Letter to the Editor

DAPA-HF study: Are the benefits uniform across non-diabetic subgroups

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Large clinical trials involving type 2 diabetes (T2D) patients have shown that sodium-glucose transporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure (HF), largely in patients without HF at baseline. Hence, benefits of SGLT2 inhibitors were largely restricted to prevention of HF.

DAPA-HF study is a landmark study as it was planned to evaluate whether these benefits extend to patients with HF with reduced ejection fraction (HFrEF) irrespective of the presence of diabetes at baseline. In this study, 4744 patients with HFrEF were randomized to receive either dapagliflozin or placebo. Over a median follow-up of 18.2 months, risk of worsening of HF or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo (HR, 0.74; 95% CI, 0.65 to 0.85; P < 0.001), regardless of the presence or absence of diabetes. However, these published results raise certain questions which are important to be answered.

While presenting baseline characteristics, authors divided the population based on their glycemic status as diabetic, pre-diabetic, and normoglycemic. However, while presenting the data of primary composite outcome, authors have given data for 2 groups i.e. patients with diabetes and those without diabetes. Among total population, almost 55% patients were non-diabetics and among these, 33% were normoglycemic and 67% were pre-diabetic. Authors have not presented the primary outcome data separately for 2 subgroups of non-diabetic population i.e. for pre-diabetes and normoglycemia.

Metabolic syndrome is a cluster of conditions that synergistically increase the risk of CVD, T2D and premature mortality. Risk factors associated with this syndrome are hypertension, dyslipidemia (high triglycerides and lower HDL), elevated fasting blood glucose, and central obesity. Pre-diabetes can be identified as either impaired fasting glucose or impaired glucose tolerance and it is closely associated with metabolic syndrome. Both, pre-diabetes and metabolic syndrome are in turn associated with obesity. Insulin resistance and systemic inflammation associated with obesity predisposes patients to pre-diabetes and metabolic syndrome. Epidemiological studies have shown that pre-diabetes is a strong predictor of CVD. In patients with HFrEF, dysglycemia is common and pre-diabetes is associated with a higher risk of adverse cardiovascular outcomes compared to normoglycemic patients i.e. cardiovascular risk in prediabetics closely resemble to that in diabetics than in normoglycemic. Glucose lowering effects of SGLT2 inhibitors are attenuated in individuals without diabetes and with reduced eGFR, and thus glucose-linked sodium excretion could be lower in normoglycemic population. SGLT2 class of drugs are not innocuous and have certain rare but serious side effects like euglycemic ketoacidosis, Fournier’s gangrene and fractures, and commonly occurring side-effects like genital mycotic infections and LDL elevation.

Thus, it is important for clinicians to know whether, in the non-diabetic group, similar extent of benefit was observed in its subgroups i.e. pre-diabetics and normoglycemic or the benefit in non-diabetic group was largely influenced by the benefits observed in pre-diabetic population. This risk-benefit assessment will help clinicians to assess whether use of SGLT2 inhibitors in normoglycemic patients is justified.

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Declaration of competing interest

Dr. Anil Pareek and Shruti Dharmadhikari are employees of Ipca Laboratories Ltd, which markets anti-diabetic drugs. Dr. Rajesh Rajput and Dr. HK Chopra do not have any conflicts of interests.

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