Robustness of outcomes in trials evaluating sodium–glucose co-transporter 2 inhibitors for heart failure

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Abstract

Aims Recent trials have evaluated sodium–glucose co-transporter 2 inhibitors in patients with heart failure (HF). We sought to assess the robustness of findings from these trials using the fragility index (FI).

Methods and results Fragility index is defined as the minimum number of patients that must be moved from the ‘non-event’ to the ‘event’ group to turn a statistically significant result to non-significant. In addition to FI, fragility quotient ([FQ]; FI divided by the sample size) was calculated to assess the proportion of events that must be moved to change the significance. For statistically non-significant outcomes, reverse fragility index (RFI) and reverse fragility quotient (RFQ) were calculated. Robustness of findings after pooling data from all three trials was also assessed. A robust reduction in first HF hospitalization or cardiovascular mortality was seen with dapagliflozin (FI = 62 and FQ = 0.013), empagliflozin (FI = 50 and FQ = 0.013), and sotagliflozin (FI = 60 and FQ = 0.049). Dapagliflozin nominally improved all-cause and cardiovascular mortality, with modest FI (n = 8 and 5) and FQ (0.002 and 0.001). Empagliflozin and sotagliflozin did not demonstrate statistically significant reductions in all-cause mortality, with modest RFI (empagliflozin: RFI = 26 and RFQ = 0.007; sotagliflozin: RFI = 6 and RFQ = 0.005). A similar trend was seen with cardiovascular mortality (empagliflozin: RFI = 24 and RFQ = 0.006; sotagliflozin: RFI = 7 and RFQ = 0.006). Upon meta-analysis, the result for first HF hospitalization or cardiovascular mortality was robust (FI = 95 and FQ = 0.010). The reductions in all-cause (FI = 12 and FQ = 0.001) and cardiovascular mortality (FI = 9 and FQ = 0.001), while statistically significant, were fragile.

Conclusion Improvement in the composite outcome of first HF hospitalization or cardiovascular death was highly concordant and robust across sodium–glucose co-transporter 2 inhibitor trials. In contrast, secondary endpoints of all-cause and cardiovascular mortality were statistically fragile, underscoring the need to power trials for mortality to fully understand the benefit of therapies on fatal events.

Keywords Fragility index; Robustness; Sodium–glucose co-transporter 2 inhibitors; Cardiac failure
**Introduction**

Recent trials show that sodium–glucose co-transporter 2 (SGLT2) inhibitors improve heart failure (HF) outcomes.\(^1\)–\(^3\) The ‘Dapagliflozin and Prevention of Adverse-Outcomes in HF’ (DAPA-HF)\(^1\) showed that dapagliflozin reduced the composite endpoint of first HF hospitalization, urgent HF visit, or cardiovascular mortality among patients with HF with reduced ejection fraction (HFrEF). The ‘Empagliflozin Outcome Trial in Patients With Chronic HFrEF’ (EMPEROR-Reduced) enrolled higher risk HFrEF patients and demonstrated a similar benefit.\(^2\) Recently, the ‘Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening HF’ (SOLOIST-WHF)\(^3\) trial evaluated the effects of sotagliflozin in HF patients with diabetes and recent hospitalization for worsening HF\(^3\) and included patients with HFrEF as well as HF with preserved ejection fraction (HfPEF). While this trial was terminated early, SOLOIST-WHF also showed a reduction in first HF hospitalization or cardiovascular mortality.

While the magnitude of benefit for the primary endpoint was consistent in all trials, the observed effects on the secondary endpoint of mortality varied. Mortality benefit was nominally significant with dapagliflozin but not with empagliflozin or sotagliflozin, raising questions regarding differences in baseline risk profiles or play of chance. None of these trials however were designed to assess mortality impact by itself. Robustness of statistically significant and non-significant dichotomous outcomes can be evaluated using fragility index (FI) and reverse fragility index (RFI).\(^4\)–\(^5\) FI can help evaluate trial results in addition to P-values and effect size estimates. In this study, we sought to assess the robustness of the results across the SGLT2 inhibitors trials in HF by assessing the FI and RFI for clinical outcomes.

**Methods**

**Study populations, definitions, and outcomes of interest**

Publicly available data were utilized, and thus, institutional review board approval was not applicable. All placebo-controlled trials designed to evaluate outcomes in HF patients using SGLT2 inhibitors were included. Three randomized controlled trials met these criteria. DAPA-HF and EMPEROR-Reduced included HFrEF outpatients with or without diabetes.\(^1\)–\(^2\) EMPEROR-Reduced enrolled a higher risk population with lower ejection fraction (EF) and estimated glomerular filtration rate, and higher natriuretic peptides. SOLOIST-WHF enrolled patients with diabetes hospitalized for worsening HF, regardless of EF.\(^3\) Sotagliflozin, studied in SOLOIST-WHF, differs from other SGLT2 inhibitors as it also has SGLT1-inhibiting activity.\(^3\)

The primary outcome varied in all three trials. In EMPEROR-Reduced, it was a composite of first HF hospitalization or cardiovascular mortality. DAPA-HF had a similar primary composite but included urgent outpatient visits for intravenous HF therapy. The number of urgent visits was few, and excluding them resulted in no meaningful change in the effect size. The primary outcome in SOLOIST-WHF was a composite of total (first and recurrent) HF hospitalizations, urgent HF visits, and cardiovascular mortality. We could not evaluate the FI/RFI for this outcome without patient-level data access, but SOLOIST-WHF also reported the composite of first HF hospitalization or cardiovascular mortality.

Fragility index and RFI were assessed for the (i) composite of first HF hospitalization or cardiovascular mortality, (ii) first HF hospitalization, (iii) cardiovascular mortality, and (iv) all-cause mortality. FI for subgroup of the primary outcome was also assessed, but this was not possible for the SOLOIST-WHF trial because the primary outcome included recurrent events.

**Statistical analysis**

For significant outcomes, FI was calculated in the manner described by Walsh et al.\(^6\) In the treatment arm with a lower event rate, patients were added to the event group while subtracting patients from the non-event group. Fisher’s exact test was used to recalculate the two-sided \(P\)-value, while iteratively adding events until the \(P\)-value became \(\geq 0.05\). For non-significant outcomes, RFI was calculated. The total number of events in each group over the entire follow-up was considered. Lower FI/RFI indicates less statistical robustness; however, there is no standardized cut-off defined for acceptable fragility. Loss of follow-up was compared with FI/RFI for each trial as it affects both the number of participants at risk and the number of events. When loss to follow-up exceeds the FI or RFI, results should be cautiously interpreted as events of interest may occur in patients lost to follow-up and factoring these may shift the results.

Fragility quotient (FQ),\(^7\)–\(^8\) which is the FI divided by the sample size, was also calculated to assess what proportion of patients must change status to change the significance of results. For instance, trial X has an FI of 2 and sample size of 500 while trial Y has an FI of 2 and sample size of 1000. Although both trials have the same FI, FQ can gauge which trial is ‘relatively’ more fragile. Trial X has an FQ of 0.004, meaning that four events per 1000 patients will be needed to change the results significance; while trial Y has an FQ of 0.002, indicating that the non-significance of trial Y is contingent on \(\sim 2\) events per 1000 patients, suggesting trial Y as more fragile.

For statistically non-significant outcomes, RFQ was calculated by dividing the RFI by the sample size. FI, RFI, FQ, and RFQ were calculated using the R Version 3.51 (R Project for...
The FI was also calculated after pooling data from all three trials. The previous meta-analysis utilized HRs for which FI or RFI cannot be calculated. For this study, (logarithm of the) risk ratios (RRs) were pooled from each study, which were calculated from dichotomous endpoints, ignoring the event times. A random-effects model was used for meta-analysis. Weights were assigned using the Mantel–Haenszel method. Fragility of meta-analysis results was assessed using the technique described by Atal et al. Review Manager (V.5.3) was used to conduct the meta-analysis, and the calculator available at http://clinicalepidemio.fr/fragility_ma/ was used to calculate FI of meta-analysis.

**Results**

**Patient population**

The baseline characteristics of patients are shown in Table 1. The three studies included a total of 9696 patients (DAPA-HF, \( n = 4744 \); EMPEROR-Reduced, \( n = 3730 \); and SOLOIST-WHF, \( n = 1222 \)). The median follow-up time was 18 months in DAPA-HF, 16 months in EMPEROR-Reduced, and 9 months in SOLOIST-WHF. The number of patient’s lost to follow-up in DAPA-HF, EMPEROR-Reduced, and SOLOIST-WHF was 36, 42, and 43, respectively.

**Fragility index, reverse fragility index, and fragility quotient**

Table 2 summarizes the findings from each trial and meta-analysis and displays the FI/RFI and FQ. Figures 1 and 2 visually represent the FI/RFI and FQ for each outcome of interest.

**Composite of first heart failure hospitalization or cardiovascular mortality**

SGLT-2 inhibitors reduced the risk of the composite endpoint of first HF hospitalization or cardiovascular mortality in DAPA-HF (hazard ratio [HR] 0.74 [0.65–0.85]), EMPEROR-Reduced (HR: 0.75 [0.65–0.86]), and SOLOIST-WHF (HR: 0.71 [0.56–0.89]) trials. The results were robust (dapagliflozin: FI = 62 and FQ = 0.013; empagliflozin: FI = 50 and FQ = 0.013; and sitagliptin: FI = 60 and FQ = 0.049), and FI was greater than patients lost to follow-up. Table 3 shows the FI/RFI of the primary outcomes of DAPA-HF and EMPEROR-Reduced stratified according to different subgroups. Meta-analysis demonstrated significant (RR: 0.75 [0.69–0.81]; \( P < 0.001 \); \( I^2 = 20\% \)) and robust (FI = 95 and FQ = 0.010) benefit.

**Discussion**

The DAPA-HF, EMPEROR-Reduced and SOLOIST-WHF trials all reported highly concordant and statistically robust results for the primary endpoint of time to first HF hospitalization or cardiovascular death. The FI for this endpoint was higher than the FI for outcomes in trials of other drugs, for example, therapies referenced in diabetes treatment guidelines (FI = 16) and anti-thrombotic therapy (FI = 5) in venous thromboembolism guidelines. The FI and RFLs of outcomes in landmark HF trials are displayed in Table 4.

In the SOLOIST-WHF trial, the initial primary endpoint was the composite of first HF hospitalization or cardiovascular mortality; however, this was later changed to a composite of first and recurrent HF hospitalization, urgent HF visits, and cardiovascular mortality. Despite enrolling only 1222 patients, this trial showed a significant and robust (FI = 60) reduction in first HF hospitalization or cardiovascular mortality, reinforcing the benefit of SGLT2 inhibitors in HF. These effects remained consistent across a range of subgroups including patients with reduced and preserved EF, in-hospital vs. post-discharge initiation, and use of sacubitril/valsartan.
|                          | EMPEROR-Reduced | Placebo | DAPA-HF | Placebo | SOLOIST-WHF | Placebo |
|--------------------------|-----------------|---------|---------|---------|-------------|---------|
| **Number of participants** | 1863            | 1867    | 2373    | 2371    | 608         | 614     |
| **Age, years (SD)**      | 67.2 (10.8)     | 66.5 (11.2) | 66.2 (11.0) | 66.5 (10.8) | 69 (63–76) | 70 (64–76) |
| **Sex, n (%)**           |                 |         |         |         |             |         |
| Male                     | 1426 (76.5)     | 1411 (75.6) | 1809 (76.2) | 1826 (77.0) | 410 (67.4) | 400 (65.1) |
| Female                   | 437 (23.5)      | 456 (24.4)  | 564 (23.8) | 545 (23.0) | 198 (32.6) | 214 (34.9) |
| **NYHA functional classification (%)** |      |         |         |         |             |         |
| II                       | 75.1            | 75.0     | 67.7    | 67.4     | 35 (28–47) | 35 (28–45) |
| III                      | 24.4            | 24.4     | 31.5    | 31.7     | 127 (20.9) | 129 (21.0) |
| IV                       | 0.5             | 0.6      | 0.8     | 1.0      | 481 (79.1) | 485 (79.0) |
| **Mean LVEF (%)**        | 27.7 (6.0)      | 27.2 (6.1) | 31.2 (6.7) | 30.9 (6.9) | 1817 (845–3659) | 1741 (843–3582) |
| **HFpEF (%)**            |                 |         |         |         |             |         |
| **NT-proBNP (pg/mL)**    | 1887 (1077–3429)| 1926 (1153–3525)| 1428 (857–2655) | 1446 (857–2641) | 1817 (845–3659) | 1741 (843–3582) |
| **Hospitalization for heart failure (%)** | 577 (31.0) | 574 (30.7) | 1124 (47.4) | 1127 (47.5) | 25 (4.1) | 20 (3.3) |
| **Diabetes (%)**         | 927 (49.8)      | 929 (49.8) | 1075 (45.3) | 1064 (44.9) | 481 (79.1) | 485 (79.0) |
| **Duration of diabetes (years)** | 61.8 (21.7) | 62.2 (21.5) | 66.0 (19.6) | 65.5 (19.3) | 49.2 (39.5–61.2) | 50.5 (40.5–64.6) |
| **Heart failure medications, n (%)** |                 |         |         |         |             |         |
| Renin–angiotensin inhibitor | 1644 (88.8) | 1673 (90.6) | >90%    | >90%    | 553 (91.0) | 563 (91.7) |
| ACE inhibitor            | 867 (46.5)      | 836 (44.8) | 1332 (56.1) | 1329 (56.1) | 254 (41.8) | 241 (39.3) |
| ARB                      | 451 (24.2)      | 457 (24.5) | 675 (28.4) | 632 (26.7) | 245 (40.3) | 270 (44.0) |
| ARNI                     | 340 (18.3)      | 387 (20.7) | 250 (10.5) | 258 (10.9) | 93 (15.3) | 112 (18.2) |
| Mineralocorticoid receptor antagonist | 1306 (70.1) | 1355 (72.6) | 1696 (71.5) | 1674 (70.6) | 403 (66.3) | 385 (62.7) |
| ICD or CRT-D             | 578 (31.0%)     | 593 (31.8%) | 622 (26.2%) | 620 (26.1%) | 564 (92.8) | 561 (91.4) |
| CRT-D or CRT-P           | 220 (11.8%)     | 222 (11.9%) | 190 (8.0%) | 164 (6.9%) |             |         |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardiac defibrillator; IQR, inter-quartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

Data are reported as n (%), mean (SD), or median (IQR).
### Table 2 Fragility of findings from SGLT2i trials and meta-analysis of these trials

|                  | DAPA-HF |                | EMPEROR-Reduced |                |                |                |                |                |                |
|------------------|---------|----------------|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                  | Events/total SGLT2i | Events/total placebo | HR [CI] | FI/RFI | FQ | Events/total SGLT2i | Events/total placebo | HR [CI] | FI/RFI | FQ |
| HFH or CVM       | 386/2373 | 502/2371       | 0.74 [0.65–0.85] | 62   | 0.0130 | 361/1863 | 462/1867       | 0.75 [0.65–0.86] | 50   | 0.0130 |
| First HFH        | 231/2373 | 318/2371       | 0.70 [0.59–0.83] | 43   | 0.0090 | 246/1863 | 342/1867       | 0.69 [0.59–0.81] | 50   | 0.0130 |
| CVM              | 227/2373 | 273/2371       | 0.82 [0.69–0.98] | 5    | 0.0010 | 187/1863 | 202/1867       | 0.92 [0.75–1.12] | 24a  | 0.0060 |
| ACM              | 276/2373 | 329/2371       | 0.83 [0.71–0.97] | 8    | 0.0020 | 249/1863 | 266/1867       | 0.92 [0.77–1.10] | 26a  | 0.0070 |

ACM, all-cause mortality; CI, confidence interval; CVM, cardiovascular mortality; FI, fragility index; FQ, fragility quotient; HF, heart failure; HFH, heart failure hospitalization; HR, hazard ratio; N/A, not available; RFI, reverse fragility index; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

*aReverse fragility index/reverse fragility quotient.

### Table 2 (continued)

|                  | SOLOIST-WHF |                | Meta-analysis |                |                |                |                |                |                |
|------------------|-------------|----------------|---------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                  | Events/total SGLT2i | Events/total placebo | HR [CI] | FI/RFI | FQ | Events/total SGLT2i | Events/total placebo | RR [CI] | FI/RFI | FQ |
| HFH or CVM       | 201/608     | 298/614        | 0.71 [0.56–0.89] | 60   | 0.0490 | 948/4844 | 1262/4852     | 0.75 [0.69–0.81] | 95   | 0.0098 |
| First HFH        | N/A         | N/A            | N/A           | N/A | N/A   | 477/4236 | 660/4238      | 0.72 [0.65–0.81] | 61   | 0.0072 |
| CVM              | 51/608      | 58/614         | 0.84 [0.58–1.22] | 7a   | 0.0060 | 465/4844 | 533/4852      | 0.87 [0.78–0.98] | 9    | 0.0009 |
| ACM              | 65/608      | 76/614         | 0.82 [0.59–1.14] | 6a   | 0.0050 | 590/4844 | 671/4852      | 0.88 [0.79–0.98] | 12   | 0.0012 |

ACM, all-cause mortality; CI, confidence interval; CVM, cardiovascular mortality; FI, fragility index; FQ, fragility quotient; HF, heart failure; HFH, heart failure hospitalization; HR, hazard ratio; N/A, not available; RFI, reverse fragility index; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

*aReverse fragility index/reverse fragility quotient.
The risk of all-cause and cardiovascular mortality was nominally reduced in DAPA-HF but not in EMPEROR-Reduced or SOLOIST-WHF. Mortality outcomes were secondary endpoints and statistically fragile, with significance dependent on less than 10 events per 1000 patients. Meta-analysis showed a robust F for the composite endpoint of first HF hospitalization or cardiovascular mortality was 95 (FQ = 0.010) but did not result in higher F for cardiovascular (F = 9) or all-cause mortality (F = 12). These findings highlight that although combining studies via random-effects meta-analysis can help detect a statistically significant treatment effect by increasing power, this does not necessarily result in an increased F and that the F and RFI are not strictly linked to statistical significance, confidence intervals, and power. While the aforementioned are related concepts, F offers additional value in interpretation of clinical trials and meta-analyses.
### Table 3

| Subgroup                        | Events/total in SGLT2 inhibitor group | Events/total in placebo group | HR [95% CI] | FI/RFI | FQ/RFQ |
|---------------------------------|---------------------------------------|-------------------------------|-------------|--------|--------|
| Diabetes                        | 215/1075                              | 271/1064                      | 0.75 [0.63–0.90] | 20     | 0.009  |
| No diabetes                     | 171/1298                              | 231/1307                      | 0.73 [0.63–0.85] | 47     | 0.013  |
| Men                             | 307/1809                              | 406/1826                      | 0.74 [0.65–0.86] | 52     | 0.012  |
| Women                           | 79/564                                | 96/545                        | 0.79 [0.69–0.91] | 38     | 0.020  |
| Age < 65 years                  | 315/1792                              | 390/1814                      | 0.72 [0.60–0.85] | 34     | 0.020  |
| Age ≥ 65 years                  | 171/1298                              | 231/1307                      | 0.73 [0.63–0.85] | 47     | 0.013  |
| History of HF hospitalization   | 315/1792                              | 390/1814                      | 0.72 [0.60–0.85] | 34     | 0.020  |
| eGFR < 60                       | 315/1792                              | 390/1814                      | 0.72 [0.60–0.85] | 34     | 0.020  |
| eGFR ≥ 60                       | 171/1298                              | 231/1307                      | 0.73 [0.63–0.85] | 47     | 0.013  |

**ARNI, angiotensin receptor/neprilysin inhibitor; Cl, confidence interval; eGFR, estimated glomerular filtration rate; FQ, fragility quotient; HF, heart failure; HR, hazard ratio; RFI, reverse fragility index; SGLT2, sodium-glucose co-transporter 2.**

The fact that a few events could change the statistical significance of the all-cause and cardiovascular mortality underscores the importance of powering trials for mortality outcomes. When the primary outcome is a composite including non-fatal events, neither the total number of fatal events nor the duration of trial follow-up supports deriving definitive conclusions regarding mortality. While it is not possible to power trials for all secondary endpoints, considering the risk for mortality in HF, strong consideration should be given to designing trials for confirming mortality results independently by either larger sample size or longer follow-up or both.

Background therapy can potentially influence the FI and RFI of clinical trials. Similar to most contemporary HF trials, patients in EMPEROR-Reduced, DAPA-HF, and SOLOIST-WHF were well treated with guideline-directed medical therapy at baseline (Table 1). In all three trials, over 90% of the participants were using beta-blockers and renin–angiotensin–aldosterone inhibitors, and over two-thirds were using mineralocorticoid receptor antagonists. There was some variation in the proportion of patients using a neprilysin inhibitor in addition to a renin–angiotensin–aldosterone inhibitor, with the highest rate of use in EMPEROR-Reduced (20%), followed by SOLOIST-WHF (17%) and then DAPA-HF (11%). Overall, the background therapies across trials were similar and unlikely to influence the FI or RFI.

There are several limitations of this study. FI does not account for the difference in time to event and can give fragile results when the number of events in each group is the same but have a difference in the timing of these events. However, studies have shown no difference when FI was applied to time-to-event vs. frequency data. Because trials are powered to detect the effect on primary outcome, interpretability of FI for secondary outcomes and subgroup analyses is limited. The use of Fisher’s exact test in calculation of FI and RFI may be limited as DAPA-HF and EMPEROR-Reduced trials analysed data in models with covariates and time-to-event techniques in which the original data if analysed with Fisher’s exact test may not yield the same \( P \)-value as the published trial. While FI may perpetuate the dichotomous \( P \)-value-oriented data interpretation, it provides a more circumspect view of assessing results than based solely on \( P \). Bayesian approaches may provide an alternate option, but the majority of trials currently are based on frequentist approaches.

In conclusion, findings for the composite endpoint of first HF hospitalization or cardiovascular death were highly consistent and robust across trials with dapaglirozin, empagliflozin, and sotagliflozin. In contrast, findings for the all-cause and cardiovascular mortality were overall significant but fragile when meta-analytically assessed, underscoring the need to design trials with adequate power and follow-up to definitely assess the impact of novel interventions on mortality.
Table 4  Fragility index of outcomes in key heart failure medication trials

| Trial                      | Sample size | Primary endpoint                                                                 | Primary endpoint | HF hospitalization/CV death | All-cause mortality | CV mortality | HF hospitalization |
|----------------------------|-------------|----------------------------------------------------------------------------------|------------------|-----------------------------|--------------------|-------------|-------------------|
|                            |             | P-value | FI/RFI | FQ/RFQ | P-value | FI/RFI | FQ/RFQ | P-value | FI/RFI | FQ/RFQ | P-value | FI/RFI | FQ/RFQ | P-value | FI/RFI | FQ/RFQ | P-value | FI/RFI | FQ/RFQ | P-value | FI/RFI | FQ/RFQ |
| SGLT2 inhibitors           |             |         |        |        |         |        |        |         |        |        |        |         |        |        |         |        |        |         |        |        |         |        |        |         |        |        |
| DAPA-HF                    | 4744        | HF hospitalization, urgent care visits due to HF or CV death                     | Sig              | 62     | 0.0131 | Sig    | 62     | 0.0130 | Sig    | 8      | 0.0020 | Sig    | 5      | 0.0010 | Sig    | 43     | 0.0090 |
| EMPEROR-Reduced SOLOIST-WHF| 3730        | HF hospitalization/CV death                                                      | Sig              | 50     | 0.0134 | Sig    | 50     | 0.0134 | NS     | 26     | 0.0070 | NS     | 24     | 0.0060 | Sig    | 50     | 0.0130 |
| SOLOIST-WHF                | 1222        | Total (first and recurrent) HF hospitalization/CV death                          | Sig              | NA     | NA     | NA     | NA     | NA     | Sig    | 3      | 0.0120 | Sig    | 4      | 0.0158 | NA     | NA     | NA     |
| ACE-I                      |             |         |        |        |         |        |        |         |        |        |        |         |        |        |         |        |        |         |        |        |         |        |        |         |        |        |
| CONSENSUS                  | 253         | All-cause mortality at 6 months                                                  | Sig              | 7      | 0.0277 | NA     | NA     | NA     | NA     | Sig    | 3      | 0.0120 | Sig    | 4      | 0.0158 | NA     | NA     | NA     |
| SOLVD-Treatment ARBs       | 2569        | All-cause mortality                                                             | Sig              | 10     | 0.0039 | NA     | NA     | NA     | NA     | Sig    | 10     | 0.0040 | Sig    | 15     | 0.0058 | Sig    | 91     | 0.0354 |
| Val-HeFT                   | 5010        | All-cause mortality/HF hospitalization/resuscitated cardiac arrest/administration of i.v. inotropic or vasodilator drugs for 4 or more hours | Sig              | 17     | 0.0034 | NA     | NA     | NA     | NA     | NS     | 63     | 0.0130 | NS     | 58     | 0.0116 | Sig    | 59     | 0.0118 |
| CHARM-Alternative Beta-blockers | 2028        | HF hospitalization/CV death                                                      | Sig              | 29     | 0.0143 | Sig    | 29     | 0.0143 | NS     | 10     | 0.0049 | NS     | 6      | 0.0030 | Sig    | 40     | 0.0197 |
| CHARM-Added                | 2548        | HF hospitalization/CV death                                                      | Sig              | 8      | 0.0031 | Sig    | 8      | 0.0031 | NS     | 10     | 0.0039 | Sig    | 3      | 0.0012 | Sig    | 5      | 0.0020 |
| CIBIS II                   | 2647        | All-cause mortality                                                             | Sig              | 37     | 0.0140 | NA     | NA     | NA     | NA     | Sig    | 37     | 0.0140 | Sig    | 11     | 0.0042 | Sig    | 37     | 0.0140 |
| MERIT-HF                   | 3991        | All-cause mortality                                                             | Sig              | 34     | 0.0085 | NA     | NA     | NA     | NA     | Sig    | 34     | 0.0085 | Sig    | 38     | 0.0095 | Sig    | 50     | 0.0125 |
| COPERNICUS                 | 2289        | All-cause mortality                                                             | Sig              | 30     | 0.0131 | NA     | NA     | NA     | NA     | Sig    | 30     | 0.0131 | Sig    | 22     | 0.0096 | Sig    | 37     | 0.0162 |
| SENIORS                    | 2128        | All-cause mortality/CV hospital admission                                       | Sig              | 2      | 0.0009 | NA     | NA     | NA     | NA     | NS     | 11     | 0.0052 | NS     | 7      | 0.0033 | NS     | 31     | 0.0146 |
| MRA                        |             |         |        |        |         |        |        |         |        |        |        |         |        |        |         |        |        |         |        |        |         |        |        |         |        |        |
| RALES                      | 1663        | All-cause mortality/CV death                                                     | Sig              | 54     | 0.0325 | NA     | NA     | NA     | NA     | Sig    | 54     | 0.0325 | Sig    | 46     | 0.0277 | Sig    | 41     | 0.0247 |
| EMPHASIS-HF                | 2737        | CV death/HF hospitalization                                                      | Sig              | 61     | 0.0223 | Sig    | 61     | 0.0223 | Sig    | 5      | 0.0018 | Sig    | 3      | 0.0011 | Sig    | 49     | 0.0179 |
| H-ISDN                     |             |         |        |        |         |        |        |         |        |        |        |         |        |        |         |        |        |         |        |        |         |        |        |         |        |        |
| A-HeFT                     | 1050        | Composite score                                                                 | Sig              | NA     | NA     | NA     | NA     | NA     | Sig    | 3      | 0.0029 | Sig    | 2      | 0.0019 | Sig    | 15     | 0.0143 |
| Digoxin                    |             |         |        |        |         |        |        |         |        |        |        |         |        |        |         |        |        |         |        |        |         |        |        |         |        |        |
| DIG                        | 6800        | All-cause mortality/CV death                                                      | Sig              | 61     | 0.0090 | NA     | NA     | NA     | NA     | Sig    | 61     | 0.0090 | NS     | 87     | 0.0128 | Sig    | 191    | 0.0281 |
| Ivabradine                 |             |         |        |        |         |        |        |         |        |        |        |         |        |        |         |        |        |         |        |        |         |        |        |         |        |        |
| SHIFT                      | 6505        | HF hospitalization/CV death                                                      | Sig              | 67     | 0.0103 | Sig    | 67     | 0.0103 | NS     | 13     | 0.0019 | NS     | 18     | 0.0028 | Sig    | 91     | 0.0140 |
| ARNI                       |             |         |        |        |         |        |        |         |        |        |        |         |        |        |         |        |        |         |        |        |         |        |        |         |        |        |
| PARADIGM-HF                | 8399        | HF hospitalization/CV death                                                      | Sig              | 118    | 0.0140 | Sig    | 118    | 0.0140 | Sig    | 49     | 0.0058 | Sig    | 66     | 0.0079 | Sig    | 54     | 0.0064 |
| Vericiguat                 |             |         |        |        |         |        |        |         |        |        |        |         |        |        |         |        |        |         |        |        |         |        |        |         |        |        |
| VICTORIA                   |             |         |        |        |         |        |        |         |        |        |        |         |        |        |         |        |        |         |        |        |         |        |        |         |        |        |
| Omecamtiv mecarbil         |             |         |        |        |         |        |        |         |        |        |        |         |        |        |         |        |        |         |        |        |         |        |        |         |        |        |
| GALACTIC-HF                | 8442        | HF hospitalization, urgent care visits due to HF or CV death                    | Sig              | 1      | 0.0001 | NS     | 33     | 0.0040 | NS     | 78     | 0.0092 | NS     | 79     | 0.0094 | NS     | 40     | 0.0047 |

ACE-I, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; ARNI, angiotensin receptor/neprilysin inhibitor; CV, cardiovascular; FI, fragility index; FQ, fragility quotient; HF, heart failure; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid antagonist; RFI, reverse fragility index; RFQ, reverse fragility quotient; SGLT2, sodium–glucose co-transporter 2.
**Conflict of interest**

G.C.F. reports consulting for Abbott, Amgen, AstraZeneca, Bayer, CHF Solutions, Janssen, Medtronic, Merck, and Novartis. S.J.G. was supported by the Heart Failure Society of America/Emergency Medicine Foundation Acute Heart Failure Young Investigator Award funded by Novartis; has received research support from the American Heart Association, AstraZeneca, Amgen, Bristol Myers Squibb, Merck, and Novartis; has served on advisory boards for Amgen and Cytokinetics; and serves as a consultant for Amgen and Merck. M. V. is supported by the KL2/Catalyst Medical Research Investigator Training Award from Harvard Catalyst (NIH/NCATS Award UL1TR002541); serves on advisory boards for Amgen, AstraZeneca, Baxter Healthcare, Bayer AG, Boehringer Ingelheim, Cytokinetics, and Relypsa; and participates on clinical endpoint committees for studies sponsored by Galmed, Novartis; has served on advisory boards for Amgen and Cytokinetics; and serves as a consultant for Amgen and Merck. T.F. reports personal fees from AstraZeneca, Baxter Healthcare, Bayer AG, Boehringer Ingelheim, Cytokinetics, and Relypsa; and participates on clinical endpoint committees for studies sponsored by Galmed, Novartis, and the NIH. T.F. reports personal fees from Novartis, Bayer, Janssen, SGS, Roche, Boehringer Ingelheim, Daiichi Sankyo, Galapagos, Penumbra, Parexel, Vifor, Biosense Webster, CSL Behring, Fresenius Kabi, Coherex Medical, and LivaNova. G.F. participated in committees of trials and registries sponsored by BI, Bayer, Medtronic, Servier, Novartis, and Vifor. A.J.S.C. reports honoraria and/or lecture fees from AstraZeneca, Bayer, Menarini, Novartis, Nutricia, Servier, Vifor, Actemted, Cardiac Dimensions, CVRx, Enopace, Faraday, Gore, Impulse Dynamics, Respircardia, Stealth Peptides, V-Wave, Corvia, Arena, and ESN Cleer. S.D.A. has received research support from Vifor International and Abbott Vascular, and fees for consultancy and/or speaking from AstraZeneca, Bayer, Boehringer Ingelheim, Respircardia, Impulse Dynamics, Janssen, Novartis, Servier, and Vifor International. J.B. is a consultant to Abbott, Amgen, Applied Therapeutics, Array, AstraZeneca, Bayer, Boehringer Ingelheim, CVRx, Eli Lilly, G3 Pharmaceutical, Impulse Dynamics, Innolife, Janssen, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Sequna, Stealth Peptides, and Vifor. All other authors report no disclosures.

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**Funding**

None.