S Afr Gen Pract. 2024;5(2):83-85
https://doi.org/10.36303/SAGP.0511

S Afr Gen Pract
ISSN 2706-9613 EISSN 2706-9621

REVIEW

Assessing the clinical impact of sodium-glucose cotransporter type 2 (SGLT2)-inhibitors in treating heart failure with reduced ejection fraction

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Heart failure with reduced ejection fraction (HFrEF), often considered life-threatening, presents a significant risk to patient health. Guideline-directed medical therapy (GDMT), comprising a four-drug regimen, is currently widely recommended to optimise patient outcomes. This article seeks to elucidate the absolute benefits of SGLT2-inhibitors in the management of HFrEF and their integration into GDMT protocols.

Keywords: heart failure with reduced ejection fraction (HFrEF), SGLT2-inhibitors, guideline-directed medical therapy (GDMT)

Heart failure

Heart failure manifests through a spectrum of symptoms reflecting its complex pathophysiology. Classification of heart failure is primarily based on ejection fraction (EF), though, dividing it into two main categories: heart failure with reduced ejection fraction (HFrEF), characterised by EF ≤ 40%, and heart failure with preserved ejection fraction (HFpEF), where EF is ≥ 50%. An intermediate category, heart failure with mid-range ejection fraction (HFmrEF), falls between these two extremes with EF ranging from 41%–49%. This classification guides treatment decisions and helps tailor management strategies to address the underlying mechanisms and severity.

Heart failure is a serious syndrome associated with significant mortality and morbidity, diminished quality of life, compromised functional capacity, and considerable financial burden. The Global Burden of Disease study has revealed a heart failure prevalence of 1–3% within the general population, a figure that escalates notably with advancing age, affecting at least one in 10 individuals aged over 70 years.[1] Moreover, the global prevalence of heart failure is on the rise. The incidence is 1–20 cases per 1 000 person-years or per 1 000 of the population. Regrettably, there is a notable scarcity of data concerning heart failure in developing nations.

Mortality rates linked to heart failure are concerning, with a 30-day mortality ranging from 2–3%, a one-year mortality of 15–30%, and a five-year mortality reaching 50–75%.[1] Undoubtedly, heart failure poses a significant threat to life.

Heart failure in Type-2 diabetes mellitus

Type-2 diabetes mellitus (T2D) presents a considerable symptom burden and elevates the risk of cardiovascular and renal complications, as well as mortality. A multinational cohort study of patients from Norway, Sweden, Germany, the Netherlands, the United Kingdom, and Japan, evaluated a total of 1 177 896 individuals with T2D.[2] Among them, 772 336 (66%) were initially free of cardiovascular-renal disease (CVRD) at the study's onset. Over a mean follow-up period of 4.5 years, the incidence of a first chronic kidney disease event was 36%, while that of heart failure was 24%. Incidences of stroke (16%), myocardial infarction (14%), and peripheral arterial disease (10%) were comparatively lower. The study's conclusion stresses that heart failure and chronic kidney disease were consistently the most prevalent initial cardiovascular disease manifestations in patients with T2D.

Guideline-directed medical therapy

Guideline-directed medical therapy (GDMT) for HFrEF, defined by an EF ≤ 40%, advises the utilisation of four specific medication classes to achieve optimal treatment outcomes.[3] These encompass the following:

1. Renin-Angiotensin-Aldosterone-System inhibitors such as ACE-inhibitors, ARB's, ARNI (ARB plus Neprilysin inhibitor)
2. Mineralocorticoid receptor antagonists (MRAs)
3. Beta-blockers (specifically Carvedilol, Bisoprolol, Metoprolol)
4. SGLT2-inhibitors

In a landmark study assessing the lifetime benefits of this GDMT approach, researchers conducted a cross-trial analysis using published randomised trials in a collaboration between the United Kingdom, United States of America, Portugal, and France.[4] This study compared the GDMT method with conventional therapy and found that GDMT was associated with a favourable hazard ratio (HR) of 0.38 (95% CI: 0.30–0.47) for cardiovascular death and first hospitalisation for worsening heart failure. The study estimated that GDMT provided an additional 2.7 years free from cardiovascular death or first hospitalisation due to heart failure for an 80-year-old patient, and 8.3 additional years for a 55-year-old.

In this enhanced management strategy for HFrEF, the role of SGLT2-inhibitors becomes a pivotal aspect to explore. Two randomised controlled trials involving SGLT2-inhibitors for HFrEF aimed to address this and other relevant research inquiries.

The primary endpoint for both trials was the combination of cardiovascular death or hospitalisation for worsening heart failure. Both trials yielded statistically significant results:

Dapagliflozin in HFrEF (DAPA-HF)[5]

A total of 4 744 patients diagnosed with HFrEF were enrolled in a study comparing the effects of dapagliflozin 10 mg daily versus placebo over a duration of 18.2 months.

Empagliflozin in HFrEF (EMPEROR-REDUCED)[6]

There were 3 730 patients with HFrEF who participated in this trial comparing empagliflozin 10 mg daily to placebo over a period of 16 months.

Number Needed to Treat (NNT) for dapagliflozin was 21 over 18.2 months; and for empagliflozin, the NNT was 19 over 16 months (See Box 1).

Event rate per 1 000 patient-years: dapagliflozin prevented four patients from experiencing the primary endpoint per 1 000 patients treated for one year; and empagliflozin prevented five patients from experiencing the primary endpoint per 1 000 patients treated for one year.

The differences between the two, while not statistically significant, could be attributed to the fact that enrolled patients receiving empagliflozin presented with more severe heart failure, as evidenced by their lower EFs.

Box 1: Number Needed to Treat (NNT)

The NNT assesses the effectiveness of a treatment. It represents the number of patients who need to be treated – in this case with an SGLT2-inhibitor – over a specific period to prevent one additional adverse cardiovascular outcome or to achieve one additional beneficial outcome compared to those not receiving the treatment. The NNT provides valuable information about the magnitude of the treatment effect and helps to evaluate the clinical significance of interventions. Lower NNT values indicate that a treatment is more effective, while higher NNT values suggest that more patients need to be treated to achieve the desired outcome.

Meta-analysis of these two trials[7]

A meta-analysis of these two trials involving a combined total of 8 474 patients with HFrEF yielded the following HRs (Box 2):

- All-cause death: HR 0.87 (95% CI: 0.77–0.98)
- Cardiovascular death: HR 0.86 (95% CI: 0.76–0.98)
- Primary endpoint of cardiovascular death or hospitalisations for heart failure: HR 0.74 (95% CI: 0.68–0.82).

These findings suggest that SGLT2-inhibitors may effectively reduce cardiovascular events in patients with HFrEF, providing reassurance regarding their therapeutic benefit.

Box 2: Hazard ratio (HR)

HRs are commonly used in survival analyses and clinical trials to compare the timing of events between two groups. HRs are often used to assess the relative risk of an event (such as death, disease progression, or treatment failure) occurring in one group compared to another.

The HR represents the ratio of the hazard rates (or risks) of the event between two groups. A HR greater than 1 indicates a higher risk or hazard of the event in the first group compared to the second group, while a HR less than 1 indicates a lower risk or hazard in the first group compared to the second group.

HRs are often accompanied by confidence intervals (CI), which provide a range of values within which the true HR is likely to lie. A HR with a CI entirely above or below 1 is typically considered statistically significant.

Example:

A clinical trial comparing two treatments for heart failure finds a HR of 0.80 for cardiovascular mortality, with a 95% CI of 0.70 to 0.90.

In this example:

The HR of 0.80 suggests that patients receiving Treatment A have a 20% *lower* risk of cardiovascular mortality compared to those receiving Treatment B.

The 95% CI of 0.70 to 0.90 indicates that we can be 95% confident that the true HR lies somewhere between 0.70 and 0.90.

Since the CI does not include 1 (which represents no difference between the two groups), the HR of 0.80 is statistically significant, suggesting a meaningful difference between the treatments in terms of reducing cardiovascular mortality.

The absolute benefit of SGLT2-inhibitors in HFrEF

Drawing from a comprehensive study analysing data from 71 545 patients across 10 randomised controlled trials of SGLT2-inhibitors,[8] the following outcomes were observed when treating 1 000 patients with HFrEF for one year: 56 fewer heart failure hospitalisations, 11 fewer cardiovascular deaths, 13 fewer total deaths, and seven fewer instances of renal deterioration. These benefits should be weighed against the potential costs, which included two urinary tract infections, three mycotic genital infections, eight episodes of volume depletion, two major hypoglycaemic events, one amputation, and one fracture.

In their guideline on heart failure treatment, the Heart Failure Society of America calculated the NNT over 36 months for the four classes of drugs used in GDMT as follows:[9] ARNI (ARB plus neprilysin inhibitor): 27; ACE-inhibitor or ARB: 26; SGLT2-inhibitor: 22; Beta-blocker: 9; and Mineralocorticoid receptor antagonist (MRA): 6.

One expert noted that the two heart failure trials involving SGLT2-inhibitors (DAPA-HF and EMPEROR-REDUCED) prevented five to eight hospitalisations per 100 patients treated for one year.[10] Referring to the publication from the Heart Failure Society

of America,[9] this article further indicated that SGLT2-inhibitors, when used in 100 patients for three years, would prevent four to five deaths, while MRAs would prevent 17 deaths, and beta blockers would prevent 11. The author concluded by stating that while SGLT2-inhibitors are a valuable addition to other treatments for HFrEF, they are not superior to many others. These data highlight the maximal benefit achievable through GDMT, consisting of four drugs, for HFrEF.

Summary points

1. HFrEF is a life-threatening condition.
2. GDMT comprises four drug classes: RAAS-inhibitor (ARNI or ACE-Inhibitor or ARB), Beta-blocker, MRA, and SGLT2-inhibitor. Evidence supports the superiority of GDMT over conventional therapy in reducing clinical events and extending lifespan. Efforts should be directed toward promoting wider adoption of GDMT.
3. When considering SGLT2-inhibitors, their calculated absolute benefits are weighed against potential harms. While SGLT2 inhibitors provide benefits that may be less pronounced than those offered by the other three components of GDMT, they are still regarded as valuable additions to complete the four-drug therapy regimen for HFrEF.

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