

A CROSS-SECTIONAL STUDY ON THE ASSOCIATION OF DPP-4 INHIBITORS AND PHYSIOLOGICAL RISK FACTORS OF HEART FAILURE

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is strongly associated with cardiovascular complications, including heart failure (HF). Dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used as oral hypoglycaemic agents; however, their cardiovascular safety remains uncertain. This study aimed to evaluate the association between DPP-4 inhibitor use and pre-existing heart failure and to compare cardiovascular risk parameters between users and non-users. **Materials and Methods:** A cross-sectional study was conducted among 218 patients with T2DM, divided equally into an exposure group using DPP-4 inhibitors (n = 109) and a control group using other oral antidiabetic drugs (n = 109). Data on demographic factors, comorbidities, blood pressure and ejection fraction were collected. Group differences were analysed using independent t-tests and chi-square tests, and logistic regression was applied to identify predictors of heart failure. **Result:** The exposure group included more males, 62 (56.9%), than females 47 (43.1%), while the control group had more females, 55 (50.5%). The mean age was higher in DPP-4 inhibitor users (64.83±11.25 years) compared to controls (59.14±15.42 years, p = 0.002). Hypertension was more common in the exposure group 78 (71.6%), than in controls 53 (48.6%). The exposure group also had higher systolic blood pressure (129.10±17.37 mmHg vs. 122.86±17.88 mmHg, p = 0.010). Logistic regression showed that DPP-4 inhibitor use was significantly associated with pre-existing HF (OR = 3.154, 95% CI: 1.245–7.993, p = 0.015), while the duration of use was not significant (p = 0.422). **Conclusion:** DPP-4 inhibitor users were older, more hypertensive, had significantly higher systolic blood pressure, and threefold higher odds of pre-existing HF compared to non-users.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is recognised as a strong cause for cardiovascular diseases (CVD) and heart failure (HF).^[1] Patients with T2DM frequently present with hypertension, coronary micro- and macrovascular dysfunction, left ventricular impairment and atrial arrhythmias, all of which contribute to HF development.^[2] Within T2DM management, oral antidiabetic therapies have evolved. The dipeptidyl peptidase-4 (DPP-4) inhibitor group is commonly used in diabetes management as it provides good blood glucose regulation, minimises the chances of low blood sugar episodes, and allows easier dosing than previous oral medicines.^[3] These agents effort by stopping the

DPP-4 enzyme, which helps raise incretin hormone levels, promotes insulin release, and lowers glucagon secretion.^[4]

Despite their metabolic advantages, the cardiovascular safety of DPP-4 inhibitors has been subject to scrutiny, especially with respect to HF outcomes. Early trials and observational studies have reported conflicting results. A large clinical trial showed that patients receiving saxagliptin had a 27% higher rate of hospital admission for HF compared with those given placebo (HR 1.27, 95% CI 1.07–1.51).^[5] However, later meta-analyses indicated that DPP-4 inhibitors had an overall neutral result on major cardiovascular outcomes such as HF, myocardial infarction, and stroke, with the relative

risk for HF admission being around 1.09 (95% CI 0.92–1.29).^[6]

Apart from the effects of specific drugs, underlying physiological risk factors in individuals with T2DM play an main part in the development of HF. Conditions such as high blood pressure, reduced ejection fraction, irregular heart rhythm, and abnormal lipid levels markedly raise the likelihood of HF among diabetic patients.^[7,8] Evidence from real-world clinical settings regarding the impact of DPP-4 inhibitors on cardiovascular function has shown inconsistent results. Data from observational research and registry studies have reported differing relationships between the use of DPP-4 inhibitors and the occurrence of hypertension, irregular heart rhythms, and left ventricular impairment in affected with diabetes mellitus (DM).^[9,10] In the setting of T2DM, assessing how antidiabetic therapies influence this intermediate risk markers can help clarify whether the drug contributes to HF vulnerability or is simply used in a higher risk group. Considering the high occurrence of cardiovascular risk factors in T2DM and the lack of clarity on how DPP-4 inhibitor therapy influences these factors, a detailed assessment is needed. Examining the link DPP-4 inhibitor treatment and physiological indicators may provide better insight into the development of HF. Hence, this study aimed to analyse the relationship between DPP-4 inhibitor use and major physiological risk factors related to HF, such as hypertension, systolic blood pressure, ejection fraction, and abnormal lipid profile and to assess the connection between DPP-4 inhibitor therapy and existing HF in patients with T2DM.

MATERIALS AND METHODS

Study design and setting: This cross-sectional study comprised 218 patients from the Department of Medicine and Diabetology. Ethical approval was got from the Institutional Ethics Committee, and all patients provided written informed consent before enrolment.

Inclusion criteria

Patients aged 30 years or above with a confirmed diagnosis of T2DM, receiving oral antidiabetic therapy containing DPP-4 inhibitors, and willing to give informed consent were included.

Exclusion criteria

Patients who had a past diagnosis of HF, those receiving insulin as the main treatment, or those

taking oral antidiabetic drugs other than DPP-4 inhibitors and patients with advanced kidney disease (estimated GFR < 30 mL/min/1.73 m²) excluded.

Methods: Eligible ones were selected and separated into two groups: 109 patients receiving DPP-4 inhibitor therapy (exposure group) and 109 patients receiving other oral antidiabetic medications without DPP-4 inhibitors (control group). Demographic information such as age, gender, and body mass index (BMI) was recorded using a structured proforma. Physiological assessments included measurement of blood pressure for evaluation of hypertension and echocardiographic assessment of ejection fraction. The presence of comorbid conditions such as hypertension, dyslipidaemia, and pre-existing cardiac disease was noted from patient medical records. Details regarding of DPP-4 inhibitors use, such as drug name (e.g. sitagliptin, linagliptin), dosage, and duration of therapy, were obtained from patient medical records.

Statistical analysis: Data were entered in Microsoft Excel and analysed using IBM SPSS Statistics version 23.0. Continuous variables were expressed as mean $\pm$ standard deviation, and categorical variables as frequency and percentage. Independent t-tests compared continuous variables, while chi-square tests assessed categorical variables. Correlation analysis evaluated the relationship between DPP-4 inhibitor duration and continuous parameters. Multiple logistic regression was performed to estimate adjusted odds ratios (OR) for HF risk factors after controlling for age, gender, and family history. A p-value < 0.05 was considered significant.

RESULTS

The exposure group included males 62 (56.9%) and females 47 (43.1%), while the control had males 54 (49.5%) and females 55 (50.5%). Patients receiving DPP-4 inhibitors were older (64.83 ± 11.25 years) compared to those on other oral antidiabetic drugs (59.14 ± 15.42 years, $p = 0.002$). Hypertension was more frequent among DPP-4 inhibitor users [78 (71.6%)] than non-users [53 (48.6%)], whereas pre-existing cardiac disease [24 (22%) vs. 27 (24.8%)] and dyslipidaemia [6 (6.9%) vs. 13 (12.1%)] were comparable. Systolic blood pressure was higher in the exposure set (129.10 ± 17.37 mmHg vs. 122.86 ± 17.88 mmHg, $p = 0.010$), with a slightly lower BMI (27.09 ± 5.10 vs. 28.51 ± 4.93 , $p = 0.067$). Ejection fraction was marginally lower among users [Table 1].

Table 1: Baseline profile and physiological parameters between groups

Variables	Exposure Group	Control Group	P value
Gender	Male	54 (49.5%)	—
	Female	55 (50.5%)	—
Comorbidity	Pre-existing cardiac disease (excluding HF)	27 (24.8%)	—
	Hypertension	53 (48.6%)	—
	Dyslipidaemia	13 (12.1%)	—
Age (years)	64.83 ± 11.25	59.14 ± 15.42	0.002
BMI (kg/m ²)	27.09 ± 5.10	28.51 ± 4.93	0.067
Systolic BP (mmHg)	129.10 ± 17.37	122.86 ± 17.88	0.010
Diastolic BP (mmHg)	77.07 ± 10.53	76.31 ± 10.69	0.602

Ejection Fraction (%)	58.59 ± 10.03	60.28 ± 8.58	0.186
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Nominal regression analysis to test the link of DPP-4 inhibitor use, duration of use, and pre-existing HF showed a significant improvement over the null model ($\chi^2 = 8.458$, $df = 2$, $p = 0.015$). The pseudo- R^2

values Cox and Snell (0.039), Nagelkerke (0.073), and McFadden (0.052) suggested modest predictive strength. DPP-4 inhibitor use was associated with HF status ($\chi^2 = 6.463$, $p = 0.011$) [Table 2].

Table 2: Model fit indices and chi-square tests assessed the link between DPP-4 inhibitor use and HF.

Model Parameter	Test Statistic / Value	p-value
Model chi-square	$\chi^2 = 8.458$, $df = 2$	0.015
Cox & Snell R^2	0.039	—
Nagelkerke R^2	0.073	—
McFadden R^2	0.052	—
Chi-square test	$\chi^2 = 6.463$	0.011

DPP-4 inhibitor use was associated with pre-existing HF, with users having higher odds of HF than non-users (OR = 3.154, 95% CI: 1.245–7.993, $p = 0.015$).

However, the duration of drug use was not significantly linked with HF status (OR = 0.948, 95% CI: 0.833–1.080, $p = 0.422$) [Table 3].

Table 3: Logistic regression showing the association of DPP-4 inhibitor use and duration with HF

Predictor	OR	95% CI	p-value
DPP-4 inhibitor use	3.154	1.245 – 7.993	0.015
Duration of DPP-4 use	0.948	0.833 – 1.080	0.422

DISCUSSION

This study tests the connection between DPP-4 inhibitor use and physiological factors associated with HF in patients with T2DM. The findings indicate that individuals taking DPP-4 inhibitors were older, had higher systolic blood pressure, and a greater frequency of hypertension compared to those not using these medications. Logistic regression analysis demonstrated that inhibitor use was significantly associated with pre-existing HF, whereas the duration of therapy showed no significant association.

In our study, patients in the exposure group were slightly older, with a higher proportion of males and a higher prevalence of hypertension than controls. Other comorbidities, such as cardiac disease and dyslipidaemia, were the same between the groups, though the exposure set showed a more mean systolic blood pressure. Similarly, Cobretti et al. the drug users were elder (mean age 68.4 years) and mostly male (95.4%), with a slightly higher but clinically insignificant prevalence of HF (9.1% vs. 8.6%, $p < 0.001$).^[11] In contrast, Ou et al. studied 196,986 individuals with type 2 DM and existing HF, among whom 15.3% were receiving DPP-4 inhibitor therapy. After applying propensity score matching, 22,510 matched pairs of users and non-users demonstrated similar demographic characteristics, duration of DM, and associated comorbidities.^[12]

Green et al. conducted the trial involving 14,671 affected with DM and CVD, with balanced baseline characteristics between sitagliptin and placebo groups (mean age 65 years, DM duration 11.6 ± 8.1 years, HbA1c $7.2 \pm 0.5\%$).^[13] Similarly, McGuire et al. included 2,643 patients (18.0%) with pre-existing HF evenly distributed between treatment groups, with comparable baseline characteristics.^[14] These findings collectively indicate that while demographic

and baseline variations exist across studies, DPP-4 inhibitor users generally have comparable cardiovascular profiles with non-users, minimising confounding influences.

In our study, regression analysis reported an association in inhibitor use and pre-existing HF, with the model showing a good fit and modest predictive strength. Similarly, Scirica et al. observed a significant increase in hospitalisation due to HF among saxagliptin users (HR = 1.27; 95% CI, 1.07–1.51; $p = 0.007$). The danger was particularly elevated in the early months of therapy and in those with pre-existing HF or reduced eGFR.¹⁵ In contrast to our findings, Cobretti et al. found 130 HF aggravations in the exposed ones ($n = 33,614$) versus 2,222 in the unexposed ones ($n = 638,651$), with 1-year exacerbation rates of 0.38% and 0.34%, respectively (HR = 1.12, $p = 0.24$). Among those with baseline rates were also comparable (3.1% vs. 2.8%; HR = 1.11, $p = 0.334$), and survival analysis showed no difference ($p = 0.26$).^[11]

Similarly, Green et al. observed no changes in HF hospitalisation in sitagliptin and placebo groups (3.1% each; HR = 1.00, 95% CI 0.83–1.20, $p = 0.98$) or in the composite outcome of HF hospitalisation or cardiovascular death (HR = 1.02, 95% CI 0.90–1.15, $p = 0.74$).^[13] Likewise, McGuire et al. reported identical HF hospitalisation rates (3.1% vs. 3.1%; HR = 1.00, 95% CI 0.83–1.19), with adjusted analyses showing consistent results (HR = 1.02, 95% CI 0.83–1.26). Composite outcomes for HF hospitalisation with cardiovascular or all-cause death also remained non-significant (HR = 1.02, 95% CI 0.90–1.14; HR = 1.00, 95% CI 0.90–1.11).¹⁴ Overall, the present findings align partly with existing evidence, suggesting a potential but inconsistent link in DPP-4 inhibitor use and HF, warranting cautious interpretation and further investigation.

In our study, logistic regression displayed that DPP-4 inhibitor use was significantly linked with a higher chance of pre-existing HF, whereas the duration of use had no significant effect on this association. Similar to our findings, Cobretti et al. observed no significant difference in time to HF exacerbation in the 2 groups over one year ($p = 0.26$), indicating that DPP-4 inhibitor duration did not affect outcomes.^[11] Ou et al. also found no impact of therapy duration on HF, with consistent hazard ratios before and after adjustment ($HR = 0.96$ vs. 1.00).^[12] Green et al. reported that long-term sitagliptin use over a period of 3 years not rise the risk of HF or cardiovascular death ($HR = 1.02$, $95\% CI 0.90-1.15$, $p = 0.74$).^[13] Similarly, McGuire et al. found that prolonged sitagliptin exposure for over 2.9 years (IQR 1.4–5.7) did not Higher the hazard of HF or composite results, even among patients with prior HF.^[14] In contrast, Kim et al. reported consistently lower hazard ratios for HF hospitalisation across various DPP-4 inhibitor subtypes: sitagliptin ($HR = 0.76$), linagliptin ($HR = 0.74$), vildagliptin ($HR = 0.82$), and saxagliptin ($HR = 0.93$), indicating either reduced or neutral risk compared with sulfonylurea use.^[16] Taken together, these findings propose that while DPP-4 inhibitor use can be related to pre-existing HF, the period of therapy appears to exert a minimal influence on the risk or progression of HF across diverse patient populations.

Limitations: This study is inadequate by its single-centre, cross-sectional design, which restricts causal inferences. Additionally, reliance on self-reported medication history may have introduced a recall bias.

CONCLUSION

DPP-4 inhibitor users were elder, had higher systolic blood pressure, and a high occurrence of hypertension than non-users. DPP-4 inhibitor use was significantly associated with pre-existing HF, with users showing three-fold higher odds, whereas the duration of therapy was not significant. These findings highlight the need for careful cardiovascular evaluation in patients with DM who are prescribed DPP-4 inhibitors. Future longitudinal studies are warranted to clarify the causal relationships and long-term cardiovascular outcomes.

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