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PERSPECTIVE

Recommended Heart Failure Medications and Adverse Drug Reactions in Women

Call for Sex-Specific Data Reporting

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Women treated with guideline-recommended cardiovascular medications experience more adverse drug reactions (ADRs) than men.[1] These women are not only at higher risk of hospitalization but may also discontinue their medications as a result of some of the adverse reactions, thus losing the potential benefit.[2] The safety of cardiovascular medications is evaluated both in clinical trials and through postmarketing surveillance. The latter is important because many ADRs rarely occur in clinical trial populations, which are generally younger and healthier than the target population. This is especially true for women, because their systematic underrepresentation in cardiovascular trials hinders the identification of gender differences in the efficacy and safety of cardiovascular medications. The underrepresentation of women is clearly illustrated in heart failure (HF) trials. Although approximately half of all HF patients are women and ≈60% of these women die from this syndrome, on average only 30% of HF trial populations are women,[3] possibly because of their older age at HF onset. The evaluation of medication safety in women is further hampered by poor inclusion of sex-specific data in trial reports.[3] The increasing prevalence of the women-dominated HF subtype with preserved ejection fraction adds impetus to this issue, as the underlying mechanism of this syndrome appears to exhibit sex differences, and therapies are lacking.[4]

We performed a systematic review of the literature to quantify sex-specific reporting of ADRs of HF medications. HF medications recommended by the 2016 HF guidelines from the European Society of Cardiology[4] were grouped into 5 groups: angiotensin-converting enzyme inhibitors, β-blockers, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, and ivabradine.[4] Digoxin was included because of its suggested harmful effects in women.[1]

First, all clinical trials cited in the European Society of Cardiology 2016 HF guidelines were extracted. Second, a systematic search of the website clinicaltrials.gov was performed on November 11, 2017. The search strategy included "heart failure" and the intervention options "ACE inhibitor," "beta blocker," "mineralocorticoid receptor antagonists," "digoxin," "ivabradine," and "angiotensin II receptor blocker." Records were excluded in the following instances:

1. The study was ongoing, had been withdrawn or terminated, or had no published report available.
2. The intervention was not part of 1 of the 6 drug families mentioned above.
3. The primary study population consisted of patients with comorbidities such as diabetes mellitus, chronic kidney disease, pulmonary hypertension, cancer, or Chagas disease.
4. The outcome of interest was not (a) the incidence of cardiovascular disease, (b) hospitalization for cardiovascular disease, or (c) (cardiovascular) mortality.

The European Society of Cardiology guidelines cited 15 trials and 2 trial substudies, adding up to 17 trials in total. The systematic search identified 6 additional

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Table. Overview of the Trials Included in the Systematic Review

Drug Class	Drug	Acronym	No.	Women, %	Average Age, y	Sex-Specific Adverse Events	Sex-Specific Efficacy	Inclusion: EF≤40%
ACEI	Enalapril	CONSENSUS	253	29.5	71	No	No	Not mentioned
		SOLVD Treatment	2569	19.7	61	Yes*	No	Yes
		SOLVD Prevention	4228	11.5	59	Yes*	No	Yes
	Lisinopril	ATLAS	3164	20.5	64	No	Yes	Yes
MRA	Eplerenone	EMPHASIS-HF	2747	22.3	69	No	No	Yes
		J-EMPHASIS-HF	221	20.4	69	No	No	Yes
		EPHESUS	6632	29.0	64	No	No	Yes
	Spironolactone	RALES	1663	27.0	65	No	No	Yes
		TOPCAT	3445	51.6	69	No	Yes	No (EF≥45%)
β-Blocker	Bucindolol	BEST	2708	22.0	60	No	No	Yes
	Carvedilol	COPERNICUS	2279	20.5	63	No	No	Yes
		US Carvedilol Heart Failure Study	1094	23.4	58	No	Yes	Yes
	Metoprolol	MERIT-HF	3991	22.5	64	Yes	Yes	Yes
	Nevibilol	SENIORS	2128	36.9	76	No	Yes	Yes
	Bisoprolol	CIBIS II	2647	19.5	61	No	Yes	Yes
ARB	Candesartan	CHARM-Alternative	2028	31.9	67	No	No	Yes
		CHARM-Overall	7599	31.6	66	No	No	No
	Losartan high	HEAAL	3834	29.5	66	No	Yes	Yes
	Valsartan	Val-HeFT	5010	20.1	63	No	No	Yes
Digitalis glycoside	Digoxin	DIG	6800	22.4	63	No	Yes	No (EF≤45%)
If channel inhibitor	Ivabradine	SHIFT	6505	23.5	60	No	Yes	Yes
		BEAUTIFUL	10 917	17.0	65	No	Yes	Yes
		SIGNIFY	19 102	27.6	65	No	Yes	No (EF≥40%)

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ATLAS, Assessment of Treatment With Lisinopril and Survival; BEAUTIFUL, Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction; BEST, Beta-Blocker Evaluation of Survival Trial; CHARM, Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; DIG, Digitalis Intervention Group; EF, ejection fraction; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HEAAL, Heart Failure End Point Evaluation of Angiotensin II Antagonist Losartan; J-EMPHASIS-HF, Japanese EMPHASIS-HF; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MRA, mineralocorticoid receptor antagonist; RALES, Randomized Aldactone Evaluation Study; SENIORS, Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors With Heart Failure; SHIFT, Systolic Heart failure treatment with the If-inhibitor ivabradine Trial; SIGNIFY, Study Assessing the Morbidity-Mortality Benefits of the I_f inhibitor Ivabradine in Patients With Coronary Artery Disease; SOLVD, Studies of Left Ventricular Dysfunction; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; and Val-HeFT, Valsartan Heart Failure Trial.

*Sex-specific adverse drug reaction data were available for the merged data from both SOLVD trials. These 2 trials were thus taken as 1, bringing the total number of studies for the calculation of the prevalence of sex-specific reporting to 22.

trials from the 235 returned records, bringing the final study database to 23 trials. The main publication and any subsequent publications for each of these trials were screened for sex-specific efficacy and safety data. For all trials, data on inclusion and exclusion criteria, efficacy and safety of the medication, total number of participants, percentage of women, and age of the participants were extracted.

In total, the 23 identified trials included 101 564 participants (25% women) with an average age of 65 years (59–76). The mean percentage of women enrolled across all trials was 25.2% (11.5–51.6). Fewer than half of the studies reported sex-specific efficacy data (11/23, 48%), and only 2 studies (9%) presented sex-specific information about ADRs (Table). In the SOLVD trial (Studies of Left Ventricular Dysfunction), the total number of ADRs reported compared with the total number of study participants was larger in women than in men in the enalapril group (35% versus 27%) but similar in the placebo group (18% versus 16%). Women were overall more likely to report ≥1 ADR (26% versus 21%), but this difference was larger in the enalapril group (odds ratio, 1.30) than in the placebo group (odds ratio, 1.15). Cough was reported by 3% of the placebo women and 10% of the women receiving enalapril, compared with 1.8% of the men on placebo

(odds ratio, 1.67) and 4.2% of the men on enalapril (odds ratio, 2.38), respectively. In the MERIT-HF trial (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure), 10% of men permanently stopped the study medication metoprolol because of an ADR compared with 8% of the women. These numbers were 12% and 10%, respectively, for the placebo group. The third largest study by study population and percentage of women (7599, 32%) did not report any sex-specific data, suggesting that insufficient statistical power may not always explain the absence of sex-specific data (Table).

These data show that sex-specific reporting of safety data is rare despite efforts to increase participation of women in cardiovascular trials.[3] The available sex-specific data suggest that women treated with enalapril may experience more ADRs whereas women treated with metoprolol were slightly less likely to permanently stop treatment as a result of ADRs than men. However, results based on 338 events in 1873 women are not sufficient to draw hard conclusions about the safety of these drugs for women. Reporting sex-stratified baseline data may help elucidate other differences between men and women that may explain the incidence of ADRs.

Next to sex-specific reporting, improvements in overall reporting of ADRs are needed. Underreporting and variability in the level of report details are common in current reporting systems, which rely on investigators and clinicians to report events. The quality of ADR reporting in clinical trials is not on par with the overall quality of clinical trial publications,[5] emphasizing the importance of addressing this matter. Potential areas for improvement include stimulating patients and healthcare professionals to more actively report ADRs, the use of comprehensive algorithms for ADR reporting in clinical trials, and in appropriate settings, the use of patient-reported outcome tools designed for ADR reporting.[5]

Although limited inclusion of women and the lack of reporting of sex-specific data may be 2 sides of the same coin and should be dealt with simultaneously, we argue that they should be tackled separately. Increasing the participation of women in clinical trials may not automatically improve sex-stratified reporting. We therefore argue that both proportionate representation of women in HF trials and sex-specific reporting of efficacy and safety data are of paramount importance for improving the quality of HF treatment.

ARTICLE INFORMATION

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