

Type 2 Diabetes Treatment Recommendations Update: Appropriate Use of Dipeptidyl Peptidase-4 Inhibitors

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Abstract

In this article, recommendations from the 2012 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement are discussed with an emphasis on the appropriate use of Dipeptidyl Peptidase-4 (DPP-4) inhibitors in individuals with Type 2 Diabetes Mellitus (T2DM). The 2012 ADA/EASD position statement emphasizes individualization of treatment, with glycated hemoglobin (A1C) targets being determined for each patient based on life expectancy, complications, disease duration, comorbidities, such as cardiovascular disease or cognitive impairment, and the risk of hypoglycemia and other adverse events. Patients' attitudes and support systems should also be considered. Recommendations for pharmacotherapy are less prescriptive and should be based on a patient's needs, preferences, and tolerances. In general, metformin is recommended as first-line therapy for most patients, although combination of 2 noninsulin agents or insulin alone should be considered in patients with baseline A1C \geq 9.0%. Add-on therapy to metformin will likely be needed to achieve and maintain glycemic control as the disease progresses. It is important to avoid therapies that increase the risk of weight gain and, especially in older patients, hypoglycemia. As discussed in this review, DPP-4 inhibitors are well tolerated and effectively lower A1C and improve β -cell function without increasing the risk of hypoglycemia and weight gain. DPP-4 inhibitors are recommended as an option for first-line therapy when metformin is contraindicated or not tolerated and are also recommended as an option for add-on therapy to metformin and to metformin plus a sulfonylurea, a thiazolidinedione, or insulin. This article reviews the appropriate use of DPP-4 inhibitors in individuals with T2DM and recently published cardiovascular outcome trials with DPP-4 inhibitors.

Keywords: Dipeptidyl peptidase-4 (DPP-4) inhibitor; Glycated hemoglobin (A1C); Pharmacotherapy; Treatment goals; Hypoglycemia; Weight gain; Metformin

Introduction

Patients with Type 2 Diabetes Mellitus (T2DM) are at an increased risk for heart disease, stroke, dementia, and Alzheimer's disease [1,2]. In patients with newly diagnosed (T2DM), intensive control of hyperglycemia can prevent or delay the onset of microvascular complications (ie, nephropathy, retinopathy, and neuropathy) [3]. However, T2DM is a heterogeneous disease, and results from recent clinical trials in patients with established T2DM and Cardiovascular (CV) disease or CV risk factors suggest that not all patients with T2DM will experience improved CV and cognitive outcomes from intensive glycemic control, especially older patients with comorbidities and those with a long duration of uncontrolled T2DM [4-10].

In 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a position statement containing updated recommendations for the management of hyperglycemia in patients with T2DM [11]. Compared with previous consensus statements, the new updated position statement emphasizes personalized treatment and contains more information regarding the efficacy and safety of newer antihyperglycemic agents, such as the incretin-based dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, and provides recommendations for their optimal use [12] (Table 1).

DPP-4 inhibitors are oral agents that achieve glycemic control with a low risk of hypoglycemia or weight gain [13]. Those approved for use in the United States are sitagliptin, saxagliptin, linagliptin, and alogliptin, and others are in development. This article reviews the appropriate use of DPP-4 inhibitors in individuals with T2DM based on the current recommendations contained in the 2012 ADA/EASD position statement and also reviews recently published CV outcome trials with DPP-4 inhibitors.

Emphasis on Patient-Centered Care

The new recommendations emphasize individualized treatment and promote the adoption of patient-centered care in the management of T2DM [11]. Choices of lifestyle modifications and treatment interventions are best made in consultation with the patient, taking into account their comorbidities, commitment level, available resources, and treatment side effects. The emphasis has shifted from tight control of glycated hemoglobin (A1C) levels for all people with T2DM, to treatment based on individual patient needs, preferences, and tolerance. Patients may achieve better control of A1C when their treatment is individualized. Patients who take an active role in their diabetes management may have improved understanding of and adherence to their therapy [14].

Therapy Goals and Treatment Regimens

The ADA/EASD position statement recommends a general goal of A1C < 7.0% for most patients. However, A1C goals may vary with patient characteristics. For example, a goal of 6.0% to 6.5% may be more appropriate for newly diagnosed patients with a long life expectancy and no significant CV disease or other comorbidities, if achievable without significant hypoglycemia or other adverse effects. In contrast,

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	2009 [12]	2012 [11]
General	Consensus approach to help healthcare providers choose the most appropriate interventions for patients with T2DM. Lifestyle intervention is important.	Less prescriptive, patient centered. Patient and disease factors drive decision making. Age and comorbidities may impose constraints on disease management. Lifestyle intervention is important.
Glycemic target (A1C)	<7.0% for most patients	<7.0% for most patients <6.5% for patients with short disease duration, long life expectancy, no significant CVD 7.5%-8.0% for patients with limited life expectancy, advanced complications, comorbidities, history of hypoglycemia, and difficulty maintaining glycemic target.
Initial drug therapy	Metformin If symptomatic hyperglycemia persists, rapid addition of other diabetes medications should be considered.	Metformin If A1C ≥ 9.0%, initiate with 2 noninsulin drugs or insulin. If A1C ≥ 10.0%, initiate insulin
Alternative to metformin if contraindicated or not tolerated	Not addressed	SU, pioglitazone, DPP-4 inhibitor. (GLP-1 receptor agonist if weight loss is essential)
2-drug combinations	Metformin+SU Metformin+basal insulin	Metformin+SU Metformin+TZD Metformin+DPP-4 inhibitor Metformin+GLP-1 receptor agonist Metformin+insulin
Additional Rx needed to reach glycemic goal	Start or intensify insulin therapy	3-drug combinations (Figure 1) and/or insulin

A1C=glycated hemoglobin; CVD=cardiovascular disease; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; SU=sulfonylurea; T2DM=type 2 diabetes mellitus; TZD=thiazolidinedione.

Table 1: Comparison of ADA/EASD 2009 and 2012 Treatment Recommendations.

a less stringent A1C goal of 7.5% to 8.0% may be more appropriate in for patients with a longer duration of T2DM, especially if not well controlled, and for patients with limited life expectancy, advanced complications, extensive comorbidities, such as CV disease or cognitive impairment, history of severe hypoglycemia, and difficulty in achieving and maintaining glycemic goals, despite intensive counseling and use of multiple diabetes medications [9].

Weight reduction or control and exercise are critical components of any program designed to manage T2DM. In patients with T2DM, intensive lifestyle interventions (diet and exercise), especially when started early in the disease process, can produce significant weight loss, improvements in glycemic control, and a reduction in CV risk factors [15]. However, lifestyle changes, particularly weight reduction, are difficult to maintain over the long term, and most individuals with T2DM will require pharmacotherapy to control their hyperglycemia [16,17].

Antihyperglycemic Agents: Characteristics

The historic course of pharmacotherapy for patients with T2DM usually begins with a single oral agent, followed by combinations of 2 and maybe 3 noninsulin medications. As β -cell function progressively decreases, patients usually require insulin in combination with 1 or 2 noninsulin agents [11].

There are 11 classes of diabetes medications, in addition to various insulin analogs. The most commonly used noninsulin classes included in the pharmacotherapy algorithm are biguanides, sulfonylureas (SUs), thiazolidinediones (TZDs), DPP-4 inhibitors, and GLP-1 receptor agonists.

Biguanide

For the past decade, metformin has been the most widely used diabetes drug and is generally considered to have the most favorable benefit-to-risk profile [18]. The primary mechanism of action of metformin is to decrease hepatic glucose production [19]. Compared with diet, metformin treatment (maximum dose of 2550 mg/d) of

overweight patients with T2DM in the United Kingdom Prospective Diabetes Study (UKPDS) resulted in a reduced risk for myocardial infarction, macrovascular complications, any diabetes-related end point, diabetes-related death, and all-cause death [20]. When used as monotherapy, metformin (1000 to \geq 1500 mg/d) reduces A1C by -0.5% to -1.8% and is associated with a low risk of hypoglycemia or weight gain [18,20,21]. The most common adverse events with metformin are nausea, diarrhea, and cramping [22]. Metformin is eliminated unchanged primarily by the kidneys and is contraindicated in individuals with decreased kidney function [23].

Sulfonylureas/Meglitinides

SUs and meglitinides interact with similar but distinct receptors on the pancreatic β cell, resulting in increased insulin secretion [22]. SUs are long-acting secretagogues that target Fasting Plasma Glucose (FPG) and Postprandial Plasma Glucose (PPG), thereby providing an effective lowering of A1C of up to -1.25% [24]. Meglitinides are short-acting secretagogues that have a faster onset of action and a shorter half-life than SUs and require more frequent dosing [22,25]. Meglitinides reduce A1C by up to approximately -1.0% [24]. The durability of glycemic control with SUs tends to be shorter than that of metformin or TZDs, and SUs can be associated with weight gain, hypoglycemia [3,18]. and increased CV risk [26]. However, the shorter-acting meglitinides may be associated with less hypoglycemia than SUs [18,26,27].

Thiazolidinediones

TZDs increase insulin sensitivity, are effective at lowering FPG and PPG, and provide durability in maintaining A1C [24,28,29]. Typically, TZDs lower A1C by up to -1.0% to -1.5% [24]. TZDs, particularly pioglitazone, have favorable effects on lipids and improve β -cell function [29-32]. Disadvantages of TZDs include weight gain, increased fractures, edema, and heart failure in susceptible individuals [29,33]. In recent years, the safety of TZDs has come under increased scrutiny as a result of a possible increased risk of myocardial infarction with rosiglitazone that led to its restricted use in the United States and its complete removal from the European market [34-36]. In addition, a

possible increased risk of bladder cancer with pioglitazone, especially in those taking the drug for >2 years, has been reported [37,38].

Newer Agents

Recently approved agents include GLP-1 receptor agonists and DPP-4 inhibitors that act through the incretin system. The incretin hormones GLP-1 and Glucose-Dependent Insulinotropic Polypeptide (GIP) are secreted by the intestine into the circulation in response to a meal. Both hormones stimulate glucose dependent insulin secretion, and GLP-1 also suppresses glucagon secretion, delays gastric emptying, and increases feelings of satiety, leading to decreased food intake [39]. GLP-1 and GIP are rapidly degraded by DPP-4, an enzyme present as both a circulating and membrane-bound form expressed in many tissues [39,40]. In individuals with T2DM, the insulinotropic effect of GLP-1 is preserved, whereas the response of β cells to GIP is reduced [41]. Two approaches have been developed to increase the levels of GLP-1. GLP-1 receptor agonists are injectable, degradation-resistant GLP-1 agents with prolonged half-lives, compared with native GLP-1 [39]. DPP-4 inhibitors are oral agents that stabilize the endogenous postprandial levels of GLP-1 by inhibiting the degradation of GLP-1 [39]. In addition to inactivating GLP-1 and GIP, DPP-4 is also involved in the degradation of other peptides that are important in CV regulation, such as stromal cell-derived factor-1 α (SDF-1 α), which is involved in the recruitment of bone marrow-derived Endothelial Progenitor Cells (EPCs) to sites of vascular damage and B-type natriuretic peptide, which plays a role in volume regulation [42-44]. Whether preventing the inactivation of peptides other than the incretin hormones is important in the action of DPP-4 inhibitors in patients with T2DM requires additional study.

Glucagon-like peptide-1 receptor agonists

Exenatide and liraglutide are currently approved GLP-1 receptor agonists that mimic the actions of endogenous GLP-1 and improve glycemic control when used in combination with metformin, SUs, TZDs, or basal insulin in patients with T2DM [45-48]. Improvements in β -cell function have also been reported [46,49]. GLP-1 receptor agonists are typically associated with weight loss and have a low risk of hypoglycemia [45-48], although the frequency of hypoglycemia may increase when these agents are used in combination with an SU or insulin [50-54]. Significant decreases in systolic blood pressure of 4 to 6 mm Hg have been observed in clinical trials of GLP-1 receptor agonists [45,46]. When used with basal insulin, there is the potential to lower daily insulin requirements [45]. Gastrointestinal effects, including nausea and vomiting, are the most frequently reported adverse events with GLP-1 receptor agonists [45-48]. GLP-1 receptor agonists are given by injection once or twice daily or once weekly [55].

Dipeptidyl peptidase-4 inhibitors

By inhibiting the enzyme responsible for the breakdown of GLP-1 and GIP, DPP-4 inhibitors prolong the half-life of endogenously released GLP-1 and GIP, leading to enhanced glucose-dependent insulin secretion and decreased glucose-dependent glucagon secretion [39]. Sitagliptin, saxagliptin, linagliptin, and alogliptin are DPP-4 inhibitors approved for use in the United States. DPP-4 inhibitors effectively improve glycemic control (significantly reduce A1C, FPG, and PPG [when measured]) when used as monotherapy [56-59], as add-on to metformin [60-64], as add-on to SUs with or without metformin [65-68], as add-on to TZDs with or without metformin [69-71], as add-on to insulin with or without metformin [72-74], and as initial combination with metformin [75] or pioglitazone [76-78]. As monotherapy, reductions in A1C with DPP-4 inhibitors are generally

less than those with agents that primarily target FPG, such as metformin or long-acting GLP-1 receptor agonists, but are comparable to those with SUs and TZDs [79]. DPP-4 inhibitors are weight neutral and pose a low risk of hypoglycemia when used as monotherapy [56-59] or as add-on to metformin [60-64]. When added to insulin therapy, they have the potential to lower daily insulin requirements [72]. When DPP-4 inhibitors are used in combination with an insulin secretagogue (eg, SU) or insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia [80]. DPP-4 inhibitors have also been shown to improve β -cell function [56-58,60,61,63,66].

Common adverse events reported in clinical trials of DPP-4 inhibitors include nasopharyngitis, upper respiratory tract infection, urinary tract infection, and headache [80-82]. However, analysis of clinical trials of >7000 patients receiving DPP-4 inhibitors found that the risk for nasopharyngitis, upper respiratory tract infection, and urinary tract infection was not different between DPP-4 inhibitors and active comparators in these trials [79]. Acute pancreatitis and hypersensitivity reactions (urticaria, angioedema, and localized skin exfoliation) have been reported with the use of DPP-4 inhibitors in clinical trials and from postmarketing surveillance [80-82].

Other Agents

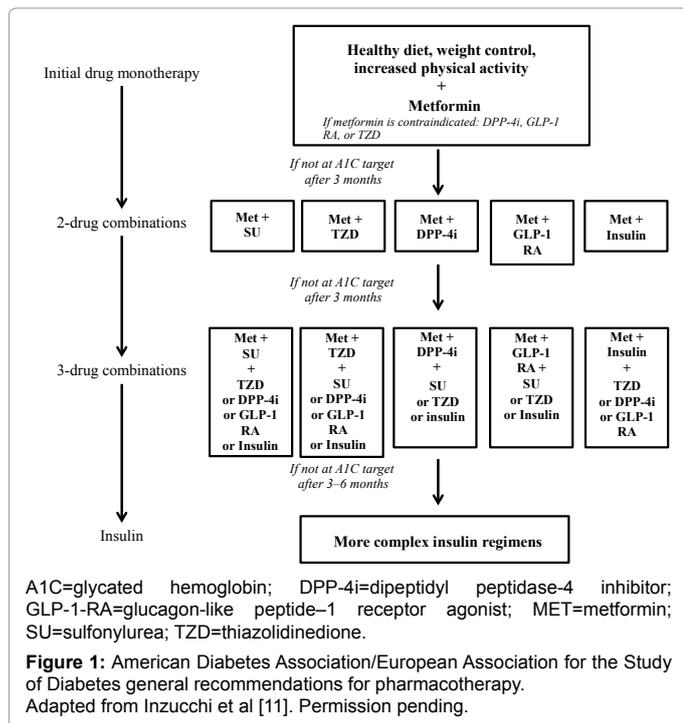
Other drugs approved for use in T2DM in the United States include α -glucosidase inhibitors, which slow the digestion and absorption of carbohydrates [83]; colesvelam, a bile acid sequestrant with an unclear mechanism of action [84]; the dopamine agonist bromocriptine, which affects the central control of metabolism [85]; pramlintide, an amylin agonist used in conjunction with insulin [86]; and canagliflozin [87], a Sodium-Glucose Cotransporter-2 (SGLT2) inhibitor that reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, resulting in increased urinary glucose excretion [88]. SGLT2 inhibitors have a low risk of hypoglycemia and are associated with reductions in body weight and blood pressure [89].

Pharmacotherapy: General Recommendations

T2DM is a progressive disease that results from the continual decrease in β -cell function [90]. Consequently, most patients require intensification and adjustments of treatment with multiple agents and insulin during the course of the disease to achieve and maintain glycemic control (Figure 1). For example, in the UKPDS trial, 3 years after diagnosis of diabetes and initiation of pharmacotherapy, approximately 50% of patients failed to achieve a target A1C <7.0% with metformin, SU, or insulin monotherapy. By 9 years, approximately 75% of patients failed to achieve A1C <7.0% with monotherapy [91]. Treatment assessments should be made regularly and therapy adjusted as target A1C goals are met or missed.

Initial therapy

Initial therapy for T2DM should be individualized and based on patients' characteristics and preferences, degree of hyperglycemia, potential for β -cell preservation, side effect profile, and potential for hypoglycemia and weight gain. In general, when diet and exercise alone have not been sufficient to achieve A1C goals, the ADA/EASD position statement recommends that metformin be considered as initial therapy for the majority of patients [11]. If metformin cannot be used, other oral agents to consider as initial therapy include SUs/meglitinides, pioglitazone, or DPP-4 inhibitors. If weight loss is a particular concern, a GLP-1 receptor agonist should be considered. At diagnosis, if patients have A1C \geq 9.0%, 2 noninsulin drugs or insulin should be considered as initial therapy instead of metformin monotherapy. When patients



have significant hyperglycemic symptoms or elevated plasma glucose concentrations (300–350 mg/dL) or A1C \geq 10.0% to 12.0%, insulin is strongly recommended as initial therapy.

Two-drug combinations

If the A1C goal is not achieved and maintained over the course of approximately 3 months with metformin monotherapy, a second oral agent (SU, TZD, or DPP-4 inhibitor), GLP-1 receptor agonist, or basal insulin (especially if A1C is high) should be added. If glycemic improvement is not apparent, the agent should be discontinued and substituted with another medication with a different mechanism of action. Although cost-effectiveness and long-term outcomes with newer agents remain to be determined, 3 recent meta-analyses have concluded that among noninsulin agents, DPP-4 inhibitors and GLP-1 receptor agonists may be good alternatives to SUs and TZDs as add-on therapy to metformin due to their glycemic efficacy, low risk of hypoglycemia, and weight neutrality or weight reduction [79,92,93].

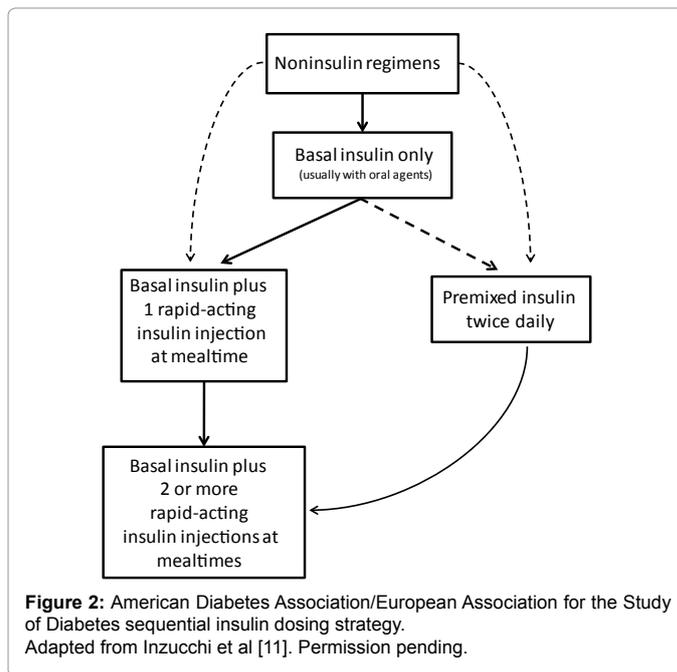
Three-drug combination

Studies have shown that the addition of a third noninsulin agent to a 2-drug combination can improve glycemic control in some patients with inadequate control. For example, addition of a TZD [94–98], GLP-1 receptor agonist [48], or DPP-4 inhibitor [66,67,99] to metformin plus SU therapy produced additional improvements in glycemic control in patients poorly controlled with metformin and an SU.

However, in patients inadequately controlled on a 2-drug combination with A1C \geq 8.5%, the best glycemic response may be achieved by transitioning to insulin. This may be especially appropriate in patients with long duration of disease and major decreases in β -cell function [100].

Insulin therapy

Initial insulin therapy usually consists of a single dose of basal insulin with up-titration, if appropriate (Figure 2). As β -cell function continues



to deteriorate such that PPG exceeds 180 mg/mL (10.0 mmol/L), daily basal insulin together with a rapid-acting insulin injection (basal-bolus regimen) should be initiated at the meal identified as producing the greatest increase in blood glucose, which is usually the evening meal [11]. If glycemic control is still not attained, increasing the prandial dose of insulin or starting prandial insulin at the second largest meal or at all 3 meals may be necessary [11]. A less flexible insulin regimen is the use of premixed insulins that consist of intermediate insulin with regular or rapid-acting insulin. Administration is before the morning and evening meals and may be appropriate for individuals who eat regularly and require a simple dosing scheme [11].

Oral agents are often continued with basal insulin. It is important to avoid agents that are associated with weight gain (eg, SUs or TZDs) or hypoglycemia and to consider agents that are weight neutral (eg, metformin or DPP-4 inhibitors) or that are associated with weight loss (eg, GLP-1 receptor agonists). In some patients, the combination of metformin and insulin produced better glycemic control, less weight gain, lower insulin requirements, and similar or less hypoglycemia than insulin alone [101,102]. Another option includes insulin combined with agents that improve PPG, such as GLP-1 receptor agonists and DPP-4 inhibitors. For example, addition of exenatide to insulin therapy reduced A1C to a greater extent than insulin alone and decreased body weight versus an increase with insulin [45]. The addition of exenatide reduced the daily insulin requirements without increasing the incidence of hypoglycemia. Similarly, DPP-4 inhibitors added to insulin therapy (with or without metformin and/or pioglitazone) produced greater reductions in A1C (sitagliptin, saxagliptin, linagliptin, and alogliptin) and PPG (sitagliptin, saxagliptin, and linagliptin) than ongoing treatment with the insulin regimen alone [72–74,103]. Changes in body weight were similar between the groups taking insulin without versus with DPP-4 inhibitors. The incidence of hypoglycemia was similar across treatment groups [72,74,103] or higher with a DPP-4 inhibitor plus insulin versus insulin alone [73].

ADA/EASD Recommendations: DPP4 Inhibitors

DPP-4 inhibitors are recommended as an option for first-line

therapy when metformin is contraindicated or not tolerated (Figure 1) [11]. A combination of 2 noninsulin agents is suggested as an option for initial therapy in patients with a high baseline A1C who are unlikely to achieve target A1C with monotherapy. Combination of a DPP-4 inhibitor with metformin, shown to be more effective than either agent alone as initial therapy in patients with T2DM, is one option for this patient population [75,104]. DPP-4 inhibitors are also recommended as an option for add-on therapy to metformin (dual therapy) and for add-on therapy to metformin and an SU, metformin and a TZD, and metformin and insulin (triple therapy).

Other Considerations

Patients with T2DM are at increased risk for CV morbidity and mortality [105-107]. One of the goals of the ADA/EASD recommendations is to make comprehensive CV risk reductions a major focus of therapy. DPP-4 inhibitors represent a treatment option that minimizes the CV risk factors of weight gain and hypoglycemia. Analyses of pooled data from clinical trials with DPP-4 inhibitors suggest that these drugs do not increase CV risk and may be associated with a decrease in CV events [108-112]. Several large CV outcome trials are addressing the CV effects of DPP-4 inhibitors [113-116]. Two of these trials, Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus – Thrombosis in Myocardial Infarction 53 (SAVOR-TIMI 53) and EXamination of cArdiovascular outcOmes with alogliptIN versus standard of care in patients with T2DM and acute coronary syndrome (EXAMINE) have recently been completed [117,118].

SAVOR-TIMI 53 evaluated the cardiovascular safety and efficacy of saxagliptin compared with placebo in patients (N=16,492) with T2DM and a history of established CV disease or multiple risk factors for vascular disease (eg, dyslipidemia, hypertension, or active smoking). Patients continued to receive standard-of-care antihyperglycemic (except for other DPP-4 inhibitors or GLP-1 receptor agonists) and CV disease therapy. Saxagliptin did not increase or decrease the risk of CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke, compared with placebo. Significantly more patients randomized to saxagliptin (3.5%) were hospitalized for heart failure compared with placebo (2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P=0.007), although these individuals did not experience an increase in CV death, nonfatal myocardial infarction, or nonfatal stroke. This finding needs to be further investigated. At study completion (median follow up of 2.1 years), saxagliptin improved glycemic control and reduced the development and progression of microalbuminuria, compared with placebo. The number of patients with acute or chronic pancreatitis was low and similar in both groups (saxagliptin, 0.3%; placebo, 0.3%). Five cases of pancreatic cancer were reported in the saxagliptin group versus 12 in the placebo group.

In the EXAMINE trial, patients (N=5,380) with T2DM and an acute coronary syndrome within 15 to 90 days before randomization received alogliptin or placebo for a median follow-up of 18 months. Patients continued to receive standard of care for T2DM and CV risk factors. Compared with placebo, alogliptin did not increase or decrease CV death, nonfatal myocardial infarction, or nonfatal stroke. Hospitalization for heart failure was also observed in this trial but occurred with similar frequency in patients receiving alogliptin (3.9%) and placebo (3.3%; hazard ratio, 1.19; 95% CI, 0.90 to 1.58; P=0.22) [119]. Alogliptin reduced A1C to a greater extent than placebo (mean change from baseline, -0.33% for alogliptin vs +0.03% for placebo). Incidences of pancreatitis were similar between alogliptin and placebo. There were no reports of pancreatic cancer.

These studies and other ongoing trials provide valuable information to guide clinicians in choosing among the various antihyperglycemic agents when treating individuals with T2DM and CV disease or at high risk for CV disease.

Case Report

Sample patient case

MG is a 78-year-old, overweight white man with T2DM for 5 years and hypertension for 8 years who is in overall good health. He lives alone at his home of 45 years and does not plan on moving. He tries to eat healthy, is active, and has good support from many family members and friends who live nearby. His current medications include metformin 1000 mg twice daily, lisinopril 20 mg daily, and aspirin 81 mg daily. His A1C has been in good control (between 6.5%–7.2%) during the past 5 years. However, today, MG's A1C is 8.1%. An adherence assessment reveals that MG takes his medications as prescribed and only misses a dose once a month at most.

Therapy approach

Because MG appears to have a good attitude, a short duration of disease that has been controlled fairly well, few comorbidities, and good support from family and friends, an A1C goal of <7% is appropriate. When selecting add-on pharmacotherapy, the clinician needs to consider that his A1C is 8.1%; therefore, PPG may be the major contributor to the elevated A1C, and an agent that targets PPG should be selected.

Additionally, because this patient is older, lives alone, and is overweight, an agent with low hypoglycemic risk and no weight gain would be preferred.

Most DPP-4 inhibitors are available in combination with metformin, such that it may be possible for the patient to take his current metformin medication with a DPP-4 inhibitor in a fixed-dose combination product, reducing concerns regarding adherence.

Summary and Conclusions

The current ADA/EASD position statement emphasizes individualization of treatment. Diet, exercise, and patient education are important components of any treatment program. Different A1C targets should be considered for each patient based on life expectancy, complications, comorbidities, risk of hypoglycemia and other adverse events, disease duration, and patients' attitudes and support system. Recommendations for pharmacotherapy are less prescriptive and should be based on a patient's needs, preferences, and tolerances. In general, metformin is recommended as first-line therapy for most patients. Add-on therapy to metformin will likely be needed as the disease progresses. It is important to avoid therapies that increase the risk of weight gain and hypoglycemia and do not preserve β -cell function. Newer therapies such as DPP-4 inhibitors and GLP-1 receptor agonists effectively lower A1C and improve β -cell function without increasing the risk of hypoglycemia and weight gain. The clinician and patient should share in the decision-making process concerning treatment goals, as this may improve adherence to therapy.

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