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ORIGINAL ARTICLE

Changes in Cardiovascular Risk-Factor Profiles among Patients with Type 2 Diabetes Mellitus Receiving Dapagliflozin and Valsartan: A Prospective Observational Cohort Study

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ABSTRACT

Background: Patients with type 2 diabetes mellitus (T2DM) often have cardiovascular risk factors, which significantly increase cardiovascular morbidity and death.

Objective: To assess cardiovascular risk variables in T2DM patients using valsartan and dapagliflozin.

Material and Methods: A prospective observational cohort research was conducted between March 2022 and March of 2023. Initially, 220 patients were enrolled, and 208 individuals were followed up with for six months. Clinical and biochemical indicators were assessed at baseline, three, and six months. The data was analyzed using multivariable logistic regression and appropriate statistical tests.

Results: Of the 208 patients, 162 (77.88%) had hypertension and 118 (56.73%) were men. Systolic blood pressure (144.80 to 127.65 mmHg), HbA1c (8.64% to 7.14%), fasting blood glucose (168.50 to 122.15 mg/dL), BMI (29.85 to 27.94 kg/m2), and lipid parameters all showed significant improvements ($p < 0.001$). Renal function didn't change much. In all, 126 individuals (60.58%) met their cardiovascular risk-factor goals. Medication adherence was a favorable predictor, but obesity, smoking, and a longer duration of diabetes were negative predictors.

Conclusion: Treatment with valsartan plus dapagliflozin was linked to steady renal function and better cardiovascular risk factor profiles.

Keywords: Type 2 diabetes mellitus; Dapagliflozin; Valsartan; Cardiovascular risk factors; Glycaemic control; Renal function; Medication adherence.

INTRODUCTION

Type 2 diabetes mellitus (T2DM), often known as hyperglycemia, is a serious metabolic condition that has a high mortality and cardiovascular disease prevalence[1]. One of the main causes of mortality for people with type 2 diabetes is cardiovascular disease (CVD), which is mostly caused by the presence of many risk factors, including smoking, dyslipidemia, obesity, hypertension, inadequate glycaemia, and renal dysfunction[2]. This is due to the fact that these variables increase the risk of atherosclerosis, heart failure, myocardial infarction, stroke, and other cardiovascular events[3]. The necessity for thorough cardiovascular risk assessment and treatment is highlighted by the fact that patients with type 2 diabetes have roughly double the cardiovascular risk of people without the disease[2,4].

The sodium-glucose cotransporter-2 (SGLT2) inhibitors are a novel family of medications that have been shown to have positive effects on blood pressure, body weight, glycemic management, and cardiorenal outcomes. As a result, they are now a significant alternative for patients with type 2 diabetes[5]. Dapagliflozin was shown to reduce cardiovascular mortality or heart failure-related hospitalization in the DECLARE-TIMI 58 clinical trial; in particular, a reduction in heart failure-related hospitalization was seen[6]. SGLT2 inhibitors may have cardiorenal advantages by slowing the course of kidney disease and heart failure events, according to further data from cardiovascular outcome studies and clinical trials[7,8].

Angiotensin II receptor blockers (ARBs), such as valsartan, are often used to treat hypertension and prevent cardiovascular and renal problems[8]. In addition to lowering blood pressure and vascular resistance, valsartan has reno-protective qualities and blocks angiotensin II receptors, particularly in individuals with diabetic nephropathy[9]. Its therapeutic importance has already been demonstrated in the control of blood pressure and the reduction of cardiovascular risk[10,11]. Additionally, the cardiovascular effects of adding dapagliflozin to other known heart failure drugs, such renin-angiotensin system (RAS) blockers, are supported by results from the DAPA-HF study[12].

There is little information on the overall cardiovascular risk profile of T2DM patients receiving combination treatment with dapagliflozin and valsartan, despite the fact that both medications have demonstrated positive cardiovascular and renal effects on their own.

Research Objective: To assess cardiovascular risk factors in T2DM patients receiving valsartan and dapagliflozin.

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MATERIAL AND METHODS

Study Design: A prospective observational cohort study was conducted to evaluate cardiovascular risk variables in individuals taking valsartan and dapagliflozin for type 2 diabetes. Patients' cardiovascular risk-factor profiles were assessed at baseline and subsequently monitored for changes.

Study Setting: The Punjab Institute of Cardiology, Lahore, a tertiary-care teaching hospital in Lahore, Pakistan that provides specialist medical and diabetes care services in Lahore.

Study Duration: The duration of this research was one year, from March 2022 to March of 2023. The individuals' clinical and biochemical cardiovascular risk variables were evaluated at baseline, three, and six months later.

Study Population: Adult patients (18 years of age or older) with a known history of type 2 diabetes who were receiving valsartan and dapagliflozin as part of their therapy made up the trial population.

Sample Size: At first, 220 patients were enrolled. Of these, 208 completed the six-month follow-up and were included in the final analysis, while 12 were lost to follow-up. 94.55% was the overall retention rate.

Sampling Technique: In order to gather the necessary number of samples, eligible patients who visited the medical and diabetic outpatient departments throughout the research period were recruited in a sequential manner.

Inclusion Criteria: Individuals with a diagnosis of T2DM who were at least eighteen years old, receiving treatment with valsartan and

dapagliflozin, and willing to participate in baseline and follow-up evaluations were eligible.

Exclusion Criteria: Individuals with severe hepatic or renal impairment, acute cardiovascular events, active cancer, type 1 diabetes mellitus, pregnancy, and other medical problems that might interfere with follow-up evaluation were excluded. Patients who refused to give their informed permission and those without baseline clinical data were also not included.

Drug Dosage and Treatment Regimen: Patients were provided 10 mg of oral dapagliflozin daily. Valiastan was administered orally at a dose of 80–320 mg daily based on the patient's blood pressure, clinical response, renal function, and physician's judgment. The attending physicians prescribed and adjusted the two medications according to clinical requirements. Throughout the trial, other drugs used to treat cardiovascular disease and diabetes were provided and monitored in a way that was clinically acceptable. During follow-up, blood pressure, serum potassium levels, and renal function were routinely monitored[13,14].

Data Collection Procedure: The data was obtained using a standardized proforma. Age, sex, duration of diabetes, family history of cardiovascular disease (CVD), smoking status, hypertension, medication usage, and relevant clinical variables made up the baseline data. At baseline and three and six months after participation, clinical and biochemical data were assessed. Measurements of cardiovascular risk variables were made and compared to baseline data.

Assessment of Cardiovascular Risk Factors: The following cardiovascular disease risk variables were evaluated: SBP, DBP, BMI, WC, FBG, HbA1c, TC, LDL, HDL, and TG. Additional information included the duration of diabetes, hypertension, and smoking status.

Laboratory Investigations: The samples were taken in order to measure the fasting blood glucose, HbA1c, and lipid profile (total cholesterol, LDL, HDL, and triglycerides). Serum creatinine, estimated glomerular filtration rate (eGFR), and serum potassium levels were measured in order to assess renal function and safety. According to protocol, laboratory testing was performed during baseline and follow-up visits.

Follow-up Assessment: Following the beginning of treatment or the baseline evaluation, patients were monitored for three and six months. At every follow-up visit, clinical data, blood pressure, BMI, compliance, and side effects were recorded. Repeated biochemical tests were used to evaluate time-dependent changes in HbA1c, fasting blood glucose, lipid profile, renal function, and serum potassium levels.

Data Analysis: IBM SPSS Statistics 26 was used to analyze the data. Descriptive statistics were used to summarize clinical and demographic data. Categorical data were displayed as frequencies and percentages, whereas continuous variables were displayed as mean ± SD. Differences in cardiovascular risk variables between baseline, three-month, and six-month assessments were evaluated using either the Friedman test or repeated-measures ANOVA. The relationship between category variables was examined using the chi-square test. After controlling for age, gender, baseline BMI, smoking status, duration of diabetes, hypertension, and medication adherence, a multivariate logistic regression model was employed to identify independent factors linked to achieving the goal. 95% confidence intervals (CIs) for adjusted odds ratios (aORs) were displayed. A statistically significant p value was defined as less than 0.05.

Ethical Considerations: The institutional ethical review committee of Punjab Institute of Cardiology, Lahore, provided ethical approval for the project. Written informed permission was provided by each subject. Throughout the study, patient privacy and identity were maintained, and the information gathered was exclusively utilized for scientific purposes.

RESULTS

The final study comprised 208 patients, whose mean age was 54.62 ± 9.84 years (table 1). The majority of participants were male (56.73%) and between the ages of 41 and 60 (53.85%). The average duration of diabetes was 7.45 ± 4.12 years. Of the patients, 47.12% were obese and 77.88% had hypertension. 40.38% of individuals had a family history of cardiovascular disease, whereas the majority of participants (64.90%) did not smoke. The most often given dosage was 160 mg of valsartan (45.19%).

Table 2 shows a substantial improvement in cardiovascular risk variables over a six-month period ($p < 0.001$). Fasting glucose dropped from 168.50 to 122.15 mg/dL, HbA1c from 8.64% to 7.14%, and systolic blood pressure from 144.80 to 127.65 mmHg. While HDL rose from 39.80 to 44.35 mg/dL and LDL fell from 134.60 to 112.40 mg/dL, BMI fell from 29.85 to 27.94 kg/m².

Renal function was comparatively steady over the follow-up period, as Table 3 demonstrates. Potassium decreased from 4.32 to 4.48 mEq/L ($p = 0.062$), eGFR from 82.40 to 81.10 ($p = 0.112$), and serum creatinine from 0.96 to 0.99 mg/dL ($p = 0.084$). Urinary tract infections and hypotension were found in 4.33% and 6.73% of patients, respectively.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (N = 208)

Characteristic	Category / Metric	Value (n [%]) or Mean ± SD
Age (years)	Mean ± SD	54.62 ± 9.84
	18–40 years	24 (11.54%)
	41–60 years	112 (53.85%)
	>60 years	72 (34.62%)
Gender	Male	118 (56.73%)
	Female	90 (43.27%)
Duration of T2DM (years)	Mean ± SD	7.45 ± 4.12
	<5 years	64 (30.77%)
	5–10 years	89 (42.79%)
	>10 years	55 (26.44%)
Hypertension	Yes	162 (77.88%)
	No	46 (22.12%)
Obesity (BMI ≥ 30 kg/m²)	Yes	98 (47.12%)
	No	110 (52.88%)
Smoking Status	Current smoker	42 (20.19%)
	Former smoker	31 (14.90%)
	Non-smoker	135 (64.90%)
Family History of CVD	Yes	84 (40.38%)
	No	124 (59.62%)
Valsartan Daily Dose	80 mg	76 (36.54%)
	160 mg	94 (45.19%)
	320 mg	38 (18.27%)

Table 2: Longitudinal Changes in Cardiovascular Risk Factors at Baseline, 3 Months, and 6 Months (N = 208)

Cardiovascular Risk Factor	Baseline	3 Months	6 Months	Test Statistic (F / χ^2)	p-value
Systolic BP (mmHg)	144.80 ± 12.45	134.20 ± 10.18	127.65 ± 9.12	F = 142.36[a]	<0.001*
Diastolic BP (mmHg)	89.40 ± 7.82	83.15 ± 6.54	79.10 ± 5.90	F = 118.54[a]	<0.001*
BMI (kg/m²)	29.85 ± 4.10	28.72 ± 3.95	27.94 ± 3.80	F = 48.20[a]	<0.001*
Waist Circumference (cm)	101.40 ± 9.60	98.85 ± 9.15	96.70 ± 8.90	F = 36.75[a]	<0.001*
Fasting Blood Glucose (mg/dL)	168.50 ± 34.20	138.40 ± 26.80	122.15 ± 21.45	F = 156.90[a]	<0.001*
HbA1c (%)	8.64 ± 1.28	7.72 ± 1.05	7.14 ± 0.92	F = 134.12[a]	<0.001*
Total Cholesterol (mg/dL)	212.30 ± 38.40	196.45 ± 34.10	184.20 ± 30.65	F = 64.18[a]	<0.001*
LDL Cholesterol (mg/dL)	134.60 ± 29.50	121.80 ± 26.40	112.40 ± 23.85	F = 58.42[a]	<0.001*
HDL Cholesterol (mg/dL)	39.80 ± 7.45	42.10 ± 7.60	44.35 ± 7.85	F = 29.64[a]	<0.001*
Triglycerides (mg/dL)	198.00 ± 54.30	176.50 ± 48.10	161.20 ± 42.75	χ^2 = 72.45[b]	<0.001*

Data are presented as Mean ± SD. [a]Repeated-measures ANOVA; [b]Friedman test for non-normally distributed data. *Statistically significant at $p < 0.05$.

Table 3: Renal Function, Safety Parameters, and Adverse Events Over 6 Months (N = 208)

Parameter	Baseline	3 Months	6 Months	p-value
Serum Creatinine (mg/dL)	0.96 ± 0.22	1.01 ± 0.24	0.99 ± 0.23	0.084[a]
eGFR (mL/min/1.73 m²)	82.40 ± 14.80	79.85 ± 14.20	81.10 ± 14.50	0.112[a]
Serum Potassium (mEq/L)	4.32 ± 0.41	4.46 ± 0.44	4.48 ± 0.43	0.062[a]
Adverse Events	3 Months (n [%])	6 Months (n [%])	Total Affected (n [%])	—
Genital mycotic infection	9 (4.33%)	5 (2.40%)	14 (6.73%)	—
Symptomatic hypotension	6 (2.88%)	3 (1.44%)	9 (4.33%)	—
Mild hyperkalaemia (>5.0 mEq/L)	4 (1.92%)	3 (1.44%)	7 (3.37%)	—
Urinary tract infection	5 (2.40%)	4 (1.92%)	9 (4.33%)	—

Evaluated using repeated-measures ANOVA. No severe adverse events or acute kidney injury cases requiring drug discontinuation were observed.

Table 4: Association between Baseline Categorical Risk Factors and Target Achievement at 6 Months (N = 208)

Risk Factor	Category	Target Achieved (n = 126, 60.58%)	Target Not Achieved (n = 82, 39.42%)	χ^2 Value	p-value
Gender	Male (n = 118)	73 (61.86%)	45 (38.14%)	0.19	0.664
	Female (n = 90)	53 (58.89%)	37 (41.11%)		
Obesity (BMI ≥ 30)	Yes (n = 98)	49 (50.00%)	49 (50.00%)	8.69	0.003*
	No (n = 110)	77 (70.00%)	33 (30.00%)		
Smoking Status	Current/Former (n = 73)	34 (46.58%)	39 (53.42%)	9.24	0.002*
	Non-smoker (n = 135)	92 (68.15%)	43 (31.85%)		
Duration of T2DM	≤10 years (n = 153)	101 (66.01%)	52 (33.99%)	7.15	0.008*
	>10 years (n = 55)	25 (45.45%)	30 (54.55%)		
Hypertension	Yes (n = 162)	91 (56.17%)	71 (43.83%)	5.96	0.015*
	No (n = 46)	35 (76.09%)	11 (23.91%)		

Associations assessed using the Chi-square (χ^2) test. Row percentages are shown for each subgroup. *Statistically significant at $p < 0.05$.

Table 5: Multivariable Regression Analysis of Independent Predictors for Cardiovascular Risk Target Achievement at 6 Months (N = 208)

Predictor Variable	Adjusted Odds Ratio (aOR)	95% Confidence Interval (CI)	p-value
Age (per 1-year increase)	0.98	0.95 – 1.02	0.318
Gender (Male vs. Female)	1.12	0.61 – 2.05	0.714
Baseline BMI (≥30 vs. <30 kg/m²)	0.48	0.26 – 0.88	0.018*
Smoking (Current/Former vs. Non-smoker)	0.44	0.23 – 0.83	0.011*
Duration of T2DM (>10 vs. ≤10 years)	0.51	0.26 – 0.99	0.047*
Baseline Hypertension (Yes vs. No)	0.49	0.22 – 1.08	0.076
Medication Adherence (High vs. Moderate/Low)	2.64	1.38 – 5.05	0.003*

Multivariable logistic regression adjusted for age, gender, baseline BMI, smoking status, duration of diabetes, hypertension, and medication adherence. *Statistically significant at $p < 0.05$.

According to Table 4, 60.58% (n = 126) of patients met their cardiovascular risk-factor goals. Patients with obesity (50.00%), smoking (46.58%), diabetes for more than ten years (45.45%), and hypertension (56.17%) had substantially worse target accomplishment ($p < 0.05$). There was no significant correlation between gender ($p = 0.664$).

Obesity (aOR = 0.48, p = 0.018), smoking (aOR = 0.44, p = 0.011), and diabetes duration over ten years (aOR = 0.51, p = 0.047) are all significant negative predictors of objective accomplishment, according to Table 5. Age, gender, and hypertension were not statistically significant ($p > 0.05$), while high medication adherence was a significant favorable predictor (aOR = 2.64, p = 0.003).

DISCUSSION

In this study, cardiovascular risk variables were evaluated in 208 T2DM patients receiving valsartan and dapagliflozin for six months. Blood pressure, glycemic parameters, obesity parameters, and lipid profile all significantly decreased, according to the data. Diastolic blood pressure dropped from 89.40 ± 7.82 to 79.10 ± 5.90 mmHg, while systolic blood pressure fell from 144.80 ± 12.45 to 127.65 ± 9.12 mmHg ($p < 0.001$). These studies' findings imply that individuals with diabetes who also have hypertension may benefit from the combined use of renin-angiotensin system and glucose-lowering medications. Since blood pressure is a major risk factor for cardiovascular problems in type 2 diabetes, its decrease is especially noteworthy.

Additionally, the anthropometric and glycemic outcomes were favorable. While HbA1c dropped from 8.64 ± 1.28% to 7.14 ± 0.92% ($p < 0.001$), fasting blood glucose fell from 168.50 ± 34.20 to 122.15 ± 21.45 mg/dL. In a similar vein, BMI dropped from 29.85 ± 4.10 to 27.94 ± 3.80 kg/m². Weber et al. (2016) found that dapagliflozin and renin-angiotensin system inhibition reduced systolic blood pressure (10.4 mmHg) and HbA1c (0.6%) in diabetic individuals with hypertension[15]. Further proof of dapagliflozin's metabolic benefits comes from our study's increased glycemic management and weight loss.

Lipid parameter improvement was also noteworthy during follow-up. Triglycerides dropped from 198.00 ± 54.30 to 161.20 ± 42.75 mg/dL, LDL from 134.60 ± 29.50 to 112.40 ± 23.85 mg/dL, and total cholesterol from 212.30 ± 38.40 to 184.20 ± 30.65 mg/dL, while HDL rose from 39.80 ± 7.45 to 44.35 ± 7.85 mg/dL ($p < 0.001$). Since dyslipidemia is a significant cardiovascular risk factor in type 2 diabetes, the study's overall findings are comforting. Zelniker et al. (2019) shown that SGLT2 inhibitors had a positive impact on major cardiovascular events by 11%, cardiovascular mortality or heart-failure hospitalization by 23%, and renal disease progression by 45% in a comprehensive review and meta-analysis of randomized controlled trials[16]. Their study focused on clinical outcomes, but their results are consistent with the cardiovascular effects of this class of drugs.

Renal safety was one of our study's other important findings. While eGFR was reasonably consistent at 82.40 ± 14.80 and 81.10 ± 14.50 mL/min/1.73 m², respectively ($p = 0.084$ and $p = 0.112$), serum creatinine only slightly increased from 0.96 ± 0.22 to 0.99 ± 0.23 mg/dL. These results are in line with those of Heerspink et al. (2020), who found that dapagliflozin decreased the risk of the primary composite renal and cardiovascular outcome by 39% when compared to a placebo (HR = 0.61, $p < 0.001$)[17]. Similarly, valsartan demonstrated clinically substantial renal protective effects in individuals with diabetic nephropathy[18].

The cardiovascular risk factor objectives were fulfilled by 60.58% (n = 126) of the patients. Obesity (aOR = 0.48, p = 0.018), smoking (aOR = 0.44, p = 0.011), and having diabetes for more than ten years (aOR = 0.51, p = 0.047) were found to be significant negative predictors; on the other hand, high medication adherence (aOR = 2.64, p = 0.003) increased the odds of reaching the goal. The findings emphasize the importance of early intervention, medication adherence, and lifestyle adjustment rather than smoking. Cahn et al. also confirmed dapagliflozin's generally favorable safety profile in a sizable group of T2DM patients, with genital infections being a major treatment-related safety issue[19].

In summary, our findings show that after six months, patients on dapagliflozin/valsartan had comparatively stable renal function and notable improvements in several cardiovascular risk factors. However, the ability to draw conclusions about causality is limited by the observational methodology, absence of a control group, single-center design, and very little follow-up. Furthermore, as clinical outcomes were not directly evaluated, the results should not be interpreted as a sign of a decline in cardiovascular events. Larger multicenter controlled trials with extended follow-up are thus necessary to validate these findings and evaluate long-term cardiovascular and renal benefits.

Strengths and Limitations: The study's prospective observational design, suitably large sample size, and 6-month follow-up duration, which allowed for the systematic assessment of cardiovascular risk variables at baseline, three months, and six months, are some of its merits. Patients on dapagliflozin and valsartan had a number of clinical and biochemical markers evaluated, including blood pressure, glycemic control, lipid profile, anthropometric measures, and renal function. Furthermore, independent predictors of reaching a target value for cardiovascular risk variables and tracking adverse events for further details on treatment safety were identified using multivariable logistic regression. However, some limitations must be acknowledged. A causal association between a therapy and improvements shown cannot be demonstrated because the data were collected in a single-center observational research without a control group, and the results are difficult to generalize. Due to the relatively short follow-up period, long-term cardiovascular and renal effects are also poorly researched. Additionally, different individuals may have adhered to their drugs differently, and the outcomes may have been impacted by concurrent cardiovascular and antidiabetic treatments. Therefore, more multicenter controlled trials with follow-up periods are needed to validate these findings.

CONCLUSION

According to the study, blood pressure, glycemic control, body weight, and lipid profile considerably improved in T2DM patients treated with dapagliflozin and valsartan over a 6-month period, whereas renal function did not significantly alter. In all, 126 individuals (60.58%) met their goals for cardiovascular risk factors. Longer duration of diabetes, obesity, smoking, and low medication adherence were all associated with poor target achievement, whereas higher adherence was associated with better results. The study's findings highlight the necessity of managing cardiovascular risk factors, lifestyle modifications, quitting smoking, and medication compliance in T2DM patients. However, longer-term controlled multicenter trials are required to validate the advantages of this combination of treatments.

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