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Dapagliflozin

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Abstract
Patients with type 2 diabetes are treated with dapagliflozin (Forxiga®), the first of a new class of glucose-lowering medications called sodium-glucose co-transporter-2 (SGLT2) inhibitors. Dapagliflozin lowers renal glucose reabsorption by blocking the kidney's SGLT2 transporter protein, which lowers blood glucose levels and causes glucose to be excreted in the urine. In contrast to various other kinds of oral antidiabetic medications, dapagliflozin's effectiveness is not dependent on insulin secretion or action. Therefore, dapagliflozin's distinct mode of action enables supplementary therapy when used in conjunction with other antidiabetic medications. Although the rate of hypoglycaemic events recorded with dapagliflozin in clinical trials varied depending on the background therapy, dapagliflozin has a low propensity to produce hypoglycaemia, especially when administered alone or in combination with metformin. We eagerly await longer-term safety and tolerability studies for dapagliflozin. Ultimately, dapagliflozin seems to be a valuable supplement to the available treatment choices for type 2 diabetes, especially when utilized as add-on therapy due to its distinct and complimentary mechanism of action.

I. Introduction

Dapagliflozin, sold under the brand names Farxiga (US) and Forxiga (EU) among others, is a medication used to treat type 2 diabetes.[1][2] It is also used to treat adults with heart failure and chronic kidney disease.[3] It reversibly inhibits sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.[4] Despite available treatment, heart failure (HF) remains a leading cause of death and recurrent hospitalization in the world. Having type 2 diabetes mellitus (T2DM) increases the chance of getting heart failure. difficulties related to heart failure, include death.

Dapagliflozin [Farxiga® (USA); Forxiga® (EU)], a sodium–glucose cotransporter 2 (SGLT2) inhibitor, was recently approved in the USA and the EU for the treatment of adults with symptomatic heart failure with reduced ejection fraction (HFrEF). The cardiovascular (CV) benefits of dapagliflozin were first observed in the DECLARE-TIMI 58 trial, in which dapagliflozin 10 mg/day significantly reduced the risk of CV death or hospitalization for HF in patients with type 2 diabetes mellitus (T2DM) who had or were at risk for atherosclerotic CV disease. In the subsequent DAPA-HF trial, dapagliflozin 10 mg/day in addition to standard of care was associated with a significantly lower risk of worsening HF or CV death than placebo in patients with HFrEF, regardless of the presence or absence of T2DM. The benefits of dapagliflozin also remained consistent regardless of background HF therapies. Dapagliflozin was generally well tolerated, with an overall safety profile consistent with its known safety profile in other indications. In conclusion, dapagliflozin is an effective and generally well-tolerated treatment that represents a valuable new addition to the options available for symptomatic HFrEF.[5]

Pharmacological properties

Dapagliflozin is a highly potent (inhibitory constant 0.55 nmol/L) and reversible SGLT2 inhibitor that is > 1400 times more selective for SGLT2 than SGLT1, the main transporter responsible for glucose absorption in the gut. [6, 7] Dapagliflozin-induced glucuresis in

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patients with T2D was associated with caloric loss and a modest reduction in bodyweight, as well as mild osmotic diuresis and transient natriuresis [7, 8]. The loss in bodyweight with SGLT2 inhibitors is less than that calculated from calorie loss due to glucuresis, which may be because of compensatory mechanisms such as increased energy intake [9]. Dapagliflozin is rapidly absorbed after oral administration, with peak plasma concentrations usually reached within 2 h (fasted state) [7].

Dapagliflozin has an absolute oral bioavailability of 78% following a dosage of 10 mg. Dapagliflozin has a mean steady-state volume of distribution of 118 L and is approximately 91% protein bound. Food does not significantly impact the pharmacokinetics of dapagliflozin in a clinically relevant way. The primary inactive metabolite of dapagliflozin is 3-O-glucuronide, which is mostly broken down by the liver and kidney enzyme UGT1A9. Dapagliflozin's other metabolites are not involved in its effects on decreasing blood sugar levels. The majority of dapagliflozin's excretion is in the urine, where 75% of the dose (less than 2% as the unmodified parent medication) is recovered, and 21% is in the feces (less than 15% as the unchanged parent drug). Following a single dose of 10 mg of dapagliflozin in healthy individuals, the average half-life of dapagliflozin's plasma terminal elimination was 12.9 hours.

Cardiovascular Outcomes

The study was originally designed to assess the effect of dapagliflozin on the primary safety outcome of major adverse CV events (MACE) [10, 11]. Dapagliflozin significantly lowered the rate of CV death/HHF versus placebo, but there was no significant between-group difference in the rate of MACE (dual efficacy endpoints assessed after confirming the non-inferiority of dapagliflozin and placebo for the primary safety outcome of MACE)[11].

Cardiovascular Safety

Dapagliflozin, a selective inhibitor of sodium–glucose cotransporter 2 that increases glucosuria in type 2 diabetic patients, has an unknown cardiovascular safety profile.

II. Method [12]

We randomly assigned patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease to receive either dapagliflozin or placebo. The primary safety outcome was a composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. Secondary efficacy outcomes were a renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.

III. Result And Outcomes

We evaluated 17,160 patients, including 10,186 without atherosclerotic cardiovascular disease, who were followed for a median of 4.2 years. In the primary safety outcome analysis, dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to MACE (upper boundary of the 95% confidence interval [CI], <1.3; P<0.001 for noninferiority). In the two primary efficacy analyses, dapagliflozin did not result in a lower rate of MACE (8.8% in the dapagliflozin group and 9.4% in the placebo group; hazard ratio, 0.93; 95% CI, 0.84 to 1.03; P=0.17) but did result in a lower rate of cardiovascular death or hospitalization for heart failure (4.9% vs. 5.8%; hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P=0.005), which reflected a lower rate of hospitalization for heart failure (hazard ratio, 0.73; 95% CI, 0.61 to 0.88); there was no between-group difference in cardiovascular death (hazard ratio, 0.98; 95% CI, 0.82 to 1.17). A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (hazard ratio, 0.76; 95% CI, 0.67 to 0.87), and death from any cause occurred in 6.2% and 6.6%, respectively (hazard ratio, 0.93; 95% CI, 0.82 to 1.04). Diabetic ketoacidosis was more common with dapagliflozin than with placebo (0.3% vs. 0.1%, P=0.02), as was the rate of genital infections that led to discontinuation of the regimen or that were considered to be serious adverse events (0.9% vs. 0.1%, P<0.001).

IV. Conclusion

Treatment with dapagliflozin in patients with type 2 diabetes and atherosclerotic cardiovascular disease did not impact MACE rates compared to placebo, but did lower rates of cardiovascular death or hospitalization for heart failure, indicating a decrease in heart failure hospitalizations. Patients with heart failure and reduced ejection fraction had a reduced risk of worsening heart failure or cardiovascular-related death if they were treated with dapagliflozin.

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