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SGLT2 inhibitors in hypertension: Role beyond diabetes and heart failure☆

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a pandemic that affects millions of patients worldwide. Diabetes affects multiple organ systems leading to comorbidities including hypertension. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) recently have been approved for the treatment of T2DM and heart failure with reduced and preserved ejection fraction. Retrospective analyses of clinical trials have noted SGLT2 inhibitors to have a promising effect on blood pressure. Moreover, the observed blood pressure reduction is not just an acute effect of treatment initiation but has been shown to have a long-term impact on both systolic and diastolic blood pressure. The mechanism of action leading to the blood pressure reduction is still unclear; however, proposed mechanisms are related to the natriuretic effect, modification of the renin-angiotensin-aldosterone system, and/or the reduction in the sympathetic nervous system, SGLT2i should be considered as second-line medication in those patients with diabetes or heart disease and concomitant hypertension. This article reviews the pharmacology, side effect profile, and clinical trials surrounding the use of SGLT2i for the treatment of hypertension.

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Introduction

The prevalence of Type II diabetes mellitus (T2DM) is expected to increase to 366 million worldwide by 2030 [1]. Diabetes affects multiple organ systems and unfortunately is associated with many comorbid conditions. Around 70% of patients with diabetes are also known to have hypertension [2,3]. Both hypertension and diabetes are major risk factors for microvascular and macrovascular complications. Hypertension has a close association with diabetes due to the increased arterial stiffness and sodium retention associated with diabetes physiology [4–6]. Arterial stiffness is caused by non-enzymatic glycosylation leading to damage and hyalinization of the arterial walls over time progressing to atherosclerosis. Atherosclerosis can lead to serious complications including sudden cardiac death, myocardial infarction, and stroke. Sodium retention associated with diabetes is due to normal renal physiology associated with the sodium-glucose transporters within the proximal tubule. Hyperglycemia in diabetics increases the activity of the sodium-glucose transporters leading to increased sodium retention and ultimately volume expansion. It is recommended to have adequate blood pressure control in patients with diabetes to help decrease the risk of cardiovascular and renal complications [7–9].

Inhibition of the sodium-glucose cotransporters within the proximal tubule has been targeted as a treatment modality for T2DM to aid in glycemic control. Further evaluation into the inhibition of the sodium-glucose cotransporter 2 (SGLT2) has shown to reduce the risk of cardiovascular death and hospitalization in patients with heart failure with reduced (HFrEF) and preserved ejection fraction (HFpEF), regardless of the presence or absence of diabetes. The 2022 American Heart Association and American College of Cardiology heart failure guidelines have given SGLT2 inhibitors (SGLT2i) a class IIa indication for its use in HFpEF and heart failure with mildly reduced ejection fraction (HFmEF) [10]. Additional studies of SGLT2 have shown to have promising effects on lowering blood pressure, reducing the risk of major cardiovascular events

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and weight loss [11,12]. This article aims to explore the role of SGLT2 outside of its already proven efficacy in the treatment of both diabetes and heart failure.

Mechanism of action

The SGLT2i are a class of drugs that target glucose reabsorption by blocking the sodium-glucose cotransporter 2 located on the apical membrane of the proximal convoluted tubules (PCT) [13]. The PCT is responsible for over 90% of glucose reabsorption within the kidneys [13–15]. In healthy individuals, glycosuria occurs when blood glucose levels exceed 180 mg/dL. In those with diabetes mellitus, SGLT2 is unregulated causing increased glucose reabsorption shifting the glycosuria threshold to 220 mg/dL. Inhibition of SGLT2 leads to glucosuria at a much lower threshold as long as blood glucose levels are above 80 mg/dL, with the degree of glucosuria proportional to the initial blood glucose levels [16]. Decreasing the reabsorption of filtered glucose within the PCT ultimately increases renal glucose excretion while reducing plasma blood glucose and lowering hemoglobin A1C by about 0.5-1% [17].

Neuroprotective properties are related to the restoration of the tubuloglomerular feedback loop. The decrease of blood volume leads to a reduction in the atrial natriuretic peptide that causes constriction of afferent renal arterioles, thereby increasing sodium concentration in the tubular fluid [13]. Macula densa senses the increased sodium levels and activates the tubuloglomerular feedback through the renin-aldosterone-angiotensin system. Renin release is inhibited leading to vasodilation of the efferent arterioles. Vasoconstriction of the afferent arterioles while simultaneous vasodilation of efferent arterioles reduces intraglomerular hydrostatic pressure as the mechanism behind the renal protective properties of SGLT2i.

By increasing glucosuria, natriuresis resulting in moderate diuresis is an observable result. An average of 300mL per day is excreted for the first few weeks of therapy with subsequent return to baseline [18]. This results in a reduction in plasma volume which is an observed benefit in heart failure patients. SGLT2i also work directly on the heart. As the myocardium is remodeling, upregulation of Na/H+ exchanger (NHE) is observed leading to increased intracellular sodium and calcium resulting in a pro-oxidant and prothrombotic state [13]. The mechanism by which SGLT2i inhibit NHE on cardiomyocytes is still unknown [19].

The mechanism of action related to the observed effects on blood pressure is still under investigation. It is hypothesized that the osmotic effect of glucose allows more sodium and water to remain within the tubules causing a consequent natriuretic effect. The accelerated natriuretic process accompanies an observed lower blood pressure in patients [20]. Another proposed mechanism involves the excess glucose and sodium excretion as observed by the nephron as a notion of excess filtration-like expansion of plasma volume or increased sodium. This could lead to the modification of the renin-angiotensin system (RAAS) [11]. The reduction in blood pressure is observed even in those with the reduction in glomerular filtration rate reduction arguing that SGLT2i may reduce the sympathetic nervous system leading to beneficial effects in both hypertension and heart failure [21,22]. The sympathetic nervous system is upregulated in a hyperglycemic state. With the observed lowering of blood glucose with the use of SGLT2i, it is presumed the sympathetic nervous system stimulation is decreased [19]. Additionally, it has been proposed that SGLT2i create a shift away from the sympathetic nervous system to that of the parasympathetic nervous system among the baroreceptors. This phenomenon is supported by the observed absence in reflex tachycardia noted with SGLT2i therapy [19]. The various proposed mechanisms of SGLT2i reducing blood pressure in T2DM are summarized in Figs. 1 and 2.

Pharmacokinetics and pharmacodynamics

The pharmacokinetics and pharmacodynamics of SGLT2i are summarized in Table 1. This includes the SGLT2i Canagliflozin, Dapagliflozin, Empagliflozin, and Ertugliflozin. SGLT2i are all primarily metabolized in the liver and the kidneys by glucuronidation by uridine diphosphate-glucuronosyltransferases (UGTs) [23]. Their breakdown metabolites are then cleared in the urine and feces [24]. Overall, SGLT2i exhibit good oral bioavailability with absorption only minimally affected by food without clinical relevance. Additionally, they all exhibit rapid absorption with a fast time to peak ranging 1-2 h after administration. Their relatively long half-life ranges from 10.6-16.6 h, allowing for once-daily dosing [24]. The effectiveness of SGLT2i ability to excrete urinary glucose decreases as renal function declines due to slight alterations of pharmacodynamics in CKD [25].

Drug interactions

The drug interactions for the SGLT2i (Canagliflozin, Dapagliflozin, Empagliflozin, and Ertugliflozin) are depicted in Table 2. Common interactions include enhanced hypoglycemic effects when used in conjunction with other antidiabetic agents.

Adverse effects

Although SGLT2i are generally well tolerated, several adverse effects are clinically relevant. Several potentially serious adverse effects may limit use in some patients. Additionally, multiple minor effects may limit patient tolerability, thereby reducing patient compliance and the overall effectiveness of the medication [26]. Safety and tolerability are important aspects to consider when prescribing medications, especially relatively new medications without long-term data.

UTI/genital infections

The first and most prominent adverse effects of SGLT2i are urinary tract infections (UTI) and genital/yeast infections [27]. The most common infections are yeast infections and can occur in both men and women. Yeast infections occur in patients tglung SGLT2i at a two to four fold increased rate. UTIs can range from simple cystitis to serious illnesses such as pyelonephritis, sepsis, or perineal necrotizing fasciitis [28].

Hypoglycemia

SGLT2i exert their effect on the nephron and do not affect insulin secretion. Therefore, they are unlikely to cause hypoglycemia by themselves. The risk of medication-induced hypoglycemia is substantially higher in patients who are prescribed insulin or other diabetic drugs that are known to increase insulin secretion or increase insulin sensitivity such as sulfonylureas or thiazolidinediones. The risk is minimal when combined with metformin [27].

Acute kidney injury

CKD is exceptionally common in patients diagnosed with diabetes. As SGLT2i act on the nephron, kidney disease often affects the drug's activity level [27]. The glucuretic effect of SGLT-2i decreases as GFR declines [25]. Additionally, there have been some post-marketing reports from the FDA of acute kidney injury (AKI) occurring after starting SGLT2i. The majority of these reports demonstrated AKI occurring in the first 1 month of therapy. Subsequent analyses of SGLT2i have demonstrated no significant increase in the risk of AKI [29].

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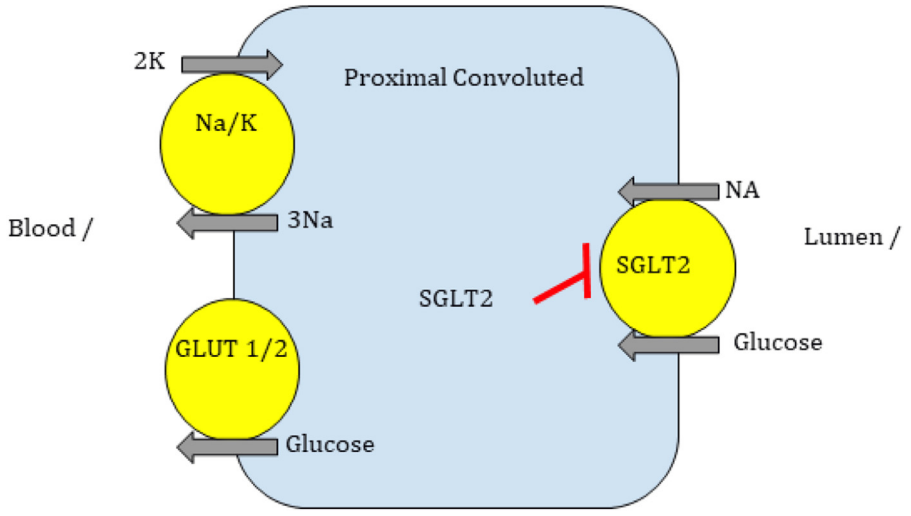

Fig. 1. Mechanism of action of SGLT2 inhibitor at cellular level.

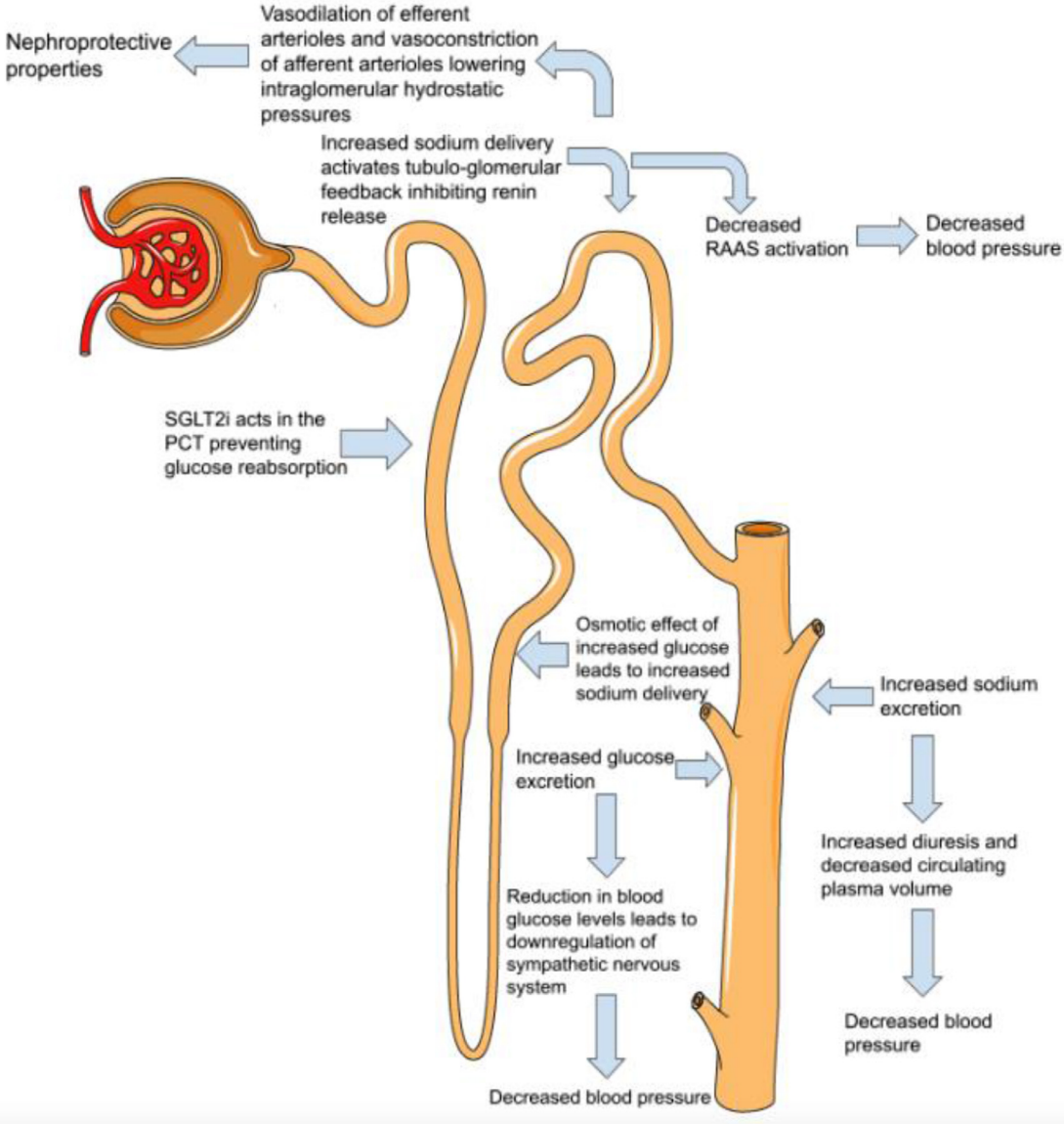

Fig. 2. Downstream effects of SGLT2 inhibitor in lowering blood pressure.

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Table 1
Pharmacokinetics and pharmacodynamics of Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin.

Medication	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Absorption	Not affected by food	Not affected by food	Absorption time slightly delayed by food but does not affect extent of absorption	Decreased max concentration by 29% and prolongs Time to max by 1 h
Vd (IV)	83.5 L	118 L	73.8 L	85.5 L
Protein Binding	99%	91%	86%	94%
Metabolism	UGT1A9, UGT2B4, CYP3A4	UGT1A9	UGT2B7, UGT1A3, UGT1A8, UGT1A9	UGT1A9, UGT2B7
Bioavailability	65%	78%	78%	~100%
Half-life elimination	10.6 h (100mg) and 13.1 h (300mg)	12.9 h	12.4 h	16.6 h
Time to peak	1-2 h	2 h	1.5 h	1 h (fasting), 2 h (with meal)
Excretion	Urine (33%) and Feces (42%)	Urine (75%) and Feces (21%)	Urine (54%) and Feces (41%)	Urine (50%) and feces (41%)

UGT=Uridine glucuronyl transferase; CYP= cytochrome; Vd=Volume of distribution.

Table 2
Drug interactions for SGLT2 inhibitors.

SGLT-2 inhibitors	Drug	Interaction	Risk Class
All	Alpha-Lipoic Acid	May enhance hypoglycemic effects	C
All	Androgens	May enhance hypoglycemic effects	C
Canagliflozin	Digoxin	May increase the serum concentration of Digoxin	C
All	Direct Acting Antiviral Agents (HCV)	May enhance hypoglycemic effects	C
Empagliflozin	Fexinidazole	May increase serum concentration of OAT1/3 substrates	D
Canagliflozin	Fosphenytoin	May decrease the serum concentration of drug	D
All	Guanethidine	May enhance hypoglycemic effects	C
All	Hyperglycemia-Associated Agents	May diminish therapeutic effect	C
All	Hypoglycemia-Associated Agents	May enhance hypoglycemic effects	C
All	Insulins	May enhance hypoglycemic effects	D
Canagliflozin, Empagliflozin	Loop Diuretics	May enhance hypoglycemic effects	C
All	Maitake	May enhance hypoglycemic effects	C
All	Monoamine Oxidase Inhibitors	May enhance hypoglycemic effects	C
Empagliflozin	Nitisinone	May increase serum concentration of OAT1/3 substrates	C
All	Pegvisomant	May enhance hypoglycemic effects	C
Canagliflozin	Phenobarbital	May decrease the serum concentration of drug	D
Canagliflozin	Phenytoin	May decrease the serum concentration of drug	D
Empagliflozin	Pretomanid	May increase serum concentration of OAT1/3 substrates	C
Canagliflozin	Primidone	May decrease the serum concentration of drug	D
All	Prothionamide	May enhance hypoglycemic effects	C
All	Quinolones	May enhance the hypoglycemic effect, and may diminish the therapeutic effect	C
Canagliflozin	Rifampin	May decrease the serum concentration of drug	D
All	Ritodrine	May diminish the therapeutic effect	C
Canagliflozin	Ritonavir	May decrease the serum concentration of drug	D
All	Salicylates	May enhance hypoglycemic effects	C
All	Selective Serotonin Reuptake Inhibitors	May enhance hypoglycemic effects	C
All	Sulfonylureas	May enhance hypoglycemic effects	D
Empagliflozin	Teriflunomide	May increase serum concentration of OAT1/3 substrates	C
All	Thiazide and Thiazide-Like Diuretics	May diminish the therapeutic effect	C

OAT1/3=Organic anion transporter 1 and 3; HCV=Hepatitis C virus
Risk Class C is classified as Monitor Therapy, Risk Class D is Consider Therapy Modification, [4–6]

Bone fractures

Some studies have suggested an increased incidence of bone fractures in patients taking canagliflozin and possibly dapagliflozin [30]. However, meta-analyses done on the safety of other SGLT2i have not found a significantly increased risk of fracture [27].

Diabetic ketoacidosis

SGLT2i have previously been shown to increase the likelihood of developing DKA [31]. The risk was thought to be substantially higher in patients with type 1 diabetes, so their use in this patient population was discouraged. However, more recent data has suggested a benefit to the use of SGLT-2i in patients with type 1 diabetes, without a significant increase in adverse events [32]. Several studies have also demonstrated an increased risk of "Euglycemic DKA" which can delay recognition and therefore treatment [31,33].

Amputations

The overall incidence of amputations in patients taking SGLT2i is very low. However, two large clinical trials demonstrated an almost two-fold increase in amputations in patients taking canagliflozin when compared to placebo [34]. As more data have emerged showing decreasing rates, the FDA has removed black box warning regarding foot and leg amputations [35].

Bladder cancer

Various trials have looked at the association of SGLT2i with different forms of cancer. Only empagliflozin has been associated with an increased risk for bladder cancer [34]. However, a subsequent meta-analysis demonstrated no significant increase in cancer risk with the use of any of the SGLT2i [33].

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Hypotension

Due to the blood pressure lowering effects of SGLT2i, there is a possibility of symptomatic hypotension. Five clinical trials explored the potential anti-hypertensive effects of SGLT2i in T2DM patients with concomitant hypertension. Among these five clinical trials, the main adverse effects reported were hypoglycemia, urinary tract/genital infections, and orthostatic hypotension [23,36–39]. Despite the blood pressure-lowering capabilities of SGLT2i, a recent meta-analysis of 16 RCTs involving ~12,000 patients found no significant increase in orthostatic hypotension [40]. In this meta-analysis, further stratification for age demonstrated a slight increase in risk in patients younger than 60-years old and in patients with a history of diabetes for greater than 9 years. When stratified based on blood pressure, patients with a baseline BP <130/80mmHg had a lower risk of orthostatic hypotension than did patients with a baseline BP >130/80mmHg.

Contraindications and warnings

Typically, SGLT2i are the second or third line for the treatment of T2DM but can be utilized as a monotherapy when metformin is contraindicated. In general, there are two main patient populations in whom SGLT2i are contraindicated. The first group includes patients with low eGFRs. The eGFR cutoffs for initiation of therapy differ based on the specific medication. The eGFR cutoff values for initiation of therapy are as follows: <60 mL/min/1.73m^2 for Ertugliflozen, <45mL/min/1.73m^2 for dapagliflozin and empagliflozin, and <30 mL/min/1.73m^2 for canagliflozin [41].

It is recommended that clinicians evaluate renal function before beginning SGLT2i and periodically after beginning the therapy [42]. SGLT2i may be continued despite a declining eGFR as long as the eGFR remains above 30 mL/min/1.73m^2. Once eGFR falls below 30 mL/min/1.73m^2, all SGLT2i should be discontinued due to a lack of benefit below this threshold.

Secondly, SGLT2i are contraindicated in patients with a prior history of diabetic ketoacidosis (DKA) [43–45]. As noted above, treatment with SGLT2i is associated with an increased risk of DKA including euglycemic DKA. Patients who are prescribed insulin in combination with an SGLT2i are at the highest risk. If DKA is suspected, any prescribed SGLT2i should be discontinued indefinitely to prevent recurrent episodes.

Previously, patients with type 1 diabetes were discouraged from being prescribed SGLT2i due to initial safety data concerning an increased risk for DKA. This was thought to be an elevated risk even more so than type 2 diabetic patients taking insulin. Studies suggest the rates of SGLT2i-associated DKA range from 5%-12% [46]. However, a more recent meta-analysis has shown a benefit to the use of SGLT-2i in patients with type 1 diabetes, without a significant increase in adverse events [32].

In addition to the above contraindications, there are some circumstances where the cost/benefit ratio may favor the avoidance of these medications. Due to the increased frequency of UTIs and yeast infections in patients taking SGLT2i, caution is recommended in patients with recurrent infections. SGLT2i should be used with caution in patients with known osteoporosis or decreased bone mineral density due to the potential for a bone mineral density lowering effect and possible increased risk for fracture in some studies. In patients with a prior history of significant neuropathy, vascular disease, open wounds or foot ulceration, or visible deformities, the use of an SGLTs inhibitor may not be recommended due to an increased rate of amputations.

Clinical trials in patients with T2DM and hypertension

In 2013, canagliflozin was the first SGLT2i to be FDA approved in the treatment of T2DM [47]. Observations from the prior trials noted multiple added benefits with the use of SGLT2i including blood pressure reduction (summarized in Table 3). This notable effect inspired more in-depth investigations into the true impact that SGLT2i has on both systolic and diastolic blood pressure (SBP and DBP respectively).

The efficacy of empagliflozin in patients with diabetes and hypertension was first evaluated in 2015 by Tikkanen et al. [39]. 825 patients with both hypertension (mean SBP 130-159 and DBP 80-99) and T2DM were evaluated in a randomized control trial to either receive empagliflozin or placebo for a 12-week duration. There was an observed reduction in BP by 3.44 mmHg with 10 mg of empagliflozin and by 4.16 mmHg with 25 mg of empagliflozin vs placebo at 12 weeks (95% CI -4.78 to -2.09; p<0.001). Empagliflozin 10 mg reduced 24 h DBP by -1.36mmHg (95% CI -2.15 to -0.56; p<0.001) compared with placebo, and empagliflozin 25 mg reduced 24h SBP by -1.72mmHg (95% CI -2.51 to -0.93; p<0.001) compared with placebo. Empagliflozin 10 mg reduced mean seated office SBP by -3.92 (95% CI -5.86 to -1.98; p<0.001) compared with placebo and empagliflozin 25 mg reduced mean seated office SBP by -4.80mmHg (95% CI -6.73 to -2.87; p<0.001) compared with placebo. Empagliflozin 10 mg reduced mean seated office DBP by -1.93 (95% CI -3.01 to -0.84; p<0.001) compared with placebo and empagliflozin 25 mg reduced mean seated office DBP by -1.89mmHg (95% CI -2.97 to -0.82; p<0.001) compared with placebo. By large, empagliflozin was associated with a clinically meaningful reduction in blood pressure vs placebo.

Weber et al. conducted a double-blinded, placebo-controlled phase three clinical trial including 311 patients [38]. Patients included had both uncontrolled T2DM (HgB A1c >7.0%) and hypertension (SBP 140-165 mmHg and DBP 85-105 mmHg) with the current medical regimen including oral antihyperglycemic medications, insulin or both and RAAS blocker and additional antihypertensive medication. Patients were given either 10 mg dapagliflozin or a placebo for 12 weeks with the primary outcome evaluating seated SBP. At week 12, mean seated SBP was reduced by -4.28mmHg (95% CI -6.54 to -2.02; p=0.0002) compared to placebo. The 24 h ambulatory SBP at week 12 was also significantly reduced in the dapagliflozin group vs placebo group by -4.45mmHg (95% CI -7.14 to -1.76; p=0.0012). Mean seated DBP was reduced by -0.97mmHg (95% CI -2.32 to 0.39; p=0.16) compared to placebo. Additionally, a post hoc analysis was performed which showed that SGLT2i also have a synergistic BP-lowering effect with calcium channel blockers and beta-blockers as their other antihypertensive, but not with thiazide diuretics]20, 38]. Overall, dapagliflozin significantly reduced blood pressure and was well tolerated.

Pfeifer et al. evaluated the effect of canagliflozin on blood pressure and markers of arterial stiffness through a post hoc analysis of data from a 26-week randomized, double-blinded control study (N=2313) and 6 week randomized double-blind controlled ambulatory blood pressure monitoring in patients with T2DM (N=169) [23]. In pooled, placebo-controlled studies, SBP was decreased by -4.0mmHg (95% CI -5.1 to -2.8) with canagliflozin 100 mg and by -4.8mmHg (95% CI -5.8 to -3.5) with canagliflozin 300 mg both compared to placebo. DBP was decreased by -1.9mmHg (95% CI -2.6 to -1.2) with canagliflozin 100 mg and by -1.9mmHg (95% CI -2.6 to -1.1) with canagliflozin 300 mg both vs placebo. For the ambulatory blood pressure monitoring (ABPM), mean 24 h SBP was decreased by -3.3mmHg (95% CI -6.7 to 0.2) with canagliflozin 100 mg and by -4.9mmHg (95% CI -8.4 to -1.5) with canagliflozin 300 mg both compared to placebo. Mean 24 h DBP was decreased by -1.9mmHg (95% CI -4.0 to 0.1) with canagliflozin 100 mg and by -2.9mmHg (95% CI -5.0 to -0.9) with canagliflozin 300 mg both

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Table 3
Summary of major SGLT2 trials in reference to effect on blood pressure.

Trial	N	Patient population	SGLT2i	Dosing	Length of Trial	SBP change (in mmHg)	DBP change (in mmHg)	24 h mean ABPM (in mmHg)
Ferdinand et al. [35]	154	African American patients with T2DM and HTN	Empagliflozin	10 mg x 4 weeks, force titration to 25 mg daily vs. placebo	24 weeks	Office SBP −7.4 (−12.4 to −2.5)	Office DBP −4.3 (−7.2 to −1.3)	24 h mean ABPM −8.4 (−13.7 to −3.0)
Kario et al. [48]	132	Adults with T2DM and uncontrolled nocturnal HTN	Empagliflozin	10 mg vs. placebo	12 weeks	Nighttime SBP: −4.3 (−10.7 to 1.7) 24 h SBP −7.7 (−12.5 to −2.8)	Nighttime DBP −1.6 (−4.4 to 1.3) 24 h DBP −2.9 (−5.0 to −0.8)	NA
Baker et al. [50]	2,098 (6 RCTs)	Meta-analysis	Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin	Double blind placebo controlled trials on SGLT2-inhibitors on 24 h ABPM	4, 6, 12 weeks	24 h ABPM SBP −3.7 (−4.2 to −2.3) Daytime SBP −4.3 (−5.1 to −3.6) Nighttime SBP −2.6 (−3.1 to −2.1)	24 h ABPM DBP −1.8 (−2.4 to −1.3) Daytime DBP −2.1 (−2.6 to −1.5) Nighttime DBP −1.5 (−2.2 to −0.8)	NA
EMPA REG-BP [51]	7,853	T2DM compared to T2DM +HTN	Empagliflozin	10 or 25 mg vs. placebo	12 weeks	25 mg 24 H SBP −4.2 (−5.5, −2.8)	24 H DBP −1.7 (−2.5, −0.9)	NA
Weir et al. [52]	2,313	T2DM	Canagliflozin	100 or 300 mg vs. placebo	26 weeks	100 mg Office SBP −4.4 (−5.9, 2.8) 300 mg Office SBP −4.9 (−6.2, −3.0)	100 mg Office DBP −1.8 (−2.7, −0.08) 300 mg Office DBP −1.7 (−2.7, −0.7)	NA
Weber et al. [36]	449	T2DM + HTN	Dapagliflozin	10 mg vs. placebo × duration	12 weeks	Office SBP −4.28 (−6.54, −2.02)	NA	NA
DECLARE [53]	17,160	T2DM + high CV risk	Dapagliflozin	10 mg vs. placebo	4-8 weeks	Office SBP −2.7 (−2.4 to −3.0)	Office DBP 0.7 (−0.6 to −0.9)	NA
CANVAS [54]	10,142	T2DM + high CV risk	Canagliflozin	100–300 mg vs. placebo	Average 188.2 weeks	Office SBP −3.9 (−4.3, −3.6)	Office DBP −1.4 (−1.6, −1.2)	NA
CREDENCE [55]	4,401	T2DM + albuminuric CKD	Canagliflozin	100 mg vs. placebo	Median 136.2 weeks	Office SBP −3.3 (−3.86, −2.73)	Office DBP −0.95 (−1.28, −0.61)	NA
DAPA-HF [56]	4,744	HFrEF < 40%	Dapagliflozin	10 mg daily vs. placebo	Median 72.8 weeks	Office SBP −1.27 (−2.09, −0.45)	NA	NA
Papadopoulou et al. [57]	85	T2DM	Dapagliflozin	10 mg daily vs. placebo	12 weeks	24 H brachial SBP -5.8±9.5 Central SBP -4.81±8.0	NA	NA

ABPM=Ambulatory blood pressure monitoring; CV=Cardiovascular; DBP=Diastolic blood pressure; HFrEF=Heart failure with reduced ejection fraction; HTN=Hypertension; SBP=Systolic blood pressure; T2DM=Type 2 Diabetes Mellitus; CKD=Chronic kidney disease
Table 3: Summary of major SGLT2 inhibitor trials with effect on blood pressure

compared to placebo [14]. A decrease in mean arterial pressure was also noted in those treated with canagliflozin (-4.2 vs -0.6 mmHg) compared to placebo. Ultimately, canagliflozin was shown to have beneficial cardiovascular outcomes in patients with T2DM.

The efficacy of dapagliflozin was evaluated in a randomized, placebo-controlled trial that included 992 patients with T2DM, pre-existing cardiovascular disease, and hypertension receiving antihypertensive agents [24]. Patients received placebo or dapagliflozin 10 mg for 24 weeks, followed by a 28-week extension time. At week 8, dapagliflozin had a statistically significant reduction in seated SBP (-1.97 mmHg), was maintained at 24 weeks (-1.95 mmHg), and again at 52 weeks (-3.58 mmHg; $p<0.0001$) [24]. For seated DBP, the dapagliflozin group showed a slight reduction from baseline at 24 weeks (-1.7 mmHg) vs. placebo (-0.4 mmHg) and again at 52 weeks with dapagliflozin (-1.7 mmHg) vs. placebo (-0.2 mmHg). A notable finding from this clinical trial was that the observed blood pressure reduction persisted over an entire year of treatment that was not previously shown in other trials.

In 2019, a placebo-controlled clinical trial of SGLT2i was executed in an African American population with concomitant T2DM and hypertension. Patients were prescribed either placebo or empagliflozin 10 mg for the first 4 weeks and then titrated to 25 mg until week 24. At week 12, empagliflozin had significantly greater reductions in 24 h ambulatory SBP compared to placebo (-5.21 mmHg; 95% CI −9.24 to −1.18; $p=0.0117$) [37]. At week 24, this difference between empagliflozin and placebo increased with -8.39 mmHg (95% CI −13.74 to −3.04; $p=0.0025$). For seated SBP, empagliflozin produced a reduction in seated SBP at weeks 12 and 24, but the difference was only statistically significant compared to placebo at week 24 (-7.43 mmHg; 95% CI −12.37 to −2.48; $p=0.0036$). For DBP, the reductions in the empagliflozin group versus the placebo group were not statistically significant at week 24, but a reduction was observed [37].

Most recently, a post hoc analysis of the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, that evaluated the value

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of SGLT2i use in kidney disease, was performed investigating the office blood pressure-lowering effect [48]. Canagliflozin showed BP reduction by 3.5mmHg compared to baseline. Although the effect was modest, it is important to take into consideration the measured blood pressures were evaluated in the office rather than home blood pressure readings which have been shown to be inferior. Interestingly, the CREDENCE trial included patients with resistant hypertension; however, patients treated with standard of care mineralocorticoid receptor antagonists were eliminated from the trial making the evaluation of SGLT2i role in resistant hypertension cumbersome.

The SACRA (SGLT2i and Angiotensin Receptor Blocker Combination Therapy in Patients With Diabetes and Uncontrolled Nocturnal Hypertension) study evaluated patients with T2DM and nocturnal hypertension with 12 weeks of treatment with empagliflozin [49,50]. Empagliflozin was noted to significantly reduce SBP vs placebo at both 12 and 24 weeks of treatment. Patients younger than 75 years of age had a reduction of 7.9 mmHg and 4.2 mmHg in those >75 years old. This corresponded to a mean 24 h SBP reduction of 11.0 and 8.7 mmHg respectively.

Resistant hypertension is defined as blood pressure above target despite the use of three or more antihypertensives with one of the medications including a diuretic [51]. There was a post hoc analysis of the EMPA-REG trial evaluating the impact of SGLT2i on patients with presumed resistant hypertension [51]. Resistant hypertension was defined by either three antihypertensive medications with SBP >140 mmHg and/or DBP >90 mmHg or the use of four antihypertensive agents. Empagliflozin was noted to decrease the SBP and DBP by 4.5 (95% CI 3.1-5.9) and 1.7 (95% CI 0.9-2.5) mmHg respectively vs placebo. Those receiving empagliflozin were able to achieve SBP <130 mmHg more frequently than placebo (38% vs 26%) [51]. The study was limited by the fact that it was a post hoc analysis of a trial that was not intended to evaluate the blood pressure lowering effects of empagliflozin. Further studies are needed to more thoroughly understand the use of SGLT2i in patients with resistant hypertension.

Conclusion

Through retrospective analysis of the various clinical trials and clinical trials investigating the effect of on blood pressure in T2DM patients, SGLT2i have an apparent beneficial effect on blood pressure. The blood pressure-lowering effect is not just in the initial setting but has been shown to continue through months of use. Current guidelines recommend hypertensive regimen to include diuretics, angiotensin converting enzyme inhibitor/angiotensin receptor blocking agents, and calcium channel blockers as first line agents. Combination therapy yields more effective blood pressure management in diabetic patients with an addition of a second agent. With the benefits seen among the hypertensive and diabetic patients, SGLT2i should be highly considered as second or third line agents, particularly in patients with proteinuria. Further clinical trials should be focused on direct comparisons with other second-line antihypertensive agents. Further evaluation is needed to delineate the use of SGLT2i in resistant hypertension as well as comparison to SGLT2i to mineralocorticoid receptor antagonists in the treatment of resistant hypertension. Overall, SGLT2i should be considered as second-line medication in those patients with comorbidities such as diabetes or heart disease and concomitant hypertension.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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