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Editorial

Heart Failure and Type 2 Diabetes

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It is well-established that type 2 diabetes mellitus (T2D) increases the risk of both developing and dying from heart failure (HF). The connection between T2D and HF is explained by pathophysiologic mechanisms including the potentially adverse effects of hyperglycemia on endothelial function and redox state, effects of excess circulating glucose and fatty acids on cardiomyocyte ultra-structure, intracellular signaling and gene expression, and the possibility that diabetes may impair recruitment of the myocardial insulin-responsive glucose transport system in response to ischemia [1]. However, the effect that antidiabetic agents have on the heart has been in the center of several clinical and experimental trials only during the last decade. The cardiovascular (CV) safety of newer antidiabetic agents, especially dipeptidyl peptidase 4 (DPP-4) inhibitor, in regards to heart failure, has been questioned after the publication of first trials (SAVOR-TIMI 53 and EXAMINE) assessing the CV risks of saxagliptin and alogliptin.

Although there were no increased risks in composite cardiovascular outcomes, the SAVOR-TIMI 53 trial reported a 27% increase in hospitalization for HF in diabetic patients who received saxagliptin.Subjects at greatest risk of hospitalization for HF had previous HF, an estimated glomerular filtration rate ≤60 mL/min, or elevated baseline levels of N-terminal pro B-type natriuretic peptide (BNP). Even in patients at high risk of hospitalization for HF, the risks of the primary and secondary end points were similar between treatment groups [2].

In the EXAMINE trial, hospital admission for HF was the first event in 3.1% patients taking alogliptin compared with 2.9% taking placebo[Hazard Ratio(HR):1.07,95% Confidence Intervals(CI):0.79-1.46).Alogliptin had no effect on composite events of CV death and hospital admission for HF in the post hoc analysis (HR: 1.00, 95% CI: 0.82-1.21) and results did not differ by baseline BNP concentration.NT-pro-BNP concentrations decreased significantly and similarly in the two groups [3]. Because of the above findings, FDA has relies an alert regarding the use of saxagliptin and alogliptin in patients with T2D and HF or increased risk for HF.

In the TECOS trial, of 14671 patients, 7332 were randomized to sitagliptin and 7339 to placebo. Hospitalization for HF occurred in 3.1% and 3.1% of the sitagliptin and placebo groups, respectively (HR: 1.00, 95% CI: 0.83-1.19). There was also no difference in total HF events between the sitagliptin and placebo groups (HR: 1.00, 95% CI: 0.80-1.25). Post-HF all-cause death was similar in the sitagliptin and placebo groups (29.8% vs 28.8%, respectively), as was CV death (22.4% vs 23.1%, respectively) [4].

Regarding the effect of glucagon-like peptide-1 receptor (GLP-1) agonists on the diabetic heart two trials have given answers.The ELIXA trial,with the GLP-1 agonist lixisenatide, showed no significant between-group differences in the rate of hospitalization for HF (HR: 0.96, 95% CI: 0.75 - 1.23) or the rate of death (HR: 0.94, 95% CI: 0.78 - 1.13) [5]. However, in the LEADER trial the GLP-1 agonist liraglutide, the rates of hospitalization for HF were lower in the liraglutide group (4.7) than in the placebo group (5.3) (HR: 0.84, 95% CI: 0.73 – 0.97) [6]. On the contrary, an increased rate of hospitalization for HF was observed in the SUSTAIN-6 trial with the weekly GLP-1 agonist, semaglutide.The rates of hospitalization for HF was non statistically higher in the semaglutide group (3.6) than in the placebo group (3.3) (HR: 1.11, 95% CI: 0.77 – 1.61) [7].Therefore, we need more data for by the ongoing clinical trials with GLP-1 analogs to answer the question if the favorable effect on hospitalization for HF is class or drug effect.

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Finally, in the EMPA-REG trial with the sodium-glucose co-transporter 2 (SGLT-2) inhibitor empagliflozin, there was a significant between-group differences in the rates of hospitalization for HF, 2.7% for the empagliflozin group and 4.1% for the placebo group, translated to a 35% relative risk reduction (HR: 0.65, 95% CI: 0.50 - 0.85) [8]. The impressive benefits with empagliflozin on CV mortality and hospitalization for HF are observed earlier, only in 3 months, since the curves for HF hospitalization begin to separate widely within 3 months and are maintained for more than 3 years.Modest improvements in glycemic, lipid, or blood pressure control unlikely contributed significantly to the beneficial CV outcomes within 3 months. A recent theory postulates that the CV benefits of empagliflozin are due to a shift in myocardial fuel metabolism away from fat and glucose oxidation, which are energy inefficient in the setting of the T2D heart,toward an energy-efficient super fuel like ketone bodies, which improve myocardial work efficiency and function. However,well-planned physiologic and imaging studies need to be done to characterize fuel energetics-based mechanisms for the CV benefits of empagliflozin [9].

In conclusion, we are in front of a new era regarding the possible cardioprotective effects of the newer antidiabetic agents especially GLP-1 agonists and SGLT-2 inhibitors. Recently the indication for empagliflozin for the treatment of T2D was expanded beyond glycemic control to encompass prevention of CV events.

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