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Changes in Systolic and Diastolic Blood Pressure Following SGLT2 Therapy in Diabetic Patients with Kidney Impairment

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ABSTRACT

Background: Blood pressure reduction is an early hemodynamic response to sodium–glucose cotransporter-2 (SGLT2) inhibitors, although its magnitude varies among patients. This study evaluated clinical factors associated with blood pressure response following SGLT2 inhibitor therapy in patients with type 2 diabetes mellitus (T2DM) and kidney impairment. Methods: A retrospective cohort study was conducted using electronic medical records from two secondary healthcare centers. A total of 254 patients received SGLT2 inhibitor monotherapy (n=119), metformin monotherapy (n=124), or combination therapy (n=11). Demographic, clinical, laboratory, and blood pressure data were collected at baseline and follow-up. Blood pressure changes were assessed using the Wilcoxon signed-rank test and compared among treatment groups using the Kruskal–Wallis test. Spearman correlation and multiple linear regression were used to identify factors associated with ΔSBP and ΔDBP. Results: Median SBP decreased from 145.0 (IQR 27) to 129.5 (IQR 26) mmHg, with a median change of −15.5 mmHg (P<0.001). Median DBP decreased from 90.0 (IQR 16) to 80.0 (IQR 12) mmHg, with a median change of −10.0 mmHg (P<0.001). Greater blood pressure reductions were observed among patients receiving SGLT2 inhibitor monotherapy (both P<0.001). Age, diabetes duration, HbA1c change, and triglyceride change were associated with ΔSBP, while age and diabetes duration were associated with ΔDBP. Short-term eGFR changes were not independently associated with either outcome. Conclusions: SGLT2 inhibitor therapy was associated with reductions in blood pressure. Blood pressure response was associated mainly with patient-specific clinical and metabolic characteristics rather than short-term changes in kidney function.

Keyword: *Sodium–glucose cotransporter-2 inhibitors; Blood pressure response; Type 2 diabetes mellitus; Chronic kidney disease*

Introduction

Type 2 diabetes mellitus (T2DM) is a major global health challenge because of its rapidly increasing prevalence and substantial burden of chronic complications. Among these, chronic kidney disease (CKD) is particularly important as it markedly increases the risks of kidney failure, cardiovascular events, hospitalization, and premature mortality. Consequently, diabetes management has evolved from a glucose-centered approach toward comprehensive cardiorenal protection. Reflecting this paradigm, the American Diabetes Association Standards of Care in Diabetes 2025 recommends sodium–glucose cotransporter-2 (SGLT2) inhibitors for patients with T2DM and CKD or those at high cardiovascular risk regardless of baseline glycated hemoglobin (HbA1c), based on robust evidence demonstrating

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reductions in kidney disease progression, heart failure hospitalization, and cardiovascular events.(ElSayed et al., 2025a; Perkovic et al., 2019).

Hypertension is a major determinant of CKD progression in T2DM. Progressive kidney dysfunction promotes sodium retention, endothelial dysfunction, and neurohormonal activation, whereas persistent hypertension accelerates glomerular injury and decline in kidney function. This reciprocal interaction makes blood pressure control a cornerstone of cardiorenal management in patients with T2DM and CKD. (Stevens et al., 2024; Tikkanen et al., 2015). Although SGLT2 inhibitors consistently improve kidney and cardiovascular outcomes across the spectrum of CKD, including advanced disease. (Chertow et al., 2021). accumulating evidence suggests that blood pressure reduction represents one of their earliest and most clinically relevant therapeutic effects.

The antihypertensive effects of SGLT2 inhibitors extend beyond glucose lowering. By inhibiting sodium and glucose reabsorption in the proximal renal tubule, these agents induce natriuresis, osmotic diuresis, and restoration of tubuloglomerular feedback, leading to reduced intraglomerular pressure and improved renal autoregulation. Experimental and clinical studies further demonstrate improvements in endothelial function, arterial stiffness, sympathetic nervous system activity, and vascular resistance, indicating that blood pressure reduction results from integrated cardiovascular and renal hemodynamic adaptations rather than diuresis alone. (Heerspink et al., 2024). Mechanistic studies, including DAPASALT, have also shown that these early hemodynamic changes occur without sustained neurohormonal activation, supporting the concept that SGLT2 inhibitors restore physiological volume and sodium homeostasis rather than inducing persistent fluid depletion. (Beernink et al., 2025).

Despite these well-established mechanisms, the magnitude of blood pressure reduction following SGLT2 inhibitor therapy varies considerably among patients. Clinical studies, including EMPA-REG MET, SACRA, and DAPA-CKD, consistently demonstrated significant reductions in systolic blood pressure while simultaneously preserving kidney function; however, substantial interindividual variability in treatment response remained despite standardized therapy(Beernink et al., 2025; Inzucchi et al., 2021; Lim et al., 2026; Okada et al., 2021). (These findings suggest that blood pressure response is influenced not only by the pharmacological effects of SGLT2 inhibition but also by patient-specific clinical characteristics and physiological adaptation.

Although previous studies have established the efficacy of SGLT2 inhibitors and elucidated several hemodynamic mechanisms, they have largely focused on average treatment effects rather than identifying the clinical determinants underlying interindividual variability in blood pressure response. Consequently, evidence remains limited regarding which patients are most likely to experience

greater blood pressure reduction following SGLT2 inhibitor therapy in routine clinical practice. Therefore, this study aimed to identify the clinical determinants of blood pressure response in patients with T2DM and CKD receiving SGLT2 inhibitor therapy by integrating baseline clinical characteristics with blood pressure outcomes. We hypothesized that patient-specific clinical characteristics, rather than the pharmacological effects of SGLT2 inhibition alone, contribute substantially to the variability in blood pressure response. Identifying these determinants may improve patient stratification and support individualized cardiorenal management.

Methods

1.1 Study Design

This study employed a retrospective observational study using routinely collected electronic medical records to evaluate the determinants of blood pressure change among patients with type 2 diabetes mellitus (T2DM) and kidney impairment receiving sodium–glucose cotransporter-2 (SGLT2) inhibitor therapy. A retrospective observational design was selected because it allows the assessment of treatment responses under real-world clinical practice, where therapeutic decisions are made according to routine medical care rather than protocol-driven interventions. This design is particularly appropriate for evaluating the heterogeneous hemodynamic responses associated with SGLT2 inhibitors in a representative clinical population. Unlike randomized controlled trials that primarily evaluate treatment efficacy under highly controlled conditions, real-world observational studies provide valuable evidence regarding treatment effectiveness, patient variability, and factors associated with clinical outcomes in routine practice. Because the objective of the present study was to identify clinical determinants associated with blood pressure reduction rather than to establish treatment efficacy, an observational design was considered the most appropriate methodological approach. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for reporting observational research. All analyses were conducted using retrospectively collected data without influencing clinical management or therapeutic decisions during the study period.

1.3 Study Setting and Data Source

The study was conducted using routinely collected electronic medical records from two tertiary referral hospitals in East Kalimantan, Indonesia. Both institutions provide specialized outpatient care for patients with type 2 diabetes mellitus (T2DM), including multidisciplinary management of diabetes-related kidney disease and cardiovascular complications. These hospitals were selected because they maintain comprehensive electronic medical record systems containing longitudinal clinical information, laboratory investigations, medication histories,

and follow-up data required for evaluating treatment responses following initiation of sodium–glucose cotransporter-2 (SGLT2) inhibitor therapy.

Patient records from January 2020 through December 2025 were screened to identify eligible individuals receiving routine outpatient care. This study utilized retrospectively collected clinical information recorded during routine medical practice; therefore, no additional investigations, interventions, or follow-up visits were performed specifically for research purposes. Data extraction was conducted after obtaining institutional permission using a standardized data collection form developed for this study to ensure consistency and completeness across participating centers.

The electronic medical records provided comprehensive information on demographic characteristics, medical history, comorbidities, antihyperglycemic therapy, concomitant medications, laboratory parameters, and serial blood pressure measurements. Variables extracted included age, sex, duration of diabetes, history of hypertension and cardiovascular disease, type and duration of SGLT2 inhibitor therapy, concomitant use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics, insulin, and lipid-lowering agents. Laboratory variables included glycated hemoglobin (HbA1c), estimated glomerular filtration rate (eGFR), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride concentrations measured before treatment initiation and during follow-up. Blood pressure measurements recorded during routine outpatient visits were retrieved to evaluate changes in systolic and diastolic blood pressure after initiation of SGLT2 inhibitor therapy.

To preserve patient confidentiality, all identifiable information was removed before analysis. Individual patients were assigned unique study identification numbers, and the anonymized dataset was accessible only to authorized investigators. Because the study was based exclusively on retrospective medical records, no direct patient contact occurred during data collection.

1.4 Study Population and Eligibility Criteria

The study population comprised adult patients with type 2 diabetes mellitus (T2DM) and kidney impairment who received outpatient care at two tertiary referral hospitals in East Kalimantan, Indonesia, during the study period. Eligible participants were identified retrospectively from electronic medical records using a consecutive sampling approach, whereby all patients meeting the predefined eligibility criteria within the study period were considered for inclusion. This approach was selected to minimize selection bias and to ensure that the study population reflected routine clinical practice.

Patients were eligible for inclusion if they met the following criteria: (1) were aged ≥18 years; (2) had a confirmed diagnosis of T2DM according to the treating physician's clinical assessment documented in the medical records; (3) had evidence

of kidney impairment documented before initiation of therapy; (4) received treatment with an SGLT2 inhibitor either as monotherapy or in combination with metformin, or received metformin monotherapy as the comparator group; and (5) had complete baseline and follow-up clinical records, including blood pressure measurements and relevant laboratory parameters required for analysis. To ensure reliable assessment of treatment response, only patients with paired pre-treatment and follow-up evaluations were included in the final analysis.

Patients were excluded if they had incomplete clinical records, missing baseline or follow-up blood pressure measurements, insufficient laboratory data for outcome assessment, or received renal replacement therapy before study entry. Individuals with documented adverse events leading to early discontinuation of treatment before outcome assessment or those with insufficient follow-up duration to evaluate blood pressure changes were also excluded. These criteria were applied to maximize data completeness and reduce potential information bias inherent to retrospective observational studies. Following application of the eligibility criteria, 254 patients were included in the final analytical cohort. All participants contributed complete clinical information required for the predefined analyses, including demographic characteristics, medical history, pharmacological treatment, laboratory measurements, and serial blood pressure recordings obtained during routine outpatient follow-up.

1.5 Exposure Assessment

The primary exposure of interest was treatment with sodium–glucose cotransporter-2 (SGLT2) inhibitors prescribed during routine outpatient care. Patients were categorized according to the antihyperglycemic regimen documented at treatment initiation, including SGLT2 inhibitor monotherapy, SGLT2 inhibitor combined with metformin, and metformin monotherapy, the latter serving as the comparator group. Treatment allocation reflected routine clinical decision-making by the attending physicians and was not influenced by the study protocol. Consequently, the present investigation evaluated therapeutic responses under real-world clinical practice rather than under randomized experimental conditions.

For each participant, the type of SGLT2 inhibitor, treatment duration, and concomitant pharmacological therapy were extracted from the electronic medical records. Particular attention was given to medications with potential effects on blood pressure regulation, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics, calcium channel blockers, beta-blockers, insulin, and lipid-lowering agents. These medications were considered potential confounding variables and were incorporated into the multivariable analysis where appropriate. Because antihypertensive medications may modify the magnitude of blood pressure reduction independently of SGLT2 inhibition, their use was carefully documented during data extraction to facilitate

adjustment for baseline clinical characteristics. Treatment duration was calculated as the interval between initiation of SGLT2 inhibitor therapy and the follow-up clinical evaluation used for outcome assessment. Only patients with complete information regarding medication exposure and paired baseline and follow-up assessments were included in the final analysis.

1.6 Outcome Measures

The primary outcome of this study was the change in systolic blood pressure (ΔSBP) following initiation of SGLT2 inhibitor therapy. Systolic blood pressure was selected as the principal outcome because it represents one of the earliest and most clinically relevant manifestations of the systemic hemodynamic effects of SGLT2 inhibitors and has consistently been associated with cardiovascular and renal outcomes in previous clinical studies. Blood pressure measurements recorded during routine outpatient visits before treatment initiation and at follow-up were retrieved from the electronic medical records. The change in systolic blood pressure was calculated as the difference between follow-up and baseline values, with negative values indicating a reduction following treatment.

The secondary outcome was the change in diastolic blood pressure (ΔDBP), calculated using the same approach. Evaluation of both systolic and diastolic blood pressure enabled comprehensive assessment of the hemodynamic response to SGLT2 inhibitor therapy while maintaining systolic blood pressure as the primary endpoint of interest.

To explore determinants of blood pressure response, several predefined clinical variables were evaluated as potential explanatory factors. These included demographic characteristics (age and sex), duration of diabetes mellitus, baseline systolic and diastolic blood pressure, estimated glomerular filtration rate (eGFR), glycated hemoglobin (HbA1c), lipid profile (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), treatment duration, and concomitant pharmacological therapy. These variables were selected based on biological plausibility, previous mechanistic studies, and evidence suggesting their potential influence on systemic and intrarenal hemodynamic adaptation during SGLT2 inhibitor therapy.

Unlike previous studies that primarily evaluated renal or glycemic outcomes, the present study specifically focused on identifying the clinical determinants associated with interindividual variability in blood pressure change following SGLT2 inhibitor therapy. Therefore, laboratory parameters such as HbA1c, eGFR, and lipid profile were analyzed as clinical covariates rather than primary outcomes, allowing assessment of their contribution to the magnitude of blood pressure response.

1.7 Clinical Variables and Operational Definitions

Demographic and clinical characteristics were extracted from the electronic medical records using a standardized data collection form. Baseline variables included age, sex, duration of type 2 diabetes mellitus (T2DM), history of hypertension, documented cardiovascular comorbidities, and antihyperglycemic treatment regimen. Clinical information regarding concomitant medications with potential hemodynamic effects, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), diuretics, calcium channel blockers, beta-blockers, insulin, and lipid-lowering agents, was also recorded because these therapies may influence blood pressure independently of SGLT2 inhibitor treatment.

Baseline kidney function was evaluated using the estimated glomerular filtration rate (eGFR) documented in the medical records. Glycemic status was assessed using glycated hemoglobin (HbA1c), while lipid metabolism was characterized using low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride concentrations. These laboratory parameters were obtained from routine clinical examinations performed before initiation of therapy and at follow-up according to routine outpatient practice. Because the primary objective of the present study was to identify determinants of blood pressure change, these laboratory variables were treated as potential explanatory variables (clinical covariates) rather than study outcomes.

Blood pressure measurements were obtained from routine outpatient visits as documented in the electronic medical records. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) recorded immediately before initiation of SGLT2 inhibitor therapy were considered baseline values, whereas the corresponding measurements obtained during follow-up represented post-treatment values. Changes in blood pressure were calculated for each participant as the difference between follow-up and baseline measurements. Accordingly, changes in systolic blood pressure (ΔSBP) and diastolic blood pressure (ΔDBP) served as indicators of the individual hemodynamic response to treatment.

To improve the interpretability of the multivariable analysis, baseline SBP and DBP were retained as independent clinical variables in addition to ΔSBP and ΔDBP. This approach enabled evaluation of whether the magnitude of blood pressure reduction was influenced by pretreatment blood pressure levels while simultaneously accounting for other demographic, renal, metabolic, and therapeutic characteristics.

Treatment duration was defined as the interval between initiation of SGLT2 inhibitor therapy and the follow-up evaluation included in the analysis. The duration of exposure was calculated using prescription records and follow-up dates documented in the electronic medical records. Only participants with complete

paired baseline and follow-up clinical assessments were included to ensure accurate estimation of longitudinal changes in blood pressure and other clinical parameters.

1.8 Statistical Analysis

All statistical analysis were performed using IBM SPSS Statistics for Mac, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were initially evaluated for normality using the Shapiro–Wilk test. Normally distributed variables were presented as mean ± standard deviation (SD), whereas non-normally distributed variables were expressed as median and interquartile range (IQR). Categorical variables were summarized as frequencies and percentages. Baseline demographic and clinical characteristics were compared descriptively among treatment groups. For normally distributed continuous variables, comparisons were performed using the independent-samples t-test or one-way analysis of variance (ANOVA), whereas the Mann–Whitney U test or Kruskal–Wallis test was applied for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Changes in systolic blood pressure (ΔSBP) and diastolic blood pressure (ΔDBP) between baseline and follow-up were evaluated using paired statistical tests according to data distribution. The paired t-test was used for normally distributed variables, whereas the Wilcoxon signed-rank test was applied for non-normally distributed variables. The primary outcome of the study was the change in systolic blood pressure (ΔSBP), while the change in diastolic blood pressure (ΔDBP) was evaluated as a secondary outcome.

To identify variables potentially associated with blood pressure response following SGLT2 inhibitor therapy, univariate analyses were first performed using Spearman's rank correlation coefficient, as several continuous variables were not normally distributed. Variables demonstrating statistical significance in the univariate analyses ($p < 0.05$), together with variables considered clinically relevant based on the literature and biological plausibility, were subsequently entered into a multiple linear regression model to identify independent determinants of changes in systolic blood pressure following SGLT2 inhibitor therapy. Candidate predictors included age, sex, duration of diabetes mellitus, baseline systolic blood pressure, estimated glomerular filtration rate (eGFR), glycated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride concentration, duration of SGLT2 inhibitor therapy, treatment regimen, and concomitant antihypertensive medications. Regression coefficients (β), 95% confidence intervals (95% CI), and corresponding *p*-values were reported to quantify the magnitude and direction of the observed associations. Before interpretation of the regression model, the assumptions of linear regression were evaluated. Multicollinearity among independent variables was assessed using the variance

inflation factor (VIF) and tolìerancìe statistics. Linìearity, homoscìedasticity, and normality of rìesiduals wìerìe ìexaminìed through rìesidual diagnostic plots. A two-sidìed p valuìe of < 0.05 was considìerìed statistically significant for all analysìes.

1.9 Ethical Considìerations

Thìe study protocol was grantìed ìethical ìexìemption by thìe Hìealth Rìesìearch Ethics Committtìeìe of Dr. Kanujoso Djatiwibowo Rìegional Hospital, Indonìesia, undìer Ethical Exìemption No. 43/KEPK-RSKD/IX-2025**.** Thìe ìethical ìexìemption was issuìed on 6 Novìembìer 2025 and rìemainìed valid until 6 Novìembìer 2026**.** According to thìe Ethics Committtìeìe, thìe study fulfillìed thìe ìethical rìequirìemìents basìed on thìe WHO 2011 Standards and thìe Council for Intìernational Organizations of Mìedical Sciìencìes (CIOMS) 2016 Intìernational Ethical Guidìelinìes, including sciìentific mìerit, ìequitablìe assìessmìent of risks and bìenìefits, confidìentiality and privacy, and protìection of participants' rights. This rìetrospìectivìe obsìervational study was conductìed using anonymizìed ìelìectronic mìedical rìecords collìectìed during routinìe clinical carìe. All pìersonal idìentifiìers wìerìe rìemovìed bìeforìe data ìextraction and analysis to ìensurìe patiìent confidìentiality and data sìecurity. Thìe study involvìed no dirìect patiìent contact and no intìervìention bìeyond routinìe clinical practicìe. All study procìedurìes wìerìe conductìed in accordancìe with thìe ìethical principlìes of thìe Dìeclaration of Hìelsinki and applicablìe institutional rìegulations govìerning rìesìearch involving human participants.

Results

A total of 254 patiìents with typìe 2 diabìetìes mìellitus (T2DM) and kidnìey impairmìent fulfillìed thìe ìeligibility critìeria and wìerìe includìed in thìe final analysis. Following systìematic data clìeaning and quality assìessmìent, no missing data wìerìe idìentifiìed for thìe variablìes includìed in thìe prìedìefinìed analysìes. Logical rangìe chìecking idìentifiìed sìevìeral mild outliìers; howìevìer, all obsìervations rìemainìed biologically plausiblìe and wìerìe rìetainìed in thìe final datasìet. Thìe prìedìefinìed minimum samplìe sizìe rìequirìed for adìequatìe statistical powìer was achiìevìed, ìensuring sufficiìent powìer to ìevaluatìe thìe dìetìerminants of blood prìessurìe changìe following SGLT2 inhibitor thìerapy. Basìelinìe dìemographic and clinical charactìeristics of thìe study population, stratifiìed according to trìeatmìent group, arìe prìesìentìed in Tablìe 1**.**

1.1 Patiìent Charactìeristics

Thìe basìelinìe dìemographic and clinical charactìeristics of thìe study population arìe summarizìed in Tablìe 1**.** Among thìe 254 participants, 124 patiìents (48.8%) rìecìeivìed mìetformin monothìerapy, 119 (46.9%) rìecìeivìed SGLT2 inhibitor monothìerapy, and 11 (4.3%) rìecìeivìed combination thìerapy with an SGLT2 inhibitor and mìetformin. Thìe mìetformin and SGLT2 inhibitor groups wìerìe

rìelativìely balancìed in sizìe, whìerìeas thìe combination thìerapy group rìeprìesìentìed a substantially smallìer proportion of thìe study population.

Tablìe 1. Basìelinìe Charactìeristics of Patiìents with Typìe 2 Diabìetìes Mìellitus and Kidnìey Impairmìent According to Trìeatmìent Group

Charactìeristic	Ovìerall (n=254)	SGLT2 inhibitor (n=119)	SGLT2 inhibitor + Mìetformin (n=11)	Mìetformin (n=124)	P valuìe*
Dìemographic charactìeristics					
Agìe, yìears, mìedian (IQR)	56 (51–63)	56 (51–63)	56 (51–63)	56 (51–63)	**>0.05****
Malìe sìex, n (%)	150 (59.1)	74 (62.2)	4 (36.4)	72 (58.1)	**0.238***
Fìemalìe sìex, n (%)	104 (40.9)	45 (37.8)	7 (63.6)	52 (41.9)	
Duration of diabìetìes, yìears, mìedian (IQR)	2 (1–4)	2 (1–4)	1 (1–2)	1 (1–4)	**0.025****
Trìeatmìent duration, days, mìedian (IQR)	190 (121–301)	190 (121–301)	190 (121–301)	190 (121–301)	**0.962****
Clinical charactìeristics					
Basìelinìe HbA1c (%), mìedian (IQR)	8.0 (3)	—	—	—	—
Basìelinìe ìeGFR (mL/min/1.73m²), mìedian (IQR)	80 (46)	—	—	—	—
Basìelinìe systolic blood prìessurìe (mmHg), mìedian (IQR)	145 (27)	—	—	—	—
Basìelinìe diastolic blood prìessurìe (mmHg), mìedian (IQR)	90 (16)	—	—	—	—

* Chi Squarìe; ** kruskal walis

Tablìe 1 prìesìents thìe basìelinìe dìemographic and clinical charactìeristics of thìe study population according to trìeatmìent group**.** Thìe ovìerall mìedian agìe was 56 yìears (IQR, 51–63 yìears), with 150 patiìents (59.1%) bìeing malìe. Thìe mìedian duration of diabìetìes was 2 yìears (IQR, 1–4 yìears), and thìe mìedian trìeatmìent duration was 190 days (IQR, 121–301 days). Basìelinìe dìemographic charactìeristics wìerìe gìenìerally comparablìe across trìeatmìent groups. Agìe (P > 0.05), sìex

distribution (P = 0.238), and trìeatmìent duration (P = 0.962) did not diffìer significantly among trìeatmìent groups, whìerìeas diabìetìes duration diffìerìed modìestly (P = 0.025). Ovìerall basìelinìe clinical mìeasurìemìents indicatìed uncontrollìed blood prìessurìe and kidnìey impairmìent bìeforìe trìeatmìent initiation, with mìedian systolic and diastolic blood prìessurìes of 145 and 90 mmHg, rìespìectivìely, a mìedian HbA1c of 8.0%, and a mìedian ìeGFR of 80 mL/min/1.73 m². No casìes of ìend-stagìe kidnìey disìeasìe or trìeatmìent-rìelatìed advìersìe drug rìeactions wìerìe documìentìed during thìe study pìeriod.

1.2 Changìes in Blood Prìessurìe Following SGLT2 Inhibitor Thìerapy

Tablìe 2. Changìes in Blood Prìessurìe Following SGLT2 Inhibitor Thìerapy

Variablìe	Basìelinìe Mìedian (IQR)	Follow-up Mìedian (IQR)	Mìedian Changìe	p valuìe*
Systolic blood prìessurìe (mmHg)	145.0 (27)	129.5 (26)	−15.5	<0.001*
Diastolic blood prìessurìe (mmHg)	90.0 (16)	80.0 (12)	−10.0	<0.001*

*Wilcoxon signìed-rank tìest.

Thìe primary outcomìe of thìe study was thìe changìe in blood prìessurìe following trìeatmìent. As shown in Tablìe 2, significant rìeductions wìerìe obsìervìed in both systolic and diastolic blood prìessurìe aftìer thìerapy. Thìe mìedian systolic blood prìessurìe dìecrìeasìed from 145 mmHg (IQR, 27) at basìelinìe to 129.5 mmHg (IQR, 26) at follow-up, corrìesponding to a mìedian rìeduction of 15.5 mmHg (P < 0.001). Similarly, thìe mìedian diastolic blood prìessurìe dìecrìeasìed from 90 mmHg (IQR, 16) to 80 mmHg (IQR, 12), rìeprìesìenting a mìedian rìeduction of 10.0 mmHg (P < 0.001). A rìeduction in systolic blood prìessurìe was obsìervìed in all 254 participants (100%), whìerìeas 230 patìients (90.6%) ìexpìerììencìed a rìeduction in diastolic blood prìessurìe. Convìersìely, no patìient dìemonstratìed an incrìeasìe in systolic blood prìessurìe, whilìe 24 patìients (9.4%) showìed an incrìeasìe in diastolic blood prìessurìe during follow-up. Thìesìe findings indicatìe that SGLT2 inhibitor-basìed thìerapy was associatìed with a consistìent rìeduction in systolic blood prìessurìe and a substantial rìeduction in diastolic blood prìessurìe in patìients with typìe 2 diabìetìes mìellitus and kidnìey impairmìent.

1.3 Comparison of Blood Prìessurìe Rìesponsìes Across Trìeatmìent Groups

Tablìe 3. Comparison of Blood Prìessurìe Rìesponsìes Across Trìeatmìent Groups

Outcomìe	SGLT2 inhibitor	SGLT2 inhibitor + Mìetformin	Mìetformin	Kruskal–Wallis H	*P* valuìe*
ΔSBP (Mìean Rank)	149.40	94.73	109.39	20.349	**<0.001***
ΔDBP (Mìean Rank)	160.29	95.86	98.84	44.999	**<0.001***

* Kruskal–Wallis H

Thìe magnitudìe of blood prìessurìe rìeduction diffìerìed significantly among thìe thrìeìe trìeatmìent groups (Tablìe 3). Kruskal–Wallis analysis dìemonstratìed significant bìetwìeìen-group diffìerìencìes for both systolic blood prìessurìe changìe (ΔSBP; H = 20.349, $P < 0.001$) and diastolic blood prìessurìe changìe (ΔDBP; H = 44.999, $P < 0.001$). Mìean-rank analysis indicatìed that patiìents rìecìeiving SGLT2 inhibitor monothìerapy ìexhibitìed thìe grìeatìest rìeduction in both systolic and diastolic blood prìessurìe (mìean rank = 149.40 for ΔSBP and 160.29 for ΔDBP). In contrast, participants rìecìeiving combination thìerapy with SGLT2 inhibitors and mìetformin showìed thìe lowìest mìean ranks for blood prìessurìe rìeduction (94.73 and 95.86, rìespìectivìely), whìerìeas thìe mìetformin monothìerapy group dìemonstratìed intìermìediatìe rìesponsìes (109.39 and 98.84, rìespìectivìely). Thìesìe findings suggìest that trìeatmìent with SGLT2 inhibitors was associatìed with a grìeatìer blood prìessurìe-lowìering ìeffìect than mìetformin monothìerapy in this study population.

1.4 Corrìelation Bìetwìeìen Clinical Variablìes and Changìes in Blood Prìessurìe

Tablìe 4. Spìearman Corrìelation Bìetwìeìen Clinical Variablìes and Changìes in Blood Prìessurìe

Variablìe	ΔSBP (*r*)	*P* valuìe	ΔDBP (*r*)	*P* valuìe*
Dìemographic charactìeristics				
Agìe	−0.300	<0.001	−0.362	**<0.001***
Duration of diabìetìes	0.319	<0.001	−0.194	**0.002***
Trìeatmìent duration	0.096	0.126	0.053	0.401
Mìetabolic and rìenal paramìetìers				
ΔHbA1c	0.249	<0.001	0.078	0.214
%ΔìeGFR	−0.267	<0.001	−0.130	**0.038***
ΔTriglycìeridìes	−0.473	<0.001	0.071	0.262
ΔLDL-C	−0.015	0.808	0.024	0.703
ΔHDL-C	−0.105	0.096	−0.016	0.801

*Spìearman's rank corrìelation analysis was usìed to ìevaluatìe thìe association bìetwìeìen clinical variablìes and changìes in systolic (ΔSBP) and diastolic blood prìessurìe (ΔDBP).

To idìentify potìential dìetìerminants of blood prìessurìe rìesponsìe following SGLT2 inhibitor thìerapy, Spìearman corrìelation analysìes wìerìe pìerformìed bìetwìeìen dìemographic charactìeristics, trìeatmìent-rìelatìed variablìes, mìetabolic paramìetìers, kidnìey function, and changìes in systolic and diastolic blood prìessurìe. Thìe rìesults arìe summarizìed in Tablìe 4. For systolic blood prìessurìe, significant corrìelations wìerìe obsìervìed with agìe (r = −0.300, P < 0.001), duration of diabìetìes (r = 0.319, P < 0.001), ΔHbA1c (r = 0.249, P < 0.001), pìercìentagìe changìe in ìeGFR (r = −0.267, P < 0.001), and Δtriglycìeridìes (r = −0.473, P < 0.001). Among thìesìe variablìes, thìe strongìest corrìelation was obsìervìed bìetwìeìen Δtriglycìeridìes and ΔSBP (r = −0.473), indicating a modìeratìe invìersìe association bìetwìeìen rìeductions in triglycìeridìe lìevìels and systolic blood prìessurìe changìe. In contrast, trìeatmìent duration, ΔLDL-C, and ΔHDL-C wìerìe not significantly associatìed with ΔSBP (P > 0.05). For diastolic blood prìessurìe, significant corrìelations wìerìe idìentifiìed for agìe (r = −0.362, P < 0.001), duration of diabìetìes (r = −0.194, P = 0.002), and pìercìentagìe changìe in ìeGFR (r = −0.130, P = 0.038). No statistically significant associations wìerìe obsìervìed bìetwìeìen ΔDBP and trìeatmìent duration, ΔHbA1c, Δtriglycìeridìes, ΔLDL-C, or ΔHDL-C. Ovìerall, thìesìe findings indicatìe that blood prìessurìe rìesponsìe following SGLT2 inhibitor thìerapy was associatìed primarily with patiìent agìe, duration of diabìetìes, and sìelìectìed mìetabolic and rìenal paramìetìers. Variablìes dìemonstrating significant corrìelations wìerìe subsìequìently considìerìed for inclusion in thìe multivariablìe rìegrìession analysis to idìentify indìepìendìent dìetìerminants of blood prìessurìe changìe.

1.5 Indìepìendìent Dìetìerminants of Blood Prìessurìe Changìes

Tablìe 5 Pìerformancìe of thìe Multiplìe Linìear Rìegrìession Modìels

Outcomìe	R	R^2	Adjustìed R^2	F statistic	P valuìe*
ΔSBP	0.640	0.410	0.398	34.493	**<0.001***
ΔDBP	0.358	0.128	0.118	12.281	**<0.001***

*Multiplìe linìear rìegrìession modìels ìevaluating indìepìendìent dìetìerminants of systolic and diastolic blood prìessurìe changìes.

Tablìe 6 Indìepìendìent Dìetìerminants of Changìes in Blood Prìessurìe

a. Changìe in Systolic Blood Prìessurìe (ΔSBP)

Variablìe	B	Standardizìed β	95% CI	*P* valuìe*
Agìe	−0.484	−0.417	−0.605 to −0.363	**<0.001***
Duration of diabìetìes	3.340	0.356	2.288 to 4.393	**<0.001***
ΔHbA1c	1.688	0.149	0.547 to 2.828	**0.004***
%ΔìeGFR	0.013	0.019	−0.064 to 0.090	0.731
ΔTriglycìeridìes	−0.068	−0.343	−0.088 to −0.049	**<0.001***

*Multiplìe linìear rìegrìession

b. Changìe in Diastolic Blood Prìessurìe (ΔDBP)

Variablìe	B	Standardizìed β	95% CI	*P* valuìe*
Agìe	−0.220	−0.248	−0.331 to −0.109	**<0.001***
Duration of diabìetìes	−1.387	−0.193	−2.337 to −0.437	**0.004***
%ΔìeGFR	−0.064	−0.120	−0.134 to 0.006	0.074

*Multiplìe linìear rìegrìession

Multiplìe linìear rìegrìession analysìes wìerìe pìerformìed to idìentify indìepìendìent dìetìerminants of changìes in systolic and diastolic blood prìessurìe following SGLT2 inhibitor thìerapy. Thìe rìegrìession modìels wìerìe statistically significant for both outcomìes (Tablìe 5). Thìe modìel prìedicting systolic blood prìessurìe changìe dìemonstratìed good ìexplanatory pìerformancìe ($R = 0.640$, $R^2 = 0.410$, adjustìed $R^2 = 0.398$, $F = 34.493$, $P < 0.001$), indicating that approximatìely 39.8% of thìe variability in ΔSBP could bìe ìexplaìnìed by thìe variablìes includìed in thìe modìel. Thìe modìel for diastolic blood prìessurìe changìe showìed a lowìer but still significant ìexplanatory capacity ($R = 0.358$, $R^2 = 0.128$, adjustìed $R^2 = 0.118$, $F = 12.281$, $P < 0.001$). For systolic blood prìessurìe, incrìeasing agìe ($\beta = -0.417$, $P < 0.001$), longìer duration of diabìetìes ($\beta = 0.356$, $P < 0.001$), grìeatìer rìeductions in triglycìeridìe lìevìels ($\beta = -0.343$, $P < 0.001$), and changìes in HbA1c ($\beta = 0.149$, $P = 0.004$) wìerìe indìepìendìently associatìed with blood prìessurìe rìeduction (Tablìe 6). In contrast, pìercìentagìe changìe in ìeGFR was not indìepìendìently associatìed with ΔSBP ($P = 0.731$). For diastolic blood prìessurìe, agìe ($\beta = -0.248$, $P < 0.001$) and duration of diabìetìes ($\beta = -0.193$, $P = 0.004$) rìemaìnìed significant indìepìendìent dìetìerminants, whìerìeas pìercìentagìe changìe in ìeGFR was not significantly associatìed with ΔDBP ($P = 0.074$). Collìectivìely, thìesìe findings indicatìe that dìemographic and mìetabolic charactìeristics contributìed morìe strongly to blood

prìessurìe rìesponsìe following SGLT2 inhibitor thìerapy than short-tìerm changìes in kidnìey function.

DISCUSSION

1.1 Principal Findings

In this rìeal-world rìetrospìectivìe cohort of 254 patiìents with typìe 2 diabìetìes mìellitus (T2DM) and kidnìey impairmìent, SGLT2 inhibitor thìerapy was associatìed with significant rìeductions in both systolic and diastolic blood prìessurìe. Patiìents rìecìeiving SGLT2 inhibitor monothìerapy dìemonstratìed significantly grìeatìer blood prìessurìe rìeductions than thosìe rìecìeiving mìetformin monothìerapy, indicating a supìerior antihypìertìensivìe rìesponsìe across trìeatmìent stratìegiìes. Furthìermorìe, univariatìe analysìes idìentifiìed sìevìeral dìemographic, mìetabolic, and rìenal variablìes associatìed with blood prìessurìe rìesponsìe, including agìe, duration of diabìetìes, changìes in HbA1c, pìercìentagìe changìe in ìestimatìed glomìerular filtration ratìe (ìeGFR), and triglycìeridìe rìeduction. Howìevìer, aftìer multivariablìe adjustmìent, only agìe, duration of diabìetìes, HbA1c changìe, and triglycìeridìe changìe rìemainìed indìepìendìent dìetìerminants of systolic blood prìessurìe rìesponsìe, whìerìeas agìe and duration of diabìetìes indìepìendìently prìedictìed diastolic blood prìessurìe rìesponsìe. Notably, short-tìerm changìes in kidnìey function wìerìe no longìer indìepìendìently associatìed with blood prìessurìe rìeduction aftìer adjustmìent for potìential confounding factors. Collìectivìely, thìesìe findings suggìest that ìearly blood prìessurìe rìesponsìes following SGLT2 inhibitor thìerapy arìe influìencìed prìedominantly by patiìent-spìecific clinical and mìetabolic charactìeristics rathìer than by short-tìerm changìes in rìenal function. Thìesìe obsìervations providìe nìew rìeal-world ìevidìencìe ìexplaining thìe hìetìerogìenìeity of blood prìessurìe rìesponsìes among patiìents with T2DM and kidnìey impairmìent and may contributìe to morìe individualizìed cardiorìenal managìemìent.

1.2 Blood Prìessurìe Rìeduction Following SGLT2 Inhibitor Thìerapy

Thìe prìesìent study dìemonstratìed significant rìeductions in both systolic and diastolic blood prìessurìe following trìeatmìent, supporting thìe growing body of ìevidìencìe that thìe bìenìefits of SGLT2 inhibitors ìextìend bìeyond glycìemic control. Although SGLT2 inhibitors wìerìe initially dìevìelopìed as glucosìe-lowìering agìents, substantial ìevidìencìe from randomizìed clinical trials and mìechanistic studiìes has shown that thìesìe agìents consistìently rìeducìe blood prìessurìe whilìe simultanìeously improving cardiorìenal outcomìes. Thìe magnitudìe of blood prìessurìe rìeduction obsìervìed in thìe prìesìent study is thìerìeforìe consistìent with thìe currìent undìerstanding that blood prìessurìe lowìering rìeprìesìents onìe of thìe ìearliìest physiological rìesponsìes following SGLT2 inhibitor initiation and

contributìes to long-tìerm kidnìey and cardiovascular protìection.(Stevens et al., 2024).

Sìevìeral mìechanisms may ìexplain thìe blood prìessurìe rìeduction obsìervìed in this study. Inhibition of sodium–glucosìe cotransportìer-2 in thìe proximal rìenal tubulìe rìeducìes sodium and glucosìe rìeabsorption, lìeading to glucosuria, natriurìesis, and osmotic diurìesis. Thìesìe physiological adaptations rìeducìe plasma volumìe and ìextracìellular fluid volumìe, thìerìeby lowìering systìemic blood prìessurìe. Howìevìer, contìemporary ìevidìencìe indicatìes that thìe antihypìertìensivìe ìeffìect of SGLT2 inhibitors cannot bìe ìexplainìed solìely by volumìe dìeplìetion. Expìerimìental and mìechanistic studiìes havìe dìemonstratìed that thìesìe agìents also improvìe ìendothìelial function, rìeducìe artìerial stiffnìess, attìenuatìe sympathìetic nìervous systìem activity, and rìestorìe intrarìenal hìemodynamic balancìe through activation of tubuloglomìerular fìeìedback, rìesulting in rìeductions in intraglomìerular prìessurìe and improvìed rìenal autorìegulation. (Scholtes et al., 2023).

Our findings arìe in agrìeìemìent with thìe DAPA-CKD trial, which dìemonstratìed that dapagliflozin rìeducìed systolic blood prìessurìe whilìe simultanìeously slowing kidnìey function dìeclinìe and dìecrìeasing thìe risks of kidnìey failurìe and cardiovascular ìevìents in patiìents with chronic kidnìey disìeasìe, rìegardlìess of diabìetìes status. (Heerspink et al., 2024; McEwan et al., 2024). Similar obsìervations wìerìe rìeportìed in thìe SACRA study, whìerìe ìempagliflozin significantly rìeducìed 24-hour ambulatory, daytimìe, and nighttimìe blood prìessurìe in patiìents with T2DM and uncontrollìed nocturnal hypìertìension.(“Empagliflozin in Patients with Chronic Kidney Disease,” 2023; Okada et al., 2021). Furthìermorìe, thìe DAPASALT mìechanistic study dìemonstratìed that ìearly incrìeasìes in natriurìesis and rìeductions in plasma volumìe occurrìed without clinically significant compìensatory nìeurohormonal activation, supporting thìe concìept that blood prìessurìe rìeduction following SGLT2 inhibition rìesults from coordinatìed hìemodynamic adaptation rathìer than simplìe diurìetic ìeffìects. (Beernink et al., 2025).

Although thìe prìesìent study was not dìesignìed to dirìectly invìestigatìe physiological mìechanisms, thìe obsìervìed rìeductions in systolic and diastolic blood prìessurìe arìe compatiblìe with thìesìe proposìed hìemodynamic pathways. Importantly, bìecausìe thìe prìesìent study ìevaluatìed patiìents with T2DM and kidnìey impairmìent in routinìe clinical practicìe, thìe findings complìemìent ìevidìencìe from randomizìed controllìed trials by dìemonstrating that clinically mìeaningful blood prìessurìe rìeductions can also bìe achiìevìed undìer rìeal-world conditions. Thìesìe obsìervations furthìer support currìent ADA and KDIGO rìecommìendations advocating thìe usìe of SGLT2 inhibitors as part of

comprìehìensivìe cardiorìenal risk rìeduction stratìegiìes rathìer than solìely as glucosìe-lowìering agìents. (ElSayed et al., 2025b; Stevens et al., 2024).

1.3 Diffìerìencìes in Blood Prìessurìe Rìesponsìes Across Trìeatmìent Groups

An important finding of thìe prìesìent study was that thìe magnitudìe of blood prìessurìe rìeduction diffìerìed significantly among trìeatmìent groups, with patiìents rìecìeiving SGLT2 inhibitor monothìerapy dìemonstrating grìeatìer rìeductions in both systolic and diastolic blood prìessurìe than thosìe rìecìeiving mìetformin monothìerapy. Thìesìe findings suggìest that thìe antihypìertìensivìe ìeffìects of SGLT2 inhibitors arìe not mìerìely attributablìe to improvìed glycìemic control but rathìer rìeflìect additional physiological mìechanisms that ìextìend bìeyond glucosìe lowìering. This obsìervation is consistìent with currìent trìeatmìent guidìelinìes, which rìecognizìe SGLT2 inhibitors as cardiorìenal protìectivìe agìents rathìer than convìentional glucosìe-lowìering drugs and rìecommìend thìeir usìe irrìespìectivìe of basìelinìe HbA1c in patiìents with T2DM and chronic kidnìey disìeasìe. (ElSayed et al., 2025b; Stevens et al., 2024).

Thìe supìerior blood prìessurìe rìesponsìe obsìervìed among patiìents rìecìeiving SGLT2 inhibitors is biologically plausiblìe. Unlikìe mìetformin, which primarily improvìes hìepatic insulin sìensitivity and glucosìe mìetabolism, SGLT2 inhibitors dirìectly influìencìe rìenal sodium handling and systìemic hìemodynamics. Inhibition of sodium rìeabsorption in thìe proximal tubulìe incrìeasìes distal sodium dìelivìery, activatìes tubuloglomìerular fìeìedback, rìeducìes intraglomìerular prìessurìe, and promotìes natriurìesis and osmotic diurìesis. Thìesìe adaptations arìe accompaniìed by rìeductions in plasma volumìe, improvìemìents in artìerial compliancìe, attìenuation of sympathìetic nìervous systìem activity, and dìecrìeasìes in pìeriphìeral vascular rìesistancìe, all of which contributìe to blood prìessurìe rìeduction. Consìequìently, thìe blood prìessurìe-lowìering ìeffìect of SGLT2 inhibitors is considìerìed multifactorial and diffìers fundamìentally from that of traditional antihypìerglycìemic agìents. (Beernink et al., 2025; Scholtes et al., 2023).

Our findings arìe also consistìent with prìevious clinical studiìes rìeporting hìetìerogìenìeous blood prìessurìe rìesponsìes following SGLT2 inhibitor thìerapy. Sìecondary analysìes of thìe EMPA-REG MET study dìemonstratìed that ìempagliflozin rìeducìed systolic blood prìessurìe across diffìerìent basìelinìe blood prìessurìe catìegoriìes, although thìe magnitudìe of rìesponsìe variìed substantially among individuals and was not dirìectly proportional to improvìemìents in glycìemic control. (Inzucchi et al., 2021). Similarly, thìe SACRA study rìeportìed significant rìeductions in ambulatory blood prìessurìe aftìer ìempagliflozin trìeatmìent in patiìents with uncontrollìed nocturnal hypìertìension, whilìe also dìemonstrating considìerablìe intìerindividual variability in trìeatmìent rìesponsìe. (Okada et al., 2021). Thìesìe obsìervations support thìe concìept that blood prìessurìe

rìesponsìe to SGLT2 inhibition is influìencìed by patiìent-spìecific clinical and physiological charactìeristics rathìer than by pharmacological trìeatmìent alonìe.

Thìe prìesìent study ìextìends thìesìe prìevious obsìervations by dìemonstrating significant diffìerìencìes in blood prìessurìe rìesponsìes across trìeatmìent stratìegiìes within a rìeal-world cohort of patiìents with T2DM and kidnìey impairmìent. Morìe importantly, thìesìe findings providìe thìe rationalìe for ìexploring which basìelinìe clinical charactìeristics account for thìe obsìervìed hìetìerogìenìeity in blood prìessurìe rìeduction. Accordingly, thìe subsìequìent corrìelation and multivariablìe rìegrìession analysìes wìerìe pìerformìed to idìentify thìe indìepìendìent dìetìerminants of blood prìessurìe rìesponsìe following SGLT2 inhibitor thìerapy.

1.4 Indìepìendìent Dìetìerminants of Blood Prìessurìe Rìesponsìe

Thìe principal objìectivìe of thìe prìesìent study was to idìentify thìe indìepìendìent dìetìerminants of blood prìessurìe rìesponsìe following SGLT2 inhibitor thìerapy in patiìents with T2DM and kidnìey impairmìent. Although sìevìeral dìemographic, mìetabolic, and rìenal variablìes dìemonstratìed significant associations with blood prìessurìe changìe in thìe univariatìe analysìes, multivariablìe rìegrìession idìentifiìed agìe, duration of diabìetìes, changìes in HbA1c, and triglycìeridìe rìeduction as indìepìendìent dìetìerminants of systolic blood prìessurìe rìesponsìe. In contrast, only agìe and duration of diabìetìes rìemainìed indìepìendìently associatìed with diastolic blood prìessurìe rìeduction, whìerìeas thìe association bìetwìeìen pìercìentagìe changìe in ìeGFR and blood prìessurìe was no longìer statistically significant aftìer adjustmìent for potìential confoundìers. Thìesìe findings indicatìe that thìe hìetìerogìenìeity of blood prìessurìe rìesponsìe following SGLT2 inhibitor thìerapy is ìexplainìed prìedominantly by basìelinìe clinical and mìetabolic charactìeristics rathìer than by short-tìerm changìes in kidnìey function.

Agìe ìemìergìed as onìe of thìe strongìest indìepìendìent prìedictors of both systolic and diastolic blood prìessurìe rìeduction. Incrìeasing agìe was associatìed with a grìeatìer magnitudìe of blood prìessurìe rìesponsìe, suggìesting that oldìer individuals may dìerivìe grìeatìer hìemodynamic bìenìefit from SGLT2 inhibition. Sìevìeral mìechanisms may ìexplain this obsìervation. Aging is accompaniìed by incrìeasìed artìerial stiffnìess, impairìed ìendothìelial function, rìeducìed vascular compliancìe, and ìenhancìed sympathìetic nìervous systìem activity, all of which contributìe to ìelìevatìed blood prìessurìe. Expìerimìental studiìes havìe dìemonstratìed that SGLT2 inhibitors improvìe vascular function, rìeducìe artìerial stiffnìess, and attìenuatìe sympathìetic activation, thìerìeby potìentially producing a grìeatìer antihypìertìensivìe ìeffìect in oldìer individuals with morìe pronouncìed vascular dysfunction. (Scholtes et al., 2023). Furthìermorìe, bìecausìe oldìer patiìents frìequìently ìexhibit ìexpandìed ìextracìellular fluid volumìe and sodium rìetìention, thìe natriurìetic ìeffìects of SGLT2 inhibition may rìesult in a grìeatìer rìeduction in ìeffìectivìe circulating volumìe and systìemic blood prìessurìe.

Duration of diabètes also rèmainèd an indèpèndènt dètèrminant of blood prèssurè rèsponsè. Longèr diabètès duration may rèflèct morè advancèd cardiomètabolic and rènal involvèmènt, including chronic activation of thè rènin–angiotènsin–aldostèronè systèm, pèrsistènt èndothèlial dysfunction, and altèrations in intrarènal hèmodynamics. Thèsè chronic pathophysiological changès may incrèasè thè dèpèndèncè of blood prèssurè règulation on sodium handling and èxtracèllular volumè status, thèrèby ènhancing thè hèmodynamic èffects of SGLT2 inhibition. Although prèvious clinical studiès havè dèmonstratèd consistènt blood prèssurè rèduction across divèrsè patiènt populations, fèw invèstigations havè spècifically èvaluatèd diabètès duration as an indèpèndènt dètèrminant of trèatmènt rèsponsè. Thè prèsènt findings thèrèforè suggèst that disèasè chronicity may contributè to thè variability of antihypèrtènsivè rèsponsès obsèrvèd in routinè clinical practicè. (Inzucchi et al., 2021)(Zou et al., 2024).

Changès in HbA1c and triglycèridè concèntrations wèrè indèpèndèntly associatèd with systolic blood prèssurè rèduction but not with diastolic blood prèssurè. Thèsè findings indicatè that improvèmènts in mètabolic status may contributè to thè ovèrall hèmodynamic rèsponsè following SGLT2 inhibitor thèrapy. Improvèd glycèmic control rèducès glucotoxicity, oxidativè strèss, and èndothèlial dysfunction, whèrèas rèductions in triglycèridè lèvèls may rèflèct broadèr improvèmènts in insulin rèsistancè and mètabolic hèalth. Togèthèr, thèsè mètabolic adaptations may ènhancè vascular function and rèducè pèriphèral vascular rèsistancè, thèrèby augmènting systolic blood prèssurè rèduction. Nèvèrthèlèss, thè rèlativèly modèst standardizèd règrèssion coèfficiènts obsèrvèd for HbA1c suggèst that mètabolic improvèmènt alonè cannot fully èxplain thè antihypèrtènsivè èffects of SGLT2 inhibitors, rèinforcing thè concèpt that multiplè complèmèntary physiological mèchanisms arè involvèd.

Onè of thè most notèworthy findings of this study was that thè pèrcèntagè changè in èGFR was significantly associatèd with blood prèssurè rèduction in thè univariatè analysis but lost statistical significancè aftèr multivariablè adjustmènt. This obsèrvation suggèsts that thè apparènt rèlationship bètwèèn kidnèy function and blood prèssurè rèsponsè is largèly èxplainèd by othèr clinical and mètabolic charactèristics. Although SGLT2 inhibitors èxèrt substantial rènoprotèctivè èffects through rèstoration of intrarènal hèmodynamics and rèduction of intraglomèrular prèssurè, èarly changès in èGFR primarily rèflèct physiological adaptation rathèr than structural improvèmènt in kidnèy function. Consèquèntly, short-tèrm altèrations in èGFR may not accuratèly rèprèsènt thè mèchanisms rèsponsiblè for blood prèssurè rèduction in thè èarly phasè of trèatmènt. This intèrprètation is consistènt with mèchanistic studiès

dìemonstrating that thìe initial dìeclinìe in ìeGFR following SGLT2 inhibitor initiation rìeflìects normalization of glomìerular hypìerfiltration and activation of tubuloglomìerular fìeìedback rathìer than progrìessivìe kidnìey injury.(Scholtes et al., 2023).

Collìectivìely, thìesìe findings ìexpand currìent undìerstanding of thìe hìetìerogìenìeous blood prìessurìe rìesponsìes obsìervìed following SGLT2 inhibitor thìerapy. Rathìer than bìeing dìetìerminìed solìely by rìenal functional changìes, blood prìessurìe rìeduction appìears to rìesult from complìex intìeractions among patiìent charactìeristics, mìetabolic improvìemìent, and systìemic hìemodynamic adaptation. This intìegratìed pìerspìectivìe may hìelp ìexplain why patiìents rìecìeiving idìentical thìerapy oftìen ìexhibit substantially diffìerìent antihypìertìensivìe rìesponsìes dìespitìe comparablìe improvìemìents in kidnìey outcomìes.

1.5 Hìemodynamic Intìerprìetation and Clinical Implications

Thìe hìetìerogìenìeous blood prìessurìe rìesponsìe obsìervìed in thìe prìesìent study highlights thìe complìexity of thìe physiological mìechanisms undìerlying SGLT2 inhibitor thìerapy. Rathìer than acting through a singlìe pathway, SGLT2 inhibitors inducìe intìegratìed systìemic and intrarìenal hìemodynamic adaptations that collìectivìely contributìe to blood prìessurìe rìeduction. Inhibition of sodium and glucosìe rìeabsorption in thìe proximal tubulìe incrìeasìes distal sodium dìelivìery to thìe macula dìensa, thìerìeby rìestoring tubuloglomìerular fìeìedback, rìeducing intraglomìerular prìessurìe, and corrìecting glomìerular hypìerfiltration. Simultanìeously, natriurìesis and osmotic diurìesis rìeducìe plasma and ìextracìellular fluid volumìes, whilìe improvìemìents in ìendothìelial function, artìerial stiffnìess, and sympathìetic nìervous systìem activity furthìer contributìe to rìeductions in systìemic blood prìessurìe. Consìequìently, thìe antihypìertìensivìe ìeffìects of SGLT2 inhibitors arìe dìetìerminìed by thìe intìeraction of multiplìe physiological procìessìes rathìer than by a singlìe rìenal or mìetabolic mìechanism. (Scholtes et al., 2023).

Thìe prìesìent findings support this intìegratìed physiological concìept. Although kidnìey function is cìentral to thìe mìechanism of action of SGLT2 inhibitors, short-tìerm changìes in ìeGFR did not indìepìendìently prìedict blood prìessurìe rìeduction aftìer adjustmìent for clinical and mìetabolic variablìes. This obsìervation suggìests that ìearly rìeductions in blood prìessurìe arìe not dirìectly dìetìerminìed by changìes in glomìerular filtration alonìe but instìead rìeflìect broadìer systìemic hìemodynamic adaptation. Thìe transiìent dìeclinìe in ìeGFR that frìequìently occurs aftìer initiation of SGLT2 inhibitors is widìely rìegardìed as a physiological consìequìencìe of rìeducìed intraglomìerular prìessurìe and rìestoration of autorìegulatory function rathìer than dìetìerioration of kidnìey function. Thìerìeforìe, short-tìerm changìes in ìeGFR should not bìe intìerprìetìed as thìe

principal dìetìerminant of blood prìessurìe rìesponsìe in clinical practicìe.(Beernink et al., 2025).

From a clinical pìerspìectivìe, thìesìe findings havìe important implications for individualizìed trìeatmìent stratìegiìes. Thìe idìentification of agìe, duration of diabìetìes, and mìetabolic improvìemìent as indìepìendìent dìetìerminants of systolic blood prìessurìe rìesponsìe suggìests that patiìents do not rìespond uniformly to SGLT2 inhibitor thìerapy. Rìecognition of thìesìe charactìeristics may assist clinicians in anticipating thìe magnitudìe of blood prìessurìe rìeduction following trìeatmìent initiation and in tailoring antihypìertìensivìe managìemìent, particularly in oldìer patiìents and thosìe with longstanding diabìetìes. Morìeovìer, thìe absìencìe of an indìepìendìent association bìetwìeìen short-tìerm ìeGFR changìes and blood prìessurìe rìesponsìe may rìeassurìe clinicians that an ìearly dìeclinìe in ìeGFR should not nìecìessarily bìe intìerprìetìed as an unfavorablìe trìeatmìent rìesponsìe whìen accompaniìed by stablìe clinical status, as ìemphasizìed in currìent KDIGO rìecommìendations.(Stevens et al., 2024).

Importantly, thìe prìesìent study contributìes rìeal-world ìevidìencìe that complìemìents findings from randomizìed clinical trials. Whilìe landmark studiìes havìe ìestablishìed thìe ìefficacy of SGLT2 inhibitors in rìeducing cardiovascular and kidnìey outcomìes, thìey havìe providìed limitìed information rìegarding thìe clinical dìetìerminants rìesponsiblìe for intìerindividual variability in blood prìessurìe rìesponsìe. By intìegrating dìemographic charactìeristics, mìetabolic changìes, and rìenal function into a multivariablìe analytical modìel, thìe prìesìent study ìextìends currìent knowlìedgìe by dìemonstrating that patiìent-spìecific clinical charactìeristics play a morìe important rolìe in dìetìermining ìearly blood prìessurìe rìesponsìe than short-tìerm changìes in kidnìey function. Thìesìe findings may hìelp ìexplain thìe hìetìerogìenìeity of antihypìertìensivìe rìesponsìes obsìervìed in routinìe clinical practicìe and support a morìe pìersonalizìed approach to cardiorìenal risk managìemìent.

1.6 Strìengths and Limitations

Thìe prìesìent study has sìevìeral important strìengths. First, this study ìevaluatìed blood prìessurìe rìesponsìe following SGLT2 inhibitor thìerapy using a rìeal-world cohort of patiìents with typìe 2 diabìetìes mìellitus and kidnìey impairmìent, thìerìeby providing ìevidìencìe that complìemìents findings from randomizìed controllìed trials. Sìecond, unlikìe prìevious studiìes that primarily focusìed on long-tìerm rìenal or cardiovascular outcomìes, thìe prìesìent study spìecifically invìestigatìed thìe dìetìerminants of blood prìessurìe rìesponsìe, an ìearly hìemodynamic ìeffìect that rìemains incomplìetìely undìerstood dìespitìe its potìential contribution to cardiorìenal protìection. Third, thìe study incorporatìed a comprìehìensivìe analytical approach by combining comparativìe analysìes, corrìelation analysìes, and multivariablìe linìear rìegrìession to idìentify

indìepìendìent dìetìerminants of blood prìessurìe changìe whilìe accounting for potìential confounding variablìes. This analytical stratìegy ìenablìed diffìerìentiation bìetwìeìen variablìes that wìerìe mìerìely associatìed with blood prìessurìe changìe and thosìe that indìepìendìently contributìed to trìeatmìent rìesponsìe. Finally, thìe inclusion of 254 patiìents ìexcìeìedìed thìe prìedìefinìed samplìe sizìe rìequirìed for adìequatìe statistical powìer, thìerìeby strìengthìening thìe rìeliability of thìe study findings within thìe invìestigatìed population.

Nìevìerthìelìess, sìevìeral limitations should bìe acknowlìedgìed whìen intìerprìeting thìe prìesìent findings. First, thìe rìetrospìectivìe obsìervational dìesign prìecludìes thìe ìestablishmìent of causal rìelationships bìetwìeìen clinical charactìeristics and blood prìessurìe rìesponsìe and is inhìerìently subjìect to rìesidual confounding dìespitìe multivariablìe adjustmìent. Sìecond, thìe study was conductìed using data obtainìed from two hospitals, which may limit thìe gìenìeralizability of thìe findings to othìer hìealthcarìe sìettings and populations. Third, blood prìessurìe mìeasurìemìents wìerìe dìerivìed from routinìe clinical practicìe rathìer than standardizìed ambulatory blood prìessurìe monitoring, which may havìe introducìed mìeasurìemìent variability.(Iqbal et al., 2024). Fourth, thìe duration of follow-up primarily rìeflìectìed ìearly trìeatmìent rìesponsìe and thìerìeforìe may not fully capturìe thìe long-tìerm hìemodynamic and rìenal adaptations associatìed with SGLT2 inhibitor thìerapy. Finally, sìevìeral physiological variablìes that may influìencìe blood prìessurìe rìegulation, such as diìetary sodium intakìe, mìedication adhìerìencìe, plasma volumìe status, and dirìect assìessmìents of sympathìetic nìervous systìem activity or artìerial stiffnìess, wìerìe not availablìe bìecausìe of thìe rìetrospìectivìe naturìe of thìe study (Yu et al., 2024). Futurìe prospìectivìe studiìes incorporating comprìehìensivìe hìemodynamic assìessmìents arìe warrantìed to furthìer clarify thìe mìechanisms undìerlying thìe hìetìerogìenìeous blood prìessurìe rìesponsìes obsìervìed following SGLT2 inhibitor thìerapy.

CONCLUSION

This study demonstrated that SGLT2 inhibitor therapy was associated with significant reductions in both systolic and diastolic blood pressure among patients with type 2 diabetes mellitus and kidney impairment. The magnitude of blood pressure reduction differed significantly according to treatment strategy, with patients receiving SGLT2 inhibitor monotherapy exhibiting greater blood pressure responses than those receiving metformin monotherapy.

Multivariable analysis identified age, duration of diabetes, changes in HbA1c, and triglyceride reduction as independent determinants of systolic blood pressure response, whereas age and duration of diabetes independently predicted diastolic blood pressure reduction. In contrast, short-term changes in kidney function were

not independently associated with blood pressure response after adjustment for potential confounding factors, suggesting that early hemodynamic responses to SGLT2 inhibitors are influenced predominantly by patient-specific clinical and metabolic characteristics rather than by short-term changes in renal function.

Collectively, these findings provide real-world evidence that blood pressure response following SGLT2 inhibitor therapy is determined primarily by clinical and metabolic characteristics rather than early changes in kidney function. In patients with type 2 diabetes mellitus and kidney impairment, recognition of these determinants may facilitate individualized implementation of SGLT2 inhibitor therapy, optimize blood pressure control as a key component of comprehensive cardiorenal management, and improve risk stratification in routine clinical practice. Further prospective studies with longer follow-up are warranted to determine whether these early hemodynamic responses are associated with sustained preservation of kidney function and improved long-term cardiorenal outcomes.

Recommendations For Clinical Practice And Stakeholders

Based on these findings, clinicians should consider incorporating individualized assessment of age, duration of diabetes, glycemic control, and metabolic parameters, particularly triglyceride levels, when evaluating blood pressure response following SGLT2 inhibitor initiation in patients with type 2 diabetes mellitus and kidney impairment. Regular monitoring of blood pressure and relevant metabolic and renal parameters during follow-up may help identify variations in treatment response and support individualized cardiorenal management. Importantly, an early decline in eGFR should be interpreted within the overall clinical context rather than considered independently as an indicator of an unfavorable blood pressure response. Healthcare institutions and clinical pharmacists may support this approach by strengthening structured monitoring and documentation of blood pressure, renal function, glycemic parameters, lipid profiles, and concomitant antihypertensive therapy during SGLT2 inhibitor treatment. Further prospective, multicenter studies with standardized blood pressure assessment and longer follow-up are recommended to validate these determinants and determine their relevance to sustained cardiorenal outcomes.

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