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Comorbidities in Heart Failure: Are There Gender Differences?

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Abstract

Compared to men, women with heart failure (HF) are often older, smoke less, and have more preserved ejection fraction (EF), and hypertensive HF rather than HF of ischemic etiology. Gender-stratified outcome on comorbidities data in HF are scarce. Women have traditionally been under-represented in HF trials. Although data suggest that overall prognosis may be better in women, they experience lower quality of life with greater functional impairment from HF compared to men. Gender-differences have been reported for comorbid diabetes, chronic obstructive pulmonary disease, renal dysfunction, anemia and depression, and may explain gender disparity in outcomes. However, possible confounding of comorbidities with known prognostic determinants in HF (such as EF) as well as gender-differences in the utilization of medical therapies obscures interpretation.

In this review, we will explore the evidence for gender differences in non-cardiovascular comorbidities in HF. Our findings may guide clinicians to individualize HF care, according to best-practice, in the hope of improving prognosis for this chronic and debilitating condition.

Keywords

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Introduction

The prevalence of heart failure (HF) is projected to increase substantially due to the ageing of populations and increased longevity[1]. The majority of HF patients suffer from comorbidities, defined as cardiovascular and non-cardiovascular chronic conditions that co-exist with the primary illness of HF[2-5]. Comorbidities put an additional burden on patients, healthcare utilization and expenditure for HF, and are associated with worse outcome[4, 6, 7]. Moreover, comorbidities may constitute risk factors for HF, trigger episodes of exacerbation, and have been proposed to drive the underlying disease process[3, 8]. A recent study providing longitudinal follow-up data of community-dwelling HF patients suggests that the percentage of HF patients with 4 or more comorbidities has increased substantially in recent years[9]. Another contemporary report showed that non-cardiovascular comorbidities constitute a greater hazard for hospitalizations and death than cardiovascular diseases in this population[10].

There is a paucity of gender-specific data on comorbidities in HF. Despite the fact that more than half of the patients with HF in routine care are women, randomized clinical trials (RCT) supporting current HF management guidelines have recruited predominantly male subjects with a lack of prospective gender-specific analyses. Some evidence, largely from registries, demonstrates important gender-differences in HF etiology, risk factors, and clinical presentation: Women, compared to men, tend to be older; with higher blood pressure and non-ischemic HF etiology, as well as more comorbidities such diabetes, renal disease and arthritis[11, 12].
Accumulating evidence suggests better overall prognosis for women with HF compared to men, although it is not possible to entirely separate the impact of these differences according to comorbidity burden[13-23].

The Meta-Analysis Global Group In Chronic Heart Failure (MAGGIC), comprising individual patient data from 31 prospective observational and randomized studies in almost 42,000 patients with a mean follow-up of three years is currently the largest database containing gender-specific data in HF. MAGGIC demonstrated better survival for women irrespective of ejection fraction (EF) and age, although the gender-specific survival benefit was attenuated in subjects with ischemic etiology and those with comorbid diabetes[9, 24]. Also, the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) in HF outpatients with reduced ejection fraction showed that women were more likely to

have advanced CKD[25]. In contrast, the multicenter Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry involving 48,612 patients with HF showed a similar burden of comorbidity and outcomes for both genders[17].

The evidence on gender-specific outcomes appears to be different between acute and chronic stable HF phenotypes. The Acute Decompensated Heart Failure National Registry (ADHERE) database and the American Heart Association Get With The Guidelines-Heart Failure (GWTG-HF) registry each comprising data from approximately 100,000 hospitalizations reported important gender differences for patient characteristics for the majority of comorbidities, but similar clinical outcomes for both genders[26, 27]. Likewise, the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) Trial in 4,133 patients hospitalized for HF and EF of ≤40% reported similar rates for all-cause mortality and CV death or HF hospitalizations for women and men[23].

Comorbidities burden in HF increase with age, may exacerbate the progression and clinical severity of HF, and possibly be of prognostic importance[28, 29]. Several important differences between HF with reduced EF (HFrEF) compared to preserved EF (HFpEF; commonly defined as EF≥40%, 45% or 50%) exist where diabetes, anemia, chronic obstructive pulmonary disease (COPD) and obesity were more commonly observed in patients with HFpEF[4, 26, 30, 31]. In general, in women HFpEF is more predominant than HFrEF[4, 10, 26, 27, 29, 32-34]. Comorbidities exacerbate morbidity and mortality in HF although close relationships with other well-established prognostic determinants such as EF likely contribute.

This manuscript discusses the available evidence from registries, administrative data from healthcare providers and clinical trials on gender-specific differences in major non-cardiovascular chronic conditions comorbid to HF.

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Diabetes

Diabetes mellitus is not only a common and important comorbidity to HF, but also exerts maladaptive cardiovascular effects such as promoting coronary atherosclerosis, adverse myocardial remodelling, endothelial dysfunction, autonomic neuropathy, renal failure[35]. Diabetes is typically defined by clinical history, although some studies have distinguished between diabetes subtypes and/or insulin dependency. The reported prevalence of diabetes in clinical trials in HF ranges

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between 11% and 50% (Table)[4, 5, 23, 34, 36]{Ghali, 2001 #13769;Simon, 2001 #13770}. Data from large registries such as OPTIMIZE-HF, ADHERE and GWTG-HF suggest a higher prevalence of diabetes of 30% to 44% in real-world patients with HF[17, 26, 31, 37]. The Framingham study reported a prevalence of 26% and 14% of women and men with HF, respectively[5, 38].

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The overall prevalence of diabetes (i.e., including both type 1 and type 2) among the 2,400 women and 5,199 men randomized in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program was similar in women (30%) and in men (28%). No significant gender differences were found for type 2 diabetes (18% in women vs 20% in men; OR 0.95 (95% CI 0.84 to 1.08)) but significantly more women suffered from type 1 diabetes (12% vs men 8%; OR 1.52 (95% CI 1.29 to 1.79); P<0.001)[22].

Gender-stratified analysis of the Cardiac Insufficiency Bisoprolol Study (CIBIS-II) reported a fairly low prevalence of diabetes with no significant differences according to gender (women 14% versus men 11%, P=0.117). Overall, women exhibited substantially lower rates of all-cause and cardiovascular mortality than men[39].

Among 5,491 patients hospitalized with new or worsening HF in relation to the Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) study, diabetes was present in 900 subjects (16%) of whom 370 were women and 530 men[33]. The investigators showed that diabetes was independently associated with increased mortality in patients hospitalized with HF (RR: 1.5; 95% CI 1.4 to 1.6; p<0.0001). Of note, diabetes was associated with a larger increase in mortality in women than in men (RR 1.7 (95% CI 1.4 to 1.9) vs RR 1.4 (1.3 to 1.6), p<0.0001).

In HF with preserved EF in the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) study, a trial with approximately 60% of patients being women, diabetes prevalence was similar in men (27%) and women (28%). On multivariable analysis, no significant gender differences were found for the association between diabetes and clinical events[40].

In the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2), a prospective observational study of HF in Japan (preserved EF in 75.1 % of women vs in 65.8% of men, P<0.001), diabetes was less prevalent in women (31.7%) vs men (36.4%; P=0.002). Overall survival was similar. Analysis of predictors for all-cause mortality between genders showed significant interaction for

diabetes although no detailed hazard ratios were reported[41]. These data are contrasted by a pooled analysis of prospective and observational studies from Spain. The multicentre Andalusian Heart Failure Registry (RAIC) examined 795 patients with a primary diagnosis of HF[42]. The relative prevalence of diabetes compared to men was higher in women (50.7% versus 41.2% in men, p<0.007). The authors did not report gender-related differences in in-hospital mortality (5.2%) or short-term morbidity (19.2%), and the relative importance of diabetes to these outcomes was not presented.

In the MAGGIC database, diabetes was found in 25.4% of women vs 22.8% of men; p<0.001)[24]. The survival benefit in women was attenuated with comorbid diabetes: the hazard ratio (95% CI) of death for men vs. women without diabetes was 1.37 (1.30-1.45), but in the presence of diabetes only 1.11 (1.03-1.20); P<0.0001 for interaction)[24].

As with most other comorbidities in HF, diabetes is more frequently reported in registries compared to prospective randomized trials. There are important differences in epidemiology related to clinical HF status, with diabetes being more prevalent in hospitalized patients than outpatients[35]. The current HF literature does not support a consistent gender differences with regards to comorbid diabetes. Given the generally adverse association between diabetes and clinical outcomes, gender-differences in its prevalence are likely of clinical relevance. Some reports have demonstrated that concomitant DM attenuates the female gender benefit in outcomes compared to men. Thus, the negative impact of diabetes on prognosis might be enhanced in women, highlighting an urgent need for gender-specific management strategies and for prospective gender-stratified analysis in future studies in HF.

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Chronic kidney disease

Chronic kidney disease (CKD) is another adverse prognostic indicator in HF subjects[4, 5, 7, 36, 43-47]. In previous analyses, CKD has usually been defined by past medical history, or determined from an estimated glomerular filtration rate (eGFR; for example <60 ml/min/1.73 m^2). The prevalence of concomitant CKD therefore differs widely between 14% up to 90% in various HF cohorts (e.g., acute vs. chronic; preserved vs. reduced EF) and with definition used (see Table 1)[17, 26, 37, 48-51]. Registries and population-based surveys reported higher prevalence figures than

prospective trials which is likely due to the presence of exclusion criteria related to renal dysfunction in most HF trials.

In a retrospective cohort study of 18,322 age- and gender-matched Medicare beneficiaries with HF (59.1% women), the relative mortality risk of comorbid CKD was higher than for comorbid diabetes or colorectal cancer, and only second to lung cancer[7].

With respect to gender, CKD has been reported more frequently in women with HF, while other authors reported male predominance or no gender-differences[11, 23, 34, 37]. A recent epidemiological study assessing healthcare utilization and outcomes in Olmsted county, Minnesota, US reported a lower prevalence of CKD in women with both preserved EF (15% compared to men 23%) and reduced EF (14% versus 17%)[29].

Of note, eGFR has usually been computed using the Modification of Diet in Renal Disease equation (MDRD) formula which is based on serum creatinine, gender, age, and ethnicity, thereby potentially introducing some gender bias[52]. In the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) the proportion of women increased with declining eGFR[25, 53]. In contrast, in the large multicenter GWTG-HF registry (n=89,127), the prevalence for CKD was higher in men both with reduced and preserved EF, and CKD was strongly associated with increased mortality for both genders[37]. There was no gender-difference in in-hospital mortality.

In HF with preserved EF in the I-PRESERVE study, CKD was more prevalent in women than in men (34 vs 26%, $p<0.001$). Despite better overall survival in female patients, the presence of an eGFR <60 ml/min/1.73 m^2 attenuated the survival advantage in women compared with men [40].

The National HF Registry under the Spanish Society of Internal Medicine (RICA) included 1,772 patients (836 men [47.2%] and 936 women [52.8%]) with HF and mean EF of 50%. CKD was seen more often in women than men (59.1% vs 53.0%, $p<0.001$) but was not associated with survival [16].

CKD is highly prevalent and an important determinant of adverse outcome in HF. Registry data likely reflect the burden of comorbid CKD in HF more accurately than prospective trials from which HF patients with significant CKD traditionally have been excluded. The fact that more women with HF have hypertension, a predisposing condition for CKD, would provide a plausible explanation for female

predominance in the prevalence of CKD. Yet, comorbid CKD in HF does not seem to exhibit a consistent gender distribution pattern, rather, its prevalence varies according to HF phenotype and clinical status. Even more important, differences in study type, methodology, investigated cohorts and employed definitions for CKD likely account for most inconsistencies. Based on the negative prognostic association of comorbid CKD in HF and the finding by some authors of gender-specific differences in its prevalence, gender-specific evaluation of CKD comorbid to HF should be the subject of prospective studies. With CKD and worsening renal function also frequently being the cause of discontinuation of medical therapies for HF, future studies should assess whether CKD requires tailored, gender-specific management in order to optimize outcomes in women and men with HF.

Anemia and iron deficiency

Anemia and iron deficiency are common in HF and are associated with worse symptoms and outcomes in HF patients[54-57]. Commonly anemia has been defined as hemoglobin levels of <12 g/dl (7.5 mmol/l) in women and <13 g/dl (<8.1 mmol/l) in men[36]. Dilutional anemia can occur in decompensated congestive HF and together with non-uniform cut-off definitions for anemia, may explain some discrepancies between HF cohorts. The reported prevalence of anemia in HF according to the above criteria ranges from 20-40%[27, 57-61]. In many HF cohorts, lower hemoglobin levels have been associated with higher morbidity and mortality[4, 37, 58-60, 62].

Anemia seems to be more frequent in women with HF compared with men [63-65]. In the Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH) biomarker analysis (n=567; mean age 71 years; 38% women), anemia was more than twice as common in women (56% vs men 26%, p<0.001).

It is important to note that anemia in heart failure is closely related to renal dysfunction, with complex and interacting pathophysiological mechanisms (cardio-renal-anemia syndrome)[66]. This notion is supported by data from the Norwegian HF Registry of outpatients with advanced HF in which baseline anemia was predictive of all-cause mortality but not in the subset of patients with renal failure or advanced HF functional class[67].

The prevalence of iron deficiency in HF is at least twice that of clinically overt anemia[55, 68]. Iron plays a key role in erythropoiesis, and normal iron metabolism is

crucial for normal function of cardiac cells[69]. Iron deficiency is associated with worse outcomes in HF[70]. In a prospective observational study of 546 predominantly male HF patients, female gender was an independent predictor of iron deficiency[69].

Anemia is associated with older age, higher mortality both in-hospital and long-term, and with reduced quality of life in patients with HF. Several reports suggest a marked female predominance in the prevalence of anemia and iron deficiency in HF. Apart from gender-specific epidemiological data, little is known on putative gender differences in the pathophysiology, clinical course and response to therapy of anemia and iron deficiency in HF. Ongoing studies evaluating the role of iron repletion strategies in anemia or iron deficiency comorbid to HF will provide further insights into putative gender-specific differences of these highly prevalent conditions and clarify a possible need for targeted therapies according to gender.

Frailty and arthritis

Frailty is often circumscribed as the presence of general muscle weakness, fatigue, limited mobility, unintentional weight loss and reduced physical reserve [71-74]. Frailty increases with age and progressive HF symptoms, and predicts death and morbidity. Given the vague definition and inability to distinguish physiologic frailty of aging from that of HF and comorbid diseases, the prevalence estimates are wide and range between 10% in HF outpatients and up to 74% in hospitalized HF patients[74-76]. No robust data exist on the gender distribution of frailty in HF.

Osteoarthritis and rheumatoid arthritis are common in HF, especially in the elderly, and may share pathogenetic links with HF[3, 5, 77-82]. In particular, pro-inflammatory mechanisms have been proposed. The reported prevalence of chronic knee pain and radiographic osteoarthritis according to gender in the general population has differed substantially, due to differences in study design definitions used[79, 83, 84].

As with osteoarthritis, the prevalence of rheumatoid arthritis in the general population, increases with age, with the presence of HF, and shows a more consistent female predominance[85-87]. Conversely, the prevalence of HF is higher in patients with arthritis[85]. In an analysis of 34,701 patients with arthritis, gender did not confer increased risk for HF, although the incidence of HF in that cohort was too low to make definitive conclusions[88]. Importantly, rheumatoid arthritis as a comorbidity to HF is associated with worse prognosis[89].

Yet, most previous HF cohort have not systematically reported comorbid arthritis. A recent study in community-dwelling HF found arthritis (of any kind) to be more prevalent in women than men, in particular in women with HF preserved EF[29].

Together, frailty and arthritis are very common comorbidities to HF, increase with age and carry prognostic importance. There is a striking scarcity of gender-specific data on the role these comorbidities in HF. Moreover, common arthritis therapies such as corticosteroids and non-steroidal anti-inflammatory drugs potentially exacerbate HF[90]. With polypharmacy being an increasing concern in HF patients, particularly in the elderly, more gender-specific evidence is also needed for medication use for arthritis in HF.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) predicts mortality in HF[91]. COPD has been reported to be more common in male compared with female HF patients [33, 92]. Registries and RCTs show substantially higher rates of smoking in men, however gender differences in rates of COPD differences are less marked or absent (table)[16, 19, 27, 34, 40, 91]. The GWTG-HF registry found smoking rates of 21% in males and 12% in females, however the prevalence of COPD was 29% in both males and females. The OPTIMIZE-HF registry had similar rates of smoking according to gender (21% males, 12 % females) with a slightly lower prevalence of COPD in females (29% vs 26%). The EuroHeart Failure Survey II (EHFS II) demonstrated higher rates of smoking in males (20%) vs females (7%) and higher rates of COPD (22% vs 15% in females).

The prevalence of COPD has decreased much more in men than in women in recent decades, a finding which has been attributed to trends in smoking patterns but is also thought to reflect women's greater susceptibility to the effects of smoking[93]. Exact mechanisms for this are not understood, and hypotheses include that women have smaller airways leading to greater per cigarette exposure, differential metabolism of tobacco products and potentially also that a decrease in oestogen in women smokers may exacerbate pulmonary disease[94]. There also may be under-diagnosis of COPD in women due in part to a distinct clinical presentation compared with men. Women are less likely to present with phlegm and more likely to present with dyspnoea[93]. One study surveying physicians found that they were less likely to give a diagnosis of COPD to a hypothetical female than male patient with the

same presenting symptoms[95]. Diagnosing COPD in the HF population may be particularly complex given the overlap of symptoms and risk factors. This is especially true in decompensated HF as pulmonary venous congestion affects pulmonary function tests. In addition, the diagnosis of COPD is often particularly difficult in HF with preserved EF, a HF phenotype which is more common in women. A recent report assessing comorbidities in COPD showed a higher prevalence of HF in women[96].

Although COPD is a common comorbidity to HF, it is not always assessed and evaluated by pulmonary function tests. COPD negatively impacts on HF prognosis. The current literature points to male predominance in the prevalence of COPD comorbid to HF. A clinical challenge is the overlap in symptoms from HF and COPD, and further, the fact that pulmonary function tests are often unreliable in patients with decompensated HF. Drug interactions are another clinical problem: beta-blockers in HF have the potential to increase airway obstruction; in particular non-selective ones[97]. Despite proven efficacy, HF patients with COPD are therefore less likely to be prescribed beta-blockers. Conversely, beta-adrenergic agents and corticosteroids for COPD may lead to tachyarrhythmia and fluid retention[98]. Whether gender differences exist for the occurrence and severity of these important drug interactions should be the subject of future research.

Depression

Depression is a common comorbid condition, and often under-recognised in the HF population as symptoms can overlap with those of HF[34, 99-105]. Depression is an independent predictor of poor outcomes in HF patients, including death and HF hospitalisation[99-102]. It is also recognised as an independent risk factor for CAD with the same weight as smoking, hypertension and hyperlipidaemia[106], and depression and HF share several biological mechanisms, including neurohormonal activation and increased inflammatory markers[107].

As with women in the general population, women with HF have a higher burden of depression than men[108]. A meta-analysis examining depression in HF found 16 studies in which gender differences were recorded, and demonstrated that the prevalence in women was 32.7% compared with 26.1% in men, which was 2-3 times the rate of the general population[99]. Prevalence estimates varied widely in this study, from 11-67% in women, and 7-63% in men depending on how depression was

defined and which investigative tool used[99]. Depressive symptoms may not be routinely assessed in HF patients, and registries and RCTs have only infrequently included details on comorbid depression (see table)[17, 31, 34]. In the OPTIMIZE-HF registry of over 48,000 patients with ADHF, only 12.3% of women and 8.8% of men had depression. A recent study examined the gender differences in comorbid conditions in HF in Olmsted County, Minnesota, using a records linkage system which allowed virtually complete capture of health care utilisation and outcomes in residents[29]. This study found higher rates of depression in women than men, and in both men and women, higher rates in HFpEF than HFrEF.

Overall, depression is a common condition in HF and exhibits a higher prevalence in women than men in most studies. Depression is a predictor of poor outcome in HF; moreover, depression severely and directly affects physical, mental and emotional wellbeing. In HF subjects, depression could potentially increase non-adherence to medication and other aspects of HF management[109] . In light of the gender disparity in prevalence, comorbid depression overall may exert greater detrimental effects in women with HF than men. Therefore, the lack of systematic gender-specific assessment of depression and the paucity of published gender-specifc analyses is striking and calls for dedicated assessment in future work.

Other non-cardiac comorbidities

Thyroid disease is common in HF, and both abnormally low and abnormally high thyroid function may increase HF event rates[110-113]. Thyroid hormone has fundamental effects on CV homeostasis[114, 115]. The reported prevalence of abnormal thyroid function in women is at least twice that of men with HF. In women, abnormal thyroid function was reported at around 20% and 11% in OPTIMIZE-HF and EHFS II respectively, contrary to less than 10% in men in both studies (table 1)[17, 19, 32]. Different definitions of comorbid thyroid disease may explain differences in the overall prevalence between studies.

Peripheral artery disease has been shown to predict adverse outcomes in acute myocardial infarction complicated with HF, reduced EF or both[116]. In HF, peripheral artery disease is another highly prevalent comorbidity, and exhibits male preponderance which may be due to the markedly higher percentage of male smokers within the same studies (table 1)[16, 17, 19, 27, 34].

The literature on gender differences of liver disease, obesity, hyperlipidemia, cognitive impairment, malignancies, mental disorders and others comorbid to HF is limited and these comorbidities are not further discussed here.

Summary and conclusion

Despite some reported gender-differences in the prevalence of non-cardiovascular comorbidities in HF, our understanding of non-cardiovascular comorbidities in HF remains incomplete. Women with HF are older and more likely than men to have comorbid hypertension, diabetes, renal failure, obesity, depression and more severe symptoms, but appear to have better overall survival. Men with HF are more often smokers and tend to have more ischemic heart disease, COPD and HF with reduced EF compared with women.

In HF clinical trials, women have traditionally been underrepresented, and interpretation of comorbidities is frequently obscured by non-uniform definitions, lack of pre-specified gender-stratification, and lack of long-term follow-up. Registries and administrative data from healthcare providers generally report higher prevalence values for comorbidities, and contrast with prospective randomized studies in the gender-specific distribution of comorbidities and their association with outcome.

There is uncertainty as to whether gender-differences exist in adherence to guideline-directed pharmacological treatment of HF as well as that of comorbidities, and whether such differences are of prognostic relevance.

Temporal changes in epidemiology suggest an increasing incidence of HFpEF compared to HFrEF, higher comorbidity burden and female predominance with the aging of HF cohorts[4, 10, 29, 117].

Combined efforts from regulators, trialists, health authorities and registry administrators are required to adequately fill our knowledge gap on gender-specific differences in epidemiology, pathogenesis, therapeutic management and prognostic significance of comorbidities in HF. There is an unmet need and a great opportunity for clinicians to assess whether gender-related differences in comorbidities of HF require specific management strategies.

Conflicts of interest

Comment [KHHSSU8]: Please complete and submit the separate disclosure form .pdf for each author

Robert Mentz receives research support from the NIH, Amgen, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Novartis, Otsuka, and ResMed; honoraria from HeartWare, Janssen, Luitpold Pharmaceuticals, Novartis, ResMed, and Thoratec; and has served on an advisory board for Luitpold Pharmaceuticals, Inc.

Thomas von Lueder has received research support from the South-Eastern Norwegian Health Authority, honoraria from Novartis and has served on advisory boards for Vifor and Novartis.

Ingrid Hopper, Dipak Kotecha, and Ken Lee Chin report no conflicts of interest.

Human and Animal Rights and Informed Consent

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This article does not contain any studies with human or animal subjects performed by any of the authors.

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Table 1. Comorbidities and demographics at baseline according to gender in important HF studies

Comment [KHHSSU10]: Due to size of Table, it may be easier to convert and relabel as a figure

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*of importance
*of major importance
(Bullet important references published in the past 3 years and provide 1 sentence annotations to explain their importance)

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