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Sex differences in heart failure

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Chapter 1

Introduction

Biological differences between men and women, referred to as sex differences, have a profound impact on the natural course of cardiovascular disease.¹ Besides environmental, cultural-behavioral factors, commonly known as gender effects, biological sex is a commonly underestimated determinant of cardiovascular risk and the epidemiology and clinical phenotype of disease.²

Cardiovascular disease currently accounts for almost 40% of all deaths in European countries and thus has enormous medical relevance.³ Historically, it has been perceived as more important in men than women. This may be attributed to a common focus on the typical male disease pattern, as well as the higher prevalence and mortality of coronary artery disease in men. This bias was termed the „Yentl syndrome“⁴, a phrase which highlighted the under-diagnosis, under-treatment and the paradoxically adverse outcomes of women with typically less obstructive coronary artery disease. Within the cardiovascular disease spectrum, ischemic heart disease is the leading cause of death, and indeed, despite rising awareness and improving outcomes it still carries considerably higher death rates of all related forms in men over women.³ However, the clinical relevance in terms of overall cardiovascular morbidity and mortality is increasing in women.³ Already in 2011, in absolute numbers more women than men died of cardiovascular diseases across Europe.³

Heart failure is the clinical syndrome at the common end of the cardiovascular disease continuum. It may result from different etiologies but in more than half of all patients, heart failure results from myocardial ischemia and there are questions on how biological sex is related to heart failure.⁵ There are currently more women than men suffering from heart failure and probably even more women will be affected by heart failure in the future because of their longer life expectancy relative to men.⁶ Men and women with heart failure share the same classic risk factors for cardiovascular disease but the onset of ischemic heart disease occurs on average 7-10 years later in women compared with men.¹

This is closely related to the changing female sex hormone levels over lifetime, with major changes occurring through menopause, leading to substantial epidemiological differences between both sexes.⁷

Men with heart failure more often suffer from ischemic cardiomyopathy and have a history of previous myocardial infarction whereas women are usually older and have typical co-morbidities, such as hypertension, diabetes and atrial fibrillation.⁸ Differences in heart failure etiologies are associated with characteristic types of remodeling and cardiac dysfunction, both of which show intimate relation with sex.⁹ Accordingly, two different types of heart failure have been differentiated over the years: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).^{10,11} A hallmark of HFpEF is diastolic dysfunction and characteristically, women are affected by HFpEF more often than men.¹² However, the underlying pathophysiology of HFpEF and its relation to female sex are not well characterized.

Overall, most data on differences between men and women with heart failure are limited and biased, because they derived from retrospective, mostly non-pre-specified subgroup analyses of randomized controlled trials including only relatively small numbers of women. Furthermore, the pathophysiological pathways underlying sex differences, as indicated by biomarkers of various disease mechanisms have thus far not been adequately addressed to characterize the female heart failure phenotype.

There is an unmet need to characterize the differences in clinical manifestation and outcome of heart failure between men and women and potential underlying sex differences in pathophysiology.

Content of the thesis

Following this introduction, Chapter 2 provides a review of sex differences of the various types of cardiomyopathies, many of which occur with different prevalence, severity, and prognosis in men and women, and may ultimately lead to heart failure.

In Chapter 3, the differences in new-onset heart failure between men and women are presented on the basis of epidemiological data for the two different types of heart failure: HFpEF and HFrEF.

Chapter 4 deals with differences in the clinical characteristics, biomarkers levels and outcome implications in men and women with chronic heart failure at discharge from hospitalization for acute decompensation.

Chapter 5 builds on Chapter 4 in terms of validating the clinical phenotype of men and women with chronic heart failure in a clinical trial cohort of acute heart failure patients with a focus on sex differences in the clinical presentation, in-hospital treatment and post-discharge outcomes.

Finally, Chapter 6 presents an analysis of the difference in the improvement of dyspnea in women versus men with acute heart failure.

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