

# Empagliflozin and the Reduction of Risk of Death in a High Cardiovascular Risk Population

REVIEW

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## Abstract

Diabetes Mellitus (DM) is a chronic cardio-metabolic disease and plays an important role on cardiovascular outcomes, most importantly when associated with an already established heart disease. Its effects in the body involve both metabolic and structural changes. To avoid such complications, in addition to the strategies already used and known, rises the Empagliflozin, a sodium glucose co-transporter inhibitor 2 (SGLT2). Its benefits and efficacy have been tried and tested in large-scale trials, with multidimensional cardiovascular effects that go beyond the adequate glycemic control. The EMPA-REG Outcome materialize such benefits, especially for people at high cardiovascular risk, when significantly reduced cardiovascular death and death from any cause in this population.

Type 2 diabetes (T2DM) is a major risk factor for cardiovascular disease [1, 2], and the presence of both type 2 diabetes and cardiovascular disease increases the risk of death [3]. T2DM is a complex cardio-metabolic disorder characterised by insulin resistance, pancreatic beta-cell failure and hyperglycemia [4, 5]. The hyperglycemia plays a critical role in the pathogenesis of diabetic complications and in the development of hypertension in patients with DM (diabetes mellitus). This is explained in part through effects on activation of the renin angiotensin aldosterone system (RAAS) and sympathetic nervous system (SNS) as well as suppression of nitric oxide [6] leading to macrovascular dysfunction including increased arterial stiffness [7, 8].

Cardiovascular complications are an important cause of morbidity and mortality in patients with diabetes, and endothelial dysfunction is

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## Keywords

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an early indicator of developing cardiovascular complications [9, 10]. Recommended strategies for reducing exacerbate cardiovascular risk in patients with T2DM include glucose management, lipid lowering, BP (blood pressure) control, smoking cessation, and weight loss [11, 12].

Empagliflozin is a novel inhibitor, which has higher selectivity for the sodium glucose cotransporter 2 (SGLT2) over other SGLT receptors compared with other class members [13, 14]. In patients with T2DM, inhibition of the SGLT2 increases urinary glucose excretion and reduces plasma glucose. Additional benefits are weight loss [15] that can lead to improvements in glycemic control [16], and a reduction in blood pressure (BP) which is probably attributable to osmotic diuresis [17, 18].

Empagliflozin used as monotherapy or add-on therapy improved hemoglobin A1c (HbA1c) approximately 0.7-1.0% -point (depending on baseline HbA1c and renal function) with a low risk of hypoglycemia, reduced body weight and BP, without increases in heart rate, and had small effects on plasma lipids (increase in HDL-cholesterol, increase in LDL-cholesterol, no change in LDL/HDL cholesterol ratio) [12, 19, 20]. Besides this, it presented favorable effects on markers of arterial stiffness and vascular resistance as well as on a marker of myocardial workload [21]. Prospective studies have shown an association of blood glucose levels and glycated hemoglobin (A1C) with cardiovascular events in diabetic and in those patients in the pre-diabetic state, with the highest incidence of cardiovascular events [22-24]

In another study In Japanese patients with T2DM, empagliflozin monotherapy for 52 weeks led to sustained reductions in HbA1c, fasting plasma glucose, body weight and Systolic blood pressure; [25-27]. Tikkanen et. al noted that Empagliflozin maintains the circadian BP rhythm, with higher reductions in daytime versus nighttime BP. Greater reductions in BP were observed in patients with a BP  $\geq$ 130/80 mmHg (ambulatory blood pressure monitoring)

compared with those with <130/80 mmHg at baseline, suggesting that the risk of hypotension in normotensive patients treated with empagliflozin may be low [28].

The mechanisms behind the cardiovascular benefits of empagliflozin are multidimensional [29] and possibly involve changes in arterial stiffness [30, 31], cardiac function, and cardiac oxygen demand (in the absence of sympathetic-nerve activation) [30], as well as cardiorenal effects [30, 32-34], reduction in albuminuria [20, 25], reduction in uric acid [19, 20], and established effects on hyperglycemia, weight, visceral adiposity, and BP [3].

In international phase III studies, empagliflozin 10 and 25mg for 24 weeks led to significant improvements in glycaemic control and reduced body weight and BP in patients with T2DM when given as monotherapy [36] add-on to metformin [37], add-on to metformin plus sulphonylurea (SU) [19] or add-on to pioglitazone with or without metformin [18, 38].

To date, few serious adverse events have been reported from clinical trials. The frequency of hypoglycaemic events was low, similar to that of placebo, and lower than comparators known to have increased risk of hypoglycaemia, with the choice of co-administered glucose-lowering agent being the major determinant of hypoglycaemic risk [5, 39] as increased incidence of urinary and genital tract infections Among Patients treated with SGLT2 inhibitors, which could potentially be attributed to the glycosuria effect of these agents [14, 40, 41].

In the EMPA-REG, among patients with type 2 diabetes at high risk for cardiovascular events, those receiving empagliflozin had a lower rate of the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than did patients receiving placebo. The reductions in the risk of cardiovascular death in the empagliflozin group were consistent across subgroups according to baseline characteristics, representing the relative reduction of 32% [3].

Empagliflozin may play an important role in diabetic patients. It has not only glycemic effects, but lowers blood pressure levels, promotes weight loss, and acts in microalbuminuria. All of this would already be reason to excitement, but EMPA-REG outcome showed us, perhaps, the greatest benefit that an anti-diabetic oral drug had ever did: the consistent cardiovascular benefits found in this trial puts empagliflozin in a level no one drug with this purposes has. The relative and absolute reduction showed in cardiovascular death and death from any causes represents strong evidence that among a high cardiovascular risk population, this drug might be recommended not only for diabetes control, but also for death prevention.

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