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Short Communication

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors in Heart Failure; So Close Yet So Far

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Abbreviations

SGLT2: Sodium-Glucose Cotransporter 2 Inhibitors; FDA: Food And Drug Administration; MACE: Major Adverse Cardiovascular Events; HFREF: Heart Failure With Reduced Ejection Fraction; ICD: Implantable Cardioverter Defibrillator; CRT: ACC/AHA/HFSA: Cardiac Resynchronization Therapy; American College Of Cardiology/American Heart Association/Heart Failure Society Of America; HFPEF: Heart Failure With Preserved Ejection Fraction

The recently published trial, the DAPA-HF trial, advocating the use of Dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor in heart failure with reduced ejection fraction (HFrEF) has raised some questions and concerns regarding the gaps in clinical trials and real world situation faced by the patients and providers [1]. At one hand, the medication proved to have a beneficial effect in the form of mortality reduction and reduced heart failure hospitalization in this large, phase III clinical trial. On the other hand, issues related to its cost, insurance approval, risk of polypharmacy (when used with other heart failure medications) arose. Moreover, where it fits in the spectrum of guideline directed medical therapy (GDMT) is also an important question that needs to be addressed in order to bridge the gap between the benefits seen in clinical trial and real-world situation.

In 2008, after observing improved cardiovascular outcomes with diabetic medications in early trials, the US Food and Drug Administration (FDA) formally approved various diabetic medications to be studied for cardiovascular outcomes in patients with diabetes [2]. The SGLT2 inhibitors were first approved for management of diabetes in 2014. Soon after their approval, EMPA-REG OUTCOME trial successfully showed a cardiovascular benefit of empagliflozin, a member of class of SGLT2 inhibitors, in the form of reduced heart failure hospitalization and cardiovascular death in patients with type II diabetes [3]. This was a great success that led the investigators in 2017 to combine the results of two different clinical trials, CANVAS and CANVAS-R (renal) trials to yet again prove the point that this time, canagliflozin was affiliated with not only reduced hospitalizations for heart failure but also with reduction in major adverse cardiovascular events (MACE) in type II diabetics [4]. The notion was again consolidated in early 2019 by the results of DECLARE-TIMI 58 trial that showed dapagliflozin to reduce heart failure hospitalization in patients with diabetes mellitus type II but no reduction in MACE. Considering the successful trials one after the other, FDA decided to approve SGLT2 inhibitors for reduction in heart failure hospitalization in patients with type II diabetes [2,5].

In the above-mentioned clinical trials, the improved cardiovascular outcomes were seen pretty soon after randomization and were independent of the control of underlying diabetes. This along with the fact that diabetes and heart failure have the same underlying pathophysiology of insulin resistance and endothelial damage, and SGLT2 inhibitors' metabolic (ketogenesis and increased glucagon storage) as well as diuretic effect are independent of presence of diabetes led the investigators to formulate a rationale of study-

ing this class of drug in patients with heart failure regardless of the presence or absence of diabetes [6].

In this recently published DAPA-HF study, dapagliflozin use in HFrEF patients not only reduced the primary outcomes of cardiovascular death and worsening heart failure but improvement was also seen across multiple secondary outcomes including heart failure symptoms, renal death as well as all-cause death. The major centers of this trial were in Europe (estimated 60%) as well as a few in North America (estimated 30%) in addition to few others in Asia. As described in the study, 93% of patients in both groups were on guideline directed medical therapy including device therapy such as implantable cardioverter defibrillator (ICD) (26%) and cardiac resynchronization therapy (CRT) when indicated. Demographically the black population number was too low, and patients overall had well controlled BMI, blood pressure and renal function. This strict selection criteria makes the general applicability of the study somewhat limited [7].

The more important dilemma, however, are the current barriers faced by providers in clinical settings in the optimizing and up-titration of the heart failure medications already approved for heart failure. As an example, sacubitril-valsartan was the last HFrEF medication approved in 2014 but it's utilization as of 2017, three years after its approval, was less than 15% in the eligible patient population [8]. This primarily in due to the medications' cost and issues surrounding its approval, even in patients with insurance who have to pay a substantial amount out of pocket cost. The fact that only 10% of patients in the DAPA-HF trial were on this medication highlights the current challenge that our general patient population is facing while not being as closely monitored as the trial population was.

FDA has place dapagliflozolin in a fast track for approval for patients with HFrEF in September 2019. However, its current cost is almost $500 for patients without an indication for insurance approval [9]. To date, there has been no change in guidelines from American College of Cardiology/American Heart Association/ Heart Faliure Society of America (ACC/AHA/HFSA) regarding management of heart failure. This being said, clinicians including primary care physicians, cardiologists as well as endocrinologists should not stop prescribing this medication for patients with HFrEF who have concomitant diabetes type II as this medication is already approved for it [10].

The next steps that investigators are now exploring is to test this medication in patients of heart failure with preserved ejection fraction (HFpEF), which accounts for more than half of our unfortunate heart failure population but with no medication to prove mortality benefit as opposed to HFrEF population [11]. However, realizing the gaps present in the real world practice and clinical trials outcomes, the authors unfortunately have to say that there is still a need for considerable time, effort and close monitoring that needs to be undertaken before we actually see the true benefits of this and other approved guideline directed heart failure medications in the real world. Future studies need to also address the compliance with the guidelines with the new therapy.

Acknowledgements

None.

Conflict of Interest

None to declare.

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