Managing type 2 diabetes:

New guidelines are transforming medication use

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This activity offers CE credit for:

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

All other attendees will receive a Certificate of Attendance.

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Statement of Need

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 target, choice of glucose-lowering medications based on cardiovascular outcome data, and treatment simplification to avoid hypoglycemia.

The educational program has several components, which include:

- Written evidence report (print monograph)
- Summary document of top 4-5 key messages
- "Academic detailing" educational sessions in physicians' offices with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
- Reference cards for easy access to key materials
- Patient education information (brochure/tear-off sheets)

This program works to synthesize the current clinical information on this topic into accessible, non-commercial, evidence-based educational material, which is taught interactively to providers by specially trained clinical educators.

For decades metformin has been the backbone of type 2 diabetes treatment, but recent data suggests starting with other medications, such as a glucagon-like peptide-1 receptor antagonist (GLP-1 RA) or a sodium-glucose co-transporter 2 inhibitor (SGLT-2i), reduces cardiovascular disease while helping patients reach an HbA1c goal. Clinicians need to understand this new recommendation and the evidence supporting it.

Learning Objectives:

Upon completing this activity, participants will be able to:

- Define an HbA1c target: 7% for most patients, modifying the goal (to <8.5%) for many frail older patients.
- Select initial treatment based on relevant comorbidities and HbA1c lowering need.
- Identify patients 1.5% or more above their goal to initiate treatment with two medications, within weeks of diagnosis.
- Revise treatment, adding insulin when other agents are not sufficient to achieve HbA1c goal.
- Plan to continuously promote weight control, exercise, and adherence to medications.

Financial Support

There is no commercial support associated with this educational activity.

Target Audience

The educational program is designed for clinicians practicing internal medicine, primary care, family medicine, and geriatrics, and nurses and other health care professionals who deliver primary care.

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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This activity is designated for 2.25 nursing contact hours.

Note to Nurse Practitioners: Nurse practitioners can apply for *AMA PRA Category 1 Credit™* through the American Academy of Nurse Practitioners (AANP). AANP will accept *AMA PRA Category 1 Credit™* from Jointly Accredited Organizations. Nurse practitioners can also apply for credit through their state boards.

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Faculty:

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Scott J. Hershman, MD, FACEHP, CHCP has nothing to disclose.

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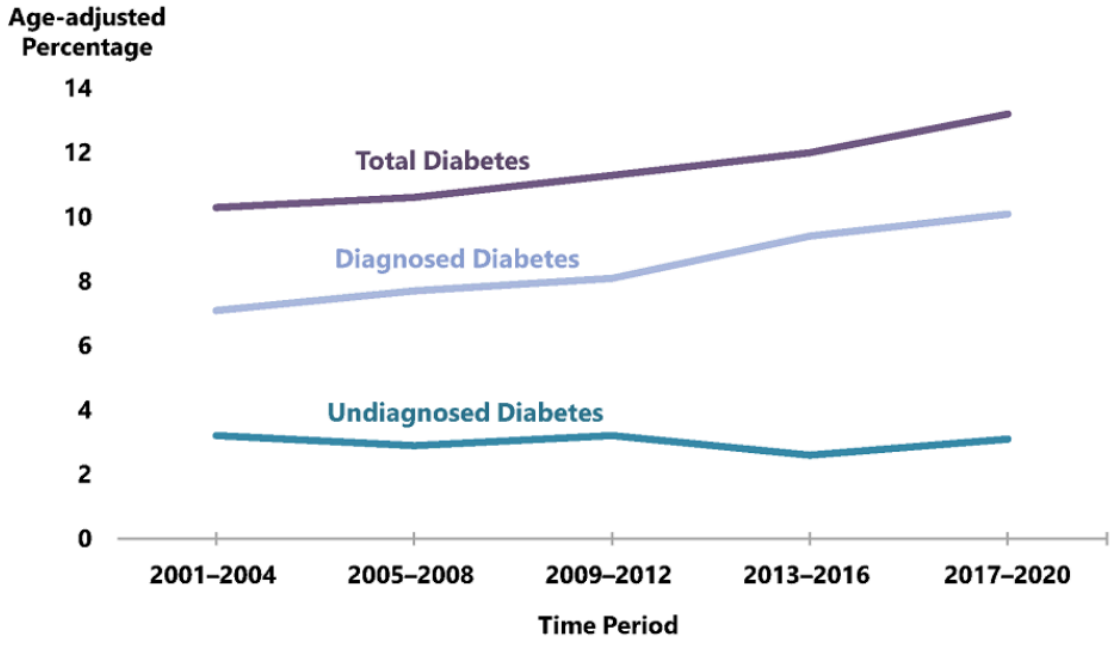
Introduction

Diabetes mellitus, of which 90-95% of cases are type 2 with most of the remaining 5-10% of cases being type 1, is one of the most common chronic conditions in the United. Type 1 and type 2 diabetes combined affect approximately 37.3 million Americans (11.3% of the adult population), and the incidence has risen steadily over the past 20 years.[1] Troublingly, nearly 1 in 4 of these people do not know they have diabetes.[1] The rising incidence is expected to continue for decades with total diabetes prevalence (diagnosed and undiagnosed) projected to increase to 25%-28% of the U.S. adult population by 2050.[2]

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



Notes: Diagnosed diabetes was based on self-report. Undiagnosed diabetes was based on fasting plasma glucose and A1C levels among people self-reporting no diabetes. Time period 2017–2020 covers January 2017 through March 2020 only.

Data source: 2001–March 2020 National Health and Nutrition Examination Surveys.

Diabetes is more common among older adults and among certain racial and ethnic groups (see Figures 2 and 3, following page).[3] Perhaps more importantly, the complications that arise from diabetes are also unequally distributed. For example, many complications, though not all,[4] are associated with older age and are more prevalent among patients who are Black (most notably progression to end-stage renal disease).[5,6]

Figure 2: Diabetes prevalence (diagnosed and undiagnosed) by age[1]

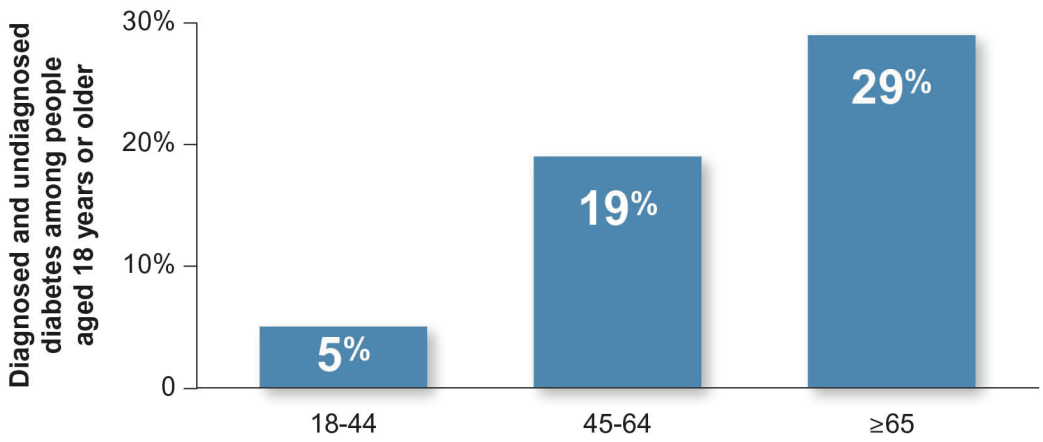
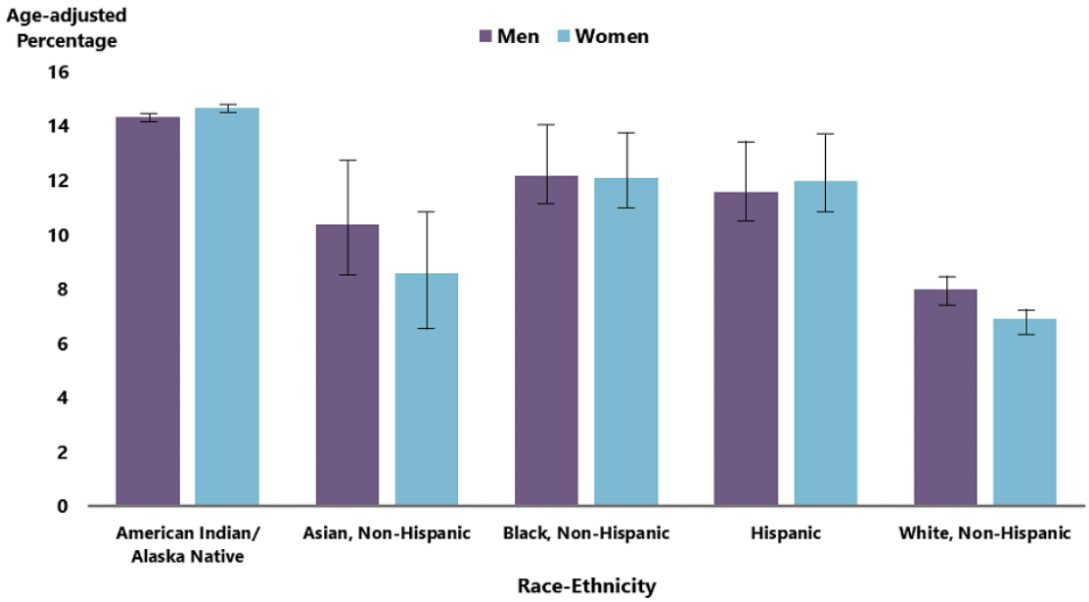


Figure 3: Percentage of U.S. adults aged 18 or older with diagnosed diabetes, by race/ethnicity 2018-2019[1]



Note: Error bars represent upper and lower bounds of the 95% confidence interval.

Data sources: 2018–2019 National Health Interview Survey; 2019 Indian Health Service National Data Warehouse (for American Indian/Alaska Native group only).

Diabetes is associated with a wide range of complications including heart disease, stroke, kidney disease, neuropathy, and retinal damage as well as increased mortality.[3] In 2019, diabetes was the 7th-leading cause of death in the U.S., with about 88,000 death certificates listing diabetes as the underlying cause of death and 282,801 death certificates listing diabetes as a related cause of death.[1]

Despite decades of attention to the problem of diabetes, and despite 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 versus 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 physicians, trying to manage multiple issues in addition to diabetes, may lack the time or resources to take all of the steps required for optimal diabetes care.

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 controlled, 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, 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.

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.[9] 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 on following page).

Table 1: Diagnosing diabetes[9]

Patient presentation	Test and threshold	Notes
Symptomatic: e.g., polyuria, polydipsia, weight loss	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 utilize second test (e.g., HbA1c). Fasting glucose 100-125 mg/dL indicates prediabetes (impaired fasting glucose, or IFG).
	HbA1c ≥6.5%	• HbA1c of 5.7-6.4% indicates prediabetes (need repeat test to confirm).
	Oral glucose tolerance test (OGTT); 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 and no proven clinical benefits over using HbA1c-based diagnostic criteria. • Glucose 140-199 mg/dL indicates prediabetes (impaired glucose tolerance, IGT); repeat test recommended for clinical confirmation.

In 2019, 96 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%,[1] which corresponds to nearly 38% of the U.S. adults over the age of 18. However, only 19% of U.S. adults reported knowing they had prediabetes, which mirrors the patients' inconsistent knowledge of having diabetes.

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.[10] While the American Diabetes Association (ADA) is careful to point out that prediabetes should not be thought of as a unique clinical entity, the prevalence and lack of awareness of prediabetes is specifically worth considering because the condition is associated with increased risk of developing diabetes.[9] However, estimates of how likely somebody with prediabetes is to develop diabetes is still a subject of some debate. For example, one estimate obtained by calculating annualized risk of developing diabetes from a set of 16 cohort studies reported that up to 50% of patients with an HbA1c of 6.0-6.5% would develop diabetes over a period of five years.[11] Other estimates are much lower; for example, the TOPICS 3 cohort study followed 2092 patients with prediabetes for nearly five years and found only 7-9% incidence of developing diabetes.[12] Moreover, in some populations there does not even appear to be 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.[13] 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 does recommend targeted screening for prediabetes and diabetes (Table 2).

Table 2: Who should be screened for prediabetes and diabetes?[9]

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/ 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 be in individuals who have overweight/obesity[14]
** For women with gestational diabetes the recommended screening is every 1-3 years (annually if on insulin in pregnancy or other high-risk characteristic).

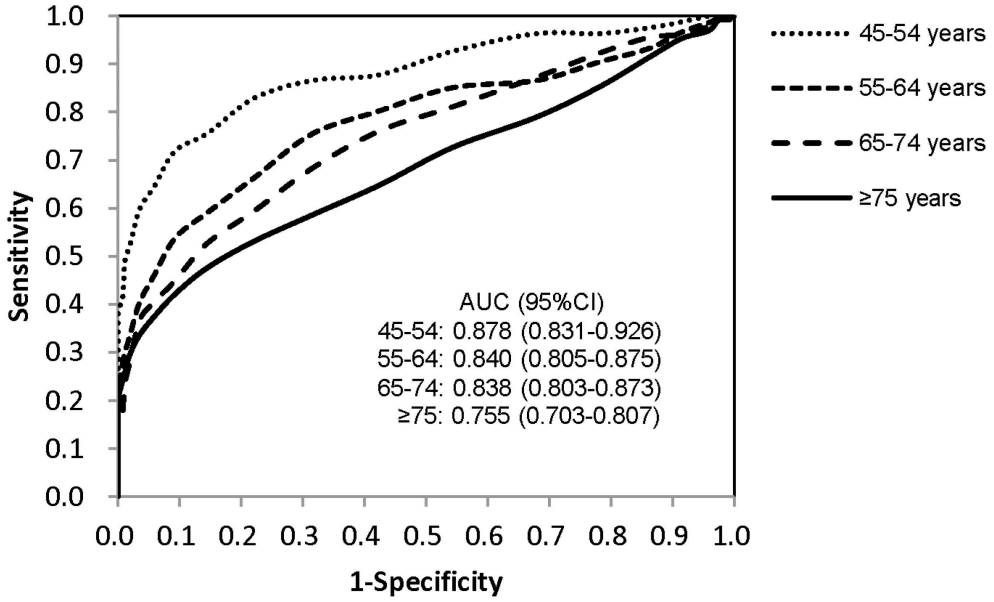
The ADA suggests that fasting plasma glucose (8 hour fast), a 2-hour plasma glucose during a 75-gram oral glucose tolerance test, or an HbA1c are equally appropriate for screening (Table 1). Regardless of which test is chosen, in the absence of symptoms (e.g., polyuria, polydipsia, weight loss) and hyperglycemia ≥200 mg/dL, two different tests from the same sample or two tests on separate samples are required to diagnose diabetes.[9]

While all tests are appropriate, HbA1c is most often used in clinical practice owing largely to its ease of use. Historically, HbA1c had been assessed using various measurement techniques that could yield different results, making the test too unreliable for diagnosis of diabetes. However, in the 1990s an international effort was taken to standardize measurement that has led to the adoption of HbA1c testing, which is logistically easier to complete than are glucose tolerance tests or fasting plasma glucose measurements, for diagnosing diabetes.[15,16]

While laboratory HbA1c assays (but not necessarily point-of-care assays) are now a reliable method for diagnosis diabetes, HbA1c is still the least sensitive of all the testing methods. For example, population cohort studies have found that using HbA1c criteria to diagnose diabetes may result in 70% fewer new diabetes diagnoses compared with using fasting plasma glucose or oral glucose tolerance tests.[17,18] Furthermore, it's important to recognize that the diagnostic accuracy of HbA1c levels may decrease with age.[19] This is because lower levels of red blood cells can lead to higher HbA1c levels, which, in turn, leads to an increased risk of false positive results, as was demonstrated in a study of 3,245 patients from China (Figure 4).[19] Aside from age, HbA1c accuracy may also be affected by other conditions that can change red blood cell density, such as anemia, hemolysis, and recent transfusion of red blood cells.

However, aside from in patients with conditions that make HbA1c inaccurate, there are not recent studies showing that patients who have normal HbA1c but have abnormal plasma fasting glucose or oral glucose tolerance tests are at significant increased risk of complications from diabetes. Furthermore, trials for the most promising anti-diabetes drugs, namely the sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists that have both been shown to reduce cardiovascular events in patients with diabetes, use HbA1c for their inclusion criteria.[20,21] As such, taken in totality, there is strong evidence for using HbA1c to diagnose diabetes and to make pharmacologic management decisions for most patients with diabetes.

Figure 4: Age and diagnostic accuracy of HbA1c levels[19]



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. 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%[22] and the ADA recommending at least 7%-10%.[9] The specific type of diet and balance of macronutrients appears

less important than adherence to whichever diet is chosen.[23] When a specific diet is requested, given 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 Dietary Approaches to Stop Hypertension, DASH, diet)[24] or cardiovascular disease risk itself (such as with the Mediterranean diet).[25] An increase in moderate-intensity physical activity to at least 150 minutes/week is also recommended by the ADA for diabetes prevention.[9]

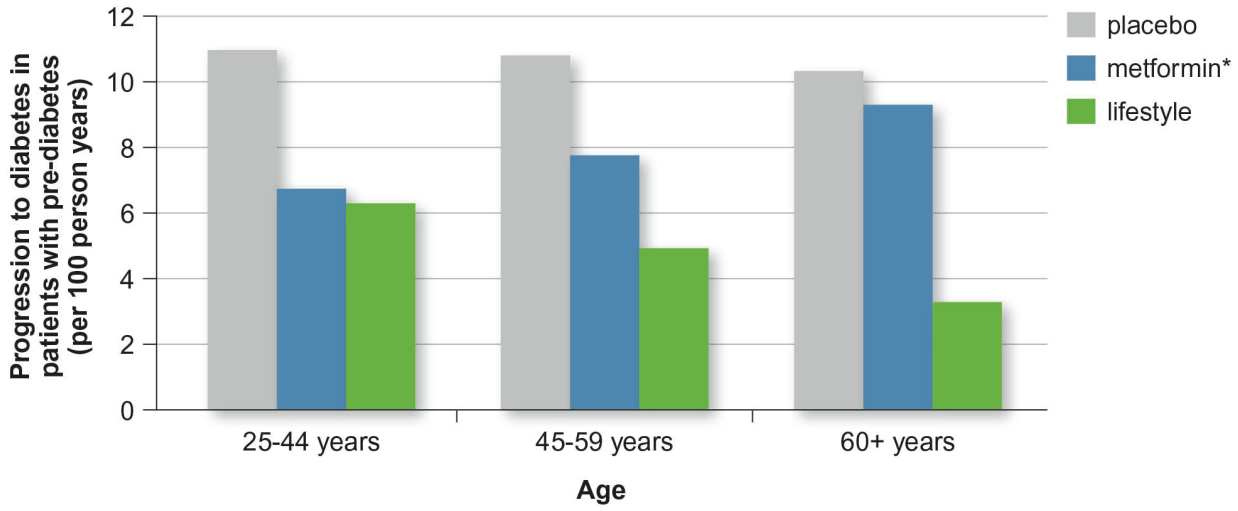
The first large trial of lifestyle modification to prevent diabetes was the **Finnish Diabetes Prevention Study** in which patients with prediabetes and had overweight were randomized to usual care (oral and written education about diabetes at baseline and annually thereafter) or a program of weight loss, reduced dietary saturated fat, and 4 hours of exercise weekly.[26] Over four years, lifestyle modification reduced the incidence of diabetes by 58% (control group: 7.8 cases of diabetes per 100 person-years; lifestyle modification group: 3.2 cases 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%.[27]

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 first 24 weeks and monthly thereafter).[28] As in the Finnish study, the incidence of diabetes over a mean 2.8 years among patients in the intensive lifestyle modification arm 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.[28]

A long-term follow-up of the DPP, the **DPP Outcomes Study (DPPOS)**, showed that the benefits of preventing or delaying diabetes with lifestyle intervention or metformin can persist for at least 10 years.[29] The DPPOS also showed that weight loss associated with metformin therapy is durable for at least 10 years of treatment.[30] Lifestyle changes were more effective in older adults than in younger individuals. (Figure 5).

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.[12] 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. It is questionable whether these small differences in HbA1c translate to meaningful clinical outcomes; for example, preliminary results from the DDPOS presented at the 2020 ADA Annual Meeting specifically suggested 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.[31] Taken in conjunction with previously discussed evidence that older adults have relatively low risk of progressing from prediabetes to diabetes,[13] lifestyle modifications for the specific purpose of reducing the progression of prediabetes to diabetes should be recommended selectively and tailored to individual patients.

Figure 5: Diabetes rates by age group in the Diabetes Prevention Program study[32]



Since 2018, Medicare has provided coverage for CDC-approved services such as the Diabetes Prevention Program. To find a nearby program, see links to CDC resources on the Pennsylvania Department of Aging website, or Medicare-approved programs at **AlosaHealth.org/Diabetes**.

Other pharmacologic treatments that reduce diabetes risk

There are multiple trials 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.[33] 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.[34] A separate study, the **SCALE** trial randomized 2,254 adults with prediabetes to liraglutide 3 mg subcutaneously once daily vs. placebo.[35] 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 ($p < 0.0001$). These 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-1 receptor agonist 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 randomized 1,961 overweight and obese participants to semaglutide or placebo plus lifestyle intervention. 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.[36] Other studies of weight loss drugs that are not used as anti-diabetes medications have also been studied in trials, including Orlistat (XENDOS trial) and phentermine/topiramate (SEQUEL trial).[37,38]

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	22%	29%	31%[28]	GI, usually transient	Twice daily, daily for XR
Acarbose 100 mg	32%	42%	25%[33]	Bloating, flatulence	Three times daily
Pioglitazone 30 mg or 45 mg	5%	17%	72%[34]	Heart failure exacerbation, weight gain	Once daily
Liraglutide 3 mg	6%	2%	79%[35]	GI, gallbladder	Once daily

None of the medications discussed or listed in the table above has an FDA-labeled indication for the prevention or delay of diabetes. The 2022 ADA guidelines suggest combining metformin with lifestyle interventions for patients with prediabetes, especially those with BMI >35 kg/m^2, those <60 years old, or with prior gestational diabetes.[9]

BOTTOM LINE: Intensive lifestyle modification, including weight loss (3%-10% of body weight or more) and increased moderate-intensity exercise (>150 minutes/week) can reduce the development of diabetes by more than 50% in patients with prediabetes. However, it is not known whether this reduction translates to reduced risk of developing complications from diabetes. Although lifestyle modification can be more effective than pharmacotherapy, especially in older adults, metformin and other some 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) and reduce the risk of macrovascular (e.g., cardiac) and microvascular (e.g., ophthalmologic, neurologic, and renal) disease. Recommended targets for fasting plasma glucose are 80-130 mg/dL and <180 mg/dL for post-prandial glucose.[9]

HbA1c levels provide a measure of average blood sugar levels in the preceding 2-3 months (Table 4 on following page). Lowering HbA1c to around 7% has been shown to reduce microvascular complications, and (with early intervention) may also be associated with a reduction in macrovascular disease,[9] although less stringent HbA1c targets are appropriate for selected patients.

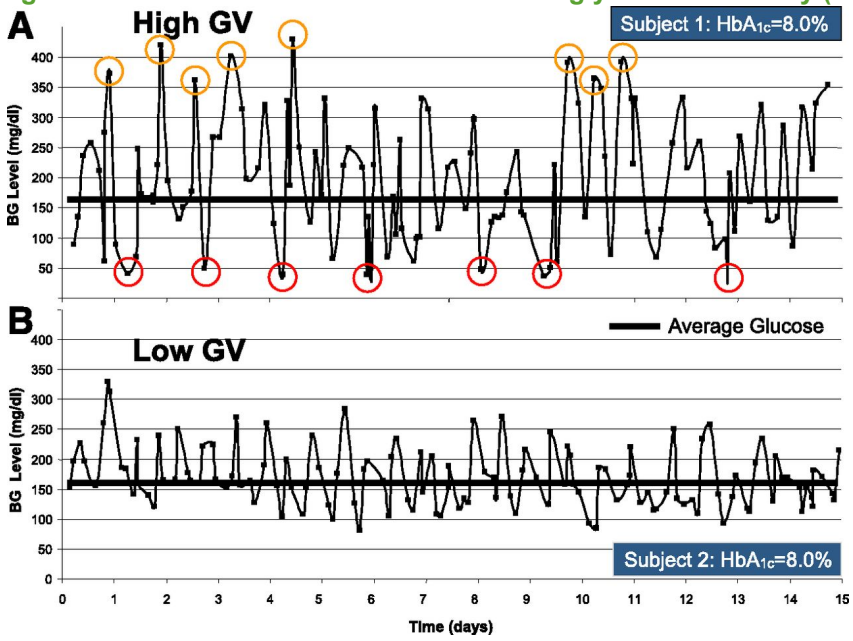
Table 4: Correlation between HbA1c level and plasma glucose levels[9]

	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

As valuable as HbA1c levels can be, clinicians should recognize that HbA1c levels can mask important variations in glycemic variability between patients. As illustrated in Figure 6, 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.[39] For example, 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.[40] 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.[41] While these specific examples come from the type 1 diabetes literature, there is little reason to think it the biologic mechanisms do not extend to patients with type 2 diabetes, and glycemic variability is now frequently posited as an important consideration for all individuals with diabetes.[42]

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.[9] 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.[43] 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.[44]

Figure 6: Identical HbA1c levels but different glycemic variability (GV) in two patients



Concerning appropriate targets for HbA1c more generally, there are several trials that inform the current recommendations for targeting a 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 diabetes were randomized 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 in patients with newly-diagnosed diabetes reduced long-term diabetes-related clinical outcomes 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 off the trial, patients randomized to the sulfonylurea–insulin group still lowered their 10-year risk for all diabetes-related endpoints (9% absolute risk reduction compared to dietary intervention alone, P=0.04), microvascular disease (24% risk reduction, P=0.001), myocardial infarction (15% risk reduction, P=0.01) and death from any cause (13%; P=0.007). In the metformin group, significant risk reductions persisted for any diabetes-related end point (21% absolute risk reduction compared to dietary intervention, P=0.01), myocardial infarction (33% risk reduction, P=0.005), and death from any cause (27% risk reduction, 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 already diagnosed with the disease. These trials showed inconsistent results (Table 5). Overall, neither the **ACCORD** trial,[46] the **ADVANCE** trial,[47] nor **VADT** trial[48] found significant reductions in macrovascular events with more intensive glycemic control compared to less-intensive control, while 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
Duration diabetes (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 an 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 that was 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 exactly why there was increased mortality in ACCORD, though review of the trial protocols can offer some potential insights. Most notably, the medications used in the trials were different; for example, ACCORD patients were on rosiglitazone, which is thought to have cardiac complications, while the plurality of patients in the ADVANCE trial were on metformin, a sulfonylurea, and/or insulin. Though subgroup analyses have not suggested that any single drug class is clearly to blame for the increased risk of mortality in the ACCORD trial, it is likely that differences in medications, along with other differences in the trial populations, can explain some of the differences in the findings across ACCORD, ADVANCE, and VADT.

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 physicians 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. However, there was a trend toward increased risk in CV or all-cause mortality (though not statistically significant), and there was 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-1receptor agonists and SGLT-2 inhibitors. As such, these trials offer only general guidance for the treatment of diabetes. 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?

Recommendations by a number of diabetes-related professional organizations regarding HbA1c targets can be summarized as follows:[9,54]

- Glycemic control (define as <7% for most patients in most guidelines) early in the natural history of diabetes substantially reduces risk of microvascular disease and, in the long term, may reduce the risk of cardiovascular events, stroke, and death in patients with type 2 diabetes.

- Pushing for targets significantly <7%, especially in individuals who have had diabetes for years, is unlikely to offer significant cardiovascular benefits and may be associated with harm (e.g., increased risk of death, hypoglycemia).
- Lower targets may specifically pose higher risk in older patients.
- Patient-specific personalized diabetes strategies are needed.

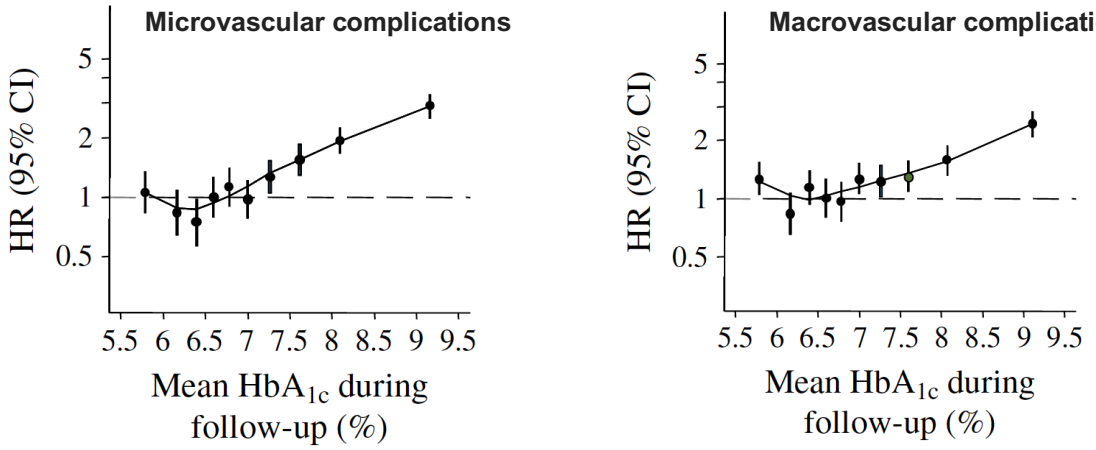
Table 7: Expert recommendations for target HbA1c levels[9,54-58] _ENREF_9

Organization	Year	HbA1c goal*
American Association of Clinical Endocrinologists (AACE) – American College of Endocrinology (ACE)	2020	<6.5%
American Diabetes Association (ADA) – European Association for the Study of Diabetes (EASD)	2018	<7%
ADA Standards of Care	2022	<7%
American College of Physicians (ACP) -- endorsed by American Academy of Family Physicians (AAFP)	2018	7-8%
American Geriatric Society (AGS)	2013	7.5-8%
Endocrine Society: Management of Diabetes in the Older Adult	2019	<7.5 - 8.5%

* All statements have caveats to allow for either more aggressive or more relaxed HbA1c goals based on patient preference and overall health.

The potential benefits of lowering HbA1c aggressively must be weighed against the potential increased risk of hypoglycemic episodes, especially in frail older patients.[59] While data shows that the risk of both microvascular and macrovascular events increases as HbA1c increases above 6.5% (Figure 7),[60] the aforementioned trials suggest that certain populations have disease that may be more readily intervened upon to prevent complications. Patients who may benefit from a more stringent HbA1c goal (e.g., <7%) include those with relatively recent diabetes diagnosis, pregnant women, and patients with a long life expectancy as long as the goal can be achieved without significant hypoglycemia or other adverse effects. On the other hand, less stringent HbA1c goals (e.g., <8.5%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, significant comorbidities, and those with long-standing diabetes who have difficulty achieving a target of <7% despite intensive education and therapy.[9,55]

Figure 7: Risk of microvascular (left) and macrovascular (right) complications by HbA1c level[60]



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. This approach is supported by the ADA[9] as well as the AACE.[54]

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 without hypoglycemia. Higher HbA1c targets may be appropriate in selected patients. For example, <8.5% may be appropriate in the frail elderly or any patients with substantial comorbidities given the many risks associated with targeting lower HbA1c levels.

Patient blood glucose self-monitoring

In addition to periodic office-based HbA1c testing, which all patients with diabetes should undergo, there is some debate about whether patients should monitor their own glucoses as part of diabetes self-management. Some studies have suggested that self-monitoring may impact health behaviors in the short term (<6 months), and these hopes were embodied in older version of guidelines that suggested self-monitoring of glucoses could be a routine part of self-management.[61-63] However, newer data suggests that, for patients with diabetes who do not require insulin therapy, any effect is small and all but disappears after 12 months.[64] As such, newer recommendations from groups such as Choosing Wisely suggest that, aside from patients taking insulin or those actively having medications titrated, most patients do not need to check their blood glucoses regularly.[65]

For patients who are monitoring their glucoses, monitoring can be done after fasting, before meals, or 1-2 hours after meals and should be tailored to patient 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.[9] 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, monitoring once per day or less may be acceptable.[66] 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.[9]

Patients must also be taught how to recognize and treat hypoglycemia (plasma glucose <70 mg/dL). Symptoms can include sweating, anxiety, palpitations, hunger, tremor, irritability, and confusion. Recommended treatments include milk or glucose–containing foods such as fruit juice and non-diet soda. Patients with recurring problematic hypoglycemia can be provided with glucagon for emergency injection at home or at work.

In addition to fasting and post-prandial glucose checks, CGM is another tool available to monitor glucose levels. As previously mentioned, glycemic variability is likely one mechanism by which diabetes can cause complications, and CGM may be able to improve patients' time in therapeutic range. Additionally, by providing real-time feedback on hypoglycemia, action can be taken and regimens revisited more frequently. For patients with type 1 diabetes, CGM has shown consistent ability to reduce hypoglycemia.[67,68] However, the data is less consistently positive in trials of patients with type 2 diabetes.

For example, the **DIAMOND** study group randomized 158 patients on multiple daily insulin injections to continuous glucose monitoring vs usual care and found no difference in severe hypoglycemia.[69] As another example, the **MOBILE** study group randomized 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 randomized to CGM (−0.24% of time; 95% CI: −0.42% to −0.05%, P = 0.02).[70]

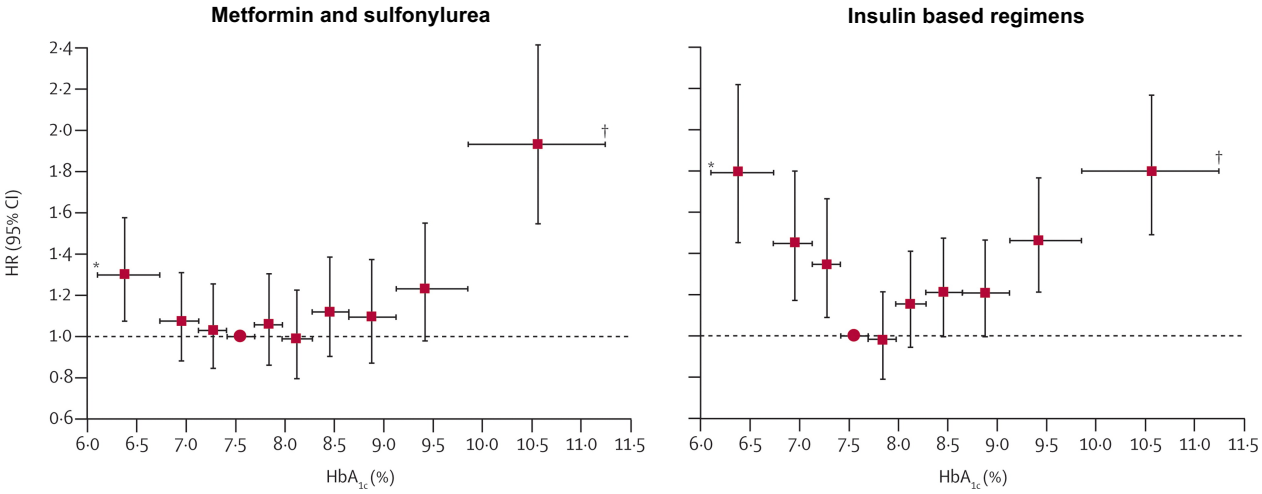
While the reduction in risk of hypoglycemia for patients with type 2 diabetes described by these studies is not overwhelming, both trials showed that HbA1c was lower in the CGM group compared with usual care (-0.3% and -0.4% in the DIAMOND and MOBILE studies, respectively, with both p=0.02). Furthermore, 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 may be more likely to 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.

BOTTOM LINE: While all patients on insulin should check their blood glucoses at home, there is likely limited value in recommending routine home blood glucose checks for most patients not on insulin. CGM should be considered in all patients using daily insulin, especially patients on multiple daily injections.

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.[71] 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.[72]

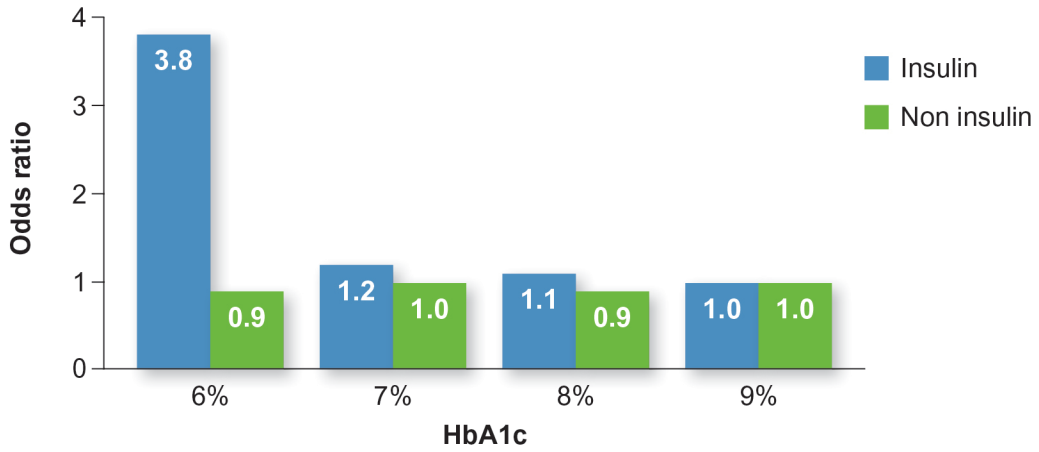
Figure 8: Mortality in adults ≥50 years old is associated with both higher and lower HbA1c levels[72]



Age and duration of diabetes are both independent risk factors for diabetes-related morbidity as well as mortality.[73] This may due to both the complications of the disease itself, but it may also due to complications from treatment of the disease. 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.[74] 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 twofold increased risk of incident dementia (RR 1.77; 95% CI: 1.35-2.33).[75] However, it is important to note that these studies are observational in nature, 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 correlations 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 (Figure 9).[76] These types of data highlight the larger magnitude of the harms older adults experience from both diabetes and the treatments for diabetes (Figure 8).

Figure 9: Association between HbA1c levels and fall risk in older patients[76]



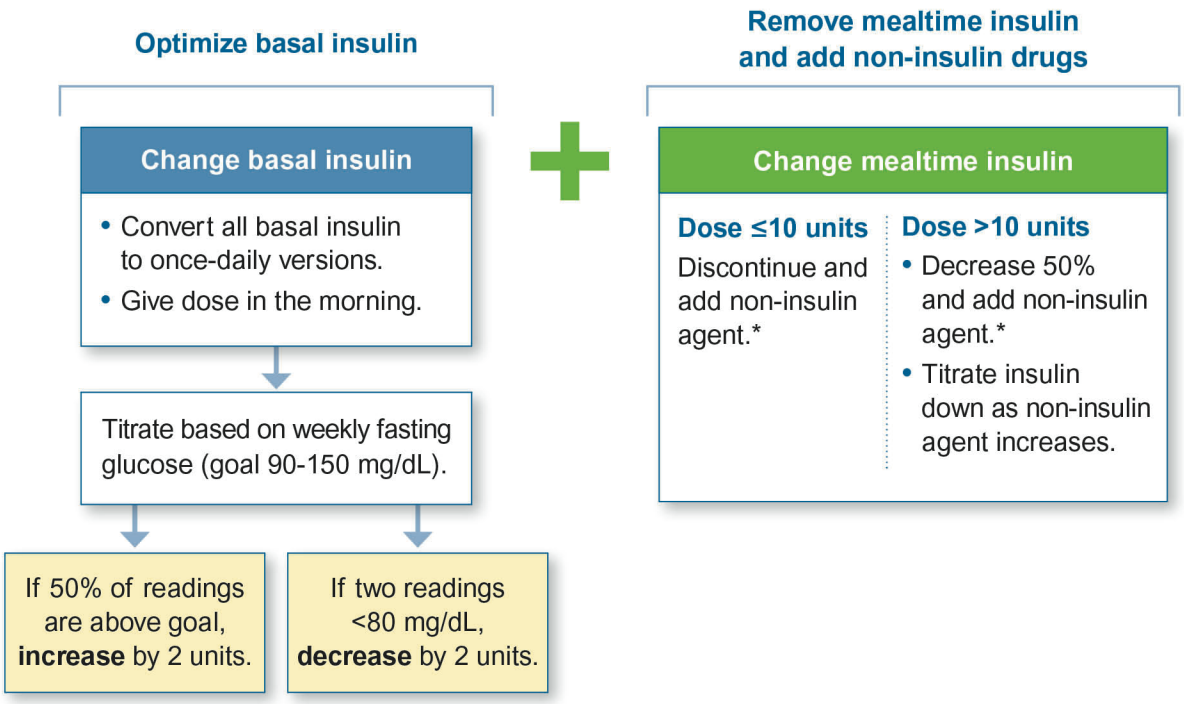
In light of this evidence, HbA1c targets should be individualized using a shared decision-making paradigm and taking into account patient characteristics and the use of other drugs with potential effects on glycemic control (Table 8 on the following page).

Table 8: Considerations for HbA1c targets in older adults[9,77]

	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	90-130	90-150	• 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

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 10 on following page).[78]

Figure 10: Simplified insulin regimen for older adults with type 2 diabetes



* Select non-insulin agents based on the algorithm on page 32, starting with metformin if tolerated and renal function permits.

BOTTOM LINE: Older adults with hypoglycemia have worse outcomes. Furthermore, older adults with lower HbA1c levels, especially those using insulin, have an increased risk of falls. Simplifying insulin regimens and personalizing HbA1c targets in high-risk older people can reduce treatment burden and the risk of hypoglycemia.

Weight management, 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.[26,28] 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.[79] Moreover, aggressive weight management also benefits other conditions associated with diabetes, such as hypertension and dyslipidemia.[80,81]

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).[82] 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.[82] Moreover, follow-up studies utilizing the Look AHEAD cohort have shown numerous benefits for individuals who lost weight; for example, there were improvements in urinary incontinence, sleep apnea, and even depression associated with weight loss.[83-85]

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.[26] 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).[23] As such, when a specific diet is requested, given 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)[24] or cardiovascular disease risk itself (such as with the Mediterranean diet).[25]

Structured exercise programs can also improve blood sugar control even if patients do not lose weight in the process.[86,87] 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.[9] 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.[88] 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 it is hard to be sure that all potential confounders (e.g., chronic illness) were adequately controlled.[89] Even moderate levels of exercise, however, can be beneficial.[86]

Combined aerobic-resistance exercise programs are the most effective for supporting blood sugar control.[9,86,90] Before undertaking exercise more intense than brisk walking, sedentary people should be evaluated by a physician. Electrocardiogram exercise stress testing for asymptomatic patients at low risk of coronary artery disease is not recommended, but may be indicated for higher-risk patients.[91] The 10-year CV risk for any given patient can be determined using an ACC/AHA risk calculator endorsed by the ADA. 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. Unfortunately, sustained success with these approaches is relatively uncommon due to the difficulty in maintaining new habits and the progressive nature of diabetes.

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 9.

Table 9: Non-insulin glucose-lowering agents

Route	Class	Examples (Brand names)
Oral	Biguanide	metformin (Glucophage)
	Sulfonylureas (SUs)	glyburide (Diabeta, Micronase) glipizide (Glucotrol) glimepiride (Amaryl)
	Thiazolidinediones (glitazones)	pioglitazone (Actos) rosiglitazone (Avandia)
	Dipeptidyl peptidase (DPP)-4 inhibitors (gliptins)	alogliptin (Nesina) linagliptin (Tradjenta) saxagliptin (Onglyza) sitagliptin (Januvia)
	Sodium glucose co-transporter (SGLT)-2 inhibitors (flozins)	canagliflozin (Invokana) dapagliflozin (Farxiga) empagliflozin (Jardiance) ertugliflozin (Steglatro)
	Glucagon-like peptide (GLP)-1 receptor agonist	semaglutide (Rybelsus)
Injectable	Glucagon-like peptide (GLP)-1 receptor agonists	dulaglutide (Trulicity) exenatide (Byetta) exenatide XR (Bydureon) liraglutide (Victoza) lixisenatide (Adlyxin) semaglutide (Ozempic)

These medications differ in their mechanisms of action, their side effects, and their cost.

Impact of non-insulin glucose-lowering agents on major clinical 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. After rosiglitazone (Avandia) was found to potentially increase the risk of cardiovascular outcomes despite lowering HbA1c,[92] the FDA began requiring newly-approved glucose-lowering medications be evaluated for CV risk through at least one randomized, placebo-controlled trial. Since then, these mandated trials have led to the discovery that select SGLT-2 inhibitors and GLP-1 receptor agonists have proven cardiovascular benefit for patients with type 2 diabetes and established cardiovascular disease (CVD). Alternatively, other glucose-lowering medications (e.g., DPP-4 inhibitors) have not been definitively proven to reduce CV events, but they have at least been shown not to increase the risk of CV events compared to placebo.

These findings, along with subsequent studies showing that SGLT-2 inhibitors and GLP-1 agonists have benefits for others 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 a HbA1c to achieve their ends.

Major randomized controlled trials evaluating cardiovascular outcomes in patients with type 2 diabetes and established CVD or high CVD risk

SGLT-2 inhibitors

Two SGLT-2 inhibitors 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.[21] 7,020 patients were randomized 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 in the pooled empagliflozin group compared to placebo (HR 0.86; CI, 0.74-0.99; P=0.04).[21] 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).[21] 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 getting 10 mg empagliflozin; and 148 (6.3%) in the group getting 25 mg empagliflozin.

The **CANVAS** and **CANVAS-R trials** randomized 10,142 patients to the SGLT-2 inhibitor 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.[93]

Two additional SGLT-2 inhibitors 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 randomized to dapagliflozin 10 mg/day vs. placebo with median follow-up 4.2 years.[94] 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%, $p<0.05$). Most recently, the **VERTIS CV** trial, another non-inferiority trial, randomized 8246 patients to ertugliflozin versus placebo and, after a median follow-up of 3.5 years concluded, concluded ertugliflozin did not reduce cardiovascular events compared with placebo (HR 0.97; 95% CI: 0.85-1.11).[95] 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-2 inhibitors, some of the clinical benefits from these medications are a medication class effect.[96]

GLP-1 receptor agonists

Multiple GLP-1 receptor agonists have been shown to reduce the risk of CVD. These include liraglutide, dulaglutide, and semaglutide (injection). Additionally, as of the writing of this document, another drug, efpeglenatide, has also shown cardiovascular benefit but is not yet on the market.

The **Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER)** trial randomized 9,340 adults to liraglutide 1.8 mg once daily vs. placebo with median follow-up 3.8 years.[20] 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 (P=0.01). Death from cardiovascular causes was also significantly lower with liraglutide (4.7% vs. 6%, P=0.007. There were no significant differences between groups, however, in rates of nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

The **REWIND** trial randomized 9901 patients over the age of 50 to dulaglutide (1.5 mg) or placebo.[97] After a median follow-up time 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 randomized to the GLP-1 receptor agonist and 13.4% of patients randomized to placebo (HR 0.88; 95% CI: 0.79-0.99), but there was no difference in all-cause mortality between the two groups.

The **SUSTAIN-6** trial randomized 3,297 adults ≥50 years old to semaglutide (0.5 or 1 mg once weekly) vs. placebo with median follow-up 2.1 years.[98] The primary outcome (composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) occurred in 6.6% vs. 8.9% respectively (P=0.02). The rate of nonfatal stroke was slightly lower with semaglutide (1.6% vs. 2.7%, P=0.04), but there were no significant differences in all-cause or cardiovascular mortality, nonfatal myocardial infarction, or hospitalization for heart failure or for unstable angina.

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-1 receptor agonists: EXSCEL (10,782 patients randomized to extended-release exenatide 2 mg per week vs. placebo)[99] and **ELIXA** (6,068 adults ≥30 years old with type 2 diabetes and an acute coronary event in the previous 180 days randomized to lixisenatide 10-20 mcg once daily vs. placebo.[100]

There is only one FDA-approved oral formulation of the GLP-1 agonist: semaglutide. In the 2019 **PIONEER 3** trial oral semaglutide to reduce HbA1c levels and body weight significantly more than sitagliptin in 1,864 patients with type 2 diabetes who had inadequate responses to either metformin alone or a sulfonylurea.[101] Oral semaglutide at doses of 7 mg/day and 14 mg/day (but not 3 mg/day) reduced HbA1c by 1% and 1.3% at 26 weeks respectively, compared to a reduction of 0.8% for sitagliptin (p<0.001 for both comparisons). Subsequently, in **PIONEER 6** trial, 3,183 patients were randomly assigned to receive oral semaglutide or placebo to study time-to-event outcomes (assessing for the first occurrence of a major adverse cardiovascular event. Technically, oral semaglutide was only shown to be non-inferior to placebo with regard to the primary outcome (HR 0.79; 95% CI: 0.57 to 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), which suggests there may yet be cardiovascular benefits associated with the drug.[97]

Multiple large trials of novel GLP-1 receptor agonists for diabetes and weight loss are still being conducted, and thus the landscape is likely to change in the coming years. One of the most recent

studies was the **AMPLITUDE-O** trial, which randomized 4,076 patients to efpeglenatide versus placebo. During a median follow-up of 1.81 years, incident major adverse cardiac events were significantly less likely to occur in the treatment group (HR 0.73; 95% CI: 0.58-0.92).[102] While efpeglenatide is not on the market as of the writing of this section, this trial is noteworthy for another reason: randomization was stratified according to baseline use of sodium–glucose cotransporter 2 inhibitors. This means that the effects of being on both a GLP-1 receptor agonist and SGLT-2 inhibitor could be studied. Subsequent exploratory analysis of the trial did this and concluded that the efficacy and safety of efpeglenatide appear to be independent of concurrent SGLT2 inhibitor use; that is, there was no additive or deleterious effect of being on both medications at once with regard to cardiac outcomes.[103] These should be considered preliminary conclusions and will need to be studied in future trials dedicated to the question.

DPP-4 inhibitors

Despite having a mechanism related to the GLP-1 pathway, DPP-4 inhibitors have not shown to have the same ability as the GLP-1 receptor agonists to reduce the risk of CVD.

For example, in the **CAROLINA** trial, 6,042 patients with poorly controlled diabetes and increased risk for CVD were randomized 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).[104] Other trials have shown other members of the DPP-4 inhibitor medication class also do not appear to reduce risk of macrovascular events. For example, in the **SAVOR-TIMI 53** trial, 1,222 patients were randomized to saxagliptin versus placebo. After a median follow-up time 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).[105]

Other studies assessing the effects of DPP-4 inhibitors on cardiovascular morbidity and mortality more generally have similarly not shown significant or consistent benefit. For example, two observational studies, a case-control study with 1,499,650 adults[106] and a retrospective cohort study with 57,737 adults,[107] 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 randomizing 176,310 participants found that use of DPP-4 inhibitors was not associated with lower mortality than placebo or no treatment (HR 1.02; 95% CI: 0.94-1.11).[108]

Older agents

As compared with studies of drugs approved around or after the FDA mandated that all drugs used to treat type 2 diabetes be studied for their cardiovascular safety, older drugs have not been studied with the same intentionality in large, randomized, 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 new diabetes diagnoses). 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 randomized to intensive therapy (defined as fasting plasma glucose target < 6 mmol/L) with insulin, intensive therapy with a sulfonylurea (chlorpropamide or glyburide), or diet alone, and were followed for 10 years.[109] 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).[109] 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 randomized 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).[110] 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.[110] Metformin did not reduce rates of microvascular complications or myocardial infarction.

The **PROactive** study **(PROspective pioglitAzone Clinical Trial In macroVascular Events)** randomized 5,238 patients with type 2 diabetes and macrovascular disease to either pioglitazone (Actos) or placebo in addition to their glucose-lowering regimen.[111] 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).

The **ADOPT** study **(A Diabetes Outcome Progression Trial)** randomized 4,360 untreated patients with diabetes to monotherapy with rosiglitazone, metformin, or glyburide.[112] Cardiovascular events were measured to evaluate the safety of these agents, but were not a pre-specified primary or secondary outcome of the study. In contrast to UKPDS, rates of all-cause mortality were similar in all groups, while the rate of serious cardiovascular events was significantly lower in patients treated with glyburide (1.8%) compared to patients treated with metformin (3.2%) or rosiglitazone (3.4%), largely due to lower rates of heart failure and non-fatal myocardial infarction in the glyburide-treated patients.

The **SPREAD-DIMCAD** study (**Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus with Coronary Artery Disease**) randomized 304 patients with type 2 diabetes and coronary artery disease to glipizide 30 mg daily or metformin 1.5 g daily for three years.[113] Mean baseline HbA1c was 7.6% in each group, and at follow up (median 5 years) had fallen to 7.1% in the glipizide group and 7.0% in the metformin group (P=0.66). Metformin was associated with a significant reduction in the primary composite endpoint of death from cardiovascular causes, death from any cause, nonfatal MI, nonfatal stroke, and arterial revascularization compared with glipizide (HR 0.54; 95% CI: 0.30-0.90; p=0.026).

These data suggest that all medication classes, especially when used early in the disease course, likely do provide cardiovascular benefit (based largely on UKPDS findings). Otherwise, data is mixed and difficult to compare across studies due to a lack of standardization of outcomes and methods (as contrasted with the literature surrounding the GLP-1 receptor agonists and SGLT-2 inhibitors). However, these data may suggest metformin has the ability to reduce cardiovascular events compared with other drug classes, especially sulfonylureas (based largely on the SPREAD-DIMCAD findings), and that pioglitazone may also have cardiovascular benefits (based largely on the 3-point MACE secondary outcome in the PROactive study).

Special cardiovascular considerations with thiazolidinediones

The FDA initially placed a black-box warning on the rosiglitazone label about the potential increased risk of myocardial infarction and placed limitations on its prescription, based on two large meta-analyses of 42 randomized trials.[92,114] _ENREF_20 In 2013, however, the FDA removed all prescribing and dispensing restrictions on rosiglitazone after determining that the data did not demonstrate an increased risk of heart attack compared to metformin and sulfonylureas. [115,116] _ENREF_71

In contrast to the data about rosiglitazone, a 2007 meta-analysis of 19 randomized controlled trials found that pioglitazone reduced by 18% the relative risk of a composite end-point of death, myocardial infarction, or stroke (P=0.005).[117] But as discussed in further detail below, both rosiglitazone and pioglitazone may increase the risk of heart failure and fracture.

BOTTOM LINE: Many SGLT-2 inhibitors and GLP-1 receptor agonists have been proven to reduce microvascular and macrovascular complications of diabetes, including risk of cardiovascular events. These cardiovascular benefits are independent of their HbA1c lowering effects. Other agents, especially as metformin and pioglitazone, may also have cardiovascular benefits, though the evidence is not as consistent and robust as it is for SGLT-2 inhibitors and GLP-1 receptor agonists. Other agents have not consistently been shown to have cardiovascular benefits, and thiazolidinediones increase heart failure risk.

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-2 inhibitors and GLP-1 receptor agonists, which showed that 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. 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 0.5-1.5% (Table 10).

Table 10: Expected reductions in HbA1c of different glucose-lowering agents

Class	HbA1c lowering
Biguanide	1-1.5%
Sulfonylureas	1-1.5%
Thiazolidinediones (glitazones)	1-1.5%
Dipeptidyl peptidase (DPP)-4 inhibitors ('gliptins')	0.5-1%
Sodium glucose co-transporter (SGLT)-2 inhibitors ('flozins')	0.5-1%
Glucagon-like peptide (GLP)-1 receptor agonists	1-1.5%

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.[55]

Combination therapy

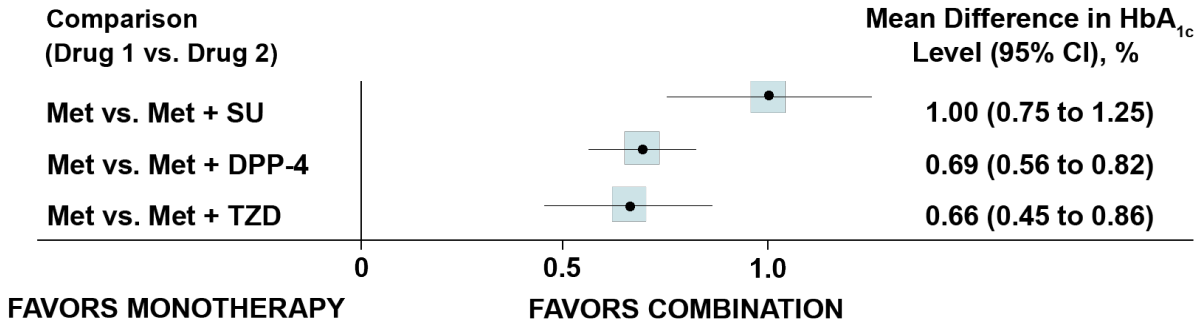
Adding a second non-insulin agent to an existing treatment regimen can help patients achieve better glycemic control. Clinical trials have consistently shown an additive effect, probably because drugs act by complementary, but different, mechanisms. In general, the addition of a second agent from a different class lowers HbA1c by an additional 1% over treatment with maximum doses of a single agent.[55,118]

In addition to achieving better glucose control, there is some evidence that early combination therapy may actually prevent the progression of diabetes (i.e., may prevent the progression of beta-cell dysfunction or recalcitrant insulin resistance). In 2019, the **VERIFY** trial randomized 1598 patients to begin monotherapy (metformin) versus combination therapy (metformin and a DPP-4 inhibitor). They found that those randomized to the combination therapy group maintained HbA1c<7% for longer even after monotherapy group participants had DPP-4i added to their regimens.[119] Furthermore, those initially randomized to the combination therapy group had a lower risk of requiring more than two agents (HR 0.74; 95% CI: 0.63–0.86).

Several other randomized studies have compared different add-on regimens (e.g., metformin + sulfonylurea vs. metformin + rosiglitazone). Despite slight under-dosing of the sulfonylurea in these trials, both treatment arms resulted in equivalent reductions in HbA1c.[120,121] The DPP-4 inhibitors appear in some studies to be as effective as other oral glucose-lowering agents when used as add-on therapy, although the data supporting their use are more limited.[122,123]

Several short-term randomized 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.[111,124-126] 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.[127] A 2012 systematic review of SGLT-2 inhibitors 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.[128]

Figure 11: Comparisons of combined treatment versus monotherapy[128]



BOTTOM LINE: Non-insulin glucose-lowering medications each reduce HbA1c by about 0.5-1.5%. Adding a second agent from a different class may lower HbA1c by about another 1.0% and could help prevent treatment failure. 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.

Other relevant outcomes

In addition to their effects on HbA1c levels, non-insulin glucose-lowering agents differ in their impact on other clinically important outcomes (Table 11).

Table 11: Cardiovascular outcomes and adverse effects of glucose-lowering drugs

Class / medication	CV outcome: ASCVD	CV outcome: HF	Worsening renal function	Weight change	Hypoglycemia	Other safety considerations
biguanide metformin (Glucophage)	potential benefit	*	*	loss	no	GI intolerance (start with low dose to minimize, or use extended release)
SGLT-2 inhibitors (flozins) canagliflozin (Invokana) empagliflozin (Jardiance)	benefit	benefit	benefit	loss	no	UTI, ketoacidosis, genital infections, hypotension, fractures (cana), amputation (cana)
dapagliflozin (Farxiga) ertugliflozin (Steglatro)	neutral		neutral			
GLP-1 receptor agonists liraglutide (Victoza) semaglutide† (Ozempic) dulaglutide† (Trulicity)	benefit	neutral	potential benefit	loss	no	GI side effects common pancreatitis
exenatide† (Bydureon) lixisenatide (Adlyxin) semaglutide (Rybelsus)§	neutral	neutral	*			
exenatide (Byetta)	*	*	*			
DPP-4 inhibitors (gliptins) linagliptin (Tradjenta) sitagliptin (Januvia)	neutral	neutral	*	*	no	joint pain, pancreatitis
alogliptin (Nesina) saxagliptin (Onglyza)	*	potential risk	*	*		
thiazolidinediones (TZD) pioglitazone (Actos)	potential benefit	increased risk	*	gain	no	fractures, bladder cancer
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; †given weekly; §oral formulation

Renal dose adjustment is required for metformin, GLP-1 receptor agonists, and SGLT-2 inhibitors.

Kidney disease

SGLT-2 inhibitors have the most robust proven renoprotective effects. Additionally, select GLP-1 receptor agonists may also be able to prevent new onset microalbuminuria.

Concerning the SGLT-2 inhibitors, multiple trials exist showing that they prevent decline in renal function in the form of reducing GFR decline and reducing the risk of a doubling of serum creatinine. For example, in the **EMPA-REG OUTCOME** trial, 4125 patients were randomized 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).[129] 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 glomerular filtration rate (eGFR) for empagliflozin was 4.7 mL/min/1.73 m^2 (95% CI: 4.0-5.5; P<0.001), showing empagliflozin offered eGFR improvements.

Multiple other trials exist showing similar results. For example, the 2019 **CREDENCE** trial randomized 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-2 inhibitor canagliflozin 100 mg/day vs. placebo with median follow-up 2.6 years (trial stopped early for benefit).[130] All patients were also on stable doses of an ACE or 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-2 inhibitors are a class effect. For example, In a 2019 systematic review of 27 studies with 7,363 patients with type 2 diabetes and chronic kidney disease (CKD), SGLT2 inhibitors attenuated the annual decline in eGFR slope (placebo-subtracted difference of 1.35 mL/1.73 m^2 /year; 95% CI: 0.78-1.93 mL/1.73 m^2 /year) and reduced the risk of the composite renal outcome (HR 0.71; 95% CI: 0.53-0.95).[131] In a more general populations, a 2018 systematic review of 25 trials evaluating renal outcomes of SGLT-2 inhibitors in 43,721 patients found a significant delay in albuminuria progression (risk ratio 0.71; 95% CI: 0.66-0.76), increased likelihood of albuminuria regression (risk ratio 1.71; 95% CI: 1.54-1.9), and reduced risk of renal replacement or death from renal causes (risk ratio 0.57; 95% CI: 0.49-0.66).[132]

In fact, the renoprotective effects of SGLT-2 inhibitors have been proven even in patients without diabetes. For example, in the **DAPA-CKD** trial, 4304 patients with CKD but without diabetes were randomized to receive dapagliflozin or placebo.[133] 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 was stopped early in 2022 for efficacy.[134]

The GLP-1 receptor agonists may also be useful for preventing progression of renal disease, but the data are less complete than they are for the SGLT-2 inhibitors. Currently, evidence supports that GLP-1 receptor agonists 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-2 inhibitors provide. 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).[20,98,135] 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.[136] 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).[137]

The magnitude of benefit GLP-1 receptor agonists will have on renal function remains an area of ongoing research with multiple dedicated trials underway.[138]

Heart Failure

There is robust evidence that SGLT-2 inhibitors can prevent clinically significant heart failure (HF) exacerbations. For example, a 2019 meta-analysis of 34,322 patients randomized to either an SGLT-2 inhibitor or placebo concluded that those randomized to an SGLT-2 inhibitor were 23% less likely to have cardiovascular death or hospitalization for heart failure (HR 0.77; 95% CI: 0.71-0.84).[139] The only SGLT-2 inhibitor not included in this meta-analysis was ertugliflozin, but analysis of the 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).[96]

Interestingly, and adding credence to their ability to improve outcomes for those with heart failure, SGLT-2 inhibitors 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 randomized 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.[140] **DAPA-HF** produced similarly significant findings for patients with reduced ejection fraction randomized to taking dapagliflozin.[141] Moreover, the **EMPEROR-Preserved** trial randomized 5,988 patients with heart failure with preserved ejection fraction (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, there is robust evidence for the use of SLGT-2 inhibitors in patients with heart failure.

Weight loss

The drugs capable of inducing the most weight loss appear to be the GLP-1 agonists. For example, in trials of exenatide, patients lost approximately 2-3 kg over six months.[125,142] In fact, these drugs may be used for the purpose of weight loss in overweight/obese patients with or without diabetes. For example, in both the **SCALE**[35] and **STEP 1**[36] trials, patients without diabetes were randomized to GLP-1 receptor agonists (liraglutide and semaglutide, respectively) and lost on average 5-12 kg more than those randomized to placebo.

While GLP-1 agonists are perhaps the most potent diabetes medications with regard to weight loss, metformin, GLP-1 agonists, and SGLT-2 inhibitors may all have some weight loss effects. For example, a 2012 systematic review of SGLT-2 inhibitors used in dual or triple therapy for patients with type 2

diabetes concluded that these agents effectively reduced weight compared with placebo.[128] By contrast, sulfonylureas and the thiazolidinediones generally cause weight gain.[118]

Cholesterol

Metformin lowers LDL cholesterol by a mean of 10 mg/dL.[118] In contrast, sulfonylureas have little effect on LDL levels, while the thiazolidinediones and SGLT-2 inhibitors tend to *increase* LDL by an average of 10 mg/dL. Rosiglitazone also elevates triglyceride levels, whereas pioglitazone and all other major classes of oral agents appear to reduce triglycerides.[118] The thiazolidinediones increase HDL levels, whereas other agents appear to have no effect on HDL. Studies of the effects of DPP-4 inhibitors have yielded variable results. Sitagliptin has been reported to be lipid neutral or beneficial, with one study reporting decreased LDL and triglyceride levels, and increased HDL levels.[120] Alogliptin, linagliptin, and saxagliptin have been reported to be lipid neutral.[143-145] A 2012 meta-analysis found that the DPP-4 inhibitors reduced total cholesterol and triglycerides.[146] Clinical studies and a meta-analysis have reported the GLP-1 receptor agonist exenatide as being lipid neutral or beneficial.[147-150] (Whether changes in cholesterol levels induced by medications actually change patients' cardiovascular risk or other clinical outcomes is not yet well-established.)

BOTTOM LINE: Among the non-insulin glucose-lowering agents, metformin, SGLT-2 inhibitors, and GLP-1 receptor agonists appear to have the most consistent beneficial effects on body weight. SGLT-2 inhibitors 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. SGLT-2 inhibitors also have robust evidence for preventing heart failure hospitalizations in patients with and without diabetes regardless of ejection fraction.

Comparative safety

Hypoglycemia

The clinical consequences of hypoglycemia include increased risk of falls, car crashes, confusion, and (possibly) increased risk of dementia.[74,76] 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).[110]

Metformin, the thiazolidinediones, SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 receptor agonists do not appear to increase the risk of hypoglycemia compared to placebo.[151,152] 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.[118] This is particularly relevant for patients whose HbA1c is close to 7%, and in the elderly.

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.[151] Accordingly, the latter agents are safer in patients with renal insufficiency and in the elderly.

BOTTOM LINE: Metformin, the thiazolidinediones, SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 receptor agonists do not appear to increase the risk of hypoglycemia. Sulfonylureas and repaglinide increase the risk of hypoglycemia more than other oral agents. Longer-acting sulfonylureas (e.g., glyburide) are more likely to cause hypoglycemia than short-acting agents (e.g., glipizide), and for this reason glipizide is the preferred sulfonylurea in the elderly or those with significant comorbidities.

Heart failure exacerbations and peripheral edema

The risk of heart failure caused by thiazolidinediones has been known for some time.[111] Even in lower-risk populations, both pioglitazone and rosiglitazone substantially elevate the risk of heart failure.[92,114,117]

The FDA issued a "black box" warning about the risk of heart failure caused by rosiglitazone and pioglitazone, a risk that is raised when these agents are used with insulin.[153,154] Rates of peripheral edema are also substantially elevated with the thiazolidinediones compared to metformin, sulfonylureas, or repaglinide. Trials comparing thiazolidinediones vs. sulfonylureas show absolute differences in the rate of peripheral edema ranging from 4% to 21%.[151]

Other glucose-lowering medications appear to have a neutral effect on heart failure,[152] with the exception of the SGLT-2 inhibitors, which have been shown to *reduce* risk of hospitalization or death from heart failure in patients with highly elevated cardiac risk at baseline, perhaps through their diuretic effects.[155]

BOTTOM LINE: The thiazolidinediones substantially increase the risk of heart failure and peripheral edema compared with sulfonylureas and metformin. Less is known about heart failure risk for many of the newer classes of non-insulin glucose-lowering agents, although SGLT-2 inhibitors lower the risk of hospitalization or death from heart failure.

Other possible side effects

Gastrointestinal (GI) intolerance

Nausea, vomiting, and diarrhea are common side effects of metformin, occurring in up 60% of patients.[118] They also occur very frequently with acarbose, but 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.

GI side effects are also common with GLP-1 receptor agonists.[111,124-127]

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.[156] The rate of pancreatitis was low and not significantly different in patients randomized 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 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-1 receptor agonists. For example, one 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-1 receptor agonists. For example, the FDA went as far as to warn that exenatide should be discontinued and not restarted if pancreatitis occurs, and that other agents be considered in patients with a history of pancreatitis.[157] Ultimately, data are inconsistent. For example, one case-controlled study (n= 2,538) reported that GLP-1 receptor agonist users had significantly increased odds of hospitalization for acute pancreatitis than non-users (OR 2.24; 95% CI: 1.36-3.68).[158] Other observational studies have produced similar results indicating that both DPP-4 inhibitors and GLP-1 receptor agonists may be associated with increased risk of pancreatitis,[159] though the connection is not uniform across all observational studies.[160] The exact mechanism of the cause of pancreatitis is unclear, but may include both the direct effects of GLP-1 receptor agonists on beta-cell function as well as the potential effects of rapid weight loss on increased risk of pancreatitis.[161,162]

Fractures

The thiazolidinediones increase 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] In the ADOPT trial, the incidence of fracture in women was 9.3% in patients treated with rosiglitazone compared with 3.5% and 5.1% in patients who received glyburide or metformin, respectively.[112] No increased risk of fracture was observed in men. In the **RECORD trial**, rosiglitazone increased the risk of upper and lower distal limb fractures, mainly in women.[163]

The SGLT-2 inhibitors 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).[93] However, this result has not been consistently seen in meta-analyses of the drug class. For example, in one meta-analysis of randomized-controlled trials, in a population of 20,895 patients being randomized to an SGLT-2 inhibitor was not associated with an increased fracture rate.[164] Similar null findings were reported in a meta-analysis limited to older adults, suggesting that any effects SGLT-2 inhibitors have on bone health and fracture risk may be small.[165]

Bladder cancer

The FDA issued a safety announcement in 2011 that the use of pioglitazone (Actos) 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).[166]

Thyroid cancer

The GLP-1 receptor agonists 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).

Urogenital infection

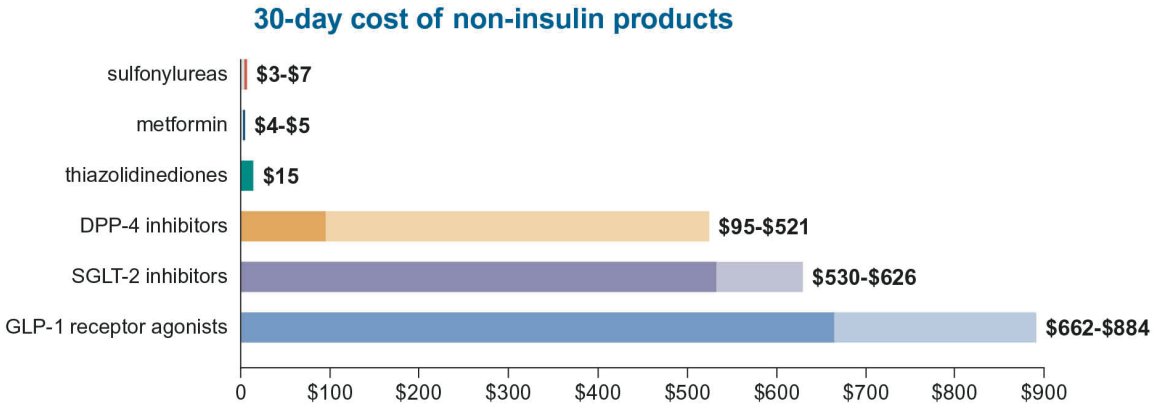
Because they increase the glucose content of urine, SGLT-2 inhibitors increase the risk of genital and urinary tract infections, particularly yeast infections, compared to other classes of glucose-lowering medications.[167] SGLT-2 inhibitors have also been associated with rare cases of ketoacidosis,[167] Fournier's gangrene,[168] and an increased risk of amputation (compared to placebo).[93]

BOTTOM LINE: Metformin and GLP-1 receptor agonists frequently cause some gastrointestinal intolerance, although for metformin and perhaps GLP-1 receptor agonists, these side effects can be reduced by gradual dose escalation, and usually diminish over time. The thiazolidinediones increase the risk of fracture. SGLT-2 inhibitors pose an increased risk of genital and urinary tract infections, particularly yeast infections.

Cost

The various non-insulin 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 extremely low. In contrast, the newer antidiabetic agents are protected by patents and cost significantly more.

Figure 12: Price for a 30-day supply of non-insulin agents



Prices from goodrx.com, March 2022. Listed doses are based on Defined Daily Doses by the World Health Organization and 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.

Initiation of therapy: Which drug to choose?

For decades, metformin had been the recommended therapeutic choice as initial therapy for most patients with type 2 diabetes. However, copious amounts of data have now proven that GLP-1 receptor agonist and SGLT-2 inhibitors have unique abilities to reduce complications from diabetes above what would be expected simply by their HbA1c lowering ability. As such, 2022 ADA Standard of Care guidelines now state that these drugs may be considered first line along with metformin.[9]

The newest recommendations now endorse the idea that patient comorbidities should be considered when selecting a first line agent. Put another way, both the final HbA1c and the route to get to that final

HbA1c matter. As such, patients with atherosclerotic cardiovascular disease (ASCVD) may benefit from beginning with either an SGLT-2 inhibitor or a GLP-1 inhibitor as initial therapy, patients with heart failure or chronic kidney disease with evidence of microalbuminuria may benefit from beginning an SGLT-2 inhibitor as initial therapy, and patients who are overweight or obese as their primary comorbidity may benefit from beginning a GLP-1 receptor agonist as initial therapy. Alternatively, metformin may still be appropriate to begin for patients without any of these comorbidities.

Given that most patients in the trials of SGLT-2 inhibitors and GLP-1 receptor agonists 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 was the case, then it would suggest that metformin might still have a role as the initial therapy in treating diabetes.[169] However, subsequent subgroup analysis of numerous trials have suggested that the effects of SGLT-2 inhibitors and GLP-1 receptor agonists are independent of metformin. For example, one meta-analysis of six trial that enrolled 51,743 patients reported that those who were randomized to receive an SGLT-2 inhibitor 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). [170] Concerning the GLP-1 receptor agonists more specifically, one meta-analysis of four trials that enrolled 43,456 patients found that those randomized to receive a GLP-1 receptor agonist 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).[171]

Of course, these guidelines may not apply to all patients due to contraindications to or intolerance of specific medications. Furthermore, as most GLP-1 receptor agonists come in an injectable form, some patients may be reticent to begin them. Table 12 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).[172] Related FDA guidance is that metformin is contraindicated in patients with eGFR <30 and should be avoided in patients with eGFR between 30 and 45.

Table 12: 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 metabolic 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
Thiazolidinediones	• heart failure • fracture in women with osteoporosis • MI (rosiglitazone)
DPP-4 inhibitors	• pancreatitis • heart failure (saxagliptin, alogliptin) • Dose adjust in CKD
GLP-1 receptor agonists	• pancreatitis history • not recommended in patients with severe renal impairment, 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-2 inhibitors	• hypotension • avoid in severe renal impairment • monitor for genital infection, bladder cancer, UTI, or ketoacidosis (in both type 1 and type 2 diabetes) • avoid in individuals at risk of fracture
Sources: Garber AJ et al. *Endocr Pract.* Jan 2016;22(1):84-113; package inserts for metformin, glyburide, glipizide, alpha-glucosidase inhibitors, meglitinides, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors; and FDA safety information for thiazolidinediones and SGLT-2 inhibitors.	

BOTTOM LINE: GLP-1 receptor agonists or SGLT-2 inhibitors 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, and contraindications to receiving certain therapies.

Monitoring and regimen intensification

After confirming that the patient has type 2 diabetes and not type 1 or a rarer type of diabetes (e.g., pancreatogenic diabetes or monogenic diabetes), and after initiation of 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.[9]

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%.[119] 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; however, the evidence that patients should be treated aggressively to HbA1c goals is clear.

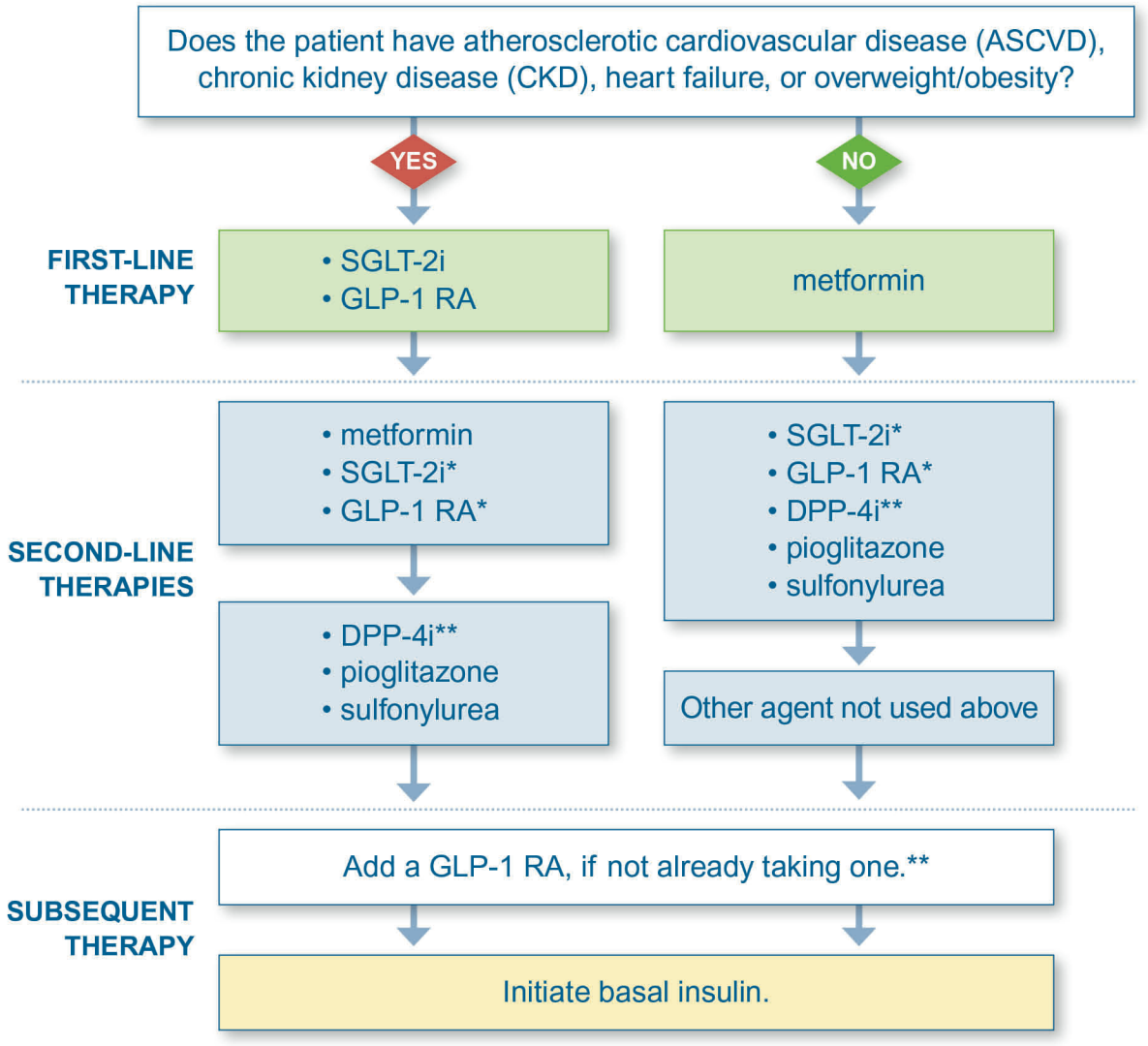
There are many therapeutic options for patients who are poorly controlled on monotherapy with metformin. Like selecting an initial agent, this should again be driven by the patient's comorbidities and HbA1c lowering needs. The algorithm in Figure 13 is based on evidence about a drug's impact on clinical outcomes such as cardiovascular risk. 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.[173]

As is the case for when considering an initial therapy, for patients with established CVD, an SGLT-2 inhibitor (empagliflozin or canagliflozin) or GLP-1 receptor agonist (dulaglutide, liraglutide, or subcutaneous semaglutide) 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-2 inhibitor is preferred over a GLP-1 receptor agonist (assuming the patient was not prescribed the agent for initial therapy), though for patients without microalbuminuria a GLP-1 receptor agonist is reasonable as well. If a patient was started on an SGLT-2 inhibitor or GLP-1 receptor agonist as a first line agent, it is also reasonable to consider metformin as a second-line agent given to date there is little evidence of additive effects of SGLT-2 inhibitors and GLP-1 receptor agonists for risk of major adverse cardiac events. 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-1 receptor agonist and avoid pioglitazone in patients with heart failure.

In patients without CVD or high risk for CVD, HF, 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 SGLT-2 inhibitors, GLP-1 receptor agonists, or metformin are preferred. If cost or insurance factors are an issue, then generic pioglitazone is an affordable medication, or in patients in whom hypoglycemia is not a concern, a sulfonylurea. Insulin may be added at any point if it is preferred, though in patients with CVD, HF, 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 will require insulin therapy (usually in combination with other agents) to maintain optimal glucose control.[55]

Figure 13: Preferred treatment options[#]



*SGLT-2is and GLP-1 RAs can be used in combination to address specific comorbidities, but this approach has not yet been formally evaluated in a randomized clinical trial.[8]

**Avoid co-prescribing a DPP-4i and 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.

BOTTOM LINE:

1. The goal of treating diabetes is to 1) select an agent that reduces macrovascular and microvascular complications independently of HbA1c lowering ability and 2) lower HbA1c to goal levels.

2. All non-insulin glucose-lowering agents reduce HbA1c levels by 0.5-1.5%.

3. Patient comorbidities should guide initial therapy. Patient at increased risk for cardiovascular disease should be started on a GLP-1 receptor agonist or SGLT-2 inhibitor. Patients with HF or CKD with microalbuminuria should be started on an SGLT-2 inhibitor. Metformin is an appropriate initial therapy for most other patients.

4. When a second agent is needed, selection should similarly be based on patient comorbidities and glucose lowering needs.

5. Some agents (e.g., thiazolidinediones) are associated with significant risks (heart failure, myocardial infarct, fractures).

6. Glucose-lowering drugs vary significantly in price.

Insulin therapy

Many patients with type 2 diabetes will eventually require insulin therapy.[55] After a successful initial response, patients in the UKPDS trial progressed despite oral therapy at a rate of 5% to 10% per year. Among patients initially controlled with a single drug, 50% required a second drug after three years, and 75% needed multiple therapies by nine years to achieve their HbA1c targets.[174] 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.[175-177] 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.[178,179] 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."[178,179]

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. The 2022 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%).[9]

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.[55] 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) or long-acting (glargine or detemir) insulins may be used.[55] Basal insulin is usually given at bedtime to control unrestricted overnight gluconeogenesis with subsequent high pre-breakfast (fasting)

glucose levels. Basal insulin may also be given in the morning if pre-dinner blood glucose levels are high, but patients should be advised to eat lunch with a morning NPH regimen to avoid hypoglycemia.

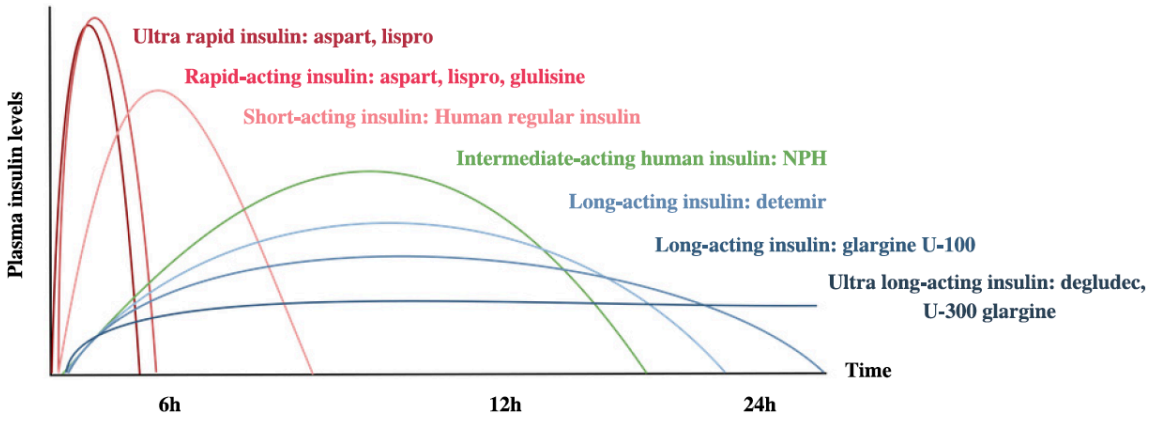
Most patients with type 2 diabetes requiring insulin therapy can be successfully treated with basal insulin alone. However, because of progressive reduction in endogenous insulin secretion, some will need prandial insulin therapy with shorter-acting insulins or pre-mixed insulins (which combine basal and short or rapid-acting insulin).[55]

Insulin is also 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.[9]

Insulin preparations

Figure 14 depicts currently available insulin preparations; they are described in more detail below.

Figure 14: Comparison of human insulin preparations and insulin analogs[180]



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: lispro, aspart, and glulisine

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 randomized controlled trials found no benefit of rapid acting insulin over regular insulin in managing HbA1c or in reducing hypoglycemic episodes.[181] 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 prescription.[182] 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 there are also ultrarapid-acting insulins 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 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.[183]

Basal insulin options (NPH, detemir, glargine U100, glargine U300, degludec)

Intermediate-acting (basal) insulin: NPH

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.[184] When used as basal insulin, it can be given once or twice daily.

Long-acting (basal) insulin analogs: glargine U100 and detemir

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, which means for some patients BID dosing is needed).[185] 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.[186]

Insulin detemir also has the favorable characteristics of prolonged action, primarily by slower absorption. Its duration of action is approximately 20 hours (shorter than glargine, with a range of 15-24 hours), and it can be used once or twice daily.[185]

Ultralong-acting insulin

There are two commonly used ultralong-acting insulins available: insulin degludec and insulin glargine U300. 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.[185]

In 2021, a trial was published exploring the safety and efficacy of a once weekly insulin. In this 26-week phase 2 randomized trial, 247 patients with sub-optimally control of diabetes (mean HbA1c ~8% on at least metformin) were assigned to receive icodec (weekly) or glargine U100 (daily). There was similar efficacy of once-weekly icodec with regard to HbA1c reduction and adverse events. However, at the time of this writing, this insulin is not readily available.[187]

Differentiating between Basal Insulin Options

There are multiple trials that can inform which of the basal insulins to initiate for a patient. Because of their different pharmacokinetic properties, they do have slightly different risk profiles (Figure 15).[185]

Concerning the decision to use NPH versus a long-acting analog, multiple studies have shown that both provide similar levels of HbA1c control. For example, the **LANMET trial** compared treatment with glargine

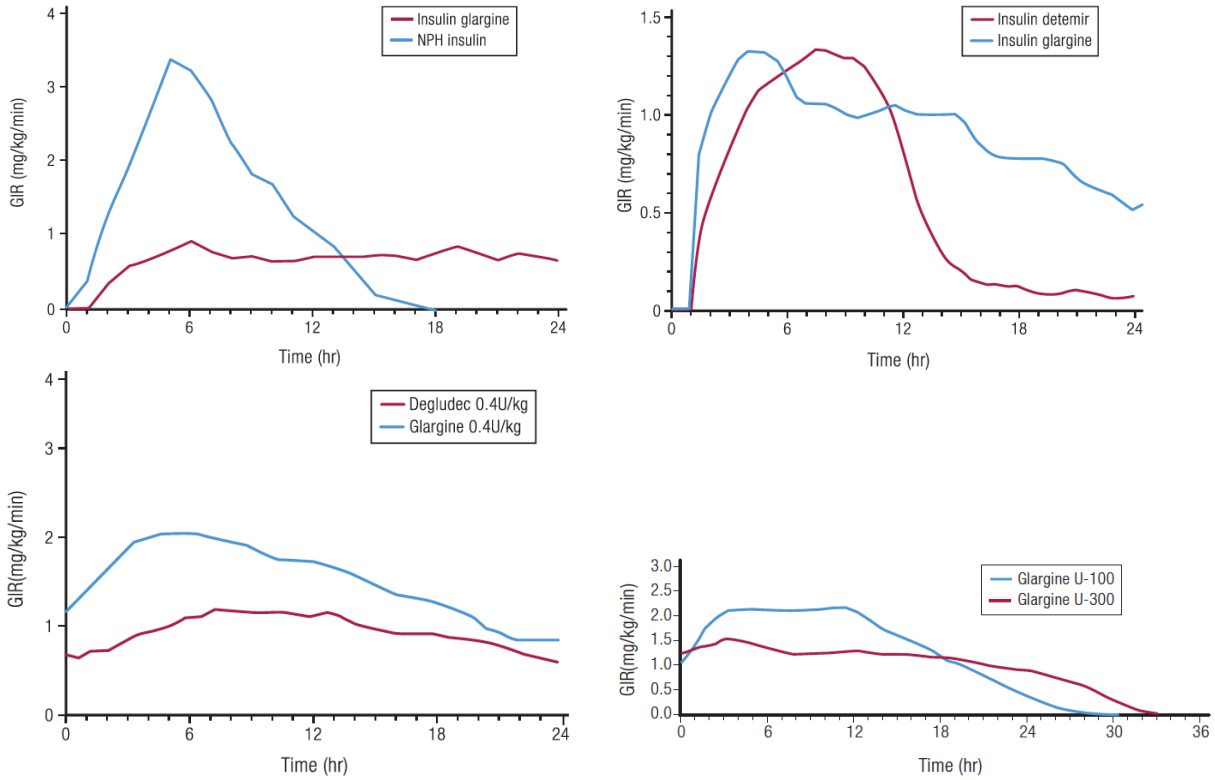
and metformin vs. NPH and metformin in type 2 diabetes.[188] It found similar glucose control in both groups, but there were fewer hypoglycemic events in the first 12 weeks in the glargine group (though this difference disappeared by the end of the trial at 36 weeks). However, as LANMET highlight, multiple other studies show using NPH often requires more injections per day and confers a higher risk of hypoglycemia compared with long-acting insulin analogues.[66,189] Data from observational studies 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.[59] While this this observational data is reassuring, and, when coupled with the data from the LANMET trial that after the initial titration period NPH was not associated with increased hypoglycemia compared with glargine, suggests that with proper patient selection NPH may be safe, the pharmacokinetic profiles and clinical trial evidence are consistent and suggest that, on average, long-acting analogs are likely a safer option.

Differences in outcomes between the long-acting basal analogs have also been studied. Concerning glargine U100 versus detemir, one Cochrane meta-analysis included 2,250 patients and found no significant difference in HbA1c or hypoglycemia between treatment groups. However, up to 57% of individuals in detemir trials required multiple injections per day to achieve the same HbA1c control as daily glargine U100, suggesting the latter may offer convenience benefits.[190]

Similarly, long-acting and ultralong-acting insulin have similar ability to lower HbA1c, but ultralong-acting analogs may have lower risk of hypoglycemia. For example, in the **DEVOTE** trial, 7637 patients with type 2 diabetes at high-risk for cardiovascular events were randomized to degludec or glargine U100 and 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).[191] 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.[192] 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.[193]

Taken together, in trial scenarios, all basal insulins provide largely equivalent HbA1c lowering ability. However, the longer-acting the insulin is, the lower the risk for hypoglycemia. As such, while insulin glargine U100 is most-often the first basal insulin used,[182] for patients with adherence issues or at particularly high-risk of hypoglycemia, ultralong-acting insulin may be reasonable alternatives to try.

Figure 15: Insulin effects over time in a population of patients with type 1 diabetes[185]



GIR: glucose infusion rate; GIR vs. time is the pharmacodynamic profile of an insulin product.

Premixed (biphasic) insulin combinations

Premixed insulin combinations contain a fixed ratio of faster and slower 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. 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,[194,195] 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 randomized 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 patients per year.[196] Moreover, in the **GINGER** trial, 310 subjects were randomized 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.[197] 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 obese patients or those who require high daily insulin needs. These products include: lispro U200 (Humalog), regular U500 (Humulin), glargine U300 (Toujeo), and degludec U200 (Tresiba). As discussed above, 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 basal insulins.[198] Concentrated insulins are available in pen devices. These can be easy and safer for patients to use because they do not require any calculations - the patient simply dials the prescribed dose in units before injecting subcutaneously.

Other insulin options

Insulin can also be delivered in a patch, pump, or as an inhalation. One type of insulin delivered by a patch-like device is Valeritas V-Go, which delivers bolus and basal insulin with a patch that is changed every day. Inhaled insulin (Afrezza) is also FDA approved to deliver rapid acting insulin.

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.

Choosing an insulin regimen

Generally, before beginning basal insulin, providers should attempt to use a GLP-1 receptor agonist for most patients with type 2 diabetes as long as the patient has a HbA1c less than 10-11%, 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.[9]

Concerning the decision to begin with initiating basal insulin over prandial insulin, this is informed by trial data that suggests that basal insulin may reduce risk of hypoglycemic events and weight gain while still providing strong HbA1c reductions. For example, in the 4-T trial, patients poorly controlled with oral glucose-lowering agents were randomized to receive biphasic insulin, prandial insulin, or detemir.[194] The study found a greater likelihood of reaching HbA1c <6.5% in the biphasic and prandial insulin arms than in the basal insulin arm (17.0%, 23.9%, and 8.1%, respectively, especially in patients with a HbA1c starting >8.5%), but also more hypoglycemia and weight gain (4.7 kg, 5.7 kg, 1.9 kg, respectively). The issue was also studied in the **APOLLO** trial. This trial found little difference in efficacy and reduced side

effects in 418 patients randomized to glargine once daily vs. fast-acting lispro three times a day. Patients receiving glargine experienced a 1.7% reduction in HbA1c, not significantly different than the 1.9% difference in those who received lispro. The incidence of hypoglycemic events was 5.2 less per year in the glargine arm than the lispro arm and treatment satisfaction was greater in the glargine group.[199]

Treating to target

A commonly-used algorithm for basal insulin intensification comes from the **Treat-to-Target** trial.[66] This randomized 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 13.

Table 13: 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

As described in the previous section, basal insulin options off roughly equivalent HbA1c control (assuming they are taken as prescribed); however, the longer-acting the insulin, the lower risk for hypoglycemia.

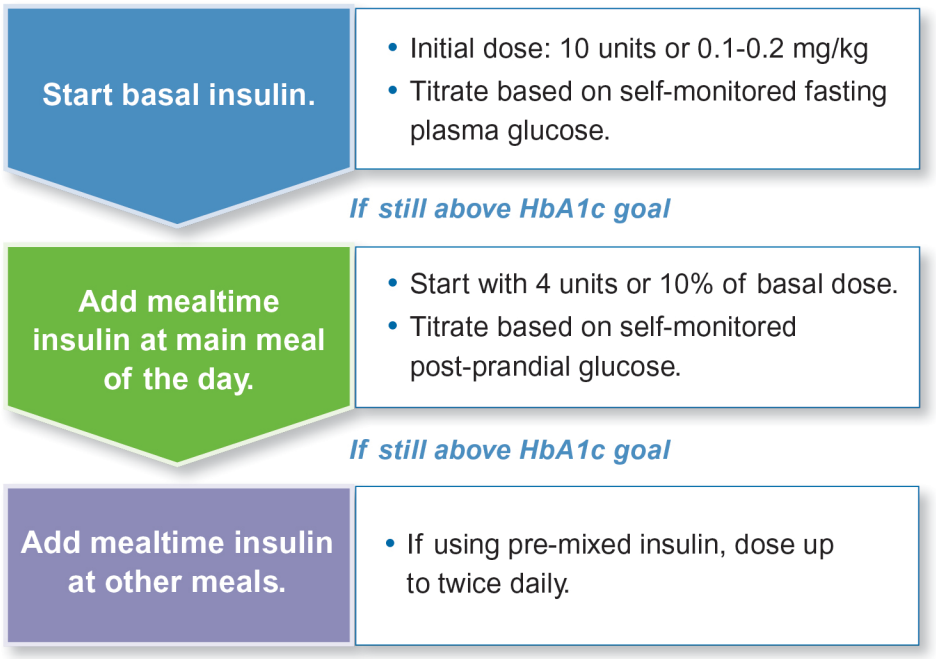
The **Treat-to-Target Trial (2003)** randomized 756 patients with overweight with type 2 diabetes and inadequate glycemic control (HbA1c 7.5%-10%) with oral glucose-lowering agents to bedtime glargine or NPH insulin titrated to target levels using a simple algorithm.[66] At the end of the 24-week study, 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 type 2 patients with diabetes with suboptimal glycemic control on oral therapy.[189] 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-1 receptor agonist 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. When considering which long-acting insulin to use, data suggests that the longer-acting the insulin is, the less risk of hypoglycemia, though most long-acting insulins are largely equivalent with regard to glycemic control. 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 (financial, number of injections required, risk of hypoglycemia, etc) and benefits to a particular patient. The algorithm in Figure 16 provides some strategies for tailoring the initiation and intensification of insulin therapy.

Figure 16: Algorithm for initiating and intensifying insulin



BOTTOM LINE: A GLP-1 receptor agonist can be trialed before insulin in many patients with type 2 diabetes and a HbA1c <10-11% without symptoms of hyperglycemia. For patients with type 2 diabetes who need insulin, most can be successfully treated 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.[200-202] A randomized 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.[203] As a result, it is often recommend that secretagogues (e.g., sulfonylureas, meglitinides) as well as DPP-4 inhibitors should be weaned or discontinued when insulin therapy is initiated or intensified, but other oral and injectable (e.g., GLP-1 receptor agonists) agents that are not secretagogues can be continued.[9]

Overall, the ADA guidelines recommend GLP-1 receptor agonist and insulin as first-line combination therapy in people with type 2 diabetes who require insulin therapy.[9] This is based on copious evidence that combination injection therapy is safe, reduces weight gain, and is equivalent or superior to adding additional insulin. For example, in the **DUAL V** trial, patients with HbA1c 7-10% on glargine and metformin were randomized 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.[204] In another study, the **DUAL VII** Trial randomized 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.[205] It should be noted that in these trials, the average HbA1c was ~8.0-8.5%, and patients were not experiencing symptoms of hyperglycemia. As such, for patients with HgbA1c greater than 10%-11% or experiencing symptoms of hyperglycemia (including weight loss, polyuria, or polydipsia), there is more experience to begin with and uptitrate insulin regimens.

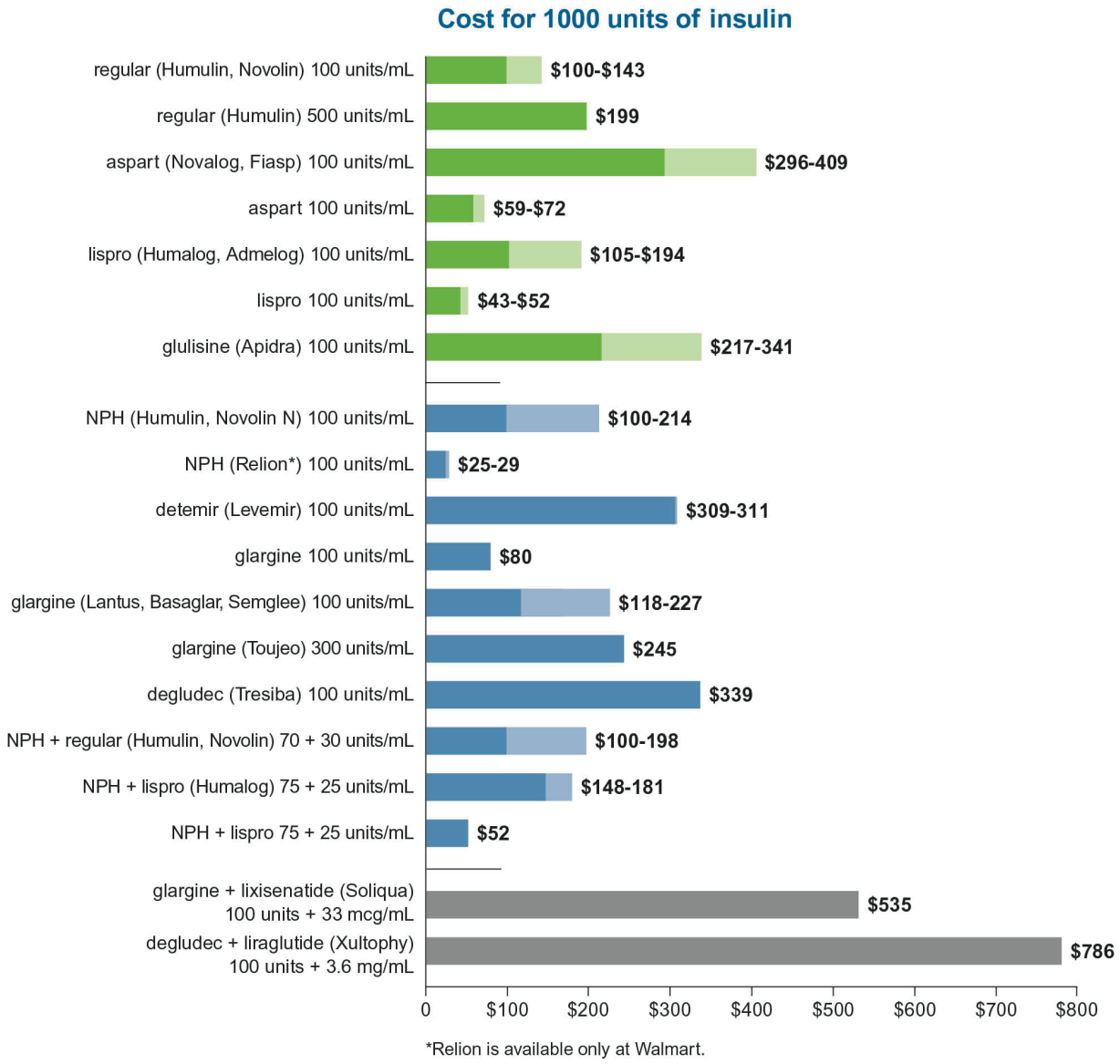
These results have also been shown in meta-analyses. For example, in a meta-analysis of 15 trials with 4,348 participants comparing the combination of GLP-1 receptor agonists and basal insulin vs. other glucose-lowering treatments showed improved mean reductions in HbA1c with the combination (-0.44%; 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).[206] 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).[207]

When placing patients on combination therapy, it is important to remember that the side effect profiles will mirror that of both drugs individuals. For example, there is evidence suggesting that insulin-thiazolidinedione combinations effectively reduce glucose,[208] but fluid retention and other safety concerns about the thiazolidinediones make other options, such as a GLP-1 receptor agonist, a better first-line combination choice.[142]

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-1 receptor agonists offer the greatest synergy for clinical effect and a relatively low risk of adverse events.

Costs of insulin preparations

Figure 17: Costs of selected insulin preparations per 1,000 units



Prices from goodrx.com, March 2022. Listed doses are based on Defined Daily Doses by the World Health Organization and 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.

Bariatric surgery

Gastric bypass and biliopancreatic diversion in 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 >35.0 (32.5 kg/m2 in Asian Americans) who do not achieve improvements in weight and diabetes control with nonsurgical methods.[9]

Multiple trials have now proven the safety and efficacy of bariatric, or metabolic, surgery for improving type 2 diabetes control. For example, a 2012 trial randomized 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.[209] 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).[209] 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).

Another study, 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.[210] Baseline average 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 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 randomized to medicine therapy alone (2.1% vs 0.3%, p<0.001).[211] The durability of these effects has been seen outside of trial scenarios as well, with multiple studies showing the HbA1c lowering effects lasts for >5 years.[212,213]

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.

End-organ damage

While diabetes can sometimes cause morbidity or mortality through acute events such as ketoacidosis or hyperosmolar coma, most complications develop slowly in the form of end-organ damage caused by prolonged hyperglycemia. Preventing diabetes complications is just as important as managing blood glucose levels, and aggressive management of other risk factors (not just hyperglycemia) is critical to the optimal management of these patients.

This effort should begin at diagnosis with careful monitoring of the eyes, heart, and kidneys.[9] This should include:

- a fundoscopic exam and referral to an ophthalmologist for periodic dilated eye exams
- blood pressure control, using an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) in patients with albuminuria (see below)
- careful management of cholesterol levels (see below)
- annual screening for microalbuminuria and eGFR so that antihypertensive therapy can be intensified if kidney function is worsening. Increased BMI and abdominal obesity are associated with albuminuria in adults with type 2 diabetes.[214] Microalbuminuria and low eGFR are both indicators of compromised renal function, and very strong predictors of cardiovascular disease and end stage renal disease

- good foot care, including patient education and referral to a podiatrist as needed

Related conditions and treatment

Patients with diabetes have high rates of hypertension and hyperlipidemia and a significantly elevated risk of cardiovascular, cerebrovascular, and peripheral vascular disease. Optimal management should include close attention to these related medical conditions and aggressive therapy where appropriate (Table 14).

Table 14: Conditions associated with type 2 diabetes and recommended interventions

Condition	Identification	Goal of therapy	Recommended interventions
Hypertension	Check BP at all visits	SBP <140 mmHg DBP <90 mmHg (lower goals may be appropriate for selected patients)*	Use a thiazide diuretic, ACEI, ARB or calcium channel blocker. ACEI or ARB if albuminuria present Start two drugs if >20/10 mm Hg above goal
Hyperlipidemia	Check lipids	Adherence to appropriate statin therapy	Treat with moderate or high intensity statins for all diabetes patients >40 years
Atherosclerotic cardiovascular disease	Assess for cardiac risk factors	Risk reduction	Aspirin for patients with ASCVD; consider SGLT-2 inhibitor or GLP-1 receptor agonist with proven CV benefit
Smoking	Ask about tobacco use	Smoking cessation	Nicotine replacement Bupropion or varenicline Counseling programs

*For patients at higher cardiovascular risk (existing ASCVD or 10-year ASCVD risk >15%), blood pressure targets <130/80 may be appropriate); ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker

Multifactorial intervention in diabetes: The Steno-2 study

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.[215] The trial randomized 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. (Results of the study are summarized in Tables 15 and 16 below.)

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.

Table 15: Clinical and biochemical variables in the Steno-2 study

Variable	End of treatment period (7.8 years)	
	Intensive group*	Conventional group
Mean HbA1c (%)	7.9	9.0
Systolic BP (mmHg)	131	146
LDL (mg/dL)	83	126
Triglycerides (mg/dL)	115	159
Urinary albumin (mg/24 hours)	46	126
* p< 0.05 for all comparisons with conventional group		

Table 16: Clinical outcomes of the Steno-2 study

Outcome	Risk reduction (intensive compared with conventional therapy) after 13.3 years
All-cause mortality	30% vs. 50%, ARR = 20% RRR = 46% (HR 0.54; 95% CI: 0.32-0.89; p=0.02)
Death from CV causes	RRR = 57% (HR 0.43; 95% CI: 0.19-0.94; p=0.04)
CV events	ARR = 29% RRR = 59% (HR 0.41; 95% CI: 0.25-0.67; p<0.001
Development of nephropathy	RRR = 56% (RR 0.44; 95% CI: 0.25-0.77; p=0.004)
Progression of retinopathy	RRR = 43% (RR 0.57; 95% CI: 0.37-0.88; p=0.01)
Progression of autonomic neuropathy	RRR = 47% (RR 0.53; 95% CI: 0.34-0.81; p=0.004)

ARR = absolute risk reduction; RRR = relative risk reduction; RR = relative risk; HR = hazard ratio

Hypertension

ADA-recommended blood pressure targets for many people with diabetes and lower 10-year ASCVD risk are <140 mmHg systolic and <90 mmHg diastolic.[9] Risk is defined using the ASCVD Risk Plus calculator (see **AlosaHealth.org/Diabetes** for links to this and other tools). Lower systolic targets, such as <130 mmHg, may sometimes also be appropriate, such as in younger patients or those with ASCVD risk scores

>15%, if this can be achieved without adverse effects.[9] Note that current AHA/ACC guidelines set a target of <130/80 mmHg for all patients with diabetes, regardless of CV risk.[216]

All patients with a blood pressure of >120/80 mm Hg should be advised about lifestyle modifications that can help reduce blood pressure, including weight reduction, salt restriction, a DASH diet, and exercise.[216] Many of these interventions may also improve glycemic control. Patients with blood pressure >140/90 mm Hg should (in addition to lifestyle therapy) have prompt initiation and titration of drug therapy to achieve blood pressure targets.

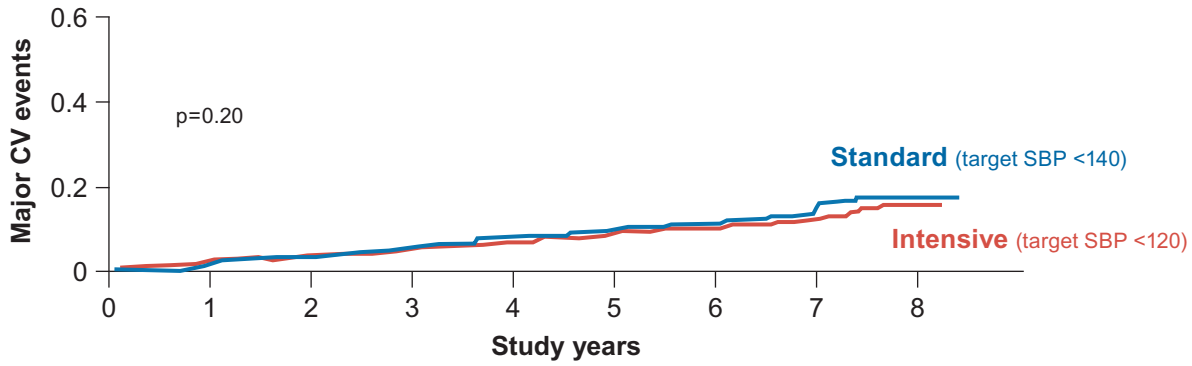
Patients with diabetes and hypertension should be started on an ACEI, ARB, thiazide diuretic, or calcium channel blocker, which have all been shown to help reduce cardiovascular risk in patients with diabetes.[217] ACEI- or ARB-based treatments can also slow the progression of nephropathy and reduce albuminuria.[217] About 10% of patients may have side effects when treated with ACEI (most often cough), and these patients can be switched to an ARB.[218] Many patients with diabetes will require treatment with multiple drugs to achieve target blood pressures. For patients who need a second drug in addition to an ACEI or ARB, a calcium channel blocker could be considered.[219] If ACEIs, ARBs, or diuretics are used, monitor eGFR and serum potassium levels.[9]

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.[220] 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 randomized 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. Accordingly, antihypertensive medications should be adjusted aggressively 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.[221]

A sub-study (ACCORD-BP) of the ACCORD trial compared intensive vs. standard BP control (<120 mmHg vs. <140 mm Hg systolic) in 4,733 patients with diabetes at high risk for CV events.[222] Patients in the intensive group had an average systolic blood pressure of 119 mm Hg, compared to an average systolic blood pressure of 134 mm Hg in the control group (Figure 18). After a mean follow up of 4.7 years, however, 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; see Figure 18) or all-cause mortality (1.3% vs. 1.2%; P=0.55). Although there were fewer strokes in the intensive BP control group (0.32% vs. 0.53%; P=0.01), serious adverse events, such as hypotension, hyperkalemia, and bradycardia, were more common (3.3% vs. 1.3%; p<0.001). Therefore, aggressive BP lowering to achieve systolic BP <120 mm Hg is not recommended for most diabetic patients. If more aggressive BP treatment is pursued in selected patients, the risk of serious adverse events, increased treatment burden, and frequent monitoring should be clearly explained.

Figure 18: Primary composite outcome in the ACCORD-BP study[222]



Some patients with diabetes and hypertension require special consideration. Pregnant women should have hypertension aggressively controlled, 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. Elderly patients may need somewhat slower adjustment of antihypertensive medications.

BOTTOM LINE: Treat blood pressure >140/90 mm Hg aggressively in 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. Adding a CCB to an ACEI reduced CV events more than a thiazide diuretic and ACEI in clinical trials.

Hyperlipidemia

All patients with diabetes should have their cholesterol checked upon diagnosis, and then every five years if not started on statin therapy and <40 years.[9] 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 age and risk factors.

Table 17: Recommendations for statin treatment in patients with type 2 diabetes[9]

Age	ASCVD or 10-year risk >20%	Recommended statin intensity*
<40 years	No Yes	None High
≥40 years	No Yes	Moderate High
* Lifestyle interventions should be continued with statin therapy		

Statin intensity is defined both by the drug and dose (Table 18). Treat most patients with diabetes requiring cholesterol reduction with a statin that has been shown to reduce the risk of cardiovascular events.[223-225] With multiple statins now available generically, most patients can use an affordable, generic statin that will lower their LDL to target levels.[226] Patients with diabetes and ASCVD and LDL ≥70 mg/dL

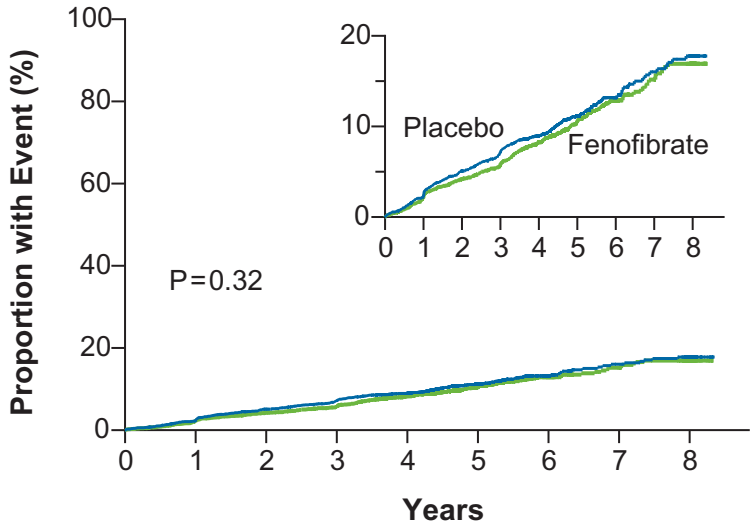
may also benefit from the addition of ezetimibe to a statin and, if LDL remains high, to a further addition of a PCSK9 inhibitor.[227]

Table 18: Classification of high- and moderate-intensity statin therapy

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

The **ACCORD-LIPID** study evaluated intensive vs. conventional lipid lowering regimens (simvastatin + fenofibrate vs. simvastatin alone) in adults with diabetes and existing cardiovascular disease or evidence of atherosclerosis. By trial's end, mean LDL had fallen to about 80 mg/dL in both groups. Triglycerides fell to 144 in the simvastatin-alone group, and to 122 in the group with added fibrate. But after a mean follow up of 4.7 years, there was no significant difference between groups in the rate of composite CV events (2.2% in the fenofibrate+simvastatin group vs. 2.4% in simvastatin alone group; P=0.32) (Figure 19) or all-cause mortality (1.5% versus 1.6%; P=0.33).[228]

Figure 19: Primary outcome in the ACCORD-LIPID study[228]



No. at Risk									
Fenofibrate	2765	2644	2565	2485	1981	1160	412	249	137
Placebo	2753	2634	2528	2442	1979	1161	395	245	131

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.[229] 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.

BOTTOM LINE: Patients with cardiovascular risk factors or cardiovascular disease should be prescribed a statin, regardless of age. Patients with diabetes over age 40 should receive a statin regardless of CV risk factors. Fenofibrate should not routinely be added to statin therapy in patients with diabetes and high CV risk.

Antiplatelet medication

Antiplatelet treatment, specifically with aspirin, has traditionally been recommended for most adults with diabetes.[230] Randomized controlled trials have indicated that aspirin can reduce the incidence of myocardial infarction in patients with *existing* cardiac disease. Virtually all patients with diabetes with 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.[231] Clopidogrel is also commonly used in patients with recent acute coronary syndromes, coronary stent insertions, or peripheral vascular disease.[232]

But the role of aspirin for primary prevention (i.e., in patients without CVD) is more 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).[233] Despite limitations of the sentinel study suggesting risk equivalence,[233] patients with diabetes have often been treated as if they have existing coronary heart disease, and aspirin has often been used for primary prevention in patients with diabetes. However, a 2009 meta-analysis (13 studies, >45,000 patients) did not support the hypothesis that diabetes is a coronary heart disease risk equivalent.[234]

Two older trials and several subsequent meta-analyses have raised questions about the role of aspirin in primary prevention in patients with diabetes. The **POPADAD study**[235] and the **JPAD study**[236] examined the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in patients with type 2 diabetes and found no differences in rates of atherosclerotic events (coronary, cerebrovascular, and peripheral vascular) or all-cause mortality compared to placebo. A 2009 meta-analysis,[237] and another in 2011,[238] came to similar conclusions.

The 2018 **ASCEND trial** randomized 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.[239] 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), although the CI includes differences that may not be clinically important. 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.

In light of the evidence, the ADA and USPSTF both have rather tepid recommendation 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.[9] Alternatively, the USPSTF suggests low-dose aspiring 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.[240]

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. 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.[241] 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.[242]

Conclusions

- Diet and exercise interventions can have a major impact on glucose control, can slow the progression of prediabetes to diabetes, and can improve glycemic control in patients with established diabetes.
- Target a HbA1c of 7% for most patients with diabetes. Modify the goal (e.g., <8.5%) for many frail older patients in whom overtreatment can pose its own risks.
- Choice of initial and step-up therapy should be driven by patient comorbidities.
  - Patients whose primary comorbidity is increased ASCVD risk should be started on an SGLT-2 inhibitor or GLP-1 receptor agonist with known cardiovascular benefits for initial therapy.
  - Patients whose primary comorbidity is CKD (with microalbuminuria) or CHF should be started on an SGLT-2 inhibitor for initial therapy.
  - Patients whose primary comorbidity is obesity may be started on a GLP-1 receptor agonist for initial therapy.
  - In patients without significant comorbidities, metformin remains a reasonable option for initial therapy.
- 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 similarly be guided by patients comorbidities and medication side effect profiles.
- Add insulin promptly when oral agents are not sufficient to achieve HbA1c target.
- Manage hypertension and hyperlipidemia aggressively and focus on smoking cessation when relevant to help prevent diabetes-related complications.
- Continuously promote healthy diet, exercise, and adherence to medications.

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; risk vs. benefit if taking		
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			
TZD	pioglitazone	15 – 20 mg	45 mg				
	rosiglitazone	4 mg	8 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	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 weekly	4.5 mg weekly				
	exenatide	10 mcg	20 mcg				
	exenatide XR	2 mcg weekly	2 mg weekly				
	liraglutide	0.6 mg	1.8 mg				Limited data
	lixisenatide	10 mcg	20 mcg				
	semaglutide injection	0.25 mg weekly	2 mg weekly				
	semaglutide oral	3 mg	14 mg				

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

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