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PHARMACOLOGIC TREATMENT OF TYPE 2 DIABETES (HE LEBOVITZ AND G BAHTIYAR, SECTION EDITORS)

Adverse Effects of Glycemia-Lowering Medications in Type 2 Diabetes

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Abstract

Purpose of Review Treatment of patients with type 2 diabetes mellitus is focused on preventing the occurrence and delaying the development of macro- and micro-vascular complications. Glycemic control can help prevent these complications, but there is concern about the adverse effects of glycemia-lowering medications. A rational approach is to balance the desired low risk of adverse events against the unwanted higher risk of major complications resulting from suboptimal glucose control.

Recent Findings Using the above approach, approved glucose-lowering agents have favorable benefit-to-risk profiles for use in most patients with type 2 diabetes. We first briefly review the mechanism of actions and benefits of the different commonly used classes of glycemia-lowering medications and then discuss adverse effects and safety concern associated with their use.

Summary Our overall assessment is that if used appropriately, the different classes of glycemia-lowering medications offer beneficial outcomes with relatively modest and, in some instances, preventable adverse events.

Keywords Severe hypoglycemia · Lactic acidosis · Euglycemic diabetic acidosis (euDKA) · Congestive heart failure · Genital infections · Necrotizing fasciitis

Introduction

Glycemic control can prevent microvascular and possibly macrovascular complications of type 2 diabetes (T2DM). However, there is continuing concern about the adverse effects of glycemia-lowering medications that can complicate the treatment plan, choice of medications to reach appropriate glycemic targets, and patient adherence. A rational approach to address this issue is to compare the desired low risk of adverse events of specific medications with the high risk of major complications associated with suboptimal glycemic control. Using this approach, the available glucose-lowering agents have an overall favorable (but variable) risk-to-benefit ratios when used appropriately in most patients with T2DM.

In this manuscript, we review the adverse effects and safety concerns associated with use of different commonly used classes of glycemia-lowering agents. The most common safety concerns include risk of iatrogenic hypoglycemia, weight gain, infections, cancer, and renal and cardiovascular (CV) events. As patients with diabetes are already at a high risk for CV morbidity and mortality, taking into account each medication's CV safety profile versus its potential benefit is crucial for recommending appropriate treatment plans.

The different classes of medications commonly used in the treatment of T2DM are detailed below. In each section, some general statements concerning their mode of action and positive attributes are mentioned. This is followed by a discussion of adverse effects associated with each class or specific medications within the class. Although most commonly used classes of medications are discussed, emphasis will be placed on recently introduced medications. The reader is frequently referred to the accompanying tables and figure in which the major adverse effects of the commonly used classes of agents are summarized.

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Therapies Based on Glucagon-Like Peptide-1 (GLP-1)

Glucagon-Like Peptide-1 Receptors Agonists (GLP-1 RA)

Incretins are hormones produced by the intestinal mucosa in response to oral intake of nutrients; they enhance glucose-stimulated insulin secretion. Hence, incretins do not stimulate insulin release when glucose levels are near-normal [1].

The physiological response to ingestion of nutrients involving the incretin system (and GLP-1 release) is reduced in most patients with T2DM [2]. The GLP-1 RAs contain amino acid modifications in GLP-1 that make the analogues resistant to degradation by circulating dipeptidyl peptidase-4 (DPP-4) enzyme. Use of GLP-1 RAs (as GLP-1-mimetics) is associated with several-fold increase in blood GLP-1-like levels [1]. These agents have multiple positive effects in the management of T2DM, namely decrease in appetite, delayed gastric emptying, stimulation of glucose-dependent insulin release, and suppression of glucagon levels. Insulin sensitivity is increased concomitant with reductions in blood glucose and insulin levels. Because GLP-1 receptors are expressed in myocardial tissue and vascular endothelium, it is possible that incretin-based therapies may also exhibit positive CV effects [3, 4]. These agents reduce glycated hemoglobin (HbA1c) by ~ 0.8–1.6%, body weight by ~ 2–4 kg, and reduce blood pressure and lipids; they appear to have a positive effect on fatty liver disease [5, 6]. Importantly, use of GLP-1 receptor agonists (in the absence of sulfonylureas or insulin) is associated with a low risk of hypoglycemia (Tables 1 and 2).

The LEADER trial evaluating the CV safety of daily injection of liraglutide indicated that the agent reduced both CV mortality and all cause death in addition to reducing proteinuria [7]. The SUSTAIN-6 trial evaluating CV safety of weekly injection of semaglutide also reported reduced primary CV outcome and nonfatal stroke; hospitalization for congestive heart failure was lowered by 39% [8].

Gastrointestinal (GI) symptoms including nausea, vomiting and diarrhea are the most common adverse events reported with use of GLP-1 RAs (up to 10–15% of cases) and are commonly the cause of discontinuation of these agents. Nausea is less common with weekly exenatide than twice daily exenatide or daily liraglutide [9]. Albiglutide also has lower rate of nausea comparing to liraglutide [10]. There was an increased risk of acute gallbladder and biliary disease with use of liraglutide versus placebo reported in the LEADER study (141 in 4668 compared to 88 in 4672 participants, respectively; $P < 0.001$) [7].

In the SUSTAIN-6 trial, weekly injection of semaglutide was associated with a significant increase in the risk of diabetic retinopathy. Many of these events were seen in those with rapid HbA1c reduction during the first 16 weeks of treatment and in patients who had pre-existing diabetic retinopathy and poor glycemic control and were treated with insulin at baseline [11].

Increased heart rate has been reported with this class of medications specifically with weekly exenatide, twice daily exenatide, daily liraglutide, and to a smaller degree with dulaglutide. Use of lixisenatide and albiglutide were not associated with increased heart rate [12].

Other untoward effects include skin reactions. Once weekly GLP-1 RAs are associated with higher incidents of injection site reactions than daily injections. In the HARMONY-7 trial injection site reactions were more common with albiglutide (13%) compared to liraglutide (5%) [10]. In the DURATION-6 trial comparing weekly exenatide vs daily liraglutide injection, higher incidence of injection site reactions was noted with exenatide weekly with formation of skin nodules at sites of injection (10% vs 1%), pruritus at injection site (3% vs 1%), and erythema (2% vs < 1%) [13]. Of note, use of weekly injected dulaglutide in the AWARD-6 trial was associated with lower rates of injection site reactions (<1%) [14].

There is risk of pancreatitis with GLP-1 RAs (Tables 1 and 2, and Fig. 1), but it is infrequent; three cases of pancreatitis (two participants with liraglutide and one with albiglutide) were reported in the HARMONY-7 trial [10]. In the LEADER study, the rate of adjudicated acute pancreatitis was 18 in the 4668 liraglutide-treated participants (0.4%) and 23 of the 4672 placebo-administered participants (0.5%), with event rates of 1.1/1000 patient years and 1.7/1000 patient years, respectively [15]. In a meta-analysis; GLP-1 RAs were not associated with excess risks of either acute pancreatitis (OR = 0.75, 95% CI 0.47–1.17) or pancreatic cancer (OR = 0.94, 95% CI 0.49–1.83) [16]. This issue continues to be scrutinized.

Antibody formation against GLP-1 RAs has been reported [10, 13, 14]. A meta-analysis of the LEAD studies showed lower immunogenicity with liraglutide than with exenatide with no differential effect on glycemic efficacy or safety [17].

In rodent models, use of GLP-1RAs has been associated with increased calcitonin levels and higher rates of medullary thyroid tumors [6]. However, in phase 3 studies on GLP-1 RAs, mean calcitonin levels were unchanged [10, 14] and only one case of papillary thyroid carcinoma in a patient treated with liraglutide was reported [14].

Dipeptidyl Peptidase-4 Inhibitors (DPP-4 Inhibitors)

The degradation of plasma GLP-1 is largely mediated by circulating DPP-4 enzyme, while renal clearance and cleavage by neprilysin (a neutral endopeptidase) also play a role [18]. By blocking the enzymatic degradation of endogenous GLP-1 by DPP-4 inhibitors, GLP-1 levels increase by ~ 2-fold [18]; there is also a decrease in plasma glucagon concentration.

Treatment with this class of oral agents is usually well tolerated and has resulted in lower discontinuation rates.

Table 1 Common adverse events associated with use of different classes of glycemia-lowering medications

Class	Hypoglycemia	Weight gain	Gastrointestinal	CV, renal, metabolic	Risk of cancer	Risk of infection
GLP-1RAs	Low risk	Low risk (cause weigh loss)	Nausea, vomiting. Pancreatitis	Favorable impact on CV risk factors Avoid in renal failure	Risk of MTC in animal studies	None
DPP-4 inhibitors	Low risk	Neutral	Risk of pancreatitis, liver dysfunction	Risk of CHF with saxagliptin Dose adjustments in CKD	None	Upper respiratory infections
SGLT2 inhibitors	Low risk	Low risk (Some weight loss)	Few reported case of pancreatitis	Risk of amputation with canagliflozin Risk of DKA and dehydration	Bladder cancer risk with dapagliflozin	Genital fungal infection and UTI. Necrotizing fasciitis
Insulin	High risk	High risk	None	None	None	At site of injection or infusion
Sulfonylurea	High risk	High risk	None	Conflicting data; most studies showed CV safety	None	None
Meglinitides	Moderate risk	Moderate risk	None	None	None	None
Metformin	Low risk	Weight neutral	Cramps, diarrhea	Possible lactic acidosis Avoid in CKD	None	None
TZDs	Low risk	High-risk weight gain/fluid retention	None	Edema and CHF, especially with insulin.	Bladder cancer risk with pioglitazone	None
Alpha Glucosidase	Low risk	Weight neutral	Flatulence, cramps	None	None	None

Each of the classes of medications has one or more specific agents. Use of different agents within a class of medications may not exhibit an equivalent severity or frequency of adverse events

Adverse events are uncommon and hypoglycemia is rare; there is no effect on body mass (Tables 1 and 2). GI symptoms including nausea, vomiting and diarrhea are far less common with DPP-4 inhibitors compared GLP-1 RAs or metformin [19]. Increased prevalence of upper respiratory infection, hepatic enzyme elevation, and pancreatitis has been reported but are infrequent [19]. In a meta-analysis, DPP-4 inhibitors significantly elevated the risk of acute pancreatitis (OR = 1.76, 95% CI 1.14–2.72) (Tables 1 and 2) but had no effect on the risk of pancreatic cancer (OR = 0.55, 95% CI 0.29–1.02); however, the risk of pancreatitis was not statistically significant in some of the reported studies [16].

Multiple clinical trials have evaluated the CV safety of various DPP-4 inhibitors, and only SAVOR-TIMI53, a large clinical trial of 16,492 participants with a follow-up of 2.9 years, showed patients treated with saxagliptin had increased rates of hospitalization due to acute heart failure (by relative risk of 27%); however, no heart failure-related mortality was detected [20]. Current data do not support congestive heart failure as an adverse effect of the class of DPP-4 inhibitors [21, 22]. These agents do not exhibit beneficial CV effects compared to placebo or GLP-1 receptor agonists.

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2 Inhibitors)

Sodium-glucose cotransporter-2 (SGLT2) proteins are highly expressed in the proximal convoluted tubule of the kidneys. These transporters are an effective target for the treatment of T2DM because they mediate the reabsorption of 80–90% of filtered glucose. The normal renal threshold for glucose reabsorption is approximately a blood glucose of 180 mg/dL. In patients with T2DM, this threshold is increased (to 220–260 mg/dL) in part due to increased expression of SGLT2 and GLUT-2 Transporters. Inhibition of SGLT2s reduces this threshold to as low as 40–120 mg/dL leading to glycosuria and reduction of hyperglycemia [23]. Their action is independent of insulin secretion or insulin sensitivity (or even diabetes).

In recent trials using SGLT2 inhibitors, weight loss of 1–4 kg over 18–104 weeks was reported [24]. Use of SGLT2 inhibitors reduces blood pressure, with greater reductions in systolic (1.7 to 6.9 mmHg) than diastolic (0.9 to 3.5 mmHg) blood pressure; they routinely cause uricosuria leading to large reductions of blood uric acid levels. The initial reductions in blood pressure are mostly attributable to their volume-depleting effects. However, longer-term effects on blood pressure may be due to inhibition of the renin-angiotensin system and weight loss [25].

Multiple trials have been established the CV safety of SGLT2 inhibitors. In addition, the trials have shown different degrees of clinically significant CV and renal benefits. In the EMPA-REG OUTCOME trial, the group receiving empagliflozin experienced significantly lower rates of hospitalization due to heart failure (35% relative risk reduction; RRR), death from CVD (38% RRR), and death from any cause (32% RRR) compared with the placebo group [26]. Also the relative risk of developing or worsening nephropathy was 39% lower in the group treated with empagliflozin (13% vs. 19%, $P < 0.001$) [26]. In the combined CANVAS study,

Table 2 Serious adverse events associated with classes of glycemia-lowering medications

Class	Severe hypoglycemia	Pancreatitis	Cancer	Serious infections	Other
GLP-1 RAs	No	Yes Rare	No	No	Yes Possible retinopathy with semaglutide
DPP-4 inhibitors	No	Yes Rare	No	No	Yes Heart failure with saxagliptin
SGLT2 inhibitors	No	No	No	Yes Genital and urinary infections	Yes Euglycemic DKA, possible higher amputations with canagliflozin
Insulins	Yes	No	No	No	No
Sulfonylureas	Yes	No	No	No	No
Metformin	No	No	No	No	Yes Lactic acidosis
TZDs	No	No	Yes Bladder cancer with pioglitazone	No	Yes Fractures of long bones in females

Each of the classes of medications has one or more specific agents. Use of different agents within a class of medications may not exhibit an equivalent severity or frequency of adverse events

the primary CVD outcome was significantly lower in those treated with canagliflozin (14% relative risk reduction), and the risk of progression to albuminuria was decreased by 27% [27]. In the CREDENCE study performed in patients with T2DM and chronic kidney disease with albuminuria, patients receiving canagliflozin had lower progression of kidney disease and CV

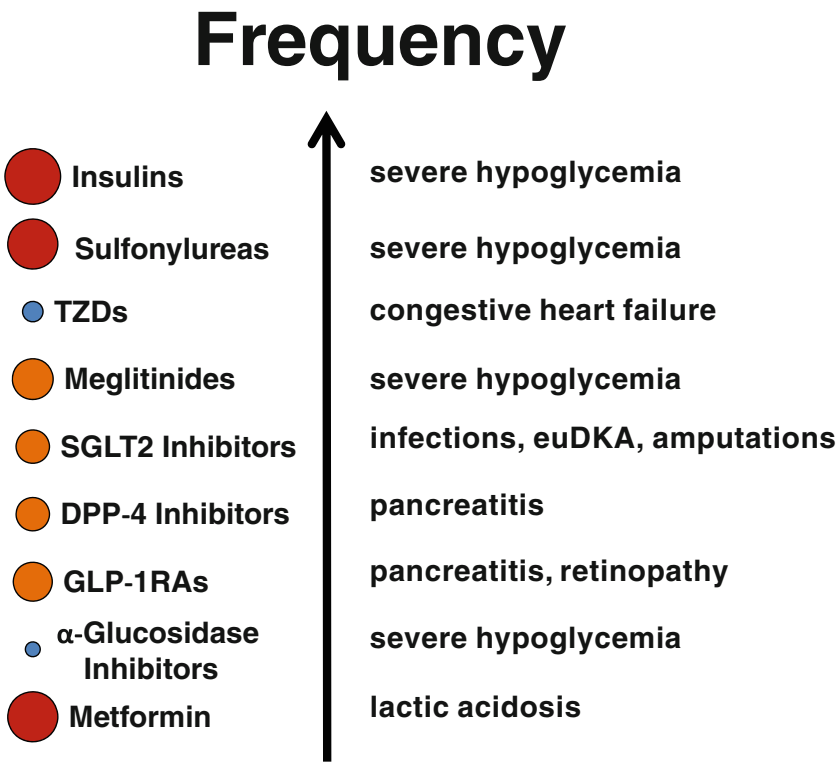

Fig. 1 Relative severity and frequency of serious life-threatening adverse events associated with use of different classes of glycemia-lowering medications. In the figure, the severity of an adverse event is depicted as being proportional to the size of the circle shown on the left; higher in *red*, moderate in *orange*, and lower in *blue*. For example, severe hypoglycemia with use of insulin and lactic acidosis with use of metformin are both depicted being clinically severe, yet they do have the same frequency. The sizes of the *circles* showing severity and position of classes of medications on the frequency scale are approximate. Use of different agents within a class of medications may not exhibit an equivalent severity or frequency of adverse events

events [28•]. These agents also appear to have a positive effect on the resolution of fatty liver. Treatment with SGLT2 inhibitors decreases both glucose and insulin levels which lead to decreased hepatic de novo lipid synthesis and improvement of hepatic steatosis [5]. Both empagliflozin and canagliflozin are approved for the specific indication of reducing the risk of CV events in individuals with T2DM and established CV disease.

The most common adverse effect of SGLT2 inhibitors is genital mycotic infections that are increased up to four-fold (Tables 1 and 2, and Fig. 1) [23, 24]. Incidences of genital bacterial infections, urinary tract infections, and osmotic diuresis-related adverse events are also higher in those receiving SGLT2 inhibitors, although the severity of these later events was generally mild to moderate [24]. It is probable that proper hygiene of areas exposed to urine containing glucose might prove effective in preventing genital mycotic infections.

Recent reports and FDA warning have identified 55 unique cases of necrotizing fasciitis (Fournier's gangrene) in patients receiving SGLT2 inhibitors between 1 March 2013 and 31 January 2019 [29, 30•, 31, 32]. The affected patients ranged in age from 33 to 87 years; 39 were men, and 16 were women. Time to onset after initiation of SGLT2-inhibitor therapy ranged from 5 days to 49 months. These patients were critically ill and required one or more surgical debridement. Eight patients had fecal diversion surgery, 2 patients developed necrotizing fasciitis of a lower extremity that required amputation, and 1 patient required a lower-extremity bypass procedure because of gangrenous toes [30•, 31, 32]. It should be noted that this serious life-threatening Fournier's gangrene can also occur in patients with T2DM who are not treated with these agents.

SGLT2 inhibition causes a rapid increase in urinary glucose excretion, ranging 50–100 g/day. Consequently, there is a decrease in both plasma glucose and insulin levels. It has been reported that glucagon expressing pancreatic alpha cells express SGLT2 transporters and their inhibition can trigger the release of glucagon [33]. The rise in glucagon level and in plasma glucagon to insulin ratio stimulates fatty acid oxidation and ketone production in liver [34, 35]. This can lead to euglycemic diabetic ketoacidosis (euDKA), defined as DKA in the presence of plasma glucose levels of <250–300 mg/dL, is more frequent in patients with type 1 diabetes (T1DM) compared to T2DM; these agents have not been approved by the FDA for use in T1DM [34, 35]. While the incidence of euDKA in patients with T2DM treated with SGLT2 inhibitors is very low (1.02–1.69 per 1000 patient-year), the risk of euDKA may be increased in patients with long-standing T2DM with marked β-cell insufficiency, in latent autoimmune diabetes in adults, or during prolonged starvation, after surgery or serious illnesses [35].

In nine pooled clinical trials with a mean duration of exposure to canagliflozin of 85 weeks, the incidence of bone fractures was 1.1, 1.4, and 1.5 per 100 patient-years of exposure to placebo, 100 mg, and 300 mg of canagliflozin, respectively. Additionally, the report documented a decline in bone mineral density and increased risk of fractures [36]. The loss of bone mineral density has not been shown with other agents in this class [37].

In 2017, the CANVAS and CANVAS-R trials reported a twofold increase in the occurrence of lower limb amputations in the group treated with canagliflozin [27, 38, 39]. These were predominantly toe or metatarsal amputations and they occurred in individuals without established peripheral vascular disease. These findings prompted FDA to issue a caution on the use of canagliflozin in individuals at risk of amputation. However, increased rates of amputations with use of canagliflozin were not noted in the recently published CREDENCE trial [28•]. A pooled analysis of 30 phase 2&3 trials did not report a statistically significant association between use of dapagliflozin and amputation [31].

In the recently published DERIVE study comparing treatment with dapagliflozin versus placebo, rates of adverse events leading to discontinuation was similar to placebo group at 1.9% [40•]. Patients in the dapagliflozin and placebo arms had similar frequencies of urinary tract infection (2.5% vs. 3.7%), genital infection (1.9% vs. 1.2%), and hypoglycemia (12.5% vs. 13.7%). No bone fractures were reported. Six cases of Fournier's gangrene were reported, one in the dapagliflozin group and five in the placebo group [41].

Finally, acute pancreatitis has been reported as a rare untoward event associated with use of canagliflozin; two case reports of acute pancreatitis associated with DKA in patients treated with canagliflozin were published in 2015 [42, 43].

Insulin and Insulin-Providing Medications

Insulin

Insulin therapy is essential in T1DM and frequently becomes a necessity in patients with long-standing T2DM. Analog insulin products have onsets and durations of action that more closely mimic the kinetics of physiologic insulin secretion. Bolus (prandial) insulin analogs mimic the physiologic response to meals, while long-acting (basal) insulin analogs provide a lower and more constant circulating insulin levels [44].

Hypoglycemia is an important adverse effect of insulin therapy; a meta-analysis of six studies in patients with T2DM including 903,510 participants and 1.0–5.6 years of follow-up reported that 0.6–5.8% patients experienced severe hypoglycemia (Tables 1 and 2, and Fig. 1) [45]; severe hypoglycemia is defined as an event in which the assistance of another person is required to treat the hypoglycemia. Additionally, insulin therapy is associated with weight gain (1.4–3.8 kg) and injection site reactions (4 in 1000 patients).

Concern has been raised regarding potential mitogenic effects of insulin analogues, but distinct evidence is lacking [46].

In the ORIGIN trial focused on efficacy and safety of glycemic control with use of glargine, 12,537 patients with CV risk factors plus prediabetes or early T2DM received insulin glargine or standard of care. The incidence of a first episode of severe hypoglycemia was 1.00 and 0.31 per 100 patient-years in the insulin-glargine and control groups, respectively ($P < 0.001$). One death was attributed to hypoglycemia in the glargine group. The incidence of an initial episode of non-severe symptomatic hypoglycemia (symptoms of hypoglycemia with a blood glucose level of ≤54 mg/dL) was 9.83 and 2.68 per 100 patient-years in the insulin-glargine and standard-care groups, respectively. Patients in the glargine group gained a median of 1.6 kg (− 2.0 to 5.5), and those in the standard of care group lost a median of 0.5 kg (− 4.3 to 3.2) during a median follow-up of 6.2 years [47].

In the DEVOTE trial in which participants with T2DM were treated with either insulin degludec or U-100 insulin glargine, lower rates of severe hypoglycemia and nocturnal severe hypoglycemia were reported in those receiving degludec (rate ratios of 0.60 versus 0.73) [48•].

In a recent systematic review of randomized controlled trials in T1DM, the efficacy and safety of short-acting insulin analogues vs regular human insulin were assessed [49]. A total of 6235 patients were included. Short-acting insulin analogues were associated with lower total, nocturnal, and severe hypoglycemic events [49].

Despite the efficacy of insulin in controlling glycemia, fear of injection as well as the cogent and well-documented risk of severe hypoglycemic events and unwanted weight gain continues to be major reasons for aversion to the use of insulin.

Sulfonylureas

Sulfonylureas constitute a group of glycemia-lowering agents that are used world-wide in the treatment of T2DM. Examples of first-generation sulfonylureas include chlorpropamide and tolbutamide, and members of the second generation include glipizide, gliclazide, and glyburide. Glimepiride is occasionally considered as a third-generation medication. Chlorpropamide, glyburide, and glimepiride have a prolonged duration of action compared to shorter-acting members including gliclazide, glipizide, and tolbutamide [50, 51].

These compounds bind to sulfonylurea receptor (SUR)-1 that is part of a complex with transmembrane potassium channels (KATP). The binding triggers the release of insulin from vesicles close to or attached to the plasma membrane of beta cells of pancreatic islets [52]. These drugs also stimulate the second phase of insulin release as more insulin-containing vesicles are transported to the plasma membrane. These agents can stimulate insulin secretion independently of plasma glucose concentration and can cause hypoglycemia [53, 54]. Sulfonyl-ureas with benzamido group (glipizide and glimepiride) can bind to SUR2A and SUR2B that are expressed in cardiac and vascular smooth muscle cells [53]; however, the clinical implications are unknown.

Hypoglycemic events associated with use of these agents are usually mild but can occasionally be severe and life-threatening (Tables 1 and 2, and Fig. 1). Severe hypoglycemia is a more likely occurrence with use of the older formulations [55]. In UKPDS severe hypoglycemia was reported as 1% annually, although higher rates were reported in the VADT and ACCORD trials with use of sulfonylureas (often used with other agents) [56, 57••, 58••]. Mortality risk from severe hypoglycemia associated with use of sulfonylurea has been reported as 0.014–0.33 per 1000 patient-years [58••]. Lower risk of hypoglycemia was reported with extended release gliclazide and glipizide [59, 60]. Other adverse events include sensitivity reactions and erythema multiforme. Fever, jaundice, blood dyscrasias, and acute porphyria have been reported rarely, and photosensitivity and facial flushing have been reported with use of chlorpropamide [61].

These agents also cause weight gain; this untoward effect is considered to be a class effect and typically amounts to 1–4 kg after 6 months of therapy [62]. Recent observational studies and meta-analyses showed no consistent CV adverse outcomes with this class or with extended release forms of these medications, although this topic remains controversial [63].

Meglitinide Analogues

Repaglinide and nateglinide are short-acting medications that increase the first phase of glucose-stimulated insulin release by binding to the SUR-1 sulfonylurea receptor; post-prandial hyperglycemia is minimized with their use [64, 65]. Repaglinide is near-exclusively metabolized in the liver and is safe to use in patients with renal failure [64]. The incidence of significant hypoglycemic events is much lower with these agents compared to sulfonylureas or insulin. Sensitivity reactions are usually transient. A small increase in weight gain is reported during initial therapy but little weight gain has been reported after switching from a sulfonylurea [64, 66].

Biguanides (Metformin)

Metformin is the only biguanide available globally after withdrawal of phenformin due to its high risk of lactic acidosis in 1970s [67]. Metformin has a variety of metabolic effects, some of which extend beyond glucose-lowering. At the cellular level, metformin improves insulin sensitivity via post-receptor insulin signaling pathways such as targeting adenosine 5-monophospate activated protein kinase (AMPK) and regulating intercellular glucose and lipid metabolism. Metformin reduces gluconeogenesis in part by increasing hepatic insulin sensitivity. Insulin-stimulated glucose uptake in skeletal muscle is increased by metformin. It also suppresses

oxidation of fatty acids and reduces triglycerides levels [68, 69]. Metformin may also reduce CV events (UKPDS) [70].

Abdominal pain and other GI adverse effects including bloating and diarrhea are not uncommon during initiation of metformin. These symptoms often resolve if the dose is up-titrated slowly. The extended release form of the medication is better tolerated in some patients. Nevertheless, about 10% of patients cannot tolerate metformin due to its GI adverse effects [71]. The most serious adverse effect associated with use of metformin is lactic acidosis which is rare (0.03 cases per 1000 patients-years) but can be lethal; it usually occurs in the setting of other serious acute illnesses (Tables 1 and 2, and Fig. 1) [72].

Thiazolidinediones (TZDs)

Medications in this class are potent agonists of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ). Stimulation of this receptor improves whole body insulin sensitivity. PPARγ is expressed at highest levels in adipose tissue and at lesser levels in liver and skeletal muscles [73]. PPARγ modulates the transcription of a wide range of insulin-sensitive genes involved in carbohydrate and lipid metabolism [74]. These agents can stimulate lipogenesis and reduce non-esterified fatty acid (NEFA) concentrations. Reduction of plasma NEFA can reduce insulin resistance and decrease the ectopic deposition of lipids in muscle and liver. Thiazolidinediones also reduce production of adipocyte derived cytokines such as TNF-alpha (which increases insulin resistance) [75].

Rosiglitazone was removed from world markets due to the possibility of causing myocardial infarction [76, 77]. However, the RECORD study showed that the risk of myocardial infarction with rosiglitazone was not significant [78]. Cardiac adverse outcomes such as the risk for myocardial infarction have been less of a concern for pioglitazone. The US package insert for both rosiglitazone and pioglitazone carries a box warning for congestive heart failure [77, 79].

A sub-analysis of the results of the PROactive trial showed that pioglitazone significantly reduced the occurrence of fatal and nonfatal myocardial infarction and acute coronary syndrome in high CV-risk patients with T2DM [80]. The IRIS trial conducted in patients without T2DM but with insulin resistance and a recent history of stroke or transient ischemic attacks found that treatment with pioglitazone resulted in significantly reduced rate of new CV events [81].

TZDs are generally well tolerated and hypoglycemia is rare. Edema and weight gain are commonly reported. Some patients develop peripheral edema, especially when treated with high doses. The risk of heart failure is elevated with these agents, especially when used in combination with insulin (Tables 1 and 2, and Fig. 1). In the RECORD trial, lower and upper extremity fractures in women treated with rosiglitazone were higher than comparator treatment group [78]. Most large studies in patients treated with TZDs noted an increased risk of bone fractures by about 1.5-fold [82].

Alpha-Glucosidase Inhibitors

Inhibitors of intestinal alpha-glucosidase enzyme delay the breakdown of complex carbohydrates and decrease the rate of their absorption thereby reducing post-prandial hyperglycemia. Acarbose was the first of this class marketed in 1990s and recently two additional agents, miglitol and voglibose, have been introduced. These medications can decrease triglycerides and post prandial hyperinsulinemia. However, they are relatively expensive in some countries [83].

The most common adverse effect is GI side effects. In STOP-NIDDM trial, 31% of patients treated with acarbose discontinued treatment due to GI symptoms including flatulence, abdominal discomfort, and diarrhea [84]. These effects usually occur during the initiation of treatment and can be minimized by slow up-titration; severe hypoglycemia is rare.

Conclusion

In the treatment of patients with T2DM, most of the effort is focused on preventing and delaying the occurrence of macro- and microvascular complications. Therefore, in choosing glycemia-lowering medications where their efficacy is measured by HbA1c reduction, those that also exhibit favorable effect on blood lipids, blood pressure, and weight as well as effects in lowering the incidence of CV and renal outcomes should be given preference. Taken together, given the wide choice of medications available for the management of T2DM, with many novel agents showing positive effects on important outcomes with reasonably low adverse effects, lead to an emerging reassuring future for patients with this disease. Nevertheless, for the vast majority of patients, only a careful individualized evaluation of clinical characteristics and lifestyle habits can result in the best treatment strategy. Choice of medications for any individual patient should rely, as always, not only on consideration of efficacy, but also on safety, cost, side effects, contraindications, tolerability and adherence, and importantly, patient preference.

Compliance with Ethical Standards

Conflict of Interest Laleh Razavi-Nematollahi declares that she has no conflict of interest. Faramarz Ismail-Beigi is a consultant to COVANCE and Sanofi and has received research grants from Novo Nordisk.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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