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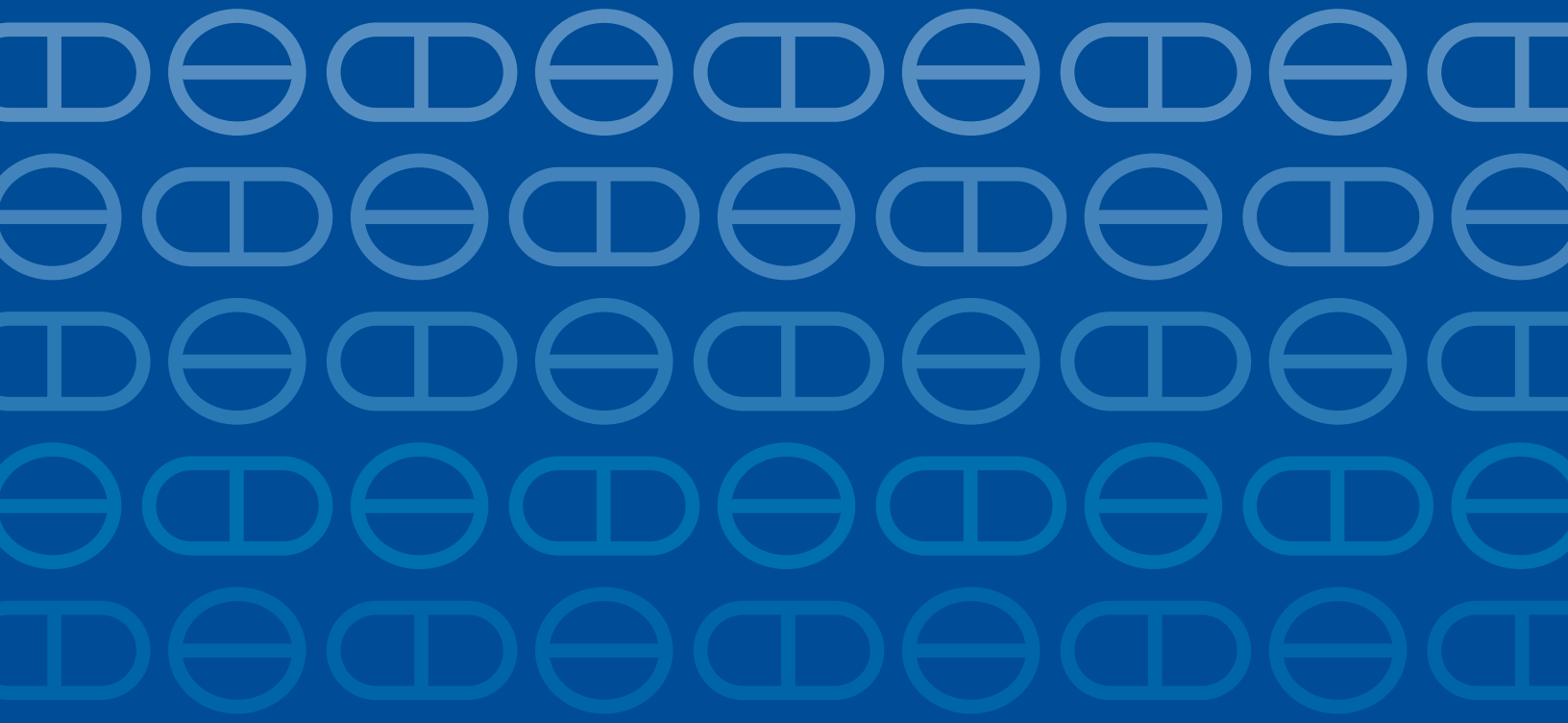
Managing type 2 diabetes

New trials and guidelines are transforming medication use



Managing type 2 diabetes:

New trials and guidelines are transforming medication use

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The Independent Drug Information Service (IDIS) is supported by the PACE Program of the Department of Aging of the Commonwealth of Pennsylvania.

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

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Accreditation:

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of Harvard Medical School and Alosa Health. The Harvard Medical School is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation:

The Harvard Medical School designates this enduring material for a maximum of 1.75 *AMA PRA* participation in the activity.

Activity Overview:

The goal of the educational program is to provide practitioners with up-to-date evidence-based treatment recommendations for type 2 diabetes, including individualized glycemic 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.

Target Audience:

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

Learning Objectives:

Upon completing this activity, participants will be able to:

- Choose an appropriate target HbA1c based on a patient's health status and response to treatments, with a goal of 7% for most patients with diabetes.
- Select metformin as first-line treatment for all patients with type 2 diabetes who require drug treatment, unless contraindicated.
- Choose appropriate additional therapeutic interventions for patients not controlled on metformin based on patient characteristics, with GLP-1 receptor agonists or SGLT-2 inhibitors as agents of choice for patients with ASCVD, heart failure, or CKD.

- Regularly recommend a healthy diet and regular exercise, and assess adherence to medications before titrating doses.
- Select insulin as the agent of choice to be initiated promptly when non-insulin agents are not sufficient to achieve HbA1c target.
- Manage hypertension and hyperlipidemia aggressively to prevent type 2 diabetes-related complications.

Disclosure Policy:

Harvard Medical School has long held the standard that its continuing medical education courses be free of commercial bias.

In accord with the disclosure policy of the Medical School as well as standards set forth by the Accreditation Council for Continuing Medical Education, course planners, speakers, and content reviewers have been asked to disclose any relevant relationship they, or their spouse or partner, have to companies producing, marketing, re-selling or distributing health care goods or services consumed by, or used on, patients. In addition, faculty have been asked to list any off-label uses of pharmaceuticals and/or devices for investigational or non-FDA approved purposes that they plan to discuss. Such disclosure is not intended to suggest or condone bias in any presentation, but is elicited to provide the course director and participants with information that might be of potential importance to their evaluation of a given presentation.

Disclosures:

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Media used:

Printed educational material.

Instructions for Participation and Credit:

There are no fees to participate in this activity. To receive credit, participants must (1) read the statements on target audience, learning objectives, and disclosures, (2) study the educational activity, and (3) complete the post−test and activity evaluation. To receive *AMA PRA Category 1 Credit*™, participants must receive a minimum score of 70% on the post−test. Tests and evaluations should be submitted to Alosa Health via email, mail, or fax.

Tests and evaluations should be submitted to Alosa Health via email, mail or fax.

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Please email any questions to **cme@alosahealth.org** or call **(617) 948-5997.**

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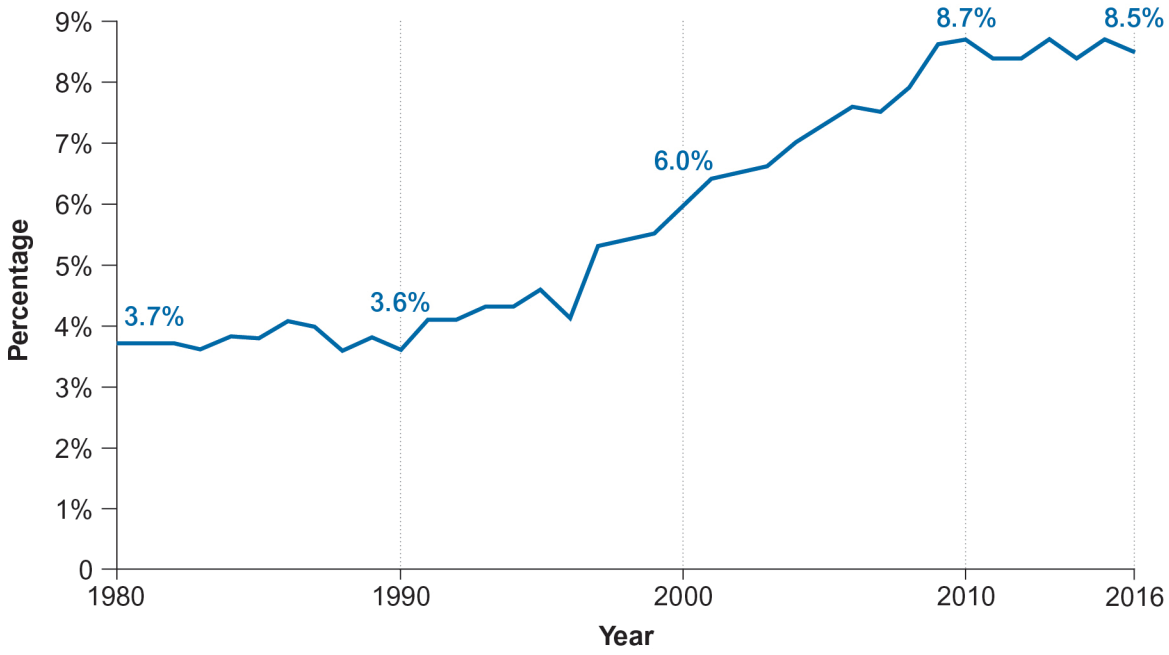
Introduction

Type 2 diabetes is one of the most common chronic conditions in the United States and poses many challenges to the clinicians who care for these patients. Type 2 diabetes accounts for 90%-95% of all diabetes cases, the remainder being type 1 diabetes. Type 1 and type 2 diabetes combined currently affect about 30.3 million Americans (9.4% of the adult population), with incidence rising steadily in the past 20 years.[1] About 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]



Diabetes is more common among older adults and among certain racial and ethnic groups (see Figures 2 and 3, following page).[1]

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

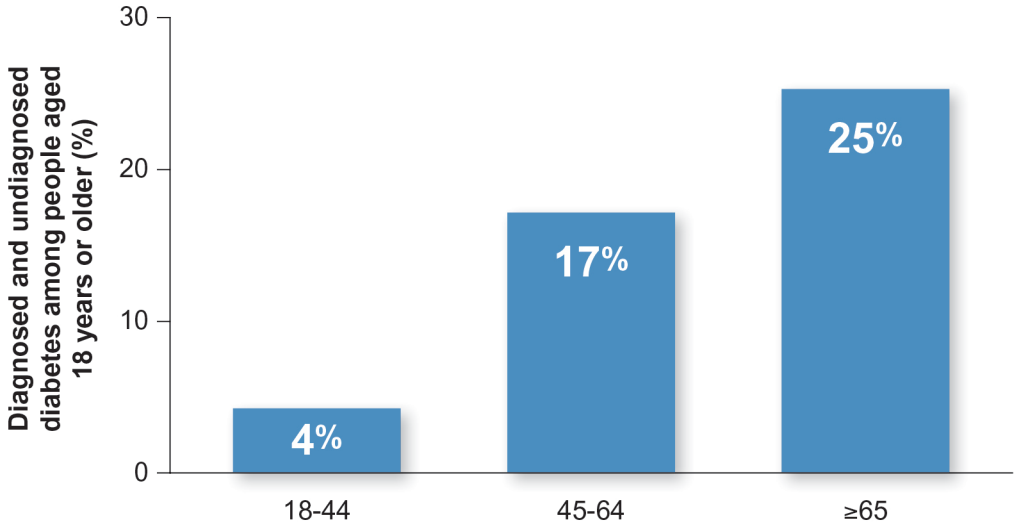
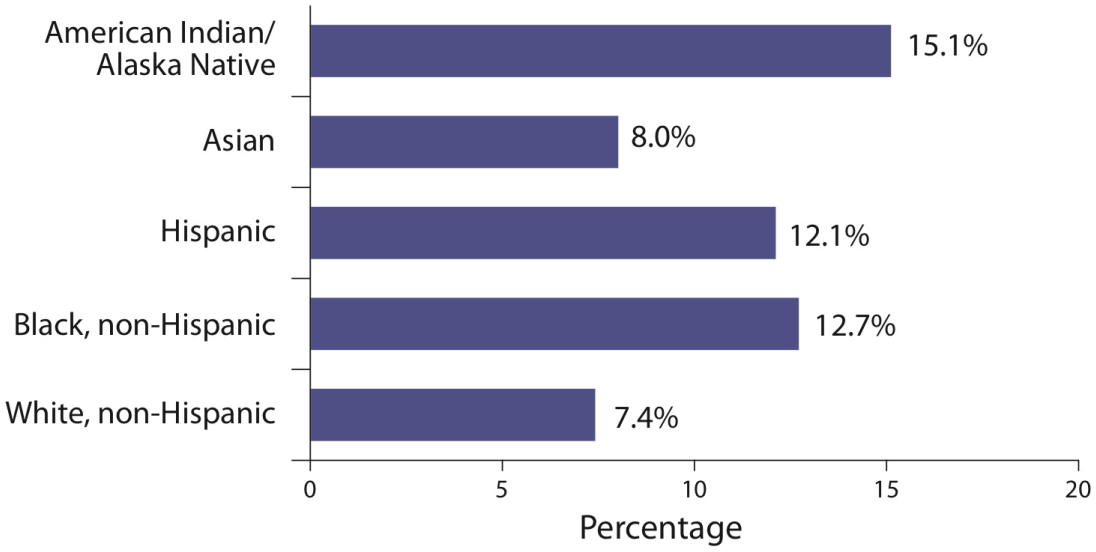


Figure 3: Percentage of U.S. adults aged 18 or older with diagnosed diabetes, by race/ethnicity 2013-2015[3]



Diabetes is associated with a wide range of complications including heart disease, stroke, kidney disease, neuropathy, and retinal damage as well as increased mortality.[1] In 2015, diabetes was the 7th-leading cause of death in the U.S., with about 80,000 death certificates listing diabetes as the underlying cause of death, and 252,806 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).[4]

This high rate of treatment 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.[5] 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[5]

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.[6] • Fasting glucose 100-125 mg/dL indicates prediabetes (impaired fasting glucose, or IFG).[7]
	HbA1c ≥6.5%	• HbA1c of 5.7-6.4% indicates prediabetes (need repeat test to confirm).
	Oral glucose tolerance test (OGTT);[8] plasma glucose ≥200 mg/dL 2 hours after 75 g glucose load	• Gold standard, and recommended by some guidelines,[9] but used infrequently due to inconvenience. • Glucose 140-199 mg/dL indicates prediabetes (impaired glucose tolerance, IGT);[8] repeat test recommended for clinical confirmation.

In 2015, 84.1 million American adults met the diagnostic criteria for "prediabetes," defined as a fasting glucose level between 100-125 mg/dL, a plasma glucose level of 140-199 mg/dL two hours after a 75 g glucose load, or an HbA1c of 5.7%-6.4%.[1,5] This condition is a risk factor for the future development of diabetes, and itself increases the risk of developing cardiovascular disease and stroke.[5] Between 15% and 30% of people with prediabetes will develop type 2 diabetes within 5 years.[1]

Although screening asymptomatic individuals (both youth and adults) for prediabetes/diabetes might appear reasonable, the evidence base for this practice is weak. Current ADA guidelines do not recommend universal screening. More targeted, screening, however, is encouraged.

Table 2: Who should be screened for diabetes?[5]

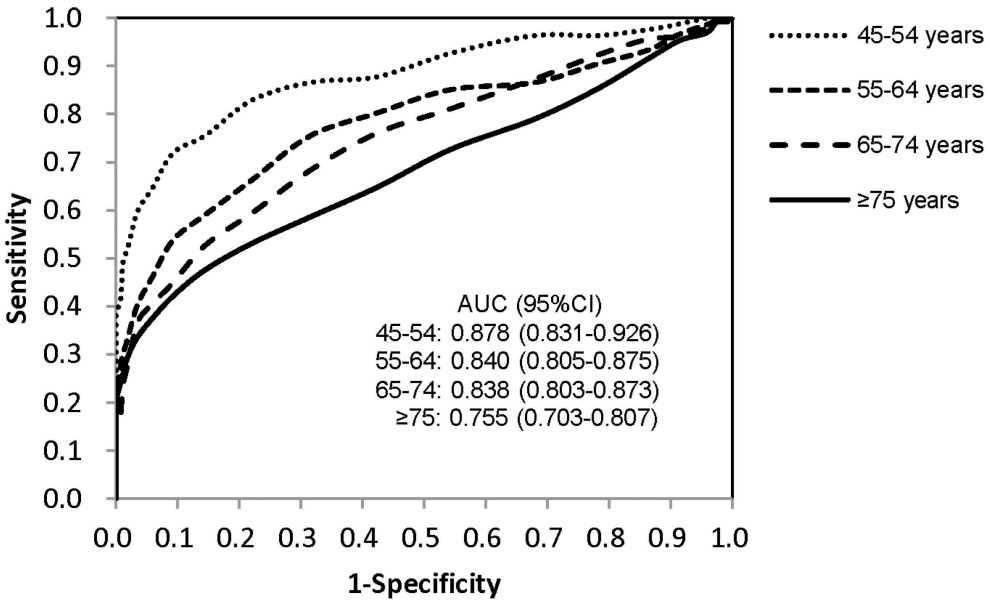
Age	BMI	Other Risk Factors	Frequency
≥45	Any	None required	Screen every 3 years
<45	≥25	*One or more of the following:* First-degree relative with diabetes Physically inactive High-risk ethnic group History of gestational diabetes or delivery of baby weighing >9 lbs* Hypertension Polycystic ovary syndrome 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
* For women with gestational diabetes the recommended screening is every 1-3 years (annually if on insulin in pregnancy or other high risk characteristic).

Screening is best done after fasting ≥8 hours with results interpreted as in Table 1. The oral glucose tolerance test is considered the "gold standard" for screening by some organizations,[9] but it is not routinely used because of its inconvenience for patients and has been largely replaced by measurement of HbA1c in routine practice. If results are normal, testing should be repeated at least every 3 years. Consider more frequent testing depending on initial results and risk status (e.g., those with prediabetes should be tested yearly and women with gestational diabetes should be tested according to current guidelines).

It's important to recognize that the diagnostic accuracy of HbA1c levels may decrease with age.[10] 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 on following page).[10] [Note that 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.]

Figure 4: Age and diagnostic accuracy of HbA1c levels[10]



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/American Heart Association recommending a loss of at least 3%-5%[11] and the American Diabetes Association (ADA) recommending at least 7%-10%.[5] The specific type of diet and balance of macronutrients appears less important than adherence to whichever diet is chosen.[12] An increase in moderate-intensity physical activity to at least 150 minutes/week is also recommended by the ADA for diabetes prevention.[5]

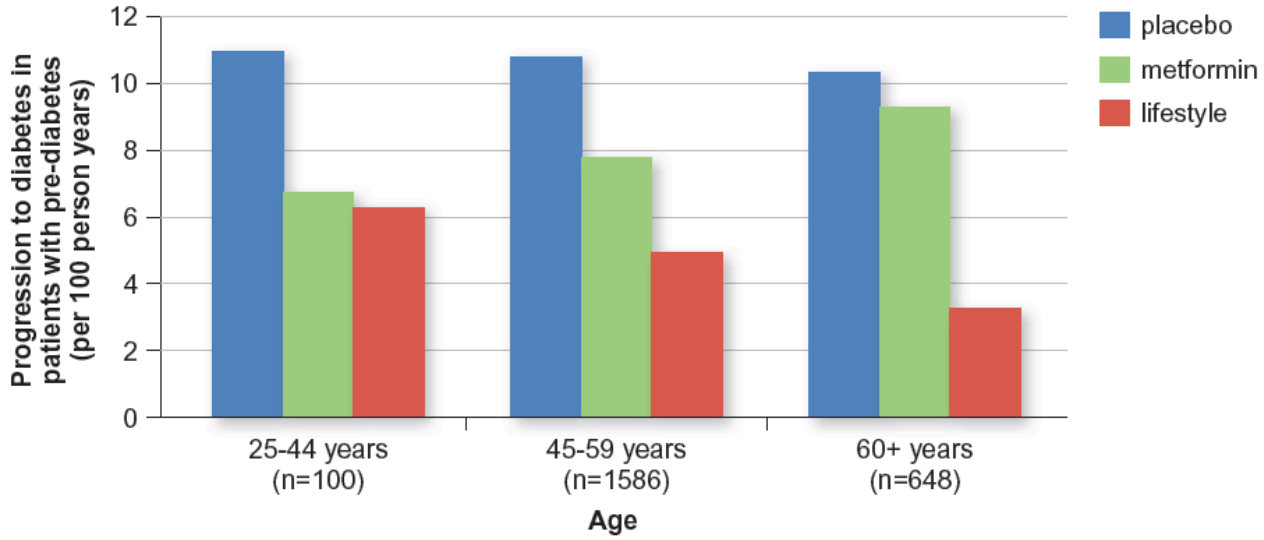
The first large trial of lifestyle modification to prevent diabetes was the **Finnish Diabetes Prevention Study** in which patients with prediabetes and overweight were randomized to usual care (oral and written education about diabetes at baseline and annually thereafter) or a program of weight loss, reduced dietary saturated fat, and 4 hours of exercise weekly.[13] 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%.[14]

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).[15] 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.[15]

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.[16] The DPPOS also showed that weight loss associated with metformin therapy is durable for at least 10 years of treatment.[17] Lifestyle changes were more effective in older adults than in younger individuals. (Figure 5).

Figure 5: Diabetes rates by age group in the Diabetes Prevention Program study[18]



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

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.[19] Another study 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.[20] The **SCALE** trial randomized 2,254 adults with prediabetes to liraglutide 3 mg subcutaneously once daily vs. placebo.[21] 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 ($p < 0.0001$).

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%[15]	GI, usually transient	Twice daily, daily for XR
Acarbose 100 mg	32%	42%	25%[19]	Bloating, flatulence	Three times daily
Pioglitazone 30 mg or 45 mg	5%	17%	72%[20]	Heart failure exacerbation, weight gain	Once daily
Liraglutide 3 mg	6%	2%	79%[21]	GI, gallbladder	Once daily

None of the medications listed in the table above has an FDA-labeled indication for the prevention or delay of diabetes. The 2019 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.[5]

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. 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 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 in order 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.[5]

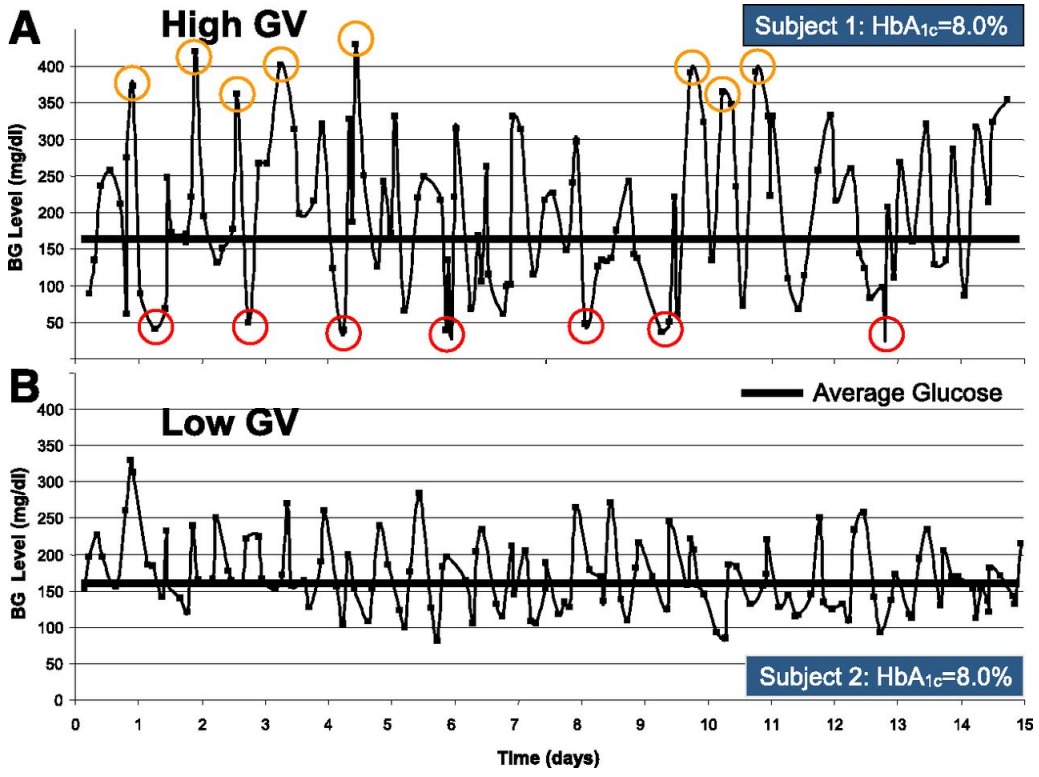
HbA1c levels provide a measure of average blood sugar levels in the preceding 2-3 months (Table 4 on following page). Lowering HbA1c to around 7% has been shown to reduce microvascular complications, and (with early intervention) may also be associated with a reduction in macrovascular disease,[5] although less stringent HbA1c targets are appropriate for selected patients.

Table 4: Correlation between HbA1c level and plasma glucose levels[5]

	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.[22]

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



Long-term outcomes from the **United Kingdom Prospective Diabetes Study (UKPDS)** found that intensive glucose control (defined as use of sulfonylurea or insulin, or, in patients with overweight or obesity, metformin) in patients with newly-diagnosed diabetes may reduce long-term diabetes-related

clinical outcomes compared to diet alone. Ten-year follow-up data from UKPDS published in 2008[23] revealed that although the between-group differences in HbA1c levels did not persist after the first year, 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).

Other trials, however, have found that intensive glycemic control provided no benefit in some key long-term outcomes or *increased* risk for some outcomes (Table 5). The **Action to Control Cardiovascular Risk in Diabetes (ACCORD)** trial,[24] **Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)** trial,[25] and the **Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes (VADT)** trial,[26] found no significant reductions in macrovascular events with more intensive glycemic control compared to less-intensive control. The implications of these data are detailed below.

Table 5: Long-term outcomes in key trials[23-26]

	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 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[25] or VADT[26] studies. It is unclear why intensive glycemic control increased mortality in ACCORD. Although patients in the intensive HbA1c lowering group in that trial used more drugs and drug combinations than patients in the standard-therapy group, their increased mortality was not attributable to any single drug or drug class. Nor did symptomatic, severe hypoglycemia appear to account for the difference in mortality between the two study arms.[27]

There was a significant reduction in microvascular events with intensive glycemic control in ADVANCE, primarily due to a reduction in nephropathy. In contrast, there was no significant reduction in microvascular events for patients randomized to intensive glycemic control in the VADT study.

Four meta-analyses published between 2009 and 2011 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, 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[28] (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)[29]	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)[30]	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)[31]	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.

What is the most appropriate HbA1c target?

Recommendations by a number of diabetes-related professional organizations regarding HbA1c targets can be summarized as follows:[32,5]

- Glycemic control early in the natural history of diabetes substantially reduces risk of microvascular disease and, in the long term, reduces the risk of cardiovascular events, stroke, and death in patients with type 2 diabetes.
- Pushing for targets < 7% late in the natural history of diabetes yields no cardiovascular benefits and may be associated with harm (increased risk of death, hypoglycemia).
- Lower targets may pose higher risk in older patients with established cardiovascular disease and higher-than-average HbA1c levels at baseline.
- Patient-specific personalized diabetes strategies are needed.

Table 7: Expert recommendations for target HbA1c levels[5,9,33-36]

Organization	Year	HbA1c goal*
American Association of Clinical Endocrinologists (AACE) – American College of Endocrinology (ACE)	2019	<6.5%
American Diabetes Association (ADA) – European Association for the Study of Diabetes (EASD)	2018	<7%
ADA Standards of Care	2019	<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.[37] Patients who may benefit from a more stringent HbA1c goal (e.g., <6.5%) include those with relatively recent diabetes diagnosis, pregnant women, and patients with a long life expectancy and no significant cardiovascular disease, if 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.[5,38]

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[5] as well as the AACE.[32]

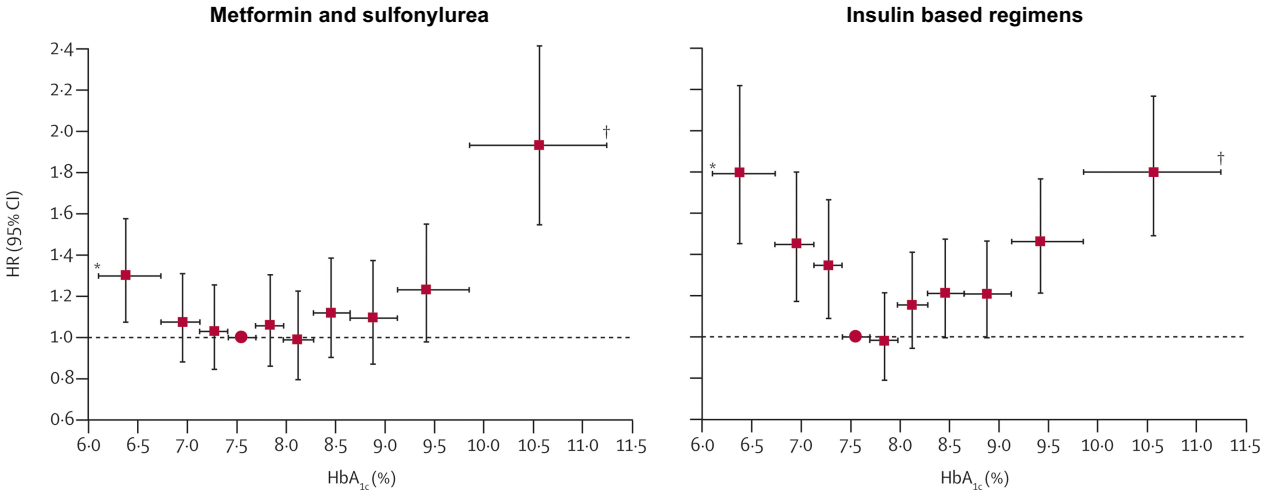
BOTTOM LINE: Aiming for HbA1c levels near or below 7% soon after the diagnosis of diabetes may reduce the risk of microvascular complications and may reduce the risk of macrovascular disease. The greatest clinical benefit of intensive glycemic control occurs early in the course of the disease. A reasonable 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 risks of falls, hypoglycemia, dementia, and mortality associated with lower HbA1c levels.

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.[39] 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.[40]

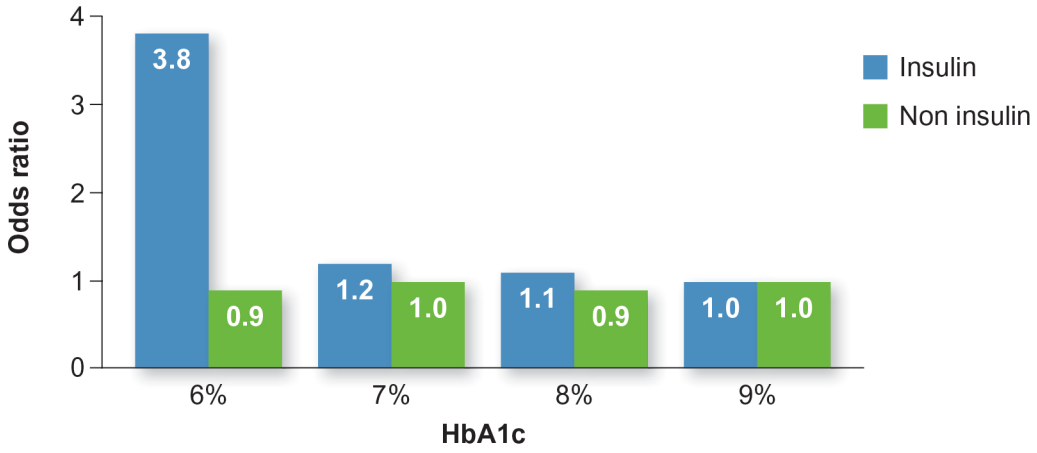
Figure 7: Mortality in adults ≥50 years old is associated with both higher and lower HbA1c levels[40]



Older patients with diabetes are at higher risk for both death from a hyperglycemic crisis and also for needing to be seen in an emergency department for hypoglycemia.[1] A bi-directional link also exists between dementia and hypoglycemia: experiencing hypoglycemic episodes appears to raise the risk of dementia, while having dementia is associated with a higher risk for future hypoglycemic episodes.[41] 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).[42]

Older patients with diabetes who have lower HbA1c levels (i.e., around 6%) on insulin therapy have a significantly higher risk for falls (Figure 8).[43]

Figure 8: Association between HbA1c levels and fall risk in older patients[43]



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.

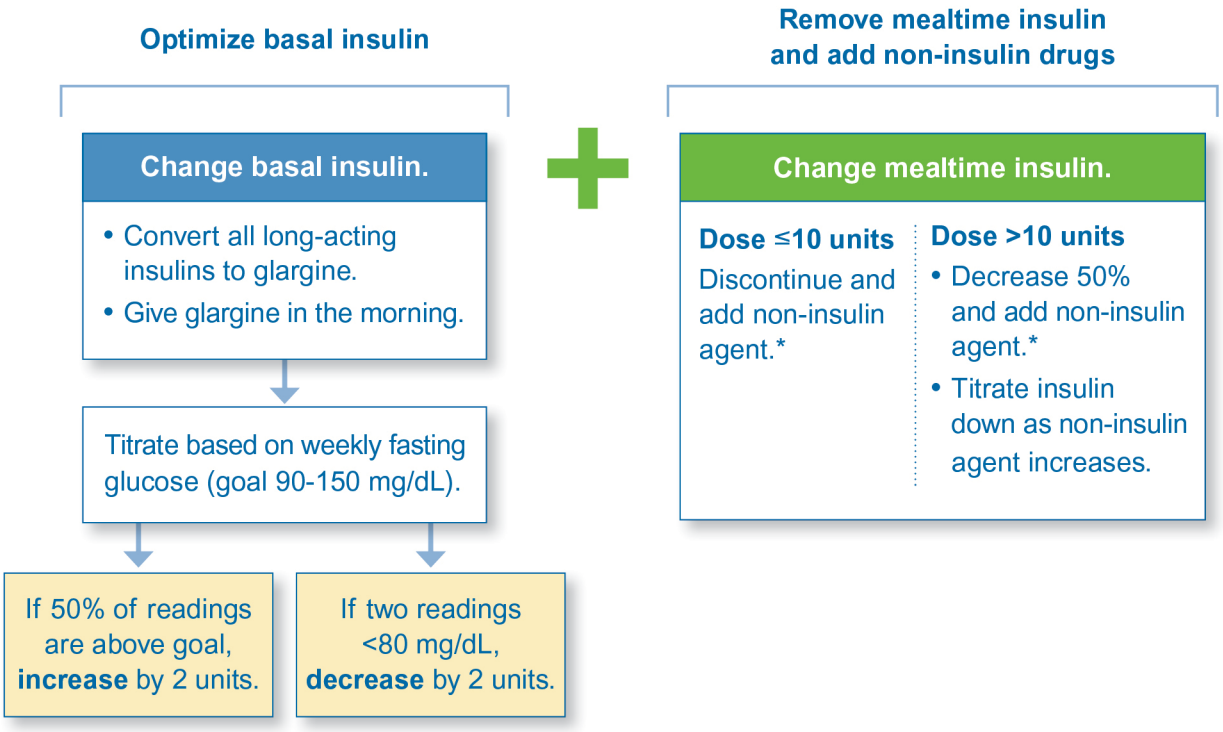
Table 8: Considerations for HbA1c targets in older adults (adapted from 2019 Endocrine Society clinical practice guideline)[9]

		Good health	Intermediate health	Poor health
Patient characteristics		≤2 chronic conditions **AND** No ADL impairments and ≤1 IADL impairment	≥3 chronic conditions **AND/OR** Any of the following: • mild cognitive impairment/early dementia • ≥2 IADL impairments	Any of the following: • end-stage medical condition • moderate to severe dementia • ≥2 ADL impairments • residence in a long-term care facility
HbA1c goal				
Use of drugs causing hypoglycemia (e.g., insulin, sulfonylureas)	No	<7.5%	<8%	<8.5%
	Yes	Keep the HbA1c no more than 0.5% under the goal. For a patient with good health, HbA1c should not be below 7%.		

ADL – activities of daily living; IADL – Instrumental activities of daily living

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 9 on following page).[44]

Figure 9: 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.

Patient blood glucose self-monitoring

In addition to periodic office-based HbA1c measurement, patients should monitor their own glucose as part of diabetes self-management.[45-47] 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.[5] 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.[48] 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.[5]

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.

BOTTOM LINE: Older adults with hypoglycemia have worse outcomes, including an increased risk for dementia. Lower HbA1c levels, especially if using insulin, are associated with increased risk of

falls. Simplifying insulin regimens and raising 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.[13,15] 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.[49] Although some physicians are skeptical about the effectiveness of such lifestyle approaches, in one large trial an aggressive program of diet and exercise actually performed better than drug therapy in controlling blood glucose.[15] Aggressive weight management also benefits other conditions associated with diabetes, such as hypertension and dyslipidemia.

Action for Health in Diabetes (Look AHEAD) was a long-term (2001-2012) clinical trial that 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).[50] 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.[50]

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.[13] 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).[12]

Structured exercise programs can improve blood sugar control even if patients do not lose weight in the process.[51,52] 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.[5] 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.[53] 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.[54] Even moderate levels of exercise, however, can be beneficial.[51]

Combined aerobic-resistance exercise programs are the most effective for supporting blood sugar control.[5,51,55] 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.[56] 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: Lifestyle modification, including diet change and increased exercise, can improve glycemic control in patients with diabetes and can slow progression from prediabetes to diabetes while offering many other health benefits. 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)
Injectable	Glucagon-like peptide (GLP)-1 receptor agonists	dulaglutide (Trulicity) exenatide (Byetta) exenatide XR (Bydureon) liraglutide (Victoza) lixisenatide (Adlyxin) semaglutide (Ozempic)*

*oral semaglutide may have become available since this document went to print in 2019.

These medications differ in their mechanisms of action (Table 10 on following page), their side effects, and their cost.

Table 10: Main mechanisms or pathophysiologic processes affected by non-insulin glucose-lowering agents

		SUs	Metformin	TZDs	Incretin (GLP-1 & DDP4i)	SGLT-2 inhibitors
	Insulin deficiency	✓			✓	
	Insulin resistance		✓	✓		
	Excess hepatic glucose output		✓	✓	✓	
	Renal glucose excretion					✓
	Intestinal glucose absorption		✓			

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 increase the risk of cardiovascular outcomes, despite lowering HbA1c, the FDA now requires that newly-approved glucose-lowering medications be evaluated for CV risk through at least one randomized, placebo-controlled trial. Select SGLT-2 inhibitors and GLP-1 receptor agonists have proven cardiovascular benefit for patients with type 2 diabetes *and* established CVD. Other glucose-lowering medications (e.g. DPP-4 inhibitors, pioglitazone) do not increase the risk of CV events compared to placebo. For older agents, only a few published trials with large sample sizes have compared individual agents to other drugs or to placebo with respect to macrovascular and microvascular outcomes.

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

SGLT-2 inhibitors

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.[57] 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).[57] 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).[57] 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.[58]

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.[59] 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).

GLP-1 receptor agonists

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.[60] 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.

SUSTAIN-6 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.[61] 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 recent trials of GLP-1 receptor agonists: **EXSCEL** (10,782 patients randomized to extended-release exenatide 2 mg per week vs. placebo)[62] 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.[63]

Although not FDA-approved as of this writing, addition of a once-daily oral formulation of the GLP-1 agonist semaglutide was shown in the 2019 **PIONEER 3** trial 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.[64] 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).

DPP-4 inhibitors

Two observational studies, a case-control study with 1,499,650 adults,[65] and a retrospective cohort study with 57,737 adults,[66] 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).[67]

Older agents

In one component of the **UKPDS** trial, non-overweight patients 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.[68] 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).[68] 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).[69] In contrast to the results in normal-weight patients, in patients with overweight metformin significantly reduced the risk of diabetes-related death, death from all causes, and stroke compared to diet alone.[69] 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.[70] 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.[71] 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.[72] 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).

Thiazolidinediones

The Food and Drug Administration (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.[73,74] 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. [75,76]

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).[77] But as discussed in further detail below, both rosiglitazone and pioglitazone may increase the risk of heart failure and fracture.

BOTTOM LINE: Emerging trials of newer agents on cardiovascular outcomes is changing the landscape of diabetes treatment. Selected SGLT-2 inhibitors and GLP-1 receptor agonists demonstrate improvements in CV and renal outcomes. SGLT-2 inhibitors reduce heart failure hospitalizations. CV benefits from SGLT-2 inhibitors and GLP-1 receptor agonists are independent of their HbA1c lowering effects. Older agents such as metformin and pioglitazone have also shown cardiovascular benefits. The CV effects of DPP-4 inhibitors have been neutral. 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. Nevertheless, 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 11).

Table 11: Expected reductions in HbA1c of different glucose-lowering agents

Route	Class	HbA1c lowering
Oral	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%
Injectable	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.[38]

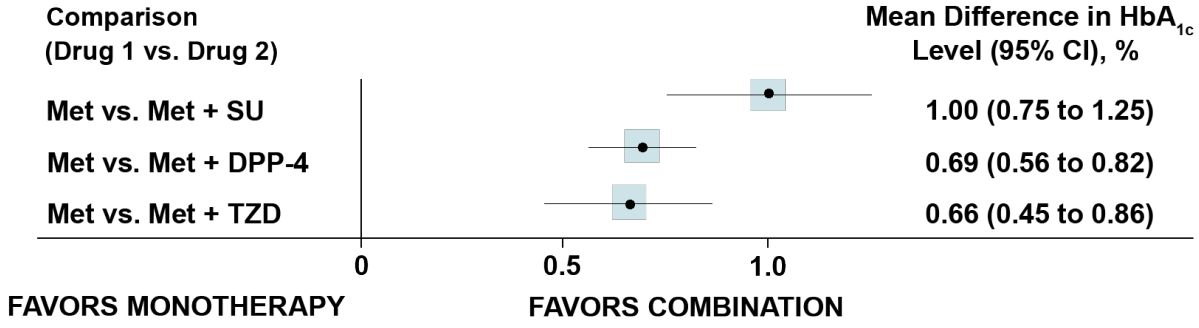
Combination therapy

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 these 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.[38,78]

Several 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.[79,80] 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.[81,82]

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.[70,83-85] 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.[86] 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.[87]

Figure 10: Comparisons of combined treatment versus monotherapy[87]



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%. Agent-and patient-specific factors such as 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 12).

Table 12: Cardiovascular outcomes and adverse effects of glucose-lowering drugs

Class / medication	CV outcome: ASCVD	CV outcome: HF	Worsening nephropathy	Weight change	Hypoglycemia	Precautions
biguanide metformin (Glucophage)	benefit	*	*	loss	no	GI intolerance (start with low dose to minimize)
SGLT-2 inhibitors (flozins) canagliflozin (Invokana) empagliflozin (Jardiance)	benefit	benefit	benefit	loss	no	UTI, ketoacidosis, genital infections, hypotension, fractures (cana), amputation (cana)
dapagliflozin (Farxiga)	neutral					
ertagliflozin (Steglatro)	*	*	*			
GLP-1 receptor agonists liraglutide (Victoza) semaglutide† (Ozempic)	benefit	neutral	benefit	loss	no	GI side effects common pancreatitis
exenatide† (Bydureon) lixisenatide (Adlyxin)	neutral	neutral	*			
dulaglutide† (Trulicity) 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)	benefit	increased risk	*	gain	no	bone fractures, bladder cancer
sulfonylureas glyburide (DiaBeta, Glynase)	neutral	*	*	gain	yes	
glipizide (Glucotrol) glimepiride (Amyarl)	*	*	*			
insulin lispro, aspart, glulisine, regular, NPH	*	*	*	gain	yes	
glargine, degludec, detemir	neutral	*	*			

*no data available; †given weekly

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

Kidney disease

SGLT-2 inhibitors and GLP-1 receptor agonists may be associated with renoprotective effects.

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).[88] 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).

In a 2019 systematic review of 27 studies with 7,363 patients with type 2 diabetes and 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).[89]

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).[90] 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).[60,61]

Weight loss

Metformin, GLP-1 agonists, and SGLT-2 inhibitors may induce weight loss. In trials of exenatide, patients lost approximately 2-3 kg over 6 months, some of which may be due to its gastrointestinal side effects. Weight loss of 2-3 kg over 6-12 months has been reported with liraglutide, both as monotherapy and when added to metformin.[86] 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.[87] By contrast, sulfonylureas and the thiazolidinediones generally cause weight gain.[78]

Cholesterol

Metformin lowers LDL cholesterol by a mean of 10 mg/dL.[78] 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.[78] 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.[79] Alogliptin, linagliptin, and saxagliptin have been reported to be lipid neutral.[91-93] A 2012 meta-analysis found that the DPP-4 inhibitors reduced total cholesterol and triglycerides.[94] Clinical studies and a meta-analysis have reported the GLP-1 receptor agonist exenatide as being lipid neutral or beneficial.[95-98] (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. Some SGLT-2 inhibitors and GLP-1 receptor agonists have been shown to delay progression of diabetic kidney disease.

Comparative safety

Hypoglycemia

The clinical consequences of hypoglycemia include increased risk of falls, car crashes, confusion, and (possibly) increased risk of dementia.[41,43] 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).[69]

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.[99,32] 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.[78] 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.[99] 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 and peripheral edema

The risk of heart failure caused by thiazolidinediones has been known for some time.[70] Even in lower-risk populations, both pioglitazone and rosiglitazone substantially elevate the risk of heart failure.[73,74,77]

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.[100,101] 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%.[99]

Other glucose-lowering medications appear to have a neutral effect on heart failure,[32] 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.[102]

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.[78] 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.[70,83-86] Exenatide is associated with a significant increased risk of pancreatitis, causing the FDA 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.[103] Pancreatitis has also been reported during liraglutide treatment, but there are no conclusive data establishing causality.[86] In five trials of ≥26 weeks duration, the incidence of withdrawal due to adverse events was 7.8% for liraglutide-treated patients and 3.4% for comparator-treated patients. Withdrawals were mainly driven by GI adverse events.[86]

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.[104] 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)

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.[71] 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.[105] 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).[58]

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).[106]

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

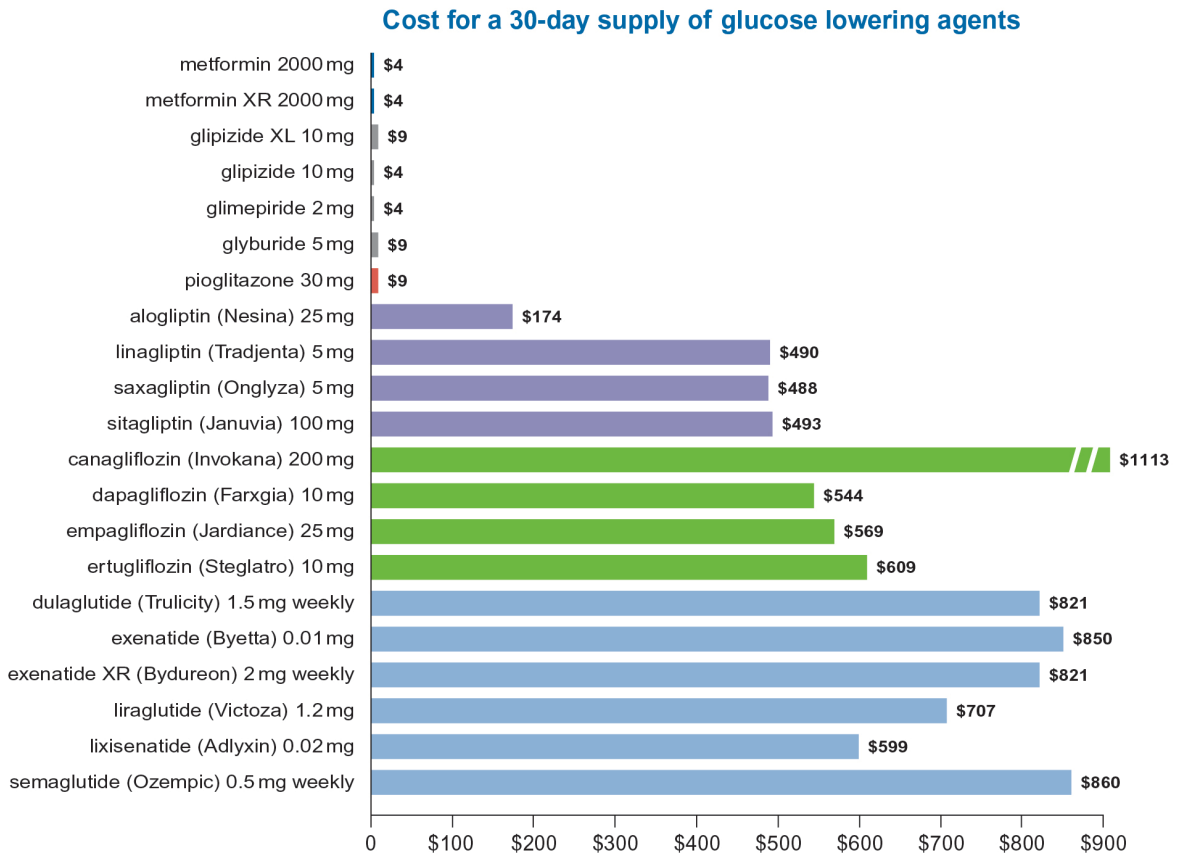
Because they increase the glucose content of urine, SGLT-2 inhibitors increase the risk of genital and urinary tract infections, particularly yeast infections, compared to other classes of glucose-lowering medications.[107] SGLT-2 inhibitors have also been associated with rare cases of ketoacidosis,[107] Fournier's gangrene,[108] and an increased risk of amputation (compared to placebo).[58]

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



Source: Prices are from goodrx.com as of January 2019.

Initiation of therapy: Which drug to choose?

Based on its therapeutic profile, relative safety, and low cost, metformin remains the best therapeutic choice as initial therapy for most patients with type 2 diabetes.

This recommendation is consistent with the most recent guidance from the ADA[5] as well as the 2019 AACE-ACE consensus statement on type 2 diabetes management.[32] These guidelines state that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first-line agent. Metformin should be initiated at (or soon after) diagnosis, particularly when lifestyle interventions alone are unlikely to achieve HbA1c goals. This recommendation is supported by results from UKPDS and other high-quality trials. Data supporting the use of other classes of agents (i.e., DPP-4 inhibitors, most GLP-1 receptor agonists, and most SGLT-2 inhibitors) are insufficient to recommend their routine use as initial therapy for most patients.

These guidelines may not apply to all patients due to contraindications to or intolerance of specific medications. Table 13 summarizes situations in which metformin and other oral agents may be contraindicated. The FDA updated its renal guidelines for metformin in 2016 with recommendations to obtain an estimated glomerular filtration rate (eGFR) prior to initiating therapy and annually thereafter (although more frequently for those at risk for renal impairment).[109] 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 13: Non-insulin glucose-lowering agents contraindications and warnings

Class	Contraindications and warnings
Metformin	• renal disease or dysfunction — avoid 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)
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: Metformin remains the drug of first choice for the initial treatment of type 2 diabetes unless contraindicated. GI side effects are common but can be minimized by gradual upward titration.

Monitoring and dose intensification

After confirming that the patient has type 2 diabetes and not type 1, 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.[5]

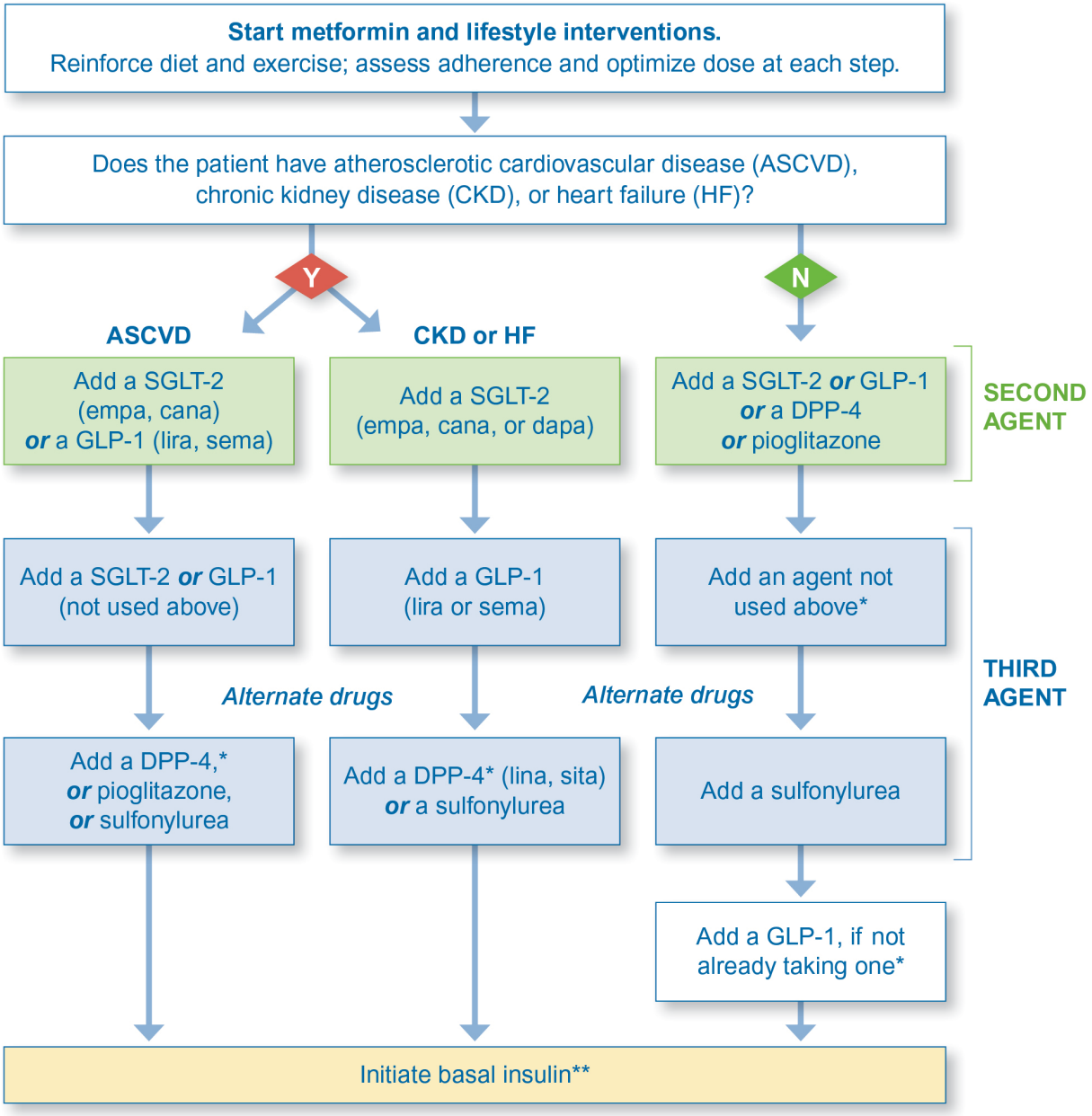
There are many therapeutic options for patients who are poorly controlled on monotherapy with metformin. In asymptomatic patients, a second agent should be added if HbA1c remains above target after approximately 3 months of optimal monotherapy. (If metformin, that would be a maximum of about 2 grams/day, titrated slowly to enhance tolerance and therefore adherence.) Which agent is chosen next can be based on a patient's cardiovascular status and risk. The algorithm in Figure 12 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. Many seemingly 'inadequate' responses to prescribed regimens are actually the result of patients not taking their medications as directed.

For patients with established CVD, an SGLT-2 inhibitor (empagliflozin or canagliflozin) or GLP-1 receptor agonist (liraglutide or semaglutide) with cardiovascular benefit is recommended as the second agent to add to baseline metformin. If patients have heart failure or CKD, then an SGLT-2 inhibitor is preferred over a GLP-1 receptor agonist given the positive impact on reducing heart failure hospitalization. If a third agent is needed, any 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 established CVD, medication-specific factors should determine which agent is the best option. If weight is a concern, then SGLT-2 inhibitors and GLP-1 receptor agonists 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. For other patients, insurance coverage, side effect profile, and patient preferences drive selection. Up to three agents may be combined to achieve an HbA1c goal before adding insulin. Insulin may be added at any point if it is preferred or if the patient has overt symptoms (e.g. polyuria, polydipsia, weight loss) associated with uncontrolled diabetes.

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.[38]

Figure 12: Preferred treatment options*



* Avoid prescribing a DPP-4 and GLP-1 together.

** **Basal insulin can be initiated if needed at any point.**

***** 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. Cardiovascular and microvascular or macrovascular benefits are demonstrated for metformin, some GLP-1 receptor agonists, some SGLT-2 inhibitors, and pioglitazone.

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

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

4. Glucose-lowering drugs vary significantly in price.

5. Based on the available evidence, metformin is the most appropriate choice to initiate pharmacologic therapy in most patients.

6. When a second agent is needed, selection should be based on patient characteristics such as the presence of established CVD or CKD at baseline.

Insulin therapy

Many patients with type 2 diabetes will eventually require insulin therapy.[38] 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.[110] Data from the National Health and Nutrition Examination Survey indicate that only 37% of patients with type 2 diabetes achieve HbA1c <7%.[111]

Unfortunately, despite convincing evidence for benefit, insulin often is not started even when clinicians and patients are aware of poor glucose control.[112-114] 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.[115,116] 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."[115,116]

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 2019 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%).[5]

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.[38] Initial therapy is usually with a "basal" insulin (unless the patient is markedly hyperglycemic and/or symptomatic).

Basal insulin provides fairly 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.[38] 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.

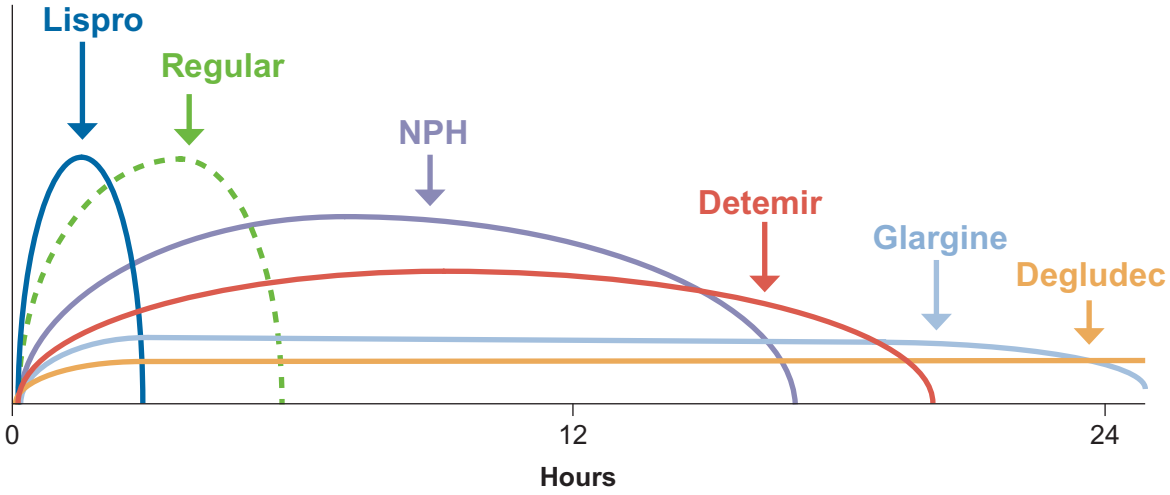
Most patients with type 2 diabetes requiring insulin therapy can be successfully treated with basal insulin alone. However, because of progressive reduction in endogenous insulin secretion, some will need prandial insulin therapy with shorter-acting insulins or pre-mixed insulins (which combine basal and short or rapid-acting insulin).[38]

Insulin is also indicated for patients who are pregnant, require high-dose glucocorticoid therapy, or are intolerant of other glucose-lowering agents,[117] as well as for hospitalized patients.[118]

Insulin preparations

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

Figure 13: Comparison of human insulin preparations and insulin analogs[119]



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.[120] However, these analogs may perform better than regular human insulin for managing 2-hour postprandial glucose, reduce the incidence of hypoglycemia in type 1 diabetes, and may be a better option than regular insulin for many patients with type 1 diabetes.[120]

Intermediate-acting (basal) insulin: NPH

NPH is absorbed more slowly than regular insulin (onset of action 2-4 hours) and has a longer duration of action (10-20 hours). It takes 6-7 hours to reach peak effectiveness. When used as basal insulin, it can be given once or twice daily.

Long-acting (basal) insulin analogs: glargine 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). 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.[121]

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.

Ultralong-acting insulin

Insulin degludec has an onset of action 2-4 hours after subcutaneous injection. It has a half-life of 25 hours, and no peaks. The level of insulin degludec is stable over 36 hours and has a duration of action up to 48 hours. Insulin degludec has similar efficacy when compared to insulin glargine. Fewer events of hypoglycemia occurred in patients taking degludec compared to glargine.[122] The timing of degludec dosing is more flexible than glargine, and may be beneficial for patients in whom compliance is a concern.[123]

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 may improve 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.

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). 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 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

Treating to target

A commonly-used algorithm for insulin intensification comes from the **Treat-to-Target** trial.[48] 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 14.

Table 14: Insulin initiation and titration

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

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

The **Treat-to-Target Trial** randomized 756 overweight subjects 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.[48] 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 study design was used to compare NPH insulin with detemir in type 2 patients with diabetes with suboptimal glycemic control on oral therapy.[124] 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.

The **LANMET trial** compared treatment with glargine and metformin vs. NPH and metformin in type 2 diabetes.[125] It found similar glucose control in both groups, but there were fewer hypoglycemic events in the first 12 weeks in the glargine group. However, at 36 weeks, the investigators found no significant differences in hypoglycemic events, suggesting that the hypoglycemic risk may be transient. NPH and glargine are both effective in reducing HbA1c, but patients prescribed NPH should be aware of the chance of hypoglycemia events within the first 3 months of treatment.

A retrospective analysis of 25,489 patients (mean age 60 years) started on basal insulin therapy (glargine vs. NPH) and followed for a mean of 1.7 years found similar rates of emergency department visits for hypoglycemia (8.8 events/1000 person years with NPH vs. 11.9 events/1000 person years with long-acting insulins, P=0.07), although patients on NPH had slightly greater reduction in mean HbA1c (mean difference -0.22%; 95% CI: -0.09% to -0.37%).[126]

Another observational study of 14,635 older adults (mean age 73 years) with type 2 diabetes (mean HbA1c 8.5%) who switched from analog (basal-bolus regimens) to human insulin (premixed 70/30 and NPH) showed a very small (and not clinically relevant) rise in mean HbA1c (0.14%) after the switch, with no significant differences in hypoglycemic events.[127] There was a decreased risk of reaching the Part D coverage gap (HR 0.45; 95% CI: 0.43-0.48).

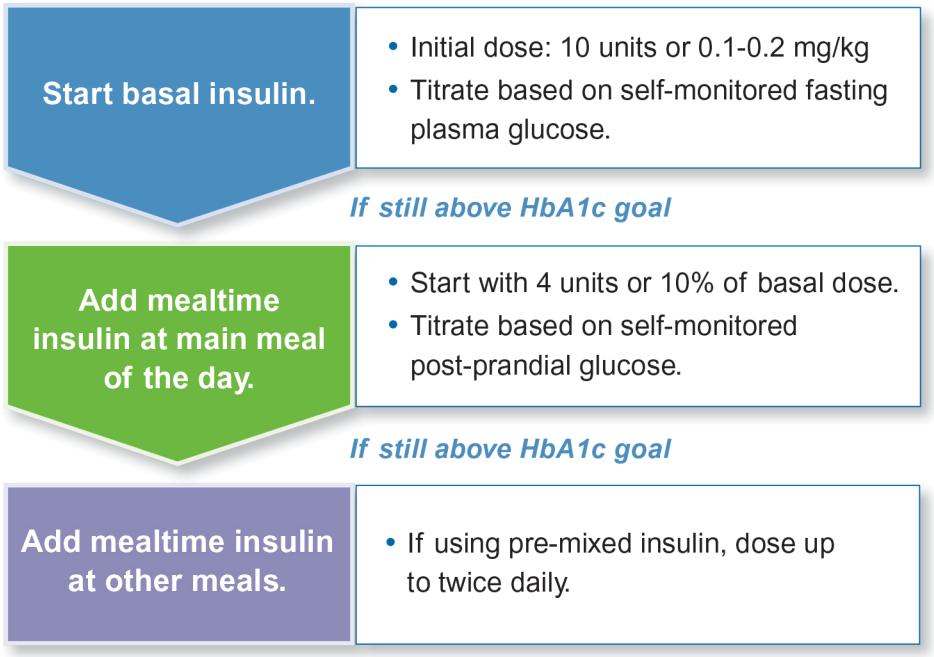
Several studies have suggested that treatment with biphasic (mixed-preparations) and prandial (ultra-fast acting) regimens offer improved glucose control, although they can increase the risk of hypoglycemia and cause more weight gain.[128-130] In the **4-T trial**, patients poorly controlled with oral glucose-lowering agents were randomized to receive biphasic insulin, prandial insulin, or detemir.[128] 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), but also more hypoglycemia and weight gain (4.7 kg, 5.7 kg, 1.9 kg, respectively). Benefits in glucose control were seen only in patients with a starting HbA1c >8.5%.

On the other hand, the **APOLLO 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.[131]

In summary, no specific insulin regimen has been shown clearly superior to any other for managing hyperglycemia in type 2 diabetes. The choice should be based on the relative costs and benefits to a

particular patient. The algorithm in Figure 14 provides some strategies for tailoring the initiation and intensification of insulin therapy.

Figure 14: Algorithm for initiating and intensifying insulin



BOTTOM LINE: Many patients with type 2 diabetes who need insulin can be successfully treated with a single dose of basal insulin at bedtime. This dosing is simple and no convincing evidence exists showing that any other approach 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.[132-134] 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.[135] As a result, it is often recommend that secretagogues (e.g., sulfonylureas, meglitinides) should be stopped when insulin therapy is initiated or intensified, but other oral agents that are not secretagogues can be continued.[5] The ADA guidelines recommend metformin and insulin as first-line combination therapy in people with type 2 diabetes who require insulin therapy.[5] Despite evidence suggesting that insulin-thiazolidinedione combinations effectively reduce glucose,[136] fluid retention and other safety concerns about the thiazolidinediones make metformin-insulin a better first-line choice.[137]

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

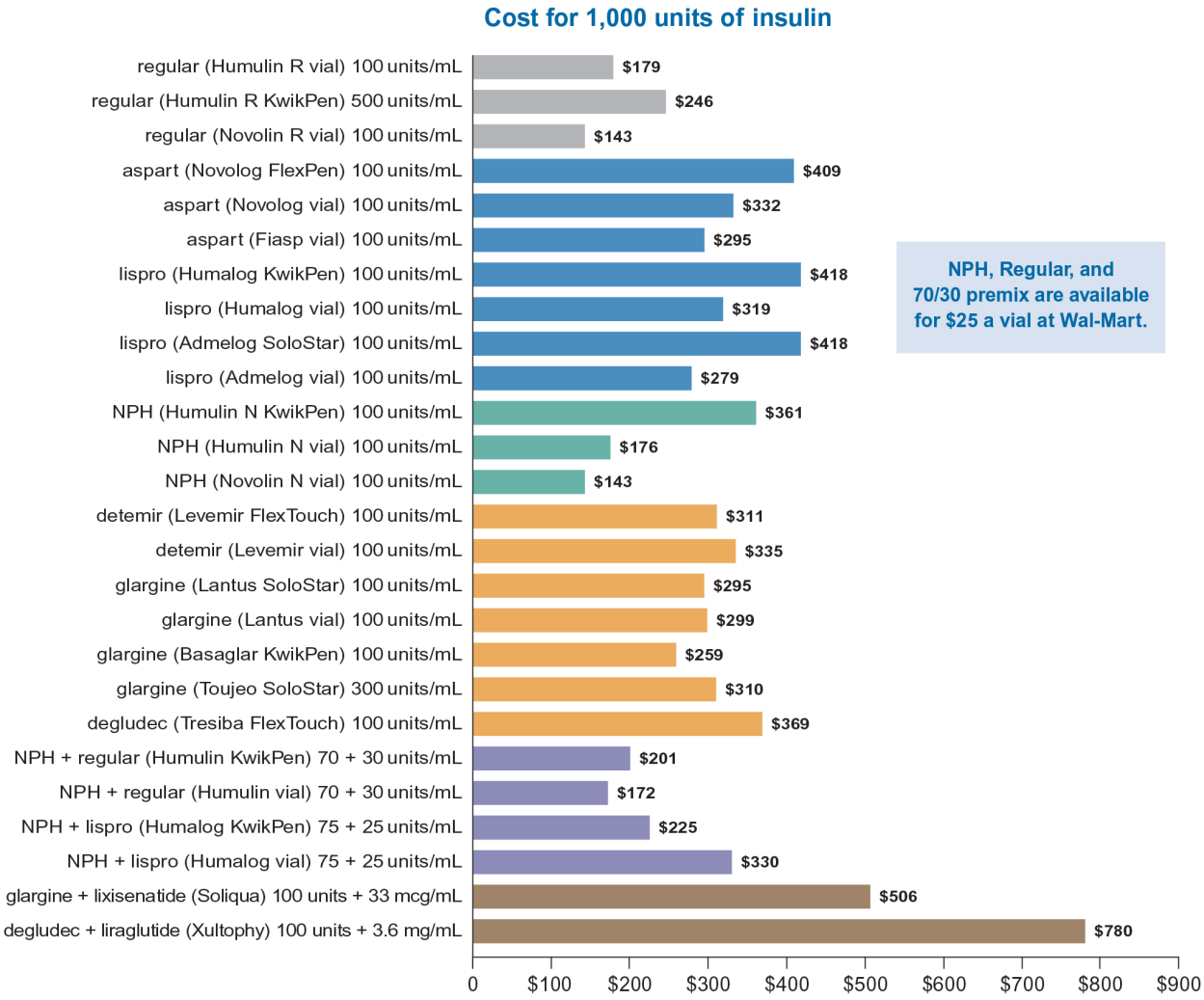
the combination (-0.44%; 95% CI: -0.60% to -0.29%), an improved likelihood of achieving the target HbA1c of 7·0% or lower (RR 1.92; 95% CI: 1.43-2.56), no increased risk of hypoglycemia (RR 0.99; 95% CI: 0.76-1.29), and a mean weight reduction 3.22 kg (1.54 kg-4.90 kg).[138]

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).[139]

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 metformin offers the greatest synergy for clinical effect and the lowest risk of adverse events.

Costs of insulin preparations

Figure 15: Costs of selected insulin preparations per 1,000 units



Source: goodrx.com (as of January 2019)

Bariatric surgery

Gastric bypass and biliopancreatic diversion in patients with morbid obesity can often result in remission of type 2 diabetes. 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.[140] At 2 years, diabetes remission had occurred in no patients in the medical-therapy group versus 75% in the gastric-bypass group, and 95% in the biliopancreatic-diversion group ($p<0.001$ for both comparisons).[140] At 2 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).[140]

Another study 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.[141] 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 ($P=0.003$).[141]

Bariatric surgery may 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. The long-term benefits of bariatric surgery compared to optimal medical/lifestyle therapy are not adequately documented, although data from cohort studies suggest a mortality benefit after 10 years.[5] Specifically, the ADA recommends bariatric surgery as a treatment option in patients with BMI >40 kg/m^2 (or BMI >35 kg/m^2 for Asian-Americans) who do not achieve durable weight loss and improvements in comorbidities with reasonable nonsurgical methods.[5] For adults with lower BMIs, (30-34.9 kg/m^2 or 27.5-32.4 kg/m^2 for Asian-Americans) the ADA suggests that bariatric surgery may be an option if other methods have failed.[5]

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.[5] 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.[142] 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 15).

Table 15: 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 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

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.[143] 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 macroabuminuria (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 16 and 17 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 16: 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 17: 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 people with diabetes and lower 10-year ASCVD risk are <140 mmHg systolic and <90 mmHg diastolic.[5] Targets for patients with higher 10-year risk (>15%) are 130/80 mmHg.[5] 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, if this can be achieved without adverse effects.[5] (Current AHA/ACC guidelines set a target of <130/80 mmHg for all patients with diabetes, regardless of CV risk).[144]

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.[144]

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.

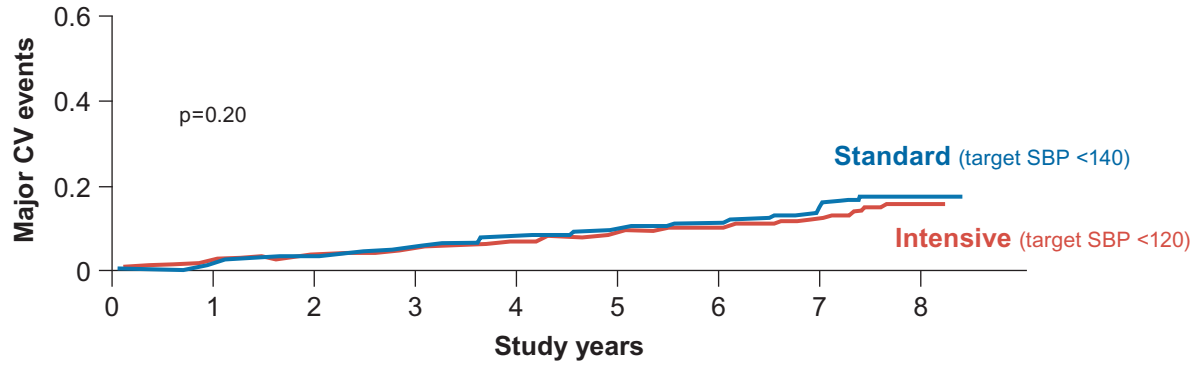
Patients with diabetes and hypertension should be started on an ACEI, ARB, thiazide diuretic, or calcium channel blocker, which have all been shown to help reduce cardiovascular risk in patients with diabetes.[145] ACEI- or ARB-based treatments can also slow the progression of nephropathy and reduce albuminuria.[145] About 10% of patients may have side effects when treated with ACEI (most often cough), and these patients can be switched to an ARB.[146] Many patients with diabetes will require treatment with multiple drugs to achieve target blood pressures.[5] For patients who need a second drug in addition to an ACEI or ARB, a calcium channel blocker could be considered.[147] If ACEIs, ARBs, or diuretics are used, monitor eGFR and serum potassium levels.[5]

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.[148] 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.[149]

A sub-study (ACCORD-BP) of the ACCORD trial compared intensive vs. standard BP control (<120 mmHg vs. <140 mmHg systolic) in 4,733 patients with diabetes at high risk for CV events.[150] Patients in the intensive group had an average systolic blood pressure of 119 mmHg, compared to an average systolic blood pressure of 134 mmHg in the control group (Figure 16). 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 16) 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 mmHg 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 16: Primary composite outcome in the ACCORD-BP study[150]



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, and maintain BP control over time. 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.[5] 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 18: Recommendations for statin treatment in patients with type 2 diabetes[5]

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 19). Treat most patients with diabetes requiring cholesterol reduction with a statin that has been shown to reduce the risk of cardiovascular events.[151-153] With multiple statins now available generically, most patients can use an affordable, generic statin that will lower their LDL to target levels.[154] Patients with diabetes and ASCVD and LDL ≥70 mg/dL

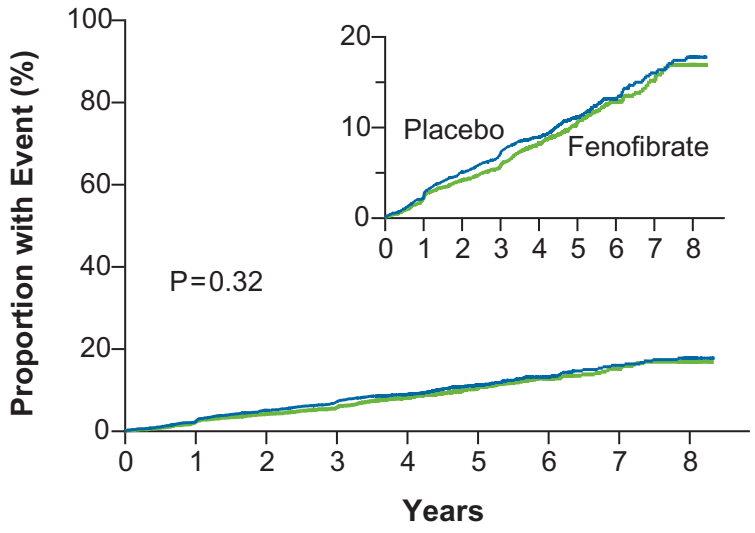
may also benefit from the addition of ezetimibe to a statin and, if LDL remains high, to a further addition of a PCSK9 inhibitor.[155]

Table 19: 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 17) or all-cause mortality (1.5% versus 1.6%; P=0.33).[156]

Figure 17: Primary outcome in the ACCORD-LIPID study[156]



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.[157] 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.[158] 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.[159] Clopidogrel is also commonly used in patients with recent acute coronary syndromes, coronary stent insertions, or peripheral vascular disease.[160]

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).[161] Despite limitations of the sentinel study suggesting risk equivalence,[161] 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.[162]

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**[163] and the **JPAD study**[164] 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,[165] and another in 2011,[166] 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.[167] 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 2019 ADA guidelines make the following recommendations:[5]

- Aspirin is not recommended for people <50 years old with diabetes and low ASCVD risk.
- For primary prevention, aspirin needs to be carefully considered and may not be recommended for all patients.
- For secondary prevention, aspirin 75-162 mg/day is recommended (i.e., in those with a history of ASCVD).

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.[168] 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.[169]

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.
- Use metformin as first-line treatment for the vast majority of patients with type 2 diabetes who require drug treatment.
- Focus on adherence before titrating doses or adding a new drug.
- Intensify treatment with a second oral agent for patients who are not controlled on metformin
  - Choose a second-line treatment based on patient characteristics.
  - Prescribe a GLP-1 receptor agonist or an SGLT-2 inhibitor for patients with established CVD, heart failure, or CKD based on trial data.
- 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	2.5mg/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 maximum			
	dapagliflozin	5 mg	10 mg				
	empagliflozin	10 mg	25 mg				
	ertugliflozin	5 mg	15 mg				
GLP-1 receptor agonists	dulaglutide	0.75 mg weekly	1.5 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				X
	semaglutide	0.25 mg weekly	1 mg weekly				

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

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About this publication

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

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