



# Personalized Management of Type 2 Diabetes

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## Abstract

**Purpose of Review** Our goal is to discuss how to personalize the management of patients with type 2 diabetes by adjusting glycemic targets and tailoring medical therapy to account for unique patient characteristics.

**Recent Findings** We review the pharmacotherapeutic options for the management of type 2 diabetes, focusing on potential advantages and disadvantages of each class of agents. We also discuss how to approach specific patient subpopulations and propose a conceptual framework for incorporating these factors into clinical practice.

**Summary** As the diabetes treatment landscape rapidly expands, physicians have the exciting opportunity to offer patients increasingly individualized care.

**Keywords** Type 2 diabetes · SGLT-2 inhibitors · GLP-1 agonists · Metformin

## Introduction

Over 30 million Americans (up to 12.2% of US adults) have diabetes mellitus; the vast majority have type 2 diabetes (T2DM) and the prevalence of this disease is expected to increase in the coming years [1, 2]. Diabetes is associated with numerous highly morbid complications and is the seventh leading cause of death in the USA [2]. Though advances in the care of these patients have led to significantly lower rates of its related complications, the cost of diabetes care continues to rise with the most recent estimates totaling \$327 billion dollars, representing a 26% increase over the past 5 years [3, 4].

Management of this costly and impactful disease relies on a multifaceted approach that has become increasingly personalized as the tools in our arsenal have multiplied. Setting a glycemic goal is no longer a straightforward task, as it must take into consideration a patient's comorbid conditions and social

context, all of which potentially change over time. In terms of therapeutic approach, lifestyle management remains the essential foundation, but fostering diabetes self-management skills, promoting medical nutrition therapy and regular physical activity, and being mindful of the potential psychosocial implications of this disease have to be addressed in an individualized way in order to promote durable and tangible effects [5]. Perhaps the most obvious realm in which personalization of therapy has become increasingly important is in diabetes pharmacotherapy. As treatment options for diabetes management have proliferated, the complexity of diabetes care has increased, allowing an opportunity to provide more thoughtful, individualized, and effective care to our patients.

## Pharmacotherapeutic Options for Patients with Type 2 Diabetes

Treatment of hyperglycemia in T2DM includes a low-carbohydrate and heart-healthy diet, exercise, weight loss, and the use of anti-diabetic agents (oral or injectable treatments). Anti-hyperglycemic treatments include agents that increase insulin availability (either through administration of insulin injections or through agents that promote insulin secretion, either directly such as sulfonylureas and meglitinides, or indirectly via incretin pathway such as dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists), improve insulin sensitivity (biguanides,

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thiazolidinediones), or increase urinary glucose excretion (sodium-glucose cotransporter-2 inhibitors). Some agents work through more than one mechanism. Navigating this long list of available anti-hyperglycemic agents can be challenging for clinicians. Since treatment should be customized based on patients' individual factors, knowledge of the unique risks and benefits of each medication class and its constituent agents is extremely important for providers treating patients with T2DM.

Table 1 outlines the main anti-hyperglycemic medication classes for treatment of T2DM including their most important benefits and disadvantages.

## Biguanides

Metformin is a biguanide which is generally considered the first choice for oral treatment of T2DM. Metformin decreases

hepatic gluconeogenesis and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. It also has an antilipolytic effect that lowers serum free fatty acid concentrations, thus decreasing substrate availability for gluconeogenesis.

## Benefits

Metformin is an effective anti-hyperglycemic agent which reduces the hemoglobin A1c (HbA1c) by about 1–2%. It does not increase the risk of hypoglycemia, is weight-neutral or provides modest weight reduction, and has overall good tolerability, long-term safety profile, and low cost. Metformin does not have adverse cardiovascular (CV) effects. On the contrary, it appears to decrease the risk of CV events in certain populations. A subset of overweight patients from the UK Prospective Diabetes Study (UKPDS) who received

**Table 1** The main benefits and disadvantages of the most commonly used glucose-lowering medication classes

Drug category and examples	Benefits	Disadvantages
Biguanides Metformin	Potent anti-hyperglycemic effect Weight loss or weight neutral Hypoglycemia risk not increased Decreased CV events in small trials Low cost	GI upset Increased risk of lactic acidosis
Sulfonylureas Glyburide Glipizide Glimepiride	Potent anti-hyperglycemic effect Low cost	Hypoglycemia Weight gain
TZDs Pioglitazone Rosiglitazone	Potent anti-hyperglycemic effect Hypoglycemia risk not increased Decreased MACE (pioglitazone)	Edema Weight gain Risk of HF
DPP-4 inhibitors Sitagliptin Saxagliptin Alogliptin Linagliptin	Hypoglycemia risk not increased No weight gain	Increased risk of HF with saxagliptin and alogliptin Increased risk of pancreatitis Expensive
GLP-1 agonists Exenatide Liraglutide Dulaglutide Lixisenatide Semaglutide	Weight loss Hypoglycemia risk not increased Decreased MACE (liraglutide, semaglutide) Decreased CV mortality (liraglutide) Beneficial effect on progression of nephropathy (liraglutide, semaglutide)	Increased risk of pancreatitis Expensive Injectable Acute kidney injury (exenatide)
SGLT-2 inhibitors Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Hypoglycemia risk is not increased Weight loss Decreased MACE (empagliflozin, canagliflozin) Decreased CV mortality (empagliflozin) Decreased HF hospitalizations (empagliflozin, canagliflozin, dapagliflozin) Beneficial effect on progression of nephropathy (empagliflozin, canagliflozin, dapagliflozin)	Polyuria, pelvic yeast infections and UTIs Dehydration Increased risk of amputations (canagliflozin) Increased risk of fractures (canagliflozin) Increased risk of DKA High cost
Insulin Various	Potent anti-hyperglycemic effect	High risk for hypoglycemia Weight gain Injectable route

metformin had a significant risk reduction of 32% for any diabetes-related endpoint (endpoints included both macrovascular and microvascular complications), 42% for diabetes-related death, and 36% for all-cause mortality compared to the group treated with sulfonylurea or insulin. Metformin also had a greater effect on any diabetes-related endpoint and all-cause mortality than intensive therapy with a sulfonylurea or insulin ( $p = 0.003$ ) [6].

### Adverse Effects and Precautions

Side effects of metformin include gastrointestinal upset (abdominal discomfort, anorexia, nausea, diarrhea etc.), vitamin B12 deficiency, and risk of lactic acidosis. Metformin should be avoided in patients at risk for lactic acidosis, such as those with a prior history of metformin-induced lactic acidosis, significantly impaired renal function, advanced liver disease, unstable heart failure, hemodynamic instability, baseline metabolic acidosis, or excessive alcohol intake. Since metformin is renally cleared, this agent should be avoided if creatinine clearance  $< 30$  mL/min/1.73 m<sup>2</sup>. Stable compensated heart failure (HF) is usually not considered a contraindication for metformin use.

### Candidates

For most patients with T2DM, in the absence of contraindications, metformin is usually the initial pharmacologic therapy. Its anti-hyperglycemic efficacy, low risk of hypoglycemia, lack of weight gain, and low cost makes it an attractive first-line treatment in addition to lifestyle modification.

### Sulfonylureas and Meglitinides

Sulfonylureas (SU) and meglitinides improve hyperglycemia by stimulating insulin release from pancreatic beta cells.

### Benefits

SU (glyburide, glipizide, glimepiride) are amongst the most effective anti-hyperglycemic agents, decreasing HbA1c by 1–2%. Meglitinides (repaglinide, nateglinide) are short-acting glucose-lowering agents which reduce the HbA1c by about 1%.

### Adverse Effects and Precautions

Hypoglycemia is the most common side effect and is especially seen with the longer-acting SU (chlorpropamide and glyburide). These should be avoided in patients at high risk for hypoglycemia (i.e., elderly patients or patients with low appetite, an irregular meal schedule, or impaired renal function). SU can also promote some weight gain.

Concerns regarding SU CV safety were raised almost 50 years ago when the first randomized trials on SU were conducted. Since then, various meta-analyses evaluating the safety of SU as a group or in association with metformin have reported contradictory results [7–9]. The recently released results of CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes (CAROLINA) showed no increase in CV events in patients with diabetes at increased CV risk or with established cardiovascular disease (CVD) who were treated with glimepiride (pending publication).

Meglitinides' CV safety is unclear but since their mechanism of action is similar to SU, theoretically, the same concerns can be raised. Meglitinides are shorter-acting medications and they possibly have less risk of hypoglycemia than SU but are more expensive.

### Candidates

Given their good anti-hyperglycemic efficacy and low cost, SU are one of the most widely used medications for the treatment of patients with T2DM.

Meglitinides can be used in patients intolerant to more conventional treatment options. They may be a good treatment option in patients who have an irregular meal schedule, since these agents are short-acting and the dose can be easily skipped if a meal is missed.

### Thiazolidinediones

Thiazolidinediones (TZDs) (rosiglitazone and pioglitazone) improve glycemic control by increasing insulin sensitivity in the adipose tissue, muscle, and liver.

### Benefits

TZDs are effective anti-hyperglycemic agents. They decrease HbA1c by 1–2% without causing hypoglycemia and have greater durability than metformin and SU.

Pioglitazone seems to be of benefit in reducing the risk of CV ischemic events. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial showed a 16% reduction in the risk of major cardiovascular event (MACE) in subjects with T2DM and established CV disease treated with pioglitazone (95% CI 0.72–0.98;  $p = 0.027$ ) [10].

The Insulin Resistance Intervention after Stroke (IRIS) trial showed that pioglitazone reduced the primary composite outcome of fatal/non-fatal myocardial infarction (MI) or stroke by 24% versus placebo (95% CI 0.62–0.93;  $p = 0.007$ ) in insulin-resistant but diabetes-free participants with a recent stroke or transient ischemic attack [11]. Most randomized trials found a more favorable lipid profile with pioglitazone than rosiglitazone [12].

Pioglitazone also has beneficial effects on non-alcoholic steatohepatitis (NASH), a prevalent comorbid condition in patients with T2DM. In a small study by Cusi et al., 58% of patients with prediabetes or T2DM and biopsy-proven NASH treated with pioglitazone and a 500-cal diet experienced histologic improvement of their disease and 51% had resolution of their NASH [13]. Promising results have also been shown in patients without T2DM, so some professional societies have included pioglitazone as a potential treatment option for NASH [14, 15].

### Adverse Effects and Precautions

Side effects of TZDs include weight gain, fluid retention, and increased risk of HF. In meta-analyses, the estimated relative risk (RR) of HF in patients assigned to TZDs compared with placebo ranged from 1.7 to 2.1 (95% CIs 1.2–2.4 and 1.1–4.1, respectively) [16, 17].

Rosiglitazone and pioglitazone seem to have different effects on ischemic events. While pioglitazone seems to confer CV benefit, a controversial 2007 meta-analysis suggested that rosiglitazone was associated with a significant increase in the risk of MI. In the rosiglitazone group, as compared with the control group, the odds ratio for MI was 1.43 (95% CI 1.03–1.98;  $p = 0.03$ ), and the odds ratio for death from CV causes was 1.64 (95% CI 0.98–2.74;  $p = 0.06$ ) [18]. However, in the randomized trial Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD), rosiglitazone proved neutral for MACE, with the caveat that the study may have been underpowered, and the results may have been affected by greater statin use in the rosiglitazone group [19].

Studies suggest that TZDs decrease bone density and increase fracture risk, particularly in women. Although the increase in fracture risk appears to be small, this class of medications should be avoided in patients at higher risk for fractures (e.g., postmenopausal women with low bone density) [20–22]. Concerns have been raised regarding an increased risk of bladder cancer with pioglitazone use though recent meta-analyses have shown conflicting results [23, 24]. Generally, it would be advisable to avoid pioglitazone use in patients with active bladder cancer or prior history of bladder cancer.

Abnormal liver function tests have occasionally been reported in patients receiving TZDs. Severe hepatic toxicity is uncommon, but TZDs should probably be avoided in patients with active liver disease (liver enzymes > 2.5–3 times above the upper reference limit) [25]. Liver function abnormalities are commonly seen in T2DM patients and are often due to NASH. As mentioned above, pioglitazone seems to have a beneficial effect on NASH and slightly elevated LFTs are not a contraindication for its use, especially when underlying NASH is suspected.

### Candidates

Since TZDs are similar in efficacy to metformin and have very good durability, this class of medications could be considered as a second-line medication in treating diabetes when more than 1% reduction in the HbA1c is desired, especially if there are contraindications to SU or if there is a need to avoid hypoglycemia. As pioglitazone has a different CV risk profile than rosiglitazone, the former is preferred and could be an appropriate treatment option for patients with overt CVD.

### Dipeptidyl Peptidase-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors (linagliptin, sitagliptin, saxagliptin, alogliptin) are a class of oral anti-hyperglycemic drugs that inhibit the enzyme DPP-4 which deactivates several peptides, including glucagon-like peptide-1 (GLP-1). GLP-1 stimulates glucose-dependent insulin release from the pancreatic beta cells, thus affecting glucose regulation.

### Benefits

DPP-4 inhibitors have a relatively modest glucose lowering effect, decreasing HbA1c by 0.5–1%. These agents are in general well-tolerated, do not cause weight gain, and carry a low risk of hypoglycemia.

### Adverse Effects and Precautions

Meta-analyses of three large randomized placebo-controlled trials with sitagliptin, saxagliptin, and alogliptin suggest an increased risk of acute pancreatitis with these agents (the absolute excess risk was small—about 1.3 cases per 1000 patients). Because of this concern, it would be best to avoid using these agents in patients with a history of acute or chronic pancreatitis or patients at risk for pancreatitis (such as alcohol abuse, high triglycerides, etc.) [26–28]. There is no clear association between this class of medications and pancreatic cancer [27, 29].

CV outcome studies suggest that DPP-4 inhibitors are neutral for MACE, but saxagliptin and alogliptin may increase the risk of HF by an unknown mechanism [30–33]. Aside from linagliptin which is eliminated via the enterohepatic system, the DPP-4 inhibitors require dose reduction in the setting of impaired kidney function. Finally, the DPP-4 inhibitors are more expensive than generic anti-hyperglycemic agents.

### Candidates

DPP-4 inhibitors can be considered as monotherapy or as a second- or third-line treatment in addition to metformin in patients at high risk for hypoglycemia who only need < 1%

reduction in HbA1c to achieve their glycemic target. Linagliptin may be a good option in patients with CKD as this agent does not require dose adjustment for low eGFR. Since DPP-4 inhibitors are weight-neutral, they may be an attractive option for patients concerned about weight gain.

### Glucagon-Like Peptide-1 Receptor Agonists

GLP-1 receptor agonists (liraglutide, dulaglutide, semaglutide, exenatide, lixisenatide) are typically injectable agents that impact glucose control by stimulating glucose-dependent insulin secretion from pancreatic beta cells, slowing gastric emptying, reducing postprandial glucagon release, and suppressing appetite. An oral formulation of semaglutide has been developed and is being evaluated in clinical trials. The oral form of semaglutide seems to have similar efficacy and side effects as the injectable form [34].

#### Benefits

GLP-1 receptor agonists reduce HbA1c by about 1%. Although expensive, this class of medications is appealing due to its appetite-suppressive effect, promotion of weight loss, and low risk of hypoglycemia.

At least two members of this class, liraglutide and semaglutide, have CV benefits. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study, in participants with T2DM at high risk for CV events, the primary MACE outcome occurred in significantly fewer participants treated with liraglutide than with placebo (HR 0.87; 95% CI 0.78–0.97), and fewer participants died from CV causes in the liraglutide group (HR 0.78, 95% CI 0.66–0.93). The rate of death from any cause was lower in the liraglutide group than in the placebo group (HR 0.85, 95% CI 0.74–0.97). The rates of nonfatal MI, nonfatal stroke, and hospitalization for HF were non-significantly lower in the liraglutide group than in the placebo group [35••].

In the Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), the primary MACE outcome occurred in fewer participants with T2DM and CV risk factors treated with semaglutide versus placebo (HR 0.74, 95% CI 0.58–0.95). The reduction in nonfatal MI between the two groups was not statistically significant (HR 0.74, 95% CI, 0.51–1.08;  $p = 0.12$ ). The occurrence of nonfatal stroke was significantly lower in the semaglutide group versus placebo (HR 0.61, 95% CI, 0.38–0.99;  $p = 0.04$ ). Rates of death from CV causes and any cause were similar in the two groups [36••].

Liraglutide and semaglutide have been associated with improved renal outcomes as well. The LEADER trial showed lower rates of the composite outcome of new-onset persistent macroalbuminuria, persistent doubling of serum creatinine, end-stage renal disease, or death due to renal disease in those

treated with liraglutide compared to placebo (HR 0.78, 95% CI, 0.67–0.92;  $p = 0.003$ ) though this result was largely driven by reductions in macroalbuminuria [37]. Similarly, SUSTAIN-6 showed that new or worsening nephropathy (defined as a composite outcome of microalbuminuria, doubling of serum creatinine, creatinine clearance  $> 45$  mL/min/1.73m<sup>2</sup>, or the need for maintenance dialysis) occurred less often in the semaglutide group versus placebo (HR 0.64, 95% CI, 0.46–0.88;  $p = 0.005$ ), a result that was also primarily driven by improvement in macroalbuminuria [36••].

Given the association between GLP-1 agonist therapy and weight loss, these agents are currently under investigation as a potential treatment option for NASH. In the Liraglutide Safety and Efficacy in Patients with Non-alcoholic Steatohepatitis (LEAN) study which enrolled patients with and without diabetes and with biopsy-proven NASH, only 9% of participants in the group treated with liraglutide had progression in their hepatic fibrosis compared to 36% in the placebo group, and 39% of participants in the liraglutide group showed resolution of their NASH [38]. Though these early results are promising, the American Association for the Study of Liver Diseases (AASLD) considers it premature to consider GLP-1 agonists as NAFLD/NASH-specific therapeutic agents [15].

#### Adverse Effects and Precautions

Common side effects of GLP-1 receptor agonists include nausea, vomiting, bloating, and constipation due to decreased gastrointestinal transit. Although some of these symptoms may get better with continuous therapy and slow dose titration, these agents would be best avoided in patients with significant baseline gastrointestinal symptoms such as chronic nausea, vomiting, acid reflux, or gastroparesis.

There is some controversy as to whether GLP-1 receptor agonists increase the risk of pancreatitis. In five liraglutide trials including over 3900 participants, there were seven cases of pancreatitis in participants randomly assigned to liraglutide and one case in a participant using another diabetes drug [39]. However, meta-analyses of randomized trials using various GLP-1 receptor agonists did not support an increased risk [40, 41]. Concerns have been raised regarding an increased risk of pancreatic cancer and pancreatic neuroendocrine tumors with the use of GLP-1 agonists, but thus far, there is no clear evidence to confirm this association. However, given these concerns, it would be best to avoid this class of medications in patients with prior history of pancreatitis or at risk for pancreatitis (excessive alcohol use, very high triglyceride levels) and pancreatic tumors. Additionally, liraglutide use has been associated with an increased risk of bile duct and gallbladder disease, representing another effect this class of agents might have on the gastrointestinal system [42–44].

In rodent studies, liraglutide and dulaglutide were associated with benign and malignant thyroid C cell tumors [45, 46].

Although it is unclear whether this risk is also increased in humans, it is recommended to avoid using GLP-1 receptor agonists in patients with a history of or at risk for medullary thyroid cancer (i.e., those with multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma).

SUSTAIN-6 found significantly increased rates of retinopathy complications in patients receiving semaglutide [36••]. However, subsequent studies including a meta-analysis, post hoc analyses of all the available SUSTAIN data, and an investigation of the FDA's adverse event reporting data did not demonstrate clear evidence of this association, raising the possibility that the worsening retinopathy might instead have been a non-specific result of the speed and magnitude of glucose-lowering in these patients rather than an effect of the medication itself [47–49].

While GLP-1 agonists are often used in patients with renal dysfunction, there have been several case reports of acute kidney injury following exenatide use, so this medication should be avoided in patients with severe renal impairment or end-stage renal disease [50].

### Candidates

GLP-1 receptor agonists can be considered a second-line treatment for T2DM after metformin in patients interested in weight loss, especially if hypoglycemia needs to be avoided. Liraglutide and semaglutide should be favored in patients at high risk of CV events given their CV benefit.

### Sodium-Glucose Co-Transporter 2 Inhibitors

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors belong to a novel class of anti-diabetic medications which improve hyperglycemia by increasing urinary glucose excretion.

### Benefits

SGLT-2 inhibitors (canagliflozin, empagliflozin, dapagliflozin, ertugliflozin) are relatively modest glucose-lowering agents, but they usually induce some weight loss and blood pressure reduction while also carrying a low risk of hypoglycemia.

Two members of this class, empagliflozin and canagliflozin, have been shown to significantly reduce CV risk in patients with underlying CVD.

In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial, participants with T2DM and CVD who were treated with empagliflozin had a lower rate of the primary MACE outcome as compared with placebo (HR in the empagliflozin group 0.86, 95% CI 0.74–0.99;  $p = 0.04$  for superiority). The primary outcome was predominately driven by a 38% reduction in the risk of CV death, whereas there

were no significant between-group differences in the rates of MI or stroke. Death from any cause was reduced by 32% and hospitalization for HF was reduced by 35% [51].

In the Canagliflozin Cardiovascular Assessment Study (CANVAS), participants with T2DM and preexisting history of symptomatic CVD or at risk for CVD who were treated with canagliflozin had significant reduction in the primary MACE outcome compared to placebo (HR 0.86, 95% CI 0.75–0.97;  $p = 0.02$  for superiority). None of the individual components of MACE nor all-cause mortality were significantly reduced by canagliflozin, but the drug did exhibit almost exactly the same benefit in reducing HF hospitalizations (HR 0.67, 95% CI 0.52–0.87) as did empagliflozin. CANVAS recruited both patients with and without established CVD, and though all were at risk for CVD, data suggests that the MACE effect may be mostly impactful in secondary prevention. In contrast, the effect on HF hospitalizations was similar in both cohorts [52••, 53].

Empagliflozin, canagliflozin, and dapagliflozin have been shown to decrease the progression of chronic kidney disease and have been associated with lower rates of clinically relevant renal events in patients with T2DM who had or were at high risk for CVD [52••, 53–55].

Early pilot data has demonstrated benefits of SGLT2 inhibitor therapy on surrogate markers of liver fat deposition, but additional studies are ongoing to more rigorously investigate the clinical impact this class of agents might have on patients with NASH [56–58].

### Adverse Effects and Precautions

The most common side effects of SGLT-2 inhibitors are polyuria and urinary urgency. These medications increase the incidence of genital mycotic infections such as balanitis and vulvovaginitis. Some but not all studies showed that the drugs are also associated with a small increase in the risk of urinary tract infections (UTIs). Upper tract UTIs, such as pyelonephritis, urosepsis, and necrotizing fasciitis of the perineum (Fournier's gangrene), are rare complications. We suggest avoiding SGLT2 inhibitors in patients with a prior history of complicated UTIs, patients with an indwelling urinary catheter, or recurrent genital mycotic infections [59]. The use of this class of medications may negatively impact the quality of life in individuals with prostatic hypertrophy or urinary incontinence.

Diabetic ketoacidosis (DKA) sometimes with serum glucose levels  $< 250$  mg/dL (and referred to as "euglycemic" DKA) has been reported as a complication of treatment with SGLT2 inhibitors. This has been more frequently observed in patients with type 1 diabetes being treated off-label with this class of medications, but this can also occur in patients with T2DM [60–62]. Because of this risk, SGLT-2 inhibitors should be avoided in patients at higher risk for developing

DKA such as those with latent autoimmune diabetes in adults (LADA) or with evidence of low endogenous insulin secretion.

An increase in lower extremity amputation rates and fractures has been seen with canagliflozin, so this medication should not be used in patients at high risk for lower extremity amputations (i.e., those with PVD, severe diabetic neuropathy, or prior history of lower amputations or foot ulcerations) or fractures [52••].

SGLT-2 inhibitors can lower the blood pressure by inducing an osmotic diuresis. This can be a beneficial effect in a patient with uncontrolled hypertension but can also lead to postural dizziness, orthostatic hypotension, and dehydration, which are of particular concern in the elderly or in patients with labile volume status. Because of reports suggesting a possible association between SGLT-2 inhibitors and acute renal failure, the Food and Drug Administration (FDA) has issued alerts regarding an increased risk of acute kidney injury with canagliflozin and dapagliflozin. Current labeling states that empagliflozin, canagliflozin, and dapagliflozin should be discontinued when the creatinine clearance is  $< 45 \text{ ml/min/1.73 m}^2$  and ertugliflozin stopped when the creatinine clearance is  $< 60 \text{ ml/min/1.73 m}^2$ .

### Candidates

Given the relatively modest reduction in hyperglycemia, high cost and absence of long-term safety data, SGLT-2 inhibitors are usually not considered first- or second-line treatment in patients with diabetes who do not have underlying CVD. However, the agents with proven CV and renal benefits should be considered as next-line to metformin in patients with established CV or diabetic renal disease. SGLT-2 inhibitors could also be considered as a second-line treatment option in patients interested in weight loss or who need to avoid hypoglycemia.

### Insulin

Many patients with T2DM will need insulin injections at some point during the course of their disease due to a progressive decline in endogenous insulin secretion. Once-daily basal insulin is the most common initial regimen with a weight-based or empiric starting dose that is then titrated to achieve a patient's individual fasting glucose goal without hypoglycemia. If HbA1c remains persistently elevated, mealtime insulin can be started at about 10% of the basal dose and titrated to target, first with the largest meal and then with subsequent meals and snacks if needed. Pre-mixed insulins are a potential alternative for patients requiring basal and bolus coverage but who prefer fewer injections per day. Generally, once insulin has been initiated, SU and DPP-4 inhibitors are stopped but most other

agents can be continued to help reduce overall insulin requirements.

### Benefits

Insulin is a very effective agent in controlling hyperglycemia and the dose can be increased as much as needed in order to improve hyperglycemia. Available data suggests that insulin has a neutral effect on MACE [63, 64]. The newer longer-acting basal analogs such as U-300 glargine and degludec show some promise in their ability to provide desired glucose-lowering with less hypoglycemia than older basal insulin formulations [65, 66]. For patients with significant insulin resistance and high insulin requirements, more concentrated formulations of insulin are now available as prefilled pens for both basal (U-300 glargine, U-200 degludec) and shorter-acting insulins (U-500 regular, U-200 lispro), which could facilitate adherence by making insulin injections easier and more comfortable [67].

### Adverse Effects and Precautions

Insulin can cause weight gain and hypoglycemia, especially the non-physiologic regimens such as premixed insulins. The insulin analogs are expensive and the route of administration may not be appealing for many patients. More frequent blood glucose monitoring is required as the complexity of the insulin regimen increases, and this can be burdensome for patients. In patients at high risk for hypoglycemia, a conservative approach should be used, keeping the number of injections to a minimum and increasing the glycemic targets.

### Candidates

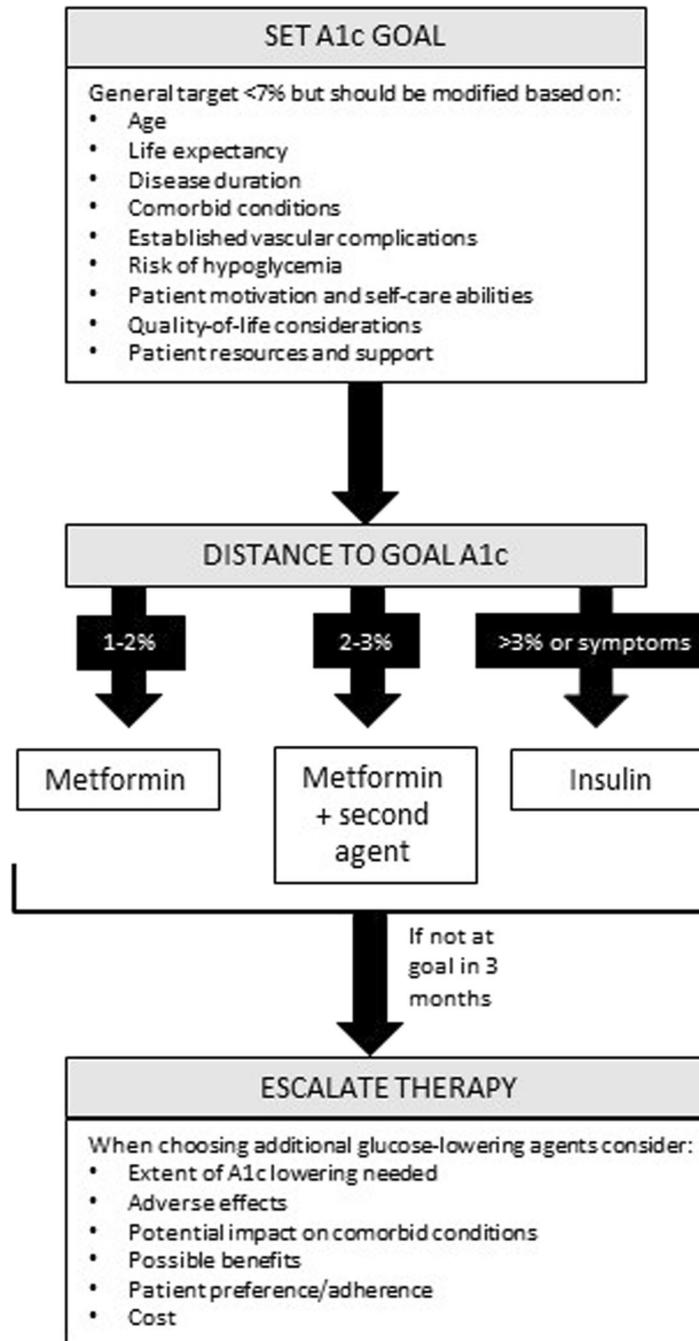
Good candidates for insulin treatment include patients with severe and/or symptomatic hyperglycemia, those unable to achieve good control on multiple agents, and patients with low endogenous insulin secretion.

### Glycemic Targets: No Longer a One-Size-Fits-All Approach

The most basic goals of diabetes care are to alleviate the symptoms of hyperglycemia and to prevent or slow the progression of its associated end-organ complications. The results of landmark trials in diabetes have demonstrated a clear link between glucose control and reduction in the rates of microvascular complications, with longer-term follow-up data suggesting benefits on CV outcomes as well [68, 69]. Despite its known unreliability in states of altered red blood cell turnover (e.g., hemoglobinopathies, pregnancy, etc.), the HbA1c test has been widely adopted as a key indicator of glucose control

due to its ease of use and generally good correlation with average glycemia. Specifically, an HbA1c of <7.0% has become the most commonly accepted glycemic goal for adults as it corresponds to a level of glycemia that strikes a reasonable balance between reducing complications while avoiding hypoglycemia [68]. However, acknowledging the complexities that arise in the care of individual patients with diabetes, most professional society guidelines in the US and Europe

have treated this as a fluid target that should be modified to account for individual patient characteristics [68, 70, 71]. Disease duration, life expectancy, comorbid conditions, established complications, resources and support, patient motivation and preference, and risks of adverse effects related to therapy including hypoglycemia must all be taken into account when deciding whether to aim for a more or less stringent target HbA1c (Fig. 1) [68]. For example, the patients that



For all patients, lifestyle modification and cardiovascular risk management should be reinforced and assessed at each visit

**Fig. 1** Approach to personalized management of type 2 diabetes

would benefit most from tight glycemic control (i.e., HbA1c < 6.5–7.0%) are those that are young with relatively recent onset of diabetes and who are without significant comorbidities. Conversely, a less stringent HbA1c < 8.0–8.5% might be appropriate for an individual with a limited life expectancy who has significant comorbidities and in whom quality of life considerations might be paramount. Many of these factors will

change over time, so the HbA1c target can and should be adjusted accordingly.

This flexibility in setting glycemic goals is especially important in older adults who often have comorbid conditions and cognitive or functional impairments that impact their ability to care for themselves or follow a complex medical regimen. Therefore, comprehensive care of these patients has to

**Table 2** Treatment considerations in specific patient populations

Patient population	Medications to use and their rationale	Medications to avoid or use only with caution
Established cardiovascular disease	Decreased MACE and CV mortality - Empagliflozin - Liraglutide Decreased MACE - Canagliflozin - Semaglutide Potential CV benefit - Metformin - Pioglitazone	Conflicting data on rosiglitazone and sulfonylureas
Heart failure	Decreased HF hospitalizations - Empagliflozin - Canagliflozin - Dapagliflozin	Increased HF risk - Pioglitazone - Rosiglitazone - Saxagliptin - Alogliptin Metformin: Avoid in decompensated CHF to limit risk of lactic acidosis
Chronic kidney disease	Decreased progression of nephropathy - SGLT2i: empagliflozin, canagliflozin, and dapagliflozin - GLP-1 agonists: liraglutide and semaglutide Can be used at any eGFR - Glipizide and glimepiride but start at low-dose - Pioglitazone but be cautious given possible fluid retention - Linagliptin - GLP-1 RA except exenatide - Insulin	Reduce dose or avoid depending on eGFR - Glyburide - SGLT2i - DPP4i (other than linagliptin) - Metformin - Exenatide IR/ER
Older adults	Use medications with less risk of hypoglycemia - DPP4i - GLP-1 RA - TZD Insulin regimens should be simplified with a focus on insulins associated with less hypoglycemia such as U-300 glargine and degludec	Glyburide: Avoid due to hypoglycemia risk SGLT2i associated with dehydration, GU infections and could increase fall risk Comorbid conditions might preclude the use of other classes of glucose-lowering agents
Obesity	Weight loss-promoting - GLP-1 RA: Semaglutide, liraglutide, dulaglutide, exenatide, and lixisenatide (from most to least effect) - SGLT2i Weight neutral - Metformin (or modest weight loss) - DPP4i	Weight gain - Sulfonylureas - TZDs - Insulin
Gastrointestinal disease	Decreased steatosis in NASH - Pioglitazone - Liraglutide Pilot data suggests possible improvements in liver fat with SGLT2i	GI symptoms - Metformin - GLP-1 RA Advanced liver disease - Metformin - TZDs Pancreatic disease - GLP-1 RA - DPP4i Gallbladder disease - Liraglutide

include ongoing, frequent assessments of functional status, fall risk, impairments in their visual or auditory acuity, and the status of their comorbid conditions in order to determine their general health status [72]. Based on this overall context, providers should set a HbA1c goal depending on how healthy or ill the older adult is [72, 73].

Overall, this patient-centered approach to setting glycemic goals acknowledges that diabetes is a complex disease that is a different experience for each person and thus requires a nuanced and flexible treatment approach.

## Approach to Specific Patient Subpopulations

Patients with diabetes are medically complex and often suffer from or at risk for other comorbid conditions that have to be considered when deciding between various pharmacotherapeutic options (Table 2). Patients with diabetes are at high risk for CVD, which remains the leading cause of death in this population [74]. Though data from landmark studies has not been particularly robust on the impact of glycemic control on reducing CV complications, the more recent CV outcome trials have identified some promising treatment options that can promote CV health in this vulnerable population. Additionally, treatment options for diabetes often have to take into consideration the potential impact on renal function as up to 40% of patients with diabetes have chronic kidney disease [75]. Finally, avoiding hypoglycemia in older adults and selecting weight loss-promoting medications in the obese are important considerations when selecting glucose-lowering agents in these frequently encountered populations.

## Conclusions

Figure 1 provides a summary of how to approach diabetes care while keeping individual patient characteristics in mind. Lifestyle management continues to be the essential backbone of diabetes care, so this should be supported and encouraged in all patients as should careful attention to modifiable CV risk factors. An HbA1c goal should account for the known benefits of glucose control while balancing the potential risks of hypoglycemia especially when considering an individual patient's social context and comorbid conditions. In terms of pharmacotherapy, metformin is widely accepted as the most appropriate initial oral glucose-lowering agent due to its demonstrated safety, efficacy, and low cost. Choice of additional medications after metformin should be driven by a combination of factors including glucose-lowering ability, adverse effects, patient preference, and potential impact on comorbid conditions. A stepwise approach is generally preferred to minimize potential side effects and cost to the patient. However, initiating dual therapy has the advantages of potentially

improving adherence (especially if available in a single pill/injection) and more quickly lowering glucose, which could be important when the HbA1c  $\geq 9\%$ . Insulin is the most appropriate initial therapy if there are signs and symptoms of glucose toxicity. Response to therapy and patient goals should be reassessed every 3–6 months and the treatment regimen should be modified accordingly.

## Compliance with Ethical Standards

**Conflict of Interest** Patricia R. Peter and Beatrice C. Lupsa declare that they have no conflict of interest.

**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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