Evidence-based Appraisal of the DAPA-HF Trial

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Patient Population: Adults (≥18 years) with ejection fraction (EF) ≤ 40%, NYHA II-IV symptoms, NT-proBNP ≥ 600 pg/mL (≥ 400 pg/mL if heart failure (HF) hospitalization in last year; ≥ 900 pg/mL if AFib/flutter) receiving standard HF device (ICD, CRT, or both) and standard drug therapy (angiotensin converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB) or angiotensin receptor neprilysin inhibitor (ARNI), beta-blocker, unless contraindicated or not tolerated, with mineralocorticoid receptor antagonist (MRA) use encouraged). Those with recent treatment with or intolerance to an SGLT2 inhibitor, T1DM, hypotension symptoms or SBP < 95 mmHg, eGFR < 30 mL/min/1.73m², or rapidly declining renal function were excluded.

Intervention (n = 2,373): Dapagliflozin 10 mg PO daily
Comparison (n = 2,371): Matching placebo PO daily

Outcome: Primary outcome: composite of worsening HF (unplanned hospitalization or urgent visit for IV HF therapy) or death from cardiovascular causes over a median of 18 months

Trial Validity

| Start of Trial | Risk of Bias |
|----------------|--------------|
| Randomization/Concealment |
| • Patients were randomized 1:1 to receive dapagliflozin or matching placebo in a fixed-randomization schedule, in balanced blocks, stratified by type 2 diabetes mellitus (T2DM) diagnosis. | Low |
| • Investigators used an interactive voice- or web-response system to determine treatment assignment, which likely concealed the randomization process. | Low |
| Baseline Characteristics |
| • Both groups had similar baseline characteristics and were well balanced between the intervention group and control group as shown in Table 1. | Low |

Categories for risk of bias include:
Low risk of bias (green), unclear/possible risk of bias (yellow), high risk of bias (red)
## Trial Validity

### During Trial

| Blinding |
|-----------------------------------------------|
| Patients, clinicians, outcome assessors, data collectors and data analysts were unaware of trial-group assignments. Per study protocol, no member of the study team, personnel at study sites, or any contract research organization handling study data had access to the randomization scheme during the study, indicating that all study personnel were blinded. |

| Equal Treatment |
|-----------------------------------------------|
| The use of cardiovascular and anti-hyperglycemic therapies was well balanced between the intervention and control group at baseline and was evaluated during the initial 14 day screening, indicating minimal potential co-intervention bias at baseline between the two groups. However, there is no information regarding concomitant therapies during the trial. |
| Dapagliflozin and placebo were stopped for reasons other than death in 10.5% and 10.9% of patients, respectively. |
| Dose reduction to 5mg daily of dapagliflozin or placebo or temporary discontinuation was permitted in case of an acute, unexpected decline in the eGFR, volume depletion, or hypotension (or to avoid these conditions) with a subsequent increase in dose or restarting of treatment, if possible. Any adverse effect leading to a dose reduction to dapagliflozin 5 mg daily occurred in 1.8% in the dapagliflozin group and 1.1% in the placebo group. Any adverse effect leading to temporary discontinuation occurred in 4.7% in the dapagliflozin group and 4.9% in the placebo group. Due to the dose reduction and/or temporary discontinuation of either dapagliflozin or placebo being permitted, this indicates that some patients may have not received the intended therapies at the dose under investigation during an unstated period of time throughout the study. The slightly higher amount of dose reduction in the dapagliflozin group would bias towards a null effect (favor placebo). However, given the small differences between groups, minimal impact would be expected as this percent is much smaller than the absolute difference in event rates between groups for the primary outcome. |
| Dapagliflozin is a prescription only medication and would prove difficult to be obtained by other means which reduces the chance of causing contamination in the trial. |

### Risk of Bias

| Blinding | Low |
| Equal Treatment | Possible/Unclear |

## End of Trial

### Completeness of Outcome Data

| There were 14 patients (0.59%) in the intervention group and 20 patients (0.84%) in the control group who lacked outcome data (lost to follow-up or withdrew consent) for the primary outcome. Since the ARR of 4.9% for the primary outcome is much larger than the percent with missing outcomes data, there is low risk of bias. |

### Method of Outcome Analysis

| Intention-to-treat analysis was performed for the efficacy outcomes. |
| Data was included from all patients who had undergone randomization to either the intervention group (n=2373, 100%) or placebo (n=2371, 100%) in the analyses of the primary and secondary outcomes. |

### Risk of Bias

| Completeness of Outcome Data | Low |
| Method of Outcome Analysis | Low |
### Trial Results - Efficacy

| Efficacy Outcome | Dapagliflozin 10 mg N=2,373 | Placebo N=2,371 | HR (95% confidence interval) | Relative Risk Reduction (RRR) | Absolute Risk Reduction (ARR) | Number Needed to Treat (NNT) | p-value |
|------------------|-----------------------------|----------------|-------------------------------|-----------------------------|-----------------------------|-----------------------------|---------|
| Primary Endpoint\(^1\) | 16.3% (386) | 21.2% (502) | HR 0.74 (95% CI 0.65 to 0.85) | 23% | 4.9% | 20 | P<0.001 |
| Secondary Endpoint\(^2\) | 16.1% (382) | 20.9% (495) | HR 0.75 (95% CI 0.65 to 0.85) | 23% | 4.8% | 21 | P<0.001 |

\(^1\)Composite of worsening heart failure, including hospitalization or an urgent visit resulting in intravenous therapy for heart failure, or cardiovascular death

\(^2\)Cardiovascular death or hospitalization due to heart failure

The primary outcome was a composite of worsening HF, including either an unplanned hospitalization or an urgent visit resulting in IV therapy, or death from cardiovascular causes. Worsening HF (hospitalization or urgent visit resulting in IV therapy for heart failure occurred in 386 patients (16.3%) in the dapagliflozin group and 502 patients (21.2%) in the placebo group (HR 0.74; 95% CI 0.65-0.85; P <0.001). A first worsening HF event occurred in 237 patients (10%) in the dapagliflozin group and 326 patients (13.7%) in the placebo group (HR 0.70; 95% CI 0.59-0.83; P-value not given). Death from cardiovascular causes occurred in 227 patients (9.6%) in the dapagliflozin group and 273 patients (11.5%) in the placebo group (HR 0.82; 95% CI 0.69-0.98; P value not given). It is evident that the event rates for all three components of the primary composite outcome favored dapagliflozin.

### Trial Results - Safety

| Adverse Event | Dapagliflozin 10 mg N=2,373 | Placebo N=2,371 | Absolute Risk Increase (ARI) | Number Needed to Treat (NNT) | p-value |
|---------------|-----------------------------|----------------|-----------------------------|-----------------------------|---------|
| Serious volume depletion\(^1\) | 1.2% (29) | 1.7% (40) | 4.9% | N/A | P=0.23 |
| Serious renal adverse event\(^1\) | 1.6% (38) | 2.7% (65) | 1.1% | 91 | P=0.009 |
| Major Hypoglycemia | 0.2% (4) | 0.2% (4) | 0% | N/A | N/A |
| Diabetic ketoacidosis | 0.1% (3) | 0 | 0.1% | N/A | N/A |

\(^1\)The total number of volume depletion events was 178 in the dapagliflozin group and 162 in the placebo group (p-value=0.40). The total number of renal adverse events was 153 in the dapagliflozin group and 170 in the placebo group (p-value=0.36).

Most adverse events that were evaluated in this study were uncommon and not statistically different between study groups. However, serious renal adverse events were significantly lower in the dapagliflozin group compared with placebo. While serious volume depletion events were numerically lower in the dapagliflozin group, the difference between groups did not reach statistical significance.
Trial Applicability

Patient Applicability

- The results of the DAPA-HF trial are applicable to adults with an EF≤40%, and NYHA class II-III HF symptoms with or without T2DM.
- The trial included patients with a mean age of 66 years, 24% were women, the mean EF was 31%. Additionally, at baseline, 68% of patients were classified as NYHA II, 32% as NYHA III, and only 1% as NYHA IV.
- The trial excluded patients who had T1DM, symptoms of hypotension or SBP<95 mmHg and eGFR<30mL/min/1.73 m² of body surface area, or rapidly declining renal function.

Intervention Applicability

- The intervention was dapagliflozin 10mg daily. This medication is an oral once-daily SGLT-2 inhibitor, which allows for a convenient dosing regimen. It is primarily indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It is also indicated as an adjunct to reduce the risk of hospitalization for HF in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors. In relation to its accessibility among patients, dapagliflozin is included in most formularies including Aetna (Tier 2, quantity limits), Blue Shield (Tier 2, quantity limits), Cigna (Tier 2, quantity limits), CVS Caremark (Tier 2), Express Scripts (Tier 2), as well as select Medicare (Tier 2) and Medicaid (Tier 1) plans. The current average wholesale cost of dapagliflozin is $500/month, with an average co-payment ranging from $20-$40/month depending on patients’ insurance type. Moreover, the manufacturer of this medication offers a savings card where most commercially insured patients can get dapagliflozin for as little as $0 per month (subject to a maximum savings of $378 per 30-day supply; excludes patients who are enrolled in a state or federally funded prescription insurance program) as long as their doctor prescribes any available dose, making it a potentially feasible option to consider for patients and providers.

Patient-Important Outcomes Measured

- In patients with HF and reduced ejection fraction, the risk of worsening HF or death from cardiovascular causes was lower among those who received dapagliflozin than those who received placebo regardless of the presence of diabetes with an NNT of 20 and an absolute risk reduction of 4.9% (p<0.001) when compared with standard care.
- Dapagliflozin was well tolerated with severe renal adverse reactions lower than placebo, with an NNT 91 (p=0.009) for dapagliflozin. The experimental group and the placebo group experienced a similar number of total renal adverse reaction events with 153 and 170 cases, respectively. The experimental group and control group experienced a similar number of volume depletion events with 178 and 162 cases, respectively. Other adverse outcomes were not statistically significant between groups, but the short follow-up duration may not be sufficient to evaluate the long term safety profile.
- If 1000 patients who suffer from HF with reduced ejection fraction with or without T2DM were treated with dapagliflozin vs placebo, there would be 49 fewer cases of worsening HF or death from cardiovascular causes and 11 fewer cases of severe renal adverse reaction events. Dapagliflozin is an efficacious agent in addition to standard therapy in the setting of HF and reduced ejection fraction to reduce the risk of worsening HF or death from cardiovascular causes, and can be considered a viable option in the management of such patients as the benefits appear to outweigh the potential risks.

Balance of Benefits vs. Harms

- The primary outcome, classified as clinical endpoints, was a composite of worsening HF, including either an unplanned hospitalization or an urgent visit resulting in intravenous therapy for HF, or death from cardiovascular causes over a median of 18 months.
- The safety analysis was performed in patients who had undergone randomization and received ≥1 dose of dapagliflozin or placebo. The trial monitored for serious adverse events including volume depletion, renal events, major hypoglycemia, bone fractures, diabetic ketoacidosis, amputations, and Fournier’s gangrene. A composite of worsening renal function was defined as a sustained decline in eGFR≥50%, end-stage renal disease (sustained (>28 days) eGFR<15mL/min/1.73m², sustained dialysis, or renal transplantation, or renal death.
- Data on other adverse events were not routinely collected due to extensive previous collection of safety data regarding dapagliflozin. However, such data was observed in patients with T2DM, and the rates for these adverse events may differ in patients suffering from heart failure. Although the frequency and focus of adverse events were evaluated appropriately, the median follow-up time of 24 months is considered insufficient in assessing the long-term safety of dapagliflozin.
Healthcare Professional Summary

The DAPA-HF trial evaluated the safety and efficacy of dapagliflozin in patients with HF with reduced ejection fraction regardless of the presence of diabetes. It was an international, multi-center, randomized, placebo-controlled study, with blinding of patients and all study personnel, a low percent of patients without final outcomes, and analyzed with the intention-to-treat principle. The primary outcome of the trial showed an absolute risk reduction of 4.9% and a relative risk reduction of 23.2%, with an NNT of 20, demonstrating that the composite outcome of worsening heart failure or death from cardiovascular causes was lower in the dapagliflozin group relative to placebo. Dapagliflozin was well tolerated with notable adverse reactions reported being volume depletion and renal adverse events in a similar number of events for both groups, and severe renal adverse events being lower with dapagliflozin. There are limitations when considering the generalizability of this study since the majority of the study population were classified as moderate heart failure. Additionally, the study demonstrated that there is a differential benefit between NYHA classes, with the primary benefit attributed to those classified as NYHA FC II. The ideal population for treatment with dapagliflozin are adults with HF with reduced ejection fraction and NYHA FC II-III symptoms, who are receiving standard HF device therapy (ICD, CRT or both) and standard drug therapy (ACEi/ARB/ARNI and beta-blocker unless contraindicated or resulting in unacceptable side effects), with MRA use being encouraged.

Patient Summary

Dapagliflozin is a medication that is taken once daily by mouth and is primarily used in patients with type 2 diabetes mellitus to lower blood sugar levels through the kidneys. Previous studies have shown that medications in the same class as dapagliflozin reduce the risk of hospitalization for heart failure. In this study, patients with a weak heart, known as, heart failure, with or without type 2 diabetes mellitus who took dapagliflozin had a lower chance of worsening heart failure (leading to a hospital admission or IV therapy) or death from heart-related problems including, heart attack, shock, and stroke compared with patients who took standard heart failure therapy. The main side effects of dehydration and kidney injury were not different between groups, and more serious kidney injury happened less often with dapagliflozin. While it may cost more to use dapagliflozin relative to other medications used to treat type 2 diabetes, this medication has the added benefit of lowering heart-related events in combination with standard treatment in patients with heart failure who may or may not have diabetes.

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