# Adverse Drug Effects Across Patients With Heart Failure: A Systematic Review

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## ABSTRACT

**OBJECTIVES:** To summarize published literature on the incidence of adverse drug effects (ADEs) associated with guideline-directed medical therapy (GDMT) for patients with heart failure with reduced ejection fraction (HFrEF).

**STUDY DESIGN:** Systematic literature review.

**METHODS:** A systematic literature review was conducted in PubMed, Ovid MEDLINE, and Clinical Key covering January 1990 to December 2018. Key search terms were ADEs for β-blockers (BBs), ACE inhibitors (ACEis), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and/or angiotensin receptor-neprilysin inhibitors (ARNis) in adult patients (≥ 18 years) with HFrEF.

**RESULTS:** A total of 279 eligible articles were identified, of which 29 reported drug-related adverse effects and were included in this review. Of the 29 studies, 11 examined BBs; 9, MRAs; 6, ARNis; 2, ACEis; and 1, ARBs. The most common reported ADEs across these therapeutic classes included bradycardia, dizziness, hypotension, hyperkalemia, cough, and renal impairment. The incidence of BB-induced bradycardia was 1% to 52% based on 9 studies, and 6 studies described dizziness as a result of BBs and ARNis (15%-43%). Fourteen studies reported induced hypotension (1.4%-63%); 13 studies, hyperkalemia (0.6%-30.2%); 3 studies, cough (37%-50%); and 4 studies, renal impairment (0.6%-7.6%).

**CONCLUSIONS:** Findings show that drug-related adverse effects are commonly reported in clinical trials and highlight the sizable burden of ADEs with medical therapy across patients with HFrEF. Additional real-world evidence and studies aiming to improve the tolerability of GDMT for patients with HFrEF are warranted.


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Heart failure (HF) is a major epidemic in the United States, with an estimated prevalence of 6.3 million adults (≥20 years) from 2013 to 2016.[1,2] In the United States, the prevalence of HF is expected to increase by 46% from 2012 to 2030.[3] HF with reduced ejection fraction (HFrEF) is a common type of HF defined as having an ejection fraction of 40% or less.[4] Based on data from the Get With The Guidelines – Heart Failure initiative, linked with Medicare claims (2005-2009), the incidence of HFrEF in 39,982 US patients admitted for HF to 254 hospitals was 46%.[5] The rates of rehospitalization for HF in the United States are high despite currently available therapies, with 30% of patients being readmitted 60 to 90 days post discharge.[6]



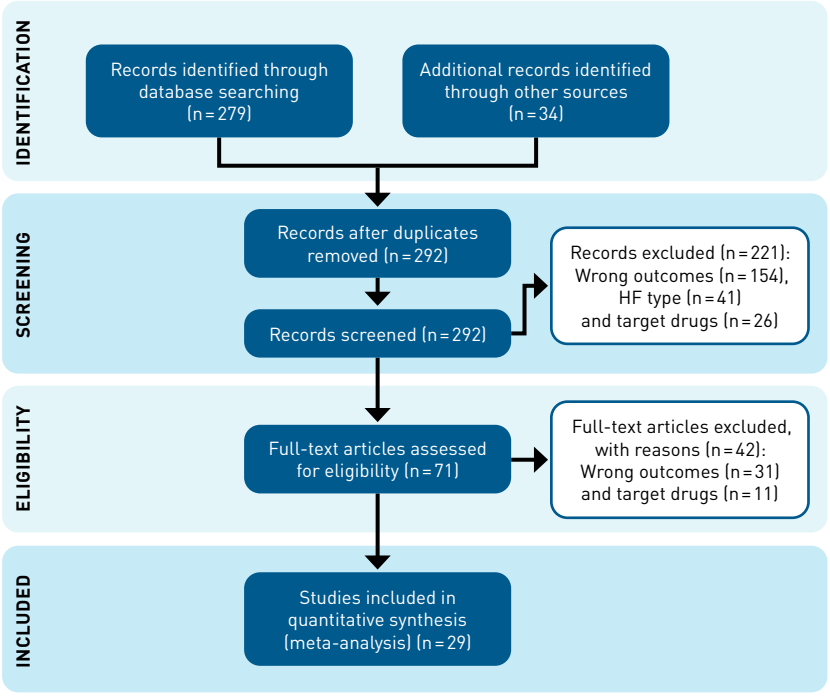
Per the 2017 update to the American College of Cardiology/American Heart Association guidelines, indicated medical treatment includes angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), β-blockers (BBs), and, most recently, angiotensin receptor-neprilysin inhibitors (ARNis) for all patients with HFrEF. The guidelines also highlight common cardiovascular adverse drug effects (ADEs), including bradycardia, dizziness, hypotension, hyperkalemia, cough, and renal impairment. Guideline-directed medical therapy (GDMT) has been shown to reduce all-cause mortality for patients with HFrEF through titration to maximum tolerated doses; however, not all patients achieve these high doses in clinical practice, in part because of ADEs.[7,8] In fact, less than 50% of patients with HFrEF reach the target dose of most GDMTs, including at discharge or in the outpatient setting.[7]

A negative contributor to drug management is patient and physician perception of ADEs.[9] Concerns about ADEs at higher doses may deter physicians from prescribing, which makes the recommended strategy problematic. Patients with HFrEF with comorbidities such as renal insufficiency and hyperkalemia are less likely to receive target doses of GDMT or may even receive none at all. Gaps in evidence include information on which ADEs have reliable evidence of induction by specific HF drugs. The ability to identify incidence of patients reporting a listed ADE that is genuinely drug related is critical, yet it is limited in the medical literature.[9] Although individual HF trials have reported ADEs, only a limited number of studies have combined

## TAKEAWAY POINTS

- Drug-related adverse effects from β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and angiotensin receptor-neprilysin inhibitors are very common in patients with heart failure who have reduced ejection fraction.
- The most common adverse drug effects (ADEs) include bradycardia, dizziness, hypotension, hyperkalemia, cough, and renal impairment.
- There is a sizable burden of these effects across patients with heart failure who have reduced ejection fraction.
- Determining the most common ADEs translates to health outcomes in real-world practice and emphasizes the importance for practitioners and stakeholders to focus on significant cardiovascular ADEs to improve health outcomes.

**FIGURE 1.** PRISMA Flow Diagram




HF, heart failure; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

the available information and reported ADEs for multiple classes of HF drugs in a single review. Because of the limited data available on the ADEs arising from guideline-directed HF therapies, the objective of this study was to summarize existing published literature on the incidence of ADEs for patients with HFrEF.

# METHODS

This systematic literature review followed the Cochrane methodology and was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist.

### Information Sources, Search Strategy, and Study Selection

A systematic literature review of studies of patients with HFrEF comparing standard-of-care HF drugs with placebo or alternative HF drugs was performed. We queried PubMed, Ovid MEDLINE, and Clinical Key and applied the following key search terms: *heart failure with reduced ejection fraction*, *reduced ejection fraction*, *HFrEF*, *adults*, *English*, *pharmacy*, *therapeutics*, and *pharmacology*. Filters were applied to identify studies that were published in English from January 1990 to December 2018 to include a broad range of clinical evidence available for ADEs. Additionally, filters were used to identify studies of adult patients (≥18 years). We included randomized controlled trials, open-label trials, and prospective and retrospective cohort studies. Included studies presented outcomes of ADEs for BBs, ACEis, ARBs, ARNis, and/or MRAs in adult patients with HFrEF. The main ADEs are defined as those most commonly reported in the literature. We excluded editorials, conference reports, systematic literature reviews, manuscript reviews, meta-analyses, and unpublished studies and abstracts. Also excluded were studies including other HF drug classes, articles with low quality ratings based on Cochrane criteria, and those missing information for extraction.

### Data Process

The PRISMA data extraction form was used to extract articles and remove duplicate records. Two authors (M.B. and P.S.) screened studies for relevance based on title and abstract and reviewed the full text of relevant articles for study inclusion. Discrepancies on whether to include specific studies were resolved through formal discussion and consensus between the same 2 authors. The PRISMA checklist was used to validate and assess the quality of all the articles meeting criteria for inclusion in this review. Additionally, we examined the reference lists of all included articles for other relevant references. Articles were excluded from the systematic literature review owing to wrong disease type, wrong drug class, and wrong outcomes. **Figure 1**, the PRISMA flow chart, outlines the data extraction methods. The following information was extracted from each article: author, trial name, year, study design, drug class, sample size, patient population, treatment group, control group, dose, follow-up time, and risk and ranges of ADEs. The articles were grouped according to HF drug class into the following categories: BB, ACEi, ARB, ARNi, and MRA.

**TABLE 1.** Distribution of Study Types Included in Review[10-38]

| Study design | Number of studies | Percentage of studies (%) | References |
|---|---|---|---|
| Randomized controlled trial | 22 | 75.9 | 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 24, 25, 27, 30, 31, 32, 36, 37, 38 |
| Retrospective cohort study | 3 | 10.3 | 23, 26, 35 |
| Post hoc analysis | 3 | 10.3 | 28, 33, 34 |
| Open-label trial | 1 | 3.5 | 29 |
| Drug class | | | |
| BB | 11 | 37.9 | 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 |
| MRA | 9 | 31.0 | 30, 31, 32, 33, 34, 35, 36, 37, 38 |
| ARNi | 6 | 20.7 | 24, 25, 26, 27, 28, 29 |
| ACEi | 2 | 6.9 | 10, 11 |
| ARB | 1 | 3.5 | 12 |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BB, β-blocker; MRA, mineralocorticoid receptor antagonist.

**TABLE 2.** Characteristics of Studies Included in Review[10-38]

| Trial | Year | Sample size | Patient population | Treatment group | Dose | Follow-up (months) |
|---|---|---|---|---|---|---|
| Woo et al[10] | 1995 | 107 | Heart failure | Captopril and enalapril vs control | Captopril 41 ± 27 mg QD<br>Enalapril 16 ± 9 mg QD | Captopril: 16<br>Enalapril: 15 |
| SOLVD[11] | 1991 | 2569 | NYHA II-III, LVEF ≤ 35% | Enalapril vs placebo | 2.5-20 mg QD | 41.4 |
| ELITE[12] | 1997 | 722 | Age ≥ 65 years, NYHA II-IV, LVEF ≤ 40% | Losartan vs captopril | Losartan 50 mg QD<br>Captopril 50 mg TID | 11 |
| BEST[13] | 2001 | 2708 | NYHA III-IV, LVEF ≤ 35% | Bucindolol vs placebo | 3 to 50-100[a] mg BID | 24 |
| COPERNICUS[14] | 2002 | 2289 | NYHA III-IV, LVEF ≤ 25% | Carvedilol vs placebo | 3.125 to 25 mg BID | 10.4 |
| PRECISE[15] | 1996 | 278 | NYHA III-IV, LVEF ≤ 35% | Carvedilol vs placebo | 25 to 50 mg BID | 6 |
| US Carvedilol HF Study Group 1[16] | 1996 | 366 | NYHA III-IV, LVEF ≤ 35% | Carvedilol vs placebo | 12.5 to 25-50 mg BID | 12 |
| Krum et al[17] | 1995 | 49 | NYHA III-IV, LVEF ≤ 35% | Carvedilol vs placebo | 25 mg BID | 3.5 |
| SENIORS[18] | 2005 | 2128 | LVEF ≤ 35% or HF hospitalization | Nebivolol vs placebo | 1.25 to 10 mg QD | 21 |
| MOCHA Study[19] | 1996 | 345 | NYHA II-III, LVEF ≤ 40% | Carvedilol vs placebo | 6.25 mg or 12.5 mg or 25 mg BID | 6 |
| US Carvedilol HF Study Group 2[20] | 1996 | 1094 | NYHA II-IV, LVEF ≤ 35% | Carvedilol vs placebo | 12.5 to 25-50[b] mg BID | 7 |

(*continued*)

# RESULTS

A total of 279 articles were identified in the initial search, 29 of which reported ADEs and were included after full text review.[10-38] Of these, 22 studies (75.9%) included in the review were randomized controlled trials (**Table 1**[10-38]). The majority of the studies evaluated ADEs of BBs (n = 11), with only 1 study evaluating ARBs. **Table 2**[10-38] summarizes the characteristics of studies included in the review. The sample sizes across these studies ranged from 30 to 8399 patients, with a mean follow-up range of 0.7 to 41.4 months. The most commonly reported ADEs across these HF drug classes included bradycardia, dizziness, hypotension, hyperkalemia, cough, and renal impairment (**Figure 2**).

**Table 3**[10-38] outlines the distribution of ADEs in the included studies and their percentage incidence. Nine studies reported bradycardia risk of 1% to 52%, caused by BB usage. Also attributable to BB usage was dizziness risk of 15% to 43%, reported in 6 studies. One other study reported an ARNi (omapatrilat)–induced dizziness risk of 19.4%; however, the clinical development of omapatrilat was discontinued and it is not a marketed drug. Fourteen studies described a high incidence of induced hypotension (1.4%-63%), resulting from treatment with a BB (9 studies), ARNi (4 studies), or ARB (1 study). Hyperkalemia was reported in 13 studies (9 with an MRA, 3 with an ARNi, 1 with an ARB) with a risk of 0.6% to 30.2%. Three studies reported cough risk of 37% to 50%, caused by ACEi (2 studies) or ARB (1 study) usage. Four studies described a high incidence of induced renal impairment (0.6%-7.6%), 3 resulting from ARNi treatment and 1 following treatment with an ARB.

**(CONTINUED ON PAGE e116)**

**TABLE 2.** (*Continued*) Characteristics of Studies Included in Review[10-38]

| Trial | Year | Sample size | Patient population | Treatment group | Dose | Follow-up (months) |
|---|---|---|---|---|---|---|
| Australian-New Zealand Group[21] | 1997 | 415 | LVEF < 45% | Carvedilol vs placebo | 25 mg BID | 19 |
| RESOLVD[22] | 2000 | 426 | LVEF < 40% | Metoprolol CR vs placebo | 12.5-25 to 200 mg QD | 6 |
| Owens et al[23] | 2018 | 225 | Age ≥ 18 years, HF admission, optimal HR control vs suboptimal control | Carvedilol vs metoprolol succinate | Carvedilol 25 mg BID<br>Metoprolol succinate 200 mg QD | 3 |
| PARADIGM HF[24] | 2014 | 8399 | NYHA II-IV, LVEF ≤ 40% | Sacubitril/ valsartan vs enalapril | Sacubitril/valsartan 200 mg BID<br>Enalapril 10 mg BID | 27 |
| OVERTURE[25] | 2002 | 5770 | NYHA II-IV secondary to DCM or non-DCM or LVEF ≤ 30% and HF hospitalization | Omapatrilat vs enalapril | Omapatrilat 40 mg QD<br>Enalapril 10 mg BID | 14.5 |
| Antol et al[26] | 2018 | 200 | Patients who initiated sacubitril/valsartan between August 2015 and March 2016 | Sacubitril/valsartan vs no sacubitril/valsartan | 24 mg/26 mg to 97 mg/103 mg BID | 4 |
| TITRATION[27] | 2016 | 540 | NYHA II-IV, LVEF ≤ 35% | Sacubitril/valsartan conservative arm vs sacubitril/ valsartan condensed arm | Conservative arm: 50 mg for 14 days, 100 mg for 21 days, then 200 mg BID<br>Condensed arm: 100 mg for 2 weeks to 200 mg BID | 2.5 |
| Jhund et al[28] | 2015 | 8399 | NYHA II-IV, LVEF ≤ 40%<br>Age category: < 55, 55-64, 65-74, and ≥ 75 years | Sacubitril/valsartan vs enalapril | Sacubitril/valsartan 200 mg BID<br>Enalapril 10 mg BID | 27 |
| Kobalava et al[29] | 2016 | 30 | NYHA II-IV, LVEF ≤ 40% | Sacubitril/valsartan | Sacubitril/valsartan 100 mg for 7 days and 200 mg for 14 days BID | 0.7 |
| RALES[30] | 1999 | 1663 | NYHA III-IV, LVEF ≤ 35% | Spironolactone vs placebo | 25-50 mg QD | 24 |
| EPHESUS[31] | 2003 | 6632 | AMI, LVEF ≤ 40% | Eplerenone vs placebo | 25-50 mg QD | 16 |
| EMPHASIS-HF[32] | 2011 | 2737 | Age ≥ 55 years, NYHA II, LVEF ≤ 35% | Eplerenone vs placebo | 25-50 mg QD | 21 |
| Eschalier et al[33] | 2013 | 2737 | Age ≥ 75 years, NYHA II, LVEF ≤ 35%, DM, CKD, and SBP < 123 mm Hg | Eplerenone vs placebo | 25-50 mg QD | 21 |
| Vardeny et al[34] | 2012 | 1658 | NYHA III-IV, LVEF ≤ 35%, worsening renal function | Spironolactone vs placebo | 25-50 mg QD | 2.8 |
| Pitt et al[35] | 2006 | 2106 | AMI, LVEF ≤ 30% | Eplerenone vs placebo | 25-50 mg QD | 16 |
| ARTS[36] | 2013 | 458 | LVEF ≤ 30%, CKD | Part 1:<br>BAY 94-8862 vs placebo<br>Part 2:<br>BAY 94-8862 vs BAY 94-8862 vs placebo vs spironolactone | Part 1: BAY 94-8862: 2.5, 5, or 10 mg QD<br>Part 2: BAY 94-8862: 2.5, 5, or 10 mg QD or 5 mg BID or spironolactone 25 mg to 50 mg QD | 1.8 |
| ARTS-HF[37] | 2016 | 1066 | HFrEF, CKD, and/or DM | Finerenone vs eplerenone | Finerenone 2.5, 5, 7.5, 10, or 15 mg QD to 5, 10, 15, 20, or 20 mg QD<br>Eplerenone 25 mg every other day to 25 mg QD on day 30 to 50 mg QD on day 60 for 90 days | 3 |
| ARTS-HF Japan Study Group[38] | 2016 | 72 | HFrEF, CKD, and/or DM | Finerenone vs eplerenone | Finerenone 2.5, 5, 7.5, 10, or 15 mg QD to 5, 10, 15, 20, or 20 mg QD<br>Eplerenone 25 mg every other day to 25 mg QD on day 30 to 50 mg QD on day 60 for 90 days | 3 |

AMI, acute myocardial infarction; BID, twice daily; CKD, chronic kidney disease; CR, controlled release; DCM, dilated cardiomyopathy; DM, diabetes mellitus; HF, heart failure; HFrEF, HF with reduced ejection fraction; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QD, once daily; SBP, systolic blood pressure; TID, 3 times daily.

[a]50 mg BID for patients who weighed less than 74 kg and 100 mg BID for patients who weighed at least 75 kg.

[b]25 mg BID for patients who weighed less than 85 kg and 50 mg BID for patients who weighed at least 85 kg.

**FIGURE 2.** Studies by Adverse Drug Effect

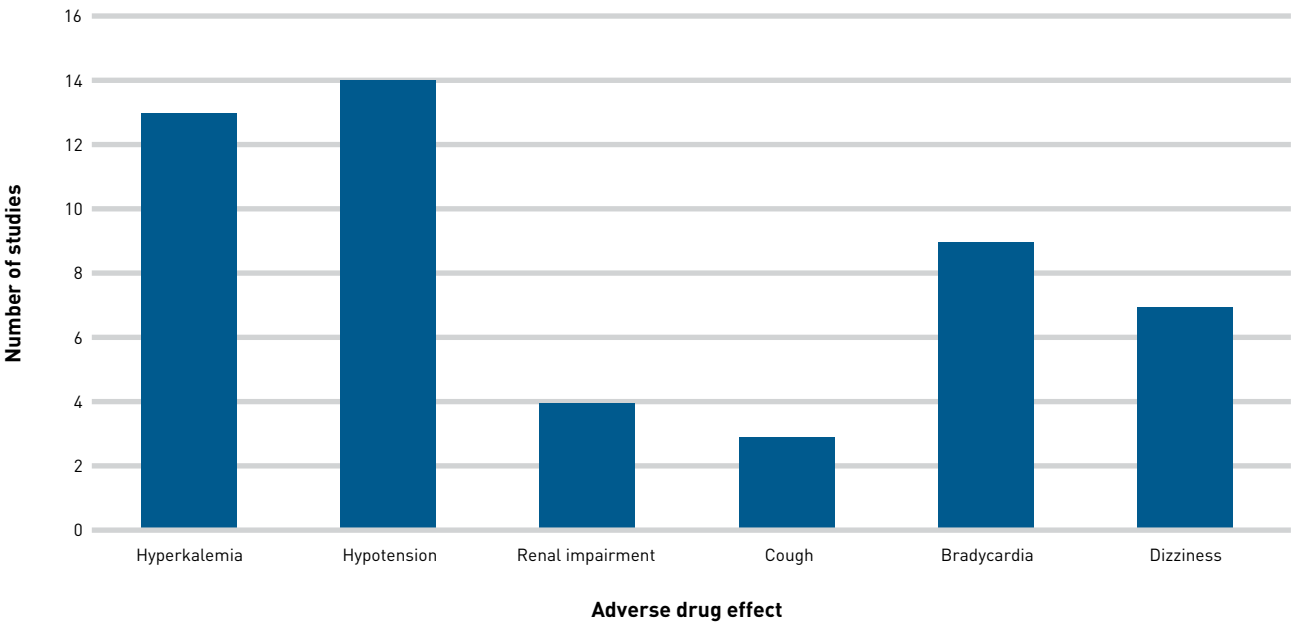



**TABLE 3.** Adverse Drug Effects From Trials[10-38]

| Trial | N | Drug class | Treatment group | Control group | Adverse drug effects (%) | |
|---|---|---|---|---|---|---|
| | | | | | Treatment group | Control group |
| Woo et al[10] | 107 | ACEi | Captopril and enalapril | Control | Cough: 50 and 43.9 | Cough: 12.5 |
| SOLVD[11] | 2569 | ACEi | Enalapril | Placebo | Cough: 37 | Cough: 31 |
| ELITE[12] | 722 | ARB | Losartan | Captopril | Cough: 0<br>Hyperkalemia: 0.6<br>Hypotension: 1.4<br>Renal impairment: 0.8 | Cough: 3.8<br>Hyperkalemia: 1.6<br>Hypotension: 2.3<br>Renal impairment: 1.4 |
| BEST[13] | 2708 | BB | Bucindolol | Placebo | Dizziness: 43<br>Hypotension: 21<br>Bradycardia: 12 | Dizziness: 39<br>Hypotension: 20<br>Bradycardia: 5 |
| COPERNICUS[14] | 2289 | BB | Carvedilol | Placebo | Bradycardia: 1.5<br>Bradycardia hospitalization: 1.6<br>Hypotension: 1.9 | Bradycardia: 1.2<br>Bradycardia hospitalization: 0.8<br>Hypotension: 1.6 |
| PRECISE[15] | 278 | BB | Carvedilol | Placebo | Dizziness: 24<br>Hypotension: 6.2<br>Bradycardia: 5.4 | Dizziness: 11.5<br>Hypotension: 2.2<br>Bradycardia: 0.7 |
| US Carvedilol HF Study Group 1[16] | 366 | BB | Carvedilol | Placebo | Dizziness: 34.9<br>Hypotension: 9.1<br>Bradycardia: 12.9 | Dizziness: 20.1<br>Hypotension: 3<br>Bradycardia: 0.7 |
| Krum et al[17] | 49 | BB | Carvedilol | Placebo | Dizziness: 15 | Dizziness: 1 |
| SENIORS[18] | 2128 | BB | Nebivolol | Placebo | Dizziness: 15.6<br>Hypotension: 7.7<br>Bradycardia: 11.1 | Dizziness: 13.4<br>Hypotension: 7.2<br>Bradycardia: 2.6 |

(*continued*)

**TABLE 3.** (*Continued*) Adverse Drug Effects From Trials[10-38]

| Trial | N | Drug class | Treatment group | Control group | Adverse drug effects (%) | |
|---|---|---|---|---|---|---|
| | | | | | Treatment group | Control group |
| MOCHA Study[19] | 345 | BB | Carvedilol | Placebo | Dizziness: 24-38[a]<br>Hypotension: 6-7[a]<br>Bradycardia: 1-11[a] | Dizziness: 23<br>Hypotension: 5<br>Bradycardia: 1 |
| US Carvedilol HF Study Group 2[20] | 1094 | BB | Carvedilol | Placebo | Bradycardia: 5.7 | Bradycardia: 1.8 |
| Australian-New Zealand Group[21] | 415 | BB | Carvedilol | Placebo | Hypotension: 7.6 | Hypotension: 6.1 |
| RESOLVD[22] | 426 | BB | Metoprolol CR | Placebo | Bradycardia: 4<br>Hypotension: 2.4 | Bradycardia: 0.9<br>Hypotension: 0.9 |
| Owens et al[23] | 225 | BB | Carvedilol and metoprolol succinate (optimal HR control) | Carvedilol and metoprolol succinate (suboptimal HR control) | Bradycardia: 52<br>Hypotension: 63 | Bradycardia: 15<br>Hypotension: 47 |
| PARADIGM HF[24] | 8399 | ARNi | Sacubitril/valsartan | Enalapril | Cough: 11.3<br>Hyperkalemia: 4.3<br>Hypotension: 14.0<br>Symptomatic hypotension: 2.7<br>Renal impairment: 3.3 | Cough: 14.3<br>Hyperkalemia: 5.6<br>Hypotension: 9.2<br>Symptomatic hypotension: 1.4<br>Renal impairment: 4.5 |
| OVERTURE[25] | 5770 | ARNi | Omapatrilat | Enalapril | Hypotension: 19.5<br>Dizziness: 19.4 | Hypotension: 11.5<br>Dizziness: 13.9 |
| Antol et al[26] | 200 | ARNi | Sacubitril/valsartan | No sacubitril/valsartan | Cough: 23.7 | Cough: 21.9 |
| TITRATION[27] | 540 | ARNi | Sacubitril/valsartan Conservative arm | Sacubitril/valsartan Condensed arm | Hyperkalemia: 4.4<br>Hypotension: 8.4<br>Renal impairment: 7.6 | Hyperkalemia: 7.7<br>Hypotension: 9.7<br>Renal impairment: 7.3 |
| Jhund et al[28] | 8399 | ARNi | Sacubitril/valsartan | Enalapril | Cough: 9.8-12.6[a]<br>Hyperkalemia: 3.4-4.8[a]<br>Hypotension: 2.5-2.9[a]<br>Renal impairment: 0.6-2.0[a] | Cough: 12.7-17.4[a]<br>Hyperkalemia: 2.9-7.2[a]<br>Hypotension: 0.9-1.5[a]<br>Renal impairment: 1.5-2.2[a] |
| Kobalava et al[29] | 30 | ARNi | Sacubitril/valsartan | Sacubitril/valsartan | Hyperkalemia discontinuation: 10 | Hyperkalemia discontinuation: 10 |
| RALES[30] | 1663 | MRA | Spironolactone | Placebo | Hyperkalemia: 2 | Hyperkalemia: 1 |
| EPHESUS[31] | 6632 | MRA | Eplerenone | Placebo | Hyperkalemia: 3.4[b]<br>Serious hyperkalemia: 5.5[b] | Hyperkalemia: 2[b]<br>Serious hyperkalemia: 3.9[b] |
| EMPHASIS-HF[32] | 2737 | MRA | Eplerenone | Placebo | Hyperkalemia: 8<br>Discontinuation rate due to hyperkalemia: 1.1 | Hyperkalemia: 3.7<br>Discontinuation rate due to hyperkalemia: 0.9 |
| Eschalier et al[33] | 2737 | MRA | Eplerenone | Placebo | Hyperkalemia: 1.9-3.8[a] | Hyperkalemia: 1.3-3.3[a] |
| Vardeny et al[34] | 1658 | MRA | Spironolactone | Placebo | Hyperkalemia: 15.4-30.2[a] | Hyperkalemia: 6.0-13.3[a] |
| Pitt et al[35] | 2106 | MRA | Eplerenone | Placebo | Hyperkalemia: 5.9 | Hyperkalemia: 3.5 |
| ARTS[36] | 458 | MRA | BAY 94-8862 | Spironolactone | Hyperkalemia: 5.3 | Hyperkalemia: 12.7 |
| ARTS-HF[37] | 1066 | MRA | Finerenone | Eplerenone | Hyperkalemia: 3.6-6.3[a] | Hyperkalemia: 4.7 |
| ARTS-HF Japan Study Group[38] | 72 | MRA | Finerenone | Eplerenone | Hyperkalemia: 18.2 | Hyperkalemia: 0 |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BB, β-blocker; CR, controlled release; HF, heart failure; HR, heart rate; MRA, mineralocorticoid receptor antagonist.

[a]Reflects range of adverse drug effects across subgroups in study.

[b]In EPHESUS, hyperkalemia was based on investigators' reports, and serious hyperkalemia (serum potassium concentration ≥6.0 mmol/L) was based on laboratory measurements.

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# DISCUSSION

As a consequence of the limited data available on the ADEs arising from guideline-directed HF therapies, the objective of this study was to summarize existing published literature on the incidence of ADEs for patients with HFrEF. This systematic literature review examines a multitude of studies reporting ADEs of guideline-directed HF therapies and is one of the few reports to summarize the incidences of common ADEs associated with GDMT for HFrEF. The results show that ADEs from clinical trials for GDMT are very common. This review highlights the sizable burden of ADEs across patients with HFrEF in the United States.

These ADEs, compared with traditional clinical outcomes for HF such as mortality and hospitalization, have been primarily studied in clinical trials and are underrepresented in the literature and, possibly, real-world practice. For example, sacubitril/valsartan was approved by the FDA in 2015 and, since approval, there has been minimal reporting on ADEs of sacubitril/valsartan in longitudinal, real-world studies for patients with HFrEF. Based on the incidence of common ADEs from randomized controlled trials in this review, these results may suggest that in real-world populations ADEs are similarly common and may result in patients discontinuing their GDMT. However, because of a lack of registry-based studies in published medical literature, risks of real-world GDMT ADEs are not well established. Owing to clinical significance, it is critical that we continue to examine the causality of ADEs related to GDMT in real-world populations. This review supports the need for future retrospective and prospective registry-based and other real-world evidence studies to evaluate ADEs across patients with HFrEF in the United States.

Additionally, ADEs have been noted to influence perceptions of HF therapies.[9] Providers have genuine concern around certain HF drug classes, dose titration schedules, or combinations thereof for the likelihood that an ADE may affect the patient's ability to tolerate continued treatment. Hyperkalemia, as noted in this review, is a very prevalent ADE of using MRAs and can be expected to only increase with additional renin-angiotensin-aldosterone system inhibitors such as ACEis, ARBs, or ARNis. Given the overwhelming burden of ADEs reported in this review, new pharmacotherapies with fewer off-target effects and more modest adverse effect profiles are needed to treat patients with HFrEF. Several pharmacologic therapies are on the horizon or recently approved for the treatment of patients with HFrEF, including sodium-glucose co-transporter 2 inhibitors (SGLT2is),[39] soluble guanylate cyclase (sGC) stimulators,[40] and a cardiac myosin activator, omecamtiv mecarbil.[41]

Dapagliflozin, an SGLT2i originally approved for the treatment of type 2 diabetes (T2D), was recently approved by the FDA for the treatment of patients with HFrEF with or without T2D. Vericiguat, a novel sGC stimulator, reduced the risk of HF hospitalization or cardiovascular death in a phase 3 clinical trial of patients with HFrEF.[42] Omecamtiv mecarbil, a selective cardiac myosin activator, was generally safe and well tolerated in a phase 2 clinical trial, with cardiac serious adverse events occurring at a similar incidence risk across treatment groups.[43] A phase 3 clinical trial of patients with HFrEF receiving omecamtiv mecarbil recently reported a lower incidence of an HF event or cardiovascular death vs placebo.[41] These new treatments may influence the profile of ADEs associated with the pharmacologic treatment of HFrEF. It remains a major evidence gap and priority to improve patients' quality of life by reducing the incidence of drug-induced adverse effects from HFrEF GDMT.

## Limitations

There are several limitations to this systematic literature review. First, the study population included only adult patients with HFrEF. The reported incidence ranges of ADEs are limited to HFrEF and are not applicable to other HF populations, such as HF with preserved or mid-range ejection fraction. Second, although this review highlights the ADEs of BBs, ACEis, ARBs, ARNis, and MRAs that have been most commonly reported in the literature, it does not cover all potential ADEs included in the medication label and, therefore, does not provide a complete list. Third, the diversity of methods of articles included did not allow for meta-analysis, nor risk or rate of ADEs. However, risks of ADEs were transparently reported and directly extracted from published articles. The risks were not combined or altered using standard meta-analysis or statistical techniques. Fourth, the quality of this review is contingent on the quality of the included studies, in which ADEs were not a prespecified outcome. The risk of bias was limited by inclusion of studies with a range of quality ratings and range of clear reporting of bias. Finally, it is possible that there are additional relevant studies that were not included in the review. Further real-world evidence studies are needed to examine and report ADEs for long-term drug use outside of controlled settings like clinical trials.

# CONCLUSIONS

This systematic literature review reported that ADEs from clinical trials for GDMT occur very commonly, and it highlights the sizable burden of these effects across patients with HFrEF in the United States. This review reports association and is not a direct assessment of ADE causality; however, pharmacologically, these ADEs have been well characterized. The decision to examine the most common ADEs translates to health outcomes in real-world practice and emphasizes the importance for practitioners and stakeholders to be mindful of the common cardiovascular ADEs vs all possible ADEs included in the medication label. Future retrospective and prospective registry-based and other real-world evidence studies to evaluate adverse drug effects across patients with HFrEF in the United States, as well as studies aiming to analyze and improve medical therapy tolerability for patients with HFrEF, are warranted. ■

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