REVIEW

The Dipeptidyl Peptidase (DPP)-4 Inhibitors for Type 2 Diabetes Mellitus in Challenging Patient Groups

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ABSTRACT

Treating hyperglycemia is a critical aspect of managing type 2 diabetes mellitus (T2DM), but can be especially challenging in patients from vulnerable groups such as those with chronic kidney disease, African Americans, and older people. The dipeptidyl peptidase (DPP)-4 inhibitors are relatively new oral antidiabetes drugs that have been incorporated into treatment algorithms over the past few years and have also been studied in these vulnerable patients. Clinical trials with DPP-4 inhibitors have now been reported for all these patient groups and have demonstrated significant improvements in measures of hyperglycemia, with a good safety profile. Based on the current evidence, it appears that the DPP-4 inhibitors are worthy of consideration not only for the most straightforward patients with T2DM, but also for these vulnerable patients.

Keywords: African American; Chronic kidney disease; Dipeptidyl peptidase-4 inhibitors; Elderly; Type 2 diabetes mellitus

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INTRODUCTION

The prevalence and incidence of diabetes are increasing worldwide, largely due to changing lifestyles characterized by reduced physical activity, rising obesity rates, and an aging population. In the US, diabetes is the leading cause of kidney failure, new cases of blindness, and non-traumatic lower limb amputations, and is a major cause of heart disease and stroke [1]. Diabetes currently affects 8.3% of the US population, some 25.8 million people [1], and type 2 diabetes mellitus (T2DM) accounts for about 90–95% of all diagnosed diabetes cases in adults.

It is well documented that good glycemic control can positively influence much of the morbidity and mortality associated with T2DM [2]. To manage hyperglycemia, expert guidelines recommend treatment to a glycated hemoglobin (HbA1c) level of below 6.5% or below 7.0%, with recognition of the need for individualization of treatment goals, for example, to minimize the risks of hypoglycemia [2–4]. The percentage of US individuals with self-reported diabetes who achieved an HbA1c level of <7% increased from 44% in 1988–1994 to 52.5% in 2007–2010 [5]. Similarly, an observational study of non-insulin–treated patients with T2DM from Spain ($n = 2,266$) indicated that 45% had suboptimal HbA1c based on the <7% criterion [6]. The International Diabetes Management Practices Study (IDMPS) of data from developing regions of Eastern Europe, Asia, and Latin America reported that 36.4% of participants with T2DM achieved an HbA1c of <7% [7]. These data were consistent with those from an observational study in Taiwan in which the percentage of patients achieving the <7% goal increased from 32.4% in 2006 to 34.5% in 2011 [8]. Taken together, these findings suggest that there has been some success in putting guidelines into practice, but that approximately one-third to one-half of patients still fail to achieve HbA1c levels below 7.0% [5–8]. Furthermore, the progressive deterioration of β-cell function, irrespective of pharmacological interventions to treat hyperglycemia, leads to an almost inevitable need for intensification of treatment [2]. There is, therefore, a recognized need for new therapeutic options that are well tolerated over the long term and have a durable effect.

The dipeptidyl peptidase (DPP)-4 inhibitors are relatively new drugs that may help meet the need for these types of treatments, and following extensive testing in phase 3 clinical trials, these agents have now been included in treatment recommendations in all major diabetes guidelines. This review will provide a brief overview regarding the positioning of DPP-4 inhibitors in the context of major clinical guidelines. Furthermore, since the majority of patients in phase 3 trials are relatively young and healthy, an additional objective of this review is to consider the DPP-4 inhibitors for the treatment of T2DM in more vulnerable patient populations, namely those with chronic kidney disease (CKD), African Americans, and older people. Current guidelines for these patients, and the clinical trials conducted with DPP-4 inhibitors in these groups, will be reviewed.

METHODS

This was a non-systematic review of the literature. A search of English-language literature was performed using PubMed and without imposing any time limitations. Search terms included combinations of the following: 'type 2 diabetes', 'DPP-4 inhibitors', 'chronic kidney disease', 'end-stage renal disease', 'renal impairment', 'African American', and 'elderly'. Articles and abstracts relevant to the subject were included. Bibliographies from retrieved articles were also searched for relevant articles. Additional references known to the author were also included. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

DPP-4 INHIBITORS

The DPP-4 inhibitors improve glycemic control mainly via potentiation of the incretin effect, that is, the postprandial augmentation of insulin secretion by the gastrointestinal

incretin hormones glucagon-like peptide (GLP)-1 and gastric inhibitory polypeptide (GIP). Increases in GLP-1 levels appear to account for the majority of the DPP-4 inhibitors' effects [9]. In addition to enhancing glucose-dependent insulin secretion, GLP-1 suppresses glucose-dependent glucagon secretion, inhibits gastric emptying, and reduces appetite and food intake [10]. It has long been known that the incretin effect is blunted in patients with T2DM, generating interest in therapies that target the incretin system [10]. Native GLP-1 itself cannot be used in therapy due to its rapid degradation by the DPP-4 enzyme, resulting in a half-life of less than 2 min. Nevertheless, therapeutic approaches for enhancing incretin action have been developed and include degradation-resistant GLP-1 receptor agonists, and increasing levels of GLP-1 indirectly by inhibition of DPP-4 [10].

Four DPP-4 inhibitors are approved in the US: sitagliptin (approved 2006), saxagliptin (approved 2009), linagliptin (approved 2011), and alogliptin (approved 2013). Vildagliptin is another DPP-4 inhibitor that has been extensively studied and is currently available in the European Union and Japan. There are also other DPP-4 inhibitors in earlier stages of development that may become available over the coming years. Although all of the DPP-4 inhibitors share the same mechanism of action, they have different chemical and pharmacokinetic properties, which may translate into clinical options with distinct profiles.

Place in Current Guidelines

In clinical trials, all available DPP-4 inhibitors have been shown to improve glycemic control, with clinically meaningful reductions in HbA1c [11]. Furthermore, they are well tolerated, are associated with a low risk of hypoglycemia, and have a favorable weight profile [11]. As evidence accumulates for their effectiveness, the DPP-4 inhibitors have been incorporated into numerous guidelines available for the management of patients with T2DM. A consensus statement and algorithm issued by the American Association of Clinical Endocrinologists (AACE) in 2013 describes several options for monotherapy and variations of combination therapy [4]. The DPP-4 inhibitors are placed among monotherapy options for patients with an entry level HbA1c of <7.5%. As with American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommendations, metformin is recommended as the first-line choice where not contraindicated. The AACE algorithm also places DPP-4 inhibitors as an option for the second component of initial dual or triple therapy in patients with entry HbA1c levels of ≥7.5% or ≥9%, respectively. The DPP-4 inhibitors may also be considered as the first component of dual or triple therapy for patients for whom metformin is contraindicated. The detailed AACE guidelines issued in 2011 noted that DPP-4 inhibitors, along with metformin, sulfonylureas, glinides, and thiazolidinediones, are all approved for use in combination with insulin [3]. However, the guidelines also highlight a raised potential for hypoglycemia when a sulfonylurea or a glinide is used with insulin, as well as several adverse effects associated with thiazolidinediones in combination with insulin, suggesting that these combinations should be carefully considered.

The ADA and EASD also issued a position statement on the management of hyperglycemia in T2DM [12]. The ADA/EASD guidelines are less prescriptive, discuss

advantages and disadvantages of all antidiabetes medicines, and highlight the need for individualization of treatment. In the general recommendations outlined in the guidelines, DPP-4 inhibitors are positioned alongside sulfonylureas, thiazolidinediones, GLP-1 agonists, and insulin, as a second-line add-on to metformin. They are prioritized along with GLP-1 agonists as an add-on to metformin when the goal is to avoid weight gain, and with GLP-1 agonists and thiazolidinediones when the goal is to avoid hypoglycemia. When metformin is not an option for first-line therapy, the ADA/EASD guidelines suggest a sulfonylurea, thiazolidinedione, DPP-4 inhibitor, or GLP-1 agonist.

Among other guidelines, the International Diabetes Federation [13], the National Institute for Health and Clinical Excellence [14], and the US Department of Veterans Affairs/Department of Defense [15], all suggest DPP-4 inhibitors as an alternative add-on to metformin, when a sulfonylurea is contraindicated or when hypoglycemia is a concern.

Guidelines are typically based on randomized trials that recruit the most straightforward patients. In the past, this is known to have led to underuse of new treatments in the very patients who could benefit the most. For example, African Americans are generally not well represented in clinical trials [16], and this, in addition to other factors, resulted in lower use of angiotensin-converting enzyme (ACE)-inhibitors (ACEI) for the treatment of hypertension in African Americans [17]. Conversely, therapies should not be used in patients when evidence is lacking. Therefore, in light of a number of recently reported studies, it is worthwhile examining the available evidence for use of DPP-4 inhibitors in vulnerable patient groups.

Use in Patients with Chronic Kidney Disease

The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) defines CKD by the presence of kidney damage or a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more [18]. It also classifies the stages of CKD as ranging between Stage 1 (kidney damage with normal or increased GFR) and Stage 5 (kidney failure). End-stage renal disease (ESRD) is included under Stage 5 of the KDOQI classification and is defined as irreversible decline in kidney function that is severe enough to be fatal in the absence of dialysis or transplantation [18].

Diabetes is considered a major risk factor for CKD, with nearly 40% of adults with T2DM having some degree of CKD [19, 20]. Furthermore, 44% of new ESRD cases in the US in 2010 had a primary diagnosis of diabetes [21]. While managing hyperglycemia is a key goal in patients with CKD, glycemic targets and choice of therapy in this patient group warrant special consideration. For example, metformin, normally the first choice of treatment for T2DM, is renally excreted, and decreased kidney function may increase the risk of lactic acidosis with its use. Current prescribing guidelines in the US contraindicate metformin when serum creatinine levels are $\geq$1.4 mg/dL in women and $\geq$1.5 mg/dL in men [22]. Furthermore, many other common antidiabetes drugs are renally excreted and have a prolonged half-life in patients with CKD, thereby increasing the risk of hypoglycemia. Recent guidelines for diabetes and CKD state that HbA1c targets of <7.0% are not recommended in patients with diabetes who are at risk for hypoglycemia, including those treated with insulin or sulfonylureas and/or who have advanced CKD. They suggest

instead extending HbA1c targets above 7.0% for patients with diabetes who are at risk of hypoglycemia and have clinically significant comorbidities or limited life expectancy [23].

The glucose-dependent stimulation of insulin release by the DPP-4 inhibitors confers a low risk of hypoglycemia [24], suggesting potential value for managing hyperglycemia in patients with T2DM and CKD. Indeed, a number of trials that specifically investigated DPP-4 inhibitors in renally impaired populations have been reported (Table 1) or completed with results anticipated in the near future (Table 2) [25–36]. Efficacy and safety data from the clinical trials reported to date are encouraging, and the DPP-4 inhibitors were generally well tolerated (Table 1). With appropriate caution, the DPP-4 inhibitors can be used in patients with all degrees of renal insufficiency, including ESRD, although dosage reduction is needed for saxagliptin, sitagliptin, and vildagliptin. Linagliptin can be used without adjustment, since it is not renally excreted (Table 3) [37–41].

Individuals with concomitant T2DM and CKD may be receiving an ACEI for management of hypertension because this class of medications may reduce cardiovascular events and protect the kidney [2]. A small increase in the risk of angioedema has been observed in patients taking concurrent ACEI and vildagliptin, but the authors were unable to determine a class effect through review of postmarketing surveillance data and the literature [42]. It is postulated that ACE inhibition shifts the metabolism of the angioedema-associated vasoactive peptides bradykinin and substance P to the secondary DPP-4 pathway [42, 43]. However, little information is available regarding the clinical relevance and frequency of ACEI and DPP-4 inhibitor interactions [43]. On the other hand,

the propensity for drug–drug interactions mediated via the p-glycoprotein (P-gp) intestinal transport system and related to cytochrome P450 3A4 (CYP3A4) metabolism have been well characterized, with some variation among the DPP-4 inhibitors [37–41, 44]. Generally, the DPP-4 inhibitors have limited drug–drug interactions via these mechanisms [37–41, 44]. However, alternatives to strong inducers of CYP3A4 or P-gp (e.g. rifampin) are strongly recommended when linagliptin is to be administered [38]. In addition, a reduction of the saxagliptin dosage to 2.5 mg once daily is recommended when coadministered with strong CYP3A4/5 inhibitors (e.g. ketoconazole) [39].

Use in African Americans

African Americans are at an increased risk of T2DM, with a prevalence of diabetes approximately double that of the white population [45]. This group also has an increased rate of complications and greater disability from complications, as well as poorer glycemic control and quality of care [46–50]. The pathophysiology of T2DM may be different in African Americans than in other populations, with studies suggesting that insulin resistance is higher in minority populations [51]. There are various theoretical reasons to consider DPP-4 inhibitors in African Americans. First, a small number of studies report racial disparities in GLP-1 levels that may have implications for efficacy of DPP-4 inhibitors in African Americans. Two studies observed that African American adolescents had lower GLP-1 concentrations than white adolescents [52, 53]. In contrast, an earlier investigation reported that obese African American adults had significantly higher fasting and post-challenge GLP-1 concentrations than obese white adults

Table 1 Prospective phase 2/3 clinical trials of DPP-4 inhibitors in renally impaired patients (with published results)

References	Study drug	N^a	RI inclusion criteria	Study design	Control	Background therapy	Change in HbA1c (reported as in original publication)
[29]	Linagliptin, 5 mg/day	133	Severe, not on dialysis[b]	52-week double-blind, randomized, placebo-controlled	Placebo	Continued (included insulin, insulin and OAD, OAD mono- and combination therapy; fixed for 12 weeks, adjusted thereafter)	Adjusted mean change from baseline, % Week 12: linagliptin −0.76; placebo −0.15 Week 52: linagliptin −0.71; placebo 0.01
[30, 31]	Saxagliptin, 2.5 mg/day	170 (Extr: 129)	Moderate/severe/ ESRD	12-week double-blind, randomized, placebo-controlled phase; 40-week extension	Placebo	Continued (included insulin, insulin and OAD, OAD monotherapy)	Adjusted mean change from baseline, % (95% CI) Week 12: saxagliptin −0.86 (−1.08, −0.64) Placebo −0.44 (−0.66, −0.23) Week 52: saxagliptin −1.08 (−1.37, −0.80) Placebo −0.36 (−0.63, −0.08)
[32]	Sitagliptin, 50 mg/day (moderate RI) or 25 mg/day (severe RI)	91	Moderate/severe/ ESRD on dialysis[c]	12-week double-blind, randomized, placebo-controlled phase; 42-week active-controlled extension	First phase: placebo Extension: glipizide 5 mg/day; titrated in 2-week intervals to maximum of 20 mg/day	All OADs washed out; +/− insulin continued	Mean change from baseline, % (95% CI) Week 12: sitagliptin −0.6 (−0.8, −0.4) Placebo −0.2 (−0.4, 0.1) Week 54: sitagliptin −0.7 (−0.9, −0.4) Placebo/glipizide: −1.0 (−1.6, −0.3)
[33]	Sitagliptin, 50 mg/day (moderate RI) or 25 mg/day (severe RI)	426	Moderate/severe, not on dialysis[b]	54-week double-blind, randomized, active-controlled	Glipizide 2.5 mg/day; titrated to maximum of 20 mg/day	All OADs washed out	Mean change from baseline[d], % (95% CI) Week 54: sitagliptin −0.8 (−0.9, −0.6) glipizide −0.6 (−0.8, −0.5)
[34]	Sitagliptin, 25 mg/day	129	ESRD, all undergoing dialysis	54-week double-blind, randomized, parallel group	Glipizide 2.5 mg/day; titrated to maximum of 20 mg/day	All OADs washed out	Mean change from baseline[d], % (95% CI) Week 54: sitagliptin −0.72 (−0.95, −0.48) glipizide −0.87 (−1.11, −0.63)
[35, 36]	Vildagliptin, 50 mg/day	515 (Extr: 369)	Moderate/severe[c] (controlled phase included four patients with ESRD on dialysis, two of these patients randomized to vildagliptin entered extension)	24-week double-blind, randomized, placebo-controlled phase; 28-week extension	Placebo	Continued (included insulin, insulin and OAD, OAD mono- and combination therapy)	Approximate adjusted mean change from baseline, %[e] Week 24, moderate RI: vildagliptin −0.74; placebo −0.24 Week 24, severe RI: vildagliptin −0.91; placebo −0.32 Week 54, moderate RI: vildagliptin −0.57; placebo −0.13 Week 54, severe RI: vildagliptin −0.8; placebo −0.07

RI renal impairment, *HbA1c* glycated hemoglobin, *OAD* oral antidiabetes drug, *ext* extension, *ESRD* end-stage renal disease, *CI* confidence interval

[a] *N* number of randomized participants

[b] Degree of RI categorized based on glomerular filtration rate estimated by the Modification of Diet in Renal Disease formula as moderate (≥30 to <50 mL/min/1.73 m²) or severe (<30 mL/min/1.73 m²)

[c] Degree of RI categorized based on creatinine clearance (CrCl) estimated by the Cockcroft-Gault formula as moderate (CrCl ≥30 to <50 mL/min), severe (CrCl <30 mL/min, and not receiving dialysis), or ESRD (receiving dialysis)

[d] Least squares mean change from baseline

[e] Number in this table estimated from bar graph of adjusted mean change in HbA1c

Table 2 Recently completed phase 3/4 trials of DPP-4 inhibitors in renally impaired patients

Study drug/comparator	ClinicalTrials identifier	Number enrolled	Design	Key inclusion criteria
Albiglutide/sitagliptin	NCT01098539	507	26-week, double-blind, randomized, active-controlled	Patients with T2DM and RI
				Inadequate glycemic control with diet and exercise, or metformin, thiazolidinediones, sulfonylurea, or any combination of these OADs
				HbA1c $\geq$7.0% and $\leq$10.0%
				BMI $\geq$20 and $\leq$45 kg/m^2
				Fasting C-peptide $\geq$0.8 ng/mL ($\geq$0.26 nmol/L)
Linagliptin/placebo and glimepiride	NCT01087502	241	12-week, double-blind, randomized, placebo-controlled phase; 40-week active-controlled extension	Patients with T2DM and with GFR <60 mL/min
				HbA1c $\geq$7.0% and $\leq$10.0%
				BMI $\leq$45 kg/m^2
				Age $\geq$18 years
Sitagliptin/placebo	NCT00740363	25	4-week, open-label, randomized, crossover	Renal transplant recipient more than 1 year post-transplant with stable renal function and stable prednisolone dose for the last 3 months before inclusion
				New onset diabetes patients with fasting plasma glucose 7–8 mmol/L, and/or 2-h plasma glucose 12–18 mmol/L after an oral glucose tolerance test OR patients already on OAD therapy, but with HbA1c $\geq$8.0% and $\leq$11.0%
				Age $\geq$18 years

T2DM type 2 diabetes mellitus, *RI* renal impairment, *HbA1c* glycated hemoglobin, *BMI* body mass index, *GFR* glomerular filtration rate, *OAD* oral antidiabetes drug

Table 3 Recommended dosing of DPP-4 inhibitors in the presence of CKD

	First approved	Standard dose	Recommended dose in context of chronic kidney disease
Alogliptin [37]	US (2013)	25 mg once daily	CrCl ≥30 to <60 mL/min (moderate RI): 12.5 mg once daily
			CrCl <30 mL/min (severe/ESRD): 6.25 mg once daily
Linagliptin [38]	US (2011)	5 mg once daily	No dose adjustment required
Saxagliptin [39]	US (2009)	5 mg once daily	CrCl ≤50 mL/min (moderate/severe/ESRD): 2.5 mg once daily
Sitagliptin [40]	US (2006)	100 mg once daily	CrCl ≥30 to <50 mL/min (moderate RI): 50 mg once daily
			CrCl <30 mL/min (severe/ESRD): 25 mg once daily
Vildagliptin [41]	EU (2007)	50 mg twice daily	CrCl <50 mL/min (moderate/severe/ESRD): 50 mg once daily

CrCl creatinine clearance, *ESRD* end-stage renal disease, *RI* renal impairment

[54]. Further studies are warranted to confirm racial differences in GLP-1 levels and to investigate any therapeutic implications.

In the meantime, there are other reasons why DPP-4 inhibitors may be a good option for this population. A significant proportion of African Americans are overweight or obese, with the prevalence of overweight and obesity combined at 76.6% (69.9% in men, 82.1% in women), and the prevalence of obesity at 49.6% (38.8% in men, 58.6% in women) [55]. Overweight and obesity are risk factors for insulin resistance, and all guidelines therefore recommend losing weight for overweight or obese patients with T2DM [2–4]. In contrast to insulin and some oral antidiabetes drugs that can result in weight gain, the weight-neutral DPP-4 inhibitors may therefore be an appropriate option for patients who are overweight or obese. African Americans are also disproportionally affected by CKD and ESRD [56, 57], with the rate of new ESRD cases being 3.4 times higher among this group than among the white population [21]. The presence of renal impairment has implications for diabetes management, but as discussed in the previous section, the DPP-4 inhibitors remain a viable choice in this setting.

Despite the prevalence of T2DM in African Americans, there is limited clinical trial information for this population. While the DPP-4 inhibitors seem theoretically appropriate for use in African Americans with T2DM, this group is characterized by higher HbA1c levels than other populations [58]. With predicted HbA1c reductions ranging between 0.4 and 1.0% with this class of drugs [11, 59], monotherapy would likely not be suitable for all patients, although larger reductions are expected in patients with higher baseline HbA1c [60].

Based on composite analyses of available pharmacokinetic data, the prescribing information for all DPP-4 inhibitors state that no dose adjustment is necessary based on race [37–41], but to date only linagliptin has been specifically investigated in African Americans. A phase 1 study (NCT00935220) assessing its pharmacodynamic and pharmacokinetic profile in African Americans with T2DM for 7 days, supported linagliptin 5 mg/day as effective for controlling blood glucose levels [61]. A subsequent phase 3 trial (NCT01194830) evaluated its efficacy and safety in black/African Americans with T2DM over 24 weeks [62]. In this study, 226 patients were randomized to linagliptin or placebo, and HbA1c levels were measured every 6 weeks. A statistically significant and clinically relevant difference

between treatment groups was found for the change in HbA1c after 24 weeks [placebo-adjusted mean change of −0.58% (95% CI −0.91 to −0.26%; $P < 0.001$)], indicating the superiority of linagliptin compared with placebo in reducing HbA1c in black/African American patients [63]. Furthermore, as expected from pivotal trials, linagliptin was well tolerated and weight neutral, with a low rate of hypoglycemic events, confirming its safety profile as well as efficacy in African American patients with T2DM [63].

Use in Older People

The latest census figures in the US indicate that people aged 65 years and older represent 13.2% of the population [64], and this proportion is expected to grow to just over 20% by 2050 [65]. The incidence of T2DM in older people is a major public health concern, and in 2010 almost 27% of people aged 65 years and older in the US had diabetes [1]. Clinical management of the older patient with T2DM is often challenging as these patients have an increased prevalence of cardiovascular risk factors, diabetes-related complications, and comorbidities such as renal impairment, congestive heart failure, cognitive impairment, and physical disability. Furthermore, they are often prescribed multiple medications, which further complicates treatment strategies and may reduce adherence [66–68]. The older T2DM patient population is, however, a highly heterogeneous group with a broad spectrum of disease duration, life expectancy, and comorbidities. A position statement issued by the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes, recommends that an HbA1c target

range of 7.0–7.5% should generally be aimed for in older patients. The caveat to this statement is that individual comorbidities, and cognitive and functional status, should be considered when determining goals. Furthermore, this position statement highlights hypoglycemia in older people as a highly prevalent and under-recognized disorder with severe consequences such as falls, cognitive impairment, and hospital admission [69].

The heterogeneity of this population is also addressed by the ADA. Their guidelines recommend that the same glycemic targets be applied to otherwise healthy older people as to younger people with diabetes; and a less ambitious target be applied to patients with more complicated conditions that include multiple comorbidities, a high level of functional dependency, and limited life expectancy [2, 70].

The DPP-4 inhibitors have generated particular interest for the treatment of older patients with T2DM for a number of reasons, namely their convenient oral dosing, the importance of avoiding hypoglycemia in the elderly, and considerations of declining renal function in this patient group. Indeed, the recent position statement mentioned above states that in selected older patients not at target or where there is poor tolerance to glucose-lowering agents, the use of DPP-4 inhibitors can be considered as second-line therapy [69]. The ADA acknowledges the few side effects associated with DPP-4 inhibitors in the context of their use in older patients; however, it also notes that their costs may be a barrier to some older patients [2]. The prescribing information available for these drugs generally agree that no overall differences in safety or effectiveness were observed between patients aged 65 years and over and younger patients [37–41]. However,

caution is advised in the context of older patients, who are more likely to have decreased renal function, and dosing adjustments are recommended for all DPP-inhibitors, except linagliptin, under these circumstances.

Three studies that prospectively assessed DPP-4 inhibitors in older patients with T2DM have been reported [71–73] (Table 4). A double-blind, randomized, active-controlled study compared vildagliptin with metformin over 24 weeks in 335 drug-naïve patients with T2DM aged ≥65 years. In this study, 41% of patients had normal renal function, 57% had mild renal insufficiency, and less than 2% had moderate renal insufficiency. The investigation showed that vildagliptin is an effective and well-tolerated treatment option in this group, demonstrating non-inferiority to metformin in terms of glycemic control, but superior gastrointestinal tolerability [71]. The second trial, a double-blind, randomized, placebo-controlled study of sitagliptin over 24 weeks in 206 patients with T2DM aged ≥65 years, concluded that sitagliptin significantly and rapidly improved glycemic control and was well tolerated in this group [72]. This study also included patients with moderate renal insufficiency (22%), but excluded those with severe renal insufficiency (estimated creatinine clearance <35 mL/min). Finally, a randomized, double-blind, placebo-controlled study investigated the efficacy and safety of linagliptin in 241 patients aged ≥70 years with T2DM and insufficient glycemic control despite metformin and/or sulfonylurea and/or insulin therapy [73]. The majority of patients in this study had either normal renal function (21%) or mild renal insufficiency (52%); 26% of patients had moderate renal insufficiency and less than 2% had severe renal insufficiency. This study concluded that linagliptin was effective and

well tolerated in elderly patients and no safety concerns were identified.

Other pooled analyses, subgroup analyses, and systematic reviews also showed that DPP-4 inhibitors in the older T2DM population were generally effective and well tolerated [74–81]. However, some studies show that when DPP-4 inhibitors are concomitantly administered with insulin or a sulfonylurea, there is an elevated risk of hypoglycemia over the concomitant administration of placebo with insulin or a sulfonylurea [82, 83]. In contrast, a pooled analysis evaluating linagliptin as add-on therapy to basal insulin showed no increased risk of hypoglycemia with the DPP-4 inhibitor [81]. Given the serious consequences of hypoglycemic events in older patients, the combination of a DPP-4 inhibitor with a sulfonylurea is perhaps ill advised; in fact, the IAGG, EDWPOP, and the International Task Force of Experts in Diabetes recommend that sulfonylurea therapy should be avoided in any older patient at risk of hypoglycemia [69].

Interestingly, there is also preliminary evidence that DPP-4 inhibitors are associated with a reduced risk of bone fractures compared with placebo or other treatments [84]. Recent evidence shows that T2DM is an independent risk factor for bone fracture [85, 86] and that older people with T2DM are at an increased risk of hip fractures [87, 88]. Furthermore, clinical trial data suggest that DPP-4 inhibitors may be associated with a lower risk of stroke compared with other therapies [89]. Patients with diabetes have an increased risk of ischemic stroke, a risk that increases in correlation with duration of diabetes [90, 91], therefore posing a particular concern for elderly patients with long-standing T2DM. If confirmed, these risk reductions will provide further compelling reasons to consider DPP-4 inhibitors in older patients. Various prospective studies of glycemic outcomes in

Table 4 Prospective phase 2/3 clinical trials of DPP-4 inhibitors in older patients (with published results)

Ref	Study drug	N^a	Age inclusion criteria	Mean age	Study design	Control	Background therapy	Change in HbA1c (reported as in original publication)
[71]	Vildagliptin, 100 mg/day	335	≥65 yrs	71 yrs	24-week double-blind, randomized, active-controlled, parallel group study	Metformin	Patients considered drug-naïve (no OADs for at least 12 weeks prior to screening; no OADs for more than 3 consecutive months at any time in the past)	Adjusted mean change from baseline, % (SE) Week 24: vildagliptin −0.64 (0.07), (P < 0.001 vs. baseline) Metformin −0.75 (0.07), (P < 0.001 vs. baseline)
[72]	Sitagliptin, 100 or 50 mg/day depending on renal function	206	≥65 yrs	72 yrs	24-week double-blind, randomized, placebo-controlled, parallel group study	Placebo	All OADs washed out	Mean change from baseline[b], % (95% CI) Week 24: sitagliptin −0.5 (−0.7, −0.2) Placebo 0.2 (0.0, 0.5)
[73]	Linagliptin	241	≥70 yrs	74.9 yrs	24-week double-blind, randomized, placebo-controlled, parallel group study	Placebo	Continued (included metformin, sulfonylureas, or basal insulin, or combinations of these drugs)	Adjusted mean change from baseline, % (SE) Week 24: linagliptin −0.61 (0.06) Placebo 0.04 (0.07)

HbA1c glycated hemoglobin, *yrs* years, *OAD* oral antidiabetes drug, *CI* confidence interval

[a] *N* number of randomized participants

[b] Least squares mean change from baseline

Table 5 Planned/recently completed prospective clinical trials of DPP-4 inhibitors in older patients

Study drug/ comparator	ClinicalTrials identifier	(Estimated) number enrolled	(Estimated) completion date	Study design	Key inclusion criteria
Saxagliptin/ glimepiride	NCT01006603 (completed)	957	June 2012	52-week, double-blind, randomized, active-controlled	Patients with T2DM treated with stable metformin monotherapy for at least 8 weeks prior to first visit; HbA1c $\geq$7.0% and $\leq$9.0%; age $\geq$65 years
Sitagliptin/ glimepiride	NCT01183104 (recruiting)	900	December 2014	52-week, open-label, randomized, active-controlled	Patients with T2DM who are OAD-naïve (or alpha-glucosidase or biguanide monotherapy, to be washed out 4 weeks prior to randomization); treatment with diet and exercise for 12 weeks or longer at screening; HbA1c $\geq$6.9% and $\leq$8.9%; age $\geq$60 years
Sitagliptin/ glimepiride	NCT01189890 (completed)	480	October 2012	30-week, double-blind, randomized, active-controlled	Patients with T2DM; community-dwelling; age 65–85 years
Vildagliptin/ placebo	NCT01257451 (completed)	431	March 2012	24-week, double-blind, randomized, placebo-controlled	Patients with T2DM; HbA1c $\geq$7.0% and $\leq$10.0% and assessed as inadequately controlled; BMI $\geq$19 and $\leq$45 kg/m^2; age $\geq$70 years

T2DM type 2 diabetes mellitus, *HbA1c* glycated hemoglobin, *OAD* oral antidiabetes drug, *BMI* body mass index

Table 6 Completed or ongoing clinical trials to investigate effects of DPP-4 inhibitors on cardiovascular morbidity and mortality

Study drug/comparator	ClinicalTrials identifier (NAME)	(Estimated) number enrolled	(Estimated) completion date	Study design	Key inclusion criteria
Alogliptin/placebo	NCT00968708 (EXAMINE)	5,380	June 2013 (completed)	4.75-year, double-blind, randomized, placebo-controlled	Patients with T2DM receiving monotherapy or combination antidiabetes therapy; HbA1c ≥6.5% and ≤11.0%; HbA1c ≥7.0% and ≤11.0% if on insulin; diagnosis of acute coronary syndrome within 15–90 days prior to randomization
Linagliptin/placebo	NCT01897532 (CARMELINA)	8,300	January 2018 (recruiting)	4-year, double-blind, randomized, placebo-controlled	Patients with T2DM who are drug-naïve or receiving monotherapy or combination antidiabetes therapy; HbA1c ≥6.5% and ≤10.0%; high risk of cardiovascular events defined by: (1) albuminuria (UACR ≥30 mg/g) plus previous macrovascular disease and/or (2) impaired renal function patients with eGFR 15 to <45 mL/min/1.73 m² are eligible with any UACR level, those with eGFR ≥45–75 mL/min/1.73 m² are required to have a UACR >200 mg/g[a]
Linagliptin/glimepiride	NCT01243424 (CAROLINA)	6,000	September 2018 (ongoing)	7.7-year, double-blind, randomized, active controlled	Patients with T2DM; HbA1c ≥6.5% and ≤8.5% if treatment-naïve or mono-/dual therapy with metformin and/or alpha-glucosidase inhibitor; HbA1c ≥6.5% and ≤7.5% if treatment with sulfonylurea/glinides in mono- or dual therapy with metformin and/or alpha-glucosidase inhibitor; pre-existing cardiovascular disease OR specified diabetes end-organ damage OR age ≥70 years OR ≥2 specified cardiovascular risk factors
Saxagliptin/placebo	NCT01107886 (SAVOR-TIMI 53)	16,492	May 2013 (completed)	4-year, double-blind, randomized, placebo-controlled	Patients with T2DM; HbA1c ≥6.5%; high risk for cardiovascular events
Sitagliptin/placebo	NCT00790205 (TECOS)	14,000	December 2014 (ongoing)	4–5-year, double-blind, randomized, placebo-controlled	Patients with T2DM; HbA1c ≥6.5% and ≤8.0% on stable dose(s) of antihyperglycemic agent(s), including insulin; pre-existing cardiovascular disease

T2DM type 2 diabetes mellitus, *HbA1c* glycated hemoglobin, *UACR* urinary albumin creatinine ratio, *eGFR* estimated glomerular filtration rate

[a] Additional study details from https://investor.lilly.com/releasedetail.cfm?ReleaseID=781539

this population are underway or recently completed (Table 5), and their findings will provide further valuable safety and efficacy data about DPP-4 inhibitors in this group, and may also allow for additional pooled analyses of outcomes of interest such as fracture. Furthermore, ongoing cardiovascular safety trials with the DPP-4 inhibitors (see below and Table 6) are expected to include substantial numbers of elderly patients, providing valuable outcome information in this particular population. In particular, patients aged ≥70 years qualify for inclusion in the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) trial, a large-scale study that aims to investigate the effects of linagliptin on cardiovascular morbidity and mortality.

Future Directions

Safety data for DPP-4 inhibitors based on registration studies are reassuring, with various meta-analyses indicating a benign and perhaps beneficial cardiovascular safety profile for the class [92–96]. However, their long-term impact on cardiovascular outcomes has yet to be firmly established by clinical trials. To address this, several large-scale trials, including EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care), CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus at High Vascular Risk), CAROLINA, SAVOR-TIMI 53 (The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53 trial), and TECOS (Sitagliptin Cardiovascular Outcome Study), have been designed to

investigate the effects of DPP-4 inhibitors on cardiovascular morbidity and mortality (Table 6), and provide further insight into the efficacy, safety, and durability of response of these drugs. Results from the first two completed trials, EXAMINE and SAVOR-TIMI 53, demonstrated no change in the risk of the composite major adverse cardiovascular event endpoint with either alogliptin or saxagliptin compared with placebo when added to the standard of care [97, 98]. In EXAMINE, the point estimate for the hazard ratio (HR) was <1 and the upper limit of the 95% CI was <1.3, which was the pre-specified non-inferiority safety margin (HR with alogliptin, 0.96; upper boundary of the one-sided repeated CI, 1.16; $P < 0.001$ for non-inferiority) [97]. Similarly in SAVOR-TIMI 53, saxagliptin met the non-inferiority criterion but did not demonstrate cardiovascular superiority versus placebo (HR with saxagliptin 1.00, 95% CI 0.89–1.12, $P = 0.99$ for superiority, $P < 0.001$ for non-inferiority) [98].

CONCLUSIONS

The DPP-4 inhibitors are clearly emerging as a useful treatment option in the general T2DM population and, as additional trials are reported, it appears their characteristics may make them particularly suitable for more vulnerable patient populations. DPP-4 inhibitors can be used in the context of CKD, a significant consideration for any antidiabetes treatment. They are also weight neutral, an important aspect when making therapy choices with a patient who is overweight or obese. Furthermore, their straightforward dosing and low risk of hypoglycemia are desirable characteristics, particularly when choosing treatments for older patients.

For various reasons, physicians may be cautious about using new therapies in vulnerable patient populations. However, these groups could potentially benefit from new treatments, and caution can be balanced by close monitoring and vigilance to ensure that all groups benefit from therapeutic advances. Given the variable progression of T2DM and the heterogeneity even within subgroups of patients, individualizing therapy will always be essential. Nevertheless, awareness of the typical issues for these high-risk groups may help physicians who are considering therapeutic options, including the DPP-4 inhibitors, when developing specific management strategies for individual patients.

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