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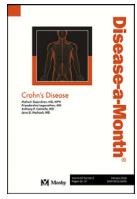

Management of type 2 diabetes without insulin: An update for the PCP

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Introduction

Diabetes Mellitus (DM) is a complex multifactorial health condition associated with several health implications. According to a 2018 study by the Centers for Disease Control and Prevention (CDC), 34.2 million Americans or 10.5% of the United States population have diabetes. It also found that the percentage of adults with diabetes increased with age, affecting 26.8% of those aged 65 years and older.[1] Given that 88 million adults have prediabetes, the overall diabetes prevalence is only expected to increase.[1] Among all patients with diabetes, around 90–95% suffer with Type 2 diabetes mellitus (T2DM) so nearly 1 in 10 Americans suffer from this illness. The incidence of T2DM has been found to increase with age, obesity, and adoption of an American diet. [2]

Uncontrolled diabetes may result in numerous complications and in fact, is the seventh leading cause of death in the U.S. T2DM remains a leading cause of cardiovascular disease, blindness, renal failure, limb amputations, hospitalizations, and other micro- and macro-vascular complications.[3]

Treating diabetes poses a significant financial burden to individuals and society. The total annual direct and indirect cost for the management of diabetes in the United States is estimated to be 327 billion dollars.[4–7] After adjusting for inflation, economic costs of diabetes increased by 26% from 2012 to 2017. This rapid increase is not only due to the increased prevalence of diabetes and but also reflects the rising cost of caring for individuals with diabetes.

Given the rising prevalence, economic burden as well as the associated morbidity and mortality of diabetes, it is essential for primary care providers to be adept at managing this impor-

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tant condition. This has become more challenging as the number of available glucose-lowering agents has multiplied in the past several years. Ultimately, the most effective treatment strategy for this complex disease requires an individualized approach that takes into account patient characteristics and preferences to achieve a durable treatment effect.[8]

Treatment of T2DM in the primary care setting

Primary care providers are the foundation for determining population health**.** According to Center for Medicare and Medicare Services (CMMS), population health is measured in terms of health outcomes (mortality, morbidity, health, and functional status), disease burden (incidence and prevalence), and behavioral and metabolic factors (diet, exercise, body mass index (BMI), and hemoglobin A1c (HbA1c).[9] To achieve an overall favorable health outcome across the population, diabetes care must be individualized for each patient while also preventing the progression of prediabetes to diabetes.

Although the proportion of patients with diabetes who achieve recommended HbA1c, blood pressure, and LDL cholesterol targets has steadily increased in recent years, a 2013 report found that 33–49% of patients still did not meet general goals for glycemic, blood pressure, or cholesterol control, and only 14% met targets for all three measures while also avoiding cigarette smoking.[5]

The Chronic Care Model (CCM), an effective framework for improving the quality of diabetes care, includes core elements which depend on the primary care health delivery system. The delivery system design shifts its focus from providing care reactively to proactively so annual wellness visits are focused on preventing problems before they occur. Along with the evolving role of the health care delivery team, engagement of primary care providers and empowerment of patient self-management are fundamental to the successful implementation of the CCM, serving as the cornerstone in preventing the development and progression of T2DM.[10]

Tailoring T2DM treatment based on individual social context

Although the Chronic Care Model (CCM) provides the framework for managing T2DM in the community, health inequalities related to diabetes and its complications are highly influenced by social determinants of health, so each primary care physician should evaluate social context in order to better tailor the treatment to the patient. The American Diabetes Association recommends that the provider assess for potential food insecurity, housing instability, and financial barriers and incorporate that information into treatment decisions. The provider should refer patients to local community resources and provide them with self-management support from community health workers when available. Health inequities related to diabetes are well documented and are heavily influenced by social determinants such as the economic, environmental, and social conditions the patient is in. Primary care providers are often most aware of their patients' financial backgrounds and are therefore most able to tailor therapy, accordingly, thereby decreasing the risk of discontinuation of therapy due to affordability issues.

Food insecurity is the unreliable availability of nutritious food and the inability to consistently obtain food without resorting to socially unacceptable practices. Food insecurity affects more than 14% of the U.S. population with higher rates in some racial/ethnic minority groups, low-income households, and homes headed by a single parent.[11] Food insecurity leads to intake of easy and cheap high-calorie foods which is associated with an increased risk of developing type 2 diabetes, worsening glycemic control, and low treatment adherence. Primary care providers should seek help from community health workers who may assist in providing diabetes self-management education and support services, particularly in underserved communities.[5]

Table 1.
Risk factors for diabetes.

First-degree relative with diabetes
High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
History of CVD
Hypertension (≥140/90 mmHg or on therapy for hypertension)
HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
Women with polycystic ovary syndrome
Physical inactivity
Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

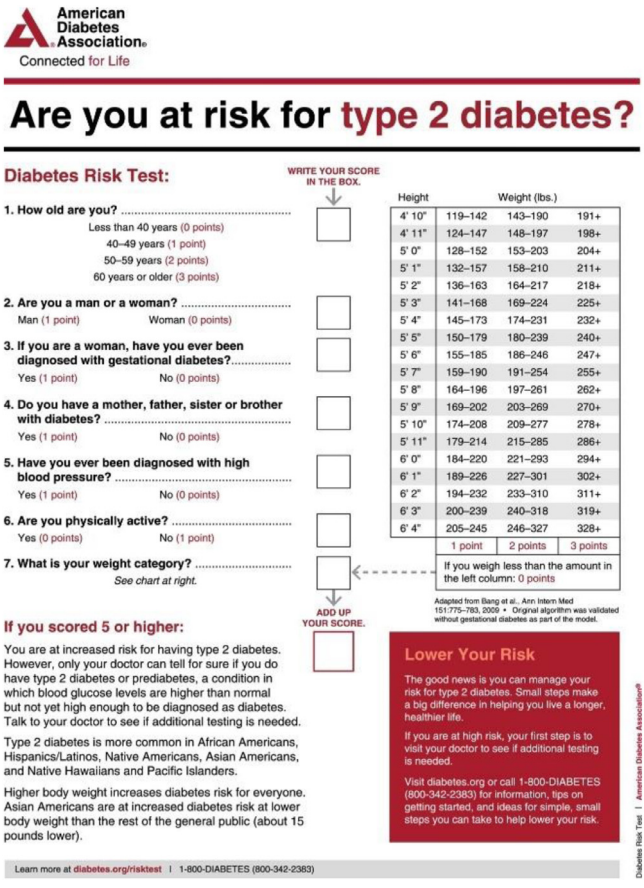

Fig. 1.. ADA diabetes risk test. Reproduced with permission from ADA.[2]

When to screen for diabetes?

Using an informal assessment of risk factors (Table 1) or an assessment tool, such as the ADA risk test (Fig. 1) (online at diabetes.org/socrisktest) can help guide providers on whether or not it is appropriate to screen for prediabetes and type 2 diabetes using a diagnostic test (Table 2). Testing for prediabetes and type 2 diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and who have one or more additional risk factor for diabetes (See Table 1).[2]

Table 2.
Diagnostic tests for prediabetes and diabetes.

	Prediabetes	Diabetes
A1C	5.7–6.4%*	≥6.5%†
FPG	100–125 mg/dL (5.6–6.9 mmol/L)*	≥126 mg/dL (7.0 mmol/L)†
OGTT	140–199 mg/dL (7.8–11.0 mmol/L)*	≥200 mg/dL (11.1 mmol/L)†
RPG		≥200 mg/dL (11.1 mmol/L)‡

* For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

† In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate samples.

‡ Only diagnostic in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

- For all other asymptomatic patients, screening should begin at age 45.
- If results are normal, testing should be repeated at a minimum of 3-year intervals.
- Women who were diagnosed with Gestational DM (GDM) should have lifelong testing at least every 3 years.
- Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.

Which diagnostic test to use?

Diabetes and prediabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2 h plasma glucose (2 h PG) value during a 75 g oral glucose tolerance test (OGTT), or A1C criteria.[2] Generally, FPG, 2 h PG during 75 g OGTT, and HbA1c are equally appropriate for diagnosis and may be used to screen for diabetes and prediabetes alike. (See Table 2)[2] HbA1c has several advantages including greater convenience (fasting not required), and less day-to-day perturbations due to stress, changes in diet, or illness. However, these advantages may be offset by the lower sensitivity of A1C at the designated cut point which is 6.5%[2] HbA1C test at the diagnostic threshold of ≥6.5% (48 mmol/mol), diagnoses only 30% of the diabetes cases identified collectively using A1C, FPG, or 2 h PG, according to National Health and Nutrition Examination Survey (NHANES) data (Table 2).[12]

The use of HbA1c is limited in conditions associated with increased red blood cell turnover, such as sickle cell disease, pregnancy, glucose-6-phosphate dehydrogenase deficiency,[13,14] hemodialysis, recent blood loss or transfusion, or erythropoietin therapy so plasma blood glucose criteria should be used to diagnose diabetes in those settings.[15] HbA1c is also less reliable in other conditions such as the postpartum state,[15] HIV treated with certain protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs),[16] and iron-deficient anemia.[17]

RPG, random plasma glucose

The ADA diabetes risk test is an additional option for assessment to determine the appropriateness of testing for diabetes or prediabetes in asymptomatic adults.[2]

Prevention or delay of type 2 diabetes

As most patients with prediabetes are only seeing their primary care physician and not a subspecialist, the primary care provider has a pivotal role to play in preventing or delaying T2DM. Targeted interventions designed to impact an individual's physical activity levels and food intake are critical parts of this management. Several well-conducted randomized clinical trials have demonstrated that lifestyle/behavioral therapy featuring an individualized reduced-calorie meal plan is highly effective in preventing type 2 diabetes and improving other cardiometabolic endpoints such as blood pressure, lipids, and systemic inflammation.[18,19]

Table 3.
Interventions for prevention or delay of T2DM.

Achieve and maintain 7% loss of initial body weight
Increase moderate-intensity physical activity to at least 150 min/week
Metformin therapy should be considered in those with prediabetes with any of the following
- BMI $\geq$35 kg/m^2
- Age $<$60 years
- Women with prior gestational diabetes mellitus.

The effectiveness of interventions for primary prevention of type 2 diabetes has mainly been demonstrated among individuals who have impaired glucose tolerance (IGT) with or without elevated fasting glucose, not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by HbA1c criteria.[10,20]

The ADA recommends referring patients with prediabetes to an intensive lifestyle behavior change program modeled on the Diabetes Prevention Program to achieve and maintain 7% loss of initial body weight and to increase moderate-intensity physical activity (such as brisk walking) to at least 150 min/week (Table 3).[21] The dietary counseling for weight loss in the Diabetes Prevention Program intervention included a reduction of total dietary fat and calories in those with an overweight or obese BMI.[21] The Centers for Disease Control and Prevention (CDC) developed the National Diabetes Prevention Program (National DPP) which is a useful online resource designed to provide evidence-based lifestyle change programs for preventing type 2 diabetes to local communities (www.cdc.gov/diabetes/prevention/index.htm). The CDC also provides the locations of CDC-recognized diabetes prevention lifestyle change programs (available at https://nccd.cdc.gov/DDT_DPRP/Programs.aspx). Patients who have a BMI in the overweight range or greater and who are at risk for diabetes based on laboratory testing or a positive risk test are eligible for this program, (available www.cdc.gov/prediabetes/takethetest/).[22]

Pharmacotherapy for prevention or delay of type 2 diabetes

Lifestyle modification therapy may be difficult to maintain long term and a proportion of patients may benefit from additional pharmacotherapeutic options.[23] Many pharmacologic agents used to treat diabetes have been evaluated for diabetes prevention. Metformin, α-glucosidase inhibitors, liraglutide, thiazolidinediones, and insulin have been shown to lower the risk of diabetes in those with prediabetes.[24–28] Some drugs like ramipril, anti-inflammatory drugs, or vitamin D showed no efficacy in preventing diabetes while valsartan seem to be effective in preventing diabetes.[29–31] Of all these drugs, metformin has the strongest evidence base and has shown long-term safety as a pharmacologic therapy for diabetes prevention.[10,32] Although metformin was overall found to be less effective than lifestyle modification in the Diabetes Prevention Program, metformin may be cost-saving over a 10-year period, demonstrating that adopting lifestyle modifications may not be affordable for everyone.[33] As of now, no pharmacologic agent has been approved by the U.S. Food and Drug Administration specifically for diabetes prevention. However, the ADA suggests that metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI $\geq$35 kg/m^2, those aged $<$60 years, and women with prior gestational diabetes mellitus.[21] Among patients who are taking metformin, periodic measurement of vitamin B12 levels is recommended as long-term use of metformin may be associated with biochemical vitamin B12 deficiency (Table 3).[21]

Degree of glycemic control related to health care outcomes

The treatment of T2DM has primarily focused on lowering blood glucose levels. Glycemic control is assessed by the HbA1c measurement, continuous glucose monitoring (CGM), and self-monitoring of blood glucose (SMBG). HbA1c is the metric used in most clinical trials demon-

Table 4.
When to check HbA1c.

Routinely in all those with T2DM at initial assessment
At least twice per year if good control
Every 3 months for patients not meeting glycemic goals

strating the benefits of improved glycemic control especially in T2DM while CGM serves as an important tool for assessing control in type 1 diabetes. HbA1c reflects average blood glucose over approximately 3 months and therefore, HbA1c should be performed routinely in all T2DM at initial assessment and periodically during treatment. ADA recommends HbA1c assessment at least two times a year in patient who are well-controlled and every 3 months for those who are not meeting glycemic goals (Table 4).[34]

It is well known that the glycemic control, as measured by HbA1c is related to risk of microvascular complications and it is presumed to influence the rate of macrovascular disease as well.[35] Randomized controlled trials have shown that the improved blood-glucose control decreases the progression of diabetic microvascular disease.[36,37] However, there is also increasing evidence that reducing blood glucose levels, while beneficial in lowering the risk of complications, is also associated with potential harms, additional patient burden, and potentially higher costs for nonpregnant adults.

Several studies looked at glycemic control on cardiovascular end points. The ACCORD (Action to Control Cardiovascular Risk in Diabetes)[38] and the VADT (Veterans Affairs Diabetes Trial)[39] targeted an HbA1c<6.0% using complex combinations of oral agents and insulin while the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation)[40] aimed for an HbA1c ≤6.5% using a less intensive approach with the sulfonylurea gliclazide. None of the trials demonstrated a statistically significant reduction in the primary combined cardiovascular end points. It was thought that high rates of hypoglycemia (threefold higher with intensive treatment when compared to conventional therapy) might be the cause for these disappointing outcomes. A meta-analysis of these trials suggested that every HbA_{1c} reduction of ~1% may be associated with a 15% relative risk reduction in nonfatal myocardial infarction but without benefits on stroke or all-cause mortality.[39]

Given the potential harms and benefits of tight control, glycemic targets can and should be personalized. As diabetes is a chronic disease that progresses over many years, the glycemic goal may change over time depending on the comorbid conditions that arise, changes in life expectancy or patient preferences and the nature of the support system the patient has. (See Fig. 2) A HbA1c goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate per ADA recommendations while the American College of Physicians (ACP) guidance recommends targeting an HbA1c between 7 and 8% in most adults with T2DM. However, newly diagnosed patients at relatively younger age may benefit the most from intensive control to prevent microvascular complications and so achieving an HbA1c lower than 7% may be acceptable and even beneficial if that can be safely achieved without significant hypoglycemia. On the other hand, among older adults and patients with limited life expectancy, less stringent HbA1c goals (such as <8% [64 mmol/mol]) may be more appropriate (Tables 5,6).[34]

With respect to older patients, the most recent American College of Physicians guidance (ACP) recommends that clinicians should aim to minimize symptoms related to hyperglycemia and to avoid setting an HbA1c target in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population (Table 5).[41]

Adapted from Qaseem et al. Ann Intern Med. 2018. Hemoglobin A1c Targets for Glycemic Control with Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians.[41]

- More or less stringent glycemic goals may be appropriate for individual patients.

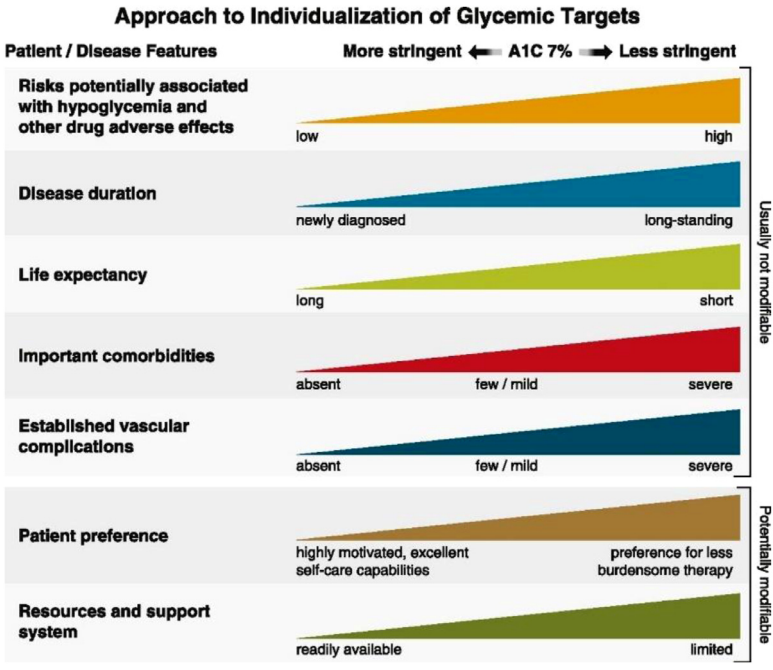

Fig. 2.. Optimal glycemic targets (Reproduced with permission from ADA[34]).

Table 5.
ACP guidance on HbA1c target for pharmacologic glycemic control in T2DM.[41]

1	Goals of glycemic control should be individualized to each patient, after discussing harms and benefits, preferences, overall health status, treatment burden, and expense
2	An A1C target of 7% to 8% is recommended for most patients, because targets of 7% or less do not appear to result in reduced risk of mortality or macrovascular events.
3	The medication regimen may be de-escalated in patients with an A1C level less than 6.5%, because there is no evidence of clinical benefit in patients at this level.
4	Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA1c level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.

Table 6.
ADA Glycemic recommendations for most adults with diabetes.

HbA1c	<7.0% (53 mmol/mol)*#
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

- # Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations
- † Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1, 2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Anti-hyperglycemic therapy for T2DM

Oral agents and non-insulin injectables

In addition to lifestyle changes, pharmacologic management of T2DM is essential to maintaining glycemic control and preventing complications. Prior to the 1990s, only a limited number of diabetes medications were available, including metformin, sulfonylureas, thiazolidinediones (TZDs), and insulin. While these agents reduce HbA1c by 0.5–1.5%, several caused hypoglycemia and weight gain. Fortunately, over the past two decades, many newer classes of medications have been approved that cause minimal hypoglycemia and/or weight gain.[42]

Some agents work by increasing insulin availability (by promoting 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), improving insulin sensitivity (biguanides, thiazolidinediones), or increasing urinary glucose excretion (sodium-glucose cotransporter-2 inhibitors) and several agents work through more than one mechanism (Table 7).[8]

Choosing the right drug for the patient from the long list of available agents can be challenging for clinicians. Ultimately, the treatment strategy should be personalized to the patient based on individual factors.[8]The ADA recommends a patient-centered approach to choosing appropriate pharmacologic treatment of blood glucose mainly by considering the drug efficacy and key patient factors: (1) important comorbidities such as atherosclerotic cardiovascular disease (ASCVD) or indicators of high ASCVD risk, chronic kidney disease (CKD), and heart failure (2) hypoglycemia risk, (3) effects on body weight, (4) side effects, (5) cost, and (6) patient preferences.[42] (Fig. 3)

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.

Metformin as first-line therapy

Metformin should be started at the time type 2 diabetes is diagnosed unless there are contraindications. For many patients this will be monotherapy in combination with lifestyle modifications.[42]

Metformin increases hepatic adenosine monophosphate-activated protein kinase activity, thus reducing hepatic gluconeogenesis and increasing insulin-mediated uptake of glucose in muscles. It also has an antilipolytic effect that lowers serum free fatty acid concentrations, thus decreasing substrate availability for gluconeogenesis.[8]

Metformin is effective and safe, is inexpensive, and may reduce the risk of cardiovascular events and death.[43] Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. When used as a monotherapy, compared with sulfonylureas, metformin as first-line monotherapy has beneficial effects on HbA1c, weight, and cardiovascular mortality.[44] Metformin has a greater effect on any diabetes-related endpoint and all-cause mortality than intensive therapy with a sulfonylurea or insulin.[45]

The principal side effects of metformin are gastrointestinal intolerance leading to diarrhea, and it should not be used in patients at risk for lactic acidosis (e.g., in advanced renal insufficiency, advanced liver disease, unstable heart failure, alcoholism).

Table 7.
Commonly used non-insulin antihyperglycemic medications in T2DM.

Class	Drugs	Primary Physiological action (s)	Advantage	Disadvantage
Biguanides	Metformin	Decreases hepatic glucose production	Extensive experience Weight loss or neutral No hypoglycemia ?Decreased CV events Low cost	Gastrointestinal side effects Lactic acidosis risk Vitamin B12 deficiency Has to be avoided in CKD and in those at risk for acidosis
Sulfonylureas	Glyburide Glipizide Glimepiride	Increases insulin secretion	Extensive experience Low cost	Weight gain Hypoglycemia risk
TZDs	Pioglitazone Rosiglitazone	Increases insulin sensitivity	No hypoglycemia Durable effect Low cost	Weight gain Edema/heart failure Bone fractures
DPP-4 inhibitors	Sitagliptin Saxagliptin Alogliptin Linagliptin	Increases insulin secretion Decreases glucagon secretion	No hypoglycemia Well tolerated	Increased risk of HF with saxagliptin and alogliptin Increased risk of pancreatitis Expensive
α-Glucosidase inhibitors	Acarbose	Delays the absorption of carbohydrates from the small intestine	No hypoglycemia Decreases post-prandial excursions	Only modest HbA_{1c} benefit GI side effects (flatulence)
GLP-1 agonists	Exenatide Liraglutide Dulaglutide Lixisenatide Semaglutide	Increases insulin secretion Decreases glucagon secretion Slows gastric emptying Increases satiety	No hypoglycemia Weight loss Decreases post-prandial excursions Decreased CV mortality (liraglutide)	GI side effects (nausea, vomiting, constipation, diarrhea) ?Acute pancreatitis Injectable
SGLT-2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Prevents the reabsorption of glucose from blood by the kidneys	Low hypoglycemia risk Weight loss Decreased CV mortality (empagliflozin) Decreased heart failure hospitalizations (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) Beneficial effect on progression of nephropathy (empagliflozin, canagliflozin, dapagliflozin)	Polyuria Yeast infections/UTIs Increased risk of DKA Expensive

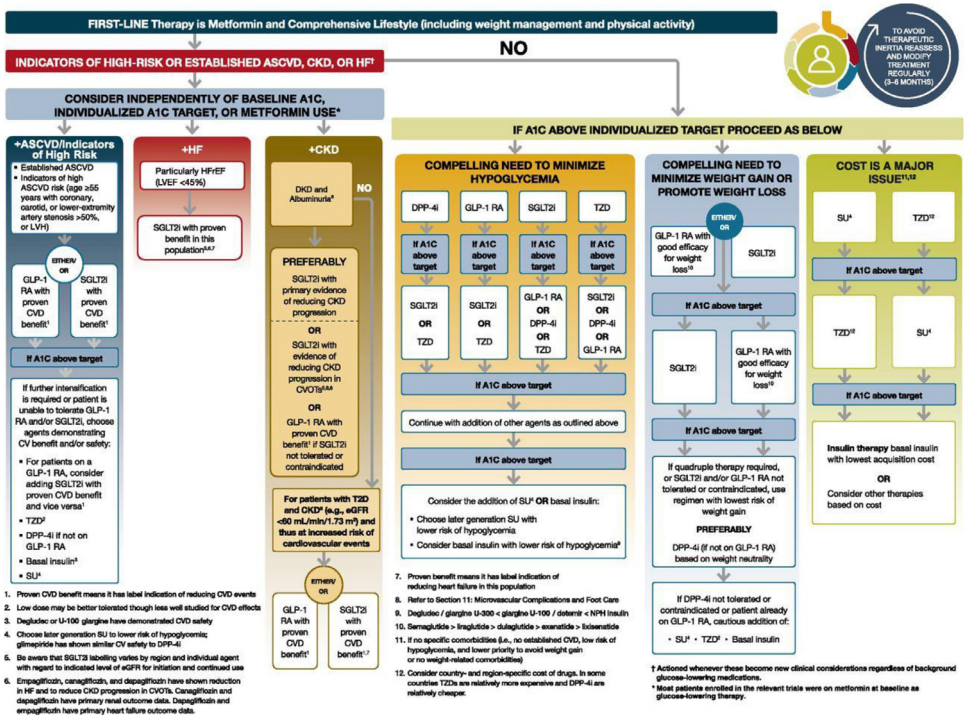

Fig. 3.. Choosing the anti-hyperglycemic agent for T2DM. Recommendations from ADA. (Reproduced with permission from Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes – 2021. American Diabetes Association).[42]

Which patients should be started on metformin?

For the majority of patients with T2DM, in the absence of contraindications, metformin is usually the first-line pharmacologic therapy. Its benefits, favorable side effect profile and low cost make it an attractive initial treatment option in addition to lifestyle modification.

Sulfonylureas

Sulfonylureas are the oldest class of oral antihyperglycemic drugs. They act by stimulating insulin release (insulin secretagogues) from pancreatic beta cells through the closure of ATP-sensitive potassium channels.[46]

Sulfonylureas (e.g., glyburide, glipizide, glimepiride) are among the most effective anti-hyperglycemic agents, decreasing HbA1c by 1, 2% although with modest weight gain and risk of hypoglycemia. Meglitinides (e.g., repaglinide, nateglinide) are short-acting insulin secretagogues that reduce the HbA1c by about 1%. A secondary failure to oral hypoglycemic agent (OHA) is said to occur when a sulfonylurea (and metformin), in appropriate doses and diet, loses its capacity to produce a desired maximal therapeutic effect (FBG $<$ 8.0 mmol/L or HBA1c $<$ 7.0%) after administration in the absence of other conditions causing hyperglycemia.[47] Some studies showed that sulfonylurea use may be associated with a secondary failure rate that may exceed other drugs due to an exacerbation of islet dysfunction.[48]

The principal side effects of sulfonylureas are hypoglycemia, and weight gain. These agents should be avoided in patients at high risk for hypoglycemia such as the elderly or those with an irregular meal schedule.

Which patients should be started on sulfonylureas?

For many patients with T2DM, after initiating metformin, sulfonylureas can be used in those who prefer an effective, low-cost, oral agent in whom hypoglycemia is not a major concern.

Thiazolidinediones

Thiazolidinediones (TZDs) (rosiglitazone and pioglitazone), are peroxisome proliferator–activated receptor γ activators that improve glycemic control by increasing insulin sensitivity in the adipose tissue, liver, skeletal muscle and reduce hepatic glucose production.[49]

TZDs do not increase the risk of hypoglycemia, and the efficacy of TZDs may be more durable than that of sulfonylureas and metformin.[48]

Pioglitazone has been shown to have a modest benefit on cardiovascular events as demonstrated in a large trial involving patients with overt macrovascular disease.[50] Several randomized trials have noted a more favorable lipid profile with pioglitazone.[51] Pioglitazone also has beneficial effects on non-alcoholic steatohepatitis (NASH), which is increasing in prevalence and is a common comorbid condition in patients with T2DM. Studies on patients with NASH, with or without T2DM, have shown histologic improvement after treatment with TZDs, prompting many hepatologists to use pioglitazone as a potential therapy for NASH.[52–54]

Apart from the most well-recognized side effects of TZDs such as weight gain, fluid retention, edema and heart failure, some studies have noted decreased bone density and fracture risk, particularly in women. Therefore, it is recommended that these agents be avoided in patients at high risk for low bone mineral density such as the elderly and in those who are on corticosteroids.[48,50,55–57]

There have been controversial reports on a possible increased risk of bladder cancer with pioglitazone use.[58] Thus, it is advisable to avoid pioglitazone in patients with prior or current bladder cancer.[8]

Which patients should be started on TZDs?

TZDs are durable, low cost-effective agents, that have good HbA1c lowering effect without an increase in the risk of hypoglycemia. Given the potential for cardiovascular and hepatic protection with pioglitazone, if a patient has overt CV disease and NASH, TZDs would be an excellent choice.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., linagliptin, sitagliptin, saxagliptin, alogliptin) are a class of oral anti-hyperglycemic drugs that inhibit the enzyme DPP-4 thereby deactivating glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). This in turn decreases glucagon release and increases glucose-dependent insulin release, decreasing gastric emptying, and increasing satiety.

DPP-4 inhibitors have relatively modest antihyperglycemic effect, decreasing HbA1c by 0.5–1% and these agents are well tolerated with low risk of hypoglycemia. DPP-4 inhibitors are weight-neutral agents that neither cause weight gain nor loss. Several meta-analyses suggested an increased risk of acute pancreatitis, although the actual estimated risk was extremely low (1.3 cases per 1000 patients).[59–61] Therefore it is better to avoid DPP-4 inhibitors in patients who have a prior history of pancreatitis or risk factors for this (e.g., high triglyceride levels, excess EtOH consumption). Among the DPP-4 inhibitors, saxagliptin and alogliptin have been shown to increase the risk of HF by an unknown mechanism.[62–65]

Which patients should be started on DDP-4 inhibitors?

DPP-4 inhibitors are well-tolerated with a low risk of hypoglycemia and are weight neutral. They are an ideal add-on therapy for patients who are overweight and/or at risk for hypoglycemia who require only modest glucose-lowering.[8]

Glucagon-like peptide-1 receptor agonists

GLP-1 receptor agonists (e.g., liraglutide, dulaglutide, semaglutide, exenatide, lixisenatide). are incretin mimetics, mimic the effects of endogenous GLP-1, thereby stimulating pancreatic insulin secretion in a glucose-dependent fashion, suppressing pancreatic glucagon output, slowing gastric emptying, and decreasing appetite.[42,66]

These are mostly injectable agents. Their main advantage is weight loss, which is modest in most patients but can be significant in some. A recent double blind randomized trial showed that the once weekly subcutaneous injection semaglutide for 68 weeks resulted in 14.9% weight loss, and so the F.D.A approved this drug as a weight loss medication for management of obesity even in the absence of diabetes.[67,68] The side effects of this class of drugs are loss of appetite, nausea, vomiting and constipation, which occur early in the course of treatment and typically resolve over time. An oral form of semaglutide has shown to be equally effective in diabetes control and so is an option for patients leery of injections.[69] Despite the limiting side effects of nausea and vomiting and occasional patient hesitance about injectables, the weight loss benefits and low risk of hypoglycemia make this group of drugs an attractive option for the right patient.

The two drugs in this class, liraglutide and semaglutide, have proven CV benefits.[70,71] Liraglutide and semaglutide have been associated with improved renal outcomes as well.[72]

With semaglutide approved as a weight loss medication for obesity, GLP-1 agonists are increasingly attractive potential options for management of NASH. In a small double-blind randomized trial, (the Liraglutide Safety and Efficacy in Patients with Non-alcoholic Steatohepatitis (LEAN) study) that enrolled patients with and without diabetes and with biopsy-proven NASH, a significant proportion of patients who received liraglutide group showed resolution of their NASH. (39% Vs 9%) $p = 0.019$[73]Although there have been some controversial reports on a possible increased incidence of acute pancreatitis, a metanalysis of 55 randomized trials showed the incidence was extremely low and therefore concluded that the drugs do not increase the risk of pancreatitis. There have also been anecdotal reports and concerns regarding a potential increased risk of pancreatic cancer and pancreatic neuroendocrine tumors with the use of GLP-1 agonists, but there is no clear evidence on this association. Nonetheless, given these concerns, it is better to avoid these agents in patients who have a prior history of pancreatitis or are at risk for pancreatitis.[74] Also, liraglutide use has been associated with a potentially increased risk of bile duct and gallbladder disease.[75]

In animal rodent studies, liraglutide and dulaglutide were associated with benign and malignant thyroid C cell tumors, although none have been observed in humans so far. However, it is recommended to avoid using GLP-1 receptor agonists in patients with a history of or at risk for medullary thyroid cancer.[76]

Which patients should be started on GLP-1 agonists?

GLP-1 receptor agonists are a great therapeutic option for those interested in avoiding hypoglycemia and losing weight, especially in those who would most benefit from a risk reduction in cardiovascular events or renal disease.

Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors (e.g., canagliflozin, empagliflozin, dapagliflozin, ertugliflozin) belong to a novel class of anti-diabetic medications which improve hyperglycemia by increasing urinary glucose excretion.

SGLT2 inhibitors inhibit sodium-glucose co-transporter 2 (SGLT-2) in proximal tubules of renal glomeruli, causing inhibition of 90% of glucose reabsorption and resulting in glycosuria in people with diabetes which in turn lowers the plasma glucose levels.[42]

These agents have relatively modest glucose-lowering efficacy, but their added benefits are from additional weight loss and blood pressure reduction while also carrying a low risk of hypoglycemia.

SGLT2 inhibitors represent a valuable class of therapy that has been shown to modify clinical course and improve life expectancy among patients with heart failure, regardless of diabetes mellitus status and ejection fraction. 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, empagliflozin was shown to reduce cardiovascular mortality when compared to placebo.[77] Similarly, canagliflozin therapy was shown to lead to a significant reduction in cardiovascular risk and heart failure hospitalizations.[78]

Empagliflozin, canagliflozin, and dapagliflozin, all have been shown to reduce the progression of chronic kidney disease in patients with T2DM.[79,80]

The most common side effect of the SGLT-2 inhibitors is polyuria or urinary urgency. Because of their mechanism of action, SGLT-2 inhibitors increase the incidence of genital mycotic infections such as balanitis and vulvovaginitis. Upper tract UTIs, such as pyelonephritis, urosepsis, and necrotizing fasciitis of the perineum (Fournier's gangrene), are other rare adverse events with SGLT-2 inhibitors.[81] When used in elderly patients with prostatic hypertrophy or urinary incontinence, these drugs can negatively impact the quality of life.[8]

SGLT-2 inhibitors are known to be associated with "euglycemic" DKA and ketosis, likely as a consequence of their noninsulin-dependent glucose clearance, hyperglucagonemia, and promotion of some volume depletion. Increased renal clearance of glucose mediated by the SGLT-2 inhibitor may lead to deceivingly low blood glucose levels in the setting of illness, and the reduced insulin doses at a time of heightened insulin resistance may tip the balance toward ketosis resulting in "euglycemic" DKA.[82] Although this is more often seen in patients with DM1 who are being treated with these agents in an "off-label" capacity, patients with T2DM who experience nausea and vomiting may develop a metabolic acidosis in the setting of SGLT-2 inhibitor therapy and should be promptly evaluated for the presence of urine and/or serum ketones. Due to this rare but serious adverse event, 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.[82]

SGLT-2 inhibitors induce an osmotic diuresis, which can sometimes lower the blood pressure by causing dehydration. This can lead to volume contraction and result in acute renal failure. It is advised that empagliflozin, canagliflozin, and dapagliflozin should be discontinued when the creatinine clearance is < 45 ml/min/1.73 m^2 and ertugliflozin stopped when the creatinine clearance is < 60 ml/min/1.73 m^2.

Which patients should be started on SGLT-2 inhibitors?

These drugs have shown great promise in improving clinically important outcomes in those with comorbid cardiovascular and renal disease and are increasingly being used as a first- or second-line glucose-lowering agent in those populations. However, potential drawbacks of these agents are their modest reduction in HbA1c along with their high cost, occasionally bothersome side effects, and lack of long-term safety data.

General implementation strategies

T2DM is a progressive chronic disease. In many patients, the maintenance of glycemic targets with a single agent is possible only for the initial few years after which they eventually require combination therapy. Metformin is often the preferred initial pharmacologic agent for the treatment of type 2 diabetes for the reasons previously discussed. Current ADA recommendations

Table 8.
Treatment considerations in specific patient groups.[8]

Patient Population	Medications to use and rationale	Medications to avoid or use with caution
Established cardiovascular disease	Decreased MACE and CV mortality - Empagliflozin - Liraglutide Decreased MACE - Canagliflozin - Semaglutide Potential CV benefit - Metformin - Pioglitazone	Conflicting data on sulfonylureas
Heart failure	Decreased HF hospitalizations - Empagliflozin - Canagliflozin - Dapagliflozin	Increased HF risk - Pioglitazone - 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	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	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
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

have been used to direct stepwise addition of second- and third-line agents based on patient selection after assessing the harms and benefits of each drug. In current practice, sequential addition of oral agents to metformin has been the standard approach.[42]

A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include effect on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (Fig. 3) (Table 8).

At the same time, there is enough data to support initial combination therapy for more rapid attainment of glycemic goals.[83] In patients with uncontrolled T2DM on oral antihyperglycemic agents, initial injectable therapy with liraglutide had shown to result in durable long term glycemic effect.[84] In patients with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible.[42]

Although this review is focused on non-insulin therapies, the early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high.[42]

Conclusion

Lifestyle modification continues to be the cornerstone for management of T2DM. Even along with all the difference classes of medication therapy, lifestyle modification and physical exercise should be strongly encouraged throughout the course of treatment.

Diabetes being a metabolic disorder, various comorbid conditions are instrumental in guiding decisions about drug regimen (Table 8). Metformin is still not only the 1st line of management for T2DM, but it also used in prevention and delaying the development of T2DM in patients with prediabetes. Based on extensive prior experience and its demonstrated efficacy, safety, low cost, and cardiovascular benefits, metformin continues to be the foundational therapy for all patients with T2DM.[85] A stepwise approach is generally preferred to minimize potential side effects and improve overall health outcomes. Glycemic targets and patient goals should be assessed at the initiation of therapy and every 3–6 months during treatment so the treatment regimen can be reassessed and modified accordingly. The choice of anti-diabetic agent must be personalized, considering associated comorbid disease and drug-related side effects.

Declaration of Competing Interest

None.

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