ISSUE 1

Management of type 2 diabetes with vildagliptin in a patient having high cardiovascular risk

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CASE PRESENTATION AND HISTORY

- A 65-year-old male patient with a long-standing diabetes reported to the physician with uncontrolled glucose levels and generalized weakness.
- He was having a 10-year history of type 2 diabetes, for which he was taking metformin 1000 mg tablet twice daily however his blood glucose parameters remained poorly controlled. He was initiated Dapagliflozin which was discontinued due to complaints of profound weakness and recurrent genital infections.
- Patient also had a history of hypertension and dyslipidemia for which he was taking telmisartan 80 mg once daily and rosuvastatin 10 mg once daily, respectively.
- He had history of breathlessness on exertion 3 years back, for which he was evaluated and diagnosed to have ischemic heart disease. However, he refused to undergo angioplasty and stenting and preferred to be treated with medication. He has been doing fine since then and is asymptomatic.
- He was a college professor and retired 6 months back.
- He preferred non-vegetarian diet and took alcohol occasionally. He has been married since last 38 years. His wife is a bank employee and he was having two sons.
- He reported no major past history of any serious illness or surgery. His family history was non-contributory.

GENERAL PHYSICAL EXAMINATION

- On examination, the patient appeared to be comfortable and had stable parameters. His height was 1.62 m, weight 76.2 kg with a BMI of 29.0 kg/m^2.
- His vital parameters were normal and his blood pressure (BP) (in right arm at sitting position) 128/84 mmHg.
- Examination of feet did not reveal any bilateral pitting edema. Carotid bruit could not be auscultated.
- Cardiovascular examination revealed a normal heart sounds.

- Chest examination were essentially normal.
- CNS examination was normal and other systemic findings were non-contributory.

LABORATORY INVESTIGATIONS

- CBC was normal, Hb 14.2%
- FPG – 150 mg/dl, PPG – 210 mg/dl
- HbA1c – 8.2%
- Total cholesterol – 200 mg/dl
- HDL-C – 46 mg/dl
- LDL-C – 120 mg/dl
- Triglycerides – 188 mg/dl
- Liver and thyroid function tests: Normal
- Renal profile: Normal
- Estimated glomerular filtration rate (eGFR): 75 mL/min/1.73 m^2
- Routine urine and microscopy: Normal
- ECG: No abnormality detected

DIAGNOSIS

Poorly controlled diabetes, hypertension, ischemic heart disease, dyslipidemia, obesity.

THERAPEUTIC INTERVENTIONS AND OUTCOMES

- Keeping in mind the co-morbid ischemic heart disease and CV risk factors, and poor diabetes control on metformin, metformin monotherapy was replaced with a combination of vildagliptin 50 mg+metformin 1000 mg twice daily.
- For management of ischemic heart disease aspirin, metoprolol, glyceryl trinitrate were continued. Rosuvastatin was increased to 40 mg daily.
- He was asked to follow-up every two weeks and keep a track of his home blood glucose parameters.
- Patient reported better quality of life with stable blood sugar parameters at 3 months follow-up visit.
- After 6 months, a laboratory investigation was conducted which revealed lowered cholesterol levels, along with HbA1c of 7.1% which was indicative of good glycemic control.

DISCUSSION

Diabetes and cardiovascular risk: An introduction

We are currently in the midst of a diabetes pandemic and the burden of diabetes is rapidly increasing around the world. According to recent estimates provided by the International Diabetes Federation (IDF),[1] globally there are more than 463 million people with diabetes and the number of affected individuals is projected to increase to 700 million by 2045. India alone harbors a large population of patients with diabetes. The population of patients with diabetes in India is estimated to be 77 million and is expected to rise to 134.2 million by 2045.[1] Diabetes is a risk factor for cardiovascular (CV) disease; patients with diabetes have 3-4-fold higher risk of suffering from CV diseases compared to those without diabetes.[2] Also, CV diseases are the leading cause of deaths in patients with type 2 diabetes, contributing to about 70% mortality rate in them.[2] Both type 1 diabetes and type 2 diabetes are the risk factors for coronary heart disease (CHD).[3] There is convincing evidence for accelerated atherosclerosis in patients with diabetes. Furthermore, majority of patients with diabetes have multivessel atherosclerosis before symptoms of coronary ischemia appear in them. Myocardial ischemia (MI) due to coronary atherosclerosis is often times silent in these patients.[3,4] Not surprisingly, survival rates in patients with diabetes with CV disease are lower compared to those patients with CV disease without diabetes.[3]

Diabetes is an independent CV risk factor. Other traditional CV risk factors such as obesity, cigarette smoking, hypertension, and hyperlipidemia also independently increase the risk of CHD in patients with diabetes.[3] These CV risk factors appear to have a multiplicative effect in amplifying CV risk, and the overall risk is likely to rise more steeply with addition of each risk factor in patients with diabetes compared to those without.[5] Risk of CV diseases in patients with diabetes also varies with age and gender. In patients with diabetes, the risk of CV disease increases with advancing age. Elderly patients with diabetes have a considerably high CV risk.[3]

The American Diabetes Association recommends a consideration of screening for coronary artery disease (CAD) in type 2 diabetes patients presenting with:[6]

- Atypical cardiac symptoms like unexplained dyspnea and chest discomfort.
- Signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease.
- Electrocardiogram abnormalities.

Dipeptidyl peptidase-4 inhibitors in patients with CV disease/risk: An insight on to its beneficial role beyond glycemic control

Dipeptidyl peptidase-4 (DPP-4) inhibitors have become a useful class of oral hypoglycemic agents (OHA) for the management of T2DM. They have been touted as promising antihyperglycemic agents due to their beneficial effects on glycemia without inducing hypoglycemia or body weight gain and their good

Table 1: Cardioprotective benefits of DPP-4 inhibitors	
Site	**Effects**
Endothelium	Vasodilatation
Vessels	Plaque reduction
Heart	Protection of ischemia/reperfusion damage
Adipose tissues	Reduction of pro-inflammatory state
Liver	Reduction of circulating lipid levels
Kidneys	Blood pressure reduction
Bone marrow	Increased angiogenesis

Source: Avogaro A, de Kreutzenberg S, Fadini G. Dipeptidyl-peptidase 4 inhibition: linking metabolic control to cardiovascular protection. *Curr Pharm Des.* 2014;20(14):2387–2394

tolerability. Beyond their glucose-lowering effects, numerous clinical trials and experimental studies have suggested that DPP-4 inhibitors may exert cardioprotective effects through their pleiotropic actions via glucagon-like peptide 1 (GLP-1) dependent mechanisms or involving other substrates. The inhibition of DPP-4 activity is associated with improvement in cardiovascular risk profile. The cardiovascular beneficial actions of DPP-4 inhibitors are summarized in Table 1.[7]

Vildagliptin: A DPP-4 inhibitor with proven efficacy and safety in T2DM patients with high cardiovascular risk

Vildagliptin is a selective and potent DPP-4 inhibitor that inhibits rapid degradation of endogenous GLP-1 and GIP, and increases α- and β-cell responsiveness to glucose, thereby improving glycemic control in T2DM. It has a strong binding ability to DPP-4 and thus may cause less glycemic variation. It has proven efficacy in lowering HbA1c with a low risk of hypoglycemia and is weight neutral. Vildagliptin is well tolerated with a low incidence of adverse effects, and does not increase the risk of adverse cardiovascular events.[8]

CLINICAL RATIONALE FOR CARDIOVASCULAR SAFETY PROFILE OF VILDAGLIPTIN

Vildagliptin in type 2 diabetes patients with high CV risk

- A meta-analysis was conducted to validate cardiovascular safety of vildagliptin in T2DM patients with high CV risk, such as those with congestive HF and/or moderate/severe renal impairment.[9]
- A total of 9599 patients (9251.4 subject-years of exposure) received vildagliptin 50 mg once daily (n=2201) or vildagliptin 50 mg twice daily (n=7398) and 7847 patients (7317.0 subject-years of exposure) were exposed to a comparator (36% placebo, 33% sulphonylurea, 10% thiazolidinediones, 15% metformin and 6% other treatments (mostly α-glucosidase inhibitors).
- The mean duration of exposure was 50.3 weeks for vildagliptin compared with 48.7 weeks for comparators.
- The primary endpoint was occurrence of major adverse CV events (MACEs; myocardial infarction, stroke and CV death). Assessments of the individual MACE components and HF events (requiring hospitalization or new onset) were secondary endpoints. The risk ratio (RR) of vildagliptin (50 mg once- and twice-daily combined) versus comparators (placebo and all non-vildagliptin treatments) was calculated using the Mantel–Haenszel (M–H) method.
- The mean age of the patients was 57 years, body mass index 30.5 kg/m^2 (nearly 50% obese), glycated hemoglobin concentration 8.1% and T2DM duration 5.5 years.
- A MACE occurred in 83 (0.86%) vildagliptin-treated patients and 85 (1.20%) comparator-treated patients, with an RR of 0.82 [95% confidence interval (CI) 0.61–1.11].
- Similar RRs were observed for the individual events. Confirmed HF events were reported in 41 (0.43%) vildagliptin-treated patients and 32 (0.45%) comparator-treated patients, with an RR 1.08 (95% CI 0.68–1.70).
- The results of the study confirmed that use of vildagliptin was associated with no increased risk of cardiovascular events and no increased risk of new or worsening of heart failure relative to the comparator.

Vildagliptin in patients with type 2 diabetes mellitus after acute coronary syndrome or acute ischemic stroke

- A study[10] evaluated the cardiovascular outcomes of vildagliptin in patients with T2DM after Acute Coronary Syndrome (ACS) or Acute Ischemic Stroke (AIS).
- The study involved a total of 3750 T2DM patients with ACS or AIS where 1250 subjects received vildagliptin with 2500 matched subjects were in the control group. The mean follow-up period was 9.9 months (SD, 6.2 months) and the maximum follow-up duration was 2.4 years.
- The primary composite outcome included cardiovascular (CV) death, nonfatal myocardial infarction (MI), and nonfatal stroke.
- The primary composite outcome occurred in 122 patients (9.8%) in the vildagliptin group and 263 patients (10.5%) in the control group (hazard ratio [HR], 0.90; 95% confidence interval [CI], 0.72–1.11) with a mean follow-up of 9.9 months.
- No significant between-group differences were observed for CV death (HR, 0.93; 95% CI, 0.56–1.52), nonfatal MI (HR, 0.79; 95% CI, 0.46–1.36), and nonfatal stroke (HR,

0.96; 95% CI, 0.74–1.24). The vildagliptin group were at similar risks of hospitalization for heart failure (HF) or coronary intervention to the control group (P = 0.312 and 0.430, respectively).

- For patients with HF at baseline, the risk of hospitalization for HF was similar between the vildagliptin and control groups (HR, 1.04; 95% CI, 0.57–1.88).
- Thus, it was concluded that in patients with T2DM after a recent ACS or AIS, treatment with vildagliptin was not associated with increased risks of CV death, nonfatal MI, nonfatal stroke, and hospitalisation for HF.

Vildagliptin versus other non-insulin antidiabetic drugs (NIADs)

- A study[11] was conducted to assess the cardiovascular (CV) safety of vildagliptin vs other non-insulin antidiabetic drugs (NIADs) using real-world data from 5 European electronic healthcare databases.
- Patients with T2DM aged ≥18 years on NIAD treatment were enrolled. Adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for the outcomes of interest (myocardial infarction [MI], acute coronary syndrome [ACS], stroke, congestive heart failure [CHF], individually and as a composite).
- Approximately 2.8% of the enrolled patients (n = 738 054) used vildagliptin at any time during the study, with an average follow-up time of 1.4 years, resulting in a cumulative current vildagliptin exposure of 28,330 person years.
- The adjusted IRRs (vildagliptin [other NIADs] vs other NIADs) were in the range of 0.61 to 0.97 (MI), 0.55 to 1.60 (ACS), 0.02 to 0.77 (stroke), 0.49 to 1.03 (CHF), and 0.22 to 1.02 (composite CV outcomes).
- The IRRs and their 95% CIs were close to 1, demonstrating no increased risk of adverse CV events, including the risk of CHF, with vildagliptin vs other NIADs in real-world conditions.
- The results of the study provide further evidence of the CV safety of vildagliptin and that exposure to vildagliptin is not associated with an increased overall CV risk or risk of any of the studied CV outcomes (MI, ACS, stroke and CHF), when compared with other NIADs.

TO CONCLUDE...

A close link exists between type 2 diabetes mellitus and cardiovascular disease. Optimal control and treatment of diabetes, along with aggressive treatment of associated CV risk factors is central to curbing the growing prevalence and progression of type 2 diabetes mellitus and cardiovascular disease. A careful selection of antidiabetic therapy with particular attention to cardiovascular safety is important in optimising diabetes management. Some antidiabetic agents are associated with increased risk of adverse cardiovascular events. Thus, the evaluation of cardiovascular risk of therapy is very important. Among, the antidiabetic drugs used, vildagliptin is a well-established dipeptidyl peptidase-4 inhibitor with significant antihyperglycemic properties and cardiovascular safety profile. Studies have shown that vildagliptin did not increase the risk of adjudicated cardiovascular events relative to all comparators in the broad population of patients with type 2 diabetes.

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