Review Article

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Cardio, renal and metabolic effects of empagliflozin: an update

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Introduction:

SGLT2 inhibitors have changed the way of diabetes management, providing a holistic approach to the management of type 2 diabetes mellitus. Empagliflozin in the EMPA-REG OUTCOME trial has shown a significant reduction in CV mortality, reduction in heart failure hospitalization, and renal benefits. Evidence of clinical benefit with Empagliflozin is rapidly evolving in various therapy areas beyond glycemic reduction based on clinical evidence. The article will focus on some of the recent updates with Empagliflozin in metabolic, renal, and cardiovascular systems.

In Metabolic:

Time in the range:

Long-term control of glycemia is usually assessed using HbA1C levels. Though HbA1C is a clinical monitoring tool, they cannot identify the hypoglycemic events or hyperglycemic excursions in patients on a day-to-day basis. Time in a range, which is a new parameter to evaluate blood glucose reduction, provides a more clear picture of what happens on a day-to-day basis in patients with diabetes[1]. ADA standards of care 2020 points that a diabetes patient should be spending 70% of the time in range (TIR -70 to 180 mg/dl)[2]. In a study by Nishimura et al., both the doses of Empagliflozin showed a significant improvement in the time in range in patients with uncontrolled type 2 diabetes mellitus from day one after initiating therapy[3].

Hypertension:

Trials with SGLT2 inhibitors have documented a modest reduction in blood pressure in patients. Certain groups of patients with higher body mass index and higher baseline BP have shown greater reductions in blood pressure[4]. Empagliflozin has shown a reduction in blood pressure in patients with uncontrolled nocturnal hypertension. In the SACRA study by Kario and colleagues in patients with uncontrolled nocturnal hypertension, Empagliflozin has shown significant reductions in 24 hour BP compared to placebo on top of standard of care drugs. In the SACRA study, a significant reduction in nocturnal BP from baseline was observed with Empagliflozin. Empagliflozin was also associated with a significant reduction in the morning BP in the SACRA study[5]. Empagliflozin has also shown a meaningful reduction in the systolic BP in patients with presumed resistant hypertension in the EMPA-REG OUTCOME study[6].

Liver:

SGLT2 inhibitors are associated with a reduction in liver enzymes and liver fat in various pre-clinical and some clinical studies. Empagliflozin has shown a significant reduction in liver fat from baseline in Indian patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease (NAFLD) in the E-LIFT study. Significant reductions in the liver enzymes were also observed in the E-LIFT study within 20 weeks[7]. A pilot study by Lai et al. provided some preliminary evidence on the improvement of histological features with Empagliflozin in patients with T2DM and non-alcoholic steatohepatitis. In comparison with historical control, Empagliflozin showed improvement in steatosis, ballooning, and fibrosis[8]. Shinozaki et al. showed there is a significant improvement in the markers of hepatic inflammation, fibrosis, and function in patients with T2DM and NAFLD with Empagliflozin[9].

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Obstructive Sleep Apnea:[10]

Obstructive sleep apnea (OSA) is one of the independent risk factors for cardiovascular diseases, and it is closely associated with patients with T2DM. Few studies are available which have analyzed the effect of SGLT2 inhibitors in patients with OSA. Neeland and colleagues performed an exploratory analysis from EMPA-REG OUTCOME in relation to obstructive sleep apnea. In this analysis, it was seen that 6% of participants had OSA at baseline and that those with OSA experienced higher overall CV and renal event rates during the trial. Empagliflozin significantly reduced the risk for CV, HHF, mortality outcomes, and incident or worsening nephropathy, regardless of OSA status. There was a 52% reduction in the new-onset Obstructive Sleep Apnoea with Empagliflozin in participants without OSA at baseline. A mediation analysis was performed to explore the possible influence of changes in mediators (weight, systolic BP, hematocrit, HbA1c) on the risk of new-onset OSA. Mediation analysis could explain only 22% of this overall benefit, to be attributable to changes in Weight, Systolic BP, Hematocrit, and HbA1c. The possible beneficial effect of SGLT2-inhibition on OSA outcomes is worthy of further exploration.

Cardiovascular:

Heart failure:[11]

EMPEROR Reduced trial assessed the effect of Empagliflozin in patients with heart failure with reduced ejection fraction (HFrEF) with or without T2DM. Empagliflozin significantly reduced the primary endpoint of CV death or hospitalization for heart failure in patients with or without diabetes. Further, the study also has shown a significant reduction in the total hospitalization for heart failure and a slower decline of eGFR. (Table 1).

Left Ventricular Mass:

EMPA-HEART Cardiolink 6 study was performed in patients with T2DM and stable coronary artery disease (CAD). In this RCT of 97 patients with Stable CAD and T2DM, Empagliflozin has shown a significant reduction in the left ventricular mass index (LVMi) over 24 weeks. The reduction in the left ventricular mass index was not associated with a reduction in BP or changes in the left ventricular volumes[12]. In other sub-studies of EMPA HEART, Empagliflozin was associated with an early increase in plasma erythropoietin levels with an accompanied increase in hematocrit and decreased ferritin levels[13]. There was a marked increase in the number of circulating proangiogenic progenitor cells and anti-inflammatory cells[14].

Table 1: Key results from EMPEROR Reduced

EMPEROR-REDUCED **(Empagliflozin vs Placebo on Top of Standard Therapy; 3730 patients; 16-month duration)** **Baseline HFrEF with LVFF ≤40%, eGFR up-to 20mL/min/1.73m^2; ≈50% without T2DM**		
CV Death or Heart-Failure Hospitalisation (Primary endpoint)	**25% Relative Risk-reduction** **5.3% absolute Risk Reduction** **NNT of 19 over 16-months***	**HR 0.75** **(95% CI 0.65, 0.86)** ***p*<0.001**
First and Recurrent Heart-Failure Hospitalisations (Key secondary endpoint)	**30% Relative Risk-reduction**	**HR 0.70** **(95% CI 0.58, 0.85)** ***p*<0.001**
eGFR slope (Key secondary endpoint)	**Stabilization of decline in eGFR, improved kidney outcomes**	**Slope difference per year 1.73 ml/min/1.73 m^2** **(95% CI 1.1. 2.4)** ***p*<0.001**

**NNT: Number of Patients Needed to Treat, to Prevent one additional event*

On the cardiac autonomic nervous system:

Patients post-myocardial infarction are at higher risk of ventricular arrhythmias due to an imbalance in the cardiac sympathetic and parasympathetic nervous system leading to sudden cardiac death. The EMBODY trial was designed to assess the effect of Empagliflozin on cardiac, sympathetic, and parasympathetic nervous systems in patients post-acute myocardial infarction. After 24 weeks of therapy, Empagliflozin showed improved cardiac autonomic activity with empagliflozin vs. placebo in post-MI patients with T2DM[15]. Further studies are ongoing, which assesses the effect of Empagliflozin on the autonomous nervous system[16].

Renal

Real-world evidence:

A Scandinavian registry study has shown that with SGLT2 inhibitors, there is a 58% lower risk of serious renal events compared to DPP4 inhibitors[17]. A large veteran affairs cohort study assessed the renal outcomes with Empagliflozin compared to non-SGLT2i antihyperglycemics. This was a Cohort study of 3-yr duration; a total of 3,79,033 new users of Empagliflozin or Non-SGLT2i antihyperglycemics were included. The main objective was to compare the Effectiveness of Empagliflozin vs. Non-SGLT2i antihyperglycemics on the risk of major adverse kidney events (Composite of eGFR decline >50%, ESKD, or All-cause mortality). 32% Lower Risk for Major Adverse Kidney Events with Empagliflozin was observed in the study. Kidney benefit with empagliflozin was consistent, regardless of eGFR or albuminuria categories, and regardless of CVD, BMI category, or use of ACE-i / ARB, metformin, statins, diuretics, or insulin. 0.99 mL/min/1.73m2 significantly lesser eGFR decline per year with Empagliflozin[18].

Conclusion:

With ever-expanding horizons for the use of SGLT2 inhibitors, substantial clinical evidence is available in the cardiac, renal, and metabolic aspects with SGLT2 inhibitors beyond HbA1C reduction. It is important that we keep ourselves updated with all the recent developments.

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