Epidemiological aspects of aortic stenosis

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Abstract

Background: Aortic stenosis (AS) is the most common heart valve disease, confers substantial morbidity and mortality after symptom onset, and is predicted to increase in importance as the population ages. AS is characterized by narrowing of the aortic valve, resulting in increasing strain on the left heart and hemostatic effects (loss of large von Willebrand factors multimers). The pathogenesis of AS remains incompletely understood but involves inflammation, lipid accumulation and calcification in a process similar to atherosclerosis. A heritable component has been suspected but has not been established. Few studies have explored the epidemiological characteristics of AS.

Aims: The aims of this thesis were to evaluate temporal trends of incidence and mortality in aortic stenosis and to evaluate the association of AS development with traditional cardiovascular risk factors, measures of atherosclerosis, and hereditary factors. Furthermore we aimed to evaluate the clinical importance of the hemostatic effects of AS.

Methods: Nationwide Swedish registers were used to identify patients with AS, for assessment of trends in incidence and mortality between 1989-2009, and to determine AS risk in siblings and spouses of AS patients. Individuals with incident AS were identified from the population-based cohort Malmö Diet and Cancer (MDC, n=5079), and related to cardiovascular risk factors and ultrasound measures of carotid plaque and intima-media thickness at baseline. In nationwide registers from both Sweden and Denmark, patients with myocardial infarction (MI) treated with dual antiplatelet therapy with and without AS were evaluated regarding risk for bleeding, recurrent MI and all-cause mortality.

Results: Despite an increase in absolute AS cases, a slight decline in age-adjusted incidence was observed between 1989-2009. The median age at diagnosis increased by 4 years. Mortality declined both in patients undergoing valvular replacement and in patients not undergoing surgery. A sibling history of AS was uncommon in the population (0.5%) but more common among patients with AS (4.8%). A sibling history conveyed a markedly increased risk for AS (hazard ratio [HR] 3.58, 95% CI=2.34-5.49) whereas a spousal history only conveyed a slight risk increase (HR 1.16, 95% CI=1.05-1.28). Higher age, diabetes, smoking, body mass index, C-reactive protein and carotid plaque were also risk factors for incident AS in the MDC. In both Sweden and Denmark, AS patients were found to have a two-fold increased risk for bleeding, recurrent MI and all-cause mortality after MI in an adjusted model.

Conclusions: The results of this thesis adds epidemiological evidence to the current understanding of the pathophysiology and risk factors of AS and provides an estimate of the expected burden of AS in Sweden in the coming decade. In particular, heritability and measures of atherosclerosis were strong risk factors for AS. The high risk after MI of both bleeding and recurrent MI in patients with AS highlight the need for individual risk assessment to optimize management of these patients. The findings have implication for future research directions and treatment strategies.

Key words: Aortic stenosis, epidemiology, valvular heart disease

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“If I have seen further, it is by standing on the shoulders of giants.”
– Isaac Newton

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I. Martinsson A, Li X, Andersson C, Nilsson J, Smith JG, Sundquist K. Temporal trends in the incidence and prognosis of aortic stenosis: a nationwide study of the Swedish population. Circulation. 2015;131:988-94.

II. Martinsson A, Östling G, Persson M, Sundquist K, Andersson C, Melander O, Engström G, Hedblad B, Smith JG**.** Carotid plaque, intima-media thickness and incident aortic stenosis: a prospective cohort study. Arterioscler Thromb Vasc Biol. 2014;34:2343-8.

III. Martinsson A, Li X, Zöller B, Andell P, Andersson C, Sundquist K, Smith JG. Familial aggregation of aortic valvular stenosis: a nationwide study of sibling risk. Manuscript submitted.

IV. Martinsson A, Li X, Torp-Pedersen C, Zöller B, Andell P, Andreasen C, Gislason G, Kober L, Sundquist K, Smith JG, Andersson C**.** Clinical outcomes of dual antiplatelet therapy after myocardial infarction in aortic stenosis patients: a nation-wide study from Sweden and Denmark**.** Manuscript submitted.

Abbreviations

95% CI – 95% confidence interval

ACE – Angiotensin-converting enzyme

ARBs – Angiotensin II receptor blockers

AS – Aortic valvular stenosis

CAD – Coronary artery disease

CDR – Cause of Death Register

DRMPS – Danish Registry of Medicinal Product Statistics

GWAS – Genome-wide association study

HF – Heart failure

HR – Hazard ratio

LVEF – Left ventricular ejection fraction

MDCS – Malmö Diet and Cancer Study

MI - Myocardial Infarction

MGR – Multi-Generation Register

NPR – National Patient Register

NSAIDs – Nonsteroidal anti-inflammatory drugs

PAR – Population attributable risk

SAVR – Surgical aortic valve replacement

SNPs – Single nucleotide polymorphisms

SPR – Swedish Pharmaceuticals Registry

TAVR – Transcatheter aortic valve replacement

vWD – von Willebrand disease

vWF – von Willebrand factor

Abstract

Background

Aortic stenosis (AS) is the most common heart valve disease, confers substantial morbidity and mortality after symptom onset, and is predicted to increase in importance as the population ages. AS is characterized by narrowing of the aortic valve, resulting in increasing strain on the left heart and hemostatic effects (loss of large von Willebrand factors multimers). The pathogenesis of AS remains incompletely understood but involves inflammation, lipid accumulation and calcification in a process similar to atherosclerosis. A heritable component has been suspected but has not been established. Few studies have explored the epidemiological characteristics of AS.

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Nationwide Swedish registers were used to identify patients with AS, for assessment of trends in incidence and mortality between 1989-2009, and to determine AS risk in siblings and spouses of AS patients. Individuals with incident AS were identified from the population-based cohort Malmö Diet and Cancer (MDC, n=5079), and related to cardiovascular risk factors and ultrasound measures of carotid plaque and intima-media thickness at baseline. In nationwide registers from both Sweden and Denmark, patients with myocardial infarction (MI) treated with dual antiplatelet therapy with and without AS were evaluated regarding risk for bleeding, recurrent MI and all-cause mortality.

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patients not undergoing surgery. A sibling history of AS was uncommon in the population (0.5%) but more common among patients with AS (4.8%). A sibling history conveyed a markedly increased risk for AS (hazard ratio [HR] 3.58, 95% CI=2.34-5.49) whereas a spousal history only conveyed a slight risk increase (HR 1.16, 95% CI=1.05-1.28). Higher age, diabetes, smoking, BMI, CRP and carotid plaque were also risk factors for incident AS in the MDC. In both Sweden and Denmark, AS patients were found to have a two-fold increased risk for bleeding, recurrent MI and all-cause mortality after MI in an adjusted model.

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Chapter I. Introduction

The human heart is essentially a muscular pump divided into four separate compartments: two atrias and two ventricles. Oxygen-depleted blood returning to the heart from tissues throughout the body circulates these compartments in a specific order. First entering the right atrium through the caval veins, from which it passed on to the right ventricle before being pumped through the pulmonary circulation for oxygenation. Thereafter the blood flow returns to the heart into the left atrium, further into the left ventricle from where it is pumped out into the systemic circulation through the aorta, the largest artery in the human body (Figure 1.1).

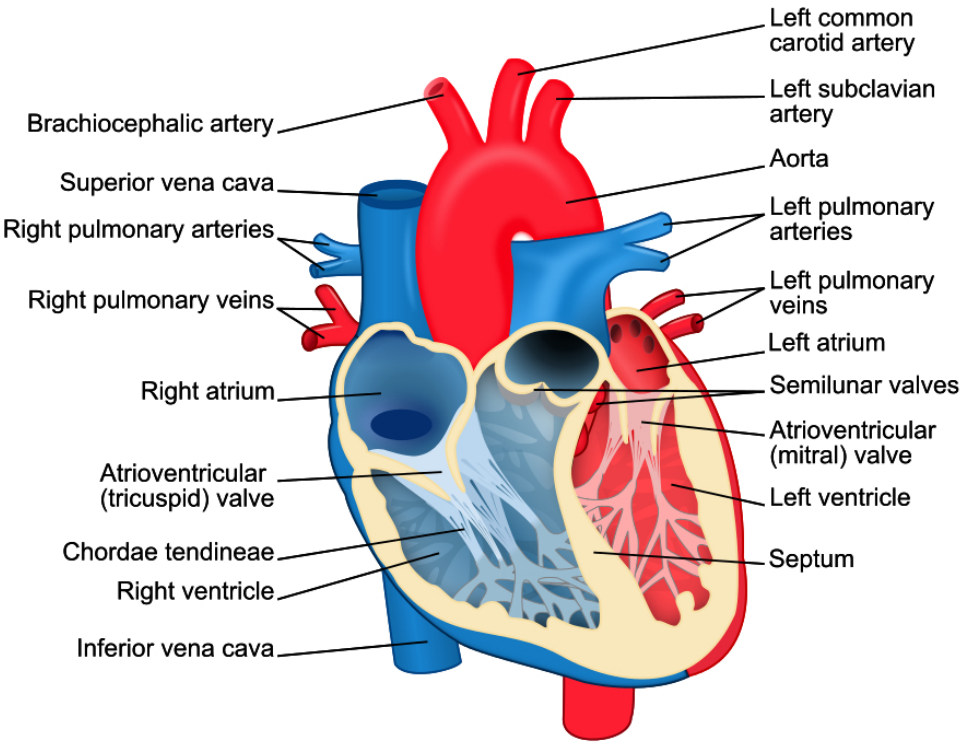

Figure 1.1. Anterior view of the human heart. The semilunar valves are the pulmonary (left in the picture) and aortic valve (right).

The orifices connecting these four compartments are the location of the heart valves; specialized structures, which enable blood flow in the intended direction but prevent regurgitation (backflow). The human heart thus has four such heart valves referred to in anatomy as the tricuspid, pulmonary, mitral and aortic valve, in order of the flow of blood through the heart as described above. The aortic valve is the final valve the blood passes after ejection at high pressure from the left ventricle into the aorta. The aortic valve consists of three components, referred to as 'cusps' or 'leaflets', which open and close in response to the increase and decrease in pressure resulting from the contraction and relaxation of the left ventricle, respectively.

Diseases of the cardiovascular system are the leading cause of death worldwide and include coronary artery disease, heart failure, rhythm disturbances, congenital cardiac malformations, and valvular heart disease.[1-2] Given the connection of the cardiovascular components, diseases in the vascular system, heart valves or heart muscle (myocardium) often affect the function of the other components as well. For example, myocardial dysfunction (heart failure) may result in valvular dysfunction while advanced valvular disease may result in heart failure.

Historically, the largest threats to human life have been predators, violence, starvation and infectious diseases. However, with the development of modern civilization, means to prevent such basic threats to survival have gradually become available to an increasing number of humans, and the disease spectrum has transitioned towards predominance of aging-degenerative and lifestyle-related diseases including, as we shall see, valvular heart disease.[3]

1.1 Historical perspectives on valvular heart disease

Looking back at the course of human history, infectious disease has been, and remains, a great challenge. The discovery of penicillin in 1928 by Dr. Alexander Fleming and the subsequent purification of the compound by Drs. Ernst Chain, Howard Florey and colleagues revolutionized the treatment of such diseases and has saved millions of lives worldwide.[4-5]

Valvular heart disease was at the beginning of the 20th century largely a disease of the young, resulting from bacterial infection with streptococci species. The infection resulted in an immunologic reaction called rheumatic fever, one of the leading causes of death in the young during the early 20th century.[6] The pathogenesis behind acute rheumatic fever remains incompletely understood but appears to include three fundamental steps: infection with a rheumatogenic streptococci strain, a vulnerable individual, and an aberrant autoimmune reaction

targeting proteins in heart tissue in a process referred to as molecular mimicry.[7-9] Rheumatic valvular disease often involves both the aortic and mitral valves, presenting with mixed regurgitation and stenosis. In parallel with emergence of antibiotics including sulfonamides and penicillin during the 20th century and improved health conditions, the incidence of rheumatic heart disease was markedly reduced in Western countries and virtually disappeared.[2] However, rheumatic heart disease remains highly prevalent in some developing parts of the world.[7]

Substantial advances have also been made in the understanding and treatment of cardiovascular disease unrelated to infectious disease during the 20th century. Cardiometabolic risk factors such as smoking, hypertension and cholesterol were described in epidemiological cohorts and shown to explain much of the increasing incidence of atherosclerotic vascular disease in the mid-20th century.[10-13] Preventive efforts targeting such risk factors, in combination with improved treatment protocols for manifest vascular disease including revascularization procedures, have resulted in declining mortality and later age at onset of cardiovascular disease.[10-13]

Valvular heart disease is currently largely a disease of the elderly, and has been considered an unavoidable consequence of aging resulting from the mechanical strain on the valve throughout the lifecycle. In recent years, valvular disease processes such as aortic stenosis has been increasingly recognized as an active, degenerative process, which may be prevented similarly to atherosclerotic vascular disease. However, as great progress has been made in the pathophysiological understanding and treatment options for atherosclerotic disease and heart failure in the last decades, valvular heart disease has remained comparably understudied with no effective medical therapies introduced. The first successful aortic valve replacement was reported in 1960. Since then significant advances have been made in prosthesis design, surgical techniques and post-operative care.[14-15] The past decade has seen the introduction of endovascular approaches to treat aortic stenosis, referred to as transcatheter aortic valve replacement (TAVR).

1.2 Epidemiology: the study of disease in human populations

Epidemiology is a scientific discipline concerned with the study of disease and health patterns in defined populations. It seeks to understand the causes and effects of disease and to guide the development of tools for prevention and therapy.

An experiment that is often referred to as the first study of modern epidemiology was carried out in the late 19th century by Dr. John Snow, who mapped outbreaks of cholera in London down to a specific water well and studied the effects of preventing use of that well, famously by removing the pump handle.[16-17] Since then, epidemiological studies have become a widely used tool in medicine, and celebrated many successes including the description of negative effects of smoking on cardiovascular health and risk of cancer and the identification of thalidomide as a teratogen. Particularly important applications of epidemiological studies include the discovery of clinical risk factors**,** as illustrated by the Framingham Heart Study, and the study of demographic information in disease transmission or development. Epidemiological methods have become a cornerstone of health studies and provide guidance in health policy decisions worldwide.[10-13,18-20]

The development of high-throughput technologies in molecular biology in recent years have facilitated a new branch of epidemiology devoted to the study of molecular disease patterns in populations; molecular epidemiology. In particular, following the complete characterization of the human genome, the field of genetic epidemiology has started to uncover the heritable basis of human disease. One important recognition in genetic epidemiology has been the rarity of diseases caused by a single genetic mutation of large impact, often resulting from negative effects on natural selection, whereas many complex diseases instead result from a complex interplay of many common genetic variants of individually modest effect (such as single-nucleotide polymorphisms [SNPs]) and environmental factors.[21-22]

For the study of common genetic variants, a high-throughput genotyping approach for SNPs referred to as genome-wide association studies (GWAS) has been highly successful. GWAS represents an attractive possibility to detect new pathophysiological mechanisms, when the effect of identified polymorphisms on nearby genes and disease development can be clarified.[22-23] Indeed, hundreds of previously unknown genes have been robustly associated with various cardiovascular diseases in GWAS, including SNPs for myocardial infarction and aortic stenosis.[22]

1.3 Aortic valvular stenosis

With intact function, the aortic valve allows the left ventricle to eject blood into the aorta during systole with minimal resistance to flow through the valvular apparatus, while minimizing any regurgitant flow during diastole. Valve function thus relies on pliable cusps to open smoothly as the left ventricle contracts. With the development of aortic valvular stenosis (AS) the cusps and surrounding

supporting structure (annulus) of the aortic valve become increasingly calcified and stiff. These alterations result in impaired opening of the aortic valve and reduced valve area, providing resistance to flow which results in an increased pressure gradient across the valve and added strain on the left ventricle. In severe AS, the increased strain on the left ventricle eventually leads to myocardial hypertrophy, heart failure and symptom development.

In early stages, aortic valvular stenosis is generally an asymptomatic disease but frequently progresses to severe, symptomatic disease, with a gradual decline in valve area and increase in calcification and pressure gradient.[24-26] Symptoms commonly include decreased tolerance for physical exercise, dyspnea, angina pectoris and syncope. After symptom onset, the prognosis for aortic valvular stenosis is poor with 2-year mortality rates estimated between 30-50% (Figure 1.2).[27-29]

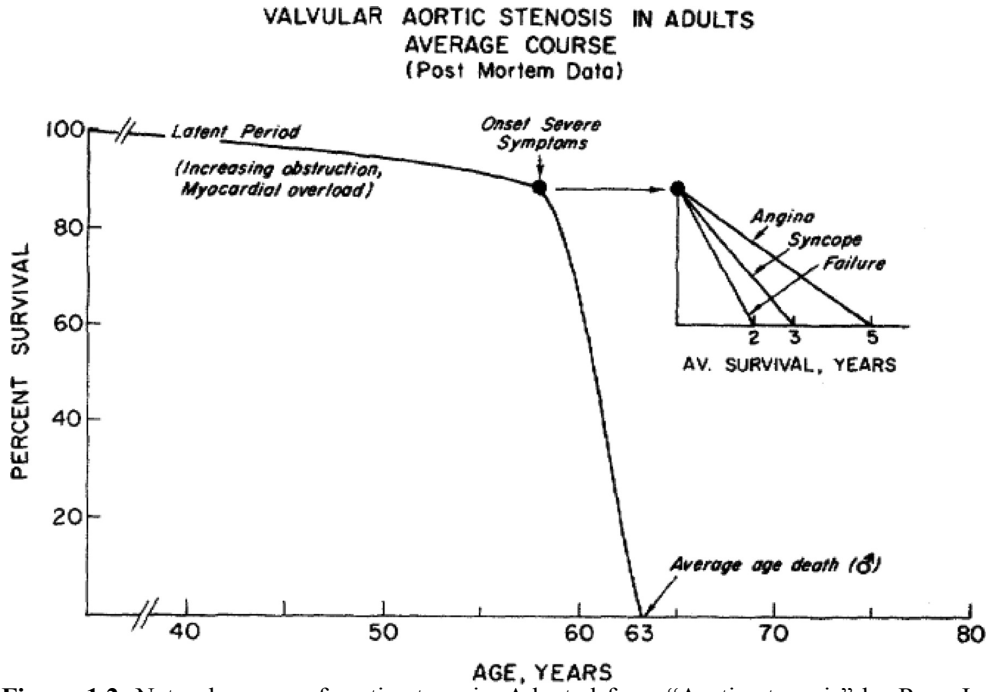

Figure 1.2. Natural course of aortic stenosis. Adapted from "Aortic stenosis" by Ross J, Braunwald E. *Circulation.* 1968;38:61-67. Published with permission.

In western countries AS today mainly constitutes a disease of the elderly with a marked increase in incidence and prevalence in the population >65 years of age.[27-28,30-31] An early precursor stage of AS, aortic sclerosis, represents the most common valvular heart defect in the population and AS is the most common valvular disease necessitating valve replacement. [27-28,30-31]

1.3.1 Diagnostic considerations

Echocardiography is the central modality for the diagnosis and severity assessment of AS.[32] Transthoracic echocardiography allows characterization of the number, thickness and mobility of leaflets, valve area, and pressure gradient. Echocardiographic evaluation also allows simultaneous assessment of ventricular function and hypertrophy, which are other important factors for AS patients. AS is commonly divided into mild, moderate and severe disease based on echocardiographic findings (Table 1.1). The classification is based on the mean transaortic pressure gradient (ΔP), transvalvular velocity (V_{max}) and valve area (which may be adjusted for body surface area).[28,32] It should be noted that some of these measures are primarily reliable in patients with normal cardiac output and patients with reduced systolic function and low-flow circulation may present with a low gradient but still have severe stenosis In these situation Dobutamine stress echocardiography can improve diagnostic accuracy.[32-33]

Measure	Unit	Mild	Moderate	Severe
Mean transaortic pressure gradient	mmHg	<20	20-40	>40
Transvalvular velocity	m/s	2.6-2.9	3.0-4.0	>4.0
Valve area	cm^2	>1.5	1.0-1.5	<1.0

Table 1.1 Most common measurements for evaluating AS in clinical practice.

1.3.2 Therapeutic alternatives

The only available and often lifesaving treatment for patients with AS is valvular replacement therapy. Valvular replacement therapy is recommended for patients with a combination of severe AS and symptoms, and for selected patients with severe AS and reduced left ventricular ejection fraction (LVEF <50%).[28,34] Until recently the single option for valvular replacement therapy was open-heart surgery with a bioprosthetic or mechanical valve (SAVR). Mortality associated with isolated SAVR is approximately 3% and increases with age but several other risk

factors are also important and risk assessment tools such as EuroSCORE II are frequently used to evaluate individual risk.[35-40] Surgery-related mortality has declined in the recent decade and, considering the natural history of AS, outcomes associated with the intervention are considered excellent. Complications do however exist, including stroke, post-operative infections and, reflecting limitations in the lifespan of prosthetic valves, re-operation.[35-40]

Patients who are considered to have too high risk for surgery have previously lacked treatment options. In the last decade TAVR has emerged as an alternative to surgery, with acceptable outcomes for patients who are inoperable or at high surgical risk in several trials.[41-44] Early data from studies comparing SAVR and TAVR in a non-inferiority design including patients at intermediate risk have also shown promising results for TAVR, but long-term data are not yet available.[45]

1.3.3 Pathophysiology and medical therapies

Early precursor lesions of aortic valvular disease, aortic valvular sclerosis, are characterized by lipid accumulation, inflammation, fibrosis and calcification.[46-49] Histological studies of such lesions have described increased amounts of intra-cellular lipids, and infiltration of foam cell macrophages and non-foam cell macrophages and increased levels of T-lymphocytes as compared to healthy valves (Figure 1.3).[50-51] T-lymphocyte infiltration appears to be most pronounced around nodules of calcium deposits, where expression of interleukin-2-receptors is also increased.[51] The sclerotic valve thus shares several features with early stages of coronary atherosclerosis.

AS also shares several cardiovascular risk factors with coronary artery disease, including diabetes, increased low-density lipoprotein cholesterol (LDL-C) and smoking.[52]There are currently several lines of evidence implicating hyperlipidemia as a causal factor in the development of aortic stenosis. One study described an association between both incident aortic stenosis and increased valve calcium with low-density cholesterol.[46] Genetically high levels of LDL cholesterol increase the risk of AS, with a particularly strong effect of high lipoprotein(a) particles.[46,53] Similarly, transgenic mouse models with genetically induced hypercholesterolemia develop early calcification of the aortic valve, and the calcification process was arrested when cholesterol levels were normalized.[54] Increased deposition of lipids in the valve extracellular matrix is thought to induce an inflammatory state, resulting in valvular tissues damage through multiple mechanisms including oxidative stress and increased superoxide levels.[55-57]

With the recognition that early development of AS is associated with increased levels of both local and circulating lipids, lipid-lowering therapy to halt the

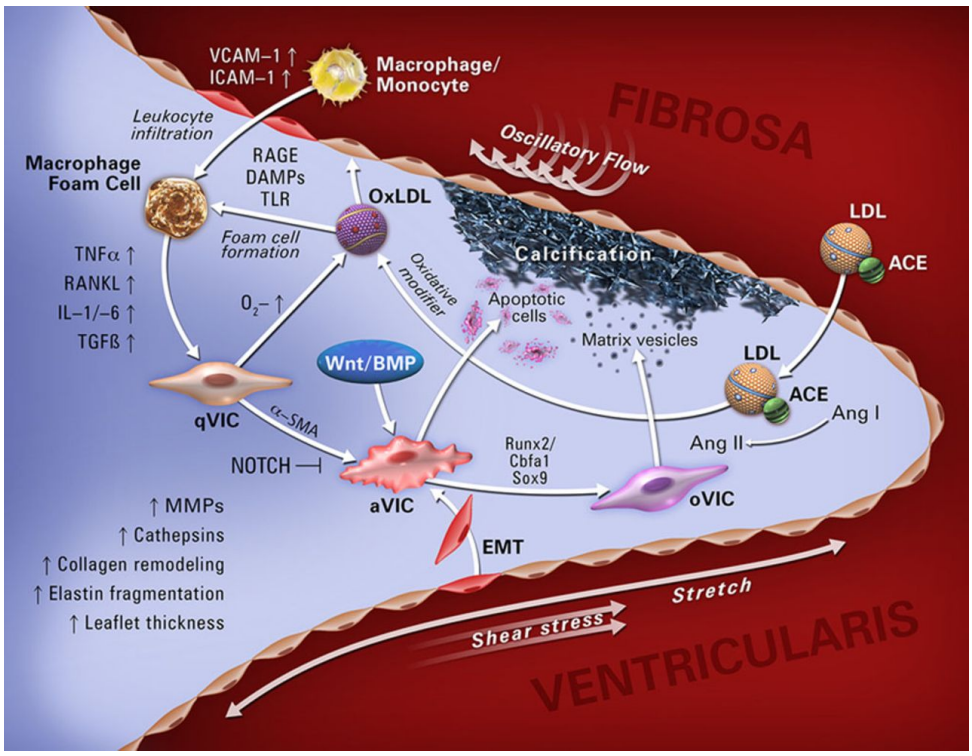

Figure 1.3. Intra- and extracellular mechanisms considered to be of importance in disease development of AS. Adapted from "Calcific aortic valve disease – A consensus summary from the alliance of investigators on calcific aortic valve disease" by Yutzey, K, Demer L, Body S, Huggins G, Towler D, Giachelli C, Hofmann-Bowman M, Mortlock D, Rogers M, Sadeghi M, Aikawa E. 2014, *Arterioscler Thromb Vasc Biol.* 34:2387-2393. Published with permission.

progression of AS was investigated in three large randomized trials, mostly including subjects with moderate AS. Unfortunately none of these trials observed any beneficial effect of lipid-lowering therapy on the progression of AS.[58-60] The reasons for this lack of effect are not completely understood, but it might be speculated that treatment might have been initiated too late in the disease process, where calcific and osteogenic factors play a more important role in disease progression. In agreement with this, studies have shown that lowering of plasma lipid levels at early stages of aortic valve disease may halt disease progression.[54,61-62]

In addition to inflammation and lipid accumulation, angiotensin-converting enzyme (ACE) and its enzymatic product angiotensin II is expressed in aortic valves with sclerosis and stenosis but not in healthy valves.[63] ACE was found to be localized near deposits of extracellular lipoproteins.[63] Angiotensin II has

previously been shown to increase the uptake of LDL cholesterol and to act as a chemotactic agent for certain inflammatory cells.[63] The expression of ACE and conversion to angiontensin II might thus contribute to AS pathogenesis through multiple mechanisms.

The beneficial effects of ACE-inhibitors in AS patients has also been explored in smaller studies with promising results, but no larger, well-powered randomized trials have been conducted.[64-67] Beneficial effects of ACE-inhibitors could potentially be related to favorable effects on cardiac remodeling or due to reduction of angiotensin II in the valvular apparatus.[64-65]

The lipid-related and inflammatory mechanisms described above are thus likely early steps in the disease process. The first event is hypothesized to be increased mechanical strain, triggering lipid accumulation and inflammation.[68] However, as the disease progresses and the valve becomes increasingly calcified other mechanisms are likely to play a more important role (Figure 1.4)[69-70]

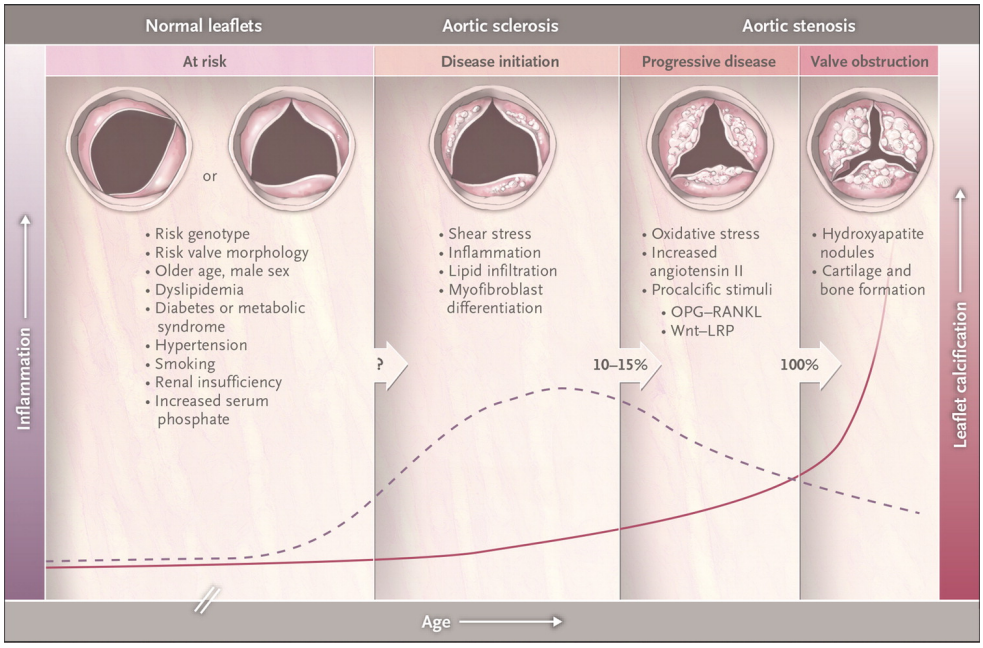

Figure 1.4. Progression of valvular aortic stenosis and the corresponding mechanisms considered associated with each step. Illustrating the shift that is seen in pathophysiology as disease progresses. Reproduced with permission from Otto CM, Prendergast B. Aortic-valve stenosis – from patients at risk to severe valve obstruction. N Engl J Med. 2014;37:744-56), Copyright Massachusetts Medical Society.

Early histological studies of stenotic valves described the presence of cells with an osteoblast-like phenotype and hydroxyapatite. Valvular interstitial cells (VICs) have been shown to have highly plastic attributes, being capable of differentiating into a variety of fibro- and osteoblastic phenotypes if presented with pathologic stimuli, and are thought to contribute to both fibrotic remodeling and hydroxyapatite deposition, which may be important pathways to increasing AS severity.[69,71-73] The presence of inflammatory proteins are also thought to contribute to transformation of the valvular extracellular matrix, with up-regulation of matrix metalloproteinases in areas of inflammation.[74-75] In combination, these mechanisms may lead to a proliferation of disorganized fibrous tissue and increased valvular stiffness.[68,74-75] Calcification, localized to areas of inflammation and lipid deposition, is present in microscopic areas of the valve early in the disease process.[68] Valve stenosis severity seems to correlate with degree of valvular calcification based on computed tomography findings.[76]

Histologically much of the calcific nodules in the valve constitute of unorganized calcium phosphate without a clear structure.[77] The differentiation of VICs into osteoblasts and osteoclasts is thought to be of importance. Several molecular cues and signaling pathways with an association to osteoblastogenesis and osteoclast differentiation are upregulated in the aortic valves of AS patients. Molecular pathways considered to be of significance include Runx-2/NOTCH-1 signaling, the Wnt3-Lrp5-β catenin pathway, and the RANKL-pathway. These pathways induce osteoblast-associated genes, and promotes matrix calcification leading to a osteogenic phenotype.[78-81] Galectin-3, involved in vascular osteogenesis, has also been shown to be overexpressed in aortic valve in AS patients.[82] In the end-stage of aortic valvular disease nodules of hydroxyapatite are present and frank osteogenesis occur with a significant obstruction of the left ventricular outflow tract.

At this point, the left ventricle undergoes structural changes in response to the increased afterload and wall stress which may have beneficial effects initially but ultimately represent a maladaptive response.[83-85] An increase in left ventricular mass is associated with myocardial fibrosis and with an accompanying decrease in stroke volume.[84-85] Myocardial fibrosis did not appear to reverse after AVR during 9 months of follow-up in a study by Hermann et al and patients with a low transvalvular gradient appeared to be at greater risk of maladaptive fibrotic remodeling.[84] A larger ventricular mass than predicted from the added ventricular strain of AS seemed to be an independent marker for adverse advents, further establishing the dysfunctional nature of this ventricular response.[85]

1.3.4 Genetic architecture of valvular aortic stenosis

Valvular AS is a complex disease and the genetic architecture of this condition remains largely unknown. A familial aggregation of cases undergoing AVR have been reported in western France, but larger studies are lacking.[86] No genetic variants of large effect have been described in AS families to date, perhaps with the exception of the NOTCH1 gene described below for bicuspid aortic valves. Recently however, GWAS was able to shed some light on common genetic determinants of AS. GWAS identified robust associations of genetically increased levels of lipoprotein(a) and low-density cholesterol with aortic valve sclerosis, which was further associated with incident AS. [46,53] Another GWAS study of aortic stenosis implicated the genes CACNA1C and RUNX2, which however have not been robustly replicated.[87] Specific polymorphisms in the IL-10 and APOB genes have also been reported to increase the risk of AS in a smaller study.[88] Collectively, these findings indicate a causal role for lipoprotein metabolism, inflammation and calcium-signaling pathways in valvular aortic stenosis. The findings support the current understanding of valvular aortic stenosis as a complex disease with several stages of disease development, and with an intricate interaction between genes and environment.

1.3.5 Bicuspid aortic valves

Bicuspid aortic valves (BAV) is a common congenital malformation characterized by the presence of an aortic valve with only two leaflets, often due to fusion of two leaflets. Most frequently BAV results from fusion of valves between the right and the left coronary sinuses, with a central raphe resulting in an asymmetrical aortic valve, although symmetrical valves have also been described.[89-91] The prevalence in the general population has been estimated to 0.5-1.0%, with a male predominance.[92-94] BAV is overrepresented in younger patients who undergo AVR, present in approximately 50% of this patient cohort.[95] BAV is also associated with development of aneurysms in the proximal aorta, likely due to a defect in fibrous tissue formation, with risk of aortic regurgitation and endocarditis.[89,92,95-96,] Patients with BAV generally have an earlier onset of AS than patients with tricuspid valves.[95,97] BAV is not simply a valvular malformation but represent a genetic disorder influencing cardiac and aortic formation.[89]

Familial clustering is well-recognized in BAV and studies have suggested an autosomal dominant inheritance pattern.[98-100] Several genes have been associated with bicuspid aortic valves, of which the most consistent finding has been of mutations in the NOTCH1 gene, which have been shown to results in abnormal valve development.[80,101] NOTCH1 is also associated with an anomalous calcium deposition in the aortic valve.[80,99]

1.3.6 Hemostatic consequences of aortic stenosis

Besides increasing strain and risk of dysfunction of the left ventricle, valvular aortic stenosis is also associated with hemostatic abnormalities. Increased bleeding risk in AS patients was reported in 1958, when Dr. Heyde first described a syndrome including valvular AS, angiodysplasias in the gastrointestinal tract, and gastrointestinal bleeding, consequently referred to as Heyde's syndrome.[102] Over the past 20 years, several case-reports and case-series have described patients with Heyde's syndrome,[103-107] for which gastrointestinal bleeding seems to be the principal hemostatic complication.[108] In the late 20th century, several groups described loss of the large multimers of von Willebrand factor (vWF), referred to as acquired von Willebrand's disease, in patients with Heyde's syndrome.[109-110] vWF has a complex multimeric structure which facilitates platelet-mediated hemostasis by binding to both platelets and collagen structures, and is of particular importance under high shear stress flow conditions.[111] The large multimers are particularly important for vWF function. Subsequent mechanistic studies suggest that as vWF multimers pass through the stenotic valve they may undergo conformational changes, exposing their cleavage site for the proteinase ADAMTS13.[112-117] The increased breakdown of vWF multimers into smaller, less potent particles induces a bleeding diathesis.[110] The hemostatic complications in AS is however not limited to an increased bleeding risk but AS has also been shown to stimulate a prothrombotic state, likely influenced by flow conditions and concurrent atherosclerotic vascular disease.[118] An increase in factor XI, and activated tissue factor with an elevation in markers of thrombin generation in severe AS have also previously been reported.[119-121] These observations could potentially have implications for the risk of thromboembolism in AS patients.

In summary, AS is associated with diverse hemostatic changes, which may predispose to both bleeding and thrombotic events.

1.4 Common comorbid conditions to AS: myocardial infarction and heart failure

Myocardial infarction (MI) and heart failure are common cardiovascular diseases that contribute a substantial part of the global burden of disease.[2] Both conditions are frequently associated with aortic stenosis, 30% of patients with either aortic sclerosis or stenosis had a history of coronary artery disease in one study and for patients undergoing aortic surgery 20% had reduced LVEF while 85% had symptoms of heart failure.[30,52]

1.4.1 Myocardial infarction

MI is caused by an insufficient oxygen supply to the cardiac myocytes, resulting in myocardial necrosis.[122-123] Coronary artery disease (CAD) is the principal common underlying cause of MI.[122-124] CAD results from a complex interplay of genetic and environmental factors, with a particularly important role of metabolic risk factors such as elevated levels of low-density lipoprotein cholesterol (LDL-C) which interacts with inflammatory mechanisms to produce lesions of atherosclerosis in the vasculature.[125] During the past decade, introduction of percutaneous coronary interventions, aggressive risk factor control, and improved secondary preventive therapy have greatly improved outcomes for patients with MI.[122-129] The introduction of potent strategies for platelet inhibition in the form of dual antiplatelet therapy (DAPT) have resulted in improved outcomes and lower risk of recurrent MI, and is currently recommended for all patients with MI in the absence of clear contraindications.[122-127] DAPT is however, due to the potent antiplatelet effect, associated with an increased risk for bleeding.[130-131] The hemostatic alterations described above in patients with AS may further add to this risk in such patients, which has not been studied.[103-110]

1.4.2 Heart failure

Heart failure is the end-stage of most conditions that negatively influence the heart, including valvular heart disease. It is a syndrome characterized by a varying set of symptoms, including dyspnea, peripheral edema and fatigue, in addition to objective measures of impaired cardiac function.[132] The symptoms are caused by a reduction in cardiac output or elevated cardiac filling pressure secondary to either impaired systolic or diastolic myocardial function.[132] The improved outcomes for heart failure patients in recent years can largely be attributed to improvement in medical therapy, with several novel pharmacologic treatment alternatives introduced with well-documented effects on mortality and morbidity.[133-138] In the context of AS, the increased outflow obstruction results in left ventricular strain, remodeling, and with severe disease, heart failure.[83-85] The role of ACE-inhibitors and angiotensin II receptor blockers (ARBs), commonly used for treatment of heart failure, have been somewhat controversial in the context of AS, given the risk of severe hypotension. In current guidelines ACE-inhibitors or ARBs may be used in patients with heart failure or hypertension awaiting, or who are not eligible for, intervention.[136-137] The pathophysiological mechanisms implicated for ACE and angiontensin II described above suggest that patients with early aortic valve lesions may derive benefits from ACE-inhibitors beyond effects on reduced afterload and blunted remodeling.

Chapter II. Aims

The aims of this thesis were to study:

- Temporal trends in incidence and prognosis of aortic valvular stenosis and changes in the utilization of aortic valvular replacement in the Swedish population between 1989-2009. (**Study I**)

- Clinical risk factors associated with aortic valvular stenosis in a large prospective cohort study, including measures of manifest atherosclerotic disease as plaque and intima-media thickening in the common carotid artery. (**Study II**)

- Sibling and spousal risk of aortic valvular stenosis in the Swedish population. (**Study III**)

- The impact of AS on outcomes after myocardial infarction in patients treated with dual antiplatelet therapy, with regard to bleeding, recurrent myocardial infarction and mortality. (**Study IV**)

Chapter III. Methods

3.1 Nationwide registers

In Study I, III and IV data on all Swedish citizens and all cases of aortic stenosis was extracted from a number of nationwide registers, including the National Patient Register (NPR), Cause of Death Register (CDR), Swedish Pharmaceuticals Registry (SPR), and the Multi-Generation Register (MGR). The registers were linked on the individual level via the Swedish personal identification numbers, introduced in 1947, unique to each Swedish citizen.[139] To preserve individual integrity the personal identification number was converted into a random serial identification number upon data extraction. The Swedish registers are internationally known to be of high coverage and validity.[140] Data on prescribed drugs were based on the SPR. Healthcare costs are covered by tax funding, pharmacotherapy is subsidized and the registries are considered nationwide and accurate.

3.1.1 National Patient Register

The (NPR) is a register that includes all hospital discharge diagnoses in Sweden and since 2005 also includes information from outpatient visits.[140-141] Diagnoses are registered according to the International Classification of Disease (ICD). Between 1987 and 1997 ICD version 9 was used and since 1997 and onwards ICD version 10 is used. Diagnosis coding in the registers are based upon a physician's clinical diagnosis. The NPR has been in use since the 1960's but has been nationwide since 1987. Reporting to the NPR is required for departments and clinics, as fiscal reimbursement is linked to diagnosis codes. As a result the Swedish NPR has excellent coverage and diagnoses in the registers in general have a high validity.[53,140,142-144]

Many cardiovascular diseases, including valvular heart diseases, are rarely cared for in a primary care setting but are typically referred to a cardiology clinic or have an acute onset such as myocardial infarction, which often leads to hospital admission. Such diseases are therefore unlikely to be cared for in a primary care setting leading to a low measure of missing data in the registers.

3.1.2 Cause of Death Register

The CDR collects information on the cause of death of all Swedish citizens on a national basis as well as information of causes of death abroad.[145] Data is included regardless of whether death occurred in a hospital, nursing home, or at home. Reporting to the CDR is mandatory and data are collected at the time of death from the reporting physician. Diagnoses are based upon ICD codes, and the register includes data since 1961.

3.1.3 Multi-Generation Register

The Multi-Generation Register (MGR) includes data on familial relations, specifically data on biological parents and siblings.[146] All Swedish inhabitants born after 1932 and registered in Sweden at any time since 1961 are included. The register does not include earlier data on parenthood as the Swedish personal identification number was introduced in 1947, and at introduction persons below 15 years of age had parenthood registered. Parenthood data have excellent coverage (100% of mothers and 96% of fathers are registered). Sibling data is based upon parenthood data. The register is updated each year.

3.1.4 Pharmaceuticals Register

The SPR contains information on all collected prescriptions in Sweden. It has been in use since 2005 and is updated monthly. Data on the amount prescribed, date of prescription and date of collection is included in the registry. The data collected are linked to the Swedish personal identification numbers. Record keeping is reimbursement-driven and provides high quality information for prescribed drugs.[147]

3.1.5. Danish registers

Study IV included data from Danish registries as well. The Danish registries, similarly to the Swedish, link data on individual level to the Danish personal identifications number and reimbursement to the departments are based on diagnosis codes. Diagnosis codes are based upon the ICD classification. The Danish NPR has had nationwide coverage since 1978 and the data collected are based on a physician's diagnosis. The positive predictive values for cardiovascular diagnoses are high.[141,143,148] The Danish CDR computerized individual records 1970. It is mandatory for physicians to complete a death certificate, including

cause of death, for all cases of death in Denmark.[149] The Danish Registry of Medicinal Product Statistics (DRMPS) have been in use since 1994 and contains information on dispensed prescriptions, which are linked on an individual level.[150]

3.2 Prospective cohort study

In study II, risk factors for AS were explored in a prospective, population-based cohort study, the Malmö Diet and Cancer Study. Both traditional cardiovascular risk factors and ultrasound measures of carotid atherosclerosis were tested for association with incident AS.

3.2.1 Malmö Diet and Cancer Study

Between January 1st 1991 and September 25th 1996, subjects living in the municipality of Malmö, Sweden, were recruited to participate in the Malmö Diet and Cancer Study (MDCS). MDCS was initiated to study the association of dietary factors with cancer and cardiovascular disease. All inhabitants in the city of Malmö born between 1923-1945 for men and 1923-1950 for women were invited to participate at a baseline examination. At the time, the city of Malmö had 230.000 inhabitants, of which most were of Swedish ancestry (80.3%). The remaining 19.7% were immigrants, primarily from northern or central Europe, or had two parents born in other countries.[151-152] In total, 30,447 subjects were included, corresponding to a participation rate of 41% (Table 3.1 illustrate the selection process for Study II).

At baseline, participants underwent an examination including anthropometric measurements, blood pressure measurement, blood sampling, and filled out a questionnaire including information on dietary habits and medical history. Anthropometric measurements included height, weight and body-mass index. In 1991-1994, a random selection of participants (n=6103) were invited to a cardiovascular cohort with comprehensive testing including carotid ultrasound with measurement of intima-media thickness (IMT) and detection of plaque.[153] After the baseline examination, follow-up data on incident disease were collected from national registers, including the NPR and the CDR.

3.2.2 Measurements of intima-media thickness

Participants in the cardiovascular cohort underwent B-mode ultrasound measurements of the right carotid artery to assess the IMT and plaque in the

common carotid artery and the bulb. IMT was measured in the far wall of the common carotid artery in a longitudinal projection, defined as a mean thickness of a 10 mm segment proximal to the bifurcation according to the leading edge principle. All measurements were made by trained, certified sonographers using an Acuson 128 Computed Sonography System with a 7-Mhz transducer. Analysis of inter- and intraobserver variability was carried out and indicated a low variability and high accuracy of the measurements. Presence of plaque was defined as a focal thickening of the intima-media complex >1.2 mm with an area of ≥10 mm^2. Details on the measurement protocol have been described in previous studies.[154-155]

3.2.3 Anthropometric measurements, questionnaire and blood samples

Height and weight was collected at the baseline visits and used to calculate the body mass index (BMI). All participants completed a questionnaire that included questions on current medication, medical history, smoking habits, dietary assessment, physical activity and socioeconomic status. Hypertension was defined as either self-reported use of hypertensive medication or a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥ 90 mmHg. Patients reporting active smoking within the last year were considered current smokers. Presence of diabetes mellitus was based on fasting blood glucose ≥6.1 mmol/L, a self-reported diagnosis of diabetes mellitus or use of anti-diabetic medications.

The differential and total leukocyte count was measured using a SYSMEX K1000 (Sysmex Europe, Germany) automatic counter using fresh, heparinized blood. Highly-sensitive C-reactive protein (CRP) was analyzed in frozen plasma sampled at the baseline examination using Tina-quant® CRP latex high sensitivity assay (Roche Diagnostic Basel, Switzerland) on an ADVIA® 1650 Chemistry System (Bayer Healtcare, NY, USA). Standard procedures at the Department of Clinical Chemistry, Malmö University Hospital were used to measure fasting levels of total cholesterol, triglycerides and high-density lipoprotein cholesterol. Friedewald's formula was used to calculate LDL-cholesterol.[156]

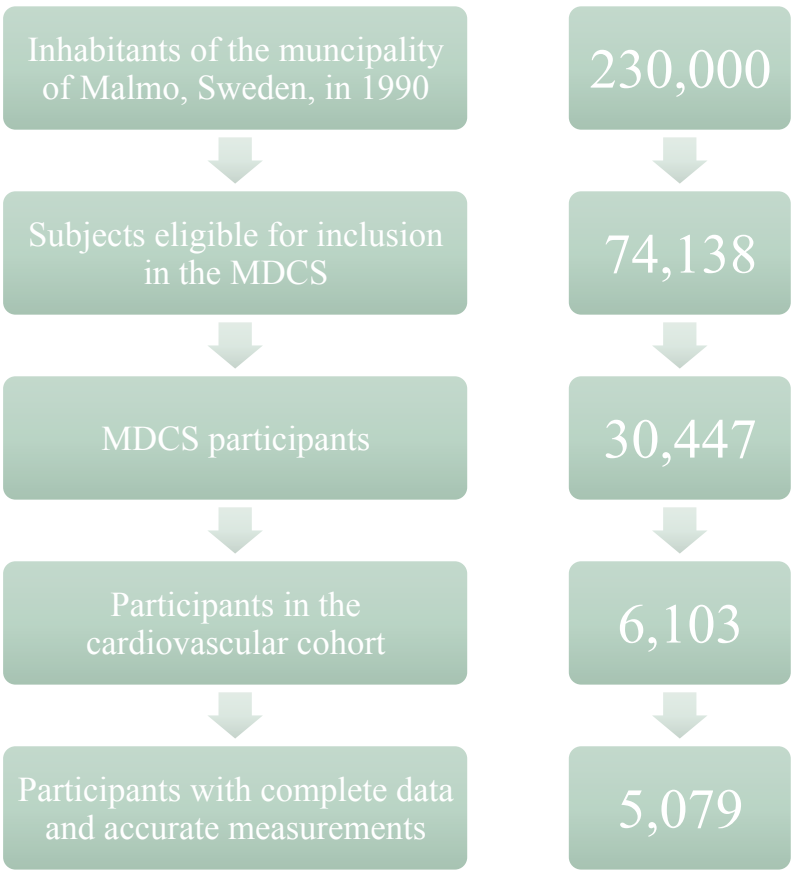

Table 3.1. Flow chart of subjects from the Malmö Diet and Cancer Study (MDCS) included in Study II.

3.3 Diagnostic definitions

In the thesis and the included papers, diagnoses of valvular aortic stenosis and comorbid conditions have been based upon the ICD codes of the World Health Organization (WHO). The 9th version of ICD was used between 1987 and 1996 and the 10th version from 1997 and onwards. Surgical and endovascular procedures are based upon the Swedish adaption of the classification of surgical procedures from the Nordic Medico-Statistical Committee (NOMESCO); the Op6 classification between 1963 and 1997 and the KKÅ classification since then.[157]

3.3.1 Definition of aortic valvular stenosis and valvular procedures

AS was defined as a diagnosis code of I35.0 (ICD-10) or 424B (ICD-9). High diagnostic validity of AS in Swedish registers (>90%) has previously been reported. The diagnosis is principally based upon echocardiographic data and cases generally represent moderate to severe AS.[43]

AVR was defined as the combination of a diagnosis code for AS and procedure code 3074, 3075, 3116, 3117 or 3078 (Op6) alternatively FMA or FMD in KKÅ. Surgical AVR was defined as FMD00, FMD10, FMD20, FMD30, FMD33, FMD40 or FMD96 (KKÅ). TAVR was defined as FMD12 or FMD13. Other surgical procedures for AS (including valve dilation and valvuloplasty) were defined as FMA00, FMA10, FMA20, FMA32 or FMA96 (KKÅ).

3.3.2 Comorbid conditions

Diagnoses codes 390-459 (ICD-9) or any I code (ICD-10) as cause of death in the CDR was considered as cardiovascular mortality. MI was defined as ICD-9 code 410 or ICD-10 code I21. MI was defined according to international consensus criteria.[122-123] HF was defined as diagnosis codes 428 in ICD-9 and I50.0, I50.1, I50.9 or I11.0 in ICD-10. High positive predictive value for a diagnosis of HF has previously been reported (95% for primary diagnoses)[158]. A diagnosis of MI has excellent validity (98-100%) in Swedish registers.[140]

For further details on the diagnosis codes used for comorbidities in individual studies please refer to the corresponding paper included in the thesis.

3.4 Statistical analyses

Descriptive data on continuous variables are reported as mean and standard deviation if normally distributed, and as median and interquartile range in the presence of a non-normal distribution. Normality assumptions were confirmed by visual inspection of histograms. Categorical values are presented as numbers and percentage of the population. In Study II, IMT, CRP and triglycerides were log-transformed due to a right-skewed distribution. Multivariable Cox proportional hazards regression analyses were used to calculate hazard ratios (HR).

The population attributable risk proportion (PAR) was calculated according to $PAR = P_c(RR_c - 1) / [1 + P_c(RR_c - 1)]$ where P_c is the prevalence of the exposure (sibling history) and RR_c is the relative risk of the exposure.[159]

3.4.1 Study I

In Study I, all patients with a first primary diagnosis of AS were included to study temporal trends. Patients diagnosed before January 1st 1989 were excluded as the registers were incomplete before this time. Patients were separated into 7 three-year time periods to study trends across time periods. Incidence and mortality rates with 95% confidence intervals were calculated under the assumption of a Poisson distribution. Age stratification was performed with weights according to the European Standard Population.[160] Cox proportional hazard regression models were used to calculate age- and sex-adjusted HRs for 1- and 3-year all-cause mortality. The first time period (1989-1991) were used as reference for all analyses. Procedural mortality was evaluated across time-periods as 30-day mortality after AVR. Cardiovascular mortality was explored in a separate Cox proportional hazards regression model.

Patients diagnosed from both hospital discharge registers or from an outpatient clinic between 2001-2009 were analyzed separately in a sensitivity analysis, as data on outpatient clinic visits were incomplete before 2001. To evaluate if the trends were consistent for different age groups, a stratified analysis of patients <75 and >75 years of age was performed. A sensitivity analysis also explored all-cause mortality in subjects who did undergo surgery.

3.4.2 Study II

In Study II, risk factors decided upon a priori including known risk factors for AS were included in Cox proportional hazard regression models in two stages. Risk factors evaluated were: BMI, CRP, LDL-C, HDL-C, triglycerides, hypertension, smoking, height, leukocytes, diabetes mellitus, IMT and presence of plaque in the common carotid artery. All statistically significant risk factors from age- and sex adjusted analyses were included in a final model to determine independent risk factors. Ultrasound measurements including IMT and presence of plaque was explored both separately and in a combined model. To examine the difference in incident AS across quartiles of IMT Kaplan-Meier curves were constructed and evaluated. Four different measures of blood pressure were explored separately, hypertension (defined as either self-reported use of hypertensive medication or a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥ 90 mmHg) or in a model with hypertensive treatment as a separate variable with either systolic blood pressure, mean arterial blood pressure or pulse pressure as a continuous variable.

3.4.3 Study III

In Study III, sibling history was explored as risk factor for AS in nation-wide registers. All Swedish siblings born after 1932 were identified from the MGR and included if at least one sibling was alive in 1997. Subjects with a hospital discharge diagnosis of AS as primary or contributing diagnosis were identified from the NPR. Cox proportional hazards regression model were used to calculate HRs with 95% CI for individuals with a sibling history of AS. Three different models were used with stepwise increasing adjustments. The first model adjusted for age and sex. The second model added family size and the final model included comorbidities (atrial fibrillation, hypertension, chronic obstructive pulmonary disease [COPD], obesity and diabetes mellitus) as well as age, sex and family size. As each family with a sibling history provides multiple cases, resulting in dependence of cases, variance was adjusted by the number of afflicted families (1/[N-M]) where N is the total of AS cases and M is the number of ascertained families.[161] Individuals with two or more siblings with AS were explored in a separate model. In an attempt to study the contribution of environmental factors to observed risk estimates, analysis of spousal history was also conduced. In spousal analyses, spouses were defined as persons living at the same address with either common children, a registered partnership or in marriage. In sensitivity analysis cases of congenital AS were excluded. Simple segregation analysis to evaluate inheritance models of AS was performed with the Li-Mantel method.[162-164]

3.4.4 Study IV

In Study IV, patients with a discharge diagnosis of MI were identified from both Swedish nationwide registers (between 2005-2010) and Danish nationwide registers (2005 until 2012) and only patients who received a prescription of DAPT were included. Patients were followed for 1 year, in agreement with current guidelines, which recommend DAPT therapy for up to 1 year after MI.[122-123] As the study period was before the widespread implementation of ticagrelor in clinical practice, DAPT typically consisted of the combination of clopidogrel and acetylsalicylic acid. To further ensure comparability, only patients with clopidogrel and acetylsalicylic acid were included. Additional warfarin therapy, referred to as triple antithrombotic therapy, was explored separately. Treatment was analyzed according to the intention to treat principle and thus treatment interruptions were not considered.

Outcomes considered were bleeding, recurrent MI and all-cause mortality. Cox proportional hazards regression analysis adjusted for potential confounders was used to calculate HRs. Confounders included age, sex, calendar year, percutaneous intervention and CABG performed within 30 days after index event, treatment

with nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, beta blockers, statins, calcium blockers, thiazides, loop diuretics, spironolactone and/or insulin, previous diagnosis of ischemic heart disease, cerebrovascular disease, peripheral artery disease, liver disease, chronic kidney disease, peptic ulcer disease, COPD, rheumatic disease, atrial fibrillation, cancer, bleeding and HF. Observational time started 30 days after discharge to allow subjects to claim DAPT prescription and undergo delayed revascularization therapy. The Swedish and Danish NPR and CDR were used to identify cases and ascertain outcomes. Data on pharmacotherapy were extracted from the SPR and the DRMPS.

In study IV, as data access restrictions made us unable to combine data on an individual-level, a meta-analysis was conducted. A random-effects model utilizing the R package "metafor" was used to combine the adjusted results for both countries.[165]

A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (version 20.0 IBM Corp., Armonk, NY, USA) SAS, versions 9.2, 9.3 and 9.4 (SAS Institute, Cary, NC, USA) and R, version 3.3.2.

Ethical approval from an independent ethics committee was obtained for all studies.

Chapter IV. Results

4.1 Temporal incidence trends for aortic valvular stenosis

In Study I the temporal trends of incidence and mortality associated with AS over two decades, between 1989-2009, were studied.

The crude incidence rate of AS in Sweden remained stable for both men (23.4 per 100.000 in 1989-1991 versus 22.9 per 100.000 in 2007-2009) and women (20.7 per 100.000 in 1989-1991; 18.7 per 100.000 in 2007-2009), as shown in Table 4.1. The total number of incident AS cases increased between 1989-1991 and 2007-2009, from 4,694 to 5,963. Median age of diagnosis increased by 4 years for both sexes.

The age-adjusted incidence declined from 15.0 to 11.4 in men and from 9.8 to 7.1 in women. Similar developments were noticed for both HF and MI during the study period.

In an age-stratified sensitivity analysis patients <75 and >75 years of age were evaluated separately. In both the younger and older patient cohort declining age-adjusted incidence rate were observed. Patients diagnosed <75 years of age were more frequently of male gender (>60% in all time periods) while a female predominance was observed in the older patient cohort (53.4% in 2007-2009).

The proportion of patients who underwent AVR did not appear to change during the study period. There was, however, a trend towards increased utilization of AVR in the later time periods. In the age-stratified analysis the proportion of patients above >75 years of age undergoing intervention increased from 27.6% to 36.3%.

In additional sensitivity analysis data from both hospital discharge and outpatient clinic diagnoses were included between 2001 and 2009. 51.5% of patients were first diagnosed in an outpatient setting. Median age at diagnosis increased from 70 to 75 for men and 72 to 76 years of age for women. A trend towards declining incidence and mortality was observed but not statistically significant in the analyses.

	1989-1991	1992-1994	1995-1997	1998-2000	2001-2003	2004-2006	2007-2009
AS cases (n)	4,694	5,583	4,940	4,893	4,702	5,038	5,963
AS cases, sex distribution (%)							
Men	52.2	52.2	52.7	50.0	52.1	54.1	54.7
Women	47.8	47.8	47.3	50.0	47.9	45.9	45.3
Age at AS diagnosis (years, median)							
Men	70	71	72	73	73	74	74
Women	75	76	77	78	78	79	79
Crude incidence rate (per 100.000)							
Men	23.4	26.3	22.3	20.0	19.1	20.2	22.9
	(22.5-24.4)	(25.4-27.3)	(21.5-23.2)	(19.2-20.8)	(18.4-19.9)	(19.5-21.0)	(22.1-23.7)
Women	20.7	23.4	19.5	19.5	17.2	16.8	18.7
	(19.8-21.5)	(22.5-24.2)	(18.7-20.2)	(18.7-20.3)	(16.5-17.9)	(16.2-17.5)	(18.0-19.4)
Age-adjusted incidence rate							
Men	15.0	15.7	12.6	10.7	9.9	10.3	11.4
	(14.4-15.6)	(15.2-16.3)	(12.1-13.1)	(10.3-11.1)	(9.5-10.3)	(9.9-10.7)	(11.0-11.8)
Women	9.8	10.5	8.1	7.5	6.6	6.4	7.1
	(9.4-10.2)	(10.1-10.9)	(7.7-8.4)	(7.2-7.8)	(6.3-6.9)	(6.2-6.7)	(6.8-7.4)
Valve replacement (%)							
1 year	8.7	7.4	5.8	6.5	5.5	6.6	4.3
3 years	40.1	40.9	37.4	37.3	38.0	39.9	42.5
Total follow-up	41.3	42.0	38.2	38.0	38.9	40.1	42.5
Procedure type (n, %)							
Surgery	1920 (99.1)	2330 (99.3)	1874 (99.3)	1859 (99.9)	1827 (99.9)	2012 (99.6)	2424 (95.7)
TAVR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.1)	30 (1.2)
Other	25 (1.3)	23 (1.0)	15 (0.8)	1 (0.1)	2 (0.1)	7 (0.3)	79 (3.1)

Table 4.1. Incidence rates for AS in the Swedish population in three-year time periods between 1989 and 2009.

4.2 Mortality trends in aortic valvular stenosis

Crude 1- and 3-year mortality rates declined for AS in both men and women, presented in Table 4.2, consistent with mortality trends observed for HF and MI. Age-adjusted mortality rates showed similar improvement with 1-year mortality declining from 5.8 (95% CI 5.3-6.3) to 4.0 (95% CI 3.6-4.3) in men and 5.4 (95% CI 4.9-5.8) to 4.1 (95% CI 3.7-4.4) in women between 1989-1991 and 2007-2009. 3-year mortality improved from 9.3 to 4.8 in men and 8.3 to 4.8 in women.

Modeling relative risk of all-cause mortality across time periods with Cox proportional hazards regression yielded similar results with improved prognosis for AS, as illustrated in Figure 4.1. Relative risk estimates were 0.58 for 1-year mortality and 0.60 for 3-year mortality, and were similar to estimates for MI as shown in Figure 4.1 and more marked than for heart failure. Similar trends were observed for cardiovascular mortality in patients with AS (HR: 0.50, 95% CI 0.46-0.55 and HR 0.55, 95% CI 0.50-0.60, for 1- and 3-year mortality respectively). Procedural mortality defined as within 30 days after AVR declined as well with relative risk estimates of 0.64 in 2007-2009 compared to the reference period 1989-1991. Prognostic improvements for patients not undergoing surgery were also observed for both 1- and 3-year mortality (HR: 0.61, 95% CI 0.55-0.67 and HR: 0.62, 95% CI 0.57-0.67, respectively).

	1989-1991	1992-1994	1995-1997	1998-2000	2001-2003	2004-2006	2007-2009
Crude mortality rate (1- year)							
AS (Men)	21.9	18.3	18.4	17.9	15.8	16.1	16.9
AS (Women)	23.5	21.1	22.0	22.0	21.0	20.3	20.4
Crude mortality rate (3- year)							
AS (Men)	31.2	27.6	28.9	27.9	25.5	26.0	21.6
AS (Women)	35.9	32.2	33.7	33.4	33.1	32.0	26.2
Age-adjusted mortality rate (1- year)							
AS (Men)	5.8	5.5	4.1	3.0	2.8	4.1	4.0
AS (Women)	5.4	4.3	4.2	4.1	2.5	2.9	4.1
Age- adjusted mortality rate (3- year)							
AS (Men)	9.3	7.8	7.8	5.0	4.7	6.2	4.8
AS (Women)	8.3	6.3	7.5	6.4	5.8	4.3	4.8

Table 4.2. Sex-specific 1- and 3-year mortality rates for AS.

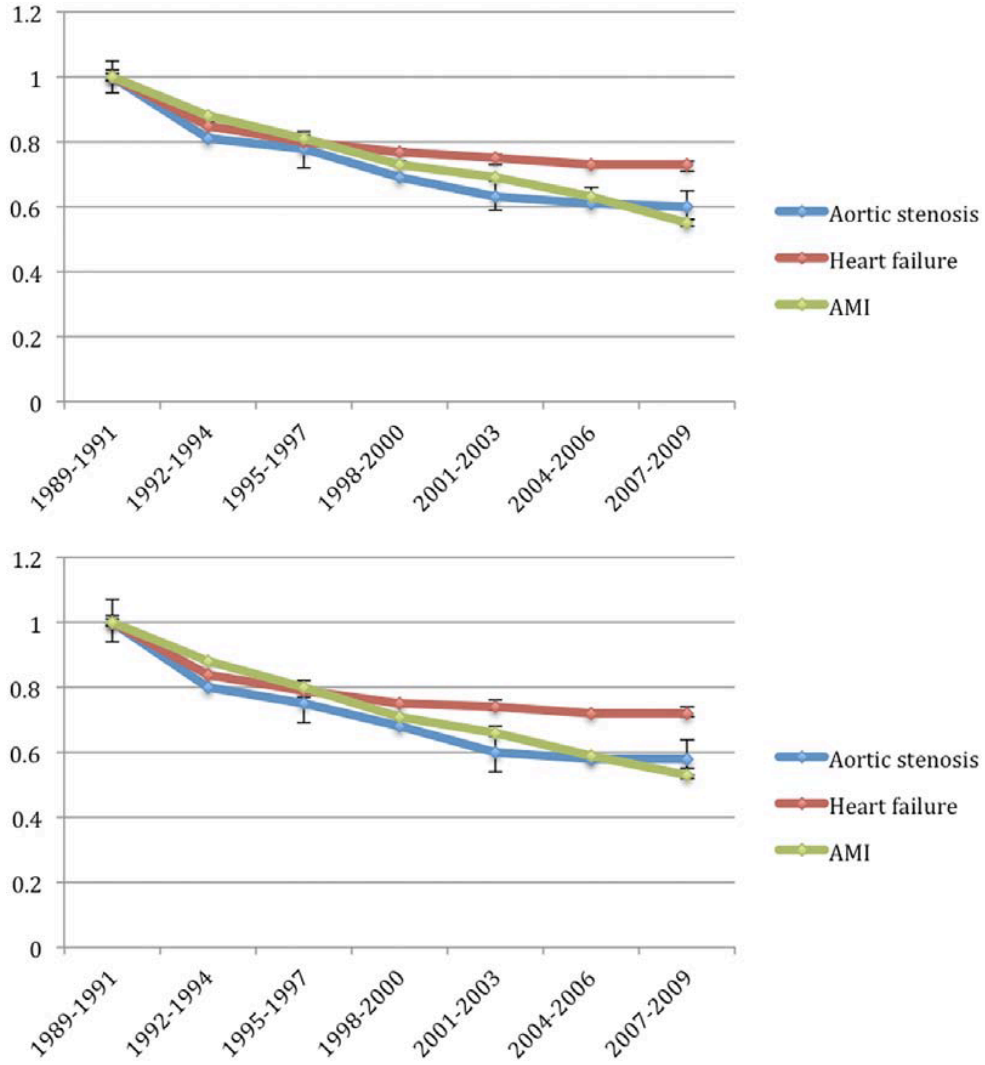

Figure 4.1. Temporal trends in mortality for patients with a first diagnosis of aortic stenosis, heart failure, and MI. Mortality at 1 year (bottom) and 3 years (top) is illustrated. Point estimates at each time period are HRs for mortality (y axis) with corresponding 95% confidence intervals from Cox proportional hazard regression models, adjusted for age and sex.

4.3 Carotid plaque, intima-media thickness and other risk factors for incident AS

Study II focused on the association of incident AS with atherosclerotic risk factors and atherosclerotic manifestations in the common carotid artery (plaque and IMT) in a prospective cohort study - the MDCS.

From a total cohort of 5,079 subjects, 69 (1.4%) participants developed AS during follow-up (mean follow-up time 16.5 years). Baseline characteristics across quartiles of IMT are presented in Table 4.3. Traditional cardiovascular risk factors such as LDL, hypertension and BMI were more common in subjects with an increased IMT.

Kaplan-Meier curves for incident AS stratified into quartiles of IMT and presence of plaque are shown in Figure 4.2. A markedly higher incidence of AS was observed in the highest quartile of IMT as well as for presence of plaque compared to no carotid plaque.

Both increased IMT (HR: 1.46 per 1-standard deviation [SD] increment, 95% CI 1.16-1.85) and presence of common carotid plaque (HR: 2.42, 95% CI 1.48-3.93) were associated with an increased risk of incident AS in age- and sex-adjusted models and were consequently included in the fully adjusted model.

In the fully adjusted model, increased IMT was associated with an increased risk of incident aortic stenosis (HR: 1.28 [per 1-SD increment], 95% CI 1.01-1.62). Presence of common carotid plaque also conferred increased risk of incident aortic stenosis (HR 2.08, 95% CI 1.27-3.42). When IMT and presence of common carotid plaque was combined into the same model, only presence of plaque remained significant (Table 4.4).

The risk for future AVR, a more rare outcome indicating severe disease, was evaluated in an age- and sex adjusted Cox regression model. In this model presence of plaque increased the risk for future AVR, (HR: 2.83, 95% CI 1.49-5.37) but IMT did not (HR 1.23, 95% CI 0.90-1.68). In the fully adjusted model, presence of plaque remained significantly associated with future AVR (HR: 2.47, 95% CI 1.29-4.74).

IMT	Q1	Q2	Q3	Q4
IMT-range				
Women	0.33-0.63	0.64-0.70	0.71-0.79	0.80-1.82
Men	0.33-0.64	0.65-0.74	0.75-0.85	0.86-2.03
N (women/men)	804/523	733/557	752/515	699/496
Age (years)	54.9 (±5.7)	56.8 (±5.8)	58.7 (±5.6)	60.2 (±5.3)
BMI (kg/m2)	25.17 (±3.79)	25.54 (±3.86)	25.70 (±3.86)	26.23 (±3.96)
LDL-C (mmol/L)	4.04 (±1.00)	4.06 (±0.93)	4.19 (±0.98)	4.41 (±1.00)
HDL-C (mmol/L)	1.41 (±0.38)	1.41 (±0.37)	1.39 (±0.37)	1.34 (±0.36)
Triglycerides (mmol/L)	1.12 (IQ: 0.69)	1.11 (IQ: 0.71)	1.15 (IQ: 0.75)	1.21 (IQ: 0.73)
CRP (mg/L)	0.12 (IQ: 0.18)	0.13 (IQ: 0.21)	0.14 (IQ: 0.24)	0.15 (IQ: 0.23)
Leukocytes (10^9 cells/L)	6.10 (±2.55)	5.98 (±1.55)	6.07 (±1.60)	6.20 (±1.67)
Hypertension, N (%)	678 (51.1)	795 (61.6)	833 (65.7)	913 (76.4)
Smoking, N (%)	376 (28.3)	361 (28.0)	338 (26.7)	347 (29.0)
Diabetes, N (%)	29 (2.2)	43 (3.3)	46 (3.6)	74 (6.2)

Table 4.3. Baseline characteristics across sex-specific quartiles of IMT. Standard deviation for continuous variables and percentage of the population for categorical variables are parenthesized. CRP and triglycerides were not normally distributed and are presented as median and interquartile range.

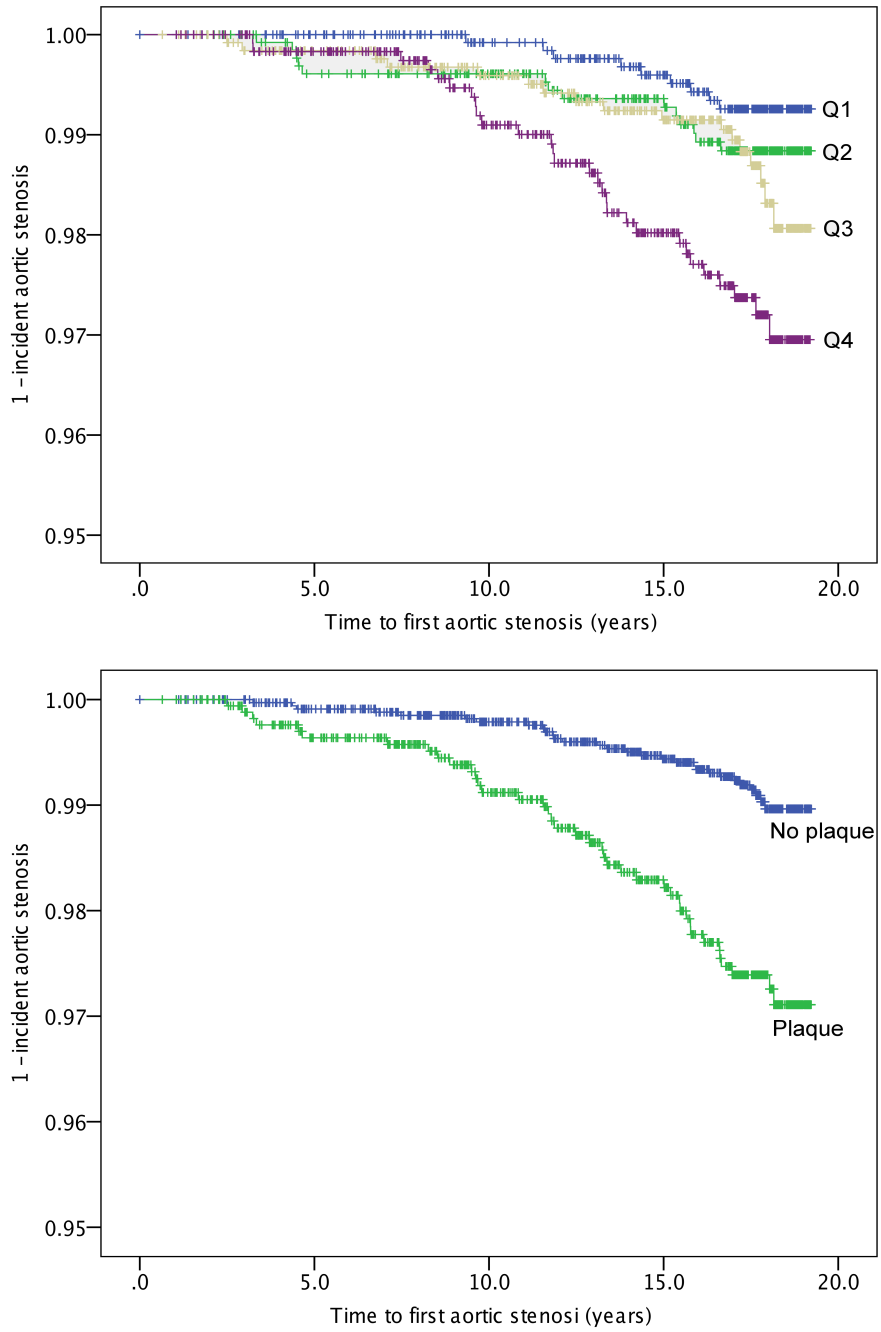

Figure 4.2. Kaplan-Meier curves illustrating risk for incident aortic stenosis across sex-specific quartiles of IMT (top) and presence of plaque (bottom).

4.4 Traditional cardiovascular risk factors and incident AS

In Study II, we also investigated the effect of traditional cardiovascular risk factors in addition to IMT and presence of plaque. Risk factors determined a priori were analyzed in age- and sex-adjusted Cox models and, if they were significantly associated with incident AS, included in the final, fully adjusted model.

In the age- and sex-adjusted model age, BMI, LDL-C, CRP, hypertension, smoking and diabetes were significantly associated with incident AS, in addition to presence of plaque and IMT. HDL, triglycerides, height and leukocytes were however not associated with incident AS.

In the fully adjusted model age, BMI, diabetes mellitus, smoking and CRP remained significant, as shown in Table 4.4 (results presented are from the combined model with both IMT and presence of plaque). Particularly strong associations were observed with age, diabetes, smoking, and common carotid plaque. Alternative measures of blood pressure were explored in additional, separate multivariate analyses. In these analyses similar risk estimates were observed for IMT and presence of plaque as in the main analysis but only presence of plaque remained statistically significant.

Combined model	HR	95% CI	p
Age (per 1-SD increment)	1.48	1.11 - 1.97	<0.01*
Female sex	0.84	0.52 - 1.37	0.50
BMI (per 1-SD increment)	1.28	1.02 - 1.60	0.03*
LDL-C (per 1-SD increment)	1.21	0.97 - 1.51	0.10
Hypertension	1.63	0.85 - 3.14	0.14
IMT (per 1-SD increment)	1.20	0.95 – 1.52	0.13
Plaque	1.95	1.17 - 3.22	0.01*
Diabetes	2.71	1.27 - 5.76	0.01*
Smoking	1.96	1.18 - 3.26	0.01*
CRP (per 1-SD increment)	1.34	1.04 - 1.72	0.03*

Table 4.4. Hazard ratios (HR) with 95% confidence intervals (CI) from multivariate Cox proportional hazards regression models, incorporating statistically significant covariates from age- and sex-adjusted analyses. SD, standard deviation of log IMT.

4.5 AS incidence rates across the lifetime of Swedish siblings

In Study III contemporary information about 6,117,263 Swedish siblings were collected from the MGR. A total of 13,442 of these siblings had a clinical diagnosis of AS in the NPR. Reflecting the prevalence of AS, a sibling history was uncommon in the general population (0.5%). However, in patients diagnosed with AS, it was tenfold more common than in the general population (4.8%). Incidence rates were low during the first ten years of life, and declined further with very few cases identified in the 2nd to 4th decade of life, as shown in Table 4.5. After the 5th decade of life, incidence increased with age. Atrial fibrillation, diabetes mellitus and hypertension were common in patients with AS (20.2%, 15.8% and 38.6%, respectively). Other comorbidities were also more frequent in subjects with AS compared to controls. The predominant type of AS according to diagnosis codes was calcific, isolated AS (n=7,620), followed by mixed stenosis and regurgitation (n=1,836), and congenital AS (n=1,166). Rheumatic AS was rare (n=144).

	Population		AS cases	
	No.	%	No.	%
Population	6,117,263			
Subtype of events			13,442	
AS (I35.0)			7,620	56.7
AS with AR (I35.2)			1,836	13.7
Rheumatic AS (I06.0)			76	0.6
Rheumatic AS with AR			68	0.5
Congenital AS (Q23.0)			1,166	8.7
Gender				
Men	3,131,437	51.2	9,030	67.2
Women	2,985,826	48.8	4,412	32.8
Age at diagnosis (years)				
<20			1,335	9.9
20-29			324	2.4
30-39			455	3.4
40-49			965	7.2
50-59			2,747	20.4
60-69			5,195	38.6
70 +			2,421	18.0
COPD				
No	5,862,536	95.8	12,191	90.7
Yes	254,727	4.2	1,251	9.3
Diabetes				
No	5,974,903	97.7	11,313	84.2
Yes	142,360	2.3	2129	15.8
Obesity				
No	6,056,355	99.0	13136	97.7
Yes	60,908	1.0	306	2.3
Hypertension				
No	5,849,636	95.6	8,257	61.4
Yes	267,627	4.4	5,185	38.6
Atrial fibrillation				
No	6,036,879	98.7	10,732	79.8
Yes	80,384	1.3	2,710	20.2
Sibling history of AS				
Without sibling history	6,088,680	99.5	12,792	95.2
With sibling history	28,583	0.5	650	4.8

Table 4.5. Baseline characteristics of subjects included in Study III

4.6 Relative risk estimates for siblings

In an age- and sex-adjusted model the risk for AS was increased by a fourfold in subjects with a sibling history of AS, as shown in Table 4.6. A moderate attenuation of the risk estimate was observed in the fully adjusted model accounting also for family size and common comorbidities (HR: 3.58. 95% CI=2.34-5.49). Additional exclusion of cases with congenital AS did not significantly alter the results (HR 3.58, 95% CI=2.33-5.49).

The population attributable risk proportion was low, estimated to 3.5%. Simple segregation analysis of families with at least one affected sibling revealed a segregation ratio of 0.023, consistent with a polygenic inheritance model.

		Model 1		Model 2	
	N	HR	95% CI	HR	95% CI
Sibling history of AS	650	4.18	2.73-6.39	3.58	2.34-5.49
Male gender		2.04	1.39-2.98	1.77	1.21-2.60
Birth year		0.94	0.66-1.33	0.96	0.67-1.35
Family size				1.02	0.71-1.46
Medical history					
COPD				1.90	1.26-2.85
Diabetes				1.80	1.21-2.68
Obesity				1.06	0.67-1.68
Hypertension				3.44	2.33-5.06
Atrial fibrillation				3.59	2.42-5.32

Table 4.6 Model 1: adjusted for gender and birth year. Model 2: adjusted for gender, birth year and family size. Model 2: full model (adjusted for gender, birth year, family size and comorbidities). AS: Aortic stenosis. COPD: Chronic obstructive pulmonary disease. N: Number of AS cases.

4.7 Individuals with multiple siblings with AS and spousal risk of AS

The subset of individuals who had more than one sibling with AS were also analyzed separately and were found to have a exceptionally high risk of AS (HR: 39.37, 95% CI=19.80-78.27) but were rare (n=34).

As the risk estimates observed with a sibling history of AS could be due to shared environmental risk factors a spousal analysis was conducted to evaluate the influence of shared adult environment. The fully adjusted model for the spousal analysis is shown in Table 4.7. A spousal history was associated with an increased risk of AS, but the effect was modest (HR: 1.16, 95% CI=1.05-1.28 for AS in a husband and HR: 1.18, 95% CI=1.07-1.30 for AS in a wife).

	N	HR	95% CI
Spouse history	407		
Wives		1.18	1.07-1.30
Husbands		1.16	1.05-1.28

Table 4.7. Subsequent risk of aortic stenosis for spouses of incident cases. N: Number of aortic stenosis cases. HR: Hazard ratio. CI: Confidence interval.

4.8 Outcomes in patients with aortic stenosis on dual antiplatelet therapy after myocardial infarction

In study IV outcomes for patients with AS after myocardial infarction were examined. Only patients treated according to contemporary guidelines with DAPT were included. The study population included both Swedish and Danish citizens hospitalized with a myocardial infarction; between 2005 to 2010 in Sweden (n = 50,460, 36% women, mean age 70±12 years) and 2005 to 2012 in Denmark (n = 30,646, 34% women, mean age 69±13 years). Patient characteristics are shown in Table 4.8. Endpoints investigated were bleeding, recurrent myocardial infarction and all-cause mortality. Concurrent AS was present in 3% of MI cases in both Sweden (n=1,287) and Denmark (n=948). 106 (8%) subjects in Sweden and 72 (8%) subjects in Denmark were censored due to valve replacement therapy. Revascularization therapy within 30 days was performed in 60% and 46% of the patients without AS in Sweden and Denmark respectively. Patients with AS were less frequently treated with revascularization therapy (28% in Sweden and 22% in Denmark).

	Denmark		**Sweden**	
	No Aortic Stenosis	**Aortic stenosis**	**No Aortic Stenosis**	**Aortic stenosis**
N	29698 (97%)	948 (3%)	49173 (97%)	1287 (3%)
Age	68 (13)	72 (13)	70 (12)	76 (11)
Male sex	66%	59%	64%	56%
Diabetes	13%	16%	15%	20%
Previous IHD	63%	69%	26%	39%
Congestive heart failure	19%	22%	16%	23%
Kidney disease	3%	3%	3%	4%
Prior bleeding	6%	7%	4%	6%
Atrial fibrillation	11%	11%	12%	16%
COPD	7%	8%	4%	5%
Cerebrovascular disease	7%	8%	7%	9%

Table 4.8. Patient characteristics of Danish and Swedish subjects included in Study IV.

4.8.1 Bleeding

As presented in Table 4.9, unadjusted bleeding rates were more common in subjects with AS (13.3 and 9.2 versus 3.2 and 5.8 per 100 person-years in Sweden and Denmark respectively). Warfarin therapy also increased bleeding rates, 5.6 and 6.8 per 100 person-years for patients without AS versus 7.1 and 13.5 for subjects with AS.

In adjusted Cox proportional hazard regression models an increased relative risk for bleeding was observed in both Sweden (HR: 2.04, 95% CI 1.61-2.59) and Denmark (HR: 1.92, 95% CI 1.53-2.42). In meta-analysis, based on the adjusted Cox-regression model, AS was associated with a twofold increased risk of bleeding (HR: 1.98, 95% CI 1.68-2.33, Figure 4.3). Warfarin therapy increased the risk of bleeding for patients without AS (HR: 1.27, 95% CI 1.03-1.57) but did not seem to further increase the risk of bleeding for subjects with AS (HR: 1.99, 95% CI 1.03-3.82).

Incidence rate (events / 100 PY)	**All-cause mortality**		**Recurrent MI**		**Bleeding**	
DAPT	7.1 (6.8-7.3)	10.1 (9.8-10.5)	8.7 (8.4-9.0)	13.1 (12.7-13.6)	3.2 (3.0-3.4)	5.8 (5.5-6.1)
DAPT + warfarin	7.8 (6.4-9.4)	12.3 (10.7-14.1)	10.1 (8.5-12.1)	15.1 (13.3-17.3)	5.6 (4.4-7.1)	6.8 (5.6-8.3)
DAPT, AS	28.7 (25.4-32.4)	49.9 (44.8-55.5)	29.5 (25.9-33.6)	28.1 (24.2-32.6)	9.2 (7.3-11.5)	13.3 (10.8-16.5)
DAPT + warfarin, AS	18.0 (9.0-36.1)	46.1 (30.1-70.8)	19.6 (9.8-39.3)	20.6 (10.7-39.6)	7.1 (2.3-21.9)	13.5 (6.1-30.1)

Table 4.9. Incidence rates of bleeding, recurrent MI and all-cause mortality per 100 person-years.

4.8.2 Recurrent myocardial infarction

For subjects without AS, rates of recurrent MI per 100 person-years were 8.7 in Sweden and 13.1 in Denmark. Patients with AS had corresponding recurrent MI rates of 29.5 and 28.1 per 100 person-years (Table 4.9).

AS patient had higher risk estimates for recurrent MI in Sweden (HR: 2.13, 95% CI 1.85-2.44) and Denmark (HR: 1.86, 95% CI 1.59-2.19). The combined analysis including both Sweden and Denmark conveyed a similar picture; patients with AS were at a higher risk for recurrent MI (HR: 2.00, 95% CI 1.75-2.29). Addition of warfarin therapy did not increase the risk of recurrent MI in subjects without AS (HR: 1.10, 95% CI 0.98-1.24) or in subjects with AS (HR 1.37, 95% CI 0.85-2.20).

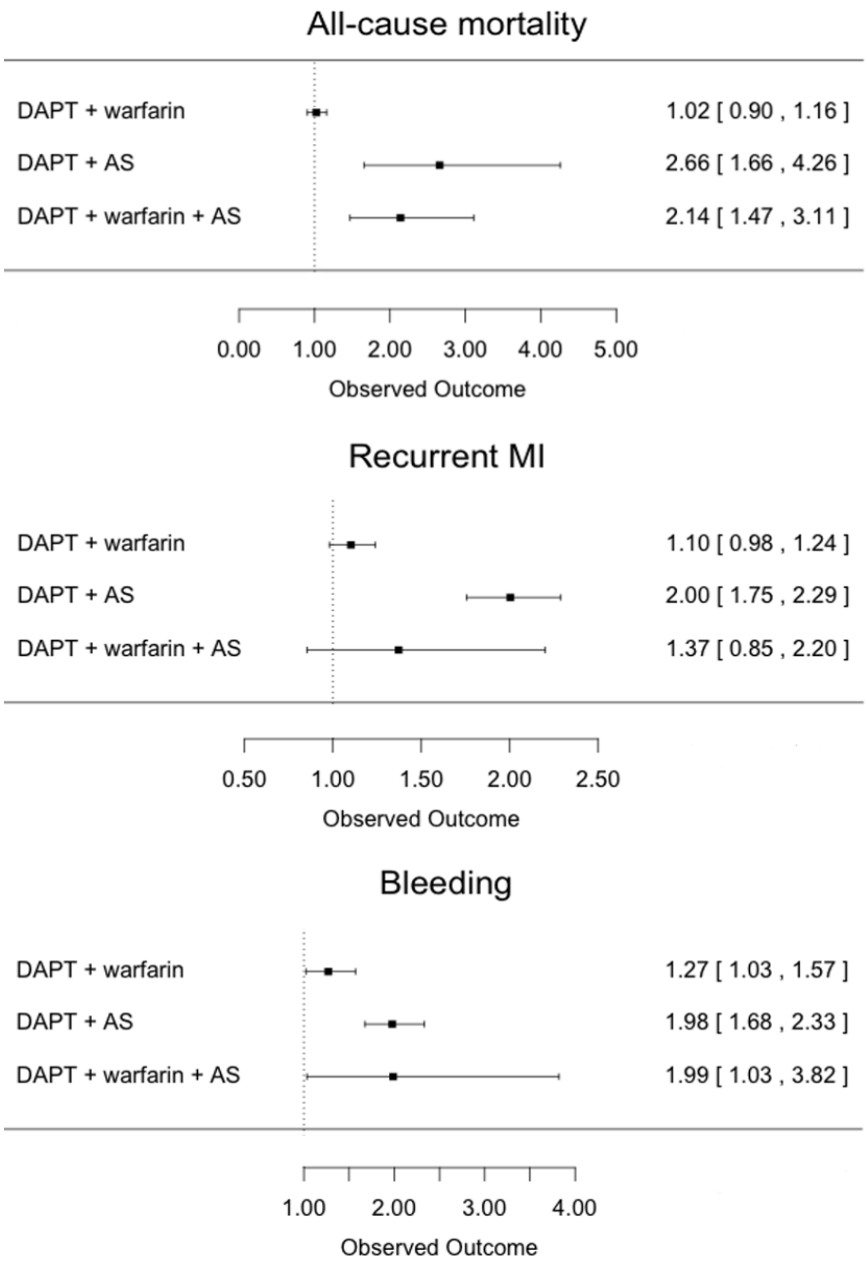

Figure 4.3. Forest plot illustrating outcomes in meta-analysis of Sweden and Denmark.

4.8.3 All-cause mortality

Kaplan-Meier estimates indicated a substantially higher mortality for patients with AS compared to patients without AS (Figure 4.4). All-cause mortality rates were 7.1 and 10.1 for subjects without AS versus 28.7 and 49.9 for patients with AS in Sweden and Denmark, respectively, per 100 person-years (Table 4.9). Patients with AS had a significantly higher risk of all-cause mortality compared to subjects without AS both in meta-analysis (HR 2.66, 95% CI 1.66-4.26) and in each country separately (HR: 2.09, 95% CI 1.85-2.35 for Sweden and HR: 3.38, 95% CI 3.00-3.81 for Denmark). Patients on warfarin therapy in addition to DAPT without AS did not have an increased risk for all-cause mortality However the combination of DAPT, warfarin and AS was associated with an increased risk (HR: 2.14, 95% CI 1.47-3.11) compared to controls without AS treated only with DAPT.

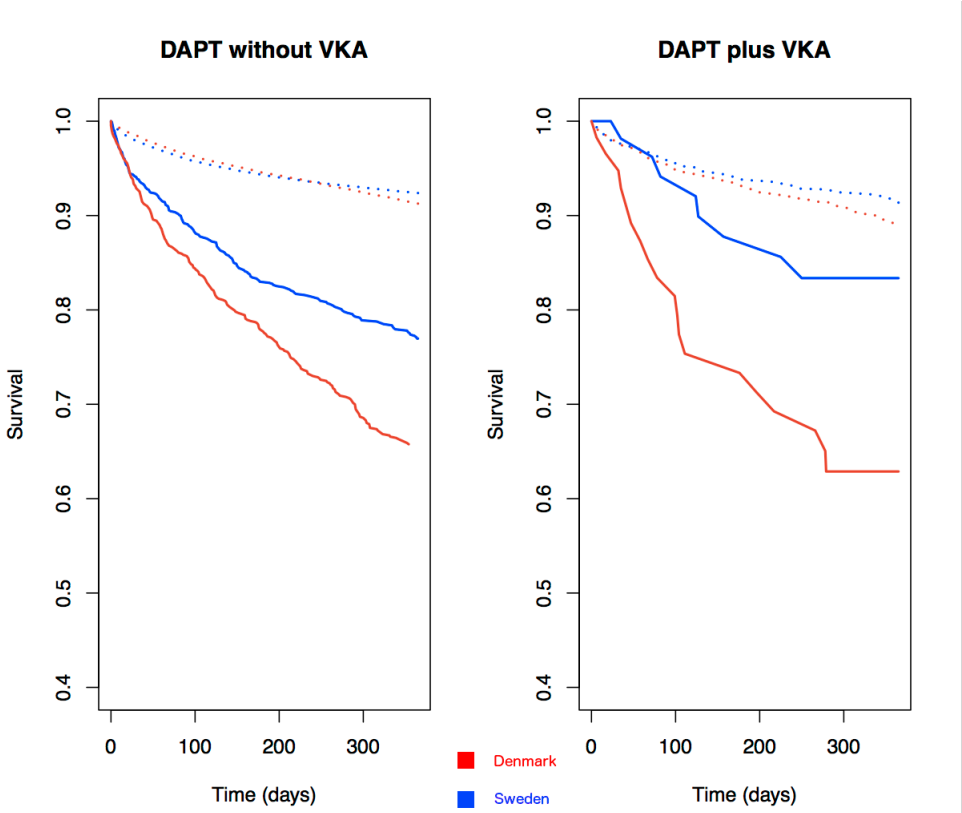

Figure 4.4. Kaplan-Meier curves illustrating all-cause mortality in patients with myocardial infarction with and without aortic stenosis. Dotted lines represent patients without AS, filled lines represents patients with AS.

Chapter V. Discussion

In this thesis, several epidemiological aspects of AS have been explored. First, a relatively stable incidence rate of AS was observed between 1989-2009, which was encouraging on the background of the aging population, and in addition improved mortality rates for the increasingly older AS patients were observed. Second, prevalent atherosclerotic vascular disease appears to strongly predict future AS and adds predictive information to the risk conferred by information on traditional cardiovascular risk factors. Third, a sibling history of AS greatly increased the risk for subsequent AS whereas spousal history was only a weak risk factor, indicating a genetic component to AS development. Fourth, the reported adverse outcomes with regard to both bleeding and thrombosis in AS patients suffering from MI and treated with DAPT highlight the importance of individualized therapeutic decisions in this high-risk patient population. Each of these findings is discussed in the following sections.

During the work on this thesis, the understanding of AS and its complications have improved. Importantly, TAVR has been adopted into routine clinical practice, providing an important therapeutic opportunity for many inoperable patients who were previously without treatment options.[41-44] In addition, the bleeding diathesis associated with AS has been described to be reversible with AVR, with normalization of von Willebrand factor multimers within minutes.[166-168] Hopefully the observations reported here will contribute to further developments to reduce the burden of AS and improve quality of life for AS patients.

5.1 Incidence trends for aortic stenosis

In Study I we observed stable unadjusted incidence rates of AS in Sweden between 1989-2009 while the age-adjusted incidence rates declined slightly. Limited information on temporal trends for valvular heart diseases are available in the literature. Another register-based study from Scotland found an increased incidence of AS between 1997-2005.[169] In the longer time period in our study however, most of the reduction in incidence occurred during the early 1990s. Indeed, a slightly increasing trend for AS during the years included in the study by Berry et al could be discerned in Study I. The observed incidence decline in the early 1990s could be consistent with AS as a potentially preventable disease and the improved risk factor control that occurred during this time period could have contributed to a decrease in disease burden. In agreement with this, several cardiovascular risk factors have been reported to decline during the last decades in Western civilization.[170] As discussed in the section 1.3.3, pathophysiological mediators of disease development in early disease stages include ACE, angiotensin II, inflammation and lipid accumulation.[46-50,63] During the study period, several medications aimed at lipid lowering, ACE-inhibition and inflammation have been introduced and received widespread use for other cardiovascular diseases. Since AS and other cardiovascular diseases frequently overlap (Table 4.8) increased utilization of these treatments, although not aimed at AS per se, might have conferred favorable effects in halting disease development in certain individuals.

5.2 Prognostic trends for aortic stenosis

Age at diagnosis increased by 4 years in the study, reflecting demographic changes in the population and the strong correlation between AS and age.[27] Despite this development, mortality rates for both men and women declined between 1989 and 2009. Women had a slightly higher mortality rate, likely resulting from the higher age at diagnosis. The crude mortality trends declined for both 1- and 3-year mortality to a similar extent. Age-adjusted mortality rates also improved during the last two decades, a marginally more pronounced effect than in the unadjusted analysis. Heart failure and MI were also investigated for comparison, representing two common comorbid cardiovascular diseases which have seen marked improvements in treatment and diagnosis during the study period with corresponding improvements in prognosis.[128,171-176] The prognostic improvements for these diseases were similar to previous reports and parallels the trends reported for AS.

Analysis of relative risk estimates with Cox proportional hazard regression analyses also supported a substantial reduction of all-cause and cardiovascular mortality in AS, with comparable improvements for heart failure and MI. Relative risk estimates of 30-day mortality after valve replacement was 0.64 for the time period 2007-2009 compared to 1989-1991, suggesting that improvements in surgical technique and postoperative care contributed to the presented results. Other studies have corroborated these findings.[36-37] Interestingly, the improvement in outcomes after AVR occurred in the time period before the broad implementation of TAVR, which thus did not contribute to the observed results.

Other mechanisms than improved outcomes after AVR are likely to contribute to the decrease in mortality in AS, as improvement in survival was not limited to subjects undergoing AVR. The development of percutaneous coronary intervention and introduction of β-blockers, ACE-inhibitors, DAPT and statin therapy are likely to also contribute to improved outcomes for patients with AS as both heart failure and MI are common comorbid conditions in these patients. Increasing use of ACE-inhibitors could also have had a direct effect on inhibiting AS pathogenesis, as experimental studies have suggested effects on reduced progress of calcification and lipid accumulation.[177-178] This hypothesis is supported by the high prevalence of aortic sclerosis in the elderly population, as ACE-inhibitors may be beneficial early during disease development.[31,69-70] As expected, relative risk for cardiovascular mortality was greatly reduced in 2007-09 compared to 1989-91 (HR 0.50 and 0.55 for 1- and 3-year respectively). The largest improvements were noticed in the first time periods (92-03) with only marginal risk reductions after 2003. Increased use of echocardiography resulting in an early recognition of AS and optimization of surgical timing might also have contributed to our findings.

5.3 Risk factors for incident AS

5.3.1 Manifest atherosclerotic disease and incident AS

Manifest atherosclerotic disease, as characterized by the presence of plaque in the common carotid artery, was associated with an increased risk for incident AS during 16.5 years of follow-up. Carotid IMT was also shown to be associated with incident AS, however when combining both IMT and presence of plaque in one model, plaque but not IMT was significantly associated with incident AS. The effect estimates, however, were similar and the lack of independent association with IMT may reflect limitations in statistical power. Carotid IMT and plaque represent somewhat different pathophysiological mechanisms: whereas plaque is

considered to represent atherosclerotic disease, increased IMT mainly reflects medial hypertrophy.[179-181] A clear dose-response relationship of IMT with incident AS was observe in Kaplan-Meier curves with increasing risk for each quartile of IMT. Another study, although limited by a case-control design, tested the association of IMT and plaque with AS reported conclusions in agreement with the present results.[182] The current study, with a prospective design strengthens the previous study and may have implication for risk stratification and disease prevention.

5.3.2 Traditional cardiovascular risk factors and incident AS

Several cardiovascular risk factors decided upon a priori were tested for association with AS. In age- and sex-adjusted analyses BMI, LDL-C cholesterol, CRP, hypertension, smoking and diabetes were significantly associated with incident AS and were included in the fully adjusted model. In the fully adjusted model age, BMI, diabetes, smoking and CRP remained significant. However LDL-C and hypertension had similar risk estimates, suggestive that the lack of association reflects limited statistical power. As lipids and inflammation have previously been shown to be involved in early stages of disease development, before extensive calcification, fibrosis and manifest disease occurs, the association is not surprising.[69-70,183] Adverse effects of smoking and hyperglycemia can also be presumed to adversely influence degenerative valvular processes. Association of these risk factors has previously been described with aortic sclerosis, the often overlooked clinical precursor of aortic sclerosis.[184]

5.3.3 Atherosclerosis and aortic stenosis

The association between atherosclerotic disease and incident AS implicates a role for risk factor management in AS prevention. Lack of benefit in trials of lipid-lowering medications[58-60] in AS may be explained by the inclusion of predominantly cases with moderate disease in such trials, whereas pathways involved in calcification may be more important in subjects with moderate and severe disease.[69-70] Accordingly, retrospective studies of statin therapy including patients with less severe disease found lower rate of calcium accumulation, decreased rate of valve area narrowing, lower degree of transaortic gradient increase and a correlation between LDL-C levels and progression of aortic valve calcification.[184-187] The finding of a direct association between AS and common treatable cardiovascular risk factors, together with a lower age-adjusted incidence and decrease in mortality provides additional support for further exploration of lipid-lowering therapy and ACE-inhibitors in earlier cases with mild aortic

stenosis, aortic sclerosis and potentially BAV. In addition to risk of incident AS, these conditions are strong risk markers for other cardiovascular events.[177,188] One potential concern is that high-dose statin therapy has been associated with increased calcium deposition in previous studies, and so could potentially have detrimental effects in AS patients. In agreement with this, studies have shown that valvular interstitial cells are capable of differentiating into cell types that respond differently with either an increase or decrease of osteoblastics markers in response to statin therapy.[189-190]

5.4 Sibling risk of aortic stenosis

5.4.1 Characteristics of AS in Swedish siblings

The Swedish MGR included information on 6,117,263 siblings, of these 13,442 individuals were diagnosed with AS. Several comorbid conditions were more frequently observed in patients with AS such as atrial fibrillation, hypertension, diabetes and COPD. This is likely caused by the strong association between AS and age as the other comorbid conditions also display an increasing frequency with age. But as previous studies suggests, and in agreement with Paper II in this thesis, atherosclerotic disease, smoking and diabetes important risk factors for coronary artery disease, also increase the risk for AS.[52]

5.4.2 Risk of AS associated with a sibling or spousal history

A sibling history of AS was strongly associated with increased AS risk. Estimates were robust in three different models with step-wise adjustments and resulted in a 3.5-fold increased risk in the fully adjusted model. To our knowledge, this is the first population-based study of the familial aggregation of AS and the results are in agreement with previous case-based studies reporting on familial patterns in AS patients undergoing AVR.[85] The strong association of sibling history contrasted against the small risk increase observed with spousal AS, suggesting that genetic or epigenetic factors may be more important than adult environmental factors. Although environmental aspects are important in the development of AS, these might also be affected by genetic predisposition.[22,69-70]

It is important to note that a number of individuals included in the study were born before the decline in rheumatic disease.[6,8] In these individuals, childhood environmental factors could potentially influence the results, and such environmental factors may to a lesser degree be shared with spouses. Rheumatic

fever is however very uncommon in modern Sweden, as observed in the Table 4.5 and recently reported by our group.[191]

Individuals with more than one sibling had a very high risk of subsequent AS with relative risk estimates of 39.5, potentially representing a genetic susceptibility with a monogenic, highly penetrant inheritance. Our segregation analyses however were suggestive of a polygenic rather than a monogenic inheritance model for AS in the general population. The population attributable proportion of a sibling history of AS was low (3.5%) reflecting the low prevalence of a sibling history in the population.

5.4.3 Genetic basis of aortic stenosis

A familial aggregation of BAV has previously been described, with prevalence estimates between 9% and 24% in first-degree relatives whereas the population prevalence is approximately 1%, with a male predominance.[89,95,192] Subjects with BAV are overrepresented in patients with AS, and in particular constitute a majority of cases among younger patients.[89,95] Investigations of the genetic background to BAV have so far only resulted in the identification of the NOTCH1 gene, encoding a transcriptional regulator. NOTCH1 mutations have been associated with defect valvulogenesis and increased progression of calcification, but are only present in a very small subset of BAV cases.[80,101]

Results from the simple segregation analysis in Study III were consistent with a polygenic inheritance model, in agreement with the current understanding of disease development.[69-70,192] The genetic architecture of AS remains largely unknown but based on pathophysiological evidence AS is likely to be the result of both genetic factors, environment and complex interactions between the two. In recent years, GWAS have been successful in robust identification of genetic associations including associations with lipoprotein(a) and LDL-C, and suggestive associations with RUNX2 and CACNA1C implicating a causal role for lipoprotein metabolism and calcium signaling in AS.[46,53,87]

The genetic substrate for AS in the population is likely based upon a myriad of small polymorphisms with individually modest effects, but which together contribute a substantial proportion of risk, as seen in other cardiovascular diseases with late onset.[22] In certain families and individuals, monogenic or strong polygenic factors may play a role as illustrated by the high risk for individuals with several siblings with AS.

5.5 Aortic stenosis and antithrombotic therapy after myocardial infarction

5.5.1 Bleeding, thromboembolism and mortality

The results presented in Paper IV include data from both Sweden and Denmark and consists of 81,106 patients with myocardial infarction treated according to contemporary guidelines with DAPT. AS was present in 3% of this cohort, a higher prevalence estimate than in the general population, reflecting the high age in the study population (mean age 70 years in Sweden and 69 years in Denmark)[27-28,30-31] and the association between coronary artery disease and AS.[193-195] As in previous studies, concurrent cardiovascular disease was common and patients with aortic stenosis were older than controls. Rates of bleeding, thromboembolism and all-cause mortality were all higher in patients with AS. Interestingly, AS had larger impact than warfarin therapy on bleeding rates, which might reflect identification by physicians of individuals with high risk for bleeding and withholding of warfarin treatment. Absolute rates for bleeding, thromboembolism and all-cause mortality were high in the Swedish population. Danish estimates were as high, or as in the case of all-cause mortality, even higher than the corresponding Swedish estimates. The high absolute rates highlight the importance of improved characterization and potentially individualized treatment for this complex patient cohort.

A substantial risk increase was noted for bleeding, recurrent MI and all-cause mortality in the adjusted meta-analyses combing data from both countries. Part of the increased risk estimates presented might be caused by a larger burden of comorbid condition and higher age. However analyses adjusted for common comorbid condition and age remained highly significant, suggestive that factors related to AS itself might confer an increased risk.

5.5.2 Underlying mechanisms for the increased risk of bleeding and recurrent MI in aortic stenosis patients

Several studies have confirmed the presence of hemostatic disturbances in AS patients, most commonly resulting in bleeding complications.[102-108] Currently the mechanism behind the increased bleeding risk is assumed to be acquired von Willebrand disease.[109-110] Flow conditions through the stenotic valve results in increased breakdown of vWF multimers, which are less efficient in maintaining hemostasis, including platelet aggregation. Implementation of DAPT has resulted in improved outcomes after MI but also increased risk of bleeding. As DAPT

treatment currently is indicated for all patients with MI in the absence of clear contraindications, such treatment has increased drastically in the last decades. Due to the increased bleeding tendency noticed in AS patient it is possible that the risk-benefit ratio of DAPT is different in this cohort. No previous studies have investigated the risk associated with DAPT in patients with AS to our knowledge.

The hemostatic condition associated with AS has also been reported to include increased factor XIa activity and thrombin generation, markers of a procoagulative state.[119-121] In agreement with this an increased risk for recurrent MI was reported in study IV for AS patients. Thrombin generation and factor XIa have recently been shown to predict recurrent events in MI patients.[196] There are also some evidence that mechanical factors could induce platelet aggregation, including shear stress which could contribute to the increased risk of recurrent MI seen in the current study.[118] Another possible mechanism could be the cessation of DAPT after an episode of bleeding resulting in stent thrombosis and subsequent recurrent MI. This population would be assumed to have a greater benefit from DAPT, highlighting the complex decision-making process involved in AS patients after an acute MI.

The results suggest that events of bleeding and recurrent MI translate to an increased risk of all-cause mortality as the adjusted risk estimates for this outcome was also significantly raised. Unmeasured confounders in this high-risk population may also contribute to the risk estimates reported.

Additional studies are required to determine the contribution of individual hemostatic components to AS outcomes in MI patients, and the risk-benefit profile of DAPT or other antihemostatic regiments in such patients.

5.6 Strengths and weaknesses

The papers presented in this thesis have limitations and strengths that need to be addressed. Three of the studies were retrospective register studies, with inherent limitations to this study design, including reporting biases, detection bias, coding biases, and lack of certain potential confounders. Data on outcomes in all studies were collected from these registers, and although representing a physician's diagnosis of the disease, echocardiographic data was lacking. We were therefore unable to assess the severity of AS in the patients. However, previous studies have showed an excellent validity of cardiovascular diagnoses in general and in particular that a diagnosis of AS generally represents moderate to severe disease based on echocardiographic data, indicating a limited effect of misclassification.[53] In study IV, only diagnoses in patients with MI were included, increasing the

likelihood that AS diagnoses are based upon echocardiographic assessment of a cardiologist and reducing the likelihood of undetected cases in the population.

The study design also has some notable strengths. The use of nation-wide registers allows for a large sample size; in the case of study I and III, the Swedish population, and in study IV the population from both Sweden and Denmark. The essentially complete coverage of hospital diagnoses in these populations and the generally high quality of the Scandinavian registers, offers a unique opportunity to study epidemiological trends of even less common diseases.

Study II was a prospective cohort study, limiting some of the weaknesses associated with a completely register-based design. However, some caution should be advised in the extrapolation of the results to the general population as they were based on a random sub-cohort from a population-based cohort with a 40% participation rate. Previous comparisons have, reassuringly, shown the MDCS to be representative of the general population but with a somewhat lower mortality.[197] Measurements of carotid plaque and IMT were based on unilateral evaluation whereas other studies frequently have applied bilateral measurement. There is however limited differences in the predictive accuracy of bi- or unilateral measurements and the reproducibility of IMT measures in the MDCS have been adequate with low intra- and interreader variability.[198-201] Finally, the small number of incident cases in the MDCS limits statistical power to detect associations.

Chapter VI. Conclusions

- Age-adjusted incidence and mortality rates declined in Sweden between 1989 and 2009. The improvements were robust for both patients with and without AVR and across different age groups. The results suggest that improved risk factor control, better surgical techniques and improved therapies for common comorbidities have translated into favorable effects for patients with AS.

- Presence of plaque and traditional cardiovascular risk factors predicts incident AS. AS is a disorder with similarities to atherosclerosis with potential implications for the prevention of the disease.

- A sibling history was strongly associated with incident AS while a spousal history of AS only conferred a modest risk increase. The results indicate that genetic factors contribute to the development of AS.

- AS was associated with an approximately twofold increased risk of bleeding, recurrent MI and mortality after MI. AS patients represent a group with high risk after MI and individualized antithrombotic therapy may be warranted.

Chapter VII. Future perspectives

Although this thesis has provided some new epidemiological perspectives on AS, many questions regarding AS development and treatment remain that needs to be addressed. First, studies are needed to explore the potential benefit of new medical therapies targeted at molecular pathways suggested by current knowledge of disease development. Further insights gained from comprehensive genetic studies might also reveal new pathways, expanding our comprehension about pathophysiologic mechanisms and opening new therapeutic alternatives. Second, with regard to valve replacement therapy, TAVR remains an exciting therapeutic alternative that is likely to expand to additional patient groups in a near future. Finally, the role of hemostatic abnormalities such as loss of large von Willebrand multimers in AS outcomes remains to be further characterized, along with how to tailor antithrombotic therapy to patients with AS.

7.1 Future medical therapies

AS has several similarities with atherosclerosis, but also important differences, as illustrated by the negative results in current studies of lipid-lowering therapy.[57-59] The failure of these trials to show a benefit might have been due to late initiation of therapy as discussed. Current studies have had encouraging results regarding the benefit of statin therapy for early stages of disease but are limited in their retrospective design.[185,202-205] If future studies of statin therapy are initiated they should target patients with mild stenosis and aortic sclerosis. As lipoprotein(a) has been implicated for both incident AS and progression of the disease[53,206] it presents a potential therapeutic target. No current randomized trials have reported results with lipoprotein(a)-lowering medications such as niacin and PCSK9 inhibitors but studies are ongoing. A list of current clinical trials evaluating medical therapy for AS is shown in Table 7.1.[207-208]

Bisphosphonates represent another promising therapy, where retrospective data have shown some conflicting results, but most with beneficial effects.[209-211] It should be noted that these studies have been retrospective, and thus subject to selection bias: patients treated with bisphosphonates have osteoporosis, which has

been shown to increase the risk for valvular calcification.[207,212] Osteoclast activation and markers of osteoclast differentiation in AS have been implicated in disease progression and increase calcification, lending a mechanism through which bisphosphonates might induce positive effects.[213-214] Hopefully randomized data on bisphosphonate therapy will soon be available. (Table 7.1)

Another suspected pathophysiological mechanism in early stages of AS, inflammation, also constitutes a potential therapeutic target, although it is currently not known if inflammation is a primary driver in the disease process or a consequential marker of tissue injury. Several potent anti-inflammatory drugs are currently available for treatment of other diseases. As for coronary artery disease, low-dose methotrexate, an anti-inflammatory drug, is tested for its effect on the progression of AS, amongst other outcomes in the ongoing Cardiovascular Inflammation Reduction Trials.[69,215]

Benefits of RAAS inhibition in AS patients are implicated through multiple mechanisms. First, there has been much discussion over the years about the role of blood pressure in AS. Antihypertensive agents have long been considered contraindicated due to the risk of hypotension. Recently, some studies have suggested that increased afterload resulting in increased strain on the heart and resulting LV remodeling may be a larger problem.[216] Increased left ventricular mass has been shown to negatively affect cardiovascular morbidity and mortality.[84-85,217] ACE-inhibitors and ARBs seem to improve myocardial remodeling in patients with AS.[218] As previously mentioned, angiotensin II has been implicated in the development of calcification of aortic valves and ACE-inhibitors seems capable of reducing disease progression.[63] Current randomized trials available for ACE-inhibitors are small but have not raised any safety concerns. Studies indicate that ACE-inhibitors/ARBs may improve left ventricular mass, and trends for slower rate of progression of AS have been reported, but larger studies are needed.[64,219]

Finally, our findings of a heritable component in AS supports the use of GWAS to discover new pathophysiological mediators and therapeutic targets. GWAS have provided many novel, previously unexplored, pathways in other cardiovascular diseases.[22] As further GWAS studies are conducted it seems likely that novel mechanisms underlying initiation and progression of AS are introduced which might present new therapeutic and diagnostic possibilities.

Trial	Therapy	Patients	Expected Enrollment (No. of Patients)	Expected Completion	Primary Outcome
ACCESS trial (NCT00252317)	Captopril and trandolapril vs placebo	AVA <1.0 cm^2	64	Unknown	Hemodynamic parameters at 8 wk
AORTICA 1 trial (NCT00404287)	Fluvastatin 80 mg/d vs placebo	Asymptomatic AS	164	Unknown	Changes in C-reactive protein concentration at 12 mo
SALTIRE II trial (NCT02132026)	Alendronic acid 70 mg once weekly vs placebo; denosumab once monthly vs placebo	AS with peak aortic jet velocity of >2.5 m/s and grade 2–4 AV calcification on echocardiography	150	August 2017	Change in AV calcium score at 6 mo and 2 y
ASPEN trial (NCT01275339)	Tadalafil 40 mg/d vs placebo	Moderate to severe AS	56	December 2016	Change in LV mass on MRI at 6 mo; change in diastolic function as measured by tissue Doppler e' at 12 wk and 6 mo; change in LV longitudinal peak systolic strain by echo at 12 wk and 6 mo
ALFA trial (NCT01589380)	Fimasartan up to 60 mg/d vs placebo	Moderate to severe AS	100	Unknown	Change of Vo_2max at 1 y
ROCK-AS (NCT00699452)	Candesartan up to 16 mg/d vs placebo	Symptomatic AS	120	Unknown	Inflammation in stenotic AV at 3–5 mo
Schuler et al (NCT00176410)	Fluvastatin up to 80 mg/d vs placebo	Mild to moderate asymptomatic AS	100	Unknown	Progression of calcified aortic stenosis, and hemodynamic parameters at echocardiography and catheterization at 24 mo
EAVaLL (NCT02109614)	Extended-release niacin 1500–2000 mg vs placebo	Aortic sclerosis or mild AS	238	September 2017	Calcium score progression by cardiac CT at 2 y
Miller et al (NCT02049203)	Ataciguat vs placebo	AV area >1.0 cm^2 and <2.0 cm^2, and AV calcium levels >300 Agatston units from chest computed tomography	40	Unknown	Orthostatic hypotension and orthostatic parameters at 14 d
Miller et al (NCT02481258)	Ataciguat 200 mg/d vs placebo	AV area >1.0 cm^2 and <2.0 cm^2, and AV calcium levels >300 Agatston units from chest computed tomography	100	May 2017	Changes in AV calcium levels measured by computed tomography at 6 mo
CALCIFIA trial (NCT01000233)	Phytine 300 mg 3 times daily vs placebo	Calcium in the AV, characterized by Rosenhek grade 2 or 3 in echocardiography	250	Unknown	Calcium in AV and in coronary arteries assessed by multidetector computer tomography at 24 mo
BICATOR trial (NCT02679261)	Atorvastatin 20 mg/d vs placebo	Bicuspid AV with moderate or less dysfunction	220	November 2018	Change of the diameter of ascending aorta by computed tomography at 3 y

ACCESS indicates Acute Haemodynamic Effects of Treatment With Angiotensin Converting Enzyme (ACE)-Inhibitors in Patients With Symptomatic Aortic Stenosis; ALFA, A Randomized Trial of Angiotensin Receptor Blocker, Fimasartan, in Aortic Stenosis; AORTICA 1, Randomized Study to Evaluate the Efficacy of Fluvastatin on Inflammatory Markers in Patients With Aortic; AS, aortic stenosis; ASPEN, Aortic Stenosis and Phosphodiesterase Type 5 Inhibition (ASPEN): A Pilot Study; AV, aortic valve; AVA, aortic valve area; BICATOR, Evaluating the Effectiveness of Atorvastatin on the Progression of Aortic Dilatation and Valvular Degeneration in Patients With Bicuspid Aortic Valve; CALCIFIA, Value of Oral Phytate (InsP6) in the Prevention of Progression of the Cardiovascular Calcifications; EAVaLL, Early Aortic Valve Lipoprotein(a) Lowering Trial; LV, left ventricle; ROCK-AS, Potential of Candesartan to Retard the Progression of Aortic Stenosis; and SALTIRE, Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis.

Table 7.1. Ongoing clinical trials for medical therapies in aortic stenosis. Adapted with permission from Marquis-Gravel G, Redfors B, Leon MB, Genereux P. Medical treatment of aortic stenosis. *Circulation*. 2016;134:1766-84

7.2 Valve replacement therapy in the future

The data reported in this thesis supports that improved outcomes in SAVR have contributed to improved outcomes in the overall AS population, with a significantly lower 30-day mortality after AVR in the last time period as compared to the first. Results after surgery, and similarly for the more recently implemented TAVR, are generally impressive[35-39,43-45] but complications do occur. Further optimization of surgical techniques, post-operative care and potentially medical treatment after AVR[218] could potentially further contribute to reduced mortality and morbidity. The complementary use of SAVR and TAVR will also likely result in improved outcomes, and discussing patients in a heart team will be important to tailor the right therapy to the right patient and highlight individual risks and benefits.[28,34] The largest benefit of TAVR has been for patients who previously lacked treatment options. A clear reduction in mortality has been reported in cases deemed unsuitable for surgery, and a large proportion of AS patients with severe AS are currently not considered for intervention. In some series as many as 30-40% of patients with symptomatic severe AS were not considered for AVR.[43,220-221] An increase in the proportion of patients eligible for intervention seems likely with increasing availability and might prove beneficial for the patient cohort as a whole.

7.3 Tailoring antithrombotic therapy to the individual patient

Previous work has established bleeding events as common in patients with severe AS.[102-117] The bleeding diathesis appears to be reversible with AVR, indicating a direct effect of flow over the stenotic valve.[112] Increased risk for thrombus generation was also noted in AS.[119-121] Speculatively, patients with these disease manifestations and severe AS might benefit from early intervention. Further studies are needed to explore this connection for optimal treatment strategies.

The results presented in Paper IV highlight the poor outcomes in AS patients with MI, and indicate that the optimal therapy for AS patients after MI needs further study. The risk-benefit profile with DAPT may be different in this population as compared to the general MI population, and other therapeutic strategies may confer a better risk-benefit profile, such as reduced duration of therapy or P2Y12 inhibitor monotherapy. Such decisions could potentially be guided by monitoring of vWF, thrombin generation and other hemostatic parameters but further studies are necessary.

Svensk sammanfattning

Kardiovaskulär sjukdom är en av vår tids stora hälsofaror och den globalt ledande orsaken till förtida död. Sjukdomar i hjärtats klaffar, vars funktion är att förhindra bakåtflöde av blod genom hjärtat efter att det pumpats ut, utgör en signifikant del av den kardiovaskulära sjukdomsbördan. I utvecklade delar av världen drabbar klaffsjukdom framförallt äldre. Den vanligaste klaffsjukdomen är förträngning av klaffen i stora kroppspulsådern (aortaklaffen), så kallad aortastenos, som ofta ses som en ålders-degenerativ process. Historiskt var klaffsjukdom i Sverige och västvärlden tvärtom en sjukdomsgrupp som framförallt drabbade yngre individer i anslutning till vissa typer av luftvägsinfektioner med en särskilt form av bakterier (streptokocker), så kallad reumatisk klaffsjukdom. I mindre utvecklade delar av världen, där bland annat tillgången till antibiotika är sämre, är reumatisk klaffsjukdom alltjämt ett betydande hälsoproblem.

Vid aortastenos blir aortaklaffen allt mer stel och öppnar sig sämre, vilket ökar trycket som hjärtat måste pumpa mot och därmed belastningen på hjärtat. Dessutom skadas vissa koagulationsfaktorer i blodet, vilket kan påverka blodets förmåga att koagulera. Sjukdomen har en lång asymtomatisk period men vid uttalad förträngning tillstöter oftast symptom i form av andnöd, svimning och bröstsmärta. Orsakerna till de förändringar i klaffen som gör att den blir allt trängre är inte helt klarlagda. Man tror dock att initiala mekanismer involverar fettinlagring i klaffen och tilltagande inflammation vilket resulterar i bildning av ärrvävnad och förkalkning, mekanismer som sjukdomen till stor del har gemensamt med de förändringar i blodkärlen som orsakar hjärtinfarkt och stroke.

I denna avhandling studerades epidemiologiska aspekter av aortastenos, främst i nationella kvalitetsregister men också i en prospektiv kohortstudie. Nationella sjukhusregister innehåller information från alla slutenvårdstillfällen inklusive diagnoser, samt information från öppenvårdsbesök, familjeförhållanden, och dödsorsaker.

I studie I studerades epidemiologiska tidstrender för aortastenos i Sverige mellan 1989-2009. Vi fann att det åldersjusterade insjuknandet i aortastenos minskat något och att genomsnittsåldern för diagnos av aortastenos ökat med fyra år. Prognosen efter aortastenos hade förbättrats både på kort och lång sikt. Både patienter som genomgick kirurgisk intervention för att byta ut den trånga aortaklaffen och de som inte genomgick operation uppvisade en förbättrad

prognos. Under de år som studerades introducerades dock ej några nya behandlingsalternativ för aortastenos. Våra resultat tyder därför på att resultaten speglar förbättrad behandling av andra samtidiga kardiovaskulära sjukdomar, framförallt hjärtinfarkt och hjärtsvikt, tillsammans med förbättrad kirurgisk teknik.

I Studie II studerades sambandet mellan insjuknande i aortastenos och förändringar i halskärlen samt traditionella riskfaktorer för hjärtinfarkt som kolesterol, högt BMI och rökning. Studien utfördes i en stor prospektiv befolkningsundersökning, ”Malmö Kost och Cancer” (MKC). För MKC undersöktes drygt 6000 slumpmässigt utvalda individer från Malmö genom insamling av hälsoinformation, analys av blodprover och utförande av ultraljud av halskärlen. Dessa deltagare följdes sedan i över 16 år för insjuknande i aortastenos med hjälp av nationella sjukhusregister. Individer med förändringar i halskärlen (plack) och med högt kolesterol, diabetes, rökning, hög ålder och höga nivåer av snabbsänka (även känd som C-reaktivt protein, CRP) hade en förhöjd risk för aortastenos. Dessa fynd tyder på att det finns kopplingar mellan riskfaktorer för hjärtkärlsjukdom, plack i halskärlen och insjuknande i aortastenos. Detta kan innebära att de mediciner som idag används för att behandla hjärtkärlsjukdom skulle kunna ha en positiv effekt även för patienter med aortastenos, som i nuläget saknar andra medicinska behandlingsalternativ än operation.

Det är inte känt huruvida en ärftlig predisposition påverkar risken för att drabbas av aortastenos. I Studie III undersökte vi därför hur risken för aortastenos påverkas av att ett syskon drabbats av aortastenos. För att försöka skilja effekten av ärftliga faktorer från den gemensamma miljön studerades också hur risken påverkades av att ha en partner med aortastenos. Resultaten visade att risken för att själv få aortastenos om man har ett syskon med aortastenos var påtagligt förhöjd. Däremot var risken endast måttligt förhöjd om individens partner hade aortastenos. Dessa fynd indikerar en ärftlig komponent av aortastenos, sannolikt medierad av genetiska faktorer.

I det sista delarbetet, studie IV, utforskade vi hur förekomst av aortastenos påverkar utfallet efter en hjärtinfarkt. Som beskrivet ovan medför aortastenos förändringar i blodets koagulativa förmåga. Vi ville därför studera huruvida den blodförtunnande behandling som ges efter hjärtinfarkt för att förebygga ny infarkt medförde större risker hos patienter med samtidig aortastenos. Aortastenos och hjärtinfarkt drabbar inte sällan samma patienter på grund av de gemensamma riskfaktorerna. Resultaten visade en fördubblad risk för blödning, men också fördubblad risk för ny infarkt samt en fördubblad mortalitet efter 1 år. Sannolikt bidrar den ökade blödningsrisken och risken för ny hjärtinfarkt till den ökade mortaliteten. Detta talar för att patienter med aortastenos som får hjärtinfarkt representerar en skör patientgrupp med hög risk, vilket motiverar noggrann individuell värdering – kanske genom monitorering av koagulationsfaktorer, vilket

får utvärderas i framtida studier. Ytterligare kliniska studier behövs innan man säkert kan uttala sig om nyttan och riskprofilen för aggressiv antitrombotisk behandling av patienter med aortastenos efter hjärtinfarkt.

Sammantaget fann vi i detta avhandlingsarbete att: (I) en förbättrad prognos och minskat åldersjusterat insjuknande i aortastenos mellan 1989-2009, (II) aortastenos har gemensamma riskfaktorer med hjärt-kärlsjukdom vilket kan ha betydelse för framtida medicinsk behandling av sjukdomen (III) en ärftlig faktor förefaller påverka risken för aortastenos, talandes för en genetisk komponent, och (IV) patienter som drabbas av hjärtinfarkt och samtidigt har aortastenos har en dubblerad risk för både blödning, ny hjärtinfarkt och mortalitet varför optimal behandling för denna patientgrupp kan skilja sig från övriga delar av befolkningen.

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