ISSN NO: 2770-2936
Date of Publication:08-03-2023

SGLT2 Inhibitors and Mechanisms of Arterial Hypertension

Raimzhanov A.A.,
Mangasaryan A.A.
Central Asian Medical University, Uzbekistan, Fergana

Annotation. The article provides information about the use of SGLT2 inhibitors in hypertensive crises, mechanisms of action as an antihypertensive drug and the normalization of endothelial function. Other generation of these drugs are also compared with empagliflazin. Studies have been conducted with placebo drugs, and information is given on the effect of drugs on reducing daily and night blood pressure.

Keywords: diabetes, hypertension, glucose, SGLT2 transporters, cardiovascular events, weight loss.

Introduction. Arterial hypertension (AH) and diabetes mellitus (DM) often occur together, and people with hypertension are at significantly higher risk of complications from cardiovascular disease (CVD) and progression of chronic kidney disease (CRF) compared with people with diabetes mellitus 2- type with normotension [1, 2]. Among people with type 2 diabetes, approximately 40% have hypertension at the time of diabetic mellitus diagnosis. The etiology of hypertension in DM cannot be associated only with diabetic kidney disease, since, in about half of patients, hypertension occurs before the onset of moderately elevated albuminuria [3].Arterial stiffness and sodium retention, which lead to volume expansion, are also additional proposed mechanisms for the development of hypertension in DM. Sodium retention is particularly associated with induced hyperglycemia in increased filtered glucose volume, as well as with an increase in insulin levels. Excess filtered glucose is reabsorbed in the proximal tubule via the sodium-glucose co-transporter (SGLT) and leads to increased sodium reabsorption [5]. Early treatment of hypertension and diabetes is especially important for the prevention of cardiovascular diseases and slowing the progression of diabetic nephropathy. Clinical trials have shown the effectiveness of intensive blood pressure (BP) control to reduce micro- and macrovascular complications in diabetes mellitus [6].

Most treatment options for DM target insulin sensitivity, insulin secretion, insulin availability, or carbohydrate absorption from the gastrointestinal tract. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are relatively new sugar-lowering agents with an insulin-independent mechanism of action. SGLT2 inhibitors reduce blood glucose, blood pressure, and body weight. SGLT2 is expressed in the proximal tubule and controls the reabsorption of approximately 90% of the filtered glucose. SGLT2 inhibitors promote renal glucose excretion and thus modestly reduce elevated blood glucose levels in diabetic patients [7, 8].

Two SGLT2 inhibitors are currently approved in Uzbekistan. (dapagliflozin, empagliflozin). In addition, there are other drugs in the world (ipragliflozin luseogliflozin, tofogliflozin) that are in the late stages of development (ertugliflozin) [4]. New evidence from clinical trials in people with a high risk of developing cardiovascular complications confirms the reduction in cardiovascular risk with canagliflozin and empagliflozin. We review the current evidence and future prospects for SGLT2 inhibitors in hypertensive patients [9].

Plasma glucose is filtered in the glomeruli, in the absence of kidney disease, the filtered glucose is reabsorbed into the proximal convoluted tubule, controlled by two classes of transport proteins: SGLTs and glucose transporters (GLUTs). SGLT transporters are located on the luminal surface of the proximal tubular epithelium, and transport glucose enters cells against a concentration gradient via the sodium-glucose cotransporter. This active transport re-needs the Na+/K+-ATPase pump, an active transporter of sodium to the extracellular space across the basolateral membrane. Two SGLT transporters are involved in renal glucose reabsorption.

Approximately 90% of the filtered glucose is reabsorbed in the early proximal tubule by the action of SGLT2, a high-throughput, low-affinity transporter, selectively expressed in the kidney. In the distal tubule, low-powered SGLT1 transports the remaining glucose (about 10% of the total). Unlike SGLT2, which is only expressed in the kidneys, SGLT1 is also expressed in the intestine, where it plays an important role in

ISSN NO: 2770-2936
Date of Publication:08-03-2023

the absorption of glucose-galactose [10]. Filtration and reabsorption of glucose are directly dependent on plasma glucose concentration. Although filtration has no limit, glucose reabsorption has a maximum threshold beyond which an increase in glucose concentration does not lead to a further increase in glucose levels. In patients with type 2 diabetes mellitus, glucose transport and the glucose threshold in the kidneys are increased compared to healthy people [11]. This increase is associated with upregulation of SGLT2 and leads to a significant increase in glucose levels in the kidney cells. As a result of the activation of the SGLT2 transporter, the release urinary glucose occurs at higher levels in diabetic patients. Inhibition of SGLT2 reduces proximal tubular glucose reabsorption and modestly lowers blood glucose levels. The ability to lower blood glucose levels is limited by the filtered load of glucose and osmotic diuresis. In addition, despite complete blockade of glucose reabsorption in the proximal tubule, measured inhibition remains less than 50% based on urinary glucose excretion. Since the sugar-lowering effect is non-insulin-dependent, these drugs do not cause hypoglycemia [12].

In 2013, the first drug approved in the US was canagliflozin, followed shortly by dapagliflozin and empagliflozin in 2014. Empagliflozin has the highest SGLT2 transporter activity compared to the other two drugs. SGLT2 inhibitors are reasonable glucose-lowering drugs, with an average decrease in hemoglobin ranging from 0.4 to 1.1% compared with the control group, depending on baseline glucose levels and kidney function. In a meta-analysis of clinical trials comparing SGLT2 inhibitors with placebo or other sugar-lowering drugs (metformin, sulfonylurea, dipeptidyl peptidase-4 [DPP-4] inhibitors, or insulin), SGLT2 inhibitors reduced hemoglobin levels by 0.5 to 0.7% compared with placebo and -0.06 to -0.13% compared with other active drugs [13, 14].

Methods and results: Although glucose control was the main end point of the clinical study with SGLT2 inhibitors, effects on BP and weight were generally studied as secondary effects. A meta-analysis of 45 placebo-controlled studies showed: a mean decrease in systolic blood pressure (SBP) of −3.77 mmHg. Art. (95% CI −4.65 to −2.90) and analysis of six active control studies showed a mean change of 4.45 mmHg. (95% CI - 5.73 to - 3.18) compared with other drugs.

In 16 studies, SGLT2 inhibitors showed a mean change in diastolic blood pressure (DBP) from baseline of 1.75 mmHg. Art. (95% CI -2.27 to -1.23), while six active controlled studies showed a mean change of -2.01 mmHg. (95% CI -2.62 to -1.39). A newer meta-analysis of 22,528 patients from 43 randomized controlled trials found significant reductions in systolic blood pressure (weighted mean pressure difference - 2.46 mm Hg (95% CI - 2.86 to - 2.06)) and DBP (mean difference of 1.46 mm Hg (95% CI 1.82 to -1.09)) with SGLT2 inhibitors compared with placebo or other drugs [15].

Because 24-hour inpatient BP is a better predictor of CV risk and mortality than out-of-hospital BP, a recent meta-analysis of 20,980 participants from six studies that used inpatient BP monitoring suggested a 24-hour steady-state decrease of −3.76 mmHg. Art. and a 24-hour ambulatory decrease in diastolic blood pressure of -1.83 mmHg, which confirms the data of previous studies.

SGLT2 inhibitors are likely to reduce nighttime BP to a lesser extent than daytime or diurnal systolic and diastolic BP without increasing heart rate and independent of diuretic or angiotensin-converting enzyme inhibitor use of angiotensin receptor blockers [16].

Further studies demonstrate a significant reduction in daytime BP and lesser degrees of nighttime systolic and diastolic BP. A multicenter, double-blind, placebo-controlled study of 451 people randomized to escalating doses of canagliflozin (50 to 300 mg daily) added to metformin, sitagliptin, or placebo found a reduction in SBP ranging from −0.9 mmHg. Art. when taking 50 mg 1 time per day up to - 4.9 mm Hg. Art. 300 mg once daily versus -1.3 mmHg when taking placebo and -0.8 mm Hg. with sitagliptin [4]. Interestingly, these studies have shown a dose-independent increased risk of urinary tract and genital infections. SGLT2 inhibitors generally do not have a significant reduction in BP; however, it has been shown that sitagliptin, although a small but significant decrease in 24-hour ambulatory systolic and diastolic blood pressure from -2.0 to -2.2 and from -1.6 to -1.8 mm Hg, respectively, in non-diabetic patients compared with placebo, while metformin, exenatide, and liraglutide failed to significantly lower 24-hour ambulatory BP. An important double-blind, placebo-controlled clinical trial conducted by Weber and colleagues evaluated 449 patients with normal renal function and elevated blood pressure despite ongoing dual antihypertensive therapy, including a renin-blocker of the angiotensin system. Patients were

ISSN NO: 2770-2936
Date of Publication:08-03-2023

randomized to receive 10 mg empagliflozin versus placebo for 12 weeks. SBP decreased by 4.3 mm with empagliflozin compared with placebo. In a retrospective analysis, empagliflozin showed an established synergistic effect in lowering blood pressure with beta-blockers and calcium channel blockers (reducing SBP with combination therapy by 5.76- and 5.13-mm Hg, respectively), but not with thiazide diuretics. Although the exact mechanisms of the antihypertensive effect of SGLT2 inhibitors are not fully understood, natriuresis is a concomitant factor in individuals with normal renal function. It is very important to note that the diuretic effects of SGLT2 inhibitors are not transient. In general, 1.70 mmol/day of sodium is reabsorbed via SGLT2 in type 2 diabetic patients with normal renal function. This mild natriuretic effect is compensated by sodium, which is reabsorbed in the last sections of the nephron. However, a 30–60% increase in urinary sodium excretion has been noted with the use of an SGLT2 inhibitor [17, 20]. SGLT2 inhibitors have been noted to improve arterial stiffness, a decrease in the activity of the sympathetic system, which activated due to hyperglycemia, improve blood circulation. As a caveat, note that despite the same direction of pooled effects across studies, the detection of modest BP reduction may be limited by differences in antihypertensive drug effects. SGLT2 inhibitors likely shift the balance of baroreceptors towards the parasympathetic pathway; however, this observation needs to be confirmed. SGLT2 inhibitors reduce weight by approximately 2–3 kg over 3 months [19]. The observed weight loss is partly due to the loss of calories due to increased excretion and volume of glucose due to osmotic diuretics. The association between weight loss and BP reduction was examined in a pooled analysis of two 12-week, randomized, placebo-controlled trials of empagliflozin as an adjunct to metformin. Two-thirds of patients were taking antihypertensive drugs at baseline. Both doses of empagliflozin 10 and 25 mg resulted in a significant decrease in systolic blood pressure by -3.8 and -4.5 mmHg. respectively. These changes were independent. In addition, a randomized placebo-controlled trial in overweight diabetic patients demonstrated that dapagliflozin 10 mg/day for 24 weeks resulted in a significant reduction in mean waist circumference and fat mass. Treatment with an SGLT2 inhibitor in type 2 DM has been associated with positive effects beyond glucose control, such as lowering blood pressure, reducing body weight and visceral adiposity, improving arterial stiffness and microalbuminuria [18, 20]. Weight, waist circumference, systolic and diastolic BP, and uric acid were significantly reduced, while lower density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol were slightly increased in patients treated with empagliflozin. Subsequent sensitivity analysis showed that the benefits of empagliflozin on CV death and hospitalization for heart failure were independent of baseline hemoglobin and change in hemoglobin from baseline, control of BP, cholesterol, LDL.

Conclusion: SGLT2 inhibitors are the first class shown to reduce CVD and mortality, improve endothelial function, and slow the progression of CKD among patients with vascular disease. They reduce not only glucose, but also BP and weight through yet to be determined mechanisms. Most of the reported effects of this class are attributed to the loss of glucose in the urine; however, benefits are still seen in people with stage 3 CKD, where osmotic glucose-lowering effects are negligible. Therefore, more research is needed to understand why this class of drugs does more than lower glucose levels.

References:

1. Fuller J.H. Epidemiology of hypertension associated with diabetes mellitus. Hypertension. 1985;7(6 Pt 2):II3–7.
2. Epstein M, Sowers JR. Diabetes mellitus and hypertension. Hypertension. 1992;19(5):403–18. https://doi.org/10.1161/01. HYP.19.5.403.
3. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation. 2002;106(16):2085–90. https://doi.org/10. 1161/01.CIR.0000033824.02722.F7.
4. Cherney DZ, et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol. 2014;13(1):28. https://doi.org/10.1186/1475-2840-13-28.

ISSN NO: 2770-2936
Date of Publication:08-03-2023

5. Nosadini R, Sambataro M, Thomaseth K, Pacini G, Cipollina MR, Brocco E, et al. Role of hyperglycemia and insulin resistance in determining sodium retention in non-insulin-dependent diabetes. Kidney Int. 1993;44(1):139–46. https://doi.org/10.1038/ki.1993.224.
6. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet, 1998. 352(9131): p. 854–65.
7. DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. Nat Rev Nephrol. 2017;13(1):11–26. Comprehensive review paper discussing all the relevant literature regarding metabolic and hemodynamic effects of the SGLT 2 class.
8. Bailey CJ. Renal glucose reabsorption inhibitors to treat diabetes. Trends Pharmacol Sci. 2011;32(2):63–71. https://doi.org/10.1016/j.tips.2010.11.011.
9. Thomson SC, Rieg T, Miracle C, Mansoury H, Whaley J, Vallon V, et al. Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. Am J Physiol Regul Integr Comp Physiol. 2012;302(1):R75–83. https://doi.org/10.1152/ajpregu.00357.2011.
10. Mancia G, Cannon CP, Tikkanen I, Zeller C, Ley L, Woerle HJ, et al. Impact of empagliflozin on blood pressure in patients with type 2 diabetes mellitus and hypertension by background antihypertensive medication. Hypertension. 016;68(6):1355–64. https://doi.org/10.1161/HYPERTENSIONAHA.116.07703.
11. Plosker GL. Dapagliflozin: a review of its use in type 2 diabetes mellitus. Drugs.2;72(17):2289–312. https://doi.org/10.2165/11209910-000000000-00000.
12. Lamos EM, Younk LM, Davis SN. Canagliflozin , an inhibitor of sodium-glucose cotransporter 2, for the treatment of type 2 diabetes mellitus. Expert Opin Drug Metab Toxicol. 2013; 9 (6): 763–75.
13. https://doi.org/10.1517/17425255.2013.791282.
14. Scheen AJ. Pharmacokinetic and pharmacodynamic profile of empagliflozin, a sodium glucose co-transporter 2 inhibitor. Clin Pharmacokinet. 2014;53(3):213–25. https://doi.org/10.1007/s40262-013-0126-x.
15. Nauck MA. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. Drug Des Devel Ther. 2014;8:1335–80. https://doi.org/10.2147/DDDT.S50773.
16. Zinman B, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28. Major CV outcome trial with empagliflozin demonstrating reduced CV risk and renoprotection.
17. Neal, B., et al., Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med, 2017.-online. Second major CV outcome trial with canagliflozin that is consistent with empagliflozin data and demonstrates major reduction in CV risk in type 2 diabetes patients.
18. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev. 2011;91(2):733–94.
19. https://doi.org/10.1152/physrev.00055.2009.
20. Hediger MA, Rhoads DB. Molecular physiology of sodium glucose cotransporters. Physiol Rev. 1994;74(4):993–1026.
21. https://doi.org/10.1152/physrev.1994.74.4.993.
22. DeFronzo RA, Hompesch M, Kasichayanula S, Liu X, Hong Y, Pfister M, et al. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. Diabetes Care. 013;36(10):3169–76. https://doi.org/10.2337/dc13-0387.
23. Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabet Med. 2010;27(2):136–42. https://doi.org/10.1111/j.1464-5491.2009.02894.x.