

REVIEW

The Role of Vildagliptin in the Therapy of Type 2 Diabetic Patients with Renal Dysfunction

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ABSTRACT

Diabetes is the leading cause of chronic kidney disease, and even in the absence of albuminuria, decreased renal function in type 2 diabetes mellitus (T2DM) patients increases the risk for major adverse cardiovascular events and death. The evidence derived from recent studies suggests that intensive glucose control not only reduces the risk for microalbuminuria and macroalbuminuria but may also decrease the rate of decline of glomerular filtration rate (GFR). Although insulin therapy is widely used in patients with T2DM and renal disease, metabolic control is particularly difficult to achieve and manage because of the limited therapeutic options and the frequent comorbidities seen in this population. Recent evidence suggests that dipeptidyl peptidase-4 (DPP-4) inhibitors may offer a better choice for improving glycemic control in T2DM patients with low GFR. This review will focus on vildagliptin, a DPP-4 inhibitor with a large body of evidence in patients with moderate to severe renal failure and a good clinical profile in terms

of efficacy and safety. In particular, vildagliptin, with appropriate dose adjustment, provides clinically important reductions in glycosylated hemoglobin, without increasing weight and the risk of hypoglycemia even in patients with severe chronic kidney disease.

Keywords: Chronic kidney disease; Dipeptidyl peptidase-4 inhibitors; Type 2 diabetes; Vildagliptin

INTRODUCTION

Diabetes is the leading cause of chronic kidney disease (CKD) in the developed world, and people with diabetes and CKD have a greatly increased risk of all-cause mortality, cardiovascular mortality, and kidney failure [1, 2]. In type 2 diabetes mellitus (T2DM) patients with proteinuria, the cardiovascular mortality is approximately eightfold greater than in the general population, as compared with a two- to fourfold increase in T2DM in general [3].

Patients with T2DM are at increased risk for the development or progression of CKD, which in turn increases the risk for major adverse cardiovascular events and death. Patients with T2DM and CKD are 16–60 times more likely to die prematurely than to reach end-stage renal disease (ESRD). Declining estimated glomerular filtration rate (eGFR) and albuminuria are both

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independent risk factors for adverse cardiovascular outcomes [4]. Once eGFR declines below 60 mL/min/1.73 m², the risk for death, major cardiovascular events, and hospitalization increases [5].

T2DM patients with renal impairment are also at greater risk of experiencing a hypoglycemic event compared with T2DM patients without renal impairment [6]. Patients with T2DM and CKD (eGFR <60 mL/min/1.73 m²) frequently have lower insulin requirements because less insulin excretion and metabolism occur. Decreased renal function also results in decreased gluconeogenesis, and half-lives for medications excreted by the kidneys are extended, which requires dose adjustment to avoid prolonged hypoglycemic events. Hypoglycemic events affect patients' lives profoundly, affecting their confidence to live independently and ability to work. Hypoglycemia has important safety implications (dizziness, convulsions, disorientation), and the risk of death is significantly increased within 1 day of a hypoglycemic event [7]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, where patients with T2DM were treated intensively for their condition, hypoglycemic episodes were significantly higher, and this could have contributed to the higher mortality rates observed [8].

The importance of intensive glycemic control for improving both microvascular and macrovascular outcomes in patients with T2DM has been demonstrated in the UK Prospective Diabetes Study [9] and in the 10-year follow-up of this study [10].

Similar results were observed in a more recent study, Action in Diabetes and Vascular Disease—Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE). After 5 years of follow-up in this study, the group of T2DM patients who received intensive glucose control had a significantly reduced HbA1c compared with standard therapy (6.5% vs 7.3%). Intensive control significantly reduced the incidence of combined major macrovascular and microvascular events (18.1% vs 20.0%) and major microvascular events (9.4% vs 10.9%), mainly because of a reduction in the incidence of nephropathy (4.1% vs 5.2%) [11].

An analysis by Perkovic et al. [12] provided more insight into the effect of intensive glycemic control in the ADVANCE study. Not only did good metabolic control prevent microalbuminuria, macroalbuminuria, and progression of albuminuria but it also promoted regression to normoalbuminuria. Furthermore the risk of ESRD was significantly reduced in patients treated with intensive glycemic control and this benefit was greater in those patients with pre-existing renal disease. These findings were consistent in various subgroups, including participants with baseline A1c above or below the median, with or without retinopathy, with an age above or below the median, and independently of the type of antihypertensive treatment.

In the ACCORD trial, patients with T2DM, high HbA1c concentrations (>7.5%), and cardiovascular disease were assigned to intensive (goal: HbA1c <6.0%) or standard (goal: HbA1c <7.0–7.9%) glycemic therapy. The ACCORD trial was stopped before study end because of increased mortality in the intensive therapy group, possibly due to an increased incidence of hypoglycemic events. However, there was a 21% reduction in development of microalbuminuria for intensive therapy compared with standard therapy. Results from this study suggest that benefits of intensive glycemic control have to be balanced against adverse events, particularly severe hypoglycemia [13].

In summary, intensive glucose control reduces not only the risk for microalbuminuria and macroalbuminuria but it may also decrease the rate of decline of GFR.

Patients with diabetes of long duration more frequently present with multiple comorbidities, especially chronic renal disease. Although insulin therapy is widely used in patients with T2DM and renal failure, metabolic control is particularly difficult to achieve and manage because of the limited therapeutic options and the frequent comorbidities seen in this population.

Treatment goals should be individualized and not be prescriptive, accounting for the needs of each patient, as outlined by the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD)

position statement [14]. Although metformin is the first-line treatment for glycemic control in patients with T2DM, there is a theoretical risk for lactic acidosis in patients with CKD, since metformin is excreted unchanged by the kidney. Thus, US prescribing guidelines contraindicate metformin in patients with moderate (<60 mL/min/ 1.73 m²) to severe (<30 mL/min/ 1.73 m²) renal insufficiency for this reason. However, there is ongoing debate, and a recent critical review of the literature supports the safe use of appropriate doses of metformin in patients with chronic stable renal impairment. The recommendation from the ADA/EASD position paper [14] is that metformin can be used down to an eGFR of 30 mL/min/ 1.73 m², but the dose of metformin should be reduced when eGFR is less than 45 mL/min/ 1.73 m². Kidney function should be checked regularly (every 6 months) and metformin should be discontinued if eGFR falls below 30 mL/min/ 1.73 m². Metformin should be prescribed with caution in patients with an eGFR less than 45 mL/min/ 1.73 m² which is rapidly deteriorating. All patients taking metformin should be warned that if they develop a condition that can lead to dehydration (e.g., vomiting or diarrhea), then they should stop metformin and seek medical advice. The risk for lactic acidosis is increased in such a scenario and applies irrespective of their baseline eGFR. It should be noted that metformin is part of some fixed-dose combinations, and the same risks apply.

Complications may arise when choosing a second antihyperglycemic agent in a patient with low GFR. The issues to be taken into account are: increased risk for hypoglycemia (due to decreased drug renal clearance, impaired renal gluconeogenesis, malnutrition, and comorbidities), increased risk for drug–drug interactions and adverse drug events (increased drug plasma concentration, advanced age, multiple drug therapies), contraindications related to comorbidities (high prevalence of cardiovascular disease, liver dysfunction, heart failure), and increased cardiovascular risk. On top of these challenging factors, many agents are not extensively studied in patients with CKD.

Among the major drug classes available, sulfonylureas, meglitinides, and insulins carry an increased risk of hypoglycemia and their use requires more intensive home blood glucose monitoring to adjust their dosage. This not only increases costs of treatment but is also a major burden to patients' lives. Because these patients are often frail with multiple comorbidities, their quality of life drastically worsens.

Although pioglitazone may also be used without need of dose reduction in any stage of CKD, its use is limited by the risk of bone fractures (all patients with CKD are at increased risk of osteoporosis) and by the risk of fluid retention and heart failure [15].

It has been recently shown that sodium-glucose transporter 2 (SGLT2) inhibitors, by reducing renal tubular glucose reabsorption, are able to decrease intraglomerular pressure and albuminuria and to slow GFR loss through mechanisms that appear independent of glycemia [16, 17]. Their efficacy, however, in lowering glucose levels is related to the filtration rate in the kidneys, so it has shown no efficacy in reducing HbA1c levels in patients with severe renal impairment, ESRD, and patients on dialysis, as well as some moderate renal impairment. For this reason, this drug class has to be prescribed with caution in patients with severe renal disease. Ongoing studies will soon clarify the role of this new class of antihyperglycemic agents in the treatment of patients with chronic renal disease.

Recent evidence has been provided that dipeptidyl peptidase-4 (DPP-4) inhibitors may offer a better choice for improving glycemic control when a T2DM patient also has a low GFR. The DPP-4 inhibitors sitagliptin, saxagliptin, vildagliptin, linagliptin, and alogliptin are orally available and have low propensity to cause hypoglycemia unless administered in combination with an agent associated with a high hypoglycemic risk, such as sulfonylureas. These agents are generally well tolerated, are weight neutral, and provide clinically important reductions in HbA1c (Table 1) [18]. While all the DPP-4 inhibitors can be used in mild (stages 1 and 2) CKD without dose adjustment in patients with T2DM, dose reductions are required for all DPP-4 inhibitors, except

Table 1 Comparison between currently available DPP-4 inhibitors

	Sitagliptin	Saxagliptin	Vildagliptin	Linagliptin	Alogliptin
Dosage	100 mg once daily	5 mg once daily	50 mg twice daily	5 mg once daily	25 mg once daily
Approximate half-life (h)	12	2	3	>120	21
Elimination	Metabolism is a minor pathway; primarily eliminated unchanged in urine (75%)	Elimination by metabolism (cytochrome P450 3A4/5) and renal clearance (24%)	Elimination by metabolism (not CYP450 enzymes) and renal clearance (23%)	Enterohepatic; eliminated unchanged in feces via biliary excretion (85%)	Metabolism is a minor pathway; primarily eliminated unchanged in urine (63%)
Effect on weight	Weight neutral	Weight neutral	Weight neutral	Weight neutral	Weight neutral
HbA1c reduction (monotherapy)	Clinically important; up to -0.8%	Clinically important; up to -0.8%	Clinically important; up to -0.8%	Clinically important; up to -0.8%	Clinically important; up to -0.8%
Use in CKD	Reduce dose to 50 mg/day for moderate CKD (CrCl ≥ 30 to ≤ 50 mL/min); reduce dose to 25 mg/day for severe CKD (CrCl < 30 mL/min); assess renal function before use and on a regular basis	Reduce dose to 2.5 mg/day for moderate CKD (CrCl ≥ 30 to ≤ 50 mL/min); give reduced dose after dialysis in chronic renal failure	Reduce dose to 50 mg/day for moderate CKD (CrCl ≥ 30 to ≤ 50 mL/min) and severe CKD (CrCl < 30 mL/min)	No dosage reduction required	Reduce dose to 12.5 mg/day for moderate CKD (CrCl ≥ 30 to ≤ 50 mL/min); reduce dose to 6.25 mg/day for severe CKD (CrCl < 30 mL/min)
Adverse events	Low	Low	Low	Low	Low

linagliptin, in T2DM patients with moderate to severe CKD (Table 1) [19]. A general review on DPP-4 inhibitors and their potential for protection against diabetes-related renal injury was recently published [20].

VILDAGLIPTIN

This review will focus on the efficacy of vildagliptin, a widely used DPP-4 inhibitor, in T2DM patients with CKD.

Relevant articles were identified through a PubMed search (publication date from 2005 to April 2017) by using the following key terms: diabetes mellitus AND chronic kidney disease, microalbuminuria, diabetic nephropathy, dialysis, DPP-4 inhibitors, vildagliptin. After exclusion of duplicates, a total of 857 unique hits remained, the titles and abstracts of which were then screened for relevance. After careful screening, a total of 22 articles were selected for full text review.

This manuscript is based on previously conducted studies and does not involve any new study of human or animal subjects performed by the author.

Vildagliptin after oral administration is rapidly absorbed within 3 h and the kidney plays a major role in the drug elimination [21, 22]. Approximately 85% of the oral dose is excreted in the urine as parental drug (25%) or metabolites [21]. Although the liver is the main site of vildagliptin metabolism, cytochrome enzymes are unlikely to be involved in the hydrolysis of the drug, and no significant association was found between the pharmacokinetic profile of vildagliptin and the degree of hepatic dysfunction (as assessed by Child–Pugh classification). However, European product information recommends that vildagliptin should not be used in patients with hepatic impairment, who have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level more than three times the upper limit of normal. No dose adjustment is required in patients with mild renal impairment. In patients with moderate or severe renal impairment or with ESRD, the recommended dose of vildagliptin is 50 mg once daily.

Preclinical Studies: Potential Beneficial Effect of Vildagliptin

There is accumulating evidence that DPP-4, glucagon-like peptide 1 (GLP-1), and the GLP-1 receptor are involved in the pathophysiology of diabetic nephropathy. The increased expression of DPP-4 in several tissues (including the kidneys) during a high-fat diet in rats with and without insulin deficiency emphasizes a possible role of DPP-4 in the pathophysiology of T2DM [23]. Furthermore, upregulation of DPP-4 expression by interferon gamma in human renal glomeruli may provide a possible mechanism involved in the development of diabetes-induced glomerulosclerosis [24]. Moreover, it was found that GLP-1 receptors were downregulated and DPP-4 activity upregulated in renal glomeruli and tubules of streptozotocin-induced diabetic rats [25]. Vildagliptin treatment for 24 weeks significantly not only decreased proteinuria and albuminuria in this animal model but also improved GFR, thereby reducing kidney injury [25]. These results were likely related to a dose-dependent delay in glomerular and tubular damage. The finding that these positive renal effects were independent of blood glucose levels suggests a possible direct role of DPP-4 inhibition in renal protection.

In another animal model of diabetes, the Zucker diabetic fatty rat, vildagliptin was able to prevent decreasing myogenic constriction of intrarenal arteries, thereby reducing glomerulosclerosis. This beneficial effect on glomerular histopathology was, however, not associated with a decrease in albuminuria [26]. These results reinforce the possibility that DPP-4 inhibitors, such as vildagliptin, may possibly exert a renoprotective action to preserve renal vascular reactivity in T2DM.

The suggestion that vildagliptin may exert a renal protective action independently of glycemic levels was also shown in a non-diabetic model of renal injury, the renal ischemia–reperfusion injury [27]. Vildagliptin was able to decrease tubular necrosis by inhibiting apoptosis signaling in the renal proximal epithelial cells.

Moreover, GLP-1 receptor is also expressed on podocytes and the administration of a GLP-1 receptor agonist, such as exendin-4, was able to reduce albuminuria, glomerular hyperfiltration, glomerular hypertrophy, and mesangial matrix expansion in the diabetic rats [28].

Although all these data provide increasing evidence that DPP-4 inhibition and GLP-1 receptor are together involved in the pathophysiology of diabetic nephropathy, at least in part, independently of their effect on glycemia, the precise mechanism of their beneficial effect is far from being clearly understood.

Vildagliptin in Patients with Renal Impairment: Potential Benefit Without Harm

Vildagliptin in Patients with Mild Renal Impairment

A retrospective analysis of the GALIANT study (GALvus In Addition to metformiN vs. TZD/metformin in T2DM) showed that the safety profile and tolerability of the combination of vildagliptin 100 mg once daily (or TZD) as add-on to metformin in T2DM patients with mild renal impairment ($n = 695$, eGFR between 50 and 80 mL/min/1.73 m²) were similar to those found in patients with normal renal function ($n = 1918$, eGFR > 80 mL/min/1.73 m²) after a 12-week treatment period [29]. No significant differences in the overall incidence of adverse events were observed between patients with mild renal impairment and those with normal renal function. Discontinuations due to adverse events were comparable for patients with normal renal function and those with mild renal impairment. Transaminase levels did not show significant change from baseline to study end in patients with either mild renal impairment or normal renal function. Serious adverse events were more frequent in TZD groups (normal renal function, 2.4%; mild renal failure, 3.0%) compared with the vildagliptin groups (normal renal function, 1.6%; mild renal failure, 2.4%). It is important to underline that the patients with reduced renal function were significantly older than those with normal renal function, thus

reinforcing the safety, efficacy, and tolerability of vildagliptin in this subset of patients.

Schweizer et al. [30] also confirmed the safety and efficacy of vildagliptin. They found that vildagliptin monotherapy (compared with metformin) was an effective and well-tolerated treatment option in 169 drug-naïve elderly patients with T2DM, 50% of whom had at least mild renal impairment (eGFR between 50 and 80 mL/min/1.73 m²).

More useful information about the safety of vildagliptin in elderly patients was derived from the INTERVAL study, a multinational, double-blind, 24-week study, that enrolled 278 drug-naïve or inadequately controlled patients with T2DM aged 70 years or older [31]. In this study the majority of patients had some degree of renal impairment: 62% had a mild eGFR reduction (between 50 and 80 mL/min/1.73 m²) and 15% had moderate eGFR impairment (eGFR between 30 and 50 mL/min/1.73 m²). Not only did this study show a significant reduction in A1c in vildagliptin-treated patients but also the overall safety and tolerability were similar in the vildagliptin and placebo groups, with low incidence of hypoglycemia and no emergence of new safety signals.

In a small ($n = 47$) 8-week, single-center, prospective, single-arm, open-label clinical trial, diabetic patients inadequately controlled by usual therapy were given vildagliptin 50 mg twice daily. It was found that vildagliptin decreased small dense-LDL and albuminuria (by 44%) [32]. These changes were unrelated to the change in glucose control. Again there is a suggestion that vildagliptin may improve some cardiorenal parameters.

Vildagliptin in Patients with Moderate to Severe Renal Impairment

Among the DPP-4 inhibitors, vildagliptin has the largest body of evidence in patients with moderate to severe kidney disease.

The efficacy, tolerability, and safety of vildagliptin 50 mg once daily in patients with moderate to severe renal failure were assessed by Lukashevich et al. in a large, multicenter, randomized, double-blind, placebo-controlled study [33]. Vildagliptin was added to current antidiabetic therapy in 515 T2DM patients with

moderate (294 patients with eGFR between 50 and 30 mL/min/1.73 m²) or severe (221 patients with eGFR < 30 mL/min/1.73 m²) renal impairment. Most patients were insulin-treated. After 24 weeks of treatment, vildagliptin significantly decreased A1c by $-0.5\% \pm 0.1\%$ ($P < 0.0001$) compared to placebo in patients with moderately impaired renal function (baseline A1c 7.9%) and by $-0.6\% \pm 0.1\%$ ($P < 0.0001$) in those with severely impaired renal function (baseline A1c 7.7%).

No difference in hepatic, pancreatic, and skin adverse events were observed between patients treated with vildagliptin or placebo. In patients with severely impaired renal function, there were more adverse events with vildagliptin, mainly due to a higher rate of influenza and a higher background risk of recurrent infections based on underlying medical history of the patients in this arm of the study. This finding, however, was not found in patients with moderate renal failure and in the recent pooled meta-analyses.

Since hypoglycemia is the major reason for concern in patients with renal failure, it is of note that in T2DM patients with severe renal failure, the incidence of hypoglycemia was comparable between patients treated with vildagliptin or placebo. Although patients with moderate renal impairment had a small increase in hypoglycemic episodes, this slight difference was due to the presence of associated drugs such as insulin or sulfonylurea. Finding of a low risk of hypoglycemia in patients with a better A1c level treated with vildagliptin is probably a consequence of the effect of vildagliptin in determining a glucose-dependent insulin secretion along with the maintenance of glucagon secretion even in the presence of low plasma glucose levels. Furthermore, despite the well-known increased CV risk in T2DM patients with reduced renal function, vildagliptin therapy was safe without any increase in the number of cardiac events, in agreement with data from patients with normal renal function or mild renal impairment.

There were no significant changes in renal function (as measured by potassium, creatinine, and eGFR changes) during this 24-week study both in patients with mild and those with

severe renal failure, suggesting again the renal safety of vildagliptin. In particular, renal function remained stable in patients with severe renal failure: the mean eGFR at baseline was 21.8 ± 0.5 and 20.7 ± 0.8 mL/min/1.73 m² in the vildagliptin and placebo group, respectively, and 20.9 ± 0.7 and 19.3 ± 1.1 mL/min/1.73 m² at week 24.

Finally it is important to note that more than 20% of the patients were older than 75 years, and this again supports the safety of vildagliptin therapy in elderly patients. This is of paramount importance since the majority of older T2DM patients have some degree of renal impairment.

Thus, adding vildagliptin to other antidiabetic drugs induced a clinically meaningful decrease in A1c in patients with moderate or severe CKD, with a safety profile similar to that of the placebo group. This was the first study with a high number of patients with moderate or severe renal failure treated with a DPP-4 inhibitor.

A post hoc analysis of this study evaluated the efficacy of vildagliptin in those patients already on insulin therapy and with severe renal impairment (eGFR < 30 mL/min/1.73 m²) [34]. There were 178 patients (100 randomized to vildagliptin, 78 randomized to placebo) with severe renal impairment (baseline eGFR approximately 21 mL/min/1.73 m²), all of them receiving insulin therapy alone or in combination with an oral hypoglycemic drug. Not only was vildagliptin able to significantly reduce A1c without weight gain but when added to insulin it demonstrated comparable hypoglycemic profiles to those of placebo. These data suggest that vildagliptin is a suitable therapeutic option in patients with low eGFR already on insulin therapy with the advantage of improving glucose control without increasing the hypoglycemic risk.

A 52-week extension of the study by Lukashovich et al. [35] confirmed the long-term beneficial effect of vildagliptin in T2DM patients with CKD. A1c level reduction achieved by the drug after 24 week of treatment was maintained after 52 weeks. This study extension supports a sustained efficacy, i.e., durability, of vildagliptin treatment in T2DM patients with impaired kidney function. It is of

note that a large proportion of vildagliptin-treated patients achieved a target A1c below 7.0%. The overall incidence of hypoglycemia in patients with severe renal impairment also remained low, without difference between vildagliptin and placebo, with the lower risk of severe hypoglycemia in vildagliptin-treated patients despite frequent insulin use. The incidence of hypoglycemia with vildagliptin in this study (26% in patients with moderate renal impairment and 18% in those with severe renal failure) appears to be lower than that expected (approximately 50%) in patients with long-standing T2DM and low baseline A1c receiving insulin with or without other oral agents. Again, the putative mechanistic explanation for such a protective effect of vildagliptin most likely relies on increased GLP-mediated stimulation of glucagon release in response to initial plasma glucose reduction.

There was a slight decline in renal function over the 1-year study in each treatment group. In patients with moderate renal failure, the mean change from baseline was -1.62 and -1.80 mL/min/1.73 m² in patients who received vildagliptin and placebo, respectively. The mean change in patients with severe renal failure from baseline was -1.98 and -2.44 mL/min/1.73 m² in patients who received vildagliptin and placebo, respectively. Mean serum potassium concentrations, similar at baseline both in patients with moderate renal failure randomized to vildagliptin (4.76 mmol/L) or placebo (4.78 mmol/L) and in those with severe renal failure (4.99 mmol/L in vildagliptin and 4.80 mmol/L in placebo group), did not change significantly over the course of the 52-week study.

Another recent multicenter, double-blind, randomized study of 24-week duration compared the safety and efficacy of vildagliptin and sitagliptin in 142 patients with T2DM and severe renal impairment (mean eGFR was 19.7 mL/min/1.73 m² in the vildagliptin group and 20.4 mL/min/1.73 m² in the sitagliptin group) [36]. It was demonstrated that vildagliptin 50 mg once daily and sitagliptin 25 mg once daily have similar efficacy and safety profiles in patients with severe renal impairment. In

particular, no deterioration of renal function was observed with either vildagliptin or sitagliptin.

In summary, these large intervention trials in T2DM patients with moderate or severe renal failure support the efficacious and safe use of vildagliptin in this vulnerable patient population. Table 2 summarizes the main efficacy and safety findings in patients with T2DM and renal dysfunction treated with vildagliptin.

Vildagliptin in Patients on Hemodialysis

There are also preliminary data on the efficacy and safety of vildagliptin in patients undergoing hemodialysis.

In a small study, 10 patients with T2DM undergoing hemodialysis received daily liraglutide 0.3 mg, vildagliptin 50 mg, and alogliptin 6.25 mg switched from insulin therapy on both the day of hemodialysis and the non-hemodialysis day, in a randomized cross-over manner [37]. Blood glucose levels were measured by continuous glucose monitoring. During treatment with incretin therapies, no severe hyperglycemia or ketosis were observed in any patients. Maximum blood glucose and mean blood glucose levels on the day of hemodialysis after treatment with liraglutide were similar to those with vildagliptin and significantly lower compared with alogliptin treatment ($P < 0.05$). On the non-hemodialysis day, the standard deviation value, a marker of glucose fluctuation, was similar with liraglutide and vildagliptin treatment and significantly lower with liraglutide compared with insulin and alogliptin ($P < 0.05$). The data suggest that in patients with T2DM undergoing hemodialysis and insulin therapy, incretin could also be an available option to improve quality of life without worsening glucose control.

Another small, open-label, single-arm clinical study in 26 Japanese patients on hemodialysis demonstrated that vildagliptin 50 mg as monotherapy was able to improve postprandial glucose levels without serious drug-related adverse events [38].

In a prospective 24-week, open-label, parallel group, controlled study 51 patients with T2DM patients undergoing hemodialysis were assigned to vildagliptin ($n = 30$) or to placebo

Table 2 Study duration, number of patients with different degrees of renal function, and A1c percentage change in five studies of vildagliptin in patients with type 2 diabetes

Study	Duration (weeks)	Patients (n)	Patients with eGFR ≥ 50 and ≤ 80 mL/min/1.73 m ² (n)	Patients with eGFR ≥ 30 and ≤ 50 mL/min/1.73 m ² (n)	Patients with eGFR < 30 mL/min/1.73 m ² (n)	A1c (%) change
GALIAN T [29]	12	2163 (1743 V/870 TZD)	695 (464 V/231 TZD)	–	–	–0.65%
INTERVAL [31]	24	278 (139 V/139 P)	173 (86 V/87 P)	40 (19 V/21 P)	–	–0.9%
Lukashevich et al. [33]	24	515 (289 V/226 P)	–	294 (165 V/129 P)	221 (124 V/97 P)	–0.5% in moderate RI; –0.6% in severe RI
Kothny et al. [35]	52	369 (216 V/153 P)	–	211 (122 V/89 P)	158 (94 V/64 P)	–0.4% in moderate RI; –0.7% in severe RI
Kothny et al. [36]	24	148 (83 V/65 S)	–	–	148 (83 V/65 S)	–0.54% vs –0.56%

P placebo, RI renal impairment, S sitagliptin, TZD thiazolidinedione, V vildagliptin

($n = 21$) [39]. Vildagliptin was administered at 50 mg/day for the first 8 weeks. Doses were then titrated to a maximum of 100 mg/day if hemoglobin A1c or glycated albumin target levels had not been reached. The average final dose of vildagliptin was 80 ± 5 mg/day. After 24 weeks, vildagliptin decreased average HbA1c levels from 6.7% at baseline to 6.1%, and average postprandial plasma glucose levels from 186 mg/dL at baseline to 140 mg/dL (all $P < 0.0001$). No hypoglycemia or liver impairment was observed in any patient.

Another small retrospective study from Japan confirmed these data on the efficacy of vildagliptin in patients on hemodialysis and peritoneal dialysis [40].

Combined, these data suggest that vildagliptin offers the opportunity to achieve better metabolic control without the risk of hypoglycemia in patients undergoing hemodialysis, and in patients that often are elderly, with multiple comorbidities and poor quality of life. The possibility to substitute, delay, or lessen insulin therapy may be of great advantage in these patients.

CONCLUSION

A good metabolic control not only plays a fundamental role in the prevention of micro- and macroalbuminuria but is also able to decrease the progression to renal failure [12]. However, the achievement of blood glucose levels close to normoglycemia is often associated with an increased risk of severe hypoglycemia.

The DPP-4 inhibitors decrease the breakdown of GLP-1 and improve both fasting and postprandial glucose levels. All can be used in CKD patients with appropriate downward dose adjustments as detailed previously. This drug class has the advantage of low risk of hypoglycemia and offers the advantage of an easy and safe therapy, avoiding the need for or decreasing the dosage of insulin or sulfonylureas.

Vildagliptin is the DPP-4 inhibitor with the largest amount of data in patients with moderate to severe renal failure and has demonstrated a good clinical profile in terms of efficacy and

safety also in “difficult-to-treat” patients over 75 years.

This is of clinical relevance, since a large proportion of diabetic patients also suffer from kidney disease. These patients present a challenge because they are often older with multiple comorbidities and frailty. Given the average slow progression of renal disease in T2DM, one limitation of the studies with currently available DPP-4 inhibitors in T2DM patients with renal impairment is the short duration of treatment. Long-term prospective studies will clarify whether vildagliptin may reduce the cardiorenal risk associated with low GFR in T2DM patients.

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