

Editorial

Welcome Empagliflozin ! ASCVD, Heart Failure and CVD death

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Diabetes is equivalent to cardiovascular disease (CVD). One of the hard risk factors for coronary artery disease (CAD) is diabetes. Leaving aside other concomitant risk factors for CVD, diabetes mellitus type 2 (DMT2) stands for 50% more risk for CAD. Essentially management of chronic hyperglycaemia delays the onset and reduce the severity of microvascular complications, as well as reduce long-term macrovascular risk. Proper hypoglycaemic control of a diabetic patient leads to decreased risk for CVD/CAD. But the hypoglycemic agents used to control DMT2 differ in their effect on CVD independent of their hypoglycemic effect. This is not surprising as we see that there are differences in antihypertensive agents in the CVD outcome effect despite having same effect on lowering of blood pressure. It was a concern that some hypoglycaemic agents (e.g. rosiglitazone) were associated with increased CV events despite lowering blood sugar. One observation in a 15 years follow-up – Veteran Affairs Diabetes Trial – was that benefits of CV outcome were independent of glycemic control. Thus, for patients with advanced diabetes, clinical focus on how glucose levels are lowered rather than on achieving intensive targets may lead to better cardiovascular outcomes.

Present recommended algorithm for routine use of hypoglycaemic agents are: metformin as the initial therapy in all cases unless there is contraindication: GLP-1 receptor agonists; Sodium glucose cotransporter 2 (SGLT-2) inhibitors; Dipeptidyl peptidase 4 (DPP-4) inhibitors; TZDs ;alpha glucosidase inhibitors (AGIs) ; insulin-secretagogue SFUs. Acceptable alternatives to metformin as initial therapy include GLP-1 receptor agonists, SGLT-2 inhibitors, DPP-4 inhibitors, and TZDs. Consensus Document of 2018 states elaborately the choice of the agent on the basis goal and comorbidity particularly CVD and renal function.

Empagliflozin Cardiovascular Outcome Events Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG

OUTCOME) included 7020 patients of DMT2 with established CVD. All the patients were on standard care of treatment. Patients of one arm received empagliflozin 10mg or 25 mg daily whereas patients of another arm had placebo. Median follow-up period was 3.1 years. There was 14% reduction in MACE (cardiovascular death, nonfatal MI, non-fatal stroke) in the empagliflozin arm. Risk of cardiovascular (CV) mortality is reduced by 38% and risk of HF hospitalizations is reduced by 35% in patients with type 2 diabetes mellitus (T2DM)

Results of the EMPA-REG OUTCOME trial added new dimension in the management of DMT2. Results of the trial are very attractive to the cardiologists. By its diuretic and natriuretic (besides glucosuric) effects, empagliflozin reduces volume load and blood pressure. Thus both pre-load and after-load of a patient is decreased. More importantly incidence of heart failure is reduced and this benefit is similar whether the patient was of heart failure or not. This finding is extended to the point that empagliflozin may be a drug for heart failure whether the patient is diabetic or not.

A meta-analysis of trials involving different SGLT 2 inhibitors had been recently published in the LANCET. There were three major trials with empagliflozin (EMPA REG OUTCOME); Canagliflozin (CANVAS); and Dapagliflozin (DECLARE TIMI-58). The authors commented that by and large the results pertaining the CVD outcome were consistent between the three different trials of SGLT2 inhibitors when analysed within similar patient subgroups. However, in patients with atherosclerotic cardiovascular disease, the effect of empagliflozin on cardiovascular death was more pronounced than that of canagliflozin or dapagliflozin, and an increased risk of amputations and fractures was only seen with canagliflozin. They observed that all the 3 drugs of the group have moderate benefits on atherosclerotic major adverse cardiovascular events that appear confined to patients with established atherosclerotic cardiovascular

disease. But there was robust reductions in hospitalisation for heart failure and progression of renal disease regardless of baseline atherosclerotic risk category or a history of heart failure.

For the SGLT2 inhibitors studied to date, it appears that among patients with established CVD, there is likely cardiovascular benefit, with the evidence of benefit modestly stronger for empagliflozin than canagliflozin. Among patients with ASCVD in whom HF coexists or is of special concern, SGLT2 inhibitors are recommended

How the drug provides CV benefit has been extensively studied leading to the conclusion that “underpinnings of empagliflozin’s CV mortality benefit are likely multifaceted” It may be attributed partly to its glucose lowering effect and mostly independent of glucose lowering effects. Osmotic diuresis accompanied by glucocuresis leads to decreased intravascular volume and blood pressure may be initial beneficial effect, It is found to reduce insulin resistance and decrease weight etc. – all extend overall CV outcome.

Benefits are found with eGFR as low as 30/ml but use is not recommended if GFR is 45ml/min or below. Another limitation of use is definitely the cost of the drug. There are reports of acute kidney injury; dehydration and orthostatic hypotension. Use of it with diuretics, ACEI or ARB should be with caution. There is chance of development of ketoacidosis in the condition of insulin deficiency. Besides there is occurrence of mycotic genital infection.

Two trials have been undertaken: EMPEROR-Reduced and EMPEROR-Preserved to see the effects empagliflozin in heart failure patients with reduced and preserved ejection fraction respectively irrespective of their glycemic status. Another trial - EMPA-TROPISM Trial (ATRU-4) – aims to see the effects empagliflozin on patients with heart failure without diabetes. It will determine whether effects of the drug are independent of its hypoglycaemic action. Results of these trials may reinforce the place of the drug for the cardiologists further.

With all the present and prospective findings, we welcome *EMPAGLOFLOZIN* as a drug for the cardiologists!

Conflict of Interest - None.

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