Hypertension and diabetic patients: how to treat in the era of SGLT2-inhibitors?

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Received: July 3, 2023, Accepted: July 15, 2023

Hypertension and diabetes are two of the most important risk factors for cardiovascular and renal disease. The prevalence of hypertension is very high in the diabetic population, while a remarkable percentage of hypertensive patients have some degree of abnormality in glucose control [1, 2]. The presence of diabetes in patients with hypertension is associated with an increase in the risk of major cardiovascular complications with a risk of cardiovascular death that is more than twice in patients with both risk factors when compared to hypertension alone [3]. The treatment of hypertension in the diabetic population has been reported to improve the clinical outcome with a significant reduction in the rate of major cardiovascular events (MACE) as well as a decrease in the separate risk of myocardial infarction, stroke, and heart failure [4]. The reduction in the absolute risk of cardiovascular complications has resulted to be greater in diabetic in comparison to the non-diabetic population and this emphasizes the importance of adequate blood pressure control in presence of glucose abnormalities. In terms of drug classes, the recent ESH Guidelines reconfirm the primary role of drug combinations [1] including RAAS-inhibitors, calcium-channel blockers, and diuretics. In particular, the results of the ADVANCE and ADVANCE-ON studies [5, 6] have clearly demonstrated a favorable effect of the combination of perindopril and indapamide in patients with hypertension and diabetes. Similar data have been observed in the diabetic population of the ACCOMPLISH trial where the treatment with an ACE-inhibitor and a calcium-channel blocker was more effective than the combined use of an ACE-inhibitor and diuretic [7]. Basically, the multi-risk dimension of the diabetic patients would suggest a more personalized choice of the different classes of drugs, with the combination of RAAS inhibitors and CCB in patients with additional metabolic risk factors (e.g. uric acid, triglyceride, etc), while the diuretic treatment would be more effective in patients with some signs of volume expansion and CCB’s contraindications.

More recently, the role of sodium-glucose co-transport 2-inhibitors (SGLT2i) in the management of diabetic patients has been well-established after the publication of a series of seminal studies focusing on the cardiovascular protective effects of this class of drugs in patients with diabetes [8, 9] (Figure 1). In particular, the treatment with SGLT2i improves serum glucose, blood pressure, serum uric acid and renal function and this is leading to an improvement in the cardiovascular and renal outcomes that was largely confirmed in the diabetic and non-diabetic population [10].

So, the next question is: How should we integrate the use of SGLT2 inhibitors with the use of more consolidated antihypertensive drugs? First, by considering that the beneficial effect of SGLT2i can be integrated with that of an effective antihypertensive treatment. The CVD-REAL 2 study, an extensive metaanalysis carried out in patients with diabetes [11], has reported a decrease in the relative risk of MI, stroke, heart failure and all-cause of death in patients treated with various SGLT2 inhibitors. According to the results of randomized clinical trials (Table 1)
the percentage of hypertensive patients among those involved in such analysis is expected to range from 82 to 90%, we can easily imagine that the benefit of SGLT2i can be additive to that of antihypertensive drugs.

The second and most important point is the treatment with SGLT2i can improve blood pressure control in the diabetic population. This has been confirmed in two large metaanalysis involving different molecules [12, 13] carried out in the hypertensive and diabetic population and showing a reduction of both systolic (-3.5 mmHg) and diastolic blood pressure (-1.7 mmHg) regardless of the method of measurement (office, 24-hour ABPM) and the intensity of antihypertensive treatment.

An improved blood pressure control has been reported in the EMPA-REG study in the subpopulation of patients with presumed resistant hypertension [14] where the effects on blood pressure control have been associated with a significant improvement in clinical outcome regardless of the previous history of hypertension.

A typical population with a high prevalence of hypertension are the patients with heart failure with preserved ejection fraction (HFpEF), as confirmed by the results of the EMPEROR-Preserved and DELIVER studies [15, 16] where a previous history of hypertension was present in about 90% of the subjects at baseline. In this patient population, the treatment with SGLT2 was highly successful in terms of cardiovascular outcome, supporting a positive interaction between the mechanisms of action of such drugs and the pathophysiology of blood pressure control. The reduction of the primary outcome in the DELIVER trial was more significant (-29 vs. -7%) in the subpopulation with blood pressure levels above the median value (128 mmHg) that included most of the patients with hypertension with a large proportion of diabetic subjects [16].

Moreover, the blood pressure-lowering effect of empagliflozin has been proven to be increased by the concomitant administration of ACE-inhibitors and diuretics [17] with a dose-dependent effect that suggests a potential for blood pressure control for doses of SGLT2i greater than those currently used for the treatment of diabetic patients. This evidence supports the possibility of future development of fixed-dose single-pill combinations of antihypertensive drugs.

Table 1. The percentage of hypertensive patients from extensive studies that included patients with type 2 diabetes mellitus and cardiovascular disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>% Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPAREG-OUTCOME</td>
<td>85.7</td>
</tr>
<tr>
<td>CANVAS</td>
<td>89.5</td>
</tr>
<tr>
<td>DECLARE-TIMI</td>
<td>82.0</td>
</tr>
<tr>
<td>VERTIS-CV</td>
<td>88.0</td>
</tr>
</tbody>
</table>
drugs and SGLT2i for the current treatment of patients with hypertension and diabetes, and new results from the secondary analysis of available clinical studies are expected for the next future. A further area of favorable synergistic interaction between some classes of blood pressure-lowering drugs and SGLT2i is renal protection. Both SGLT2i and RAAS inhibitors have some positive effect on glomerular hemodynamics (involving both afferent and efferent arteriole) and intra-glomerular pressure resulting in a lesser decline in renal function and reduction in albumin excretion [18–21]. This renal protective effect may significantly prevent the progression toward chronic kidney disease (CKD) but can also contribute to cardiovascular prevention according to the primary role of CKD as a risk factor for myocardial infarction, stroke and heart failure [22]. The net benefit on renal function has been clearly demonstrated in patients with diabetes and heart failure, where the rate of decline in GFR [23] was cumulatively reduced in patients treated with SGLT2 inhibitors after an initial worsening due to tubule-glomerular balance during the first weeks of treatment.

Among the many “pleiotropic effects” of SGLT2i, one of the most important in terms of cardiometabolic prevention is the reduction of the circulating levels of uric acid. It is the final product of protein catabolism, and its production is closely related to the activity of the enzyme xanthine-oxidase (XO) which is responsible for the two final steps of purine catabolism. The activity of XO is associated with the release of oxygen radicals responsible for a remarkable amount of oxidative stress that is largely involved in the negative cardiovascular effects of hyperuricemia. A decrease in the circulating levels of uric acid has been demonstrated in patients treated with different SGLT2i without a dose-dependent effect [10] that clearly suggest a rate-limiting step in the mechanism of action urate-lowering effect of SGLT2 inhibitors that is largely based on the increase of renal urate excretion through the renal tubule. This uricosuric effect could be largely integrated with the action of xanthine-oxidase inhibitors with a synergistic effect on circulating serum urate levels.

The effect of SGLT2i on serum urate can contribute to their preventive cardiovascular effects in patients with diabetes and hypertension, where they have been reported to affect many of the components of cardiac and renal damage. A meta-analysis of data involving empagliflozin has reported a significant reduction in both systolic and diastolic blood pressure [24] associated with a decrease in serum urate levels. These results are largely in agreement with those of several randomized clinical trials investigating the cardiovascular protective role of SGLT2 inhibitors in patients with or without diabetes and/or heart failure (Table 2).

Inzucchi et al. [25] have provided a quantification of the clinical impact of serum uric acid reduction on the positive results of the EMPAREG-OUTCOME study reporting a cumulative contribution of over 25% after adjustment for all the possible confounding risk factors. In absolute term, this benefit largely corresponds to that reported in the LIFE study [26] where the urate-lowering effects of losartan were reported to statistically explain about 30% of the overall benefit reported in comparison to atenolol. This means that the future treatment of patients with hypertension and diabetes should primarily consider the use of drugs with a mechanism of action beyond blood pressure and glucose control that will remain the primary targets of treatment but whose control is not sufficient to prevent the overall risk of cardiovascular and renal disease. The use of SGLT2 inhibitors in combination with RAAS inhibitors and CCB’s is expected to play this “all-around” role and new studies and clinical observations are expected to confirm this promising pharmacological approach to the management of the most dangerous combination of cardiovascular risk factors.

**References**


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### Table 2. Effects of SGLT2-I on serum uric acid levels and clinical outcome in patients with DM, HFrEF, HFpEF.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Patients</th>
<th>Uric acid (all significant)</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>EMPAREG-OUTCOME</td>
<td>DM2</td>
<td>-1.04 mg/dL vs. Placebo</td>
<td>Reduced MACE</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>EMPEROR-RED</td>
<td>HFrEF</td>
<td>-1.11 mg/dL vs. Placebo</td>
<td>Reduced MACE</td>
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<tr>
<td>Empagliflozin</td>
<td>EMPEROR-PRES</td>
<td>HFpEF</td>
<td>-0.8 mg/dL vs. Placebo</td>
<td>Reduced MACE</td>
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<tr>
<td>Dapagliflozin</td>
<td>DAPA-HF</td>
<td>HFrEF</td>
<td>-0.84 mg/dL vs. Placebo</td>
<td>Reduced MACE</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>DELIVER</td>
<td>HFpEF</td>
<td>-0.93 mg/dL vs. Placebo</td>
<td>Reduced MACE</td>
</tr>
</tbody>
</table>


19. Seidu S, Kunutsor SK, Cos X, Gillani S, Khunti K; for and on behalf of Primary Care Diabetes Europe. SGLT2 inhibitors and renal outcomes in type 2 diabetes with or without renal impairment: A systematic review and meta-analysis. Prim Care Diabetes. 2018;12(3):265-283.


