Επίκαιρο Άρθρο

Beneficial effects on blood pressure and central hemodynamics of newer anti-glycaemic drugs – An update 2022

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ABSTRACT

Newer glucose-lowering drugs for the treatment of type 2 diabetes have been introduced in recent years, such as the SGLT-2 inhibitors and GLP-1 receptor agonists/analogues, with their well-documented clinical benefits from large trials. These drugs are able to reduce both macro- and microvascular events in patients with type 2 diabetes and to prevent worsening of diabetic nephropathy. One important aspect of these new drugs is the ability to lower blood pressure and to improve central hemodynamics, including arterial stiffness of the aorta. In the updated review, the evidence for these effects is discussed for each drug class separately and in combination. In the future there may come new opportunities for fixed drug combinations to improve cost-effectiveness and compliance of diabetes treatment when antihypertensive, lipid-lowering and glucose-lowering drugs are combined. Such preparations must be carefully designed and tested before a wider use, at least for some categories of patients with type 2 diabetes. As control of hypertension is of great importance for patients with diabetes in general, the combination of traditional antihypertensive drugs (i.e. blockers of the renin-angiotensin system) with newer glucose-lowering drugs that may also lower blood pressure could prove to be a successful and very useful combination.

Key-words: *SGLT-2 inhibitors and GLP-1 receptor agonists/analogues, blood pressure type 2 diabetes antihypertensive drugs Combination therapy*

The emergence of newer glucose-lowering drugs for the treatment of type 2 diabetes (T2D) has provided rich opportunities for not only control of cardiovascular risk but also reduction of morbidity and mortality based on results from large clinical trials. Both the sodium glucose transporter 2 (SGLT-2) inhibitors and the glucagon-like peptide 1 (GLP-1) receptor agonists/analogues (RA) have shown impressive effects on prevention on both macrovascular and microvascular endpoints[1-4], including slowing the progression of diabetic nephropathy[5]. Still the mechanistic explanations for these clinical benefits are not well understood, as they go beyond the effects of traditional control of hyperglycaemia. Among the pleiotropic effects of these newer drugs, also the blood pressure (BP) lowering properties have been observed[6,7], both based on observations from conventional office blood pressure measurements and by use of 24-hour ambulatory blood pressure monitoring (ABPM). In addition, also beneficial effects on central hemodynamics and aortic stiffness have been reported[8]. These findings will here be briefly reviewed and discussed. Such effects are of great clinical importance as hypertension is a common and important cardiovascular and renal risk factor in most T2D patients[9], often complicated by special features linked to diabetes such as masked hypertension[10], orthostatic reactions upon standing[11], or even resistant hypertension[12].

SGLT-2 inhibitors

This is a class of drugs with a number of effects that may contribute to BP lowering, as well as an improvement of central hemodynamics, including the

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lowering of aortic pulse wave velocity (aoPWV) as a marker of arterial stiffness. Among these contributing mechanisms are noted weight reduction[13], increased natriuresis[13] and vascular relaxation[14]. The increased natriuresis is combined with increased glucosuria, one of the very hallmarks of this class of drugs leading to reduced hyperglycaemia.

Already the first large-scale intervention study (EMPA-REG) in 2015 could document lowering of office BP (a few mmHg) by use of the SGLT-2 inhibitor empagliflozine versus placebo in patients with T2D and previous cardiovascular events[15]. No reflex increase of heart rate was noted. That was later followed by a study showing similar BP lowering effects based on 24-h ABPM, with or without background antihypertensive drug medication such as hydrochlorothiazide[16]. Also other SGLT-2 inhibitors (canagliflozin, dapagliflozin, etc.) have later on shown similar effects that go in parallel with weight reduction.

In one study, treatment with dapagliflozin significantly reduced ambulatory, brachial and central BP levels and aoPWV in DM2 patients versus placebo[17].

More recently a meta-analysis could show that SGLT-2 inhibitor treatment leads to an average reduction of systolic/diastolic BP 3.62/1.70 mmHg in 24-h ambulatory BP. This BP-lowering effect remains unmodified regardless of the dose of SGLT-2 inhibitor used and is comparable with the BP-lowering efficacy of low-dose hydrochlorothiazide[18], i.e. a mild diuretic effect.

In cases of resistant hypertension, SGLT-2 inhibitors have been added for better BP control[19], a new way to achieve this goal when previously the addition of an aldosterone antagonist was recommended (spironolactone, eplerenone), which still is a useful alternative in patients with resistant hypertension.

A beneficial effect on arterial stiffness and aoPWV has been documented by use of SGLT-2 inhibition[20,21] in both patients with type 1 and type 2 diabetes, even if sometimes surrogate markers and not a direct measurement of aoPWV was used. The reduction of arterial stiffness could be secondary to a lowering of BP, but it could be speculated that also other, more direct effects on the arterial wall could be present, for example improvement of endothelial dysfunction[22].

It is noteworthy that the rapidly occurring preventive effect on congestive heart failure of SGLT2 inhibition in clinical trials (after a few weeks) could most likely be explained by a reduction of arterial stiffness and normalization of the reflex wave that impacts on cardiac function, a mechanism called ventriculo-arterial coupling (VAC)[23]. This provides another argument in favor of using SGLT-2 inhibitors for prevention of heart failure in many cardiovascular risk patients, irrespective of diabetes status, as increased arterial (aortic) stiffness is a very common phenomenon in such individuals.

The SGLT-2 inhibitors are well tolerated in general, but some adverse effects may affect a few patients like urinary tract infection and dermatitis caused by candida infection. Other more rare side effects are normoglycaemic ketoacidosis and worsening of peripheral artery disease (in one study), etc[24].

GLP-1 receptor agonists/analogues

These drugs increase the activity of glucagon-like peptide 1 (GLP-1), a secreted incretin from the gastrointestinal mucosa, and thereby facilitating insulin secretion from pancreatic beta-cells. One of the main effects is weight reduction[25] that can sometimes be substantial with more recent incretin-active drugs such as tirzepatide that combines GLP-1 and gastric inhibitory peptide (GIP), another incretin secreted from the gastrointestinal mucosa[26]. There is even a triple drug combination with the two incretin-active drugs plus glucagon that may further reduce body weight[27]. This weight reduction is mainly caused by a reduction of gastric emptying and increased satiety due to central nervous effects[28].

Besides weight loss that promotes BP reduction[29] these injectable drugs also improve vascular relaxation and are supposed to prevent atherosclerosis, an effect also achieved with newer oral preparations[30]. The slowing of atherosclerosis could be linked to beneficial effects on chronic inflammation in the vascular wall[31]. Secondary to vasodilatation an increase of heart rate has been noticed, but this is still debated whether it can increase cardiovascular risk or not. Taken together, the benefits achieved for reduction of cardiovascular disease manifestations in clinical studies overshadow the untoward effect of a slight increase in heart rate.

Among side effects of GLP-1 receptor agonists/analogues (RA) are noticed most importantly nausea and vomiting that may affect up to one third of all patients, at least during initiation of the drug therapy. In most cases such initial side effects will disappear after some time. In a few cases also pancreatitis has been encountered, but the risk seems to be very low.

Combination therapy

As many subjects with the metabolic syndrome have hyperglycaemia linked to insulin resistance and ab-

dominal obesity they are prone to develop different states of pre-diabetes or even overt T2D, when these new classes of glucose lowering drugs may prove to be useful, often in combination with first-line drug metformin according to current guidelines[32]. Other useful combinations could be with blockers of the renin-angiotensin system[33], or even a combination of SGLT-2 inhibitors with GLP-1 RA drugs[32]. A recent randomized study reported that a 12-month treatment with GLP-1 RA, SGLT-2 inhibitor, and their combination, showed a greater improvement of vascular markers and effective cardiac work than insulin treatment in T2D. The combined therapy as second line was superior to either insulin or GLP-1 RA and SGLT-2 inhibitor prescribed separately[34].

This way of thinking paves the way for a fixed drug combination (FDC) in patients with T2D, when also a statin and antihypertensive drugs can be added. Such fixed combinations based on a statin, antihypertensive drugs and aspirin (PolyPill, PolyCaps) have recently been shown to be efficient based on a meta-analysis[36]. The addition of one or more glucose-lowering drugs[37] to such a FDC could become a more cost-effective way in the future to help many T2D patients due to the simplification of treatment and improved compliance.

Conclusions

The newer glucose-lowering drugs for T2D (i.e. SGLT-2 inhibitors and GLP-1 RA) have contributed to our understanding of how to improve prevention of macro- and micro-vascular complications in these patients. Among the beneficial effects of these drugs also BP-lowering and improvement of central hemodynamics can be of great importance to explain the reduction of cardiovascular events. For the SGLT-2 inhibitors there is increased natriuresis and weight loss, and for the GLP-1 RA drugs there is most of all weight loss but also improvement of endothelial function. However, still the exact mechanisms behind the hemodynamic changes of the two classes of drugs are not fully known. As hypertension poses a substantial risk for these patients, the use of anti-hypertensive drugs in combination with these newer glucose-lowering drugs may prove to be important for BP control, normalization of central hemodynamics and lowering of the BP-dependent risk. In the future it is expected that more fixed drug combinations will be used and this may involve also these two promising classes of drugs to treat T2D patients and lower their cardiovascular and renal risk.

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