

# Association of Optimal Implementation of Sodium-Glucose Cotransporter 2 Inhibitor Therapy With Outcome for Patients With Heart Failure

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 Supplemental content

**IMPORTANCE** Sodium-glucose cotransporter 2 inhibitor (SGLT2-i) therapy provided incremental survival benefit to patients with heart failure and reduced ejection fraction (HFrEF) who received guideline-directed medical therapy regardless of type 2 diabetes status in a recent clinical trial. To date, estimation of the potential benefits that could be gained from optimal implementation of SGLT2-i therapy at the population level has not been quantified.

**OBJECTIVE** To quantify the projected gains for deaths prevented or postponed with comprehensive implementation of SGLT2-i therapy for patients with HFrEF in the United States.

**DESIGN, SETTING, AND PARTICIPANTS** This decision analytical model, performed from September 25 to October 20, 2019, used published sources to estimate the US population of patients with HFrEF eligible for SGLT2-i therapy and the numbers needed to treat to prevent or postpone overt death. Sensitivity analyses were performed to account for the range of potential benefits.

**MAIN OUTCOMES AND MEASURES** All-cause mortality.

**RESULTS** Of the 3.1 million patients with HFrEF in the United States, 2 132 800 (69%) were projected to be candidates for SGLT2-i therapy. Optimal implementation of SGLT2-i therapy was empirically estimated to prevent up to 34 125 deaths per year (range 21 840-49 140 deaths per year). A secondary analysis excluding patients on the basis of N-terminal-pro brain natriuretic peptide levels and other trial entry criteria would yield a potential benefit of 25 594 deaths per year prevented (range, 16 380-36 855 deaths per year prevented).

**CONCLUSIONS AND RELEVANCE** This study suggests that a substantial number of deaths in the United States could be prevented by optimal implementation of SGLT2-i therapy. These data support implementation of the current evidence into practice in a timely manner to achieve important public health benefits and to reduce the mortality burden of HFrEF.

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Sodium-glucose cotransporter 2 inhibitor (SGLT2-i) therapy was initially directed toward the management of type 2 diabetes. The first cardiovascular clinical outcome trial of SGLT2-i therapy, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), demonstrated an unexpected and substantial reduction in all-cause mortality, cardiovascular death, and heart failure (HF) hospitalizations among patients with type 2 diabetes.<sup>1</sup> Significant reductions in HF hospitalizations were also demonstrated with the SGLT2-i canagliflozin in the Canagliflozin Cardiovascular Assessment Study<sup>2</sup> and with dapagliflozin in the Dapagliflozin Effect on Cardiovascular Events trial,<sup>3</sup> thus confirming the EMPA-REG OUTCOME findings. Sodium-glucose cotransporter 2 inhibitors are now established as among the most effective therapies to prevent HF in patients with type 2 diabetes.<sup>4</sup>

More recently, the SGLT2-i dapagliflozin has been demonstrated to reduce HF events, cardiovascular death, and all-

cause mortality among patients with HF with reduced ejection fraction (HFrEF) irrespective of whether or not they had type 2 diabetes in the Dapagliflozin and Prevention of Adverse outcomes in Heart Failure (DAPA-HF) trial.<sup>5</sup> These landmark data argue for the addition of the SGLT2-i class to the therapeutic armamentarium for HFrEF. Our study aimed to estimate the potential magnitude of benefit with optimal implementation of SGLT2-i therapy at the population level.

## Methods

This decision analytical model was performed from September 25 to October 20, 2019. Eligibility for SGLT2-i therapy was based on the population of patients with HF in the American Heart Association Heart Disease and Stroke Statistics 2019 Update.<sup>6</sup>

The magnitude of mortality reduction for SGLT2-i was determined from the DAPA-HF trial.<sup>5</sup> The number needed to treat

at 12 months was calculated to estimate the potential lives saved per year with SGLT2-i therapy, as previously described.<sup>7</sup> We evaluated the range of benefits using a multilevel analysis-of-extremes method.<sup>8</sup> This approach assigns a lower value and an upper value using  $\pm 20\%$  relative differences for the number of patients eligible for treatment and risk reduction variables. We further estimated population-level benefits in HF hospitalizations and whether treatment with SGLT2-i therapy was confined to only patients meeting the N-terminal-pro brain natriuretic peptide cutpoints in the DAPA-HF trial.

## Results

The prevalence of HF is 6 200 000 cases per the entire US population,<sup>6</sup> and 50% of these patients have a left ventricular ejection fraction of 40% or less.<sup>9</sup> Of the 3 100 000 patients with HF<sub>rEF</sub>, additional exclusions were applied for those receiving hospice or comfort care—only measures (124 000 [4%]); for those receiving continuous inotropic agents, requiring ventricular assist devices, or requiring urgent heart transplantation (31 000 [1%]);<sup>7</sup> and for those with New York Heart Association class I HF (465 000 [15%]) (Figure).<sup>10</sup> For the remaining 2 480 000 patients with HF<sub>rEF</sub>, 297 600 (12%)<sup>11</sup> were excluded on the basis of having a glomerular filtration rate less than 30 mL/min/1.73 m<sup>2</sup>, and 49 600 (2%) were excluded on the basis of having type 1 diabetes, leaving 2 132 800 patients as candidates for SGLT2-i therapy. The magnitude of benefit demonstrated with SGLT2-i therapy incremental to guideline-directed medical therapy is shown in Table 1 and Table 2. Based on the DAPA-HF trial, the number needed to treat to prevent 1 death, standardized to 12 months, was calculated to be 62.5 (based on a mortality rate of 7.9 per 100 patient-years with dapagliflozin vs 9.5 per 100 patient-years with placebo added to standard background therapy).<sup>5</sup> The number of deaths prevented each year with optimal implementation of SGLT2-i therapy was calculated as 34 125; multiple-way sensitivity analyses using the analysis-of-extremes method yields a range of 21 840 to 49 140 estimated deaths prevented per year with SGLT2-i therapy.

In the sensitivity analysis that accounts for N-terminal-pro brain natriuretic peptide cutoffs and other exclusions in the DAPA-HF trial, an additional 25% of all eligible patients were excluded. Doing so would yield a total number of 1 599 600 eligible patients and a potential to prevent death in 25 594 patients (range, 16 380-36 855 patients).

## Discussion

Heart failure is a reported comorbid condition for 1 in every 9 deaths in the United States.<sup>12</sup> The prevention of incident HF is the most effective population health strategy through lifestyle interventions, including a heart-healthy diet, abstaining from smoking, and daily physical exercise.<sup>13</sup> Second, intensive medical management of modifiable risk factors, such as hypertension, dyslipidemia, and type 2 diabetes, is critical in the prevention of HF. Although there have been many therapeutic advances for patients with HF<sub>rEF</sub>, there remains sub-

## Key Points

**Question** What would the reduction be in all-cause mortality for the US population if all eligible patients with heart failure with reduced ejection fraction were prescribed sodium-glucose cotransporter 2 inhibitor therapy?

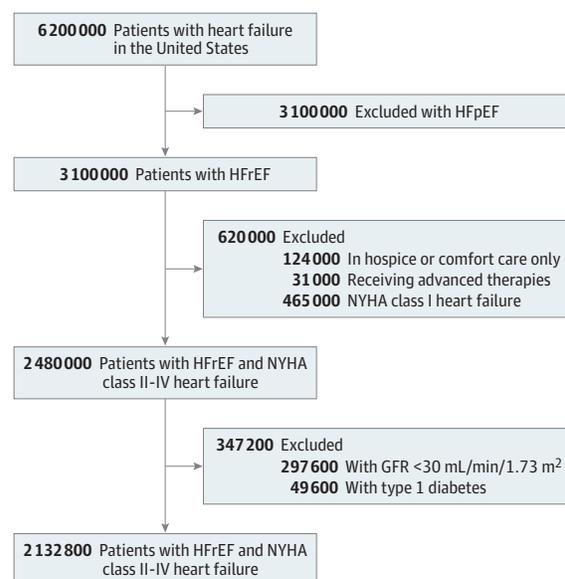
**Findings** This decision analytical model found that optimal implementation of sodium-glucose cotransporter 2 inhibitor therapy for patients with heart failure with reduced ejection fraction would be estimated to result in as many as 34 125 lives saved per year (range, 21 840-49 140 lives saved per year).

**Meaning** The timely addition of sodium-glucose cotransporter 2 inhibitor therapy to standard guideline-directed medical therapy, even if not fully deployed, has the potential to substantially reduce all-cause mortality among patients with heart failure in the United States.

stantial residual risk for mortality and rehospitalization. This study defines the population-level projected gains for deaths prevented or postponed with optimal implementation of SGLT2-i therapy for patients with HF<sub>rEF</sub>.

With the introduction of SGLT2-I therapy, a new class of medications is now available that demonstrates reductions in incident HF, in exacerbations of chronic HF, in cardiovascular death, and in all-cause mortality. More important, for patients with HF<sub>rEF</sub> in the DAPA-HF trial, the benefits were in addition to the high rates of guideline-directed medical therapy: 96% of patients were receiving  $\beta$ -blockers; 95% were

Figure. Sodium-Glucose Cotransporter 2 Inhibitor (SGLT2-i) Therapy Eligibility Flow Diagram



Derivation of the population of patients with heart failure and reduced ejection fraction eligible for SGLT2-i therapy. GFR indicates glomerular filtration rate; HF<sub>rEF</sub>, heart failure with reduced ejection fraction; HF<sub>pEF</sub>, heart failure with preserved ejection fraction; and NYHA, New York Heart Association.

Table 1. Demonstrated Benefits of Evidence-Based Therapies for Patients With Heart Failure and Reduced Ejection Fraction<sup>a</sup>

Evidence-based therapy	Relative risk reduction in all-cause mortality in pivotal randomized clinical trial(s), %	NNT to prevent all-cause mortality over time <sup>b</sup>	NNT for all-cause mortality	
			Standardized to 12 mo	Standardized to 36 mo
ACEI or ARB	17	22 for 42 mo	77	26
ARNI <sup>c</sup>	16	36 for 27 mo	80	27
β-Blocker	34	28 for 12 mo	28	9
Aldosterone antagonist	30	9 for 24 mo	18	6
Hydralazine and nitrate <sup>d</sup>	43	25 for 10 mo	21	7
CRT	36	12 for 24 mo	24	8
ICD	23	14 for 60 mo	70	23
Transcatheter MVR	38	6 for 24 mo	12	4
SGLT2-i	17	43 for 18 mo	63	22

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; MVR, mitral valve repair; NNT, number needed to treat; SGLT2-i, sodium-glucose cotransporter 2 inhibitor.

<sup>a</sup> See the eTable in the Supplement for randomized clinical trials used.

<sup>b</sup> Median duration of follow-up in the respective clinical trial.

<sup>c</sup> Benefit of ARNI therapy incremental to that achieved with ACEI therapy. For the other medications shown, the benefits are based on comparisons with placebo control.

<sup>d</sup> Benefit of hydralazine and nitrate combination therapy was limited to African Americans in this trial.

Table 2. Estimated Cumulative Benefits for All-Cause Mortality of Evidence-Based Medical Therapies for Patients With Heart Failure and Reduced Ejection Fraction<sup>a</sup>

Evidence-based therapy	Relative risk reduction in all-cause mortality, %	Mortality at 24 mo, %	Absolute reduction in all-cause mortality, %
None	NA	35	NA
ARNI (vs imputed placebo)	28	25	10
β-Blocker	35	16	9
Aldosterone antagonist	30	12	5
SGLT2-i	17	10	2
Quadruple therapy <sup>b</sup>	73	10	26

Abbreviations: ARNI, angiotensin receptor neprilysin inhibitor; NA, not applicable; SGLT2-i, sodium-glucose cotransporter 2 inhibitor.

<sup>a</sup> The number needed to treat for 24 months with all 4 medical therapies to prevent 1 death = 3.9. This number is based on the premise that the efficacy

demonstrated for each successive therapy is cumulative, without overlap or attenuation, and each therapy is optimally dosed, monitored, and adhered to.

<sup>b</sup> ARNI, β-blocker, aldosterone antagonist, and SGLT2-i therapy.

receiving angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor neprilysin inhibitors; and 71% were receiving mineralocorticoid receptor antagonists.<sup>5</sup> Based on the findings of our study, which is the first, to our knowledge, to quantify the magnitude of survival benefit in the United States, if SGLT2-i therapy were comprehensively applied to eligible patients with HF<sub>rEF</sub>, then up to 34 125 deaths per year could be prevented or postponed.

Establishing the potential population-level benefits with optimal implementation of a new HF therapy may be informative when considering the commitment of resources and national quality improvement efforts toward implementation of the new therapy. The fact that tens of thousands of lives could be saved with appropriate adoption of SGLT2-i therapy for eligible patients suggests that there may be downsides to delaying implementation of this new therapy in clinical practice. Although this study focused on mortality, SGLT2-i therapy has been shown to have other clinical benefits, including improved health status and reduced HF hospitalizations.<sup>5</sup> Given the variable and slow uptake of other evidence-based HF therapies, compelling guideline recommendations as well as other effective performance improvement interventions will be required for meaningful population-level implementation, as previously described.<sup>11</sup>

The underlying premise of this analysis is that the magnitude of efficacy demonstrated in the DAPA-HF trial will be similar for patients with HF<sub>rEF</sub> encountered in clinical practice. This premise may or may not be the case, particularly for patient subgroups not adequately represented in the trial. In addition, the expected survival benefits of implementation of SGLT2-i therapy is contingent on being able to apply this therapy with similar levels of safety, tolerability, and dosing as achieved in clinical trials. This study does not account for a potential increase in adverse events at the population level, including diabetic ketoacidosis, infections, fracture, and Fournier gangrene, although these rates did not differ from those seen with placebo in the DAPA-HF trial. The DAPA-HF trial demonstrated substantial benefits to patients regardless of whether the patients had type 2 diabetes or not. There was no heterogeneity for the primary composite end point or for mortality reduction by diabetes status in the DAPA-HF trial. If subsequent trial data reveal different magnitudes of survival benefits by diabetes status, the population-wide estimations may need to be further refined.

### Limitations

There are important limitations to our analysis with respect to inclusion and exclusion criteria, cost, access, and adherence. The

DAPA-HF trial studied 4744 carefully selected patients for a median of 18.2 months and excluded many patients with HF seen in daily practice with the following attributes: New York Heart Association class I HF, advanced-stage chronic kidney disease, and type 1 diabetes. The exact proportion of eligible patients with contraindications for SGLT2-i therapy may deviate from the estimates used in this study. Second, SGLT2-i therapy represents an additional cost burden to patients with HF and health systems. Although formal cost-effectiveness analyses are warranted, the financial implications of a population-level implementation are likely to be prohibitive at current price levels. Third, dapagliflozin was provided to patients enrolled in the DAPA-HF trial, and adherence was supported and evaluated by a team of health care professionals—2 key attributes that may not be available to many patients in clinical practice. Fourth, as with any novel and efficacious therapy representing a paradigm shift, widespread adoption of SGLT2-i therapy into clinical practice will be a challenge. Given the fact that many outpatient registry patients with HF<sub>rEF</sub> are not receiving optimal therapy with the current armamentarium of guideline-directed medical therapy (ie,  $\beta$ -blockers, mineralocorticoid receptor antagonists, or angiotensin receptor neprilysin inhibitors),<sup>14</sup> it represents an extra challenge for the

prescriber and patient to add yet another medication to the medication list. Yet our analysis demonstrates that this is an effort worth undertaking given the substantial increase in potential lives saved.

The DAPA-HF trial is the first trial to demonstrate substantial benefit in patients with HF<sub>rEF</sub> without type 2 diabetes. The results from the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction,<sup>15</sup> which will study the use of the SGLT2-i empagliflozin in the treatment of patients with HF<sub>rEF</sub>, half of whom do not have type 2 diabetes, as well as other HF outcome trials, are upcoming.

## Conclusions

This study suggests that a substantial mortality benefit can be achieved with the implementation of SGLT2-i therapy on a population-wide basis for appropriately selected patients with HF<sub>rEF</sub>. Given the substantial HF burden and potential benefits of implementation of SGLT2-i therapy for preventing deaths, new and potentially disruptive efforts to ensure comprehensive implementation of SGLT2-i therapy should be considered.

### ARTICLE INFORMATION

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**Drafting of the manuscript:** Bassi, Yancy.  
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**Statistical analysis:** Bassi, Ziaeian, Fonarow.  
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**Supervision:** Ziaeian, Yancy, Fonarow.

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