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CARDIOVASCULAR AND RENAL EFFECTS OF EMPAGLIFLOZIN AND DAPAGLIFLOZIN: A COMPARATIVE REVIEW

General Medicine

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ABSTRACT

Sodium-glucose cotransporter 2 inhibitors (SGLT2i), including Dapagliflozin and Empagliflozin, represent a paradigm shift in cardiovascular and renal therapies [1]. Originally utilized for glycaemic control in patients with Type 2 Diabetes Mellitus (T2DM), these agents have been demonstrated in randomized controlled trials to reduce major adverse cardiovascular events (MACE) and hospitalizations for heart failure (HF) across the entire spectrum of ejection fraction[1,2]. The cardioprotective effects of SGLT2i are pleiotropic, involving modulation of cardiac metabolism, inhibition of the Na+/H+ Exchanger 1 (NHE1), modulation of mitochondrial dynamics, and effects on epigenetic pathways and iron metabolism [1, 3]. Comparative effectiveness studies between Dapagliflozin and Empagliflozin have generally indicated similar outcomes for MACE in patients with T2DM [1]. However, some observational data suggest potential differences in specific outcomes, such as hospitalization rates in HF patients and the risk of incident atrial fibrillation in T2DM patients. Both agents provide renal protection by decreasing estimated Glomerular Filtration Rate (eGFR) and reducing renal-specific outcomes [1].

KEYWORDS

Sodium-glucose Cotransporter 2 Inhibitors (SGLT2i), Dapagliflozin, Empagliflozin, Heart Failure (HF), Type 2 Diabetes Mellitus (T2DM), Renal Protection.

INTRODUCTION

Heart failure is a leading cause of global morbidity and mortality [4]. The efficacy of SGLT2i in improving cardiovascular and renal outcomes has led to their broad use in patients presenting with T2DM, Chronic Kidney Disease (CKD), or HF regardless of ejection fraction [4]. The mechanisms explaining the benefits of SGLT2i are still not fully understood, but their efficacy across these diverse conditions suggests that they intersect at metabolic, renal, and cardiac pathways, interrupting maladaptive cycles and mitigating direct organ damage [5].

Methodology

Comparisons between Empagliflozin and Dapagliflozin must rely on outcomes derived from individual landmark trials, observational real-world studies, and network meta-analyses, as direct head-to-head randomized controlled trials comparing their cardiovascular efficacy are currently absent [6]. The differences in chemical structure and selectivity for SGLT2/SGLT1 could potentially lead to divergent pharmacodynamic effects [6].

RESULT AND DISCUSSION

1. Comparative Cardiovascular Outcomes in Clinical Trials

Differences in chemical structure and SGLT2/SGLT1 selectivity, potentially cause divergent pharmacodynamics effects. Direct head-to-head randomized controlled trials comparing Empagliflozin and Dapagliflozin for cardiovascular efficacy are currently absent. Therefore, comparisons rely on outcomes from individual landmark trials, network meta-analyses, and observational real-world studies [7].

Major Adverse Cardiovascular Events (MACE) in Diabetes

- Empagliflozin (EMPA-REG OUTCOME): Showed a significant reduction in CV mortality, all-cause mortality, and hospitalization for HF [8].
- Dapagliflozin (DECLARE-TIMI 58): Showed a decline in hospitalization for HF and participants showed a 19% lower risk of developing AF [8].

Heart Failure Outcomes (HFrEF and HFpEF)

- The EMPEROR-Reduced (Empagliflozin) and DAPA-HF (Dapagliflozin) trials both showed a 25% reduction in the composite outcome of cardiovascular death or hospitalization for worsening HF [8].
- Both trials demonstrated consistency in reducing HF hospitalization by approximately 30% [8].
- DAPA-HF reported a statistically significant reduction in cardiovascular death and all-cause mortality, whereas the corresponding hazard ratios in EMPEROR-Reduced were numerically lower but not statistically significant. This discrepancy potentially attributed to differences in patient populations, higher discontinuation rates in EMPEROR-Reduced, and statistical power limitations since primary outcome caused reductions in HF hospitalizations [9].
- In patients with preserved or mildly reduced ejection fraction (HFpEF/HFmREF), both agents proved beneficial, as in EMPEROR-Preserved (Empagliflozin) and DELIVER (Dapagliflozin) studies, both of which demonstrated a reduction in HF hospitalization [9].

Atrial Fibrillation (AF)

- The studies comparing Dapagliflozin and Empagliflozin in T2DM patients demonstrated that Dapagliflozin users had a significantly lower risk of incident nonvalvular AF compared with Empagliflozin users [7].
- Meta-analyses of RCTs also indicated that the observed reduction in AF incidence across the SGLT2i class was largely driven by Dapagliflozin trials [11].

2. Renal Protection in CKD

- The DAPA-CKD trial and the EMPA-KIDNEY trial both showed a lower risk of renal-specific outcomes, defined as a composite of progression of kidney disease or death from cardiovascular causes [11].
- In the HFrEF trials, EMPEROR-Reduced and DAPA-HF reported a similar and significant effect of SGLT2 inhibitors in decreasing eGFR [12].

3. Molecular Targets and Mechanistic Comparisons

Cardiac Metabolism and Energy Shift

Both Empagliflozin and Dapagliflozin induce a metabolic shift away from inefficient glucose utilization towards ketone bodies, fatty acids, and branched-chain amino acids [12].

- In HF, the increase in circulating ketone bodies due to SGLT2i administration seems to improve overall cardiac function [12].
- Ketone bodies provide a higher energy yield for cardiac mitochondria to produce ATP, compared to glucose [13].
- Preclinical studies, specifically using Empagliflozin, demonstrated that infusion before reperfusion elevates ketonemia, improve myocardial ischemia-reperfusion injury and reducing infarct size [13].

Cardioprotective Signaling Pathways

- Empagliflozin, Dapagliflozin and canagliflozin have been reported to reduce myocardial cytoplasmic Na+ through inhibition of the cardiac NHE1 in animal models [13]. NHE1 inhibition may reduce intracellular calcium and thereby inhibit calmodulin-dependent protein kinase II (CaM kinase II) [13].
- Empagliflozin was shown to reduce CaMKII activity in isolated ventricular cardiomyocytes [15]. Sotagliflozin also inhibits the activation of the TLR4 (Toll-like receptor 4) /CaMKII signaling pathway.
- Empagliflozin has direct effects on myocardial contractility in HF, improving diastolic function and myofibril passive stiffness by enhancing the phosphorylation of myofilament regulatory proteins. This process involves the NO/sGC/cGMP/PKG

pathway, which is often impaired in HF [15].
- SGLT2i actively restore mitochondrial metabolism and dynamics [15]. Both Empagliflozin and Dapagliflozin enhance autophagy and antioxidant capacity in distressed hearts, reducing mitochondrial dysfunction and apoptosis [15]. Empagliflozin notably reduced left ventricular dysfunction by mitigating hyper-autophagy and Connexin 43 (Cx43) lateralization.
- Dapagliflozin reduced arrhythmic vulnerabilities by regulating Cx43 expression via the AMPK (AMP-activated protein kinase) pathway in post-infarcted rats [14]. Empagliflozin has also been shown to influence Cx40 and Cx43 expression.
- SGLT2 inhibitors also act as "epidrugs" by influencing key epigenetic and metabolic pathways [14]. Empagliflozin has been shown to reduce high glucose-induced inflammation through suppression of HDAC2 (Histone deacetylases) [14]. Additionally, the cardioprotective effects of SGLT2i—including dapagliflozin—may be mediated by increased ketogenesis and elevated β-hydroxybutyrate (β-OHB) levels, which function as indirect HDAC inhibitors [14]. Beyond epigenetic modulation, SGLT2i promote favourable adaptations in erythropoiesis and iron metabolism, potentially via hepcidin downregulation, increased iron mobilization, and improved myocardial iron handling, collectively supporting enhanced mitochondrial efficiency and cardiac function [14].

4. Guidelines and Clinical Recommendations

- SGLT2 inhibitors are now considered essential cardiorenal therapies, having moved beyond their traditional role as solely glucose-lowering agents.
- They have emerged as two pivotal pillars of Heart Failure management [5].
- The therapeutic benefits of SGLT2i are generally considered to be class effects across diverse conditions [5].

Recommendations for Heart Failure

- SGLT2 inhibitors are strongly recommended in clinical practice guidelines for the management of HF [16].
- They are approved and recommended for use in HF irrespective of the patient's ejection fraction status, covering HF with reduced, preserved, or mildly reduced EF [5].
- Current guidelines recommend treating patients with Heart Failure with reduced Ejection Fraction (HFrEF) with quadruple therapy, which includes SGLT2 inhibitors alongside with ARNI, Beta-blockers, and Mineralocorticoid Receptor Antagonists (MRA) [16].

Recommendations for Type 2 Diabetes Mellitus

- Danish, ESC, ADA, and EASD guidelines advocate for SGLT2i as first-line treatment in T2DM patients who have coexisting atherosclerotic cardiovascular disease, HF, or kidney disease [16].
- In T2DM patients without existing cardiovascular or kidney disease, SGLT2i are recommended as an adjunct to metformin if they are at high cardiovascular risk and require additional glucose control [16].
- SGLT2i are also recommended as second-line glucose-lowering therapy, equally with other classes, for those without increased cardiovascular risk [10].

Comparative Recommendations

- Major guidelines (Danish, European, and US) generally treat Empagliflozin and Dapagliflozin equally for T2DM management based on the evidence supporting a class effect [10].
- Observational and other data suggest that Dapagliflozin confers a significantly lower risk of incident nonvalvular AF compared with Empagliflozin.
- One retrospective cohort study suggested that Empagliflozin initiation might be associated with a lower rate of hospitalization over one year in HF patients compared with Dapagliflozin.

CONCLUSION

Empagliflozin and dapagliflozin recognized as cornerstone therapies in contemporary cardiorenal management, signifying a major paradigm shift beyond their function as glucose-lowering agents [2]. Their established efficacy, supported by numerous randomized controlled trials (RCTs), includes significant reductions in major adverse cardiovascular events (MACE), Heart Failure (HF) hospitalizations across the entire ejection fraction spectrum, and the mitigation of kidney disease progression in patients with Type 2 Diabetes Mellitus (T2DM) and Chronic Kidney Disease (CKD) [2].

Extensive data and cross-trial comparisons consistently support a generalized class effect for SGLT2 inhibitors regarding MACE reduction and major renal outcomes, indicating largely comparable efficacy between Empagliflozin and Dapagliflozin. Current clinical guidelines endorse both agents equally for HF management and as cardiorenal protective therapy in T2DM [7].

Empagliflozin initiation was associated with lower rates of the composite outcome of all-cause mortality or hospitalization compared with Dapagliflozin initiation in HF patients, a finding primarily driven by a reduction in hospitalization endpoints. Dapagliflozin confers a significantly superior protective effect against incident nonvalvular AF when compared to Empagliflozin.

These subtle variations exist despite the agents sharing fundamental mechanistic actions, such as enhancing metabolic efficiency by shifting energy utilization toward ketone bodies, inhibiting the cardiac Na+/H+ Exchanger 1, and modulating mitochondrial dynamics and epigenetic pathways [3]. While guidelines acknowledge the need to consider these variations, continued head-to-head research is essential to fully clarify these pharmacological distinctions and guide personalized therapeutic strategies [3].

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