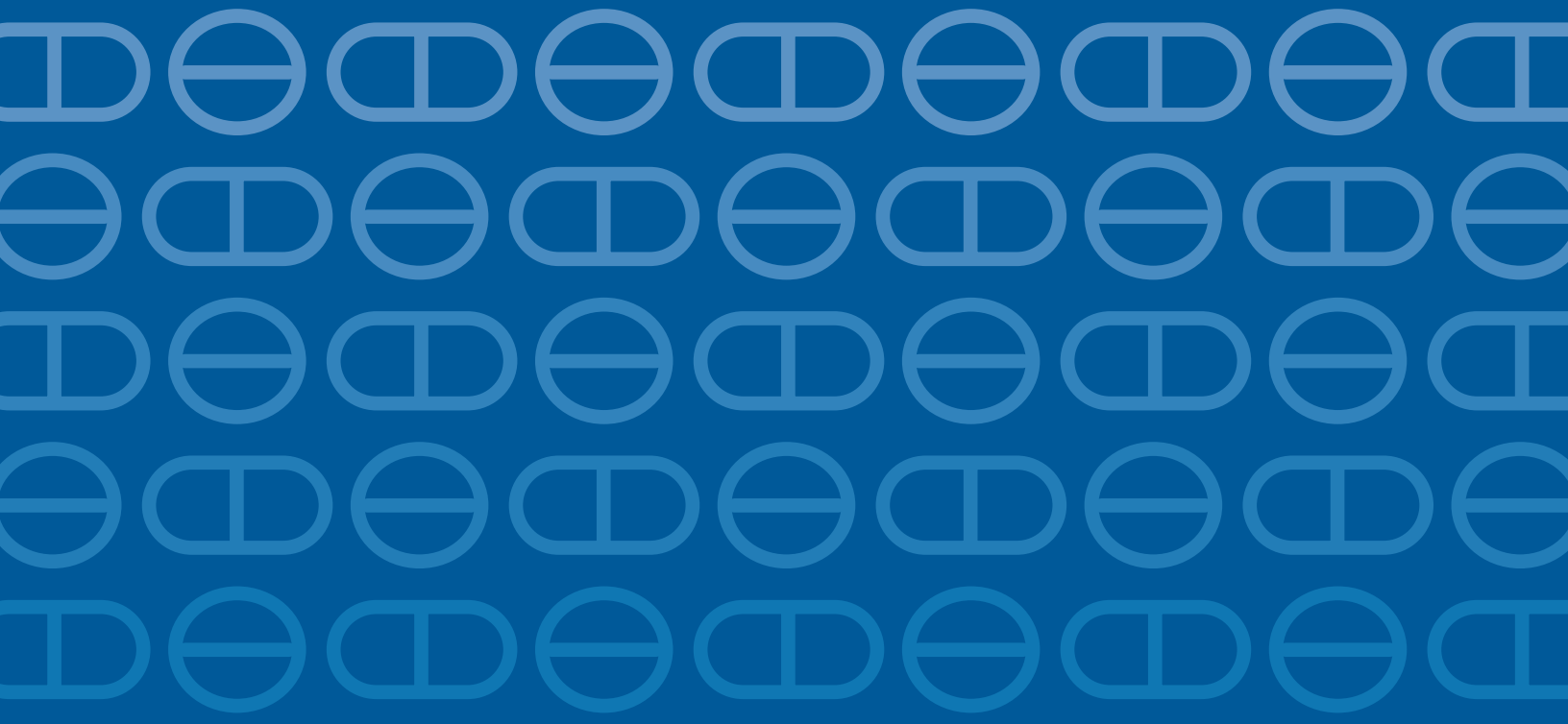
PACE Pharmaceutical Assistance Contract for the Elderly

Alosa Health
Bringing unbiased evidence to clinical care

Transforming treatment for patients with type 2 diabetes



Transforming treatment for patients with type 2 diabetes

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

Alosa Health

Transforming treatment for patients with type 2 diabetes

Activity Start Date: January 8, 2026
Activity Termination Date: January 7, 2029

This activity offers CE credit for:

1. Medicine (AMA)
2. Nurses (ANCC)
3. Other

All other attendees will receive a Certificate of Attendance

Activity Overview:

The goal of the educational program is to provide practitioners with up-to-date evidence-based treatment recommendations for type 2 diabetes, including individualized glycemic targets, choice of glucose-lowering medications based on end-organ protection and HbA1c lowering, and strategies to avoid hypoglycemia by adjusting insulin regimens.

The educational program includes a written evidence report (print monograph) and several non-CME/CE components:

1. Summary document of top 4-5 key messages
2. “Academic detailing” educational sessions in clinicians’ offices with specially trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
3. Patient education information (brochure/tear off sheets)

This program synthesizes current clinical information on this topic into accessible, non-commercial, evidence-based educational material, to be taught interactively to providers by specially trained clinical educators.

Learning Objectives:

Upon completing this activity, participants should be able to:

- Individualize the HbA1c target (often around 7% for most patients, but adjusting the goal based on co-occurring conditions, hypoglycemia risk, functional status, and other patient factors).
- Select initial treatment based on relevant comorbidities and HbA1c lowering need.
- Assess response to treatment, ensure appropriate medication taking behaviors, and optimize doses before adding insulin to achieve HbA1c goal.
- Continuously encourage exercise and healthy diet strategies for weight management.
- Manage overall health by preventing complications and screening for diabetes-related complications.

Financial Support:

There is no commercial support associated with this activity.

Target Audience:

The educational program is designed for primary care providers, including general internal medicine doctors, family practice physicians, nurse practitioners, physician assistants, nurses, and all other clinicians caring for patients with diabetes.

Credit Information:

In support of improving patient care, this activity has been planned and implemented by CME Outfitters, LLC and Alosa Health. CME Outfitters, LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Nurses: This activity is designated for 2.0 nursing contact hours.

California Residents: This continuing nursing education activity was approved by the California Board of Registered Nursing. CME Outfitters LLC's provider number is CEP15510.

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Disclosures:

This material is provided by Alosa Health, a nonprofit organization which accepts no funding from any pharmaceutical company. All individuals including planners, authors, reviewers, academic detailers, staff,

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All identified Conflicts of Interest have been mitigated.

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Table of contents

Introduction **1**

Making the diagnosis **3**

Preventing or delaying diabetes **7**

Lifestyle modification 7

Pharmacologic treatments that reduce diabetes risk 9

Overall goals of diabetes care **10**

Intensive vs. conventional glucose control 13

What is the most appropriate HbA1c target? 14

Patient blood glucose self-monitoring 15

Special considerations for older adults with diabetes 17

Non-insulin pharmacologic treatment of diabetes **19**

Reductions in HbA1c 20

Cardiovascular outcomes 22

Heart failure 26

Kidney disease 27

Weight loss 28

Liver disease 29

Potential adverse events **30**

Hypoglycemia 30

Initiation of therapy: Which drug to choose? **33**

Combination therapy 36

Monitoring and regimen intensification 37

Insulin therapy **38**

When should insulin therapy be initiated for type 2 diabetes? 38

Insulin preparations 38

Choosing an insulin regimen **42**

Treating to target 42

Combining insulin with other glucose-lowering agents 44

Maintaining overall health **46**

Diet and exercise 47
Controlling hypertension 48
Hyperlipidemia 49
Antiplatelet medication 51
Smoking 52
The importance of screenings 52

Bariatric surgery 53

Supporting treatment goals for older adults 54

Putting it all together 56

Appendix 1: Renal adjustments for glucose-lowering agents in type 2 diabetes . 57

Appendix 2: Costs 58

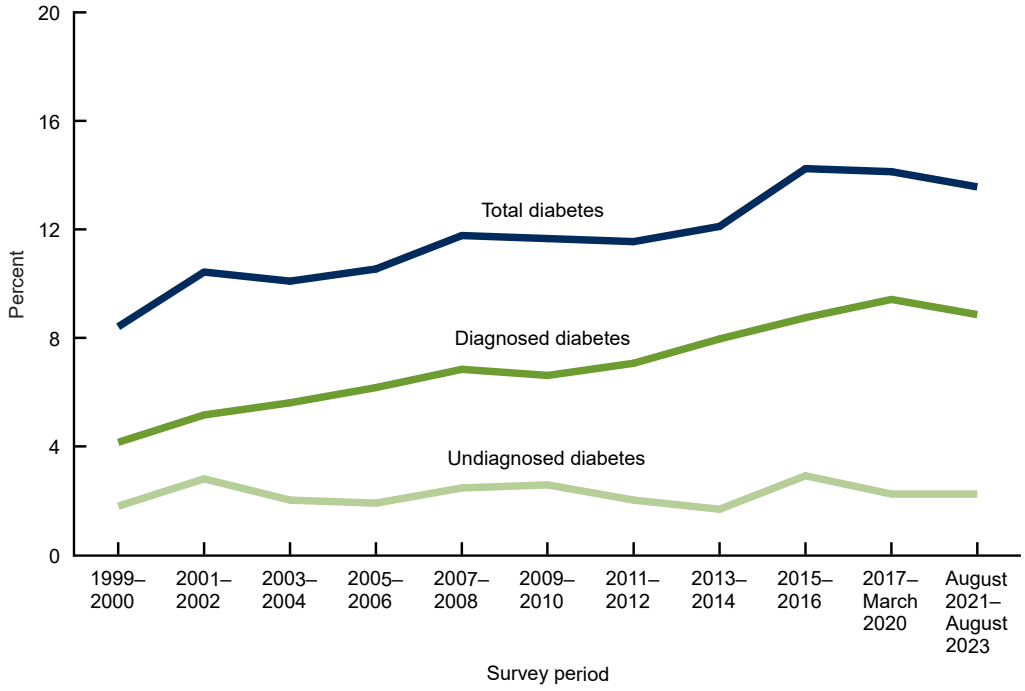
References 59

Continuing education exam 72

Introduction

Diabetes mellitus, of which 90-95% of cases are type 2, is one of the most common chronic conditions in the U.S.[1] Of the remaining 5-10% of diabetes cases, the majority are type 1, with pancreatic, monogenetic, secondary, and other forms of diabetes comprising a small percentage of cases. Type 1 and type 2 diabetes combined affect approximately 38.4 million Americans (11.6% of the adult population).[1] The incidence has risen steadily over the past 20 years with some flattening of the trend in recent years, primarily among non-Hispanic white individuals.[2] Troublingly, nearly 1 in 4 affected people do not know they have diabetes.[1] Despite the relative flattening in recent years, the number of U.S. adults with diagnosed diabetes is projected to nearly triple by 2060.[3]

Figure 1: Prevalence of diabetes (type 1 and type 2) in U.S. adults[2]



Diabetes is more common among older adults and among certain racial and ethnic groups (Figures 2 and 3, next page).

Figure 2: Diabetes prevalence (diagnosed and undiagnosed) by age[2]

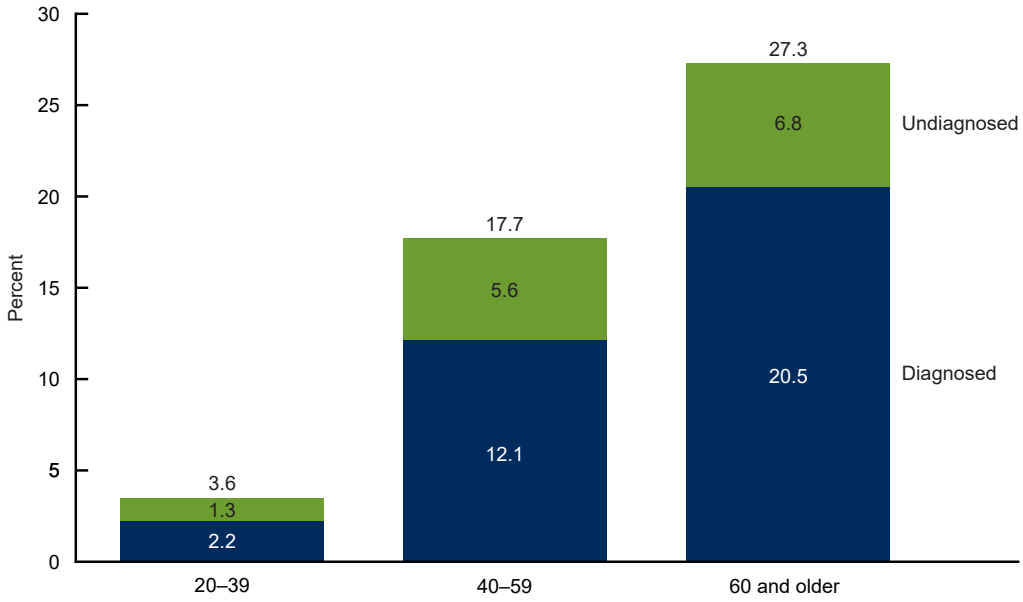
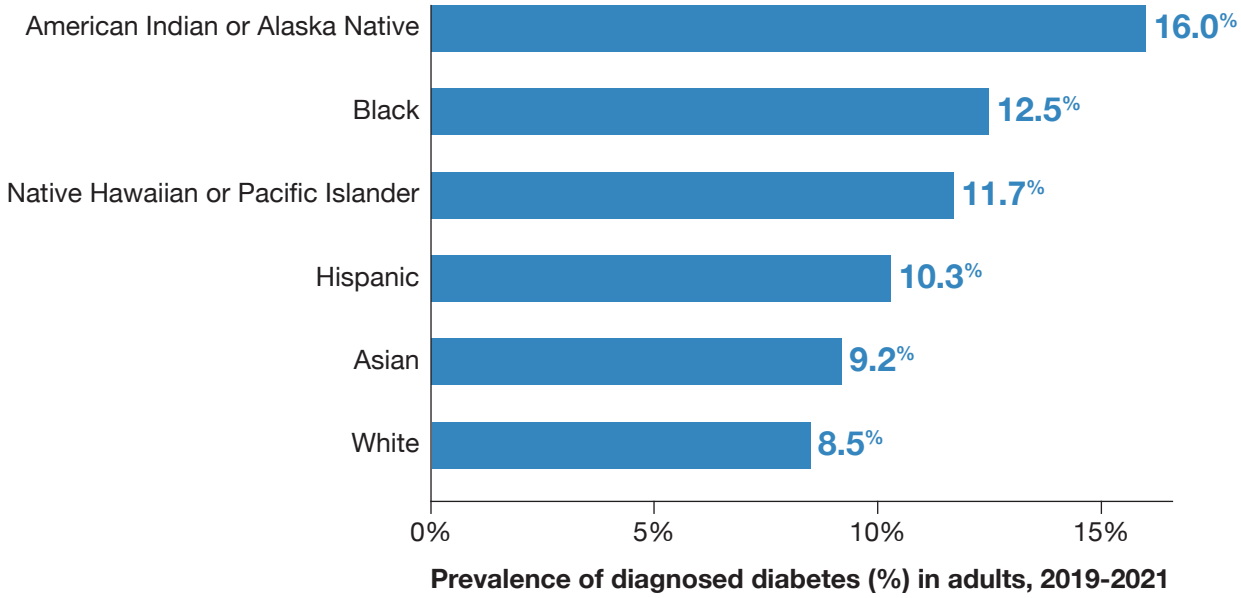


Figure 3: Percentage of U.S. adults aged 18 or older with diagnosed diabetes, by race/ethnicity[1]



Diabetes is associated with a wide range of complications including heart disease, stroke, kidney disease, neuropathy, and retinal damage as well as increased mortality.[4] Rates of complications vary significantly by race. For example, diabetes-related end-stage renal disease is much more prevalent among patients who are Black than patients of other races or ethnicities.[5,6] In 2021, diabetes was the 8th-leading cause of

death in the U.S., with about 103,000 death certificates listing diabetes as the underlying cause of death and almost 400,000 death certificates listing diabetes as a related cause of death.[1]

Despite decades of attention to the problem of diabetes, the advent of new pharmacological treatment options, and better means of monitoring blood glucose levels, roughly half of those currently treated for diabetes are not achieving the general target of 7% glycated hemoglobin (HbA1c).[7] In fact, the average HbA1c at initiation of second-line anti-diabetic therapies actually increased from 7.7% to 8.6% in 2003 compared to 2015.[8]

This high rate of treatment inertia and inadequacy is driven by many factors. Patients often find it difficult to make the lifestyle changes needed for better glycemic control, and clinicians, trying to manage multiple issues in addition to diabetes, often lack the time or resources to take all of the steps required for optimal diabetes care.[9,10]

Successful management is based on the following elements:

- patient education, lifestyle modification, and self-monitoring
- ongoing clinical contact to determine whether glucose and other cardiovascular risk factors are optimized, and if medication initiation or adjustment is necessary
- detection and prevention of complications
- treatment of related conditions such as hypertension and hypercholesterolemia

This monograph provides practical, evidence-based information to help clinicians manage diabetes more successfully, with a specific emphasis on older adults. The monograph has been updated with the most recent guidance from professional organizations such as the American Diabetes Association (ADA), as well as data from new clinical trials and systematic reviews related to type 2 diabetes care. Although it focuses largely on medication therapy, the monograph also addresses diagnosis, monitoring, and other practice-relevant areas.

BOTTOM LINE: Diabetes is very common and is associated with a wide range of complications. Despite decades of work, about half of those currently treated for diabetes are not achieving target glucose levels.

Making the diagnosis

Diabetes is sometimes detected when a patient presents with symptoms of uncontrolled hyperglycemia such as polyuria or polydipsia. In such patients, a single plasma glucose measurement of ≥200 mg/dL is generally adequate to make the diagnosis.[11] More often, however, the diagnosis is made in an asymptomatic patient either through routine screening or when hyperglycemia is detected incidentally as part of a panel of laboratory tests (Table 1, next page).

Table 1: Diagnosing diabetes (American Diabetes Association criteria)[12]

Patient presentation	Test and threshold	Notes
Symptomatic e.g., polyuria, polydipsia, weight loss, diabetic ketoacidosis	Random plasma glucose ≥200 mg/dL	
Asymptomatic	Fasting plasma glucose ≥126 mg/dL	• Fasting is defined as no caloric intake for at least 8 hours before the test. • Repeat on a second day to confirm or use second test (e.g., HbA1c). • Fasting glucose 100-125 mg/dL indicates impaired fasting glucose (IFG).
	HbA1c ≥6.5%	• HbA1c of 5.7-6.4% indicates prediabetes (need repeat test to confirm).
	Oral glucose tolerance test; plasma glucose ≥200 mg/dL 2 hours after 75 g glucose load	• Most sensitive and listed as conditional recommendation by some guidelines for select high-risk individuals who are diagnosed with prediabetes by HbA1c. — However, used infrequently due to inconvenience, despite being potentially helpful in older adults, for whom HbA1c may be less accurate. • Glucose 140-199 mg/dL indicates impaired glucose tolerance (IGT); repeat test recommended for clinical confirmation.

HbA1c: non-enzymatic glycation of red blood cells accrued over the lifespan of the red blood cell and measured on average in the red blood cell population.

In 2021, 97.6 million American adults met the diagnostic criteria for "prediabetes," defined as a fasting glucose level between 100-125 mg/dL or an HbA1c of 5.7%-6.4%, which corresponds to 38% of the U.S. adults over the age of 18.[1] However, only 19% of U.S. adults reported knowing they had prediabetes, which mirrors the high rates of underdiagnosis for diabetes.[1]

While it has only been more explicitly addressed in guidelines published over the past two decades, the concept of prediabetes has been in the medical lexicon since at least the 1960s.[13] The American Diabetes Association (ADA) is careful to point out that prediabetes should not be thought of as a unique clinical entity. The high prevalence and lack of awareness of prediabetes, however, is worth considering because the condition is associated with increased risk of developing diabetes.[11] Estimates of how likely somebody with prediabetes is to develop diabetes are still debated, however, and depend on which test or diagnostic criteria are used and in which population.

For example, the TOPICS 3 cohort study followed 2,092 patients with prediabetes for nearly five years and found that the probability of progression to diabetes was only 7-9% (depending on which type of test was used).[14] Moreover, in some populations there does not appear to be *any* increased risk of developing clinically-important diabetes. For example, one study of 3,412 community-based older adults (mean age

75) found that patients with prediabetes were more likely to die (19%) than develop diabetes (9%) over the subsequent five-year period.[15] This may be due to the known modest rise in HbA1c with aging, related to changes in red blood cell half-life among other factors, which can result in the over-diagnosis of clinically relevant diabetes in this age group.

Other estimates, however, suggest a higher risk. Calculations from a set of 16 cohort studies of the annualized risk of developing diabetes reported that between 25% and 50% of patients with an HbA1c of 6.0-6.5% would develop diabetes over a period of five years.[16] Further complicating matters is the fact that most of these studies do not address whether individuals with prediabetes are more likely to progress to having the microvascular or macrovascular complications of diabetes, nor do they address whether treating prediabetes delays the onset of these complications.

Limitations notwithstanding, among a general population, being diagnosed with prediabetes is associated with at least some increased risk of developing diabetes. As such, the ADA recommends targeted screening for prediabetes and diabetes (Table 2).

Table 2: Who should be screened for prediabetes and diabetes?[12]

Age	BMI	Other Risk Factors	Frequency
≥35	Any*	None required	Screen every 3 years
<35	≥25 (≥23 if Asian)	*One or more of the following:* First-degree relative with diabetes Physically inactive High-risk race or ethnicity History of gestational diabetes or delivery of baby weighing >9 lbs** Hypertension Polycystic ovary syndrome Low HDL/high triglycerides Vascular disease	Screen every 3 years
Any	Any	Prediabetes on previous testing (IFG, IGT, HbA1c of 5.7-6.4%)	Screen annually

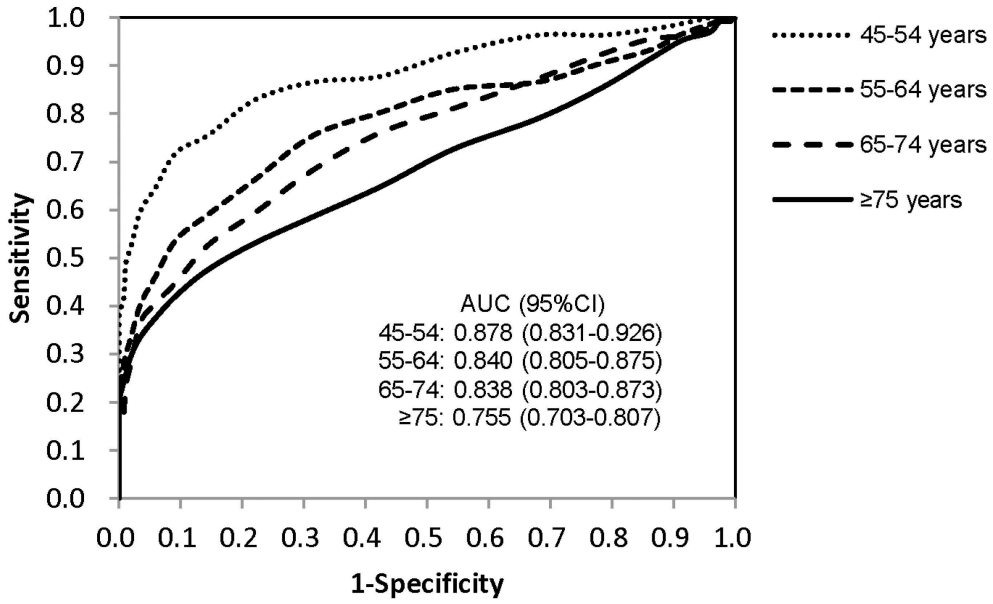
IFG = impaired fasting glucose; IGT = impaired glucose tolerance
*United States Preventative Task Force (USPSTF) recommends screening only for individuals who have overweight/obesity[17]
** For women with gestational diabetes the recommended screening is every 1-3 years (annually if on insulin in pregnancy or other high-risk characteristic).

Regardless of which test of glucose level is chosen, in the absence of symptoms (e.g., polyuria, polydipsia, weight loss) and hyperglycemia ≥200 mg/dL, two different tests from the same sample or two tests (same or different test types) on separate samples are required to diagnose diabetes or prediabetes.[12]

Currently, HbA1c is the most commonly used test in clinical practice owing largely to its ease of use and general reliability. However, it is important to recognize the limitations of HbA1c testing in screening for diabetes. For most adults, HbA1c remains the least sensitive of all the testing methods. For example, one

study found that using HbA1c criteria alone to diagnose diabetes may result in 70% fewer new diabetes diagnoses compared with using fasting plasma glucose or oral glucose tolerance tests.[18,19] HbA1c accuracy may also be affected by any condition that can change red blood cell half-life, such as anemia, hemolysis, hemodialysis, red cell dyscrasias (sickle cell, G6PD deficiency), or recent transfusion of red blood cells. It's particularly important to recognize that the diagnostic accuracy of HbA1c levels may decrease with age.[20] This is because the lower rate of red blood cell turnover with age increases the time hemoglobin is exposed to circulating blood glucose levels which can, in turn, lead to higher HbA1c levels. This can increase the risk of false positive results, as was demonstrated in a study of 3,245 patients from China (Figure 4).[20]

Figure 4: Age and diagnostic accuracy of HbA1c levels[20]



However, aside from in patients with conditions that make HbA1c inaccurate, no recent studies show that patients who have normal HbA1c but have abnormal plasma fasting glucose or oral glucose tolerance tests are at significantly increased risk of complications from diabetes. Furthermore, trials for the newest anti-diabetes drugs, namely the sodium-glucose cotransporter-2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), use HbA1c for their inclusion criteria.[21,22] Taken in totality, there is strong evidence for using HbA1c to diagnose diabetes and to make pharmacologic management decisions for most patients with diabetes.

BOTTOM LINE: Diabetes can be diagnosed with HbA1c, fasting plasma glucose, or 2-hr. plasma glucose testing following an oral glucose load. HbA1c testing is commonly used because it is easy to administer and provides a long-term picture of glucose levels. HbA1c tests are less accurate in older adults and in patients with certain comorbidities.

Preventing or delaying diabetes

Lifestyle changes, medication-based interventions, or a combination of both may reduce the risk of progression to type 2 diabetes in some patients with prediabetes.

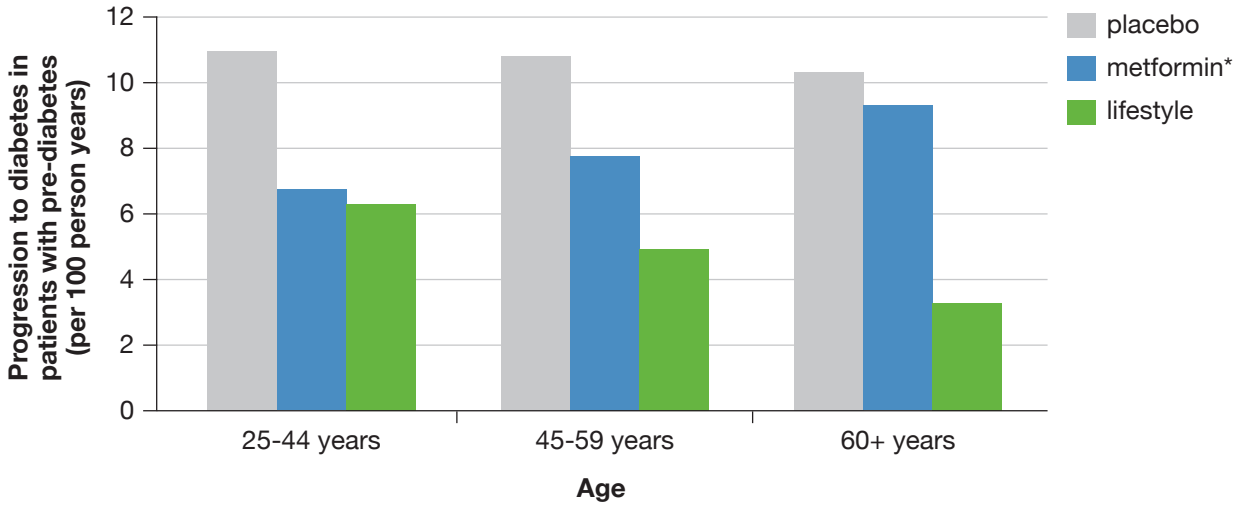
Lifestyle modification

Relatively modest weight loss is associated with significant reductions in diabetes-related risk factors with the American College of Cardiology (ACC)/American Heart Association (AHA) recommending a loss of at least 3%-5%[23] and the ADA recommending at least 7%-10%.[11] The specific type of diet and balance of macronutrients appears less important than adherence to any calorie-restricted diet that avoids highly processed foods and excessive amounts of sugar, salt, and saturated fats.[24] When a specific diet is requested, given that diabetes is a risk factor for cardiovascular disease, it may be appropriate to recommend one with known benefits for reducing cardiovascular risk factors (such as the Dietary Approaches to Stop Hypertension, DASH, diet)[25] or cardiovascular disease risk itself (such as the Mediterranean diet).[26] An increase in moderate-intensity physical activity to at least 150 minutes/week is also recommended by the ADA for diabetes prevention.[11]

The first large trial of lifestyle modification to prevent diabetes was the **Finnish Diabetes Prevention Study** in which patients with prediabetes and overweight were randomly assigned to usual care (oral and written education about diabetes at baseline and annually thereafter) or a program of weight loss, reduced dietary saturated fat, and 4 hours of exercise weekly.[27] Over four years, lifestyle modification reduced the incidence of diabetes by 58% (lifestyle modification group: 3.2 cases per 100 person-years; control group: 7.8 cases of diabetes per 100 person-years). After an additional three years of follow-up, the effect of lifestyle modification remained substantial, reducing the incidence of diabetes by 43%.[28]

The **Diabetes Prevention Program (DPP)** also studied patients with prediabetes and overweight, randomizing them to general lifestyle modification plus placebo, general lifestyle modification plus metformin, or an intensive lifestyle modification program (diet, exercise ≥150 minutes/week targeting a 7% reduction in body weight, and individualized counseling sessions weekly for the first 24 weeks and monthly thereafter).[29] As in the Finnish study, the incidence of diabetes among patients in the intensive lifestyle modification arm (mean follow-up 2.8 years) was reduced by 58% compared to placebo (lifestyle modification group: 4.8 cases per 100 person-years; control group: 11.0 cases of diabetes per 100 person-years). Patients in the metformin arm had a 31% relative risk reduction (7.8 cases of diabetes per 100 person-years) compared to placebo.[29] In addition, lifestyle modification was more effective with increasing age (6.3, 4.9, and 3.3 cases per 100 person-years, in the 25-44, 45-59, and 60-85 year age groups, respectively, see Figure 5).[30]

Figure 5: Diabetes rates by age group in the Diabetes Prevention Program study[30]



Long-term follow-up of the DPP showed that the benefits of preventing or delaying diabetes with lifestyle intervention or metformin can persist for at least 20 years.[31] Compared with placebo, patients with intensive lifestyle had a 24% relative decrease in incident diabetes (rate difference -1.59 cases per 100 person years; 95% CI: -2.25 to -0.93) and patients prescribed metformin had a 17% relative decrease (rate difference -1.17 per 100 person years; 95% CI: -1.85 to -0.49). By age group, metformin and lifestyle intervention slowed progression to diabetes in the 25-44 year group and the 45-59 year group, but among those 60 years and over, only lifestyle slowed progression to diabetes (by 36%, rate difference -1.91 cases per 100 person years; 95% CI: -3.15 to -0.67), while metformin was no different than placebo.

The 2025 **Prevención con Dieta Mediterránea (PREDIMED)** trial found that an intensive intervention using a Mediterranean diet with a 600 kcal/day reduction plus increased physical activity was more effective than an ad libitum Mediterranean diet for reducing diabetes incidence in overweight/obese persons with metabolic syndrome.[32] With a median 6-year follow-up, the absolute risk for developing diabetes in the control group was 12.0% (95% CI: 11.9%-12.1%, 349 cases) and 9.5% in the intervention group (95% CI: 9.4%-9.5%, 280 cases) with an adjusted hazard ratio (HR) of 0.69; 95% CI: 0.59-0.82.

While these trials have shown that lifestyle modification can reduce the risk of developing diabetes among patients with prediabetes, there are several caveats. First, these trials used fasting plasma glucose or oral glucose tolerance tests rather than the now more commonly used HbA1c assays to assign prediabetes and diabetes status to trial participants. Because these measures are more sensitive than HbA1c, the risk of progressing to diabetes was much higher in the trial populations that population-based estimates suggest using HbA1c measurements; for example, over 30% of patients in the placebo group of the DPP trial developed diabetes within four years, which is higher than the 7-9% incidence over five years seen in previous studies.[14] In fact, by the end of the DPP trial, the average HbA1c differed by less than approximately 0.2% between groups, and the average HbA1c was less than 6.4% in all groups.

Whether these small differences in HbA1c translate to meaningful clinical outcomes is unclear. For example, results from the **Diabetes Prevention Program Outcomes Study** specifically suggest that there were no significant benefits seen with either metformin or lifestyle intervention with regard to heart disease or the development of kidney disease or diabetic retinopathy.[33] Taken in conjunction with previously discussed evidence that older adults have relatively low risk of progressing from prediabetes to

diabetes,[15] lifestyle modifications for the specific purpose of reducing the progression of prediabetes to diabetes should be recommended selectively and tailored to individual patients.

Since 2018, Medicare has covered CDC-approved services such as the DPP. To find a nearby program, see links to Medicare-approved programs at AlosaHealth.org/Prediabetes.

Pharmacologic treatments that reduce diabetes risk

Multiple trials have been conducted of pharmacologic treatments aimed at reducing the progression of prediabetes to diabetes. For example, the **STOP-NIDDM** trial found that treatment with acarbose reduced the development of diabetes in people with prediabetes by 25% with mean follow-up 3.3 years, but gastrointestinal symptoms limited adherence.[34] Another study, the **ACT NOW** trial, found that pioglitazone reduced the risk of type 2 diabetes progression by 72% compared to placebo after a median follow-up of 2.4 years but caused significant weight gain and edema.[35] A separate study, the **SCALE** trial randomly assigned 2,254 adults with prediabetes to liraglutide 3 mg subcutaneously once daily vs. placebo.[36] After 160 weeks, 47% of participants in the liraglutide group and 55% of the placebo group had dropped out, but in the 1,128 remaining adults diabetes was diagnosed in 2% vs. 6% respectively (66% reduction). These results are in addition to the DPP that showed the efficacy of metformin for reducing the risk of diabetes.

Building off the SCALE trial, which studied a GLP-1RA with known weight loss properties, there have been multiple studies exploring whether weight loss drugs may reduce the risk of developing diabetes. Most notably, the **STEP 1** trial randomly assigned 1,961 overweight and obese participants to semaglutide plus lifestyle interventions or placebo plus lifestyle interventions. Of these participants, 43.7% had prediabetes. They found that among participants with prediabetes at baseline, 84.1% of participants in the semaglutide group, as compared with 47.8% of participants in the placebo group, reverted to normoglycemia by trial end.[37] More recently, the **STEP 10** trial randomly assigned 138 patients with obesity and prediabetes to either subcutaneous semaglutide 2.4 mg weekly or placebo with a 52-week follow-up.[38] Patients in the semaglutide group lost a mean of 13.9% of bodyweight (standard deviation [SD] 0.7%) compared to 2.7% (SD 0.6%) in the placebo group, and 81% of the semaglutide group reverted to normoglycemia vs. 14% of the placebo group (OR 19.8; 95% CI: 8.7-45.2).

Other studies of weight loss drugs that are not typically used as anti-diabetes medications have also been studied in trials, including orlistat (**XENDOS** trial) and phentermine/topiramate (**SEQUEL** trial), both of which showed modest reductions in progression to diabetes.[39,40]

The dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1RA tirzepatide was evaluated in the **SURMOUNT-1** trial of 1,032 patients with prediabetes, a BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 plus one obesity-related complication.[41] Patients were randomly assigned to one of three dosing regimens (5 mg, 10 mg, or 15 mg once weekly) or placebo. At three-year follow-up the mean percent change in body weight among the participants who received tirzepatide was -12.3% with the 5-mg dose, -18.7% with the 10-mg dose, and -19.7% with the 15-mg dose, compared with -1.3% among those who received placebo (P<0.001 for all comparisons with placebo). Fewer participants received a diagnosis of type 2 diabetes in the tirzepatide groups than in the placebo group (1.3% vs. 13.3%; HR 0.07; 95% CI: 0.0 to 0.1).

Table 3: Medications to help prevent development of diabetes

Intervention	Intervention (% w/diabetes)	Placebo (% w/diabetes)	Relative risk reduction	Side effects	Dosing schedule
metformin 850 mg[29]	22%	29%	31%	GI, usually transient	Twice daily, or daily for XR
acarbose 100 mg[34]	32%	42%	25%	Bloating, flatulence	Three times daily
pioglitazone 30 mg or 45 mg[35]	5%	17%	72%	Heart failure exacerbation, weight gain	Once daily
liraglutide 3 mg[36]	6%	2%	79%	GI, gallbladder	Once daily
tirzepatide 5 mg, 10 mg, and 15 mg[41]	1.3%	13.3%	93%	GI, mild to moderate	Once weekly

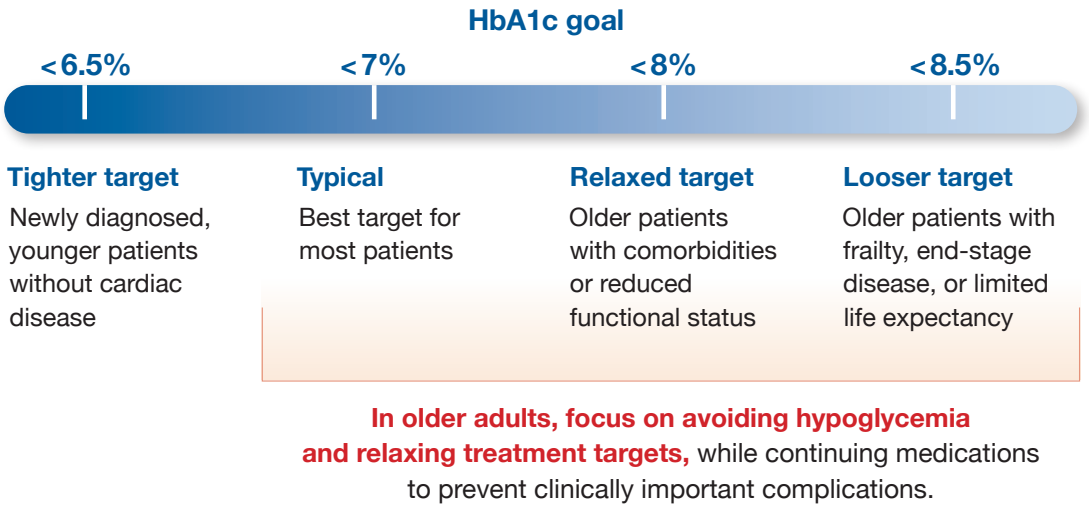
None of the medications discussed or listed in the table above has an FDA-labeled indication for the prevention or delay of diabetes. The 2025 ADA guidelines for prevention or delay of diabetes suggest lifestyle interventions for patients with prediabetes (i.e., weight loss of at least 7%, and moderate-intensity exercise) with metformin for those at high risk of type 2 diabetes, especially those aged 25-59 with BMI >35 kg/m^2, fasting glucose ≥110 mg/dL, or HbA1c ≥6%, and those with prior gestational diabetes.[42]

BOTTOM LINE: Intensive lifestyle modification, including weight loss and increased moderate-intensity exercise can reduce the risk of developing diabetes. Although lifestyle modification can be more effective than pharmacotherapy, especially in older adults, metformin and other glucose-lowering agents may also reduce the risk of diabetes, but the variable benefits must be weighed carefully against side effects and costs.

Overall goals of diabetes care

The goal of diabetes treatment is to optimize plasma glucose levels to relieve symptoms (when present), prevent diabetic emergencies, and reduce the risk of macrovascular (e.g., cardiac) and microvascular (e.g., ophthalmologic, neurologic, and renal) disease. An HbA1c goal of <7% is appropriate for many nonpregnant adults, although this goal can be modified in light of variables such as age, comorbidities, or vulnerability to hypoglycemia (Figure 6).

Figure 6: Individualized HbA1c goals[43]



HbA1c levels provide a measure of average blood sugar levels in the preceding 2-3 months (Table 4). Lowering HbA1c to around 7% has been shown to reduce microvascular complications, and (with early intervention) may also be associated with a lower risk of macrovascular disease,[44] although less stringent HbA1c targets are appropriate for selected patients.

Table 4: Correlation between HbA1c level and plasma glucose levels[43]

	Mean plasma glucose (past 3 months)	
HbA1c (%)	**mg/dL**	**mmol/L**
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

Several trials inform the current recommendations for targeting an HbA1c of <7% in most individuals. These studies include the United Kingdom Prospective Diabetes Study (UKPDS), the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and the Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes (VADT) trial.

The oldest trial is the **UKPDS**, which ran from 1977 until 1997. Patients with newly diagnosed type 2 diabetes were randomly assigned to intensive glucose control with medication (insulin/sulfonylurea or, in patients who had overweight/obesity, metformin) versus dietary interventions. In the trial, the intensive

group achieved a mean HbA1c of ~7% compared with ~8% in the diet group. Long-term outcomes from the study found that intensive glucose control with medications reduced long-term diabetes-related clinical outcomes (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal myocardial infarction, angina, heart failure, fatal or nonfatal stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction),compared to diet alone. Ten-year follow-up data from UKPDS published in 2008[45] revealed that although the between-group differences in HbA1c levels did not persist after the first year of the trial, patients randomly assigned to the sulfonylurea–insulin group still lowered their 10-year risk for all diabetes-related endpoints (9% relative risk [RR] reduction compared to dietary intervention alone, P=0.04), microvascular disease (24% RR, P=0.001), myocardial infarction (15% RR, P=0.01) and death from any cause (13% RR; P=0.007). In the metformin group (compared to dietary group), significant risk reductions persisted for any diabetes-related end point (21% RR, P=0.01), myocardial infarction (33% RR, P=0.005), and death from any cause (27% RR, P=0.002). In summary, the UKPDS study showed that early intensive blood glucose control can reduce both microvascular and macrovascular events in patients with diabetes.

While UKPDS studied the effects of medication versus diet on diabetes outcomes in patients newly diagnosed with the disease, other trials more explicitly studied intensive versus standard glucose goals in patients with longer diabetes duration. These trials showed inconsistent results (Table 5). Overall, neither the **ACCORD** trial,[46] the **ADVANCE** trial,[47] nor the **VADT** trial[48] found significant reductions in macrovascular events with more intensive glycemic control compared to less-intensive control, with ACCORD actually showing increased mortality in the intensive control arm (aiming for a HbA1c target of 6% or lower), and only the ADVANCE trial found evidence that an intense HbA1c goal reduced microvascular events. The implications of these data are detailed below.

Table 5: Long-term outcomes in key trials[45-48]

	UKPDS	ACCORD	ADVANCE	VADT
Mean diabetes duration (years)	0 (just diagnosed)	10	8	11
Target HbA1c		<6% vs. 7-7.9%	<6.5% vs. local guidelines	<6% vs. difference of 1.5%
Median follow-up	10 years & 20 years	3.5 years (stopped early)	5 years	5.6 years
Outcomes				
Achieved HbA1c	~7% vs. ~ 8%	6.4% vs. 7.5%	6.5% vs. 7.3%	6.9% vs. 8.4%
Macrovascular events	**Significant reduction**	No significant difference	No significant difference	No significant difference
Microvascular events	**Significant reduction**	No data	**Significant reduction**	No significant difference
CV death	**Significant reduction**	**Significant increase**	No significant difference	No significant difference
All-cause mortality	**Significant reduction**	**Significant increase**	No significant difference	No significant difference

Intensive vs. conventional glucose control

The ACCORD trial found that patients assigned to a target HbA1c level under 6% had an increased risk of death. In contrast, no increase in mortality with similarly intensive glycemic control was seen in the ADVANCE[47] or VADT[48] studies. Furthermore, of these three trials, only ADVANCE found a decreased risk of microvascular complications in the intervention group. Given that the actual HbA1c achieved by the intervention group in each of these three studies was similar, it is unclear exactly why intensive glycemic control did not have consistent results across the trials. Most pertinently, it remains unclear why there was increased mortality in ACCORD.

While considering what may have caused the differences in results, it is also important to note that an increased risk of hypoglycemic events in ACCORD is unlikely to be the culprit. While hypoglycemic events in both the intervention and control groups were associated with increased risk of mortality in ACCORD, subsequent analysis of the trial data suggest symptomatic severe hypoglycemia did not account for the difference in mortality between the two study arms.[49] This is important as it suggests that the excess mortality was not necessarily from attempting to gain adequate control of diabetes, but possibly secondary to other factors like patient selection or the therapeutic route clinicians took to achieve a lower HbA1c.

Given these disparate results, four large meta-analyses published between 2009 and 2011 were published on the topic (Table 6). They showed reductions in the risk of myocardial infarction with intensive vs. standard glycemic control, although a greater than two-fold increase in the risk of severe hypoglycemic events.

Table 6: Summary of meta-analyses of intensive versus standard glycemic control

Analysis	CV disease or events	Myocardial infarction	CV death	All-cause mortality	Risk of severe hypoglycemia
	All comparisons are more-intensive glucose control versus conventional control				
Turnbull 2009[50] (4 studies, N=27, 049)	Major CV events reduced by 9%	MI reduced by 15%	Not significantly different	Not significantly different	Significantly increased (HR 2.48; 95% CI: 1.91-3.21)
Ray 2009 (5 studies, N= 33,040)[51]	Coronary heart disease reduced by 15%	Non-fatal MI reduced by 17%	Not assessed	Not significantly different	Not assessed
Boussageon 2011 (13 studies (N= 34,533)[52]	Not assessed	Non-fatal MI reduced by 15%	Not significantly different	Not significantly different	Significantly increased (RR 2.33; 95% CI: 1.62-3.36)
Hemmingsen 2011 (14 studies, N= 28,614)[53]	Not assessed	Non-fatal MI reduced by 15%	Not significantly different	Not significantly different	Significantly increased (RR 2.39; 95% CI: 1.71-3.34)

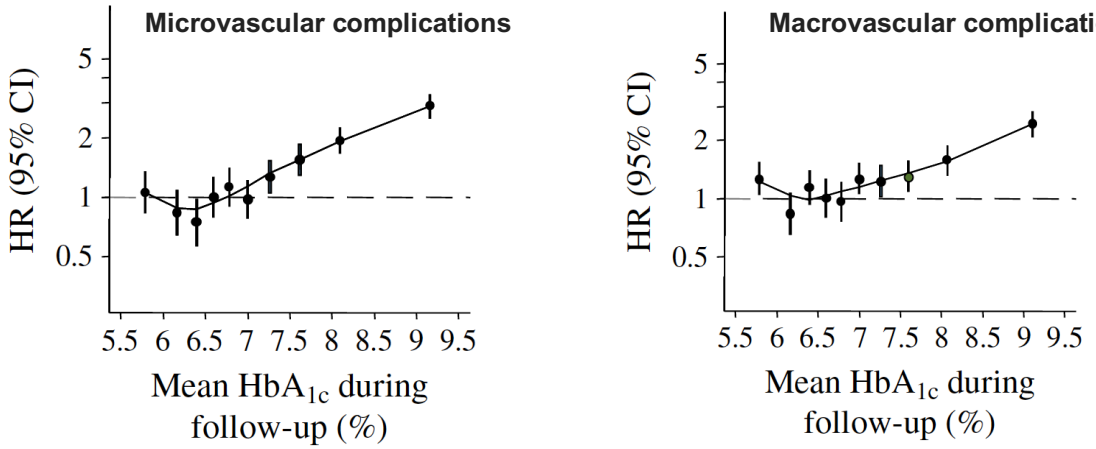
CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; RR = risk ratio.

The UKPDS, ADVANCE, ACCORD, and VADT differ across multiple variable categories including but not limited to patient populations, disease characteristics, treatment goals, and medications used. Furthermore, they were all conducted in an era during which diabetes was treated very differently than it is since the advent of medication classes with known cardiovascular benefits, specifically GLP-1RAs and SGLT-2is. As such, these trials offer only general guidance for the treatment of diabetes which may be especially relevant in individuals with inadequate glycemic control despite use of first-line medications with cardiorenal benefits. Namely, UKPDS suggests that early control of diabetes is easier to achieve with medications and doing so likely reduces both microvascular and macrovascular events, while all the trials suggest limited benefit to aiming for an HbA1c lower than 7% regardless of the population studied.

What is the most appropriate HbA1c target?

The potential benefits of lowering HbA1c aggressively must be weighed against the potential increased risk of hypoglycemic episodes, especially in frail older patients.[54] While data shows that the risk of both microvascular and macrovascular events increases as HbA1c increases above 6.5% (Figure 7),[55] the aforementioned trials suggest that certain populations may benefit more than others. While for most adults, an HbA1c target of <7% remains appropriate, it is important to recognize that microvascular complications typically take years to develop so there is little to no benefit of intensive glycemic control in individuals with limited life expectancy or advanced comorbid illnesses. Thus in individuals with advanced long-term illnesses, advanced age, those with cognitive impairment, or advanced chronic disease where the risk of hypoglycemia is high, an HbA1c target of <8% may be appropriate alongside the goal of preventing symptomatic hyperglycemia. It is important to consider individualized HbA1c targets that balance long-term complication risks with overall safety and quality of life.

Figure 7: Risk of microvascular (left) and macrovascular (right) complications by HbA1c level[55]



Given that the UKPDS and other studies showed protection from microvascular disease with an HbA1c target <7% compared with higher targets, it is reasonable to target the lowest possible HbA1c achievable without hypoglycemia during the first 10 years of the disease.

BOTTOM LINE: Aiming for HbA1c levels near or below 7% soon after the diagnosis of diabetes may reduce the risk of microvascular and macrovascular complications. The greatest clinical benefit of intensive glycemic control occurs early in the course of the disease. A reasonable HbA1c target is 7% for most non-pregnant adults with few comorbidities if it can be achieved with

minimal hypoglycemia. A looser target may be appropriate based on patient factors, such as comorbidities, frailty and life-expectancy. Higher HbA1c targets may be appropriate in selected patients. For example, <8% may be appropriate in older adults or any patients with substantial comorbidities given the many risks associated with targeting lower HbA1c levels.

Patient blood glucose self-monitoring

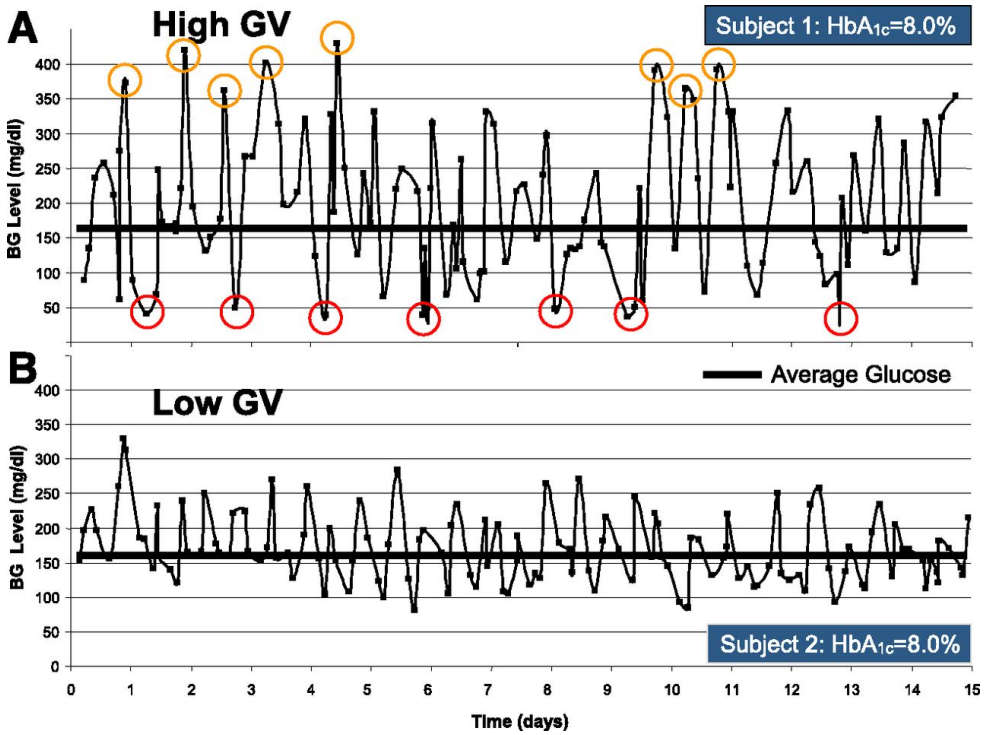
Although periodic office-based HbA1c testing is unquestionably valuable, some debate exists about whether all patients with diabetes should monitor their own glucose levels as part of diabetes self-management, either with finger-stick blood tests (i.e., blood test monitoring [BTM]), or continuous glucose monitoring (CGM). Some studies have suggested that self-monitoring with either approach may positively impact health behaviors in the short term (<6 months), and this evidence was used in older guidelines suggesting that glucose self-monitoring be a routine part of self-management.[56-58] However, newer data suggests that, for patients with diabetes who do not require insulin therapy, any effect of self-monitoring is small and all but disappears after 12 months.[59] While the effectiveness of glucose self-monitoring (BTM or CGM) in patients not on insulin therapy remains questionable, self-monitoring remains vital in people on insulin therapy for dose titration and for monitoring hypoglycemia. In fact, the latest ADA guidelines recommend CGM for all patients on insulin therapy (whether with type 1 or type 2 diabetes) and that CGM be "considered" for adults with type 2 diabetes treated with non-insulin glucose-lowering medications.[60]

For patients who are monitoring their glucose levels, monitoring can be done after fasting, before meals, or 1-2 hours after meals and should be tailored to their glucose pattern, medication regimen, and circumstances. The general blood glucose goals are between 80 and 130 mg/dL when fasting, with postprandial (1-2 hours after meal) glucose levels below 180 mg/dL.[11] These targets can be raised for patients at increased risk of hypoglycemia. For patients on insulin or making rapid changes in therapy, monitoring 3-4 times per day is optimal. For patients meeting their HbA1c targets and not on insulin, monitoring once per day or less may be acceptable.[61] In patients with normal fasting blood sugars in the morning but high pre-meal glucose throughout the day, adding postprandial glucose monitoring can help identify isolated postprandial glucose elevation and achieve better glycemic control.[11]

Patients must also be taught how to recognize and treat hypoglycemia (plasma glucose <70 mg/dL). Symptoms can include adrenergic symptoms (sweating, anxiety, palpitations, hunger, tremor, irritability), and in severe cases, neuroglycopenic symptoms (confusion, lethargy, seizure, or even death). Neuroglycopenic symptoms in the absence of preceding adrenergic symptoms are diagnostic of hypoglycemia unawareness. Recommended treatments include taking 15g of carbohydrate (about 4oz of milk or glucose–containing beverages such as fruit juice and non-diet soda, 2 glucose tabs), waiting 15 minutes to recheck the glucose, and treating with another 15g of carbohydrate if blood glucose remains low. Patients with recurring problematic hypoglycemia can be provided with glucagon for emergency injection at home or at work, which can be administered by a bystander in the situation where the patient has neuroglycopenic symptoms.

In addition to fasting and post-prandial glucose checks, CGM is another tool available to monitor glucose levels, especially given that HbA1c levels can mask important variations in glycemic variability between patients. As illustrated in Figure 8, two patients with identical HbA1c levels may have very different patterns of glycemic variation, with wide swings in glucose levels being more problematic in terms of both symptoms and long-term outcomes.[62]

Figure 8: Identical HbA1c levels but different glycemic variability (GV) in two patients[62]



Results from the **Diabetes Control and Complications Trial**, a study of intensive vs standard control of blood sugar in patients with type 1 diabetes, found that nearly 90% of the difference in risk of retinopathy between groups was due to factors other than glycemic exposure (i.e., HbA1c times duration of diabetes), suggesting other factors, and specifically glycemic variability, likely contribute directly to diabetes complications.[63] Another example from an analysis of data from the Diabetes Control and Complications Trial found an 80% increased hazard for nephropathy for every 1% increase in HbA1c standard deviation.[64] While these specific examples come from the type 1 diabetes literature, there is little reason to think that the biologic mechanisms do not extend to patients with type 2 diabetes, and glycemic variability, along with HbA1c level, is now frequently posited as an important consideration for all individuals with diabetes.[65]

Based on this understanding, the ADA recommends continuous glucose monitors (CGM) for patients on multiple daily insulin injections while also suggesting providers may consider CGM for patients on only basal insulin regimens as well.[43] CGM tracks many metrics that can be acted upon, most notably time in range values that refer to time per day spent within a prespecified glucose range, below a target glucose range, and above a target glucose range.[66] While trials studying whether CGM itself reduces macrovascular or microvascular complications of diabetes have not been conducted, experts have extrapolated the robust literature showing poor outcomes related to having glucoses that are out of range to conclude CGM-driven management of insulin regimens can likely play an important role in preventing complications from diabetes.[67]

For patients with type 1 diabetes, CGM has shown consistent ability to reduce hypoglycemia.[68,69] However, the data is less consistently positive in trials of patients with type 2 diabetes. For example, the **DIAMOND** study group randomly assigned 158 patients on multiple daily insulin injections to continuous glucose monitoring vs usual care and found no difference in severe hypoglycemia.[70] As another example,

the **MOBILE** study group randomly assigned 175 patients on basal insulin to continuous glucose monitoring vs usual care and similarly found no differences in severe hypoglycemia. Alternatively, in an exploratory analysis of data from the MOBILE trial, there was slightly less time spent with glucose <70 mg/dL for patients assigned to CGM (−0.24% of time; 95% CI: −0.42% to −0.05%, P = 0.02).[71]

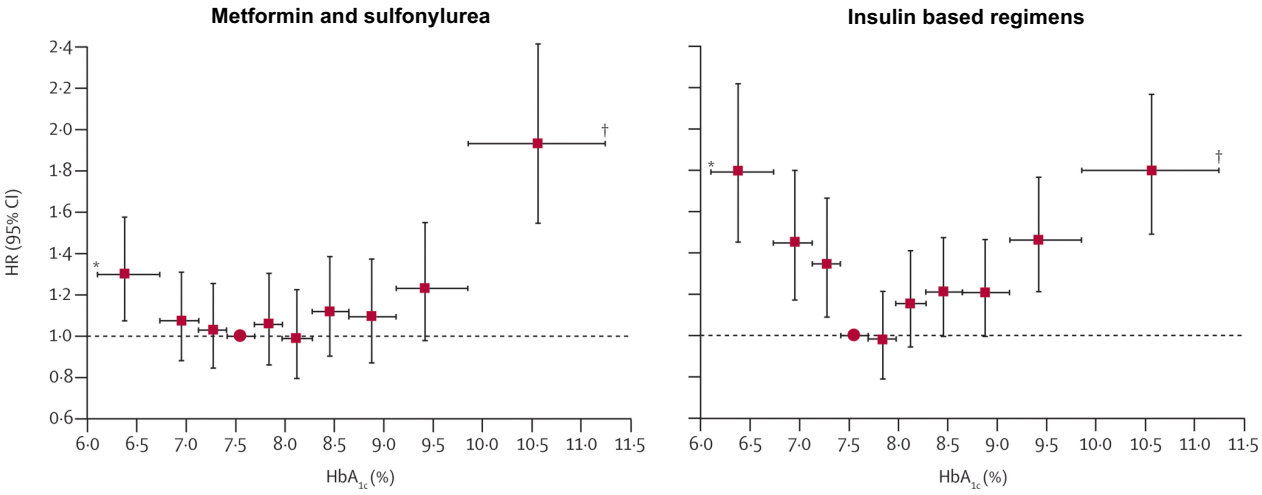
While the reduction in risk of hypoglycemia for patients with type 2 diabetes described by these studies is not overwhelming, both trials showed that HbA1c was lower in the CGM group compared with usual care (-0.3% and -0.4% in the DIAMOND and MOBILE studies, respectively, with both p=0.02). Thus, these individuals on regimens with high risk for hypoglycemia (particularly the MDI population in DIAMOND) were able to achieve lower HbA1c without an increase in hypoglycemia. Furthermore, these trials were small and included populations that may have been lower risk of having hypoglycemia (for example, the MOBILE study group excluded patients with significant renal disease). As such, it may be that CGM for patients with type 2 diabetes can reduce the risk of clinically significant hypoglycemia in specific higher-risk patient populations, and it is still recognized as having benefits for glucose monitoring over standard intermittent glucose checks for many patients on insulin, including increased levels of patient satisfaction with treatment.[72,73]

BOTTOM LINE: All patients on insulin should check their blood glucose levels at home with either blood glucose monitors or, ideally, a CGM. CGM may be considered in patients with type 2 diabetes being treated with non-insulin glucose-lowering medications.

Special considerations for older adults with diabetes

Many geriatric syndromes can impact the management of diabetes, including multimorbidity, polypharmacy, cognitive and sensory impairments, frailty, and a lack of financial or social supports.[74] These issues can raise the risk of diabetes treatment-related adverse events, impede adherence to diet and lifestyle interventions, and introduce problematic drug-disease and drug-drug interactions. Observational data show that both higher and lower HbA1c levels are associated with higher mortality rates in older adults.[75]

Figure 9: Mortality in adults ≥50 years old is associated with both higher and lower HbA1c levels[75]



Age and duration of diabetes are both independent risk factors for diabetes-related morbidity as well as mortality.[76] This may be due to the complications of the disease itself as well as complications from treatment of the disease. Even a single episode of acute hypoglycemia is associated with cognitive decline which over time may have detrimental effects.[77] For example, in one prospective cohort study of older adults with diabetes, hypoglycemic episodes were more likely to occur both before and after a diagnosis of dementia, raising the question of whether there is a bidirectional relationship between hypoglycemia and dementia.[78] Other observational data supports this possibility; for example, a 2018 meta-analysis of 13 studies found that severe hypoglycemic episodes were associated with a nearly two-fold increased risk of incident dementia (RR 1.77; 95% CI: 1.35-2.33).[79] However, it is important to note that these studies are observational, and it is certainly possible that this correlation between hypoglycemia and subsequent risk of dementia is due to residual confounding such as undiagnosed mild-cognitive impairment.

Regardless, other examples of associations between diabetes treatments and complications in older adults are ubiquitous in the literature. For example, patients with diabetes who have lower HbA1c levels (i.e., around 6%) on insulin therapy have a significantly higher risk for falls (OR 4.36 for risk of falling in patients with HbA1c ≤6% vs. HbA1c >8%; 95% CI: 1.32-14.46).[80] The potential benefit of tight glycemic control is also diminished in individuals with either low life expectancy (no time to develop complications) or in people who already have end-stage microvascular complications (nothing to prevent). Such concerns highlight the larger magnitude of the harms older adults experience from both diabetes and diabetes treatments. HbA1c targets should, therefore, be individualized using a shared decision-making paradigm and taking into account patient characteristics and the use of other drugs with potential effects on glycemic control (Table 7).

Table 7: Considerations for HbA1c targets in older adults[11,81]

	HbA1c goal	Average FBG target range (mg/dL)	Average bedtime glucose target range (mg/dL)	Rationale
Healthy • few comorbidities • functionally and cognitive intact	<7.5	80-130	80-150	• significant life expectancy • goal is to prevent future macrovascular and microvascular complications
Complex/intermediate • multiple chronic comorbidities OR • two or more IADL impairments OR • mild to moderate cognitive impairment	<8	90-150	100-180	• intermediate life expectancy • high treatment burden • at risk for hypoglycemia and falls
Very complex/poor health • residency in a long-term care facility OR • end-stage chronic illnesses OR • two or more ADL impairments OR • moderate to severe cognitive impairment	<8.5*	100-180	110-200	• limited life expectancy • uncertain benefit • high risk of hypoglycemia and falls

BOTTOM LINE: Older adults with hypoglycemia or lower HbA1c levels have worse outcomes (cognition, falls, mortality, etc.). Simplifying insulin regimens and personalizing HbA1c targets in high-risk older people can reduce treatment burden and the risk of hypoglycemia.

Non-insulin pharmacologic treatment of diabetes

The major classes of oral glucose-lowering agents and non-insulin injectable agents for treating patients with type 2 diabetes are summarized in Table 8.

Table 8: Non-insulin glucose-lowering agents

Route	Class	Examples (Brand names)
Oral	Biguanide	metformin (Glucophage)
	Sulfonylureas (SUs)	glyburide (Diabeta, Micronase) glipizide (Glucotrol) glimepiride (Amaryl)
	Thiazolidinediones	pioglitazone (Actos)
	Dipeptidyl peptidase (DPP)-4 inhibitors	alogliptin (Nesina) linagliptin (Tradjenta) saxagliptin (Onglyza) sitagliptin (Januvia)
	SGLT-2is	bexagliflozin (Brenzavy) canagliflozin (Invokana) dapagliflozin (Farxiga) empagliflozin (Jardiance) ertugliflozin (Steglatro)
	GLP-1RA	semaglutide (Rybelsus)
Injectable	GLP-1RAs	dulaglutide (Trulicity) exenatide (Byetta) exenatide XR (Bydureon) liraglutide (Victoza) lixisenatide (Adlyxin) semaglutide (Ozempic)
	Dual agonist (glucose-dependent insulinotropic polypeptide [GIP] and GLP-1RA)	Tirzepatide (Mounjaro)

These medications differ in their mechanisms of action, their side effects, and their cost. Other medications such as meglitinides, repaglinide (Prandin, generics) and nateglinide (generics), and acarbose, are still available but not typically recommended, though may be continued in patients who are at treatment goal and not having side effects.

Reductions in HbA1c

Many studies have compared the ability of non-insulin glucose-lowering agents to reduce HbA1c, a surrogate for long-term glycemic control in patients with diabetes. The controversy surrounding rosiglitazone has prompted questions about how well this surrogate marker, in isolation, can provide a complete picture of a drug's clinical worth. The importance of HbA1c reduction was again revisited with the advent of the SGLT-2is and GLP-1RAs, which showed that these agents could reduce the risk of macrovascular events independent of HbA1c reduction. However, the trials of HbA1c control (especially UKPDS) and epidemiologic studies linking higher HbA1c with significantly more morbidity highlight why HbA1c reduction remains important. Patients may also experience physical symptoms or psychological distress related to inadequate glycemic control. As such, understanding how different agents lower HbA1c is still important for making rational therapeutic choices.

Numerous trials have evaluated the effectiveness of individual agents to reduce HbA1c compared to placebo, and results show these agents can lower HbA1c by about 0.5-2.5% (Table 9).

Table 9: Expected reductions in HbA1c of different glucose-lowering agents[82-84]

Class	HbA1c lowering
Biguanide	1-1.5%
Sulfonylureas	1-1.5%
Thiazolidinediones	1-1.5%
DPP-4 inhibitors	0.5-1%
SGLT-2is	0.5-1%
GLP-1RAs	1-1.5%
GIP/GLP-1RA	2-2.5%

In general, older drugs have been tested in patients with higher baseline HbA1c levels, a situation in which greater reductions in HbA1c are possible regardless of therapy type.[85]

Table 10: Other relevant outcomes

Class / medication	CV outcome: ASCVD	CV outcome: HF risk	Diabetic kidney disease progression	Weight change	Hypoglycemia	Precautions
SGLT-2 inhibitors canagliflozin (Invokana) empagliflozin (Jardiance)	benefit	benefit	benefit	loss	no	UTI, ketoacidosis, genital infections, hypotension, fractures (cana)
bexagliflozin (Brenzavvy) dapagliflozin (Farxiga) ertugliflozin (Steglatro)	neutral					
GIP/GLP-1 RA tirzepatide (Mounjaro)	benefit	benefit	*	loss	no	GI side effects common, pancreatitis
GLP-1 RA dulaglutide (Trulicity) liraglutide (Victoza) semaglutide (Ozempic) semaglutide (Rybelsus)	benefit	neutral†	potential benefit	loss	no	GI side effects common, pancreatitis
exenatide (Bydureon) lixisenatide (Adlyxin)	neutral	neutral	*			
biguanide metformin (Glucophage)	potential benefit	*	*	potential benefit	no	GI intolerance (start low, or use extended release)
thiazolidinediones (TZD) pioglitazone (Actos)	potential benefit	increased risk	*	gain	no	fractures, bladder cancer
DPP-4 inhibitors linagliptin (Tradjenta) sitagliptin (Januvia)	neutral	neutral	*	*	no	joint pain, pancreatitis
alogliptin (Nesina) saxagliptin (Onglyza)		potential risk	*	*		
sulfonylureas glyburide (DiaBeta, Glynase) glimepiride (Amaryl)	neutral	*	*	gain	yes	
glipizide (Glucotrol)	*	*	*			
insulin lispro, aspart, glulisine, regular, NPH	*	*	*	gain	yes	
glargine, degludec, detemir	neutral	*	*			

*No data available. †Semaglutide (Ozempic) improves quality of life metrics.
GIP = glucose-dependent insulinotropic polypeptide; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; UTI = urinary tract infection

In addition to their effects on HbA1c levels, non-insulin glucose-lowering agents differ in their impact on other clinically important outcomes, which are summarized in the table below and detailed in the following pages.

Cardiovascular outcomes

All glucose-lowering medications reduce HbA1c, but the true goal when treating diabetes is to reduce clinically important outcomes such as end-organ damage (e.g., cardiovascular disease, nephropathy, neuropathy, and retinopathy) or death. Although this was ultimately disproven, after an analysis suggested that rosiglitazone (Avandia) was associated with increased risk of cardiovascular outcomes despite lowering HbA1c,[86] the FDA required, between 2008 and 2020, that newly-approved glucose-lowering medications be evaluated for CV risk through at least one randomly assigned, placebo-controlled trial. These mandated trials led to the discovery that select SGLT-2is and GLP-1RAs provide cardiovascular benefit for patients with type 2 diabetes and established cardiovascular disease (CVD).

Conversely, other glucose-lowering medications (e.g., DPP-4 inhibitors) have not been definitively proven to reduce CV events, but many have been shown not to increase CV risk compared to placebo.

These findings, along with subsequent studies showing that SGLT-2is and GLP-1RAs have benefits for other health outcomes, have fundamentally altered the precision with which diabetes can be treated. While older agents had been proven to reduce HbA1c, few published trials with large sample sizes compared individual agents to other drugs or to placebo with respect to macrovascular and microvascular outcomes. As such, attempting to prevent complications from diabetes was largely attempted via targeting a surrogate outcome (e.g., HbA1c) using medications with the most appropriate side-effect and cost profile for the patients. Now, the goal remains the same (to prevent complications from diabetes), but clinicians can consider how to tailor specific pharmacologic choices to target patients' specific complication profiles and not rely solely on targeting an HbA1c to achieve their ends.

Note that as they relate to SGLT-2 inhibitors and GLP-1 RAs, cardiovascular disease (CVD) typically refers to 3-point MACE outcomes, which includes a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. All SGLT-2 inhibitors, and some GLP-1 RAs, also have been shown to reduce heart failure, which is typically considered separately despite still being a cardiovascular outcome and which is captured by broader measures (e.g., 4- and 5-point MACE).

SGLT-2 inhibitors

Two SGLT-2is have been shown to reduce the risk of CVD: empagliflozin and canagliflozin.

The 2015 **Empa-Reg Outcome Study** looked at the effects of empagliflozin, when added to standard care (which could include other glucose-lowering agents), on CV morbidity and mortality.[22] 7,020 patients were randomly assigned to one of three arms: 10 mg empagliflozin/day; 25 mg empagliflozin/day; or placebo. After a median follow-up of 3.1 years, there was a 14% reduction in CV events (i.e., death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) in the pooled empagliflozin group compared to placebo (HR 0.86; CI, 0.74-0.99; P=0.04).[22] There were no significant between-group differences in the rates of myocardial infarction or stroke, but the empagliflozin group had significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% vs. 4.1%; 35% relative risk reduction), and death from any cause (5.7% vs. 8.3%; 32% relative risk reduction).[22] Because the drug works by increasing urinary glucose excretion, there were significantly more cases of genital infection among both male and female

patients in the empagliflozin group: 42 cases (1.8%) in the placebo group vs. 153 cases (6.5%) in the group assigned to 10 mg empagliflozin; and 148 (6.3%) in the group assigned to 25 mg empagliflozin.

The **CANVAS** and **CANVAS-R trials** randomly assigned 10,142 patients to the SGLT-2i canagliflozin (100 or 300 mg/day) vs. placebo and found a reduced risk of CV events (HR 0.86; 95% CI: 0.75-0.97), but increased risks for amputation, fracture, and genital infections in males and females.[87]

Two additional SGLT-2is have not been found to reduce CVD risk, but both have been shown to be noninferior to placebo with regard to cardiovascular safety. **DECLARE-TIMI 58** was a noninferiority trial with 17,160 adults randomly assigned to dapagliflozin 10 mg/day vs. placebo with median follow-up 4.2 years.[88] Dapagliflozin did not reduce major adverse cardiovascular events (HR 0.93; 95% CI: 0.84-1.03 vs. placebo) but did reduce the rate of hospitalization for heart failure (in 2.5% vs. 3.3%, respectively, $p<0.05$) and renal adverse events (in 4.3% vs. 6.6%, $p<0.05$). The **VERTIS CV** trial, another non-inferiority trial, randomly assigned 8,246 patients to ertugliflozin versus placebo and, after a median follow-up of 3.5 years , concluded ertugliflozin did not reduce cardiovascular events compared with placebo (HR 0.97; 95% CI: 0.85-1.11).[89] Similar to the DECLARE-TIMI 58 study, subsequent analyses of the VERTIS CV trial did show that ertugliflozin reduces the risk of first hospitalization for heart failure (HR, 0.70; 95% CI, 0.54–0.90). This latter finding adds credence to the belief that while CV event reduction may not apply to all SGLT-2is, some of the clinical benefits from these medications are a medication class effect.[90]

GLP-1RAs

Multiple GLP-1RAs have been shown to reduce the risk of CVD. These include liraglutide, dulaglutide, and semaglutide (injection).

The **Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER)** trial randomly assigned 9,340 adults to liraglutide 1.8 mg once daily vs. placebo with median follow-up 3.8 years.[21] Both groups received “standard care” which could include other glucose-lowering agents. The primary end point (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) occurred in 13% of the liraglutide group vs. 14.9% in the placebo group (HR 0.87; 95% CI: 0.78-0.97). Death from cardiovascular causes was also significantly lower with liraglutide (4.7% vs. 6%, HR 0.78; 95% CI: 0.66-0.93). There were no significant differences between groups, however, in rates of nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

The **REWIND** trial randomly assigned 9901 patients over the age of 50 to dulaglutide (1.5 mg) or placebo.[91] After a median follow-up of 5.4 years, the primary composite endpoint (non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes) occurred in 12% of patients assigned to the GLP-1RA and 13.4% of patients assigned to placebo (HR 0.88; 95% CI: 0.79-0.99), but there was no difference in all-cause mortality between the two groups. Of note, REWIND was the only cardiovascular outcome trial involving GLP-1RAs or SGLT-2is which included many patients at risk of a first event (i.e. for primary prevention) unlike other studies involving mostly, or all, patients with established ASCVD.

The **SUSTAIN-6** trial randomly assigned 3,297 adults ≥50 years old to semaglutide (0.5 or 1 mg once weekly) vs. placebo with median follow-up of 2.1 years.[92] The primary outcome (composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) occurred in 6.6% vs. 8.9% respectively (HR 0.74; 95% CI: 0.58-0.95). The rate of nonfatal stroke was lower with semaglutide (1.6% vs. 2.7%, HR 0.61; 95% CI: 0.38-0.99), but there were no significant differences in all-cause or

cardiovascular mortality, nonfatal myocardial infarction, or hospitalization for heart failure or for unstable angina.

As of this writing only one FDA-approved oral formulation of a GLP-1RA is on the market: semaglutide (Rybelsus). In the **PIONEER 6** trial, 3,183 patients were randomly assigned to receive oral semaglutide or placebo in a cardiovascular outcome trial. Oral semaglutide was shown to be non-inferior to placebo with regard to the primary composite CV outcome (HR 0.79; 95% CI: 0.57-1.11; P<0.001 for noninferiority; P=0.17 for superiority). However, death from cardiovascular causes was substantially lower in the oral semaglutide group (HR 0.49; 95% CI: 0.27-0.92). [91] In part because of the mortality findings, the cardiovascular safety of oral semaglutide was also evaluated in the **SOUL** trial. This superiority trial randomly assigned 9,650 patients with type 2 diabetes and high cardiovascular risk to daily oral semaglutide (maximum dose 14 mg) or placebo with a mean follow-up of 47.5 months.**[93]** The primary outcome (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) occurred in 12% of the semaglutide group vs. 13.8% in the placebo group (HR 0.86; 95% CI: 0.77-0.96). Rates of serious adverse events were relatively high in both groups, but less in the oral semaglutide group (47.9% vs. 50.3%, P=0.02). Gastrointestinal disorders were more common with oral semaglutide than with placebo 5.0% vs. 4.4%.

In 2025, preliminary results from the **SURPASS-CVOT** trial showed that tirzepatide was noninferior to low-dose dulaglutide for protection from cardiovascular events.[94] This is the first cardiovascular outcomes trial assessing the effect of a diabetes agent compared to an active comparator (dulaglutide) that has already showed CV risk reduction (dulaglutide in REWIND study). The study randomly assigned 13,165 patients with established atherosclerotic disease and diabetes to weekly tirzepatide (maximum dose 15 mg) or dulaglutide 1.5 mg for a median duration of 4 years. Patients in the tirzepatide group showed an 8% risk reduction for the composite endpoint of CV death, myocardial infarction, or stroke compared to dulaglutide (absolute event rates of 12.2% and 13.1%, respectively). This met the prespecified criteria for noninferiority (p<0.001), but not for superiority (p=0.09). Additionally, in an imputed placebo analysis, the study showed that tirzepatide reduced 3-point MACE by 28% and all-cause mortality by 39% compared to placebo, suggesting possible extended cardioprotective effects with this dual incretin therapy.[95]

There were no significant differences in major CV events, CV mortality, all-cause mortality, hospitalization for heart failure, or serious adverse events in two other trials of GLP-1RAs: **EXSCEL** (10,782 patients randomly assigned to extended-release exenatide 2 mg per week vs. placebo)[96] and **ELIXA** (6,068 adults ≥30 years old with type 2 diabetes and an acute coronary event in the previous 180 days randomly assigned to lixisenatide 10-20 mcg once daily vs. placebo).[97]

DPP-4 inhibitors

Despite having a mechanism related to the GLP-1RA pathway, DPP-4 inhibitors have not been shown to have the same ability as the GLP-1RAs to reduce CVD risk. Even though the DPP-4 inhibitors saxagliptin and alogliptin have been associated with higher risk of heart failure relative to placebo, these agents have not been found to increase the risk of major adverse cardiovascular events.[98,99]

Other studies have found a similar absence of increased cardiovascular risk with DPP-4 inhibitors. For example, in the **CAROLINA** trial, 6,042 patients with poorly controlled diabetes and increased risk for CVD were randomly assigned to linagliptin or a sulfonylurea (glimepiride). The primary outcome (3-point MACE) was not significantly different between groups (HR 0.98; 95% CI: 0.84-1.14; P <0.001 for noninferiority, P = 0.76 for superiority).[100] Other trials have shown other members of the DPP-4 inhibitor medication class also do not appear to reduce risk of macrovascular events.[101] For example, in the

SAVOR-TIMI 53 trial, 1,222 patients were randomly assigned to saxagliptin versus placebo. After a median follow-up of over two years, there was no difference between cardiovascular events between the groups (HR 1.00; 95% CI: 0.89-1.12; P=0.99 for superiority; P<0.001 for noninferiority).[99]

Studies assessing the effects of DPP-4 inhibitors on cardiovascular morbidity and mortality more generally have not shown significant or consistent benefits. For example, two observational studies, a case-control study with 1,499,650 adults[102] and a retrospective cohort study with 57,737 adults,[103] found no significant differences in rates of heart failure hospitalization between patients using DPP-4 inhibitors vs. other oral anti-diabetic drugs. A network meta-analysis of 236 trials including 176,310 participants found that use of DPP-4 inhibitors was not associated with lower mortality compared to placebo or no treatment (HR 1.02; 95% CI: 0.94-1.11).[104]

Older agents

Compared with studies of drugs approved around or after the FDA mandated that drugs for type 2 diabetes be studied for their cardiovascular safety, older drugs have not been studied with the same intentionality in large, randomly assigned, controlled trials. Those that have been studied were often also assessing other aspects of treating diabetes (for example, the UKPDS studied multiple medication regimens and different intervention targets) or included only select populations (for example, the UKPDS included only individuals with newly diagnosed diabetes). Some of the trials of metformin, sulfonylureas, and thiazolidinediones are described here.

In one component of the **UKPDS** trial, patients without overweight or obesity with newly-diagnosed diabetes were randomly assigned to intensive therapy (defined as fasting plasma glucose target < 6 mmol/L [108 mg/dL]) with insulin, intensive therapy with a sulfonylurea (chlorpropamide or glyburide), or diet alone, and were followed for 10 years.[105] Intensive drug therapy with either regimen was substantially more effective than diet alone for lowering HbA1c, reducing the risk of microvascular complications, and reducing CV morality, although the reduction in the risk of myocardial infarction was borderline significant (RR 0.84; 95% CI: 0.74-1.00).[105] No differences in CV outcomes were found between patients treated with sulfonylurea versus insulin.

In a second component of UKPDS, patients with >120% ideal body weight were randomly assigned to a conventional regimen (primarily diet alone), intensive therapy (defined as fasting plasma glucose target < 6 mmol/L) with metformin, or intensive therapy with insulin or a sulfonylurea (glyburide or chlorpropamide).[106] In contrast to the results in patients without overweight, in patients with overweight metformin significantly reduced the risk of diabetes-related death, death from all causes, and stroke compared to diet alone.[106] Other smaller trials have also suggested that metformin may perform favorably compared with sulfonylureas with regard to CVD outcomes.[107] Metformin did not reduce rates of microvascular complications or myocardial infarction.

The **PROactive** study **(PROspective pioglitAzone Clinical Trial In macroVascular Events)** randomly assigned 5,238 patients with type 2 diabetes and macrovascular disease to either pioglitazone (Actos) or placebo in addition to their glucose-lowering regimen.[108] The primary endpoint was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, or amputation above the ankle. This endpoint was not significantly reduced in patients treated with pioglitazone (HR 0.90; 95% CI: 0.80-1.02), but a secondary composite outcome (all-cause mortality, non-fatal myocardial infarction, or stroke) was reduced by 16% in pioglitazone-treated patients (HR 0.84; 95% CI: 0.72-0.98).

Data are mixed and difficult to compare across studies due to a lack of standard outcomes and methods (as contrasted with the literature surrounding the GLP-1RAs and SGLT-2is). However, these data may suggest that intensive control of blood sugar early in the disease course could have cardiovascular benefits, that metformin may reduce cardiovascular events compared with other drug classes, especially sulfonylureas, and that pioglitazone may also have cardiovascular benefits (based largely on the **PROactive** and **IRIS** trials).[109]

Heart failure

Robust evidence demonstrates that SGLT-2is, as a class, can prevent clinically significant heart failure (HF) exacerbations. For example, a 2019 meta-analysis of 34,322 patients randomly assigned to either an SGLT-2i or placebo concluded that those randomly assigned to the SGLT-2i were 23% less likely to have cardiovascular death or hospitalization for heart failure (HR 0.77; 95% CI: 0.71-0.84).[110] The only SGLT-2i not included in this meta-analysis was ertugliflozin, but analysis of that drug in the **VERTIS CV** trial did show reduction in the risk of first hospitalization for heart failure (HR, 0.70; 95% CI: 0.54–0.90).[90]

SGLT-2is have been proven to reduce risk of hospitalization due to heart failure even in patients without diabetes. For example, in the **EMPEROR-Reduced** trial, 3,730 patients with heart failure with reduced ejection fraction (ejection fraction<40%) were randomly assigned to empagliflozin versus placebo. They found a 25% reduction in cardiovascular death or hospitalization due to heart failure (HR 0.75; 95% CI: 0.65-0.86), which remained significant regardless of patients' diabetes status.[111] **DAPA-HF** produced similarly significant findings for patients with reduced ejection fraction randomly assigned to taking dapagliflozin.[112] Moreover, the **EMPEROR-Preserved** trial randomly assigned 5,988 patients with heart failure with preserved ejection fraction (HFpEF, ejection fraction >40%) to empagliflozin versus placebo and also found benefit: cardiovascular death or hospitalization due to heart failure was 21% less likely in the empagliflozin group (HR 0.79; 95% CI: 0.69-0.90).

Regardless of diabetes status and ejection fraction, evidence supports the use of SLGT-2is in patients with heart failure.

GLP-1RAs, too, may offer benefits for those with heart failure. The dual-agent tirzepatide, for example, was shown in the **SUMMIT** trial to improve heart failure outcomes in 731 patients with type 2 diabetes and HFpEF.[113] At 104 weeks of follow-up, patients in the tirzepatide group had a 38% reduced risk of death from CV causes or worsening heart failure compared to the placebo group (HR 0.62; 95% CI: 0.41-0.95). In addition, with 52 weeks of follow-up, quality of life scores increased by 19.5 points in the tirzepatide group vs. 12.7 points in the placebo group (P<0.001).

For semaglutide, the **STEP-HFpeF-DM** trial evaluated quality of life outcomes among 616 patients with HFpEF, obesity, and type 2 diabetes and found significant improvements in 6-minute walk distance and changes in quality of life scores among patients randomly assigned to semaglutide vs. those randomly assigned to placebo.[114]

Semaglutide may also improve symptoms of frailty among patients with heart failure. A 2025 analysis of data from the **Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity (STEP-HFpEF)** program (N=1,145) found that semaglutide-mediated weight loss was similar across frailty strata, with the greatest improvements in quality of life scores at 52 weeks among the most frail patients (mean difference on frailty index 11%; 95% CI 8.1%-13.8%) compared to non-frail patients.[115] Semaglutide also reduced the burden of frailty during follow-up (OR for being non-frail at 52 weeks 3.16; 95% CI: 2.44-4.09).

Pioglitazone increases the risk of heart failure events (mainly due to fluid retention). In the PROactive trial, 281 patients (11%) taking pioglitazone reported any heart failure compared to 198 patients (8%) of patients who were in the placebo arm (p<0.0001). This included a significant increase in patients requiring hospitalization for heart failure but not mortality. A meta-analysis of 19 trials of pioglitazone found a 1.41-fold risk in serious heart failure with pioglitazone vs. placebo (95% CI: 1.14-1.76).[116,117] Current diabetes guidelines therefore recommend avoiding pioglitazone in people with symptomatic heart failure.[118,119]

BOTTOM LINE: Non-insulin glucose-lowering medications each reduce HbA1c by about 0.5-2.5%. Selected SGLT-2is and GLP-1RAs have been proven to reduce the risk of cardiovascular events. Other agents, especially metformin and pioglitazone, may also have cardiovascular benefits, though the evidence is not as consistent and robust as it is for SGLT-2is and GLP-1RAs. Other agents have not consistently been shown to have cardiovascular benefits. SGLT-2is also have robust evidence for preventing heart failure hospitalizations in patients with and without diabetes regardless of ejection fraction while GLP-1RAs have emerging evidence of benefit in people with heart failure and preserved ejection fraction. Pioglitazone should be avoided in patients with heart failure.

Kidney disease

SGLT-2is have the most robust proven renoprotective effects. Additionally, some GLP-1RAs may also be able to prevent new onset microalbuminuria.

Multiple trials show that SGLT-2is prevent decline in renal function as evidenced by reducing glomerular filtration rate (GFR) decline and reducing the risk of a doubling of serum creatinine. For example, in the **EMPA-REG OUTCOME** trial, 4,125 patients were randomly assigned to empagliflozin or placebo. A composite outcome of nephropathy was 39% less likely to occur in the empagliflozin group (HR 0.61; 95% CI: 0.53-0.70).[120] Especially noteworthy, doubling of serum creatinine was 44% less likely to occur in the empagliflozin group, and progression to renal replacement therapy was 55% less likely to occur in the empagliflozin group (both statistically significant findings). Moreover, the difference from placebo in the change from baseline in the estimated GFR (eGFR) for empagliflozin was 4.7 mL/min/1.73 m^2 (95% CI: 4.0-5.5; P<0.001), meaning that empagliflozin improved eGFR relative to placebo.

It's important to note that a small drop in GFR upon initiation of an SGLT-2i is expected, but this drop is related to changes in tubuloglomerular feedback rather than a true change in renal function and is generally reversible; these agents have been shown to be renoprotective over longer time frames.[121] Post hoc analyses from major trials (e.g., **EMPA-REG OUTCOME**, **CREDENCE**) show that an initial eGFR decline ≥10% is not associated with increased risk or loss of benefit, and that most patients experience a smaller initial GFR dip.[122]

Multiple other trials show similar results. For example, the 2019 **CREDENCE** trial randomly assigned 4,401 patients with type 2 diabetes and reduced kidney function (eGFR 30 to 90 mL/min/1.73 m^2 and albuminuria) to the SGLT-2i canagliflozin 100 mg/day vs. placebo with median follow-up of 2.6 years (trial stopped early for benefit).[123] All patients were also on stable doses of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). The risk of the renal-specific composite outcome (end-stage kidney disease, doubling of serum creatinine, or death from renal or CV causes) was 34% lower with canagliflozin (HR 0.66; 95% CI: 0.53-0.81), and the risk of end-stage kidney disease was lower by 32% (HR 0.68; 95% CI: 0.54-0.86).

These types of results are consistent across nearly all trials, suggesting the renoprotective effects of SGLT-2is are a class effect. In fact, the renoprotective effects of SGLT-2is have been proven even in patients without diabetes. For example, in the **DAPA-CKD** trial, 4304 patients with CKD but without diabetes were randomly assigned to receive dapagliflozin or placebo.[124] The trial was stopped early for efficacy – the composite primary outcome (decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes) was 39% (HR 0.61; 95% CI: 0.51-0.72) less likely to occur in the dapagliflozin group. Similarly, the **EMPA-KIDNEY** trial, which included patients with a GFR as low as 20, was stopped early in 2022 for efficacy.[125]

The GLP-1RAs may also be useful for preventing progression of renal disease (typically defined as new-onset or persistent macroalbuminuria, a persistent doubling of serum creatinine, a persistent decline in eGFR <45, the need for renal replacement therapy, or death from kidney disease). Current evidence supports that GLP-1RAs can prevent the formation of new persistent albuminuria, but they may not prevent GFR decline or provide patients already experiencing albuminuria with as much improvement in renal function as the SGLT-2is. In the **LEADER** trial, the incidence of a composite outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group (HR 0.84; 95% CI: 0.73-0.97), a difference driven by a lower rate of nephropathy in the liraglutide group (1.5 vs. 1.9 events per 100 patient-years of observation (HR 0.78; 95% CI: 0.67-0.92). In the **SUSTAIN-6** trial, new or worsening nephropathy occurred in 62 patients (3.8%) in the semaglutide group vs. 100 (6.1%) in the placebo group (HR 0.64; 95% CI: 0.46-0.88).[21,92,126]

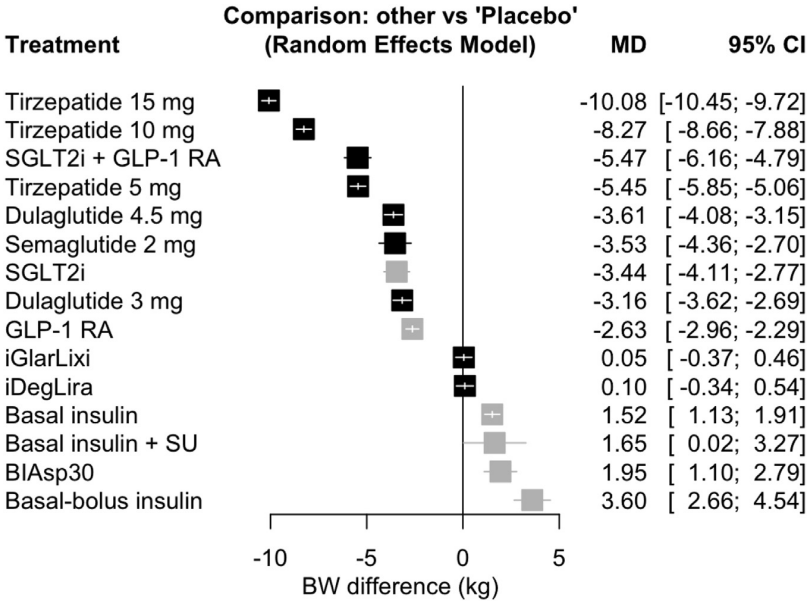
Pooled analysis from these trials was published in early 2022 and found semaglutide/liraglutide lowered albuminuria from baseline to 2 years after randomization by 24% (95% CI: 20%–27%; P<0.001) versus placebo and concluded that semaglutide/liraglutide reduced the rate of GFR decline compared with placebo.[127] Finally, in an exploratory analysis of the **REWIND** trial, the composite renal outcome (defined as the first occurrence of new macroalbuminuria, a sustained decline in eGFR of 30% or more from baseline, or chronic renal replacement therapy) was 15% less likely to occur in the dulaglutide group (HR 0.85; 95% CI: 0.77–0.93). Again, this effect was driven by reducing incidence of new macroalbuminuria (HR 0.77; 95% CI: 0.68–0.87).[128]

The 2024 **FLOW** trial randomly assigned 3,533 patients with type 2 diabetes and kidney disease to semaglutide 1 mg vs. placebo with a mean follow-up of 3.4 years (15.6% of patients in the trial were on an SGLT-2i at baseline, but no significant interactions were observed in subgroup analyses).[129] Patients in the semaglutide group had a 24% lower risk for the primary outcome of major kidney disease events compared to placebo (HR 0.76; 95% CI: 0.66-0.88) and a 21% reduced risk for kidney-specific events (HR 0.79, 95% CI: 0.66-0.94).

Weight loss

Because 80-90% of people with type 2 diabetes have overweight or obesity, weight management is an important goal of diabetes management. The medications capable of inducing the most weight loss appear to be the GLP-1RA and dual GIP/GLP-1RA medications. A 2023 meta-analysis of 40 studies (26,490 patients) found that tirzepatide 15 mg was associated with the most weight loss (mean difference compared to placebo 10 kg) with other GLP-IRAs, SGLT2is and combinations being associated with lower, but still clinically meaningful, weight reductions (Figure 10).[82]

Figure 10: Meta-analysis of diabetes medications and associations with changes from baseline bodyweight [82]



Because of their efficacy for inducing weight loss, GLP-1RAs and dual GIP/GLP-1RAs medications are being used for weight loss in patients with or without diabetes. For example, the **SURMOUNT-5** trial compared the efficacy for weight loss of tirzepatide vs. subcutaneous semaglutide in 751 patients with obesity but without type 2 diabetes.[130] At 72 weeks of follow up, the mean percent change in weight was −20.2% (95% CI: −21.4% to −19.1%) with tirzepatide and −13.7% (95% CI: −14.9% to −12.6%) with semaglutide (P<0.001).

Similar results were shown in the **SURPASS-2** trial comparing three doses of tirzepatide (5 mg, 10 mg, and 15 mg) to subcutaneous semaglutide 1 mg in 1,879 patients with type 2 diabetes.[131] Reductions in body weight were greater with tirzepatide than with semaglutide (the mean reductions in body weight with tirzepatide at the respective doses were −7.6 kg, −9.3 kg, and −11.2 kg, as compared with −5.7 kg with semaglutide (P<0.001 for all comparisons).

While GLP-1RAs and dual GIP/GLP-1RAs are perhaps the most potent diabetes medications with regard to weight loss, SGLT-2is may also have some weight loss effects. For example, a 2012 systematic review of SGLT-2is used in dual or triple therapy for patients with type 2 diabetes concluded that these agents effectively reduced weight compared with placebo.[132] By contrast, sulfonylureas and pioglitazone generally cause weight gain and metformin has variable effects on weight.[133]

Liver disease

Approximately 70% of patients with type 2 diabetes have either metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic-associated steatohepatitis (MASH), both of which are leading causes of cirrhosis.[134] MASLD (formerly called nonalcoholic fatty liver disease) is the presence of steatotic liver disease with at least one cardiometabolic risk factor associated with insulin resistance (e.g., prediabetes, diabetes, atherogenic dyslipidemia, or hypertension) without other identifiable causes of

steatosis.[134] MASH is a more severe stage of MASLD involving not only fat accumulation in the liver but also inflammation and liver cell injury.

Clinicians may underestimate the prevalence of MASLD and MASH and not use appropriate screening strategies in people with prediabetes or type 2 diabetes. The fibrosis-4 index (FIB-4) is a cost-effective strategy for screening patients with prediabetes or with type 2 diabetes for at-risk MASH, with a cutoff value of 1.3 suggesting a higher risk of future cirrhosis and a need for ultrasound elastography testing. [134] Because the FIB-4 may be less reliable in older adults, a cutoff of ≥ 2.0 may be a better threshold for referral for ultrasound elastography in adults over age 65.[134] In patients with low FIB-4 scores, repeat the screening every 2-3 years. If FIB-4 is high, do elastography and if it shows moderate to advanced fibrosis, consider referral to hepatology.[134]

The 2025 ADA guidelines recommend that in adults with type 2 diabetes, MASLD, and overweight or obesity, consider treatment with a GLP-1RA or a GIP/GLP-1RA based on evidence from some recent trials.[134]

Results of an ongoing phase 3 randomly assigned trial comparing subcutaneous semaglutide (2.4 mg once weekly) to placebo in 800 patients with biopsy-defined MASH and moderate or advanced (F2 or F3) fibrosis, with or without type 2 diabetes found a resolution of steatohepatitis in 62.9% in the semaglutide group vs. 34.3% in the placebo group (P<0.001) at 72 weeks of follow-up.[135] A reduction in fibrosis without worsening steatohepatitis was reported in 36.8% of the semaglutide group vs. 22.4% of the placebo group (P<0.001). In August 2025, the FDA approved semaglutide for treating adults with noncirrhotic MASH who have moderate to advanced fibrosis.[136]

Preliminary data about tirzepatide demonstrate similar findings. A phase-2 dose-finding trial randomly assigned 190 patients with biopsy-confirmed MASH and stage F2 or F3 fibrosis to one of three doses of tirzepatide (5 mg, 10 mg, or 15 mg) vs. placebo.[137] At one-year follow-up the percentages of patients who met criteria for resolution of MASH without worsening of fibrosis was 62% in the 15 mg group; 56% in the 10 mg group; 44% in the 5 mg group; and 10% in the placebo group (P<0.001 for all comparisons).

A meta-analysis of 25 trials involving 2,600 patients with MASLD/MASH who used GLP-RAs for a median of 24 weeks found decreases in liver fat deposition and improved histological steatosis, hepatocellular ballooning, and lobular inflammation in patients on a GLP-RA vs. placebo or another active agent.[138]

BOTTOM LINE: GLP-1RAs and dual GIP/GLP-1RAs appear to have the most consistent beneficial effects on body weight. SGLT-2is have robust evidence for renoprotective effects in patients with chronic kidney disease both with and without diabetes, while GLP-1 receptor agonists may delay progression of diabetic kidney disease. GLP-1RAs and GIP/GLP-1RAs are recommended for patients with MASLD and overweight or obesity.

Potential adverse events

Hypoglycemia

The clinical consequences of hypoglycemia include increased risk of falls, car crashes, confusion, and increased risk of dementia.[78,80] Many patients with diabetes experience episodes of hypoglycemia, even without drug therapy. The occurrence of such episodes in patients with obesity on diet therapy alone over

the 10-year follow-up of the UKPDS were 0.7% (major episodes) and 7.9% (minor episodes).[106] Importantly, some patients may not realize they are having symptoms of hypoglycemia ("hypoglycemia unawareness") which increases the adverse effects of this condition. Hypoglycemia unawareness may be rooted in factors such as altered brain glucose sensing, cerebral adaptations, or impaired hormonal regulation.[139]

Metformin, pioglitazone, SGLT-2is, DPP-4 inhibitors, and GLP-1RAs do not appear to increase the risk of hypoglycemia compared to placebo.[140,141] In contrast, because the sulfonylureas act by increasing insulin secretion, they increase the absolute risk of hypoglycemia by 4-9% compared to both placebo and other oral agents.[133] This is particularly relevant for patients whose HbA1c is close to 7%, and in older adults. Longer-acting sulfonylureas such as glyburide increase the absolute risk of hypoglycemia by 2% (95% CI: 0.5%-5%) compared to shorter-acting sulfonylureas such as glipizide and glimepiride.[140] Accordingly, the latter agents are safer in patients with renal insufficiency and in older adults .

Gastrointestinal (GI) intolerance

Nausea, vomiting, and diarrhea are common side effects of metformin, occurring in up 60% of patients.[133] They are substantially lower in patients receiving sulfonylureas, thiazolidinediones, meglitinides, and the DPP-4 inhibitors. To minimize the side effects of metformin, the ADA recommends beginning with a low dose (500 mg taken once or twice a day with meals), and if GI side effects have not occurred after 5-7 days, increasing the dose to 850 mg or 1000 mg before breakfast and dinner. Alternatively, an extended release formulation of metformin could be tried.

GI side effects are also common with GLP-1RAs. The general approach to reduce the risk of GI side effects is to start with low doses, titrate slowly and remain on lower doses if therapeutic effectiveness is achieved, treat specific symptoms (e.g., GERD) as needed, alter eating behaviors (eat smaller meals, eat slowly, avoid trigger foods), consider proton-pump inhibitors or H2-blockers, and adjust the dose, pause, or switch agents if GI symptoms persist. The QR code below links to an article by Wharton et al. that reviews current strategies for managing GI side effects of GLP-1RAs.

Figure 11: QR code for clinical recommendations for managing GI side effects[142]

The 3 Es of managing side effects

- education and explanation to patients
- escalation to an appropriate dose
- effective management of GI side effects

Pancreatitis

The **Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)** evaluated the incidence of acute pancreatitis and pancreatic cancer in 14,671 patients with type 2 diabetes and cardiovascular disease who were treated with the DPP-4 inhibitor sitagliptin.[143] The rate of pancreatitis was low and not significantly different in patients randomly assigned to sitagliptin vs. placebo (0.3% vs. 0.2%, P=0.065). Cases of pancreatic cancer were numerically fewer with sitagliptin (9 [0.1%]) vs. placebo (14 [0.2%] P=0.32). The study authors also performed a meta-analysis with two other DPP-4 inhibitor studies

(involving alogliptin[98] and saxagliptin[99]) with cardiovascular outcomes and found an increased risk for acute pancreatitis (RR 1.78; 95% CI: 1.13-2.81) but no significant effect for pancreatic cancer (RR 0.54; 95% CI: 0.28-1.04).

Similar evaluations have been done for the GLP-1RAs. For example, a 2025 meta-analysis of 62 trials (N=66,232 patients taking GLP1RAs) evaluating rates of pancreatitis and pancreatic cancer found no significant risks for pancreatitis when data were stratified by background medications (RR 1.28; 95% CI: 0.87-1.87) and no observed overall risk for pancreatic cancer (RR 1.30; 95% CI: 0.86-1.97).[144]

Another meta-analysis of 36,397 patients concluded there was no increased risk for pancreatic cancer compared with other treatments (OR 1.06; 95% CI: 0.67-1.67). However, there may be an increased risk of pancreatitis with some GLP-1RAs. For example, the FDA has warned that exenatide should be discontinued and not restarted if pancreatitis occurs, and that other agents be considered in patients with a history of pancreatitis.[145] And a case-controlled study (n= 2,538) reported that GLP-1RA users had significantly increased odds of hospitalization for acute pancreatitis than non-users (OR 2.24; 95% CI: 1.36-3.68).[146] Other observational studies have produced similar results indicating that both DPP-4 inhibitors and GLP-1RAs may be associated with increased risk of pancreatitis,[147] though the connection is not uniform across all observational studies.[148] The exact mechanism of the cause of pancreatitis is unclear, but may include both the direct effects of GLP-1RAs on beta-cell function as well as the potential effects of rapid weight loss on increased risk of pancreatitis.[149,150]

Although the observed associations are weak and absolute risks of pancreatitis and pancreatic cancer are very low, if a patient develops acute pancreatitis on therapy without a clear alternative cause, a GLP-1RA or DPP-4 inhibitor should be stopped.

Fractures

Pioglitazone increases the risk of fracture in women. In the **PROactive trial**, 5.1% of pioglitazone-treated women had a fracture compared with 2.5% of patients on placebo.[33] No increased risk of fracture was observed in men.

The SGLT-2is have been implicated in increasing fracture risk. For example, in the **CANVAS trials**, canagliflozin was associated with an increased rate of fracture (15.4 per 1,000 patient years vs. 11.9 per 1,000 patients years, p=0.02).[87] However, this result has not been consistently seen in meta-analyses of the drug class. For example, in one meta-analysis of randomly assigned-controlled trials, in a population of 20,895 patients being randomly assigned to an SGLT-2i was not associated with an increased fracture rate.[151] Similar null findings were reported in a meta-analysis limited to older adults, suggesting that any effects SGLT-2is have on bone health and fracture risk may be small or may not be a class effect.[152]

Bladder cancer

The FDA issued a safety announcement in 2011 that the use of pioglitazone for more than one year may also be associated with an increased risk of bladder cancer. A 2017 meta-analysis of 26 trials of pioglitazone, however, found no significant increased risk, although the CI includes differences that may be clinically important (RR 1.13; 95% CI: 0.96-1.33).[153]

Thyroid cancer

The GLP-1RAs all carry a black box warning advising that the drugs are contraindicated in patients with a personal or family history of medullary thyroid carcinoma, or in patients with multiple endocrine neoplasia syndrome type 2 (MEN-2). Patients could be counseled that the data on which the warning is based are from preclinical studies in rodents and that similar issues have not been found in human clinical data likely due to differences in GLP-1 receptor expression between rodents and humans.

Ketoacidosis

SGLT-2is increase the risk of diabetic ketoacidosis, often with more modest glucose elevation than expected (known as "euglycemic DKA"). Counsel patients about the risk of diabetic ketoacidosis and advise them to pause an SGLT2i during febrile or GI illnesses, if they decrease their intake of food or are on a ketogenic diet, or if they have planned surgery.

Genital infection

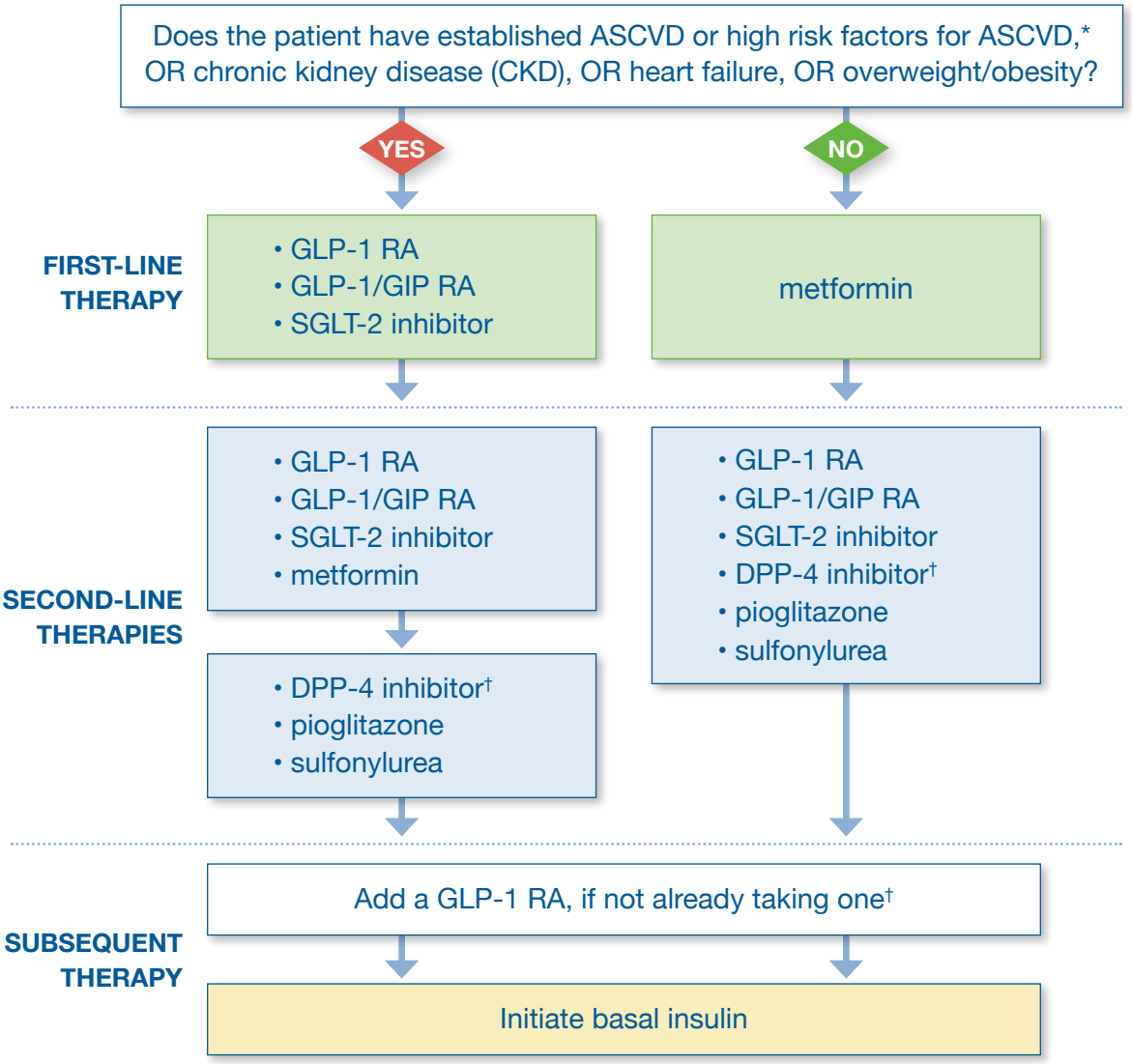
Because they increase the glucose content of urine, SGLT-2is increase the risk of genital mycotic infections, particularly yeast infections, compared to other classes of glucose-lowering medications[154] as well as Fournier's gangrene (compared to placebo).[155] Counsel patients about these risks so that they seek help quickly for any suspected genital infection. Encourage good hygiene practices in women and men, especially uncircumcised men (i.e., "clean under the hood").

BOTTOM LINE: Metformin, pioglitazone, SGLT-2is, DPP-4 inhibitors, and GLP-1RAs do not appear to increase the risk of hypoglycemia. Sulfonylureas increase the risk of hypoglycemia more than these agents. Metformin and GLP-1RAs frequently cause some gastrointestinal intolerance, although for metformin and GLP-1RAs, these side effects can be reduced by gradual dose escalation and behavioral change and usually diminish over time. Pioglitazone increases the risk of fracture. SGLT-2is pose an increased risk of genital infections, particularly yeast infections, and DKA.

Initiation of therapy: Which drug to choose?

For decades, metformin had been recommended as first-line therapy for most patients with type 2 diabetes. However, copious amounts of data have now proven that GLP-1RAs, GIP/GLP-1RAs, and SGLT-2is have unique abilities to reduce complications from diabetes above what would be expected simply by their HbA1c lowering ability. As such, 2025 ADA Standard of Care guidelines state that these drugs are considered first line for patients with established or high risk of CVD, CKD, heart failure, or overweight/obesity, with metformin still first-line for patients without these factors.[156]

Figure 12: Preferred treatment options[#]



* risk factors: age ≥ 55 with two or more risk factors (e.g., obesity, hypertension, smoking, dyslipidemia, or albuminuria). † Avoid co-prescribing a DPP-4 inhibitor with any GLP-1 RA because they act through overlapping mechanisms. # These recommendations are based on current evidence about medication efficacy in relation to clinical outcomes and not only HbA1c levels, as well as data on drug side effects.

Given that most patients in the trials of SGLT-2is and GLP-1RAs were taking metformin, there is still some debate about whether their ability to modify ASCVD risk is dependent on patients being on metformin. If this were the case, then it would suggest that metformin might still have a role as the initial therapy in treating diabetes.[157] However, subsequent subgroup analysis of numerous trials have suggested that the effects of SGLT-2is and GLP-1RAs are independent of metformin. For example, one meta-analysis of six trials that enrolled 51,743 patients reported that those who were randomly assigned to receive an SGLT-2i and were not on metformin still had an 18% reduction in risk of having a major adverse cardiovascular event compared with placebo (HR 0.82; 95% CI: 0.71-0.86). [158] Concerning the GLP-1RAs more specifically, one meta-analysis of four trials that enrolled 43,456 patients found that those randomly

assigned to receive a GLP-1RA and who were not on metformin still had a 20% reduction in risk of having a major adverse cardiovascular event compared with placebo (HR 0.80; 95% CI: 0.72-0.90).[159]

Of course, these guidelines may not apply to all patients due to contraindications to or intolerance of specific medications. Furthermore, as most GLP-1RAs come in an injectable form, some patients may be reticent to begin them. Table 11 summarizes situations in which metformin and other agents may be contraindicated. The FDA updated its renal guidelines for metformin in 2017 with recommendations to obtain an eGFR prior to initiating therapy and annually thereafter (although more frequently for those at risk for renal impairment).[160] Metformin is contraindicated in patients with eGFR <30 due to increased risk of lactic acidosis without appropriate renal clearance and should be avoided or dose-reduced in patients with eGFR between 30 and 45.

Table 11: Non-insulin glucose-lowering agents contraindications and warnings

Class	Contraindications and warnings
Metformin	• renal disease or dysfunction — avoid initiating if eGFR <45, dose reduce if eGFR is between 30-45, and do not continue if eGFR <30 • acute or chronic lactic acidosis
Sulfonylureas	• hypoglycemia • renal impairment: — glyburide not recommended if CrCl <50 mL/min — glipizide not recommended if CrCl <10 ml/mL • avoid glyburide in older adults due to its prolonged action
Pioglitazone	• heart failure • fracture in women with osteoporosis
DPP-4 inhibitors	• pancreatitis • heart failure (saxagliptin, alogliptin) • dose adjust in CKD (except linagliptin)
GLP-1RAs GIP/GLP-1RAs	• idiopathic pancreatitis • use with caution in patients with severe renal impairment, severe gastroparesis, or other causes of delayed gastric emptying • contraindicated in patients with a personal or family history of medullary thyroid carcinoma, or in patients with MEN 2
SGLT-2is	• hypotension, orthostasis • avoid in severe renal impairment (GFR<20) • monitor for genital infection, or ketoacidosis (in both type 1 and type 2 diabetes)

Sources: package inserts for metformin, glyburide, glipizide, alpha-glucosidase inhibitors, meglitinides, DPP-4 inhibitors, GLP-1RAs, SGLT-2is; and FDA safety information for thiazolidinediones and SGLT-2is.

BOTTOM LINE: GLP-1RAs, dual GIP/GLP-1RAs, or SGLT-2is are appropriate as initial agents for patients with increased ASCVD risk, HF, CKD, or obesity as indicated. Metformin remains an appropriate first line agent for patients without these comorbidities. All medication decisions should be made considering cost, side effect profiles, contraindications to receiving certain therapies, and patient preferences.

Combination therapy

Using a dual-agent medication such as a GIP/GLP-1RA, or adding a second non-insulin agent to an existing treatment regimen can help patients achieve better glycemic control. Clinical trials have consistently shown an additive effect of such combinations, probably because drugs act by complementary, but different, mechanisms. In general, the addition of a second agent from a different class lowers HbA1c by an additional 1% over treatment with maximum doses of a single agent.[85,133]

Dual agents

A 2025 meta-analysis of 10 randomly assigned controlled trials with 42,651 participants (2,820 on a combination of an SGLT-2i and GLP-1RA, the rest on either SGLT-2i (37.1%) or GLP-1RA (20.1%) monotherapy or treatment as usual (TAU) (42.8%).[161] Patients using combination therapy had superior cardiovascular, weight, and HbA1c outcomes versus monotherapy, although they also had higher rates of GI adverse events. Patients on combination therapy had a lower risk of hospitalization for heart failure vs. GLP-1RA monotherapy (RR 0.37; 95% CI: 0.22-0.65) or vs. SGLT-2i monotherapy (RR 0.37; 95% CI: 0.19-0.75).

GIP/GLP-1RA therapy was also associated with a significantly lower risk of major adverse cardiac events versus TAU (RR 0.73; 95% CI: 0.61-0.88). Patients on combination therapy had greater weight loss and HbA1c reduction versus SGLT-2i monotherapy (MD = -2.20 kg; 95% CI: -3.09 kg to -1.31 kg and MD -0.74%; 95% CI: -1.21% to -0.27%), respectively, while no difference was observed in comparison to GLP-1RA monotherapy. The incidence of nausea and diarrhea was higher with combination therapy versus SGLT-2i monotherapy (MD = 3.34; 95% CI: 1.74-6.43 and MD = 1.75; 95% CI: 1.10-2.77), respectively than vs. GLP-1RA monotherapy.

Combinations

In 2019, the **VERIFY** trial randomly assigned 1598 patients to begin monotherapy (metformin) versus combination therapy (metformin and a DPP-4 inhibitor). They found that those randomly assigned to the combination therapy group maintained HbA1c <7% for longer even after monotherapy group participants had DPP-4i added to their regimens.[162] Furthermore, those initially randomly assigned to the combination therapy group had a lower risk of requiring more than two agents (HR 0.74; 95% CI: 0.63–0.86).

Studies of older medications such as metformin, sulfonylureas, and pioglitazone demonstrate modest add-on reductions in HbA1c.[163,164] Several short-term randomly assigned trials have shown that exenatide reduces HbA1c by 0.5%-1.0% when added to sulfonylureas and/or metformin in patients whose glucose was poorly controlled.[108,165-167] In two separate 6-month trials, liraglutide added to metformin or a sulfonylurea reduced HbA1c by about 1.0% compared to metformin or sulfonylurea alone.[168] A 2012 systematic review of SGLT-2is used in dual or triple therapy for patients with type 2 diabetes concluded that these agents were effective in reducing HbA1c levels compared with placebo.[132]

BOTTOM LINE: Adding a second agent from a different class may lower HbA1c by an additional 1.0% and could help prevent treatment failure. Combining an SGLT-2i with GLP-1RA may enhance cardioprotective and HbA1c effects, but also increases the risk of GI side effects. Agent- and patient-specific factors such as comorbidities, dosing frequency, adverse effect profiles, and cost often guide choice rather than comparative effects on HbA1c lowering.

Monitoring and regimen intensification

After confirming that a patient has type 2 diabetes and not type 1 or a rarer type of diabetes (e.g., pancreatogenic diabetes or monogenic diabetes), and after initiating therapy, the ADA recommends repeating an HbA1c every 3 months until a target HbA1c is achieved (typically <7%) and at least every 6 months thereafter.[156]

In asymptomatic patients, a second agent is often added if HbA1c remains above target after approximately 3 months of optimal monotherapy. However, as discussed previously, evidence from the **VERIFY** trial suggests that beginning combination therapy within weeks of diagnosis may reduce the risk of treatment failure by over 25%.[162] This was in a trial setting, and the ability to quickly uptitrate medications in practice is much more likely to be limited by side effects, cost, or patient preference.

Many therapeutic options exist for patients who are poorly controlled on monotherapy with GLP-1RAs, SGLT-2is, or metformin. Like selecting an initial agent, this should again be driven by the patient's comorbidities and HbA1c-lowering needs. Before advancing the regimen, titrate the existing medication(s) to their optimal doses and inquire about adherence as seemingly 'inadequate' responses to prescribed regimens may be the result of patients not taking their medications as directed.[169] Lifestyle measures should be assessed and optimized, as feasible.

As is the case when considering an initial therapy, for patients with established CVD, an SGLT-2i or GLP-1RA with cardiovascular benefit is recommended as the second agent if a patient is not already on the medication. If patients have heart failure or CKD with microalbuminuria, then an SGLT-2i is preferred over a GLP-1RA (assuming the patient was not prescribed the agent for initial therapy), though for patients without microalbuminuria a GLP-1RA is reasonable as well. If a patient was started on an SGLT-2i or GLP-1RA as a first line agent, it is also reasonable to consider metformin as a second-line agent. If a third agent is needed, many of the other classes may be tried, with the caveats that clinicians should avoid adding a DPP-4 inhibitor to a GLP-1RA and avoid pioglitazone in patients with heart failure.

In patients without CVD or high risk for CVD, heart failure, or CKD, then medication-specific factors should determine which agent is the best option for step-up therapy. For example, if weight is a concern, then an SGLT-2i, GLP-1RA, or a GIP/GLP-1RA are preferred. If cost or insurance factors are an issue, then metformin, pioglitazone, and sulfonylureas are affordable options. Insulin may be added at any point if it is preferred, though in patients with CVD, heart failure, or CKD, patients should be encouraged to begin a non-insulin agent with proven benefit. Alternatively, if the patient has overt symptoms (e.g., polyuria, polydipsia, weight loss) associated with uncontrolled diabetes, insulin should be recommended.

Monitor patients regularly for side effects, and continue education and motivation to achieve lifestyle changes. For all patients, reinforce weight control and exercise recommendations at every visit, even after medications have been started. Ultimately, many patients may require insulin therapy (usually in combination with other agents) to maintain optimal glucose control, particularly with longer diabetes duration which is associated with progressive insulin deficiency.[85]

BOTTOM LINE: Repeat HbA1c testing every 3 months until a target level is achieved (typically <7%) and at least every 6 months thereafter. When a second agent is needed, selection should be based on patient comorbidities, glucose lowering needs, and cost.

Insulin therapy

Many patients with type 2 diabetes will eventually require insulin therapy.[85] Data from the National Health and Nutrition Examination Survey indicate that only 50% of patients with type 2 diabetes achieve HbA1c <7%.[7]

Unfortunately, despite convincing evidence for benefit, insulin often is not started even when clinicians and patients are aware of poor glucose control.[170-172] Patients' fear of injections and the discomfort of injections are major barriers to use, as well as low perceived efficacy and a belief that adding insulin therapy is a sign of treatment and lifestyle failure.[173,174] Physicians worry about hypoglycemia, lack of time to adequately instruct patients regarding insulin use, a sense of failure at being unable to manage blood glucose with non-insulin medications, and the belief that insulin should only be started when "absolutely essential."[173,174]

When should insulin therapy be initiated for type 2 diabetes?

Generally, insulin is required for patients who do not respond adequately to non-insulin glucose-lowering therapy or who have high baseline blood glucose. Current ADA guidelines suggest initiation of insulin in newly-diagnosed patients if they have hyperglycemic symptoms and/or very high plasma glucose levels (≥300 mg/dL or HbA1c ≥10%).[156]

Most patients with type 2 diabetes produce some endogenous insulin even in the latter stages of disease. Accordingly, the more complex and intensive strategies needed for type 1 diabetes are not typically needed.[85] Initial therapy is usually with a basal insulin (unless the patient is markedly hyperglycemic and/or symptomatic).

Basal insulin provides relatively uniform insulin coverage throughout the day and night to control blood glucose by suppressing hepatic glucose production between meals and during sleep. Either intermediate-acting (NPH, dosed once or twice daily) or long-acting (glargine or deludec, dosed once daily) insulins may be used.[85] Weekly insulins are also nearing regulatory approval and marketing. Basal insulin is usually given at bedtime to control unrestricted overnight gluconeogenesis with subsequent high pre-breakfast (fasting) glucose levels. NPH may also be given in the morning if pre-dinner blood glucose levels are high, but patients may need to be advised to eat lunch if using a morning NPH dose to avoid hypoglycemia especially if the morning dose is higher than the evening dose.

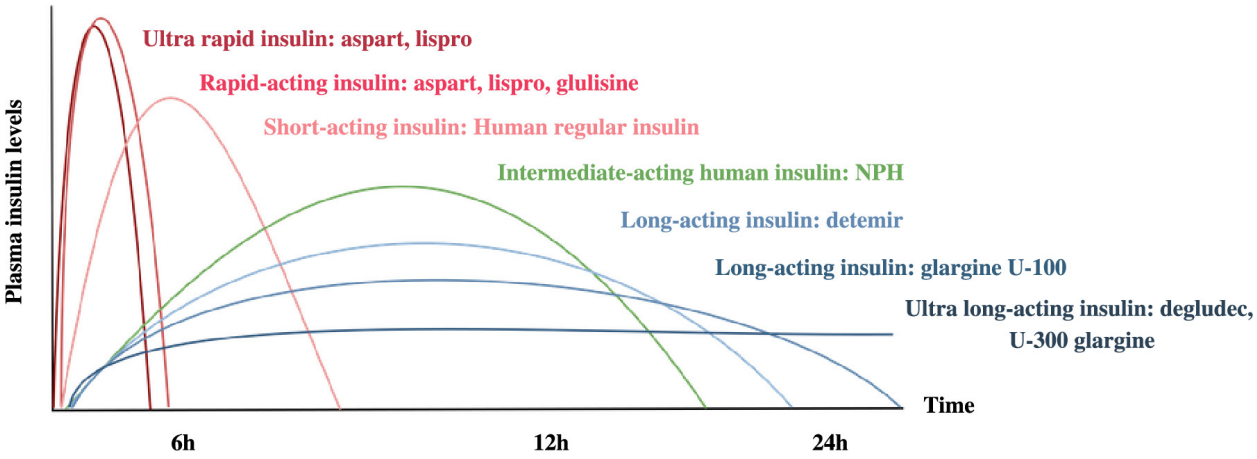
Most patients with type 2 diabetes requiring insulin therapy can be successfully treated with basal insulin alone. However, because of progressive reduction in endogenous insulin secretion, particularly in the early post-prandial phase, some will need prandial insulin therapy with shorter-acting insulins or pre-mixed insulins (which combine intermediate-acting and short or rapid-acting insulin).[85]

Insulin may also be indicated for patients who are pregnant, require high-dose glucocorticoid therapy, or are intolerant of other glucose-lowering agents, as well as for hospitalized patients.[156]

Insulin preparations

Figure 13 depicts currently available insulin preparations; they are described in more detail below.

Figure 13: Comparison of human insulin preparations and insulin analogs[175]



Short-acting insulin (regular insulin)

Regular (short-acting) insulin was the first insulin used to manage the rapid glucose increase that occurs after meals. Its onset, however, does not closely mimic that of the normal postprandial insulin burst. Onset for regular insulin occurs 30-60 minutes after injection, with a peak at 2-3 hours. This means that for maximum effect, regular insulin should be administered at least 30 minutes prior to mealtime.

Rapid-acting insulin analogs

Recombinant DNA technology has led to the development of insulin analogs with pharmacokinetic profiles that more closely mimic post-meal endogenous insulin release. They are rapidly absorbed, peak at 1 hour, and have a shorter duration of action than regular insulin. For patients with type 2 diabetes, a meta-analysis of 42 randomly assigned controlled trials found no benefit of rapid acting insulin over regular insulin in managing HbA1c or in reducing hypoglycemic episodes.[176] Still, outside of clinical trial settings, because these analogs are given closer to mealtime, they do confer theoretical benefits of reducing the likelihood that a patient takes insulin and then has an interruption that leads to a delayed meal and may therefore be a better option for many patients, and they represent the vast majority of non-long acting insulin prescriptions.[177] Given their similar pharmacokinetic profile, there is also little evidence that any of the rapid-acting analogs would provide consistent benefit over another for most patients with type 2 diabetes.

Note that ultrarapid-acting insulins are also available. These are insulin analogs formulated with additional compounds, for example with niacinamide (aspart) or treprostinil and citrate (lispro), to increase speed of absorption. In multiple trials these agents were found to be non-inferior to rapid-acting insulin; however, given that their onset of action is only minutes earlier than their rapid-acting counterparts, it's unclear if they offer a clinically significant benefit for most patients with type 2 diabetes.[178]

Basal insulin options

Intermediate-acting (basal) insulin

NPH is absorbed more slowly than regular insulin (onset of action 1-3 hours) and has a longer duration of action (10-20 hours). It takes 4-8 hours to reach peak effectiveness; because there is a peak effect, there

is a modest increase in hypoglycemia during this period.[179] When used as basal insulin, it can be given once or twice daily.

Long-acting (basal) insulin analogs

Insulin glargine is a long-acting insulin analog. Its onset of action is about 1-2 hours after subcutaneous injection. It has a steady activity plateau with minimal evidence of a peak, and a 24-hour duration of action (the range is approximately 18-26 hours, with shorter duration when low doses are used, which means for some patients BID dosing is needed).[180] As a basal insulin, it is usually injected once daily, and is frequently given at bedtime. However, if nighttime hypoglycemia occurs, the timing of the injection should be changed to the morning. One trial suggests that morning glargine may provide better glucose control than bedtime glargine.[181]

Ultralong-acting insulin

There are two commonly used ultralong-acting insulins available: insulin degludec and insulin glargine U300 (3x concentrated version of glargine). Both have an onset of action ~2-4 hours after subcutaneous injection. Insulin degludec has a half-life of ~25 hours while insulin glargine U300 has a half-life of ~19 hours, and both have no substantial peaks. Both ultralong-acting insulins are stable for over 36 hours and can have a duration of action up to 48 hours.[180]

Differentiating between basal insulin options

All basal insulins provide largely equivalent HbA1c lowering ability when titrated appropriately. However, the longer-acting the insulin is, the lower the risk for hypoglycemia.

Multiple studies have shown that NPH and long-acting analogs provide similar levels of HbA1c control. For example, the **LANMET trial** compared treatment with glargine and metformin vs. once-daily NPH at bedtime and metformin in type 2 diabetes.[182] It found similar glucose control in both groups, but there were fewer hypoglycemic events in the first 12 weeks in the glargine group (though this difference disappeared by the end of the trial at 36 weeks). NPH, however, often requires more injections per day and confers a higher risk of hypoglycemia compared with long-acting insulin analogues.[61,183] Data from observational studies, in which NPH is generally dosed BID as opposed to in most comparative trials, are more mixed, and one propensity-matched study of 25,489 patients initiated on basal insulin found HbA1c was 0.22% lower in patients taking NPH (compared with long-acting analogs) while there were no differences in hypoglycemia-related emergency department visits.[54]

Long-acting and ultralong-acting insulin have similar abilities to lower HbA1c, but ultralong-acting analogs may have lower risk of hypoglycemia. For example, in the **DEVOTE** trial, 7,637 patients with type 2 diabetes at high-risk for cardiovascular events were randomly assigned to degludec or glargine U100 and were followed for 24 months. There were no differences between cardiovascular outcomes or HbA1c between groups, but there were fewer hypoglycemic events in the degludec group (absolute difference of 1.7 percentage points, $p<0.001$ for superiority).[184] These findings of similar HbA1c control and slightly fewer hypoglycemic episodes with ultralong-acting analogs (including both degludec and glargine U300 compared with glargine U100) have been further replicated in meta-analyses of multiple clinical trials.[185]

Furthermore, the timing of degludec dosing may be more flexible than glargine U100, and may be beneficial for patients in whom compliance is a concern.[186]

Taken together, the trial evidence shows that all basal insulins may provide largely equivalent HbA1c lowering with longer-acting insulins possibly posing a lower risk for hypoglycemia. As such, while insulin

glargine U100 is frequently the first basal insulin used in the US, when insurance coverage allows,[177] for patients with adherence issues or at particularly high-risk of hypoglycemia, ultralong-acting insulin or once-weekly insulin may be reasonable alternatives to try.

Premixed (biphasic) insulin combinations

Premixed insulin combinations contain a fixed ratio of faster and intermediate-acting insulins. These combinations can be used to provide both steady state and prandial insulin requirements. Premixed insulin combinations are available for both human insulin preparations (regular and a formulation with a similar activity to NPH), as well as newer insulin analogs (lispro and aspart combined with an NPH-like insulin).

These combinations can simplify treatment by reducing the number of injections needed, while providing both basal and postprandial coverage. As a result, these products provide the theoretical benefit of improving adherence. The fixed ratios, however, can be limiting when attempting to tailor therapy to individual needs, particularly in patients with variable carbohydrate intake. Evening dosing of a premixed formulation can cause nocturnal hypoglycemia, as the NPH-component peaks during a time of minimal glucose intake and production. The combinations are generally given twice a day, before breakfast and dinner, but can be given at once-a-day or three-times-a-day intervals.

While there are theoretical benefits to premixed insulin, and while some clinical trials suggest that HbA1c may be improved over basal insulin alone,[187,188] other clinical trials have suggested they are generally equivalent or inferior to commonly used basal and basal/bolus regimens. For example, in the **DURABLE** trial, patients were randomly assigned to either glargine U100 or lispro protamine/lispro (75/25) mix. After 24 weeks, HbA1c reduction was similar (-1.8 vs -1.7%) in both premixed and glargine groups, but patients in the premixed group had higher doses of insulin and 5 more hypoglycemic events per patient per year.[189] Moreover, in the **GINGER** trial, 310 subjects were randomly assigned to glargine U100 and glulisine vs. twice daily premixed insulin. After the 52-week trial, HbA1c was significantly lower in the basal-bolus group (-1.31% vs. -0.80%) while there were no significant differences in hypoglycemic events.[190] As such, while premixed insulin may be used in select clinical circumstances, it is most often reserved for individuals who eat fixed meals and otherwise have issues with medication adherence.

Concentrated insulins

Concentrated insulins may be useful for patients with significant insulin resistance who require high daily insulin needs by allowing higher insulin dosing at lower injection volumes (as higher volumes may have unreliable absorption and may increase the risk of scarring or lipoatrophy). These products include: lispro U200 (Humalog), regular U500 (Humulin), glargine U300 (Toujeo), and degludec U200 (Tresiba). Some of these concentrated insulins have been directly compared with alternative options (for example, glargine U100 versus glargine U300). Additionally the pharmacokinetic profiles of these drugs do differ by varying degrees. For example, while glargine U100 and U300 are generally similar, there are large pharmacokinetic differences between regular insulin and regular U500. More specifically, regular U500 insulin has a significantly longer time-to-peak concentration and time to maximum effect, which gives it some characteristics of intermediate-acting insulins.[191] Given the unique pharmacokinetics of regular U500, consultation with an endocrinologist is recommended due to the high risk of hypoglycemia.

Insulin delivery options

In addition to traditional vials/syringes, all insulins can be delivered with pen devices that can be easier and safer for patients to use because they do not require any calculations and needles are retractable. Some pens include features such as smart phone app integration to suggest dosing, keep a record of insulin administrations, and remind patients of missed injections. In addition, some insulins can also be delivered in a patch, pump, or as an inhalation.

BOTTOM LINE: Insulin is indicated in patients with high plasma glucose levels that have not responded to non-insulin pharmacologic therapy or patients with baseline glucose levels ≥300 mg/dL or HbA1c ≥10%. In most patients, the introduction of insulin should not be delayed when HbA1c targets are unlikely to be met with non-insulin agents. All basal insulins provide roughly equivalent HbA1c lowering ability, but longer-acting insulins may pose lower risks for hypoglycemia.

Choosing an insulin regimen

Generally, before beginning basal insulin, providers should attempt to use a non-insulin medication for most patients with type 2 diabetes as long as the patient has a HbA1c less than 10%, is not having symptoms of hyperglycemia, and has no other contraindications to the medication class. When patients meet criteria to begin insulin, it is reasonable to begin with basal insulin (rather than prandial or premixed). Therapy can then be stepped-up by adding prandial insulin.[11]

Treating to target

A commonly-used algorithm for basal insulin intensification comes from the **Treat-to-Target** trial.[61] This randomly assigned controlled trial demonstrated that most patients who were inadequately controlled on one or two oral agents could achieve an HbA1c <7% by following the simple schedule shown in Table 12.

Table 12: Insulin initiation and titration

- Start with 10 units of **basal** insulin (either intermediate or long-acting insulin) at bedtime.
- Adjust insulin dose every week, based on the mean self-monitored fasting blood glucose (FBG) values from the previous 2 days.

If mean FPG is:	Increase insulin by:
100-120 mg/dL	2 units
120-140 mg/dL	4 units
140-180 mg/dL	6 units
≥180 mg/dL	8 units

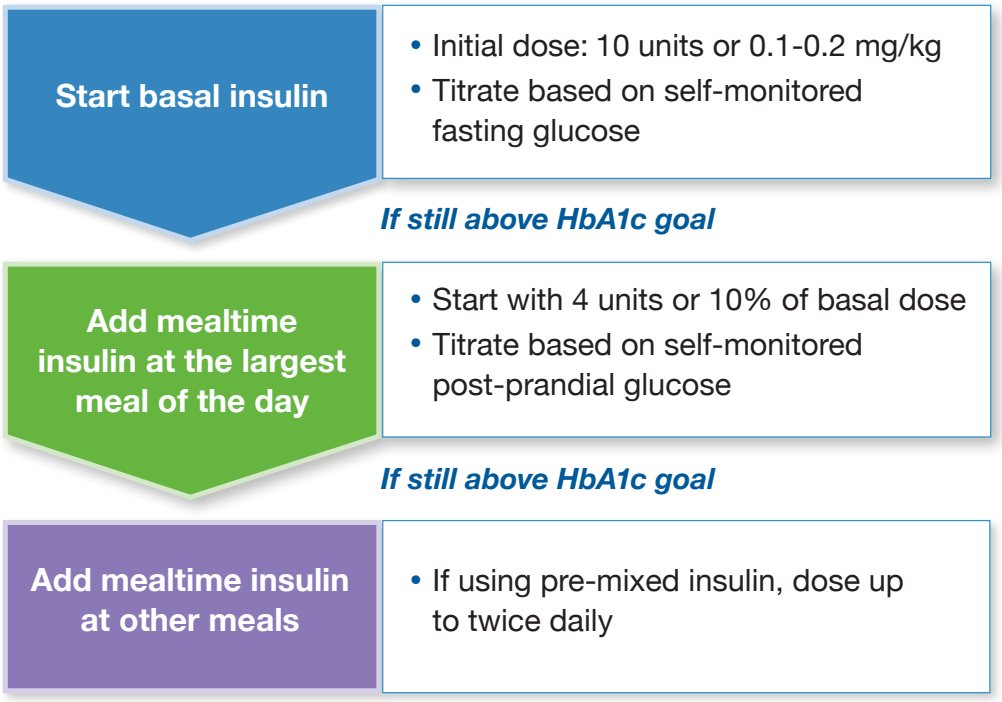
The **Treat-to-Target Trial (2003)** randomly assigned 756 patients with overweight with type 2 diabetes and inadequate glycemic control (HbA1c 7.5%-10%) with oral glucose-lowering agents to bedtime glargine or NPH insulin titrated to target levels using a simple algorithm.[61] At the end of the 24-week

study, NPH and glargine were equally effective in achieving HbA1c levels of ≤ 7%, with about 60% of patients reaching this goal in each group. More nocturnal hypoglycemic events occurred in the NPH group (33% vs. 27%; p<0.05).

A similar **Target-To-Treat (2006)** trial was conducted to compare NPH insulin with detemir in patients with type 2 diabetes with suboptimal glycemic control on oral therapy.[183] HbA1c reductions were similar in both groups. About two-thirds of participants in each group reached an HbA1c of 7%. Patients treated with detemir had significantly fewer hypoglycemic events than patients treated with NPH (26% vs. 16%; P=0.008). Both long-acting insulin (glargine and detemir) and NPH were equally effective in reducing HbA1c, but long-acting insulins may be preferred in patients at higher risk for hypoglycemic events.

In summary, trials suggest that there is likely little benefit to initiating a multi-dose insulin regimen compared with either basal insulin (or even a GLP-1RA for those not already on one) with regard to HbA1c lowering ability, and there is increased risk of hypoglycemia and weight gain with more frequent insulin dosing regimens. There are likely few differences between rapid-acting analogs and outcomes. Ultimately, the choice of which insulin regimen to initiate should be based on the relative costs, number of injections required, and risk of hypoglycemia for the particular patient. The algorithm in Figure 14 provides some strategies for tailoring the initiation and intensification of insulin therapy.

Figure 14: Algorithm for initiating and intensifying insulin

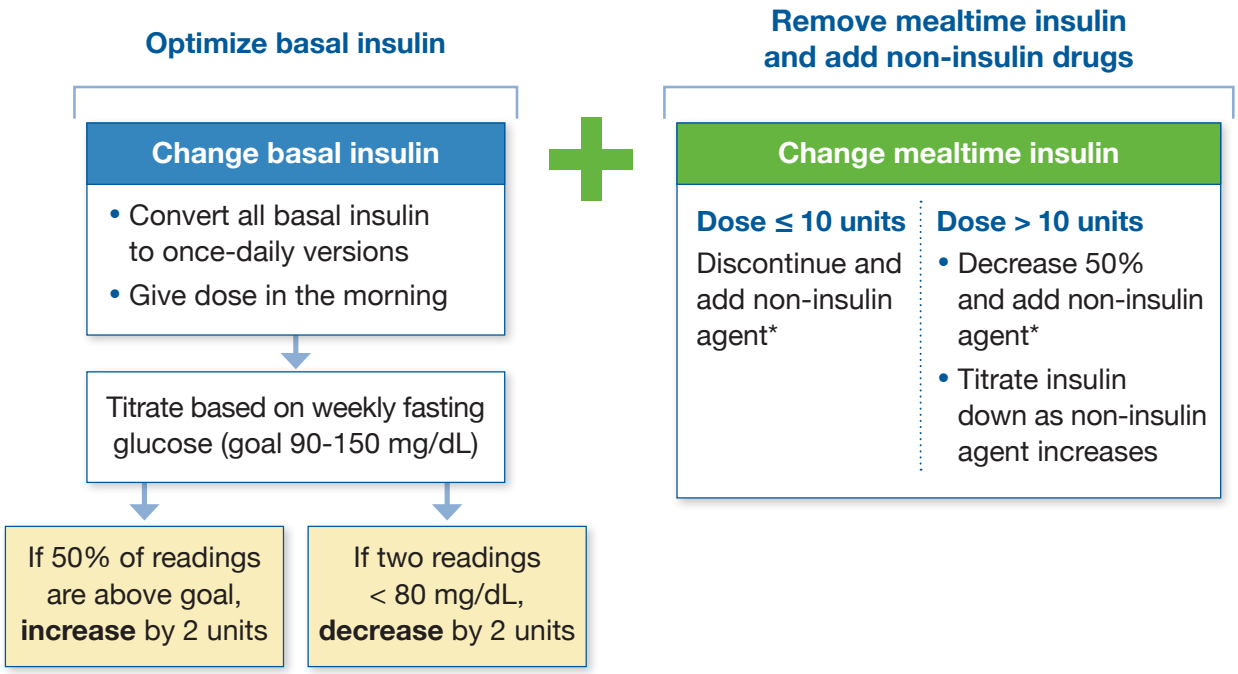


Dosing regimens for older adults

Older adults using complex insulin regimens (e.g., basal-bolus regimens) may be at increased risk of hypoglycemia. A simplified insulin regimen for older adults has been proposed by Munshi et al., which

was shown in a small, single-arm implementation study to reduce hypoglycemic events at 8 months without compromising control of hyperglycemia or HbA1c levels (Figure 15).[192]

Figure 15: Simplified insulin regimen for older adults with type 2 diabetes



BOTTOM LINE: For patients with type 2 diabetes who need insulin, most can be successfully treated with a single dose of basal insulin at bedtime. This dosing for basal insulin is simple and no convincing evidence exists showing that any other initial approach (such as starting with prandial or premixed insulin) provides superior glucose control or safety.

Combining insulin with other glucose-lowering agents

When initiating insulin, most guidelines recommend adding it to existing therapy. Meta-analyses have demonstrated significant reductions in fasting serum glucose and HbA1c levels, and a lower daily insulin dose (11 units less a day) when insulin is added to existing therapy compared to using insulin alone.[193-195] A randomly assigned controlled trial comparing different combinations of oral therapy with insulin found that adding insulin to metformin caused more weight loss, fewer hypoglycemic events, and better glucose control than adding insulin to a sulfonylurea.[196] As a result, it is often recommend that secretagogues (e.g., sulfonylureas, meglitinides) should be weaned or discontinued when insulin therapy is initiated or intensified, but other oral and injectable (e.g., GLP-1RAs) agents that are not secretagogues can be continued.[11]

Current ADA guidelines recommend GLP-1RA and insulin as first-line combination therapy in people with type 2 diabetes who require insulin therapy.[11] This is based on evidence that combination therapy is safe, reduces weight, and is equivalent or superior to adding additional insulin.

For example, the **TRANSITION-T2D** open-label trial showed that in patients with well-controlled type 2 diabetes (HbA1c ≤7.5%) who were on multiple daily insulin (MDI) prandial injections (≤120 units/day) replacing the multiple injections with once-weekly subcutaneous semaglutide maintained, or improved HbA1c levels after 26 weeks.[197] Mean change in HbA1c in the semaglutide group was -0.5% vs. 0.0% for the MDI group (P=0.009), and insulin total daily dose decreased 56% with semaglutide and increased 6.7% with MDI.

Similar findings came from the **SURPASS-6** trial, which randomly assigned 1,428 patients with type 2 diabetes who were taking basal insulin to one of three doses of tirzepatide (5 mg, 10 mg, or 15 mg weekly) or thrice-daily insulin lispro with a 52-week follow up.[198] In an analysis that pooled the tirzepatide groups, the mean change from baseline in HbA1c with tirzepatide was −2.1% vs −1.1% with insulin lispro, resulting in mean HbA1c levels of 6.7% vs 7.7% (estimated treatment difference; −0.98% 95% CI: −1.17% to −0.79%). Patients in the tirzepatide group also lost more weight (mean change from baseline -9.0 kg vs. 3.2 kg with insulin lispro) and had fewer hypoglycemia events (0.4 events per patient-year with tirzepatide vs. 4.4 events per patient-year with insulin lispro).

These results have also been shown in meta-analyses. For example, in a meta-analysis of 15 trials with 4,348 participants comparing the combination of GLP-1RAs and basal insulin vs. other glucose-lowering treatments showed improved mean reductions in HbA1c with the combination (-0.44%; 95% CI: -0.60% to -0.29%), an improved likelihood of achieving the target HbA1c of 7·0% or lower (RR 1.92; 95% CI: 1.43-2.56), no increased risk of hypoglycemia (RR 0.99; 95% CI: 0.76-1.29), and a mean weight reduction 3.22 kg (1.54 kg-4.90 kg).[199] Another meta-analysis of 26 trials with 11,425 patients comparing the same combination vs. other injectable treatments showed similar results: reduced HbA1c with combination treatment (weighted mean difference [WMD] -0.47%; 95% CI: -0.59% to -0.35%), more patients at HbA1c target (RR 1.65; 95% CI: 1.44-1.88), similar hypoglycemic events (RR 1.14; 95% CI: 0.93-1.39), and weight reduction (WMD -2.5 kg; 95% CI: -3.3 to -1.7, result limited by significant heterogeneity).[200]

Many other trials using older diabetes medications have shown improved reductions in HbA1c levels with combination therapy. For example, in the **DUAL V** trial, patients with HbA1c 7-10% on glargine and metformin were randomly assigned to either increased glargine dose or combination degludec/liraglutide. HbA1c reduction was greater with degludec/liraglutide group (−1.81% vs −1.13% for the glargine group, P<0.001 for superiority), and there was also more weight loss and less hypoglycemia with the combination drug.[201] In another study, the **DUAL VII** Trial randomly assigned patients with HbA1c 7-10% on basal insulin to degludec/liraglutide versus glargine and prandial aspart. They found HbA1c reductions were similar and there was a 60% lower risk of hypoglycemia in the degludec/liraglutide group.[202] It should be noted that in these trials, the average HbA1c was ~8.0-8.5%, and patients were not experiencing symptoms of hyperglycemia.

When placing patients on combination therapy, remember that the side effect profiles will mirror that of both drugs individually. For example, evidence suggests that insulin-thiazolidinedione combinations effectively reduce glucose,[203] but fluid retention and other safety concerns about the thiazolidinediones make other options, such as a GLP-1RA, a better first-line combination choice, particularly in patients at risk for heart failure.[204] When combining insulin with a GLP-1RA, insulin dose reductions vary with HbA1c levels and patient factors, as summarized in Table 13.

Table 13: Insulin titration when starting a GLP-1RA[197,205]

HbA1c level & patient factors		% basal dose reduction	% bolus dose reduction
< 7%		20%	50%
7.1-8.0%		10-20%	25%
> 8.0%	**WITH** glycemic variability, hypoglycemia unawareness, or severe hypoglycemic events	10%	25%
	WITHOUT glycemic variability, hypoglycemia unawareness, or severe hypoglycemic events	No adjustment	10-20%

BOTTOM LINE: Combining insulin with other glucose-lowering agents can improve glucose control and enhance weight loss to a greater extent than therapy with insulin alone. Insulin combined with GLP-1RAs offer the greatest synergy for clinical effect and a relatively low risk of adverse events.

Maintaining overall health

Patients with diabetes have high rates of hypertension, hyperlipidemia, liver disease, cardiovascular disease and many other comorbidities. Optimal management should include close attention to these related medical conditions and aggressive therapy where appropriate using multifactorial interventions.

For example, the **Steno-2 study** examined the effects of multifactorial interventions on microvascular and macrovascular complications and mortality in middle-aged adults recently diagnosed with type 2 diabetes.[206] The trial randomly assigned 160 patients with type 2 diabetes and microalbuminuria to conventional treatment or to intensive target-driven therapy involving a combination of medications and focused behavior modification. Targets for intensive therapy included HbA1c ≤6.5%, fasting total cholesterol ≤175, triglycerides ≤150, systolic BP ≤130, and diastolic BP ≤85. All patients received ACEI/ARB and aspirin in addition to a range of antihyperglycemic agents to treat their diabetes. The multicomponent intervention was associated with reductions in mortality (HR 0.55; 95% CI: 0.36-0.83), CV mortality (HR 0.38; 95% CI: 0.19-0.75), and microvascular complications such as retinopathy progression (HR 0.67; 95% CI: 0.51-0.89) and progression to diabetic nephropathy (HR 0.52; 95% CI: 0.32-0.84) over a median follow-up of 21.2 years.

Interestingly, the achieved HbA1c in the intensive-treatment group was 7.9%, much higher than the achieved HbA1c levels of the intensive groups in **ACCORD** (6.4%), **ADVANCE** (6.5%), and **VADT** (6.9%) These trials focused primarily on lowering glucose levels, and found no benefit, or even harms, from such aggressive glycemic control.

Diet and exercise

Much of the steady increase in diabetes prevalence stems from increasing rates of obesity. As described earlier, good evidence suggests that weight loss of 3%-10% can reduce insulin resistance and the risk of developing diabetes.[27,29] Once a patient has been diagnosed with the disease, weight management programs for patients with type 2 diabetes and obesity or overweight are associated with improved health-related quality of life and physical fitness, and reduced diabetes symptoms.[207] Moreover, aggressive weight management also benefits other conditions associated with diabetes, such as hypertension and dyslipidemia.[208,209]

The most rigorous exploration of how lifestyle modification can impact diabetes outcomes is the **Action for Health in Diabetes (Look AHEAD)** study. This long-term (2001-2012) clinical trial examined the effects of intensive lifestyle intervention compared with diabetes support and education on cardiovascular outcomes in 5,145 adults with type 2 diabetes and overweight (most patients used glucose-lowering drugs).[210] Look AHEAD found that intensive lifestyle intervention can produce sustained weight loss and improvements in fitness, glycemic control, and some cardiovascular risk factors, although no differences in cardiovascular event rates were observed after a median follow-up of 4 years.[210] However, compared to the usual care arm, those in the intensive lifestyle intervention arm who successfully lost at least 10% of their body weight did experience reduced cardiovascular events.[211] Moreover, follow-up studies using the Look AHEAD cohort have shown numerous benefits for individuals who lost weight; for example, there were improvements in urinary incontinence, sleep apnea, and depression.[212-214]

Working with patients on a structured program to reduce caloric intake can help promote weight reduction, although sustained weight loss remains challenging for many patients.[27] Evidence does not support the superiority of any particular diet type or mix of macronutrients (e.g., carbohydrate restriction or diets based on glycemic index/load).[24] As such, when a specific diet is requested, given that diabetes is a risk factor for cardiovascular disease, it may be appropriate to recommend one with known benefits for reducing cardiovascular risk factors (such as with the DASH diet[25] or Mediterranean diet[26]).

Structured exercise programs can also improve blood sugar control even if patients do not lose weight in the process.[215,216] Current guidelines recommend at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days per week with no more than two consecutive days without exercise, if possible and clinically appropriate.[217] A 2011 study found that structured exercise training consisting of aerobic exercise, resistance training, or both, lasting more than 150 minutes per week, leads to greater HbA1c reductions than less demanding regimens.[218] A 2012 meta-analysis of five observational studies of high vs. low total physical activity in patients with diabetes found a 40% reduction in all-cause mortality in patients with high physical activity (HR 0.60; 95% CI: 0.49-0.73), but residual confounding may exist.[219] Even moderate levels of exercise, however, can be beneficial.[215]

Combined aerobic-resistance exercise programs are the most effective for supporting blood sugar control.[11,215,220] Before undertaking exercise more intense than brisk walking, sedentary people should be evaluated by a clinician. Electrocardiogram exercise stress testing for asymptomatic patients at low risk of coronary artery disease is not recommended, especially in patients starting low to moderate intensity regimens or who are at low cardiovascular risk. In higher-risk patients or those who are proposing high-intensity exercise regimens, careful screening for symptoms, including atypical anginal equivalents, should be conducted at a healthcare visit. In select high risk patients, especially those going from sedentary to high-intensity exercise, professional societies have suggested stress testing prior to regimen initiation, with weak evidence to support the recommendation.[118,221] The 10-year CV risk for any given patient can be determined using an ACC/AHA risk calculator. A link to the tool is available at

AlosaHealth.org/Diabetes. Patients prone to hypoglycemia or who have developed symptoms of retinopathy or neuropathy will require extra caution in devising an appropriate exercise regimen.

BOTTOM LINE: In addition to slowing the progression from prediabetes to diabetes, lifestyle modifications can also improve glycemic control and have many other health benefits in patients with diabetes. Programs combining diet and exercise are especially effective. While sustained success with these approaches alone can be difficult, they remain an important component of a multimodal approach to treating diabetes.

Controlling hypertension

ADA-recommended blood pressure (BP) targets for many people with diabetes are <130 mmHg systolic (SBP) and <80 mmHg diastolic (DBP), targets that are also endorsed by the American Heart Association.[118,222] Blood pressure should be checked at every visit, with two or more measurements (or an average of two or more readings) of SBP ≥130 mm Hg or DBP ≥ 90 mg suggesting clinical intervention.

All patients with a blood pressure >120/80 mm Hg should be advised about lifestyle modifications that can help reduce blood pressure, including weight reduction, salt restriction, a DASH diet, quitting smoking, and exercise.[223] Many of these interventions may also improve glycemic control. Patients with blood pressure >130/80 mm Hg should (in addition to lifestyle therapy) have prompt initiation and titration of drug therapy to achieve blood pressure targets.

Patients with diabetes and hypertension should be started on an angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), thiazide diuretic, or calcium channel blocker (CCB), all of which have been shown to help reduce cardiovascular risk in patients with diabetes.[224] ACEI- or ARB-based treatments can also slow the progression of nephropathy and reduce albuminuria.[224] About 10% of patients may have side effects when treated with ACEI (most often cough), and these patients can be switched to an ARB, or, because ACEIs and ARBs are equally effective for reducing blood pressure, patients can simply be started on an ARB.[225,226] Many patients with diabetes will require treatment with multiple drugs to achieve target blood pressures, especially if initial BP is > 140/90 mm Hg. For patients who need a second drug in addition to an ACEI or ARB, a CCB could be considered.[227] If ACEIs, ARBs, or diuretics are used, monitor eGFR and serum potassium levels 7–14 days after initiation or after a dose change and then at least annually.

The central importance of blood pressure control for reducing morbidity and mortality in patients with diabetes was demonstrated in the UKPDS 10-year follow-up study.[228] As with glycemic control, the differences in blood pressure initially achieved between the two study groups (tight control vs. less tight control) disappeared within 2 years of trial termination. While patients with tight glycemic control had persistent improvements in clinical status, patients randomly assigned to tight blood pressure control did not sustain in the post-trial follow-up the risk reductions found during the trial for diabetes-related endpoints, diabetes-related death, microvascular disease, and stroke.

These findings suggest that good control of hypertension must be continued if its benefits are to be fully realized and that, in general, BP targets even lower than those recommended in guidelines may be beneficial. By contrast, more lenient blood pressure control was not associated with reduced CV events in the ACCORD trial.

For example, the 2025 **BPROAD** trial randomly assigned 12,821 patients with type 2 diabetes in China to intensive treatment targeting SBP <120 mm Hg or standard treatment targeting an SBP <140 mm Hg.[229] The primary outcome was a composite of nonfatal stroke, nonfatal myocardial infarction, treatment or hospitalization for heart failure, or death from cardiovascular causes. After a median follow-up of 4.2 years primary outcome events occurred in 393 patients in the intensive-treatment group and 492 patients in the standard-treatment group (HR 0.79; 95% CI: 0.69-0.90). The treatment groups did not differ significantly in the incidence of serious adverse events, but symptomatic hypotension and hyperkalemia occurred more frequently in the intensive-treatment group.

These results have caused a reassessment of BP goals that had been based on older studies such as the **ACCORD-BP** trial, which also compared intensive vs. standard BP control (<120 mmHg vs. <140 mm Hg systolic) in patients with diabetes at high risk for CV events.[230] After a mean follow up of 4.7 years, patients assigned to intensive BP reduction did not have a significant benefit in the composite CV events outcome (1.9% in the intensive group versus 2.1% in the usual care group; P=0.2) or all-cause mortality (1.3% vs. 1.2%; P=0.55). Serious adverse events, such as hypotension, hyperkalemia, and bradycardia, were more common (3.3% vs. 1.3%; p<0.001).

In light of current evidence, antihypertensive medications should be adjusted aggressively in patients with diabetes to maintain blood pressure at or below target levels. Clinicians should be aware of “clinical inertia,” the reluctance of both patients and prescribers to add new medications, even when the potential benefits are large.[231]

Some patients with diabetes and hypertension require special consideration. Pregnant women should have hypertension aggressively controlled to <140/90 mm Hg, but ACEIs and ARBs are contraindicated. Patients with very elevated blood pressure or with poorly-controlled blood pressure despite multiple medications may require specialist consultation. Older patients may need somewhat slower adjustment of antihypertensive medications.

BOTTOM LINE: Treat blood pressure >130/80 mm Hg in most patients with diabetes. Prescribe a thiazide diuretic, ACEI, ARB or CCB to lower blood pressure, using an ACEI or ARB if albuminuria is present. Multiple agents may be needed.

Hyperlipidemia

All patients with diabetes should have their cholesterol checked upon diagnosis, and then annually thereafter or more frequently if indicated.[118] Lifestyle interventions including diet modification and exercise are warranted for all patients with CV risk factors or CV disease. Treatment with statins for patients with diabetes is based on presence of existing or previous cardiovascular disease (i.e., primary vs. secondary prevention), age, and risk factors.

Primary prevention

Table 14: Recommendations for primary prevention with statin in patients with type 2 diabetes

Age	Qualifier	Recommended statin intensity*
20-39 years	With ASCVD risk factors	Moderate
40-75 years	No ASCVD risk factors With ASCVD risk factors	Moderate High
>75 years	Already on statin Not on statin	Continue statin Moderate (after discussion of risks/benefits)

* Lifestyle interventions should be continued with statin therapy
ASCVD= Atherosclerotic cardiovascular disease

Statin intensity is defined both by the drug and dose (Table 15). With multiple statins now available generically, most patients can use an affordable, generic statin that will lower their LDL to target levels.[232] Patients with diabetes and ASCVD and LDL ≥70 mg/dL may also benefit from the addition of ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to a statin.[233]

Table 15: Classification of high- and moderate-intensity statin therapy[118]

High-intensity statin therapy	Moderate-intensity statin therapy
Lowers LDL cholesterol by ≥50%	Lowers LDL cholesterol by 30% to 50%
atorvastatin 40-80 mg rosuvastatin 20-40mg	atorvastatin 10-20 mg rosuvastatin 5-10 mg simvastatin 20-40 mg pravastatin 40-80 mg lovastatin 40 mg fluvastatin XL 80 mg pitavastatin 2-4 mg

Note that statins are associated with a small increased risk of developing incident diabetes. A 2010 meta-analysis (13 trials, 91,140 patients) found that statin therapy was associated with a 9% increased risk for the development of diabetes (OR 1.09; 95% CI: 1.02-1.17), with the risk highest in trials with older participants. Treatment of 255 (95% CI: 150-852) patients with statins for 4 years was estimated to result in one extra case of diabetes, so the risk is low both in absolute terms and when compared with the reduction in coronary events.[234] The well-demonstrated benefit of statins in preventing cardiovascular events is more clinically important than the small increase in risk of inducing or exacerbating diabetes.

Secondary prevention

For people of all ages with diabetes and existing ASCVD, high-intensity statin therapy should be added to lifestyle therapy to obtain an LDL cholesterol reduction of ≥50% from baseline with an LDL cholesterol goal of <55 mg/dL for those with established ASCVD and <70 for those at high risk of ASCVD.[118] Add ezetimibe or a PCSK9 inhibitor if these goals are not achieved on the maximum tolerated dose.

BOTTOM LINE: Patients with cardiovascular risk factors or cardiovascular disease should be prescribed a statin, regardless of age. Patients with diabetes over age 75 should continue a statin if they are already on one or consider a statin if they are not.

Antiplatelet medication

Primary prevention

Antiplatelet treatment, specifically with aspirin, was once recommended for most adults with diabetes.[235] Now aspirin for primary prevention (i.e., in patients without CVD) is uncertain. Diabetes has often been considered to be a coronary heart disease "risk equivalent" (i.e., people with diabetes without prior myocardial infarction are seen as having the same risk of fatal or non-fatal MI as non-diabetic patients with a previous MI), yet data have not supported this risk equivalency.[236]

The 2018 **ASCEND trial** randomly assigned 15,480 people (mean age 63 years) with diabetes but no CVD to aspirin 100 mg/day vs. placebo with mean follow-up 7.4 years.[237] No significant differences were found in rates of nonfatal MI, nonfatal ischemic stroke, transient ischemic attack, or any arterial revascularization. The rate of any serious vascular events was lower in the aspirin group (RR 0.88; 95% CI: 0.79-0.97). Rates of serious gastrointestinal bleeding, however, were significantly higher in the aspirin group (RR 1.36; 95% CI: 1.05-1.75), as was the rate of "other major bleeding" (RR 1.7; 95% CI: 1.18-2.44). In subgroup analyses by age, the evidence for CV benefit with aspirin was less robust for patients >60 years, while the evidence for major bleeding was clearly significant. Similar results were also found in the **ASPREE** trial in 19,114 older adults without CVD or diabetes. Low-dose (i.e., 100 mg) aspirin resulted in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of CVD compared to placebo.[238]

In light of the evidence, the ADA and the U.S. Preventive Services Task Force (USPSTF) have tepid recommendations for the use of aspirin for primary prevention. The ADA suggests that low-dose aspirin may be considered for primary prevention in those with diabetes who are at increased risk of cardiovascular disease, between the ages of 50 and 70, and not at increased risk of bleeding.[118] The USPSTF suggests low-dose aspirin may be considered for primary prevention in those with an increased risk of cardiovascular disease, who are between the ages of 40 and 59, and who do not have any increased risk of bleeding.[239] But for adults age 70 and older, the bleeding risk from aspirin may outweigh the benefit, as demonstrated by the data from **ASCEND** and **ASPREE**.

Secondary prevention

Randomly assigned controlled trials have indicated that aspirin can reduce the incidence of myocardial infarction in patients with existing cardiac disease. Virtually all patients with diabetes and known coronary artery disease should be treated with aspirin unless there is a compelling contraindication. For patients who cannot tolerate aspirin, clopidogrel (Plavix) may be an alternative antiplatelet agent.[240] Clopidogrel is also commonly used in patients with recent acute coronary syndromes, coronary stent insertions, or peripheral vascular disease.[241]

BOTTOM LINE: The benefit of aspirin for the primary prevention of cardiovascular events in patients with diabetes is unclear. An individual clinical decision must be made weighing the degree of cardiovascular risk and the risk of bleeding. For adults > 70, the risks may outweigh the

benefits. However, patients with diabetes and established coronary artery disease should generally be treated with low-dose aspirin unless contraindicated.

Smoking

All patients with diabetes should be strongly encouraged not to smoke because smoking significantly increases the risks for CVD, stroke, and death—risks already raised by diabetes itself. A study in smokers with newly-diagnosed type 2 diabetes found that at 1-year follow-up, smoking cessation was associated with amelioration of metabolic parameters as well as reduced blood pressure and albuminuria.[242] Although tobacco smoking is one of the hardest habits to break, several effective interventions are available. These include nicotine replacement therapy (e.g., patches or gum), bupropion (Zyban, Wellbutrin SR), varenicline (Chantix), and counseling programs. The addition of pharmacological therapy to counseling may be more effective than either therapy alone.[243]

The importance of screenings

Because patients with diabetes are at higher risk for a wide range of diseases, screening tests play an important role in health maintenance. The table below summarizes current screening recommendations for some common conditions.

Table 16: Screening tests for diseases associated with diabetes

Complication	Recommended screening
Cardiovascular diseases	• Continuously assess blood pressure and increase medications to achieve and maintain goals • Peripheral arterial disease: — Use ankle-brachial index testing for peripheral artery disease
Hyperlipidemia	• Annual lipid panel
Renal disease	• Annual screening of: — Urinary albumin to creatinine ratio — Estimated glomerular filtration rate (eGFR)
Retinopathy	• Typically annual screening with a dilated eye exam or retinal photography
Liver disease (MASLD/MASH)	• Screen all patients with the FIB-4, regardless of liver enzymes • A cutoff of ≥ 2.0 may be a better threshold for referral for ultrasound elastography or an enhanced liver fibrosis test in older adults
Peripheral neuropathy	• Comprehensive foot exam annually, which may include monofilament testing. • Encourage patients to conduct daily foot exams
Bone health	• Assess fracture risk using a tool like FRAX, although this may underestimate true risk in patients with diabetes • Recommend DEXA in women age 65 and older or if younger with 2-3 additional risk factors • Advise patients to consume 1000 mg calcium daily, ideally from dietary sources • Use bone-directed medications (e.g., alendronate) when indicated.
Vaccination	• Get recommended vaccinations — Influenza, COVID-19, pneumococcal, RSV, zoster, Tdap, and Hep B
Smoking	• Ask about tobacco use and recommend nicotine replacement, bupropion, varenicline, or counseling programs as appropriate
Mental health	• Screen for depression and anxiety • Assess for cognitive changes throughout the lifespan, especially in patients who have severe hypoglycemia.
Sleep health	• Ask patients about sleep quality • Counsel patients on healthy sleep behaviors • Refer patients who require assessment for sleep disorders
Oral health	• American Dental Association recommends at least once or twice yearly visits for patients, more if needed[244]
Cognitive function	• Use tests such as the Mini-Mental State Examination, Mini-Cog, or Montreal Cognitive Assessment for early detection of mild cognitive impairment or dementia in adults ≥65 years

Bariatric surgery

Bariatric surgery for patients with morbid obesity can often result in remission of type 2 diabetes. Termed “metabolic surgery” in some guidelines, it should be considered as an option to treat type 2 diabetes in

surgical candidates with a BMI ≥30.0 kg/m^2 (≥27.5 kg/m^2 in Asian Americans) who do not achieve improvements in weight and diabetes control with nonsurgical methods.[217]

Multiple trials have proven the safety and efficacy of bariatric surgery for improving type 2 diabetes control or even achieving diabetes remission. For example, a 2012 trial randomly assigned 60 patients between the ages of 30 and 60 years with BMI ≥35, a history of at least 5 years of type 2 diabetes, and HbA1c ≥7.0% to receive conventional medical therapy or undergo either gastric bypass or biliopancreatic diversion.[245] At two years, diabetes remission had occurred in no patients in the medical-therapy group, 75% in the gastric-bypass group, and 95% in the biliopancreatic-diversion group (p<0.001 for both comparisons).[245] At two years, the average baseline HbA1c of 8.7% had decreased in all groups, but patients in the two surgical groups had the greatest degree of improvement (mean HbA1c 7.7% in the medical-therapy group, 6.4% in the gastric-bypass group, and 5.0% in the biliopancreatic-diversion group).

The **STAMPEDE** trial, compared the efficacy of intensive medical therapy alone versus medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy in 150 patients with obesity and uncontrolled type 2 diabetes.[246] Baseline mean HbA1c was 9.2%. After 12 months, glycemic control significantly improved in all three groups, although with better control in the two surgery arms: mean HbA1c was 7.5% in the medical-therapy group; 6.4% in the gastric-bypass group (p<0.001); and 6.6% in the sleeve-gastrectomy group (P=0.003). These results were reassessed 5 years after the trial and continued to show benefit for the surgery groups: patients who underwent surgical procedures had nearly 2% larger decreases from their baseline HbA1c than did those randomly assigned to medicine therapy alone (2.1% vs 0.3%, p<0.001).[247] The durability of these effects has been seen outside of trial scenarios as well, with multiple studies showing HbA1c lowering effects lasting for >5 years.[248,249]

As such, bariatric surgery can be a useful therapeutic alternative for adults with type 2 diabetes, especially when the diabetes or its associated comorbidities are difficult to control with lifestyle interventions and medication.

Supporting treatment goals for older adults

As noted previously, older adults with diabetes have higher rates of comorbid conditions such as functional disability, muscle loss, mobility impairment, frailty, and coexisting illnesses. These patients may also require greater caregiver support and are at greater risk for cognitive impairment, depression, urinary incontinence, falls, and polypharmacy.

Given the complexity and breadth of health concerns among older adults with diabetes, a holistic team approach to care can be useful for some patients. This may include the participation of such professionals as dieticians, diabetes educators, social workers, physical therapists, home health care workers, and a host of medical specialists such as podiatrists, endocrinologists, and cardiologists. Primary care clinicians do help coordinate such care teams when they are needed, but their most common role remains to perform the monitoring summarized above and managing medications to achieve the personal goals created for each patient.

Clinicians can encourage healthy lifestyle habits at each visit, such as supporting weight loss if appropriate and recommending a diet rich in whole grains, nuts, fruits, and vegetables instead of processed foods. Exercise can be promoted at whatever level is achievable by the patient, with a minimum goal of 150 minutes of moderate intensity activity every week. Combining aerobic activity with

some form of resistance training has been shown to be more effective than resistance or aerobic exercise alone.[220]

Another core part of overall diabetes care is attending to patients' psychosocial needs, including family issues, behavioral and emotional factors, and social determinants of health such as socioeconomic status.[250] Diabetes poses complex challenges for people with diabetes and their families or caregivers. These challenges can result in clinically significant behavioral or mental health problems. These, in turn, are associated with reduced short-term (i.e., <6 months) glycemic stability and increased mortality risk.[250]

Clinicians should routinely monitor and screen for psychosocial concerns and, when appropriate, refer to appropriate associated health care professionals. Brief, person-centered psychosocial interventions can be integrated into routine diabetes care by creating an emotionally safe and supportive environment for disclosure of sensitive information. Validating an individual's experiences, asking open-ended questions, and employing empathetic listening can foster trust and increase engagement with diabetes treatment decisions.

Older adults are also at especially high risk for hypoglycemia, which should be considered in selecting their regimens.[251] The ADA recommends that all individuals taking insulin or who are at risk for hypoglycemia should receive structured education for hypoglycemia prevention and treatment, with ongoing education for those who experience hypoglycemic events.[43] One common point of emphasis is the "rule of 15", which is to suggest to patients with hypoglycemia that they consume 15 grams of fast-acting carbohydrates (that include high-sugar low-fat options like glucose tablets, juice, or candy), waiting 15 minutes, then recheck blood sugar anytime readings are <70 mg/dL.[252]

Another point of emphasis is ensuring older adults using insulin have glucagon prescriptions (specifically premixed or nasal forms that are ready to use in emergencies). Patients who experience one or more episodes of level 2 or 3 hypoglycemia should have their treatment plan re-evaluated, which may include deintensifying or switching diabetes medications if appropriate (see Table 13 on page 46).

In patients using insulin, who are by definition at high risk of hypoglycemia, CGMs are recommended. If available and affordable, CGMs can allow tailoring of treatment for older adults with diabetes and a reduced risk of hypoglycemia episodes even when they are not on insulin.[253] CGMs were also associated with reduced HbA1c levels (0.33%) over 12 weeks in one meta-analysis of 14 RCTs, regardless of use of insulin.[254]

Putting it all together

- Diet and exercise interventions can have a major impact on glucose control, can slow the progression of prediabetes to diabetes, and can improve other CV risk factors in patients with established diabetes.
- Target a HbA1c of 7% for most patients with diabetes. Modify the goal (e.g., <8%) for older patients because the benefit of tight glycemic control in this population is generally diminished and risks are greater.
- Choice of initial and step-up therapy should be driven by patient comorbidities.
- Use a GLP-1RA, GIP/GLP-1RA, or an SGLT-2i as first-line treatment for patients with established or high risk of CVD, CKD, heart failure, or overweight/obesity. Consider metformin as first-line for patients without these risk factors.
- Focus on adherence before titrating doses or adding a new drug.
- Intensifying treatment regimens early with additional oral agents may slow time to treatment failure and should be guided by patient comorbidities and medication side effect profiles.
- Add insulin promptly when oral agents are not sufficient to achieve HbA1c target or initially if patient has severe hyperglycemia.
- Manage hypertension and hyperlipidemia aggressively and focus on smoking cessation when relevant to help prevent diabetes-related complications.
- Continuously promote the importance of a diet rich in whole grains, fresh fruits, and vegetables, and encourage moderate-intensity exercise.
- Recommend continuous glucose monitors for all patients on insulin therapy and tailor time in range to promote normoglycemia.
- Adjust insulin therapy when adding a GLP-1RA or to reduce treatment burden in older adults.

Appendix 1: Renal adjustments for glucose-lowering agents in type 2 diabetes

Class	Medications	Starting daily dose	Maximum daily dose	Action if eGFR (mL/min)			
				<60 but >45	<45 but >30	<30 but >15	<15 or ESRD
Biguanide	metformin	250 – 500 mg	2,550 mg		Do not start*		
Sulfonylureas	glyburide	2.5 – 5 mg	20 mg 12 mg (micronized)				
	glipizide	5 mg 2.5 mg in elderly	40 mg (IR) 20 mg (XL)	2.5 mg/d, slow titration	2.5 mg/d, slow titration		
	glimepiride	1 – 2 mg	8 mg	1 mg/d, slow titration			
Thiazo-lidinedione	pioglitazone	15 – 20 mg	45 mg				
DPP-4 inhibitors	alogliptin	25 mg	25 mg	12.5 mg/d	12.5 mg/d	6.25 mg/d	6.25 mg/d
	linagliptin	5 mg	5 mg				
	saxagliptin	2.5 – 5 mg	5 mg		2.5 mg/d	2.5 mg/d	2.5 mg/d
	sitagliptin	100 mg	100 mg		50 mg/d	25 mg/d	25 mg/d
SGLT-2 inhibitors	bexagliflozin	20 mg	20 mg				
	canagliflozin	100 mg	300 mg	100 mg/d	100 mg/d	**	**
	dapagliflozin	5 mg	10 mg		#	#	
	empagliflozin	10 mg	25 mg			&	
	ertugliflozin	5 mg	15 mg				
GLP-1 receptor agonists	dulaglutide	0.75 mg wkly	4.5 mg weekly				
	exenatide	10 mcg	20 mcg				
	exenatide XR	2 mcg wkly	2 mg wkly				
	liraglutide	0.6 mg	1.8 mg				Limited data
	lixisenatide	10 mcg	20 mcg				
	semaglutide injection oral	 0.25 mg wkly 3 mg	 2 mg wkly 14 mg				
GIP/GLP-1 RA	tirzepatide	2.5 mg wkly	15 mg wkly				

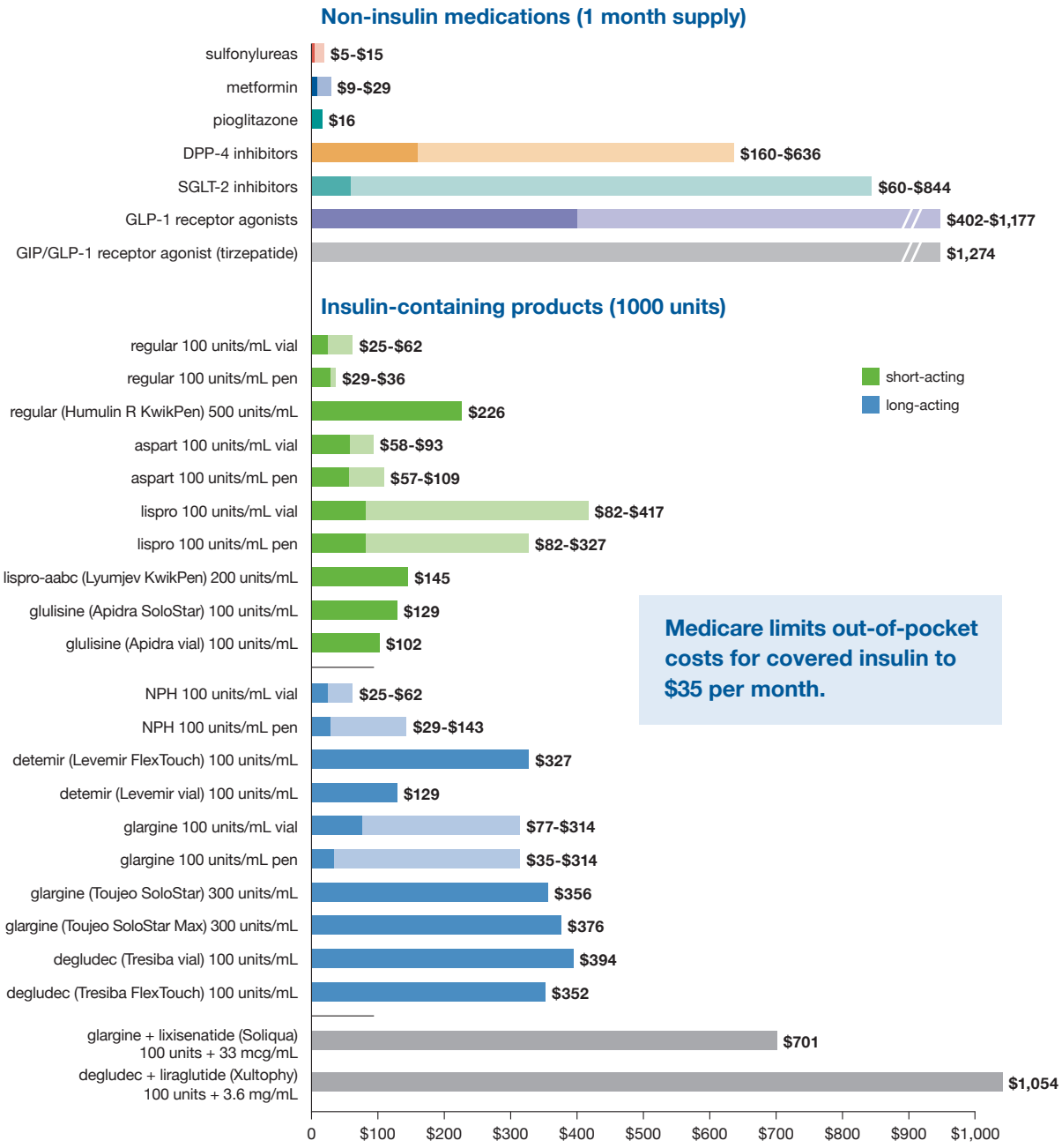
Green = no adjustment needed; yellow = dose reduction, limited data, or use with caution; red = avoid or contraindicated; wkly = weekly

* risk vs. benefit if taking, max dose: 1000mg; ** may continue canagliflozin 100 mg if albuminuria > 300 mg/day; # don't start dapagliflozin for diabetes in patients with eGFR <45, and discontinue it for patients with diabetes without CKD if eGFR < 30. For patients with CKD, do not start if eGFR is < 25; & empagliflozin can be started in patients with eGFR > 20 with CKD and HF, not for glycemic control

Appendix 2: Costs

The various glucose-lowering agents vary widely in cost. Because sulfonylureas, metformin, and pioglitazone have been on the market for many years, generic versions exist, and their monthly cost is low. In contrast, the newer antidiabetic agents are protected by patents and cost significantly more. Insulin products now include biosimilars for insulins lispro and glargine.

Costs of medications



Prices from goodrx.com, October 2025. Listed doses are based on Defined Daily Doses by the World Health Organization, when available, or package inserts; they should not be used for dosing in all patients. All doses shown are generics when available, unless otherwise noted. These prices are a guide; patient costs will be subject to copays, rebates, and other incentives.

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

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