Are There Differences in Potency Between SGLT-2 Receptor Blockers Utilized in The Therapy of Heart Failure?

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Commentary

SGLT-2 receptor inhibitors, when used to treat type 2 diabetes, show differences in the achieved HbA1c when used in the same patients. In a retrospective study there was a decrease in HbA1c of 0.2% when patients were forced by third party payors to change from canagliflozin to empagliflozin (Bell and Goncalves, 2018). From a large database patients starting canagliflozin 300 mg versus dapagliflozin 10 mg daily over six months had a 0.26 mg % significantly greater fall in HbA1c with canagliflozin (Blonde *et al.*, 2018). The ability of canagliflozin to have a greater effect on the HbA1c than other SGLT-2 inhibitors is due to the 300 mg dose being unique in that it's effects lasts for at least 24 hours which results in a greater daily urine glucose excretion (Plosker, 2014).

More recently the SGLT-2 inhibitors have been approved for use in the therapy of heart failure (HF). Dapagliflozin is approved for treatment of HF in both diabetic and non-diabetic subjects while canagliflozin has been approved to reduce the risk of hospitalization for HF in adults with type 2 diabetes, nephropathy and albuminuria (McMurray *et al.*, 2019; Perkovic *et al.*, 2019). Empagliflozin, while not receiving an indication for use in HF, has been shown in a prospective study to reduce HF hospitalizations and cardiac death even when HF was not present at the start of the study (Fitchett *et al.*, 2016). Based on these prospective studies we cannot compare the efficacy of the available SGLT-2 inhibitors in HF and differences may exist that are more significant than differences between SGLT-2 receptor therapy of hyperglycemia. In addition, effects other than an osmotic diuresis (weight loss, lowering of blood pressure, increased ketone production and utilization decreasing cardiac workload and blockade of the Na+/H+ exchanger in the myocardium) of SGLT-2 inhibitors may differ between these compounds and result in differing potencies in the therapy of HF (Bell and Goncalves, 2019).

A single clinical observation has led us to question whether there could be differences in the

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efficacy of SGLT-2 receptor blockers in the treatment of HF. A 62-year-old white type 2 diabetic patient had well controlled type 2 diabetes (HbA1c 6.2%) and adequately controlled HF (NYHA2) utilizing sacabritil/valsartan, carvedilol, spironolactone and canagliflozin had a toe amputation. For medicolegal reasons he was changed from canagliflozin 300 mg daily to dapagliflozin 10 mg daily. Following this change his NT-pro BNP (normal less than 125 pg/ml) rose from 221 pg/ml to 891 pg/ml. On returning to canagliflozin 300 mg daily the NT-pro BNP dropped back to 238 pg/ml and on changing, again for medicolegal reasons, to empagliflozin 25 mg daily his NT-pro BNP dropped to 164 pg/ml (normal less than 125 pg/ml).

Was this decrease in myocardial function as measured by NP-pro BNP with dapagliflozin and which was corrected with both canagliflozin and empagliflozin, unique to this patient or was there evidence of the same phenomenon occuring in randomized controlled clinical trials? In the DEFINE-HF trial where 263 HF subjects with or without diabetes and who had a low ejection fraction were randomized to either placebo or to dapagliflozin 10 mg daily, there was a suggestion of an improvement in symptoms but no change in NT-pro BNP (Nassif *et al.*, 2019). On the other hand, in a study of established class 2, 3, 4 NYHA heart failure in both diabetic and non-diabetic subjects with reduced ejection fraction, dapagliflozin 10 mg daily significantly reduced the NP-pro BNP by 46% (196 to 101 pg/ml) (McMurray *et al.*, 2019). While from these results we might conclude, based on the biomarkers of HF, that the efficacy of dapagliflozin in HF is controversial, there is no doubt that the other SGLT-2 inhibitors reduce the biomarkers of HF.

Canagliflozin, in two human studies has clearly been shown to lower BNP in both Japanese and older patients with type 2 diabetes and chronic heart failure. NT-pro BNP was significantly ($p=0.001$) decreased with canagliflozin 100 mg daily in 35 Japanese patients with HF and type 2 diabetes (Sezai *et al.*, 2019). When 666 type 2 older diabetic patients with HF receiving either canagliflozin 100 mg or 300 mg, were compared with those receiving placebo canagliflozin over two years delayed the rise in serum NT-pro BNP and this effect was greater with the 300 mg dose (Januzzi *et al.*, 2017). In addition, in animal studies empagliflozin has been clearly shown to lower BNP (Shi *et al.*, 2017).

Therefore, there is good evidence of a positive effect of canagliflozin and empagliflozin on cardiac biomarkers and conflicting evidence for dapagliflozin's effect. The only way this confusion could be reconciled is with "head to head" trials, rather than placebo-controlled trials, of the effects of different SGLT-2 inhibitors used in the therapy of HF. Until then the choice of an SGLT-2 inhibitor for the therapy of HF should be based on clinical judgement and monitored closely for changes in symptoms and cardiac biomarkers. Should the response to therapy be less than optimal, then changing to another member of the class would be justified.

What is NOT justified is to exchange an SGLT-2 receptor inhibitor by anyone other than the treating physician. Therefore, when being utilized to treat HF, SGLT-2 receptor agonists should not be changed on the basis of cost or insurance coverage by pharmacists and/or third-party payors.

While SGLT-2 inhibitors can safely and justifiably be interchanged when being utilized to treat diabetes, only the treating physician should make the decision when these drugs can be exchanged for the therapy of HF.

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