diseases.

Pathophysiological explanations for postoperative AF in patients undergoing CABG are not precisely understood, but are probably multifactorial. Studies have found several risk factors that are associated with risk of AF in patients undergoing cardiac surgery, including factors such as advanced age, history of AF, male gender, valvular heart surgery, left ventricular dysfunction, diabetes mellitus, renal failure and obesity. In addition to mentioned risk factors, it is believed that some patients undergoing cardiac surgery might develop an atrial substrate during atrial incision making them more vulnerable for postoperative AF. Also, it is believed that postoperative inflammation, both systemic and locally in the atrium, might promote AF. This theory is supported by reports showing that an increase in inflammatory biomarkers, e.g. C-reactive protein, follows a similar time frame as AF onset. Other proposed explanatory mechanisms linking cardiac surgery and postoperative AF include activation of the sympathetic nervous system and increased vagal tone due to surgery induced stress. Moreover, it is believed that postoperative AF might be linked to surgery-induced alterations of ion-channel function and volume-pressure changes.
2.5 Management

2.5.1 Coronary artery disease

Management of ACS can simplified be divided into two strategies; initial therapy and secondary prevention. The goal with initial therapy is to stabilize the patient’s condition, to relieve the patient from symptoms and to reduce myocardial damage and further ischemia.\textsuperscript{92,93} In contrast, the main goal with secondary prevention is to avoid recurrent cardiovascular events after an episode of ACS.\textsuperscript{92,93}

Invasive treatment

Today, patients with ACS are treated invasively using two different methods, CABG or PCI. With both methods, the goal is to improve blood flow though the occluded coronary arteries. CABG was introduced in clinical practice during the 1960s after the development of the cardiopulmonary bypass machine and uses vessel grafts to improve coronary blood flow.\textsuperscript{94} A decade later during the 1970s, coronary angiography and PCI was commenced in clinical practice and has during recent years undergone substantial improvements with introduction of newer and better catheters, balloons and stents to improve the coronary circulation.\textsuperscript{95} Recent guidelines recommend both treatments and that the choice between the two methods depend on the clinical setting, patient comorbidities and angiographic findings.\textsuperscript{96}

In patients with STEMI, urgent revascularization of occluded arteries is of importance.\textsuperscript{97} Hence, current guidelines recommend acute PCI within 90 minutes from first medical contact. If PCI is not possible within given time-frame, guidelines recommend pre-hospital fibrinolysis followed by routine coronary angiography.\textsuperscript{96,98} In patients where PCI cannot be performed due to unsuitable anatomy, CABG should be considered.\textsuperscript{96} In patients with NSTEMI or unstable angina, revascularization guidelines differ from that of patients with STEMI. For these patients, urgent coronary angiography is recommended when there is a high ischemic risk, e.g. cardiogenic shock and hemodynamic instability. In all other cases, routine coronary angiography is recommended for patients with high risk of CAD, especially in patients with positive biomarkers reflecting CAD.\textsuperscript{96,99,100} Current guidelines recommend that in patients undergoing invasive treatment, revascularization strategy with either culprit lesion PCI, multivessel PCI or CABG is to be selected based on patient comorbidities, the clinical setting and angiographic findings by a multidisciplinary team.\textsuperscript{96} To facilitate the selection of optimal treatment, the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) score is recommended.\textsuperscript{101}
Antithrombotic therapy

Antithrombotic therapy is of core importance in the initial treatment and for the secondary prevention after an episode of ACS. Aspirin, one of the cornerstones in treatment of ACS was first introduced for public use in the beginning of the 1900s. However, it was not until the 1980s when aspirin was studied in an orderly fashion after ACS and was associated with marked reduction in death and recurrent MI. Aspirin irreversibly inhibits the enzymatic activity of cyclooxygenase, resulting in a reduced production of thromboxane A2. As previously mentioned, thromboxane A2 stimulates the thromboxane prostanoid receptors, which results in platelet activation. Thus, treatment with aspirin almost completely blocks the activation of platelets thought this pathway, with the effect enduring for the lifetime of the platelets.

In addition to aspirin, P2Y12 inhibitors are recommended to patients with ACS in a dual antiplatelet strategy. This combination is recommend for patients managed using a non-invasive strategy, but more importantly in patients undergoing PCI with coronary stenting to reduce risk of stent thrombosis. The first P2Y12 inhibitor to be used in clinical practice was ticlopidine during the 1990s, which in addition to aspirin showed a reduction ischemic events, however, with increased risk of neutropenia or thrombocytopenia. Thus, ticlopidine was soon replaced with clopidogrel, which was shown to have similar beneficial effects in reducing risk of ischemic events, but without above mentioned adverse effects. Moreover, clopidogrel in addition to aspirin was shown to be beneficial in reducing ischemic events in patients with STEMI and NSTEMI, but with the cost of increased risk of bleeding events. During recent years, new generation of P2Y12 inhibitors have been introduced and include prasugrel and ticagrelor which are more efficient and have faster onset compared to clopidogrel. In phase III trials and compared to clopidogrel, prasugrel and ticagrelor were associated with reduced risk of ischemic events, however, with increased risk of bleeding events. Ticlopidine, clopidogrel and prasugrel belong to the thienopyridine class of drugs and compromise inactive pro-drugs that needs to be metabolized before they irreversibly inhibit the P2Y12 receptors and platelet aggregation. In contrast, ticagrelor belong to the cyclo-pentyl-triazolo-pyrimidines class and acts as an analogue to adenosine triphosphate which reversibly binds to the P2Y12 receptors, thereby inhibiting platelet aggregation.

Prior to interventional strategies involving PCI with stenting and the widespread clinical use of P2Y12 inhibitors, several trials between the 1960s and early 2000s demonstrated the efficacy of oral anticoagulants in preventing recurrent ischemic events in patients post-MI. In one of the largest placebo-controlled trials, oral anticoagulation with warfarin was associated
with a 24% reduced risk of all-cause mortality and recurrent MI in patients after MI. In another trial, oral anticoagulation showed limited effect on mortality, but was associated with a 53% reduction in risk of recurrent MI. Following these pivotal trials and after the widespread use of aspirin, a trial comparing warfarin alone, aspirin alone or a combination of aspirin and warfarin in patients with acute MI was published in 2002. In this trial, warfarin, in combination with aspirin or as monotherapy was superior to aspirin alone in reducing the risk of death, recurrent MI or thromboembolic stroke after an acute MI. Similar results were seen in two meta-analysis that compared the combination of aspirin and warfarin to aspirin alone, in which the authors concluded that the combined therapy reduced the risk of ischemic events, but with the cost of excessive bleeding events. However, after the introduction of PCI and coronary stenting in a majority of patients with ACS, dual antiplatelet therapy with aspirin and P2Y12 inhibitors became mainstream due to lower rate of stent thrombosis as compared to aspirin alone or in combination with oral anticoagulants. Briefly, warfarin inhibits vitamin K reductase depleting the active form of vitamin K. As a result, the subsequent activation of the vitamin K-dependent coagulation factors II, VII, IX and X, and anticoagulant proteins C and S is inhibited which in turn decreases the levels of thrombin generated.

Renin-angiotensin system inhibitors
RAS inhibitors include angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) which exhibit their effect by promoting vasodilation and renal sodium excretion, blocking sympathetic nervous system activity, and by inhibiting cardiac and vascular remodeling. This is achieved by inhibiting the generation of the active peptide angiotensin II (the effector in the RAS), or by blocking its action via the angiotensin II receptors. Several studies have established the mortality and recurrent MI benefits of RAS inhibitors in patients post-ACS, and current guidelines recommend ACEI or ARBs especially to patients with left ventricular dysfunction, CHF, hypertension and/or diabetes mellitus.

Other pharmacological therapy and long-term management
In addition to invasive procedures, antithrombotic therapy and RAS inhibition, a number of other therapeutic strategies are beneficial in the management of patients with ACS, and include beta blockers, lipid-lowering treatment and nitrates. Furthermore, secondary prevention after an ACS also includes risk factor modification including exercise, diet and smoking cessation. These treatment and risk factor modification aspects are beyond the scope of this thesis.
2.5.2 Atrial fibrillation
Management of AF can simplified be divided into three strategies; rate control, rhythm control and prevention of thromboembolism. The overall aim with the different strategies is to regulate the ventricular rate, to reduce symptoms and to prevent mortality and morbidity associated with AF.

Heart rate and rhythm control
With heart rate control the aim is to regulate the ventricular rate with drugs, to reduce symptoms and to prevent tachycardia-induced cardiomyopathy. In contrast, rhythm control aims to restore and maintain sinus rhythm with electrical cardioversion, antiarrhythmic drugs and/or surgical intervention. Several trials comparing the two treatment strategies have found that rate control is non-inferior to rhythm control for the prevention of death and morbidity associated with AF. Thus, current guidelines recommend rhythm control therapy for patients in whom symptom improvement is not attained with rate control. Irrespective of rate or rhythm control, guidelines recommend stroke risk assessment and oral anticoagulation therapy if indicated.

Antithrombotic therapy
As previously mentioned, AF can lead to formation of blood clots, especially in the left atrial appendage, and is associated with increased risk of ischemic stroke. However, the risk of stroke varies considerably across patients, whereby the use of predictive risk stratification scores such as the CHA$_2$DS$_2$-VASc score (CHF, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, female sex) are recommended prior to initiation of treatment. For patients with increased risk of ischemic stroke, treatment with an oral anticoagulant is recommended. However, it was not until the 1990s that randomized trials and meta-analysis verified the efficacy of warfarin in preventing mortality and ischemic stroke in patients with AF. In one meta-analysis, warfarin was associated with an approximate 25% risk reduction in mortality and a 60% risk reduction in ischemic stroke compared to no antithrombotic treatment.

Antiplatelet therapy with aspirin has for many years been studied and used for patients with AF and risk for ischemic stroke. Seven large trials have compared aspirin to placebo or control, however, only one study was able to show a significant risk reduction of thromboembolic events with aspirin. Subsequently, meta-analyses have concluded that warfarin and antiplatelet agents reduce stroke, but that warfarin is substantially more efficacious. Additionally, a randomized clinical trial has shown that oral anticoagulation therapy is superior to clopidogrel plus aspirin for prevention
of stroke, non-central nervous system systemic embolus, MI or vascular death.\textsuperscript{149}

Despite the benefits with warfarin, the drug has some limitations. High therapeutic values of warfarin, as measured using blood samples and a value called international normalized ratio, entails an increased bleeding risk and subtherapeutic values is associated with poor stroke prevention. Thus, regular blood sample monitoring is required due to a narrow therapeutic window.\textsuperscript{150,151} Moreover, warfarin metabolism interacts with other drugs and food.\textsuperscript{151} To resolve these limitations, new and safer oral anticoagulants have been introduced and include dabigatran, rivaroxaban, apixaban and edoxaban. All of these drugs have been shown to be at least as effective and safe as warfarin in patients with AF.\textsuperscript{152-155}

2.5.3 Coronary artery disease and atrial fibrillation

Management of patients with AF in the setting of CAD compromises several treatment strategies. This thesis focuses on antithrombotic therapy and RAS inhibition post-MI. Also, some management aspects of AF in the setting of isolated CABG are covered.

Antithrombotic therapy

As previously mentioned, dual antiplatelet therapy with aspirin and P2Y\textsubscript{12} inhibitors are recommended after an ACS, especially in patients undergoing coronary artery stenting to reduce the risk of recurrent ischemic events.\textsuperscript{92,93} However, there is scarce evidence regarding optimal antiplatelets therapy for patients with AF in whom long-term oral anticoagulation therapy is needed to reduce risk of ischemic stroke.\textsuperscript{138-142,156} Thus, optimal antithrombotic drug combinations and duration of such therapy is unknown for patients with AF post-ACS. For these patients, current guidelines recommend treatment during a short period (between 1 – 6 months) with triple therapy (aspirin, clopidogrel and oral anticoagulants) followed by a period of dual antiplatelet therapy (aspirin or clopidogrel plus oral anticoagulant). After one year, guidelines recommend monotherapy with one oral anticoagulant.\textsuperscript{26} Also, use of prasugrel and ticagrelor in combination with aspirin and oral anticoagulants is not recommended due to increased risk of major bleeding events as compared to clopidogrel.\textsuperscript{26,157}

Several studies, most of them small, single-center and/or retrospective, have shown that triple therapy, as compared to dual antiplatelet therapy, is associated with higher risk of bleeding events in patients with ACS.\textsuperscript{158-164} In aggregate, these studies also suggest that patients discharged without oral anticoagulants are at higher risk of adverse cardiovascular outcomes.\textsuperscript{158-164} Recently, the use of one oral anticoagulant plus a single antiplatelet agent was
proposed in a randomized trial in which patients undergoing PCI (a majority of whom were non-ACS patients) treated with oral anticoagulants, regardless of indication, were randomly assigned to either triple therapy or one oral anticoagulant plus clopidogrel. This study was powered to show differences in the primary endpoint of any bleeding events within one year and showed that the use of an oral anticoagulant plus clopidogrel, as compared to triple therapy, reduced the risk of bleeding events with no increase in rate of thromboembolic events. Following this trial, retrospective registry data has shown similar findings. Moreover, a recent randomized clinical trial presented that triple therapy with aspirin, clopidogrel and warfarin was associated with significantly higher bleeding risk compared to two treatment strategies with either rivaroxaban 15 mg once daily plus one P2Y\textsubscript{12} inhibitor, or triple therapy with a lower dose of rivaroxaban 2.5 mg twice daily plus aspirin and one P2Y\textsubscript{12} inhibitor. In contrast, the cardiovascular event rates seemed similar in all treatment arms, however, the trial was not powered to evaluate efficacy outcomes. Despite above results, the available evidence does not allow robust conclusions regarding antithrombotic therapy for patients with ACS and AF.

Renin-angiotensin system inhibitors
RAS inhibitors have been shown to inhibit cardiac and vascular remodeling, inhibit the arrhythmogenic effects of angiotensin II and to reduce inflammation. Several retrospective analyses from large randomized clinical trials, and consequent meta-analyses, on patients with CHF or left ventricular dysfunction have reported a lower incidence of new-onset AF in patients treated with RAS inhibitors. Similar trends have been seen for patients with hypertension treated with RAS inhibitors compared to placebo. Two retrospective analyses of trials on patients post-acute MI have studied RAS inhibition and risk of AF, both presenting conflicting results. In one of the trials, RAS inhibition with trandolapril was associated with lower risk of new-onset AF, a finding which was not observed in a trial studying the effects of lisinopril. In a meta-analysis including these two trials, no effect of RAS inhibition was noted in relation to new-onset AF.

Coronary artery bypass grafting
Management of AF in the setting of CABG compromises several different treatment strategies. Studies on treatment and preventive strategies have shown that antiarrhythmic therapies such as beta-blockers, sotalol, amiodarone, magnesium and temporary pacing might reduce the incidence of AF post-open-heart surgery. Despite this, incidence rates of AF are high with approximately one-third of patients undergoing CABG having episodes of postoperative AF. Currently, there is a lack of evidence regarding optimal management of patients with postoperative AF. Thus, current
guidelines cautiously recommend oral anticoagulants as for patients with ordinary AF based on beneficial findings reported from one retrospective single-center study. In patients with symptomatic AF, rhythm control therapy is recommended and a rate control strategy is stated as reasonable for patients with none or acceptable symptoms.
3. Aims

The overall aim of this thesis was to describe the prevalence of AF, the characteristics of patients with AF, the risks with AF, and the management of patients with AF in the setting of CAD.

Specifically, the aim with the thesis was to answer the following questions:

I What is the prevalence of different subtypes of AF (new-onset, paroxysmal and chronic) in patients hospitalized due to acute MI? What is the association between different subtypes of AF and short-term outcomes?

II What antithrombotic agents are prescribed to patients with a known or newly diagnosed AF after an acute MI and PCI? What is the association between antithrombotic treatment regimens and short- and long-term outcomes?

III Is RAS inhibition associated with beneficial outcomes in patients post-acute MI with and without CHF and/or AF? In patients with no history or in-hospital diagnosis of AF post-acute MI, is RAS inhibition associated with lower risk of new-onset AF?

IV In patients undergoing CABG, what is the prevalence of AF and what is the impact of preoperative AF and new-onset postoperative AF on long-term outcomes? Is the presence of new-onset postoperative AF associated with future risk of recurrent AF?
4. Methods

4.1 Study design

All of the studies included in this thesis (papers I – IV) were designed as retrospective observational cohort studies, with the purpose to examine the associations between risk factors and exposures to given outcomes. A summary of all studies is presented in Table 3.

Table 3. Overview of design and methods in papers I – IV

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<tr>
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<td>Post-coronary artery bypass grafting</td>
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<td><strong>Sample size</strong></td>
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<td>9,107</td>
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<td>Propensity-score matched analysis</td>
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4.2 Data collection

4.2.1 National quality registries

A unified definition of national quality registries has been proposed by the Swedish Association of Local Authorities and Regions:

“The registries contain individualized data about medical interventions, procedures and outcomes. They are integrated into clinical workflows and have the capacity to generate data in real time. Each registry is supported by an organization of health care professionals, researchers and patient representatives. They are jointly responsible for developing the registry.”

Sweden with over 100 national quality registries covering healthcare aspects from cardiovascular disease to psychiatric disorders has a unique and strong position in the world as data derived from national quality registries continuously enables health care professionals to follow-up and improve the quality of medical care provided. However, participation in national quality registries is not mandatory for hospitals, health care professionals and patients. On admission, patients receive written information about national quality registries but do not provide written consent. However, they are informed about their inclusion and have the right to decline participation. According to Swedish law (Patientdatalagen, 2008:355, chapter 7), written consent is not required because quality control is an inherent element of healthcare.

4.2.2 SWEDHEART

The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDHEART) registry was launched in December 2009 and is a national quality registry within the field of cardiovascular healthcare. However, the history of SWEDHEART began much earlier. In 1991, the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA) was launched by Dr. Lars Wallentin and Dr. Ulf Stenestrand in Linköping, Sweden. In 1995 the registry was approved as a national quality registry, and in 2008 that all coronary care units in Sweden reported data to the registry. Today SWEDHEART constitutes of six sub-registries; RIKS-HIA, the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), the Swedish Heart Surgery Registry, the National Registry of Secondary Prevention (SEPHIA), the Percutaneous Valve Registry and the Swedish Cardiogenetic Registry. In the present thesis, data was collected from RIKS-HIA, SCAAR and the Swedish Heart Surgery Registry.
RIKS-HIA, the longest-running member of SWEDEHEART, collects data about patients admitted to all coronary care units in Sweden due to symptoms suggestive of ACS. Over 100 variables are registered, including data about patient characteristics upon arrival, during the in-hospital course and at discharge. RIKS-HIA currently covers approximately 84% of all patients diagnosed with MI as some patients with MI are treated in other wards than coronary care units. SCAAR was launched in 1998 and collects data on all patients undergoing a coronary procedure in any of the 29 cardiac catheterization labs in Sweden. Approximately 150 variables are collected, including information about angiographic findings, procedures and medication at the catheterization laboratory. Furthermore, the Swedish Heart Surgery Registry was launched in 1992 and captures over 100 variables including patient characteristics and peri- and postoperative data in patients undergoing open heart surgery in any of the eight thoracic surgery departments in Sweden.

Today, data registered in SWEDEHEART is managed using an online web based interface that prompts for user identifications and transfers data in an encrypted format to servers at the Uppsala Clinical Research Center, Uppsala, Sweden, see Figure 1. Using the online interface, users are able to access customized feedback reports with comparisons made to other hospitals and national target levels. The online registry also enables automatic error checks on data entered, preventing input of incorrect data. Moreover, the online registry forces the users to enter a majority of the variables, as many of them are mandatory. In addition to the above steps, a monitor visits approximately 20 centers each year comparing data entered with patient records to ensure data quality, with reports showing a 96% agreement between the data entered in the registry and the patient records.
4.2.3 Registries maintained by the National Board of Health and Welfare

The National Board of Health and Welfare is an organization in Sweden under the Ministry of Health and Social Affairs. Among many duties, the organization provides national healthcare guidelines, manages licenses given to healthcare professionals and maintains health data registries with complete coverage, such as the National Patient Register, the National Cause of Death Register and the National Dispensed Drug Register.

The National Patient Register was launched in 1964, and initially collected data on patients treated at selected country councils in Sweden. It was not before 1987 the National Patient Register became a mandatory registry for all country councils. Since then, all hospitals in Sweden provide data, including patient data, geographical data, administrative data and medical data, to the register on regular basis. Further, the register contains primary and secondary diagnosis codes for all admissions based on the International Classification of Diseases (ICD). The quality of data is regularly monitored, with an external review and validation of the register showing a positive predictive value of 85-95% for different diagnoses. The National Cause of Death Register was created in 1961 and includes mortality data on all patients residing in Sweden. In addition to time of death, information about the underlying cause of death based on the ICD-classification is collected. The National Dispensed Drug Register contains information about all prescribed drug purchases at Swedish pharmacies since July 2005. The database includes information about Anatomical Therapeutic Chemical (ATC) codes, dosage, prescription dates, dispense dates, size and numbers of packages dispensed and pricing.

4.2.4 Data linkage and ethics

For the studies in this thesis, data linkage between SWEDEHEART, the National Patient Register, the National Cause of Death Register and the National Dispensed Drug Register was performed by the National Board of Health and Welfare. In Sweden, each citizen has a unique 10-digit person registration number. This number made it possible for the different registries to be linked and merged. After linkage, personal identifiers were removed and replaced with serial numbers to protect the anonymity of patients included.

All of the included papers (paper I – IV) were approved by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden.
4.3 Study populations

Papers I – III included patients admitted to coronary care units due to MI, and data was collected from RIKS-HIA and SCAAR. In papers I and III, all patients with MI, irrespectively of type and revascularization strategy were included. In paper II, patients with MI undergoing PCI were included. In paper IV, all patients undergoing isolated CABG were identified in the Swedish Heart Surgery Registry, with additional data obtained from RIKS-HIA and SCAAR. For detailed inclusion and exclusion criterions, see Figures 2 – 4.

Figure 2. Selection of study population in paper I

Figure 3. Selection of study population in paper II
In all papers, data about previous comorbidities and outcome was obtained from the National Patient Register and the National Cause of Death Register. In papers II – IV, drug dispense data was obtained from the National Dispensed Drug Register.
4.4 Risk factors and medical interventions

In papers I and IV, AF status as a risk factor for cardiovascular outcome was studied. In paper I, data about AF status was based on physician interpretation of ECGs on arrival and at discharge. Data on previous diagnosis of AF, preceding the current hospital admission, was collected from the National Patient Register. In the study, patients were categorized into five groups:

- New-onset AF with sinus rhythm at discharge – No history of AF but AF on arrival ECG and sinus rhythm on discharge ECG.
- New-onset AF with AF at discharge – No history of AF but AF on discharge ECG, regardless of arrival ECG.
- Paroxysmal AF – History of AF, but sinus rhythm on either the arrival or discharge ECG.
- Chronic AF – History of AF and AF on both the arrival and discharge ECG.
- Sinus rhythm – Patients with no diagnosis of AF preceding admission and with no AF during the in-hospital course. These patients were used as controls.

In paper IV, risk for cardiovascular outcome was studied in patients with pre- or postoperative AF:

- Preoperative AF – History of AF preceding surgery as indicated by the SWEDEHEART registry or if a diagnosis of AF appeared in the National Patient Registry prior to admission.
- Postoperative AF – Patients with no history of AF according to SWEDEHEART and the National Patient Registry, but with an episode of AF post-surgery according to SWEDEHEART.
- No AF – Patients with no diagnosis of AF pre-or post-CABG. These patients were used as controls.

In paper II, antithrombotic medication post-acute MI and PCI was studied in patients with AF. Exposure to antithrombotic medication was studied post-discharge and over time within one year from discharge. Medication at discharge was determined using data from SWEDEHEART and was cross-matched with prescription data from the National Dispensed Drug Register. Only information about warfarin (ATC: B01AA03), aspirin (ATC: B01AC06) and clopidogrel (ATC: B01AC04) was collected in the study, since newer antithrombotic agents were not routinely used in the setting of MI and AF in Sweden during the study period. For aspirin and clopidogrel, the purchased quantity was used to determine the duration of treatment. An interruption gap of 20 days between dispenses was allowed to consider the treatment as continuous. For warfarin, as dosing may vary over time, each purchase was estimated to last three months with an interruption gap of three months.
between dispenses being allowed. The following antithrombotic treatment groups were defined:

- Single antiplatelet therapy – Exposure to either aspirin or clopidogrel.
- Warfarin monotherapy – Treatment with warfarin monotherapy.
- Dual antiplatelet therapy – Treatment with aspirin and clopidogrel. Patients with dual antiplatelet treatment were used as controls.
- Aspirin plus warfarin – Exposure to a combination of aspirin and warfarin.
- Clopidogrel plus warfarin – Exposure to a combination of clopidogrel and warfarin.
- Triple therapy – Treatment with a combination of aspirin, clopidogrel and warfarin.

In paper III, exposure to RAS inhibition, either ACEI (ATC: C09A, C09B), ARB (ATC: C09C, C09D) or both, was studied in relation to cardiovascular outcomes. Patients with no treatment with ACEI and/or ARB were used as controls. Information about medication was collected from SWEDHEART and was cross-matched with prescription data from the National Dispensed Drug Register. The duration of treatment after discharge was estimated to last three months. Thereafter, each drug dispense within six months resulted in an exposure for an additional six months. An interruption gap of six months or above in drug dispense, or drug dispense in an unexposed patient, resulted in censoring from the analysis as patients were assumed to have initiated/discontinued treatment.

4.5 Outcomes

Using the unique 10-digit person registration number, outcome during follow-up was obtained from the National Patient Register and the National Cause of Death Register. In paper I, the efficacy endpoint was a composite of all-cause mortality, recurrent MI (ICD-10: I21, I22) and ischemic stroke (ICD-10: I63) within 90 days from discharge. Other endpoints were all-cause mortality, acute MI and ischemic stroke, respectively.

In paper II, the same composite cardiovascular endpoint was defined as in paper I. However, outcome was studied in landmark periods between 0 to 90 days and 91 to 365 days from discharge. Further, a safety endpoint was studied and including all major bleeding events requiring in-hospital care (ICD-10 and procedure codes: I60, I61, I62, I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922, N02, R310, R311, R318, R040, R041, R042, R048, R049, R58, T810, I983, D629, DR029). Several other endpoints were studied and included all-cause mortality, acute MI or coronary death (ICD-10:

In paper III, the efficacy outcome was all-cause mortality. Additional outcomes included recurrent MI, ischemic or hemorrhagic stroke (ICD-10: I60, I61, I63, I64) and new-onset AF (ICD-10: I48).

In paper IV, the efficacy endpoint was all-cause mortality. In addition, risk for cardiovascular mortality (ICD-10: I00 – I99), acute MI, ischemic stroke, recurrent symptomatic AF (procedure codes: DF010, DF026, DF027) and recurrent AF (ICD-10: I48) was assessed.

4.6 Statistics

Several statistical methods were applied in papers I – IV. In all papers, descriptive statistics for baseline characteristics were presented using a tabular format with continuous variables as medians with interquartile ranges (25th and 75th percentiles) and categorical variables as frequencies with percentages. In paper II, for tests of differences among groups, the Kruskal-Wallis test was used for continuous variables and the Pearson’s $\chi^2$ test was used for categorical variables.

When analyzing outcome, patients were censored at the end of follow-up. For all-cause mortality, no other censoring scheme was applied. All other individual endpoints were censored for mortality. For the composite cardiovascular endpoints in papers I and II, time until first event was evaluated. The risk of event was reported using crude event rates, which was calculated by dividing the total number of events by the total number of person-years in units of 100 years during follow-up. In papers I, III and IV, Kaplan-Meier estimated events rates were plotted to illustrate outcome in relation to AF status and drug treatment. In paper II, Simon–Makuch plots were used to illustrate the effect of antithrombotic treatment during follow-up as a time-dependent factor.

The relationship between risk factors, medication and outcome in all papers were investigated using Cox proportional hazards regression models, with testing for the proportional hazard assumption fulfilled using Schoenfeld residuals. Unadjusted hazard ratios (HR) with 95% CI were reported using univariable Cox proportional hazards regression models and adjusted HRs were reported using multivariable Cox proportional hazards regression
models. In papers I, II and IV, adjustment was made for established risk factors included in the CHA\textsubscript{2}DS\textsubscript{2}-VASc scoring system; CHF, hypertension, age (3 knot restricted cubic spline), diabetes mellitus, ischemic stroke, transient ischemic attack or thromboembolism, vascular disease and sex.\textsuperscript{137} In paper I, additional adjustment was also made for admission year, hospital (\(\Gamma\) distributed random frailty effect), in-hospital revascularization and antithrombotic medication at discharge. In addition to the factors in the CHA\textsubscript{2}DS\textsubscript{2}-VASc scoring system, adjustment was done for new-onset AF during the in-hospital course in paper II. In paper IV, additional factors adjusted for included admission year and hospital (\(\Gamma\) distributed random frailty effect). In paper III, the adjusted Cox proportional-hazards regression analyzes included the following covariates; age (3 knot restricted cubic spline), sex, diabetes mellitus, hypertension, peripheral vascular disease, prior ischemic stroke, type of infarction (STEMI or NSTEMI), Killip class on admission, new-onset AF during hospital course, left ventricular ejection fraction (LV-EF), creatinine level (3 knot restricted cubic spline), discharge hospital (\(\Gamma\) distributed random frailty effect), PCI or CABG during the in-hospital course, and concomitant medication at discharge (oral anticoagulants, aspirin, P2Y\textsubscript{12}-inhibitors, \(\beta\)-blockers, diuretics, digoxin and statins). In paper II, two combined statistical approaches were implemented to assess the association between antithrombotic medication and outcome over time after discharge. Time-varying Cox proportional hazards regression models were used allowing patients to switch between antithrombotic regimen during follow-up.\textsuperscript{191} To assess the early and late benefits and risks with different antithrombotic medication, a landmark approach was implemented with time periods studied between 0 to 90 days post-discharge and between 91 to 365 days post-discharge.\textsuperscript{192} No data was missing in regard to the variables included in the adjusted Cox proportional hazards regression models in papers I, II and IV. In paper III, data was missing for some of the included variables in the adjusted analyses. For missing data, multiple imputation with chained equations was performed generating 25 imputed data sets, replacing missing values with imputed values. In a second step, the pooled imputed data was used to generate single set of estimates presented in the paper.\textsuperscript{193} In papers III and IV, as a sensitivity analysis, propensity-score matched analysis\textsuperscript{194} were performed in which propensity scores for the likelihood of AF status and treatment with RAS inhibition, respectively, were obtained using random effects logistic regression models with all variables in the adjusted Cox proportional hazards regression models as explanatory variables. Matching was done in a 1:1 fashion based on estimated propensity scores.

All statistical tests were two-sided using an P-value of < 0.05 as significant. Statistical analyses were performed using R software environment version 2.15.9 and 3.1.0 (https://www.r-project.org/).
5. Results

5.1 Atrial fibrillation and myocardial infarction (Paper I)

5.1.1 Baseline characteristics
AF was observed in 24,023 (15.5%) patients in the setting of acute MI. Approximately half of the patient with AF had new-onset AF, n = 11,742 (7.6%). Roughly half of the patients with new-onset AF had sinus rhythm at discharge, n = 5,769 (3.7%), with the remaining having AF at discharge, n = 5,973 (3.9%). Paroxysmal AF was documented in 7,633 (4.9%) and chronic AF in 4,648 (3.0%) patients. Patient characteristics are summarized in Table 4.

5.1.2 Outcome in relation to atrial fibrillation status
Figure 6 illustrates unadjusted Kaplan-Meier plots within 90 days from discharge for the composite cardiovascular outcome (all-cause mortality, recurrent MI or ischemic stroke) and the individual components of the composite cardiovascular outcome. Outcomes including event rates per 100 person years, unadjusted and adjusted HRs with 95% CI are presented in Table 5. Clinical outcomes were examined according to AF status versus sinus rhythm. Moreover, clinical outcomes were compared between each AF strata. After adjustment for patient, hospital and treatment characteristics, AF was significantly and independently associated with increased risk of 90-day composite cardiovascular outcome (adjusted HR 1.28, 95% CI 1.19 – 1.37). The highest event rate of 90-day composite cardiovascular outcome was observed among patients with chronic AF followed by new-onset AF with AF at discharge. As compared to sinus rhythm, all subtypes of AF were significantly associated with increased risk of 90-day composite cardiovascular outcome. However, no significant difference was observed between the different subtypes of AF.

In individual outcome analysis, patients with AF versus sinus rhythm were at higher risk of all-cause mortality (adjusted HR 1.59, 95% CI 1.41 – 1.80). A similar finding was observed among all subgroups of AF. The adjusted HR for recurrent MI was higher among patients with AF (adjusted HR 1.14, 95% CI 1.05 – 1.24), and in a subgroup analyses among patients with paroxysmal
AF. However, no significant difference was found across the different subtypes of AF. The cumulative incidence of ischemic stroke was higher in patients with AF compared to sinus rhythm, and this association persisted after adjustment (adjusted HR 2.29, 95% CI 1.92 – 2.74). All subtypes of AF were significantly associated with higher risk of ischemic stroke, but no significant difference between AF subtypes was observed.

Table 4. Patient characteristics and in-hospital characteristics of acute myocardial infarction patients in relation to pattern occurrence of atrial fibrillation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sinus rhythm (n = 131,048)</th>
<th>New-onset AF, SR at discharge (n = 5,769)</th>
<th>New-onset AF, AF at discharge (n = 5,973)</th>
<th>Paroxysmal AF (n = 7,633)</th>
<th>Chronic AF (n = 4,648)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR), years</td>
<td>69 (59–78)</td>
<td>78 (70–83)</td>
<td>79 (73–84)</td>
<td>78 (70–83)</td>
<td>80 (74–85)</td>
</tr>
<tr>
<td>Sex, women</td>
<td>45,967 (35.1)</td>
<td>2,341 (40.6)</td>
<td>2,259 (37.8)</td>
<td>3,249 (42.6)</td>
<td>1,834 (39.5)</td>
</tr>
<tr>
<td>Comorbidities and presentation at admission, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28,121 (21.5)</td>
<td>1,477 (25.6)</td>
<td>1,472 (24.6)</td>
<td>2,038 (26.7)</td>
<td>1,436 (30.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64,900 (49.5)</td>
<td>3,175 (55.0)</td>
<td>3,278 (54.9)</td>
<td>5,165 (67.7)</td>
<td>3,138 (67.5)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>31,676 (24.2)</td>
<td>1,773 (30.7)</td>
<td>1,654 (27.7)</td>
<td>3,498 (45.8)</td>
<td>1,998 (43.0)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>11,196 (8.5)</td>
<td>1,010 (17.5)</td>
<td>1,270 (21.3)</td>
<td>2,968 (38.9)</td>
<td>2,536 (54.6)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>5,638 (4.3)</td>
<td>401 (7.0)</td>
<td>348 (5.8)</td>
<td>799 (10.5)</td>
<td>489 (10.5)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>8,374 (6.4)</td>
<td>636 (11.0)</td>
<td>668 (11.2)</td>
<td>1,283 (16.8)</td>
<td>1,095 (23.6)</td>
</tr>
<tr>
<td>COPD</td>
<td>10,232 (7.6)</td>
<td>599 (10.4)</td>
<td>517 (8.7)</td>
<td>1,004 (13.2)</td>
<td>748 (16.1)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>2,184 (1.7)</td>
<td>153 (2.7)</td>
<td>126 (2.1)</td>
<td>461 (6.0)</td>
<td>265 (5.7)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>5,387 (4.1)</td>
<td>352 (6.1)</td>
<td>328 (5.5)</td>
<td>709 (9.3)</td>
<td>565 (12.2)</td>
</tr>
<tr>
<td>Cancer within 3 years</td>
<td>2,276 (1.7)</td>
<td>168 (2.9)</td>
<td>133 (2.2)</td>
<td>363 (4.8)</td>
<td>232 (5.0)</td>
</tr>
<tr>
<td>Hospital course, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>81,029 (61.8)</td>
<td>3,789 (65.7)</td>
<td>3,869 (64.8)</td>
<td>5,508 (72.2)</td>
<td>3,397 (73.1)</td>
</tr>
<tr>
<td>STEMI</td>
<td>50,019 (38.2)</td>
<td>1,980 (34.3)</td>
<td>2,104 (35.2)</td>
<td>2,125 (27.8)</td>
<td>1,251 (26.9)</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>85,828 (65.5)</td>
<td>2,309 (40.0)</td>
<td>2,196 (36.8)</td>
<td>3,825 (50.1)</td>
<td>1,639 (35.3)</td>
</tr>
<tr>
<td>PCI</td>
<td>62,566 (47.7)</td>
<td>1,440 (25.0)</td>
<td>1,349 (22.6)</td>
<td>2,529 (33.1)</td>
<td>1,035 (22.3)</td>
</tr>
<tr>
<td>CHA2DS2-VASc score at discharge, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc = 0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 1</td>
<td>19,675 (15.0)</td>
<td>261 (4.5)</td>
<td>175 (2.9)</td>
<td>183 (2.4)</td>
<td>39 (0.8)</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 2</td>
<td>111,373 (85.0)</td>
<td>5,506 (95.5)</td>
<td>5,798 (97.1)</td>
<td>7,450 (97.6)</td>
<td>4,609 (99.2)</td>
</tr>
<tr>
<td>Discharge medication, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>118,828 (90.7)</td>
<td>4,881 (84.6)</td>
<td>4,356 (72.9)</td>
<td>6,086 (79.7)</td>
<td>2,992 (64.4)</td>
</tr>
<tr>
<td>P2Y12 inhibitors</td>
<td>75,719 (57.8)</td>
<td>2,231 (38.7)</td>
<td>1,925 (32.2)</td>
<td>3,431 (44.9)</td>
<td>1,457 (31.3)</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>4,642 (3.5)</td>
<td>575 (10.0)</td>
<td>1,730 (29.0)</td>
<td>1,431 (18.7)</td>
<td>1,913 (41.2)</td>
</tr>
</tbody>
</table>
Figure 6. Kaplan-Meier plots depicting cumulative event rates within 90-days post-discharge for (A) composite cardiovascular outcome, (B) all-cause mortality, (C) recurrent myocardial infarction and (D) ischemic stroke according to atrial fibrillation status.
Figure 6 (continued). Kaplan-Meier plots depicting cumulative event rates within 90-days post-discharge for (A) composite cardiovascular outcome, (B) all-cause mortality, (C) recurrent myocardial infarction and (D) ischemic stroke according to atrial fibrillation status.
Table 5. Crude event rate and unadjusted/adjusted HR for the comparison between sinus rhythm and atrial fibrillation and different subtypes of atrial fibrillation.
5.2 Antithrombotic therapy after percutaneous coronary intervention (Paper II)

5.2.1 Baseline characteristics

There were 7,116 patients with first admission for MI undergoing PCI with a history of AF or in-hospital diagnosis of AF who fulfilled the inclusion criteria. The median age of the population was 76 years. Further patient characteristics are presented in Table 6.

5.2.2 Antithrombotic therapy during follow-up

Among those included, 96.6% had a CHA2DS2-VASc score ≥ 2. At discharge, 12.3% of the patients received a single antiplatelet (aspirin or clopidogrel), 1.6% warfarin, 60.8% dual antiplatelets (aspirin and clopidogrel), 1.9% aspirin plus warfarin, 7.3% clopidogrel plus warfarin and 16.2% triple therapy (aspirin, clopidogrel and warfarin); in total, 26.9% received warfarin in any combination. Several patients underwent treatment cross-over during the one-year follow-up, n = 5,466 (76.8%). Figure 7 illustrates the mean duration of antithrombotic therapies during follow-up according to discharge medication.

5.2.3 Outcome in relation to antithrombotic therapy

Figure 8 illustrates unadjusted Simon-Makuch plots with a landmark at 90 days after discharge for the composite cardiovascular outcome (all-cause

Figure 7. Treatment cross-over during a one-year follow-up. Mean duration of various antithrombotic drug combinations over time in relation to antithrombotic treatment at discharge
<table>
<thead>
<tr>
<th>Variable</th>
<th>Single antplatelet (n = 874)</th>
<th>Warfarin (n = 111)</th>
<th>Dual antplatelet (n = 4,328)</th>
<th>Aspirin + warfarin (n = 134)</th>
<th>Clopidogrel + warfarin (n = 516)</th>
<th>Triple therapy (n = 1,153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR), yrs</td>
<td>78 (71–83)</td>
<td>76 (71–80)</td>
<td>76 (68–81)</td>
<td>77 (70–81)</td>
<td>76 (70–80)</td>
<td>74 (68–79)</td>
</tr>
<tr>
<td>Sex, women</td>
<td>297 (34.0)</td>
<td>44 (39.6)</td>
<td>1,319 (30.5)</td>
<td>44 (32.8)</td>
<td>125 (24.2)</td>
<td>276 (23.9)</td>
</tr>
<tr>
<td>Comorbidities and presentation at admission, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>166 (19.0)</td>
<td>28 (25.2)</td>
<td>954 (22.0)</td>
<td>43 (32.1)</td>
<td>128 (24.8)</td>
<td>531 (46.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>727 (83.2)</td>
<td>96 (86.5)</td>
<td>3,244 (75.0)</td>
<td>100 (74.6)</td>
<td>404 (78.3)</td>
<td>931 (80.7)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>480 (54.9)</td>
<td>39 (35.1)</td>
<td>1,647 (38.1)</td>
<td>55 (41.0)</td>
<td>201 (39.0)</td>
<td>353 (30.6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>303 (34.7)</td>
<td>49 (44.1)</td>
<td>998 (23.1)</td>
<td>36 (26.9)</td>
<td>158 (30.6)</td>
<td>314 (27.2)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>118 (13.5)</td>
<td>23 (20.7)</td>
<td>427 (9.9)</td>
<td>17 (12.7)</td>
<td>74 (14.3)</td>
<td>130 (11.3)</td>
</tr>
<tr>
<td>COPD</td>
<td>106 (12.1)</td>
<td>10 (9.0)</td>
<td>331 (7.6)</td>
<td>12 (9.0)</td>
<td>37 (7.2)</td>
<td>83 (7.2)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>60 (6.9)</td>
<td>1 (0.9)</td>
<td>194 (4.5)</td>
<td>4 (3.0)</td>
<td>16 (3.1)</td>
<td>37 (3.2)</td>
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<tr>
<td>Liver disease</td>
<td>5 (0.6)</td>
<td>0 (0.0)</td>
<td>22 (0.5)</td>
<td>1 (0.7)</td>
<td>4 (0.8)</td>
<td>8 (0.7)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>126 (14.4)</td>
<td>12 (10.8)</td>
<td>374 (8.6)</td>
<td>11 (8.2)</td>
<td>51 (9.9)</td>
<td>95 (8.2)</td>
</tr>
<tr>
<td>Dementia</td>
<td>4 (0.5)</td>
<td>0 (0.0)</td>
<td>18 (0.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Cancer within 3 years</td>
<td>47 (5.4)</td>
<td>6 (5.4)</td>
<td>185 (4.3)</td>
<td>4 (3.0)</td>
<td>15 (2.9)</td>
<td>44 (3.8)</td>
</tr>
<tr>
<td>Arrival antithrombotic medication, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>579 (76.4)</td>
<td>19 (32.2)</td>
<td>2,380 (55.0)</td>
<td>48 (35.8)</td>
<td>106 (41.2)</td>
<td>300 (26.0)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>98 (13.8)</td>
<td>3 (8.3)</td>
<td>380 (8.8)</td>
<td>2 (10.5)</td>
<td>27 (5.2)</td>
<td>62 (5.4)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>133 (49.8)</td>
<td>67 (80.4)</td>
<td>469 (36.5)</td>
<td>67 (50.0)</td>
<td>330 (64.0)</td>
<td>719 (62.4)</td>
</tr>
<tr>
<td>Hospital course</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>341 (39.0)</td>
<td>60 (54.1)</td>
<td>1,751 (40.5)</td>
<td>70 (52.2)</td>
<td>182 (35.3)</td>
<td>371 (32.2)</td>
</tr>
<tr>
<td>PCI</td>
<td>260 (29.7)</td>
<td>38 (34.2)</td>
<td>1,619 (37.4)</td>
<td>54 (40.3)</td>
<td>162 (31.4)</td>
<td>402 (34.9)</td>
</tr>
<tr>
<td>Procedure-related medication, n(%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>619 (70.8)</td>
<td>76 (68.5)</td>
<td>3,113 (71.9)</td>
<td>106 (79.1)</td>
<td>344 (66.7)</td>
<td>901 (78.1)</td>
</tr>
<tr>
<td>LMWH</td>
<td>216 (24.7)</td>
<td>26 (23.4)</td>
<td>1,063 (24.6)</td>
<td>25 (18.7)</td>
<td>130 (25.2)</td>
<td>204 (17.7)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>140 (16.0)</td>
<td>7 (6.3)</td>
<td>870 (20.1)</td>
<td>13 (9.7)</td>
<td>83 (16.1)</td>
<td>210 (18.2)</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>259 (29.6)</td>
<td>37 (33.3)</td>
<td>1,222 (28.2)</td>
<td>27 (20.1)</td>
<td>174 (33.7)</td>
<td>333 (28.9)</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inh.</td>
<td>187 (21.4)</td>
<td>25 (22.5)</td>
<td>972 (22.5)</td>
<td>34 (25.4)</td>
<td>73 (14.1)</td>
<td>131 (11.4)</td>
</tr>
<tr>
<td>Heparin</td>
<td>619 (70.8)</td>
<td>76 (68.5)</td>
<td>3,113 (71.9)</td>
<td>106 (79.1)</td>
<td>344 (66.7)</td>
<td>901 (78.1)</td>
</tr>
<tr>
<td>PCI characteristics, n(%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Vascular access approach</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial-artery</td>
<td>295 (33.8)</td>
<td>45 (40.5)</td>
<td>1,725 (39.9)</td>
<td>58 (43.3)</td>
<td>232 (45.0)</td>
<td>628 (54.5)</td>
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<tr>
<td>Femoral-artery</td>
<td>520 (59.5)</td>
<td>61 (55.0)</td>
<td>2,377 (54.9)</td>
<td>67 (50.0)</td>
<td>256 (49.6)</td>
<td>444 (38.5)</td>
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<td>Radial and femoral</td>
<td>58 (6.6)</td>
<td>5 (4.5)</td>
<td>219 (5.1)</td>
<td>9 (6.7)</td>
<td>28 (5.4)</td>
<td>78 (6.8)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td>7 (0.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Finding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/atheroma</td>
<td>7 (0.8)</td>
<td>2 (1.8)</td>
<td>48 (1.1)</td>
<td>1 (0.7)</td>
<td>5 (1.0)</td>
<td>7 (0.6)</td>
</tr>
<tr>
<td>One-vessel disease</td>
<td>308 (35.2)</td>
<td>52 (46.8)</td>
<td>1,676 (38.7)</td>
<td>64 (47.8)</td>
<td>218 (42.2)</td>
<td>505 (43.8)</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>228 (26.1)</td>
<td>26 (23.4)</td>
<td>1,234 (28.5)</td>
<td>31 (23.1)</td>
<td>124 (24.0)</td>
<td>334 (29.0)</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>235 (26.9)</td>
<td>23 (20.7)</td>
<td>1,047 (24.2)</td>
<td>21 (15.7)</td>
<td>133 (25.8)</td>
<td>222 (19.3)</td>
</tr>
<tr>
<td>Bare metal stents, n = 6,389</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug eluting stents, n = 6,389</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc score at discharge, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc = 0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 1</td>
<td>0 (0.9)</td>
<td>2 (1.8)</td>
<td>187 (4.3)</td>
<td>5 (3.7)</td>
<td>9 (1.7)</td>
<td>30 (2.6)</td>
</tr>
<tr>
<td>CHA2DS2-VASc ≥ 2</td>
<td>866 (99.1)</td>
<td>109 (98.2)</td>
<td>4,141 (95.7)</td>
<td>129 (96.3)</td>
<td>507 (98.3)</td>
<td>1,123 (97.4)</td>
</tr>
<tr>
<td>HAS-BLED score at discharge, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAS-BLED = 0/1</td>
<td>50 (5.7)</td>
<td>14 (12.6)</td>
<td>851 (19.7)</td>
<td>33 (24.6)</td>
<td>110 (21.3)</td>
<td>266 (23.1)</td>
</tr>
<tr>
<td>HAS-BLED = 2</td>
<td>221 (25.3)</td>
<td>45 (40.5)</td>
<td>1,278 (29.5)</td>
<td>42 (31.3)</td>
<td>191 (37.0)</td>
<td>453 (39.3)</td>
</tr>
<tr>
<td>HAS-BLED ≥ 3</td>
<td>603 (69.0)</td>
<td>52 (46.8)</td>
<td>2,199 (50.8)</td>
<td>59 (44.0)</td>
<td>215 (41.7)</td>
<td>434 (37.6)</td>
</tr>
</tbody>
</table>
Figure 8. Simon–Makuch plots with 0–90-day and 91–365-day landmark periods illustrating (A) composite cardiovascular outcome; all-cause mortality, myocardial infarction or ischemic stroke and (B) major bleeding events in relation to use of antithrombotic therapy over time.
mortality, recurrent MI or ischemic stroke) and for major bleeding events requiring in-hospital attention. Clinical outcomes were examined using time-varying analyses comparing single antiplatelet therapy, warfarin monotherapy, aspirin plus warfarin, clopidogrel plus warfarin and triple therapy versus dual antiplatelet therapy as presented in Figures 9–11.

Figure 9. Forest plot depicting (A) composite cardiovascular outcome; all-cause mortality, myocardial infarction or ischemic stroke and (B) major bleeding events in relation to use of antithrombotic therapy over time

The 90-day unadjusted and adjusted risks for the composite cardiovascular outcome were similar between patients treated with aspirin plus warfarin, clopidogrel plus warfarin and triple therapy versus dual antiplatelet therapy, see Figure 9. In the landmark period between 91 to 365 days, warfarin monotherapy, aspirin plus warfarin and clopidogrel plus warfarin were associated with lower risk for cardiovascular events than dual antiplatelet therapy, see Figure 9. The adjusted HR was lower at 0.78 with triple therapy versus dual antiplatelet therapy, however, this association was non-significant.

The cumulative event rates for major bleeding events requiring in-hospital attention within 0 to 90 days and 91 to 365 days were higher among patients treated with triple therapy versus dual antiplatelet therapy, with persistent significant results in an adjusted analysis between 0 to 90 days (adjusted HR 2.16, 95% CI 1.48 – 3.13) and with a non-significant trend between 91 to 365 days (adjusted HR 1.61, 95% CI 0.98 – 2.66).

For all-cause mortality, similar associations as for the composite cardiovascular outcome were observed with all treatment combinations. In the
Figure 10. Forest plot depicting (A) all-cause mortality, (B) myocardial infarction or coronary death, (C) stent thrombosis and (D) ischemic stroke in relation to use of antithrombotic therapy over time

landmark analysis from 0 to 90 days, single antiplatelet therapy versus dual antiplatelet therapy was associated with higher HR of MI or coronary death (adjusted HR 1.47, 95% CI 1.19 – 1.83), with no other significant associations observed. Between 91 to 365 days, the HR for MI or coronary death was lower among patients treated with warfarin monotherapy and aspirin plus warfarin, with no other associations observed. Only 43 events of stent thrombosis were documented in the total population during a one-year follow-up, with single antiplatelet therapy and warfarin monotherapy associated with a higher risk during 0 to 90 days than dual antiplatelet therapy. Triple therapy versus dual antiplatelet therapy was associated with lower 0 – 90-day risk of ischemic
stroke, with no association observed between 91 – 365 days. Moreover, the combined cohort of patients with single antiplatelet therapy (aspirin or clopidogrel) plus warfarin was associated with lower risk of ischemic stroke during 0 – 90 days (adjusted HR 0.47, 95% CI 0.23 – 0.97) and 91 – 365 days (adjusted HR 0.54, 95% CI 0.33 – 0.88) compared to dual antiplatelet therapy. All other treatment strategies showed no significant differences when compared to dual antiplatelet therapy.

### Figure 11.

Forest plot depicting (A) intracranial bleeding events and (B) gastrointestinal bleeding events according to use of antithrombotic therapy over time

Few events of intracranial bleeding were documented during follow-up. Compared to dual antiplatelet therapy, only aspirin plus warfarin was associated with a higher risk for intracranial bleeding events during 0 – 90 days (adjusted HR 4.23, 95% CI 1.16 – 15.36). All other treatment strategies were comparable to dual antiplatelet therapy. For gastrointestinal bleeding events, no significant differences were observed across all treatment strategies, see Figure 11.
5.3 Inhibition of the renin-angiotensin system (Paper III)

5.3.1 Baseline characteristics

A total of 112,648 patients post-MI were included in this study. The median age at MI was 72 years and 35.5% were female. At discharge, 73.9% of the patients were treated with RAS inhibition (ACEI, ARB or both). Further patient characteristics are presented in Table 7.

Table 7. Patient characteristics and in-hospital characteristics of acute myocardial infarction patients in relation to treatment with ACEI and/or ARB at discharge

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n = 112,648)</th>
<th>No ACEI/ARB (n = 29,357)</th>
<th>ACEI/ARB (n = 83,291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR), years</td>
<td>72 (62–81)</td>
<td>74 (62–83)</td>
<td>71 (62–79)</td>
</tr>
<tr>
<td>Sex, women</td>
<td>39,987 (35.5)</td>
<td>11,729 (40.0)</td>
<td>28,258 (33.9)</td>
</tr>
<tr>
<td>Smoking, n = 106,886</td>
<td>25,714 (24.1)</td>
<td>6,451 (23.8)</td>
<td>19,263 (24.1)</td>
</tr>
<tr>
<td>BMI, median (IQR), n = 97,204</td>
<td>26 (24–29)</td>
<td>25 (23–28)</td>
<td>27 (24–29)</td>
</tr>
<tr>
<td>Comorbidities and presentation at admission, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27,149 (24.1)</td>
<td>4,959 (16.9)</td>
<td>22,190 (26.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67,436 (59.9)</td>
<td>13,571 (46.2)</td>
<td>53,865 (64.7)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>29,330 (26.0)</td>
<td>7,087 (24.1)</td>
<td>22,243 (26.7)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>12,039 (10.7)</td>
<td>2,903 (9.9)</td>
<td>9,136 (11.0)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>6,143 (5.5)</td>
<td>1,618 (5.5)</td>
<td>4,525 (5.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>13,038 (11.6)</td>
<td>3,618 (12.3)</td>
<td>9,420 (11.3)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>7,390 (6.6)</td>
<td>2,174 (7.4)</td>
<td>5,216 (6.3)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>7,855 (7.0)</td>
<td>2,262 (7.7)</td>
<td>5,593 (6.7)</td>
</tr>
<tr>
<td>Cancer diagnosis within 3 years</td>
<td>3,160 (2.8)</td>
<td>1,033 (3.5)</td>
<td>2,127 (2.6)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>12,727 (11.3)</td>
<td>2,667 (9.1)</td>
<td>10,060 (12.1)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>9,461 (8.4)</td>
<td>2,100 (7.2)</td>
<td>7,361 (8.8)</td>
</tr>
<tr>
<td>Creatinine, median (IQR), μmol/L, n = 110,143</td>
<td>83 (70–102)</td>
<td>84 (70–106)</td>
<td>83 (70–100)</td>
</tr>
<tr>
<td>Hospital course, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>36,472 (32.4)</td>
<td>6,949 (23.7)</td>
<td>29,523 (35.4)</td>
</tr>
<tr>
<td>PCI</td>
<td>63,821 (56.7)</td>
<td>12,621 (43.0)</td>
<td>51,200 (61.5)</td>
</tr>
<tr>
<td>CABG</td>
<td>3,935 (3.5)</td>
<td>1,181 (4.0)</td>
<td>2,754 (3.3)</td>
</tr>
<tr>
<td>LV-EF &lt; 50%, n = 82,026</td>
<td>35,679 (43.5)</td>
<td>4,924 (27.1)</td>
<td>30,755 (48.2)</td>
</tr>
<tr>
<td>Congestive heart failure (including history of)</td>
<td>43,165 (38.3)</td>
<td>7,136 (24.3)</td>
<td>36,029 (43.3)</td>
</tr>
<tr>
<td>New-onset atrial fibrillation</td>
<td>9,853 (8.9)</td>
<td>2,636 (9.2)</td>
<td>7,218 (8.9)</td>
</tr>
<tr>
<td>Atrial fibrillation (including history of)</td>
<td>21,555 (19.1)</td>
<td>5,936 (20.2)</td>
<td>15,619 (18.8)</td>
</tr>
<tr>
<td>Discharge medication, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>104,283 (92.8)</td>
<td>26,459 (90.5)</td>
<td>77,824 (93.6)</td>
</tr>
<tr>
<td>P2Y12 inhibitors</td>
<td>86,889 (77.2)</td>
<td>19,770 (67.7)</td>
<td>67,119 (80.6)</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>7,921 (7.0)</td>
<td>1,655 (5.7)</td>
<td>6,266 (7.5)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>100,285 (89.1)</td>
<td>24,537 (83.8)</td>
<td>75,748 (91.0)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>17,711 (15.7)</td>
<td>4,327 (14.8)</td>
<td>13,384 (16.1)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>3,613 (3.2)</td>
<td>1,016 (3.5)</td>
<td>2,597 (3.1)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>37,220 (33.1)</td>
<td>8,834 (30.2)</td>
<td>28,386 (34.1)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>19,301 (17.2)</td>
<td>5,874 (20.1)</td>
<td>13,427 (16.2)</td>
</tr>
<tr>
<td>Statins</td>
<td>94,871 (84.3)</td>
<td>21,382 (73.1)</td>
<td>73,489 (88.3)</td>
</tr>
</tbody>
</table>
5.3.2 Outcome in relation to treatment with renin-angiotensin system inhibitors

Clinical outcomes were examined according to ACEI/ARB treatment versus no treatment. Event rates per 100 person years, unadjusted and adjusted HRs with 95% CI for all outcomes are presented in Table 8. Figure 12 illustrates Kaplan-Meier plots within 3 years from discharge for the efficacy outcome of all-cause mortality.

A total of 17,121 patients died during the 3-year follow-up. In an adjusted analysis, treatment with ACEI/ARB versus no treatment was related with lower risk of 3-year all-cause mortality (adjusted HR 0.73, 95% CI 0.71 – 0.76). Similar outcome estimates were observed in four prespecified subgroups; patients with CHF and AF, patients with CHF without AF, patients without CHF and with AF, and patients without both CHF and AF, see Table 8. For cardiovascular mortality, lower outcome estimates were similarly observed among patients treated with ACEI/ARB, however, the comparison remained non-significant for patients without CHF and with AF, see Table 8.

For recurrent MI, a lower outcome estimate was observed among patients receiving ACEI/ARB versus no treatment (adjusted HR 0.95, 95% CI 0.92 – 0.98). However, this association was only present in patients with CHF and not among patients with no history or in-hospital diagnosis of CHF, see Table 8.

Figure 12. Kaplan-Meier plot depicting the cumulative event rate for all-cause mortality stratified by use of ACEI and/or ARB in patients with and without congestive heart failure and atrial fibrillation.
8. The rates of stroke did not differ among patients treated with or without ACEI/ARB. Similarly, no significant association in regard to stroke was found among subgroups of patients with or without CHF and/or AF, see Table 8.

5.3.3 Risk of new-onset atrial fibrillation in relation to treatment with renin-angiotensin system inhibitors

In a cohort of patients with no history of AF and in-hospital diagnosis of AF (n = 91,093), the risk of new-onset AF during follow-up was estimated. Figure 13 illustrates unadjusted Kaplan-Meier plots within 3 years from discharge and Table 8 depicts event rates per 100 person years, unadjusted and adjusted HRs with 95% CI for the risk of new-onset AF. The cumulative incidence per 100 person years for 3-year risk of new-onset AF was 2.9 in patients treated with ACEI/ARB versus 2.9 in non-treated patients. In an adjusted analysis, ACEI/ARB was not associated with a lower risk of new-onset AF (adjusted HR 1.07, 95% CI 1.00 – 1.15). Similar results were observed among patients with CHF (adjusted HR 0.96, 95% CI 0.84 – 1.10). For patients without CHF, higher risk of new-onset AF was observed with ACEI/ARB versus no treatment (adjusted HR 1.12, 95% CI 1.02 – 1.22).

Figure 13. Kaplan-Meier plot depicting the cumulative event rate for new-onset atrial fibrillation stratified by use of ACEI and/or ARB in patients with and without congestive heart failure
Table 8. Number of events, events rate, and adjusted hazard ratios for outcomes stratified by ACEI and/or ARB treatment in patients with and without congestive heart failure and atrial fibrillation.

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of Events</th>
<th>Rate (per 1000)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CHF</td>
<td>No AF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1025</td>
<td>0.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2024</td>
<td>0.01</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3036</td>
<td>0.02</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4036</td>
<td>0.03</td>
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<td>5</td>
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<td>6</td>
<td>6036</td>
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<tr>
<td>7</td>
<td>7036</td>
<td>0.06</td>
<td>1.00</td>
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</tr>
<tr>
<td>8</td>
<td>8036</td>
<td>0.07</td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td>9036</td>
<td>0.08</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10036</td>
<td>0.09</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>11036</td>
<td>0.10</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>12036</td>
<td>0.11</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>13036</td>
<td>0.12</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>14036</td>
<td>0.13</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>15036</td>
<td>0.14</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>16036</td>
<td>0.15</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>17036</td>
<td>0.16</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>18036</td>
<td>0.17</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>19036</td>
<td>0.18</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>20036</td>
<td>0.19</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

CHF = congestive heart failure, AF = atrial fibrillation, HR = hazard ratio.
5.4 Atrial fibrillation and coronary artery bypass grafting (Paper IV)

5.4.1 Baseline characteristics

In this study, a total of 9,107 consecutive patients undergoing CABG in all 8 thoracic surgery sites in Sweden between January 2010 and June 2013 were included. The median age among included patients was 68 years and 18.9% were female. History of AF was present in 8.1% and new-onset postoperative AF occurred among 25.1% of the patients. See Table 9 for detailed patient characteristics.

5.4.2 Outcome in relation to atrial fibrillation status

Figure 14 illustrates Kaplan-Meier plots for the efficacy outcome of all-cause mortality. All outcomes were examined according to pre- and postoperative AF versus no AF, with event rates per 100 person years, unadjusted and adjusted HRs with 95% CI presented in Figure 15.

![Figure 14. Cumulative event rate of all-cause mortality in relation to in-hospital atrial fibrillation status](image)

The unadjusted cumulative incidence rates per 100 person years for all-cause mortality were numerically higher for patients with pre- and postoperative AF versus no AF (5.0 and 2.4 versus 1.5). A similar finding was observed for
cardiovascular mortality, MI, CHF and ischemic stroke. In an adjusted analysis, pre- and postoperative AF were associated with a higher risk of all-cause mortality (adjusted HR 1.76, 95% CI 1.33 – 2.33 and adjusted HR 1.27, 95% CI 1.01 – 1.60). A similar finding was observed for cardiovascular mortality and CHF. For MI and ischemic stroke, the adjusted HR was higher among patients with pre- and postoperative AF versus no AF, however, these comparisons remained non-significant, see Figure 15.

The crude incidence rates per 100 person years for symptomatic recurrent AF during follow-up was numerically higher for patients with postoperative AF versus no AF (0.7 versus 0.2), see Figure 15 and 16. This association persisted after adjustment for relevant variables (adjusted HR 4.38, 95% CI 2.46 – 7.78).
Table 9. Patient characteristics and in-hospital characteristics of coronary artery bypass graft surgery patients in relation to atrial fibrillation status

<table>
<thead>
<tr>
<th>Variable</th>
<th>No AF (n = 6,080)</th>
<th>Preoperative AF (n = 737)</th>
<th>Postoperative AF (n = 2,290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR), years</td>
<td>66 (60–72)</td>
<td>72 (67–77)</td>
<td>70 (64–75)</td>
</tr>
<tr>
<td>Sex, women</td>
<td>1,171 (19.3)</td>
<td>141 (19.1)</td>
<td>406 (17.7)</td>
</tr>
<tr>
<td>Smoking, n = 8,493</td>
<td>1,031 (18.3)</td>
<td>84 (12.2)</td>
<td>302 (14.0)</td>
</tr>
<tr>
<td>BMI, median (IQR), n = 8,990</td>
<td>27.1 (24.7–29.7)</td>
<td>27.2 (24.6–30.1)</td>
<td>27.0 (24.7–29.7)</td>
</tr>
<tr>
<td>Comorbidities and presentation at admission, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1,851 (30.4)</td>
<td>285 (38.7)</td>
<td>675 (29.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4,128 (67.9)</td>
<td>594 (80.6)</td>
<td>1,697 (74.1)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3,595 (59.1)</td>
<td>560 (76.0)</td>
<td>1,421 (62.1)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>974 (16.0)</td>
<td>280 (36.0)</td>
<td>406 (17.7)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>264 (4.3)</td>
<td>56 (7.6)</td>
<td>110 (4.8)</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>14 (0.2)</td>
<td>3 (0.4)</td>
<td>10 (0.4)</td>
</tr>
<tr>
<td>Ischemic / unknown stroke</td>
<td>287 (4.7)</td>
<td>60 (8.1)</td>
<td>114 (5.0)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>115 (1.9)</td>
<td>37 (5.0)</td>
<td>69 (3.0)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>44 (0.7)</td>
<td>4 (0.5)</td>
<td>15 (0.7)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>291 (4.6)</td>
<td>63 (8.5)</td>
<td>98 (4.3)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>125 (2.1)</td>
<td>50 (6.8)</td>
<td>56 (2.4)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>319 (5.2)</td>
<td>62 (8.4)</td>
<td>138 (6.0)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>1,365 (22.5)</td>
<td>184 (25.0)</td>
<td>490 (21.4)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>99 (1.6)</td>
<td>21 (2.8)</td>
<td>35 (1.5)</td>
</tr>
<tr>
<td>Hospital course, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication for CABG, n = 8,886</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable coronary artery disease</td>
<td>2,533 (42.8)</td>
<td>232 (32.4)</td>
<td>921 (41.0)</td>
</tr>
<tr>
<td>Unstable angina / acute myocardial infarction</td>
<td>3,389 (57.2)</td>
<td>485 (67.6)</td>
<td>1,326 (59.0)</td>
</tr>
<tr>
<td>EuroSCORE I, median (IQR), n = 9,062</td>
<td>4 (2–6)</td>
<td>6 (4–8)</td>
<td>5 (3–7)</td>
</tr>
<tr>
<td>Extracorporeal circulation</td>
<td>6,014 (98.9)</td>
<td>724 (98.2)</td>
<td>2,256 (98.5)</td>
</tr>
<tr>
<td>No. central anastomoses, median (IQR), n = 7,434</td>
<td>1 (0.5–1.5)</td>
<td>2 (1–3)</td>
<td>1 (0.5–1.5)</td>
</tr>
<tr>
<td>No. peripheral anastomoses, median (IQR), n = 7,434</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
</tr>
<tr>
<td>Internal mammary artery, left, n = 7,434</td>
<td>4,352 (89.2)</td>
<td>497 (86.9)</td>
<td>1,834 (92.4)</td>
</tr>
<tr>
<td>Internal mammary artery, right, n = 7,434</td>
<td>92 (1.9)</td>
<td>6 (1.0)</td>
<td>30 (1.5)</td>
</tr>
<tr>
<td>Vein graft, n = 7,434</td>
<td>4,465 (91.5)</td>
<td>525 (91.8)</td>
<td>1,882 (94.9)</td>
</tr>
<tr>
<td>Radial artery graft, n = 7,434</td>
<td>59 (1.2)</td>
<td>15 (2.6)</td>
<td>49 (2.5)</td>
</tr>
<tr>
<td>Postoperative bleeding, n = 9,080</td>
<td>207 (3.4)</td>
<td>31 (4.2)</td>
<td>113 (4.9)</td>
</tr>
<tr>
<td>Postoperative stroke, n = 9,093</td>
<td>48 (0.8)</td>
<td>12 (1.6)</td>
<td>35 (1.5)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt; 50%, n = 8,160</td>
<td>1,466 (27.0)</td>
<td>307 (44.7)</td>
<td>609 (29.7)</td>
</tr>
<tr>
<td>Creatinine, median (IQR), µmol/L, n = 9,100</td>
<td>87 (75–105)</td>
<td>100 (83–129)</td>
<td>93 (79–120)</td>
</tr>
<tr>
<td>CHA2DS2-VASc score at discharge, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc = 0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 1</td>
<td>638 (10.5)</td>
<td>13 (1.8)</td>
<td>113 (4.9)</td>
</tr>
<tr>
<td>CHA2DS2-VASc ≥ 2</td>
<td>5,442 (89.5)</td>
<td>724 (98.2)</td>
<td>2,177 (95.1)</td>
</tr>
<tr>
<td>Discharge medication, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>5,539 (91.1)</td>
<td>512 (69.5)</td>
<td>1,958 (85.5)</td>
</tr>
<tr>
<td>P2Y12 inhibitors</td>
<td>955 (15.7)</td>
<td>61 (8.3)</td>
<td>311 (13.6)</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>278 (4.6)</td>
<td>338 (45.9)</td>
<td>417 (18.2)</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>4,158 (68.4)</td>
<td>522 (70.8)</td>
<td>1,558 (68.0)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1,146 (18.8)</td>
<td>158 (21.4)</td>
<td>473 (20.7)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>2,155 (35.4)</td>
<td>402 (54.5)</td>
<td>1,075 (46.9)</td>
</tr>
<tr>
<td>Statins</td>
<td>5,492 (90.3)</td>
<td>617 (83.7)</td>
<td>2,034 (88.8)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>37 (0.6)</td>
<td>89 (12.1)</td>
<td>44 (1.9)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>5,433 (89.4)</td>
<td>629 (85.3)</td>
<td>1,973 (86.2)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>39 (0.6)</td>
<td>27 (3.7)</td>
<td>229 (10.0)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>127 (2.1)</td>
<td>111 (15.1)</td>
<td>417 (18.2)</td>
</tr>
<tr>
<td>Verapamil / Diltiazem</td>
<td>59 (1.0)</td>
<td>16 (2.2)</td>
<td>30 (1.3)</td>
</tr>
</tbody>
</table>
6. Discussion

In this thesis, several aspects of AF in the setting of CAD were studied. The overall aim was to assess the prevalence of AF in the setting of CAD and to describe the patient characteristics, risks, current treatment and short and long-term outcome in patients with AF in the setting of CAD.

6.1 Atrial fibrillation in the setting of coronary artery disease

The results in this thesis show that AF is an arrhythmia that commonly complicates acute MI. In data from SWEDEHEART, approximately 16% of patients hospitalized for acute MI had AF. In detail, approximately 4% had new-onset AF with sinus rhythm at discharge, 4% new-onset AF with AF at discharge, 5% paroxysmal AF and 3% chronic AF. In patients undergoing isolated CABG the proportion of patients with AF were almost doubled, with approximately 33% having concomitant AF. History of AF prior to CABG was found in almost 8% of the patients and new-onset postoperative AF complicated 21% of the patients.

Several previous studies have reported that AF is a common finding among patients hospitalized for acute MI or in patients undergoing CABG. However, few studies have focused on the distribution of different subtypes of AF and its prognostic implications. An important and novel finding in this thesis was that new-onset AF was a common finding among patients hospitalized for acute MI. In contrast, previous smaller studies have reported that history of AF is more often seen than new-onset AF. The difference in results between paper I and previous findings could be explained by the fact that AF in many cases goes undetected, resulting in some cases of new-onset AF being misinterpreted. Also, data about history of AF in the studies was collected from registries linked to inpatient hospitalizations and specialized outpatient care, but not primary care practice. Thus, the true prevalence of AF cannot be reported. However, the findings in this thesis imply that careful evaluation of ECG rhythm during the in-hospital course is important as new-onset AF is a potential finding that could alter treatment strategies and outcome. Probably, the longer the in-hospital cardiac monitoring is, the more
likely you are to find AF. In patients undergoing isolated CABG, a high rate of postoperative AF was observed as previously reported in other studies. Moreover, a large proportion of patients had a history of AF prior to surgery, a finding which has previously only been reported in a handful of studies.

From the data collected in papers I and IV, observations were made that patients with AF were considerably older than patients with no AF. Not a surprising finding given the fact that the prevalence of AF increases with age. Epidemiologic data suggest that AF is more prevalent in men than in women, however, in paper I there were relatively more women in the AF cohort than in the non-AF cohort. This difference can probably be explained by women generally being older than men at hospitalization for MI, resulting in a higher age-related prevalence of AF. Furthermore, patients with AF, regardless of subtype, had a higher burden of comorbidities at admission such as diabetes mellitus, hypertension, prior MI, CHF, stroke, renal disease and episodes of previous bleeding events. Not a surprising finding, and similar to other observational studies, given that patients with AF were older than non-AF patients at admission.

6.2 Prognostic implication of atrial fibrillation

In paper I, patients with AF versus sinus rhythm had an almost doubled unadjusted risk of a composite cardiovascular outcome that included all-cause mortality, MI or ischemic stroke within 90 days from discharge after an acute MI. However, compared to patients with sinus rhythm, patients with AF were older and more likely to have concomitant diseases. Despite this and after adjustment for relevant confounders, the risk perpetuated and was approximately 30% higher in patients with AF. Additionally, AF versus sinus rhythm was independently associated with increased risk of all individual cardiovascular outcomes, including all-cause mortality, recurrent MI and ischemic stroke. Also, different subtypes of AF (new-onset AF, paroxysmal AF and chronic AF) were associated with higher risk of all-cause mortality and ischemic stroke.

Similar to our findings, previous studies including two meta-analyses on patients with MI have reported that the presence of pre-existing AF and new-onset AF is associated with increased risk of all-cause mortality. Also, AF in the setting of CAD has been reported to be associated with increased risk of stroke and recurrent MI. However, few studies have reported stroke risk based on subtype classification of AF. In two retrospective studies similar to paper I, new-onset AF, irrespectively of discharge ECG, was associated with increased risk of ischemic stroke. Given the findings in paper I and
previous observations, it is important to bear in mind that AF, irrespectively of subtype, is an important risk factor when considering future stroke risk and oral antithrombotic management. Furthermore, it was observed in paper I that patients with AF were at an 14% increased risk of recurrent MI, a finding which has previously been reported in a handful of observational studies.\textsuperscript{46,49,55,58} This finding might be explained by AF and CAD sharing several similar risk factors and pathophysiological pathways, including systemic inflammation and structural remodeling of the heart.\textsuperscript{77–81}

In paper IV, pre- and postoperative AF after isolated CABG were associated with higher long-term risk of all-cause mortality, cardiovascular mortality and hospitalization due to CHF. However, no significant associations between AF and risk for future ischemic stroke and MI were observed. Several observational studies on patients with postoperative AF, but only one single center study on patients with both pre- and postoperative AF, have found AF in the setting of CABG to be associated with short- and long-term all-cause mortality and cardiovascular mortality.\textsuperscript{52,53,177,198,199} Despite this, only speculative mechanisms between AF and mortality have been proposed and include; AF recurrence leading to adverse outcomes including hemodynamic instability, and a higher prescription of proarrhythmia associated antiarrhythmic drugs among patients with AF.\textsuperscript{200–202} However, these theories are hypothetical and the underlying pathological mechanisms are still uncertain. In paper IV, both pre- and postoperative AF were associated with substantially higher risk of hospitalization for CHF, a novel finding which to some extent could explain the higher risk of mortality seen in patients with AF. Another important finding in paper IV was that patients with postoperative AF were at increased risk of recurrent AF. During a median follow-up of approximately 2 years, patients with postoperative AF had a more than 4-time higher risk of relapse in symptomatic AF compared to patients with no AF. A finding which supports previous smaller and single-center observations.\textsuperscript{52,203} Despite increased risk of recurrent AF, no independent association between postoperative AF and risk of ischemic stroke was observed. However, previous observational studies have contrary reported that AF post-cardiac surgery might be associated with increased risk of stroke,\textsuperscript{204,205} a difference that could be explained by even longer follow-up in those studies than in paper IV, and due to differences in prescription of oral anticoagulants at discharge. Also, it has previously been shown that patients post-CABG, irrespectively of AF, have an increased risk of stroke,\textsuperscript{206} an observation which might make it more difficult to show an independent association between postoperative AF and stroke. Given the current lack of knowledge regarding postoperative AF and ischemic stroke risk, current AF guidelines recommend oral anticoagulants as reasonable for patients with postoperative AF and risk for stroke. Nonetheless, this strategy has not been proven and has only been studied in one observational single center study in
6.3 Management and treatment

Management of patients with AF in the setting of CAD compromises several treatment strategies. This thesis focused on antithrombotic therapy after MI in patients with AF undergoing PCI, and on treatment with RAS inhibition in patients with and without AF post-MI.

Antithrombotic therapy

Paper II reported that approximately 27% of the patients with AF received oral anticoagulation therapy, with or without concomitant antiplatelet therapy, at discharge post-MI and PCI. Moreover, treatment with either aspirin or clopidogrel in combination with warfarin was associated with similar 0 – 90-day, and lower 91 – 365-day risk of the composite cardiovascular outcome of mortality, MI or ischemic stroke compared to dual antiplatelet therapy. Furthermore, treatment with aspirin or clopidogrel plus warfarin was associated with similar risk of short- and long-term bleeding events requiring in-hospital attention compared to dual antiplatelet therapy. In contrast, triple therapy with aspirin, clopidogrel plus warfarin was associated with a similar risk of the composite cardiovascular outcome, but with an almost doubled risk of major bleeding events than dual antiplatelet therapy.

Current guidelines recommend triple therapy during 1 – 6 months after PCI with stenting. These recommendations are mainly based on small, single-center and/or retrospective studies with inherent limitations. Thus, ideal antithrombotic therapy and duration post-PCI in patients with AF is not defined. As previously mentioned, patients after an ACS, especially post-PCI and stenting, are in need of aspirin and P2Y12 inhibitors to reduce the risk of recurrent ischemic events. In contrast, patients with AF are in need of long-term oral anticoagulation therapy to reduce the risk of ischemic stroke. Recently, two randomized clinical trials have suggested that omitting aspirin in favor of one oral anticoagulant plus P2Y12 inhibitor lower rates of bleeding events compared to triple therapy post-PCI and stenting. In both trials, one oral anticoagulant (warfarin or rivaroxaban) plus one P2Y12 inhibitor was associated with lower rates of any bleeding events compared to triple therapy, with no significant increase in thromboembolic events. Unfortunately, both trials had several limitations, with the most significant limitation being that they were underpowered to evaluate efficacy outcomes. Nonetheless, similar findings have been confirmed in this thesis and in recently published observational studies. In this context it is also important to remember that pre-PCI era trials reported
that oral anticoagulant post-MI reduced the risk of mortality and recurrent MI compared to placebo or aspirin.\textsuperscript{118–122}

The most noticeable conclusion to be drawn from paper II and from earlier studies is that the management of patients with AF post-MI and PCI provides a clinical challenge where hemorrhagic and thrombotic risks have to be intricately balanced. There is no doubt that triple therapy is associated with increased risk of major bleeding events as observed in this thesis and in previous trials.\textsuperscript{165,166} However, robust data regarding ischemic events and duration of therapy with combinations other than aspirin and P2Y\textsubscript{12} inhibitors is not available. Until such data is available, physicians have to carefully balance treatment provided to their patients keeping in mind that current guideline recommendations are based on weak evidence and that triple therapy might do more harm than good.\textsuperscript{26,92,93} In addition, duration of triple therapy is a challenge with guidelines recommending treatment between 1 – 6 months post-PCI.\textsuperscript{26} Unfortunately, no robust data is available on treatment duration and no data is available regarding drug treatment beyond the initial months and prior to the initiation of long-term monotherapy with an oral anticoagulant. Hopefully, results from upcoming trials with novel antithrombotic drugs may bring some insight into the challenges associated with these patients.\textsuperscript{207}

\textbf{Renin-angiotensin system inhibitors}

In paper III it was observed that RAS inhibition with ACEI and/or ARB post-MI was associated with lower risk of all-cause mortality and cardiovascular mortality. A similar association was found in subgroup analysis among patients with or without CHF and/or AF. A lower risk of recurrent MI was observed among patients treated with ACEI/ARB and with concomitant CHF, irrespective of AF presence or not. Among patient with no history of AF at discharge, no benefit was observed with RAS inhibition in deterring the development of new-onset AF.

Prior to this study, several randomized trials and meta-analyses have reported similar favorable outcomes in regard to all-cause mortality and cardiovascular mortality with ACEI and ARBs in patients with CHF or left ventricular dysfunction post-MI.\textsuperscript{128–132} Also, previous studies suggest that RAS inhibition post-MI might be beneficial for all patients, not only those suffering from CHF or left ventricular dysfunction.\textsuperscript{208,209} The association between RAS inhibition and recurrent MI is still unsettled, with studies presenting diverging results.\textsuperscript{128,131} Paper III confirms that ACEI and/or ARB are beneficial for all patients post-MI, with a novel finding being that the treatment also seems beneficial for patients with concomitant AF. These findings are in accordance with current ACS guidelines were ACEI and ARBs are recommended to all patients with CHF and/or left ventricular dysfunction, and suggested to
patients without signs or symptoms of CHF post-MI. However, based on the findings in this thesis it is important to stress that all patients post-MI, including patients with AF, should receive treatment with ACEI or ARBs.

Pre-clinical studies have reported that RAS inhibition might inhibit inflammation and cardiac, electrical and vascular remodeling associated with new-onset of AF. These theories have further been confirmed in post-hoc analysis of randomized controlled trials, and consequent meta-analyses, in patients with CHF and/or left ventricular dysfunction receiving RAS inhibition. In patients post-MI, two retrospective analyses of randomized clinical trials have reported conflicting results, with a meta-analysis including these two trials reporting no association between RAS inhibition and future risk of AF. The findings in paper III confirm the results from the meta-analysis. Thus, RAS inhibition post-MI cannot be recommended as upstream therapy to prevent new-onset AF.

6.4 Limitations

The present thesis has limitations that have to be considered when interpreting the results. First, all papers in this thesis were retrospective observational studies and patients were not randomized to the different comparison arms. In papers I and IV, randomization was not possible as different patient cohorts were compared. In papers II and III, different antithrombotic regimes and RAS inhibition were compared based on treatment received at discharge and during follow-up. Therefore, it is inevitable that residual confounding may occur and that unknown and unmeasured confounders may exist. However, this thesis presents multicenter data adjusted for several relevant clinical factors that might differ at baseline. Despite this, it is important to remember that national quality registries run as part of routine care and can only register a limited number of variables reflecting patient characteristics, in-hospital care and discharge treatment.

Second, the definition of AF in papers I and IV have some limitations. In paper I, incomplete data regarding ECG records resulted in some patients being excluded from the analysis. Furthermore, classification of AF in paper I did not follow current AF definitions. In the study, AF was categorized into new-onset, paroxysmal and chronic AF based on data about history of AF prior to arrival and physician interpretation of ECG on arrival and at discharge. Thus, patients with undetected AF prior to arrival might be misclassified into new-onset AF, and in some patients uncertainty remains whether the AF diagnosis was persistent or permanent. In paper IV, pre- and postoperative AF were defined based on history of AF prior to arrival and on data entered by physicians in SWEDEHEART. Again, silent and undiagnosed AF prior to
admission might be misclassified. In paper IV, the definition of AF during follow-up had some limitations as the outcome was based on DC cardioversion as a surrogate marker of symptomatic relapse in AF. This probably resulted in an underestimated relapse risk as silent and non-DC cardioversion episodes of AF were not captured. This was addressed in a sensitive analysis where all diagnosis codes of AF during follow-up was accounted for. Unfortunately, this method had its own drawbacks as patients with follow-up visits due to earlier episodes of AF might have mistakenly been classified as having a relapse in AF.

In papers II and III, drug treatment at discharge and during follow-up was assessed using data from SWEDEHEART and the National Dispensed Drug Register. This made it possible to alter treatment arms and to censor for drug initiation or discontinuation during follow-up. Despite this possibility, no accurate date for initiation and withdrawal of treatment was available, but was instead based on advanced calculations using drugs dispense data. Furthermore, no data on reasons for drug initiation, termination and adverse effects was available. Despite these limitations, the results in the thesis were confirmed in numerous sensitivity analyses, including intention-to-treat analysis.

Finally, and despite all the limitations, it is important to acknowledge that the data included in this thesis consists of real-life consecutive patients admitted to all coronary care units or cardiothoracic centers in Sweden, with no loss in follow-up. Thus, the belief is that this thesis provides some valuable findings about risks associated with AF and benefits and risks associated with treatment provided to patients with AF in the setting of CAD.
7. Conclusions

In patients with AF in the setting of acute MI:

- AF is an arrhythmia that occurred in approximately 16% of patients with acute MI. The most common type of AF was new-onset AF (8%), followed by paroxysmal AF (5%) and chronic AF (3%). AF versus sinus rhythm was associated with an increased risk of a composite cardiovascular outcome of all-cause mortality, MI or ischemic stroke post-acute MI. Similar associations were observed for all individual outcomes. All subtypes of AF (new-onset, paroxysmal, chronic AF) were associated with higher risk of composite cardiovascular outcome, including individual components of all-cause mortality and ischemic stroke, with no major difference between different subtypes of AF.

- Approximately 1 in 4 patients post-acute MI and PCI with concomitant AF received oral anticoagulation, with or without antiplatelet therapy, at discharge. Treatment with a single antiplatelet agent plus warfarin or triple therapy versus dual antiplatelet therapy was associated with similar or lower risk of the composite of mortality, MI or ischemic stroke. Single antiplatelet therapy plus warfarin was associated with similar risk of major bleeding events compared to dual antiplatelet therapy. In contrast, triple therapy versus dual antiplatelet therapy was associated with an almost doubled risk of major bleeding events requiring in-hospital attention.

- Treatment with ACEI and/or ARB was associated with lower risk of all-cause mortality and cardiovascular mortality in patients with acute MI, irrespectively if the patients had CHF and/or AF. Lower risk of recurrent MI was observed in patients with CHF, but not in patients without CHF.

- Treatment with ACEI and/or ARB was not associated with lower long-term risk of new-onset AF in patients post-acute MI without AF at baseline.

In patients with AF in the setting of CABG:

- History of AF prior to CABG was documented in approximately 8% of the patients and new-onset postoperative AF complicated approximately 25%
of the patients. Pre- and postoperative AF was associated with an increased long-term risk of all-cause mortality, cardiovascular mortality and CHF. However, no significant association was observed between AF status and risk for ischemic stroke and MI.

- Postoperative AF was associated with higher long-term risk of relapse in symptomatic AF.
8. Clinical implications and future perspective

This thesis reported that AF was a common finding among patients with acute MI and in patients undergoing isolated CABG. Moreover, all subtypes of AF, irrespectively of new-onset, paroxysmal, chronic or postoperative, were associated with future detrimental outcome. Thus, patients with AF in the setting of CAD should be thoughtfully managed and future studies are needed to identify patients in this setting with a high risk of morbidity and mortality.

AF is a common heart arrhythmia, with an increasing prevalence and incidence globally. As previously mentioned, it is estimated that approximately 33.5 million individuals had AF in 2010. However, this is probably an underestimation as AF can go undetected, and cardiac monitoring is likely to identify AF in additional individuals. Thus, systematic screening of high risk populations, e.g. patients post-acute MI should be studied. Also, considering that postoperative AF after CABG in this thesis was associated with relapse in symptomatic AF, systematic screening for AF post-CABG is warranted to evaluate the true relapse risk.

To tailor treatment for patients post-acute MI and CABG there is a need to better understand what treatment options are effective, but also safe. For instance, few patients with AF received oral anticoagulants after an acute MI or CABG in this thesis, despite the verified efficacy of oral anticoagulants in preventing mortality and ischemic stroke in patients with AF. Moreover, patients with AF undergoing PCI due to acute MI received a wide array of antithrombotic drug combinations, further strengthening the fact that optimal antithrombotic therapy in this cohort is unknown. Thus, there is an urgent need for randomized clinical trials evaluating optimal antithrombotic therapy, and duration of therapy, in patients with AF undergoing PCI. Also, there is a need for trials evaluating antithrombotic therapy in patients with AF post-CABG. Furthermore, improved cardiovascular and bleeding risk scores are highly warranted in these populations to tailor treatment strategies.

Today, treatment options for the management of AF are based on rate control, rhythm control and prevention of thromboembolism. These strategies, mainly based on the electrical and thromboembolic aspects of AF, have not approached the aspects of cardiac remodeling that is associated with AF. Previous studies have shown that the RAS is associated with atrial
proarrhythmia such as AF.\textsuperscript{126,167} However, there is conflicting evidence whether or not treatment with RAS inhibitors such as ACEI and ARBs reduce the incidence of AF.\textsuperscript{57,172} Unfortunately, no beneficial effects with RAS inhibition was observed in this thesis. Despite this finding, it would be interesting to study other drug targets that could potentially inhibit cardiac remodeling associated with AF.

Although this thesis hopefully adds a small piece to the puzzle, there are still a lot of questions that remain to be answered before we can properly identify high risk individuals and tailor treatment for patients with AF in the setting of CAD.

\begin{quote}
\textit{``The important thing is not to stop questioning. Curiosity has its own reason for existing.''}
\end{quote}

- Albert Einstein

Under de senaste årtionden har forskare och sjukvårdspersonal upptäckt flera riskfaktorer som kan orsaka och förklara uppkomsten av båda sjukdomarna. Dessutom har betydande framsteg gjorts vad gäller behandling av både hjärtinfarkt och förmaksflimmer. T.ex. har ingrepp i kranskärlen med bypassoperation och ballongvidgning, med efterföljande medicinsk behandling och riskfaktormodifikation, inneburit att fler personer idag överlever sin hjärtinfarkt. Hos patienter med förmaksflimmer har medvetandet om riskerna med sjukdomen, t.ex. ökad risk för stroke (slaganfall), inneburit att behandling med potenta blodförtunnande läkemedel minskat risken för efterföljande allvarlig sjukdom. Trots att vården förbättrats och dödligheten för patienter med hjärtinfarkt och förmaksflimmer minskat utgör dessa sjukdomar fortsatt en betydande belastning för befolkningen. Målet med fortsatt hjärtforskning är att bl.a. upptäcka patienter som ligger i riskzonen för att drabbas av t.ex. hjärtinfarkt eller förmaksflimmer, samt att individanpassa den medicinska behandlingen för att förbättra utfall och minska risken för allvarliga biverkningar. Syftet med denna avhandling var att undersöka olika aspekter av förmaksflimmer hos patienter med kranskärlssjukdom, både när det gäller riskerna med samsjuklighet samt långtidsbehandlingen för att förebygga nya hjärt-kärlhändelser. För att besvara dessa frågor i avhandlingen inhämtades data från flera nationella register, inklusive SWEDEHEART som...
är ett nationellt kvalitetsregister som bl.a. registrerar information om given hjärtintensivvård, kranskärlsröntgen, ballongsprängning och hjärtkirurgi.


förenat med snarlik risk för allvarliga blödningar jämfört med behandling med endast acetylsalicylsyra och P2Y12-hämmare, utan att öka risken för ny hjärtinfarkt eller död. Följaktligen föreslår fynden i arbete två att man möjligen kan avstå från en av de specifika blodfordunnande läkemedlen som vanligtvis används efter ballongsprängning.


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References


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)