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Mini Review

SGLT2 Inhibitors; Not If but When

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The diagnosis and management of heart failure is one of modern medicine's success stories. As both cardiac imaging and treatment modalities have evolved, the prognosis for managing structurally diseased hearts has improved dramatically [1]. Firmly ensconced in this process are ACE inhibitors, ARBs, Beta blockers, ARNIs, MRAs and CRT [2]. With the advent of the SGLT2 trials heralding CV benefit beginning with EMPA-REG OUTCOME in 2015 [3] and culminating most recently in the publication of the DELIVER trial in 2022[4,5], a new concept in HF treatment has also been established. Now part of guideline directed management of all forms of symptomatic heart failure with and without DM2, SGLT2i therapy has gained wide acceptance [6].

In light of the role SGLT2 therapy now plays in the management of heart failure and considering its concomitant role in the place where it was designed to reside, type 2 diabetes mellitus, the issue of its use in HF prevention has been brought to the forefront. In a meta-analysis from the diabetes literature which included all SGLT2i randomized clinical trials with a duration of treatment longer than 52 weeks and in which HF of any degree was not listed as an inclusion or exclusion criteria leading indirectly to the assumption that a component of the patients could have been categorized as NYHA1 Stage A, Silveri, et al. conclude, "SGLT2 inhibitors reduce all-cause mortality" [7].

While standard risk factor reduction for at risk hearts has long been practiced, the role for a new mechanism inside the preemptive HF prevention armamentarium utilizing SGLT2i is now also being directly considered for primary prevention of HF. Thus far the major SGLT2i trials have excluded NYHA stage 1 patients and thus Stage a HF patients limiting their utility to draw direct conclusions on the role of preventative SGLT2i therapy. In analyzing three nested case-control studies involving patients with DM2 in England and Wales, Wright et al. have concluded "SGLT2i…may be beneficial in primary prevention of MACCE and HF. These data call for primary prevention trials using these agents" [8].

The proposed pathophysiologic mechanisms underlying SGLT2i cardiac benefit are numerous and debated. In addition to/along with the basic mechanism of SGLT2i to inhibit the coupled reabsorption of sodium and glucose from the proximal tubules thereby increasing renal glucose and sodium excretion [9], they have more widespread renal effects including diuresis/natriuresis, blood pressure reduction, erythropoiesis, improved cardiac energy metabolism, inflammation reduction, inhibition of the sympathetic nervous system, prevention of adverse cardiac modeling, prevention of ischemia/reperfusion injury among others [10]. One particularly interesting mechanism that may be active in primary prevention is decreasing oxidative stress which may decrease the potential for "cardiac glucotoxicity" [10].

That hyperglycemia is cardio toxic as an independent effect on the development of heart failure is well established [11-13]. Thus, diabetic cardiomyopathy can be considered a risk for the development of HF in addition to other standard risk factors. While clear guidelines are in place for the management of hypertension [14], hyperlipidemia [15] and diabetes proper [16], how early in the prevention process a SGLT2i can be started is unclear?

Clues to the answer to this question may be seen in re-in visioning the role for HbA1c in the heart failure diagnosis and management process. Well known for its role in the diagnosis and management of diabetes mellitus in all its forms, a recent study has shown an independent correlation between rising HbA1c and direct measures of cardiac diastolic dysfunction when controlling for standard risk factors. In particular, an HbA1c of 6.5 or greater was found to be associated with a higher E/e' ratio and LAVI [17]. While diabetic pharmacologic therapy is not recommended until an HbA1c of 7.5 [16], using an earlier cutoff for at risk but asymptomatic hearts solely for the purpose of preventing glycemic cardio-toxicity may be reasonable.

An ideal candidate for early initiation of SGLT2i preventive therapy may be one with NYHA 1, Stage a heart failure. Stage a heart failure, defined as those patients at risk for but not demonstrating clinical symptoms or Echo demonstrated depressed LVEF [18], could define a standardized patient population for multifactorial cardio protection to include prediabetes SGLT2i. The Emperor-Preserved trial included patients with preserved EF but excluded the NYHA1 functional class [19]. Additional subgroup analyses of the EMPA-REG, CANVAS, DELCARE-TIMI and CREDENCE trials showed that only a minority subgroup of treatment arm patients were shown to have "heart failure" clinically (from 9.9%-14.9 %) implying that the majority were not clinically in heart failure[3, 20-22].

All of the treatment group patients in these trials showed a reduction in risk of hospitalization for heart failure. This lends further evidence to the need for clinical trials that directly assess HF prevention in non-diabetics with NYHA 1n Stage A patients with the use of SGLT2i.

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