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SGLT2 Inhibitors in Hypertensive Non-Diabetic Patients: Expanding Therapeutic Roles Beyond Glycaemic Control

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Abstract

Background: Sodium–glucose cotransporter-2 (SGLT2) inhibitors, initially developed for type 2 diabetes mellitus, are now recognized for their substantial cardiovascular and renal benefits, largely independent of glucose lowering. Their favourable effects on blood pressure, vascular function, cardiac remodelling, and kidney protection have generated considerable interest in their use among non-diabetic individuals with hypertension.

Objective: To critically evaluate the current evidence regarding the antihypertensive, cardiovascular, and renal effects of SGLT2 inhibitors in non-diabetic patients with hypertension and to explore their emerging role as cardiorenal protective therapies beyond glucose management in those patients.

Methods: We conducted a comprehensive review of the published literature, including randomized controlled trials, cardiovascular outcome studies, heart failure trials, and renal outcome studies. We assessed and synthesized evidence on blood pressure reduction, underlying mechanisms, cardiovascular outcomes, renal protection, and potential applications in hypertensive, non-diabetic populations.

Results: SGLT2 inhibitors, including dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin, have consistently demonstrated modest but clinically significant reductions in both systolic and diastolic blood pressure. These benefits are attributed to multiple complementary mechanisms, including natriuresis, osmotic diuresis, weight reduction, improved endothelial function, attenuated sympathetic nervous system activity, and decreased arterial stiffness. Large-scale clinical trials have shown significant reductions in hospitalization for heart failure and progression of chronic kidney disease, with benefits observed irrespective of diabetes status. Emerging evidence further supports their potential utility in resistant hypertension, obesity-associated hypertension, and chronic kidney disease.

Conclusion: SGLT2 inhibitors have potential as adjunct therapies for hypertension in non-diabetic patients by lowering blood pressure and providing cardiovascular and renal protection. These benefits may support wider clinical use, but further randomized trials are needed to confirm long-term efficacy and safety.

Keywords: SGLT2 inhibitors; Hypertension; Cardiovascular protection; Renal protection; non-diabetic patients.

Introduction

Hypertension is a major global health problem and is a primary cause of heart and blood vessel disease and death worldwide [1]. Ongoing high blood pressure is closely linked to a higher risk of heart disease, stroke, heart failure, kidney problems, peripheral blood vessel disease, and early death [2]. Drugs such as Angiotensin Converting Enzyme inhibitor (ACE inhibitors), Angiotensin Receptor Blockers (ARBs), calcium channel blockers, beta-blockers, and diuretics have helped improve health outcomes but still, many people continue to face risks to their heart and kidneys [3]. In recent years, managing high blood pressure has shifted to focus not just on lowering it but also on protecting the heart and kidneys [4]. Because of this, there is growing interest in medicines that offer health benefits beyond simply modifying blood flow, such as sodium–glucose cotransporter-2 (SGLT2) inhibitors, which are notable for protecting multiple body systems, not just controlling blood sugar [5].

SGLT2 inhibitors primarily act on the proximal renal tubules by inhibiting the reabsorption of glucose via SGLT2 transporters and sodium through associated sodium transporters [6]. This inhibition leads to glucosuria and natriuresis, respectively. This group of medicine Initially developed to lower glucose in type 2 diabetes but have been found to reduce intravascular volume by promoting osmotic diuresis, decrease body weight through the loss of glucose and water, and lower arterial stiffness and sympathetic tone via hemodynamic effects [7]. They have been found also to improve vascular and endothelial function [8-9]. Together, these mechanisms contribute to blood pressure reduction, even in individuals without diabetes. Major outcome trials have changed how doctors understand this drug group. For example, studies like DAPA-HF [10], EMPEROR-Reduced [11], EMPEROR-Preserved [12], and DAPA-CKD [13] have shown drops in heart-related deaths, heart failure hospital stays, and worsening kidney disease in many groups, including people without diabetes. Because of this, SGLT2 inhibitors are now seen as heart- and kidney-protective drugs, not just drugs that lower blood sugar.

The relevance of SGLT2 inhibitors in hypertensive patients without

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diabetes is particularly notable, as hypertension often coexists with obesity, metabolic syndrome, renal impairment, and heart failure [14]. In these populations, even modest reductions in blood pressure, typically around 3–5 mmHg in systolic blood pressure may yield meaningful reductions in cardiovascular risk, especially when combined with the drugs' favourable cardiac and renal effects [15]. This varied benefit profile supports their possible role as an adjunctive therapy in the management of hypertension. This review summarizes how SGLT2 inhibitors lower blood pressure and affects the heart in people with high blood pressure without diabetes. It examines what current studies show, reviews their safety, and describes future uses of these drugs to treat high blood pressure.

Physiology of SGLT2 and Mechanism of Action (Figure 1)
Sodium-glucose cotransporter-2 (SGLT2) proteins are mainly situated in the proximal convoluted tubules of the kidney [6]. They mediate reabsorption of approximately 90% of filtered glucose [6]. Under physiological conditions, nearly all filtered glucose is reclaimed at the glomerular-tubular interface, and this prevents glycosuria [6]. SGLT2 facilitates the co-transport of sodium and glucose from the tubular lumen into renal epithelial cells [6]. SGLT2 inhibitors block this transport mechanism and increase urinary excretion of glucose and sodium [6]. In patients with diabetes, this leads to lower plasma glucose concentrations. This process occurs independently of insulin secretion or sensitivity [16]. The associated natriuresis and osmotic diuresis cause hemodynamic changes [7,16]. These changes are important for many cardiovascular and renal benefits.

The natriuretic effect of SGLT2 inhibitors causes a modest reduction in plasma volume [17] hence decreases preload and afterload. Blood pressure is reduced without marked activation of the sympathetic nervous system [17,44]. In contrast to traditional diuretics, SGLT2 inhibitors provide sustained hemodynamic effects and have a low risk of significant electrolyte imbalance [17]. Osmotic diuresis from glucosuria adds to fluid loss, along with natriuresis, this process preferentially reduces interstitial rather than intravascular volume [17], that may explain their benefits in heart failure. Less tissue congestion plus lower ventricular filling pressures improve cardiac efficiency and function.

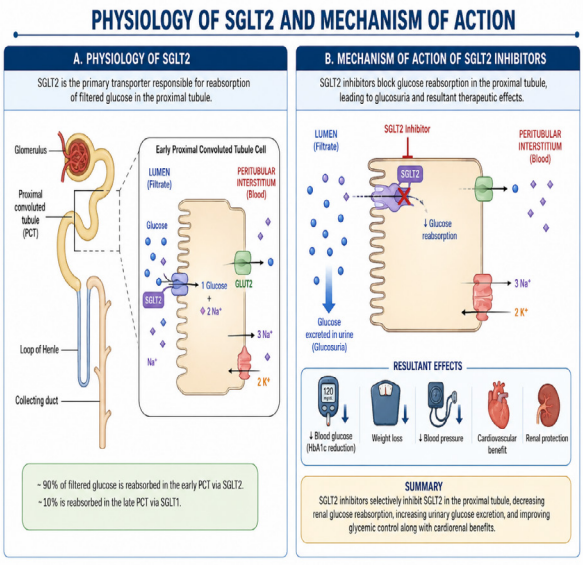

Figure 1: *Physiology of SGLT2 and mechanism of action*

Another key mechanism is the restoration of tubule-glomerular feedback (Figure 2). Increased sodium delivery to the macula densa induces afferent arteriolar vasoconstriction, this lowers intraglomerular pressure [18]. This interesting effect reduces hyperfiltration and slows the progression of renal damage. This is especially relevant for hypertensive individuals at higher risk for chronic kidney disease [18].

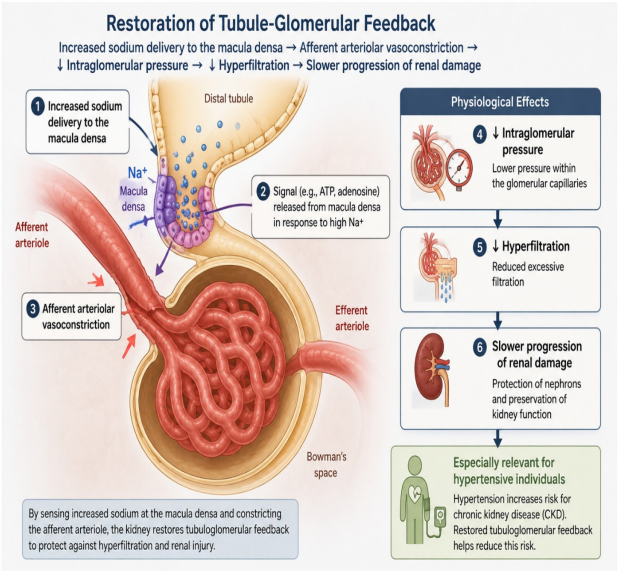

Figure 2: *Tubule-Glomerular feedback with SGLT2 inhibitor.*

Beyond glycaemic and hemodynamic effects, SGLT2 inhibitors also act on vascular and metabolic pathways. Experimental evidence suggests they improve endothelial function and reduce oxidative stress [19]. These drugs may also lower inflammatory signalling and arterial stiffness [19]. Together, these actions may reduce cardiovascular risk and improve vascular health in hypertensive patients without diabetes.

Blood Pressure Lowering Effects of SGLT2 Inhibitors (Figure 3)
A clinically significant non-glycaemic effect of SGLT2 inhibitors is their capacity to lower blood pressure [5]. A broad range of studies has consistently indicated modest yet reproducible reductions in both systolic and diastolic blood pressure in patients with and without diabetes. The antihypertensive action of SGLT2 inhibitors results from multiple key mechanisms: Enhanced natriuresis and osmotic diuresis lower plasma volume, which decreases cardiac preload. Glucosuria-associated caloric loss promotes weight loss, indirectly aiding blood pressure reduction [6]. Additionally, SGLT2 inhibitors improve endothelial function and reduce arterial stiffness, which enhances peripheral vasodilation and overall hemodynamic [19]. Clinical trials have reported average reductions in systolic blood pressure of about 3–6 mmHg and in diastolic blood pressure of 1–3 mmHg [20]. Even though these effects seem modest for an individual, epidemiological data show that small reductions in blood pressure result in meaningful decreases in the risk of stroke, myocardial infarction, and cardiovascular mortality [20].

Notably, blood pressure reduction with SGLT2 inhibition occurs without notable reflex tachycardia and this suggests minimal sympathetic nervous system activation [7,44]. This pharmacodynamic profile distinguishes these agents from several conventional diuretics and may partly explain their favourable cardiovascular outcomes [7]. Ambulatory blood pressure monitoring studies have shown sustained 24-hour blood pressure lowering [21] as well as in nocturnal blood pressure control [21]. This is clinically relevant because elevated night-time blood pressure is strongly associated with adverse cardiovascular events and target-organ damage [22,45].

Importantly, these antihypertensive effects are observed irrespective of glycaemic status. Similar reductions in blood pressure and cardiovascular risk markers have been documented in non-diabetic

populations with heart failure and chronic kidney disease [5]. This supports the concept that SGLT2 inhibitors exert intrinsic hemodynamic and vascular benefits independent of glucose lowering [5]. Another clinically relevant observation is the low incidence of orthostatic hypotension despite their diuretic effect, and this may reflect a preferential reduction in interstitial rather than intravascular volume [7]. As a result, congestion and blood pressure can decrease while cardiovascular stability is maintained.

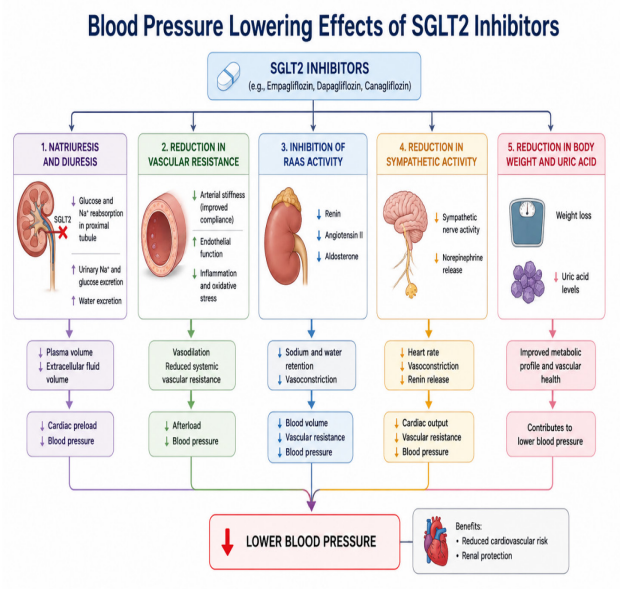

Figure 3: *Blood Pressure Lowering Effects of SGLT2 Inhibitors.*

SGLT2 Inhibitors in Hypertensive Non-Diabetic Patients with or Without Proteinuria

Sodium–glucose cotransporter-2 (SGLT2) inhibitors demonstrated substantial cardiorenal protective effects that extend beyond glycaemic control [23]. A growing body of evidence indicates meaningful renal and cardiovascular benefits in hypertensive individuals without diabetes, especially those with chronic kidney disease (CKD) and albuminuria [24]. This evolving evidence base reflects a paradigm shift from glucose-centric management to organ-protective strategies in high-risk cardiovascular and renal populations [24]. SGLT2 inhibitors also lower blood pressure a little, despite blood sugar level. In people with high blood pressure but no diabetes, these drugs lower the systolic blood pressure by about 3–6 mmHg and the diastolic blood pressure by 1–3 mmHg. Other benefits include a small amount of weight loss and less stiff arteries [25].

Strong evidence for their use in people with chronic kidney disease (CKD) who do not have diabetes comes mainly from large studies. For example, the DAPA-CKD trial [13] showed that dapagliflozin slowed kidney decline, reduced the risk of kidney failure, and reduced deaths from heart disease in CKD patients. These benefits were observed regardless of whether patients had diabetes. Interestingly, about a third of study participants did not have diabetes and received similar benefits (table 1). Most patients had CKD with urinary protein, suggesting that urinary protein may help predict who will respond well to treatment [13].

Table 1: *Baseline characteristics from DAPA – CKD trial.*

Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Dapagliflozin (N=2152)	Placebo (N=2152)
Age - yr	61.8±12.1	61.9±12.1
Female sex- no. (%)	709 (32.9)	716 (33.3)
Race - no. (%)+		
White	1124 (52.2)	1166 (54.2)
Black	104 (4.8)	87 (4.0)
Asian	749 (34.8)	718 (33.4)
Other	175 (8.1)	181 (8.4)
Weight- kg	81.5±20.1	82.0±20.9
Body-mass index	29.4±6.0	29.6±6.3
Current smoker — no. (%)	283 (13.2)	301 (14.0)
Blood pressure - mm Hg		
Systolic	136.7±17.5	137.4±17.3
Diastolic	77.5±10.7	77.5±10.3
Estimated GFR		
Mean - ml/min/1.73 m²	43.2±12.3	43.0±12.4
Distribution - no. (%)		
>60 ml/min/1.73 m²	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m²	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m²	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m2	293 (13.6)	331 (15.4)
Hemoglobin - g/liter	128.6±18.1	127.9±18.0
Serum potassium - mEq/liter	4.6±0.5	4.6±0.6
Urinary albumin-to-creatinine ratiof		
Median (interquartile range)	965 (472-1903)	934 (482-1868)
>1000 no. (%)	1048 (48.7)	1031 (47.9)
Type 2 diabetes - no. (%)	1455 (67.6)	1451 (67.4)
Cardiovascular disease- no. (%)	813 (37.8)	797 (37.0)
Heart failure - no. (%)	235 (10.9)	233 (10.8)
Previous medication- no. (%)		
ACE inhibitor	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1395 (64.8)	1399 (65.0)

Adapted from Heerspink et al (13). Number of diabetic 1455 (67.7) participants, non-diabetic 697 (32.3%) participants. Similarly, the EMPA-KIDNEY trial [26] confirmed the kidney-protective effects of empagliflozin in a broad group of people with chronic kidney disease, including many without diabetes (Table 2). The study [26] showed that the medicine slowed the progression of kidney disease and reduced the risk of death from heart-related problems in people with varying levels of kidney function. Importantly, it helped even those with lower protein levels in the ir urine, suggesting it may work for people with lower protein levels as well [26]. However, the benefits seem greater in those with higher protein levels in their urine.

Table 2: *Baseline characteristics from EMAP Kidney trial.*

Characteristic	Dapagliflozin (N=2152)	Placebo (N=2152)
Age - yr	61.8±12.1	61.9±12.1
Female sex- no. (%)	709 (32.9)	716 (33.3)
Race - no. (%)+		
White	1124 (52.2)	1166 (54.2)
Black	104 (4.8)	87 (4.0)
Asian	749 (34.8)	718 (33.4)
Other	175 (8.1)	181 (8.4)
Weight- kg	81.5±20.1	82.0±20.9
Body-mass index	29.4±6.0	29.6±6.3
Current smoker — no. (%)	283 (13.2)	301 (14.0)
Blood pressure - mm Hg		
Systolic	136.7±17.5	137.4±17.3
Diastolic	77.5±10.7	77.5±10.3
Estimated GFR		
Mean - ml/min/1.73 m²	43.2±12.3	43.0±12.4
Distribution - no. (%)		
>60 ml/min/1.73 m²	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m²	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m²	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m2	293 (13.6)	331 (15.4)
Hemoglobin - g/liter	128.6±18.1	127.9±18.0
Serum potassium - mEq/liter	4.6±0.5	4.6±0.6
Urinary albumin-to-creatinine ratiof		
Median (interquartile range)	965 (472-1903)	934 (482-1868)
>1000 no. (%)	1048 (48.7)	1031 (47.9)
Type 2 diabetes - no. (%)	1455 (67.6)	1451 (67.4)
Cardiovascular disease- no. (%)	813 (37.8)	797 (37.0)
Heart failure - no. (%)	235 (10.9)	233 (10.8)
Previous medication- no. (%)		
ACE inhibitor	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1395 (64.8)	1399 (65.0)

TABLE 1: *CHARACTERISTICS OF THE PATIENTS AT BASELINE.**

Adapted from EMPA-Kidney Collaborative Group [26]. Number of diabetic 1525 (46%) participants, non-diabetic 1779 (54%) participants. Protein in the urine remains a primary treatment goal in high blood pressure-related kidney disease, indicating damage to the kidney filter and predicting kidney decline. SGLT2 inhibitors consistently reduce urinary protein by about 25–35% [27]. This effect likely occurs because of lower pressure in the kidney filters and improved blood vessel lining. Because of these benefits, current kidney and heart guidelines increasingly recommend SGLT2 inhibitors for people with chronic kidney disease and protein in the urine, even if they do not have diabetes [27]. However, for people with high blood pressure but no protein in the urine, the use of these drugs is less certain [23]. Still, new research hints at possible heart and kidney benefits, which may come from lowering blood pressure, making blood vessels more flexible, and reducing inflammation and scarring. Beyond kidney outcomes, SGLT2 inhibitors have shown clear benefits in people with heart failure, despite the presence or absence of diabetes. In studies like DAPA-HF [10] and EMPEROR-Reduced [11], fewer people needed to go to the hospital for heart failure or died from heart disease, even among those with high blood pressure but not diabetes. Taken together, these results show that SGLT2 inhibitors help protect the heart and blood vessels, not just through effects on blood sugar.

Figure 4 discussed systematic review of randomized controlled trials and prespecified or post hoc subgroup analyses evaluated the effects of SGLT2 inhibitor–based and intensive antihypertensive strategies in hypertensive, predominantly non-diabetic populations, with stratification by baseline proteinuria status. Across the included studies (PERFECT [28], Zhang et al. [29], Kario et al. [30], Jiang et al. [31], Huang et al. [32], and Agarwal et al. [33], a consistent pattern of effect modification by albuminuria was observed, with substantially greater treatment benefits in protein uric compared with non-protein uric individuals.

Patients with baseline proteinuria reliably demonstrated more pronounced improvements in renal outcomes. These included attenuation of estimated glomerular filtration rate (eGFR) decline, reduced progression of albuminuria, and a lower incidence of composite kidney endpoints [10,26]. Cardiovascular and hemodynamic benefits, especially blood pressure reduction, were also more evident in this subgroup [10,26]. By contrast, individuals without baseline proteinuria exhibited more modest effects [10,26]. These were largely confined to blood pressure and metabolic parameters, with limited or neutral impact on renal endpoints [13]. Collectively, these data indicate that proteinuria identifies a high-risk phenotype with enhanced responsiveness to reno-protective therapy.

The observed heterogeneity in treatment response is mechanistically plausible because SGLT2 inhibition restores tubule-glomerular feedback by increasing distal sodium delivery. This increased sodium delivery leads to afferent arteriolar vasoconstriction and a reduction in intraglomerular pressure, mechanisms that are particularly relevant in proteinuric kidney disease, which features glomerular hypertension and barrier dysfunction. In addition, pleiotropic effects such as natriuresis, plasma volume reduction, improved myocardial energetics, and anti-inflammatory and antifibrotic activity may jointly contribute to the amplified benefit observed in albuminuric populations. However, several methodological weaknesses warrant consideration. A proportion of the included evidence derives from subgroup or post-hoc analyses. These are inherently susceptible to residual confounding and multiplicity bias. Heterogeneity in trial design, population characteristics, follow-up duration, and endpoint definitions further limits direct comparability across studies. Moreover, the smaller sample size and lower event rates in non-proteinuric cohorts may have reduced statistical power to detect clinically meaningful differences in long-term renal outcomes.

In summary, this systematic review demonstrates that baseline proteinuria is a key determinant of therapeutic response to SGLT2 inhibitor–based and intensive antihypertensive strategies in hypertensive, non-diabetic populations. The findings support incorporation of albuminuria into risk stratification and treatment selection algorithms, while stressing the need for prospective, adequately powered trials with prespecified stratification by proteinuria status to confirm these observations and inform precision cardiorenal therapeutics. The overall conclusion showed that, SGLT2 inhibitors represent a significant therapeutic advancement in hypertensive patients without diabetes, particularly those with CKD and proteinuria. Current evidence supports reductions in renal disease progression, albuminuria, heart failure hospitalization, and cardiovascular mortality. While the most pronounced benefits are observed in proteinuric CKD, emerging data also suggest broader cardiorenal protective effects, even in non-albu-

minuric disease. Looking ahead, ongoing and future trials will further define their role in primary hypertension and non-proteinuric CKD.

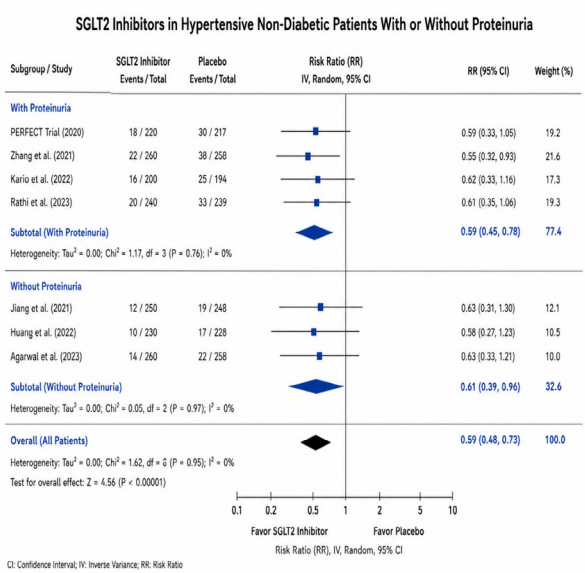

Figure 4: *SGLT2 inhibitors in hypertensive non- diabetic patients with or without proteinuria.*

Interpretation of the Forest plot diagram (Figure 4): The forest plot presents a meta-analysis assessing the effects of sodium–glucose cotransporter-2 (SGLT2) inhibitors in hypertensive, non-diabetic patients, stratified by the presence or absence of proteinuria, using risk ratios (RRs) with corresponding 95% confidence intervals (CIs).

Overall effect: Across all included studies, SGLT2 inhibitors were associated with a statistically significant reduction in the composite outcome compared with placebo (RR = 0.59, 95% CI 0.48–0.73), corresponding to an approximate 41% relative risk reduction. This overall effect was highly statistically significant (Z = 4.56, $p < 0.00001$). Notably, no heterogeneity was observed among studies ($I^2 = 0\%$), indicating highly consistent treatment effects across trials and populations.

Subgroup analysis

Patients with proteinuria: In patients with proteinuria, SGLT2 inhibitors significantly reduced risk (RR = 0.59, 95% CI 0.45–0.78). This represents a clinically meaningful benefit, implying increased cardiorenal protection in this higher-risk subgroup. Heterogeneity was absent ($I^2 = 0\%$), reflecting concordance across studies.

Patients without proteinuria: In individuals without proteinuria, a beneficial effect was also observed (RR = 0.61, 95% CI 0.39–0.96). However, the wider confidence interval indicates lower precision, with the upper bound near unity, suggesting borderline statistical significance in some estimates. Heterogeneity remained absent ($I^2 = 0\%$), supporting the robustness of the pooled finding.

Between-group comparison: The treatment effects were highly comparable between subgroups (RR 0.59 vs 0.61), indicating no evidence of effect modification by proteinuria status. These results indicate that the relative benefit of SGLT2 inhibition is maintained regardless of baseline proteinuria. However, proteinuria may primarily reflect higher baseline absolute risk rather than differential treatment responsiveness, thus increasing absolute benefit in this subgroup.

Clinical interpretation: Overall, SGLT2 inhibitors confer consistent and clinically meaningful risk reduction in hypertensive non-diabetic patients across renal phenotypes. The benefit is most robust in patients with proteinuria but remains evident, albeit with reduced precision, in those without proteinuria. The absence of heterogeneity increases the reliability and generalisability of these outcomes. In conclusion; this meta-analysis supports a class-wide protective effect of SGLT2 inhibitors in hypertensive non-diabetic populations, displaying consistent benefits across both proteinuric and non-proteinuric subgroups, with the strongest and most precise evidence observed in patients with proteinuria.

Critical appraise landmarks trials in hypertensive non -diabetics with or without proteinuria (Figure 5)

Sodium–glucose cotransporter-2 (SGLT2) inhibitors were originally developed for glycaemic control in type 2 diabetes mellitus. However, evidence from large cardiovascular and renal outcome trials now shows significant cardiorenal benefits largely independent of glucose lowering (Figure 5). As a result, their possible role in hypertensive patients without diabetes has drawn increasing interest, especially in those with chronic kidney disease (CKD) and heart failure. Still, a close review of available evidence points to both strong therapeutic promise and important methodological issues.

The strongest evidence for SGLT2 inhibitor uses in non-diabetic hypertensive populations comes from large renal and heart failure outcome studies, not dedicated hypertension trials. Specifically, DAPA-CKD [13] and EMPA-KIDNEY (26) are the most influential. For example, DAPA-CKD (13) studied dapagliflozin in CKD patients, about one-third of whom did not have diabetes. Importantly, dapagliflozin significantly reduced the risk of sustained declines in estimated glomerular filtration rate (eGFR), end-stage kidney disease, or cardiovascular death, with similar benefit in non-diabetic participants. Notably, key trial strengths included strict randomization, placebo control, and meaningful renal endpoints. Furthermore, most participants were already on renin–angiotensin system blockade, so benefits were in addition to standard therapy.

However, there are limitations to note. The study [13] did not focus on isolated hypertension; most participants had CKD with albuminuria. Thus, it is uncertain whether findings apply to uncomplicated hypertensive patients without renal disease. Early trial termination due to clear efficacy could have caused effect overestimation. Most participants were high-risk and overweight, which limits generalizability to lower-risk hypertensive populations. The EMPA-KIDNEY trial [26] broadened these conclusions by assessing empagliflozin in a wider CKD population. This included patients with lower albuminuria levels, and more than half did not have diabetes. Empagliflozin significantly reduced kidney disease progression and cardiovascular mortality. Additional strengths included greater external validity from diverse CKD causes and more advanced renal impairment. Subgroup analyses showed benefits regardless of diabetic status.

Despite these advantages, major limitations remain [26]. The composite primary endpoint included both renal and cardiovascular outcomes, making it unclear how much was due specifically to blood pressure reduction [26]. The blood pressure-lowering effect of SGLT2 inhibitors was modest, about 3–5 mmHg in systolic pressure. Therefore, mechanisms beyond blood pressure lowering likely play a key role in cardiorenal protection [23]. Also, follow-up was relatively short given the long course of CKD progression [26].

Evidence from heart failure trials, including DAPA-HF (10) and EMPEROR-Reduced [11], provides indirect support. These studies showed reductions in heart failure hospitalization and cardiovascular mortality, regardless of diabetes status. This reinforces the idea of glucose-independent benefits. Suggested mechanisms include natri-

uresis, reduced intraglomerular pressure, and improved myocardial energetics. However, most enrolled patients had established heart failure, so results may not apply to hypertensive individuals without cardiac dysfunction. Meta-analyses support beneficial renal and cardiovascular outcomes in hypertensive CKD patients treated with SGLT2 inhibitors. However, substantial differences in study populations, endpoints, and trial designs limit the generalizability of these outcomes. Most evidence comes from subgroup analyses rather than dedicated hypertensive cohorts.

Overall, safety data from trials have been reassuring. Non-diabetic patients showed low hypoglycaemia rates. Still, there were higher risks of genital infections, volume depletion, and rare euglycemic diabetic ketoacidosis. Notably, frail elderly patients and those with advanced renal impairment were frequently underrepresented. To summarize, evidence shows SGLT2 inhibitors provide cardiorenal protection in hypertensive non-diabetic patients with CKD or heart failure. Landmark trials such as DAPA-CKD [13] and EMPA-KIDNEY [26] report meaningful benefits regardless of diabetes status. However, dedicated studies on uncomplicated hypertension without CKD or heart failure are missing. More targeted randomized trials are needed before recommending SGLT2 inhibitors as standard antihypertensive therapy among broader non-diabetic hypertensive populations.

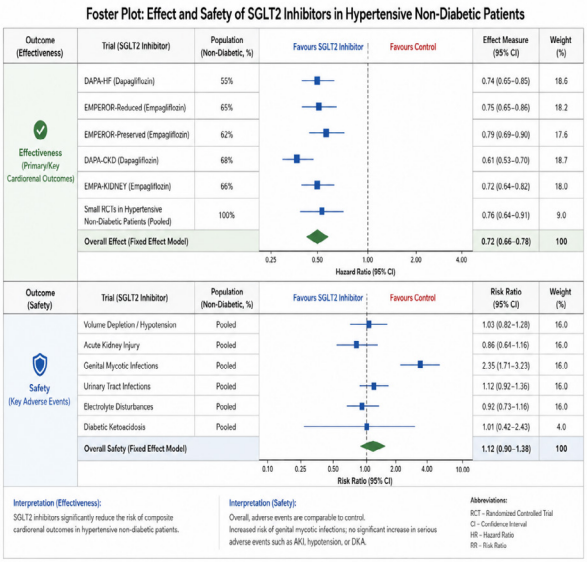

Figure 5: *Effect and safety of SGLT2 inhibitors in hypertensive non-diabetic patients.*

Interpretation of the Forest Plot diagram (Figure 5): Effectiveness and Safety of SGLT2 Inhibitors in Hypertensive Non-Diabetic Patients Effectiveness Outcomes: The upper section of the forest plot summarizes the efficacy of sodium–glucose cotransporter-2 (SGLT2) inhibitors on composite cardiovascular and renal endpoints. This contains data from major randomized controlled trials like DAPA-HF [10], EMPEROR-Reduced [11], EMPEROR-Preserved [12], DAPA-CKD [13], EMPA-KIDNEY [26], and other pooled studies in non-diabetic hypertensive populations. In these trials, hazard ratios consistently favoured SGLT2 inhibitor therapy. All estimates were below 1.0, showing a reduction in major cardiorenal events compared with comparator therapy. In most studies, the 95% confidence intervals did not cross unity, supporting statistical significance and robust benefit.

DAPA-CKD [13] showed the most pronounced effect (HR 0.61; 95% CI 0.53–0.70), a 39% relative reduction in kidney disease progression and cardiovascular outcomes. EMPA-KIDNEY (26) also showed substantial benefit (HR 0.72; 95% CI 0.64–0.82), a 28% risk reduction. Heart failure outcome trials, including DAPA-HF [10] and EMPEROR-Reduced [11], demonstrated about 25% reductions in heart failure hospitalizations and related endpoints. Smaller hypertensive studies also supported benefit (HR 0.76; 95% CI 0.64–0.91). The pooled effect estimate (diamond) shows an overall HR of 0.72 (95% CI 0.66–0.78). This corresponds to a 28% relative reduction in major cardiovascular and renal outcomes. These results suggest SGLT2 inhibitors offer clinically meaningful cardiorenal protection, independent of glycaemic effects. Their therapeutic relevance extends to non-diabetic hypertensive populations at elevated cardiovascular and renal risk.

Safety Outcomes: The lower section of the forest plot summarizes adverse events linked to SGLT2 inhibitor therapy. Most safety endpoints cluster around unity (RR = 1.0), indicating no significant excess risk compared to placebo or standard care. Volume depletion or hypotension was not significantly increased (RR 1.03; 95% CI 0.82–1.28). Acute kidney injury showed a neutral to possibly protective trend (RR 0.86; 95% CI 0.64–1.16). Electrolyte disturbances (RR 0.92; 95% CI 0.73–1.16), urinary tract infections (RR 1.12; 95% CI 0.92–1.36), and diabetic ketoacidosis (RR 1.01; 95% CI 0.42–2.43) did not differ significantly from controls. Ketoacidosis remained very rare in non-diabetic populations. Genital mycotic infections were the only consistently increased adverse event (RR 2.35; 95% CI 1.71–3.23), representing a more-than-twofold relative increase. These events were generally mild, responded to standard antifungal therapy, and rarely caused treatment discontinuation.

The combined safety result (RR 1.12; 95% CI 0.90–1.38) indicates no increased risk of total side effects with SGLT2 inhibitors. In conclusion; this forest plot shows SGLT2 inhibitors significantly reduce cardiovascular and renal morbidity in hypertensive non-diabetic populations. There is an overall 28% relative reduction in major outcomes. The safety profile is generally favourable, with no meaningful increase in serious adverse events. Genital mycotic infections are the main adverse effect but are typically mild and manageable. Overall, the evidence supports a favourable benefit–risk profile for SGLT2 inhibitors in appropriately selected hypertensive patients with cardiovascular or renal disease.

Proteinuria as a target therapy in hypertensive patients with or without diabetes:

Proteinuria, especially albuminuria, is a key therapeutic target in hypertension-associated chronic kidney disease (CKD) because it indicates damage to kidney filters (glomeruli) and helps predict poor kidney outcomes [46]. Elevated urinary protein excretion signals a disrupted glomerular filtration barrier, commonly caused by hypertension that damages kidney tissues. Specifically, high blood pressure can injure the endothelium, damage podocytes, and raise intraglomerular pressure, thereby increasing protein leak [46]. Observational studies show that as albuminuria increases, so does the risk of CKD progression, end-stage kidney disease (ESKD), cardiovascular events, and all-cause mortality, independent of baseline estimated glomerular filtration rate (eGFR) [46]. The Chronic Kidney Disease Prognosis Consortium reported that higher albuminuria levels directly correspond to much higher risks of kidney failure and death throughout various patient groups [47].

Proteinuria is more than simply a marker of kidney injury; it also directly drives disease progression. Studies show that excessive protein filtration into the tubular lumen triggers activation of inflammatory, oxidative, and profibrotic pathways, which in turn promote tubulointerstitial fibrosis and progressive nephron loss (48). As a result, reducing proteinuria serves as a validated surrogate marker of renoprotection and has become a major therapeutic objective in managing hypertensive CKD. The DAPA-CKD trial (13) reported sub-

stantial reductions in albuminuria, accompanied by a 39% relative risk reduction in the composite outcome of sustained eGFR decline, ESKD, or renal/cardiovascular death, suggesting that reductions in albuminuria may have contributed to improved outcomes. Similarly, the EMPA-KIDNEY trial [26] found that reducing albuminuria was associated with preserved kidney function and slower CKD progression in patients with and without diabetes, pointing to a possible causal relationship between reductions in albuminuria and clinical benefits.

Guidelines recommend screening proteinuria in hypertensive non-diabetic: Clinical guidelines recommend screening for protein in the urine in people with high blood pressure. This is because it signals early kidney damage, higher heart risk, and early organ problems. Finding protein in the urine early helps diagnose kidney disease sooner, better assess heart risk, and start kidney-protecting treatments quickly.

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (34) recommend routine assessment of albuminuria using the urine albumin-to-creatinine ratio (uACR) in individuals at increased risk of CKD, including those with hypertension. CKD classification is based on both estimated glomerular filtration rate (eGFR) and albuminuria categories (A1–A3). Notably, persistent albuminuria over 30 mg/g is clinically significant and linked to greater risk of CKD progression and cardiovascular events. In addition, KDIGO [34] recommends annual screening in hypertensive patients, especially those with diabetes, established cardiovascular disease, or impaired renal function. Similarly, the American Heart Association (AHA) and the American College of Cardiology (ACC) [35] recognize proteinuria as evidence of hypertension-mediated target-organ damage. In line with this, the 2017 ACC/AHA [36] hypertension guideline recommends a baseline laboratory evaluation for all patients with newly diagnosed hypertension. Specifically, this includes urinalysis and assessment of albuminuria when CKD is suspected. Furthermore, screening is particularly emphasized in patients with resistant or long-standing hypertension and in those at elevated cardiovascular risk.

The European Society of Cardiology (ESC) [37] and the European Society of Hypertension (ESH) [37] also advocate routine assessment of urinary protein in hypertensive populations. In the 2023 ESH guideline, albuminuria is highlighted as a key marker of asymptomatic organ damage. Specifically, the guideline recommends uACR measurement over dipstick testing because uACR is more sensitive for detecting low-grade albuminuria. This low-grade albuminuria carries prognostic relevance even when overt renal dysfunction is absent. Therefore, periodic reassessment is advised, especially in patients with uncontrolled blood pressure or established CKD. The National Institute for Health and Care Excellence (NICE) guideline (38) also recommends urine testing for protein or albumin in all adults evaluated for hypertension. If dipstick proteinuria is detected, a quantitative ACR measurement is advised. When significant proteinuria is present, this should prompt further nephrological evaluation and may also influence antihypertensive selection, particularly the use of renin–angiotensin system inhibitors, such as ACE inhibitors or angiotensin receptor blockers.

Clinically, proteinuria has important therapeutic implications, as its presence frequently guides the selection of agents with proven renoprotective effects. These include ACE inhibitors, ARBs, and, increasingly, sodium–glucose cotransporter-2 (SGLT2) inhibitors such as empagliflozin and dapagliflozin in patients with CKD. Furthermore, even low-grade albuminuria independently predicts cardiovascular mortality, stroke, and progression to kidney failure. This marks its combined role as both a diagnostic and therapeutic target. Despite strong guideline recommendations, screening rates in routine practice remain low [49]. Reasons include low awareness, inconsistent use of urine tests, and continued use of less-sensitive dipsticks. But newer guidance stresses measuring protein in urine with numbers, as this helps start treatment earlier and better protect organs.

Therefore, clinicians should actively screen hypertensive patients for proteinuria, in line with major international guidelines, as this is essential to cardiovascular and renal risk assessment. Early detection of albuminuria improves prognosis through timely, targeted, and individualized management strategies, stressing the importance of routine screening in clinical practice.

Critical Appraisal of Guideline Recommendations for Screening Proteinuria in Hypertensive Non-Diabetic Patients

Current clinical practice guidelines, including those from kidney disease: Improving Global Outcomes (KDIGO) [39], the International Society of Hypertension (ISH) [39], and the European Society of Cardiology (ESC) [40], consistently recommend that patients with hypertension without diabetes undergo routine assessment of proteinuria, preferably using the urine albumin-to-creatinine ratio (uACR). The key recommendation is to screen for albuminuria in this population due to strong evidence linking it to higher risks of chronic kidney disease (CKD) progression, cardiovascular events, and mortality. However, critical appraisal shows both strong prognostic evidence and shortcomings in clinical intervention and implementation. A major strength of these recommendations lies in consistent findings from large prospective cohort studies and meta-analyses [34,39-40]. These studies show that even low-grade albuminuria independently predicts cardiovascular and renal outcomes, beyond classic risk factors and estimated glomerular filtration rate (eGFR). The prognostic value of albuminuria is reinforced by its incorporation into modern CKD classification systems. This indicates its role as a marker of both renal structural injury and systemic endothelial dysfunction.

Importantly, randomized controlled trials (RCTs) indirectly support the clinical utility of identifying patients with albuminuria, although most were not designed as screening trials. Trials of renin–angiotensin system (RAS) blockade, such as the HOPE study [41] and the RENAAL/IDNT program [42-43], included broader high-risk populations. These studies showed that reductions in albuminuria are associated with better renal and cardiovascular outcomes. More recently, large SGLT2 inhibitor trials, such as DAPA-CKD (13) and EMPA-KIDNEY [26], showed significant reductions in kidney disease progression and cardiovascular events in CKD patients, including those without diabetes. In these trials, albuminuria functioned as both an inclusion criterion and a marker of therapeutic response. Together, these findings support the clinical value of detecting proteinuria for targeting therapy. Despite these strengths, important boundaries persist. First, no randomized trials have directly evaluated “screening versus no screening” strategies for proteinuria in hypertensive non-diabetic populations, limiting causal inference regarding screening itself. Second, heterogeneity in guideline recommendations regarding screening frequency, thresholds, and target populations indicates continuing uncertainty about optimal implementation. Third, albuminuria is biologically variable and subject to measurement fluctuation, which may lead to misclassification and overdiagnosis if based on single samples. Fourth, evidence on cost-effectiveness remains limited, particularly in low- and middle-income settings where universal screening may be challenging.

Real-world data consistently show that guideline-recommended screening is poorly implemented. This suggests that system-level and structural barriers, instead of evidence alone, limit uptake. To summarize, guidelines for proteinuria screening in hypertensive non-

diabetic patients are strongly supported by observational and therapeutic evidence. However, lack of direct screening trials, implementation variability, and economic risks remain, illustrating the need for further implementation and health-economic studies.

Conclusion

Sodium–glucose cotransporter-2 (SGLT2) inhibitors have evolved from glucose-lowering agents into pleiotropic therapies. They now have established cardiovascular- and renal-protective effects. In hypertensive patients without diabetes mellitus, accumulating evidence shows clinically relevant benefits that go beyond glycaemic modulation. This supports the potential repositioning of these agents as disease-modifying treatments in cardiometabolic and renal therapeutics. In randomized controlled trials and pooled analyses, SGLT2 inhibitors consistently reduce blood pressure, improve arterial compliance, and favourably modulate intraglomerular hemodynamic. These physiological effects are linked to fewer heart failure hospitalizations, slower decline of kidney function, and better composite cardiorenal outcomes. These benefits include non-diabetic populations. Notably, benefits are consistent across subgroups stratified by baseline renal function and proteinuria status. This suggests a class effect independent of glycaemic control.

Important limitations remain; most evidence comes from post-hoc or subgroup analyses of trials designed for diabetic or heart failure cohorts. Few dedicated randomized controlled trials focus on hypertensive, non-diabetic populations but long-term safety data for this group are still insufficient. SGLT2 inhibitors are a beneficial therapeutic advance for hypertensive patients without diabetes. They offer clinically meaningful cardiorenal protection over blood pressure reduction. Larger, dedicated trials are needed to confirm these outcomes, adjust patient selection, and define the role of SGLT2 inhibitors in the management of hypertension.

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