Title

Medication-Attributable Adverse Events in Heart Failure Trials.

Journal

JACC: Heart Failure, 11(4)

Authors

Harrington, Josephine
Fonarow, Gregg
Khan, Muhammad
et al.

Publication Date

2023-04-01

DOI

10.1016/j.jchf.2022.11.026

Peer reviewed

HHS Public Access

Author manuscript

JACC Heart Fail. Author manuscript; available in PMC 2023 April 10.

Published in final edited form as:

JACC Heart Fail. 2023 April ; 11(4): 425–436. doi:10.1016/j.jchf.2022.11.026.

Medication-Attributable Adverse Events in Heart Failure Trials

Josephine Harrington, MD[1,2], **Gregg C. Fonarow, MD**[3], **Muhammad S. Khan, MBBS MSc**[2], **Adrian Hernandez, MD MHS**[1,2], **Stefan Anker, MD PhD**[4,5], **Michael Böhm, MD**[6], **Stephen J. Greene, MD**[1,2], **G. Michael Felker, MD MHS**[1,2], **Muthiah Vaduganathan, MD MPH**[7], **Javed Butler, MD MPH MBA**[8,9]

[1]Duke Clinical Research Institute, Durham, North Carolina

[2]Department of Medicine, Division of Cardiology, Duke University Hospital, Durham North Carolina

[3]Division of Cardiology, David Geffen School of Medicine, University of California, Los Angeles Medical Center

[4]Department of Cardiology (CVK); and Berlin Institute of Health Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Germany

[5]Institute of Heart Disease, Wroclaw Meidcal University, Wroclaw, Poland

[6]Department of Medicine, Saarland University Hospital, Hombug/Saar, Germany

[7]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[8]Baylor Scott and White Research Institute, Dallas TX

[9]Department of Medicine, University of Mississippi, Jackson, MS

Abstract

Background: Initiation and up-titration of guideline-directed medical therapies (GDMT) for heart failure with reduced ejection fraction (HFrEF) remains suboptimal, in part due to concerns regarding tolerability and adverse events (AE).

Objectives: To compare rates of adverse events in patients randomized to GDMT medication vs placebo in a meta-analysis of landmark cardiovascular outcomes trials.

Methods: We assessed rates of reported AE in 17 landmark HFrEF clinical trials across each class of GDMT in the placebo and intervention arms. The overall rates of AE for each drug class, the absolute difference in frequency in AEs between the placebo and intervention arms, and the odds of each AE according based on randomization strata were calculated.

Results: AE were reported commonly in trials across each class of GDMT, with 75-85% of participants reporting at least one AE. There was no significant difference in the frequency of AE between the intervention and placebo arms, except for angiotensin converting enzyme

Corresponding Author: Javed Butler, MD MPH MBA, Baylor Scott and White Research Institute, 3434 Live Oak St Ste 501, Dallas TX 75204 Javed.butler@bwshealth.org. 214-820-2687.

(ACE) inhibitors (87.0% [85.0-88.8%] vs 82.0% [79.8-84.0%], absolute difference +5% with intervention, P<0.001). There was no significant difference in drug discontinuation due to AE between placebo and intervention arms in ACE inhibitors, mineralocorticoid receptor antagonists (MRA), sodium glucose co-transporter 2 (SGLT2) inhibitor or angiotensin receptor neprilysin inhibitor (ARNI)/angiotensin II receptor blocker (ARB) trials. Patients randomized to beta blocker were significantly less likely to stop study drug due to AE than placebo (11.3% [10.3 to12.3%] vs 13.7% [12.5 to 14.9%], absolute difference −1.1%, P=0.015). When individual types of AE were assessed, initiation of intervention vs placebo resulted in small differences in absolute frequency of AE that were largely not statistically significant.

Conclusions: In clinical trials of GDMT for HFrEF, AE are frequently observed. However, rates of AE are similar between active medication and control, suggesting these may reflect the high risk nature of the HF disease state rather than be attributive to a specific therapy.

Condensed Abstract

To understand the actual impact of GDMT on adverse events for patients with heart failure and reduced ejection fraction (HFrEF), rates of AE in 17 landmark HFrEF clinical trials were compared between the placebo and intervention arms. Though AE were frequently reported in trials of GDMT (between 75-85% of all patients), there was generally no substantial difference in the frequency of AE between the intervention and placebo arms. Individual AEs such as cough rarely occurred more frequently for patients randomized to GDMT vs placebo. These findings suggest that many of the AEs observed in patients with HFrEF are not related to GDMT, and support the use of GDMT whenever possible to prevent morbidity and mortality.

Keywords

Guideline-Directed Medical Therapy; Adverse Events; Heart Failure

Patients with heart failure with reduced ejection fraction (HFrEF) are at risk for poor clinical and quality of life outcomes (1–3). These risks are reduced with the use of guideline-directed medical therapy (GDMT), which consists of beta-blockers, renin-angiotensin aldosterone system (RAAS) agents, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose co-transporter 2 (SGLT2) inhibitors, which each have a Class 1 recommendation for use in patients with HFrEF without contraindication (4). Compared with therapy with a RAAS and beta-blocker, comprehensive therapy with all four drugs is estimated to extend life of a 55 year-old patient by over 6 years, and by over a year even in octogenarians (5).

However, patients with HFrEF are often not prescribed these drugs or generally receive doses below the target (6, 7). These gaps in use and dosing of GDMT have important implications. It is estimated that optimal use of angiotensin receptor-neprilysin inhibitors would prevent 28,000 deaths in the United States annually, with an additional 34,000 deaths prevented with SGLT2 inhibitor use (8, 9). One possible reason that clinicians are hesitant to escalate these therapies is the perceived risk of adverse events (AE) or side effects (10–12). Providers may worry that GDMT will provoke hypotension, kidney injury, or metabolic disturbances in patients vulnerable to such events (13). Likewise, patients who experience

HF or other symptoms while on GDMT may have these symptoms attributed to GDMT, which may result in medication discontinuation and/or patients being labeled intolerant, without further attempts to use them.

Patients with HFrEF have a high burden of symptoms overall (3). Though patients may truly be unable to tolerate GDMT, in some cases these symptoms may be a manifestation of HFrEF and other co-morbidities, and not related to a medication. In this case, use of GDMT may not impact or may even improve symptoms over time, while reducing risk of hospitalization and death. To assess the frequency of AE in patients with HFrEF, and to understand the percentage are attributable to the use of GDMT, we evaluated relative rates of common AE in major cardiovascular trials of GDMT, comparing rates in both the placebo and intervention arms, and calculating a placebo-adjusted frequency of AE to understand the impact of GDMT on them.

METHODS

Eligibility Criteria

To assess the frequency of AEs and the impact of randomization to intervention vs. placebo arm on the rate of AEs, we evaluated rates of AEs from landmark clinical trials of GDMT, including RAAS agents such as angiotensin-converting enzyme (ACE) inhibitors (14–17), angiotensin 2 receptor blockers (ARBs),(18) and angiotensin receptor-neprilysin inhibitors (ARNIs),(19, 20) beta-blockers (21–25), MRAs (26–28), and SGLT2 inhibitors (29–31), both in patients with chronic HFrEF and in patients following myocardial infarction with signs of left ventricular dysfunction or symptoms of HF. Trials were considered landmark trials if they evaluated the impact of a drug within one of the GDMT classes for HF on mortality and heart failure outcomes in comparison to placebo or (for ARNI and ARB trials) against an active comparator and were cited in HF guidelines to support the use of a class of medication for GDMT.

Search Strategy and Data Extraction

AEs were assessed in the primary publications of 17 landmark GDMT trials (Table 1). The Cardiac Insufficiency Bisoprolol Study II and the Survival and Ventricular Enlargement (SAVE) trials were not included based on inadequate AE information reports (24, 32). When available, overall rates of AEs, serious AEs, and drug discontinuation secondary to AEs were collected. Information on AEs, as reported either in the main manuscript or in a supplement, were compiled, as was the size of each study arm. AEs in the overall study were assessed and tabulated between the intervention and the comparator arm. In instances where an individual trial reported several hundred types of AEs (29), only those occurring more than 0.5% of the time, or with corresponding information on the occurrence of the same AE from other trials, were included. AEs that were only reported in a single trial, or which were not relevant to the known mechanisms of these drugs (e.g., neoplasm, which was reported in only a single MRA trial (28)) were not included. Heart failure hospitalization and death, which were typically efficacy endpoints in each trial, were not recorded as AEs. As some trials did not report the size of the on-treatment, or safety, population of the trial, and reported only the intention to treat size, intention-to-treat was chosen as the population size

for each trial for consistency: however, the difference between these populations for trials reporting the size of each cohort was <0.5% in all instances (26–31).

Statistical Analysis

The overall frequency of each AE type was calculated across each GDMT class for the placebo and the intervention arms, and 95% confidence intervals (CI) were calculated. To compare AE frequencies between the groups, odds ratios (ORs) were calculated. Meta-analyses were performed based on a generalized linear mixed effects model under trial-specific random effects, with 95% Cis computed by the restricted maximum likelihood. Significance was set at 2-sided $P < .05$. Data management and statistical analyses were performed using Microsoft Excel (Microsoft Corporation) and the R-based software. For trials of ARBs and ARNIs, AE rates were calculated for the active comparator (an ACE inhibitor) in lieu of placebo. In instances where only a percentage or a total number of patients experiences an AE was reported, the missing data were manually calculated. To calculate the placebo-adjusted rates of each AE, the rate observed in the placebo arm was subtracted from the rate observed in the intervention arm to determine the absolute difference in frequency of each AE seen with intervention vs placebo. Because rates of AEs were high regardless of length of study, and because there was no difference in length between the two arms of any study, no adjustment was made for length of trial.

RESULTS

Trial Populations

This analysis included data from 51,419 patients across 17 trials, including 4 ACE inhibitor, 4 beta blocker, 3 MRA, 3 SGLT2 inhibitor, and 3 ARB or ARNI trials (Supplemental Table 1). Average follow-up time ranged from 6.3 (15) to 41.4 months (14). The average age across trials was 65 (58 to 74) years. Across trials, 73% of patients were male and the average ejection fraction was 29%.

Adverse Events Across Trials

AEs were commonly observed regardless of randomization status, with rates ranging from 74.9% (SGLT2 inhibitors) to 84.5% (ACE inhibitors) trials (Figure 1). The overall frequency of AEs was not reported in the beta-blocker trials, though one trial did report serious AEs, which were experienced by 42.5% of patients overall. Compared with placebo, patients in the intervention arm of trials generally did not have a meaningfully different frequency of AEs (absolute differences ranged from 5% higher for ACE inhibitor to 0.8% lower for SGLT2 inhibitor). These differences were not statistically significant, except for ACE inhibitor vs. placebo (87.0% [85.0-88.8%] vs 82.0% [79.8- 84.0%], absolute difference +5% in ACE inhibitor arm, $p<0.001$). Risk of serious AEs was lower for patients randomized to a beta blocker (39.0% [36.2-41.9%] vs 45.5% [42.7-48.5%], absolute difference −6.5% for beta-blocker, $p=0.002$); ACE inhibitor (57.3% [54.2-60.3%] vs 63.0% [60.0-66.0%], net difference −5.7%, $p=0.009$) or SGLT2i (39.3% [37.9-40.7%] vs 44.1% [42.7-45.5%], absolute difference −4.9%, $p<0.001$) as compared to placebo.

Discontinuation of Study Drug

Across trials, 4.7% to 13.4% of patients discontinued study drug due to AEs. There was no significant difference in rates of drug discontinuation due to AEs in trials of ACE inhibitors (7.4% [6.1-9.1%] vs. 12.3% [10.5-14.4%], absolute difference −4.9%, p=0.68, OR 0.80 [0.28-2.32]), MRAs (8.2% [7.2-9.5%] vs. 11.8% [10.7-13.2%], absolute difference −3.66%, p=0.84, OR 0.89 [0.27-2.89]), SGLT2 inhibitors (4.7% [4.0-5.5%] vs. 4.7% [4.0-5.4%], absolute difference 0%, p=0.94, OR 1.01 [0.79-1.28]) in intervention vs placebo arms respectively, or ARNI vs. ARB (12% [11.2-12.7%] vs 12.7% [11.9-13.5%], absolute difference −0.7%, p=0.61, OR 1.15 (0.67-1.99). Patients randomized to beta blocker were less likely to stop study drug due to AEs compared with placebo (11.3% [10.3-12.3%] vs 13.7% [12.5-14.9%], absolute difference −1.1%, p=0.015, OR 0.84 [0.73-0.97]).

Renin-Angiotensin Aldosterone System Modulator Trials

The most common AEs were dizziness or syncope, cough, and angina (Table 2). Adjusting for rates observed in the placebo group, patients randomized to an ACE inhibitor were 3.9% more likely to experience dizziness/syncope and 8.9% more likely to experience cough (Figure 1 **Panel A,** Table 2). When proportion of symptoms attributable to randomization to ACE inhibitor was assessed, the study drug accounted for 11.9% of dizziness or syncope and 24.7% of coughs (absolute difference 3.9%, p<0.001, OR 1.32 [1.14-1.54] for dizziness/ syncope, and 8.9%, p=0.014, OR 1.55, [1.09-2.23] for cough). The AEs most likely to be attributable to ACE inhibitor use were hyperkalemia, worsening renal function, and cough: the absolute increase in frequency was 2.3%, 1.5%, and 8.9% respectively (Table 2). For patients enrolled in ARB or ARNI trials, most common AEs overall were hyperkalemia, cough, and dizziness or syncope, (Supplemental Table 2, Supplemental Figure). These trials used an ACE inhibitor as comparator and the difference between the two arms are shown in Supplemental Table 2.

Beta Blocker Trials

The most frequently reported AE were upper respiratory infection, cough, and pain (Figure 1 **Panel B,** Table 3), however there was no significant difference between placebo and intervention groups (p=0.84, 0.34, and 0.73, respectively). The AEs most likely to be attributable to beta blocker were dizziness and nausea, which occurred in 5.5% and 4.1% more patients randomized to beta blocker (p<0.001, OR 1.99 [1.52-2.64] for dizziness and p=0.013,OR 1.99 [1.16-3.42]] for nausea). Bradycardia was reported in 1.9% more patients in the intervention arm; this difference was not significant (p=0.06, OR 3.25 [0.95-11.02]).

Mineralocorticoid Receptor Antagonist Trials

Cough and musculoskeletal disorders were the most frequently reported AEs (Table 4, Figure 1 **Panel C**). There was no significant difference in musculoskeletal disorders between the two study arms, and rates of cough were lower in patients randomized to MRA (p=0.029, OR 0.83, 0.70-2.59]). AEs most attributable to MRA were male gynecomastia (+5.7%, p<0.001, OR 7.61 [3.60-16.12] and male breast pain (+1.1%; p=0.026, OR 10.38 [1/32-80.64]), though these events were driven by spironolactone and not eplerenone, followed by hyperkalemia (+2.3%, p=0.001, OR 1.97 [1.51-2.59]).

SGLT2 Inhibitor Trials

Common AEs were symptomatic hypotension, renal impairment, and volume depletion (Table 5, Figure 1 **Panel D**). These did not occur at statistically significantly different rates between placebo vs. intervention arms (p=0.82, OR 1.03 [0.78 – 1.36]) for symptomatic hypotension, p=0.32, OR 0.90 [0.71-1.12] for renal impairment, and p=0.23, 1.09 [0.92-1.26] for volume depletion). Hypoglycemia and severe hypoglycemia did not occur at significantly different rates either (Table 5). The AEs attributable to SLGT2 inhibitors were genital mycotic infection (+0.9%, OR 2.77 [1.46-5.26] p=0.002 and ; dysuria +1.4% OR 5.10 [1.11-23.57] p=0.036).

DISCUSSION

In this analysis of patients enrolled in landmark clinical trials of GDMT for HFrEF, overall burden of AEs was high, however, patients randomized to the intervention arm in general did not have substantially more AEs than those randomized to placebo. There was no significant difference in rates of AEs between the intervention and placebo arm for SGLT2 inhibitors or MRAs. Importantly, patients randomized to intervention experienced either similar (ARNI/ARB trials) or significantly lower (beta blockers, ACE inhibitor, and SGLT2 inhibitor) rates of serious AEs than patients randomized to placebo. Rates of study drug discontinuation due to AEs were not statistically different between intervention and control arms for trials of ACE inhibitors, MRAs, SGLT2 inhibitors, or ARNIs/ARBs. Patients randomized to a beta blocker were in fact less likely to stop study drug due to an AE than placebo. The only drug class for which significantly more AEs were observed was ACE inhibitors, with a modest absolute increase in AE rate of 5%; this was countered by lower rates of serious AEs (−5.7%) with ACE inhibitor use. In instances where a specific AE was seen more frequently with randomization to GDMT, such as gynecomastia with MRA use, the absolute difference in frequency intervention and placebo arm was generally small and rarely above 2%.

These data suggest that the overall burden of AEs in patients with HFrEF is high, even for patients enrolled in the placebo arm. In the most recent trials that closely resemble contemporary HFrEF populations, AEs were reported in 75% to 80% of all patients. These findings are consistent with HFrEF's substantial impact on quality of life, and underscores the high symptom burden associated with HFrEF and its associated comorbidities (33, 34). Symptoms such as hypotension, one of the most concerning AEs related to the initiation of new therapies, occurred slightly more often in intervention arms (1.8% for beta blocker, 5.6% for ACE inhibitors, 3.4% for ARB or ARNI, 0.6% for MRA and 0.3% for SGLT2 inhibitors). Most hypotension events could not be reliably attributed to the addition of GDMT. Since most of the hypotension, dizziness, and syncope was not related to the initiation of an additional GDMT, providers should be thoughtful about whether such symptoms should prompt discontinuation of therapies, especially if patients are not very symptomatic or have a borderline blood pressure. When a drug is discontinued because of concerns for side effects, providers should plan to re-attempt in the future when possible.

There were some instances when an AE was more likely to be attributable to GDMT, however, the absolute rates of these events were low, and these AEs were typically

"nuisance" events that could be avoided through specific drug choices. For instance, just over half all noted episodes of gynecomastia could be attributed to MRA use, but on average only 0.9% more patients (i.e., less than one patient out of every hundred patients) experienced this in the intervention arm as compared to the placebo arm of MRA trials. Notably, gynecomastia is observed with spironolactone and not eplerenone, making this AE easily avoidable for those who may be concerned. Similarly, the most likely AE attributable to any form of GDMT was cough, which occurred in 8.9% more patients randomized to ACE inhibitor vs placebo. However, this side effect could be easily addressed through preferential use of an ARB or ARNI over ACE inhibitor.

Overall, the absolute difference rates for most individual AEs were less than 5% between intervention and placebo: in some cases, AEs occurred less often with intervention, such as hypokalemia with MRA use. The addition of single GDMT drug resulted in between 0.8% fewer to 5% more patients experiencing any AE at all, a difference which was often not statistically significant. Since it has been estimated that the use of all four therapies in GDMT reduces mortality in HFrEF patients by 25% over 2 years, with each additional therapy providing incremental benefit, the relatively low risk that AEs can actually be attributed to initiation of GDMT must be weighed against the benefit in mortality and hospitalization risk (8).

As we consider the large gaps in use and dosing of GDMT in practice, one key factor is the potential misclassification of symptoms due to worsening of the HF disease state versus medication-related AEs. Indeed, events like worsening functional status, acute kidney injury, and syncope occur at non-trivial rates among patients receiving placebo in trials. However, it is important to recognize that worsening symptoms and decreasing functional status are less likely to occur with prompt initiation and titration of GDMT. Beyond mortality benefit, GDMT is associated with improved symptoms and functional class: for instance, patients with HFrEF randomized to empagliflozin were more likely to improve and less likely to worsen their New York Heart Association class. These effects were evident as early as 28 days after randomization, and persisted for the length of the trial (35). It is therefore possible that failure to initiate or withdrawal of GDMT could actually lead to more symptoms, which could paradoxically make it more likely that a provider would withdraw more GDMT in response to a patient's escalating symptom burden, creating a downward spiral of worsening outcomes. Early use of one class GDMT may decrease key AE's to the point of enabling other drug classes (36). For example, initiation of SGLT2i decreases risk of hyperkalemia, slows progression of kidney disease, and decrease risk of MRA discontinuation (37). Similar trends have been reported with ARNI therapy (38). Our results suggest that though AEs occur commonly in HF patients, these AEs cannot be clearly attributed to GDMT. Clinicians therefore should be thoughtful about whether symptoms should prompt a change in GDMT, and whether drugs, once stopped, should be re-trialed, especially given concerns that stopping GDMT may in fact worsen symptoms. Though more work is needed, but it is likely that the issue is not simply that that failure to tolerate GDMT is a poor prognosticator, but that withdrawal of GDMT directly contributes to higher symptom burdens and poor outcomes.

LIMITATIONS

There are limitations to our analysis. AEs were not reported uniformly across trials and definitions of AEs may have varied. Older trials tended to not have available supplemental sections and reported fewer AEs. The frequency of AEs sometimes differed across trials even for the same drug class, likely related to changes in thresholds for reporting, and to differences in definitions or regulatory requirements. It is therefore not possible to compare burden of AEs between different classes of GDMT or across trials. Despite this, AE reporting would be consistent within trials and the absolute change in frequency with intervention vs placebo is unlikely to be biased. Severity of AEs was generally not systematically categorized, but AEs leading to death or drug discontinuation were assessed. Specific side effects, such as gynecomastia, are known to be related to specific drugs (spironolactone) and are not considered to be a class effect. It is also possible that the patients enrolled in trials tended to be healthier than the overall HFrEF population and may therefore have been less likely to experience AEs. However, prior research has suggested that patients enrolled in recent trials closely mirrors those observed in real-world clinical practice (39, 40). Finally, trials are powered to look at efficacy endpoints and not adverse events. While patients in these trials were much more likely to experience any AE overall than a primary outcome, these AE reflect diverse symptoms and safety events. As such, trials are typically not powered to assess composite AE, despite their frequency.

In conclusion, AEs occurred often in trials, but at similar rates for patients in the placebo and intervention arms. In general, AEs were infrequently attributable to initiation of a GDMT. When AEs did appear to occur more often in the intervention arm, the absolute frequency was low. Given the high burden of symptoms and AEs observed in the placebo arm of trials and the low additive risk of symptoms with initiation of GDMT, physicians should consider whether their patients symptoms may be related to HFrEF or other comorbidities, and not necessarily to GDMT. As such, clinicians should balance the threshold to discontinue or to retry GDMT in the setting of symptoms against the risk for clinical deterioration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures

JH receives salary support from T32 training grant T32HL069749. GCF reports consulting for Abbott, Amgen, AstraZeneca, Bayer, Cytokinetics, Janssen, Medtronic, Merck, and Novartis. MSK has no disclosures. GMF has received research grants from NHLBI, American Heart Association, Amgen, Bayer, BMS, Merck, Cytokinetics, and CSL-Behring; he has acted as a consultant to Novartis, Amgen, BMS, Cytokinetics, Medtronic, Cardionomic, Boehringer-Ingelheim, American Regent, Abbott, Astra-Zeneca, Reprieve, Myovant, Sequana, Windtree Therapuetics, and Whiteswell, and has served on clinical endpoint committees/data safety monitoring boards for Amgen, Merck, Medtronic, EBR Systems, V-Wave, LivaNova, Siemens, and Rocket Pharma. MB is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939) and reports personal fees from Abbott, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, Servier and Vifor during the conduct of the study. AFH: Reports research grants from American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squib, Merck, Novartis, Verily and consulting from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squib, Myokardia, Novo Nordisk. SDA: reports receiving fees from Abbott, Bayer, Boehringer Ingelheim, Cardiac Dimension, Impulse Dynamics, Novartis, Occlutech, Servier, and Vifor Pharma, and grant support from Abbott and Vifor Pharma SJG has received research support from the Duke University Department of Medicine Chair’s Research Award, American Heart Association, National Heart Lung and Blood Institute, Amgen, AstraZeneca,

Bristol Myers Squibb, Cytokinetics, Merck & Co., Inc., Novartis, Pfizer, and Sanofi; has served on advisory boards for Amgen, AstraZeneca, Boehringer Ingelheim/ Lilly, Bristol Myers Squibb, Cytokinetics, Roche Diagnostics, and Sanofi; serves as a consultant for Amgen, Bayer, Bristol Myers Squibb, Merck & Co., Inc., PhamaIN, Roche Diagnostics, Sanofi, Tricog Health, Urovant Pharmaceuticals, and Vifor; and has received speaker fees from Boehringer Ingelheim. MV has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health, speaker engagements with Novartis, AstraZeneca, and Roche Diagnostics, and participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. JB has served as a consultant to Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Berlin Cures, Boehringer Ingelheim, Bristol-Myers Squib, CVRx, G3 Pharmaceutical, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Occlutech, Relypsa, Roche, Sanofi, SC Pharma, V-Wave Limited, and Vifor.

Abbreviations

ACE	angiotensin converting enzyme
AE	adverse event
ARB	angiotensin II receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
GDMT	guideline-directed medical therapy
HFrEF	heart failure with reduced ejection fraction
MRA	mineralocorticoid receptor antagonists
SGLT2i	sodium glucose co-transporter 2

REFERENCES

1. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National Burden of Heart Failure Events in the United States, 2006 to 2014. Circulation: Heart Failure 2018;11:e004873. [PubMed: 30562099]
2. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among Patients in the Medicare Fee-for-Service Program. New England Journal of Medicine 2009;360:1418–1428. [PubMed: 19339721]
3. Juenger J, Schellberg D, Kraemer S, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. Heart 2002;87:235–241. [PubMed: 11847161]
4. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895–e1032. [PubMed: 35363499]
5. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. The Lancet 2020;396:121–128.
6. Greene SJ, Butler J, Albert NM, et al. Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. Journal of the American College of Cardiology 2018;72:351–366. [PubMed: 30025570]
7. Brunner-La Rocca H-P, Linssen GC, Smeele FJ, et al. Contemporary Drug Treatment of Chronic Heart Failure With Reduced Ejection Fraction: The CHECK-HF Registry. JACC Heart Fail 2019;7:13–21. [PubMed: 30606482]

8. Bassi NS, Ziaeian B, Yancy CW, Fonarow GC. Association of Optimal Implementation of Sodium-Glucose Cotransporter 2 Inhibitor Therapy With Outcome for Patients With Heart Failure. JAMA Cardiol 2020;5:948–951. [PubMed: 32374344]
9. Fonarow GC, Hernandez AF, Solomon SD, Yancy CW. Potential Mortality Reduction With Optimal Implementation of Angiotensin Receptor Neprilysin Inhibitor Therapy in Heart Failure. JAMA Cardiology 2016;1:714–717. [PubMed: 27437874]
10. Savarese G, Bodegard J, Norhammar A, et al. Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: a multinational observational study (US, UK and Sweden). Eur J Heart Fail 2021.
11. Ferreira JP, Rossignol P, Machu J-L, et al. Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF. Eur J Heart Fail 2017;19:1284–1293. [PubMed: 28580625]
12. Khan MS, Segar MW, Usman MS, et al. Frailty, Guideline-Directed Medical Therapy, and Outcomes in HFrEF: From the GUIDE-IT Trial. JACC Heart Fail 2022;10:266–275. [PubMed: 35361446]
13. Smith KV, Dunning JR, Fischer CM, et al. Reasons for Failure to Optimize Guideline-Directed Medical Therapy for Heart Failure with Reduced Ejection Fraction Patients in Clinical Practice. Journal of Cardiac Failure 2018;24:S100–S101.
14. The SOLVD Investigators. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. New England Journal of Medicine 1991;325:293–302. [PubMed: 2057034]
15. The Consensus Trial Study Group. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. New England Journal of Medicine 1987;316:1429–1435. [PubMed: 2883575]
16. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet 1993;342:821–828. [PubMed: 8104270]
17. Køber L, Torp-Pedersen C, Carlsen JE, et al. A Clinical Trial of the Angiotensin-Converting–Enzyme Inhibitor Trandolapril in Patients with Left Ventricular Dysfunction after Myocardial Infarction. New England Journal of Medicine 1995;333:1670–1676. [PubMed: 7477219]
18. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997;349:747–752. [PubMed: 9074572]
19. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. NEJM 2014;371:993–1004. [PubMed: 25176015]
20. Pfeffer MA, Claggett B, Lewis EF, et al. Angiotensin Receptor-Neprilysin Inhibition in Acute Myocardial Infarction. N Engl J Med 2021;385:1845–1855. [PubMed: 34758252]
21. Packer M, Fowler MB, Roecker EB, et al. Effect of Carvedilol on the Morbidity of Patients With Severe Chronic Heart Failure. Circulation 2002;106:2194–2199. [PubMed: 12390947]
22. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;357:1385–1390. [PubMed: 11356434]
23. Hjalmarson Å, Goldstein S, Fagerberg B, et al. Effects of Controlled-Release Metoprolol on Total Mortality, Hospitalizations, and Well-being in Patients With Heart FailureThe Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). JAMA 2000;283:1295–1302. [PubMed: 10714728]
24. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13. [PubMed: 10023943]
25. Packer M, Bristow MR, Cohn JN, et al. The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure. New England Journal of Medicine 1996;334:1349–1355. [PubMed: 8614419]
26. Pitt B, Zannad F, Remme WJ, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. N Engl J Med 1999;341:709–717. [PubMed: 10471456]

27. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11–21. [PubMed: 21073363]
28. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N. Engl. J. Med 2003;348:1309–1321. [PubMed: 12668699]
29. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. NEJM 2019:1995–2008. [PubMed: 31535829]
30. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. NEJM 2020;383:1413–1424. [PubMed: 32865377]
31. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. NEJM 2021;384:117–128. [PubMed: 33200892]
32. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of Captopril on Mortality and Morbidity in Patients with Left Ventricular Dysfunction after Myocardial Infarction. New England Journal of Medicine 1992;327:669–677. [PubMed: 1386652]
33. Dunbar SB, Tan X, Lautsch D, et al. Patient-centered Outcomes in HFrEF Following a Worsening Heart Failure Event: A Survey Analysis. J Card Fail 2021;27:877–887. [PubMed: 34364664]
34. Jorge AJL, Rosa MLG, Correia DM da S, et al. Evaluation of Quality of Life in Patients with and without Heart Failure in Primary Care. Arq Bras Cardiol 2017;109:248–252. [PubMed: 28832746]
35. Packer M, Anker SD, Butler J, et al. Effect of Empagliflozin on the Clinical Stability of Patients With Heart Failure and a Reduced Ejection Fraction. Circulation 2021;143:326–336. [PubMed: 33081531]
36. Greene SJ, Khan MS. Quadruple Medical Therapy for Heart Failure: Medications Working Together to Provide the Best Care. J Am Coll Cardiol 2021;77:1408–1411. [PubMed: 33736822]
37. Ferreira JP, Zannad F, Pocock SJ, et al. Interplay of Mineralocorticoid Receptor Antagonists and Empagliflozin in Heart Failure: EMPEROR-Reduced. J Am Coll Cardiol 2021;77:1397–1407. [PubMed: 33736821]
38. Desai AS, Vardeny O, Claggett B, et al. Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared With Enalapril: A Secondary Analysis of the PARADIGM-HF Trial. JAMA Cardiol 2017;2:79–85. [PubMed: 27842179]
39. Fudim M, Sayeed S, Xu H, et al. Representativeness of the PIONEER-HF Clinical Trial Population in Patients Hospitalized With Heart Failure and Reduced Ejection Fraction. Circulation: Heart Failure 2020;13:e006645. [PubMed: 32248695]
40. Vaduganathan M, Greene SJ, Zhang S, et al. Applicability of US Food and Drug Administration Labeling for Dapagliflozin to Patients With Heart Failure With Reduced Ejection Fraction in US Clinical Practice. JAMA Cardiol 2021;6:1–10.

Perspectives

Competency in Medical Knowledge

- The use of guideline-directed medical therapies (GDMT) for heart failure with reduced ejection fraction (HFrEF) remains suboptimal, likely in part due to concerns that these drugs will be poorly tolerated by patients
- Though adverse events occurred commonly in clinical trials of GDMT medications, it was at similar rates in the placebo and intervention arms, suggesting the initiation of GDMT was uncommon as the driver of patient symptoms and that GDMT is generally very well tolerated in patients with HFrEF
- Providers should consider whether their patients' symptoms may not be related to GDMT therapies, and, if medications are stopped for symptoms, consider re-trialing them in the future

Translational Outlook

More research is needed to understand the frequency with which side effects are truly attributable to GDMT. However, by examining rates of reported adverse events in landmark clinical trials of GDMT, we see that these events tend to occur at very similar rates between placebo and intervention arms. This suggests that though adverse events are common in patients with HFrEF, they may be more related to the condition of heart failure itself rather than GDMT usage.

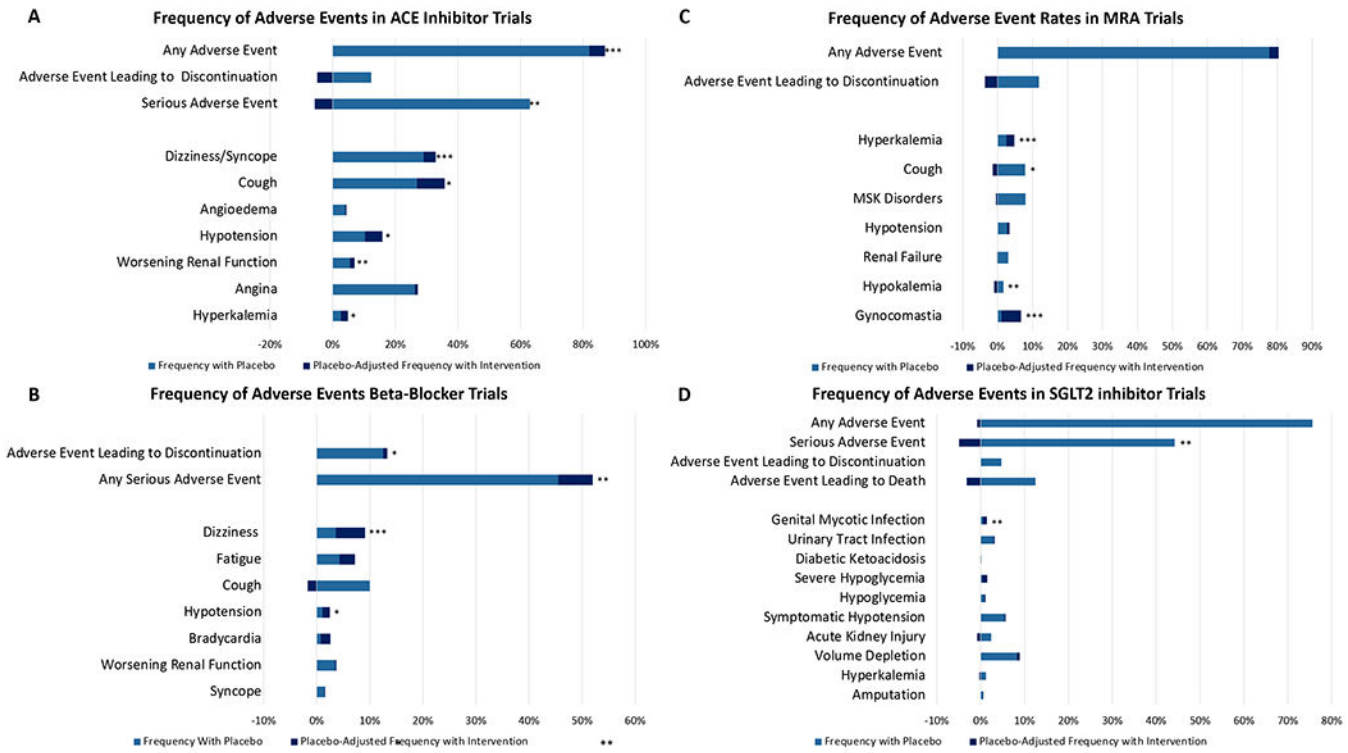
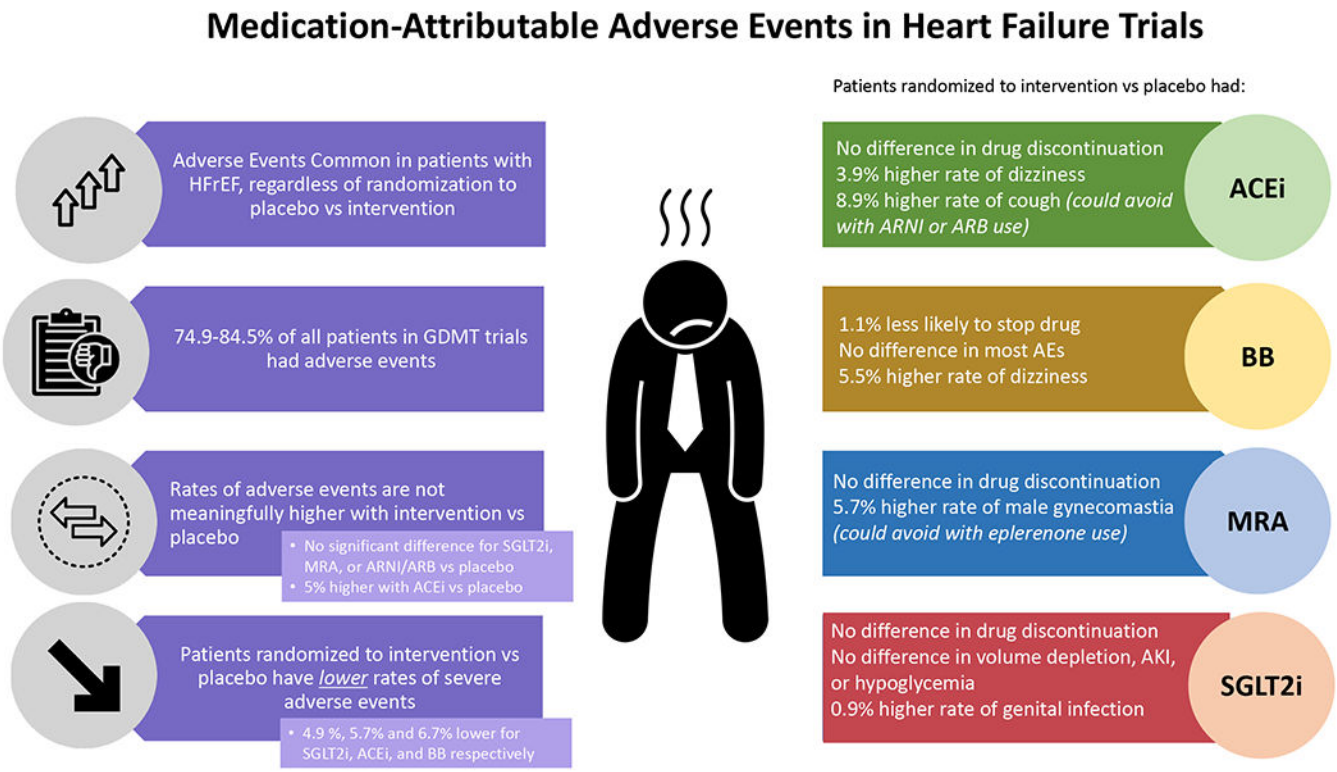


Figure 1: Frequency of AEs.

Frequency with Placebo and Absolute Difference in Frequency of Adverse Events in Intervention Arm. Placebo-adjusted rate frequency shows the difference in rates of an adverse event in the intervention arm as compared to the placebo arm. Note that some AEs occurred less frequently in the intervention arm than in the placebo arm. ACE: angiotensin converting enzyme AE: adverse event **Panel A:** Frequency of AEs in ACE Inhibitor Trials. **Panel B:** Frequency of AEs in Beta-Blocker Trials. **Panel C:** Frequency of AEs in MRA Trials. **Panel D:** Frequency of AEs in SGLT2 Inhibitor Trials. Single asterisk: $p<0.05$, double asterisk: $p<0.01$, triple asterisk: $p<0.001$



Central Illustration: Medication-Attributable Adverse Events in Heart Failure Trials.

ACE: angiotensin-converting enzyme; AE: adverse event; AKI: acute kidney injury; BB: beta blocker; GDMT: guideline-directed medical therapy; HFrEF: heart failure with reduced ejection fraction; mineralocorticoid receptor antagonist; SGLT2i: sodium-glucose co-transporter 2 inhibitor

JACC Heart Fail. Author manuscript; available in PMC 2023 April 10.

Table 1:

Trials Included in Analyses

ACEi Trials
The Studies of Left Ventricular Dysfunction (SOLVD)
Cooperative North Scandinavian Enalapril Survival (CONSENSUS)
Acute Infarction Ramipril Efficacy (AIRE)
Trandolapril Cardiac Evaluation (TRACE)
ARB and ARNI Trials
Evaluation of Losartan in the Elderly Study (ELITE)
Prospective Comparison of ARNI with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM HF)
Prospective ARNI vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after MI (PARADISE MI)
Beta Blocker Trials
Carvedilol Heart Failure Study Group
Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS)
Carvedilol Post-infarct Survival Controlled Evaluation (CAPRICORN)
Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT HF)
MRA Trials
Randomized Aldactone Evaluation Study (RALES)
Eplerenone in Mild Patients Hospitalization Survival Study in Heart Failure (EMPHASIS-HF)
Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)
SGLT2i Trials
Dapagliflozin and Prevention of Averse-Outcomes in Heart Failure (DAPA-HF)
Empagliflozin Outcomes Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-REDUCED)
Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF)

Table 2:

AEs Noted in ACE Inhibitor Cardiovascular Outcomes Trials.

Median follow-up	Enalapril				Ramipril		Trandolapril		Frequency with Intervention	Frequency with Placebo	Overall Frequency	Placebo-Adjusted Frequency in Intervention Arm	Odds Ratio with 95% confidence interval	P-value
	SOLVD		CONSENSUS		AIRE		TRACE							
	41.4 mo		6.3 mo		15 mo									
	Enalapril	Placebo	Enalapril	Placebo	Ramipril	Placebo	Trandolapril	Placebo						
	n=1284	n=1285	n=127	n=126	n=1014	n=992	n=876	n=873						
Any side effect	1117 (87.0%)	1054 (82.0%)	-	-	-	-	-	-	87.0% (85.0 – 88.8)	82.0% (79.8 – 84.0)	84.5% (83.1 – 85.9)	5.0%	1.46 (1.19-1.82)	<0.001
SE leading to permanent discontinuation of drug	-	-	17 (13.4%)	12 (9.5%)	68 (6.7)	126 (12.7%)	-	-	7.4% (6.1 – 9.1)	12.3% (10.5 – 14.4)	9.9 %(8.7 – 11.1)	−4.9%	0.80 (0.28-2.32)	0.68
Serious SE	-	-	-	-	581 (57.3%)	625 (63%)	-	-	57.3% (54.2 – 60.3)	63.0% (60.0 – 66.0)	60.1% (58.0 – 62.2)	−5.7%	0.79 (0.66-0.94)	0.009
Dizziness/ Syncope	732 (57.0%)	643 (50.0%)	-	-	24 (2.4%)	17 (1.7%)	-	-	32.9% (31.0 – 34.8)	29.0% (27.2 – 30.9)	30.9% (29.6 – 32.3)	3.9%	1.32 (1.14-1.54)	<0.001
Cough	475 (37.0%)	398 (31.0%)	-	-			297 (33.9%)	183 (21.0%)	35.7% (33.7 – 37.8)	26.9% (25.1 – 28.8)	31.3% (30.0 – 32.7)	8.9%	1.55 (1.09-2.23)	0.014
Angioedema	49 (3.8%)	53 (4.1%)	-	-			-	-	3.8% (2.9 – 5.0)	4.1% (3.2 – 5.4)	4.0% (3.3 – 4.8)	0.3%	0.92 (0.62-1.38)	0.69
Hypotension	-	-	7(5.5%)	0.00%	42(4.2%)	12(1.2%)	272 (31.0%)	194 (22.2%)	15.9% (14.4 – 17.6)	10.3% (9.1 – 11.8)	13.1% (12.1 – 14.2)	5.6%	2.59 (1.13-6.05)	0.025
Worsening Renal Function	-	-	6(4.7%)	4(3.1%)	15 (1.5%)	12(1.2%)	120 (13.7%)	94 (10.8%)	7.0% (6.0 – 8.2)	5.5% (4.6 – 6.6)	6.3% (5.6 – 7.1)	1.5%	1.45 (1.12 0 1.90)	0.005
Angina	-	-	-	-	181 (18%)	171 (17.2)	334 (38.1%)	318 (36.4%)	27.2% (25.3 – 29.3)	26.2% (24.3 – 28.2)	26.7% (25.3 – 28.2)	1.0%	1.06 (0.91-1.23)	0.43
Hyperkalemia	-	-	-	-			43 (4.9%)	23 (2.6%)	4.9% (3.7 – 6.5)	2.6% (1.8 – 3.9)	3.8% (3.0 – 4.8)	2.3%	1.92 (1.14-3.19)	0.014

ACE: angiotensin-converting enzyme; AE: adverse event

Table 3:

AEs Noted in Beta Blocker Cardiovascular Outcomes Trials.

	Carvedilol						Metoprolol		Frequency with Intervention	Frequency with Placebo	Overall Frequency	Placebo-Adjusted Frequency in Intervention Arm	Odds Ratio with 95% confidence interval	P-value
	Carvedilol Heart Failure Study Group		COPERNICUS		CAPRICORN		MERIT-HF							
Median Follow-up	6.5 mo		10.4 mo*		15.6 mo		12 mo*							
	Carvedilol	Placebo	Carvedilol	Placebo	Carvedilol	Placebo	Metoprolol Succinate	Placebo						
	n=696	n=398	n=1156	n=1133	975	984	n=1990	n=2001						
Any SAE	-	-	451 (39%)	516 (45.5%)	-	-	-	-	39.0% (36.2 to 41.9)	45.5% (42.7 to 48.5)	42.2% (40.2 to 44.3)	−6.5%	0.76 (0.65-0.90)	0.002
AE leading to discontinuation of study drug	40 (5.7%)	31 (7.8%)	-	-	176 (18.0%)	197 (20.0%)	196 (9.8%)	234 (11.7%)	11.3% (10.3 to 12.3)	13.7% (12.5 to 14.9)	12.4% (11.7 to 13.2)	−2.4%	0.84 (0.73-0.97)	0.015
Dizziness	233 (33.4%)	80 (20.1%)	-	-	-	-	12 (0.6%)	6 (0.3%)	9.1% (8.1 to 10.3)	3.6% (2.9 to 4.4)	6.5% (5.9 to 7.2)	5.5%	1.99 (1.52-2.64)	<0.001
Fatigue	177 (25.4%)	93 (23.3%)	-	-	-	-	14 (0.7%)	9 (0.4%)	7.1% (6.2 to 8.1)	4.3% (3.5 to 5.1)	5.8% (51.5 to 64.3)	2.9%	1.16 (0.88-1.52)	0.29
Dyspnea	150 (21.6%)	101 (25.4%)	19 (1.6%)	26 (2.3%)	-	-	15 (0.8%)	12 (0.6%)	4.8% (4.2 to 5.5)	3.9% (3.3 to 4.6)	4.4% (3.9 to 4.9)	0.9%	0.83 (0.65-1.06)	0.13
Upper Resp Infection	133 (19.1%)	74 (18.6%)	-	-	-	-			19.1% (16.4 to 22.2)	18.6% (15.1 to 22.7)	18.9% (16.7 to 21.3)	0.5%	1.03 (0.76-1.42)	0.83
Chest pain	104 (14.9%)	61 (15.3%)	38 (3.3%)	46 (4.1%)	-	-	9 (0.5%)	20 (1.0%)	3.9% (3.4 to 4.6)	3.6% (3.0 to 4.3)	3.8% (3.4 to 4.2)	0.3%	0.82 (0.61-2.66)	0.19
Hyperglycemia	88 (12.6%)	34 (8.5%)	-	-	-	-			12.6% (10.4 to 15.3)	8.5% (6.2 to 11.7)	11.1% (9.4 to 13.2)	4.1%	1.55 (1.02-2.34)	0.039
Diarrhea	83 (11.9%)	24 (6%)	-	-	-	-			11.9% (9.7 to 14.5)	6.0% (4.1 to 8.8)	9.8% (8.2 to 11.7)	5.9%	2.11 (1.32-3.39)	0.0019
Weight Gain	71 (10.2%)	30 (7.5%)	-	-	-	-			10.2% (8.2 to 12.7)	7.5% (5.3 to 10.6)	9.2% (7.7 to 11.1)	2.7%	1.39 (0.90-2.18)	0.14
Cough	58 (8.3%)	40 (10.1%)	-	-	-	-			8.3% (6.5 to 10.6)	10.1% (7.5 to 13.4)	8.9% (7.4 to 10.8)	−1.7%	0.81 (1.88-1.25)	0.34
Pain	62 (8.9%)	33 (8.3%)	-	-	-	-			8.9% (7.0 to 11.3)	8.3% (6.0 to 11.4)	8.7% (7.2 to 10.5)	0.6%	1.08 (0.70-1.68)	0.73

JACC Heart Fail. Author manuscript; available in PMC 2023 April 10.

	Carvedilol						Metoprolol		Frequency with Intervention	Frequency with Placebo	Overall Frequency	Placebo-Adjusted Frequency in Intervention Arm	Odds Ratio with 95% confidence interval	P-value
	Carvedilol Heart Failure Study Group		COPERNICUS		CAPRICORN		MERIT-HF							
Median Follow-up	6.5 mo		10.4 mo*		15.6 mo		12 mo*							
	Carvedilol	Placebo	Carvedilol	Placebo	Carvedilol	Placebo	Metoprolol Succinate	Placebo						
	n=696	n=398	n=1156	n=1133	975	984	n=1990	n=2001						
Headache	57 (8.2%)	30 (7.5%)	-	-	-	-			8.1% (6.4 to 10.5)	7.5% (5.3 to 10.6)	7.9% (6.5 to 9.7)	0.7%	1.09 (0.69-1.73)	0.70
Nausea	60 (8.6%)	18 (4.5%)	-	-	-	-			8.6% (6.8 to 10.9)	4.5% (2.9 to 7.0)	7.1% (5.8-8.8)	4.1%	1.99 (1.16-3.42)	0.013
Hypotension	60 (8.6%)	15 (3.8%)	22(1.9%)	18 (1.6%)	-	-	12 (0.6%)	5 (0.2%)	2.4% (2.0 to 3.0)	1.1% (0.8 to 1.5)	1.8% (1.5 to 2.1)	1.4%	1.84 (1.11-3.06)	0.019
Asthma	49 (7%)	27 (6.8%)	-	-	-	-			7.0% (5.4 to 9.2)	6.8% (4.7 to 9.7)	6.9% (5.6 to 8.6)	0.3%	1.04 (0.64-1.70)	0.87
Bradycardia	65 (9.3%)	4 (1%)	17 (1.5%)	14 (1.2%)	-	-	16 (0.8%)	5 (0.2%)	2.6% (2.1 to 3.1)	0.7% (0.4 to 1.0)	1.6% (1.4 to 2.0)	1.9%	3.25 (0.95-11.02)	0.06
Vomiting	46 (6.6%)	20 (5%)	-	-	-	-			6.6% (5.0 to 8.7)	5.0% (3.3 to 7.6)	6.0% (4.8 to 7.6)	1.6%	1.34 (0.78-2.29)	0.29
Worsening Renal Function	46 (6.6%)	18 4. (5%)	22 (1.9%)	35 (3.1%)	-	-			3.7%(2.9. to 4.6)	3.5% (2.7 to 4.5)	3.6% (3.0 to 4.3)	0.2%	0.95 (0.39-2.29)	0.91
Syncope	-	-	19 (1.6%)	17 (1.5%)	-	-			1.6% (1.1 to 2.6)	1.5% (0.9 to 2.4)	1.6% (1.1 to 2.2)	0.1%	1.09 (0.57-2.12)	0.78

AE: adverse event

Table 4:

AEs Noted in MRA Cardiovascular Outcomes Trials.

In RALES gynecomastia only recorded in men, n=603 for spironolactone n=614 placebo.

Median Follow-up	Spironolactone		Eplerenone				Frequency with Intervention	Frequency with Placebo	Overall Frequency	Placebo-Adjusted Frequency in Intervention Arm	Odds Ratio with 95% confidence interval	P-value
	RALES		EMPHASIS-HF		EPHESUS							
	24 mo		21 mo		16 mo							
	Spironolactone	Placebo	Eplerenone	Placebo	Eplerenone	Placebo						
	n=822	n=841	n=1364	n=1373	n=3313	n=3319						
Any Event	674 (82.0%)	667 (79.3%)	979 (71.8%)	1007 (73.6%)	2608 (78.9%)	2623 (79.5%)	77.5% (76.4 to 78.6)	77.7% (76.5 to 78.7)	77.6% (76.8 to 78.3)	2.7%	0.99 (0.90-1.08)	0.83
AE Leading to Discontinuation of Study Drug	62 (7.5%)	40 (4.8%)	118 (13.8%)	222 (16.2%)	-	-	8.2% (7.2 to 9.5)	11.8% (10.6 to 13.2)	10.0% (9.2 to 11.0)	−3.7%	0.89 (0.27-2.89)	0.84
Hyperkalemia	-	-	109 (8.0%)	50 (3.7%)	113 (7.4%)	66 (2%)	4.7% (4.2 to 5.4)	2.5% (2.1 to 3.0)	3.6% (3.2 to 4.0)	2.3%	1.97 (1.51-2.59)	<0.001
Cough	103 (12.5%)	117 (13.9%)	-	-	167 (5%)	207 (6.3%)	6.5% (5.8 to 7.3)	7.9% (7.1 to 8.8)	7.2% (6.7 to 7.8)	−1.4%	0.83 (0.70-2.59)	0.029
MSK Disorders	101 (12.3%)	118 (14.0%)	-	-	209 (6.3%)	213 (6.5%)	7.5% (6.7 to 8.3)	7.9% (7.2 to 8.8)	7.7% (7.2 to 8.3)	−0.5%	0.94 (0.80-1.11)	0.45
Hypotension	-	-	46 (3.4%)	37 (2.7%)	-	-	3.4% (2.5 to 4.5)	2.7% (2.0 to 3.7)	3.0% (2.5 to 3.7)	0.7%	1.26 (0.81-1.95)	0.30
Renal Failure	-	-	38 (2.8%)	41 (3.0%)	-	-	2.8% (2.0 to 3.8)	3.0% (2.2 to 4.0)	2.9% (2.3 to 3.6)	−0.27%	0.93 (0.59-1.46)	0.75
Hypokalemia	-	-	16 (1.2%)	30 (2.2%)	15 (0.5%)	49 (1.5%)	0.7% (0.47 to 0.94)	1.7% (1.4 to 2.1)	1.2% (0.98 to 1.4)	−1.0%	0.40 (0.23-0.69)	0.001
Gynecomastia*	55 (9.1%)	8 (1.3%)	-	-	-	-	9.1% (7.1to 11.7)	1.3% (0.7 to 2.5)	5.2% (4.1 to 6.6)	5.7%	7.61 (3.60-16.12)	<0.001
Breast pain *	10 (1.7%)	1 (0.2%)	-	-	-	-	1.2% (0.66 to 2.2)	0.11% (0.02 to 0.67)	0.7% (0.37 to 1.2)	1.1%	10.38 (1.32-80.64)	0.026
Either gynecomastia or breast pain *	61 (10.1%)	9 (1.5%)	10 (0.7%)	14 (1%)	12 (0.5%)	14 (0.6%)	1.5% (1.2 to 1.9)	0.7% (0.5 to 0.9)	1.1% (0.9 to 1.3)	0.9%	1.68 (0.38-7.39)	0.49
Serious Hyperkalemia	14 (1.7%)	10 (1.2%)	-	-	180 (5.5%)	126 (3.9%)	4.7% (4.1 to 5.4)	3.3% (2.8 to 3.9)	4.0% (3.6 to 4.4)	1.4%	1.46 (1.16-1.82)	0.001

AE: adverse event; MRA: mineralocorticoid receptor antagonist; MSK: musculoskeletal

Table 5:

AEs Noted in SGLT2i Cardiovascular Outcomes Trials.

	Dapagliflozin		Empagliflozin		Sotagliflozin		Frequency with Intervention	Frequency with Placebo	Overall Frequency	Placebo-Adjusted Frequency in Intervention Arm	Odds Ratio with 95% confidence interval	P-value
	DAPA-HF		Emperor-Reduced		SOLOIST-WHF Trial							
Median Follow-up time	18.2 mo		16 mo		9 mo							
	Dapagliflozin	Placebo	Empagliflozin	Placebo	Sotagliflozin	Placebo						
	n=2372	n=2371	n=1863	n=1867	n= 608	n=614						
Patients with at least one AE			1420 (76.2%)	1463 (78.5%)	420 (69.4%)	412 (67.4%)	74.1% (72.4 to 75.8)	75.6% (73.8 to 77.2)	74.9% (73.6 to 76.0)	−0.8%	0.96 (0.79-1.19)	0.73
Patients with at least one SAE	895 (37.8%)	994 (42%)	772 (41.4%)	896 (48.1%)	235 (38.8%)	251 (41.1%)	39.3% (37.9 to 40.7)	44.1% (42.7 to 45.5)	41.7% (40.7 to 42.7)	−4.9%	0.82 (0.76-0.89)	<0.001
AE leading to permanent discontinuation of drug	111 (4.7%)	116 (4.9%)	-	-	29 (4.8%)	23 (3.8%)	4.7% (4.0 to 5.5)	4.7% (4.0 to 5.4)	4.7% (4.2 to 5.2)	0%	1.01 (0.79-1.28)	0.94
SAE leading to permanent discontinuation of study drug	-	-	-	-	18 (3%)	17 (2.8%)	3.0% (1.9 to 4.6)	2.8% (1.7 to 4.4)	2.9% (2.1 to 3.9)	0.2%	1.07 (0.55-2.10)	0.84
AE leading to death	227 (9.6%)	250 (10.6%)	-	-	51 (8.4%)	54 (8.8%)	9.3% (8.3 to 10.4)	10.2% (9.1 to 11.3)	9.6% (9.0 to 10.5)	−3.2%	0.90 (0.76-1.07)	0.26
Symptomatic Hypotension	-	-	106 (5.7%)	103 (5.5%)	-	-	5.7% (4.7 to 6.8)	5.5% (4.6 to 6.6)	5.6% (4.9 to 6.4)	0.2%	1.03 (0.78 −1.36)	0.82
Diarrhea	-	-	-	-	37 (6.1%)	21 (3.4%)	6.1% (4.4 to 8.3)	3.4% (2.2 to 5.2)	4.7% (3.7 to 6.1)	2.7%	1.82 (1.06 −3.16)	0.031
Severe Hypoglycemia	4 (0.2%)	4 (0.2%)	-	-	9 (1.5%)	2 (0.3%)	0.3% (0.2 to 0.6)	0.1% (0.01 to 0.2)	0.2% (0.1 to 0.3)	1.2%	2.08 (0.46 −9.21)	0.34
Hypotension	7 (0.3%)	11 (0.5%)	176 (9.4%)	163 (8.3%)	36 (6%)	28 (4.6%)	4.5% (4.0 to 5.1)	4.2% (3.6 to 4.8)	4.3% (4.0 to 4.8)	0.3%	1.09 (0.90 −1.34)	0.39
AKI	23 (1.0%)	46 (1.9%)	-	-	25 (4.1%)	27 (4.4%)	1.6% (1.2 to 2.1)	2.4% (1.9 to 3.1)	2.0% (1.7 to 2.4)	−0.8%	0.68 (0.36-1.25)	0.21
UTI	11 (0.5%)	17 (0.7%)	91 (4.9%)	83 (4.5%)	29 (4.8%)	31 (5.1%)	2.7% (2.3 to 3.2)	2.7% (2.3 to 3.2)	2.7% (2.4 to 3.0)	0.00%	1.01 (0.79 −1.28)	0.97
Pneumonia	76 (3.2%)	82 (3.5%)	-	-	27 (4.5%)	31 (5.1%)	3.5% (2.9 to 4.2)	3.8% (3.2 to 4.5)	3.6% (3.2 to 4.1)	−0.3%	0.91 (0.69-1.20)	0.50

	Dapagliflozin		Empagliflozin		Sotagliflozin		Frequency with Intervention	Frequency with Placebo	Overall Frequency	Placebo-Adjusted Frequency in Intervention Arm	Odds Ratio with 95% confidence interval	P-value
	DAPA-HF		Emperor-Reduced		SOLOIST-WHF Trial							
Median Follow-up time	18.2 mo		16 mo		9 mo							
	Dapagliflozin	Placebo	Empagliflozin	Placebo	Sotagliflozin	Placebo						
	n=2372	n=2371	n=1863	n=1867	n= 608	n=614						
Hyperkalemia	2 (0.1%)	5 (0.2%)	-	-	26 (4.3%)	31 (5.1%)	0.9% (0.65 to 1.4)	1.2% (0.9 to 1.7)	1.1% (0.8 to 1.4)	−0.3%	0.78 (0.47-1.30)	0.34
Hypoglycemia	1 (0%)	4 (0.2%)	27 (1.4%)	18 (1.5%)	26 (4.3%)	17 (2.8%)	1.1% (0.9 to 1.5)	0.8% (0.6 to 1.1)	1.0% (0.7 to 1.2)	0.3%	1.43 (0.94-2.20)	0.093
Renal Impairment/ Event	153 (6.5%)	170 (7.2%)	-	-	12 (2%)	13 (2.1%)	5.5% (4.8 to 6.4)	6.1% (5.3 to 7.0)	5.8% (5.3 to 6.5)	1.8%	0.90 (0.71-1.12)	0.32
Renal Failure	8 (0.3%)	8 (0.3%)	-	-	9 (1.5%)	12 (2.0%)	0.6% (0.4 to 0.9)	0.7% (0.4 to 1.0)	0.6% (0.5 to 0.9)	0.2%	0.85 (0.44-1.63)	0.63
CKD	4 (0.2%)	8 (0.3%)	-	-	9 (1.5%)	12 (2.0%)	0.4% (0.3 to 0.7)	0.7% (0.4 to 1.0)	0.6% (0.4 to 0.8)	0%	0.65 (0.32-1.32)	0.24
Dysuria	-	-	-	-	10 (1.7%)	2 (0.3%)	1.6% (0.9 to 3.0)	0.3% (0.1 to 1.2)	1.0% (0.7 to 1.7)	1.4%	5.10 (1.11-23.57)	0.036
Bone Fractures	49 (2.1%)	50 (2.1%)	45 (2.4%)	42 (2.3%)	12 (2%)	9 (1.5%)	2.2% (1.8 to 2.6)	2.1% (1.8 to 2.6)	2.2% (1.9 to 2.5)	0.1%	1.05 (0.79-1.39)	0.72
Diabetic Ketoacidosis	3 (0.1%)	0	-	-	2 (0.3%)	4 (0.7%)	0.2% (0.07 to 0.4)	0.1% (0.05 to 0.3)	0.2% (0.08 to 0.3)	0.0%	0.71 (0.11-17.46))	0.79
Genital Mycotic Infection	-	-	31 (1.7%)	12 (0.6%)	5 (0.8%)	1(0.2%)	1.5% (1.4 to 1.7%)	0.5% (0.3 to 0.9)	1.0% (0.7 to 1.3)	0.9%	2.77 (1.46-5.26)	0.0018
Complicated Genital Mycotic Infection	-	-	6 (0.3%)	5 (0.3%)	-	-	0.3% (0.2 to 0.7)	0.3% (0.1 to 0.6)	0.3% (0.2 to 0.5)	0.1%	1.21 (0.37-3.94)	0.76
Complicated UTI			19 (1.0%)	15 (0.8%)			1% (0.7 to 1.6)	0.8% (0.5 to 1.3)	0.9% (0.7 to 1.3)	0.2%	1.27 (0.64-2.51)	0.49
Volume Depletion	178 (7.5%)	162 (6.8%)	197 (10.6%)	184 (9.9%)	57 (9.4%)	54 (8.8%)	8.9% (8.1 to 9.8)	8.2% (7.5 to 9.1)	8.6% (8.0 to 9.2)	0.7%	1.09 (0.92-1.26)	0.23
Pancreatitis	6 (0.3%)	4 (0.2%)	-	-	0	3 (0.5%)	0.2% (0.1 to 0.4)	0.2% (0.1 to 0.5)	0.2% (0.1 to 0.4)	−0.0%	0.69 (0.08-5.99)	0.74
Venous Thrombotic Events	1 (0%)	0%	-	-	4 (0.7%)	1 (0.2%)	0.2% (0.07 to 0.4)	0.0 (0 to 0.2)	0.1% (0.1 to 0.2)	0.1%	3.67 (0.60-22.42)	0.16

JACC Heart Fail. Author manuscript; available in PMC 2023 April 10.

	Dapagliflozin		Empagliflozin		Sotagliflozin		Frequency with Intervention	Frequency with Placebo	Overall Frequency	Placebo-Adjusted Frequency in Intervention Arm	Odds Ratio with 95% confidence interval	P-value
	DAPA-HF		Emperor-Reduced		SOLOIST-WHF Trial							
Median Follow-up time	18.2 mo		16 mo		9 mo							
	Dapagliflozin	Placebo	Empagliflozin	Placebo	Sotagliflozin	Placebo						
	n=2372	n=2371	n=1863	n=1867	n= 608	n=614						
Amputation	13 (0.5%)	12 (0.5%)	13 (0.7%)	10 (0.5%)	4 (0.7%)	1 (0.2%)	0.6% (0.4 to 0.9)	0.5 (0.3 to 0.7)	0.6% (0.4 to 0.7)	0.1%	1.28 (0.73-2.23)	0.38

AE: AE; AKI: acute kidney injury; CKD: chronic kidney disease; SAE: serious AE; SGLT2i: sodium-glucose co-transporter 2 inhibitor; UTI: urinary tract infection