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Mini Review

Clinical Implication of SGLT-2 Inhibitors on Diuretics Dose in Outpatient Heart Failure Patients

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ABSTRACT

Inhibitors of Sodium Glucose Co-transporter 2 (SGLT-2) reduce the risk of hospitalization for heart failure. Recent studies showed evidence supporting the effects of SGLT-2 inhibitors on broad spectrum of Heart Failure (HF) regardless of left ventricular ejection fraction. There have been many changes in the guideline if HF and several studies of SGLT-2 have played a key role.

In stable outpatients HF patients, the event such as cardiovascular death or HF hospitalization is less likely to occur. So, intensification of diuretic therapy also is a representative indicator of worsening HF. The current study's objective was to examine the effect of SGLT-2 inhibitors on change of diuretics dose in outpatient HF patients.

Keywords: Sodium-glucose cotransporter-2 inhibitors; Diuretics; Outpatient; Heart failure

INTRODUCTION

HF is a clinical syndrome and the single greatest unmet need in cardiovascular medicine [1]. Especially, as the population ages increases, the prevalence of HF with Preserved Ejection Fraction (HFpEF) increases considerably [2]. Sodium-Glucose Co-Transporter 2 (SGLT-2) inhibitors have been emerging as a powerful therapeutic option to reduce the risk of HF and hospitalization for HF. Recent landmark studies showed evidence supporting the effects of SGLT-2 inhibitors on HF with or without diabetes regardless of left ventricular ejection fraction [3,4]. There are several potential mechanisms of SGLT-2 inhibitors that lead to a beneficial cardio-renal effect, such as decreasing intraglomerular pressure, increasing natriuresis, improving metabolic parameters and increasing oxygenation of tubular cells [5-7]. Especially, the role of SGLT-2 inhibitors in renal protection of patients with HF has received considerable attention and it was proved in real-world trials [8,9]. The impact on an increase of natriuresis is a hemodynamically important factor, and it plays a similar role to that of diuretics in HF management [10].

LITERATURE REVIEW

Outcome improvement in HFpEF

The diagnosis of HFpEF is challenging, because symptoms are nonspecific and can be explained by several alternative non-cardiac conditions [11]. There have been a lot of efforts to defining phenotypes of HFpEF according to their pathophysiology, but failed to prove benefits of potential pharmacologic treatments in this heterogeneous syndrome [12,13].

Recently, based on the results from further analysis of 'The Prospective Comparison of ARNI (Angiotensin Receptor Neprilysin Inhibitor) with ARB (Angiotensin-Receptor Blockers) Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF)', sacubitril-valsartan is proved to have benefit in HFpEF, the US Food and Drug Administration expanded indication to sacubitril-valsartan that would allow for use of the therapy in some patients with HFpEF [14]. In aspect of SGLT-2 inhibitors, 'Emperor Preserved trial' showed that SGLT2-inhibitors improved cardiovascular outcome, however

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empagliflozin's effect did not show statistical significance in patients with Left Ventricular Ejection Fraction (LVEF) of 60% or more [3]. So, this finding indicates that patients with HF mild reduced Ejection Fraction (EF) (Left Ventricular Ejection Fraction 40%-50%) would have contributed to improving the entire primary CV outcome. Recently, the 'Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) study' showed that the effect of SGLT-2 inhibitors was verified even in HF with normal EF, this study verified that SGLT-2 inhibitors are effective even in stable outpatient HF patients.

Assessment of outpatient HF

It is not easy to evaluate the treatment effect in stable outpatients HF patients. It is difficult to frequently perform echocardiography or blood tests such as Brain Natriuretic Peptide (BNP) or N-terminal pro BNP in outpatient settings. In addition, hard end points such as cardiovascular death or HF hospitalization are less likely to occur. Thus, focusing only on HF hospitalization underestimates the frequency of clinical worsening in HF, and fails to recognize the other manifestations of deteriorating that have serious implications. These episodes of outpatient worsening may be more important given the current emphasis on attempting to minimize hospital admissions in patients with HF [15]. So, intensification of HF therapy can also be an indicator of HF worsening in a broad sense. In particular, requiring intensification of diuretic therapy can be a representative indicator of worsening HF. This concept has been demonstrated through a recent pre specified analysis of Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study [16].

In this study, authors revealed that initiating SGLT-2 inhibitors could reduce the diuretics in outpatients with stable HF. About 23.1% of patients experienced diuretic dose reduction and mean dose of furosemide was reduced by about half during the 430 days of the mean follow-up period. The interesting aspect of this study was that more than 80% of enrolled patients were HF preserved EF. These findings suggested that it may be reasonable to consider empirical loop diuretic dose reduction when initiating an SGLT-2 inhibitor in an outpatient clinical setting.

DISCUSSION

Beyond the reduction of diuretics

This study has other important clinical implications. Reducing the diuretic dose is significant in that it not only reduces fluid retention, but also provides an opportunity to more actively use other medications. It is important to up-titrate medications in the treatment of HF, but it is not well practiced due to side effects of drugs in real clinical practice. Treatment with renin-angiotensin system blockers or angiotensin receptor-neprilysin inhibitor is frequently accompanied by hypotension as well as renal dysfunction [17]. Mineralocorticoid receptor antagonists also have the risk of reducing glomerular filtration rate. Therefore, use of these drugs is limited, or there is reluctance to up-titration when combined with other diuretics. Recent updated HF guidelines suggest initial simultaneous combination (four-pillar) of evidence-based medications [18]. However, there is no definitive conclusion as to which drug should be used first. Interestingly, beta-blockers have an absolute advantage in HF, but there is a concern about fluid retention in the condition's early stages. The volume reduction effects of SGLT-2 inhibitors can compensate for this concern of beta-blockers. Based on the evidence of the diuretic effect of SGLT-2 inhibitors, suitable recommendations have been presented [19]. This study result that empagliflozin can reduce diuretic dose supports the recent suggestion for initial combination of beta-blockers and SGLT2-inhibitors in management of HF.

CONCLUSION

In outpatient clinic HF patients, SGLT-2 inhibitors significantly reduced diuretics dose in some patients, and the mean dose of furosemide was reduced by about half. This suggests that SGLT-2 inhibitors have clinical advantages in managing outpatient HF patients. The recommended strategy could offset the side effects and maximize the benefits of SGLT-2 inhibitors, which appear to be a markedly reasonable and relatively easy approach in clinical practice. A large-scale prospective study is needed in the future.

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