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Original Article

THEEFFECT OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS ON CARDIOVASCULAR DISEASE RISK IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Objective: The aim of this study was is to investigate the proposed beneficial cardiovascular effects of a novel class of antidiabetic drugs named; dipeptidyl peptidase 4 inhibitors. In this study, we compared the effect of using add-on therapy of vildagliptin (dipeptidyl peptidase-4 inhibitor; DPP-4i) and gliclazide (sulphonylurea; SU) to that when using gliclazide monotherapy in patients with type 2 diabetes mellitus (T2DM) and acute coronary syndrome (ACS) on different cardiovascular outcomes.

Methods: A total of 60 patients diagnosed with T2DM, and ACS were randomly recruited into two treatment groups each of 30 patients to receive either gliclazide monotherapy (SU) or vildagliptin (DPP4i)+gliclazide (SU) add-on therapy, administered in a double-blind fashion. Outpatient visits were scheduled at 3, 6, and 12 mo where patient was reevaluated for cardiovascular (CV) outcomes and followed up for any arising cardiovascular complication.

Results: The vildagliptin (DPP4i) plus gliclazide (SU) add-on therapy group have significantly shown more improved glycemic control, lipid profile and ventricular performance compared to gliclazide (SU) monotherapy group with p values<0.05.

Conclusion: Vildagliptin as a DPP4i provides favourable cardiovascular effects beyond glucose control. Yet, its long-term safety and efficacy data still needs further investigations.

Keywords: Diabetes mellitus, Dipeptidyl peptidase-4 inhibitor, Cardiovascular disease

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INTRODUCTION

Cardiovascular disease (CVD) complications is considered fastest growing health concerns for many diabetic patients [1]. Type 2 diabetes mellitus (T2DM) doubles the risk of major cardiovascular complications for patients with or without established cardiovascular diseases [2-4], and causing up to 50-60% of T2DM patients death cases [5-8].

Accumulating evidence suggests that T2DM can negatively affect cardiovascular (CV) status by different pathogenic processes, which include accelerated atherosclerosis, as well as abnormalities in inflammatory pathways and in endothelial, myocardial, and platelet function [9-12].

Many antidiabetic agents such as metformin, sulfonylurea derivatives, and insulin have been found to improve glycemic control in T2DM significantly. However, none of them hardly had any favourable effect on cardiovascular complications associated with the disease such as dyslipidemia, hypertension, and obesity. On the other hand, many of these drugs even caused more harm than benefit to the cardiovascular (CVS) either by increasing weight gains such as insulin and sulphonylurea or by increasing CV risks such as thiazolidinedione [13, 14].

Therefore, it has become a requirement by FDA that newly developed antidiabetic drugs' cardiovascular outcomes should be prioritized in clinical trials [15]. Consequently, the new focus for ideally developing an oral antidiabetic agent aimed not only to target a proper glycemic control in patients but also to improve CV outcomes. Therefore generally speaking it has been stressed that diabetes therapies with beneficial effects on glycemic control, vascular function and CV risks should be considered as more desirable future trends in T2DM treatment. A novel class of oral antihyperglycemic agents used to treat T2DM have been found promising in that respect named Dipeptidyl peptidase 4 (DPP4) inhibitors. These incretin-based drugs are GIT hormones that is released in response to nutrient ingestion. Incretins such as; glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) enhance glucose-dependent insulin secretion, suppresses glucagon secretion, which all contribute beneficially to the proper glycemic control. However, these actions are limited by their rapid inactivation *in vivo* by Dipeptidyl peptidase enzymes. Thus inhibition of these enzymes should prolong and enhance the activity of incretins that play a desirable role in insulin secretion and blood glucose control regulation [16].

Recently, Data have shown an increased expression of DPP-4 enzymes in visceral adipose tissue which raises the possibility about the pathophysiological role of these enzymes in diabetes development in obese patients [17]. In addition, DPP4i have been found to exert favourable cardiovascular effect mediated partially through specific receptors on cardiomyocytes, vascular endothelium and vascular smooth muscle cells [18]. Consequently, speculations have arisen that DPP4i might have a potential to reduce the cardiovascular diseases (CVD) burden among patients with T2DM. It has been postulated that using these drugs may offer a dual benefit of targeting proper glycemic control with CVS regulation and protection in T2DM patients.

Evidence from preclinical and small observational studies in humans showed that DPP4i have pleiotropic actions in T2DM patients resulting in favourable effects on postprandial glycemia, lipedema, blood pressure, silent inflammation, oxidative stress, and endothelial dysfunction [19, 20].

Thus regarding their anticipated favourable effects on several CV risk factors and mechanisms contributing to CV pathology, researchers now have become keener on investigating their actual potential to reduce CV events in T2DM. Contradicting, several other safety trials have shown that DPP-4i do not increase or decrease major adverse CV events over several years of use in individuals with T2DM and CV diseases [21].

As a matter of fact, the debate about DPP4i benefit in improving CV risks associated with T2DM, need more ongoing and future CV studies in order to provide the body of evidence needed to select these drugs for patients with T2DM optimally. Most studies in literature targeted investigating a specifically targeted CV event by comparing DPP4i with a placebo [22, 23]. However, researchers targeting comparison of DPP4i main CVS outcomes with other antidiabetic drugs remains few.

Thus our study aimed to compare between two treatment study groups; group 1 and 2 who received a monotherapy of a sulphonylurea named gliclazide (SU) or an add-on therapy of gliclazide plus vildagliptin (SU+DPP4i), respectively on different therapeutic outcomes such as glycated hemoglobin (HBA1c), fasting blood glucose level (FBG), lipid profile, body weight, and left ventricular ejection fraction (LVEF%) in patients with type 2 diabetes mellitus and Acute coronary syndrome.

MATERIALS AND METHODS

Study patients

A total of 60 patients (31 males and 29 females) aged between 40-75, diagnosed with type 2 diabetes mellitus (T2DM), and had had a recent acute coronary syndrome (ACS) within 15 to 90 d were randomly recruited from intensive care unit at Fayoum general hospital. The study protocol was approved by the ethics committee of Fayoum general Hospital, Fayoum, Egypt (FM FU). All patients were asked to sign a consent form prior to participation in the study. Patients should have a confirmed history of T2DM proved by blood glucose and glycated haemoglobin test (HBA1c, 6.5 to 8.0% at screening). Selected patients should be hemodynamically stable and had a recent acute coronary syndrome (ACS) proved by the history of chest pain with evolving changes on the electrocardiogram; ST-segment elevation myocardial infarction (STEMI; anterior MI or inferior MI) or non-ST-segment elevation myocardial infarction (NSTEMI) and positive troponin. Major exclusion criteria were a diagnosis of type 1 diabetes, history of ketoacidosis or requirements for insulin therapy within 1 y of first diagnosis of diabetes, receiving DPP4i therapy for either more than 14 d total or within the past 3 mo prior to the study, unstable cardiac disorders (e. g., uncompensated heart failure, refractory angina,, or severe uncontrolled hypertension), kidney or liver diseases, pregnancy, and dialysis within 14 d before screening.

Study drugs and procedures

During ICU admission, all eligible patients received the standard conservative therapy for ACS (statin, aspirin, clopidogrel, heparin and nitrates) with standard doses according to the most updated guidelines [24]. Any patient contraindicated with any of the above drugs were excluded. The eligible patients' baseline demographic and clinical data were recorded after ICU discharge. Patients were subjected to a complete and detailed medical history, physical and clinical examination (ECG, Echo) and laboratory investigation (lipid profile, fasting blood glucose test and HbA1c). Informed consent was obtained from all individual participants included in the study.

After ICU discharge eligible diabetic patients with acute coronary syndrome (STEMI or NSTEMI) were randomly assigned into two treatment groups each of 30 patients to receive either gliclazide monotherapy (SU) or vildagliptin (DPP4i)+gliclazide (SU) add-on therapy, administered in a double-blind fashion till the end of the follow-up period.

Group 1 received an oral once or twice daily dose of 60 mg gliclazide; a sulphonylurea monotherapy (diamicron® MR 60 mg; Servier, Egypt). Group 2 received an add-on therapy of an oral once or twice daily dose of 60 mg gliclazide (SU) a sulphonylurea (diamicron® MR 60 tablets; Servier, Egypt) plus an oral once daily dose of vildagliptin; a DPP-4i (vildagluse 50 mg; Inspire pharma, Egypt). The once or twice daily dose of gliclazide was adjusted as needed to reach the HBA1c target level according to american society of endocrinologist guidelines (HbA1C ≤6.5%) [25, 26]. Any therapeutic changes needed for the management of the patient's diabetes and ACS during the study was at the discretion of the responsible physician but with stressing that no concomitant DPP4i should be allowed.

Outpatient visits were scheduled at 3, 6, and 12 mo after randomization during the first year of the study. Patients of each treatment group were evaluated at these different time periods regarding glycated haemoglobin (HbA1c), fasting blood glucose (FBG), lipid profile (LDL, HDL, TG, and weight) and echocardiography measurements (ejection fraction; EF%). All patients were followed up for any arising cardiovascular complication.

Statistical analysis

SPSS V18.0 (SPSS Inc, Chicago, USA) was used for statistical comparison of cardiovascular effects in type 2 diabetes mellitus patients when using a monotherapy of gliclazide (SU) or an add-on therapy of gliclazide (SU) plus vildagliptin (DPP4i). Comparison of the two treatment groups was accomplished using Paired t-test. The calculated P-value is considered significant if ≤ 0.05.

RESULTS

A total of 60 randomly selected diabetic patients, registered in the intensive care unit at Beni-Suef general hospital as cases of acute coronary syndrome were recruited in the study and randomly assigned into two treatment groups. Group 1 of 30 patients (17 males and 13 females) with mean±SD age (year) and weight (kg) of 56.9±6.1, and 84.5±4.1, respectively. Group 2 of 30 patients (14 males and 16 females) with mean±SD (year) and weight (kg) of 56.3±7, 83.±75.1 respectively. The two study treatment groups were well balanced with respect to baseline demographic and clinical characteristics or with respect to their smoking history and current medical condition as presented in table 1.

Table 1: Baseline characteristics of the study patients (n=60)

Demographic details		Group 1 (SU, n=30)	Group 2 (SU+DPP4i, n=30)
mean±SD or No (%)			
Age (y)		56.9±6.1	56.3±7
Weight (kg)		84.5±4.1	83.±75.1
Sex	Male	17±56.7%	14±46.7%
	Female	13±43.3%	16±53.3%
Smoking	Smokers	20±66.7	16±53.3
	Non smokers	10±33.3	14±46.7
ACS History	Inferior MI	14±46.7%	13±43.3%
	Anterior MI	12±40%	11±36.7%
	NSTEMI	4±13.3%	6±20%
Lipid profile (mg/dl) e	LDL	132.9±9.6	132.3±12.3
	HDL	36.2±4.4	35.8±3.9
	TG	180.03±10.3	181.5±9.1
FBG (mg/dl)		173.6±8.7	170.03±30.4
HBA1c %		7.7±0.27	7.8±0.27
EF%		58.1±3.3	59.1±9.5

SU; sulfonylurea, DPP4I; dipeptidyl peptidase 4 inhibitors, ACS; acute coronary syndrome, MI; myocardial infarction, NSTEMI; non ST segment elevation myocardial infarction, LDL; low density lipoprotein, HDL; low density lipoprotein, TG; triglyceride, FBG; fasting blood glucose, HBA1c; glycated hemoglobin, EF%; ejection fraction %.

As shown fig. 1 and 2, the diabetic profile of patients in each study group showed a non-significant difference prior to treatment administration as regards to HBA1c and FBG. However, on the other hand, the glycemic profile regarding the same parameters differed significantly ($p<0.05$) after treatment for both groups. Notably, a more significant ($p<0.05$) reduction in HBA1c and FBG were found in group 2 receiving SU+DPP4i than in group 1 receiving the SU monotherapy. The mean±SD change from baseline in HBA1c and FBG post, one year of treatment, is 1.3±0.16, 1.9±0.1 %, and 52.7±3.7, 61.33±21.5 mg/dl for group 1 (SU) and group 2 (SU+DPP4i), respectively.

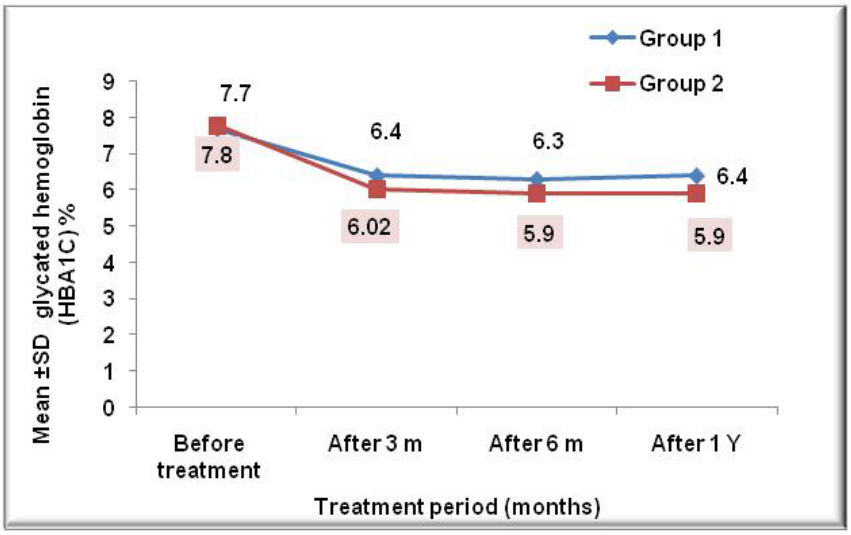

Fig. 1: Comparisons of HBA1c level follow-up in each study group

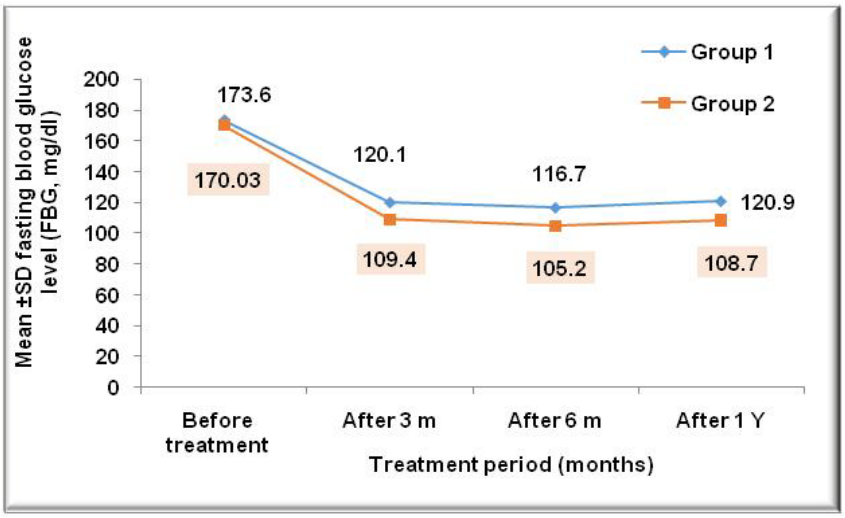

Fig. 2: Comparisons of FBS level follow-up in each study group

Similarly, as shown in the following table 2, the lipid profile of patients in both groups were non-significant prior to treatment. However, three and six months post-treatment group 2 (DPP4i+SU) showed more significant ($p<0.001$) improvement regarding LDL, HDL and TG values.

Table 2: Mean lipid profile (HDL, LDL, TG) mg/dl at baseline and post 3, 6 and 12 mo of treatment (n=60)

Mean±SD (mg/dl)	Group 1 (SU, n=30)			Group 2 (SU+DPP4i, n=30)		
	LDL	HDL	TG	LDL	HDL	TG
Pretreatment	132.9±9.6	36.2±4.5	180.0±10.3	132.3±12.3	35.8±3.3	181.5±9.1
Post 3 mo	90.03±5.5	44.1±1.9	136.2±3.9	88±5.6	46.9±.2.5	132.3±5.6
Post 6 mo	89.2±5.5	44.8±7.9	133.8±6	85.7±5.8	48.5±3.1	130±5.8

SU; sulfonylurea, DPP4i; dipeptidyl peptidase inhibitors, LDL; low-density lipoprotein, HDL; High-density lipoprotein, TG; triglyceride.

However, regarding LVEF% of study patients, it was found that EF% of group 2 was not significantly affected, whereas group 1 EF% showed a significant decline ($p<0.001$). The results were represented in fig. 3.

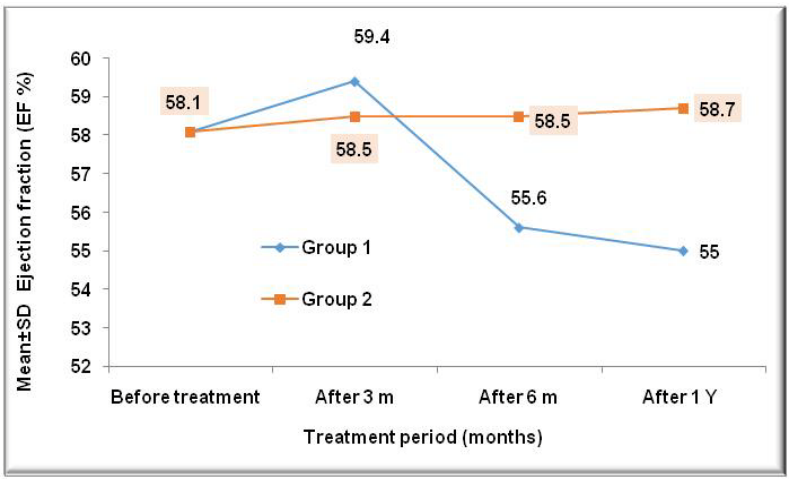

Fig. 3: Comparisons of EF% follow-up in each study group

Regarding the effect of each treatment on patients' weight, group 1 patients (SU) weight significantly ($p<0.01$) increased from 82.5 kg pretreatment to 85.6 kg, and 86.5 kg post 3 and 6 mo of treatment. However, On the other hand, group 2 patients (SU+DPP4i) weight were not affected by treatment. In addition, statistical comparison of patient's weight between both groups pre and post treatment were non-significant. Patients were also followed for any arising complications due to either treatment, however, as illustrated in table 3, it was found that both groups showed non-significance regarding Hospitalization and hypoglycemia incidences.

Table 3: No. (%) percent incidence of hospitalization and hypoglycemia risk in study patients groups, (n=60)

Risk incidence No. (%)	Group 1 (SU, n=30)	Group 2 (SU+DPP4i,n=30)
Hospitalization		
Post 6 mo	5 (16.7)	2 (6.7)
Hypoglycemia		
Post 3 mo	1 (3.3)	2 (6.7)
Post 6 mo	1 (3.3)	2 (6.7)
Risk incidence No. (%)	Group 1 (SU, n=30)	Group 2 (SU+DPP4i,n=30)
Re-hospitalization		
Post 3 mo	5 (16.7%)	2 (6.7%)
Hypoglycemia		
Post 3 mo	1 (3.3%)	2 (6.7%)
Post 6 mo	1 (3.3%)	2 (6.7%)
Risk incidence No. (%)	Group 1 (SU, n=30)	Group 2 (SU+DPP4i,n=30)
Re-hospitalization		
Post 3 mo	5 (16.7%)	2 (6.7%)
Hypoglycemia		
Post 3 mo	1 (3.3%)	2 (6.7%)
Post 6 mo	1 (3.3%)	2 (6.7%)

SU; sulfonylurea, DPP4i; dipeptidyl peptidase inhibitors, All values are No. (%)

As shown for the above table, only 5 (16.7) patients of group1 and 2 (6.7%) patients of group 2 were hospitalised during the study period. Regarding hypoglycemia, both groups showed a similar number of patients showing hypoglycemic episodes.

DISCUSSION

Despite the fact that DPP-4 inhibitors (DPP4i) are widely spread in clinical use for the treatment of type 2 diabetes, however their cardiovascular safety has not been yet properly established. Thus more studies are still needed to clarify their effects on many cardiovascular events in diabetic patients. Patients with T2DM and recent acute coronary syndrome (ACS) selected for this study are considered the real candidate that should benefit from cardio protective effects of DPP4i if any.

The CVD risks associated with DPP4i treatment have been investigated in different studies but have shown many conflicting results. With DPP4i some studies showed an increased risk of MI and ischemic stroke [23, 27-29] or HF [22]. Contradictingly, other studies have shown a significantly lower HF risk [30] or a neutral effect on CV events [28].

Our study aimed to assess the cardiovascular outcomes associated with adding vildagliptin (DPP4i) to gliclazide (SU) versus gliclazide mono-therapy in diabetic patients with acute coronary syndrome (ACS).

As shown from the above data using vildagliptin as add-on therapy to gliclazide caused a highly significant ($p<0.001$) reduction in HBA1c and FBG levels compared to gliclazide monotherapy. However, the beneficial effect of DPP4i addition on glycemic profile in this study was not at all surprising and comes in agreement with several previous studies [31]. Vildagliptin improved glycemia in T2DM patients have been reported when it was used as a monotherapy [32] as well as, a combination therapy with metformin [33], thiazolidinedione's [34], sulfonylureas [35] or insulin [36].

However, the issue here is not proving the improved glycemic control of diabetic patients using DPP4i which was confirmed by several studies, but the real debate is whether this glycemic improvement would have any pronounced effect regarding decreasing incidence of cardiovascular risks in those ACS diabetic patients.

Patients' lipid profile is considered a crucial factor that determines patients CV risks.

As noted from our results the lipid parameters (HDL, LDL, and TG) significantly improved when vildagliptin therapy was added to gliclazide in group 2 at 3, 6, and 12 mo post treatment. This confirms the beneficial effects of vildagliptin add-on therapy on diabetic patients' lipid profile.

Similarly, a previous study by Matikainen *et al.*, assessed the effects of vildagliptin on postprandial lipid and lipoprotein metabolism in diabetic patients and recorded an improvement in triglyceride metabolism following a fat-rich meal [37]. In addition, this is in accordance with several previous studies that also demonstrated a significant drop in triglyceride and LDL concentration post-DPP4i treatment [38, 39].

Several mechanisms, have been proposed to explain such beneficial effects on lipid profile by DPP4i other than improving glycemic control such as GLP-1 induced myocardial protection [40], improving endothelial function [41], and even having an anti-inflammatory role by reducing C-reactive protein levels [42].

The above results gave researchers the hope that DPP4i might be the answer to resolving the common dyslipidemia concern in diabetic patients thus protecting them from subsequent CVD.

Pre and post patient's weight were not affected by vildagliptin plus gliclazide treatment. However, a significant increase was noted in patients' weight post-treatment with gliclazide monotherapy. However post-treatment weight results of both groups were non-significant. Although our results did not reach significance but SU group was more noted to increase patients' weight

This might be explained by the proposed enhanced postprandial lipid mobilisation and oxidation with vildagliptin, which is thought to decrease insulin resistance in T2DM patients as the otherwise accumulation of such lipid intermediates, may interfere with insulin signalling through receptors. Furthermore, such increased postprandial lipid oxidation could increase postprandial thermogenesis, thus explaining why vildagliptin does not lead to weight gain, as in the case with insulin, sulfonylurea, and thiazolidinedione therapy [43].

Over time, weight reduction may have an indirect benefit on cardiovascular risk, including blood pressure, cholesterol levels, inflammatory markers, and insulin resistance.

Regarding echo finding measurements (EF %), our results have shown a significantly ($p<0.05$) improved Ejection fraction (EF %) with group 2 (DPP4i+SU) than that observed with group 1 (SU) post different treatment periods.

The beneficial effect of 100 mg sitagliptin on ejection fraction was previously confirmed by khan *et al.*, 2010 who recorded an improved ejection fraction of 72.6±7.2% vs 63.9±7.9%, $p = 0.001$ compared to placebo in coronary heart diseases patients [40].

The first study to assess the effect of vildagliptin on ejection fractions in T2DM patients with left ventricular ejection fraction [LVEF]<40% has shown that vildagliptin increased the size of the left ventricle but without any decline in the its contraction and emptying which might speculate that this anti-diabetes drug may have improved the dispensability and compliance of the left ventricle **[**44].

Both groups of patients reported a similar incidence of hospitalisation and hypoglycemia. Although the non-significant difference in hypoglycemia demonstrated in this study, but several other studies have shown persistent fears from the tendency of insulin secretagogue such as the sulphonylurea groups to induce hypoglycemia that may impose additional myocardial ischemic risk in diabetic CAD patients. Consequently, SU drugs have been recommended to be used cautiously at the lowest effective dose, with ongoing regular glucose level monitoring for such patients [45]. Otherwise, DPP4i have been reported to have decreased the incidence of hypoglycemia which might be due to its effect on inhibiting glucagon levels during meal ingestion but sustaining glucagon counter-regulation during hypoglycemia. Thus vildagliptin may offer a potential add-on therapy for even T1DM patients without increasing the risk for hypoglycemia [46].

CONCLUSION

In conclusion, selection of the optimal antihyperglycemic agents in diabetes patients with cardiovascular complications pose many challenges to prescribers.

Our study has shown that the use of vildagliptin as a DPP4i plus gliclazide (SU) was not associated with increased CVD risks. Vildagliptin can be considered as a reasonably safe and effective medication option in T2DM with high CV risk. With comparable efficacy and more favourable CV outcomes, vildagliptin offers a more tailored approach to diabetes control in such a challenging group of patients.

CONFLICT OF INTERESTS

The authors state that they have no conflict of interest

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