

**The Efficacy of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor
Blockers in Men and Women with Heart Failure with Reduced Ejection Fraction**

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Abstract

Background. Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are essential to the treatment of heart failure with reduced ejection fraction (HFrEF). However, little data are available to determine whether their efficacy in reducing hospitalizations and mortality may differ between men and women with HFrEF.

Purpose. To explore whether differences exist in the efficacy of ACEi/ARBs in HFrEF by sex.

Methods. We conducted a pooled analysis of individual data from 4 randomized clinical trials: The Study of Left Ventricular Dysfunction (SOLVD) Treatment, SOLVD Prevention, Candesartan in Heart Failure: Assessment of Morbidity and Mortality (CHARM) Alternative and Added trials. The primary outcome was a composite of death or hospitalization for heart failure. Multivariable analyses were conducted using Cox proportional hazards models, adjusting for confounders, to obtain sex specific hazard ratios (HRs) and the interaction was tested by a sex-by-randomized treatment term.

Results. Among the 11,373 participants (19% women; mean age 61.5), women were older, with a higher prevalence of type 2 diabetes and hypertension, and a lower prevalence of ischemic heart disease than men regardless of treatment group. The ACEi/ARBs group had a lower incidence of the primary outcome compared to placebo [13.3 vs 16.6 per 100 person-year], with a similar efficacy in both men and women [adjusted-HR men 0.76 vs women 0.88, $p_{\text{sex-by-drug interaction}}=0.12$]. However, women were more likely than men to be hospitalized for HF despite treatment [adjusted-HR men 0.65 95%CI 0.54-0.79 vs women 0.82 95%CI 0.74-0.90, $p_{\text{sex-by-drug interaction}}=0.09$].

Conclusions. The association between ACEi/ARB and the primary outcome of death or HF hospitalization did not differ between men and women. However, women were more likely than men to have HF hospitalizations despite ACEi/ARB treatment. Future trials should include a larger enough sample size of women and men to enable sex-specific recommendations about HF drug efficacy.

Résumé

Contexte. Les inhibiteurs de l'enzyme de conversion de l'angiotensine (ACEi) et les inhibiteurs des récepteurs de l'angiotensine (ARB) sont essentiels au traitement de l'insuffisance cardiaque avec fraction d'éjection réduite (HFrEF). Cependant, peu de données sont disponibles pour déterminer si leur efficacité peut différer entre les hommes et les femmes atteints de HFrEF.

Objectif. Explorer s'il existe des différences dans l'efficacité des ACEi / ARB dans le HFrEF selon le sexe.

Méthodes. Nous avons effectué une analyse groupée des données individuelles de 4 essais cliniques randomisés: The Study of Left Ventricular Dysfunction (SOLVD) Treatment, SOLVD Prevention, Candesartan in Heart Failure: Assessment of Morbidity and Mortality (CHARM) Alternative and Added. Le critère de jugement principal était un composite de décès et d'hospitalisation pour insuffisance cardiaque. Des analyses multivariées ont été menées à l'aide des modèles de risques proportionnels de Cox, ajustés pour tenir compte des facteurs confondants, pour obtenir des rapports de risque (HR) spécifiques au sexe et l'interaction a été testée par un terme du traitement randomisé et du sexe.

Résultats. Parmi les 11373 participants (19% de femmes; âge moyen de 61,5 ans), les femmes étaient plus âgées, avec une prévalence plus élevée de diabète de type 2 et d'hypertension, et une prévalence plus faible de cardiopathie ischémique que les hommes, quel que soit le groupe de traitement. Le groupe ACEi / ARB avait une incidence plus faible du critère de jugement principal par rapport au placebo [13,3 vs 16,6 pour 100 personnes-an], avec une efficacité similaire chez les hommes et les femmes [HR ajusté hommes 0,76 vs femmes 0,88, $p^{\text{sexe}} = 0,12$]. Cependant, les femmes étaient plus susceptibles que les

hommes d'être hospitalisées pour IC malgré le traitement [HR ajusté pour hommes 0,65 IC à 95% 0,54-0,79 vs femmes 0,82 IC à 95% 0,74-0,90, interaction p sexe par médicament = 0,09] .

Conclusions. L'association ACEi / ARB et le critère principal de décès ou d'hospitalisation pour l'insuffisance cardiaque ne différait pas entre les hommes et les femmes. Cependant, les femmes étaient plus susceptibles que les hommes d'avoir des hospitalisations pour l'insuffisance cardiaque malgré le traitement. Les essais futurs devraient inclure un échantillon suffisamment plus grand de femmes et d'hommes pour permettre des recommandations spécifiques sur l'efficacité des médicaments contre HFrEF selon le sexe.

Preface

This manuscript-based thesis incorporates one manuscript:

Manuscript #1 “Efficacy of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Men and Women with Heart Failure with Reduced Ejection Fraction”

The thesis conforms to the requirements of McGill University for manuscript-based theses. The manuscript was integrated with the mandatory thesis components, and connecting texts were included to provide a logical progression. Since manuscripts are concisely written research reports intended for scientific journals, additional sections were also incorporated to provide a more detailed description of some aspects of the manuscripts. Some redundancy is inevitable in a manuscript-based thesis, regarding the general introduction and discussion of the thesis and those of the individual manuscripts, but all effort was made to present a coherent scholarly work.

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Contribution of Authors

As the first author of the manuscript, I was involved in the study conception and design, the planning of the statistical analysis, interpretation of the results and the manuscript writing and revision.

Dr Pilote, as thesis supervisor and one of the senior authors supervised all aspects of the work executed. Dr Raparelli was closely involved in advising and reviewing all parts of the work as well. Dr Jhund was instrumental in providing access to the dataset and running the statistical analyses that I designed. Drs Giannetti and McMurray, as well as the previous authors, contributed to the review of the paper.

Literature Review

1. Epidemiology of Heart Failure

Heart failure is a disease with a rapidly growing prevalence. Data from the United States show that 6.5 million people were affected in 2014, up from 5.7 million in 2012. This increase is mirrored globally¹. Despite advances in treatment, the mortality rate of heart failure remains high- 1 in 5 people with heart failure die within 1 year of diagnosis². Heart failure is also a disease with great morbidity, leading to frequent hospitalizations, which aside from the human cost, leads to a significant economic cost, estimated at 30 billion dollars annually in the US³. Heart failure is therefore a large public health concern.

Heart failure is a complex clinical syndrome that lies at the endpoint of many conditions, such as obesity, diabetes, hypertension, coronary artery disease. The prevalence of heart failure is therefore intimately linked to the prevalence of these underlying conditions and risk factors. For example, the number of people living with diabetes is projected to increase by 25% over the next decade⁴, which will have a direct impact on the prevalence of heart disease and heart failure.

There are 2 major types of heart failure, determined by ejection fraction (EF)- the percentage of blood pumped out of the heart ventricle. The types are heart failure with reduced ejection fraction (HFrEF), usually defined by an $EF \leq 40\%$ and heart failure with preserved ejection fraction (HFpEF), defined by an $EF \geq 50\%$ ⁵. Heart failure with mid-range ejection fraction (HFmEF) is a new and relatively less well understood entity, defined by an EF of 41%-49%⁵. HFpEF patients make up half of the population

of patients with HF and is the more prevalent type of HF in women⁶. Despite this, HFpEF remains a poorly understood entity, with few treatment options⁷. Our study will focus primarily on HFrEF, as this was the subtype that was first recognized and in which there is a large body of evidence regarding effective therapy⁵.

2. Sex differences in Heart Failure

There is wide ranging evidence for sex differences in heart failure. Firstly, the epidemiology of heart failure, its incidence and prevalence, as well as the epidemiology of related diseases has been found to vary by sex⁸. Secondly, there are numerous intrinsic, biological differences between men and women, including in their cardiovascular anatomy and physiology⁹. Gender and psychosocial factors may also play also affect the development of heart failure¹⁰. All of these factors ultimately may lead to differences in outcomes such as quality of life and mortality¹¹.

a. Epidemiology

The epidemiology of sex differences in heart failure is reviewed by Lam et al⁸, using data from multiple large, longitudinal studies such as the Framingham Heart Study and the Rotterdam study . Half of all patients with heart failure are women, but differences become apparent when looking at the type of heart failure. Women are more likely to develop HFpEF than men by a factor of 2:1⁶, while they make up only 25-30% of the HFrEF population. Heart failure secondary to valvular disease is also more common in women. Finally, women also tend to develop heart failure later in life. From ages 40-80 years, the prevalence of heart failure is higher in men but in the 80+ age group, the prevalence in women is greater. Women with heart failure tend to live longer than men, leading to their over representation in the older age group¹². There is

evidence therefore that heart failure is distributed differently across the sexes, with women comprising a smaller proportion of patients with HFrEF.

There are also sex differences in the epidemiology of the multiple risk factors that predispose to heart failure and the degree to which they contribute to heart failure - the population attributable risk (PAR)¹². Hypertension is the most important risk factor in women (PAR of 59% in women vs 39% in men), whereas ischemic heart disease is more important in men (PAR of 34% in men vs 13% in women). The management of hypertension has improved to a greater degree than that of ischemic heart disease, which has also affected the incidence of heart failure by sex¹³. Diabetes also acts differentially by sex- it increases the risk of heart failure in men two fold, while increasing the risk in women five fold⁸. Obesity is more prevalent amongst women and increases the risk of developing heart failure, though of HFpEF more than HFrEF. Women are also more likely to suffer from iron deficiency and depression, both of which are associated with worse outcomes in heart failure¹⁴.

b. Biological Factors

There are varied biological systems that are different between men and women many of which impact the heart. These changes, reviewed in an article from Beale et al⁶, arise from differences in genetics and hormones -namely estrogen- and are mediated through differences in cardiac function, vascular function, metabolism and inflammation.

Men and women differ in their normal cardiac anatomy and physiology, which contributes to the differences they exhibit in heart failure. Women have smaller ventricular chambers and stroke volumes, even when accounting for body size.

Therefore, to maintain cardiac output they must rely on an increased heart rate at baseline. In addition to being smaller, women's ventricles are also stiffer. Women's ventricles also tend to be stiffer in both contraction and relaxation of the heart muscle. This hinders their ability to adapt to higher blood pressures and increasing arterial stiffness with age. The process of cardiac aging is also altered in response to this strain, with attenuated death of cardiac myocytes and altered remodeling of the heart muscle¹⁵.

Vascular function is also markedly different in women. They have increased vascular stiffening with age, accentuated by menopause. This leads to an increased incidence of hypertension and pressure overload or increased strain on the heart⁹. They also have increased microvascular dysfunction rather than obvious vascular obstruction which is more common in men. This phenomenon is poorly understood but can impair blood supply to the heart muscle. Microvascular and endothelial dysfunction is also one of the proposed mechanisms by which pre-eclampsia, a disease of pregnancy which exclusively affects women, leads to heart failure⁶.

Physiological systems outside the cardiovascular system also contribute to sex differences. The immune system and inflammation is now being implicated in the pathogenesis of heart failure. Women are known to have stronger immune responses, which has certain survival advantages but also predisposes them to auto-immune diseases and overall increased systemic inflammation¹⁵. Women also have altered metabolics compared to men, with increased dependence on lipid metabolism and altered oxygen consumption. This in turn is related to the altered cardiac modeling, as

myocytes are less likely to die through apoptosis and instead become inefficient and hypertrophied⁶.

c. Other Factors

Psychosocial Factors

Apart from the purely biological factors, psychological and social factors can play a large role in the care and in outcomes of heart failure, such as readmissions or hospitalizations for heart failure. Heart failure is a chronic condition that requires management of medications, diet, exercise and a host of other factors, meaning patients need to be proficient in self care¹⁶. Studies investigating the self care of heart failure patients have shown that women are less confident about being able to manage this complex chronic condition and this has a distinct negative impact on their quality of life^{10,17}. The presence of social supports or a caregiver is also an important determinant of heart failure outcomes and women are less likely than men to have these kinds of social supports- they tend to be caregivers rather than be given care¹⁸.

Women are also more likely to suffer from depression, more frequently experiencing negative emotions and a lack of hope in the face of heart failure. As the fatigue and decreased energy of depression mimics that of heart failure, this depression may be underdiagnosed¹⁴. Overall, this points to women being a vulnerable population, prone to frequent hospitalizations and often lacking appropriate psychological and social support.

Gaps in Care

Some of the sex differences seem to arise from differences in management of the comorbidities. Diabetes and obesity are two risk factors that increase the risk for HFrEF more in women than men. Mortality due to these factors has decreased overall, but that decrease has been less steep in women¹⁹. Furthermore, they are less likely to be prescribed preventative medications such as aspirin. Women are also less likely to receive ICD or CRT therapy, despite the fact that it is often medically indicated and shown to have concrete benefits¹⁹.

There was an accumulation of evidence that showed women were less likely to receive ACE inhibitors- evidence based and life prolonging treatment in heart failure. More recent studies have revisited the issue and found conflicting results, with some finding similar prescription rates for men and women, and others finding less prescription to women. Overall it seems that receiving appropriate treatment is dependent on the provider, where specialized heart failure centers provide equal care, while some less experienced providers may undertreat women^{11,20}.

d. Differences in outcomes

Overall, women have a worse quality of life with heart failure, suffering from more dyspnea, bronchitis and edema, but with improved mortality¹¹. Despite living longer with heart failure, they have seen less of an improvement than men- analyses of the data from the Framingham study that advances of care have led to greater improvements in mortality in men than in women¹⁹.

This discrepancy persists in both trial data and in registries. An analysis of the CHARM data found that women had better survival that was not explained by higher EF or by etiology of the HF, both of which are usually different between men and women²¹. A study of patients from the OPTIMIZE-HF registry found that they had similar outcomes. Furthermore, there seemed to be a greater survival benefit in non-ischemic heart failure¹¹. Overall, women are affected differently by heart failure and it remains unclear why.

3. Pathophysiology of Heart Failure

The role of the heart is to pump blood to the rest of the body, with the amount of blood pumped out referred per minute referred to as cardiac output. The cardiac output depends on the heart rate, the contractility of the heart, the preload and the afterload. The contractility refers to the strength of the contraction of the heart muscle. The preload refers to the ventricular filling of the heart with blood or fluid with the subsequent stretching of the muscle priming it for contraction. The afterload refers to the force against which the heart must contract and is largely dependent on the body's vascular tone. Understanding of these factors and the physiology of cardiac output allows us to better understand the pathophysiology and subsequent treatment of heart failure²².

HFrEF is a reduction in the cardiac output of the heart, or an inability to maintain that cardiac output under normal conditions. The injury or damage can be due to cardiovascular disease, such as coronary artery disease, or due to causes such as chemotherapy, infection or autoimmune disease. However, coronary artery disease is the major contributor and HFrEF is often diagnosed after a recent myocardial infarction

leading to impaired ventricular contraction¹. The impaired function then leads to the activation of compensatory mechanisms such as the sympathetic nervous system (SNS) and the renin angiotensin aldosterone system (RAS) which, in the short-term lead to an increased heart rate and increased fluid retention or preload, maintaining cardiac output. However, in the long term these changes are maladaptive, leading to increased systemic vascular resistance or afterload and increased strain on the heart. Ultimately, this chronic injury and stress leads to the development of HFrEF.

At the cellular and molecular level, there are many changes to the cardiac tissue. The cytoskeletal proteins that make up the contractile elements of heart muscle, the sarcomeres, are altered leading to impaired contractility. Calcium signaling, which regulates the contraction and relaxation of the cardiac muscle, is also impaired. Changes to the cell membrane and the functioning of the ion channels predisposes the tissue to aberrant electrical activity and arrhythmias. Myocardial cells begin to die under the strain, through apoptosis and autophagy²³.

To compensate for the decreased cardiac output that these changes cause, there is an activation of the SNS. This activation increases the heart rate as well as myocardial contractility to maintain the cardiac output in the short run. However, in the long run, this leads to increased strain on the heart and left ventricular remodeling which result in decreased efficiency and increased energy demand²³.

The decreased cardiac output leads to decreased renal perfusion, which in turn leads to activation of the RAS. This system will be discussed in greater depth later, but its activation results in fluid retention and maintains organ perfusion. Once again, the increased preload, though initially beneficial leads to further cardiac strain and

remodeling. RAS activation, through the hormone aldosterone, has also been found to promote cardiac interstitial fibrosis and myocyte hypertrophy which further reduces contractility and worsens heart failure¹.

4. Overview of Heart Failure Treatment

The understanding of heart failure therapy has evolved significantly over the past few decades. It was initially thought to be a disease primarily of contractility to be treated with inotropes- medications that increase contractility. Studies of digoxin, derived from foxglove, and other inotropes found that they did not improve mortality and were possibly causing harm²⁴. Therapy then went to focus on vasodilators that would decrease preload and afterload and improve the heart's hemodynamic function. The Vasodilator- Heart Failure Trial (V-Heft I) did improve cardiac function in the short term but showed no improvement in long term mortality. It was the understanding of heart failure as a neuroendocrine disease that changed the paradigm of heart failure and led to significant improvements in mortality²⁴.

The backbone of chronic HF treatment involves targeting of the neurohormonal pathways involved, including the RAS and the SNS⁵, which, as previously discussed, worsen heart failure in the long run by increasing preload and afterload. Guideline directed medical therapy (GDMT) recommends triple therapy for patients with heart failure, including an angiotensin converting enzyme inhibitor (ACEi), a beta blocker and a mineralocorticoid antagonist (MRA). For patients that are intolerant to ACEi, such as those who develop a dry cough, hyperkalemia or hypotension, an angiotensin receptor blocker (ARB) is a suitable replacement.

There are adjuncts to basic triple therapy. Ivabradine is an inhibitor of the pacemaker current in the sinus node of the heart with heart rate lowering effects and has been shown to decrease heart failure hospitalizations even in patients already on a beta blocker. Hydralazine and isosorbide dinitrate (H-ISDN) are vasodilators that are an alternative means of decreasing afterload or preload. They are used for black patients as they have a “less active” RAS, or as additional therapy in patients whose symptoms are not controlled by triple therapy⁵.

Recent clinical trials have provided novel pharmacological therapy for heart failure, namely angiotensin receptor and neprilysin inhibitors (ARNIs) and sodium-glucose transfer protein 2 inhibitors (SGLT2i). ARNIs work by enhancing the effect of the vasodilatory and natriuretic peptides and have been found to have a mortality benefit compared to ACEi²⁵, leading to their incorporation into international guidelines^{5,26}. SGLT2is were initially developed for the treatment of diabetes but have recently been found to be an effective treatment for heart failure²⁷, though the mechanism remains unclear. Further clinical trials are ongoing.

Device therapy, in addition to pharmacotherapy, may also be of benefit. Implantable Cardiac Defibrillators (ICDs) improve outcomes in patients with a history of ventricular arrhythmias and other selected patients. Cardiac Resynchronization Therapy (CRT) devices improve cardiac function and symptoms in patients who have abnormal rhythms (widened QRS) leading to uncoordinated and inefficient ventricular contractions.

Other therapeutic considerations include diet and exercise. Moderate intensity exercise has been shown to improve mortality and decrease hospital admissions. Salt

and fluid intake should also be monitored, although there is little evidence to support the traditional view of salt and water restriction.

Patients with HF often suffer from acute decompensation, leading to fluid overload, pulmonary edema and hospital admissions. These are generally managed with diuretics and supportive therapy. Management of acute decompensation is outside the scope of this thesis⁵.

5. RAS Blockers

a. Overview of RAS and relationship with Heart Failure

The RAS is the hormonal system in the body that is activated in response to decreased blood flow or perfusion to the kidneys (Figure 1). It plays an important role in systemic vasoconstriction, which led to investigation of the RAS as a target for the treatment of heart failure. Decreased perfusion to the kidneys is sensed by cells in the juxtaglomerular apparatus, leading to secretion of renin. This enzyme clips 10 amino acids off the inactive angiotensinogen peptide, converting it to the angiotensin 1 (AT I). Angiotensin converting enzyme (ACE) further cleaves AT1 into Angiotensin II (AT II)²⁸.

AT II acts primarily through the AT₁ receptor and has multiple effects. Systemically, it causes vasoconstriction. At the level of the kidneys, it causes renal arteriolar vasoconstriction to maintain perfusion, increases reabsorption in the renal tubules and stimulates secretion of aldosterone from the adrenal glands. Aldosterone acts on the renal collecting ducts to cause further reabsorption of sodium and water and secretion of potassium. The immediate effect of AT II is to maintain blood pressure through vasoconstriction, followed by an increase in the body's extra cellular volume²⁸.

In the setting of heart failure, there is decreased perfusion to the kidneys and activation of the RAS functions to maintain cardiac output, blood pressure and organ perfusion in the short term. However, chronic activation of the RAS negatively impacts the cardiovascular system. Aldosterone and AT II cause endothelial damage, sympathetic activation and decreased nitric oxide production²⁸. Chronic vasoconstriction increases the afterload that the heart must pump against. This strain leads to increased energy demand and hypertrophy of cardiac muscle.

AT II, through the AT₁ receptor on the cardiac myocyte, directly leads to myocyte hypertrophy. Furthermore, it activates fibroblasts in the heart, leading to increased production of collagen and cardiac fibrosis. Aldosterone may have similar effects in cardiac tissue. The ventricular remodeling that occurs as a result also leads to worsening of heart failure²⁸.

There are also novel elements of the RAS that have been found to have clinical implications. For example, ACE2 is an enzyme that breaks down AT II into ACE (1-7), which is a peptide with vasodilatory rather than vasoconstrictive properties. ACE2 is currently under investigation for its potential therapeutic value in hypertension and cardiovascular disease²⁹. Of note, it is expressed at differing levels in men and in women³⁰.

b. ACEi/ARB

Mechanism of Action

ACE inhibitors bind to the ACE enzyme, preventing production of AT II from AT I, affecting the all the subsequent effects of the RAS activation. There is less vasoconstriction, leading to afterload reduction and subsequently improved hemodynamics. The effect on the kidneys can also lead to decreased fluid reabsorption and decreased preload, also decreasing strain on the heart. Finally, and perhaps more importantly, it prevents cardiac myocyte hypertrophy and fibrosis, slowing adverse cardiac remodeling and improving mortality.

ACE is also responsible for the regulation of the vasodilatory molecule bradykinin, which it cleaves and inactivates. Increased bradykinin levels in the lungs are thought to be responsible for the dry cough that is a common side effect of ACEi³¹. Bradykinin is also partially responsible for the most serious side effect of ACEi: angioedema. It is a potentially life threatening “hypersensitivity reaction” that causes swelling, primarily of the face, and can lead to blockage of the airway. The other side effects of ACEi are the expected consequences of blocking the RAS, namely, hypotension, hyperkalemia and decreased perfusion to the kidneys causing acute kidney injury (AKI). Any of these side effects may lead to discontinuation of the drug³¹. Of note, women are more likely to suffer these side effects, most commonly the dry cough, than men³².

Further research found that despite inhibition of ACE, circulating levels of AT II often remained high, implying there were non-ACE dependent pathways by which AT II was formed. Angiotensin Receptor (AT₁) Blockers (ARBs) were therefore

developed to prevent the action of ATII, regardless of how it was formed. This also had the benefit of allowing continued stimulation of the AT₂ receptors, which are thought to have vasodilatory effects³³. Furthermore, since ARBs do not interfere with bradykinin regulation, they have fewer related side effects, such as the cough.

c. Sex differences in RAS and RAS blockers

Multiple differences have been found between the RAS in men and women, in the production, regulation and response to AT II. The genetic expression of the elements of the RAS vary between men and women³⁴. For example, polymorphisms in angiotensinogen, the AT₁ receptor and ACE are closely linked to cardiovascular disease in men while it is polymorphisms in ACE2, a recently discovered enzyme that breaks down AT II, that are more closely linked to disease in women³⁰. Women also have significantly higher levels of the AT₂ receptor, which is expressed on the X chromosome (Figure 2)³⁰. The impact of this receptor is not fully understood; most of the impact of the RAS seems to be mediated by the AT₁ receptor³⁵.

Sex hormones have also been found to modulate the response to AT II³⁶. Increased levels of estradiol lead to a decrease in production of AT II from AT I. There is also some evidence that sex hormones may affect the metabolism of AT II, as women seem to have, on average, greater circulating levels of AT II than men. Hormones may influence the expression and activity of regulatory enzymes such as ACE2³⁶.

Men and women also differ in their response to drugs, with respect to both pharmacodynamics, i.e. the effect of the medications, and pharmacokinetics, i.e. how the drug was metabolized and excreted by the body. For example, women have lower oral drug absorption and differing levels of CYP enzymes¹⁹. These may lead to

clinically relevant differences in the effect of drugs. Animal as well as human studies have found that the pharmacodynamics of ACEi's are different between men and women. A study of healthy men and women found that women had lower levels of ACE activity at all concentrations of the drug³⁷. The differential action of the drug by sex is reflected clearly in the side effect profile, where the odds of women developing side effects is up to 2.5 times higher than men³².

Evidence for ACEi/ARB in HFrEF

CONSENSUS was the first trial comparing an ACEi, enalapril, to placebo in late stage heart failure and was stopped early due to a significant mortality benefit (relative risk RR 0.73, p=0.003) found in the trial arm³⁸. The Study of Left Ventricular Dysfunction (SOLVD) was another landmark trial that studied enalapril in a broader range of HF patients (stages II to III) and found to have significant mortality benefit (RR 0.84, p=0.004) and a reduction in HF hospitalizations (RR 0.78, p<0.001)³⁹. Other trials such as SAVE⁴⁰ (RR 0.81, p=0.019), TRACE⁴¹ (hazard ratio HR 0.78, p=0.001) and AIRE⁴² (HR 0.73, p=0.002) provided further evidence of the benefit of ACEi's in cardiovascular disease (Table 1)²⁸.

The CHARM program was one of the largest studies of ARBs⁴³. It had three different components, namely Added, Alternative and Preserved. CHARM Added compared both medications to only an ACEi. CHARM Alternative enrolled patients intolerant to ACEi and compared them to placebo. Overall, it found that ARBs led to similar outcomes as ACEi, though the addition did not yield any clinical benefit in the Added trial. Other large trials included ELITE II and Val-HeFT (Table 2). Current

guidelines recommend ACEi as the first line therapy, as there is more robust evidence for their benefit, and ARBs in patients who are ACEi intolerant³³.

d. Sex differences in efficacy of RAS blockers in HFrEF

The sex differences in the RAS pathophysiology detailed above could lead to differences in the efficacy of the RAS blockers in patients with HFrEF. Trials of these medications primarily enroll men, with women comprising only approximately up to 20% of the study population, making it difficult to get a true assessment of the benefit these medications have in women. A meta-analysis of four large trials of ACEis found that though women appeared to benefit for the combined endpoint of death, myocardial infarction and heart failure, there appeared to be no survival benefit for women. Although there is less data available regarding ARBs, data from the CHARM trial indicated that the benefit of ARBS was similar in men and women¹¹.

In summary, there is a large body of evidence for sex differences in the epidemiology, pathophysiology and outcomes of heart failure. There are also established sex differences in RAS biology. Together, this evidence forms a biological rationale for sex differences in the efficacy of ACEi/ARBs. However, conclusive evidence for the latter is lacking, in large part due to the small number of women enrolled in clinical trials of these medications. Our study will aim to overcome this sample size limitation to better assess whether the efficacy of ACEi/ARBs varies between men and women.

Table 1: Large ACEi Trials in HFrEF, ACEi vs placebo

Study (year)	n	% women	Primary Outcome*	Overall (95% CI)	Women	Men
SAVE ⁴⁰	2231	18	All-cause mortality	19 (3-32) RRR	2 (-53-37)	22 (6-36)
AIRE ⁴²	1461	26	All-cause mortality	0.73 (0.60-0.89) HR	~0.70 (0.35-0.98)	~0.75 (0.56-0.98)
TRACE ⁴¹	1749	28	All-cause mortality	0.78 (0.63-0.89) HR	0.9 (0.69-1.18)	0.74 (0.62-0.89)
SOLVD ³⁹	2569	20	All-cause mortality	16 (5-26) RRR	n/a	n/a
Flather ⁴⁴ (meta analysis)	12763	18.8	All-cause mortality	0.73 (0.61-0.88) OR	0.85 (0.71-1.02)	0.79 (0.72-0.87)

*Sex stratified results were not available for other outcomes.

Abbreviations: RRR: relative risk reduction, HR: hazard ratio, OR: odds ratio.

Table 2: Large ARB Trials in HF

Study (year)	n	% women	Comparison	Outcome	Overall	Women	Men
CHARM-Overall ⁴⁵	7599	31.5	ARB vs placebo (Alt) ARB + ACEi vs ACEi (Added) ARB vs placebo in HFpEF	Death or HF Hospitalization	0.84 (0.77-0.91)	~0.83 (0.70-0.96)	~0.84 (0.76-0.92)
ELITE II ⁴⁶	3152	30.5	ARB vs ACEi	All-cause mortality	1.13 (0.95-1.35)	~1.10 (0.93-1.270)	~1.14 (0.83-1.45)

Figure 1: Renin Angiotensin System Activation

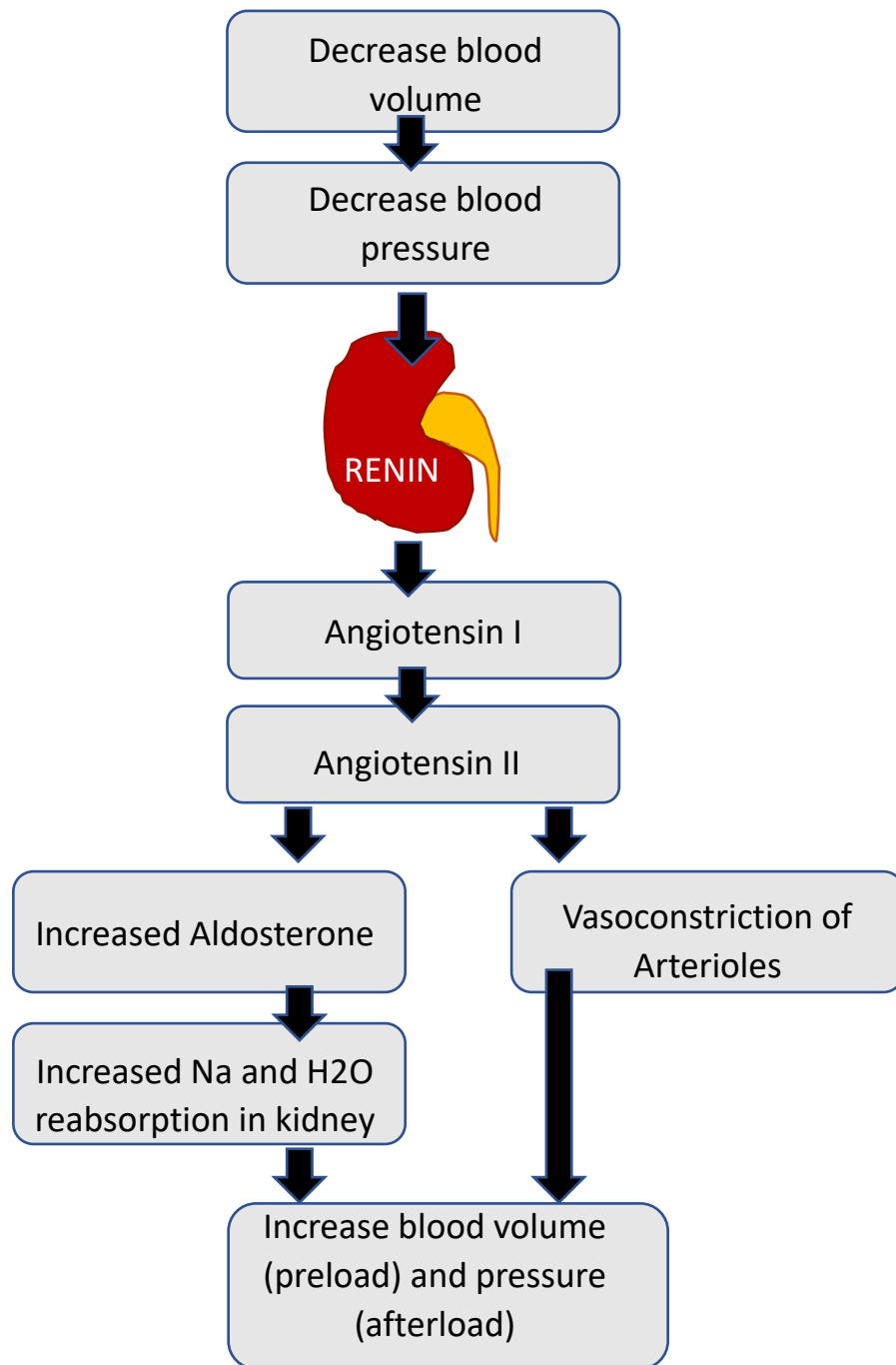
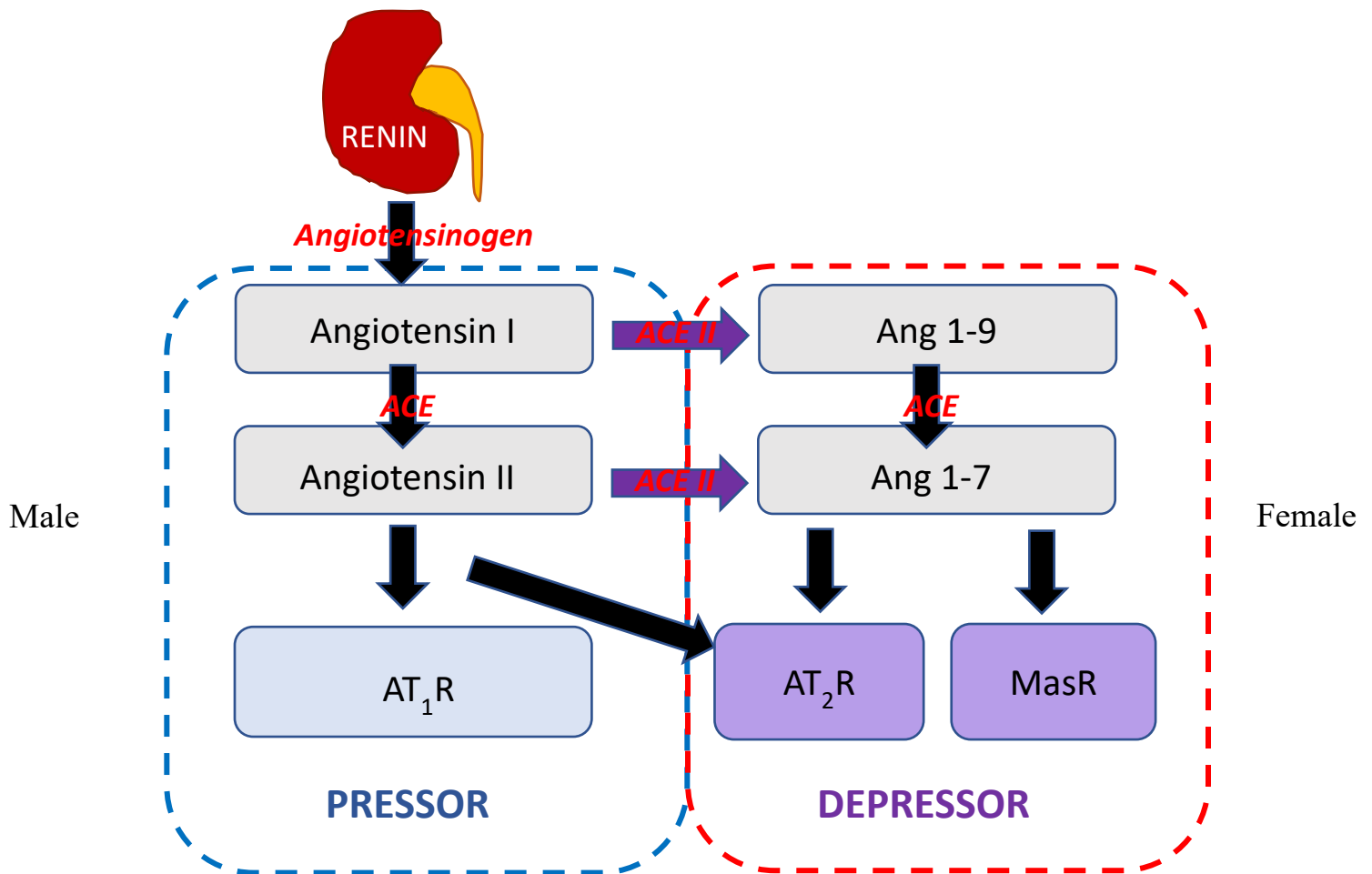


Figure 2: Sex Differences in RAS- ACE2 enzyme

Adapted from Collafella et al.³⁰



Manuscript

**The Efficacy of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor
Blockers in Men and Women with Heart Failure with Reduced Ejection Fraction**

Running Title: ACEi/ARBs Efficacy in Women

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Manuscript Word Count: 3455

Tables: 3

Figure: 2

Abstract

Background. Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are essential to the treatment of heart failure with reduced ejection fraction (HFrEF). However, little data are available to determine whether their efficacy may differ between men and women with HFrEF.

Purpose. To explore whether differences exist in the efficacy of ACEi/ARBs in HFrEF by sex.

Methods. We conducted a pooled analysis of individual data from 4 randomized clinical trials: The Study of Left Ventricular Dysfunction (SOLVD) Treatment, SOLVD Prevention, Candesartan in Heart Failure: Assessment of Morbidity and Mortality (CHARM) Alternative and Added trials. The primary outcome was a composite of death and hospitalization for heart failure. Multivariable analyses were conducted using Cox proportional hazards models, adjusting for confounders, to obtain sex specific hazard ratios (HRs) and the interaction was tested by a sex-by-randomized treatment term.

Results. Among the 11,373 participants (19% women; mean age 61.5), women were older, with a higher prevalence of type 2 diabetes and hypertension, and a lower prevalence of ischemic heart disease than men regardless of treatment group. The ACEi/ARBs group had a lower incidence of the primary outcome compared to placebo [13.3 vs 16.6 per 100 person-year], with a similar efficacy in both men and women [adjusted-HR men 0.76 vs women 0.88, $p_{\text{sex-by-drug interaction}}=0.12$]. However, women

were more likely than men to be hospitalized for HF despite treatment [adjusted-HR men 0.65 95%CI 0.54-0.79 vs women 0.82 95%CI 0.74-0.90, $p_{\text{sex-by-drug interaction}}=0.09$].

Conclusions.

The association between ACEi/ARB and the primary outcome of death or HF hospitalization did not differ between men and women. However, women were more likely than men to have HF hospitalizations despite ACEi/ARB treatment. Future trials should include a larger enough sample size of women and men to enable sex-specific recommendations about HF drug efficacy.

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Word Count: 293

Key Words: Heart Failure with Reduced Ejection Fraction, Sex, Renin Angiotensin System Blockers, Randomized Control Trials, Efficacy

Introduction

Heart failure with reduced ejection fraction (HFrEF) increases as the population ages¹, reaching epidemic proportions². Despite recent advances in treatment, the 5-year mortality remains high, ranging from 20% to 60%³. Sex differences in the epidemiology, clinical presentation and prognosis in HFrEF have been reported⁴, nevertheless limited sex-stratified data are available for the efficacy of drugs with the exception of subgroup analysis of randomized controlled trials (RCTs) that usually are underpowered for detecting sex differences due to the low participation of women⁵.

The angiotensin converting enzyme inhibitor (ACEi) and angiotensin receptor blocker (ARBs) are essential to the pharmacological management of HFrEF⁶. Current guidelines recommend the same approach in men and women.^{7,8} However, in RCTs testing the efficacy of these medications among individuals with HFrEF, women constitute on average only 20-30% of participants⁹. Though this is approximately representative of the percentage of the HFrEF epidemiology¹⁰, such sample sizes might be insufficient for reporting that these medications have an effect in women when they might not. In this light, two meta-analysis have shown consistent benefits of ACEi for men across multiple outcomes, but inconsistent benefits for women^{9,11}. Furthermore, pharmacological studies conducted in healthy subjects and hypertensive adults suggested that the response to the blockade of the renin angiotensin aldosterone system (RAS) differ in men and in women^{12,13}. Finally, studies using administrative databases have reported a sex-specific cardiovascular effectiveness of RAS blockers^{14,15}. Given this inconsistent data, the aim of this study was to determine whether the efficacy of

ACEi/ARBs in adults with HFrEF differs by sex, analyzing pooled individual-level data from previous RCTs thereby increasing the sample size for women.

Methods

Trials and Participants

This is a retrospective analysis of pooled, individual-level data from four large RCTs of ACEi/ARBs in HFrEF: the CHARM (Candesartan in Heart Failure: Reduction in Mortality and Morbidity)-Alternative, the CHARM-Added, the SOLVD (Study of Left Ventricular Dysfunction Treatment)-Treatment and the SOLVD-Prevention trials, investigating the efficacy of candesartan and enalapril respectively. Each trial was approved by the ethics committee at participating centers and all participants provided written informed consent.

The study design and the main results of these trials have been reported previously^{16–19}. In the CHARM-Alternative trial, 2028 (31.8% women) individuals with a history of HF, a left ventricular ejection fraction (LVEF) $\leq 40\%$ and a previously documented intolerance to ACEi, were randomized to candesartan or placebo. The trial found a significant reduction in the primary outcome of cardiovascular death or an unplanned hospitalization for HF with candesartan. In CHARM-Added, 2548 (21.3% women) individuals with HF and a LVEF $\leq 40\%$ who were being treated with ACE inhibitors were randomized to the addition of candesartan or placebo. The trial found a significant reduction in the same primary outcome. In SOLVD-Treatment, 2569 (19.6% women) individuals with a history of heart failure and a LVEF $\leq 35\%$ were randomized to enalapril or placebo. The trial found a significant relative risk (RR)

reduction in the composite outcome of death from any cause or hospitalization for HF. In SOLVD-Prevention, 4228 (12.4% women) individuals with asymptomatic left ventricular systolic dysfunction with a LVEF $\leq$ 35% were randomized to enalapril or placebo. The trial found a significant RR reduction in the same composite outcome of death from any cause or hospitalization for HF.

Outcomes

The primary outcome for the CHARM trials was the composite of first hospitalization for HF or cardiovascular death, while for SOLVD trials it was death from any cause. Therefore, in this study, we defined our primary outcome as a composite of death from any cause or hospitalization for HF. Our secondary outcomes included the individual components of our primary outcome and cardiovascular death. All deaths were considered cardiovascular unless there was an unequivocal non-cardiovascular cause. A hospitalization for HF was defined as an unexpected admission to the hospital primarily for the treatment of HF. The need for diuretics was not formally included in the event definition. In CHARM, an independent blinded committee adjudicated study outcomes. In SOLVD, outcomes were determined by a study physician with oversight from the site's principal investigator.

Statistical Analysis

We described the baseline characteristics of men and women randomized in the trials and by randomized treatment arm in each sex. Data are described using the mean and standard deviation for continuous variables and numbers and percentages for

categorical variables. For each group, we calculated incidence rates (IR) per 100 patient years, with 95% CI for the primary and secondary outcomes.

Unadjusted Kaplan-Meier curves, estimated separately for men and women, were plotted to compare the incidence between the treatment and placebo groups. Differences between groups were compared using the log-rank test.

For each outcome, Cox proportional hazards models were used to estimate the treatment effect of randomized therapy as hazard ratios (HRs) with 95% confidence intervals (CI). Univariable analyses were conducted and variables that were associated with the outcome ($p < 0.10$) and those that were considered clinically relevant were included in a multivariable model. These variables were age, LVEF, systolic blood pressure (SBP), heart rate, NYHA class, race, smoking status, history of myocardial infarction (MI), hypertension, type 2 diabetes mellitus (T2DM), atrial fibrillation (AF), and stroke. Additionally, we accounted for clustering within trials using robust standard errors across our analyses.

For each outcome, both unadjusted and adjusted regression models were calculated. These were calculated in the overall population and stratified by sex. The interaction between sex and randomized therapy was tested using a Wald test which was considered statistically significant at $p < 0.05$. The results of this model were used to determine the separate adjusted HRs for women and men²⁰.

We only included variables in our analysis that were common across the 4 RCTs (Table 1). A smaller subset of patients in the pooled dataset had some missing values such as history of AF (3%) and serum creatinine level (28%).

Sensitivity Analysis

We conducted multiple sensitivity analyses. An analysis was done using only CHARM-Alternative and SOLVD-Treatment. This was done to have a more homogenous population, excluding the patients from SOLVD-Prevention who were primarily asymptomatic, and to have a better comparison of ACEi/ARBs vs placebo, excluding CHARM-Added which compared dual inhibition with candesartan and enalapril to enalapril only. A separate analysis was done with SOLVD-Treatment and SOLVD-Prevention to assess sex differences in ACEi. Finally, competing risk regression was used to account for the risk of multiple potential competing events. Specifically, hospitalization for HF was tested for competing risk of all-cause death. We used the fully adjusted multivariable model to run this analysis.

Results

A total of 11,373 participants with HF_rEF were included in the analysis. The participants included 2168 women (19%) and 9205 men (81%) (Figure 1).

Overall, women were older, with a higher prevalence of hypertension and diabetes, a lower prevalence of ischemic heart disease than men and a higher NYHA class (Table 1). Women were also more likely to be treated with digoxin and diuretics. However, within each sex, placebo and treatment groups had similar baseline characteristics (Table 1).

During a mean follow up of 37.8 ± 0.6 months, 438 women in the placebo group and 400 women in the ACEi/ARBs group experienced the primary outcome (IR placebo=16.7 per 100 person-year, PY, 95% CI 15.2-18.3; IR ACEi/ARBs =14.7 per

100 PY, 95% CI 13.3-16.2) whereas during a mean follow up of 41.1 ± 0.4 months among men, 1836 and 1558 primary events occurred in placebo and ACEi/ARBs groups, respectively (IR placebo=16.6 per 100 PY, 95% CI 15.8-17.3; IR ACEi/ARBs =12.9 per 100 PY, 95% CI 12.3-13.6) (Table 2). In the treatment group, men had a lower IR than women (Table 2), as illustrated by Kaplan-Meier curves (Figure 2a) and the sex-specific log-rank test.

The unadjusted survival analysis for the primary outcome showed it was not different between men and women (HR 0.79 95% CI 0.72-0.86 vs HR 0.89 95% CI 0.83-0.94, , $p_{\text{interaction}}=0.10$) (Table 3a).

In the adjusted multivariate analysis of the comparative efficacy, the risk of primary outcome was significantly lower for ACEi/ARBs group compared with placebo (aHR 0.79, 95% CI 0.72-0.86) (Table 3b). In the multivariate model that considered potential effect modification by sex, the two-way sex-by-randomized treatment interaction was not statistically significant ($p=0.12$) (Table 3b), indicating that the efficacy of ACEi/ARBs, relative to placebo, was similar for women and men. In the analysis of the secondary outcomes, we found that women were hospitalized for HF more often than men despite treatment. (aHR women 0.82 95% CI 0.74-0.90 vs aHR men 0.69 95% CI 0.60-0.79 in men, $p_{\text{interaction}}=0.09$) (Table 3b, Fig 2 c).

In our sensitivity analysis that included only the CHARM-Alternative and SOLVD-Treatment trials, we observed similar results (Supplemental Table 2). In the analysis that included only SOLVD-Treatment and SOLVD-Prevention, there was a statistically significant difference between men and women in both the primary outcome (aHR 0.72 95% CI 0.65-0.79 in men vs aHR 0.95 95% CI 0.77-1.17, p -

interaction=0.01) and the secondary outcome of hospitalization for HF (aHR 0.58 95% CI 0.51-0.66 in men vs aHR 0.88 95% CI 0.68-1.13, $p_{\text{interaction}} < 0.01$) (Supplemental Table 3). Adjusting for differences in diuretics, digoxin and betablocker use did not change the results. Our analysis of the competing risk of death showed that it did not significantly impact our findings.

Discussion

The main findings of our sex stratified analysis is that the treatment with ACEi/ARBs was equally effective in men and women with HFrEF in reducing the incidence of a composite outcome of death or hospitalization for heart failure. However, women were more frequently hospitalized for HF during the follow-up period despite treatment with ACEi/ARBs.

Our study builds on previous analyses of sex differences in RAS blockade. A meta-analysis of ACEi to treat HFrEF⁹, including the SOLVD-Treatment trial, found no statistically significant benefit in women for the composite outcome of death, HF and MI, but the sex-by-drug interaction term was not significant. An analysis of pooled data from the CHARM trials²¹ found no sex difference in the HR for the composite outcome of cardiovascular death and HF hospitalization. However, these results came from the subgroup analysis not adjusted for confounders. Conversely, we performed a multivariate analysis adjusted for sex-by-treatment interaction allowing us to better characterize sex differences²². A similar approach was recently used to retrospectively analyze data from the TOPCAT trial and found a potential mortality benefit of aldosterone in women, but not men²³. Furthermore, a large retrospective study of individuals with HFrEF using administrative data showed that ARBs may be more

effective than ACEi in women, but equally effective in men¹⁴. A pharmacological study of RAS stimulation through angiotensin II peptide infusions in healthy volunteers found that women had less kidney injury than men in response to RAS stimulation¹³. A study using mathematical models of the RAS found that female rats had a smaller absolute decrease in angiotensin I and II than males in response to RAS blockade²⁴. Together these studies suggest biologically plausible mechanisms supporting sex differences in the efficacy of ACEi/ARBs in HFrEF. So far, we can only speculate on other potential mechanisms which may be involved, such as the hormonal regulation of the RAS. In fact, estrogen leads to a net downregulation of the RAS, while testosterone leads to a net upregulation^{25,26}. Women with HFrEF included in the RCTs were predominantly post-menopausal and their RAS activity might be upregulated compared to pre-menopausal women. On the other hand, men may have a higher baseline RAS activity due to higher level of testosterone and hence benefit more from RAS blockade than women. A second mechanism might be related to the sex differences in the genetic expression of RAS components. A study of the genetic expression of these components, such as renin and ACE, found sex specific polymorphisms²⁷ which could impact the efficacy of RAS blockade differentially by sex. Finally, women are known to experience more adverse effects from ACEi²⁸, which may lead to decreased compliance and decreased benefit from RAS blockade. This hypothesis is difficult to explore as the sex specific rates of adverse events and subsequent discontinuation were not available in our dataset. Furthermore, these sex specific data are rarely reported in clinical trials²⁹. Given these varied possible explanations, a further effort should be supported for understanding how the RAS differs based on the individual sex.

Furthermore, there is recently reported evidence on a sex difference in the efficacy of a relatively new class of medication, the angiotensin receptor and neprilysin inhibitors (ARNIs), which enhances the effect of the vasodilatory and natriuretic peptides. The PARAGON-HF trial (51.7% women)³⁰, which compared an ARNI to an ARB in HF with preserved ejection fraction (HFpEF), found a greater benefit of the ARNI in women in reducing hospitalizations for HF and death from cardiovascular causes³¹. It is intriguing that PARAGON-HF, which had a large proportion of women, found a sex difference in the same outcome as our study, namely heart failure hospitalizations. However, it is important to note that this study was in HFpEF and the PARADIGM-HF trial (21.6% women)³², which studied ARNIs in HFrEF, found no sex differences. Considering this growing evidence of sex-specific effects, it is mandatory to explore sex-specific evidence-based management of HFrEF in greater depth.

There were several strengths to our study approach. Firstly, we had access to individualized patient data. Secondly, we conducted multivariate analyses of the sex subgroups rather than the univariate analysis that is usually done and represented in Forest plots of RCTs. Thirdly, we merged data from multiple trials, which increased the number of women and hence our power to detect a difference.

There were also some limitations to be mentioned. Firstly, we assumed that the clinical effect of RAS blockade was similar across both ACEi and ARBs, however we also performed sensitivity analysis on ACEi. Secondly, we were missing data on some prognostic variables for certain patients such as previous history of hospitalization for

HF as well as biomarkers such as NT-proBNP. Thirdly, this was a non-prespecified outcome of the trial and therefore may be subject to bias. Finally, our study was not fully powered to detect an interaction by sex³³. Future studies could address these limitations through access to more detailed data that focus on the specific classes of RAS blockers.

In conclusion, our study shows that ACEi/ARBs are equally effective in women and men in treating HFrEF. However, women suffer more than men from hospitalizations for heart failure despite treatment. This highlights the need for a continued focus on addressing health inequities faced by women. Though there has been significant progress, with increased enrollment of women in clinical trials since CHARM and SOLVD were conducted⁵, much work still remains to be done³⁴. Our hope is that continued research in the field of HF will be designed to allow for data to support treatment strategies that are tailored to and effective in both men and women.

Tables and Figures

Table 1. Baseline Characteristics by Sex and Treatment Group

	Women Placebo (N=1092)	Women Treatment (N=1076)	Men Placebo (N=4596)	Men Treatment (N=4609)
Age, years (mean, SD)	64 (11)	64 (11)	61 (11)	61 (11)
LVEF, % (mean, SD)	28.7 (7.1)	28.6 (7.0)	27.5 (6.8)	27.5 (6.8)
SBP, mmHg (mean, SD)	128 (19)	129 (19)	126 (18)	125 (17)
DBP, mmHg (mean, SD)	76 (10)	76 (11)	77 (10)	77 (10)
HR, beats/min (mean, SD)	77 (13)	77 (13)	75 (13)	75 (13)
Non-white race	207 (19)	211 (19.6)	539 (11.7)	590 (12.8)
NYHA Class 3-4	479 (43.9)	503 (46.8)	1450 (31.6)	1397 (30.3)
Current smoker	157 (14.4)	139 (12.9)	991 (21.6)	980 (21.3)
Ischemic Etiology	671 (61.5)	667 (62.1)	3487 (76)	3500 (76)
Angina	507 (46.4)	471 (43.8)	1985 (43.2)	1967 (42.7)
Myocardial Infarction	593 (54.4)	607 (56.5)	3245 (70.7)	3288 (71.5)
CABG	98 (9.0)	108 (10.0)	559 (12.2)	599 (13.0)
Hypertension	555 (50.8)	585 (54.4)	1903 (41.4)	1852 (40.2)
Diabetes	303 (27.8)	305 (28.4)	1013 (22.1)	995 (21.6)
Atrial Fibrillation*	162 (15.1)	171 (16.2)	627 (14.0)	661 (14.7)
Stroke	85 (7.8)	78 (7.3)	342 (7.5)	337 (7.3)
Treatment (%)				
Digoxin	512 (46.9)	488 (45.4)	1867 (40.6)	1794 (39.0)
Diuretics	818 (74.9)	813 (75.6)	2654 (57.8)	2643 (57.4)

Beta Blocker	369 (33.8)	375 (34.9)	1487 (32.4)	1500 (32.6)
Pacemaker	65 (6.0)	73 (6.8)	261 (5.7)	248 (5.4)
ICD	9 (0.8)	15 (1.4)	72 (1.6)	72 (1.6)
Lab Results				
EGFR*, ml/min/1.73 cm ² (mean, SD)	69.2 (29.8)	70.1 (31.5)	71.7 (25.7)	70.8 (24.6)

Legend: Data are reported as n (%) unless reported otherwise;

*missing data in the harmonized dataset.

For missing data, the percentage and standard deviation was calculated based on available data

Abbreviations: LVEF: Left Ventricular Ejection Fraction, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, NYHA: New York Heart Association, HF: Heart Failure, CABG: Coronary Artery Bypass Graft, ICD: Implantable Cardiac Defibrillator.

Table 2. Incidence of Primary and Secondary Outcomes by Sex

	Overall Placebo N=5688	Overall Treatment N=5685	Women Placebo N=1092	Women Treatment N=1076	Men Placebo N=4596	Men Treatment N=4609
Death or HHF						
No. of events	2274	1958	438	400	1836	1558
Incidence per 100 PY	16.6 (15.9-17.3)	13.3 (12.7-13.9)	16.7 (15.2-18.3)	14.7 (13.3-16.2)	16.6 (15.8-17.3)	12.9 (12.3-13.6)
Death(all cause)						
No. of events	1552	1407	295	267	1257	1140
Incidence per 100 PY	9.9 (9.4-10.4)	8.7 (8.3-9.2)	9.8 (8.8-11)	8.8 (7.8-9.9)	9.9 (9.4-10.5)	8.7 (8.2-9.2)
HHF						
No. of events	1381	1037	292	246	1089	791
Incidence per 100 PY	10.1 (9.5-10.6)	7.0 (6.6-7.5)	11.1 (9.9-12.5)	9.1 (8-10.3)	9.8 (9.2-10.4)	6.6 (6.1-7.0)
CV Death						
No. of events	1356	1177	265	217	1091	960
Incidence per 100 PY	8.7 (8.2-9.1)	7.3 (6.9-7.7)	8.8 (7.8-10)	7.2 (6.2-8.2)	8.6 (8.1-9.2)	7.3 (6.9-7.8)

Legend: Data are provided as numbers of events or incidence rate (95% confidence interval);

HHF: hospitalization for heart failure, CV: Cardiovascular; PY, person-year

Table 3a. Unadjusted Hazard Ratios for Primary and Secondary Outcomes

	Overall (N=11373)	Men (N=9205)	Women (N=2168)	P_{sex-by-drug} interaction
Death or HHF	0.81 (0.75-0.86) p<0.001	0.79 (0.72-0.86) p<0.001	0.89 (0.83-0.94) p=0.0001	0.10
All-cause death	0.88 (0.85-0.92) p<0.001	0.88 (0.85-0.90) p=0.001	0.90 (0.79-1.01) p=0.078	0.69
HHF	0.71 (0.63-0.79) p<0.001	0.68 (0.57-0.80) p<0.001	0.82 (0.76-0.88) p<0.001	0.09
CV Death	0.84 (0.83-0.86) p=0.010	0.85 (0.84-0.86) p<0.001	0.81 (0.72-0.91) p=0.0003	0.42

Abbreviations: HHF: Hospitalization for Heart Failure, CV: Cardiovascular

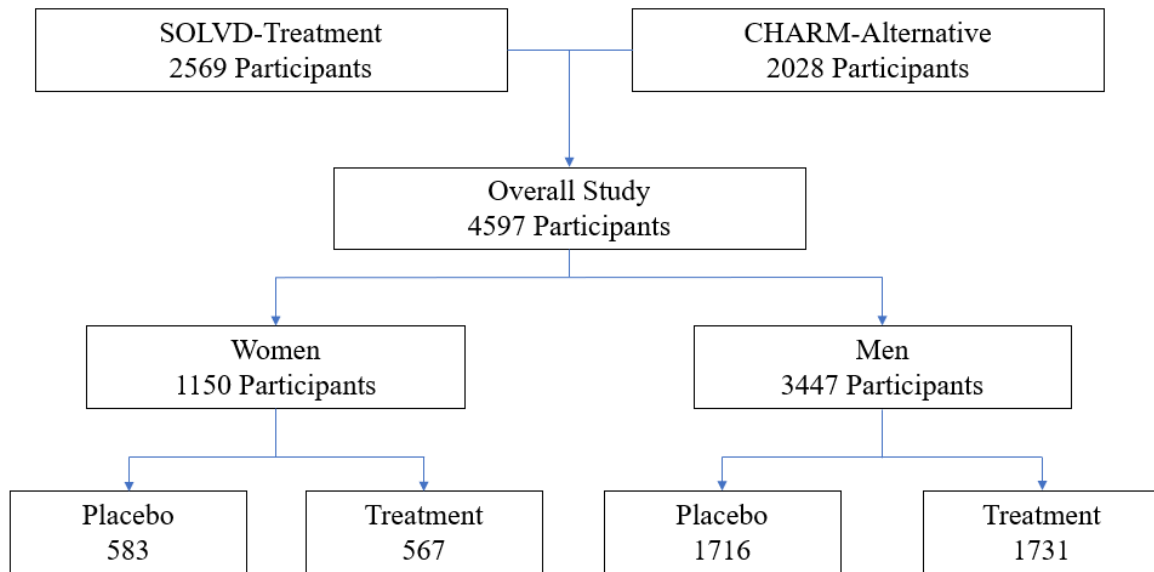
Table 3b. Adjusted Hazard Ratios for Primary and Secondary Outcomes

	Overall (n=11373)	Men (n=9205)	Women (n=2168)	P_{sex-by-drug} interaction
Death or HHF	0.79 (0.72-0.86) p<0.001	0.76 (0.68-0.86) p<0.001	0.88 (0.81-0.95) p=0.001	0.12
All-cause death	0.87 (0.83-0.92) p<0.001	0.87 (0.84-0.90) p<0.001	0.87 (0.75-1.02) p=0.08	0.97
HHF	0.69 (0.60-0.79) p<0.001	0.65 (0.54-0.79) p<0.001	0.82 (0.74-0.90) p=0.012	0.09
CV Death	0.84 (0.81-0.87) p<0.001	0.85 (0.83-0.86) p<0.001	0.80 (0.70-0.91), p=0.016	0.33

Abbreviations: HHF: Hospitalization for Heart Failure, CV: Cardiovascular

Adjusted for age, LVEF, systolic blood pressure (SBP), heart rate, NYHA class, race, smoking status, history of myocardial infarction (MI), hypertension, diabetes mellitus, atrial fibrillation, and stroke.

Figure 1



Note: 3 participants were lost to follow up from the treatment group, and 2 from the placebo group, but this information was not stratified by sex.

Figure 2 KM Curves, Placebo vs Treatment for Women and Men

Fig 2a. Primary Outcome: Hospitalization for Heart Failure or Death

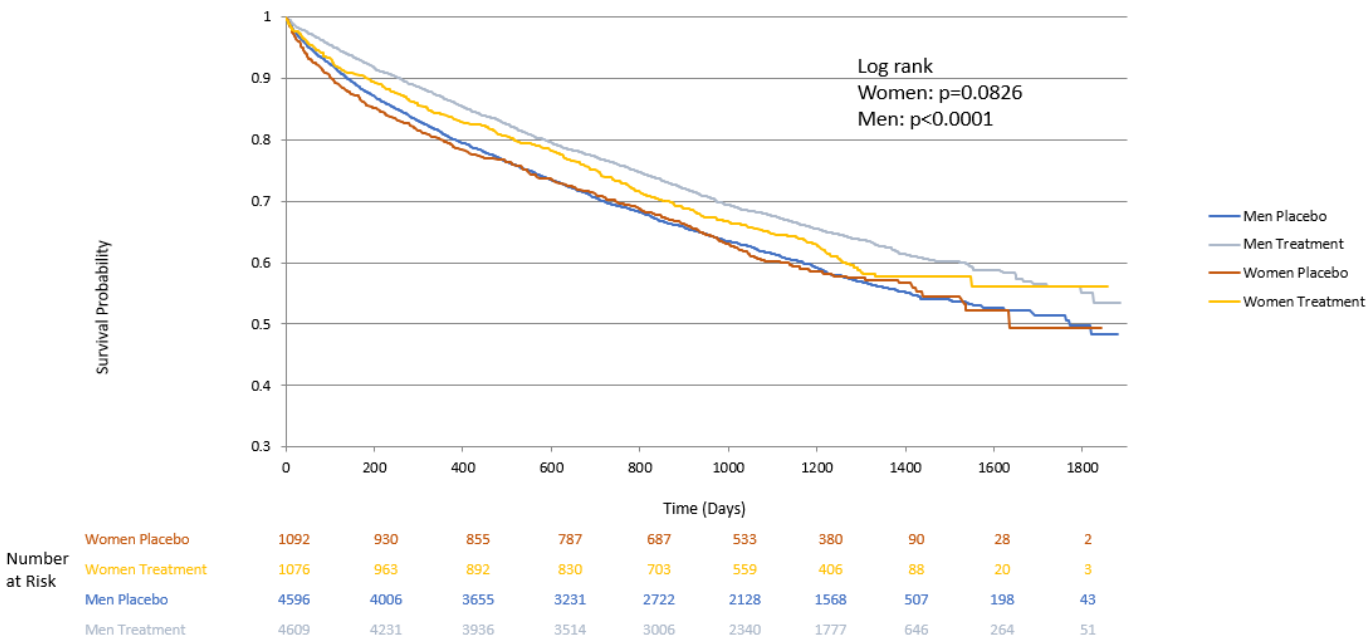


Fig 2b. All Cause Death

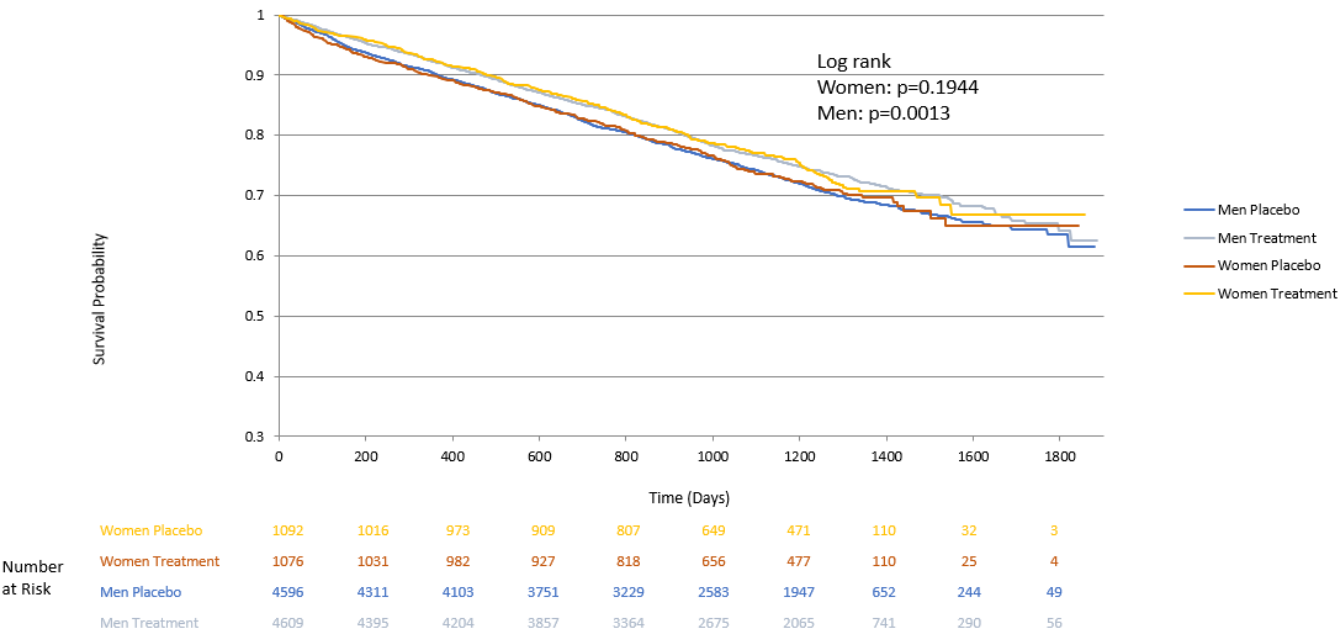


Fig 2c. Hospitalization for Heart Failure

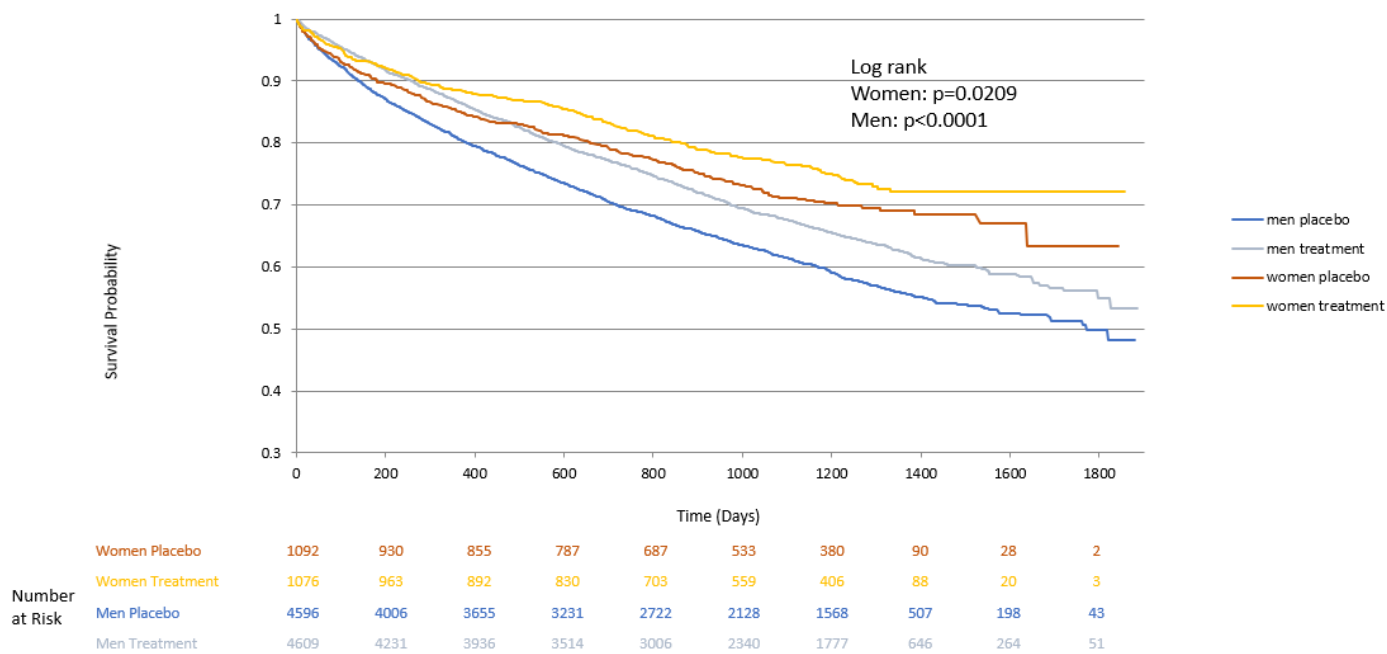
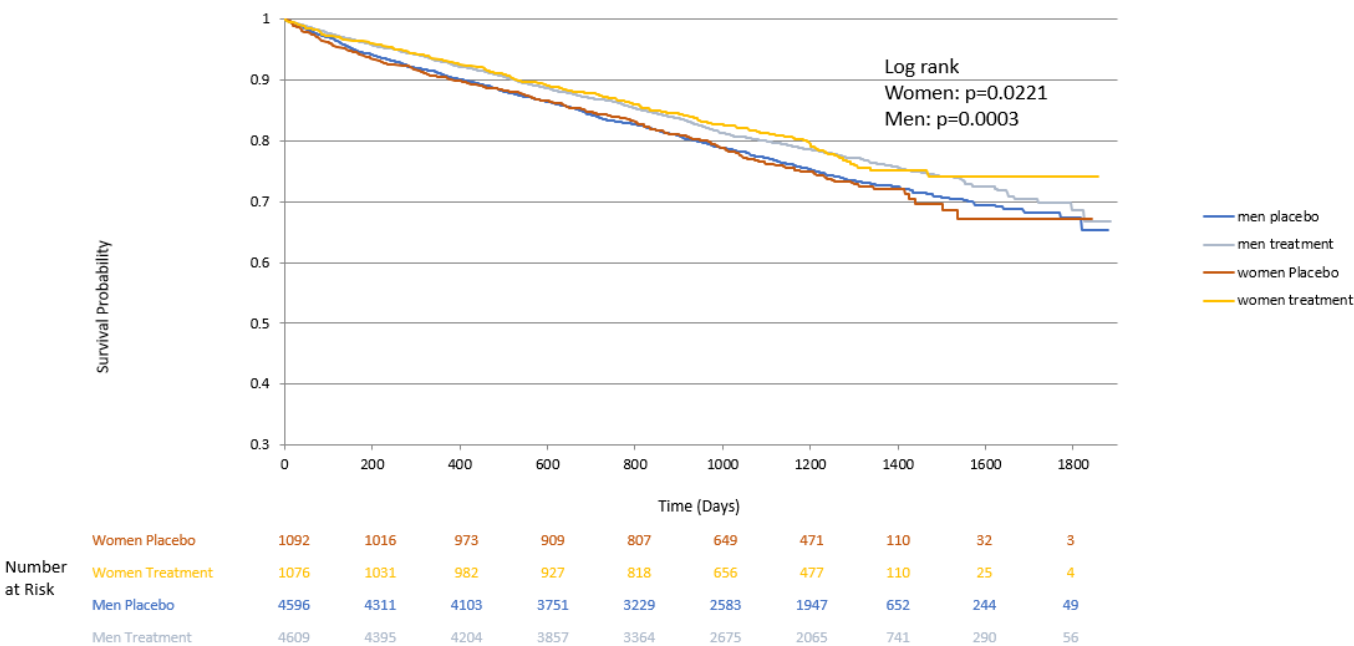


Fig 2d. Cardiovascular Death



Supplemental Data

Supplemental Table 1: Baseline Characteristics by Sex

	Women Overall (N=2168)	Men Overall (N=9205)
Age, years (mean, SD)	64 (11)	61 (11)
LVEF, % (mean, SD)	28.6 (7.1)	27.5 (6.8)
SBP, mmHg (mean, SD)	128 (19)	126 (17)
DBP, mmHg (mean, SD)	76 (10)	77 (10)
HR, beats/min (mean, SD)	77 (13)	75 (13)
Non-white race	418 (19.3)	1129 (12.3)
NYHA Class 3-4	982 (45.3)	2847 (30.9)
Current smoker	296 (13.7)	1971 (21.4)
Ischemic Etiology	1338 (61.8)	6987 (76)
Angina	978 (45.1)	3952 (43)
Myocardial Infarction	1200 (55.4)	6533 (71.1)
CABG	206 (9.5)	1158 (12.6)
Hypertension	1140 (52.6)	3755 (40.8)
Diabetes	608 (28.1)	2008 (21.8)
Atrial Fibrillation*	333 (15.7)	1288 (14.4)
Stroke	163 (7.5)	679 (7.4)
Treatment		
Digoxin	1000 (46.1)	3661 (39.8)
Diuretics	1631 (75.2)	5297 (57.6)

Beta Blocker	744 (34.3)	2987 (32.5)
Pacemaker	138 (6.4)	509 (5.5)
ICD	24 (1.1)	144 (1.6)
Lab Results		
EGFR*, ml/min/1.73 cm ² (mean, SD)	69.6 (30.7)	71.3 (25.2)

Legend: Data are reported as n (%) unless reported otherwise;

*missing data in the harmonized dataset.

For missing data, the percentage and standard deviation was calculated based on available data

Abbreviations: LVEF: Left Ventricular Ejection Fraction, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, NYHA: New York Heart Association, HF: Heart Failure, CABG: Coronary Artery Bypass Graft, ICD: Implantable Cardiac Defibrillator.

Supplemental Table 2: Multivariate analysis of sex interaction of SOLVD-Treatment and CHARM-Alternative

	Overall (n=4597)	Men (n=3447)	Women (n=1150)	P_{sex-by-drug} interaction
Death or HHF	0.73 (0.69-0.77), p<0.0001	0.70(0.63-0.76), p<0.001	0.86 (0.72-1.03), p=0.11	0.12
All-cause death	0.84 (0.84-0.84), p<0.001	0.84 (0.82-0.86), p<0.001	0.80 (0.75-0.86), p<0.001	0.97
HHF	0.63 (0.63-0.64), p<0.0001	0.58 (0.54-0.62), p<0.001	0.82 (0.66-1.03), p=0.091	0.09
CV Death	0.81 (0.80-0.83), p<0.0001	0.83 (0.82-0.84), p<0.0001	0.74 (0.71-0.78), p<0.0001	0.33

Abbreviations: HHF: Hospitalization for Heart Failure, CV: Cardiovascular

Adjusted for age, LVEF, systolic blood pressure (SBP), heart rate, NYHA class, race, smoking status, history of myocardial infarction (MI), hypertension, diabetes mellitus, atrial fibrillation, and stroke.

Supplemental Table 3 . Multivariate analysis of sex interaction of SOLVD-Treatment and SOLVD-Prevention

	Overall (n=6797)	Men (n=5817)	Women (n=980)	P_{sex-by-drug interaction}
Death or HHF	0.75 (0.69-0.82) p<0.001	0.72 (0.65-0.79) p<0.001	0.95 (0.77-1.17) p=0.650	0.01
All-cause death	0.88 (0.79-0.97) p<0.001	0.86 (0.77-0.96) p=0.008	0.96 (0.75-1.24) p=0.771	0.44
HHF	0.63 (0.56-0.71) p<0.001	0.58 (0.51-0.66) p<0.001	0.88 (0.68-1.13) p=0.315	<0.01
CV Death	0.84 (0.76-0.94) p=0.002	0.84 (0.75-0.94) p=0.003	0.87 (0.66-1.15), p=0.328	0.80

Abbreviations: HHF: Hospitalization for Heart Failure, CV: Cardiovascular

Adjusted for age, LVEF, systolic blood pressure (SBP), heart rate, NYHA class, race, smoking status, history of myocardial infarction (MI), hypertension, diabetes mellitus, atrial fibrillation, and stroke

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Discussion

The main findings of our sex stratified analysis is that the treatment with ACEi/ARBs was equally effective in men and women with HFrEF in reducing the incidence of a composite outcome of death or hospitalization for heart failure. However, women were more frequently hospitalized for HF during the follow-up period.

Previous analyses of these trials and of these medications have been done. A meta-analysis of ACEi to treat HFrEF⁴⁴, including the SOLVD-Treatment trial, found no statistically significant benefit in women for the composite outcome of death, HF and MI, but the sex-by-drug interaction term was not significant. An analysis of pooled data from the CHARM trials⁴⁷ found no sex difference in the HR for the composite outcome of cardiovascular death and HF hospitalization. However, these results came from the subgroup analysis not adjusted for confounders. Conversely, we performed a multivariate analysis adjusted for sex-by-treatment interaction allowing us to better characterize sex differences⁴⁸. A similar approach was recently used to retrospectively analyze data from the TOPCAT trial and found a potential mortality benefit of aldosterone in women, but not men⁴⁹. Furthermore, a large retrospective study of individuals with HFrEF using administrative data showed that ARBs may be more effective than ACEi in women, but equally effective in men⁵⁰

There is evidence for multiple different etiologies that lend biological plausibility to our findings. Hormones have wide ranging effects on the RAS system (as well as effects on other aspects of heart failure) and do differ markedly between men and women. There is growing evidence of pharmacokinetic differences, i.e. that

women process all medications, including ACEi/ARBs, differently from men. Genetics lie at the root of biological systems and gene polymorphisms in the components RAS may be able to explain our findings as well.

Estrogen leads to a net downregulation of the RAS, while testosterone leads to a net upregulation^{36,51}. Women with HFrEF included in the RCTs were predominantly post-menopausal and their RAS activity might be upregulated compared to pre-menopausal women. On the other hand, men may have a higher baseline RAS activity due to higher level of testosterone and hence benefit more from RAS blockade than women. This hypothesis is consistent with the long observed “cardioprotective” role of estrogen as well as the improved mortality in women compared to men in heart failure seen in certain studies⁵².

There is a large body of evidence supporting sex differences in pharmacokinetics. A pharmacological study of RAS stimulation through angiotensin II peptide infusions in healthy volunteers found that women had less kidney injury than men in response to RAS stimulation³⁵. A study using mathematical models of the RAS found that female rats had a smaller absolute decrease in angiotensin I and II than males in response to RAS blockade⁵³. A recently published post-hoc analysis of prospective cohort study BIOSTAT-CHF⁵⁴ reported that when comparing different doses of ACEi/ARBs in men and in women the best outcomes, i.e. the lowest HR of death or hospitalisation for HF, occurred at 100% of the recommended dose of ACEi/ARBs and β blockers in men, but at only 50% of the recommended dose in women. Other trials looking at differential dosing of lisinopril (ACEi) and losartan (ARB) showed higher doses benefiting men but not women⁵⁵. Once again, this is

consistent with our findings that ACEi/ARBs have differential effects in men and women.

Sex differences in the genetic expression of RAS components may also explain our findings. A study of the genetic expression of these components, such as renin and ACE, found sex specific polymorphisms³⁴ which could impact the efficacy of RAS blockade differentially by sex. Finally, women are known to experience more adverse effects from ACEi³², which may lead to decreased compliance and decreased benefit from RAS blockade. This hypothesis is difficult to explore as sex specific rates of adverse events and subsequent discontinuation in clinical trials, including CHARM and SOLVD, are rarely reported⁵⁶. Finally, women are known to have greater levels of ACE2, an enzyme which opposes the traditional maladaptive response of the RAS leading to a lower activity of the RAS at baseline^{30,57}. This in turn may explain why women derive less benefit than men in further pharmacological lowering or blockade of RAS activity. Given these varied possible explanations, a further effort should be supported for understanding how the RAS differs based on the individual sex.

There were several strengths to our study approach. Firstly, we had access to individualized patient data. Secondly, we conducted multivariate analyses of the sex subgroups rather than the univariate analysis that is usually done and represented in Forest plots of RCTs. Thirdly, we merged data from multiple trials, which increased the number of women and hence our power to detect a difference.

There were also some limitations to be mentioned. Firstly, we assumed that the clinical effect of RAS blockade was similar across both ACEi and ARBs, though we also performed sensitivity analysis on ACEi. Secondly, we were missing data on some

prognostic variables for certain patients such as previous history of hospitalization for HF. Future studies could address these limitations through access to more detailed data that focus on the specific classes of RAS blockers.

These findings must be interpreted in context of the limitations of the statistical analysis, the existing literature on sex differences and as well as evidence of biological plausibility. Any analysis may be limited by its statistical power and must strike a balance between making a Type I or II error. The existing literature is equivocal about the existence of sex differences of ACEi/ARB, but recent studies have shed new light on the topic.

Our analysis originally found a statistically significant difference in the secondary outcome, with $p_{\text{-interaction}}=0.03$. A more stringent analysis then found some overlap with a p value of 0.09. Though this does not meet the generally accepted mark for statistical significance, it does merit further investigation, especially given the recognition of the limitation of p values⁵⁸. That is to say, an arbitrary cut off should be interpreted alongside mounting evidence of difference and with appropriate caution against a Type II error.

The power of our pooled study to detect a difference is higher than that of the individual trials, though it remains limited. Most studies are powered to detect a pre-determined difference at the 80-90% power. The individual subgroups from these studies are almost by definition underpowered and must be interpreted with caution⁵⁹. Furthermore, interaction analyses require a significantly higher sample size, from 5-100 times larger, to be powered to the same degree depending on the size of the interaction, which is usually not feasible in the current model of clinical trials⁶⁰.

However, simulations have shown that subgroup analyses can detect true effects even in context of a null overall findings⁶¹. Studies such as ours, i.e. retrospective analyses of multiple pooled clinical trials, therefore, represent the best chance of detecting a difference, barring further trials that recruit primarily women.

Conclusion

In conclusion, our study shows that ACEi/ARBs are equally effective in women and men in treating HFrEF. However, women suffer more than men from hospitalizations for heart failure despite treatment. It highlights the need for a continued focus on addressing health inequities faced by women, particularly in clinical research and therapeutics in cardiovascular disease. Though there has been significant progress, with increased enrollment of women in clinical trials since CHARM and SOLVD were conducted⁶², much work still remains to be done⁶³. Our hope is that continued research in the field of sex differences will allow for treatment strategies that are tailored to and effective in women.

Appendix: Methodological Considerations

This chapter aims to discuss the details of our methodology. We conducted multiple different analyses of the data in addition to those presented in the final manuscript. These analyses took a different approach to building our statistical models. Firstly, they included adjustment for treatment variables, primarily medications, which may lead to a risk of confounding by indication. Secondly, they adjusted for potential differences between the SOLVD and CHARM trial participants by adjusting for trial type rather than using robust standard errors, i.e. clustering. The results generated by using this alternate approach are presented below. Thirdly, we included the results of the competing risk analysis used in the manuscript. Finally, we discuss the limitations of subgroup analyses and their power to detect an effect.

Confounding by Indication

Firstly, this analysis was different from that included in our main manuscript in that it included adjustment for treatment variables. When adjusting for medications, there is a risk for confounding by indication where the adjustment may represent either the effect of the medication itself or may represent underlying severity⁶⁴. Diuretics are an illustrative example, where increased prescription and use of diuretics in women is likely representative of worse symptoms of edema and dyspnea, but likely have similar impacts in men and women. However, excluding these medications from the analysis may miss capturing true differences between men and women that are not accounted for by other measures of severity such as NYHA class, as well as potential differential effects of the medications by sex, e.g. digoxin⁶⁵.

Clustering

In our study, we combined two large trials, SOLVD and CHARM, into a single dataset. Though these had similar inclusion criteria, the patient populations were not identical. Furthermore, they occurred more than a decade apart, during which time the standard of care of heart failure had advanced. Our statistical analysis must therefore account for the differences in these populations. We used two different statistical approaches to do so. One approach used robust standard errors, or clustering, while the other used default standard errors, with differing results.

Regression analyses require that certain assumptions be met for the results to be unbiased and consistent. One of these assumptions is that of homoskedasticity, where the errors or variance of the outcome is evenly distributed across the range of the dependent variable. Another assumption is that the outcomes are independent among individuals and not related to other covariates⁶⁶. In our case, if the two trial populations do cluster with participants in the same trial behaving more similarly than participants from the other, it challenges the assumption of independence where outcomes may depend not only on the drug administered but also the trial in which the participant was enrolled. This can be measured using the intra-cluster correlation⁶⁷.

Robust standard errors help account for this clustering and generally lead to estimates that are less biased, though often with wider confidence intervals. Robust standard errors and default standard errors will tend to overlap if there is homoskedasticity and diverge if there is a degree of dependence or variance of the error term on a third covariate⁶⁷.

The results of our alternate and main analyses are detailed in Table 1 and Table 3b (from the manuscript) respectively. The alternate analysis adjusted for treatment variables and used default standard errors rather than robust standard errors. In the alternate analysis, there was no statistically significant effect of sex on the primary outcome ($p_{\text{interaction}}=0.12$). However, for the secondary outcome of hospitalizations for heart failure there was a statistically significant difference in efficacy by sex (HR 0.65 95% CI 0.59-0.71 in men vs HR 0.80 95% CI 0.68-0.95 in women, $p_{\text{interaction}}=0.03$). This differed from the main analysis which had a $p_{\text{interaction}}=0.09$.

The two approaches give p-values that are quite similar but on opposite sides of the conventional threshold of 0.05. This was likely driven by clustering of participants within each trial- the inclusion of medications in the multivariate analysis did not change our estimates significantly in sensitivity analyses (not shown). In the presence of clustering, the robust standard errors used in our main analysis are generally accepted to give less biased estimates⁶⁷. However, looking at the estimates generated in our main analysis, we see that the confidence intervals have minimal overlap (HR 0.65 95% CI 0.54-0.79 in men vs HR 0.82 95% CI 0.74-0.90 in women). It remains possible that through our strict statistical analyses we are committing a Type II error i.e. falsely accepting the null hypothesis that there is no difference in the efficacy of RAS inhibitors between men and women. Our results should be interpreted with that possibility in mind.

Table 1. Adjusted Hazard Ratios for Primary and Secondary Outcomes, with adjustments for medications and without Clustering

	Overall (n=11373)	Men (n=9205)	Women (n=2168)	P_{sex-by-drug interaction}
Death or HHF	0.79 (0.74-0.83) p<0.001	0.76 (0.71-0.82) p<0.001	0.87 (0.76-1.00) p=0.052	0.09
All-cause death	0.87 (0.81-0.94) p<0.001	0.87 (0.76-0.99) p<0.001	0.88 (0.74-1.04) p=0.133	0.92
HHF	0.68 (0.63-0.74) p<0.001	0.65 (0.59-0.71) p<0.001	0.80 (0.68-0.95) p=0.012	0.03
CV Death	0.84 (0.77-0.91) p<0.001	0.85 (0.78-0.93) p<0.001	0.80 (0.67-0.96), p=0.016	0.57

Adjusted for age, LVEF, systolic blood pressure (SBP), heart rate, NYHA class, race, smoking status, history of myocardial infarction (MI), hypertension, diabetes mellitus, atrial fibrillation, and stroke, as well as medications and devices, trial

Abbreviations: HHF, hospitalization for heart failure; CV, cardiovascular.

Table 3b. Adjusted Hazard Ratios for Primary and Secondary Outcomes

	Overall (n=11373)	Men (n=9205)	Women (n=2168)	P_{sex-by-drug interaction}
Death or HHF	0.79 (0.72-0.86) p<0.001	0.76 (0.68-0.86) p<0.001	0.88 (0.81-0.95) p=0.001	0.12
All-cause death	0.87 (0.83-0.92) p<0.001	0.87 (0.84-0.90) p<0.001	0.87 (0.75-1.02) p=0.08	0.97
HHF	0.69 (0.60-0.79) p<0.001	0.65 (0.54-0.79) p<0.001	0.82 (0.74-0.90) p=0.012	0.09
CV Death	0.84 (0.81-0.87) p<0.001	0.85 (0.83-0.86) p<0.001	0.80 (0.70-0.91), p=0.016	0.33

Abbreviations: HHF: Hospitalization for Heart Failure, CV: Cardiovascular

Adjusted for age, LVEF, systolic blood pressure (SBP), heart rate, NYHA class, race, smoking status, history of myocardial infarction (MI), hypertension, diabetes mellitus, atrial fibrillation, and stroke.

Subgroup Analyses

Women have long been under-represented in medical research. This stretches from animal models to inclusion in clinical trials with significant long-term consequence such as the marketing and sale of medications that are unsafe for women. The treatment for many women-only conditions remains insufficient. And for many diseases that affect both sexes, the evidence base is primarily based on men with unclear evidence regarding women.

Consequences of lack of inclusion of women have been significant⁶⁸. Early examples of such adverse consequences include the marketing of thalidomide for morning sickness and diethylstilberol to reduce complications of pregnancy. The first led to birth defects in many children while the second led to birth defects and cancer in the children of treated mothers. Though this spurred policy changes in the US to include more women, it also led to the exclusion of women of childbearing age. More recent examples include alosetron and tegaserod, medications for irritable bowel syndrome that increased the risks for cardiovascular disease in women⁶⁸.

There have been policy changes to try and improve inclusion of women as well as efforts to direct funding towards research on sex and sex-based differences across a spectrum of clinical conditions⁶⁹. Governmental institutions such as the National Institutes for Health (NIH) in the United States and the Canadian Institute for Health Research (CIHR) are also enacting changes in funding to heighten enrollment of women into research⁷⁰.

Different approaches have been proposed to address the lack of inclusion of women in clinical trials. One such approach is the population prevalence ratio (PPR).

For example, if 50% of the people suffering from hypertension are women, then approximately 50% of the participants in the clinical trial should be women; here the PPR would be 1⁷¹. A PPR ranging from 0.8-1.2 is considered appropriate representation. By this metric, some argue that most of the new drugs approved by the FDA have had an appropriate number of women⁷². Though this is definitely a step forward, there are some limitations to this approach from a statistical perspective. Namely, although the representation of women equates the prevalence of a specific condition- such a metric may not lead to sufficient sample size of women to determine whether or not there is a benefit.

Assessing the effect of a particular treatment on women within a study would require a subgroup analysis which presents some inherent challenges. Subgroup analyses are a commonly used tool in randomized controlled trials (RCTs) that aim to determine whether treatment effects vary across groups of clinical interest, such as age groups, sex, race, etc. However, the interpretation of the results from subgroup analyses can be controversial. Criteria exist to assess the credibility of subgroup analyses. Key criteria are that subgroups be pre-specified, that they be of a sufficient size and that a statistical test for interaction be carried out. A full list of criteria are listed in the paper by Sun et al⁷³. The same paper found many studies fail to meet or report these criteria thereby limiting their credibility. One of the limitations of subgroups include their limited statistical power. Studies are powered to be able to make conclusions for the whole population and therefore subgroups, by definition, will be underpowered. For example, for a similar sample size, a subgroup that makes up half the study population is only powered at 60% to detect the same effect as the

overall study. For a subgroup that makes up 20% of the population, the approximate PPR for women with HFrEF, will only have 30% power⁶⁰.

Furthermore, for subgroup analyses to be credible, a formal test of interaction must be carried out. Interaction tests assess whether the effect of a causal variable, e.g. a drug, on an outcome, such as mortality, is modified by a third variable, e.g. sex. Effect sizes for subgroups may differ from the main effect but they cannot be directly compared reliably without conducting a formal test of interaction. However, obtaining adequate power for to carry out an interaction test may require very large sample sizes—easily 10 times that of the original studies⁶⁰. Estimates of required sample sizes to adequately power a sex*drug interaction, as done in our study, are shown in Table 1, with variations based on the predicted effect size and the proportion of women and a significance level of 0.05. These calculations are based on a logistic regression⁷⁴ rather than a Cox Proportional Hazards model, but do illustrate the very large sample sizes required. For example, our study, despite its large sample size, only has a power of approximately 60%.

Randomized controlled trials of appropriate size to power an interaction analysis require very large sample sizes, which may be considered too costly or unfeasible. However, the costs of not addressing this deficit in health research and healthcare could be higher. Though progress has been made, further work must be done to obtain results that are relevant and applicable to both men and women⁶³.

Table 1. Power and sample size for sex*drug interaction

Sample Size	Proportion of Women	OR 0.5	OR 0.8	OR 0.9
25000	0.2	100	91	35
	0.5	100	99	51
	0.8	100	92	36
20000	0.2	100	84	29
	0.5	100	96	43
	0.8	100	86	29
11000	0.2	100	60	18
	0.5	100	79	26
	0.8	100	75	19
5000	0.2	99	32	11
	0.5	100	47	14
	0.8	97	33	11
2000	0.2	79	15	7
	0.5	94	22	8
	0.8	83	16	7

The odds ratio (OR) calculated with an estimated effect size of 0.8 and the reported sample sizes and proportion of women, using an online tool⁷⁴

Competing Risk Analysis

Conventional survival analysis uses the concept of censoring. A feature of censoring is that it is assumed for subjects who have not experienced the event of interest by the end of study, they would eventually have experienced it if the study had been prolonged. The statistical analysis of survival data assumes that censoring is independent or noninformative and the subjects who remain under follow-up have the same risk as those who have been censored⁷⁵. However, this assumption is not always correct.

A competing risk is an event which precludes the occurrence of the event of interest. In our study, where we looked at the outcomes of death or hospitalization for heart failure (HF), there is a competing risk as an individual who has experienced death can no longer experience a hospitalization. These events are not independent, and this can lead to an inaccurate estimate of the survival function. We therefore conducted an analysis to assess whether the competing risk of death affected the hazard ratio for hospitalization for heart failure.

The results of this analysis are presented in the table below. The hazard ratio for hospitalization for heart failure did not change significantly (HR 0.68 95%CI 0.63-0.74 in the original model vs HR 0.70 95% CI 0.65-0.76 in the competing risk model). Therefore, our results were not biased by competing risks.

Table 1: Competing Risk Analysis

	Original Model Hazard Ratio	Competing Risk Model Hazard Ratio
HHF (Death OR HHF)		
Overall	0.68 (0.63-0.74)	0.70 (0.65-0.76)
Women	0.80 (0.67-0.95)	0.82 (0.69-0.97)
Men	0.65 (0.59-0.71)	0.67 (0.61-0.74)

Adjusted for sex, age, LVEF, systolic blood pressure (SBP), heart rate, NYHA class, race, smoking status, history of myocardial infarction (MI), hypertension, diabetes mellitus, atrial fibrillation, and stroke, as well as medications and devices, trial

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