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# Potential Global Impact of Sodium-Glucose Cotransporter-2 Inhibitors in Heart Failure

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## ABSTRACT

**Aims:** Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are effective across the spectrum of the left ventricular ejection fraction (LVEF) in heart failure (HF); however, population-wide medication use in eligible patients remains suboptimal. We evaluated the potential implications of optimal global implementation of SGLT-2 inhibitors in HF.

**Methods and Results:** A decision analytical study was performed using the global prevalence of HF from the Global Burden of Disease 2017 report. Exclusion criteria were applied using the NHANES to ascertain an SGLT-2 inhibitor-eligible population, which was mapped onto global LVEF distributions from the REPORT-HF registry. The number needed to treat for 3 years for the composite of worsening HF events and cardiovascular deaths was calculated from estimated event rates in the EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, and DELIVER trials and projected onto the eligible population. An estimated 49,329,000 (95%CI, 43,882,000–54,929,000) HF patients would be eligible for SGLT-2 inhibitors across all LVEFs, including 25,651,000 (95%CI, 22,818,000–28,563,000) with LVEF of ≤40% and 23,678,000 (95%CI, 21,063,000–26,366,000) with LVEF >40%. Optimal implementation of SGLT-2 inhibitors would be projected to prevent/postpone 4,512,011 (95%CI, 4,013,686–5,024,232) to 5,986,943 (95%CI, 5,325,721–6,666,604) total worsening HF events and cardiovascular deaths over 3 years in patients with LVEF <40%. An additional 2,102,606 (95%CI, 1,870,394–2,341,301) to 2,557,224 (95%CI, 2,274,804–2,847,528) events would be prevented/postponed in patients with LVEF >40%. Among all eligible HF patients, irrespective of LVEF, 7,069,235 (95%CI, 6,288,490–7,871,760) to 8,089,549 (95%CI, 7,196,115–9,007,905) total worsening HF events and cardiovascular deaths would be prevented/postponed over this period.

**Conclusions:** Optimal implementation of SGLT-2 inhibitors globally in HF is projected to prevent approximately 7-8 million worsening HF events and cardiovascular deaths over 3 years.


**Keywords:** sodium-glucose cotransporter-2; heart failure; implementation; global; hospitalization; cardiovascular death.

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are efficacious in heart failure (HF) across the spectrum of left ventricular ejection fraction (LVEF), based on the evidence from the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) [1], EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) [2], EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) [3] and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trials [4]. Their use is further supported in patients with recent worsening HF by the SOLOIST-WHF [5] (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) and the EMPULSE [6] (The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure) trials.

Efforts toward achieving broader utilization of SGLT-2 inhibitors in eligible patients would be expected to have substantial impact. For example, in a contemporary analysis of the benefits of SGLT-2 inhibitors in HF based on trial data in the United States, a maximum of 630,000 worsening HF events and cardiovascular deaths were projected to be prevented over 3 years [7]. Global uptake of SGLT-2 inhibitors for HF would also lead to major patient and population-level benefits in the setting of a nearly 2-fold increase in global HF cases from 1990 to 2017 [8], especially in low- and middle-income countries but represents a major challenge with regional variation in health system infrastructure, health policy, and access to healthcare. In this decision analytical model study, we sought to examine the potential global impact of optimal implementation of SGLT-2 inhibitor therapy in HF across the LVEF spectrum.

## METHODS

### Study Cohort

The Global Burden of Disease (GBD) is a comprehensive and systematic report that provides an estimation of disease prevalence, injuries, and risk factors at a regional, national, and global level stratified by age, sex, and location. The census is administered by the Institute of Health

Metrics and Evaluation (IHME) at the University of Washington and is funded by the Bill and Melinda Gates Foundation. The details of how GBD collects and classifies data have been described previously [9]. Estimates of global HF prevalence were obtained from an investigation by Bragazzi et al. who reported the collective burden of HF in 21 regions and 195 countries from 1990 to 2017 using the 2017 GBD report [10].

The National Health and Nutritional Examination Survey (NHANES) [11], which is a biannually conducted survey designed to project national prevalence estimates of diseases in the US, was used to obtain baseline characteristics of the HF population in the US from 2015 to 2018 (N=19,255). The data from the NHANES cohort were used to apply the following exclusions to the total HF prevalence estimate obtained from GBD 2019: patients with an estimated glomerular filtration rate (eGFR [<20 mL/min/1.73 $m^2$]) (7.2%) and systolic blood pressure (SBP) <95 mm Hg (5.8%), those with New York Heart Association Class I functional status (5.0%), those receiving hospice care or comfort measures only (4.0%), inotropic agents, ventricular assist devices, urgent transplantation (1.0%), and those with type 1 diabetes mellitus (0.02%). Blood pressure measurements were obtained by physical examination and eGFR was determined based on creatinine measurements. These data from a global registry were not reliably available, hence the NHANES data for HF patients in the US was used to estimate patients that would not be eligible for SGLT-2 inhibitor therapy.

**Estimation of Left Ventricular Ejection Fraction Subgroups**

The International Registry to assess medical Practice and Longitudinal Observation for Treatment of Heart Failure (REPORT-HF) is a global registry of HF patients prospectively collected at 358 sites across 44 countries [12]. A total of 18,102 patients that were hospitalized for new-onset HF or decompensation of chronic HF between July 2014 and March 2017 were recruited over 32 months. We used the data from the registry to estimate the global distribution of HF with reduced ejection fraction (HFrEF) and HF with mildly reduced ejection fraction (HFmrEF)/HF with preserved ejection fraction [HFpEF])., e.g., LVEF $\leq$40% and LVEF >40%,

respectively [13]. The LVEF distribution estimates were also compared to those reported in the Global Congestive Heart Failure (G-CHF) study [14]. The estimates were mapped onto the HF population estimate from the GBD to obtain estimates of the total HF population with LVEF ≤40% and LVEF >40%.

**Endpoint Assessment**

We designated the following endpoints for assessment of population-level impact, standardized over 1 and 3 years; a) total (first and recurrent) HF hospitalizations, b) composite of total (first and recurrent) HF hospitalizations and CV deaths, and c) composite of worsening HF event (expanded composite inclusive of urgent HF visits and total HF hospitalizations) or CV death, as done in a prior similar study [7]. Urgent HF visits were defined as urgent outpatient or emergency room visits for worsening HF that required intravenous therapy. Event rates for these endpoints were obtained from the DAPA-HF and EMPEROR-Reduced trials for LVEF ≤40% and from the EMPEROR-Reduced and DELIVER trials for LVEF >40%.

**Adverse events**

The following adverse events of interest were included in this analysis, standardized at 1 and 3 years: a) symptomatic hypotension (events defined by investigators with no specific cut-off for blood pressure), and b) mycotic genital infections (urinary tract infections are not included). Projected population-level adverse events were only reported for the EMPEROR-Reduced and EMPEROR-Preserved trials. The DAPA-HF and DELIVER trials only reported data on serious adverse events, adverse events that led to drug discontinuation and select other adverse events, which was different from how adverse events were reported in the EMPEROR-Reduced and EMPEROR-Preserved trials.

**Numbers Needed to Treat for Recurrent Events**

We calculated incidence rates for total (first and recurrent) HF hospitalizations, CV death and HF hospitalizations, and worsening HF events or CV death using trial-level data from the EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, and DELIVER trials. The number

needed to treat (NNT) is defined as the number of patients that need to be treated with the study drug (SGLT-2 inhibitor in this case) for a specific time to prevent one patient from having an event. The NNT for the investigated recurrent events was calculated as per patient-year observed using data at 1- and 3 years following randomization for each endpoint. The NNT for all LVEFs was calculated using pooled data from the EMPEROR-Reduced and EMPEROR-Preserved trials, and DAPA-HF and DELIVER trials, and was reported separately for each set of trials. The NNT for LVEF ≤40% was calculated using data from the EMPEROR-Reduced and DAPA-HF trials and was reportedly separately. The NNT for LVEF >40% was calculated using data from the EMPEROR-Preserved and DELIVER trials and was reported separately. We calculated an event based NNT that represents the number of patients that must be treated for 1 and 3 years to prevent 1 event. The NNT was estimated by calculating the inverse of the rate difference (reported as events per 100 patient-years) **(Table 1)**. These NNTs were then mapped onto the HF population groups as derived earlier for LVEF ≤40%, LVEF >40%, and all LVEFs that would be eligible for SGLT-2 inhibitor therapy.

**Numbers Needed to Harm for Adverse Events**

The number needed to harm (NNH) is defined as the number of patients that needed to be treated with the study drug to cause one patient to have an adverse event. The NNH was computed as event-based for the first occurrences of symptomatic hypotension and genital infections. Assuming an exponential distribution, we calculated expected event rates using data for up to 1 and 3 years from the EMPEROR-Reduced and EMPEROR-Preserved trials. NNH was then computed using the inverse of the estimated event rate difference between the SGLT-2 inhibitor and placebo groups. The rate difference confidence intervals (CI) were calculated based on the exponential model. The inverse of the rate difference CI was calculated to determine the CI for NNH **(Table 2)**. Data until 7 days after treatment discontinuation was used in line with the safety analyses of the trial. These NNHs were then mapped onto the HF population groups as derived earlier for LVEF ≤40%, LVEF >40%, and all LVEFs that would be

eligible for SGLT-2 inhibitor therapy. All analyses were performed using SAS, version 9.4 (SAS Institute).

**RESULTS**

The global prevalence of HF was estimated to be 64,300,000 (95% CI: 57,200,000 – 71,600,000). After exclusions were applied, 49,329,000 (95% CI: 43,882,000 – 54,929,000) HF patients eligible for SGLT-2 inhibitors were identified **(Figure 1)**. Among 18,102 patients hospitalized for HF in the REPORT-HF registry, 1562 (9%) did not have available data for LVEF. Among those with available data (n = 16,540), relative proportions of patients based on LVEF subgroups, ≤40% and >40%, were 52% and 48% respectively. Similar proportions were reported in the G-CHF study (LVEF ≥40, 46%, LVEF <40%, 54%). When mapped onto the global population estimates, an estimated 25,651,000 (95% CI, 22,818,000 – 28,563,000) individuals had an LVEF of ≤ 40% and would have met the eligibility criteria for SGLT-2 inhibitor therapy based on results of the DAPA-HF and EMPEROR-Reduced trials. An estimated 23,678,000 (95% CI, 21,063,000 – 26,366,000) individuals had an LVEF >40% and would have potentially met the eligibility criteria for SGLT-2 inhibitor therapy based on the results of the EMPEROR-Preserved and DELIVER trials.

**LVEF ≤40%**

In the DAPA-HF trial, the 3-year NNTs for total HF hospitalizations, the composite of HF hospitalizations and CV deaths, and worsening HF event or CV death were 9, 7, and 6, respectively **(Table 1)**. In the EMPEROR-Reduced trial, the 3-year NNT for total HF hospitalizations, the composite of HF hospitalizations and CV deaths, and worsening HF event or CV death was 5 for all endpoints **(Table 1)**. Using these estimates, optimal implementation of SGLT-2 inhibitors in HF with LVEF ≤40% is projected to prevent/postpone 2,978,081 (95% CI, 2,649,170 – 3,316,164) to 5,132,765 (95% CI, 4,565,882 –5,715,456) total HF hospitalizations, 4,068,249 (95% CI, 3,618,935 – 4,530,092) to 5,579,093 (95% CI, 4,962,915 – 6,212,453) total HF hospitalizations and CV deaths, and 4,512,011 (95% CI, 4,013,686 – 5,024,232) to

5,986,943 (95% CI, 5,325,721 – 6,666,604) worsening HF events and CV deaths over 3 years **(Table 3) (Figure 2)**.

**LVEF >40%**

The 3-year NNT among 5988 participants in the EMPEROR-Preserved trial for total HF hospitalizations, the composite of HF hospitalizations and CV deaths, and worsening HF event or CV death were 16, 13, and 12, respectively **(Table 1)**. Among 6263 participants in the DELIVER trial, the 3-year NNTs for total HF hospitalizations, the composite of HF hospitalizations and CV deaths, and worsening HF event or CV death were 12, 10, and 10, respectively **(Table 1)**. Using these estimates, the optimal implementation of SGLT-2 inhibitors in HF with LVEF >40% is projected to prevent/postpone 1,562,748 (95% CI, 1,390,158 – 1,740,156) to 2,088,400 (95% CI, 1,857,757 – 2,325,481) total HF hospitalizations, 1,832,677 (95% CI, 1,630,276 – 2,040,728) to 2,400,949 (95% CI, 2,135,788 – 2,673,512) total HF hospitalizations and CV deaths, and 2,102,606 (95% CI, 1,870,394 – 2,341,301) to 2,557,224 (95% CI, 2,274,804 – 2,847,528) worsening HF events and CV deaths over 3 years **(Table 3) (Figure 2)**.

**All LVEFs**

The estimated population-level benefit was calculated by the addition of the number of events prevented/postponed in the LVEF $\leq$40% and LVEF >40% groups in the EMPEROR-Reduced and EMPEROR-Preserved trials, and the DAPA-HF and DELIVER trials, respectively. Optimal implementation of SGLT-2 inhibitors across the LVEF spectrum is projected to prevent/postpone to 5,066,481 (95% CI, 4,506,927 – 5,641,645) to 6,695,513 (95% CI, 5,956,040 – 7,455,612) total HF hospitalizations, 6,469,198 (95% CI, 5,754,723 – 7,203,604) to 7,411,770 (95% CI, 6,593,151 – 8,253,181) total HF hospitalizations and CV deaths, and 7,069,235 (95% CI, 6,288,490 – 7,871,760) to 8,089,549 (95% CI, 7,196,115 – 9,007,905) worsening HF events and CV deaths over 3 years **(Table 3) (Figure 2)**.

**Adverse events**

Among patients with LVEF ≤40% in the EMPEROR-Reduced trial, the 3-year NNH for symptomatic hypotension and genital infections was 447 and 41, respectively **(Table 2)**. Optimal implementation of SGLT-2 inhibitor therapy would cause a projected 57,385 (95% CI, 51,047 – 63,899) patients to experience a symptomatic hypotension event and 625,634 (95% CI, 556,537 – 696,659) patients to experience a genital infection over 3 years **(Table 3)**. Among patients with LVEF >40% in the EMPEROR-Preserved trial, the 3-year NNH for symptomatic hypotension and genital infections was 52 and 42, respectively **(Table 2)**. Optimal implementation of SGLT-2 inhibitor therapy would cause a projected 455,346 (95% CI, 405,058 – 507,038) patients to experience a symptomatic hypotension event and 563,762 (95% CI, 501,500 – 627,762) patients to experience a genital infection over 3 years **(Table 3)**. The estimated population-level benefit was calculated by the addition of the number of events caused in the LVEF ≤40% and LVEF >40% groups in the EMPEROR-Reduced and EMPEROR-Preserved trials. Optimal implementation of SGLT-2 inhibitor therapy would cause a projected 512,713 (95% CI, 456,105 – 570,937) patients to experience a symptomatic hypotension event and 1,189,396 (95% CI, 1,058,037 – 1,324,421) patients to experience a genital infection event over 3 years **(Table 3)**. The data for adverse events from the DAPA-HF and DELIVER trials were not included in the study as only serious adverse events, adverse events that led to treatment discontinuation and select other events were reported in these trials.

## DISCUSSION

This study provides critical insight into the potential benefits of global implementation of SGLT-2 inhibitor therapy for HF across the LVEF spectrum. We estimate that up to 7.5 million worsening HF events and cardiovascular deaths would be prevented or postponed with optimal implementation of SGLT-2 inhibitors globally across the LVEF spectrum. This includes the prevention or postponement of approximately 5.2 million worsening HF events and cardiovascular deaths in patients with HFrEF and approximately 2.3 million worsening HF

events and cardiovascular deaths in patients with HFmrEF and HFpEF. Such benefits would be offset by a substantially smaller number of projected adverse events.

These findings are important in the context of a high global prevalence of HF. According to data from GBD, there has been a nearly 2-fold increase in the total HF cases from 1990 to 2017, however, there has been a decrease in age-standardized prevalence rates from 895 per 100,000 persons to 831 per 100,000 persons from 1990 to 2017 [8]. The GBD 2017 report also reported marked variation in prevalence rates across different geographic regions. The trends for prevalence are well-documented in the US and Western Europe with a projected 34% rise in HF in the US by 2060 [15]; however, the rest of the world shares an equal, if not greater, burden of HF, with rising estimates reported in Southeast Asia, South Asia, and South America. Moreover, the proportion of patients with HFrEF and HFpEF is largely similar, although epidemiological data over the past 20 years suggest a rising trend in HFpEF and a relatively stable/declining trend in HFrEF.

An analysis from the REPORT-HF registry [13] reported a great disparity in outcomes in HFrEF – a higher risk of 1-year mortality was observed in patients from lower-income countries and in countries with greater income inequality, supporting earlier findings in a global analysis of ambulant patients [16]. The outcomes were especially poor in Southeast Asia, followed by Eastern Mediterranean and Africa, and Central and South America. In the G-CHF study, health-related quality of life declined linearly across country income categories[14]. Another analysis from REPORT-HF reported that only about one-third of HF patients were on optimal medical therapy at hospital discharge and at 6-month follow-up[17].

Prescription and uptake of HF therapies in clinical practice in low-, middle-, and even high-income countries is suboptimal. Low rates of GDMT in low- and middle-income countries are mainly attributed to limited accessibility and affordability. Up to 2 billion people in the world lack access to essential cardiovascular medications for various reasons, and up to 60% in low- and middle-income countries, mostly in Asia and Africa, cannot afford essential cardiovascular

medications [18]. Khatib et al. reported in the PURE study (Prospective Urban and Rural Epidemiology) [19] that patients with CV disease living in communities where access to medications is limited are less likely on optimal therapy. The unaffordability and unavailability of these medications were also found to be associated with a high risk of major cardiac adverse events in patients with CV disease [20]. According to an analysis of 53 low- and middle-income countries' national essential medications list, only 47% included all recommended drug classes for HFrEF at that time, which were ACEi, beta-blockers, MRA, and diuretics [21]. Although one can infer several reasons for low rates of medication use in low- and middle-income countries including lack of adequate insurance and high out-of-pocket costs, there is a lack of high-quality evidence to assess barriers and facilitators to important CV medication use in these regions [22] which may preclude focused efforts to improve medication uptake. Moreover, most CV trials, including HF, were historically based in high-income countries in terms of research infrastructure and recruitment [23]. This leads to concerns about the generalizability of trial results to heterogenous populations globally and may impede the optimal use of medications.

Our study provides an important projection of the benefits that can be achieved with optimal medical therapy augmented with SGLT-2 inhibitors both in HFrEF and HFpEF. Optimal implementation of SGLT2 inhibitors globally in HF, if achievable, is projected to prevent 7 to 8 million worsening HF events and cardiovascular deaths over 3 years. The prevalence of HFpEF has been on the rise but therapies for HFpEF remain limited. SGLT-2 inhibitors are the only drugs that have been found to reduce worsening HF events in HFpEF and HFmrEF based on results from the EMPEROR-Preserved and DELIVER trials. If optimally implemented, we estimate that SGLT-2 inhibitors have the potential to prevent/postpone approximately 2.3 million worsening HF events and cardiovascular deaths in those with HFpEF alone.

Given that the traditional HF drug therapies recommended decades before the introduction of SGLT-2 inhibitors have still not achieved optimal uptake globally, it is necessary to consider the challenges of the implementation of SGLT-2 inhibitors. Cardinal among them is

cost; SGLT-2 inhibitors are part of a recommended 4-drug regimen for HFrEF, and a novel treatment option for HFpEF, and carry a substantial out-of-pocket cost even in insured patients in some high-income countries [24]. For example, in the US, annual out of pocket costs for 4-drug medical therapy for HFrEF was found to be ~$3000 for patients under Medicare[25]. Moreover, patients with HF are often older with multiple cardiovascular and non-cardiovascular co-morbidities and are already on multiple medications, so the addition of another medication would contribute to polypharmacy and medical expenditure. Current data regarding prescription rates of SGLT-2 inhibitors specifically for HF are scarce as indication for use in HF is rather new. However, SGLT-2 inhibitors also have multiple potential unique advantages that may favor improved implementation compared with other therapies. SGLT-2 inhibitors were originally considered to be anti-hyperglycemic drugs and are currently indicated as first-line therapy for patients with type 2 diabetes in patients at high cardiovascular risk [26] and can potentially replace routine use of alternative expensive medications like dipeptidyl-peptidase 4 inhibitors. They are also indicated in the management of CKD. The drug is already included in the list of essential medications by the World Health Organization for the management of type 2 diabetes [27]. Hence, the use of SGLT-2 inhibitors has already been well-established for multiple conditions for the past 5 to 10 years, and its safety profile is well-known. We also predict low symptomatic hypotension and genital infection event rates with optimal implementation over 3 years (500,000 and 1.2 million respectively) compared to projected benefits, and neither of these is an absolute contraindication to continuing therapy. Moreover, relative to other HF medications, the use of SGLT-2 inhibitors is remarkably safe and straightforward thus favoring improved utilization across a spectrum of global regions and available resources, including one dose with no titration, one pill per day, and no absolute requirement for routine serial laboratory monitoring. Moreover, widespread implementation of SGLT-2 inhibitors may facilitate the use of MRAs by reducing the risk of hyperkalemia[28]. Further, optimal GDMT may avoid or postpone the need for additional devices, e.g., implantable cardioverter-defibrillators, which could further reduce costs

for patients. Formal cost-effectiveness analyses have shown that use of comprehensive quadruple GDMT is cost effective compared to double or triple medical therapy[29]. Efforts toward reducing barriers to the administration of these beneficial drugs are needed. This includes addressing the social determinants of health that create disparities in access to quality healthcare, more universal insurance coverage for favorable therapies, and earlier application of treatments such as SGLT-2 inhibitors among at-risk or affected individuals.

**LIMITATIONS**

There are several limitations to this study. First, the results of this analysis are based on the integration of estimates of global HF prevalence, baseline characteristics to determine SGLT-2 inhibitor eligibility, and LVEF distribution obtained from different, non-overlapping datasets. The multiplicative assumptions make these projections general estimates. Second, a global database was not available to reliably identify estimates of baseline characteristics to determine eligibility for SGLT-2 inhibitors in HF; hence, we used a US-based self-reported database (NHANES) to obtain these estimates, which may not truly reflect the actual number of eligible patients globally and within each specific region. Third, we provide an estimate of the population-level benefit of the *maximal* implementation of SGLT-2 inhibitors and did not consider geographic variations in prescription rates and adherence patterns. The design of the study inherently assumes that all patients eligible for SGLT-2 inhibitors would take the drug consistently for 3 years. Fourth, GBD provides an estimated prevalence of HF in 2017 across all age groups and did not provide an estimate of HF prevalence in patients 18 and older, while NHANES, REPORT-HF, and all SGLT-2 inhibitor trials provide data for patients aged 18 years and older. This may have led to an overestimation of projected benefits and adverse events, though the number of individuals with HF in childhood is likely low. Fifth, the REPORT-HF reported data for LVEFs in patients hospitalized for HF which may not be a true representation of LVEF measurements in ambulatory patients though the data were comparable to G-CHF. Sixth, drug-related event rates and NNH were used from the EMPEROR-Reduced and

EMPEROR-Preserved trials, as DAPA-HF and DELIVER trials only reported safety data related to serious adverse events and those that led to treatment discontinuation for genital infections. Lastly, urgent HF visits that led to HF hospitalization were counted as two separate events in the EMPEROR-Reduced and EMPEROR-Preserved trials. This could have caused duplication of worsening HF events and overestimation of projected benefits.

**CONCLUSIONS**

Evidence-based use with optimal implementation of SGLT-2 inhibitors in HF is projected to prevent/postpone approximately 7-8 million worsening HF events and cardiovascular deaths across the LVEF spectrum of HF globally over 3 years. Such quantification of potential global population-level benefits should further affirm trial results and drive concerted, targeted efforts to improve the uptake of GDMT in HF, including SGLT-2 inhibitors, to achieve projected benefits in low-, middle-, and high-income countries.

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## FIGURE LEGENDS

**Figure 1:** A diagrammatic illustration of the total heart failure population estimated from the Global Burden of Disease report that would be eligible for SGLT-2 inhibitor therapy. DELIVER: Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; eGFR: estimated glomerular filtration rate; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; EMPEROR-Reduced: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPEROR-Preserved: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; LVEF: left ventricular ejection fraction.

**Figure 2:** The estimated reduction in the number of worsening heart failure events and cardiovascular deaths during event rates from the EMPEROR-Reduced and EMPEROR-Preserved trials and DAPA-HF and DELIVER trials.

**Table 1:** Overall, 1-year, and 3-year event rates, rate differences, and number needed to treat with SGLT-2 Inhibitors in the EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, and DELIVER trials.

| Endpoint | Overall rate (per 100 patient years) | | Overall rate measure* (95% CI) | Rate difference 1-year outcome | Event rate (per 100 patient years) in the first 3 years | | Rate difference 3-year outcome | Number Needed to Treat (NNT) | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo | SGLT-2 inhibitor | | | Placebo | SGLT-2 inhibitor | | 1-year outcome | 3-year outcome |
| **EMPEROR-Reduced and EMPEROR-Preserved trials, all LVEFs** | | | | | | | | | |
| Total HF hospitalizations | 12.49 | 9.07 | 0.72 (0.63, 0.83) | 5.13 | 12.56 | 9.09 | 10.41 | 20 | 10 |
| Total HF hospitalizations and CV deaths | 17.58 | 13.70 | 0.77 (0.69, 0.87) | 5.41 | 17.64 | 13.73 | 11.73 | 19 | 9 |
| Worsening HF event† or CV death | 19.17 | 14.84 | 0.76 (0.68, 0.86) | 6.22 | 19.22 | 14.88 | 13.02 | 17 | 8 |
| **DAPA-HF/DELIVER trials, all LVEFs** | | | | | | | | | |
| Total HF hospitalizations | 11.44 | 8.20 | 0.72 (0.63, 0.82) | 4.78 | 11.47 | 8.21 | 9.78 | 21 | 11 |
| Total HF hospitalizations and CV deaths | 17.34 | 13.28 | 0.76 (0.69, 0.85) | 5.50 | 17.40 | 13.29 | 12.33 | 19 | 9 |
| Worsening HF event or CV death | 17.78 | 13.46 | 0.76 (0.68, 0.84) | 6.15 | 17.83 | 13.47 | 13.08 | 17 | 8 |
| **EMPEROR-Reduced trial, LVEF ≤ 40%** | | | | | | | | | |
| Total HF hospitalizations | 22.44 | 15.77 | 0.71 (0.58, 0.86) | 7.53 | 22.44 | 15.77 | 20.01 | 14 | 5 |
| Total HF hospitalizations and CV deaths | 30.63 | 23.38 | 0.76 (0.64, 0.91) | 8.26 | 30.63 | 23.38 | 21.75 | 13 | 5 |
| Worsening HF event or CV death | 32.90 | 25.12 | 0.75 (0.62, 0.89) | 9.83 | 32.90 | 25.12 | 23.34 | 11 | 5 |
| **DAPA-HF trial, LVEF ≤ 40%** | | | | | | | | | |
| Total HF hospitalizations | 13.64 | 9.77 | 0.72 (0.59, 0.86) | 3.98 | 13.64 | 9.77 | 11.61 | 26 | 9 |
| Total HF hospitalizations and CV deaths | 21.59 | 16.30 | 0.75 (0.65, 0.88) | 5.41 | 21.59 | 16.30 | 15.86 | 19 | 7 |
| Worsening HF event or CV death | 22.43 | 16.57 | 0.74 (0.64, 0.86) | 5.85 | 22.43 | 16.57 | 17.59 | 18 | 6 |
| **EMPEROR-Preserved trial, LVEF >40%** | | | | | | | | | |
| Total HF hospitalizations | 8.60 | 6.46 | 0.73 (0.60, 0.89) | 3.74 | 8.64 | 6.44 | 6.60 | 27 | 16 |
| Total HF hospitalizations and CV deaths | 12.47 | 9.93 | 0.78 (0.66, 0.93) | 3.75 | 12.48 | 9.90 | 7.74 | 27 | 13 |
| Worsening HF | | | | | 13.78 | 10.82 | 8.88 | | 12 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| event or CV death | 13.79 | 10.83 | 0.77 (0.65, 0.91) | 4.14 | | | | 25 | |
| **DELIVER trial, LVEF >40%** | | | | | | | | | |
| Total HF hospitalizations | 10.25 | 7.35 | 0.72 (0.60, 0.85) | 5.31 | 10.30 | 7.36 | 8.82 | 19 | 12 |
| Total HF hospitalizations and CV deaths | 14.04 | 10.69 | 0.76 (0.66, 0.88) | 5.50 | 14.11 | 10.73 | 10.14 | 19 | 10 |
| Worsening HF event or CV death | 15.33 | 11.79 | 0.77 (0.67, 0.89) | 6.40 | 15.39 | 11.79 | 10.80 | 16 | 10 |

† Worsening HF events include CV death, HF hospitalizations, and urgent visits for HF requiring intravenous therapy. HF: heart failure; CV: cardiovascular; EMPEROR-Reduced: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPEROR-Preserved: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER: Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; LVEF: left ventricular ejection fraction.

**Table 2:** Overall, 1-year, and 3-year adverse event rates, rate differences and numbers needed to harm with SGLT-2 inhibitors in the EMPEROR trials.

| Endpoint | Rate (95% CI) (per 100 patient years) | | Measure (95% CI) | Rate difference (95% CI) | | Number needed to Harm (NNH) (95% CI) ¶ | |
|---|---|---|---|---|---|---|---|
| | Placebo | SGLT-2 inhibitor | | 1-year outcome | 3-year outcome | 1-year outcome | 3-year outcome |
| **EMPEROR-Reduced and EMPEROR-Preserved, all LVEFs** | | | | | | | |
| **Symptomatic hypotension** | 3.39 (2.99, 3.82) | 3.98 (3.54, 4.44) | 1.16 (0.99, 1.37) | 1.47 (0.52, 2.42) | 0.54 (-0.07, 1.15) | 72 (45, 181) | 70 (38, 440) |
| **Genital infections** | 0.43 (0.30, 0.59) | 1.25 (1.02, 1.51) | 2.90 (1.96, 4.28) | 1.29 (0.84, 1.73) | 0.83 (0.54, 1.12) | 79 (60, 117) | 42 (33, 56) |
| **EMPEROR-Reduced trial, LVEF ≤40%** | | | | | | | |
| **Symptomatic hypotension** | 4.75 (3.87, 5.71) | 4.83 (3.96, 5.79) | 1.01 (0.77, 1.32) | 0.59 (-1.12, 2.30) | 0.09 (-1.21, 1.38) | 181 (≥ 50, NNT*≥ 109) | 447 (≥ 42, NNT*≥ 51) |
| **Genital infections** | 0.53 (0.28, 0.88) | 1.38 (0.94, 1.91) | 2.57 (1.32, 5.01) | 1.09 (0.32, 1.85) | 0.85 (0.28, 1.42) | 94 (57, 262) | 41 (29, 71) |
| **EMPEROR-Preserved trial, LVEF >40%** | | | | | | | |
| **Symptomatic hypotension** | 2.86 (2.43, 3.32) | 3.63 (3.14, 4.16) | 1.28 (1.04, 1.58) | 1.97 (0.84, 3.09) | 0.71 (0.03, 1.40) | 54 (35, 117) | 52 (30, 212) |
| **Genital infections** | 0.39 (0.25, 0.57) | 1.20 (0.93, 1.51) | 3.06 (1.89, 4.96) | 1.40 (0.86, 1.94) | 0.82 (0.48, 1.16) | 73 (53, 115) | 42 (32, 62) |

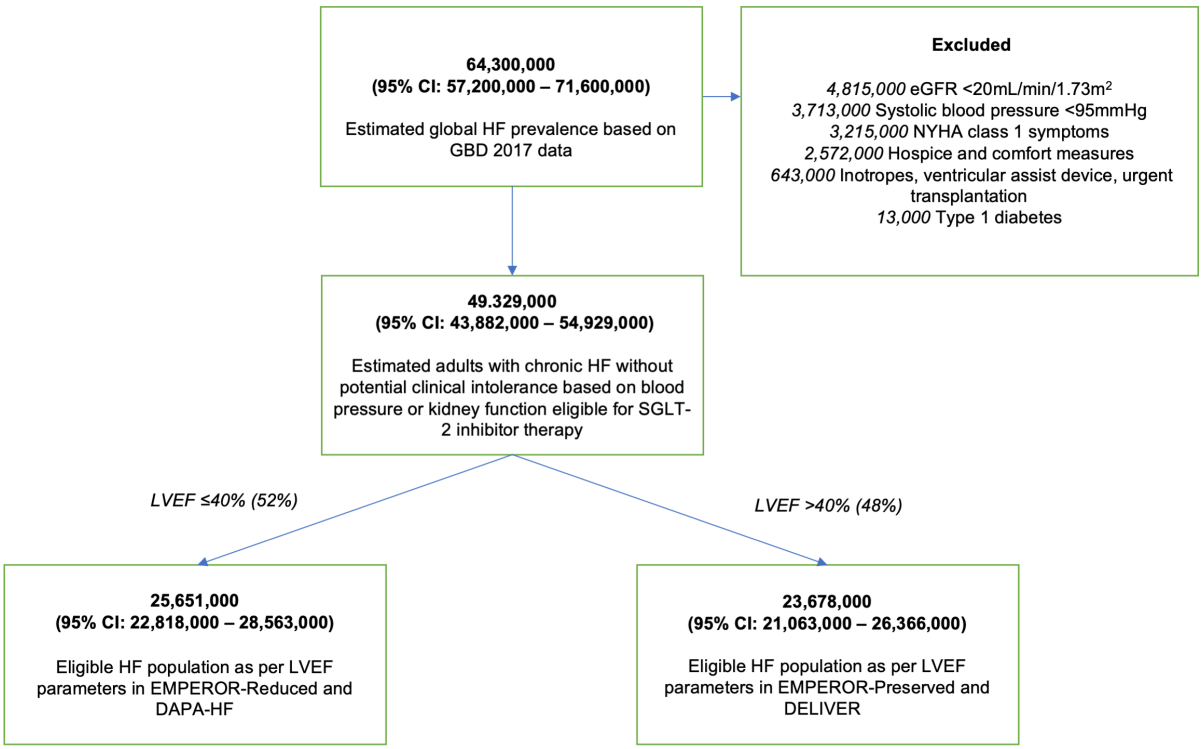
¶ The data for safety events from the DAPA-HF and DELIVER trials were not included in the study due as only serious adverse events, adverse events that led to treatment discontinuation and select other adverse events were reported in these trials.

* The confidence interval of the difference between treatment and placebo groups extends across no effect in the EMPEROR-Reduced trial. Therefore, the confidence interval of the NNH includes the possibility of a beneficial effect denoted by NNT.

**Table 3:** Projected events prevented/postponed or caused by SGLT-2 inhibitor therapy among newly eligible patients treated for 3 years.

| LVEF range | Potentially newly eligible candidates, No. (95% CI) | Estimated events prevented/postponed by the implementation of SGLT-2 inhibitors among newly eligible patients for 3 years, No. (95% CI) * | | | Estimated events caused by the implementation of SGLT-2 inhibitors among newly eligible patients for 3 years, No. (95% CI) * | |
|---|---|---|---|---|---|---|
| | | Total HF hospitalizations | Total HF hospitalizations and CV deaths | Worsening HF event† and CV death | Symptomatic hypotension | Genital infections |
| **DAPA-HF and DELIVER trials** | | | | | | |
| **LVEF ≤40%** | 25,651,000 (22,818,000 – 28,563,000) | 2,978,081 (2,649,170 – 3,316,164) | 4,068,249 (3,618,935 – 4,530,092) | 4,512,011 (4,013,686 – 5,024,232) | - | - |
| **LVEF >40%** | 23,678,000 (21,063,000 – 26,366,000) | 2,088,400 (1,857,757 – 2,325,481) | 2,400,949 (2,135,788 – 2,673,512) | 2,557,224 (2,274,804 – 2,847,528) | - | - |
| **All LVEFs** | 49.329,000 (43,882,000 – 54,929,000) | 5,066,481 (4,506,927 – 5,641,645) | 6,469,198 (5,754,723 – 7,203,604) | 7,069,235 (6,288,490 – 7,871,760) | - | - |
| **EMPEROR-Reduced and EMPEROR-Preserved trials** | | | | | | |
| **LVEF ≤40%** | 25,651,000 (22,818,000 – 28,563,000) | 5,132,765 (4,565,882 – 5,715,456) | 5,579,093 (4,962,915 – 6,212,453) | 5,986,943 (5,325,721 – 6,666,604) | 57,385 (51,047 – 63,899) | 625,634 (556,537 – 696,659) |
| **LVEF >40%** | 23,678,000 (21,063,000 – 26,366,000) | 1,562,748 (1,390,158 – 1,740,156) | 1,832,677 (1,630,276 – 2,040,728) | 2,102,606 (1,870,394 – 2,341,301) | 455,346 (405,058 – 507,038) | 563,762 (501,500 – 627,762) |
| **All LVEFs (addition)** | 49.329,000 (43,882,000 – 54,929,000) | 6,695,513 (5,956,040 – 7,455,612) | 7,411,770 (6,593,151 – 8,253,181) | 8,089,549 (7,196,115 – 9,007,905 | 512,713 (456,105 – 570,937) | 1,189,396 (1,058,037 – 1,324,421) |

† Worsening HF events include CV death, HF hospitalizations, and urgent visits for HF requiring intravenous therapy.
* Using 95% CI of the potentially newly eligible candidates and the estimates of differences in event rates.

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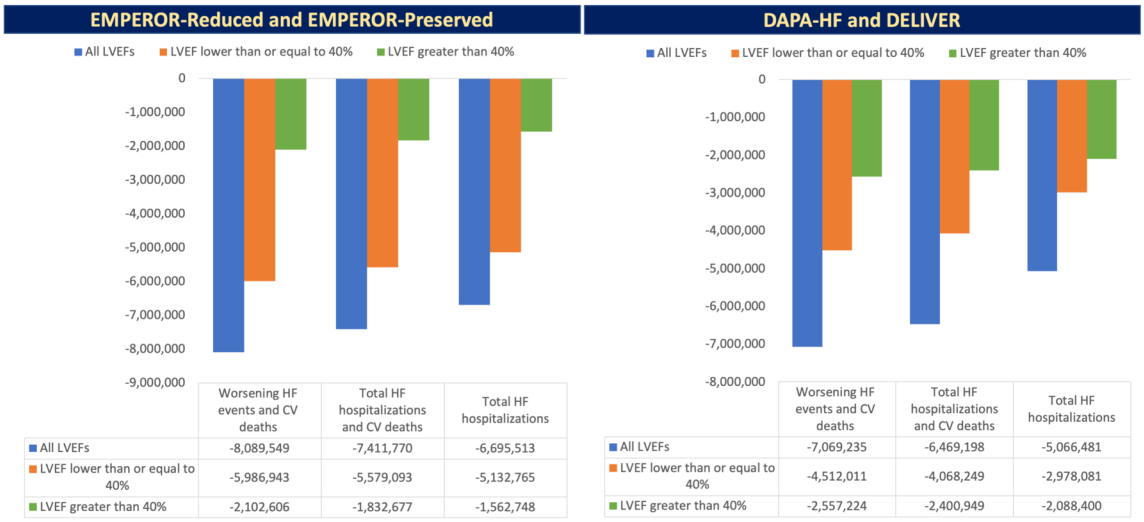


EJHF_2864_Fig 2 HF Global SGLT2i EJHF Revised.tiff