From the Department of Medicine, Cardiology Unit
Karolinska Institutet, Stockholm, Sweden

# Prognostication In Heart Failure Across Ejection Fraction Phenotypes And Challenging Subgroups:

## Data From The Swedish Heart Failure Registry

Davide Stolfo


Karolinska Institutet

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*To Marta, Tommaso, Lorenzo and…*

# Prognostication in Heart Failure Across Ejection Fraction Phenotypes and Challenging Subgroups: Data from the Swedish Heart Failure Registry

Thesis for doctoral degree (Ph.D.)
By
Davide Stolfo

The thesis will be defended in public at Torsten Gordh - Norrbacka S2:02 Karolinska University Hospital, Stockholm, 03 June 2022, h 9.00 AM

*Principal Supervisor:*
Prof. Gianluigi Savarese
Karolinska Institutet
Department of Medicine
Division of Cardiology

*Co-supervisor(s):*
Prof. Lars H Lund
Karolinska Institutet
Department of Medicine
Division of Cardiology

Prof. Gianfranco Sinagra
University of Trieste (Italy)
Cardiothoracovascular Department
Division of Cardiology

PhD Camilla Hage
Karolinska Institutet
Department of Medicine
Division of Cardiology

Prof. Nicola Orsini
Karolinska Institutet
Department of Public Health Sciences

*Opponent:*
Prof. Dan Atar
University of Oslo
Department of Cardiology
Division of Medicine

*Examination Board:*
Prof. Michael Henein
Umeå University
Department of Public Health
and Clinical Medicine

PhD Jonas Spaak
Karolinska Institutet
Department of Clinical Sciences

Prof. Kurt Boman
Umeå University
Department of Public Health
and Clinical Medicine

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# POPULAR SCIENCE SUMMARY OF THE THESIS

The population of patients affected by heart failure is dramatically growing worldwide determining an increasing demand in terms of economical and individual resources. Validated treatments are strongly recommended to manage symptoms and to improve survival. However, their implementation remains poor in the real-world and this is especially true in more challenging subgroups. Our overall aim is to explore the current status of treatment implementation in specific subgroups of patients with heart failure which are classically excluded from large randomized studies, in order to define the associations between treatment use and mortality/morbidity, the reasons for underuse of treatments and the potential solutions for improve the physicians' adherence to guidelines recommendations.

# ABSTRACT

**Background.** The growing prevalence of heart failure (HF) worldwide determines an increasing burden on healthcare systems. HF phenotypes differ for several patient characteristics. Treatments with proven efficacy are mainly available for HF with reduced ejection fraction (HFrEF), whereas for HF with mildly reduced (HFmrEF) and preserved (HFpEF) ejection fraction evidence on treatment effect is more recent and limited to a single randomized control trial (RCT) and post-hoc/subgroup analyses of former RCTs. Although therapies affect survival in HFrEF, treatment implementation remains poor in particular in specific and more challenging subgroups.

**Aims**. The overall purpose is to provide a thorough characterization in terms of prognostication, to explore associations with outcomes and reasons for underuse of HF treatments while focusing on challenging settings underrepresented in RCTs and the different HF phenotypes (HFrEF, HFpEF and HFmrEF). Specific aims are:

- to assess gender-related differences in clinical characteristics, therapeutic strategies and outcomes in order to characterize the specific features of women affected by HF across the HF phenotypes (study I)
- to evaluate the use and the predictors of use of betablockers in older HFrEF patients, and the association between betablocker therapy and outcomes (study II)
- to assess the state of implementation of evidence-based treatments for HFrEF in older patients (study III)
- to explore the burden of HF on an healthcare system, with particular attention to the impact of the increasing burden of comorbidities on cardiovascular (CV) and non-CV mortality and morbidity (study IV)

These specific aims are assessed in a large and unselected contemporary cohort of HF patients, such as the Swedish HF Registry (SwedeHF).

**Sex-based differences in heart failure across the ejection fraction spectrum: Phenotyping, and prognostic and therapeutic implications.** In the SwedeHF Registry population, of 42,987 patients, 37% were females (55% with HFpEF, 39% with HFmrEF, 29% with HFrEF). Females were older, had more symptoms and more likely hypertension and kidney disease. There were differences in treatment use, with higher rates of beta-blocker and digoxin use in women vs men. Females less likely received HF devices. Adjusted risk of mortality/HF hospitalization was lower in females regardless of EF. The observed sex-related differences suggest to implement strategies for higher recruitment of women in RCTs.

**Association between beta-blocker use and mortality/morbidity in older patients with heart failure with reduced ejection fraction: A propensity score-matched analysis from the Swedish Heart Failure Registry.** We assessed the association between beta-blocker use, all-cause mortality and CV mortality/HF hospitalization in a 1:1 propensity score-matched cohort of patients with HFrEF and aged ≥80 years. Of 6562 patients aged ≥80 years, 5640 (86%) received beta-blocker. In the matched cohort (n=1732) beta-blocker use was associated lower risk of all-cause mortality. There was no signifantly lower risk of CV mortality/HF with vs. without beta-blocker in the matched cohort due to the lack of association between beta-blocker use and the outcome HF hospitalization. However, after adjustment rather than matching for the propensity score in the overall cohort, beta-blocker use was associated with reduced risk of all-cause mortality and CV mortality/HF hospitalization.

**Use of evidence-based therapy in heart failure with reduced ejection fraction across age strata.** We studied 27430 patients with HFrEF: 31% were <70, 34% 70-79 and 35% ≥80 years old. Use of renin-angiotensin-system/angiotensin receptor neprilysin inhibitors, beta-blockers and mineralocorticoid receptor antagonists progressively decreased with increasing age. Older patients were less likely treated with target doses of or combinations of HF medications. Except that for cardiac resynchronization therapy, after extensive adjustments age was inversely associated with the probability of guideline-directed medical therapy (GDMT) use and target dose achievement.

**Persistent high burden of heart failure across the ejection fraction spectrum in a nationwide setting.** A total of 76510 HF patients (53% HFrEF, had reduced EF 23% HFmrEF, 24% HFpEF) from the SwedeHF Registry were compared 1:3 with a sex, age, and county matched non-HF population. The incidence of cardiovascular and non-cardiovascular mortality/morbidity outcomes, as well as the in-hospital length of stay, was up to 5 times higher in HF vs non-HF patients. Across the EF spectrum, HFrEF was more exposed to HF hospitalization, whereas HFpEF to all-cause and non-cardiovascular hospitalization and mortality.

**Conclusions.** In the overall management of patients with HF, there are challenging subgroups that remain underexplored and frequently under-represented in RCT. Weaker evidence supporting the use of treatments and clinical inertia lead to lower adherence to current therapeutic recommendations. In our study women presented peculiarities in characteristics and treatments across the whole EF spectrum compared with men, with better survival/morbidity after adjustment for other patient characteristics. Patients in the older age range represent another group with a great representation in the overall real-world HF population, but often poorly considered and represented in clinical trials and by the scientific community in terms of treatment use implementation. Concerns regarding lower or no efficacy of treatments in older groups are not supported by post-hoc analyses of RCTs, and we observed a convincing lower mortality/morbidity risk associated with beta-blockers treatment in HFrEF over 80 years old, without any safety concerns. Despite the available data support evidence-based treatments regardless of age, in our cohort study we demonstrated that, with the exception of cardiac resynchronization therapy, medical treatments and devices are largely under-used and under-dosed in older patients with HFrEF. Finally, the increasing complexity of the contemporary HF population, partially given by the growing age and the increasing number of comorbidities, heavily burdens on the whole healthcare system, with HF patients experiencing a dramatically higher rate of cardiovascular and non-cardiovascular mortality/morbidity events. This claims for further efforts in the optimization of resources allocation and design of future RCTs.

# LIST OF SCIENTIFIC PAPERS

**Study I**

Sex-Based Differences in Heart Failure Across the Ejection Fraction Spectrum. Phenotyping, and Prognostic and Therapeutic Implications

Davide Stolfo, Alicia Uijl, Ola Vedin, Anna Strömberg, Ulrika Ljung Faxén, Giuseppe M.C. Rosano, Gianfranco Sinagra, Ulf Dahlström, Gianluigi Savarese

*J Am Coll Cardiol HF 2019;7:505–15*

**Study II**

Association between beta-blocker use and mortality/morbidity in older patients with heart failure with reduced ejection fraction. A propensity score-matched analysis from the Swedish Heart Failure Registry

Davide Stolfo, Alicia Uijl, Lina Benson, Benedikt Schrage, Marat Fudim, Folkert W. Asselbergs, Stefan Koudstaal, Gianfranco Sinagra, Ulf Dahlström, Giuseppe Rosano, Gianluigi Savarese

*European Journal of Heart Failure (2020) 22, 103–112*

**Study III**

Use of evidence-based therapy in heart failure with reduced ejection fraction across age strata

Davide Stolfo, Lars H Lund, Peter Moritz Becher, Nicola Orsini, Tonje Thorvaldsen, Lina Benson, Camilla Hage, Ulf Dahlström, Gianfranco Sinagra, Gianluigi Savarese.

*Eur J Heart Fail. 2022 Mar 12. Online ahead of print*

**Study IV**

Persistent High Burden of Heart Failure across the Ejection Fraction Spectrum in a Nationwide Setting

Davide Stolfo, Lars H. Lund, Lina Benson, Camilla Hage, Gianfranco Sinagra, Ulf Dahlström, Gianluigi Savarese

*Submitted*

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACE | Angiotensin converting enzyme |
| ARNI | Angiotensin receptor neprilysin inhibitor |
| CI | Confidence interval |
| CRT | Cardiac resynchronization therapy |
| CV | Cardiovascular |
| EF | Ejection fraction |
| ESC | European Society of Cardiology |
| eGFR | Estimated glomerular filtration rate |
| GDMT | Guidelines directed medical therapy |
| HF | Heart failure |
| HFmrEF | Heart failure with mildly reduced ejection fraction |
| HFpEF | Heart failure with preserved ejection fraction |
| HFrEF | Heart failure with reduced ejection fraction |
| HR | Hazard ratio |
| ICD | Implantable cardioverter defibrillator |
| IRR | Incidence rate ratio |
| MRA | Mineralocorticoid receptor antagonists |
| NYHA | New York Heart Association |
| NT-proBNP | N-terminal pro–B-type natriuretic peptide |
| RASI | Renin angiotensin system inhibitors |
| RCT | Randomized controlled trial |
| SCD | Sudden cardiac death |
| SGLT2 | Sodium-glucose cotransporter 2 |
| SwedeHF | Swedish Heart Failure Registry |
| UK | United Kingdom |
| US | United States |

# 1 INTRODUCTION AND LITERATURE REVIEW

**The overall burden of Heart Failure**

Heart failure (HF) is a global pandemic with increasing prevalence in the general population. Due to the overall aging of the worldwide population, carrying a higher burden of HF-related hospital admissions and an increasing demand of HF therapies, the HF-related health-care costs are increasing dramatically(1,2). Indeed, health expenditures for the yearly 1.1 million hospital stays for chronic HF in the United States amount to nearly $29 billion, corresponding to 10% of total health expenditures(3).

**Prognosis of heart failure**

Despite the improvement in treatment strategies and prognosis since the publication of the first RCTs in HF, overall survival improved but mortality still remains high and quality of life poor. Several prognostic markers became available over the years, including clinical factors, biomarkers and imaging. However, the performance of prognostic models is still unsatisfactory and the risk stratification of individual patients frequently fails.

Survival rates in HF shows broad variation which depends on several factors, including study design, diagnostic criteria, characteristics of study populations. Data from observational studies and registries typically report higher mortality rates compared with RCTs, that in a large part is the consequence of the selection process. Registries enroll patients from the "real world", who are generally older and with higher burden of comorbidities compared with trials. These patients are also exposed to non-cardiovascular (CV) events which are not directly explained by HF and that account for more than half of 30-days readmissions after diagnosis (4-6). In a Spanish cohort of 1876 patients with EF <50%, non-CV deaths accounted for 17.4% of deaths in 2002, increasing to 65.8% in 2018, mainly due to an increase in cancer deaths(4). Patients included in RCTs are instead younger, with less and less severe comorbid conditions and usually receiving optimal therapies.

In a recent U.S. registry-based study overall 5-years mortality rates were 24% and 54% for 60 and 80 year-old HF patients, respectively, and were stable over time(7). In a recent large meta-analysis, estimated 1, 2, 5 and 10-year survival was 87%, 73%, 57% and 35%, respectively(8).

In the last decades a drastic decrease in mortality in HF has not been observed. In the Olmsted County, mortality rates remained stable during the last 10 years, reflecting the changing epidemiology with HF with preserved ejection fraction (HFpEF) becoming more prevalent and with less therapeutic opportunities, and the increasing burden of comorbidities(7). In a large U.K. cohort, trends in mortality in patients with HF have been assessed over 20 years(9). Mortality risk slightly decreased, but absolute mortality rates remained high (i.e. >20% at 1 year). Important differences were observed according to age group, sex and socioeconomic status.

*Hospitalizations*

HF hospitalizations represent 1% to 2% of all hospital admissions and HF is the leading diagnosis in hospitalized patient aged >65 years(10,11). Absolute numbers of hospital admissions for HF are projected to increase by about 50% over the next 25 years, due to a growing and aging population(12).

In U.K. trends in risk of hospitalization have increased over the last 20 years, with a 28% increase in the first-year rates of all-cause hospitalization, 28% increase in the first-year rates of HF hospitalization and a 42% increase in the first-year rates of non-CV admissions. Older vs younger patients, women vs men, patients with an in-hospital vs a community-based diagnosis of HF and most deprived patients showed the worst patterns in terms of increasing hospitalization rates for both HF and non-CV reasons(9). The transition in causes of hospitalization, with non-HF and non-CV causes currently representing the most frequent reason of hospitalization in HF patients, has been confirmed in several studies(6,13). In the Olmsted County, >60% of hospitalizations were due to non-CV causes(7). Also, the predominant phenotype of hospitalized patients with HF is changing, with HFpEF becoming dominant(14). In the Get With The Guidelines-Heart Failure cohort, the proportion of patients admitted for acute decompensated HF who had HFpEF increased from 33% in 2005 to 39% in 2010(15).

**Current classification of chronic heart failure**

Several classifications have been proposed for chronic HF, but the most used is based on left ventricular EF. Indeed, according to the most recent European guidelines, HF is defined as with reduced EF (HFrEF; EF ≤40%), with mildly reduced EF (HFmrEF; EF: 41-49%) and with preserved EF (HFpEF; EF≥50%)(2).

**Contemporary treatment of heart failure**

*Heart Failure with Reduced Ejection Fraction (HFrEF)*

The largest benefit from anti-neurohormonal drugs is observed in HFrEF whereby several RCTs support the use of different classes of medications(2).

The historical milestones of drug therapy for HFrEF are the inhibitors of the renin-angiotensin system (RASI, angiotensin converting enzyme (ACE)-inhibitors and angiotensin receptor blockers), beta-blocker and the mineralocorticoid-receptor antagonists (MRA) that have dramatically improved the prognosis of patients with HFrEF in the last 30 years by improving survival, decreasing the risk of sudden cardiac death (SCD), and preventing HF hospitalizations(2).

The cumulative reduction in mortality associated with the combined use of evidence-based treatments is close to 60% according to data from a large network meta-analysis(16). The implementation of medical therapies has led also to a reduction in risk of SCD till below 5%(17).

After about two decades without convincing advances in the medical care of HFrEF, new classes of drugs recently emerged that clearly demonstrates to provide additional benefit on top, or alternatively in place of, conventional antineurohormonal classes.

The PARADIGM-HF trial drastically modified the landscape of HFrEF medical therapy after decades of disappointing results from RCTs. In this trial, sacubitril/valsartan, compared with enalapril, strongly reduced the combined primary endpoint of CV death or HF hospitalizations, as well as all-cause mortality. Following these results, sacubitril–valsartan is now recommended by international guidelines with class IA recommendation in order to reduce HF-related hospitalizations and mortality(2,18). Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of medications initially proposed as pure glucose-lowering

drugs, that demonstrated to improve mortality/morbidity in patients with HF regardless the presence of diabetes. Two large RCTs support the use of this pharmacological class in symptomatic HFrEF with class IA recommendation(19,20). The estimated treatment effects of comprehensive disease-modifying pharmacological therapy (i.e. MRA, ARNI, SGLT2i and beta-blocker) vs conventional therapy (i.e. ACE-inhibitor and beta-blocker alone) has been tested in a cross-trial analysis(21). Three pivotal RCTs were compared, EMPHASIS-HF (n=2737), PARADIGM-HF (n=8399), and DAPA-HF (n=4744)(18,19,22) and the composite primary endpoint of CV death or first hospital admission for HF was assessed. The hazard ratio (HR) for the aggregate treatment effects of comprehensive disease-modifying therapy versus conventional therapy on the primary endpoint of CV death or hospital admission for HF was 0.38 (95% CI 0.30–0.47) and the lifetime estimated weighted benefit ranged between 2.7 additional years of survival free from HF-hospitalizations (for a 80-year-old patient) and 8.3 years (for a 55-year-old-patient). These conclusions support the early adoption of combined interventions including ARNI, betablockers, MRA and SGLT2-inhibitors recommended in the last European Society of Cardiology (ESC) guidelines as the new therapeutic standard in order to reduce mortality (Figure 1)(2).


**Figure 1.**
Adapted from Mc Donagh et al. European Heart Journal (2021) 00, 1-128

Devices also have largely contributed to the improvement in survival and to the reduction in SCD among HFrEF patients. Cardiac resynchronization therapy (CRT) and primary prevention implantable cardioverter defibrillators (ICD) are first-line therapies that, if correctly used, exert a strong prognostic role(23-28).

*Heart failure with Mildly Reduced Ejection Fraction (HFmrEF)*

In 2016 the ESC guidelines introduced a category of HF in between the two classical entities, namely preserved and reduced EF, and this new entity was named HF with mid-range EF (HFmrEF)(29). The aim of the guidelines committee was to stimulate dedicated research into the "underlying characteristics, pathophysiology and treatment of this group of patients"(29). Data acquired following the publication of 2016 ESC guidelines and results of retrospective analyses of RCTs suggesting a potential benefit in treating HFmrEF with evidence-based drugs for HFrEF led to rename this entity from 'heart failure with mid-range ejection fraction' to 'heart failure with mildly reduced ejection fraction'(2). This revised category includes patients in the 41 to 49% range of EF. The proportion of HFmrEF within the overall HF population ranges between 10 and 25%(30-36).

HFmrEF cannot be simply defined as an intermediate phenotype between HFrEF and HFpEF. For some characteristics, in particular coexisting comorbidities, it can resemble more HFpEF, but for others it looks much more close to HFrEF. Ischemic etiology is important in the interpretation of HFmrEF as a milder form of HFrEF as the prevalence of ischemic

heart disease, including adjusted prevalence, is similar in these two phenotypes (31,36-38). Regarding the gender distribution, the proportion of females in HFmrEF was intermediate between HFrEF and HFpEF, but more similar to HFrEF(39). Prognosis in large observational studies appeared more favorable compared to HFpEF and HFrEF(31-33,35). Differences in outcome between real-world studies and RCTs are also evident for HFmrEF patients, since events rates in HFmrEF and HFpEF were generally lower than in HFrEF in RCTs(40). Neurohormonal antagonists have demonstrated to be effective in HFrEF, whereas until the recent release of RCTs on SGLT2-inhibitors(41), no therapy demonstrated proven benefit in the two other categories of HF. However, the rate of guidelines directed medical therapy (GDMT) use in registries is high in the HFmrEF population, suggesting that in clinical practice these patients are frequently assimilated to the HFrEF, have alternative indications to these treatments (i.e. systemic hypertension, atrial fibrillation) or alternatively, are "in transition" from HFrEF(31-33,36,37,42). In most of RCTs on HFpEF the lower threshold of EF was set to include completely, or partially, the HFmrEF spectrum(43-46). In the CHARM as well as in the TOPCAT trial, the primary outcome and/or the risk of recurrent HF hospitalizations was reduced in HFmrEF(40,47). An individual patient data meta-analysis on betablockers demonstrated an HR for CV mortality in HFmrEF patients of 0.48 (95% CI 0.24–0.97)(48). More recently, in the PARAGON-HF a subgroup analysis demonstrated a benefit in patients with EF below the median (i.e. <57%)(46). Due to the post-hoc design of the analysis, the gap in EF with values >40% and <45% excluded from both the RCTs, and the different treatment in the placebo arms, these observations should be considered as hypotheses generating. Pooled together on a continuous scale, data from these studies suggest HFrEF treatments might provide benefit also in HFmrEF, as also reported by the recently published ESC guidelines on HF (Figure 2)(2,49).

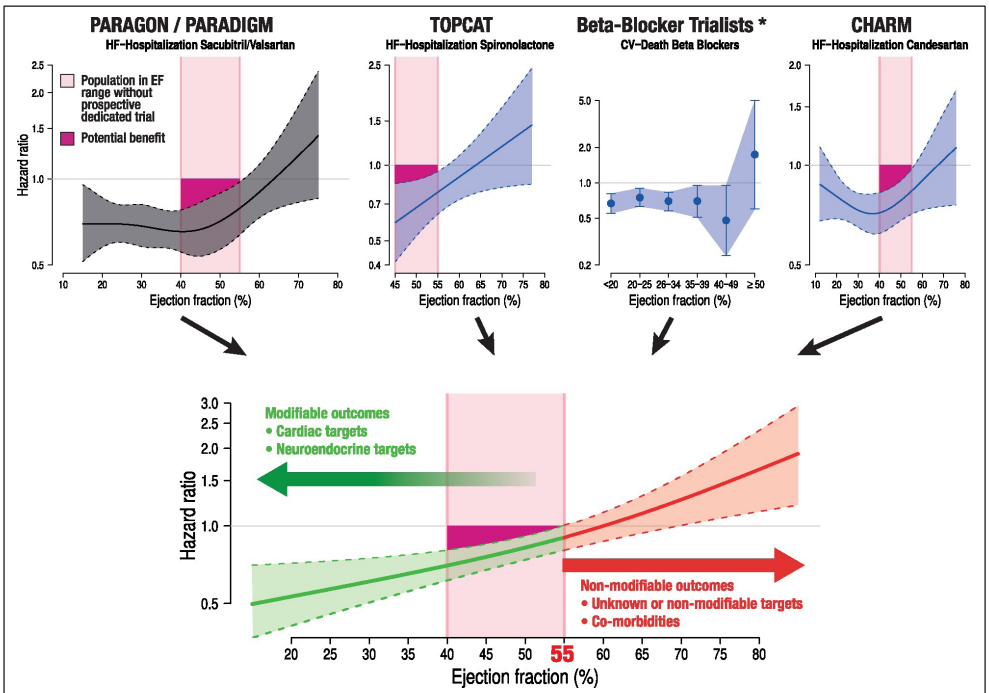


**Figure 2.**

Adapted from Bohm et al. Eur Heart J. 2020 Jul 1;41(25):2363-2365.

After the success of the two major RCTs on SGLT2-inhibitors in HFrEF, this class of drugs confirmed the expectations of the scientific community also in the setting of HFmrEF/HFpEF with the publication of the EMPEROR-PRESERVED trial. One-third of the trial population had HFmrEF and the results were consistent across the entire EF spectrum (41).

*Heart Failure with Preserved Ejection Fraction (HFpEF)*

The advances in the management of HFrEF were not counterbalanced by an improvement in the treatment of HFpEF. Diagnostic work-up may be more difficult in HFpEF due to the EF in the normal ranges. Symptoms can be confounded by potential alternative causes (i.e. chronic respiratory diseases, etc). Novel diagnostic criteria have been recently formulated that include echo parameters, natriuretic peptides and, if uncertainty persists, stress testing and/or invasive hemodynamics can be considered(50).

Data from registries demonstrate that patients with HFpEF exhibit critical differences compared to other HF phenotypes(51,52). They are older, more likely female, and carry a higher burden of comorbidities(51,52). Outcomes in HFpEF are comparable to those of HFrEF, with 1-year mortality ranging between 10% and 30%(33,53). Data from the GWTG-HF registry found no difference in 1-year mortality between HFrEF and HFpEF, and whereas HFrEF patients had higher rates of HF readmission, HFpEF patients had higher rates of all-cause readmission(51). In the Swedish HF Registry (SwedeHF), adjusted all-cause mortality at 1 and 3-years in HFmrEF was lower compared with HFrEF and numerically higher but not statistically significantly different compared with HFpEF(33). In addition, although mortality rates for HFrEF have decreased over the past 15 years, they are stable in HFpEF, likely due to the paucity of evidence-based treatments for HFpEF (54).

Antineurohormonal therapies that drastically modified the natural history of HFrEF and dramatically reduced mortality, failed to demonstrate a benefit in HFpEF. The PARAGON-HF trial tested the effect sacubitril/valsartan in HFpEF and did not meet the primary outcome, although with borderline significance(46). In 2021, the EMPEROR-PRESERVED study, that included patients with HF and EF>40%, has finally become the first RCT that provided solid evidence of benefit in the treatment of HFpEF(41), with a 21% reduction in CV mortality/HF hospitalization in the treatment arm compared to the placebo group, although with not significant effect on mortality. The results were consistent across the entire EF spectrum investigated in the trial. In the SOLOIST-WHF, that tested the SGLT1-SGLT2 inhibitor sotagliflozin in diabetic patients with recent worsening HF, around 25% of patients had EF≥50%. This study demonstrated a reduction in the composite of CV death/HF hospitalization/urgent visits for HF in the treatment arm that was consistent in the EF<50% and ≥50% groups(55). The recently published EMPULSE trial enrolled 530 patients with acute de-novo or decompensated chronic HF regardless of EF and demonstrated a significant clinical benefit in the treated arm, defined by a hierarchical composite of all-cause death, number of HF events and time to first HF event, or change in symptoms at 90 days, without significant interaction with EF(56). If the upcoming results of the second dedicated outcome trial in HFpEF/HFmrEF with a SGLT2-inhibitor, the Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER)(57), will be confirmatory, SGLT2-inhibitors will be the first class of drugs with proven positive effect on the prognosis of patients with HFpEF (and HFmrEF).

## Gaps in treatment of heart failure with reduced ejection fraction

Despite the strong level of recommendations and the data from an international registry that demonstrated the positive association between the adherence to guideline-recommended medications in HFrEF and survival(58), underprescription and underdosing of HF medications are frequent in clinical practice compared to the setting of a RCTs, due to several factors including the excessive concerns about adverse events (Figure 3)(59,60). In the U.S. registry CHAMP-HF only 72%, 67% and 33% of patients with chronic HFrEF received, respectively,

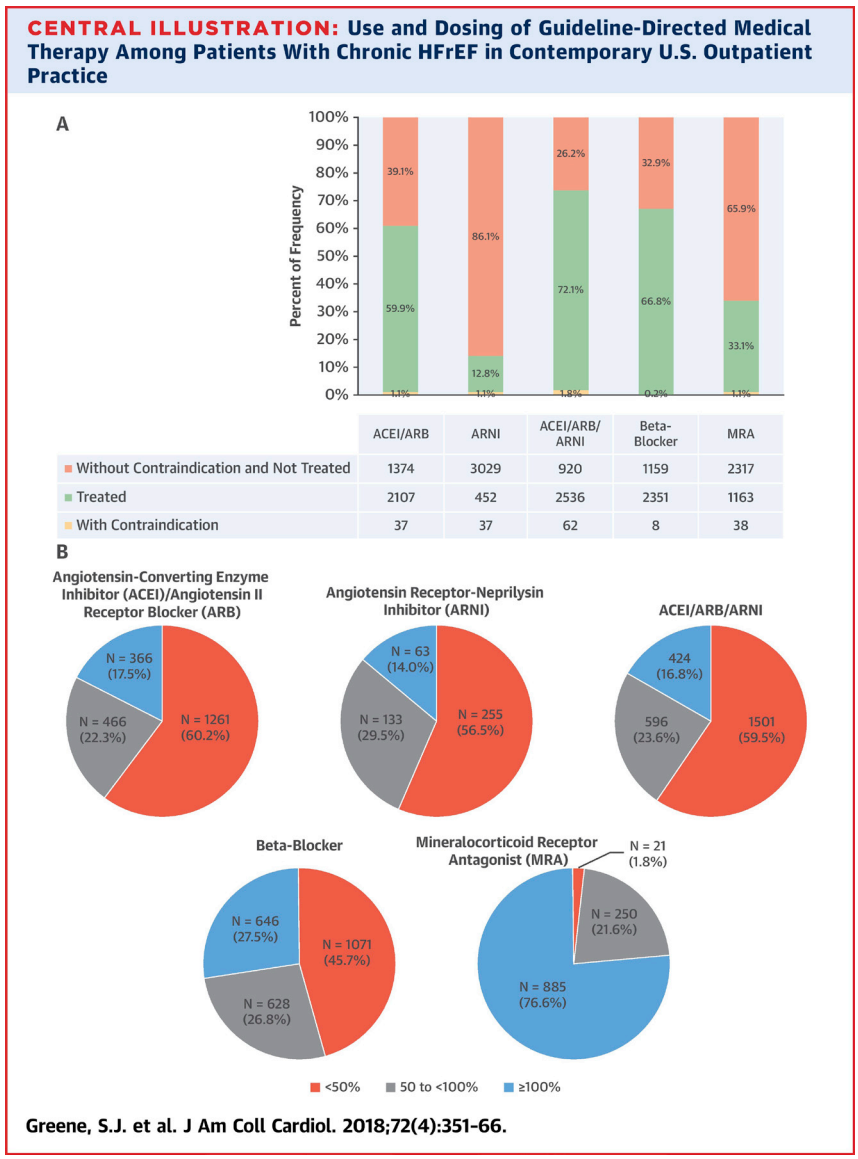


**Figure 3.**
Adapted from Greene et al. J Am Coll Cardiol 2018;72(4):351-66

RASI/ARNI, beta-blockers and MRAs(59).
European studies reported higher use of evidence-based treatments in HFrEF. In the ESC-HF Long-term Registry patients treated with RASI were 94%, with beta-blockers 93% and with MRA 67%(61). More recently, similar rates were reported in the SwedeHF Registry(62,63).

Although the prescription rates of medications improved overtime in the European cohorts (61), optimization of doses remains limited. In the ESC-HF Long-term Registry less than one third of patients received medications at recommended doses(61). As shown in Figure 3, in the CHAMP-HF registry, less than 20% and 30% of patients received target doses of RASI/ARNI and beta-blockers, respectively(59). In the SwedeHF Registry the reported rate of target dose achievement was higher compared to previous studies, with 46% on target dose of RASI/ARNI and 37% on target dose of beta-blockers in the overall HFrEF population. Notably, simultaneous use of intermediate doses of RASI/ARNI and beta-blockers yielded a lower risk of CV mortality/HF hospitalization than the use of a single drug at 100% target dose(62) (Figure 4).

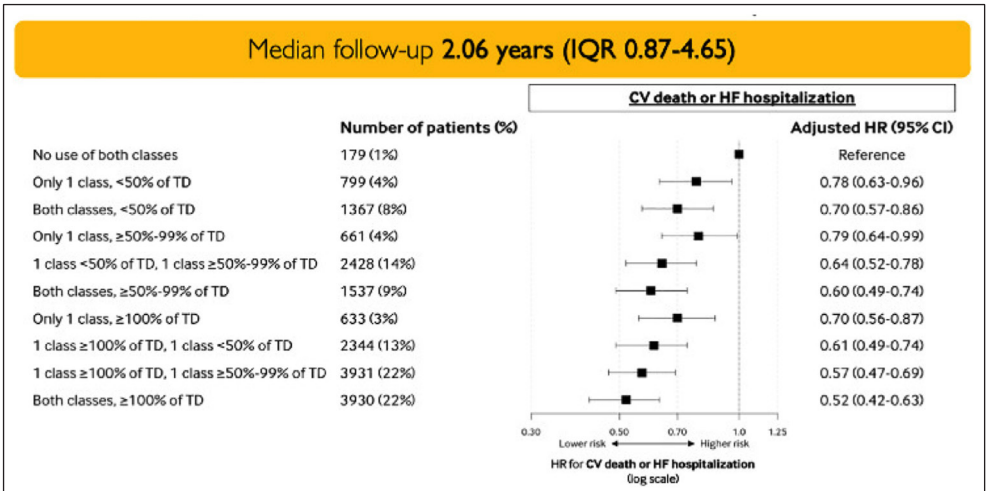


**Figure 4.**
Adapted from D'Amario, et al. Eur J Heart Fail. 2022 Mar 8. doi: 10.1002/ejhf.2477. Online ahead of print.

Several reasons behind the underuse and underdosing of HF medications can be summarized into three categories: 1) patient-related factors, including medical (e.g. comorbidities, vulnerable groups such as women, frail or older people) and socio-demographic (e.g. deprived socio-economical condition) characteristics, and challenges inherent to managing comorbidities and polypharmacy, 2) treatment-related aspects including actual or perceived tolerability concerns or side-effects (e.g. bradycardia with beta-blockers, hyperkalaemia with MRAs, hypotension etc.), and 3) healthcare-related/organizational factors with an impact on delivery and quality of care (e.g. primary rather than specialty care, clinical inertia)(64).

The rate of access to HF devices in patients with HFrEF is also of further concern. Data from registries attested very low prevalence of ICD and CRT implantation in patients eligible for these interventions(65,66).

## Challenging subgroups

### *Gender differences in heart failure*

Women have been systematically undertreated in HF clinical practice and underrepresented in all the HF RCTs, raising concerns regarding generalizability of RCT results. Sex-related differences in HF involve multiple aspects of the syndrome, including epidemiology, pathophysiology, phenotyping, prognosis, and can influence the course of the disease and the response to treatments. Moreover, with the increasing aging of the population the prevalence of HF within women is progressively approaching the one in men(67). Although in previous studies outcome was reported to be worse in men compared with women with HF, faster increases in rates of HF and non-CV hospitalizations and slower decreases in mortality in women than men have resulted in a similar overall outcome across sexes over the past decade(9,68,69). Such observations may be at least partially due to the increasing prevalence of non-CV comorbidities in women. However, a more severe HF or the lack of effective therapies, partially because of the higher prevalence of HFpEF, in women compared with men cannot be excluded(9,70). Moreover, the under-representation of women in RCTs also questions the applicability and the efficacy of maximal doses in females since target doses have been validated in settings where males were predominantly enrolled. Recently, an analysis of the BIOSTAT-CHF study suggested that women showed approximately 30% lower risk of death or hospitalization for HF at only 50% of the recommended doses of RASI and beta-blockers, without any additional benefit at higher doses, whereas men achieved the best reduction in risk with 100% target dose of these drugs. These findings have been validated in the ASIAN-HF Registry showing similar results(71).

Differences in the use of devices in HF have been also reported. In particular CRT is less used in women although current evidence suggests potential higher efficacy in females(72,73).

### *Older age classes with heart failure*

Patients enrolled in HF clinical trials poorly represent the real-world HF population. Patients in trials are younger, less exposed to drugs-related complications and with less comorbidities, compared with real-world populations, and all these aspects influence the access to evidence-based treatments and the long-term outcome. Therefore, the picture provided by HF RCTs cannot be always translated into clinical practice. Among the subgroups poorly represented in clinical trials, the elderly, along with women, are probably the most largely represented population in daily clinical practice, i.e more than one-third of the overall HF population in Europe(74,75). Indeed, with the aging of the population, HF has become particularly prevalent in the elderly(76). Nevertheless, mean age in large randomized studies is systematically below 70 years. Older HF patients present higher burden of comorbidities and might be more difficultly treated because of lower tolerance to medications or more likely drugs interactions due to polipharmacy. Indeed, aging carries a greater burden of comorbidities that is associated with increased severity of HF symptoms and reduced tolerance to HF treatments(77). However, beyond these aspects that may negatively influence the adherence to recommended HF treatments, age by itself should not be considered a contraindication to evidence-based drugs and devices for HF. In the current guidelines, treatments' recommendations are independent of age(2). In post-hoc analyses of RCTs, including the most novel classes ARNI and SGLT2i, age did not affect treatment effect(78-82). The only study designed to assess the efficacy of beta-blockers in older HF patients was the SENIORS trial (inclusion criteria ≥70 years, mean

age 76 years), which showed a significant reduction in the combined risk of death or CV hospitalization, but no effect on survival with beta-blockers vs. placebo (83). In older patients with HFrEF dose uptitration of HF medications could seem more difficult. Moreover, the evidence on additional benefit of higher doses is less solid in older vs younger patients. In the two largest RCTs comparing low vs. high-dose of RASI there was no interaction with age, with older patients (>65 years) having similar outcome compared to younger patients(84,85). In the SENIORS trial, however, patients on 50% of target dose had similar outcome compared to those on 100% of target dose(83).

The efficacy of the use of combined therapies in older patients has not been specifically investigated. However, in an indirect comparison of three major RCTs (EMPHASIS, PARADIGM-HF and DAPA-HF), the estimated gain in survival free-from HF hospitalization provided by comprehensive treatment with ARNI, beta-blocker, MRA, and SGLT2-inhibitor versus RASI plus beta-blocker in a hypothetical 80-years old patient was 2.7 years(21), which was less than in younger patients. Therefore, in absence of contraindications, the medical approach to HFrEF should be the same in younger and older patients, and efforts toward therapy implementation and dose optimization should be pursued regardless the age. In the real-world management of HF, however, data on use of HF treatments in the older vs younger patients remain conflicting(86-88), and evidence on treatment efficacy in the elderly is poor(74,75). A recent large retrospective study from the SwedeHF Registry provided data supporting the efficacy of renin-angiotensin system inhibitors (RASI) in patients >80 years old(89). Nevertheless, the adherence to evidence-based treatments for HFrEF in older patients remains incompletely explored in large HFrEF populations, in particular in the current era of new available drugs for HF management.

*Comorbidities*

The majority of patients with HF has ≥3 coexisting comorbidities and the overall amount of CV and non- CV comorbidities is increasing overtime (90,91). The increasing number of comorbidities is influenced by several factors, such as population ageing, enhanced screening and diagnostics, physician awareness, and changes in risk factors overtime(90). CV comorbidities have a well-known unfavorable effect on the outcome in HF(92), but also non- CV comorbidities has been shown to negatively affect prognosis(93). Multimorbidity increases the complexity of the management of patients with HF, and comorbidities can impair the introduction and titration of evidence-based therapies by increasing the risk, or the perception of risk, of intolerance and side effects, by discouraging physicians to implement treatments in patients already taking multiple medications, or by the perception of lower efficacy. Data from registries indicated that chronic kidney disease and hyperkalaemia were the most frequent reasons for not use or discontinuation of RASI and MRAs, respectively, whereas asthma and bradycardia were the most frequent contraindications or reasons for discontinuation of beta-blockers(61,94).

As previously reported, patients with HFpEF have higher prevalence of CV and non-CV comorbidities compared with HFrEF and HFmrEF(95).

# 2 RESEARCH AIMS

Based on this background, the overall aim is to investigate the most controversial and complex subgroups of patients with HF which have been traditionally excluded or under-represented in RCTs, by providing a comprehensive overview on their characteristics, treatment implementation and related benefits in terms of outcomes, while considering their impact on the overall HF management.

Specific aims are:

1. to assess sex-based differences in demographic and clinical characteristics, treatments, and outcomes in a large and unselected cohort of HF patients across the EF spectrum (Study I).
2. to assess the use of beta-blockers in HFrEF patients aged ≥80 years, and to test their association with outcomes in a large, contemporary, real-world HFrEF cohort (Study II).
3. to define the current status of implementation of HFrEF evidence-based therapies and explore the reasons for underuse/underdosing across different age strata and within specific subgroups of interest (Study III).
4. to comprehensively compare a large HF population across the EF spectrum with a control non-HF population with regard to demographic features, comorbidities, treatments and outcomes, in order to explain the significant burden of HF on healthcare resources (Study IV).

# 3 MATERIALS AND METHODS

**Data Source – The Swedish Heart Failure Registry (SwedeHF)**

For all the four studies, data have been derived from the SwedeHF Registry. SwedeHF has been previously described(96). Briefly, it is an ongoing voluntary health care quality registry founded in 2000 and implemented on a national basis in 2003. A majority of Swedish hospitals (~60 out of 75 hospitals) and to a minor extent also primary care centers enroll patients without financial compensation, and collect approximately 80 variables, i.e. data on demographics, comorbidities, clinical parameters, biomarkers, treatments and organizational aspects, from adult in-patient wards and out-patient clinics (www.swedehf.se). The inclusion criterion was clinician-judged HF until April 2017 and after that defined as a diagnosis of HF according to the following ICD-10 codes: I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0 and I13.2. EF is not mandatory, but recorded as a categorical variable (i.e. <40%, 40-49%, ≥ 50%) in around 90% of the registrations, and, thus, distinctions can be made between HFrEF, HFmrEF, and HFpEF patients. Reported coverage of SwedeHF in 2019 was 30.4% of the prevalent HF population in Sweden (54% in the inpatient setting). In addition to data directly available in the SwedeHF Registry, linkage to Statistics Sweden can provide socioeconomic data. The National Patient Registry, a national mandatory registration of administrative records from hospitalizations and non-primary outpatient care maintained by The National Board of Health and Welfare, provides data on additional comorbidities and hospital accesses outcomes. The Dispensed Drug Registry (DDR) (established in July 2005) provides data on medications prescribed and actually dispensed to the individual patients. Linkage between the registries was allowed by the personal identification number, which all residents in Sweden have.

For **Study IV** a control age, sex and county matched population without HF was derived from Statistics Sweden.

**Statistical analysis – general approach**

In each study baseline characteristics in the overall population and across the subgroups of interest were compared by using t-test or Wilcoxon-Mann-Whitney U-tests for continuous variables and chi-square test for categorical variables. The EF spectrum was defined according to the categorical classification recorded in the SwedeHF Registry: HFrEF (EF<40%), HFmrEF (EF 40% to 49%) and HFpEF (EF≥50%). In all multivariable models, missing data in baseline characteristics were handled by chained equation multiple imputation (10 datasets generated). Unadjusted survivor functions were estimated using the Kaplan-Meier method. A p value of <0.05 was considered statistically significant for all analyses. Statistical analyses were performed using Stata version 14.2 software (Stata Corp., College Station, Texas) (**Study I and III)** or R software v.3.5.1 (**Study II)** and v.4.0.2 (**Study IV**) (R Core Team 2019).

## Study I

**Patients**

Patients registered in SwedeHF between May 11, 2000, and December 31, 2012, without missing data for EF and with follow-up ≥1 day were included. When a patient reported more than one registration, the first one was selected. The index date was defined as the date of the outpatient clinic visit for HF or hospital discharge. The end of follow-up was December 31, 2012.

### Outcomes

Outcomes of interest were: time to all-cause death or HF hospitalization (composite primary outcome), time to all-cause death, time to CV death, time to non-CV death, time to CV hospitalization, time to HF hospitalization, and time to non-CV hospitalization.

### Statistical analyses

- Multivariable logistic regression analysis was used to calculate the adjusted odds ratios for HF treatments use in females vs males;
- Multivariable Cox regression analyses were used to: 1) calculate the adjusted proportional HR of outcomes in females vs males; 2) to investigate the predictors of outcomes in females and in males within each EF category
- The presence of a statistically significant interaction between sex and EF in the risk of outcomes was tested by the Wald test. Similarly, an interaction term between each baseline characteristic and sex was included in the multivariable Cox regression models to identify sex-based differences in predictors of the primary outcome within each EF strata.

## Study II

### Patients

In this study we included patients registered between 11 May 2000 and 31 December 2015, with EF <40%, HF duration ≥3 months, follow-up ≥1 day and available information on beta-blocker use. We excluded patients receiving beta-blockers other than those recommended by 2016 ESC HF guidelines (i.e. bisoprolol, carvedilol, or metoprolol)(29). If the same patient was registered more than once, we considered the first registration. End of follow-up was 31 December 2015. Patients with age ≥80 years represented the study population, whereas patients <80 years old were included as the positive control population where beta-blockers are well known to improve outcomes.

### Outcomes

Primary outcomes were 5-year all-cause mortality and a 5-year composite of CV mortality and first HF hospitalization. Additional outcomes of interest were 5-year CV mortality, first HF hospitalization, hospitalization for syncope (safety analysis) and hospitalization for cancer (falsification analysis).

### Statistical analysis

This is a propensity score matched designed study.

- A logistic regression model that included all clinically relevant variables was used to calculate the propensity score for beta-blocker use in each imputed dataset. Beta-blocker users and non-users were matched 1:1 using the nearest neighbour method with caliper <0.01 and no replacement.
- The association between beta-blocker use and outcome was assessed by Cox proportional hazard model in the matched population.
- In order to overcome the reduction in sample size determined by the matching process, an additional Cox proportional hazard models was fitted in the overall cohort adjusting, rather than matching, for the propensity score.

- A positive and negative (falsification) control analysis was also performed. Patients with HFrEF and <80 years old from the SwedeHF represented the positive control population where beta-blockers are well known to improve outcomes. Negative control analysis consisted of a model fitted in HFrEF patients aged ≥80years with hospitalization for cancer as outcome, since this is not expected to be associated with beta-blocker use and whether an association is retrieved, it might indicate the presence of residual confounding.

## Study III

### Patients

We included patients with HFrEF and HF duration ≥3 months (to allow for treatment optimization) registered between May 11th, 2000 and December 31st, 2018. When a patient was registered more than once, the last registration was selected as more representative of contemporary care. Patients were divided into three age categories: <70 years, 70-79 years and ≥80 years old. Specific subgroups of interest were specifically explored: caregiver location (in- vs outpatient) for all treatments (i.e. RASI/ARNI, beta-blockers, MRA, ICD and CRT); males vs females for all treatments; estimated glomerular filtration rate (eGFR) <30 vs 30-60 vs ≥60 ml/min/1.73m2 for RASI/ARNI and MRA; presence of dyskalemia for RASI/ARNI and MRA; heart rate for beta-blockers; atrial fibrillation for beta-blockers and CRT; EF< vs ≥30% for ICD and CRT. Variations in use of treatments across the different regions in Sweden were also assessed.

### Treatments

Analyzed treatments were RASI, ARNI (from 2016), beta-blockers, MRA, ICD and CRT.
Analyses on HF devices were conducted in patients who fulfilled the above-reported inclusion criteria and had Class I-IIa recommendation for ICD or CRT implantation according to the 2016 ESC HF guidelines(29).

Proportion of received target dose of treatments according to 2016 ESC HF guidelines(29), trends in use of HF treatments over time (starting from 2003, with MRA doses available in the registry from 2015) and the combined use of HF treatments were also assessed.

### Statistical analysis

- Multivariable logistic and multinomial regression models were fitted to investigate factors associated with use/non-use of treatments and with the the achieved target dose (<50% of target dose, 50-99% of target dose, ≥100% of target dose).
- Risk-adjusted probabilities of HF treatments use and of ≥100% target dose achievement over time were assessed in the overall population and across age categories by multivariable logistic regression analysis, with calendar year included in the models.
- To evaluate whether the probability of drug/device use or targed dose achievement changed over time, logistic regression models were fitted including calendar year of registration as continuous covariate and drug/device use or target dose achievement as dependent variables.

## Study IV

### Patients

Study IV included patients with HF registered between December 1st, 2005 and December 31st, 2018. HF patients who died during the index hospitalization or had reused/changed personal identification numbers were excluded. The first registration was selected for those patients who had multiple registrations in SwedeHF.

Patients with HF were matched by sex, year of birth and county of residence at index with a control cohort of individuals without HF derived from Statistics Sweden. The ratio was 1:3 for each observation in SwedeHF.

### Outcomes

We assessed all-cause, CV and non-CV mortality. Morbidity outcomes were first and repeated all-cause, HF, CV and non-CV hospitalizations; first and repeated all-cause outpatient visits and first emergency visits (defined as unplanned adimssion to an emergency ward). Length of in-hospital stay (LoS), defined as total in-hospital time from index date to end of follow-up, calculated per follow-up year, was also calculated.

### Statistical analysis

Time to first event was presented by Kaplan-Meier curves for all-cause mortality, and by cumulative incidence curves treating death as competing event for the other outcomes. Mean cumulative function was used for repeated events. A negative binomial generalized linear model which included the log of time as an offset was used to model repeated events. Crude Cox proportional hazards regression models were fitted to model the time to first event. Repeated events were modelled by a negative binomial generalized linear model including the log of time as an offset. Censoring time was December 31st, 2019 or death/emigration, and, for the controls a diagnosis of HF.

### Ethical Considerations

All the studies were performed in accordance with good clinical practice guidelines (ICH-GCP) and fulfilled the recommendations of the Helsinki Declaration. In the health quality and research registry SwedeHF, individual written consent is not required, but patients are informed of registration and allowed to opt-out. Foundation of the SwedeHF and its linking with the abovementioned registries, as well as all the analyses that are part of this thesis, were approved by an ethics committee. The reference numbers of the ethical permits are:

- Study I: DNR 2012 406-31
- Study II: DNR 2019-02698
- Study III: DNR 2019-02698
- Study IV: DNR 2019-02698

# 4 RESULTS

## Study I

Among a total of 42987 patients (mean age 76±12 years), 37% were female. More females had HFpEF (55% of the whole HFpEF population) and more males had HFmrEF (61%) or HFrEF (71%). Median follow-up was 2.2 years (range 0.9 to 4.1 years). Main baseline characteristics according to sex and EF category are summarized in **Table 1**.

**Table 1.** Baseline Characteristics According to Sex and HF phenotype including Missing data.

| Variables | HFpEF n=9957 | | | HFmrEF n=9225 | | | HFrEF n=23805 | | | Missing Data |
|---|---|---|---|---|---|---|---|---|---|---|
| | Males (n=4515, 45%) | Females (n=544, 55%) | p | Males (n=5596, 61%) | Females (n=3629, 39%) | p | Males (n=16949, 71%) | Females (n=6856, 29%) | p | n (%) |
| **Demographics** | | | | | | | | | | |
| **Age, mean (SD), y*#** | 75 (11) | 79 (10) | <0.001 | 73 (12) | 77 (11) | <0.001 | 71 (12) | 74 (12) | <0.001 | 0 |
| **Caregiver at SwedeHF registration *#** | | | | | | | | | | 2295 (5) |
| Inpatient | 2811 (62%) | 3868 (71%) | <0.001 | 2780 (50%) | 2215 (61%) | <0.001 | 8958 (53%) | 4076 (59%) | <0.001 | |
| Outpatient | 1704 (38%) | 1574 (29%) | | 2816 (50%) | 1414 (39%) | | 7991 (47%) | 2780 (41%) | | |
| **Specialty at SwedeHF registration *#** | | | | | | | | | | 2637 (6) |
| Cardiology | 2008 (49%) | 2439 (50%) | 0.96 | 2800 (54%) | 1712 (51%) | 0.003 | 9397 (57%) | 3644 (55%) | 0.002 | |
| Internal medicine or Geriatrics | 2052 (51%) | 2487 (50%) | | 2409 (46%) | 1677 (49%) | | 7069 (43%) | 2998 (45%) | | |
| **Follow-up referral specialty (physician specialty; not same as the HF nurse FUP)*#** | | | | | | | | | | |
| Primary care or Other care | 2034 (48%) | 2998 (60%) | <0.001 | 1880 (35%) | 1659 (49%) | <0.001 | 4367 (27%) | 2463 (38%) | <0.001 | |
| Cardiology or Internal medicine | 2169 (52%) | 2014 (40%) | | 3417 (65%) | 1755 (51%) | | 11595 (73%) | 3999 (62%) | | |
| **Follow-up referral to outpatient HF nurse clinic*#** | | | | | | | | | | 2688 (6) |
| No | 3002 (71%) | 3870 (77%) | <0.001 | 3246 (61%) | 2299 (67%) | <0.001 | 8237 (52%) | 3742 (58%) | <0.001 | |
| Yes | 1198 (29%) | 1143 (23%) | | 2047 (39%) | 1113 (33%) | | 7692 (48%) | 2710 (42%) | | |
| **Clinical** | | | | | | | | | | |
| **Duration of HF, months*#** | | | | | | | | | | 281 (0.6) |
| <6 | 2155 (48%) | 2597 (48%) | 0.96 | 2750 (49%) | 1801 (50%) | 0.67 | 8451 (50%) | 3669 (54%) | <0.001 | |
| ≥6 | 2323 (52%) | 2803 (52%) | | 2817 (51%) | 1812 (50%) | | 8384 (50%) | 3144 (46%) | | |
| **NYHA*#** | | | | | | | | | | 11816 (27) |
| I-II | 1876 (64%) | 1960 (59%) | <0.001 | 2873 (69%) | 1668 (66%) | <0.001 | 7257 (55%) | 2590 (52%) | <0.001 | |
| III-IV | 1070 (36%) | 1385 (42%) | | 1263 (31%) | 871 (34%) | | 5920 (45%) | 2438 (48%) | | |
| **BMI, mean (SD), kg/m2 *#** | 28 (6) | 27 (7) | 0.050 | 27 (5) | 27 (6) | 0.001 | 27 (5) | 26 (6) | <0.001 | 23296 (54) |
| <22.5 | 330 (16%) | 566 (24%) | <0.001 | 390 (15%) | 391 (24%) | <0.001 | 1485 (18%) | 892 (29%) | <0.001 | |
| 22.5-30 | 1120 (55%) | 1088 (47%) | <0.001 | 1507 (58%) | 798 (50%) | <0.001 | 4872 (61%) | 1525 (49%) | <0.001 | |
| >30 | 596 (29%) | 673 (29%) | <0.001 | 694 (27%) | 425 (26%) | <0.001 | 1663 (21%) | 676 (22%) | <0.001 | |
| **Mean arterial blood pressure, mean (SD), mmHg*#** | 93 (13) | 93 (13) | 0.14 | 93 (13) | 93 (13) | 0.50 | 90 (13) | 91 (13) | 0.21 | 605 (1) |
| **Heart Rate, mean (SD), beats/min*#** | 73 (15) | 75 (16) | <0.001 | 72 (15) | 75 (16) | <0.001 | 74 (16) | 76 (16) | <0.001 | 2922 (7) |
| **Laboratory Values** | | | | | | | | | | |
| **eGFR, median (IQR), ml/ min/1.73m² §*#** | 60 (44, 78) | 54 (39, 71) | <0.001 | 64 (47, 81) | 56 (41, 73) | <0.001 | 65 (47, 82) | 58 (41, 76) | <0.001 | 134 (0.3) |
| >60 | 2254 (50%) | 2150 (40%) | <0.001 | 3166 (57%) | 1595 (44%) | <0.001 | 9627 (57%) | 3152 (46%) | <0.001 | |
| 30-59 | 1864 (41%) | 2599 (48%) | <0.001 | 2010 (36%) | 1629 (45%) | <0.001 | 6078 (36%) | 2923 (43%) | <0.001 | |
| <30 | 388 (9%) | 668 (12%) | <0.001 | 407 (7%) | 387 (11%) | <0.001 | 1214 (7%) | 742 (11%) | <0.001 | |
| **NT-proBNP, median (IQR), pg/mL*#** | 1786 (764, 3980) | 2221 (991, 4690) | <0.001 | 1963 (875, 4463) | 2625 (1024, 5693) | <0.001 | 2940 (1293, 6473) | 3618 (1560, 8240) | <0.001 | 29635 (69) |

**Table 1.** Continuing

| Variables | HFpEF n=9957 | | | HFmrEF n=9225 | | | HFrEF n=23805 | | | Missing Data |
|---|---|---|---|---|---|---|---|---|---|---|
| | Males (n=4515, 45%) | Females (n=544, 55%) | p | Males (n=5596, 61%) | Females (n=3629, 39%) | p | Males (n=16949, 71%) | Females (n=6856, 29%) | p | n (%) |
| **Concomitant Medications** | | | | | | | | | | |
| **RAS inhibitors*#** | 3311 (74%) | 3749 (70%) | <0.001 | 4744 (85%) | 2904 (81%) | <0.001 | 15333 (91%) | 6037 (89%) | <0.001 | 294 (0.7) |
| **MRA*#** | 1139 (25%) | 1461 (27%) | 0.070 | 1259 (23%) | 909 (25%) | 0.004 | 5543 (33%) | 2210 (32%) | 0.50 | 305 (0.7) |
| **Digoxin*#** | 678 (15%) | 1117 (21%) | <0.001 | 761 (14%) | 724 (20%) | <0.001 | 2967 (18%) | 1220 (18%) | 0.63 | 246 (0.6) |
| **Diuretic*#** | 3699 (82%) | 4716 (87%) | <0.001 | 3950 (71%) | 2892 (80%) | <0.001 | 13311 (79%) | 5588 (82%) | <0.001 | 208 (0.6) |
| **Nitrate*#** | 769 (17%) | 1037 (19%) | 0.009 | 876 (16%) | 647 (18%) | 0.006 | 2596 (15%) | 1151 (17%) | 0.005 | 305 (0.7) |
| **Beta-Blocker*#** | 3451 (77%) | 4302 (80%) | 0.003 | 4735 (85%) | 3132 (87%) | 0.029 | 15226 (90%) | 6169 (90%) | 0.77 | 214 (0.5) |
| **ICD and/or CRT*#** | 58 (1.3%) | 46 (0.9%) | <0.001 | 151 (2.7%) | 49 (1.4%) | <0.001 | 1218 (7.3%) | 245 (3.6%) | <0.001 | 432 (1) |
| **History and Comorbidity** | | | | | | | | | | |
| **Smoking*#** | | | | | | | | | | 9557 (22) |
| Never | 1347 (39%) | 2326 (61%) | <0.001 | 1689 (37%) | 1530 (57%) | <0.001 | 4775 (35%) | 2784 (54%) | <0.001 | |
| Previous | 1760 (51%) | 1100 (29%) | | 2263 (50%) | 853 (32%) | | 6832 (49%) | 1684 (32%) | | |
| Current | 342 (10%) | 362 (10%) | | 567 (13%) | 280 (11%) | | 2217 (16%) | 719 (14%) | | |
| **Hypertension*#** | 3121 (69%) | 3935 (72%) | <0.001 | 3384 (60%) | 2440 (67%) | <0.001 | 9002 (53%) | 3918 (57%) | <0.001 | 0 |
| **Diabetes Mellitus*#** | 1345 (30%) | 1471 (27%) | 0.002 | 1557 (28%) | 922 (25%) | 0.011 | 4669 (28%) | 1731 (25%) | <0.001 | 0 |
| **Ischemic heart disease*#** | 2203 (50%) | 2291 (43%) | <0.001 | 3338 (61%) | 1792 (51%) | <0.001 | 9767 (60%) | 3485 (53%) | <0.001 | 1478 (3) |
| **Atrial fibrillation/ flutter*#** | 2902 (64%) | 3444 (63%) | 0.31 | 3239 (58%) | 2136 (59%) | 0.35 | 8965 (53%) | 3250 (47%) | <0.001 | 0 |
| **Anemia*#$** | 2095 (46%) | 1983 (36%) | <0.001 | 2084 (37%) | 1110 (31%) | <0.001 | 5643 (33%) | 1863 (27%) | <0.001 | 3 |
| **Cancer history*#** | 855 (19%) | 643 (12%) | <0.001 | 828 (15%) | 400 (11%) | <0.001 | 2229 (13%) | 726 (11%) | <0.001 | 0 |
| **COPD*#** | 944 (21%) | 1225 (23%) | 0.054 | 940 (17%) | 683 (19%) | 0.013 | 2578 (15%) | 1216 (18%) | <0.001 | 0 |
| **Socio-economic variables** | | | | | | | | | | |
| **Family type*#** | | | | | | | | | | 88 (0.2) |
| Living alone | 1864 (41%) | 3893 (72%) | <0.001 | 2300 (41%) | 2393 (66%) | <0.001 | 7264 (43%) | 4352 (64%) | <0.001 | |
| Married/ cohabitating | 2646 (59%) | 1541 (28%) | | 3290 (59%) | 1234 (34%) | | 9627 (57%) | 2495 (36%) | | |
| **Income £*#** | | | | | | | | | | 201 (0.5) |
| ≤ median | 1844 (41%) | 3817 (70%) | <0.001 | 2136 (38%) | 2443 (67%) | <0.001 | 6622 (39%) | 4498 (66%) | <0.001 | |
| > median | 2659 (59%) | 1613 (30%) | | 3436 (62%) | 1177 (33%) | | 10213 (61%) | 2328 (34%) | | |

Abbreviations: HFpEF: heart failure with preserved ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction; fup: follow-up; NYHA: New York heart association; BMI: body mass index; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro-B-type natriuretic peptide; COPD: chronic obstructive pulmonary disease; RAS: renin-angiotensin-system; MRA: mineralocorticoid receptor antagonist; ICD: implantable cardioverter defibrillator; CRT: cardiac resynchronization therapy; SD: standard deviation; IQR: interquartile range. eGFR is calculated by the CKD-EPI formula, anemia defined as hemoglobin <120 g/L in females and <130 g/L in males. *Variables included in multivariable models together with year of registration in SwedeHF. In multivariable models, NT-proBNP has been categorized according to its different median value in HFpEF, HFmrEF and HFrEF; eGFR and BMI were included as strata as defined in the Table; mean arterial pressure was categorized as > or < 90 mmHg; heart rate was categorized as > or < 70 bpm; the income was categorized according its median value; number of children was categorized as < or >2. #Variables included in the multiple imputation models together with year of registration in SwedeHF and time to and occurrence of the primary outcome (continuous variables were stratified as in multivariable models). £ Disposable income earned during the year prior to the index date has been considered. Disposable income is the amount of money that household have available for spending and saving after taxes have been accounted for. Median (interquartile range) was 133600 (110200-176400) SEK

### Patient characteristics

Briefly, compared with males, females were older, had a more deprived socio-economic status, were less likely followed up in a specialty care setting. Females had worse New York Heart Association (NYHA) functional class and higher N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels. Among comorbidities, females more likely reported hypertension, valve disease, chronic kidney disease, and lung disease, but less likely diabetes, ischemic heart disease, and anemia. Atrial fibrillation/flutter prevalence was higher in males than in females in the HFrEF group and similar in the other EF phenotypes.

### Use of treatments

Regarding therapy, unadjusted analysis demonstrated for females lower probability to receive RASI, devices (ICD and/or CRT) and higher probability to receive diuretics regardless of EF. MRA, digoxin, and beta-blockers were more likely prescribed in females with HFpEF and HFmrEF, but similarly in males vs females in HFrEF. After extensive adjustments for confounding factors, use of RASI was similar in females vs males, whereas females were more likely treated with beta-blockers and digoxin across the whole EF spectrum, and HFrEF females were less likely to receive ICD and/or CRT (**Figure 5**).

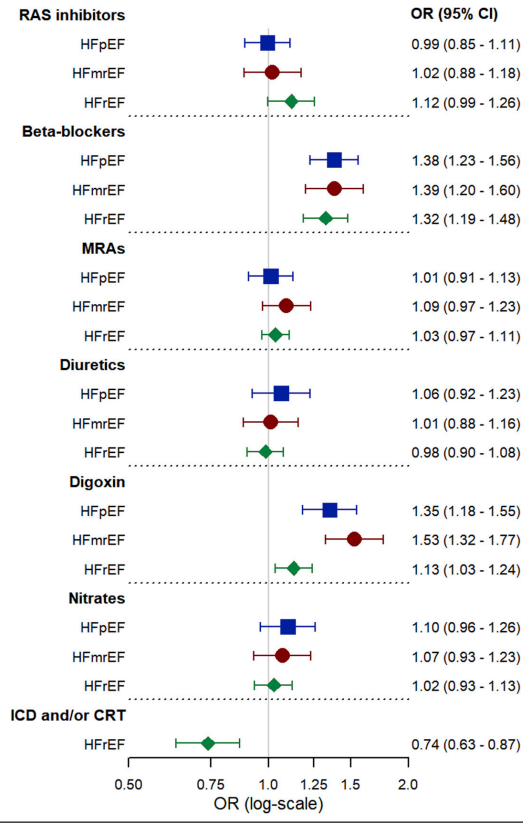


**Figure 5.** Forest Plot Reporting the Use of Treatments in Females Versus That in Males After Adjustments for Patient Characteristics.

ORs refer to females versus males. *p < 0.05. CI = confidence interval; CRT = cardiac resynchronization therapy; HFpEF = heart failure with preserved ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist; OR = odds ratio; RAS = renin angiotensin system.

## Prognosis (Table 2)

The crude risk of all-cause mortality/HF hospitalization was higher in females than in males with HFpEF and HFmrEF but lower in HFrEF. After adjustments, females reported significantly lower risk of all-cause mortality/HF hospitalization in all HF phenotypes. Differences were greater for lower EF ranges as p for interaction between sex and EF phenotype was statistically significant (**Figure 6**).

**Table 2.** Unadjusted and adjusted rates of study endpoints in females vs males across the EF spectrum.

| | Males | | Females | | | |
|---|---|---|---|---|---|---|
| | Event rate (%) | Event rate (per 100 patient-yrs) | Event rate (%) | Event rate (per 100 patient-yrs) | HR (95% CI) Unadjusted Females vs. Males | HR (95% CI) Adjusted Females vs. Males |
| **All-cause death/HF hospitalization** | | | | | | |
| **HFpEF** | 1,929 (42.7) | 20.45 (19.56–21.39) | 2,545 (46.8) | 23.79 (22.88–24.73) | 1.14 (1.07–1.21)† | 0.93 (0.88–0.99)† |
| **HFmrEF** | 2,258 (40.4) | 17.45 (16.74–18.18) | 1,601 (44.1) | 20.67 (19.68–21.71) | 1.16 (1.08–1.23)† | 0.91 (0.85–0.97)† |
| **HFrEF** | 8,546 (50.4) | 25.09 (24.57–25.63) | 3,302 (48.2) | 23.89 (23.09–24.72) | 0.95 (0.92–0.99)† | 0.80 (0.77–0.84)† |
| **All-cause death** | | | | | | |
| **HFpEF** | 1,888 (41.8) | 16.27 (15.54–17.02) | 2,373 (43.6) | 17.54 (16.85–18.26) | 1.07 (1.01–1.14)* | 0.81 (0.76–0.87) |
| **HFmrEF** | 2,009 (35.9) | 12.73 (12.18–13.30) | 1,459 (40.2) | 15.27 (14.50–16.07) | 1.19 (1.11–1.27)* | 0.82 (0.77–0.89) |
| **HFrEF** | 6,433 (38.0) | 13.6 (13.32–13.98) | 2,701 (39.4) | 14.55 (14.01–15.11) | 1.06 (1.02–1.11)* | 0.80 (0.74–0.84) |
| **Cardiovascular death** | | | | | | |
| **HFpEF** | 1,102 (24.4) | 9.49 (8.95–10.07) | 1,506 (27.7) | 11.13 (10.58–11.71) | 1.17 (1.08–1.26)* | 0.82 (0.76–0.89) |
| **HFmrEF** | 1,231 (22.0) | 7.80 (7.38–8.25) | 917 (25.3) | 9.58 (8.98–10.22) | 1.22 (1.12–1.32* | 0.78 (0.72–0.86) |
| **HFrEF** | 4,441 (26.2) | 9.42 (9.15–9.70) | 1,844 (26.9) | 9.94 (9.49–10.40) | 1.05 (0.99–1.11)* | 0.75 (0.70–0.79) |
| **Noncardiovascular death** | | | | | | |
| **HFpEF** | 786 (17.4) | 6.77 (6.31–7.26) | 867 (15.9) | 6.41 (6.00–6.85) | 0.94 (0.85–1.04)* | 0.80 (0.73–0.89) |
| **HFmrEF** | 778 (13.9) | 4.93 (4.59–5.29) | 542 (15.0) | 5.69 (5.23–6.19) | 1.15 (1.03–1.28)* | 0.90 (0.80–1.01) |
| **HFrEF** | 1,992 (11.8) | 4.23 (4.04–4.41) | 857 (12.5) | 4.62 (4.32–4.94) | 1.09 (1.01–1.18)* | 0.89 (0.82–0.97) |
| **HF hospitalization** | | | | | | |
| **HFpEF** | 1,398 (31.0) | 14.82 (14.07–15.62) | 1,799 (33.1) | 16.82 (16.06–17.61) | 1.11 (1.03–1.19)† | 0.98 (0.91–1.05)† |
| **HFmrEF** | 1,665 (29.8) | 12.87 (12.26–13.50) | 1,124 (31.0) | 14.51 (13.69–15.39) | 1.10 (1.02–1.18)† | 0.94 (0.86–1.02)† |
| **HFrEF** | 6,686 (39.5) | 19.63 (19.17–20.11) | 2,439 (35.6) | 17.65 (16.96–18.36) | 0.90 (0.86–0.94)† | 0.81 (0.77–0.86)† |
| **Cardiovascular hospitalization** | | | | | | |
| **HFpEF** | 2,498 (55.3) | 36.57 (35.17–38.04) | 3,050 (56.1) | 38.84 (37.49–40.24) | 1.04 (0.99–1.10)† | 0.97 (0.92–1.03)* |
| **HFmrEF** | 2,985 (53.3) | 31.11 (30.01–32.24) | 1,940 (53.5) | 33.21 (31.77–34.73) | 1.04 (0.98–1.10)† | 0.95 (0.90–1.01)* |
| **HFrEF** | 9,759 (57.6) | 37.21 (36.48–37.96) | 3,728 (54.4) | 34.54 (33.45–35.66) | 0.94 (0.90–0.97)† | 0.90 (0.86–0.93)* |
| **Noncardiovascular hospitalization** | | | | | | |
| **HFpEF** | 2,778 (61.5) | 43.62 (42.02–45.27) | 3,399 (62.5) | 48.23 (46.64–49.88) | 1.07 (1.02–1.13) | 0.99 (0.94–1.04) |
| **HFmrEF** | 3,176 (56.8) | 33.37 (32.23–34.55) | 2,116 (58.3) | 38.73 (37.12–40.42) | 1.12 (1.06–1.19) | 0.99 (0.94–1.05) |
| **HFrEF** | 8,678 (51.2) | 29.26 (28.65–29.88) | 3,587 (52.3) | 32.06 (31.02–33.12) | 1.08 (1.04–1.12) | 1.00 (0.96–1.04) |

*Significant interaction ($p < 0.05$) in the sex ejection fraction category. †Significant interaction ($p < 0.01$) in the sex ejection fraction category. HR = hazard ratio; CI = confidence interval; CV = cardiovascular.

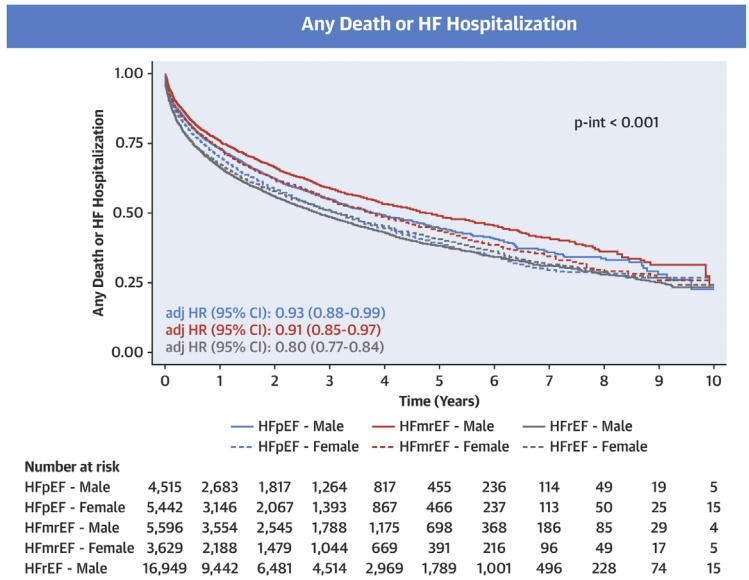


**Figure 6.** Kaplan-Meier Unadjusted Curves for Time to All-Cause Mortality/HF Hospitalization in Females Versus That in Males According to HF Phenotype.
Abbreviations: HFpEF = heart failure with preserved ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio.

The unadjusted risk of all-cause, CV and non-CV mortality was higher in females than in males across the EF spectrum. However, after adjustments, females reported a lower risk of all-cause death and CV mortality. Risk of non-CV death was also significantly lower in females than in males in the HFpEF and HFrEF groups, and of borderline statistical significance in HFmrEF, in the absence of a significant interaction between sex and EF (**Figure 7**).

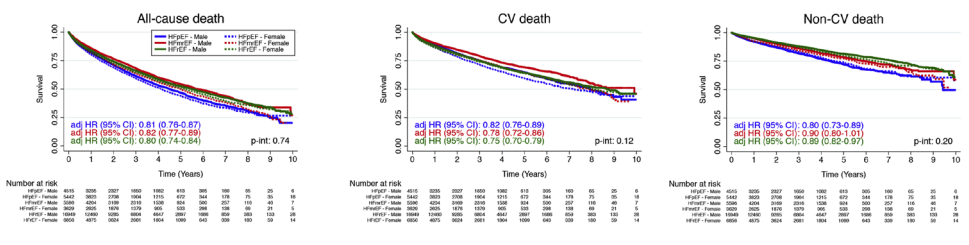


**Figure 7.** Kaplan-Meier Unadjusted Curves for Time to All-Cause Mortality, Time to Cardiovascular Death, and Time to Non-Cardiovascular Death in Females Versus Those in Males According to HF Phenotype
Abbreviations. CI = confidence interval; CV = cardiovascular; other abbreviations as in Figure 6.

There were no sex-based differences in the risk of CV hospitalization in HFpEF and HFmrEF but significantly lower risk in females than in males with HFrEF in unadjusted and adjusted analysis, with a statistically significant interaction between sex and EF. No differences in risk of non-CV hospitalization were observed after adjustments. Unadjusted risk of HF hospitalization was higher in females than in males in HFpEF and HFmrEF but lower in females than in males with HFrEF. After adjustments, results in HFrEF were confirmed but no sex-based differences in risk were observed in HFpEF and HFmrEF patients, with a statistically significant interaction between sex and EF (**Figure 8**).

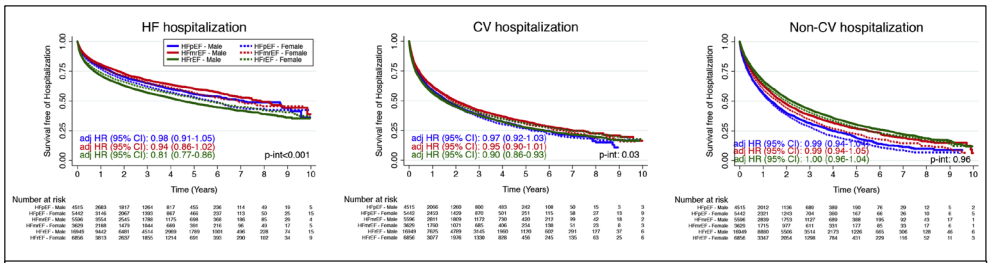


**Figure 8.** Kaplan-Meier Unadjusted Curves for Time to HF Hospitalization, Time to CV Hospitalization, and Time to Non-Cardiovascular Hospitalization in Females Versus Those in Males According to HF Phenotype.
Abbreviations as in Figure 6 and Figure 7

## Prognostic predictors

Independent predictors of mortality/ HF hospitalization were overall similar across sexes and HF phenotypes (**Figure 9**). Main patient characteristics associated with worse prognosis regardless of sex and EF were longer HF duration, higher NT-proBNP, ischemic etiology, chronic kidney disease, and atrial fibrillation. Few sex-related differences in prognostic predictors were found: diabetes and NYHA class were associated with increased risk of outcome regardless of EF and sex, but they predicted higher risk in males than in females with HFrEF. In HFmrEF, anemia was a prognostic predictor only in males. The association of age with the increased risk of outcome was evident across the range of EF, but stronger in males than in females with HFmrEF. Obesity was associated with a statistically significant increased risk of outcome in males but not in females with HFpEF and HFrEF in the absence of any significant statistical interaction between BMI and sex.

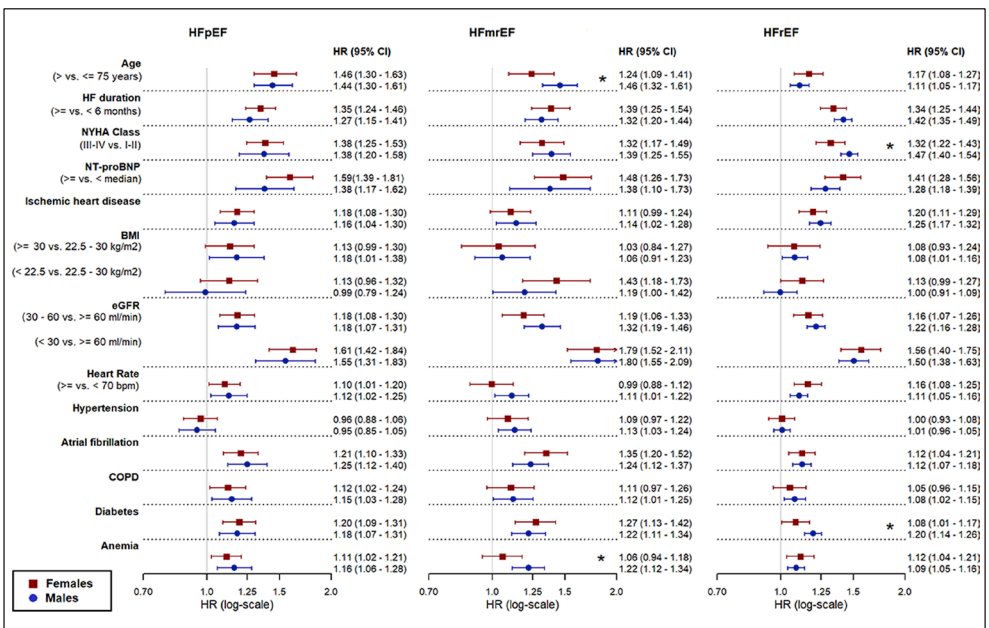


**Figure 9.** Forest Plot Reporting Selected Predictors of All-Cause Mortality/HF Hospitalization in Females Versus Those in Males According to HF Phenotype
*Significant interaction between sex and variable of interest ($p < 0.05$). BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro–B-type natriuretic peptide; other abbreviations as in Figure 6.

## Study II

Among 6562 patients aged ≥80 years (median age 84, interquartile range: 82–87, 34.7% women) fulfilling the inclusion criteria, 5640 (86%) were treated with beta-blockers and 922 (14%) were untreated. Median follow-up was 1.76 (interquartile range: 0.64–3.39) years. Treated patients received target dose in 21.1% of the cases, 50-99% target dose in 36.4% and <50% in 42.5%. Propensity score matched analysis included 1732 patients, 866 (50%) treated and 866 (50%) untreated. Matched beta-blocker users received target dose in 19.0% of the cases, 50-99% target dose in 33.4% and <50% in 47.6%.

Baseline characteristics in treated vs untreated patients are summarized in **Table 3**. Patients treated with beta-blockers were younger, more likely female and followed up in specialist care, had less severe HF, higher BMI, different pattern of co-morbidities and higher use of pharmacological and device therapies except for MRA. Consequently, in the overall cohort, propensity scores were differently distributed across the study arms (**Figure 10**). After matching, there were no statistically significant differences in baseline characteristics between beta-blocker users and non-users (Figure 10 and Table 3).

**Table 3.** Baseline characteristics of patients ≥80 years old in the overall and matched cohort

| | Overall cohort | | | Matched cohort | | |
|---|---|---|---|---|---|---|
| | Beta-blocker non-users | Beta-blocker users | p-value | Beta-blocker non-users | Beta-blocker users | Absolute standardized difference* |
| n | 922 (14%) | 5640 (86%) | | 866 (50%) | 866 (50%) | |
| Age (years, mean (SD))[a, b] | 85.4 (4.2) | 84.6 (3.6) | <0.001 | 85.2 (4.0) | 85.3 (3.8) | 1.1% |
| Sex = Female (%)[a, b] | 30.5 | 35.4 | 0.004 | 30.9 | 31.5 | 1.2% |
| Location = Out-patient (%)[a, b] | 36.7 | 40.2 | 0.052 | 37.5 | 34.9 | 5.5% |
| Follow-up location = Specialty (%)[a, b] | 36.6 | 47.0 | <0.001 | 38.5 | 39.2 | 1.5% |
| NYHA class (%)[a, b] | | | <0.001 | | | 3.8% |
| NYHA-I | 5.7 | 3.5 | | 4.8 | 4.0 | |
| NYHA-II | 31.9 | 37.6 | | 33.3 | 33.4 | |
| NYHA-III | 51.7 | 51.8 | | 52.0 | 52.6 | |
| NYHA-IV | 10.7 | 7.1 | | 9.9 | 10.0 | |
| EF = 30 - 39% (%)[a, b] | 55.3 | 53.8 | 0.385 | 55.5 | 54.0 | 3.8% |
| **Clinical measures** | | | | | | |
| BMI (kg/m$^2$, mean (SD)) | 24.3 (4.2) | 25.1 (4.3) | 0.001 | 24.4 (4.2) | 24.5 (4.0) | 2.9% |
| SBP (mmHg, mean (SD)) | 124.8 (19.8) | 124.7 (20.1) | 0.862 | 124.9 (19.7) | 123.9 (20.5) | 4.9% |
| DBP (mmHg, mean (SD)) | 69.3 (11.5) | 70.4 (11.3) | 0.008 | 69.3 (11.6) | 70.0 (11.3) | 6.0% |
| MAP (mmHg, mean (SD))[a, b] | 87.8 (12.5) | 88.5 (12.5) | 0.122 | 87.8 (12.6) | 87.9 (12.6) | 1.0% |
| Heart Rate (bpm, median [IQR])[a, b] | 72.0 [63.0, 82.0] | 72.0 [64.0, 82.0] | 0.611 | 72.0 [63.0, 82.0] | 71.0 [63.0, 82.0] | 4.7% |
| <60 bmp | 14.4% | 12.2% | | 14.6% | 11.6% | |
| eGFR (mL/min/1.73m$^2$, median [IQR])[a, b] | 45.3 [34.2, 59.6] | 44.5 [33.5, 58.0] | 0.222 | 44.9 [34.1, 59.4] | 45.1 [33.6, 59.0] | 1.4% |
| >60 | 24.9% | 22.3% | | 24.4 | 23.4 | |
| 30-60 | 57.3% | 59.2% | | 57.8 | 57.8 | |
| <30 | 17.9% | 18.5% | | 17.9 | 18.8 | |
| NT-proBNP (pg/L, median [IQR]) | 4773.5 [2106.3, 10454.8] | 5228.5 [2410.0, 11805.3] | 0.195 | 4761.0 [2143.5, 9926.0] | 5711.0 [2456.5, 13234.5] | 14.6% |
| Smoking (%)[a, b] | | | 0.966 | | | 7.6% |
| never | 51.6 | 52.0% | | 50.6 | 52.5 | |
| former | 44.2 | 43.7% | | 45.0 | 44.5 | |
| current | 4.2 | 4.3% | | 4.4 | 3.0 | |

**Table 3.** Continuing

| | Overall cohort | | | Matched cohort | | |
|---|---|---|---|---|---|---|
| | Beta-blocker non-users | Beta-blocker users | p-value | Beta-blocker non-users | Beta-blocker users | Absolute standardized difference* |
| **Medical history (%)** | | | | | | |
| Atrial fibrillation [a, b] | 65.5 | 68.4 | 0.088 | 65.9 | 67.1 | 2.4% |
| Anemia [a, b] | 50.0 | 44.7 | 0.003 | 48.7 | 49.8 | 2.1% |
| COPD [a, b] | 15.2 | 15.9 | 0.641 | 15.7 | 13.3 | 6.9% |
| Dilated Cardiomyopathy [a, b] | 10.1 | 9.8 | 0.797 | 9.6 | 11.3 | 5.7% |
| Diabetes [a, b] | 21.9 | 28.9 | <0.001 | 22.6 | 22.5 | 0.3% |
| Hypertension [a, b] | 58.8 | 69.2 | <0.001 | 60.9 | 62.1 | 2.6% |
| Ischemic heart disease [a, b] | 66.8 | 74.4 | <0.001 | 68.4 | 70.2 | 4.0% |
| Peripheral artery disease [a, b] | 16.3 | 13.3 | 0.016 | 16.3 | 16.2 | 0.3% |
| Stroke and/or TIA [a, b] | 19.3 | 20.1 | 0.604 | 19.7 | 19.4 | 0.9% |
| Valvular disease [a, b] | 40.9 | 38.5 | 0.178 | 41.2 | 40.9 | 0.7% |
| Cancer in the previous 3 years [a, b] | 14.1 | 12.9 | 0.346 | 14.0 | 14.8 | 2.3% |
| Dementia | 2.4 | 2.6 | 0.828 | 2.4 | 2.4 | 0.1% |
| **Procedures (%)** | | | | | | |
| Coronary revascularization [a, b] | 32.8 | 37.1 | 0.012 | 33.6 | 34.2 | 1.2% |
| Devices[§, a, b] | 3.3 | 5.5 | 0.008 | 3.5 | 2.5 | 5.4% |
| CRT or ICD | 3.3 | 5.4 | 0.008 | 3.5 | 2.5 | 5.4% |
| Pacemaker (CRT-D, CRT-P or pacemaker) | 19.2 | 19.5 | | 19.2 | 20.6 | |
| No device | 80.0 | 78.9 | | 80.0 | 78.8 | |
| **Medication use (%)** | | | | | | |
| RAS-inhibitors [a, b] | 72.4 | 81.7 | <0.001 | 75.5 | 73.7 | 4.1% |
| MRA [a, b] | 32.3 | 32.5 | 0.958 | 32.8 | 34.9 | 4.4% |
| Digoxin [a, b] | 15.6 | 17.1 | 0.281 | 15.8 | 17.6 | 2.1% |
| Diuretics [a, b] | 89.9 | 91.0 | 0.321 | 90.6 | 90.0 | 2.1% |
| Statins [a, b] | 31.4 | 44.4 | <0.001 | 33.4 | 35.0 | 3.4% |
| Anticoagulants [a, b] | 34.5 | 42.3 | <0.001 | 36.0 | 36.6 | 1.3% |
| Anti-platelets [a, b] | 50.9 | 53.0 | 0.256 | 52.4 | 50.6 | 3.6% |
| Nitrates [a, b] | 24.2 | 28.0 | 0.018 | 24.9 | 26.5 | 3.5% |
| **Social economic characteristics (%)** | | | | | | |
| Marital status [a, b] | | | 0.723 | | | 2.3% |
| Married | 45.7 | 47.0 | | 46.9 | 45.7 | |
| Single | 15.8 | 15.2 | | 15.1 | 15.5 | |
| Widowed | 38.5 | 37.8 | | 38.0 | 38.8 | |
| Education level [a, b] | | | 0.867 | | | 3.3% |
| Compulsory school | 57.9 | 57.4 | | 57.3 | 58.9 | |
| Secondary school | 30.5 | 31.3 | | 31.2 | 30.0 | |
| University | 11.6 | 11.3 | | 11.5 | 11.1 | |
| Income > median [a, b] | 42.2 | 42.8 | 0.763 | 42.7 | 41.6 | 2.3% |

NYHA: New York heart association; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); COPD: Chronic obstructive pulmonary disease; TIA: Transient ischemic attack; CRT: Cardiac resynchronization therapy; ICD: Implantable cardioverter defibrillator; RAS-inhibitor: Renin-angiotensin-system inhibitor; MRA: Mineralocorticoid receptor antagonist; SD: Standard deviation; IQR: Interquartile range.

a = variables included in multiple imputation together with index year, duration of HF, the composite outcome, and beta-blocker use (yes/no);

b = variables included to estimate the propensity score together with index year and duration of HF.

* = Absolute standardized differences are defined as the difference in means, proportions or ranks divided by the mutual standard deviation

§ = The variable devices was included in the multiple imputation and propensity score models as yes (CRT or ICD) /no.

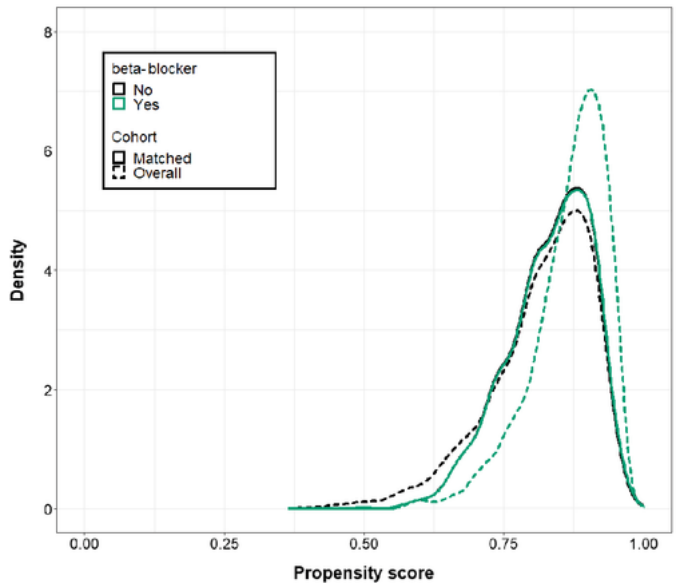


**Figure 10.** Kernel density plot reporting the propensity score distribution in the overall (n = 6562) and matched (n = 1720) cohort of patients ≥80 years of age by treatment arm.

**Outcome Analysis**

*All-cause mortality.* In the overall cohort 4658 (71%) patients died from any cause over a median follow-up of 1.76 (interquartile range: 0.64–3.39) years. The 5-year rate of all-cause death was 32.2 per 100 patient-years for beta-blocker users vs. 42.8 per 100 patient-years for non-users, with a HR of 0.76 (95% CI 0.71–0.83) (**Figure 11A**). After matching, the 5-year event rate was 36.7 vs. 41.8 per 100 patient-years for beta-blocker users vs non-users (HR 0.89, 95% CI 0.79–0.99). In the unmatched overall cohort, the use of beta-blocker was associated with lower 5-year all-cause mortality adjusting rather than matching for the propensity score (HR 0.89, 95% CI 0.82–0.97).

There were no significant interactions between beta-blocker use and any variable defining the subgroups of interest (including atrial fibrillation) (**Figure 12A**).

*Composite outcome (CV mortality or HF hospitalization)*. In total, 4701 (71.6%) CV mortality/HF hospitalization events were observed. The 5-year event rate for beta-blocker users was lower compared with non-users (46.7 vs. 58.8 per 100 patient-years, HR 0.83, 95%CI 0.76 – 0.90) (**Figure 11B**). In the matched cohort, the 5-year event rate for beta-blocker users was 54.4 vs. 58.2 per 100 patient-years in non-users with a non statistically significant reduction in risk for beta-blocker users (HR 0.94, 95% CI 0.85–1.05). However, adjusting rather than matching for propensity score yielded a statistically significant association between beta-blocker use and lower risk of the composite outcome (HR 0.90, 95% CI 0.83–0.97). Results were consistent across the subgroups of interest (**Figure 12B**). When CV mortality and HF hospitalization were assessed separately, the crude risk of CV mortality was lower in beta-blocker users vs non-users (23.2 vs. 32.0 per 100 patient-years, respectively, HR 0.74, 95% CI

0.67 – 0.81). After matching beta-blocker users had a lower 5-year risk of CV death (event rate 26.2 vs. 31.1 per 100 patient-years in beta-blocker users vs non-users, HR 0.86, 95% CI 0.75 – 0.97). The lower risk of CV mortality in beta-blocker users was consistent after adjusting rather than matching for the propensity score (HR 0.87, 95% CI 0.79 – 0.95). Concerning the risk of HF hospitalization, 5-year event rate in beta-blocker users vs non-users was 33.8 vs. 40.4 per 100 patient-years (crude HR 0.87, 95% CI 0.79–0.96), whereas in the matched cohort was 38.5 vs. 41.0 per 100 patient-years for beta-blocker users vs. non-user, with a non statistically significant lower risk of HF hospitalization for beta-blocker users (HR 0.94, 95% CI 0.83–1.07). However, the propensity-adjusted association in the whole cohort showed a lower risk of HF hospitalization in beta-blocker users compared with non-users (HR 0.90, 95% CI 0.82–0.99).

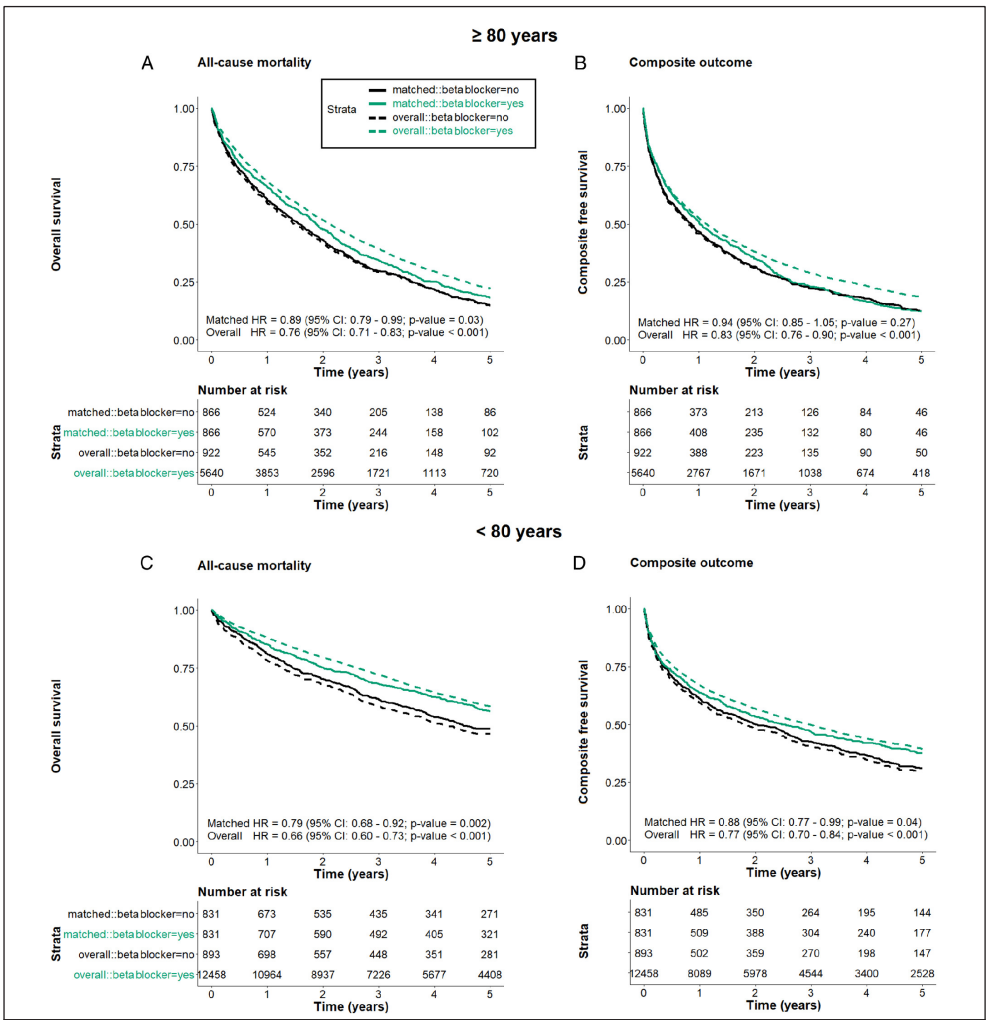


**Figure 11.** Kaplan–Meier curves for the association between beta-blocker use and all-cause mortality and the composite outcome (cardio- vascular mortality or heart failure hospitalization). (A) and (B) patients aged ≥80 years. (C) and (D) patients aged <80 years (positive control analysis).

CI, confidence interval; HR, hazard ratio.

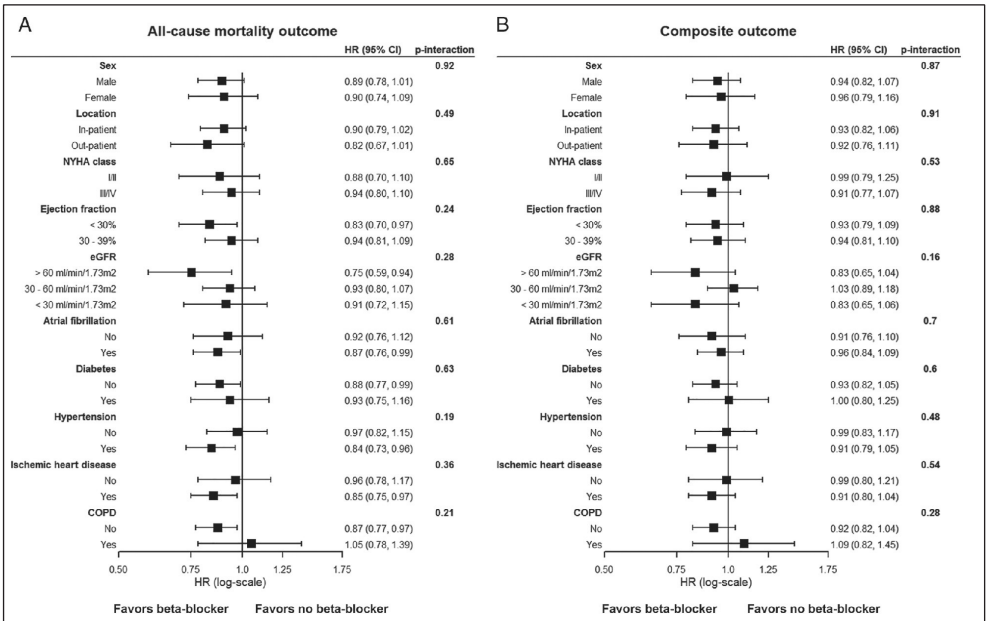


**Figure 12.** The association between beta-blocker use, all-cause mortality and the composite of cardiovascular mortality and heart failure hospitalization in prespecified subgroups in the matched cohort ≥80 years of age.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate (calculated by the Modification of Diet in Renal Disease formula); HR, hazard ratio; NYHA, New York Heart Association.

*Safety outcome*. No statistically significant difference in the 5-year risk of hospitalization for syncope in beta-blocker users vs. non-users was observed in the overall cohort (crude HR 1.09, 95% CI 0.69–1.71), in the propensity score matched (HR 1.04, 95% CI 0.69–1.58) and in the propensity score adjusted analysis (HR 1.03, 95% CI 0.65–1.64).

*Positive control and falsification (negative control) analysis*. In the positive control analysis (patients <80 years of age, $n = 13\,351$, 93.3% treated with beta-blockers), the crude risk (event rates 11.0 vs. 16.8 per 100 patient-years, HR 0.66, 95% CI 0.60 – 0.73) and the risk in the matched population (12.1 vs. 15.5 per 100 patient-years, HR 0.79,95% CI 0.68 – 0.92) for 5-years mortality were lower in beta-blocker users vs non-users, as well as the risk of the composite outcome was lower in beta-blocker users vs non-users in both the overall cohort (event rates 23.5 vs. 31.9 per 100 patient-years, HR 0.77, 95% CI 0.70 – 0.84) and after matching for the propensity score (event rates 25.2 vs. 30.0 per 100 patient-years, HR 0.88, 95% CI 0.77 – 0.99). Similar results were obtained when we adjusted rather than matching for propensity score in the overall cohort. Secondary outcome analysis reported results that were consistent with the ≥80 years cohort.

As a falsification analysis, we assessed the risk of 5-years hospitalization for cancer and demonstrated that in the propensity score matched study cohort use of beta-blocker was not associated with a lower risk of outcome (HR 1.04, 95% CI 0.69–1.58). The propensity score adjusted model in the overall cohort yielded a similar neutral association between use of beta-blocker and the 5-year risk of hospitalization for cancer (HR 0.97, 95% CI 0.70–1.36). Corresponding HRs in the cohort aged <80 years were also not significant.

# Study III

## Patients characteristics

In 27430 HFrEF patients (27% females), mean age was 74±12 years (31% <70 years old, 34% being 70-79 years old and 35% ≥80 years old). The proportion of females increased with aging. Main characteristics of the study patients are summarized in **Table 4.** Older patients were more likely to be registered as in-patients and less likely followed up in a specialty care setting. They had a more deprived socio-economic status, a longer and more severe HF (higher NYHA class and NT-proBNP) and a higher comorbidity burden (e.g. kidney disease, atrial fibrillation/atrial flutter, anemia, hypertension, valve disease, ischemic heart disease, history of stroke/transient ischemic attack, cancer, musculoskeletal disease/connective tissue disease, dementia and depression).

**Table 4.** Main characteristics of the study population according to age category.

| | | Age category | | | |
|---|---|---|---|---|---|
| | **Total** | **<70 years** | **70-79 years** | **≥80 years** | **p-value** |
| | **27430** | **8515 (31%)** | **9392 (34%)** | **9523 (35%)** | |
| **Demographics** | | | | | |
| **Age, yrs¶, mean (SD)** | 74 (12) | 60 (9) | 75 (3) | 85 (4) | <0.001 |
| **Female¶, n (%)** | 7484 (27) | 1836 (22) | 2428 (26) | 3220 (34) | <0.001 |
| **Caregiver at SwedeHF registration¶, n (%)** | | | | | <0.001 |
| Inpatient | 10079 (37) | 2188 (26) | 3038 (32) | 4853 (51) | |
| Outpatient | 17351 (63) | 6327 (74) | 6354 (68) | 4670 (49) | |
| **Follow-up referral to outpatient HF nurse-led clinic¶, n (%)** | | | | | <0.001 |
| No | 12155 (47) | 3127 (38) | 3876 (44) | 5152 (58) | |
| Yes | 13679 (53) | 4990 (62) | 4982 (56) | 3707 (42) | |
| **Follow-up referral specialty¶, n (%)** | | | | | <0.001 |
| Hospital | 17788 (68) | 7035 (85) | 6520 (73) | 4233 (47) | |
| Primary care | 7519 (29) | 998 (13) | 2156 (24) | 4365 (49) | |
| Other | 828 (3) | 194 (2) | 281 (3) | 353 (4) | |
| **Socio-economic** | | | | | |
| **Family type¶, n (%)** | | | | | <0.001 |
| Cohabitating | 14463 (53) | 4538 (54) | 5378 (57) | 4547 (48) | |
| Living alone | 12931 (47) | 3951 (46) | 4008 (43) | 4972 (52) | |
| **Education¶, n (%)** | | | | | <0.001 |
| Compulsory | 12155 (45) | 2775 (33) | 4233 (46) | 5147 (55) | |
| Secondary | 10508 (39) | 4021 (48) | 3498 (38) | 2989 (32) | |
| University | 4197 (16) | 1573 (19) | 1465 (16) | 1159 (13) | |
| **Income¶, n (%)** | | | | | <0.001 |
| Low | 9589 (35) | 2606 (31) | 3313 (35) | 3670 (39) | |
| Medium | 10537 (39) | 2356 (28) | 4026 (43) | 4155 (44) | |
| High | 7268 (26) | 3527 (41) | 2047 (22) | 1694 (17) | |
| **Children¶, n (%)** | 22792 (83) | 6434 (76) | 8026 (85) | 8332 (88) | <0.001 |

| **Table 4.** Continuing | | | | | |
|---|---|---|---|---|---|
| | | **Age category** | | | |
| | **Total** | **<70 years** | **70-79 years** | **≥80 years** | |
| | **27430** | **8515 (31%)** | **9392 (34%)** | **9523 (35%)** | **p-value** |
| | **Clinical** | | | | |
| **HF duration < 6 months¶, n (%)** | 5467 (20) | 2052 (24) | 1771 (19) | 1644 (17) | <0.001 |
| **BMI category, kg/m2¶, n (%)** | | | | | <0.001 |
| <22.5 | | 627 (13) | 901 (17) | 1566 (29) | |
| 22.5-30 | | 2443 (52) | 3095 (59) | 3177 (58) | |
| >30 | | 1641 (35) | 1269 (24) | 698 (13) | |
| **NYHA class III-IV¶, n (%)** | 10798 (50) | 2737 (39) | 3862 (51) | 4199 (61) | <0.001 |
| **Blood pressure, mmHg, mean (SD)** | | | | | |
| Systolic | 122 (20) | 121 (20) | 122 (20) | 123 (20) | <0.001 |
| Diastolic | 71 (12) | 73 (12) | 71 (11) | 70 (11) | <0.001 |
| Mean¶* | 88 (13) | 89 (13) | 88 (13) | 88 (13) | <0.001 |
| **Heart rate, bpm¶, mean (SD)** | 73 (15) | 72 (15) | 73 (15) | 74 (15) | <0.001 |
| **LVEF<30%¶, n (%)** | 13410 (49) | 4394 (52) | 4627 (49) | 4389 (46) | <0.001 |
| **QRS duration, msec, mean (SD)** | 125 (32) | 120 (30) | 126 (32) | 128 (32) | <0.001 |
| **left bundle-branch block, n (%)** | 5880 (28) | 1478 (22) | 2048 (29) | 2354 (32) | <0.001 |
| | Laboratory | | | | |
| **Hb, g/l, mean (SD)** | 132 (17) | 137 (17) | 132 (17) | 127 (16) | <0.001 |
| **Potassium, mEq/l, median (Q1,Q3)** | 4.3 (4.0, 4.6) | 4.3 (4.0, 4.6) | 4.3 (4.0, 4.6) | 4.2 (3.9, 4.5) | <0.001 |
| **Dyskalemia¶, n (%)** | | | | | <0.001 |
| Hypokalemia | 780 (4) | 184 (3) | 252 (3) | 344 (5) | |
| Normakalemia | 19647 (91) | 6289 (93) | 6829 (92) | 6529 (90) | |
| Hyperkalemia | 1032 (5) | 296 (4) | 385 (5) | 351 (5) | |
| **eGFR category, ml/min/1.73m2^¶, n (%)** | | | | | <0.001 |
| <30 | 3238 (12) | 428 (5) | 954 (10) | 1856 (20) | |
| 30-60 | 12191 (45) | 2054 (25) | 4583 (50) | 5554 (59) | |
| ≥60 | 11486 (43) | 5850 (70) | 3653 (40) | 1983 (21) | |
| **NT-proBNP, pg/ml¶, median (Q1,Q3)** | 2669 (1040, 6544) | 1305 (509, 3420) | 2624 (1165, 6000) | 4820 (2311, 10681) | <0.001 |
| | **Comorbidities** | | | | |
| **Atrial fibrillation/atrial flutter¶, n (%)** | 16343 (60) | 3807 (45) | 5925 (63) | 6611 (69) | <0.001 |
| **Smoking¶, n (%)** | | | | | <0.001 |
| Current | 2553 (12) | 1480 (21) | 785 (11) | 288 (4) | |
| Former | 10169 (47) | 3212 (47) | 3852 (51) | 3105 (43) | |
| Never | 8845 (41) | 2211 (32) | 2846 (38) | 3788 (53) | |
| **Anemia†¶, n (%)** | 9625 (37) | 2063 (26) | 3278 (38) | 4284 (47) | <0.001 |
| **Diabetes¶, n (%)** | 8922 (32) | 2807 (33) | 3453 (37) | 2662 (28) | <0.001 |
| **Hypertension¶, n (%)** | 17480 (64) | 4694 (55) | 6238 (66) | 6548 (69) | <0.001 |
| **Valve disease¶, n (%)** | 8346 (31) | 1906 (23) | 2866 (31) | 3574 (38) | <0.001 |
| **Ischemic heart disease¶, n (%)** | 18351 (67) | 4610 (54) | 6673 (71) | 7068 (74) | <0.001 |
| **Previous revascularization, n (%)** | 11493 (42) | 3194 (37) | 4505 (48) | 3794 (40) | <0.001 |
| **Peripheral Artery disease¶, n (%)** | 3158 (11) | 729 (9) | 1318 (14) | 1111 (12) | <0.001 |
| **Stroke or transient ischemic attack¶, n (%)** | 5802 (21) | 1281 (15) | 2072 (22) | 2449 (26) | <0.001 |
| **COPD¶*, n (%)** | 4289 (16) | 1161 (14) | 1705 (18) | 1423 (15) | <0.001 |
| **Liver disease¶, n (%)** | 759 (3) | 450 (5) | 190 (2) | 119 (1) | <0.001 |
| **Cancer history last 3 years¶, n (%)** | 4025 (15) | 692 (8) | 1505 (16) | 1828 (19) | <0.001 |
| **Muscoloskeletal/connective tissue disease last 3 years¶, n(%)** | 8844 (32) | 2293 (27) | 3170 (34) | 3381 (35) | <0.001 |
| **Dementia¶, n(%)** | 538 (2) | 31 (0.4) | 206 (2) | 301 (3) | <0.001 |
| **Depression¶, n(%)** | 1163 (4) | 474 (6) | 362 (4) | 327 (3) | <0.001 |

| **Table 4.** Continuing | | | | | |
|---|---|---|---|---|---|
| | | **Age category** | | | |
| | **Total** | **<70 years** | **70-79 years** | **≥80 years** | **p-value** |
| | **27430** | **8515 (31%)** | **9392 (34%)** | **9523 (35%)** | |
| **Therapy and devices** | | | | | |
| **RASI/ARNI¶, n (%)** | 23904 (88) | 7995 (95) | 8384 (90) | 7525 (80) | <0.001 |
| **RASI, n (%)** | 22732 (83) | 7375 (87) | 7917 (85) | 7440 (79) | <0.001 |
| **ARNI, n (%)** | 1349 (17) | 669 (25) | 524 (17) | 156 (7) | <0.001 |
| **RASI target dose, n (%)** | | | | | <0.001 |
| <50% | 6490 (29) | 1405 (19) | 2165 (27) | 2920 (39%) | |
| 50-99% | 6157 (27) | 1741 (24) | 2129 (27) | 2287 (31%) | |
| ≥100 | 10056 (44) | 4222 (57) | 3612 (46) | 2222 (30%) | |
| **ARNI target dose, n (%)** | | | | | 0.005 |
| <50% | 311 (23) | 140 (21) | 120 (23) | 51 (33) | |
| 50-99% | 472 (35) | 223 (33) | 198 (38) | 51 (33) | |
| ≥100 | 566 (42) | 306 (46) | 206 (39) | 54 (34) | |
| **Beta-blocker¶, n (%)** | 25094 (92) | 8049 (95) | 8734 (93) | 8311 (88) | <0.001 |
| **Beta-blocker target dose, n (%)** | | | | | <0.001 |
| <50% | 7237 (29) | 1692 (21) | 2332 (27) | 3213 (40) | |
| 50-99% | 8490 (35) | 2608 (33) | 3038 (35) | 2844 (35) | |
| ≥100% | 8901 (36) | 3645 (46) | 3209 (38) | 2047 (25) | |
| **MRA¶*, n (%)** | 12360 (45) | 4572 (54) | 4433 (47) | 3355 (35) | <0.001 |
| **MRA target dose, n (%)** | | | | | <0.001 |
| <50% | 864 (13) | 239 (9) | 319 (13) | 306 (19) | |
| 50-99% | 4769 (71) | 1820 (70) | 1802 (73) | 1147 (72) | |
| ≥100% | 1052 (16) | 550 (21) | 356 (14) | 146 (9) | |
| **Diuretics¶, n (%)** | 22593 (83) | 6238 (74) | 7751 (83) | 8604 (91) | <0.001 |
| **Digoxin¶, n (%)** | 4281 (16) | 1260 (15) | 1537 (16) | 1484 (16) | 0.015 |
| **Antiplatelet therapy¶, n (%)** | 11840 (43) | 3497 (41) | 3935 (42) | 4408 (47) | <0.001 |
| **Anticoagulant therapy¶, n (%)** | 13445 (49) | 3836 (45) | 5121 (55) | 4488 (47) | <0.001 |
| **Statin¶, n (%)** | 14569 (53) | 4653 (55) | 5738 (61) | 4178 (44) | <0.001 |
| **Nitrates¶, n (%)** | 4708 (17) | 781 (9) | 1536 (16) | 2391 (25) | <0.001 |
| **ICD¶*, n (%)** | 3755 (19) | 1803 (29) | 1529 (22) | 423 (7) | <0.001 |
| **CRT¶*, n (%)** | 3141 (37) | 1140 (50) | 1309 (42) | 692 (23) | <0.001 |

Values are mean (SD), n (%), or median (Q1,Q3). ˆCalculated by the CKD-EPI formula. †Anemia, defined as hemoglobin <120 g/l in females and <130 g/l in males. ¶ Variables included in the multiple imputation models and as covariates in the multivariable models. *among patients with indication according to current guidelines (see methods). Legend: ARNI=angiotensin receptor neprilysin inhibitors; BMI=body mass index; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; COPD=chronic obstructive pulmonary disease; CRT=cardiac resynchronization therapy; eGFR=estimated glomerular filtration rate; Hb=hemoglobin; HF=heart failure; ICD=implantable cardioverter cardioverter-defibrillator; LVEF=left ventricle ejection fraction; MRA=mineralocorticoid receptor antagonists; NT-proBNP=N-terminal pro–B-type natriuretic peptide; NYHA=New York Heart Association; RASI =renin-angiotensin system inhibitors

## Use of HF treatments according to age (Figures 13 and 14)

In the overall population, 88% received RASI or ARNI, 17% ARNI, 92% beta-blocker and 45% MRA. Use of medical treatments steadily decreased with aging. Of patients ≥80 years old, 78%, 7%, 88% and 35%, received treatment with RASI, ARNI, beta-blocker and MRA, respectively. Target dose of medications was achieved in less than 50% of the total study population (44% for RASI/ARNI, 36% for beta-blocker and 16% for MRA), with older vs. younger patients less likely to be treated with target dose or to receive combinations of HF treatments.

In patients with an indication for a HF device (ICD=19444 patients; CRT=8444 patients), 19% had an ICD and 37% a CRT. The crude use of ICD and CRT was nearly 4-fold and 2-fold lower in patients ≥80 vs. <70 years old, respectively.

After comprehensive adjustments, there was still a significant independent association between older age and non-use and lower use of target dose of antineurohormonal drugs, and lower use of ICD but not of CRT.

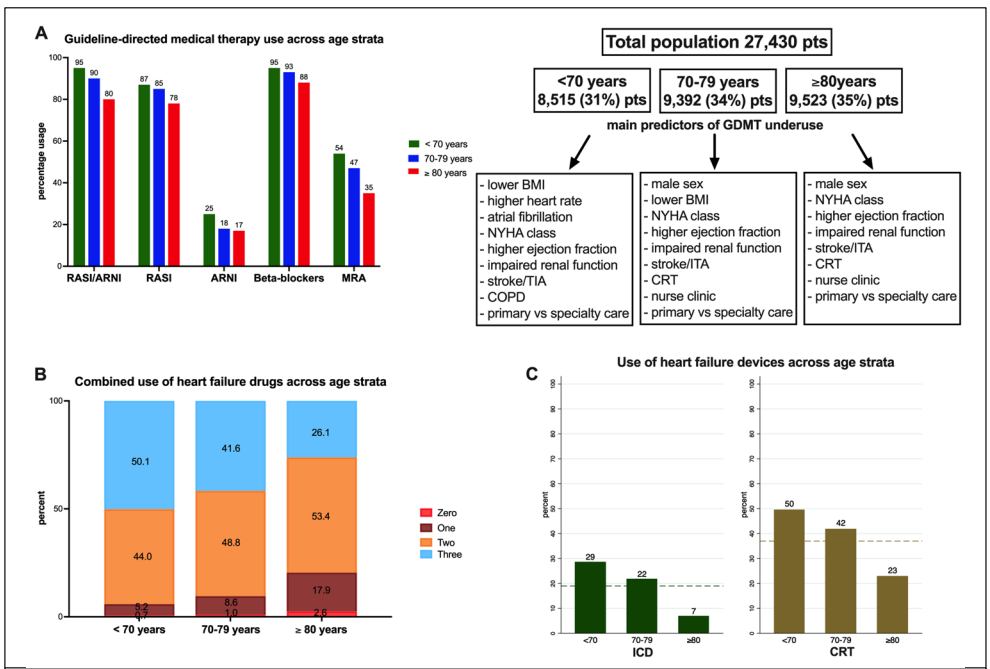


**Figure 13.** Use of guideline-directed medical therapy across age strata in heart failure with reduced ejection. Panel A. Crude rate of guideline-directed medical therapy use in the overall cohort and across age strata. Panel B. Combined use of heart failure drugs in the overall cohort and across age strata. Panel C. Crude use of heart failure devices across age strata.
ARNI rates refer to patients enrolled from 2016 onward. Dashed lines indicate the rates of implantation in the total population. GDMT = guidelines-directed medical therapy. Other abbreviations as in Table 1.

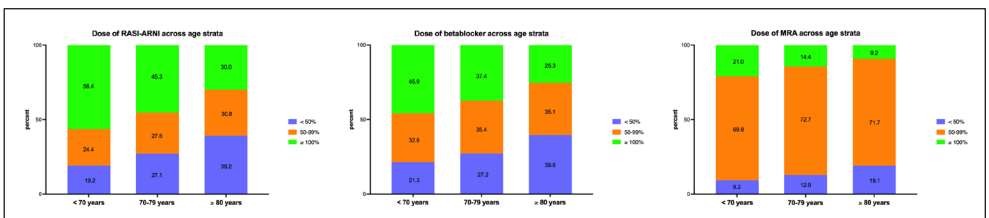


**Figure 14.** Percentage of target dose achievement for guideline-directed medical therapies in the overall cohort and across age strata. Abbreviations as in Table 1. Doses of MRA were available from 2015.

### Age-related differences in the use of HF treatments in specific subgroups

Use of treatments was overall lower in older vs. younger patients in all the explored subgroups (**Table 5**).

Females in the <70 years old category were less likely treated with RASI/ARNI and beta-blocker compared with males. Use of ARNI was lower in females vs. males aged ≥70 years. Use of devices was consistently lower in females across all the age categories. After extensive adjustments, older age was independently associated with non-use of RASI/ARNI and beta-blocker in males but not in females, whereas for MRA this association was consistent regardless of sex.

**Table 5.** Use of guideline-directed medical therapy across subgroups.

| | | Age category | | |
|---|---|---|---|---|
| | **Total** | **<70 years** | **70-79 years** | **≥80 years** |
| | **27430** | **8515 (31%)** | **9392 (34%)** | **9523 (35%)** |
| **RASI/ARNI** | | | | |
| **Sex, %** | | | | |
| Male (n=19,946) | 88 | 95 | 90 | 80 |
| Female (n=7,484) | 87 | 93 | 91 | 80 |
| p-value | <0.001 | 0.005 | 0.434 | 0.556 |
| **Dyskalemia, %** | | | | |
| Hypokalemia (n=780) | 72 | 86 | 75 | 63 |
| Normakalemia (n=19,647) | 89 | 95 | 91 | 82 |
| Hyperkalemia (n=1,032) | 88 | 93 | 89 | 83 |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 |
| **eGFR category, ml/min/1.73m2, %** | | | | |
| <30 (n=3,238) | 65 | 75 | 66 | 62 |
| 30-60 (n=12,191) | 87 | 92 | 91 | 83 |
| ≥60 (n=11,486) | 95 | 97 | 95 | 88 |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 |
| **Caregiver at SwedeHF registration, %** | | | | |
| Inpatients (n=10,079) | 79 | 90 | 82 | 72 |
| Outpatients (n=17,351) | 93 | 96 | 94 | 88 |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 |
| **ARNI** | | | | |
| **Sex, %** | | | | |
| Male (n=19,946) | 18 | 25 | 20 | 7 |
| Female (n=7,484) | 12 | 24 | 11 | 5 |
| p-value | <0.001 | 0.612 | <0.001 | 0.036 |
| **Dyskalemia, %** | | | | |
| Hypokalemia (n=780) | 9 | 18 | 9 | 3 |
| Normakalemia (n=19,647) | 17 | 25 | 18 | 7 |
| Hyperkalemia (n=1,032) | 20 | 28 | 21 | 11 |
| p-value | 0.005 | 0.351 | 0.081 | 0.049 |
| **eGFR category, ml/min/1.73m2, %** | | | | |
| <30 (n=3,238) | 7 | 13 | 9 | 3 |
| 30-60 (n=12,191) | 15 | 27 | 19 | 7 |
| ≥60 (n=11,486) | 21 | 26 | 18 | 9 |
| p-value | <0.001 | 0.017 | 0.001 | 0.002 |
| **Caregiver at SwedeHF registration, %** | | | | |
| Inpatients (n=10,079) | 4 | 12 | 3 | 1 |
| Outpatients (n=17,351) | 19 | 26 | 20 | 9 |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 |

| **Table 5.** Continuing | | | | |
|---|---|---|---|---|
| | | **Age category** | | |
| | **Total** | **<70 years** | **70-79 years** | **≥80 years** |
| | **27430** | **8515 (31%)** | **9392 (34%)** | **9523 (35%)** |
| **Beta-blocker** | | | | |
| **Sex, %** | | | | |
| Male (n=19,946) | 92 | 95 | 93 | 87 |
| Female (n=7,484) | 91 | 93 | 94 | 89 |
| p-value | 0.167 | <0.001 | 0.363 | 0.020 |
| **Heart rate, %** | | | | |
| >70 bpm (n=12,819) | 91 | 94 | 93 | 87 |
| ≤70 bpm (n=13,285) | 93 | 96 | 94 | 88 |
| p-value | <0.001 | <0.001 | 0.093 | 0.082 |
| **Atrial fibrillation, %** | | | | |
| Yes (n=16,343) | 92 | 95 | 93 | 88 |
| No (n=11,087) | 92 | 95 | 93 | 86 |
| p-value | 0.402 | 0.403 | 0.696 | 0.005 |
| **Caregiver at SwedeHF registration, %** | | | | |
| Inpatients (n=10,079) | 88 | 93 | 91 | 86 |
| Outpatients (n=17,351) | 93 | 95 | 94 | 90 |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 |
| **MRA** | | | | |
| **Sex, %** | | | | |
| Male (n=19,946) | 46 | 54 | 48 | 35 |
| Female (n=7,484) | 43 | 53 | 47 | 36 |
| p-value | <0.001 | 0.136 | 0.350 | 0.849 |
| **Dyskalemia, %** | | | | |
| Hypokalemia (n=780) | 39 | 47 | 39 | 35 |
| Normakalemia (n=19,647) | 46 | 55 | 48 | 35 |
| Hyperkalemia (n=1,032) | 51 | 57 | 52 | 44 |
| p-value | <0.001 | 0.088 | 0.005 | 0.003 |
| **eGFR category, ml/min/1.73m2, %** | | | | |
| <30 (n=3,238) | 26 | 27 | 29 | 24 |
| 30-60 (n=12,191) | 44 | 54 | 48 | 37 |
| ≥60 (n=11,486) | 51 | 56 | 51 | 40 |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 |
| **Caregiver at SwedeHF registration, %** | | | | |
| Inpatients (n=10,079) | 40 | 52 | 43 | 33 |
| Outpatients (n=17,351) | 48 | 55 | 49 | 38 |
| p-value | <0.001 | 0.026 | <0.001 | <0.001 |
| **ICD** | | | | |
| **Sex, %** | | | | |
| Male (n=19,946) | 22 | 30 | 25 | 8 |
| Female (n=7,484) | 12 | 23 | 14 | 4 |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 |
| **LVEF, %** | | | | |
| <30% (n=13,410) | 12 | 14 | 21 | 7 |
| ≥30% (n=14,020) | 16 | 18 | 13 | 4 |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 |
| **Caregiver at SwedeHF registration, %** | | | | |
| Inpatients (n=10,079) | 20 | 38 | 24 | 6 |
| Outpatients (n=17,351) | 19 | 26 | 21 | 7 |
| p-value | 0.082 | <0.001 | 0.003 | 0.185 |

| **Table 5.** Continuing | | | | |
|---|---|---|---|---|
| | | **Age category** | | |
| | **Total** | **<70 years** | **70-79 years** | **≥80 years** |
| | **27430** | **8515 (31%)** | **9392 (34%)** | **9523 (35%)** |
| **CRT** | | | | |
| **Sex, %** | | | | |
| Male (n=19,946) | 40 | 52 | 44 | 26 |
| Female (n=7,484) | 29 | 41 | 36 | 15 |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 |
| **LVEF, %** | | | | |
| <30% (n=13,410) | 41 | 53 | 44 | 25 |
| ≥30% (n=14,020) | 32 | 44 | 39 | 20 |
| p-value | <0.001 | <0.001 | 0.002 | <0.001 |
| **Atrial fibrillation, %** | | | | |
| Yes (n=16,343) | 40 | 56 | 46 | 26 |
| No (n=11,087) | 33 | 44 | 35 | 17 |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 |
| **Caregiver at SwedeHF registration, %** | | | | |
| Inpatients (10,079) | 33 | 57 | 39 | 18 |
| Outpatients (17,351) | 39 | 47 | 43 | 27 |
| p-value | <0.001 | <0.001 | 0.057 | <0.001 |

For abbreviations see Table 4

**Independent predictors of use of HF treatments according to age (Table 6)**

Some predictors of use were consistent across age categories, including better renal function for RASI/ARNI and MRA use, referral to specialty care and nurse-led HF clinic for all the HF drugs. Higher comorbidity burden was associated instead with lower use/uptitration of HF drugs and lower use of ICD.

Female sex was independently associated with higher use of RASI/ARNI and MRA, higher use and higher target dose achievement of beta-blocker, and lower use of ICD in patients ≥80 years old, whereas in the younger subgroup female sex was independently associated with less target dose achievement, but not with underuse of HF drugs or devices.
Atrial fibrillation was independently associated with lower use of RASI/ARNI and MRA in <70 years old patients and with lower use/dosing of RASI/ARNI in age ≥80 years, higher dose of beta-blocker across age subgroups, higher use of CRT in age=70-79 and ≥80 years.

**Temporal trends in use of HF treatments across age categories**

We assessed crude rates of HF treatments use/dosing and adjusted probabilities of treatment use/dosing over time. The adjusted predicted probabilities of using HF treatments and of target dose achievement, and of use of devices over time are reported in **Figures 15 and 16.** Use of RASI/ARNI tended to decrease over time regardless of age, but more in the ≥80 years old class, whereas beta-blocker use increased in age ≥70 vs. <70 years. Use of MRA increased over time in age <80 years. Adjusted use of target dose decreased over time regardless of age for RASI/ARNI and increased in age≥70 years but not in age<70 years for beta-blocker.

Adjusted use of ICD increased over time regardless of age, whereas adjusted probabilities of CRT use was overall stable in age≥80 years, but increased and then decreased in age<80 years.

**Table 6.** Factors associated with the use of heart failure guideline-directed medical therapy in the overall population.

| Variables | RASI/ARNI | | Beta-blocker | | MRA | |
|---|---|---|---|---|---|---|
| | HR (95%CI) | p | HR (95% CI) | p | HR (95% CI) | p |
| **Male sex** | 0.79 (0.72-0.88) | <0.001 | 0.82 (0.73-0.91) | <0.001 | 0.92 (0.86-0.98) | 0.007 |
| **Caregiver** (Outpatient vs. inpatient) | 1.72 (1.56-1.89) | <0.001 | 1.18 (1.05-1.33) | 0.004 | 0.91 (0.86-0.98) | 0.007 |
| **Follow-up location** | | | | | | |
| Primary care vs hospital | 0.80 (0.72-0.88) | <0.001 | 0.77 (0.68-0.86) | <0.001 | 0.78 (0.73-0.83) | <0.001 |
| Other vs hospital | 0.76 (0.62-0.94) | 0.011 | 0.76 (0.60-0.97) | 0.028 | 0.68 (0.58-0.79) | <0.001 |
| **Referral to HF nurse clinic** | 1.28 (1.15-1.42) | <0.001 | 1.12 (1.00-1.26) | 0.052 | 0.98 (0.93-1.05) | 0.627 |
| **HF duration** (≥6 vs. <6 months) | 0.88 (0.78-0.98) | 0.024 | 0.81 (0.72-0.91) | 0.001 | 1.23 (1.16-1.32) | <0.001 |
| **NYHA** (III-IV vs. I-II) | 0.75 (0.68-0.84) | <0.001 | 0.8 8(0.79-0.99) | 0.039 | 1.17 (1.10-1.24) | <0.001 |
| **BMI** | | | | | | |
| BMI 22.5-30 kg/m2 vs <22.5 | 1.38 (1.18-1.62) | <0.001 | 1.16 (1.00-1.34) | 0.055 | 0.99 (0.90-1.08) | 0.826 |
| BMI >30 kg/m2 vs <22.5 | 1.40 (1.12-1.74) | 0.004 | 1.25 (1.03-1.53) | 0.027 | 1.20 (1.04-1.39) | 0.013 |
| **MAP** (≥90 vs <90 mmHg) | 1.03 (0.94-1.13) | 0.489 | 1.06 (0.97-1.17) | 0.201 | 0.76 (0.72-0.80) | <0.001 |
| **HR** (≥70 vs. <70 bpm) | 0.76 (0.70-0.83) | <0.001 | 0.89 (0.81-0.98) | 0.019 | 0.93 (0.89-0.98) | 0.007 |
| **EF < 30%** | 1.29 (1.18-1.40) | <0.001 | 1.07 (0.98-1.18) | 0.147 | 1.20 (1.14-1.27) | <0.001 |
| **NT-proBNP** (≥ median vs. <median) | 0.65 (0.55-0.89) | <0.001 | 1.35 (1.09-1.67) | 0.007 | 0.99 (0.90-1.10) | 0.891 |
| **eGFR** | | | | | | |
| eGFR 30-60 vs <30 ml/min/1.73m2 | 2.92 (2.63-3.24) | <0.001 | 0.89 (0.77-1.02) | 0.097 | 2.16 (1.96-2.37) | <0.001 |
| eGFR>60 vs <30 ml/min/1.73m2 | 5.17 (4.50-5.94) | <0.001 | 0.84 (0.71-0.99) | 0.047 | 2.77 (2.50-3.07) | <0.001 |
| **Dyskalemia** | | | | | | |
| Normo vs hypo | 2.10 (1.69-2.60) | <0.001 | 0.90 (0.64-1.27) | 0.542 | 1.10 (0.92-1.31) | 0.200 |
| Hyper vs hypo | 2.89 (2.22-3.75) | <0.001 | 0.92 (0.62-1.36) | 0.677 | 1.54 (1.27-1.88) | <0.001 |
| **Ischemic heart disease** | 0.80 (0.72-0.89) | <0.001 | 0.95 (0.85-1.06) | 0.382 | 0.96 (0.90-1.02) | 0.180 |
| **Hypertension** | 1.09 (1.00-1.20) | 0.057 | 1.20 (1.09-1.33) | <0.001 | 1.12 (1.06-1.19) | <0.001 |
| **Diabetes Mellitus** | 0.92 (0.83-1.01) | 0.065 | 1.09 (0.98-1.21) | 0.104 | 1.01 (0.95-1.08) | 0.686 |
| **COPD** | 0.90 (0.80-1.01) | 0.070 | 0.92 (0.81-1.05) | 0.221 | 0.95 (0.88-1.02) | 0.155 |
| **Anemia** | 0.94 (0.86-1.02) | 0.152 | 0.87 (0.79-0.96) | 0.007 | 0.89 (0.84-0.94) | <0.001 |
| **Atrial fibrillation/ flutter** | 0.82 (0.74-0.91) | <0.001 | 1.00 (0.90-1.13) | 0.934 | 0.96 (0.90-1.03) | 0.281 |
| **Peripheral artery disease** | 0.85 (0.75-0.96) | 0.008 | 0.87 (0.76-0.99) | 0.048 | 0.94 (0.87-1.02) | 0.144 |
| **Stroke or transient ischemic attack** | 0.83 (0.76-0.91) | <0.001 | 0.87 (0.78-0.96) | 0.008 | 0.87 (0.82-0.93) | <0.001 |

**Table 6.** Continuing

| Variables | RASI/ARNI | | Beta-blocker | | MRA | |
|---|---|---|---|---|---|---|
| | HR (95%CI) | p | HR (95% CI) | p | HR (95% CI) | p |
| **Valvular disease** | 0.70 (0.64-0.76) | <0.001 | 0.83 (0.76-0.92) | <0.001 | 1.14 (1.08-1.21) | <0.001 |
| **Liver disease** | 0.71 (0.57-0.90) | 0.004 | 1.01 (0.77-1.33) | 0.949 | 1.12 (0.96-1.31) | 0.140 |
| **Cancer history** | 0.87 (0.79-0.97) | 0.013 | 0.90 (0.80-1.01) | 0.076 | 0.94 (0.84-1.01) | 0.117 |
| **Muscoloskeletal/ connective tissue disease last 3 years** | 0.86 (0.79-0.93) | <0.001 | 0.83 (0.75-0.91) | <0.001 | 0.90 (0.85-0.95) | <0.001 |
| **Dementia** | 0.86 (0.67-1.08) | 0.182 | 1.21 (0.91-1.62) | 0.195 | 0.81 (0.67-0.98) | 0.034 |
| **Depression** | 1.03 (0.84-1.26) | 0.775 | 0.73 (0.60-0.88) | 0.002 | 1.04 (0.92-1.19) | 0.482 |
| **Smoking** | | | | | | |
| Previous vs. current | 0.86 (0.70-1.04) | 0.116 | 0.78 (0.65-0.93) | 0.007 | 1.12 (1.03-1.23) | 0.012 |
| No vs. current | 0.82 (0.68-1.00) | 0.052 | 0.72 (0.60-0.87) | 0.001 | 1.11 (1.01-1.23) | 0.028 |
| **Living alone vs married/ cohabitating** | 0.95 (0.87-1.04) | 0.290 | 0.96 (0.87-1.06) | 0.433 | 0.97 (0.92-1.03) | 0.336 |
| **Education** | | | | | | |
| Secondary vs compulsory | 1.09 (0.99-1.20) | 0.064 | 1.01 (0.91-1.11) | 0.963 | 0.98 (0.92-1.04) | 0.457 |
| University vs compulsory | 1.20 (1.04-1.37) | 0.011 | 0.98 (0.84-1.13) | 0.756 | 0.98 (0.91-1.06) | 0.681 |
| **Income** | | | | | | |
| Medium vs low | 1.02 (0.92-1.12) | 0.756 | 1.00 (0.90-1.11) | 0.963 | 1.06 (0.99-1.12) | 0.067 |
| High vs low | 0.99 (0.88-1.12) | 0.952 | 1.13 (0.99-1.29) | 0.078 | 1.13 (1.05-1.21) | 0.001 |
| **Children** | 1.00 (0.89-1.13) | 0.995 | 0.89 (0.78-1.01) | 0.068 | 1.04 (0.97-1.12) | 0.274 |
| **Diuretics** | 1.16 (1.00-1.34) | 0.046 | 1.18 (1.03-1.35) | 0.018 | 1.48 (1.37-1.59) | <0.001 |
| **Digoxin** | 1.13 (1.00-1.28) | 0.045 | 1.12 (0.98-1.28) | 0.094 | 1.28 (1.19-1.38) | <0.001 |
| **Nitrates** | 1.02 (0.92-1.13) | 0.743 | 1.22 (1.08-1.38) | 0.002 | 0.98 (0.92-1.06) | 0.665 |
| **Anticoagulants** | 1.68 (1.49-1.89) | <0.001 | 1.60 (1.41-1.83) | <0.001 | 1.11 (1.03-1.20) | 0.007 |
| **Antiplatelets** | 1.19 (1.07-1.33) | 0.002 | 1.30 (1.15-1.47) | <0.001 | 0.95 (0.88-1.02) | 0.123 |
| **Statins** | 1.58 (1.44-1.73) | <0.001 | 1.46 (1.32-1.62) | <0.001 | 1.07 (1.01-1.13) | 0.026 |
| **RASI** | - | - | 1.99 (1.77-2.24) | <0.001 | 1.07 (0.98-1.17) | 0.132 |
| **Beta-blocker** | 2.09 (1.86-2.35) | <0.001 | 2.00 (1.78-2.25) | <0.001 | 1.09 (0.99-1.20) | 0.065 |
| **MRA** | 1.09 (0.99-1.19) | 0.065 | 1.11 (1.01-1.22) | 0.027 | - | - |
| **CRT** | 1.00 (0.85-1.18) | 0.995 | 1.29 (1.05-1.58) | 0.015 | 1.15 (1.05-1.26) | 0.003 |
| **ICD** | 1.15 (0.97-1.36) | 0.117 | 1.86 (1.50-2.32) | <0.001 | 1.49 (1.36-1.63) | <0.001 |

ARNI=angiotensin receptor neprilysin inhibitors; BMI=body mass index; COPD=chronic obstructive pulmonary disease; CRT=cardiac resynchronization therapy; eGFR=estimated glomerular filtration rateHF=heart failure; ICD=implantable cardioverter cardioverter-defibrillator; LVEF=left ventricle ejection fraction; MAP=mean arterial pressure; MRA=mineralocorticoid receptor antagonists; NT-proBNP=N-terminal pro–B-type natriuretic peptide; NYHA=New York Heart Association; RASI =renin-angiotensin system inhibitors.

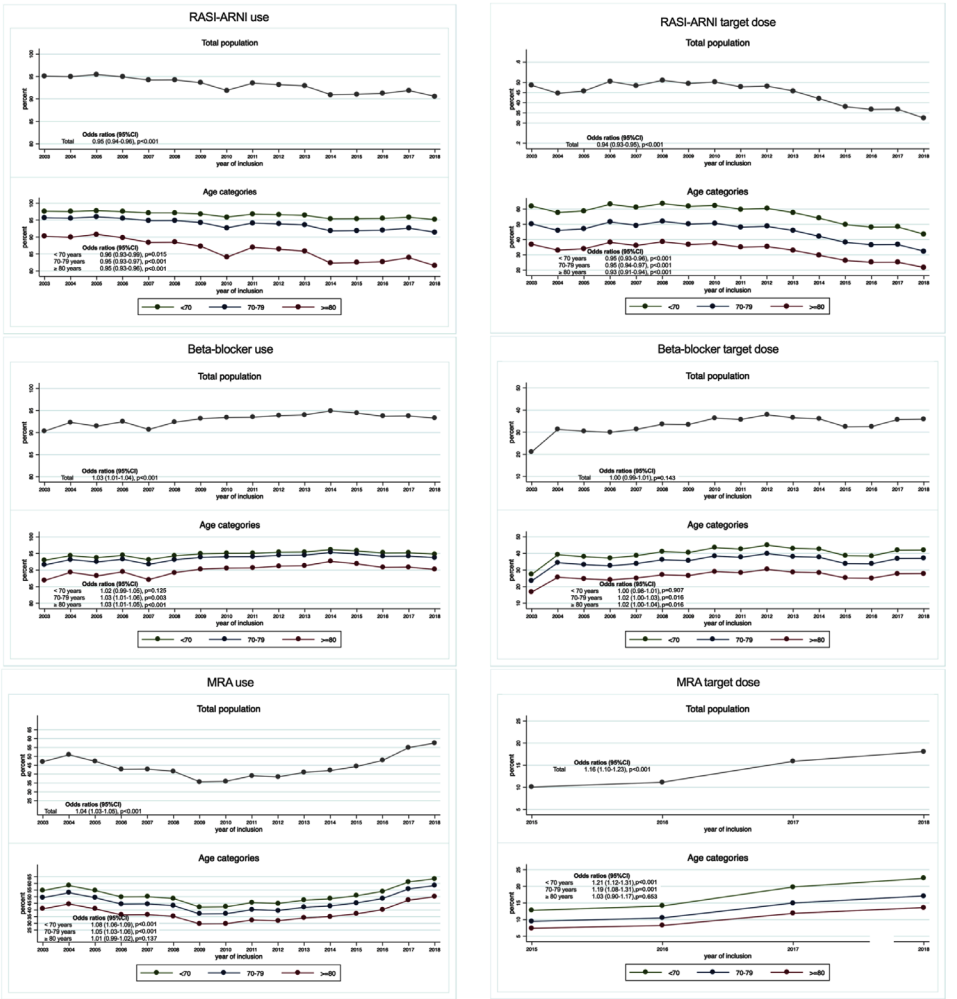


**Figure 15.** Temporal trends in the adjusted probability of guideline-directed medical therapy (left panel) and target dose achievement (right panel) across age strata.
Trends in use of HF treatments starts from 2003 when SwedeHF was implemented; doses of MRA were available from 2015.

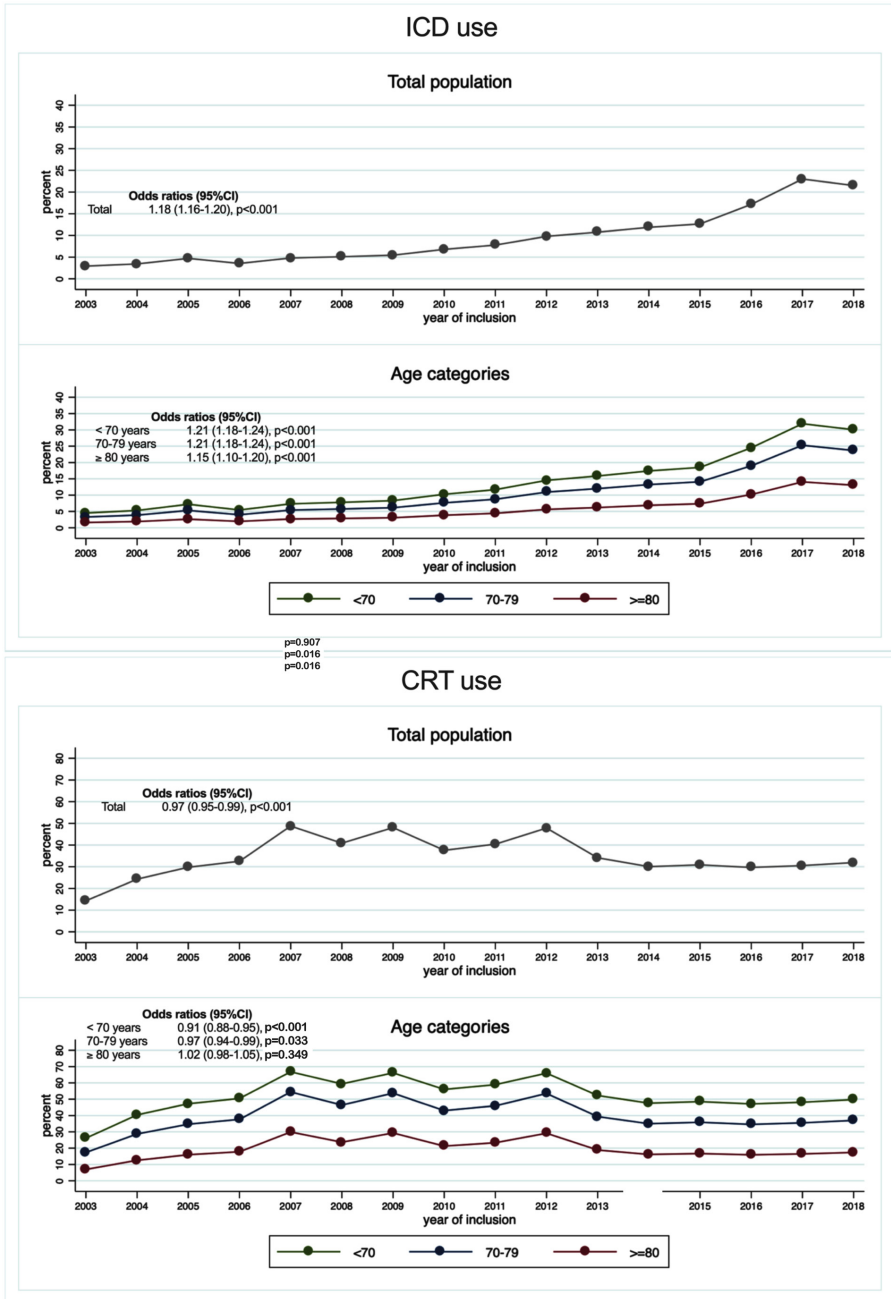


**Figure 16.** Temporal trends in the adjusted probability use of devices in the overall cohort and across age strata.

# Study IV

## Main characteristics of the HF and non-HF population

The overall HF population included 76510 patients (53% had HFrEF, 23% HFmrEF, and 24% HFpEF) and the control population without HF 229359 patients. Median age was 76 (67-83) years, 36.9% were females. As shown in **Table 7 and Figure 17**, compared with subjects without HF, patients with HF showed an overall higher CV (i.e. ischemic heart disease in 52.4% of patients with HF vs 14.6% without HF, diabetes in 25.2% vs 8.5%, atrial fibrillation in 51.8% vs 7.8%, hypertension in 56.1% vs 22.2%, obesity in 5.2% vs 0.8%, history of stroke in 14.3% vs 9.1%, peripheral artery disease in 8.8% vs 2.8%) and, with the exception of dementia, non-CV comorbidity burden (i.e. renal failure in 12.4% in the HF cohort vs 1.8% in the non-HF cohort, chronic obstructive pulmonary disease in 13.1% vs 3.0%, anemia in 14.2% vs 4.1%, cancer in 14.2% vs 11.9% and liver disease in 2.0% vs 0.6%). HF patients were also more likely to have lower education level and income. Treatments, including non-HF drugs (i.e. antiplatelet drugs, anticoagulants, oral glucose lowering drugs and statins), were more likely prescribed to HF patients.

**Table 7.** Baseline characteristics of the HF population compared with the non-HF population.

| | HF | Non-HF | p |
|---|---|---|---|
| **n** | 76,453 | 229,359 | |
| ***Demographic/Organizational characteristcs*** | | | |
| **Sex Male, n (%)** | 48,214 (63.1) | 144,642 (63.1) | 1.000 |
| **Age, years, median (IQR)** | 76.0 [67.0, 83.0] | 76.0 [67, 83] | 1.000 |
| **Outpatient, n (%)** | 39,872 (52.2) | - | |
| **Follow-up referral HF nurse clinic, n (%)** | 40,813 (56.7) | - | |
| **Follow-up referral speciality, n (%)** | | | |
| **Hospital** | 48,209 (66.1) | - | |
| **Primary care** | 22,657 (31.1) | - | |
| **Other** | 2,018 (2.8) | - | |
| **Year of registration, n (%)** | | | 1.000 |
| **2005-2010** | 27,514 (36.0) | 82,542 (36.0) | |
| **2011-2015** | 28,256 (37.0) | 84,768 (37.0) | |
| **2016-2018** | 20,683 (27.1) | 62,049 (27.1) | |
| ***Clinical characteritics*** | | | |
| **EF category, n (%)** | | | 1.000 |
| **HFrEF** | 40,893 (53.5) | | |
| **HFmrEF** | 17,395 (22.8) | | |
| **HFpEF** | 18,165 (23.8) | | |
| **HF duration > 6 months, n (%)** | 36,178 (48.6) | - | |
| **NYHA class, n (%)** | | | |
| **I** | 6,181 (11.8) | - | |
| **II** | 25,423 (48.4) | - | |
| **III** | 19,183 (36.6) | - | |
| **IV** | 1,693 (3.2) | - | |
| **SBP, mmHg, median (IQR)** | 125 [112, 140] | - | |
| **DBP, mmHg, median (IQR)** | 72.0 [65, 80] | - | |
| **HR, bpm, median (IQR)** | 72.0 [63, 83] | - | |
| **HR >70 bpm, n (%)** | 39,108 (52.7) | - | |
| **LBBB, n (%)** | 11,550 (18.2) | - | |
| ***Laboratory measurements*** | | | |
| **Hb (g/L), median (IQR)** | 133 [120, 145] | - | |
| **eGFR (mL/min/1.73 m$^2$)*, median (IQR)** | 62.2 [45.1, 80.2] | - | |
| **eGFR <60 mL/min/1.73** m$^2$, n (%) | 35,145 (46.6) | - | |
| **NT-proBNP (pg/ml), median (IQR)** | 2,399 [1044, 5338] | - | |
| **Hyperkalemia, n (%)** | 1,099 (1.4) | 345 (0.2) | <0.001 |
| **Hypokalemia, n (%)** | 1,567 (2.0) | 1,117 (0.5) | <0.001 |

| **Table 7.** Continuing | | | |
|---|---|---|---|
| | **HF** | **Non-HF** | **p** |
| **n** | 76,453 | 229,359 | |
| ***Medical history/comorbidities*** | | | |
| **BMI, kg/m², median (IQR)** | 26.5 [23.4, 30.2] | - | |
| **BMI ≥30, n (%)** | 12,092 (26.5) | - | |
| **Former/current smoker, n (%)** | 32,764 (56.0) | - | |
| **Diabetes, n (%)** | 19,258 (25.2) | 19,429 (8.5) | <0.001 |
| **Renal failure, n (%)** | 9,449 (12.4) | 4,124 (1.8) | <0.001 |
| **AF, n (%)** | 39,593 (51.8) | 17,950 (7.8) | <0.001 |
| **Ischemic heart disease, n (%)** | 40,056 (52.4) | 33,591 (14.6) | <0.001 |
| **Anemia, n (%)** | 10,866 (14.2) | 9,456 (4.1) | <0.001 |
| **Hypertension, n (%)** | 42,910 (56.1) | 50,935 (22.2) | <0.001 |
| **Peripheral artery disease, n (%)** | 6,715 (8.8) | 6,378 (2.8) | <0.001 |
| **PCI, n (%)** | 10,076 (13.2) | 4,563 (2.0) | <0.001 |
| **CABG, n (%)** | 17,014 (22.3) | 8,442 (3.7) | <0.001 |
| **Stroke, n (%)** | 10,959 (14.3) | 20,871 (9.1) | <0.001 |
| **Valvular disease, n (%)** | 15,373 (20.1) | 5,297 (2.3) | <0.001 |
| **Malignant cancer, n (%)** | 10,853 (14.2) | 27,332 (11.9) | <0.001 |
| **COPD, n (%)** | 10,002 (13.1) | 6,821 (3.0) | <0.001 |
| **Liver disease, n (%)** | 1,552 (2.0) | 1,482 (0.6) | <0.001 |
| **Dementia, n (%)** | 1,310 (1.7) | 7,520 (3.3) | <0.001 |
| **Severe bleeding, n (%)** | 13,486 (17.6) | 16,594 (7.2) | <0.001 |
| **Muscoloskeletal/connective tissue disease, n (%)** | 23,616 (30.9) | 46,145 (20.1) | <0.001 |
| **Alcohol abuse, n (%)** | 2,430 (3.2) | 3,117 (1.4) | <0.001 |
| **Charlson comorbidity Index** | 2.0 [1.0, 4.0] | 0.0 [0.0, 2.0] | <0.001 |
| ***Treatments*** | | | |
| **Devices (ICD/CRT)** | 3,530 (4.6) | 78 (0.0) | <0.001 |
| **RASI/ARNI, n (%)** | 66,654 (87.2) | 68,008 (29.7) | <0.001 |
| **Diuretics, n (%)** | 59,022 (77.2) | 54,737 (23.9) | <0.001 |
| **Beta-blocker, n (%)** | 67,377 (88.1) | 61,882 (27.0) | <0.001 |
| **Calcium Channel Blockers, n (%)** | 16,804 (22.0) | 44,029 (19.2) | <0.001 |
| **MRA, n (%)** | 27,721 (36.3) | 4,255 (1.9) | <0.001 |
| **Antiplatelet therapy, n (%)** | 37,776 (49.4) | 60,663 (26.4) | <0.001 |
| **Anticoagulant therapy, n (%)** | 34,936 (45.7) | 17,775 (7.7) | <0.001 |
| **Insulin, n (%)** | 9,309 (12.2) | 9,714 (4.2) | <0.001 |
| **Oral glucose lowering therapy, n (%)** | 10,733 (14.0) | 17,906 (7.8) | <0.001 |
| **Lipid lowering therapy, n (%)** | 38,270 (50.1) | 54,300 (23.7) | <0.001 |
| **Digoxin, n (%)** | 12,389 (16.2) | 3,438 (1.5) | <0.001 |
| **Nitrates, n (%)** | 22,696 (29.7) | 13,108 (5.7) | <0.001 |
| **Antiarrhythmic therapy, n (%)** | 2,694 (3.5) | 807 (0.4) | <0.001 |
| ***Socio-economic characteristics*** | | | |
| **Family type Living alone, n (%)** | 36,985 (48.5) | 100,138 (43.7) | <0.001 |
| **Children, n (%)** | 63,815 (83.5) | 194,416 (84.8) | <0.001 |
| **Education, n (%)** | | | <0.001 |
| **Compulsory school** | 33,681 (45.0) | 91,255 (40.5) | |
| **Secondary school** | 29,013 (38.8) | 84,227 (37.4) | |
| **University** | 12,107 (16.2) | 49,671 (22.1) | |
| **Income above median, n (%)** | 34,588 (45.3) | 118,275 (51.6) | <0.001 |

AF=atrial fibrillation, BMI=body mass index, CABG=coronary artery by-pass graft, COPD=chronic obstructive pulmonary disease, CRT=cardiac resynchronization therapy, DBP=diastolic blood pressure, EF=ejection fraction, eGFR=estimated glomerular filtration rate, Hb=hemoglobin, ICD=implantable cardioverter defibrillator, HF=heart failure, HFmrEF=mildly reduced ejection fraction heart failure, HFpEF=preserved ejection fraction heart failure, HFrEF= reduced ejection fraction heart failure, HR=heart rate, IQR=interquartile range, LBBB=left bundle branch block, MRA=mineralocorticoid receptor antagonists, NYHA=New York Heart Association, NT-proBNP= N-terminal pro–B-type natriuretic peptide, PCI=percutaneous coronary intervention, RASI/ARNI=renin-angiotensin system inhibitors/angiotensin receptor neprilysin inhibitor, SBP=systolic blood pressure. Categorical variables are presented with number and percentage, continuous variables with median and interquartile range. * GFR estimation derived from CKD-EPI formula.

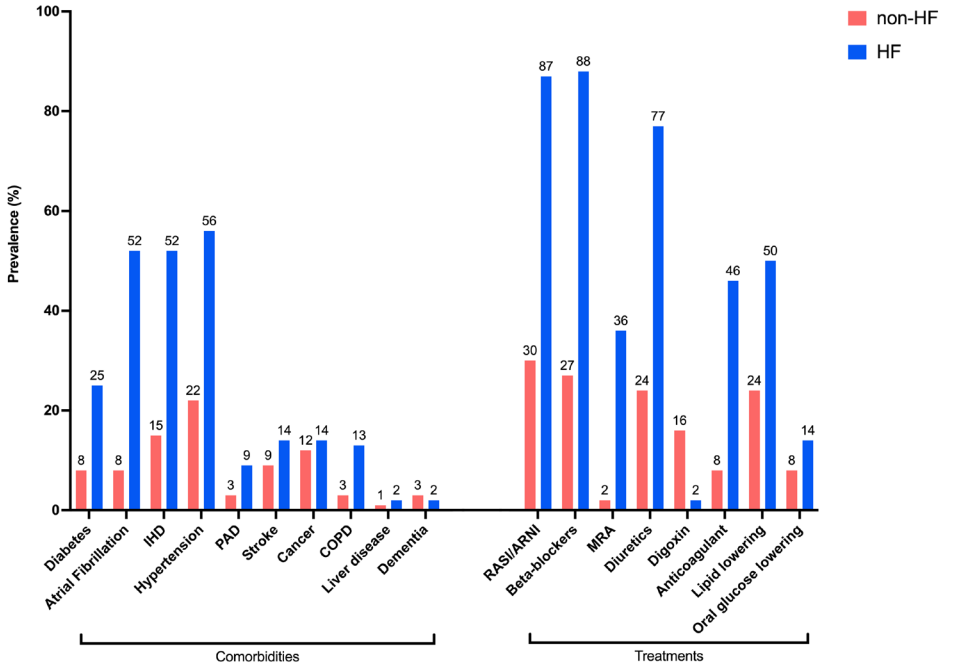


**Figure 17.** Differences in comorbidities and treatments and outcomes between patients with HF and control individuals without HF.
CV=cardiovascular, HHF=hospitalization for heart failure, HF=heart failure, IHD=ischemic heart disease, PAD=peripheral artery disease. * *x 10*. See Table 1 for other abbreviations.

**Main characteristics of the HF population across EF categories (Table 8, Figure 18)**

Patients with HFpEF were more likely to be female (54%) and were older (median 80 years, interquartile range 72-85) compared to HFmrEF and HFrEF. They were also more likely to live alone rather than cohabitate, to have lower education level and income, to be in-patients at the time of registration in SwedeHF, less likely to be followed in specialized care and to be referred to HF nurse-led clinics.

The highest burden of comorbidities was observed in HFpEF patients (i.e. diabetes, impaired renal function, anemia, atrial fibrillation, history of stroke, chronic obstructive pulmonary disease, cancer and dementia), with the exception of ischemic heart disease which was more frequent in HFrEF and HFmrEF. HF drugs were more likely prescribed in HFrEF. Use of RASI/ARNI and diuretics in HFmrEF was more similar to HFrEF.

The higher comorbidity burden and the larger use of HF and non-HF drugs in the HF vs non-HF population were consistent across the range of EF.

| **Table 8.** Baseline characteristics of the HF population across the EF categories. | | | | |
|---|---|---|---|---|
| **Variable** | **HFrEF** | **HFmrEF** | **HFpEF** | **p** |
| **n** | 40,893 | 17,395 | 18,165 | |
| ***Demographic/Organizational characteristics*** | | | | |
| **Sex Male, n (%)** | 29,047 (71.0) | 10,733 (61.7) | 8,434 (46.4) | <0.001 |
| **Age, years, median (IQR)** | 73 [64, 81] | 76 [68, 83] | 80 [72, 85] | <0.001 |
| **Outpatient, n (%)** | 22,347 (54.6) | 9,899 (56.9) | 7,626 (42.0) | <0.001 |
| **Follow-up referral HF nurse clinic, n (%)** | 24,691 (63.7) | 9,143 (55.6) | 6,979 (41.6) | <0.001 |
| **Follow-up referral speciality, n (%)** | | | | <0.001 |
| **Hospital** | 29,757 (75.9) | 10,324 (62.1) | 8,128 (47.6) | |
| **Primary care** | 8,437 (21.5) | 5,852 (35.2) | 8,368 (49.1) | |
| **Other** | 1,012 (2.6) | 444 (2.7) | 562 (3.3) | |
| **Year of registration, n (%)** | | | | <0.001 |
| **2005-2010** | 15,174 (37.1) | 5,971 (34.3) | 6,369 (35.1) | |
| **2011-2015** | 15,075 (36.9) | 6,355 (36.5) | 6,826 (37.6) | |
| **2016-2018** | 10,644 (26.0) | 5,069 (29.1) | 4,970 (27.4) | |
| ***Clinical characteristics*** | | | | |
| **HF duration > 6 months, n (%)** | 18,326 (45.8) | 8,458 (50.0) | 9,394 (53.8) | <0.001 |
| **NYHA class, n (%)** | | | | <0.001 |
| **I** | 2,753 (9.2) | 1,872 (15.6) | 1,556 (14.8) | |
| **II** | 14,160 (47.2) | 6,436 (53.6) | 4,827 (46.0) | |
| **III** | 11,962 (39.9) | 3,451 (28.7) | 3,770 (35.9) | |
| **IV** | 1,100 (3.7) | 257 (2.1) | 336 (3.2) | |
| **SBP, mmHg, median (IQR)** | 120 [110, 140] | 130 [117, 140] | 130 [120, 145] | <0.001 |
| **DBP, mmHg, median (IQR)** | 71 [65, 80] | 74 [65, 80] | 70 [65, 80] | <0.001 |
| **HR, bpm, median (IQR)** | 72 [64, 84] | 71 [62, 81] | 72 [63, 82] | <0.001 |
| **HR >70 bpm, n (%)** | 21,539 (54.1) | 8,438 (50.1) | 9,131 (52.2) | <0.001 |
| **LBBB, n (%)** | 8,352 (24.5) | 2,026 (14.1) | 1,172 (7.8) | <0.001 |
| ***Laboratory measurements*** | | | | |
| **Hb (g/L), median (IQR)** | 135 [122, 147] | 132 [120, 144] | 127 [115, 139] | <0.001 |
| **eGFR (mL/min/1.73 m²)*, median (IQR)** | 64 [47, 82] | 63 [46, 80] | 57 [41, 75] | <0.001 |
| **eGFR <60 mL/min/1.73** m², n (%) | 17522 (43.3) | 7833 (45.7) | 9790 (55.0) | <0.001 |
| **NT-proBNP (pg/ml), median (IQR)** | 2904 [1270, 6440] | 1932 [799, 4247] | 2020 [913, 4163] | <0.001 |
| **Hyperkalemia, n (%)** | 541 (1.3) | 226 (1.3) | 332 (1.8) | <0.001 |
| **Hypokalemia, n (%)** | 708 (1.7) | 361 (2.1) | 498 (2.7) | <0.001 |
| ***Medical history/comorbidities*** | | | | |
| **BMI, kg/m², median (IQR)** | 26 [23, 30] | 27 [24, 30] | 27 [24, 31.] | <0.001 |
| **BMI ≥30, n (%)** | 5875 (23.8) | 2958 (28.2) | 3259 (31.2) | <0.001 |
| **Former/current smoker, n (%)** | 19172 (59.4) | 7243 (54.7) | 6349 (49.1) | <0.001 |
| **Diabetes, n (%)** | 10125 (24.8) | 4212 (24.2) | 4921 (27.1) | <0.001 |
| **Renal failure, n (%)** | 4757 (11.6) | 2078 (11.9) | 2614 (14.4) | <0.001 |
| **AF, n (%)** | 19290 (47.2) | 9304 (53.5) | 10999 (60.6) | <0.001 |
| **Ischemic heart disease, n (%)** | 22076 (54.0) | 9569 (55.0) | 8411 (46.3) | <0.001 |
| **Anemia, n (%)** | 4790 (11.7) | 2508 (14.4) | 3568 (19.6) | <0.001 |
| **Hypertension, n (%)** | 20401 (49.9) | 10196 (58.6) | 12313 (67.8) | <0.001 |
| **Peripheral artery disease, n (%)** | 3450 (8.4) | 1574 (9.0) | 1691 (9.3) | 0.001 |
| **PCI, n (%)** | 5970 (14.6) | 2671 (15.4) | 1435 (7.9) | <0.001 |
| **CABG, n (%)** | 9723 (23.8) | 4198 (24.1) | 3093 (17.0) | <0.001 |
| **Stroke, n (%)** | 5491 (13.4) | 2486 (14.3) | 2982 (16.4) | <0.001 |

| **Table 8.** Continuing | | | | |
|---|---|---|---|---|
| **Variable** | **HFrEF** | **HFmrEF** | **HFpEF** | **p** |
| **n** | 40,893 | 17,395 | 18,165 | |
| **Valvular disease, n (%)** | 6806 (16.6) | 3660 (21.0) | 4907 (27.0) | <0.001 |
| **Malignant cancer, n (%)** | 5332 (13.0) | 2557 (14.7) | 2964 (16.3) | <0.001 |
| **COPD, n (%)** | 4788 (11.7) | 2253 (13.0) | 2961 (16.3) | <0.001 |
| **Liver disease, n (%)** | 849 (2.1) | 309 (1.8) | 394 (2.2) | 0.020 |
| **Dementia, n (%)** | 623 (1.5) | 263 (1.5) | 424 (2.3) | <0.001 |
| **Severe bleeding, n (%)** | 6,120 (15.0) | 3,208 (18.4) | 4,158 (22.9) | <0.001 |
| **Muscoloskeletal/connective tissue diseases, n (%)** | 11,162 (27.3) | 5,574 (32.0) | 6,880 (37.9) | <0.001 |
| **Alcohol abuse, n (%)** | 1,502 (3.7) | 464 (2.7) | 464 (2.6) | <0.001 |
| **Charlson comorbidity Index** | 2.0 [1.0, 4.0] | 2.0 [1.0, 4.0] | 3.0 [1.0, 4.0] | <0.001 |
| ***Treatments*** | | | | |
| **Devices (ICD/CRT)** | 2,917 (7.1) | 422 (2.4) | 191 (1.1) | <0.001 |
| **RASI/ARNI, n (%)** | 37,606 (92.0) | 15,117 (86.9) | 13,931 (76.7) | <0.001 |
| **Diuretics, n (%)** | 31,563 (77.2) | 12,345 (71.0) | 15,114 (83.2) | <0.001 |
| **Beta-blocker, n (%)** | 37,291 (91.2) | 15,137 (87.0) | 14,949 (82.3) | <0.001 |
| **Calcium Channel Blocker, n (%)** | 6,706 (16.4) | 4,137 (23.8) | 5,961 (32.8) | <0.001 |
| **MRA, n (%)** | 16,693 (40.8) | 5,053 (29.0) | 5,975 (32.9) | <0.001 |
| **Antiplatelet therapy, n (%)** | 21,157 (51.7) | 8,718 (50.1) | 7,901 (43.5) | <0.001 |
| **Anticoagulant therapy, n (%)** | 18,291 (44.7) | 7,908 (45.5) | 8,737 (48.1) | <0.001 |
| **Insulin, n (%)** | 4,803 (11.7) | 2,036 (11.7) | 2,470 (13.6) | <0.001 |
| **Oral glucose lowering therapy, n (%)** | 5,795 (14.2) | 2,358 (13.6) | 2,580 (14.2) | 0.113 |
| **Lipid lowering therapy, n (%)** | 21,198 (51.8) | 9,086 (52.2) | 7,986 (44.0) | <0.001 |
| **Digoxin, n (%)** | 6,691 (16.4) | 2,572 (14.8) | 3,126 (17.2) | <0.001 |
| **Nitrates, n (%)** | 12,352 (30.2) | 5,394 (31.0) | 4,950 (27.3) | <0.001 |
| **Antiarrhythmic therapy, n (%)** | 1,807 (4.4) | 480 (2.8) | 407 (2.2) | <0.001 |
| ***Socio-economic characteristics*** | | | | |
| **Family type Living alone, n (%)** | 18,854 (46.2) | 8,167 (47.0) | 9,964 (54.9) | <0.001 |
| **Children, n (%)** | 33,655 (82.3) | 14,736 (84.7) | 15,424 (84.9) | <0.001 |
| **Education, n (%)** | | | | <0.001 |
| **Compulsory school** | 17,414 (43.4) | 7,524 (44.2) | 8,743 (49.5) | |
| **Secondary school** | 16,115 (40.2) | 6,617 (38.8) | 6,281 (35.6) | |
| **University** | 6,572 (16.4) | 2,892 (17.0) | 2,643 (15.0) | |
| **Income above median, n (%)** | 19,857 (48.7) | 7,996 (46.0) | 6,735 (37.1) | <0.001 |

For abbreviations see Table 1. Categorical variables are presented with number and percentage, continuous variables with median and interquartile range. * GFR estimation derived from CKD-EPI formula.

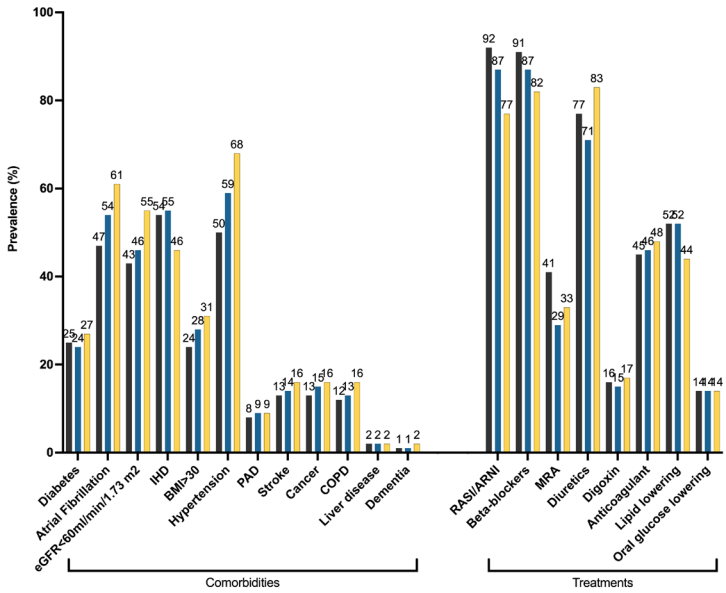


**Figure 18.** Distribution of the main cardiovascular and non-cardiovascular comorbidities, and of HF and non-HF treatments across the EF spectrum.
For abbreviations see Figure 17

## Study Outcomes

The median follow-up was 4.0 (2.0-7.3) years. Compared with non-HF, the HF cohort was characterized by three-fold and four-fold higher incidence of first (HR: 2.86, 95% CI: 2.83-2.89) and repeated (incidence rate ratio [IRR]: 3.93, 95% CI: 3.89-3.98) all-cause hospitalizations, respectively; five-fold and ten-fold higher incidence of first (HR: 5.47, 95% CI: 5.39-5.54) and repeated (IRR: 10.4, 95% CI: 10.3-10.6) CV hospitalizations, respectively; two-fold higher incidence of first (HR: 2.03, 95% CI: 2.01-20.5) and repeated (IRR: 2.44, 95% CI: 2.41-2.47) non-CV hospitalizations; three-fold and 2-fold higher incidence of first (HR: 2.95, 95% CI: 2.92-2.97) and repeated (IRR: 2.26, 95% CI: 2.24-2.28) all-cause outpatient visits, respectively; and two-fold higher incidence of repeated emergency visits (IRR 2.38, 95%CI 2.34-2.43) (**Figure 19**).

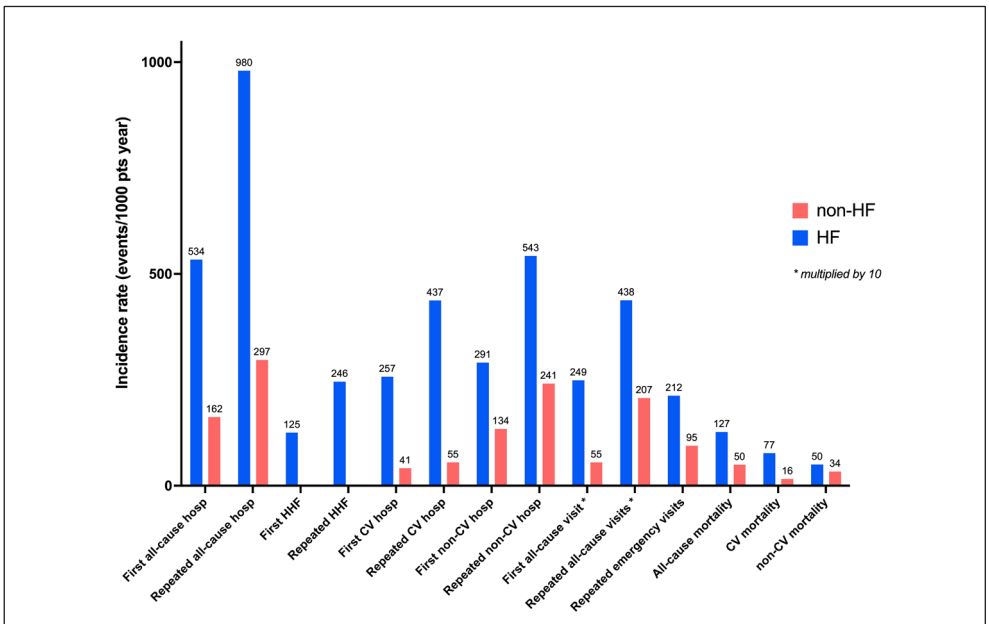


**Figure 19.** Differences in outcomes between patients with HF and control individuals without HF. CV=cardiovascular, HHF=hospitalization for heart failure, HF=heart failure, IHD=ischemic heart disease, PAD=peripheral artery disease. * x 10. See Table 7 for other abbreviations

The average in-hospital LoS for any cause per follow-up year was 7.1 days in HF vs 2.1 days in non-HF subjects and was mainly driven by non-CV causes. The risk of all-cause death was two-fold higher (HR: 2.53, 95% CI: 2.50-2.56), the risk of CV death was five-fold higher (HR 4.67, 95%CI 4.59-4.76) and the risk non-CV death 1.5-fold higher (HR: 1.49, 95% CI: 1.46-1.52) in the HF compared with the non-HF population. As summarized in **Figure 20** patients with HFrEF reported the highest, HFpEF patients intermediate and HFmrEF patients the lowest risk of first and repeated HF hospitalizations. For first and repeated all-cause hospitalizations and non-CV hospitalization, patients with HFpEF were at higher risk. Similarly, HFpEF was at higher risk of all-cause, CV and non-CV death and had the longest average in-hospital LoS for any cause, CV causes and non-CV causes. The higher risk in outcomes in HF vs non-HF was consistent regardless of EF.

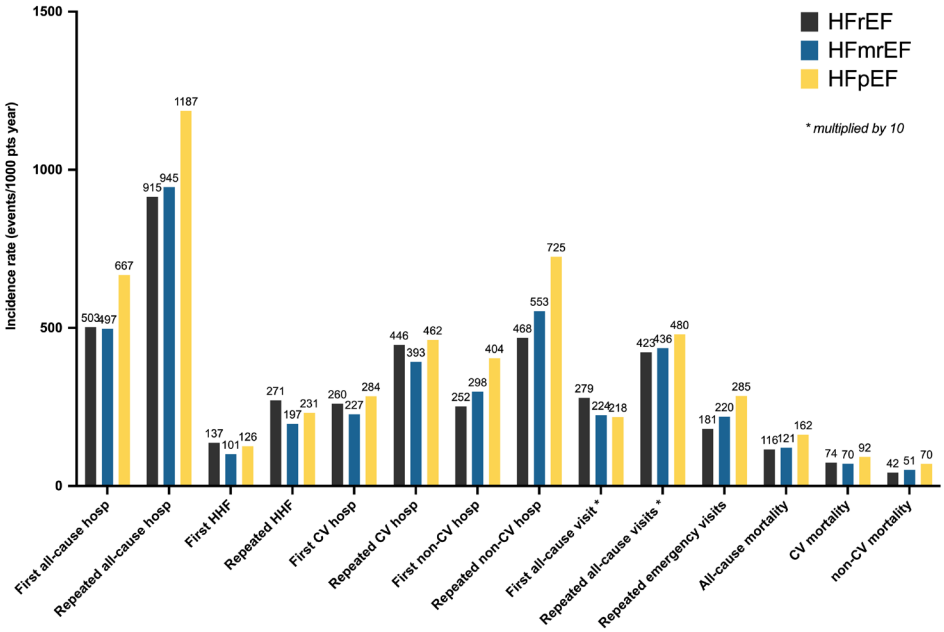


**Figure 20.** Incidence of the study outcomes in the HF population across the EF categories.
See Table 7 and Figure 19 for abbreviations

# 5 DISCUSSION

Despite the advances in diagnostic work-up, risk stratification and treatments, prognosis in HF remains poor(2,63). Underprescription and underdosing of HF medications are frequent in clinical practice and limited implementation of available therapeutic strategies is a major concern in the overall care of HF(59,60). There are challenging subgroups of patients with HF that, for several reasons, are more likely exposed to under-treatment, but are also of major impact for the whole healthcare system due to their increasing prevalence or worse outcome. The four studies included in the present thesis provided a comprehensive overview on two of the more important subgroups of patients with HF, women and older patients (**Study I** and **III**), aimed to confirm the safety and effectiveness of evidence-based treatments in a scenario neglected by RCTs (**Study II**) and defined the overall burden of HF on the healthcare system, which is importantly influenced in the contemporary era by the progressive aging of the population and by the increasing burden of comorbidities (**Study IV**).

**Differences in characteristics and outcome between the overall HF population and non-HF controls and distinctive features of specific subgroups (i.e. women and older patients)**

Representation of specific subgroups of patients with HF has been historically limited in the setting of RCTs, which reduces the trust toward the evidence supporting the use of evidence-based therapies in specific settings. Nevertheless, current recommendations from HF guidelines do not discriminate between sex or age, and therapy for HF should be indistinctly prescribed in women vs men and in older vs younger patients(2). However, specific aspects differ across sexes as well as in older vs younger individuals. In **Study I** we specifically explored the characteristics of women with HF across the EF spectrum, and in **Study III** we assessed the characteristics and the status of treatment implementation in a large population of older patients with HFrEF compared with younger strata. **Study I** showed different characteristics in women compared with men with HF that were largely consistent across the EF spectrum. In particular women presented higher prevalence of chronic kidney disease, hypertension, valve and lung disease, but a lower prevalence of ischemic heart disease, diabetes and anemia. When in **Study IV** we quantified the comorbidity burden in the overall HF population from SwedeHF, there was a higher number of comorbidities in HFpEF compared to HFrEF and HFmrEF. For instance, the prevalence of diabetes was 27% in HFpEF vs 24.2% and 24.8% in HFmrEF and HFrEF, respectively; the prevalence of impaired renal function was 14% in HFpEF vs 11.9% and 11.6% in HFmrEF and HFrEF, respectively; and the prevalence of atrial fibrillation was 60.6% in HFpEF vs 53.5% and 47.2% in HFmrEF and HFrEF, respectively. This is strictly related with another important characteristic of the contemporary HF population, that is the ageing(90,97,98). In **Study III**, indeed, octogenarians were the 35% of the overall HFrEF study cohort and, as expected, they carried a higher burden of comorbidities and a less favorable socio-economic condition. Of note, as already found in **Study I**, the prevalence of females increased with aging, and this is another partial explanation of the higher proportion of females in the HFpEF category.

Sex-related differences have been previously reported regarding HF prognosis(99-102). In our **Study I** the higher crude risk of mortality/morbidity observed in females with HFpEF and HFmrEF was not confirmed after extensive adjustment. Females had a lower adjusted

risk of the primary outcome (i.e. a composite of all-cause death and HF hospitalization) and the differences in risk in males vs females increased with decreasing EF. The risk of all-cause, CV and non-CV mortality was lower in females, but regarding hospitalizations, females were exposed to a lower adjusted risk of CV and HF hospitalization compared to males only in the HFrEF range. The higher unadjusted risk of mortality/morbidity is likely due to the different characteristics of women vs men. Women were older, presented worse HF in terms of both symptoms and higher NT-proBNP values, had higher prevalence of comorbidities with known negative prognostic impact (e.g. impaired renal function, chronic obstructive pulmonary disease), had a more deprived socio-economic status and less likely were followed in specialized care and referred to an HF nurse-led clinic. The better outcome that was instead observed in females in the adjusted analysis is probably explained by biological differences including the role of sex hormones. These aspects worth to be specifically investigated in dedicated studies.

Differences in outcomes were also found in **Study II** when analyzing patients with HFrEF aged ≥ 80 years old and the positive control cohort of patients aged < 80 years old. For instance, the crude 5-year event rate was 32.2 per 100 patient-years for beta-blocker users vs. 42.8 per 100 patient-years for non-users in the ≥ 80 years old cohort and 11.0 per 100 patient-years for beta-blocker users vs. 16.8 per 100 patient-years for non-users in the < 80 years old cohort. Similarly, older patients were exposed to higher rate of HF hospitalizations. This is an obvious observation, but the three-fold higher mortality and the two-fold higher exposure to HF hospitalization in the older population must be considered as it is one major explanation of the increasing overall burden that HF exerts on the worldwide healthcare systems (**Study IV**).

**Physicians' adherence to prescribe evidence-based HF therapies in specific subgroups**

Sex-related disparities in treatment have been previously reported and involve both medical therapies and devices(99,103). In the CHAMP-HF registry women resulted to be undertreated compared to men(59). In **Study I** we have observed that after adjustments, females were more likely to receive beta-blocker and digoxin, and we hypothesized that it might be explained by the higher need in females to achieve a successful heart rate control. The higher use of digoxin is noteworthy considering the findings from the DIG trial that reported a significantly higher absolute risk of death associated with digoxin use in women(104).

Recently, a multicenter study by Santema et al. collecting data from two major cohorts (i.e. BIOSTAT-CHF and ASIAN-HF) suggested that women might need lower doses of RASI/ARNI and beta-blocker than men(71). In our **Study III**, female sex was associated with lower target dose achievement for RASI and beta-blocker in patients aged <70 years old but with higher target dose achievement for beta-blocker in patients aged ≥80 years old. No differences in the use of GDMT between sexes were observed in the <70 years old age stratum, whereas in patients aged ≥80 years, female sex was associated with higher use of RASI/ARNI, beta-blocker and MRA. This is concordant with what we have reported in **Study I**, where females with HFrEF were older, had higher heart rate and blood pressure, higher NYHA class and NT-proBNP compared to males. These aspects might have promoted larger adoption of HF medications in older classes, where females were more largely represented.

However, in general, the lower use and lower dosing of HF treatments was strongly associated with increasing age in **Study III**, according to previous data from literature(59,105-109). In our cohort, the absolute rate of HF drugs use in ≥80 years old patients with HFrEF was higher compared to previous studies (i.e. 80% received RASI/ARNI, 88% received beta-blocker and 35% received MRA)(105,107-109), but significantly lower than in younger categories. The limited enrollment of older patients in RCTs might limit the generalizability of the evidence on the efficacy of GDMT in older groups. However, in the SENIORS trial, the only RCT specifically designed to enroll a population ≥70 years old, nebivolol reduced the risk of all-cause mortality/cardiovascular hospitalization(83). A former observational study from the SwedeHF registry showed a similar magnitude for the association between RASI use and mortality in older vs. younger patients(110). In **Study II** we assessed the association between beta-blocker use and prognosis in octogenarians with HFrEF, including one of the largest available cohort of ≥80 years HFrEF patients. Use of beta-blocker was significantly associated with a lower 5-year risk of all-cause death/HF hospitalization, which was consistent with the results of the SENIORS trial(83), although in our analysis we documented a statistically significant lower mortality with beta-blockes that might be explained by the higher exposure to the risk of death in a real-world cohort compared to the RCT setting. Our findings support the recommendations from the current guidelines which do not report age-related distinctions for treatment strategies(2).

**The overall impact of HF on the healthcare system in the contemporary era.**

In **Study IV** we showed that the comorbidity burden is much higher in patients with HF compared to non-HF controls. Ageing of the population is one of the determinants of the increasing comorbidity burden that is currently observed in the HF population(90). Multimorbidity and growing age may have important consequences in terms of healthcare system management and costs. For instance, in a Spanish study the reported annual average cost per patient is €3,110 and €1,803 for diabetic and non-diabetic subjects, respectively, whereas impaired renal failure has been reported to be one of the major determinants of increasing costs in patients with HF. (111,112). In Spain, the average expenditure per HF patient was €1147/year in patients with one co-morbidity and €16,806/year in patients with >9 co-morbidities(113). Multimorbidity also influences the overall cost of medications in patients with HF. In U.S. non-HF medications accounted for the largest part of the total medication cost per patient(114).

The complexity of the HF population has dramatic consequences in terms of prognosis. We observed a ~3-fold higher risk for first and repeated all-cause hospitalizations and 2-fold higher risk for all-cause mortality in HF vs non-HF. The risk of non-CV events was also increased. The overall costs attributed to HF have been estimated to account for 1-2% of the total healthcare expenditure, reaching 7% in Spain(113,115). Of note, HF specific costs accounted for 69% of the total costs in the first year, but only 49% and 46% in the second and third year after the diagnosis, when costs related to non-CV events became predominant(116). The distribution of comorbidities and outcomes varied across the EF spectrum. Older patients were more largely represented in the HFpEF phenotype, which showed more CV and non-CV comorbidities. The older age, along with the higher burden of CV and non-CV comorbidities, can explain the higher crude risk of all-cause and non-CV hospitalizations we have observed in HFpEF compared to HFmrEF and HFrEF, whereas patients with HFrEF were more exposed to HF hospitalizations. Similar findings have important implications in the process of resource

allocation and might aid the identification of the better targets of intervention that could not necessarily be the same across the EF spectrum. In Sweden, CV hospitalizations accounted for the largest part of the total secondary care costs in the first year after the diagnosis of HF, but then declined afterwards(116). In a previous analysis focusing on HFpEF, non-CV hospitalizations accounted for ~40% of the overall hospitalizations-related costs (i.e. € 3,618/patient/year)(117). Moreover, higher annual costs of re-hospitalizations were reported in HFpEF (€ 5396) vs. HFrEF (€ 4287) which might be at least partially explained by the high burden of comorbidities in patients with HFpEF(118). Therefore, use of treatments with proven efficacy in reducing HF hospitalizations can be convenient in terms of economical net benefit. Post-hoc analyses from RCTs supported the cost-effectiveness of more recent HFrEF drugs(119,120). The recent demonstration of benefit in terms of HF hospitalization risk reduction for the SGLT2-inhibitor empagliflozin in HFpEF/HFmrEF(41) might also determine an important reduction in the cost expenditures.

# 6 CONCLUSIONS

In the real world, there are important differences in characteristics and outcome in specific subgroups of patients with HF (i.e. women and older patients, see **Study I** and **Study III**) that have important implications in treatment adherence. Females have better survival/ morbidity profile, which may be explained by biological sex differences, but not by lower use of HF drugs since in females adjusted use of RASI and MRA was similar and use of beta-blocker was higher than in males, whereas devices were less used in females vs males (**Study I**). In older categories, GDMT was less used and less likely uptitrated, although they are currently recommended regardless of age as available data suggest similar benefit from GDMT regardless of sex (**Study II**). The increasing complexity of HF patients, including the growing age and the large amount of co-existing comorbidities, determines an exponential increase in costs, with a dramatically growing burden on the healthcare system (**Study IV**). Improving the understanding of challenging subgroups and expanding their representation in RCTs might increase generalizability and improve use of treatments in clinical practice.

# 7 POINTS OF PERSPECTIVE

The present thesis highlighted the need for further and deeper research focused on the most neglected subgroups of patients with HF. Adequate representation of women and older patients in future RCT might increase the generalizability of RCTs' findings and their application in clinical practice. Future studies focused on the assessment of treatment tolerability and efficacy in presence of multiple comorbidities are advocated. Educational programs, structured active follow-up and multidisciplinarity are important fields worth to be implemented in order to improve adherence to guidelines recommendations.

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# 9 REFERENCES


1. Yancy CW, Jessup M, Bozkurt B et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137-e161.
2. McDonagh TA, Metra M, Adamo M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-3726.
3. Roger VL, Go AS, Lloyd-Jones DM et al. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation 2011;123:e18-e209.
4. Moliner P, Lupon J, de Antonio M et al. Trends in modes of death in heart failure over the last two decades: less sudden death but cancer deaths on the rise. Eur J Heart Fail 2019;21:1259-1266.
5. Dunlay SM, Redfield MM, Weston SA et al. Hospitalizations after heart failure diagnosis a community perspective. J Am Coll Cardiol 2009;54:1695-702.
6. Dharmarajan K, Hsieh AF, Lin Z et al. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA 2013;309:355-63.
7. Gerber Y, Weston SA, Redfield MM et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med 2015;175:996-1004.
8. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. Eur J Heart Fail 2019;21:1306-1325.
9. Lawson CA, Zaccardi F, Squire I et al. 20-year trends in cause-specific heart failure outcomes by sex, socioeconomic status, and place of diagnosis: a population-based study. Lancet Public Health 2019;4:e406-e420.
10. Alla F, Zannad F, Filippatos G. Epidemiology of acute heart failure syndromes. Heart Fail Rev 2007;12:91-5.
11. Braunwald E. The war against heart failure: the Lancet lecture. Lancet 2015;385:812-24.
12. Goff DC, Jr., Pandey DK, Chan FA, Ortiz C, Nichaman MZ. Congestive heart failure in the United States: is there more than meets the I(CD code)? The Corpus Christi Heart Project. Arch Intern Med 2000;160:197-202.
13. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail 2012;5:720-6.
14. Chang PP, Wruck LM, Shahar E et al. Trends in Hospitalizations and Survival of Acute Decompensated Heart Failure in Four US Communities (2005-2014): ARIC Study Community Surveillance. Circulation 2018;138:12-24.
15. Steinberg BA, Zhao X, Heidenreich PA et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation 2012;126:65-75.
16. Burnett H, Earley A, Voors AA et al. Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction: A Network Meta-Analysis. Circ Heart Fail 2017;10.

17. Shen L, Jhund PS, Petrie MC et al. Declining Risk of Sudden Death in Heart Failure. N Engl J Med 2017;377:41-51.
18. McMurray JJ, Packer M, Desai AS et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
19. McMurray JJV, Solomon SD, Inzucchi SE et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019;381:1995-2008.
20. Packer M, Anker SD, Butler J et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 2020;383:1413-1424.
21. Vaduganathan M, Claggett BL, Jhund PS et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet 2020;396:121-128.
22. Zannad F, McMurray JJ, Krum H et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11-21.
23. Cazeau S, Leclercq C, Lavergne T et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873-80.
24. Cleland JG, Daubert JC, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.
25. Tang AS, Wells GA, Talajic M et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385-95.
26. Bardy GH, Lee KL, Mark DB et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37.
27. Normand C, Linde C, Singh J, Dickstein K. Indications for Cardiac Resynchronization Therapy: A Comparison of the Major International Guidelines. JACC Heart Fail 2018;6:308-316.
28. Linde C, Ellenbogen K, McAlister FA. Cardiac resynchronization therapy (CRT): clinical trials, guidelines, and target populations. Heart Rhythm 2012;9:S3-S13.
29. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-2200.
30. Kapoor JR, Kapoor R, Ju C et al. Precipitating Clinical Factors, Heart Failure Characterization, and Outcomes in Patients Hospitalized With Heart Failure With Reduced, Borderline, and Preserved Ejection Fraction. JACC Heart Fail 2016;4:464-72.
31. Tsuji K, Sakata Y, Nochioka K et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study. Eur J Heart Fail 2017;19:1258-1269.
32. Chioncel O, Lainscak M, Seferovic PM et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2017;19:1574-1585.
33. Koh AS, Tay WT, Teng THK et al. A comprehensive population-based characterization

of heart failure with mid-range ejection fraction. Eur J Heart Fail 2017;19:1624-1634.

34. Bhambhani V, Kizer JR, Lima JAC et al. Predictors and outcomes of heart failure with mid-range ejection fraction. Eur J Heart Fail 2018;20:651-659.
35. Lam CSP, Gamble GD, Ling LH et al. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. Eur Heart J 2018;39:1770-1780.
36. Rickenbacher P, Kaufmann BA, Maeder MT et al. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). Eur J Heart Fail 2017;19:1586-1596.
37. Ibrahim NE, Song Y, Cannon CP et al. Heart failure with mid-range ejection fraction: characterization of patients from the PINNACLE Registry(R). ESC Heart Fail 2019;6:784-792.
38. Vedin O, Lam CSP, Koh AS et al. Significance of Ischemic Heart Disease in Patients With Heart Failure and Preserved, Midrange, and Reduced Ejection Fraction: A Nationwide Cohort Study. Circ Heart Fail 2017;10.
39. Stolfo D, Uijl A, Vedin O et al. Sex-Based Differences in Heart Failure Across the Ejection Fraction Spectrum: Phenotyping, and Prognostic and Therapeutic Implications. JACC Heart Fail 2019;7:505-515.
40. Lund LH, Claggett B, Liu J et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail 2018;20:1230-1239.
41. Anker SD, Butler J, Filippatos G et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med 2021;385:1451-1461.
42. Shah KS, Xu H, Matsouaka RA et al. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. J Am Coll Cardiol 2017;70:2476-2486.
43. Yusuf S, Pfeffer MA, Swedberg K et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.
44. Massie BM, Carson PE, McMurray JJ et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456-67.
45. Pitt B, Pfeffer MA, Assmann SF et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383-92.
46. Solomon SD, McMurray JJV, Anand IS et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med 2019;381:1609-1620.
47. Solomon SD, Claggett B, Lewis EF et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J 2016;37:455-62.
48. Cleland JGF, Bunting KV, Flather MD et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J 2018;39:26-35.
49. Bohm M, Bewarder Y, Kindermann I. Ejection fraction in heart failure revisited- where does the evidence start? Eur Heart J 2020;41:2363-2365.

50. Pieske B, Tschope C, de Boer RA et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J 2019;40:3297-3317.
51. Cheng RK, Cox M, Neely ML et al. Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicare population. Am Heart J 2014;168:721-30.
52. Fonarow GC, Stough WG, Abraham WT et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50:768-77.
53. Dhingra A, Garg A, Kaur S et al. Epidemiology of heart failure with preserved ejection fraction. Curr Heart Fail Rep 2014;11:354-65.
54. Benjamin EJ, Blaha MJ, Chiuve SE et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 2017;135:e146-e603.
55. Bhatt DL, Szarek M, Steg PG et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med 2021;384:117-128.
56. Nassif ME, Windsor SL, Borlaug BA et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med 2021;27:1954-1960.
57. Solomon SD, de Boer RA, DeMets D et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail 2021;23:1217-1225.
58. Komajda M, Cowie MR, Tavazzi L et al. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. Eur J Heart Fail 2017;19:1414-1423.
59. Greene SJ, Butler J, Albert NM et al. Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. J Am Coll Cardiol 2018;72:351-366.
60. Greene SJ, Fonarow GC, DeVore AD et al. Titration of Medical Therapy for Heart Failure With Reduced Ejection Fraction. J Am Coll Cardiol 2019;73:2365-2383.
61. Maggioni AP, Anker SD, Dahlstrom U et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2013;15:1173-84.
62. D'Amario D, Rodolico D, Rosano GMC et al. Association between dosing and combination use of medications and outcomes in heart failure with reduced ejection fraction: data from the Swedish Heart Failure Registry. Eur J Heart Fail 2022.
63. Thorvaldsen T, Benson L, Dahlstrom U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003-2012. Eur J Heart Fail 2016;18:503-11.
64. Seferovic PM, Polovina M, Adlbrecht C et al. Navigating between Scylla and Charybdis: challenges and strategies for implementing guideline-directed medical therapy in heart failure with reduced ejection fraction. Eur J Heart Fail 2021;23:1999-2007.
65. Schrage B, Uijl A, Benson L et al. Association Between Use of Primary-Prevention Implantable Cardioverter-Defibrillators and Mortality in Patients With Heart Failure: A

Prospective Propensity Score-Matched Analysis From the Swedish Heart Failure Registry. Circulation 2019;140:1530-1539.

66. Lund LH, Svennblad B, Dahlstrom U, Stahlberg M. Effect of expanding evidence and evolving clinical guidelines on the prevalence of indication for cardiac resynchronization therapy in patients with heart failure. Eur J Heart Fail 2018;20:769-777.
67. Lam CSP, Arnott C, Beale AL et al. Sex differences in heart failure. Eur Heart J 2019;40:3859-3868c.
68. Akwo EA, Kabagambe EK, Wang TJ et al. Heart Failure Incidence and Mortality in the Southern Community Cohort Study. Circ Heart Fail 2017;10.
69. Gerber Y, Weston SA, Enriquez-Sarano M et al. Mortality Associated With Heart Failure After Myocardial Infarction: A Contemporary Community Perspective. Circ Heart Fail 2016;9:e002460.
70. Pina IL, Kokkinos P, Kao A et al. Baseline differences in the HF-ACTION trial by sex. Am Heart J 2009;158:S16-23.
71. Santema BT, Ouwerkerk W, Tromp J et al. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. Lancet 2019;394:1254-1263.
72. Zusterzeel R, Selzman KA, Sanders WE et al. Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. JAMA Intern Med 2014;174:1340-8.
73. Zusterzeel R, Spatz ES, Curtis JP et al. Cardiac resynchronization therapy in women versus men: observational comparative effectiveness study from the National Cardiovascular Data Registry. Circ Cardiovasc Qual Outcomes 2015;8:S4-11.
74. Lazzarini V, Mentz RJ, Fiuzat M, Metra M, O'Connor CM. Heart failure in elderly patients: distinctive features and unresolved issues. Eur J Heart Fail 2013;15:717-23.
75. Maggioni AP, Orso F, Calabria S et al. The real-world evidence of heart failure: findings from 41 413 patients of the ARNO database. Eur J Heart Fail 2016;18:402-10.
76. Levy D, Kenchaiah S, Larson MG et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347:1397-402.
77. van Deursen VM, Urso R, Laroche C et al. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail 2014;16:103-11.
78. Cohn JN, Tognoni G, Valsartan Heart Failure Trial I. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667-75.
79. Kotecha D, Manzano L, Krum H et al. Effect of age and sex on efficacy and tolerability of beta blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis. BMJ 2016;353:i1855.
80. Young JB, Dunlap ME, Pfeffer MA et al. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation 2004;110:2618-26.
81. Martinez FA, Serenelli M, Nicolau JC et al. Efficacy and Safety of Dapagliflozin in Heart Failure With Reduced Ejection Fraction According to Age: Insights From DAPA-HF. Circulation 2020;141:100-111.

82. Jhund PS, Fu M, Bayram E et al. Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF. Eur Heart J 2015;36:2576-84.

83. Flather MD, Shibata MC, Coats AJ et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215-25.

84. Konstam MA, Neaton JD, Dickstein K et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet 2009;374:1840-8.

85. Packer M, Poole-Wilson PA, Armstrong PW et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation 1999;100:2312-8.

86. Flather MD, Yusuf S, Kober L et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000;355:1575-81.

87. Cohen-Solal A, McMurray JJ, Swedberg K et al. Benefits and safety of candesartan treatment in heart failure are independent of age: insights from the Candesartan in Heart failure--Assessment of Reduction in Mortality and morbidity programme. Eur Heart J 2008;29:3022-8.

88. Dulin BR, Haas SJ, Abraham WT, Krum H. Do elderly systolic heart failure patients benefit from beta blockers to the same extent as the non-elderly? Meta-analysis of >12,000 patients in large-scale clinical trials. Am J Cardiol 2005;95:896-8.

89. Savarese G, Orsini N, Hage C et al. Associations With and Prognostic and Discriminatory Role of N-Terminal Pro-B-Type Natriuretic Peptide in Heart Failure With Preserved Versus Mid-range Versus Reduced Ejection Fraction. J Card Fail 2018;24:365-374.

90. Conrad N, Judge A, Tran J et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet 2018;391:572-580.

91. Pandey A, Vaduganathan M, Arora S et al. Temporal Trends in Prevalence and Prognostic Implications of Comorbidities Among Patients With Acute Decompensated Heart Failure: The ARIC Study Community Surveillance. Circulation 2020;142:230-243.

92. Mountantonakis SE, Grau-Sepulveda MV, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure: an analysis of get with the guidelines-heart failure. Circ Heart Fail 2012;5:191-201.

93. Sharma A, Zhao X, Hammill BG et al. Trends in Noncardiovascular Comorbidities Among Patients Hospitalized for Heart Failure: Insights From the Get With The Guidelines-Heart Failure Registry. Circ Heart Fail 2018;11:e004646.

94. Komajda M, Schope J, Wagenpfeil S et al. Physicians' guideline adherence is associated with long-term heart failure mortality in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. Eur J Heart Fail 2019;21:921-929.

95. Savarese G, Stolfo D, Sinagra G, Lund LH. Heart failure with mid-range or mildly reduced ejection fraction. Nat Rev Cardiol 2021.

96. Savarese G, Vasko P, Jonsson A, Edner M, Dahlstrom U, Lund LH. The Swedish Heart Failure Registry: a living, ongoing quality assurance and research in heart failure. Ups J Med Sci 2019;124:65-69.

97. Taylor CJ, Ordonez-Mena JM, Roalfe AK et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. BMJ 2019;364:l223.

98. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail 2016;18:242-52.

99. Dewan P, Rorth R, Jhund PS et al. Differential Impact of Heart Failure With Reduced Ejection Fraction on Men and Women. J Am Coll Cardiol 2019;73:29-40.

100. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). Circulation 2001;103:375-80.

101. Martinez-Selles M, Doughty RN, Poppe K et al. Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. Eur J Heart Fail 2012;14:473-9.

102. O'Meara E, Clayton T, McEntegart MB et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation 2007;115:3111-20.

103. Chatterjee NA, Borgquist R, Chang Y et al. Increasing sex differences in the use of cardiac resynchronization therapy with or without implantable cardioverter-defibrillator. Eur Heart J 2017;38:1485-1494.

104. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med 2002;347:1403-11.

105. Brunner-La Rocca HP, Linssen GC, Smeele FJ et al. Contemporary Drug Treatment of Chronic Heart Failure With Reduced Ejection Fraction: The CHECK-HF Registry. JACC Heart Fail 2019;7:13-21.

106. Mordi IR, Ouwerkerk W, Anker SD et al. Heart failure treatment up-titration and outcome and age: an analysis of BIOSTAT-CHF. Eur J Heart Fail 2021;23:436-444.

107. Oh GC, Cho HJ, Lee SE et al. Management and Prognosis of Heart Failure in Octogenarians: Final Report from the KorAHF Registry. J Clin Med 2020;9.

108. Komajda M, Hanon O, Hochadel M et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. Eur Heart J 2009;30:478-86.

109. Forman DE, Cannon CP, Hernandez AF et al. Influence of age on the management of heart failure: findings from Get With the Guidelines-Heart Failure (GWTG-HF). Am Heart J 2009;157:1010-7.

110. Savarese G, Dahlstrom U, Vasko P, Pitt B, Lund LH. Association between renin-angiotensin system inhibitor use and mortality/morbidity in elderly patients with heart failure with reduced ejection fraction: a prospective propensity score-matched cohort study. Eur Heart J 2018;39:4257-4265.

111. Mata-Cases M, Casajuana M, Franch-Nadal J et al. Direct medical costs attributable to type 2 diabetes mellitus: a population-based study in Catalonia, Spain. Eur J Health Econ 2016;17:1001-1010.

112. Wang V, Vilme H, Maciejewski ML, Boulware LE. The Economic Burden of Chronic Kidney Disease and End-Stage Renal Disease. Semin Nephrol 2016;36:319-30.
113. Farre N, Vela E, Cleries M et al. Medical resource use and expenditure in patients with chronic heart failure: a population-based analysis of 88 195 patients. Eur J Heart Fail 2016;18:1132-40.
114. Lam CSP, Wood R, Vaduganathan M et al. Contemporary economic burden in a real-world heart failure population with Commercial and Medicare supplemental plans. Clin Cardiol 2021;44:646-655.
115. Malek M. Health economics of heart failure. Heart 1999;82 Suppl 4:IV11-3.
116. Boman K, Lindmark K, Stalhammar J et al. Healthcare resource utilisation and costs associated with a heart failure diagnosis: a retrospective, population-based cohort study in Sweden. BMJ Open 2021;11:e053806.
117. Stalhammar J, Stern L, Linder R et al. The burden of preserved ejection fraction heart failure in a real-world Swedish patient population. J Med Econ 2014;17:43-51.
118. Murphy TM, Waterhouse DF, James S et al. A comparison of HFrEF vs HFpEF's clinical workload and cost in the first year following hospitalization and enrollment in a disease management program. Int J Cardiol 2017;232:330-335.
119. McEwan P, Darlington O, McMurray JJV et al. Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. Eur J Heart Fail 2020;22:2147-2156.
120. King JB, Shah RU, Bress AP, Nelson RE, Bellows BK. Cost-Effectiveness of Sacubitril-Valsartan Combination Therapy Compared With Enalapril for the Treatment of Heart Failure With Reduced Ejection Fraction. JACC Heart Fail 2016;4:392-402.