REVIEW ARTICLE

Ten years of experience with DPP-4 inhibitors for the treatment of type 2 diabetes mellitus

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Abstract

Achieving and maintaining recommended glycemic targets without causing adverse e ffects, including hypoglycemia, is challenging, especially in older patients with type 2 diabetes mellitus (T2DM). The introduction of dipeptidyl peptidase-4 (DPP-4) inhibitors, more than 10 years ago, has provided an alternative to conventional medications for the intensification of glucose-lowering treatment after failure of metformin monotherapy, and therefore, marked an important advance in the management of T2DM. By prolonging the activity of incretin hormones, DPP-4 inhibitors induce insulin release and decrease glucagon secretion in a glucose-dependent manner. This results in a more physiologic glycemic control as compared to that ensured by insulin secretagogues (sulfonylureas and glinides). Overall, DPP-4 inhibitors have a favorable safety profile and can be used without dose adjustments in older adults and in patients with mild renal impairment; they have a neutral effect on body weight and do not cause hypoglycemia by themselves. Safety issues, reported mainly in post-marketing surveillance programs and including cardiovascular outcomes and the risk of acute pancreatitis, are being extensively investigated. The aim of this review is to discuss the impact of DPP-4 inhibitors on the treatment of T2DM, after 10 years of experience, with an emphasis on diabetes care in Italy. We will first describe T2DM treatment in Italy and then provide an overview of the main findings from randomized controlled trials, real-world studies and post-marketing surveillance programs with DPP-4 inhibitors.

Keywords DPP-4 inhibitors · Diabetes · Hypoglycemia · Cardiovascular outcome trial

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Introduction

Type 2 diabetes mellitus (T2DM) is a widespread, chronic and complex disease which is associated with severe complications including chronic kidney disease (CKD) and cardiovascular (CV) disease [1, 2]. T2DM largely affects the elderly population, with a prevalence of approximately 25% among individuals aged ≥ 65 years [3–5]. Achieving and maintaining recommended glycemic targets without causing adverse effects, such as hypoglycemia and weight gain, is challenging when using traditional antihyperglycemic medications. This problem is particularly relevant in older patients [4, 6, 7].

The oral glucose-lowering dipeptidyl peptidase-4 (DPP-4) inhibitors, or gliptins, were introduced for the treatment of T2DM 10 years ago [8]. By inhibiting DPP-4, a protease that degrades the incretin hormones glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), gliptins prolong the activity of incretins leading to increased postprandial glucose-dependent insulin secretion and decreased glucagon secretion [9, 10]. The main representatives of this class are vildagliptin, sitagliptin, saxagliptin, linagliptin, and alogliptin [11–15]. DPP-4 inhibitors are indicated in adult patients with T2DM as an adjunct to diet and exercise, as monotherapy when metformin is not tolerated or contraindicated, or in combination with other antihyperglycemic medications, including insulin. DPP-4 inhibitors are characterized by a low risk of hypoglycemia and neutral effects on body weight [10]. Current guidelines recommend DPP-4 inhibitors as add-on to metformin or other glucose-lowering agents in dual or triple therapy [16, 17].

The aim of this review is to discuss the impact of DPP-4 inhibitors on the treatment of T2DM, after 10 years of experience, with an emphasis on diabetes care in Italy. We will first deal with T2DM treatment in Italy and the position of DPP-4 inhibitors in routine diabetes practice. We will then provide an overview of the main findings from randomized controlled trials (RCTs) and real-world studies with DPP-4 inhibitors.

The current status of diabetes care in Italy

According to the Italian National Institute of Statistics (ISTAT), the known cases of diabetes in Italy were > 3 million in 2016, corresponding to a prevalence of > 5.3% of the entire population [18]. Estimates based on the data collected by the Italian ARNO Osservatorio Diabete—a database launched in 2007 to document treatment patterns of diabetes in Italy—have shown a prevalence of

6.3% which may underestimate the true prevalence of the disease, as diabetes patients that are not treated pharmacologically are not recorded in the database [3]. Furthermore, diabetes remains undiagnosed in a substantial proportion of patients. More than 60% of the diabetes patients in the ARNO database were aged more than 65 years and about one-fifth were more than 80 years.

According to the ISTAT, the standardized mortality rate due to diabetes was 28.4 per 100,000 Italian residents in 2014 [18]. Over the past 5 years, an improvement in the management of patients with diabetes has occurred as highlighted by the decrease in the hospitalization rate due to T2DM from 22.4/100,000 in 2010 to 13.7/100,000 in 2015 [18]. This improvement was observed across all Italian Regions [18]. CKD and CV disease are the most frequent complications associated with T2DM, with an estimated prevalence of 37.5% and 23.2%, respectively, among T2DM patients, according to the Italian multicenter RIACE study [19]. A recent study comparing the incidence of major CV events, deaths and drug prescriptions in patients with or without diabetes in a Northern Italian Region found a decrease in the incidence of CV morbidity and mortality between 2002 and 2012 in both groups [20]. These findings were paralleled by an increase, over the same period, in the use of drugs for CV disease and for diabetes.

With regard to the prescription of antihyperglycemic drugs in Italy, recent data from the Medicines Utilization Monitoring Centre (OsMed) of the Italian medicines agency (AIFA) have shown a considerable reduction from 2015 to 2016 in the use of insulins and insulin analogues [21]. The utilization of sulfonylureas in association with metformin or as monotherapy has also decreased from 2015 to 2016, while a 6.8% increase in the use of DPP-4 inhibitors has been reported [21]. According to the ARNO database mentioned above, in 2016 metformin was the most frequently used oral antihyperglycemic (62.2% of 516,073 treated individuals) followed by sulfonylureas (19.2%), repaglinide (8.9%), and metformin plus sulfonylureas (8.2%) [3]. DPP-4 inhibitors were used by 7.0% of patients in combination with metformin and by 5.0% as monotherapy. Among the five currently available gliptins, sitagliptin was the most frequently used in association with metformin or alone. The other newer oral antihyperglycemics, GLP-1 analogues and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, were used by 2.4% and 2.5% of patients recorded in the ARNO database, respectively.

The relatively low use of DPP-4 inhibitors in Italy can be explained, at least in part, by the prescribing limitations issued by the AIFA [22]. According to these limitations, incretin-based therapies are reimbursed only if they are prescribed by a diabetes specialist. Furthermore, the prescription of incretin-based drugs is restricted to cases of therapeutic failure defined by levels of glycated hemoglobin

$(HbA_{1c}) \geq 7.5\%$ (≥ 58 mmol/mol) with the maximum tolerated dose of the current glucose-lowering agent [22]. In addition, HbA_{1c} levels must be < 8.5–9.0% (< 69–75 mmol/mol), a limit established based on the fact that the average HbA_{1c} reduction associated with incretin-based therapy is $\leq 1\%$ [22]. Evidence suggests that current prescribing regulations for incretin-based therapies result in limited access to appropriate treatment for patients not referred to diabetes centers.

In contrast, an analysis of electronic health record systems and national registers in Finland showed that DPP4-inhibitors were the most common agent for treatment intensification after metformin failure and that the increased use of DPP4-inhibitors occurred after the introduction of a policy for full reimbursement (in 2010) [23]. Similar to Italy, treatment intensification tended to occur at relatively high HbA_{1c} levels (at approximately 7.5%, 58 mmol/mol), which is higher than recommended international and international guidelines (at 7.0%, 53 mmol/mol) [23].

According to the 2015 data from the ARNO database concerning the diabetes population aged ≥ 65 years, a substantial proportion of elderly patients were treated with insulin secretagogues (43.4%), including sulfonylureas and glinides, which are associated with a higher risk of hypoglycemia compared with other oral antihyperglycemics [24]. These findings are in line with the results from real-life observational studies. For example, the RIACE study showed that sulfonylureas and repaglinide are widely used in clinical practice in elderly patients with impaired renal function and that their use tend to increase with increasing age [25]. According to the ARNO database, only 10.7% of elderly patients were treated with DPP-4 inhibitors alone or in association with metformin, and the proportion of older patients treated with gliptins decreased with increasing age [24]. In Italy, the underprescribing of gliptins to older T2DM patients after failure of metformin monotherapy may also be a consequence of the fact that these patients, who are usually treated by general practitioners (GPs), will more likely be prescribed the add-on of traditional medications, like sulfonylureas, than be referred to a diabetologist for prescription of DPP-4 inhibitors.

T2DM management 10 years after the introduction of DPP-4 inhibitors

The development of DPP-4 inhibitors was made possible by the improvements in our understanding of the pathophysiology of diabetes leading to the design of drugs able to target the mechanisms responsible for hyperglycemia and, therefore, to provide a more physiologic control of blood glucose [9]. The introduction of DPP-4 inhibitors has brought about an important conceptual change in the management of T2DM and caused a shift from an approach focused on lowering glucose levels to strategies targeting the underlying pathophysiological processes [8]. DPP-4 inhibitors have also contributed to the recognition of hypoglycemic adverse events and weight gain as important clinical barriers to optimal glucose-lowering therapy [8].

Specifically targeting some of the various causes of hyperglycemia, newly introduced agents—gliptins as well as GLP-1 receptor agonists and SGLT-2 inhibitors—have substantially enlarged the available therapeutic armamentarium, which now includes as many as 7 classes of non-insulin anti-hyperglycemia drugs. This large armamentarium allows physicians to tailor anti-hyperglycemic treatment to fit the specific needs of each individual patient and to achieve personalized glucose/HbA1c targets with an improved safety profile [7].

Compared with other oral antihyperglycemics, DPP-4 inhibitors induce a less rapid and marked glucose-lowering effect. This more gradual effect on glucose levels is counterbalanced by a more favorable safety profile: gliptins have a neutral effect on body weight and, by stimulating insulin secretion in a glucose-dependent manner, they do not cause hypoglycemia by themselves [26–29]. Thus, the introduction of DPP-4 inhibitors has no doubt provided a valid and overall safer alternative to insulin secretagogues (sulfonylureas and glinides) for the intensification of glucose-lowering treatment after failure of metformin monotherapy [27]. Furthermore, DPP-4 inhibitors can be used in elderly patients and in the presence of CKD [11–15, 30]. Of note, large real-life observational studies comparing the effectiveness of DPP-4 inhibitors vs sulfonylureas have demonstrated that the addition of a DPP-4 inhibitor to ongoing therapy allows for better glycemic control than the addition of a sulfonylurea, and that HbA_{1c}-lowering is directly proportional to baseline HbA_{1c} levels and indirectly proportional to T2DM duration [31, 32]. Evidence also exists that treatment with gliptins potentiate glucose-dependent insulin secretion in T2DM and, more recently, in latent autoimmune diabetes in adults [33–36].

Overall, DPP-4 inhibitors are characterized by intermediate glucose-lowering efficacy, low risk of hypoglycemia, neutral effect on body weight, low frequency of side effects, and high costs [17, 37]. Efficacy appears comparable among class members, but very few head-to-head comparisons of gliptins are available. Vildagliptin and sitagliptin were the first to be granted marketing authorization by the European Medicines Agency (2007) followed by saxagliptin (2009), linagliptin (2011), and alogliptin (2013). All five gliptins can be used in elderly patients and in the presence of mild renal impairment, with no need for dose adjustments [11–15]. Table 1 summarizes relevant information concerning the treatment with each member of the gliptin family.

Table 1 Main characteristics of DPP-4 inhibitors currently licensed by the European Medicines Agency [11–15]

DPP-4 inhibitor	Posology and administration	Drug–drug interactions	Renal impairment	Hepatic impairment	Further precautions
Alogliptin	25 mg, once daily. When used in combination with SU or insulin, consider a lower dose of SU or insulin. Oral, with or without a meal		Mild impairment[a]: no dose adjustment. Moderate impairment: 12.5 mg, once daily. Severe impairment or ESRD: 6.25 mg, once daily. Renal function tests recommended before and during treatment	Mild–moderate impairment[d]: no dose adjustment. Severe impairment: not recommended	Obtain liver function tests promptly in pts with symptoms of liver injury
Linagliptin	5 mg, once daily. When used in combination with SU or insulin, consider a lower dose of SU or insulin. Oral, with or without a meal		No dose adjustment required	No dose adjustment required	Discontinue if bullous pemphigoid is suspected
Saxagliptin	5 mg, once daily. When used in combination with SU or insulin, consider a lower dose of SU or insulin. Oral, with or without a meal	If used with potent CYP3A4/5 inducer, glycemic control should be assessed	Mild impairment: no dose adjustment. Moderate–severe impairment: 2.5 mg, once daily. ESRD: not recommended. Renal function tests recommended before and during treatment	Mild impairment: no dose adjustment. Moderate impairment: use with caution. Severe impairment: not recommended	Discontinue if hypersensitivity reactions are suspected. Monitoring for skin disorders recommended. Caution warranted in pts with known risk factors for hospitalization for HF
Sitagliptin	100 mg, once daily. When used in combination with SU or insulin, consider a lower dose of SU or insulin. Oral, with or without a meal		Mild impairment[c]: no dose adjustment if GFR ≥45 to <60 ml/min; 50 mg, once daily, if GFR ≥30 to <45 ml/min. Severe impairment or ESRD: 25 mg, once daily. Renal function tests recommended before and during treatment	Mild–moderate impairment: no dose adjustment. Severe impairment: use with caution	Discontinue if hypersensitivity reactions or bullous pemphigoid are suspected
Vildagliptin	50 mg, twice daily. 50 mg, once daily, when used in combination with SU; or reduce the SU dose. Oral, with or without a meal		Mild impairment[a]: no dose adjustment. Moderate–severe impairment: 50 mg, once daily. ESRD: use with caution	Should not be used[b]	Not recommended in pts with NYHA functional class IV

For all DPP-4 inhibitors, there is a low potential of clinically relevant drug–drug interactions, no dose adjustment is required in patients with a history of acute pancreatitis, and DPP-4 inhibitor should be discontinued if pancreatitis is suspected

DPP-4 dipeptidyl peptidase-4, *ESRD* end-stage renal disease, *HF* heart failure, *NYHA* New York Heart Association, *pts* patients, *SU* sulfonylurea

[a] Mild, moderate, and severe renal impairment are defined by creatinine clearance ≥ 50 to <80 ml/min, ≥ 30 to <50 ml/min, and <30 ml/min, respectively

[b] Any grade of hepatic impairment including pre-treatment alanine aminotransferase (ALN) or aspartate aminotransferase (AST) > 3x upper limit of normal

[c] Mild, moderate, and severe renal impairment are defined by a glomerular filtration rate (GFR) ≥60 to <90 ml/min, ≥ 30 to <60 ml/min, and ≥ 15 to <30 ml/min, respectively; ESRD is defined by GFR <15 ml/min

[d] Mild–moderate impairment: Child-Pugh scores of 5 to 9; severe impairment: Child-Pugh score >9

DPP-4 inhibitors have been extensively studied in clinical trials over the past decade and a number of studies are ongoing. Real-world evidence supporting the effectiveness of DPP-4 inhibitors is also available. In the next sections, relevant efficacy, safety, and effectiveness of DPP-4 inhibitors will be discussed.

Efficacy of DPP-4 inhibitors

General diabetes population

Most trials with DPP-4 inhibitors were designed to test the agents as add-on to the standard treatment of T2DM, usually metformin. In these trials, DPP-4 inhibitors were compared with placebo or with other add-on treatments. Several systematic reviews and meta-analyses of trials evaluating DPP-4 inhibitors have been performed [26, 28, 29, 38–45].

In an evaluation of 63 systematic reviews of DPP-4 inhibitors for the treatment of T2DM, all DPP-4 inhibitors were shown to significantly reduce HbA_{1c} levels compared with placebo and had similar ability to metformin in reducing HbA1c levels, but were less effective when compared with GLP-1 receptor agonists and sulfonylureas [44]. Similarly, a Bayesian network meta-analysis of 58 randomized controlled trials ($n = 31,356$ participants with T2DM), which assessed the efficacy and safety of DPP-4 inhibitors compared with placebo and with each other, showed a decrease in HbA_{1c} for all DPP-4 inhibitors vs placebo, except for alogliptin; vildagliptin 50 mg twice daily showed the highest probability in reduction effect on HbA_{1c} [45]. In addition, all DPP-4 inhibitors, and especially linagliptin 10 mg once daily, significantly reduced fasting plasma glucose when compared with placebo [45].

The efficacy of DPP-4 inhibitors on HbA_{1c} levels appears to fall within a suitable range. A meta-regression analysis of 78 RCTs evaluating the efficacy of gliptins on HbA_{1c} levels and including 20,503 patients with T2DM estimated a mean decrease of HbA_{1c} levels from baseline [mean baseline HbA_{1c} 8.03% (64 mmol/mol)] of -0.74% [46]. Treatment duration ranged from 12 to 104 weeks. The analysis found that baseline HbA_{1c} and fasting glucose levels influenced the response to gliptins, with greater HbA_{1c} reductions being achieved in patients with higher baseline HbA_{1c} and lower fasting glucose levels.

Overall, the evidence from trials comparing DPP-4 inhibitors with sulfonylureas, the oral antihyperglycemics most commonly used as add-on to metformin in the second-line setting, shows a greater efficacy of sulfonylureas in lowering HbA_{1c} levels during the first 3 months' of treatment, while DPP-4 inhibitors have demonstrated efficacy in the long-term maintenance of glycemic control. A meta-analysis including 12 RCTs of ≥ 18-week duration, which compared head-to-head DPP-4 inhibitors with sulfonylureas in T2DM patients ($n = 10,982$, overall), found that sulfonylureas lowered HbA_{1c} significantly more than DPP-4 inhibitors [28]. However, DPP-4 inhibitors had a more favorable safety profile than sulfonylureas, as highlighted by a reduction in body weight, total adverse events and CV events, and a lower risk of hypoglycemia [28]. A meta-analysis of 16 studies with 15,176 patients (8,047 treated with a DPP-4 inhibitor and 7,129 with a sulfonylurea) specifically addressed the efficacy of gliptins vs sulfonylureas, both as add-on therapy to metformin [42]. Sulfonylureas were associated with a significantly greater reduction in HbA_{1c} from baseline to 12 weeks; however, at 52 and 104 weeks, differences between the two treatments were no longer statistically significant. At all-time points, sulfonylureas, but not DPP4-inhibitors, were associated with weight gain. The incidence of hypoglycemia at 12, 52, and 104 weeks was substantially and significantly greater with sulfonylureas (20%, 24%, and 27%, respectively) compared with DPP-4 inhibitors (6%, 3%, and 4%, respectively). Notably, the proportion of patients achieving, at 52 and 104 week, the recommended target of $HbA_{1c} < 7\%$ (< 53 mmol/mol), without hypoglycemia, was significantly higher among patients on DPP-4 inhibitors.

Patients with renal impairment

Metformin, the recommended first-line option in T2DM patients not adequately controlled by diet and lifestyle interventions, is contraindicated in patients with moderate–severe renal impairment. Before the introduction of the newer oral antihyperglycemics, these patients had few treatment options. The fact that renal dysfunction is associated with an increased risk of hypoglycemia further complicates the management of these patients [30]. Several studies have shown that DPP-4 inhibitors are effective in lowering HbA_{1c} levels in patients with T2DM and renal impairment, without increasing the risk of hypoglycemia or other adverse events, especially vs active comparators [30, 47–51]. This is reflected in the labels of the five approved gliptins, according to which, these agents are not contraindicated in patients with mild–moderate renal dysfunction (Table 1) [11–15].

Elderly patients

Evidence from more recent studies has, however, shown that DPP-4 inhibitors can also be used successfully in patients aged ≥ 65 years and with long-standing disease. Older T2DM patients are a difficult-to-treat group as they often have multiple comorbidities and are at increased risk of severe hypoglycemia due to different age-related conditions, including progressive renal failure, CV disease, reduced glucagon secretion, and hypoglycemia unawareness [4]. According to national and international guidelines, older adults can use

all currently available glucose-lowering agents [4, 16, 17]. When selecting the glucose-lowering agent, great care must be taken to prevent hypoglycemic events, especially in this age group. The cognitive status of the patient, the drug–drug interactions related to polytherapy, and the CV risk must be carefully evaluated, as well, to provide a care plan as individualized as possible.

Studies of DPP-4 inhibitors in older adults have clearly suggested the potential of gliptins for the management of T2DM in this important age group [6, 7, 52–56]. A summary of efficacy outcomes of DPP-4 inhibitors in elderly patients with T2DM is shown in Table 2 [6, 7, 53, 56–60]. Alogliptin was shown to be non-inferior to glipizide with consistent and comparable glycemic control in mildly hyperglycemic elderly T2DM patients [59] and to be effective and well tolerated in elderly T2DM patients (aged ≥ 65 years) with similar HbA_{1c} improvements to younger patients (aged < 65 years) and no increased risk of hypoglycemia, weight gain, or other adverse events [58]. Linagliptin improved glycaemia and had a safety profile similar to placebo in elderly T2DM patients with inadequate glycemic control despite receiving other glucose-lowering drugs [6]. Linagliptin was also efficacious in reducing HbA_{1c} and well tolerated, and appears to reduce the risk of hypoglycemia when added to basal insulin [53]. Improved glycemic control was achieved with saxagliptin as monotherapy, add-on therapy, or initial combination therapy with metformin in elderly T2DM patients [57]. The efficacy and safety of sitagliptin was confirmed in elderly T2DM patients (≥ 75 years) with improved HbA_{1c} levels and no increased risk of hypoglycemia [60]. Treatment with vildagliptin achieved individualized glycemic target levels with no safety or tolerability issues in elderly T2DM patients [7] with significantly improved compliance and persistence to treatment and lower rates of hypoglycemic events [56].

The favorable safety profile of DPP-4 inhibitors, especially in terms of reduced risk of hypoglycemia, may also result in improved ease of use of these drugs, as compared with other glucose-lowering agents that require regular food intake to prevent hypoglycemic events. Improved ease of use is no doubt a major advantage, especially for elderly T2DM patients. Additional characteristics that may constitute an advantage over other antihyperglycemics in older diabetes patients, who are often frail and on polytherapy, include the lack of clinically meaningful drug interactions for most gliptins (Table 1), and a neutral or protective effect on the risk of bone fractures [11–15, 61, 62].

Real-world evidence

Real-world evidence is crucial for demonstrating the effectiveness of a novel drug, that is, its ability to work under real-life conditions and to provide benefits that are important for patients. Regulatory authorities and decision-makers,

along with the evidence from RCTs, increasingly request it. The worldwide, real-life observational EDGE study was conducted in more than 45,000 patients from 27 countries to compare the effectiveness of vildagliptin in dual therapy with other commonly used glucose-lowering agents for second-line, mostly metformin–sulfonylureas or metformin–pioglitazone combinations [63]. Vildagliptin not only achieved a reduction in HbA_{1c} of 1.19% over 12 months, comparable to that observed in RCTs, but was also superior to the comparators at every time point over the year. Similarly, a sub-analysis of the DARWIN-T2D real-world study [64] demonstrated significant benefits of DPP-4 inhibitors in terms of reductions in HbA1c, fasting glucose, and body weight compared with the sulfonylurea, gliclazide, after a median of 6-month follow-up [32]. Together these studies highlight the importance of real-world evidence in enhancing our understanding of the potential role that therapeutic drugs have in clinical practice.

Following the introduction of the newer oral antihyperglycemics in 2008, the AIFA launched the Anti-diabetics Monitoring Registry to monitor the use of incretin-based therapies and for post-marketing safety surveillance [65]. Of 77,864 records entered between February 2008 and August 2010, 75,283 were of patients initiating a DPP-4 inhibitor or a GLP-1 receptor agonist (38,811 sitagliptin, 21,064 exenatide, and 17,989 vildagliptin). Patients aged ≥ 75 years were approximately 10% of the patients treated with a DPP-4 inhibitor. Reductions of HbA_{1c} levels were − 0.88% and − 0.94% for sitagliptin and vildagliptin, respectively. The probability of achieving the HbA_{1c} target of 7% (53 mmol/mol) with both gliptins decreased rapidly with increasing baseline HbA_{1c}. Body weight decreased with treatment by approximately 1%. The safety profile of sitagliptin and vildagliptin was similar to that reported in RCTs.

Safety of DPP-4 inhibitors

Overall, a favorable safety and tolerability profile of DPP-4 inhibitors has emerged from RCTs [27]. Indeed, the incidence of hypoglycemia was found to be lower with DPP-4 inhibitors compared with sulfonylureas but was not significantly different compared with placebo or GLP-1 receptor agonists in an evaluation of 63 systematic reviews of DPP-4 inhibitors for the treatment of T2DM [44]. DPP-4 inhibitors also had similar effects in reducing the incidence of CV events, CV mortality, infections, diarrhea and nausea compared with placebo, but were associated with an lower risk of CV events compared with sulfonylureas treatment [44]. Similarly, DPP-4 inhibitors were also associated with no increase in the incidence of adverse events in a Bayesian network meta-analysis of 58 randomized controlled trials, although vildagliptin 100 mg once daily and sitagliptin

Table 2 Summary of efficacy outcomes of the DPP-4 inhibitors in elderly patients with T2DM

DPP-4 inhibitor	Study type	Patient population	Efficacy outcomes
Alogliptin [58, 59]	Rosenstock et al. 2013 [59] Global, multicenter, randomized, double-blind, active-controlled study	441 T2DM pts (aged 65–90 years) with HbA1c 6.5–9.0% (48–75 mmol/mol) on diet/exercise alone or HbA$_{1c}$ 6.5–8.0% (48–64 mmol/mol) on oral antidiabetic monotherapy	LS mean changes in HbA$_{1c}$ from baseline at wk 52 were −0.14% with alogliptin and −0.09% with glipizide (treatment-group difference −0.05%; one-sided 97.5% CI −∞, 0.13)
	Pratley et al. 2009 [58] Pooled analysis of six randomized, double-blind, phase 2 and 3, placebo-controlled studies	455 T2DM pts aged ≥ 65 with inadequate glycemic control	Compared with baseline, LS mean HbA$_{1c}$ decreased significantly at 26 wks (12 wks in phase 2 study) by 0.7% and 0.8% in pts receiving alogliptin 12.5 and 25 mg, respectively ($p < 0.001$ for both alogliptin doses vs placebo)
Linagliptin [6, 53]	Barnett et al. 2013 [6] Randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial	241 T2DM pts aged ≥ 70 years with HbA$_{1c}$ ≥ 7.0% (≥ 53 mmol/mol) receiving stable doses of common antidiabetic treatments for at least 8 wks	Placebo-adjusted mean change from baseline in HbA$_{1c}$ with linagliptin was −0.64% (95% CI −0.81 to −0.48, $p < 0.0001$) at wk 24
	Inzucchi et al. 2015 [53] Prespecified retrospective analysis of two phase 3, multinational, randomized, double-blind, placebo-controlled, parallel-group clinical trials	247 T2DM pts aged ≥ 70 years receiving basal insulin therapy with or without oral glucose-lowering drugs	Placebo-adjusted change from baseline in HbA$_{1c}$ with linagliptin of −0.77% (95% CI −0.95 to 0.59; $p < 0.0001$) after 24 wks
Saxagliptin [57]	Post hoc analysis of pooled data from five 24-week phase III, multicenter, randomized, double-blind trials	428 T2DM pts aged ≥ 65 years with HbA$_{1c}$ 7–10.5% (53–91 mmol/mol) who were either treatment-naïve or had not achieved adequate glycemic control on monotherapy with metformin, thiazolidinedione or sulfonylurea	Placebo-adjusted mean change in HbA$_{1c}$ with saxagliptin 2.5 mg of −0.60% (95% CI, −0.99% to −0.21%) and −0.55% (−0.97% to −0.14%) for saxagliptin 5 mg after 24 wks
Sitagliptin [60]	Post hoc age-stratified analysis	Elderly Japanese T2DM pts (aged 65–74 [n = 281], and ≥ 75 [n = 126] years) on diet/exercise alone or with HbA$_{1c}$ ≥ 6.9% (≥ 52 mmol/mol) despite treatment with hypoglycemic agents	HbA$_{1c}$ decreased significantly from baseline to 24 months for pts aged 65–74 years (from 7.6 to 7.0% [60 to 53 mmol/mol]) and aged ≥ 75 years (from 7.7 to 7.1% [61 to 54 mmol/mol]) ($p < 0.05$ for both age groups)
Vildagliptin [7, 56]	Strain et al. 2013 [7] Randomized, double-blind, placebo-controlled study	276 T2DM pts aged ≥ 70 years either treatment-naïve or inadequately controlled by conventional oral antidiabetic drugs	Significantly more pts in the vildagliptin group achieved their individualized HbA1c targets vs the placebo group (52.6% vs 27.0%, respectively; adjusted odds ratio 3.16, 96.2% CI 1.81–5.52; $p < 0.0001$) Clinically relevant 0.9% reduction in HbA1c from a baseline value of 7.9% (63 mmol/mol) with vildagliptin at wk 24, with a between-group difference of −0.6% (98.8% CI −0.81 to −0.33; $p < 0.0001$)

Table 2 (continued)

DPP-4 inhibitor	Study type	Patient population	Efficacy outcomes
	Sicras-Mainar et al. 2014 [56]		
	Multicenter, retrospective, observational study analysis	T2DM pts aged ≥ 65 years receiving either metformin + vildagliptin (n = 270) or metformin plus sulfonylureas or glitazones (reference group, n = 717)	Significantly (p < 0.05) improved compliance (68.3% vs 62.5%), persistence (61.5% vs 55.1%), and metabolic control (63.3% vs 57.6%) and significantly (p < 0.05) lower rates of CVE (4.4% vs 8.6%) and hypoglycemia (17.4% vs 42.8%) for vildagliptin-treated pts vs the reference group

CI confidence interval, CVE cardiovascular events, HbA_{1c} glycated hemoglobin, LS least squares, n number, pts patients, SU sulfonylurea, T2DM type 2 diabetes mellitus, wk week

100 mg once daily were associated with the lowest probability in reducing the incidence of hypoglycemia and upper respiratory tract infection, respectively [45].

This favorable safety and tolerability profile has been largely confirmed in vulnerable D2TM subpopulations, such as elderly patients and patients with renal impairment, as well as in the real-world observational and the post-marketing setting [27, 63, 66, 67]. Table 3 provides an overview of the safety profile of the five available gliptins that has emerged from clinical trials and post-marketing surveillance.

Over the past decade, new regulatory guidelines have enforced the adjudication of all CV events when testing novel diabetes drugs. Endpoints of CV mortality, myocardial infarction, stroke, and hospitalization for heart failure were, therefore, included in most clinical studies on DPP-4 inhibitors. Five large, placebo-controlled, CV safety outcome trials in T2DM patients with established CV disease were conducted with saxagliptin (SAVOR-TIMI 53 trial, ~ 16,500 patients), alogliptin (EXAMINE trial, ~ 5400 patients), sitagliptin (TECOS trial, ~ 15,000 patients), and linagliptin (CARMELINA trial, 6,979 patients; CAROLINA trial, ~ 6000 patients) (Table 3) [68–72]. The EXAMINE trial revealed the non-inferiority of alogliptin vs placebo in terms of CV events [71]. Findings from the SAVOR-TIMI 53 trial confirmed the overall CV safety of saxagliptin, but raised a warning related to the increase in the risk of hospitalization for heart failure in the saxagliptin group [70]. No CV safety issues emerged from the TECOS trial evaluating sitagliptin [68]. The CARMELINA trial demonstrated a non-inferior risk of a composite CV outcome over a median of 2.2 years for linagliptin vs placebo when added to standard care in T2DM patients with established CV and/or kidney complications [72]. The results concerning the CV outcomes associated with linagliptin (CAROLINA trial) are expected soon. No CV outcome trial was planned for vildagliptin, but several trials have addressed its CV safety [73, 74]. In a meta-analysis (40 trials, 17,446 patients), vildagliptin was not associated with an increased risk of adjudicated major adverse CV events vs the comparators (any non-vildagliptin agent) (Table 3) [73]. The analysis did not find a significant increased risk of heart failure in patients treated with vildagliptin. The VIVIDD trial evaluated the effect of a 52-week treatment with vildagliptin on left ventricular ejection fraction (LVEF) in 254 subjects with T2DM and congestive heart failure [74]. The results showed no major effect on LVEF, but a statistically significant increase in left ventricular end-diastolic volume in the vildagliptin arm vs the placebo arm. The clinical implications of this observation are currently unclear. Based on the available evidence on CV outcomes associated with DPP-4 inhibitors, the general consensus in the field is that more data are needed for most gliptins, notably in patients with established heart failure and left ventricular systolic dysfunction [43, 74, 75].

Table 3 Summary of the safety profiles of the DPP-4 inhibitors approved by the European Medicines Agency

DPP-4 inhibitor	Phase 3/4 clinical trials	Cardiovascular outcome trials	Post-marketing surveillance reports
Alogliptin [15, 71]	Headache Overall comparable incidence of AEs, SAEs, and AEs requiring treatment discontinuation in pts treated with alogliptin or placebo/active control Pancreatitis	EXAMINE trial MACE in 11.3% (alogliptin) vs 11.8% (placebo), HR 0.96; $p < 0.001$ Similar rates of pancreatitis	Hypersensitivity reactions Acute pancreatitis Hepatic dysfunction Skin and subcutaneous tissue disorders
Linagliptin [14, 69, 72]	Hypoglycemia (when used in triple therapy with metformin and SU) Pancreatitis	CARMELINA trial MACE in 12.4% (linagliptin) vs 12.1% (placebo); HR, 1.02; 95% CI 0.89–1.17; $p < 0.001$ for non-inferiority Similar rates of acute or chronic pancreatitis CAROLINA trial Ongoing	Angioedema, urticaria, rash, bullous pemphigoid
Saxagliptin [13, 70]	Upper respiratory tract infections Urinary tract infections Headache Arthralgia Pancreatitis	SAVOR-TIMI 53 trial MACE in 7.3% (saxagliptin) vs 7.2% (placebo); HR 1.00, 95% CI 0.89–1.12, $p = 0.99$ for superiority and $p < 0.001$ for non-inferiority Hospitalization rates for HF: 3.5% vs 2.8%, HR 1.27, 95% CI 1.07–1.51, $p = 0.007$ Similar rates of acute or chronic pancreatitis	Hypersensitivity and anaphylactic reactions Abdominal pain, nausea, pancreatitis Rash Arthralgia
Sitagliptin [12, 68]	Headache Hypoglycemia in combination with SU and insulin Pancreatitis	TECOS trial MACE in 11.4% (sitagliptin) vs 11.6% (placebo); HR 0.98, 95% CI 0.88–1.09; $p < 0.001$ Similar rates of hospitalization for HF (HR 1.00, 95% CI 0.83–1.20; $p = 0.98$) Similar rates of acute pancreatitis and pancreatic cancer	Acute pancreatitis Hypersensitivity reactions Arthralgia, myalgia, back pain Skin and subcutaneous tissue disorders Impaired renal function
Vildagliptin [11, 73]	AEs mostly mild and transient, not requiring treatment discontinuation Rare cases of hepatic dysfunction Rare cases of angioedema (especially pts on ACE-inhibitor) Pancreatitis	Meta-analysis of 40 phase III/IV trials (9,599 vildagliptin-treated pts) Composite MACEs in 0.86% (vildagliptin) vs 1.20% (comparator); M-H RR 0.82 (95% CI 0.61–1.11) Similar RRs for the individual events Confirmed HF events in 0.43% (vildagliptin) vs 0.45% (comparator); M-H RR 1.08 (95% CI 0.68–1.70)	Pancreatitis Hepatitis, abnormal liver function tests Myalgia Urticaria, exfoliative and bullous skin lesions

ACE angiotensin converting enzyme, *AE* adverse event, *CI* confidence interval, *HF* heart failure, *HR* hazard ratio, *MACE* major adverse cardiovascular event (myocardial infarction, stroke, and death from cardiovascular causes), *M-H RR* Mantel–Haenszel risk ratio, *pts* patients, *SAE* severe adverse event, *SU* sulfonylurea

Patients with T2DM have a twofold increased risk of developing acute pancreatitis compared with healthy individuals [67]. All incretin-based therapies have been extensively evaluated for pancreatic safety, due to the potential risk of pancreatic events, although no conclusive evidence of a causal relationship is available. Although an extensive evaluation of non-clinical and clinical data by the European Medicines Agency and the US Food and Drug Administration suggested no causal association between incretin-based therapies and pancreatic adverse events, the risk of acute pancreatitis has been added to the label of all DPP-4 inhibitors (Table 1) [76]. Notably, similar rates of acute or chronic pancreatitis have been reported in four large, placebo-controlled, CV safety outcome trials in T2DM patients with established CV disease: EXAMINE (alogliptin), CARMELINA (linagliptin), SAVOR-TIMI (saxagliptin), and TECOS (sitagliptin) (Table 3) [68, 70–72].

Results concerning pancreatic safety obtained in meta-analyses are conflicting [77]. A meta-analysis, including the large CV outcome trials discussed above, demonstrated an

increased relative risk of acute pancreatitis (odds ratio 1.79; 95% CI 1.13–2.82) versus placebo, although the absolute risk increase was low (0.13%) [78]. A recent meta-analysis of 38 trials (59,404 patients), which compared DPP-4 inhibitors with placebo or other antihyperglycemic agents, found an increased risk of acute pancreatitis (Peto odds ratio 1.72, 95% CI 1.18–2.53) with DPP-4 inhibitors, but no relationship with pancreatic cancer [77]. The estimated number needed to harm was 1066, confirming that the risk of developing acute pancreatitis is low [77–79].

Conclusions and perspectives

Ten years of use in clinical practice, along with the evidence from an extensive program of clinical research and post-marketing surveillance, show that the development of DPP-4 inhibitors has been a valuable addition to the available therapies for T2DM. DPP-4 inhibitors, which stimulate insulin secretion in a glucose-dependent manner, are characterized by a gradual and durable lowering effect on HbA_{1c} levels. Compared with commonly used oral glucose-lowering medications, DPP-4 inhibitors are associated with a low risk of hypoglycemic events and body weight increase. Due to the favorable safety and tolerability, DPP-4 inhibitors are indicated for the treatment of patients at high risk of hypoglycemia, including older patients and patients with renal impairment. They can be added at any stage of the treatment plan, with no major clinical barriers to their prescription, and are easy to administer.

With regard to diabetes care in Italy, evidence from national registries and databases suggests that DPP-4 inhibitors are underused, and that sulfonylureas and glinides continue to be the first choice when glycemic control with metformin monotherapy needs to be intensified. The prescribing limitations issued by the AIFA for incretin-based therapies are among the reasons for the underuse of DPP-4 inhibitors. According to these limitations, incretin-based therapies are reimbursed only if prescribed by a diabetes specialist; furthermore they cannot be prescribed to patients with $HbA_{1c} < 7.5\%$ (< 58 mmol/mol) even if the current medication has a less favorable risk–benefit profile, or to patients with $HbA_{1c} > 8.5$–9.0% (> 69–75 mmol/mol). A loosening of the prescribing limitations would be desirable in Italy to improve access to appropriate treatment, especially for patients, such as older individuals with CKD and other comorbidities, who have very few treatment options besides DPP-4 inhibitors. Such a change will require educational efforts directed to GPs to train them in the use of the newer glucose-lowering therapies.

Further research on DPP-4 inhibitors is needed. Important safety issues, including CV outcomes and the risk of acute pancreatitis, are still under investigation and need to be conclusively established. Clinical research in this area is also ongoing and will hopefully improve our understanding of central questions on the pathophysiology of diabetes.

Compliance with ethical standards

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