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Adverse Drug Reactions to Guideline-Recommended Heart Failure Drugs in Women

A Systematic Review of the Literature

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ABSTRACT

OBJECTIVES This study sought to summarize all available evidence on sex differences in adverse drug reactions (ADRs) to heart failure (HF) medication.

BACKGROUND Women are more likely to experience ADRs than men, and these reactions may negatively affect women's immediate and long-term health. HF in particular is associated with increased ADR risk because of the high number of comorbidities and older age. However, little is known about ADRs in women with HF who are treated with guideline-recommended drugs.

METHODS A systematic search of PubMed and EMBASE was performed to collect all available information on ADRs to angiotensin-converting enzyme inhibitors, β-blockers, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, ivabradine, and digoxin in both women and men with HF.

RESULTS The search identified 155 eligible records, of which only 11 (7%) reported ADR data for women and men separately. Sex-stratified reporting of ADRs did not increase over the last decades. Six of the 11 studies did not report sex differences. Three studies reported a higher risk of angiotensin-converting enzyme inhibitor–related ADRs in women, 1 study showed higher digoxin-related mortality risk for women, and 1 study reported a higher risk of mineralocorticoid receptor antagonist–related ADRs in men. No sex differences in ADRs were reported for angiotensin II receptor blockers and β-blockers. Sex-stratified data were not available for ivabradine.

CONCLUSIONS These results underline the scarcity of ADR data stratified by sex. The study investigators call for a change in standard scientific practice toward reporting of ADR data for women and men separately. (J Am Coll Cardiol HF 2019;7:258–66) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Women have an approximately 1.5 times higher risk of developing adverse drug reactions (ADRs) than men (1,2). They are not only at a higher risk of hospitalization because of the severity of their ADRs but are also more likely to discontinue their treatment and thereby lose its potential benefit (1-4). A precise assessment of sex-specific ADRs is complicated by the rare reporting of such events in younger, predominantly male clinical trial groups with few comorbidities (5-7), as well as the lack of women in phase I clinical trials that collect data on tolerability and dose-related ADRs (8). As a result, it is unclear which ADRs to look for during post-marketing surveillance, a system that itself is also limited by high rates of underreporting and reporting bias (9).

The lack of sex-specific ADR data is especially pertinent in heart failure (HF) because of the high prevalence of comorbidities (10) and polypharmacy in these patients (11). Women with HF are less likely to receive guideline-recommended treatment (12,13), possibly because of an increased risk for certain ADRs (14). Given the under-representation of women in all phases of clinical trials, little is known about female-specific ADRs in patients with HF who are treated with guideline-recommended drugs. To expand on an earlier effort evaluating sex-specific reporting in clinical trials (15), we performed a systematic review to identify sex-specific ADRs to guideline-recommended HF drugs.

METHODS

SEARCH STRATEGY AND SELECTION CRITERIA. We combined search results from PubMed Medline and the EMBASE database. Both databases were searched on February 20, 2018 using a pre-defined search strategy consisting of both text words and MeSH headings. The text words were limited to title and abstract only. We used the terms *female, women, male, men, sex, gender* for the sex-specific part of the search strategy; the terms *heart failure, heart decompensation, cardiac decompensation* for the HF domain; and the terms *drug-related side effects and adverse reactions, side effect, adverse effect* for the ADR component. We specifically excluded chemotherapy-induced HF and studies in children. We included all ejection fractions. The search was updated on October 18, 2018.

Guideline-recommended HF drugs were based on the 2016 HF treatment guidelines from the European Society of Cardiology (16). There are 5 groups of HF drugs: angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and ivabradine (16). We added digoxin because of its suggested harmful effects in women (1).

Only original research articles written in English or Dutch were considered for inclusion. Records were included if they mentioned any sex-specific ADRs related to 1 of the recommended HF drugs. We excluded studies with study groups too small for sex-stratified analyses (n = <50), where the primary study group was not HF specific or had reduced left ventricular function secondary to a recent myocardial infarction. We excluded studies where the results could not be linked back to 1 specific drug or where the drug was administered intravenously. We excluded studies where the drug was administered only once to evaluate first-dose effects. Finally, we excluded all studies for which the full text could not be retrieved.

For all included studies, the population size, the percentage of women and mean age of the study group, the description of the ADR type(s) reported, and the sex-specific ADR results were extracted. Meta-analysis of the results was not possible because of heterogeneity. The data are presented separately for each of the 5 drug categories.

RESULTS

The search returned 9,424 unique articles, 356 of which were eligible for full-text screening. Most of these studies were excluded because of the lack of sex-specific data (n = 144, 40%) or because the study design did not match our search criteria (n = 96, 27%). Of the remaining articles (n = 116), 25 did not provide ADR data, 19 were written in a different language, 13 were duplicates, and for 48 the full text could not be located. Eleven articles met the inclusion criteria and were included in the analyses (**Figure 1**). The articles were distributed relatively equally across the 3 decades in which they were published and showed no upward trend in sex-specific ADR reporting over time (**Figure 2**).

Importantly, these 11 studies comprised only 7% of the 155 studies that reported ADR data. The 11 studies included 153,945 individuals with a mean age of 64 years (52 to 75 years) and included on average 25% women (13% to 49%), similar to the 144 excluded studies (29%). Four studies (36%) reported more ADRs in women compared with men, whereas 1 study (9%) reported more ADRs in men. The remaining 6 studies (55%) reported no difference in ADRs between the sexes. Six studies were post hoc analyses

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ADR = adverse drug reaction

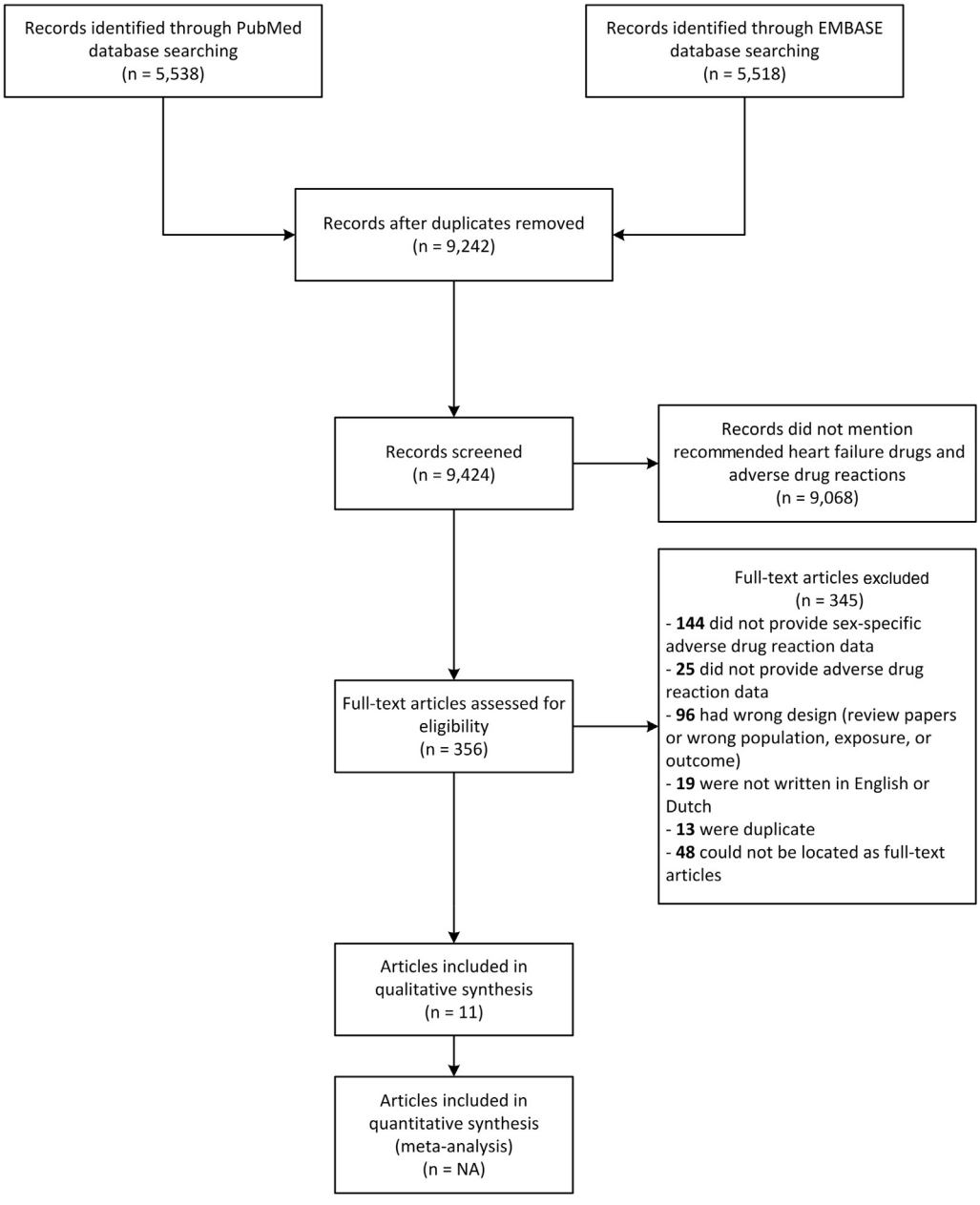
ARB = angiotensin II receptor blocker

HF = heart failure

MRA = mineralocorticoid receptor antagonist

QOL = quality of life

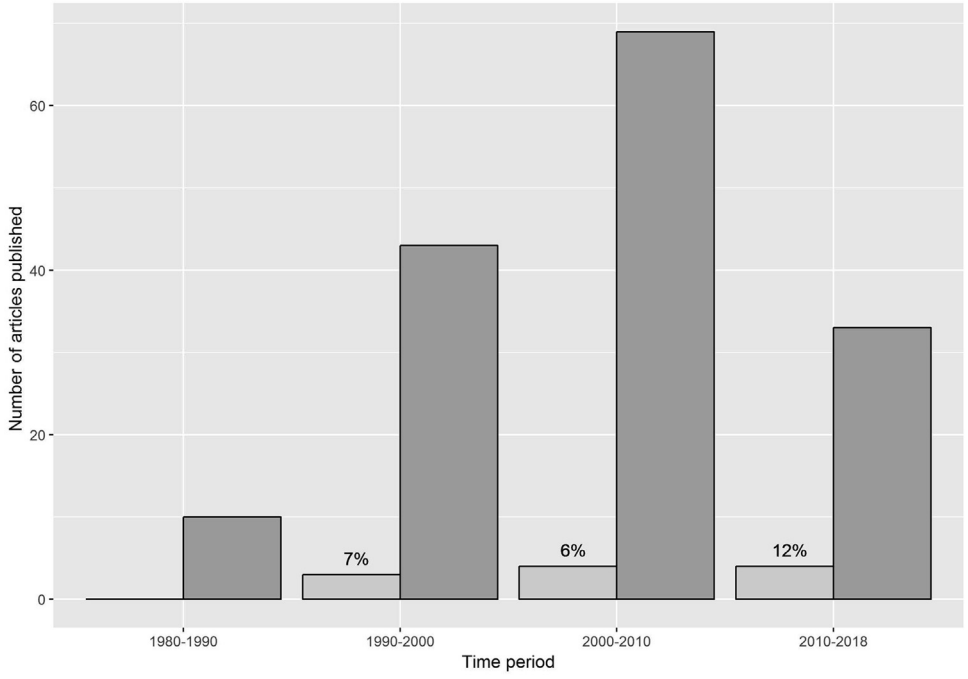
FIGURE 1 Overview of the Systematic Search Process



PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram depicting the flow of information through the different phases of a systematic review. It shows the number of records identified in the original search, the number of records included and excluded in the screening process, and the reasons for exclusion during the full-text screening phase.

from randomized clinical trials, 2 used data from health care insurance claims databases, and the remaining 3 used patient cohorts from HF clinics (Table 1). The availability of sex-specific ADR data varied across the different drug categories. Two of 7 digoxin studies reported sex-specific data (28.6%), and this decreased to 1 in 8 for ACE inhibitors (5 of 40, 12.5%) and even lower fractions for the other drugs. Sex-specific data were unavailable for ivabradine (Table 1).

FIGURE 2 Sex-Specific ADR Reporting Across the Past 4 Decades



The total number of articles that reported adverse drug reaction (ADR) data **(dark gray)** and the number of articles that reported sex-specific adverse drug reaction data **(light gray).** The articles have been divided by decade of publication. The percentage of sex-specific adverse drug reaction papers of all adverse drug reaction papers published that period are presented on **top of the light gray bars**.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS. There were 40 articles with ADR data for ACE inhibitors, 5 of which contained sex-specific ADR data (**Table 1**). These 5 studies enrolled 137,956 patients with a mean age of 63 years (60 to 75 years) and on average 26% women. The BIOSTAT-CHF (Systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure) study looked at 3 different HF drugs, including ACE inhibitors, bringing the total number of ACE inhibitor studies to 6 (**Table 1**).

Data from an American claims database showed that the incidence of angioedema was 5.16 (3.37 to 7.92) per 1,000 person-years in women who initiated ACE inhibitor treatment compared with 2.32 (1.48 to 3.64) per 1,000 person-years in men (17). Similarly, 2 post hoc analyses of the SOLVD (Studies Of Left Ventricular Dysfunction) reported more ADRs in women than in men (18,19). The difference was especially pronounced for cough, which was almost 2.5 times more prevalent in women compared with men (18). However, this difference was not found in a Japanese hospital-based study, where the percentage of cough-related ADRs was similar between men and women (20). A third post hoc analysis of the SOLVD trial showed that a similar percentage of men and women experienced at least 1 episode of anemia during enalapril treatment (38% vs. 41%) (21). Similarly, a post hoc analysis of the BIOSTAT-CHF study found no significant difference in the number of men and women who failed to reach the target dose of ACE inhibitor or ARB as a result of ADRs (25% vs. 27%) (22).

ANGIOTENSIN II RECEPTOR BLOCKERS. The search returned 23 articles with ADR data for ARBs, of which 1 contained sex-specific ADR data (**Table 1**). The BIOSTAT-CHF study also evaluated ARBs, bringing the total number of sex-specific ARB studies to 2. A post hoc analysis of the HEAAL (Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan) study, which enrolled 3,834 participants with a mean age of 67 years and 29% women, reported that there were no significant differences in risk of kidney impairment, hyperkalemia, or hypotension between men and women treated with losartan (23) (**Table 1**). As mentioned earlier, a similar percentage of men and women failed to reach the target dose of ARB or ACE inhibitors in the BIOSTAT-CHF study (22).

TABLE 1 Characteristics of All Studies Reporting Sex-Specific Adverse Drug Reaction Data per Drug Class

Drug Class	Number of Studies Reporting ADR Data	Studies Reporting Sex-Specific ADR Data (Ref. #)	Total Study Population (% Women) (Ref. #)	Mean Age, yrs	Number of Studies Reporting More ADRs in Women/Men	Number of Studies Reporting No Sex Difference in ADRs	Number of Studies per Design Type: Clinical Trial, Cohort, Claims Database	Description of ADRs Reported (Number of Studies)
ACE inhibitor	40	5 (12.5) (17–21)	137,956 (27)	63 (60–75)	3 (w)	2	3 (ct), 1 (ch), 1 (cd)	Cough (3), angioedema (1), anemia (1)
ARB	23	1 (4.3) (23)	3,834 (30)	67		1	1 (ct)	Kidney impairment, hyperkalemia, hypotension
BB	45	1 (2.2) (24)	230 (13)	52		1	1 (ch)	Fatal and nonfatal ADRs
Digoxin	7	2 (28.6) (25,26)	9,691 (29)	67 (65–69.5)	1 (w)	1	1 (ct), 1 (cd)	Death, hospitalization
MRA	18	1 (5.6) (27)	134 (32)	66	1 (m)		1 (ch)	Discontinuation of treatment due to ADRs
Ivabradine	3	0 (0.0)						
Combination of drugs	19	1 (5.3) (22)	2,100 (25)	68		1	1 (ct)	Failure to reach target dose due to ADRs
Total	155	11 (7.1)	153,945 (26)	64 (52–75)	4 (w) / 1 (m)	6	6 (ct), 3 (ch), 2 (cd)	

Values are n, n (%), or mean (interquartile range).

ACE = angiotensin-converting enzyme; ADR = adverse drug reaction; ARB = angiotensin II receptor inhibitor; BB = β-blocker; cd = claims database; ch = cohort; ct = clinical trial; m = men; MRA = mineralocorticoid receptor antagonist; w = women.

β-BLOCKERS. In total, 45 articles provided ADR data for β-blockers, and 1 of these articles reported sex-specific ADR data (Table 1). The BIOSTAT-CHF study included an evaluation of β-blockers, bringing the total number of β-blocker studies to 2. A study from an HF clinic in Australia, which included 230 patients with HF with a mean age of 52 years and 13% women, reported that men and women treated with carvedilol reported similar numbers of ADRs (12% vs. 10%, respectively) (24). Data from the BIOSTAT-CHF study suggest that a similar percentage of men and women failed to reach target dose as a result of ADRs (20% vs. 22%, respectively) (22).

DIGITALIS GLYCOSIDES. There were 7 articles with ADR data for digoxin, of which 2 evaluated the effects of sex (Table 1). Together these 2 studies included 9,691 patients with a mean age of 67 years (65 to 70 years) and on average 28% women (Table 1). A post hoc analysis of the DIG (Digitalis Intervention Group) study data suggested that women treated with digoxin had an approximately 20% higher risk of death compared with the placebo group (hazard ratio: 1.23; 95% confidence interval: 1.02 to 1.47), although this difference was not seen for men (hazard ratio: 0.93; 95% confidence interval: −0.85 to 1.02) (25). This sex difference was not present in data from an American claims cohort, where the risk for death and hospitalization was similar for men and women (26).

MINERALOCORTICOID RECEPTOR ANTAGONISTS. The search returned 18 articles with ADR data for MRAs, 1 of which reported sex-specific ADR data (Table 1). This study enrolled 134 patients with HF with a mean age of 66 years and 31% women. The patients were followed up for discontinuation of treatment because of hyperkalemia, deterioration of renal function on the basis of serum creatinine, and gynecomastia in men. These investigators found that 16% of the women treated with spironolactone withdrew from treatment because of ADRs compared with 28% of the men (27).

IVABRADINE. In total, 3 studies provided ADR data for ivabradine, of which none reported sex-specific results (Table 1).

DISCUSSION

We show a general lack of information about sex-specific ADRs for guideline-recommended HF drugs. Of the 155 ADR records returned by the search, only 11 (7%) provided sex-specific ADR data. The majority of these 11 studies (55%) reported no sex differences in ADRs. Women may have more ADRs related to ACE inhibitors and digoxin, whereas men may experience more ADRs related to MRAs. However, the low number of studies and participants in some studies make it difficult to draw solid conclusions.

LACK OF SEX-SPECIFIC DATA. We show that the lack of sex-specific ADR data is widespread in observational studies. Only 7% of all available studies, spanning a large range of study group sizes and publication years, reported sex-specific ADR results. In line with the limited effect of efforts to increase the participation of women in cardiovascular trials (28), there was no upward trend in sex-specific reporting over time. We therefore argue that sex-specific reporting should receive attention separately from

the proportionate representation of women, even though these problems are connected.

Sex-specific data reporting should be regarded as standard practice instead of a statistical power-dependent subgroup analysis. Reporting data for women and men separately reflects proper scientific conduct to support future meta-analyses. In situations where data are scarce, even the smallest studies can contribute, an argument also made for dementia trials (29).

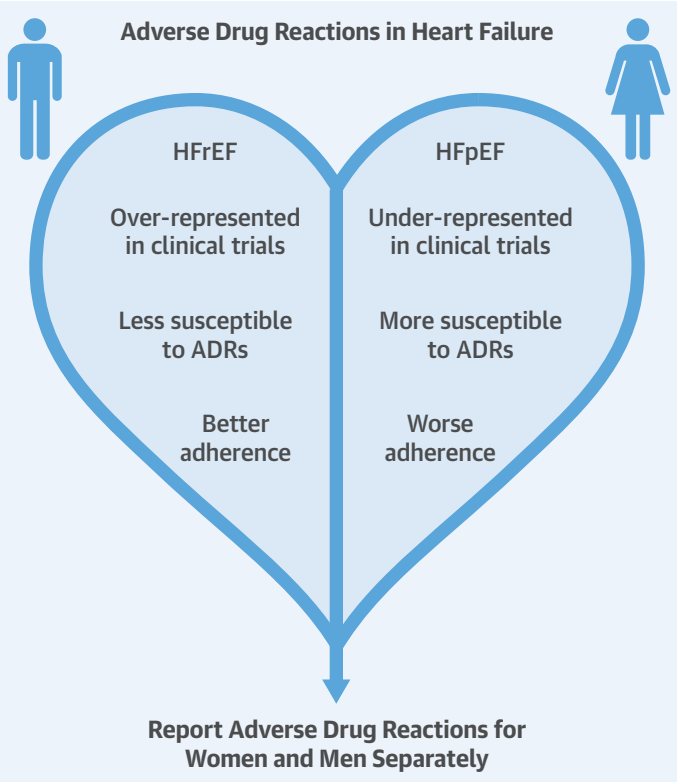
UNDER-REPRESENTATION. The persistent under-representation of women in clinical trials (6,28,30–32) calls for a new approach to address the lack of female-specific data (**Central Illustration**). ADRs that may be relatively common in women become too rare to be detected in a clinical trial population with only few women, thereby creating an evidence gap. In addition, the lack of sex-stratified data hinders the identification of sex-specific ADR trends. Observational studies have the unique potential to fill this evidence gap because they include more women and are thus able to stratify their results by sex. Early-stage safety and dose-finding trials should also be included in this effort because they have the opportunity to detect sex differences early on without the need to conduct large-scale studies. Observations from these studies can lead to interesting insights (14) that can inform health care professionals and treatment guidelines on optimal treatment for both sexes until sufficient clinical trials with a proportionate amount of women and sex-stratified ADR data have been conducted.

SUSCEPTIBILITY TO ADVERSE DRUG REACTIONS. Patients with HF often also have 5 or more comorbidities and take on average 10 different medications (11,33,34). Women more often have HF with preserved ejection fraction than men (**Central Illustration**), a subtype characterized by additional comorbidities and older age compared with other HF subtypes (10,33). In addition, women seem to use more medications than men (4,35). These factors increase the risk for drug-drug interaction ADRs in women with HF, which is indeed 1 of the 3 driving factors behind sex differences in ADR reporting (2) (**Central Illustration**). The other 2 are sex differences in pharmacokinetics and pharmacodynamics (2), of which differences in distribution volume, hepatic and renal clearance, and sex hormones seem to be the key players. The biological processes underlying these differences have been discussed in detail elsewhere (36,37).

ADHERENCE AND QUALITY OF LIFE. Interestingly, women with HF with preserved ejection fraction report a poorer quality of life (QOL) than men regardless of disease severity (38,39). Women report lower QOL as a result of worsening symptoms or decreased physical functioning and overall health, among others (40). This lower QOL may be induced by ADRs directly or indirectly by poor adherence, the latter view supported by the observations that QOL is positively related with adherence (41) and that women are more likely to be poor adherers (42). However, much is still unclear about sex differences in QOL (40), and further research is needed to evaluate sex-specific effects of ADRs on QOL properly.

SEX DIFFERENCES IN ADVERSE DRUG REACTIONS. Three of the 6 ACE inhibitor articles included in our review suggested that women were more likely to experience ACE inhibitor–induced ADRs, whereas the other 3 showed no sex differences. The higher incidence of ACE inhibitor–induced cough in women has been observed previously (43–45). In addition, ARBs

CENTRAL ILLUSTRATION Underlying Sex Differences in Heart Failure That Necessitate Sex-Specific Reporting



Bots, S.H. et al. J Am Coll Cardiol HF. 2019;7(3):258–66.

This figure summarizes the underlying sex differences in heart failure that support the need to report adverse drug reactions (ADRs) for women and men separately. HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

seem to have better efficacy and adherence profiles than ACE inhibitors in women with congestive HF but not in men (14). Women may thus be at higher risk of ACE inhibitor-induced ADRs, which negatively affects their adherence and treatment benefit, but more data are needed to draw a solid conclusion. The small Japanese study identified by our search reported no sex differences in ACE inhibitor-induced ADRs, whereas other studies suggest these ADRs to be more prevalent among Asian populations (46,47). This finding may be explained by the small study size in combination with the small number of reported ADRs (n = 37, 19 women), or the sex difference may be masked by the higher ADR prevalence. Regarding angioedema the results are less clear, with some previous studies showing a higher incidence in women (48) and others showing no sex differences (49). Additional data on angioedema may lead to more insight into this matter.

We did not find evidence for sex differences in ADRs for ARBs and β-blockers. Our results on digoxin are contradictory because the higher risk of hospitalization and death in women related to digoxin treatment observed in a post hoc analysis from the DIG trial was not observed in a large cohort. Similarly, data from a British cohort study did not observe any sex differences in the risk of all-cause mortality in patients treated with digoxin (50), and there is some evidence that digoxin is equally beneficial in both men and women at low blood concentrations (51). Scientific evidence claiming no sex differences may outweigh the evidence that suggests the presence of sex differences in digoxin-related ADRs. More data are needed to support this claim.

The only MRA article returned by our search showed a higher number of spironolactone-related ADRs in men than women. Spironolactone is known to induce gynecomastia (52) and hyperkalemia, which occur more frequently in men than women (53). This could explain why men more often withdrew from MRA treatment than women, but additional data may shed more light on the issue.

STUDY LIMITATIONS. This systematic review combines all available knowledge on sex-specific ADRs for guideline-recommended HF drugs. Because of the lack of data and heterogeneity of the available data, however, the results could not be meta-analyzed. The definition of HF was not identical across included studies, possibly leading to some misclassification in individual studies. As a result, we were unable to split our result by HF subtype. We excluded diuretic agents and sacubitril-valsartan from our search because the first agents are used only to treat symptoms and the second drugs were discovered too recently for sex-specific post hoc studies to be published but should be included in future efforts. The low number of returned studies obliges us to interpret our results with care. We were unable to discuss sex-specific ADRs for ivabradine because of the lack of data. However, the scarcity of data in itself is an important finding that hopefully inspires future researchers to sex-stratify their results.

CONCLUSIONS

The scarcity of sex-specific ADR data for guideline-recommended HF drugs data hampers the identification of female-specific ADRs. The currently available evidence hints at the existence of sex-specific ADRs but remains inconclusive given the scarcity of data. Sex-specific ADR reporting in articles has not increased over the past 3 decades. A call to action is needed to incorporate sex-specific reporting into scientific practice.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study suggests that women may experience different ADRs than men when treated with the same HF drugs. However, given the scarcity of data, this conclusion should be interpreted with care. We hope these results will stimulate clinicians to consider the sex of their patients when they prescribe HF drugs and that they will report sex-specific data in their own scientific work.

TRANSLATIONAL OUTLOOK: The identification and scientific evaluation of ADRs caused by HF medications used in the clinic require large amounts of sex-specific data, which are currently not available. We believe that observational studies can play a large role in filling this evidence gap. Viewing sex-stratified reporting as an example of good scientific conduct instead of a power-driven subgroup analysis will aid the discovery of sex-specific ADRs to HF drugs. In turn, this will help clinicians to make more informed decisions when prescribing HF drugs.

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