Heart Failure and Aortic Stenosis

Factors Influencing Prognosis and Development

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"A daring smile on my face, I turn my look within
and my heart
I clutch with my hand. Trembling
I clasp my treasure to my ear and listen.

I feel like
I hold a shell in my hands
in which,
long and ununderstood,
the murmur of an unfathomable sea resounds.

Oh, will I ever, will I ever
reach the shore
of that sea I now
sense
but cannot see?"

"The Shell" by Lucian Blaga

To my family

ABSTRACT

Background: An ageing population increases the prevalence of heart failure (HF) and aortic stenosis (AS). Several studies have investigated prognosis and predictors of HF with preserved ejection fraction (HFpEF) compared to heart failure with reduced ejection fraction (HFrEF), with inconsistent results. Valvular heart diseases gain importance in HF aetiology. How often AS occurs with age, the factors that might predict it, how aortic valvular interventions influence outcome of HF remain inadequately studied.

Methods: In *the first study* we analysed patients ≥65 years hospitalised for HF. The 5-year all-cause mortality and prognostic factors were compared between HFpEF and HFrEF. In *the second study*, we created a study cohort consisting of HF with aorta valve intervention due to AS by linking the Swedish Heart Failure Registry with the National Patient Register (NPR) and divided it into two subgroups: AS-HFrEF and AS-HFpEF. For each individual, three matched controls with HF were identified. The outcomes were all-cause and cardiovascular mortality. In *the third study*, we included men who were a part of the 'Study of Men Born in 1943' and studied the prevalence and factors predicting AS or aortic sclerosis. In *the fourth study*, we analysed men participating in the Multifactor Primary Prevention Study and identified the outcome (AS) and its associated factors by linking this database to the NPR.

Results: In *Paper I*, 5-year mortality was high (67.5%). After adjusting for age, HFpEF had better survival than HFrEF; different factors predicted mortality in HFpEF and HFrEF. In *Paper II*, crude all-cause mortality was 50.3% and no statistically significant differences in all-cause or CV mortality were found between AS-HFpEF and AS-HFrEF or between those with AS-HF and matched HF controls. Prognostic predictors were similar between the two groups, except of diabetes mellitus. In *Paper III*, 2.6% of the individuals developed AS. Body mass index (BMI) correlated with the risk of developing AS after 21 years, whereas BMI and hypercholesterolemia correlated with the development of AS/aortic sclerosis. In *Paper IV,* the cumulative incidence of AS was 3.2%. The factors significantly associated with its development were higher BMI, obesity, cholesterol, arterial hypertension, atrial fibrillation, and smoking.

Conclusions: HF has a high mortality, but HFpEF has better prognosis than HFrEF, at least in women. This difference in survival was not apparent if HF developed after AS and subsequent aortic valvular intervention. The cumulative incidence of AS is about 3% and atherosclerotic factors might be involved in its development. These risk factors are modifiable, implying that AS-caused HF could be preventable.

Keywords: heart failure, prognosis, predictive factors, aortic stenosis, obesity

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LIST OF PAPERS

This thesis is based on the following papers:

I. Kontogeorgos S, Thunström E, Johansson MC, Fu M. Heart failure with preserved ejection fraction has a better long-term prognosis than heart failure with reduced ejection fraction in old patients in a 5-year follow-up retrospective study**.** *Int J Cardiol, 2017 Apr 1;232:86-92.*

II. Kontogeorgos S, Thunström E, Pivodic A, Dahlström U, Fu M. Prognosis and outcome determinants after heart failure diagnosis in patients who underwent aortic valvular intervention.
Revised and resubmitted ESC Heart Failure

III. Kontogeorgos S, Thunström E, Basic C, Hansson PO, Zhong Y, Ergatoudes C, Morales D, Mandalenakis Z, Rosengren A, Caidahl K, Fu M. Prevalence and risk factors of aortic stenosis and aortic sclerosis: a 21-years follow-up of middle-aged men.
Scand Cardiovasc J. 2020 Apr;54(2):115-123.

IV. Kontogeorgos S, Thunström E, Lappas G, Rosengren A, Fu M. Lifelong cumulative incidence and predictors of acquired aortic stenosis in a large population of middle-aged men followed for up to 43 years
In manuscript

SAMMANFATTNING PÅ SVENSKA

Bakgrund: Allteftersom andelen äldre i befolkningen ökar, så ökar också åldrandets sjukdomar som t ex hjärtsvikt och degenerativa klaffsjukdomar. Flera studier har undersökt prognos och prediktorer för hjärtsvikt med bevarad pumpförmåga jämfört med hjärtsvikt med reducerad pumpförmåga, men med motstridiga resultat. Klaffsjukdomarna har kommit att spela en allt större roll i hjärtsviktens etiologi. Hur förekomsten av aortastenos ökar med stigande ålder, vilka faktorer som kan prediktera aortastenos och hur klaffintervention påverkar prognosen vid hjärtsvikt är inte klarlagt.

Metod: I den *första studien* analyserade vi 289 patienter äldre än 65 år, inlagda på grund av hjärtsvikt och utfallet var 5-årsmortalitet. Patienterna indelades i två grupper, en med bevarad och en med reducerad pumpförmåga. Vi undersökte grupperna med avseende på vilka faktorer som predikterade sämre överlevnad. I den *andra studien* skapade vi en kohort av hjärtsviktspatienter med aortastenos och aortaklaffintervention före hjärtsviktsdiagnosen genom att länka kvalitetsregistret Rikssvikt med Patientregistret. Vi delade in patienterna beroende på om de hade bevarad eller reducerad pumpförmåga och jämfört mortalitet av alla orsaker och kardiovaskulär mortalitet samt identifierade faktorer som var förknippade med högre mortalitet i dessa två grupper. För varje individ i kohorten identifierade vi 3 matchade kontroller från hjärtsviktspopulationen som inte hade aortastenos. I den *tredje studien* inkluderade vi 780 män, varav 535 genomgick ultraljud vid 71 års ålder, som ursprungligen var en del av ”Studien av män födda 1943”. Vi studerade prevalens och faktorer som predikterade utvecklingen av aortastenos eller aortaskleros under 21 års uppföljning. I den *fjärde studien* analyserade vi 7494 män ur den multifaktoriella primärpreventiva studien som under en genomsnittlig uppföljningstid 27 år fått diagnosen aortastenos enligt Patientregistret, där vi undersökte vilka faktorer som var associerade med risk för att utveckla aortastenos.

Resultat: I den *första studien* fann vi en hög 5-årsmortalitet (67.5%). Efter justering för ålder, så hade patienter med hjärtsvikt med bevarad pumpförmåga bättre överlevnad jämfört med dem med hjärtsvikt med reducerad pumpförmåga, en skillnad som var mest påtaglig hos 70-åriga kvinnor. Faktorer som var förknippade med sämre överlevnad skilde sig delvis åt mellan dem med hjärtsvikt med bevarad och med reducerad pumpförmåga. I den *andra studien*

fanns det ingen skillnad i kardiovaskulär mortalitet eller total mortalitet, vare sig mellan patienter med hjärtsvikt efter aortaklaffsinterven-tion med bevarad eller reducerad pumpförmåga eller mellan patienter med hjärtsvikt efter aortaklaffsintervention och matchade kontroller. Samma faktorer predikterade högre mortalitet i dem båda grupperna, med undantag för diabetes mellitus (som predikterade död bara hos patienter med reducerad pumpförmåga). I den *tredje studien* utvecklade 2,6% aortastenos bland de studerade männen. Högre body mass index (BMI) var associerat med högre risk för aortastenos, medan hyperkolesterolemi var förknippat med högre risk för aortastenos eller utveckling av aortaskleros. I den *fjärde studien* var den kumulativa incidensen av aortastenos 3.2% och faktorer som var associerade med framtida aortastenos var högre BMI, högt kolesterol, hypertoni, förmaksflimmer och rökning.

Slutsatser: Hjärtsvikt har hög mortalitet, bättre hos patienterna med bevarad pumpförmåga, åtminstone hos kvinnor. Denna skillnad i överlevnad fanns inte hos patienter som utvecklade hjärtsvikt efter aortaklaffintervention på grund av aortastenos. Aortastenosens kumulativa incidens upp till 97 år är 3,2% för män och aterosklerotiska riskfaktorer förefaller vara involverade i dess utveckling. Dessa faktorer är påverkbara och aortastenos och hjärtsvikt orsakad av aortastenos skulle därför kunna förebyggas.

CONTENT

ABBREVIATIONS

ACC	American College of Cardiology
ACEi/ARBs	Angiotensin-converting enzyme inhibitors
AHA	American Heart Association
ARBs	Angiotensin II receptor blockers
ARNI	Angiotensin receptor neprilysin inhibitors
AS	Aortic stenosis
AS-HFpEF	Heart failure with preserved ejection fraction and aortic stenosis
AS-HFrEF	Heart failure with reduced ejection fraction and aortic stenosis
AVI	Aortic valvular intervention
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CV mortality	Cardiovascular mortality
ECG	Electrocardiography
EF	Ejection fraction
ESC	European Society of Cardiology
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
GLP-1	Glucagon-like peptide-1 receptor agonists
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
hs-TnT	High sensitive troponin T
hs-CRP	High sensitive C-reactive protein

HR	Hazard ratio
ICD	International Classification of Diseases
IQR	Interquartile range
KKÅ	Swedish version of the classification of surgical procedures from the Nordic Medico-Statistical Committee
LV	Left ventricle
LVEF	Left ventricle ejection fraction
MRA	Mineralocorticoid receptor antagonists
NPR	National Patient Registry
NT-pro-BNP	N-terminal proB-type natriuretic peptide
OR	Odds ratio
PCI	Percutaneous coronary intervention
RCT	Randomized clinical trials
SAVR	Surgical aortic valve replacement
SGLT2	Sodium glucose co-transporter-2 inhibitors
SwedeHF	Swedish Heart Failure Registry
TAVI	Transcatheter aortic valve implantation
VHD	Valvular heart diseases

INTRODUCTION

HEART FAILURE

Definition and historical perspective

Heart failure (HF) is a progressive, clinical syndrome secondary to many cardiovascular and non-cardiovascular diseases, a common phase before death. Globally, it is estimated that approximately 63.4 million people suffer from HF[1, 2].

The definition and criteria used to diagnose HF have varied over the years. Below is the latest definition of HF issued in 2016 by the European Society of Cardiology (ESC):

> HF is a clinical syndrome characterised by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress[3].

The history of HF can be traced to the ancient Greeks and Egyptians, who recognised some symptoms and signs of HF but could not understand their cause. In 1628, Harvey described the heart as a pump with a detailed description of the circulatory system. Richard Lower provided the first definition of HF in 1669 and several advances in HF diagnosis were made afterwards. Still, therapy was unsuccessful, although some symptom relief was offered, first with digitalis, and later with diuretics. The first most important breakthrough in HF treatment was the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), a randomised controlled trial published in 1987. This study demonstrated for the first time improved survival in patients with severe HF treated with angiotensin-converting enzyme inhibitors (ACEi)[4]. The first European guidelines for the diagnosis and assessment of HF were published in 1995[5].

The concept of HF with preserved systolic function had been suggested nearly 50 years ago[6] and was included in the 1995 guidelines but termed “diastolic

heart failure" and defined as "symptoms and/or signs of HF in the presence of normal ejection fraction at rest"[5]. Later, this term was thought to be inappropriate given that systolic and diastolic dysfunction often coexist. In addition, preserved systolic function and normal LVEF are not entirely synonymous because other imaging examinations can indicate systolic dysfunction even when LVEF is normal[7].

Classification

Heart failure can be classified according to four aspects of this syndrome.

a. Left ventricular ejection fraction

While HF with reduced ejection fraction (HFrEF) has been uniformly defined as symptoms and signs typical of HF and reduced left ventricular ejection fraction (LVEF), the definition of HF with preserved ejection fraction (HFpEF) has been subject to several changes and development. In 2012, the ESC guidelines defined HFpEF as symptoms and signs typical of HF, with normal or only mildly reduced LVEF, normal or mildly dilated left ventricle (LV) and relevant structural heart disease (left ventricular hypertrophy, left atrial enlargement and/or diastolic dysfunction)[8]. This definition was updated in 2016, introducing elevated natriuretic peptides as a prerequisite in HFpEF diagnosis. At the same time, a new HF category was introduced, HF with mid-range ejection fraction (HFmrEF), with nearly the same definition as HFpEF, except that LVEF was required to be between 40 and 49%.

b. Duration or onset

HF may be classified based on how urgently the symptoms or signs occur in acute or chronic HF. Acute HF is defined as rapid onset or rapid deterioration (within 24 hours), with symptoms and/or signs of HF requiring urgent evaluation and treatment, usually leading to emergent hospitalisation. It may present *de novo,* as the first manifestation of HF, with acute pulmonary oedema or cardiogenic shock or, more often, as decompensation of chronic HF[3]. On the other hand, chronic HF is an ongoing process with progressive deterioration, with episodes of decompensation requiring hospitalisation and may ultimately lead to death.

c. Symptoms/functional limits

Based on the limitation imposed by the symptoms on the daily activity, HF may be classified using the criteria defined in 1964 by the New York Heart Association (NYHA)[9] (Table1).

Table 1. NYHA classification

New York Heart Association Classification System	
Class I	No symptoms with ordinary activity
Class II	Mild limitation of physical activity; symptoms with ordinary physical activity
Class III	Marked limitation of physical activity; symptoms with less than ordinary physical activity
Class IV	Symptoms with any physical activity or at rest

d. Disease development and progression

The American College of Cardiology/American Heart Association (ACC/AHA) classifies HF according to development stages, listed in the Table 2, below[10].

Table 2. ACC/AHA stages of HF

ACC/AHA stages of heart failure	
Stages	
A	Patients at risk for developing HF, who have not yet developed structural heart changes (i.e. those with diabetes, hypertension, with coronary disease without prior infarct, valvular heart diseases). No history of signs or symptoms of HF
B	Patients with structural heart disease (i.e. reduced ejection fraction, left ventricular hypertrophy, chamber enlargement) strongly associated with the development of HF. No history of signs or symptoms of HF
C	Patients who have developed clinical HF, with current or prior symptoms
D	Patients with HF refractory to maximal medical treatment with advanced structural heart disease, requiring advanced intervention (i.e. biventricular pacemaker, left ventricular assist device, transplantation)

Epidemiology

In general, the prevalence of HF is estimated to 1-2% and the incidence to approximately 5-10 per 1000 persons per year in developed countries[11, 12]. The prevalence increases steeply with age, from about 1% in those 55-64 years to over 17% in those ≥85 years[12]. The lifetime risk for 55 years old individuals to develop HF has been estimated at 33% in men and 28% in women[12]. The prevalence of HF is predicted to rise by 2030, reaching 3%, mainly because of increasing life expectancy. In patients >80 years the increase is estimated to be 66% by 2030[13]. The mean age of the patients with HF increased from 60 years in 1950-1969 to 80 years in 1990-1999[14].

In Sweden, the prevalence of HF is about 2.2% and the incidence 3.8/1000 person-years[15]. The mean age varies according to the studied population. For instance, the mean age of HF patients is 75 years in those included in the Swedish Heart Failure Registry, the majority after hospital admission[16], 77 years if both primary and secondary care patients are investigated[15] and 79 years

when including only primary care patients[17]. In 1990, the overall age-adjusted prevalence was 1.73% and increased with an estimated annual percentage change of 4.3% from 1990 to 1995, without a significant change until 2002. From 2002, the prevalence declined slowly to 1.99% in 2007. A different trend was observed in individuals <65 years, where the prevalence increased markedly. In absolute numbers an increase was found among very old individuals, in accordance with demographic changes[18].

Looking in more detail, the dynamic of the HF prevalence depends on how HFpEF and HFrEF evolve in relation to each other. HFpEF patients represent about 50% of all HF patients[19-21]. An ageing population, acquiring more comorbidities (e.g., hypertension, diabetes mellitus, obesity) leads to an increase in HFpEF prevalence. At the same time, improved control of risk factors, combined with better therapy for the prevention and treatment of coronary artery disease (CAD) decreases HFrEF prevalence. To date, the prevalence of HFrEF seems to have reached a plateau and may begin to decline. However, HFpEF continues to increase, driving up the prevalence of HF[22]. The increase in the prevalence of HFpEF in relation to HFrEF was 1% per year[23, 24].

The incidence of HF also varies according to subtype, partly explaining the dynamic relationship between HFpEF and HFrEF. While the incidence of HFrEF decreased due to successful strategies for prevention and treatment of CAD[25], HFpEF incidence increased[26] and is estimated to become the predominant HF category in the future[23, 24]. Age is an important factor in changes in the incidence of HF. In a Danish study the incidence between 1995 and 2012 decreased in those ≥50 years but increased in those <50 years. This finding was observed in men and women and in ischemic and non-ischemic HF[27], confirming the findings of another Swedish study[28]. This increase in HF among the young might be potentially explained by rising obesity rates, where obesity is a powerful predictor of early HF[29, 30].

Aetiology and pathogenesis

Several conditions lead to HF, with ischemic heart disease, hypertension and valvular heart disease among the most frequent aetiologies. Ischemic heart disease is the most common underlying cause of HF[31]. However, it is challenging to be confident about the primary aetiology of HF in a patient with multiple coexisting potential causes (e.g., ischemic heart disease, hypertension, diabetes mellitus, atrial fibrillation, valvular heart disease, etc.). For instance, in the elderly, although ischemic heart disease is common, hypertensive heart disease may predominate and account for the high prevalence of HFpEF. In a study conducted on the Framingham cohort[32] HF aetiology varied by phenotype. In HFrEF 63% of HF cases were caused by CAD, hypertension came second (19%), "other aetiologies" third (13%) and valvular heart disease causing only a relatively small proportion (5%). For HFpEF, the distribution of the aetiologies differed, with CAD (37%) and hypertension contributing equally (36%). In comparison, "other aetiologies" were assigned as the cause of HF in 16% of the cases and valvular heart disease in 11%, or twice as often as in HFrEF. Dilated cardiomyopathy and valvular heart diseases are two important causes of non-ischemic HF, with the former being more common in younger patients and the latter in elderly patients.

Given the multitude of causes and predisposing factors, it is difficult to understand the underlying pathophysiology without considering the different phenotypes, comorbidities or aetiologies. For instance, CAD is a well-recognised pathogenic factor in HFrEF, but it is gaining more importance as an aetiology in HFmrEF and HFpEF[33]. To date, accumulating data show that HFpEF and HFrEF are two entities with different physiopathology at both macro and cellular levels[34]. Briefly, HFrEF is characterised by an eccentric remodelled left ventricle[35], without increased wall thickness, with increased end-diastolic volume and decreased mass to volume ratio, response to an extensive myocardial insult caused by ischemia, toxins, infections, etc. At the cellular level, the myocytes are elongated, with lower collagen content in the extracellular matrix[36,37]. By contrast, in HFpEF the left ventricle is usually non-dilated, with increased wall thickness and concentric hypertrophy, with an increased ratio between mass and volume. The myocytes have an increased diameter, and in the extracellular matrix, there is higher collagen content[36, 37].

However, these two HF categories share some common functional changes, albeit to a different extent. These changes include diastolic dysfunction and even systolic dysfunction (evident only during exercise in HFpEF)[38], chronotropic incompetence, abnormal vasorelaxation and endothelium-dependent vasodilation in the systemic and pulmonary circulation, neurohormonal activation and renal dysfunction[34].

Aortic stenosis (AS) is one of the most common degenerative valvular heart diseases, particularly in the elderly. The narrowed aortic orifice resulting from the diseased aortic valve leads to increased wall pressure and left ventricle responses with hypertrophy as a compensatory mechanism. This event results in diastolic dysfunction, and subsequently, without timely valvular intervention, to left ventricular dilatation and systolic dysfunction. Usually, this is a slow-developing process, taking decades until the emergence of symptoms. Aortic valvular intervention is the only therapy that can change the natural history of AS. However, HF can also develop despite valvular intervention (Figure 1), as the changes induced by AS take months to years to revert (e.g., left ventricular hypertrophy, left atrial dilation)[39, 40] or could be irreversible once fibrosis develop[41]. To date, there is a substantial knowledge gap concerning how often HF develops after valvular intervention and subsequent prognosis.

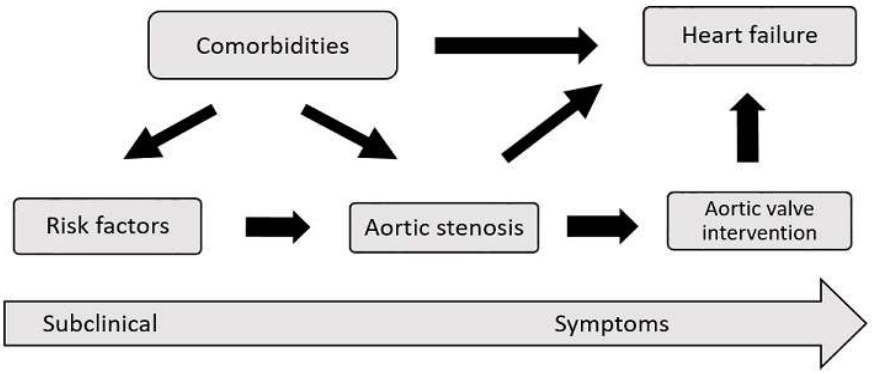


Figure 1. Relationship between AS and HF.

Treatment

HFrEF has a well-established therapy algorithm[3], resulting from several large randomised clinical trials (RCTs) showing an effect on mortality and morbidity. Therapy with ACEi[4, 42-44] or angiotensin II type I receptor blockers (ARB)[45, 46], beta-blockers[47-50], aldosterone receptor antagonists[51, 52], and a combination of the angiotensin receptor neprilysin inhibitor (ARNI), sacubitril and an ARB (valsartan), sold under the commercial name Entresto[R],[53] have all been shown to have a positive effect on morbidity and mortality. In addition, coronary revascularization[54, 55], cardiac resynchronisation therapy (CRT)[56, 57] and treatment with implantable cardioverter defibrillators (ICD)[58, 59] also have had positive effects on the survival of HFrEF patients.

Lately, progress has been made in developing new treatment modalities. The availability of sodium-glucose co-transporter-2 (SGLT2) inhibitors has opened new opportunities for effective treatment and prevention of HF. Hence, empagliflozin and dapagliflozin were shown to positively affect a composite outcome of hospitalisation for HF and cardiovascular mortality in patients with HFrEF, with or without diabetes mellitus[60, 61]. Sotagliflozin, another SGLT1 and 2 inhibitor, was recently shown to decrease cardiovascular death and hospitalisations in patients with diabetes mellitus and recent worsening of HF[62].

Moreover, vericiguat, an oral soluble guanylate cyclase stimulator, was investigated in the Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction (VICTORIA) trial. Vericiguat was administered to patients with high-risk HF and evidence of clinical worsening for which hospitalisation or urgent treatment were warranted. Death from cardiovascular causes or hospitalisations for HF were lower among those who received vericiguat than those who received placebo[63].

Very recently, a new type of positive inotropic agent has been developed. In the Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure (GALACTIC-HF) trial patients with HFrEF who were administered omecamtiv mecarbil had an 8% lower relative risk of the composite primary outcome defined as a first HF event (hospitalisation or urgent visit) or death from cardiovascular causes than those in the placebo group. This modest but significant lowering of the incidence of the primary outcome was observed across a broad range of both inpatients and outpatients[64]. Concerning these

two latest drugs, it remains to be shown if they affect survival as a primary outcome.

Unfortunately, until now, no trials could demonstrate any mortality benefit in HFpEF patients. For instance, the CHARM-Preserved trial with candesartan (n=3023 patients with LVEF >40%)[65], the I-PRESERVE trial with Irbesartan (n=4128 patients with LVEF≥45%)[66] or the PEP-CHF trial with Perindopril (n=850 patients with LVEF>40-50%)[67] could not demonstrate that these drugs influenced survival. Nor could an observational study from the OPTIMIZE registry show a positive effect of ACEi/ARB[68]. Furthermore, although beta-blockers are used frequently in HFpEF, no impact on survival could be demonstrated[68]. Nebivolol was shown to have a positive effect on the SENIORS trial. However, in this trial HFpEF was defined as LVEF ≥35% and only a limited number of patients had LVEF >50%[69]. Digitalis[70], sacubitril/valsartan[71] and spironolactone[72] did not affect hospitalisation or mortality in HFpEF. However, a benefit was shown in some subgroups of HFpEF patients[73], suggesting that further characterisation of this heterogeneous population is needed to determine the benefits of the therapy.

In conclusion, the path forward concerning HFpEF therapy is still far from clear. In addition, HFpEF patients differ from HFrEF patients in a significant way: they are older, more often women and with a high prevalence of comorbidities (e.g., hypertension, atrial fibrillation, diabetes)[23, 68, 74, 75], indicating that the way forward to improve prognosis may be to identify and treat comorbidities in HFpEF.

Prognosis

HF, irrespective of phenotype, is a lethal condition, with higher mortality than many common cancer forms[76, 77]. In a recent meta-analysis the 1-year, 2-year, 5-year and 10-year survival rates were 87%, 73%, 57% and 35%, respectively[78].

Over the past decades, we have witnessed declining mortality in HF with increased 5-year survival from 1970-1979 and 2000-2009 in the USA[79], the UK[80] and worldwide[78]. In Sweden, several studies have demonstrated similar trends, with a decrease in hospitalisation rates and 1-year mortality from 1993 to 2000[81], improved 30-day and 5-year survival from 1988 to 2004[77] and

from 2006 to 2010[15]. A recent study evaluating 1-year mortality in a Swedish population reached the same conclusion, with a decreasing trend in all-cause and cardiovascular mortality between 2005 and 2013 and a decrease in the proportion of deaths caused by CAD[82]. The improved survival was undoubtedly driven by multiple factors, including the reduction of mortality in patients with CAD[82-85], successful therapies for HFrEF, innovative interventional techniques, such as percutaneous coronary interventions (PCI), and transcatheter aortic valve implantation (TAVI). However, the initial positive trend in HF mortality came to a halt and even reversed in 2012-2015[86]. One reason for this reversal might be the observed increase in HF mortality caused by atrial fibrillation or degenerative valvular diseases[82], both age-dependent conditions.

Prognosis in HF results from the interaction between several factors, including age, hospitalisations, comorbidities, available therapy, aetiology and the structure of the healthcare system. With increasing age, patients have more comorbidities[87], complicating diagnosis and clinical care. Diabetes mellitus continues to increase globally[88] and in Sweden[89], similar to obesity[90], atrial fibrillation[91] and hypertension[92]. Concerning aetiology, more patients survive an acute myocardial infarction[82] and develop HF later in their life course. Likewise, more patients are being operated on for valvular diseases, and at older ages, more patients develop HF because of diabetes or hypertension.

To date, there are still debates about how HFrEF and HFpEF differ in prognosis because the studies addressing this issue have provided inconsistent results[20, 74, 93-96]. The discrepant results might be due to different designs, many definitions of HFpEF, varying periods of the studies in which HF therapy may vary and diverse study populations. Therefore, contemporary studies using the same definition for HFpEF in a real-world cohort are warranted.

Risk factors and comorbidities

According to the ACC/AHA guidelines for HF[97], the first stadium of HF is "at high risk for HF but without structural heart disease or symptoms of HF" (Table 2). In this phase the patient does not have symptoms or signs of HF and, with adequate measures against risk factors, the development of HF can be avoided or delayed. The most prominent risk factors for HF are hypertension, diabetes mellitus, metabolic syndrome and atherosclerotic disease. The preva-

lence of these risk factors is dynamic over time. Over the past 50 years, although body weight increased, the total cardiovascular risk factor burden decreased[90]. In addition, comparing two cohorts of middle-aged men from the general population born 30 years apart (1913 vs. 1943), the men born in 1943 had half the risk of HF after their 50s than those born 30 years earlier. However, in both cohorts atrial fibrillation, obesity, CAD, diabetes mellitus and hypertension were important precursors of HF[98].

The prevalence of hypertension and CAD is expected to increase slightly in the future[19], but the prevalence of diabetes mellitus[99] and obesity[90, 100] is expected to continue increasing considerably. This pattern is already reflected in the epidemiology of HF because HFrEF, caused more often by CAD and hypertension, decreases in prevalence, whereas HFpEF, in which diabetes and obesity play an essential part, increases.

Comorbidities in HF can be cardiovascular (hypertension, CAD, atrial fibrillation, peripheral arterial disease, etc.) or non-cardiovascular (diabetes mellitus, obesity, anaemia, renal failure, dementia, etc.). With increasing age, the comorbidity burden increases, affecting the complexity of clinical care and HF severity[101]. Advanced age also impacts survival and quality of life in HF patients. The Charlson comorbidity index is calculated by assigning a score to each comorbidity depending on the mortality risk of each condition. As an indicator of the comorbidity burden, it is a strong independent predictor of mortality in HF in the elderly[102]. In addition, the comorbidities appear to increase in prevalence. The prevalence of hypertension, diabetes mellitus and atrial fibrillation increased from 1987-2001 in patients with HF, whereas CAD was unchanged[23].

The comorbidity profile is different between HFpEF and HFrEF. HFpEF patients (men and women) have, on average, one more comorbidity than HFrEF patients[103]. In a registry study 91% of all patients with HFpEF had hypertension, diabetes or CAD[75]. In another Swedish registry study HFpEF patients had a higher number of non-cardiovascular comorbidities. They had more often hypertension, diabetes, stroke/TIA, anaemia, pulmonary or liver disease compared to HFrEF patients[104]. Still, the negative effect of comorbidities on survival was similar in the two HF phenotypes.

AORTIC STENOSIS

Definition

The aortic valve has a distinct and vital function. It is located at the aorta's base, permitting the anterograde flow from the left ventricle into the aorta and hindering the aorta's retrograde blood flow. It usually has three cusps (right, left, non-coronary), named after their anatomical relation with the Valsalva sinuses. If two leaflets fuse during embryological development, the valve becomes bicuspid, a condition estimated to be present in 1-2% of the population[105]. The normal aortic orifice in adults is 2.5-4 cm^2.

The aortic valve opens and closes approximately 3 billion times in a lifetime, functioning in a highly demanding mechanical environment, subject to considerable shear stress, leaflet flexure and tension. The aortic valve may, in some cases, degenerate, resulting in AS.

AS is defined as an obstruction in anterograde blood flow from the left ventricle into the aorta, most commonly at the valvular level. The aetiology is degenerative (the most common form in developed countries), rheumatic (prevalent in developing countries) and congenital (unicuspid valve, bicuspid valve, subvalvular or supravalvular AS). AS induces compensatory changes in the left ventricle during a long asymptomatic phase. Symptoms are angina, syncope and dyspnea. The symptoms usually appear at an advanced age (70 to 80 years), although it may develop 20 years earlier in individuals with bicuspid aorta valve[106].

Pathophysiology

AS was previously considered a degenerative disease and that the “wear and tear” caused by normal ageing was the primary pathophysiologic mechanism. However, this belief was not borne out in an echocardiographic study of elderly persons where only a small fraction (2.9%) had developed critical valve stenosis[107]. Consequently, the theory of a proliferative, inflammatory process involving cardiovascular risk factors in common with atherosclerosis was developed[108-110]. Pathological changes in blood flow, with low shear stress and abnormal flow on the aortic side of the valve are the triggers that initiate the process leading to AS, promoting defective tissue remodelling. The valve en-

dothelium's basement membrane disrupts, lipids, proteins, and calcium accumulate, leading to subendothelial thickening and a subendothelial lesion is initiated. In this early lesion inflammatory cells, macrophage (inclusive lipid-laden) and T lymphocytes infiltrate the lesion and proteins (e.g., osteopontin and osteocalcin) are produced. Simultaneously, the myofibroblasts transform into osteoblast-like cells. In the next phase a process of mineralisation and bone formation takes place. This process resembles to the atherosclerotic process[108, 111] (Figure 2).

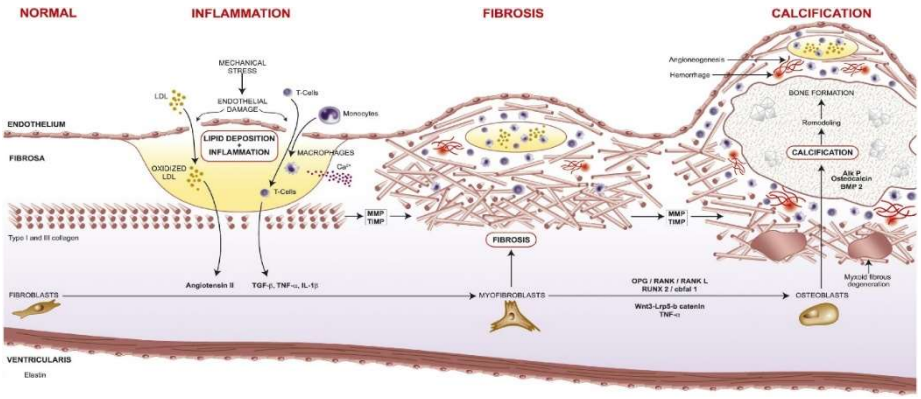
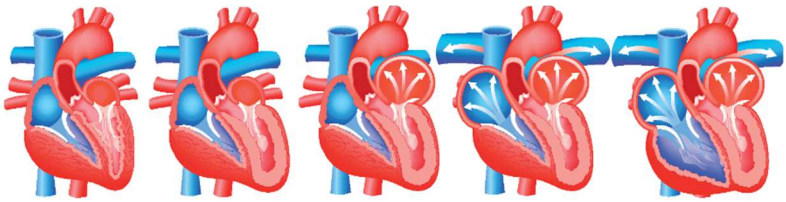


Figure 2. Summary of the pathological processes occurring within the valve during aortic stenosis: Reproduced with permission from Marc R. Dweck et al. J Am Coll Cardiol 2012; 60:1854-1863.

The stenotic aortic valve imposes a pressure overload on the LV, which compensates through remodeling and hypertrophy. Hypertrophy leads to increased myocardial mass and, in extreme cases, the heart can weigh up to 1000 g. The pattern of hypertrophy in AS is different in men and women. In women, the LV is small, hyperdynamic, with increased wall thickness. In men, the LV tends to be dilated and hypokinetic, with normal wall thickness[112, 113]. Patients with eccentric hypertrophy had a worse prognosis than those with concentric hypertrophy, even after adjusting for sex and myocardial infarction in addition to other variables, associated with poor left ventricular function[114]. In addi-

tion, with hypertrophy, the compliance of LV decreases, and the need for oxygen increases simultaneously with reduction of blood flow reserve[115, 116]. Diastolic function is also disturbed[36]. The rate of cardiomyocyte apoptosis is accelerated and fibrosis is initiated, linking hypertrophy with systolic dysfunction[117-119] (Figure 3).



Stages/Criteria	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Damage	LV Damage	LA or Mitral Damage	Pulmonary Vasculature or Tricuspid Damage	RV Damage
Echocardiogram		Increased LV Mass Index >115 g/m² (Male) >95 g/m² (Female)	Indexed left atrial volume >34mL/m²	Systolic Pulmonary hypertension ≥60 mmhg	Moderate-Severe right ventricular dysfunction
		E/e' >14	Moderate-Severe mitral regurgitation	Moderate-Severe tricuspid regurgitation	
		LV Ejection Fraction <50%	Atrial Fibrillation		

Figure 3. Cardiac stratification of aortic stenosis based on the extent of cardiac damage. Reproduced with permission from Généreux et al. Eur Heart J, Volume 38, Issue 45, 01 December 2017, Pages 3351–3358, https://doi.org/10.1093/eurheartj/ehx381.

Diagnosis

Clinically, AS is characterised by a systolic murmur with an intensity that usually, but not always reflects the severity of the lesion[120] and typically raises the suspicion of AS. The diagnosis is determined with echocardiography and is based on aortic jet velocity, maximal and mean pressure gradient over the aortic valve and aortic valve area. Echocardiography is used to assess valve anatomy and AS severity, as well as the effect on left ventricular function and structure. At the same time, it identifies associated lesions and excludes differential diagnoses (e.g., hypertrophic cardiomyopathy, mitral valve insufficiency).

Aortic sclerosis, defined as an aortic valve with increased echogenicity and diminished systolic opening and a maximal velocity over the aortic valve between 2 and 2.5 m/s on echocardiography[121], is considered an early stage of AS[122].

AS is graded according to parameters listed in Table 3 using Doppler echocardiography[121].

Table 3. Recommendations for AS severity grading according to current guidelines

	Aortic sclerosis	Mild AS	Moderate AS	Severe AS
Maximum velocity (m/s)	≤ 2.5	2.6-2.9	3.0-4.0	≥ 4.0
Mean gradient (mm Hg)		<20	20-40	≥40
Aortic valve area (cm²)		>1.5	1.0-1.5	<1.0
Indexed aortic valve area (cm²/m²)		>0.85	0.60-0.85	<0.6
Velocity ratio		>0.50	0.25-0.50	<0.25

However, the grading is not always straightforward, as the different parameters might be discordant with each other, usually with area indicating severe AS and mean gradient indicating moderate AS. Low gradient severe AS has recently been described and the dobutamine stress echocardiography and cardiac computed tomography were integrated into the assessment of AS severity[123,124].

Risk factors

The theory underlying the pathophysiology of AS led to the idea that the factors involved in the atherosclerotic process (such as hypertension, obesity, diabetes mellitus, hypercholesterolemia, male sex, smoking) could also be involved in AS development.

Hypertension affects the haemodynamic forces around the aortic valve and imposes mechanical stress on the valves. It induces similar changes on the LV, with hypertrophy and diastolic dysfunction. Although several studies have investigated the role of hypertension in development[125-129] and AS progression[130], the results are inconsistent and questionable.

Obesity is a major and increasing health problem across the world[131]. In Sweden, the prevalence of obesity in adults was estimated at 16.6% in 2016-2017. This figure has increased dramatically over the two preceding decades[132]. Obesity, associated with diabetes mellitus, dyslipidaemia and hypertension, induces a low-grade inflammatory state[133, 134], changes in heart function (increased cardiac output, diastolic dysfunction) and structure (LV hypertrophy, increased LV mass, left atrial dilation)[135]. Several studies have investigated the role of obesity in development of aortic valve calcification, AS development[125, 129, 136, 137], or AS progression[138-140]. Other studies found no correlation between BMI and AS[141, 142]. However, many of these studies had a design or follow-up that limited the possibility to investigate the effect of obesity on AS over time.

Hypercholesterolemia is an important factor in atherosclerosis. The relationship between hypercholesterolemia and AS has also been studied but again with inconsistent and mixed results[125, 129, 141, 143]. Genetic factors might also be involved in the development of AS, and factors associated with vitamin D receptor polymorphism have been described[144].

Epidemiology

Aortic valve stenosis is one of the most frequent valvular heart diseases in the Western world[145-147]. The prevalence increases with age[107, 142, 147, 148] and is expected to increase[147]. Ageing increases the risk of incident AS threefold for every 10 years[127]. AS is more prevalent in men than women[128, 147]. The inci-

dence rate is 4.9‰/year in adults[148] and a decreasing trend has been demonstrated in Sweden[149]. Aortic sclerosis is encountered in 25% of those between 65 and 74 years and in 48% in those ≥84 years[122, 142].

Natural history

Asymptomatic patients have a better prognosis than symptomatic patients, with a 1-year survival rate of 92.8% and a 5-year survival rate of 73.6%[150]. However, with the onset of symptoms, the prognosis deteriorates. In 1968, Ross and Braunwald described how survival is affected by the appearance of symptoms: expected survival was approximately 5, 3 and 2 years after the onset of angina, syncope and symptoms of HF, respectively. This description is still considered accurate[151, 152]. Symptomatic, medically treated patients with severe AS have a 5-year mortality rate of 50% and a 10-year mortality rate of 90%[153, 154].

In prospective studies the jet velocity's progression rate is 0.3±0.3m/s per year, of the mean gradient of 7±7 mmHg/year, and the valve area of 0.12±0.19 $cm/m^2/year$[155]. The disease progresses more rapidly in patients with homozygous type II hypercholesterolemia, Paget's disease and renal failure[156-159].

Treatment

No medical therapy can improve survival or delay AS progression[160-163]. The only treatment that influences the natural history is aortic valve intervention (AVI). AS is the valvular heart disease that leads most often to intervention in developed countries[146]. Briefly, AVI is indicated in patients with severe AS who have symptoms, have an LVEF <50% or undergo CABG or have other characteristics considered to have a high risk for an adverse outcome[124]. Surgical aortic valve replacement (SAVR) has been performed since 1950 and various valve types with improved haemodynamic properties have since been developed. Nowadays, under SAVR, the diseased aortic valve is replaced with a mechanical or biological prosthesis. TAVI, used in humans for the first time in 2002, evolved initially as an alternative to percutaneous aortic valvuloplasty, a procedure that has virtually been abandoned, as a solution for patients deemed inoperable due to unacceptably high risk. During TAVI, a biological valve is delivered into the place of the diseased aortic valve. TAVI is indicated in patients with high surgical risk[124]. Being non-inferior and even superior to

surgery in patients with intermediate risk[164-166] and with the rapid improvement of the transcatheter valves and implantation techniques, TAVI's indications extend gradually to patients with lower surgical risk. The overall in-hospital mortality rate was 2.9% for SAVR and 2.6% for TAVI in 2016 in Germany[167]. Three-year survival after SAVR was 90% compared to 51.6% in patients treated medically[168].

In mechanical prosthesis the major problems induced by prosthesis are the lifelong treatment with anticoagulants and its complications and, in biological prosthesis, degeneration. A biological valve's lifespan is estimated to 15 years on average in the elderly, but lower in younger individuals[169]. However, interventions ameliorate the prognosis, bringing the life expectancy of an operated patient for AS close to that of an individual without AS, especially in the elderly[170, 171] and should not be delayed when indicated.

FROM AORTIC STENOSIS TO HEART FAILURE

With ageing of the population, degenerative valvular heart diseases become more frequent and contribute to HF aetiology to a greater extent. As stated above, valvular heart diseases account for 11% of the HFpEF and 5% of the HFrEF cases.

Classically, in patients with AS it is considered that the LV function is preserved as long as the compensatory hypertrophy maintains normal wall stress despite pressure overload[172, 173]. LVEF <50% is considered a sign of disturbed systolic function and a negative prognostic factor preoperatively[174,175]. The diastolic dysfunction that intervenes in the pathophysiology of AS before deterioration of the systolic function was considered only a phase and the phenotype of HFpEF in AS is only lately being described. Indeed, in a study characterising HFpEF, 11% of the patients with AS had HFpEF and 8% HFrEF[176]. In a more recent study of severe AS patients, it was observed that LVEF started to deteriorate even when AS was still moderate and accelerated when the aortic valve area was ≤1.2 cm². At the same time, patients with LVEF between 50 and 60% had a worse prognosis than those with LVEF ≥60%, even after AVI[114]. These findings raise questions of whether other mechanisms in addition to the reduced EF impair prognosis in these patients, if the cut-off used to define LV dysfunction is too low or if the use of other echocardiographic parameters to determine systolic dysfunction besides LVEF should be used.

LVEF mainly reflects the left ventricular radial function, whereas in AS the longitudinal function is impaired earlier due to myocardial replacement fibrosis. It has been shown that left ventricular global longitudinal strain might be a more sensitive parameter to diagnose subclinical left ventricular dysfunction and to discern patients who have a poorer prognosis after AVI[177].

Moreover, the paradoxical low gradient AS (area <1 cm², mean transaortic gradient <40 mm Hg and indexed LV stroke volume <35 ml/m²) shares common features with HFpEF for pathophysiology, patient characteristics and comorbidity-driven prognosis. This form of AS is considered a systemic disease rather than a primary valvular disease[178, 179]. Therefore, HFpEF in AS patients should be studied further concerning prognosis and its influencing factors.

With an ageing population coupled with longer life expectancy, more patients develop severe AS. In addition, owing to progress in surgical and interventional techniques, more patients are operated on for AS and survive AVI. Consequently, there is an increasing population at risk to develop HF, despite intervention. It is therefore crucial to study the prognosis of HF in this population. Regrettably, differences in prognosis between HFpEF and HFrEF developed after AVI remain inadequately studied. Furthermore, it is unclear if low LVEF has the same negative importance in prognosis in these post-AVI HF cases.

The challenge in studying HF due to AS is that most patients will ultimately undergo AVI in the natural history of AS, except for those in whom intervention is delayed or considered to have an unacceptable risk/benefit ratio. Thus, to study HF development from AS in contemporary time we need to evaluate patients who underwent AVI.

Moreover, HF in AS is often multifactorial in most cases, as these patients often have CAD (approximately 50% of the patients)[180], atrial fibrillation (about 30% of the patients)[164, 165, 181] or hypertension (approximately 30% of the patients)[182]. Accordingly, HF might precede AS, be a result of AS, or appear after AVI. HF developed after AVI can be caused by complications that may occur during the intervention, by irreversible adverse cardiac remodelling despite AVI, by comorbidities, or by a combination of all these factors.

AIMS

The overall aims of this thesis were to study 1) the prognosis of HF and its influencing factors and 2) the cumulative incidence and the influencing factors of AS development, as an increasingly important causal factor of HF. This knowledge would provide better risk stratification in patients with HF and to better understanding whether and how we can prevent AS, and eventually HF.

The specific aims of the thesis were:

- To compare 5-year all-cause mortality between HFrEF and HFpEF in an elderly cohort and which factors correlate with survival.

- To study clinical phenotype and prognosis for all-cause and cardiovascular mortality and prognostic factors in patients with incident HF after valvular intervention due to AS according to HF subtypes and compared to HF without AS.

- To examine the prevalence and predictive factors of AS in a random population cohort of 50-year-old men, with a subsequent 21-year follow-up.

- To ascertain the cumulative incidence and predictive factors of AS over an extended follow-up of 43 years.

PATIENTS AND METHODS

Table 4. The participants and study design of Paper I-IV

	I	II	III	IV
TYPE OF STUDY	Retrospective	Retrospective	Retrospective	Retrospective
DATA SOURCE	Hospital cohort	SwedeHF	General population	General population
STUDY POPULATION	Patients≥65 years, hospitalized for HF	Patients operated with SAVR/TAVI for AS and HF diagnosis; matched controls	Men born in Gothenburg 1943	Men born in Gothenburg 1915-1925
NUMBER OF PATIENTS	289	549 (1748 HF + matched controls)	535	7494
MEAN AGE	79 years	77 years	71 years	51 years at screening, 61 years at final examination
FOLLOW-UP (MAX)	61 months	11 years	21 years	43 years
MAIN OUTCOMES	5 years all-cause mortality	All-cause mortality, cardiovascular mortality	Aortic stenosis	Aortic stenosis
STATISTICAL ANALYSES	Cox regression	Kaplan Meier survival analysis, Cumulative incidence function, Cox regression	Logistic regression	Cox regression

Study population

Paper I

In this paper we included consecutive patients older than 65 years, hospitalised for HF from 1 April 2007 until 30 May 2008 at the Sahlgrenska University Hospital/Östra and examined with echocardiography during hospital stay (n=386). HF was diagnosed according to the 2012 ESC guidelines, in use when the study began[8]. After the exclusion of patients without a detailed echocardiographic examination and those with severe valve disease, the final study population comprised 289 patients (Figure 4).

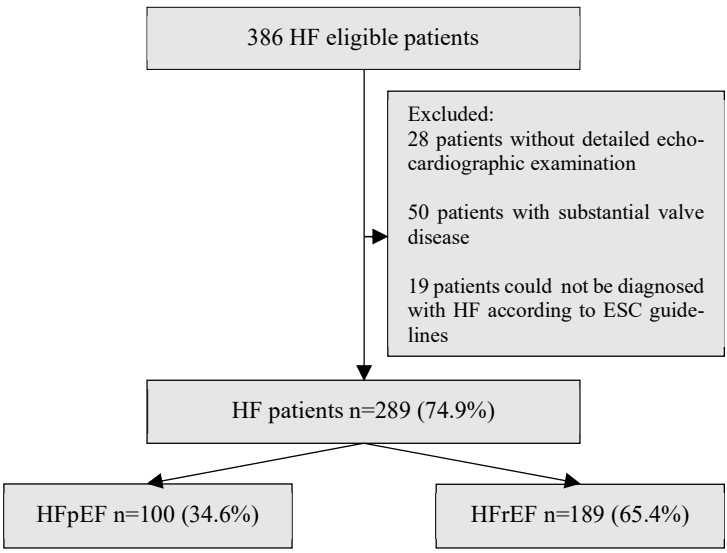


Figure 4. Flow chart of study participants, Paper I.

Paper II

The Swedish Heart Failure Registry (SwedeHF) is a noncompulsory quality registry. Established in 2001, the registry contains data about approximately half of all patients over 18 years old with HF hospitalized in a Swedish hospital, with the purpose to improve quality of life, morbidity and survival in patients with HF[16]. The inclusion criterion is HF diagnosed by a physician at any hospital. The registry contains around 80 variables that are recorded either at the discharge from the hospital or at an outpatient clinic visit. On the website http://www.ucr.uu.se/rikssvikt the protocol, registration form, and annual reports may be accessed.

The reported data are demographic (e.g. age, sex, civil status), clinical (e.g. symptoms, blood pressure, heart rate, New York Heart Association class), paraclinical (blood tests, X-ray, ECG, spirometry), comorbidities, and cardiovascular treatment. Most of the patients have a recorded LVEF, but echocardiography is not mandatory. Patients are informed about their inclusion in the registry and about their right to opt out, but individual informed consent is not requested.

In this study, we included patients from SwedeHF, registered 2003-2016, with available data on LVEF. The baseline date was the index visit in SwedeHF. The patients with AS diagnosis and SAVR or TAVI due to AS before HF diagnosis represented the study population. Patients with CABG performed before AS and those diagnosed with HF before their AS procedure were excluded. The cohort was divided into two subgroups, with LVEF ≥50% (AS-HFpEF) and <50% (AS-HFrEF). For each individual we identified three patients from SwedeHF, without history of preceding AS (control group), matched on sex, age at the index visit, age at HF diagnosis, year of HF diagnosis and LVEF, resulting in 1311 controls for the 437 patients (Figure 5).

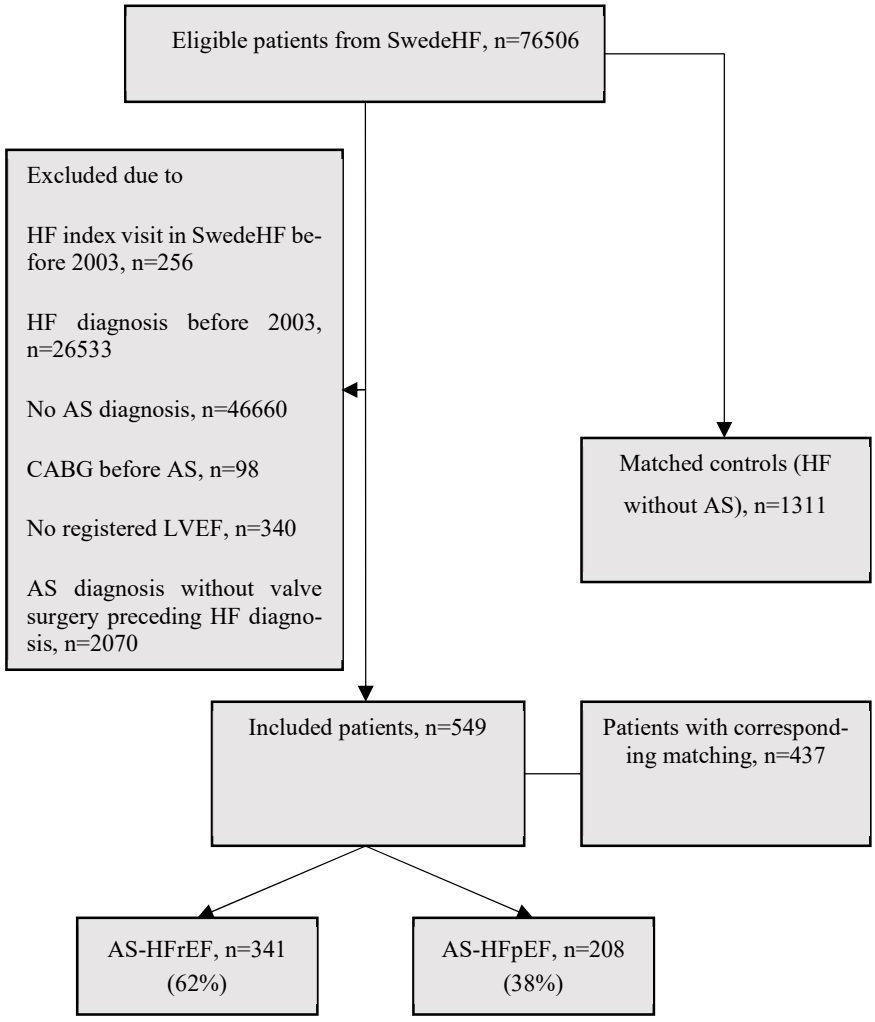


Figure 5. Flow chart of the study participants, Paper II.

Paper III

The study population derives from the 'Study of Men Born in 1943', a longitudinal, prospective population-based study of middle-aged men born 1943. A random sample (n=1463) of half of all men born in 1943 and living in the city of Gothenburg was invited in 1993 to participate. Fifty-four % (798 men) agreed to take part in the study (Figure 6).

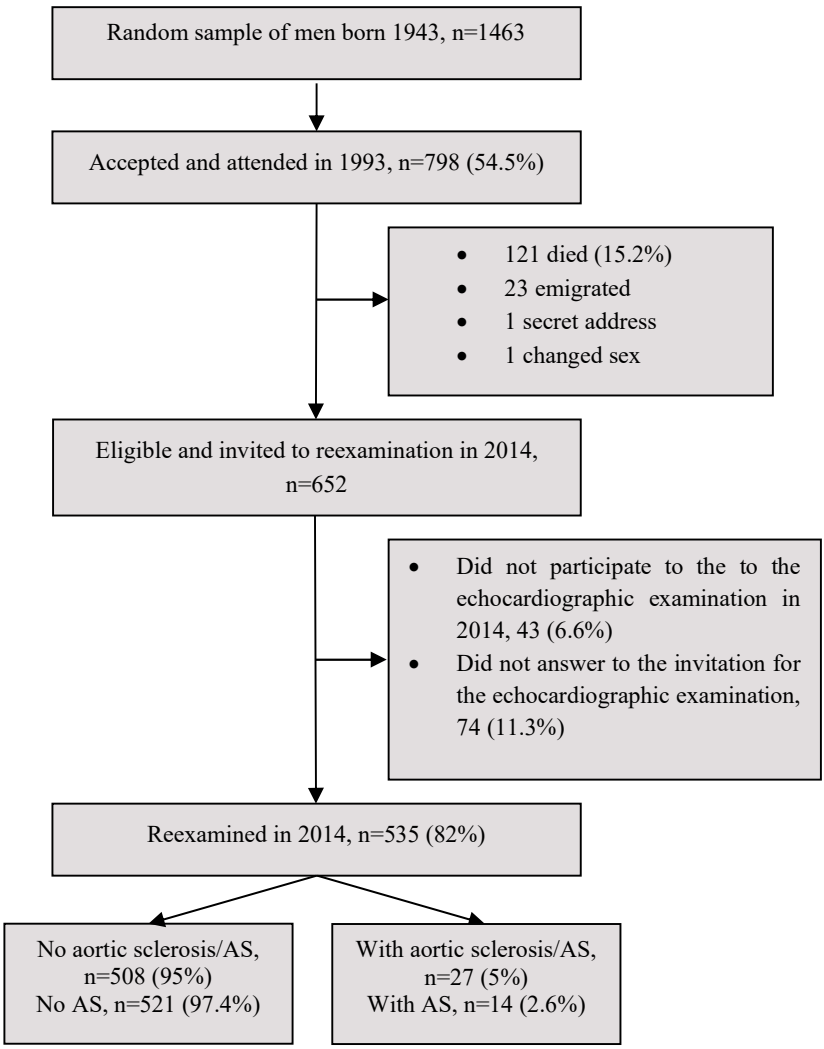


Figure 6. Flow chart of the study participants, Paper III.

Paper IV

Participants in the multifactor Primary Prevention Study (PPS) formed the study basis for this investigation. The PPS started in 1970 in Gothenburg, Sweden. All men born 1915-1925 (except 1923) in Gothenburg (30,000 individuals) were randomized into three groups, an intervention group (9998 men) and two equally large control groups (Figure 7). The participants were 47-55 years at the screening (mean age 51 years) and 57-65 years (mean age 61 years) at the reexamination/end of the intervention. The intervention was directed towards high blood pressure, high serum cholesterol and heavy smoking, but since there was no difference neither in risk factor levels nor in outcomes, this group is considered to be representative of men in the city during this period[183].

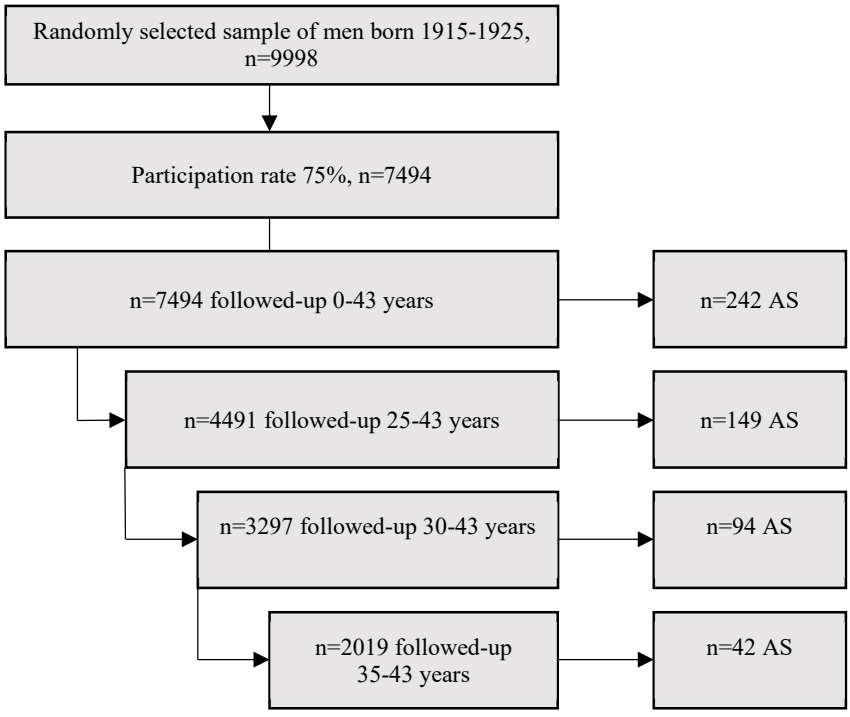


Figure 7. Flow chart of study participants, Paper IV.

Data collection and validation procedures

Paper I

All clinical, medical history and paraclinical data were collected by reviewing medical records. The patients were examined by echocardiography. We followed the patients from the index echocardiographic examination to the end of the follow-up, 1 January 2013, for an average of 61 months (range 56-69 months). HFrEF was defined as symptoms or signs of HF and an EF <50%, while HFpEF was defined as symptoms or signs of HF, EF ≥ 50%, without left ventricle dilatation (left ventricular end diastolic volume indexed <97 ml/m²) and at least one objective sign of diastolic dysfunction or structural abnormality (left ventricular hypertrophy, left atrial volume index >34 ml/m² or left ventricular mass index >95 g/m² (women) and 115g/m² (men), or a mitral annular diastolic velocity of <8cm/s).

Paper II

We identified the patient cohort and their comorbidities by accessing SwedeHF, linked with Swedish National Patient Registry (NPR) from 1997 and onwards, using the personal identification number and the ICD 10 codes shown in Table 5. The patients were followed from the index visit in SwedeHF until December 31, 2016.

The NPR was established in 1964, with nationwide coverage since 1987, with registration mandatory for all hospitalizations, and from 2001 for outpatient visits to specialized hospital clinics also. Diagnoses from primary care are not included[184]. The diagnoses are reported using the International Classification of Diseases (ICD) coding. Data from the NPR were validated through numerous studies and a review of these studies concluded that the validity of major diagnoses was high (positive predictive value 85-95%)[185]. NPR contains codes for primary and secondary diagnoses, and for procedures, alongside with data on hospital and clinic, length of the hospitalization, admission and discharge dates, or, for outpatients, date of visit.

The Swedish Cause of Death Registry contains data since 1961 and is updated annually. The registry, similar to the NPR, is kept by the Swedish National Board of Health and Welfare. Underlying and contributing causes of death are

reported by the physician in charge, either in Sweden or abroad. If the data are not of sufficiently good quality, additional data are requested[186].

Table 5. ICD 10 codes and KKÅ codes used in Paper II

DISEASE	ICD-10 CODES/KKÅ CODES
AORTIC STENOSIS	I35.0
HEART FAILURE	I50
CV MORTALITY	I00-I99
HYPERTENSION	I10,I11,I12,I13,I15
DIABETES MELLITUS	E10,E11,E12,E13,E14
ATRIAL FIBRILLATION/ FLUTTER	I48
LUNG DISEASE/COPD	J40,J41,J42,J43,J44,J45,J46, J47
STROKE/TIA	I61,I62,I63,I64, G458,G459,I639
LIVER DISEASE	B18,I85,I864,I982,K70,K711,K713,K714,K715,K717,K72, K73,K74,K760,K762,K763, K764,K765,K766,K767,K768, K769,Z944
RENAL DISEASE	Z491,Z492,DR014,DR015, DR016,DR020,DR012,DR013, DR023,DR024,TJA33,TJA35
PERIPHERAL VASCULAR DISEASE	I70,I71,I72,I73
OBSTRUCTIVE SLEEP APNEA	G473
AORTA VALVE SURGERY	FMD00, FMD10, FMD20, FMD30, FMD33, FMD40, or FMD96
TAVI	FMD12
CABG	FNA, FNB, FNC, FND, or FNE

Paper III

The participant men underwent a medical examination in 1993. Those still alive and living in Sweden in 2003 were examined again in 2003 and 2014. The medical examination included a physical examination, blood tests, and data concerning lifestyle, medical history and medical treatments were collected by questionnaires. BMI was calculated as weight (kg)/body area (m^2); BMI ≥30 kg/m² was defined as obesity. In 2014, echocardiography was added to these examinations and the aortic valve was evaluated. The groups that were analysed were men with AS or aortic sclerosis compared with men without AS or aortic sclerosis and a strictly defined group with only AS compared with men without AS.

Paper IV

The participants were examined at three occasions, 1970-1973, 1974-1977 and 1980-1983 (20% of the sample). The men included in the intervention group (9998 men) were screened for cardiovascular risk factors by filling in a questionnaire, physical examination and blood tests. The men who were considered to have high risk were treated: medical treatment for those with systolic blood pressure >175 mmHg or diastolic blood pressure >115 mm Hg, dietary recommendation for those with cholesterol >6.8 mmol/L, advice for smoking cessation for those who smoked more than 15 cigarettes/day. The participants were followed from the baseline examination, until October 2012 or their death. The follow-up time was maximum 42.8 years, mean 26.8 years. By linking the database with NPR and the Swedish Cause of Death, we identified the individuals with AS, comorbidities and death in a time-updated manner.

Outcomes

Paper I

The outcome in this study was all-cause 5-year mortality. We obtained data on death from the Swedish Death Registry and validated them by reviewing the medical journals until the end of the follow-up (1 January 2013).

Paper II

All-cause mortality and cardiovascular mortality were studied as outcome and defined as main cause of death that included ICD 10 codes I00-I99. We obtained data concerning date and underlying cause of death for cases and matched controls by linking the SwedeHF with the Swedish Cause of Death Registry.

Paper III

The outcome in this study was aortic sclerosis and aortic stenosis. Aortic sclerosis was defined as anterograde velocity recorded with continuous Doppler across the aortic valve of between 2 and 2.49 m/s and aortic stenosis as anterograde velocity of ≥2.5 m/s and thickened leaflets with reduced systolic opening. AS was considered to be mild (maximal velocity 2.5-2.9 m/s), moderate (3-3.99 m/s) and severe (≥4 m/s or operated with aortic valve replacement for AS during follow-up).

Paper IV

The outcome in this study was the same as in the third study, AS obtained from NPR. The ICD codes used were 424.10 (ICD8), 424B (ICD9), or I35.0, I35.2 (ICD10). Patients with isolated aortic insufficiency were manually identified and excluded.

Statistical analysis

Paper I, II, III, IV

The data were analysed using SAS software version 9.4 (SAS Institute Inc, Cary NC, USA) and R 3.6.2[187]. Continuous variables were expressed as mean ± standard deviation or median and IQR according to their distribution. Categorical variables were expressed as frequencies and percentages. All tests were two-tailed and conducted at 0.05 significance level, while the interaction terms were considered statistically significant at 0.10 level.

Paper I

The univariate association between the baseline variables and the HFpEF and HFrEF group were determined by the Mann-Whitney U test (for continuous variables) and Fisher´s exact test (for dichotomous variables). Cox regression analysis was used to find the independent endpoint predictors of time to death in all patients, all patients with HFpEF and all patients with HFrEF. We adjusted first for age, in a univariate Cox regression and the statistically significant predictors were further introduced in a stepwise Cox regression analysis, resulting in a multivariable model that included only statistically significant predictors. We calculated the p-values for interaction between the group variable and the predictors to find the variables that statistically differentiate the two groups with respect to mortality.

Paper II

We used Fisher's exact test for dichotomous variables, Mantel-Haenszel Chi-square trend test for ordered categorical variables, Chi-square test for not ordered variables, and Mann-Whitney U-test for continuous variables for testing between two groups (AS-HFpEF vs AS-HFrEF). We described time-to-event by n (%), event rate with 95% CI, and Kaplan-Meier curves presented time to all-cause mortality. The cumulative incidence function was used for time to CV mortality, considering other reasons for death as competing risk. In order to evaluate the relative difference between AS-HFrEF vs AS-HFpEF and between AS-HF vs control group, we used adjusted Cox proportional hazards models. We analyzed also the interaction between LVEF category and patient/control group. We identified predictors for time to death in AS-HFpEF and AS-HFrEF patients, using age and sex adjusted Cox regression. The interactions between the predictive factors and the two LVEF groups (AS-HFpEF, AS-HFrEF) with respect to the outcome were studied.

Paper III

Logistic regression was used to detect the univariable and multivariable associations between the baseline variables and the two subgroups of individuals (with and without aortic sclerosis or AS). We used stepwise selection to choose the best set of independent (explanatory) variables. Odds ratios (ORs) with 95% confidence intervals (95%CIs) were presented to describe the effect size.

The area under the receiver-operating curve (ROC) with its 95%CI was presented as goodness of fit. We analysed separately a subgroup with patients strictly with AS. We controlled the results by using the Firth's logistic regression method considering the low outcome prevalence, and obtained the same results.

Paper IV

Taking into account the long follow-up (43 years), in order to control, at least partially, the effect of the baseline factors on the death as a competing risk, we divided the follow-up period into three overlapping intervals: 1) between 25 and 43 years, 2) between 30 and 43 years and 3) between 35 and 43 years. The comorbidities were time-updated. These associations between the risk of AS and the baseline factors and the time-updated comorbidities were analyzed with Cox proportional hazards regression model, covariates being age and the baseline factor. The cumulative incidences of AS and the association for some baseline factors were analyzed and presented in diagrams.

Ethical approvals

All the studies were approved by the Ethical Committee at the University of Gothenburg and conformed to the ethical guidelines issued in the 1975 Declaration of Helsinki. The record number of the approvals (DNR) are: *Paper I* 709-13; *Paper II* 2013/392-32; *Paper III* 886-13,T187-16; *Paper IV* L103-99, T051-99, Ö375-00.

RESULTS

Paper I

Long–term prognosis of patients with heart failure in a hospitalised cohort

Clinical characteristics:

The study population had a mean age of 79 years and the HFpEF patients were 5 years older than HFrEF patients. In the HFpEF group women were more numerous compared to men in the HFpEF group (56%), while in the HFrEF group men predominated (36% women). The patients with HFpEF were more often diagnosed with atrial fibrillation, hypertension and less often with ischemic heart disease and diabetes mellitus. The HFpEF patients were, despite their high mean age of 80 years, frequently treated with beta-blockers (80%) and ACEIs/ARBs (82%). However, as expected, the HFrEF patients were more often treated with ACEIs/ARBs and statins.

Outcome

The study population had a high 5-year mortality, of 67.5%. After adjustment for sex, age led to 7.2% higher risk to die per year. Adjusting for age, we found that HFrEF patients had a 42% higher mortality compared with HFpEF patients. Even after adjustment for sex and age, HFrEF patients tended to have a poorer survival than HFpEF patients did and this was more obvious in women. The risk to die for a woman of 70 years with HFrEF was 135% higher than for a woman of same age with HFpEF (Figure 8), while for men the difference was not statistically significant. In the very old (over 90 years), there was no difference in mortality.

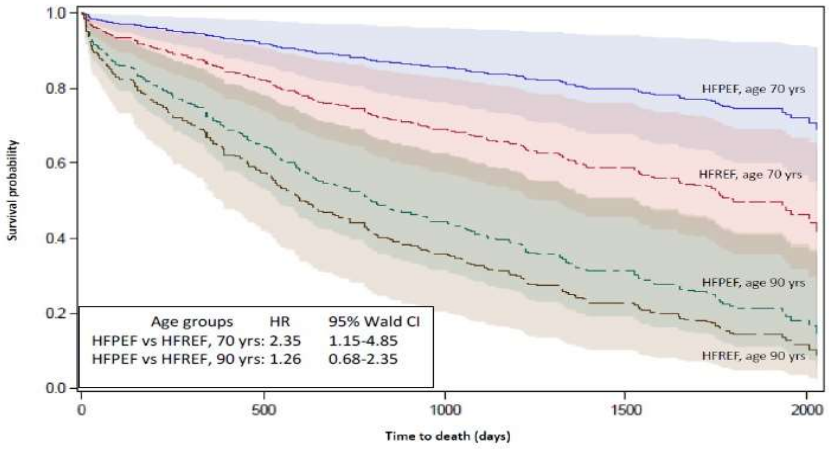


Figure 8. Estimated survival in HFpEF and HFrEF in two age groups (70- and 90-year- old) in women.

Prognostic predictors

The factors that predicted higher mortality in the whole cohort were sex, age, hypertension, atrial fibrillation, PCI, LVEF, treatment with ACEIs/ARBs, aldosterone receptor antagonists and loop diuretics. Aldosterone receptor antagonist and loop diuretics predicted lower survival, whereas treated hypertension, PCI, LVEF and treatment with ACEIs/ARBs predicted better survival in multivariable analysis.

Analyzing separately the two groups, with HFpEF and HFrEF, we found that they had different prognostic risk profiles, with different prognostic factors negatively associated with prognosis in HFpEF (age, female sex, pulmonary disease renal dysfunction, aldosterone receptor antagonist and loop diuretics) and HFrEF (age, atrial fibrillation, NT-proBNP and loop diuretics). The factors that were positively associated with survival were also different in HFpEF (ACEIs/ARBs and statins) and HFrEF (sinus rhythm, treated hypertension, percutaneous coronary intervention, ACEIs/ARBs and BBs).

Paper II

Prognosis and determinants of prognosis in heart failure patients who underwent aortic valvular intervention

Clinical characteristics

Between 2003 and 2016, 76506 patients were registered in the SwedeHF. After exclusion of the patients according to the exclusion criteria described in "Methods", 549 patients remained. Of these, 341 (62%) had LVEF <50% (AS-HFrEF) and 208 (38.0%) ≥50% (AS-HFpEF).

Comparing AS-HFrEF and AS-HFpEF patients, the AS-HFpEF patients were older (77.4% vs. 65.4% were ≥75 years), more often women, had a lower heart rate, lower mean hemoglobin value and more often were diagnosed with atrial fibrillation (as a comorbidity) and less often with left bundle branch block and peripheral arterial disease. They were treated more often with mineralocorticoid receptor antagonists (MRA) and diuretics and less often with ACEi/ARBs.

We matched the whole cohort with three controls with HF, without AS, resulting in a control group of 1311 individuals. The AS patients had lower diastolic blood pressure, mean arterial pressure and hemoglobin values, more often pacemaker rhythm, or other arrhythmias (except atrial fibrillation at the index visit), atrial fibrillation as a comorbidity, peripheral arterial disease, treatment with statins and anticoagulants.

Outcome

Concerning outcomes, all-cause mortality in the whole group of 549 patients was 50.3%, 47.8% in AS-HFrEF group and 54.3% in the AS-HFpEF group. The crude CV mortality was 30.2% in the whole group, 29.6% in the AS-HFrEF group and 31.3% in the AS-HFpEF group (Table 6).

Table 6. Event rate for all patients included in Paper II, grouped by LVEF

ENDPOINT	SUBGROUP	EVENTS, N (%)	FOLLOW-UP TIME (YEARS) MEDIAN (IQR)	EVENT RATE PER 100 PERSON YEARS (95% CI)*
ALL-CAUSE MORTALITY	**All patients**	276 (50.3%)	2.53 (0.98-4.87)	16.0 (14.2 - 18.1)
	LVEF <50%	163 (47.8%)	2.42 (0.93-4.87)	15.4 (13.1 - 18.0)
	LVEF ≥50%	113 (54.3%)	2.70 (1.10-4.86)	17.1 (14.1 - 20.5)
CV MORTALITY	**All patients**	166 (30.2%)	2.53 (0.98-4.87)	9.7 (8.2 - 11.2)
	LVEF <50%	101 (29.6%)	2.42 (0.93-4.87)	9.5 (7.8 - 11.6)
	LVEF ≥50%	65 (31.3%)	2.70 (1.10-4.86)	9.8 (7.6 - 12.5)

95%CI computed by using exact Poisson limits

All-cause mortality in AS-HF, grouped by EF and compared to matched controls is presented in Table 7. The median follow-up time was 2.80 years, IQR (1.18-5.07) for AS patients and 2.88 years, IQR (1.02-5.45) for the matched controls.

Table 7. Event rate for all patients included in Paper II, grouped by LVEF

		AS PATIENTS		MATCHED HF PATIENTS WITHOUT AS	
ENDPOINT	**SUB-GROUP**	**EVENTS N (%)**	**EVENT RATE PER 100 PERSON-YEARS (95% CI)***	**EVENTS N (%)**	**EVENT RATE PER 100 PERSON-YEARS (95% CI)***
ALL-CAUSE MORTALITY	**ALL PATIENTS**	214 (49.0%)	14.7 (12.8 - 16.9)	586 (44.7%)	13.0 (12.0 - 14.1)
	LVEF <50%	120 (44.6%)	13.4 (11.1 - 16.1)	341 (42.3%)	12.2 (11.0 - 13.6)
	LVEF ≥50%	94 (56.0%)	16.9 (13.6 - 20.6)	245 (48.6%)	14.2 (12.5 - 16.1)
CV MORTALITY	**ALL PATIENTS**	122 (27.9%)	8.4 (7.0 - 10.0)	349 (26.6%)	7.7 (6.9 - 8.6)
	LVEF <50%	72 (26.8%)	8.1 (6.3 - 10.1)	207 (25.7%)	7.4 (6.4 - 8.5)
	LVEF ≥50%	50 (29.8%)	9.0 (6.7 - 11.8)	142 (28.2%)	8.2 (6.9.7)

95%CI computed by using exact Poisson limits

Even if the all-cause mortality and CV mortality seemed to be different comparing AS-HFpEF to AS-HFrEF patients, and patients with AS and HF with matched controls without AS, after adjusting for age at index visit and sex, we did not find a statistically significant difference between these groups. In addition, we adjusted for age at HF diagnosis, years between AVI and HF diagnosis, smoking, mean arterial pressure, haemoglobin, eGFR and comorbidities (atrial fibrillation, stroke/TIA, renal disease, peripheral vascular disease, hypertension, diabetes and lung diseases), but there were still no significant differences in mortality between AS-HFpEF and AS-HFrEF, or between these patients and their matched controls (Figure 9).

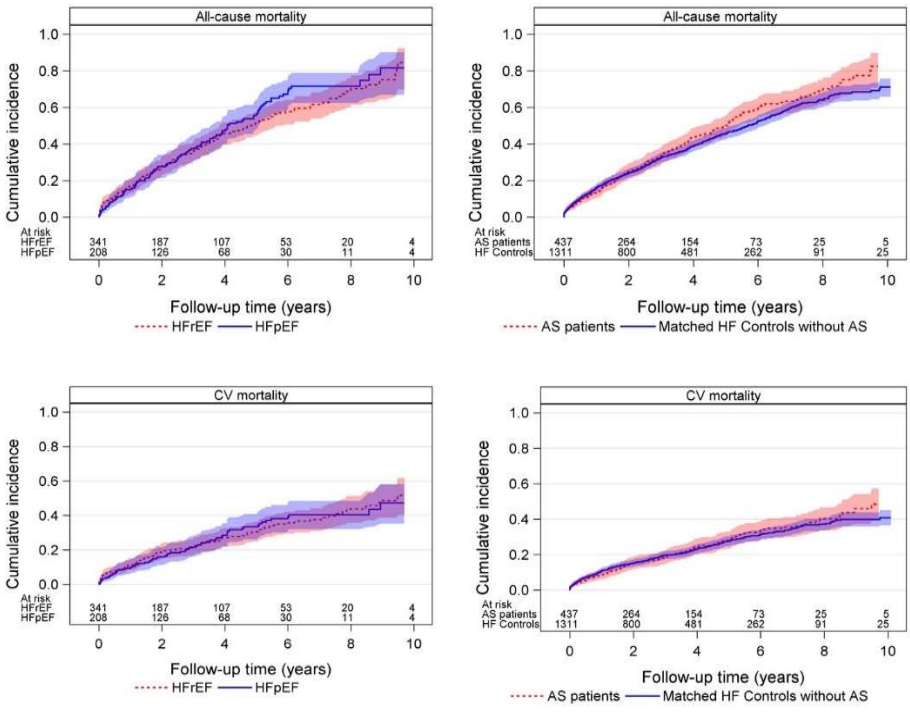


Figure 9. Comparison of all-cause mortality and CV mortality for AS-HFpEF compared with AS-HFrEF (left) and patients with AS and HF compared with matched controls (right).

Prognostic predictors

We addressed the issue if there are different predictive factors for higher survival in the two subgroups, AS-HFpEF and AS-HFrEF. Age (both at HF diagnosis and index visit), duration between AVI and index HF visit were predictive factors for lower survival in both AS-HFpEF and AS-HFrEF. However, atrial fibrillation (HR 1.43; 95%CI 1.02-2.02) and diabetes mellitus (HR 1.67; 95%CI 1.21-2.31) predicted lower survival only in HFrEF, while only for diabetes mellitus the p for interaction was statistically significant (p for interaction 0.041).

Paper III

Prevalence and risk factors of aortic stenosis and aortic sclerosis during 21-year follow-up of middle-aged men

Prevalence

The prevalence of AS or aorta sclerosis among the 535 men who were examined in 2014 was 5% and of AS 2.6%, with 36% having mild, 21% moderate and 43% severe AS.

Baseline characteristics

The baseline characteristics of the men diagnosed with aortic sclerosis or AS were similar with the individuals without AS or aortic sclerosis concerning smoking habits, physical activity, occurrence of hypertension, levels NT-proBNP, high sensitive troponin T (hs-TnT), calcium, and high sensitive C-reactive protein (hs-CRP). However, men with aortic sclerosis or AS were more often obese (29.6% vs. 9.3%), had a higher prevalence of hypercholesterolemia (51.9% vs 32.1%) and diabetes mellitus (7.4% vs. 1.2%). Regarding the strictly defined group with AS, the only difference was concerning baseline BMI ≥30 kg/m² (28.6% vs. 9.8%).

Risk factors

Baseline BMI, both as a continuous and a categorical variable (BMI≥30 kg/m²), was significantly correlated with the diagnosis AS or aortic sclerosis after 21 years (OR [95%CI] 1.23[1.10-1.38], p=0.0002, respective OR [95%CI] 4.13 [1.71-9.95], p=0.0016), as well as hypercholesterolemia at baseline. These two factors in combination had a higher prediction value than hypercholesterolemia alone (OR 4.73 vs. 2.28), Figure 10. In the multivariable stepwise regression model applied to compare these two groups, BMI increased the odds of developing aortic sclerosis/AS, with an OR per unit of 1.23 (95%CI 1.10-1.38; p=0.0003). The other factor that was significantly correlated with development of aortic sclerosis/AS after 21 years was a combined variable of total cholesterol >6.2 mmol/l and hs-CRP >1 (OR [95%CI] of 2.66 [1.18-6.00], p=0.019) Figure 10. In the strictly defined group with only AS

compared to the group without AS, in univariable analysis only BMI as a continuous and as a categorical variable was associated with increased odds to develop AS diagnosis after 21 years, see Figure 11.

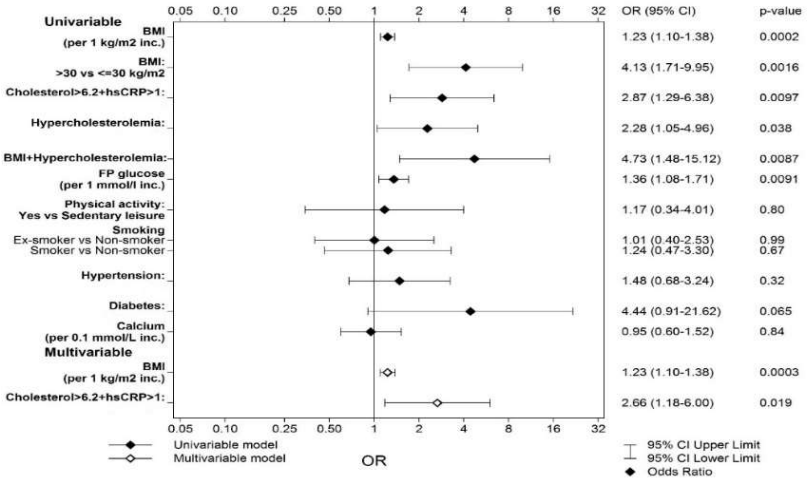


Figure 10. Forest plot illustrating factors associated with aortic sclerosis or AS in univariable and multivariable analysis.

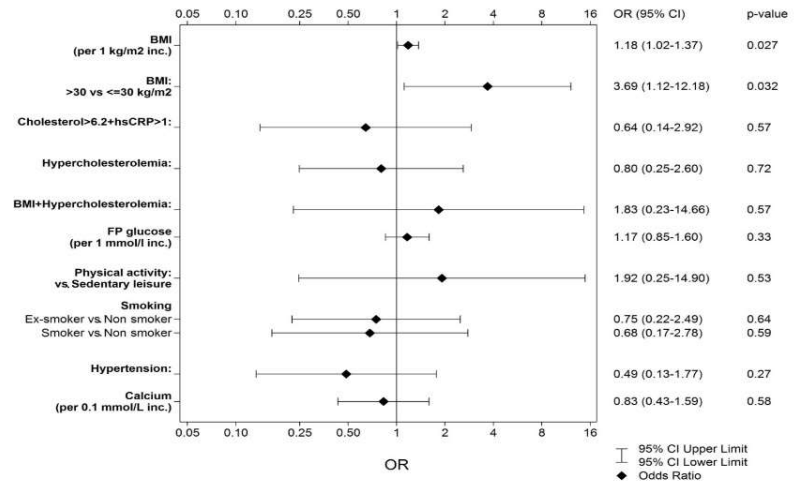


Figure 11. Forest plot illustrating factors associated with AS univariable analysis.

Paper IV

Lifelong cumulative incidence and predictors of acquired aortic stenosis in a large population of middle-aged men followed for up to 43 years

Cumulative incidence

Following the 7494 participants, we found that 242 were diagnosed with AS under the 43 years of follow-up, resulting in a cumulative incidence of 3.2%.

Baseline characteristics

The participants had a mean age of 51 at the baseline examination. The participants with the longest follow-up, surviving more than 35 years had a lower weight and BMI at screening, had gained less weight from age 20, had lower levels of blood pressure, pulse pressure, heart rate, and total cholesterol. They were also less sedentary, with fewer smokers and family history of stroke or myocardial infarction. The comorbidities of the participants were time-updated and, as expected, had higher prevalence in the group surviving longest.

Risk factors

The associations between baseline variables and time-updated comorbidities with AS diagnosis were investigated with age-adjusted analyses and are presented in Table 8. There were statistically significant associations between AS and the following variables: weight, BMI, obesity, serum cholesterol. In addition, hypertension, CAD, atrial fibrillation, heredity of stroke in siblings, current smoking compared with nonsmoking were also correlated with the risk to develop AS (Table 8).

We present in Figure 12 the cumulative incidence of AS generally and in Figure 13 and 14 the cumulative incidence of AS in relationship with several baseline factors.

We analyzed closely the association between baseline BMI and AS. It was a curvilinear relationship, with wider CI at higher BMI levels. Using BMI 20-22.5 kg/m² as reference category, we found that men with BMI 25-27.5 kg/m² had a HR of 1.99 (CI 95% 1.12-3.55, p=0.019) to develop AS, while the HR

was 2.98 (CI 95% 1.65-5.40 p<0.001) in those with BMI 27.5-30 kg/m² and 3.55 (CI 95% 1.84-6.87, p<0.001) in those with BMI ≥30 kg/m².

Table 8. Baseline levels and prevalence of risk factors in the study population in Paper IV at four overlapping periods shrinking towards the end of follow-up

Follow-up interval	0 – 43 years	25 - 43 years	30 – 43 years	35 – 43 years
	Screening age- adjusted HR (95% CI)			
BMI (per BMI unit)	1.08(1.04-1.12)	1.09(1.03-1.15)	1.07(1.00-1.15)	1.12(1.01-1.24)
Weight at screening (per kg)	1.02(1.01-1.03)	1.02(1.01-1.04)	1.02(1.00-1.04)	1.03(1.00-1.06)
Obesity (yes/no)	1.64(1.08-2.51)	1.83(1.07-3.12)	1.62(0.78-3.35)	3.13(1.31-7.45)
Cholesterol (per mmol/L)	1.26(1.15-1.39)	1.29(1.15-1.46)	1.22(1.04-1.43)	1.07(0.82-1.40)
Smoking never vs current	1.32(0.99-1.77)	1.54(1.05-2.25)	1.89(1.18-3.03)	2.08(1.07-4.07)
Family history of stroke, siblings (yes/no)	2.02(1.07-3.80)	2.86(1.40-5.84)	3.61(1.58-8.27)	4.35 (1.34-14.09)
Hypertension (yes/no)	1.40(1.09-1.80)	1.57(1.14-2.17)	1.86(1.23-2.82)	1.77(0.95-3.31)
CAD (yes/no)	1.54(1.09-2.18)	1.47(1.03-2.08)	1.61(1.06-2.45)	1.49(0.80-2.75)
Atrial fibrillation (yes/no)	-	2.00(1.19-3.37)	2.25(1.37-3.69)	2.30(1.19-4.44)

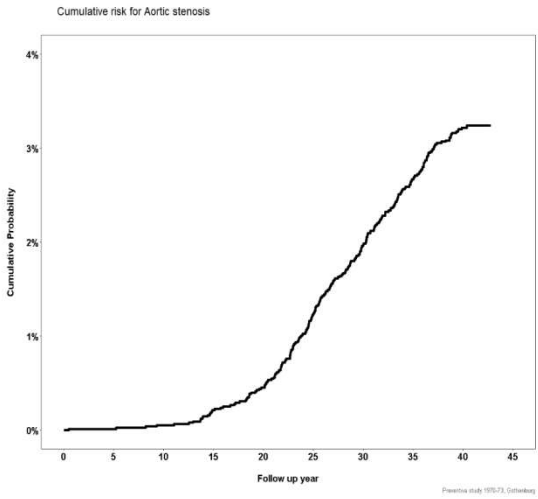


Figure 12. Cumulative incidence of AS in the overall study population.

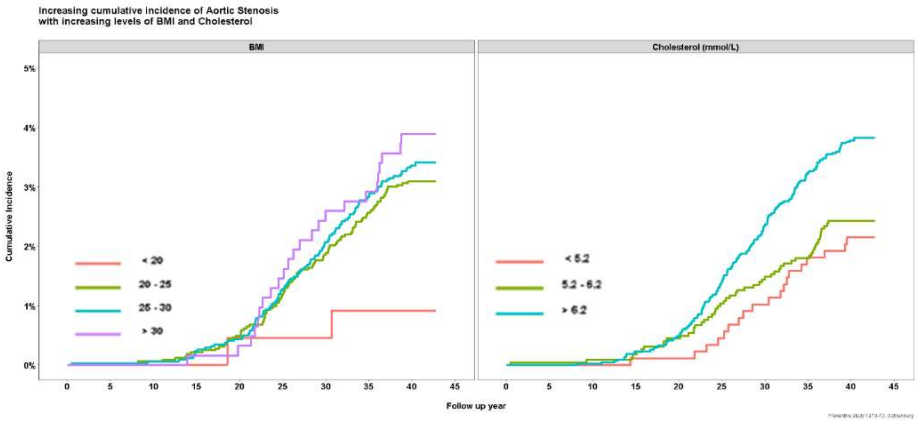


Figure 13. Cumulative incidence of AS according to BMI and cholesterol.

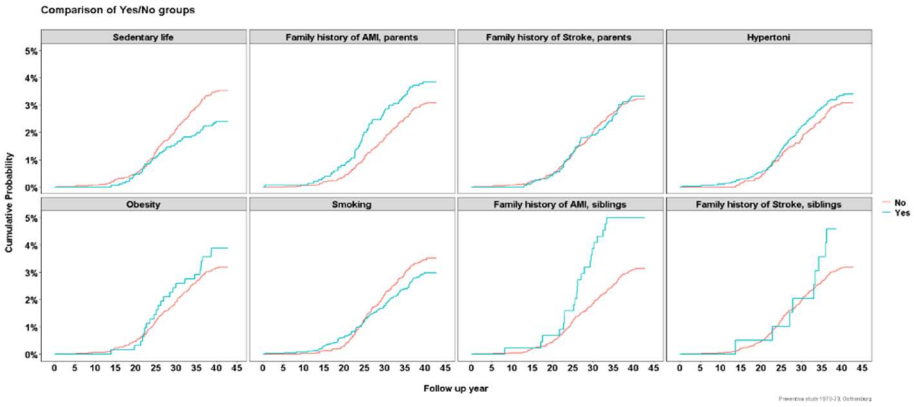


Figure 14. Cumulative incidence of AS according to categorical baseline factors.

DISCUSSION

Discussion of the results

Prognosis of HF: HFpEF vs. HFrEF

A controversial issue is whether HFrEF and HFpEF are independent and separate entities and have a different prognosis. Previous findings have not been conclusive on this matter and have even been contradictory. One of the supporting articles of this thesis found that mortality in HFrEF was higher than in HFpEF, most notably in 70-year-old women but with no difference in those aged >90 years. However, other studies have reported that patients with HFpEF have either better[93, 94, 188-193] or the same survival[20, 74, 96, 194-197] as HFrEF patients. For example, Shah et al, studying hospitalised patients with HF with a mean age of 80 years (HFpEF patients were 2 years older than HFrEF patients), found high 5-year mortality of about 75%, which is similar to the mortality rate in our paper. Contrary to our results, there was no difference in mortality between patients with HFpEF and HFrEF, even after adjusting for age and multiple other variables[20]. However, patients with LVEF between 41-49% were analysed separately and not included in the HFrEF group, as in our study.

In a prospective multicentre study, age- and sex-adjusted 2-year all-cause mortality was similar between HFpEF and HFmrEF patients but lower than in HFrEF patients[193]. A Danish study of patients admitted to hospital for new or worsening HF showed that patients with a systolic dysfunction carried a higher mortality risk than those with normal LVEF. The difference in survival between patients with and without systolic dysfunction was no longer evident in patients >80 years[94]. These results are comparable to ours, showing that the survival benefits that patients with HFpEF have over those with HFrEF disappear in very old age. A meta-analysis found that HFpEF patients had better-adjusted survival compared to HFrEF patients. This difference was more pronounced in ambulatory than in hospitalised patients and, similar to our findings, decreased with increasing age[95].

In Paper I, we only examined hospitalised HF patients, partly explaining why the difference in survival was not significant in men. In addition, patients with HFpEF, being older and with a considerable comorbidity burden, might be prone to be evaluated as not suitable for advanced life-sustaining treatments and palliation might be more often used, mostly without the need to hospitalise the patient. This evaluation strategy might influence the prognosis despite appropriate adjustment for age.

One reason for the discrepant results regarding prognosis in HFrEF compared to HFpEF is the lack of a universal definition of HFpEF. The definition of HFpEF has changed over time, from symptoms and LVEF ≥50%[5], afterwards adding criteria for diastolic dysfunction[8] and later on adding biomarkers in the latest guidelines from 2016[3]. Our study strictly applied the criteria defined in the 2012 European guidelines, which were in use when the present study began. Besides symptoms and EF ≥50%, these guidelines required echocardiographic signs of structural abnormalities or diastolic dysfunction. The patients who did not have all the diastolic parameters needed to diagnose HFpEF were excluded from our study to ensure a 'real' HFpEF population.

Another cause for the heterogeneity of the HFpEF prognosis results is the use of different LVEF cut-off values (values varied from ≥40 to ≥55%)[198]. We used the cut-off value of 50% to differentiate HFpEF and HFrEF and did not have an HFmrEF group because the guidelines in 2012 did not define HFmrEF.

In this thesis 5-year all-cause mortality was high, nearly 68% in these patients with a baseline mean age of 79 years; age increased the death risk by 7.2% per year, even after adjusting for sex. Comparing HFpEF with HFrEF patients, the HFpEF patients were typically older, more often female and with a history of hypertension and AF. After adjusting for age and sex, the mortality in HFrEF women was higher than in HFpEF women, and the difference was most pronounced by age 70, levelling off in those >90.

In our study not only were the results on mortality in accordance with those previously published, but the clinical characteristics of our cohort also were similar to those customarily recognised as a typical HFpEF phenotype (older, more often women, with a higher prevalence of hypertension and atrial fibrillation and lower CAD)[74, 94, 95, 199].

Impact of sex difference on prognosis in HF

In our study the difference in survival was most pronounced and statistically significant in women. There are several reasons for this finding. Because most RCTs include fewer women than men, sex differences could not be established. However, some studies investigated HF prognosis, comparing men and women. For instance, an epidemiologic study in the Framingham cohort showed that women with HF, regardless of the type of HF and aetiology, had better survival than men[200]. A study using the ancillary arm of the Digitalis Investigation Group trial showed the same crude 3–year mortality (25%) for men and women with HFpEF; however, after adjusting for age and other variables, better survival was observed in women than in men with HFpEF[201]. In this study the cohort was younger than ours, with a median age of 70 years. Women had greater HF severity and half had ischemia as the cause of their HFpEF. Another study, assessing HFrEF patients, demonstrated sex differences in survival. This study analysed five randomised trials in HFrEF patients and found that women had better survival than men despite comparable LVEF. The difference was most pronounced in those with HFrEF of non-ischemic aetiologies[202]. In conclusion, there are sex-dependent differences in HF prognosis and women tend to have a better prognosis than men across the entire HF spectrum. Moreover, there is a greater HF therapeutic benefit in women compared to men. In a subgroup analysis of the PARAGON-HF, sacubitril-valsartan seemed to reduce the risk of HF hospitalisation more in women than in men[203].

Impact of other factors on prognosis in HF

In this thesis, in HFrEF, factors associated with higher mortality were age, atrial fibrillation, high NT-proBNP and treatment with loop diuretics. Factors associated with a positive effect on survival were sinus rhythm, PCI, treatment with ACEi/ARB and beta-blockers. Factors associated with higher mortality in HFpEF patients were age, female sex, renal dysfunction, pulmonary disease and treatment with aldosterone receptor antagonist or loop diuretics. Factors that correlated with lower mortality were treatment with statins and ACEIs/ARBs. Consistent with our study, a previous study that included patients with HF from the SwedeHF registry showed a positive effect of renin-angiotensin system antagonists on survival in patients with HFpEF[204]. Although there is a theoretical basis to explain a positive impact of ACEi/ARB in

HFpEF, the RCT[65-67] did not show that this group of medicines positively affects mortality or rehospitalisations[65, 67]. The most recent trial with the combination sacubitril-valsartan compared with valsartan could not demonstrate improved survival in HFpEF patients[71].

Comorbidities contribute to increased morbidity and mortality and impaired quality of life in HFrEF and HFpEF[101, 104], which was confirmed in our study, in which pulmonary disease and renal dysfunction were associated with worse survival. Because in HFpEF there are virtually no effective treatments, treating comorbidities becomes even more important.

The prognostic factors were also investigated in Paper II. In this case factors correlating with higher mortality were roughly the same in the AS-HFpEF and AS-HFrEF groups. Only diabetes mellitus predicted worse survival in the AS-HFrEF group but not in the AS-HFpEF group. The relationship between diabetes mellitus and HF is multifactorial through a cardiotoxic tetrad, including CAD, hypertension, diabetic cardiomyopathy and fluid overload[205]. Our findings suggest that patients with HFrEF, in which AS had an important part in HF aetiology, are more prone to be affected negatively by this factor.

Impact of aortic valvular intervention on HF prognosis

Structural valvular heart disease may lead to HF unless valvular intervention is performed. In paper I we found that 14% of patients with HF identified by echocardiography had significant valvular diseases. However, the exact incidence and prognosis of HF with valvular heart disease as the primary aetiology remain unclear. Studying this issue is challenging because a significant structural valvular heart disease will be actively considered for valvular intervention before HF develops in clinical practice. Consequently, a natural development of valvular heart disease to HF without valvular intervention is uncommon, occurring only in patients for which the intervention has been delayed or has an unacceptable high risk-benefit ratio.

Nevertheless, the post-AVI population will probably increase as more patients with severe AS undergo AVI before HF develops. In addition, AS prevalence keeps increasing along with the ageing of the population and AVI, especially with TAVI becomes more common. However, HF developing in patients who undergo valvular intervention remains inadequately studied.

In this thesis we investigated the prognosis of incident HF after SAVR or TAVI due to AS by two parallel comparisons: comparing AS-HF and matched HF without precedent AS (general HF population) and comparing patients with HF after AVI for HF phenotype. The all-cause and CV mortality were similar between the incident HF after AVI and HF in the general population. This observation suggests that intervening on the aortic valve, considering the peri- and postoperative complications and the complications rendered by a valve prosthesis, AVI alters the disease course of AS, considerably improving survival. This improvement has been shown in other studies, where AS patients who underwent surgery had nearly the same survival as the general population, especially among the elderly[148, 171, 206].

Considering the findings from Paper I, we hypothesised in Paper II that the mortality in the AS-HFpEF group should be lower than in the AS-HFrEF group. However, both all-cause and CV mortality were the same between these two phenotypes, suggesting that, despite AVI, the post -AVI population is still different from a general HF population in which HFrEF appears to have a worse prognosis than HFpEF (as shown in Paper I). Accordingly, factors correlating with higher mortality were roughly the same comparing the AS-HFpEF and AS-HFrEF groups post-AVI, but different in the HFpEF and HFrEF patients generally, as demonstrated in Paper I. However, for clinical characteristics, we did not observe differences between AS-HFpEF and HFpEF from the general HF population: they were older, more often women, with a higher prevalence of atrial fibrillation and lower prevalence of left bundle branch block, peripheral arterial disease or PCI. Thus, these patients were part of a typical HFpEF population.

The stenotic aortic valve produces a pressure overload on the left ventricle, which compensates with hypertrophy to maintain cardiac output. Hypertrophy leads to impaired blood flow reserve[115], apoptosis of the cardiomyocytes and myocardial fibrosis[117, 119]. In this way the left ventricle begins to fail, first in its diastolic function[36] and then in its systolic function[173]. Although the reduced LVEF is considered occurring in a more advanced AS stage and a marker of severity[207], our results show that patients operated for AS have the same grim prognosis, irrespective of LVEF. One explanation might be that, by intervening on the aortic valve with SAVR or TAVI, the differences in survival between HFpEF and HFrEF patients are virtually eliminated. In addition, in Paper II we excluded patients with prior CAGB, i.e. patients in whom LVEF

might play a more critical role. Moreover, the LVEF, while being a central parameter in decision taking in AS patients, may not be the most appropriate parameter to evaluate LV systolic function, or the cut-off to define reduced systolic function might be inappropriate. However, in our study we could not investigate HF incidence in patients with AS because SwedeHF, as an HF registry, does not contain AS patients without HF, nor does it have complete coverage of all HF patients.

Aortic stenosis - prevalence and cumulative incidence over decades

Structural valvular heart disease occur in a large number of HF cases, although the exact prevalence of HF caused by valvular heart disease remains unclear. Obviously, with the increasing severity of valvular heart disease, more HF cases occur. Among patients with severe AS, HF was highly prevalent and LVEF <55% was seen in ~30–50% of the patients with severe AS[165, 208, 209], leaving little doubt that severe AS is an important cause of HF.

AS is a slowly progressing disease that develops over decades. In this thesis we focused on its prevalence and cumulative incidence over 2-4 decades. After a follow-up of 21 years, we found an AS prevalence of 2.6% among Swedish men aged 71 and a cumulative incidence of 3.2% over a follow-up of 43 years.

The AS prevalence has been investigated before, with variable results[107,142,147,148]. These differences were possibly due to many factors: lack of a common definition of AS, use of different echocardiographic criteria (e.g., peak flow, mean gradient), heterogeneous study populations, diverse study designs and different study periods. In the European and American echocardiography society guidelines, the cut-off to diagnose AS was maximal transvalvular velocity ≥2.5 m/s and for aortic sclerosis from 2-2.5 m/s[210]. In the AHA/ACC 2014 guidelines the velocity between 2 and 2.5 m/s was used to define mild AS[211]. We used both cut-offs in our study, analysing separately patients with only AS and those with aortic sclerosis or AS. Our results are comparable with the prevalence of 2.4% reported among participants in the "Cardiovascular Health Study", where their AS definition was similar to ours. Higher prevalence values had been reported in other studies: 4.8% in a Finnish study on older participants (75-86 years)[107] and 3.9% in 70-79 years old in a

recent Norwegian study, where AS was defined as a transvalvular mean gradient ≥15 mm Hg[148].

Factors correlating with the development of AS

In the pathophysiology of AS an inflammatory process similar to that involved in atherosclerosis plays a part in the incipient phases[108, 109, 212]. Consequently, factors promoting atherosclerosis are believed to be involved in AS development. In Paper III, overweight, obesity and hypercholesterolemia combined with inflammation at the age of 50 correlated with the development of aortic sclerosis/AS during a 21-year follow-up. In Paper IV, higher BMI, obesity, cholesterol level, hypertension, atrial fibrillation, smoking and heredity for stroke correlated with the development of AS during a follow-up of 43 years.

Obesity

In Paper III and IV, we found that patients with obesity have a higher risk to develop AS compared to those without obesity and that the correlation is curvilinear. To date, previous studies have been inconsistent. Several studies found a positive correlation between obesity and either aortic valve calcification or AS[125, 129, 136, 137, 213, 214]. Some of these studies had aortic valve calcification diagnosed with computer tomography as an outcome[125, 129, 136] or used ICD codes to define AS[213]. Another investigated the correlation between BMI and severe AS in patients with a mean age of 65 using echocardiography as the diagnostic method[137] or between BMI and aortic sclerosis diagnosed using echocardiography (in a population-based study)[214]. Other studies examined the effect of obesity[138] or metabolic syndrome[139, 140] on AS progression and found positive associations between them.

However, other studies did not find a link between BMI and AS development. In a sub-study of SEAS (Simvastatin and Ezetimibe in AS)[215], overweight or obesity did not correlate with the progression rate of AS, but in this study patients with diabetes mellitus and hypercholesterolemia were excluded. In another study from the Cardiovascular Health Study, no relationship was found between body weight and echocardiographically diagnosed aortic sclerosis or AS[142]. However, this study was cross-sectional, limiting the possibility to study the time-updated effect of risk factors on the development of AS. By contrast, a study found an inverse association between BMI and aortic valve

calcification in the elderly[141]. However, that study was also cross-sectional, without the necessary follow-up to study time-dependent effects of risk factors on AS development. Our study provided more robust data and could confirm a close positive association between BMI and AS development during the life course.

A theoretical background is available for the role of obesity in the pathophysiology of AS. Patients with overweight or obesity are predisposed to hypertension, dyslipidaemia, diabetes mellitus, factors also involved in atherosclerosis that might prompt aortic valve degeneration[108]. Moreover, a low-grade, chronic inflammatory process is triggered and sustained by specialised metabolic cells in patients with weight excess[133, 134]. A similar inflammatory phase is also found in the incipient lesion in degenerative AS[108]. In conclusion, a higher than normal BMI might be a part of the pathological pathway leading to aortic sclerosis or AS.

Hypercholesterolemia

Hypercholesterolemia is another factor described in literature as being associated with AS. In Paper III, hypercholesterolemia combined with hs-CRP increased the odds of developing aortic sclerosis or AS. In Paper IV, the increased risk was found in all groups except the group with the longest surviving participants. The theory behind this correlation is that lipid accumulation is found in the early lesion that develops in the aortic valve[108, 109] and hypercholesterolemia induces lipid accumulation in atherosclerosis. This association has been described in mice[216] and humans[142, 143, 217, 218]. In addition, several retrospective, smaller studies suggest that statins might delay AS development, apparently independent of cholesterol levels[162, 219-222].

By contrast, an older study presented contradictory findings for dyslipidaemia and aortic valve calcification; however, this study was cross-sectional and biochemical data were available only for the participants >75 years[141]. In addition, no RCT investigating calcified AS could find an effect of statins (or statins combined with ezetimibe) on AS progression. However, two of the RCT studies included participants with an advanced calcified AS with a mean age of 68 years and a short follow-up of about 2 years[161, 223]. With the longer follow-up and less advanced AS, two other studies excluded all patients with an

indication for statins for other causes, such as CAD, diabetes mellitus, peripheral arterial disease, cerebrovascular disease, i.e. less representative of "real world" patients[160, 163].

The relationship between hypercholesterolemia and AS appears to be age-dependent. In both our studies participants had a mean age of about 50 years. In a study using cross-sectional baseline information from the Multi-Ethnic Study of Atherosclerosis an association between low-density lipoprotein and AS was only found in those <65 years[143]. In another study an association between low-density lipoprotein and AS was found only in those aged 50-59 years[218]. Taken together, these studies suggest that it requires sufficient time to establish a time-dependent relationship as AS develops gradually over decades. The pathophysiology of the AS is most probably initiated by an early phase, predominated by an inflammatory phase, followed by lipid accumulation, thickening of the fibrosa and, finally, mineralisation of the lesion. It is reasonable to consider that to prevent AS the actions should be taken early and throughout the lesion's incipient phases. In Paper III, we found that hypercholesterolemia could predict aortic sclerosis or AS, but only in association with inflammation, which covers these two early phases.

Hypertension

Hypertension was shown to be correlated with AS[125, 141, 142, 217, 224] and to indicate a worse prognosis[225] and a faster progression rate[130]. In Paper IV, the participants with hypertension at screening had a higher risk of being diagnosed with AS during follow-up. The association could be explained by shared common risk factors or by simultaneous diagnoses of AS and hypertension in the same individuals. In addition, it is considered that hypertension affects tensile and shear stress on the aortic valve[142]. In Paper III, we did not find an association between AS and hypertension, but the event rate was low in this study, limiting the possibility to identify potential correlations.

Discussion of the methods used in this thesis

Sample size

In Paper I, our cohort consisted of a relatively small sample, of 289 patients. Nevertheless, the outcome was 5-year mortality and the event rate was high, with 67% of the participants attaining the outcome until the end of follow-up.

In Paper III, a serious problem was the low event rate despite long-term follow-up beyond two decades in which a general population was studied. We identified only 14 patients (2.6%) with AS from the 535 men and 27 (5%) with either AS or aortic sclerosis. Having few cases limits our possibility to identify all the factors that could influence AS development. Statistically, we verified the results using Firth's logistic regression method and obtained the same results. In Paper IV, a larger cohort (242 individuals [3.2%] with AS) was studied to ascertain the results from Paper III.

Random error/systematic error

In Paper I, we included consecutive patients to limit selection bias. In addition, the diagnosis of HF was based strictly on the criteria of the guidelines, minimising the risk of misclassification. Moreover, we adjusted for known confounders.

In Paper II, we matched each individual with AS, HF and AVI for sex, age of index visit in the SwedeHF, age at HF diagnosis, LVEF and year of HF diagnosis with three individuals with HF without AS to reduce bias by confounding. We also adjusted for known confounders in our data analysis.

In Paper III and IV, random samples of individuals from the general population were included to avoid selection bias. However, in both studies the possibility of misclassification, albeit nondifferential, could occur. For instance, in Paper III, patients with AS were defined according to peak velocity over the aortic valve instead of the mean gradient area, whilst in Paper IV, the outcome (i.e. AS) was defined according to ICD codes.

Generalisability

Paper I investigated elderly patients with a mean age of 79 years. Only hospitalised patients were included, likely in a more severe stage of HF. Accordingly, the findings can be applied only to this particular group of patients. Still, most HF cases occur in the elderly, so the findings are likely representative of a large group of patients.

In Paper II, the patients were diagnosed with HF and had all undergone AVI. Therefore, our findings may not be generalisable to patients without an AVI before HF diagnoses, nor to patients with AS without AVI. In addition, the data were collected from registries containing information on hospitalised patients. Moreover, patients with CABG before the AS diagnosis were excluded, limiting further the generalisability of our results.

In Paper III and IV, only middle-aged men were included. Therefore, we cannot apply our findings to women or other age categories. Moreover, the men were from the same geographical region, from a developed country and the great majority were of Caucasian origin, limiting our findings' external validity.

Applicability

Our findings on HF prognosis in general and in patients with AS and AVI specifically are clinically relevant because they are commonly seen in our daily clinical practice. Knowledge about prognosis prediction and AS development provides insight into how to optimally manage HF care and the possibilities to prevent HF caused by AS.

Strengths and limitations

Paper I

One of this study's strengths is that we included consecutive patients hospitalised for HF in our hospital. Also, we defined HF strictly according to the ESC Heart failure guidelines, creating the possibility to compare our results with studies using the same definition.

Moreover, only patients with detailed echocardiographic data were included. The extended follow-up of 5 years and that our cohort was older than those included in most previous studies are features that allow us to characterise better this growing group of "real-life" patients. However, there are several inherent limitations in a retrospective study design, such as the quality of data, which were gathered during hospitalisation, and not for research purposes. Furthermore, in some cases there were many missing values. Referral bias is an issue here because the study was conducted in a tertiary care unit.

Paper II

This study is based on the SwedeHF registry and included a large number of patients. We intended to examine the patients in which AS had a central aetiological role. Therefore, we were careful to exclude those patients who already had an HF diagnosis before AVI intervention or patients with AS without an AVI intervention. In this way, we excluded the less severe AS cases, where it could not be considered an important part of HF aetiology. In addition, we also excluded patients with CABG to achieve a more homogenous population. We also had data from a large number of matched controls from the HF population and thus were able to compare these two groups (HF with and without an AVI due to AS).

However, not all the data were available in the registries. The most important missing information involved echocardiographic parameters on aortic valve morphology and stenosis severity. Moreover, the patients with severe AS who did not undergo an AVI were omitted. We could not study HF incidence in individuals with AS because SwedeHF does not contain AS patients without HF. Furthermore, this registry does not have complete coverage of all HF patients.

Because of the nature of registry studies, the possibility of validating the diagnoses by consulting the medical charts is limited. Because we included only patients after an AVI, we cannot generalise our results to all patients with valvular disease as HF aetiology. Moreover, we did not investigate how much CAD influenced these patients' prognosis or if AS was the most important aetiology in these patients.

Paper III and IV

The major strength of Paper III and IV is the long follow-up time. Because AS progresses slowly, cross-sectional or short follow-up studies are not appropriate to characterise this disease. By including men from the same region and about the same age, enabled us to exclude several confounders. The reverse of the coin was that this sampling process influenced the external validity of our results negatively.

The small number of participants diagnosed with AS is the major limitation in Paper III. Two other limitations are the lack of an echocardiographic examination at baseline and the lack of information about how many individuals had a bicuspid aortic valve. The AS diagnosis was also based on maximum velocity over the aortic valve, instead of the recommended mean gradient and valve area. Although we had a high event rate in Paper IV, the lack of echocardiographic data was a major limitation. In addition, without access to echocardiographic data, we could not evaluate the severity of AS.

Scientific relevance of this thesis

This thesis has added novel data with a significant scientific impact at two levels:

At the first level, the thesis facilitates understanding HF prognosis and its influencing factors in a real-world cohort. It also addresses more specifically HF post-AVI. The thesis fills a knowledge gap in that few studies have investigated this topic at length and the available results are questionable. There is considerable interest in comparing the prognosis of HFpEF to HFrEF. This interest lies in the fact that there has been tremendous progress in HFrEF therapy but virtually no effective treatment for HFpEF. Meanwhile, the landscape of HF has changed due to the dynamic relationship between HFrEF and HFpEF, with a predominance of HFpEF cases among the elderly. We also tried to underline that AVI improves the prognosis of AS. Moreover, the fact that LVEF does not play the same role in patients who develop HF afterwards is crucial to not underestimate the prognosis in patients with preserved LVEF and AS.

At the second level, this thesis facilitates the understanding of how AS develops during the life course and what factors influence AS development. The factors that we found to influence the development of AS are modifiable. Consequently, there is at least a theoretical ground that we might be able to slow down or even prevent AS and its eventual development into HF in patients with AS. Scientifically, this is a crucial issue as the focus in HF should shift to early treatment and prevention. Perhaps the best treatment for HF is not treatment, but prevention. We have witnessed a decline in CAD as the most important cause of HF; in this context, we suspect that degenerative valvular heart disease may soon become one of the important causes of HF. Moreover, valvular heart diseases are usually slowly progressive diseases, requiring a long-term strategy. To achieve the goal of preventing HF, a thorough understanding of AS progression is needed. Our findings provide robust data in this field.

Clinical relevance of this thesis

To understand the prognosis of HFpEF to HFrEF is essential. An increasing number of patients are diagnosed and treated for HFpEF, both in hospitals and outpatient clinics. Yet, lacking disease-modifying drugs, we can only treat them symptomatically and therefore we need to have sufficient knowledge about prognosis. This information is necessary to inform our HF patients correctly about their disease, take the right clinical decisions regarding the level of HF care (life-prolongation therapy, symptomatic relief, supportive or palliative care) and the frequency or need to follow-up these patients. For instance, HF also occurs after AVI and has a similar prognosis as in the general HF population, strongly suggesting the need to follow-up this post-AVI patient group to diagnose and treat HF in a timely fashion.

Moreover, knowing that AVI alters the prognosis of AS in such a meaningful way should motivate the physicians not to delay it and consider the procedure even in high-risk patients. The grim prognosis of 70-year-old women with HFrEF is another significant finding because this group of patients is often ignored. To improve quality of life and survival in HFrEF and HFpEF in the future it is vital to optimise the treatment of these women. In addition, knowledge about prognostic factors is overriding if we wish to design and develop effective therapies in the future.

The fact that obesity and other atherosclerotic risk factors were associated with AS is also important because it opens the possibility to target them to prevent AS and ultimately HF in patients with AS.

Public health relevance of this thesis

Even though HF incidence is relatively stable, the prevalence is estimated to rise because of the ageing of the population and improved survival rates from heart and circulatory events. This increase makes HF an escalating global public health problem with increased care costs, mostly because of frequent re-hospitalisations associated with HF. Having the correct picture concerning prognosis in HF will enable clinicians to inform the patients correctly about their condition, decide the optimal therapy, follow-up, ultimately reducing re-hospitalisations with high costs for the healthcare systems.

Calcific AS is also a significant and increasing public health issue, being one of the most prevalent heart valve disorders in developed countries. The AVI is costly, no matter what kind of procedure is used. Our knowledge about risk factors in the development of AS could facilitate effective measures to prevent AS, and ultimately, HF. The prevention of AS is similar to the prevention of CAD: keeping a normal BMI, refrain from smoking, avoid hypercholesterolemia and hypertension. Measures are needed to increase awareness about this disease, which constitutes a burden for health systems worldwide.

CONCLUSION

Elderly patients with HF have a grim prognosis, regardless of LVEF, although the prognosis is slightly better in HFpEF. This fact underscores the need to find new methods to treat these patients or prevent HF development. Because women with HFrEF have a dismal prognosis, we need to pay more attention to these patients, usually underrepresented in studies and often ignored in real life.

Factors influencing prognosis in HFpEF and HFrEF vary, supporting the idea that these disorders, elements of the same syndrome, differ pathophysiologically in significant ways and are therefore not a part of the same continuum. Consequently, different treatment strategies should be developed.

Patients who develop HF after an AVI have the same prognosis irrespective of LVEF and the same prognosis as the general HF population. Factors predicting prognosis are largely the same irrespective of LVEF. Intervention on the aortic valve for AS improves the prognosis and should not be delayed when indicated.

Several atherosclerotic factors, especially obesity, might be involved in the development of AS. Although modifiable, their influence is slow and to demonstrate their effect, an extended follow-up is needed. Eventually, AS might be prevented, along with the development of HF in these patients. However, given the disease's slow progression, steps should be taken early on to prevent AS.

FUTURE PERSPECTIVES

With the ageing population and associated comorbidities, HF becomes increasingly complex. Old age and multiple high-impact comorbidities will become key targets to overcome in future clinical studies. As a complement to RCTs with a strict selection of HF patients, cohort study or registry data have broader generalisability. Considering that elderly patients with multiple comorbidities form the major component of the HF population, a real-world study, based on validated diagnosis and with complete data should be used as an alternative approach for clinical decision making when randomisation is impractical. Such studies must use the same strict definition of HF to obtain the best results concerning prognosis and possible therapies.

Moreover, that prognosis in AS patients with AVI and HF did not depend on LVEF is another issue that deserves further attention. It is possible that the used modality to determine LVEF is not the best or the cut-off value used is inappropriate.

For a slowly progressive disease like AS, which takes decades to develop, a long-term, preferable lifetime follow-up is necessary to capture all the events. We suggest that prospective studies be conducted in a contemporary era of cardiovascular prevention and treatment to verify the hypothesis that AS might be prevented. There is a need to show that targeting obesity, hypercholesterolemia, hypertension and smoking under a sufficient period can influence AS.

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