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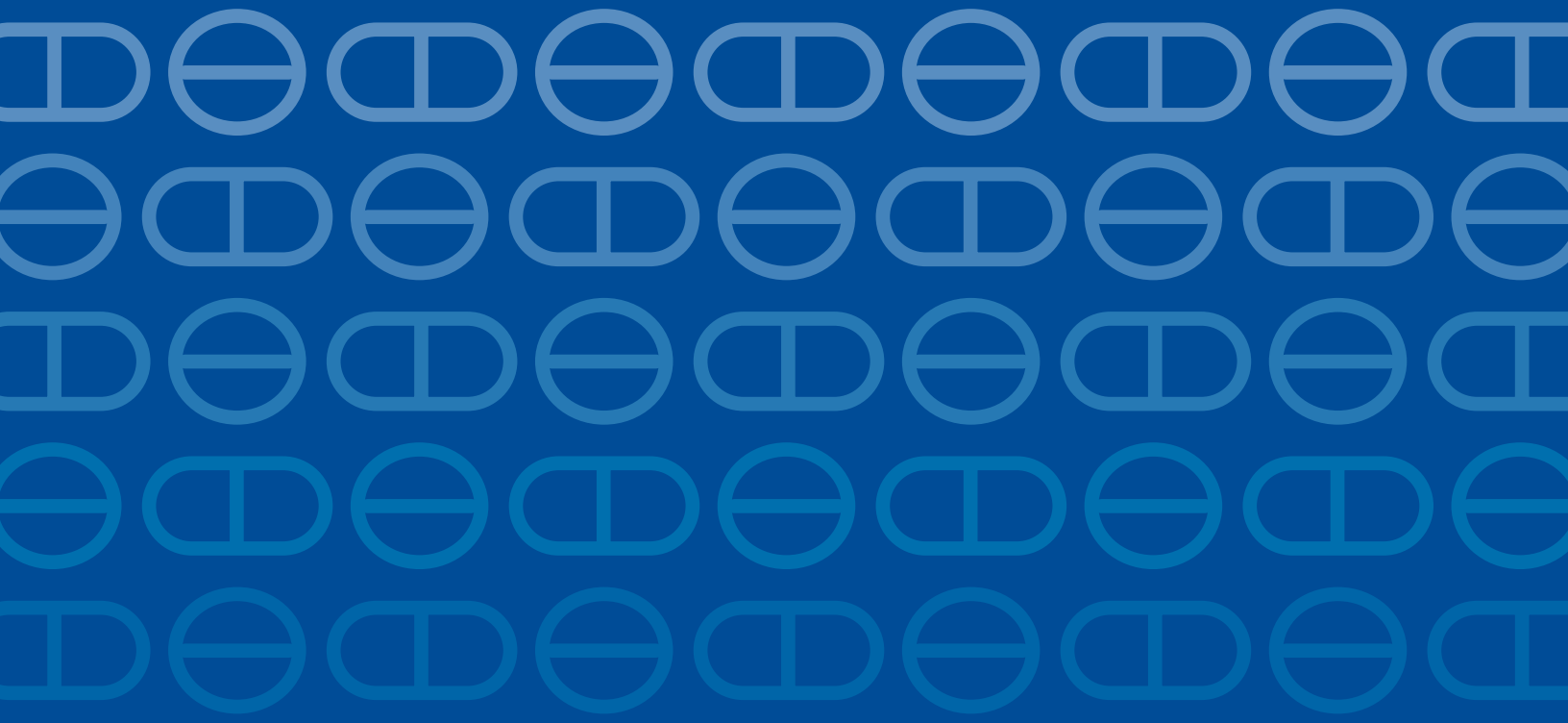
Just a spoonful of medicine helps the sugar go down:

Improving the management of type 2 diabetes



Just a spoonful of medicine helps the sugar go down:

Improving the management of type 2 diabetes

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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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Alosa Health
Just a spoonful of medicine helps the sugar go down: Improving the management of type 2 diabetes

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 Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Activity Overview:

The goal of the educational program is to help practitioners assess the comparative effectiveness and safety of type 2 diabetes medications; understand the evidence regarding appropriate therapy; weigh the benefits, risks, and value of treatment options; and improve the quality of prescribing and patient care. In addition to providing this evidence report, the education program uses an innovative approach, academic detailing, one-on-one educational sessions in physicians' offices with trained outreach educators (pharmacists, nurses, physicians) who present the educational material interactively. Reference cards for clinicians and education materials for family members are also provided.

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 completion of this activity, participants will be able to:

- Target hemoglobin A1C of 7% for most patients with diabetes; however, modify the goal (e.g., 8%) for frail older patients in whom overtreatment can pose its own risk.
- Use metformin as first-line treatment for all patients with type 2 diabetes who require drug treatment.
- Intensify treatment with a second agent for patients not controlled on metformin based on patient characteristics.
- Add insulin promptly when oral agents are not sufficient to achieve hemoglobin A1c goal.
- Manage hypertension and hyperlipidemia aggressively to prevent type 2 diabetes-related complications.
- Recommend a focus on healthy diet, exercise and most importantly, adherence to medications before titrating doses.

Disclosure Policy:

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Disclosures:

This material is provided by Alosa Health, a nonprofit organization which is not affiliated with any pharmaceutical company. No commercial support has been received for this activity. None of the planners/authors have any financial relationships to disclose. The Independent Drug Information Service (IDIS) is supported by the PACE Program of the Department of Aging of the Commonwealth of Pennsylvania.

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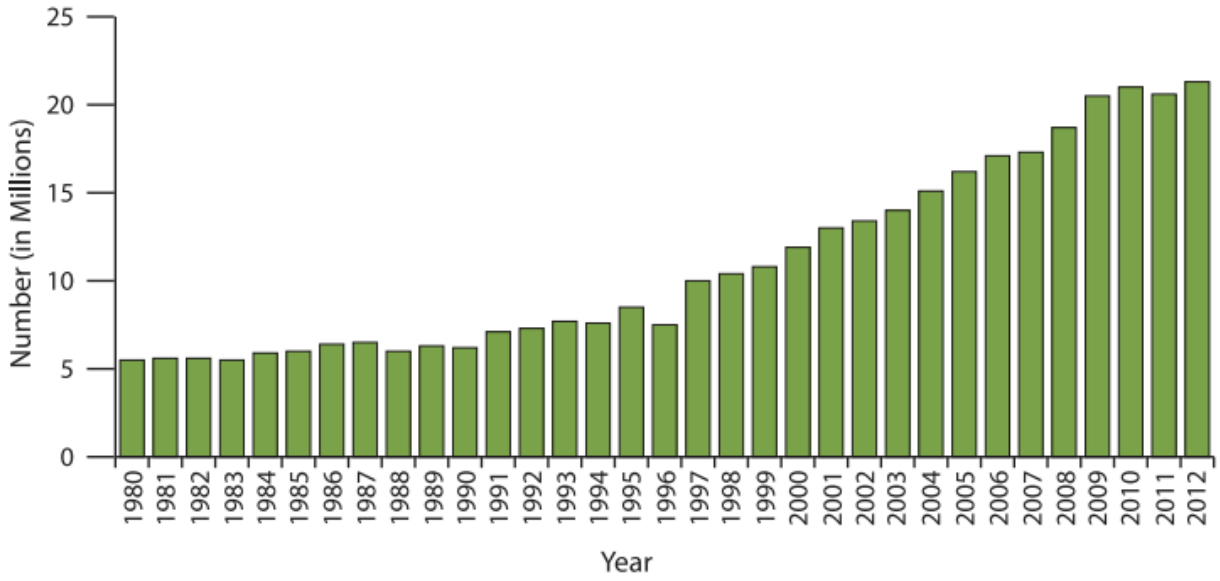
Please email any questions to **cme@alosahealth.org** or call **(617) 948-5997.**

Table of contents

Introduction

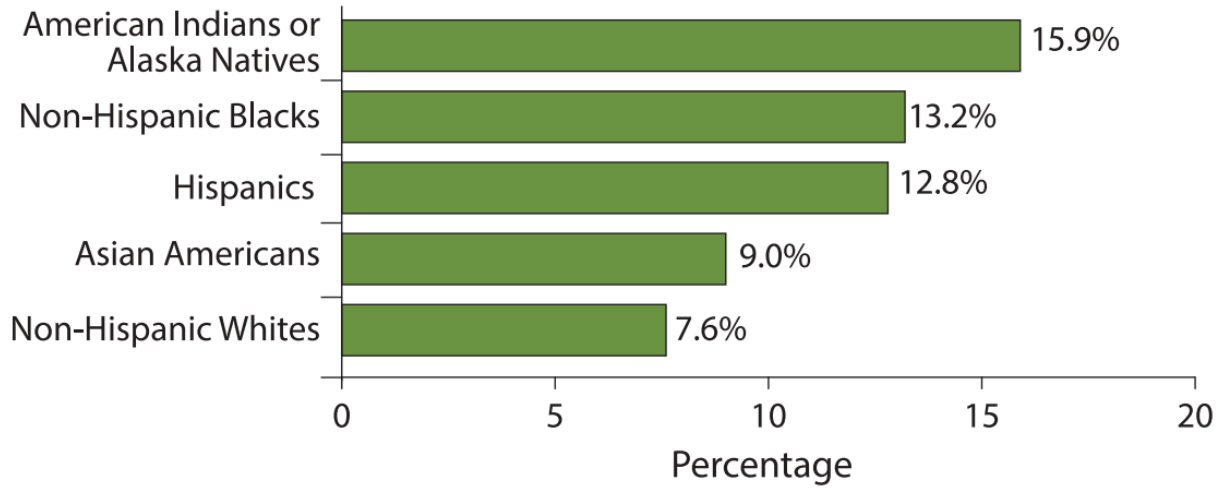
Type 2 diabetes is one of the most common chronic conditions in the United States and poses many challenges to the clinicians who coordinate care for these patients. Diabetes currently affects over 29 million Americans, with incidence rising steadily in the past 20 years.[1] About 1 in 4 of these people do not know they have diabetes.[1] The rising incidence is expected to continue for decades, from about 8 cases per 1,000 in 2008 to about 15 per 1,000 in 2050.[2] Assuming low incidence and relatively high diabetes-related mortality, total diabetes prevalence (diagnosed and undiagnosed cases) is projected to increase from 14% in 2010 to 21% of the US adult population by 2050.[2]

Figure 1. Number of US adults age 18 or older diagnosed with diabetes each year[1]



Type 2 diabetes is far more common among older adults and among certain racial and ethnic groups (see Figure 2, following page).[1]

Figure 2. Percentage of US adults age 20 or older with diagnosed diabetes, by race/ethnicity in 2012[3]



Diabetes continues to be under-treated and patients continue to suffer from preventable complications.[4-6] It's been estimated that every 5 minutes 2 people in the US die of diabetes-related causes.[7]

Many factors contribute to this public health crisis. 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 guiding principles:

- 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 information to help clinicians manage diabetes more successfully. Although it focuses largely on medication therapy, it also addresses diagnosis, monitoring, and other practice-relevant areas. The Independent Drug Information Service (IDIS) has also produced educational materials for patients to help them adhere to their physician's recommendations; these are available at AlosaHealth.org.

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 random blood glucose ≥200 mg/dL is generally adequate to make the diagnosis.[8] More often, however, the diagnosis is made in an asymptomatic patient in whom hyperglycemia is detected incidentally as part of a panel of laboratory tests (Table 1).

Table 1: Diagnosis of diabetes[8, 9]

Patient presentation	Test and threshold	Notes
Symptomatic: e.g., polyuria, polydipsia, weight loss	Random plasma glucose ≥200 mg/dL	
Asymptomatic	Fasting plasma glucose ≥126 mg/dL	Fasting is defined as no caloric intake for at least 8 hours before the test Repeat on a second day to confirm[10] Fasting glucose 100-125 mg/dL indicates prediabetes (impaired fasting glucose, or IFG)[11]
	HbA1c ≥6.5%	HbA1c of 5.7-6.4% indicates prediabetes (need repeat test to confirm)
	Oral glucose tolerance test (OGTT);[12] plasma glucose ≥200 mg/dL 2 hours after 75 gm glucose load	Used infrequently due to inconvenience Glucose 140-199 mg/dL indicates prediabetes (impaired glucose tolerance, IGT);[12] repeat test recommended for clinical confirmation

Currently about 86 million Americans over age 20 do not fulfill the diagnostic criteria for diabetes but instead have “prediabetes,” defined by a fasting glucose level between 100-125 mg/dL, a plasma glucose level of 140-199 2 hours after a 75 gram glucose load, or an HbA1c of 5.7-6.4%.[1,8] This condition is a risk factor for the future development of diabetes, and itself increases the risk of developing cardiovascular disease.[8] Between 15% and 30% of people with prediabetes will develop type 2 diabetes within 5 years.[1]

Current evidence does not support screening all asymptomatic patients for diabetes. Screening is most appropriate in the groups noted in Table 2 (next page).

Table 2. Who should be screened for diabetes?[13]

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 GDM the recommended screening is q1-3 years (q1 year if on insulin in pregnancy or other high risk characteristic.

Screening is best done under fasting conditions, and results interpreted as in Table 1. The oral glucose tolerance test was once the "gold standard" for screening, but it is not routinely used because of its inconvenience,[14-16] and is now 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).

Preventing or delaying diabetes

The concept of prediabetes has focused attention on the possibility of preventing diabetes from developing, or slowing its onset, in the millions of patients found each year to have mildly abnormal glucose metabolism. Both lifestyle interventions and medication-based interventions have been shown capable of preventing frank type 2 diabetes in some patients; data from several studies demonstrate that the most effective single intervention is a 3-5% sustained weight loss, regardless of the composition of the diet used to achieve the loss.[17]

Trials of lifestyle intervention

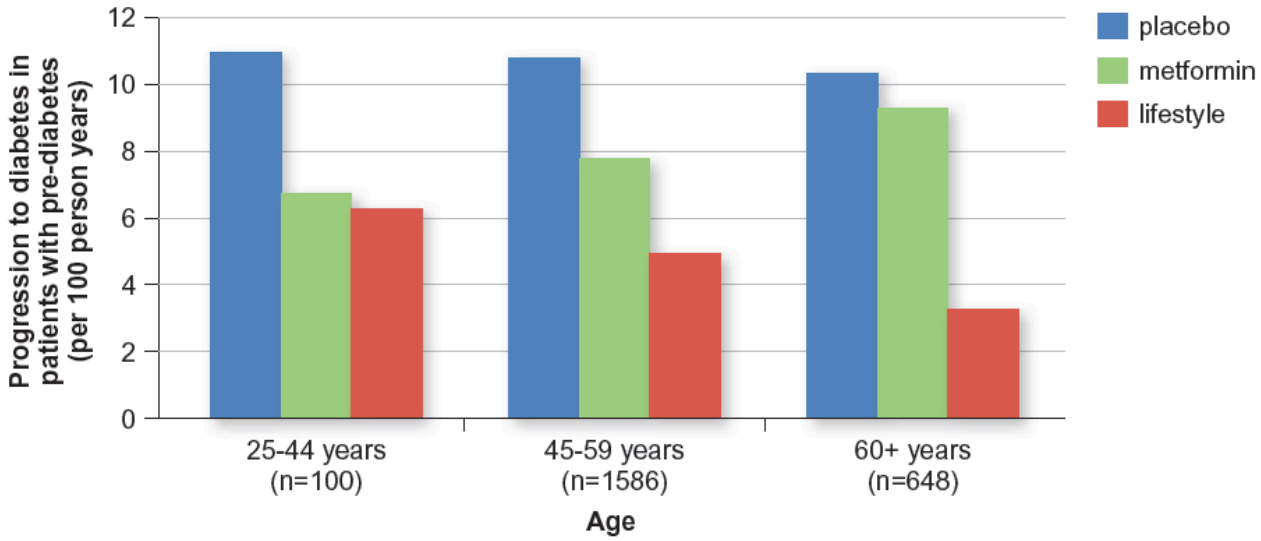
The first large trial of lifestyle modification was the **Finnish Diabetes Prevention Study** in which overweight patients with prediabetes were randomized to usual care or a program of lifestyle modification including weight loss, reduced dietary saturated fat, and substantial amounts of exercise (4 hours weekly).[18] Over four years, lifestyle modification sharply 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 highly significant, reducing the incidence of diabetes by 43%.[19]

The **Diabetes Prevention Program (DPP)** also studied overweight patients with prediabetes, randomizing them to general lifestyle modification plus placebo; general lifestyle modification plus metformin, or an intensive lifestyle modification program.[20] As in the Finnish study, the incidence of diabetes among patients in the intensive lifestyle modification arm was reduced by 58% compared to the placebo group (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% risk reduction (7.8 cases of diabetes per 100 person-years) compared to placebo.[20]

A long-term follow-up of the DPP, the **DPP Outcomes Study (DPPOS)**, showed that the benefits of prevention or delay of diabetes with lifestyle intervention or metformin can persist for at least 10 years.[21] The DPPOS also showed that weight loss associated with metformin therapy is durable for at least 10 years of treatment.[22] A 10-year cost-effectiveness analysis of these interventions found that lifestyle was cost-effective and that metformin was marginally cost-saving compared with placebo.[23]

Importantly, data from the DPP showed that lifestyle changes were particularly effective for older adults (see Figure 3).

Figure 3. Diabetes rates by age group in the Diabetes Prevention Program study[24]



Other medication trials in prediabetes

The **STOP-NIDDM** trial found that treatment with acarbose reduced the development of diabetes in people with prediabetes by 25% in the mean follow-up of 3.3 years, but gastrointestinal symptoms limited adherence.[25] In the **DREAM** trial, patients with prediabetes treated with rosiglitazone were 62% less likely to develop diabetes (10.6% vs. 25% in placebo) after being followed for a median of 3 years,[26] but more recent concerns about the cardiovascular toxicity of rosiglitazone[27-29] outweigh the benefits of its use for preventive treatment in this population. Another study found that pioglitazone reduced the risk of progression to type 2 diabetes by 72% compared to placebo after a median follow-up of 2.4 years, but caused significant weight gain and edema.[30] Finally, the use of valsartan for 5 years along with lifestyle modification in patients with prediabetes and CV disease or risk factors led to a reduction of 14% in the incidence of diabetes.[31]

A 2010 study of nateglinide in patients with prediabetes and established cardiovascular disease or cardiovascular risk factors found that nateglinide taken for 5 years did not reduce the incidence of diabetes or adverse cardiovascular outcomes.[32]

Table 3: Treatment to prevent development of diabetes

Intervention	Intervention (% w/diabetes)	Placebo (% w/diabetes)	Relative risk reduction	Side effects	Dosing schedule
Lifestyle modification • weight loss • decreased saturated fat • exercise	11%	23%	58%	N/A	N/A
Metformin 850 mg BID	22%	29%	31%	Diarrhea, usually transient	Twice daily, Daily for XR
Acarbose 100 mg TID	32%	42%	25%	Bloating, flatulence	Three times daily
Rosiglitazone 8 mg daily	11%	25%	62%	Heart failure exacerbation, weight gain	Once daily
Pioglitazone 30 mg or 45 mg daily	5%	17%	72%		
Valsartan 160 mg daily	33%	37%	14%	Hypotension	Once daily

None of the medications listed in the table above has an FDA-labeled indication for the prevention or delay of diabetes. Some guidelines propose that metformin (along with lifestyle interventions) should be considered for patients with prediabetes, especially those with BMI >35 kg/m^2, <60 years of age, or prior gestational diabetes mellitus (GDM).[8]

BOTTOM LINE: Intensive lifestyle modification, including weight loss (3%-5% of body weight or more) and increased moderate-intensity exercise (4 hours weekly) can reduce the development of diabetes by more than 50% in patients with prediabetes. Metformin and other hypoglycemic agents can also reduce the risk of diabetes, but the benefits must be weighed carefully against side effects and costs.

Overall goals of care

The goal of diabetes treatment is to optimize the plasma glucose level 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.

Glycosylated hemoglobin (HbA1c) provides an indication of a patient's average blood sugar levels in the preceding 2-3 months (Table 4). Lowering HbA1c to around 7% has been shown to reduce microvascular complications of diabetes, and (with early intervention) is associated with reduction in macrovascular disease,[8] although less stringent HbA1c targets may be appropriate for selected patients.

Table 4: Correlation between HbA1c level and plasma glucose levels[8]

	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

Intensive vs. conventional glucose control

Large trials such as the United Kingdom Prospective Diabetes Study (UKPDS), have found that intensive glucose control for patients newly diagnosed with diabetes can reduce diabetes-related clinical outcomes. Ten-year follow-up data from UKPDS were published in 2008[33] and 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%; p=0.04) and microvascular disease (24%; p=0.001). Further, risk reductions for myocardial infarction (15%; p=0.01) and death from any cause (13%; p=0.007) emerged over time. In the metformin group, significant risk reductions persisted for any diabetes-related end point (21%; p=0.01), myocardial infarction (33%; p=0.005), and death from any cause (27%; p=0.002).

Other trials, however, have found that there may be limits below which HbA1c levels should not be pushed. Three trials of patients with long-standing diabetes, the Action to Control Cardiovascular Risk in Diabetes (ACCORD),[34] Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)[35] and the Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes (VADT) study,[36] found no significant reduction in macrovascular events with more intensive glycemic control.

Table 5: Summary of the ACCORD, ADVANCE, and VADT trials

	ACCORD	ADVANCE	VADT
Number of patients	10,251	11,140	1,791
Mean age, years	62	66	60
Duration of diabetes, years	10	8	11
History of CVD, %	35	32	40
BMI, kg/m^2	32	28	31
Median baseline HbA1c	8.1%	7.2%	9.4%
Target HbA1c	<6.0% vs. 7.0–7.9%	<6.5%	<6.0% vs. a planned difference of 1.5% between groups
Median follow-up	3.5 years (trial stopped early)	5 years	5.6 years
Outcomes (intensive glycemic control compared to standard control)			
HbA1c achieved	6.4% vs. 7.5%	6.5% vs. 7.3%	6.9% vs. 8.4%
Macrovascular events	No significant difference	No significant difference	No significant difference
Microvascular events	Not measured	Significant reduction	No significant difference
Death (CV)	Significant increase	No significant difference	No significant difference
Death (all causes)	Significant increase	No significant difference	No significant difference

The ACCORD study found that patients assigned to a target HbA1c level under 6% had an increased risk of death. In contrast, no increase in mortality with intensive glycemic control was seen in the ADVANCE[35] or VADT[36] studies. It is unclear why intensive glycemic control (i.e., targeting HbA1c levels below 6%) increased mortality in ACCORD. Although patients in the intensive HbA1c lowering group in that study 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.[37]

There was a significant reduction in microvascular events with intensive glycemic control in ADVANCE, primarily as a consequence of 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[38] (4 studies, N=27, 049)	Major CV events reduced by 9% (HR 0.91; 95% CI: 0.84-0.99)	MI reduced by 15% (HR 0.85; 95% CI: 0.76-0.94).	Not significantly different (HR 1.10; 95% CI: 0.84-1.42)	Not significantly different (HR 1.04; 95% CI: 0.90-1.20)	Significantly increased (HR 2.48; 95% CI: 1.91-3.21)
Ray 2009 (5 studies, N= 33,040)[39]	Coronary heart disease reduced by 15% (OR 0.85; 95% CI: 0.77-0.93)	Non-fatal MI reduced by 17% (OR 0.83; 95% CI: 0.75-0.93)	Not assessed	Not significantly different (OR 1.02; 95% CI: 0.87-1.19)	Not assessed
Boussageon 2011 (13 studies (N= 34,533)[40]	Not assessed	Non-fatal MI reduced by 15% (RR 0.85; 95% CI: 0.74-0.96) NNT 117-150 for 5 years	Not significantly different (RR 1.11; 95% CI: 0.86-1.43)	Not significantly different (RR 1.04; 95% CI: 0.91-1.19)	Significantly increased (RR 2.33; 95% CI: 1.62-3.36) NNH=15-52 for 5 years
Hemmingsen 2011 (14 studies, N= 28,614)[41]	Not assessed	Non-fatal MI reduced by 15% (RR 0.85; 95% CI: 0.76-0.95)	Not significantly different (RR 1.11; 95% CI: 0.92-1.35)	Not significantly different (RR 1.02; 95% CI: 0.91-1.13)	Significantly increased (RR 2.39; 95% CI: 1.71-3.34)

CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; NNH = number needed to harm; NNT = number needed to treat; NSD = not significantly different; OR = odds ratio; RR = risk ratio.

What is the most appropriate HbA1c target?

Consensus statements have been issued by a number of diabetes-related professional organizations; their recommendations regarding HbA1c targets can be summarized as follows:[42,8]

- Glycemic control early in the natural history of diabetes substantially reduces risk of microvascular disease and, in the long term, results in reduced cardiovascular events, stroke and death in patients with type 2 diabetes.
- Pushing for lower targets late in the natural history of diabetes yields no cardiovascular benefits.
- Lower targets pose higher risk in older patients with established cardiovascular disease.
- Patient-specific personalized diabetes strategies are needed.

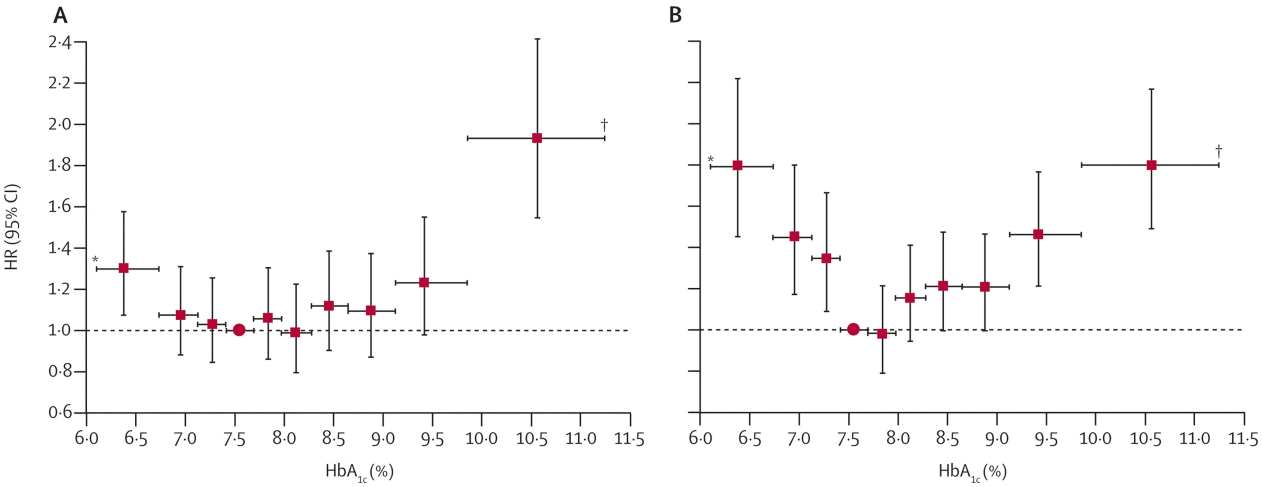
The potential benefits of lowering HbA1c aggressively must be weighed against the potential increased risk of hypoglycemic episodes, especially in frail older patients.[43] The decision to pursue more aggressive control (i.e., HbA1c below 7%) should be made on a patient-by-patient basis. Patients who may benefit from a more stringent HbA1c goal (e.g., 6.5%) include those with short duration of diabetes, 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%) 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.[8,44] Given that the UKPDS[45] and other studies showed protection from micro-vascular disease at HbA1c levels below 7 compared with higher levels, a reasonable approach is to target the lowest possible HbA1c achievable without hypoglycemia during the first 10 years of the disease. This approach is supported by the American Diabetes Association (ADA)[8] as well as the American Association of Clinical Endocrinologists (AACE)[42].

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.[46] 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. As previously noted, caution is warranted in using hypoglycemic agents in older adults because data show that both higher and lower HbA1c levels are associated with higher mortality rates.[47]

Figure 4. Mortality in older adults is associated with both higher and lower HbA1c levels[47]

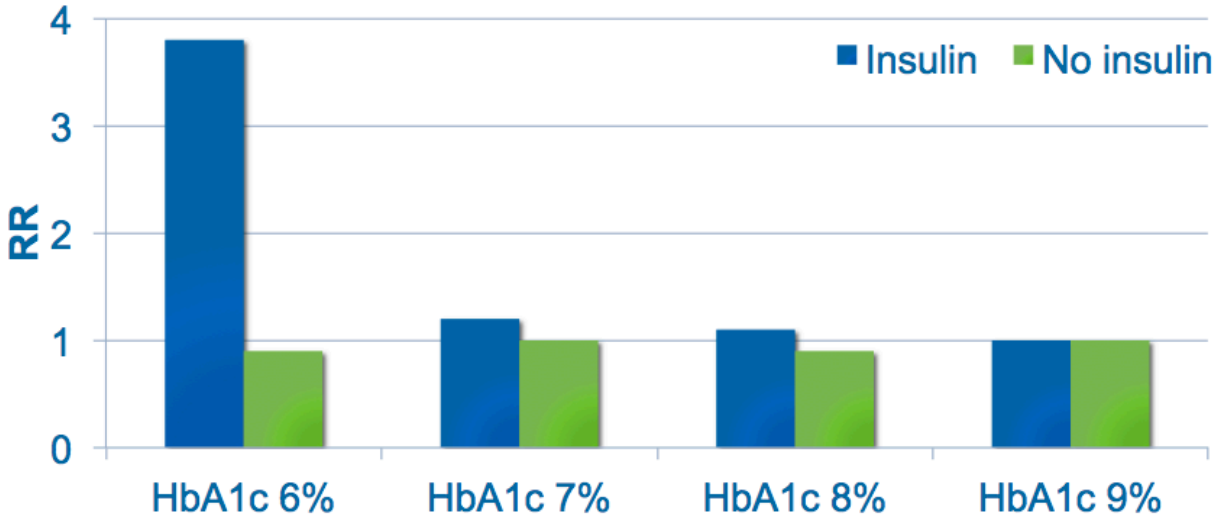


(A) Non-insulin patients (B) Insulin patients

Older patients with diabetes are also at higher risk for death from a hyperglycemic crisis and 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.[48]

Older patients with diabetes who have lower HbA1c levels (i.e., around 6%) on insulin therapy have a significantly higher risk for falls (see Figure 5).[49]

Figure 5. Association between HbA1c levels and fall risk in older patients[49]



Patient blood glucose self-monitoring

In addition to periodic HbA1c measurement, patients should monitor their own blood glucose as part of their diabetes management.[50-52] Monitoring options include fasting, before meals, or 1 or 2 hours after meals and should be tailored to patient glucose patterns, medication regimen, and circumstances. The general blood glucose goals are between 70 and 130 mg/dL when fasting, with postprandial (1-2 hours after meal) glucose levels below 180 mg/dL.[8] For patients on insulin or making rapid changes in therapy, monitoring of blood glucose 3-4 times per day is optimal, if possible. For patients who are meeting their targets for HbA1c, less frequent monitoring (once per day or occasionally less often) may be acceptable.[53] In patients with normal fasting blood sugars in the morning but high pre-meal glucose throughout the day, adding postprandial glucose monitoring can be helpful in identifying isolated postprandial glucose elevation and achieving better glycemic control.[8]

Patients must also be taught how to recognize and treat hypoglycemia (plasma glucose <70 mg/dL). Its symptoms can include sweating, anxiety, palpitations, hunger, tremor, irritability, and confusion. Recommended treatments include milk, and 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: Aiming for HbA1c levels near or below 7% soon after the diagnosis of diabetes reduces 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% 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.

Weight management, diet, and exercise

Much of the steady increase in the prevalence of diabetes in recent years is the result of increasing rates of obesity in the United States. Correspondingly, there is good evidence from studies of patients with prediabetes that weight loss can reduce insulin resistance and reduce the risk of developing frank diabetes.[18,20] Weight management programs for obese patients with type 2 diabetes have also been shown to improve health-related quality of life, improve physical fitness, and reduce symptoms.[54] Although many physicians despair 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 serum glucose.[20] Aggressive weight management also benefits other conditions associated with diabetes, such as hypertension and dyslipidemia.

The **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 overweight adults with type 2 diabetes.[55] (For more information visit lookaheadtrial.org/public/home.cfm) It found that intensive lifestyle intervention can produce sustained weight loss and improvements in fitness, glycemic control, and cardiovascular risk factors in patients with type 2 diabetes.[55]

Working with patients on a structured program to reduce overall caloric intake can help promote weight reduction, although sustained weight loss remains challenging for many patients.[18] The current evidence is insufficient to recommend diets that focus solely on carbohydrate restriction, diets based on glycemic index/load, or diets focused on one particular food group.

Structured exercise programs can improve the control of diabetes, even if patients do not lose weight in the process.[56,57] 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 2 consecutive days without exercise, if possible and clinically appropriate.[8] 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.[58] A 2012 meta-analysis of 5 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.[59] Even moderate levels of exercise, however, can be beneficial.[56]

Combined aerobic-resistance exercise programs are the most effective.[8,56,60] Before undertaking exercise more intense than brisk walking, sedentary people will benefit from an evaluation by a physician. Electrocardiogram exercise stress testing for asymptomatic patients at low risk of coronary artery disease is not routinely recommended, but may be indicated for higher risk patients.[61] The 10-year risk for any given patient can be determined using a calculator endorsed by the American Diabetes Association (ADA). A link to the tool is available at alosahealth.org/modules/diabetes. Patients prone to hypoglycemia or who have developed symptoms of retinopathy or neuropathy will require extra caution in devising an 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 multiple other health benefits. Programs combining diet and exercise are especially effective.[62] 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 treatment of diabetes

Six major classes of oral hypoglycemic agents and a non-insulin injectable are now available to treat patients who have developed type 2 diabetes.

Table 7. Non-insulin hypoglycemic agents

Route	Class	Examples (Brand names)
Oral	Biguanide	metformin (Glucophage)
	Sulfonylureas	glyburide (Diabeta, Micronase) glipizide (Glucotrol) glimepiride (Amaryl)
	Thiazolidinediones (glitazones)	pioglitazone (Actos) rosiglitazone (Avandia)
	α-glucosidase inhibitors	acarbose (Precose) miglitol (Glyset)
	Meglitinides	nateglinide (Starlix) repaglinide (Prandin)
	Dipeptidyl peptidase (DPP)-4 inhibitors (‘gliptins’)	sitagliptin (Januvia) saxagliptin (Onglyza) linagliptin (Tradjenta) alpogliptin (Nesina)
	Sodium glucose co-transporter (SGLT)-2 inhibitors (‘flozins’)	canagliflozin (Invokana) dapagliflozin (Farxiga) empagliflozin (Jardiance)
Injectable	Glucagon-like peptide (GLP)-1 receptor agonists	exenatide (Byetta) exenatide XR (Bydureon) liraglutide (Victoza) dulaglutide (Trulicity) albiglutide (Tanzeum)

These medications differ in their hypoglycemic mechanisms of action (see Table 8 on following page), their side effects, and their cost. Some agents (i.e., metformin, sulfonylureas, glitazones, and SGLT-2 inhibitors) have been carefully evaluated in trials that demonstrated benefit in terms of actual clinical outcomes, while others have been shown only to improve surrogate measures such as glucose or HbA1c levels.

Table 8. Major mechanisms or pathophysiologies affected by non-insulin hypoglycemic agents

		SUs	Metformin	TZDs*	α-glucosidase inhibitors	Meglitinides	Incretin (GLP-1 & DDP4i)	SGLT-2 inhibitors
Major pathophysiologies	Insulin deficiency	✔				✔	✔	
	Insulin resistance		✔	✔				
	Excess hepatic glucose output		✔	✔			✔	
	Renal glucose excretion							✔
	Intestinal glucose absorption		✔	✔				

* TZDs = Thiazolidinediones (glitazones)

Impact of non-insulin hypo heglycemic agents on major clinical outcomes

The fundamental goal of diabetes medications is to reduce clinically important outcomes such as end-organ damage (e.g., cardiovascular disease, nephropathy, neuropathy and retinopathy), and death. Unfortunately, only a few published trials with sufficiently large sample sizes have compared individual agents to other drugs or to placebo with respect to these actual clinical outcomes. Instead, many oral agents have been shown only to reduce serum glucose or HbA1c levels. The importance of distinguishing between these two outcomes was vividly illustrated by rosiglitazone (Avandia), which successfully lowered HbA1c levels, but actually increased the risk of myocardial infarction.[27]

Placebo-controlled trials

The **United Kingdom Prospective Diabetes Study (UKPDS)** was a landmark trial published in *The Lancet* in 1998. In one component, non-overweight patients with newly diagnosed diabetes were randomized to receive intensive therapy with insulin, or intensive therapy with a sulfonylurea (chlorpropamide or glyburide), or diet alone. Subjects were followed up for 10 years.[63] Intensive drug therapy with either regimen was substantially more effective than diet for lowering HbA1c and reducing the risk of microvascular complications, but resulted in only a small reduction in the risk of myocardial infarction (RR 0.84; 95% CI: 0.74-1.00).[63] No differences were found between patients treated with sulfonylurea versus insulin. These findings are in contrast to earlier evidence from a trial conducted by the University Group Diabetes Program, in which patients treated with sulfonylureas had a higher incidence of myocardial infarction than patients managed with diet alone.[14]

In a second component of UKPDS, overweight patients (>120% ideal body weight) were randomized to a conventional regimen (primarily diet alone), or intensive therapy with metformin, or intensive therapy with insulin or a sulfonylurea (glibenclamide or chlorpropamide).[64] In contrast to the results in normal-weight

patients, in overweight patients metformin significantly reduced the risk of diabetes-related death and death from all causes, compared to diet alone.[64] Metformin did not reduce the rate of microvascular complications.

The **PROactive** study **(PROspective pioglitAzone Clinical Trial In macroVascular Events)** randomized 5,238 patients with type 2 diabetes and macrovascular disease to receive either pioglitazone (Actos) or placebo in addition to their glucose-lowering regimen.[65] The primary study 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 composite endpoint was not reduced in patients treated with pioglitazone, but a secondary outcome (all-cause mortality, non-fatal myocardial infarction, or stroke) was significantly reduced by 16% in pioglitazone-treated patients.

The 2015 **Empa-Reg Outcome Study** looked at the effects of empagliflozin, an inhibitor of sodium-glucose cotransporter 2 (SGLT-2) in addition to standard care, on CV morbidity and mortality in patients with type 2 diabetes at high CV risk.[66] 7020 patients were randomized to one of three arms: 10 mg empaglflozin/daily; 25 mg empagliflozin/daily; or placebo. After a median observation time of 3.1 years, there was a 24% reduction in CV events in the pooled empagliflozin group compared to placebo (HR 0.86; CI, 0.74 – 0.99; P=0.04).[66] 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% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction).[66] Because the drug works by having the patient excrete glucose through the urine, there were significantly more cases of genital infection among both male and female patients receiving empagliflozin than placebo: 42 cases (1.8%) in the placebo group compared with 153 cases (6.5%) in the group getting 10 mg empagliflozin; and 148 (6.3%) in the group getting 25 mg empagliflozin.

Most recently, the **Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER)** trial followed 9340 high-risk adults with type 2 diabetes for 5 years, comparing those randomly assigned to liraglutide or placebo, along with standard treatment. The composite primary end point was defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Initial results show that liraglutide significantly reduced the risk of major adverse CV events, although the full data set and final results have not yet been published or presented as of this writing.[67]

Trials directly comparing different agents

In addition to comparing different non-insulin hypoglycemic agents to placebo, the UKPDS study directly compared several hypoglycemic medications. In the study component involving overweight patients, metformin resulted in lower rates of all-cause mortality and stroke (but not myocardial infarction or microvascular events) compared to sulfonylurea or insulin.[64] The benefits of metformin observed in the UKPDS have not been tested in other randomized trials.

The **ADOPT** study **(A Diabetes Outcome Progression Trial)** randomized 4,360 untreated patients with diabetes to monotherapy with rosiglitazone, metformin, or glyburide.[4] 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, and the rate of serious cardiovascular events was significantly lower in patients treated with glyburide (1.8%) than

in patients treated with metformin (3.2%) or rosiglitazone (3.4%), largely due to lower rates of congestive heart failure and non-fatal myocardial infarction in the glyburide-treated patients.

In 2012, results from the **SPREAD-DIMCAD** study (**Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus with Coronary Artery Disease**) were published.[68] This trial randomized 304 patients with type 2 diabetes and coronary artery disease to glipizide or metformin for three years. Baseline HbA1c was 7.6% in each group, and at the end of follow up had fallen to 7.1% in the glipizide group and 7.0% in the metformin group (p=0.66). Over a median follow-up of 5 years, treatment with metformin reduced the primary composite endpoint of death from cardiovascular causes, death from any cause, nonfatal MI, nonfatal stroke, and arterial revascularization by 46% compared with glipizide (HR 0.54; 95% CI: 0.30-0.90; p=0.026).

The glitazone controversy

In mid-2007, an analysis of 42 randomized controlled trials that had allocated patients to rosiglitazone (Avandia) vs. placebo or another oral hypoglycemic regimen found that use of rosiglitazone ***increased*** the risk of myocardial infarction by 43% (p=0.03), and resulted in a 64% increased risk of death from cardiovascular causes (p=0.06).[27] A subsequent meta-analysis of four large, longer-term trials that prospectively collected information on cardiovascular events confirmed the findings of the original meta-analysis.[27,28] Later studies, however, found conflicting results.[69]

The Food and Drug Administration (FDA) initially placed a black-box warning on the rosiglitazone label warning of the potential increased risk of myocardial infarction and placed limitations on its prescription. In 2013, however, the FDA removed all prescribing and dispensing restrictions on rosiglitazone after determining that data did not demonstrate an increased risk of heart attack compared to metformin and sulfonylureas.[70]

In contrast to the data about rosiglitazone, a late 2007 meta-analysis of 19 randomized controlled trials of pioglitazone found that this drug *reduced* the relative risk of a primary end-point of death, myocardial infarction or stroke by 18% (p=0.005).[71] But as discussed in further detail below, both rosiglitazone and pioglitazone increase the risk of heart failure and fracture.

BOTTOM LINE: Existing clinical endpoint data provide the most consistent evidence for metformin in reducing cardiovascular events. Individual trials have also found cardiovascular benefits from sulfonylureas, pioglitazone, and empagliflozin; and neutral cardiovascular effects for gliptins and GLP1 receptor antagonists (although emerging evidence may suggest a cardiovascular benefit for the latter). Clinical endpoint data are currently lacking for other non-insulin hypoglycemics; several trials are underway. The glitazones increase the risk of heart failure and fracture.

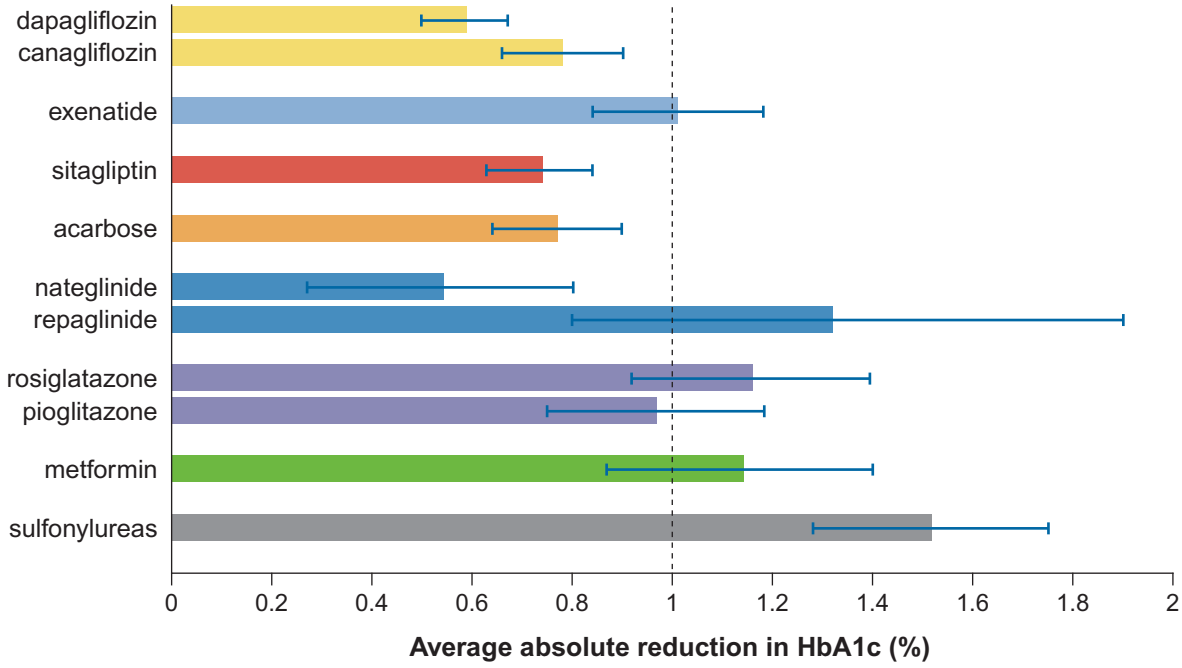
Reductions in HbA1c

Many studies have compared the ability of non-insulin anti-diabetic 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.

Indirect comparisons of oral hypoglycemic agents

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% (see Figure 6).[72,73,74]

Figure 6. Expected reductions in HbA1c from indirect comparisons of different hypoglycemic agents[72, 75,74]

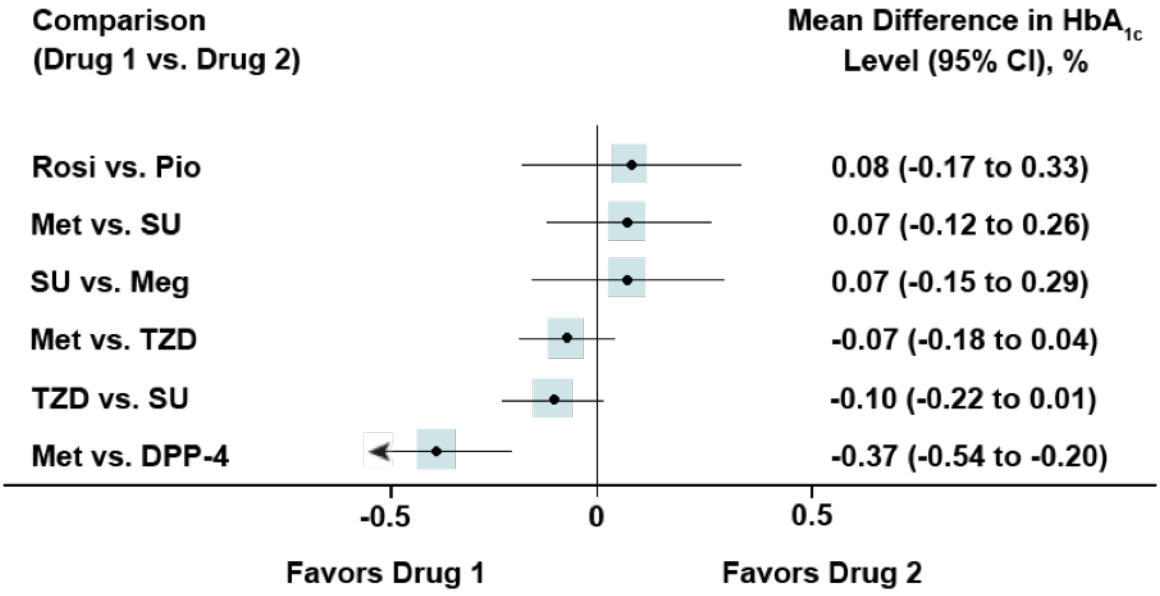


In general, older drugs have been tested in patients with higher baseline HbA1c, which itself is associated with greater reductions in HbA1c irrespective of therapy type.[44]

Direct comparisons of oral hypoglycemic agents

A number of head-to-head trials have directly compared the capacity of various oral agents to lower HbA1c. A meta-analysis of these trials confirms the observation that most drug classes produce similar reductions in HbA1c as monotherapy (see Figure 7, next page).[76]

Figure 7. Direct comparisons of different oral hypoglycemic agenda. Differences were modest across all drug classes.[72]



Several studies have compared HbA1c lowering with gliptins compared with other oral agents (sulfonylureas, metformin and the glitazones). When the results of these studies were pooled in a meta-analysis, gliptins achieved reductions in HbA1c that were 0.21% (95% confidence interval 0.02% to 0.39%) smaller than those achieved by other oral hypoglycemic agents (i.e., gliptins were less effective than the agents to which they were compared).[75]

In general, any differential effects on glucose control seen in head-to-head studies of non-insulin agents are small.[44] Agent- and patient-specific factors such as dosing frequency, adverse effect profiles, and cost often guide choice rather than comparative effects on HbA1c lowering.[44]

Combination therapy

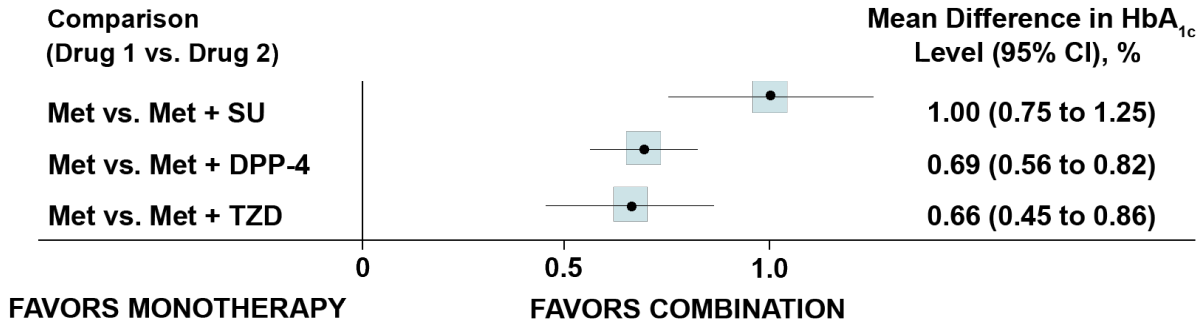
Adding a second non-insulin agent to an existing treatment regimen can help patients achieve better glycemic control. Clinical trials have consistently shown an additive effect, probably because these drugs act by complementary mechanisms. In general, the addition of a second agent from a different class lowers HbA1c by an additional 1% over treatment with maximum doses of a single agent.[44,76]

Several randomized studies have compared different add-on regimens (metformin + sulfonylurea versus metformin + rosiglitazone). Despite slight under-dosing of the sulfonylurea in these trials, both treatment arms resulted in equivalent reductions in HbA1c.[15,16,72] The gliptins appear in some studies to be as effective as other oral hypoglycemic agents when used as add-on therapy, although the data supporting their use are more limited.[77,78]

Several short-term randomized trials have shown that exenatide reduces HbA1c by 0.5-1.0% when added to treatment with sulfonylureas and/or metformin in patients whose glucose was poorly controlled.[65,79-81] 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.[73] 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.[82]

Figure 8: Comparisons of combined treatment versus monotherapy[72]



BOTTOM LINE: Non-insulin hypoglycemics each lower HbA1c by about 0.5-1.5%. Adding a second agent from a different class lowers 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 clinical outcomes

In addition to their effects on HbA1c levels, non-insulin hypoglycemic agents differ in their impact on other clinically important outcomes (See Table 9

on page 23 for details). Metformin lowers LDL cholesterol, resulting in average reductions of 10 mg/dL.[76] In contrast, sulfonylureas, repaglinide, and acarbose have little effect on LDL levels, while the glitazones 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.[76] The glitazones 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.[83] Alogliptin, linagliptin, and saxagliptin have been reported as being lipid neutral.[84-86] A 2012 meta-analysis found that the gliptins reduced total cholesterol and triglycerides.[87] Clinical studies and a meta-analysis have reported the GLP-1 agonist exenatide as being lipid neutral or beneficial.[88-91]

Metformin, GLP-1 agonists, and flozins may induce weight loss. By contrast, sulfonylureas, the glitazones, and repaglinide generally cause equivalent amounts of weight gain, whereas patients taking metformin consistently *lose* weight or remain weight-neutral.[76] Nateglinide may cause less weight gain than repaglinide and acarbose appears to have similar effects on weight as metformin.[72] 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 as monotherapy and when added to metformin.[73] A 2012 systematic review of flozins used in dual or triple therapy for patients with type 2 diabetes concluded that these agents were effective in reducing weight compared with placebo.[82]

BOTTOM LINE: Among the non-insulin hypoglycemic agents, metformin appears to have the most consistent beneficial effects on the clinically important parameters of LDL and body weight.

Comparative safety

Hypoglycemia

The clinical consequences of hypoglycemic episodes include increased risk of falls, car crashes, confusion, and (possibly) increased risk of dementia.[48,49] Many patients with diabetes experience episodes of hypoglycemia, even without drug therapy. The occurrence of such episodes in obese patients on diet therapy alone over the 10-year follow-up of the UKPDS were 0.7% (major episodes) and 7.9% (minor episodes).[64]

Metformin, the glitazones, SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 agonists do not appear to increase the risk of hypoglycemia compared to placebo.[72,42] In contrast, because the sulfonylureas and the meglitinides (in particular repaglinide) act by increasing insulin secretion, they increase the absolute risk of hypoglycemia by 4-9% compared to both placebo and other agents.[76] This is particularly relevant for patients whose HbA1c is close to 7%, and in the elderly. There are limited data about the risks of hypoglycemia from nateglinide and α-glucosidase inhibitors, although the risks from these agents appear to be low.[75]

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

BOTTOM LINE: Metformin, the glitazones, SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 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 comorbidites.

Heart failure and peripheral edema

The risk of heart failure caused by both glitazones has been known for some time.[65] Even in lower risk populations, both pioglitazone and rosiglitazone substantially elevate the risk of heart failure.[27,28,71]

In light of the mounting evidence, 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 in conjunction with insulin.[29,62] Rates of peripheral edema are also substantially elevated with the glitazones as compared to either metformin, sulfonylureas, or repaglinide. Randomized controlled trials comparing glitazones to sulfonylureas show absolute differences in the rate of peripheral edema ranging from 4 to 21%.[72]

Other antidiabetic medications appear to have a neutral effect on heart failure,[42] with the exception of the SGLT-2 inhibitors, which appear to somewhat *reduce* risk of hospitalization or death from heart failure, perhaps through the diuretic effect of the glycosuria that they produce.[92]

BOTTOM LINE: The glitazones substantially increase the risk of heart failure and peripheral edema compared with sulfonylureas and metformin. There is less information about heart failure risk for many of the newer classes of non-insulin hypoglycemic agents, although studies of SGLT-2 inhibitors suggest that they lower the risk of hospitalization or death from heart failure.

Other side effects

Although an older biguanide no longer available in the U.S. (phenformin) caused lactic acidosis, a systematic review found no cases of lactic acidosis in clinical trials of metformin.[93] However, randomized trials generally exclude patients with renal insufficiency or impaired creatinine clearance (such as many elderly), in whom the risk of lactic acidosis may be elevated. The official FDA label for metformin says lactic acidosis can be expected in is 3 cases per 100,000 patients treated.

In contrast, gastrointestinal intolerance (e.g., nausea, vomiting, and diarrhea) is a common side effect for metformin, occurring in up 60% of patients.[76] It also occurs very frequently with acarbose, but is substantially lower in patients receiving sulfonylureas, glitazones, meglitinides, and the DPP4 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 gastrointestinal side effects have not occurred after 5-7 days, increasing the dose to 850 mg or 1000 mg before breakfast and dinner.

Gastrointestinal side effects are also common with the GLP-1 receptor agonists (exenatide and liraglutide).[65,73,79-81] Exenatide is also associated with a significant increase in the risk of pancreatitis, causing the FDA to warn that exenatide should be discontinued and not restarted if pancreatitis occurs, and other agents be considered in patients with a history of pancreatitis.[94] Pancreatitis has also been reported during liraglutide treatment, but there are no conclusive data establishing causality.[73] In five trials of ≥26 week 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 reactions.[73]

The glitazones 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.[4] 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.[95]

The FDA issued a safety announcement in 2011 that the use of Actos (pioglitazone) for more than one year may also be associated with an increased risk of bladder cancer. An interim analysis of an ongoing 10-year epidemiological study found an increased risk of bladder cancer among patients with the longest exposure to pioglitazone, and in those exposed to the highest cumulative dose of the drug.

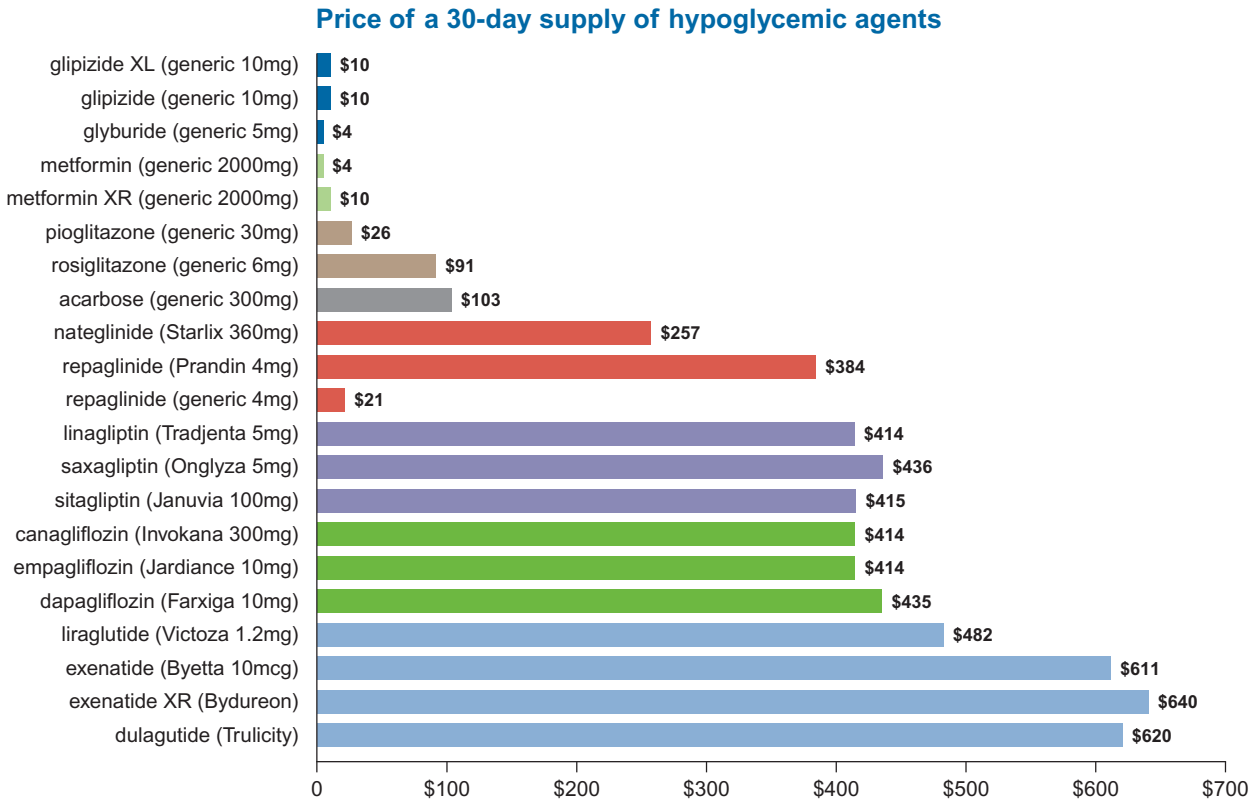
The GLP-1 receptor agonists all carry a black box warning advising that the drugs are contraindicated in patients with a personal or family history of medullary thyroid carcinoma, or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2). Data from animals taking 8 times the amounts of these agents that humans take suggest a possible increased risk, although the risk is considered very low by the FDA.[96]

BOTTOM LINE: Metformin, GLP-1 receptor agonists, and acarbose frequently cause some gastrointestinal intolerance, although for metformin these side effects can be reduced by gradual dose escalation, and usually diminish over time. Metformin was not associated with an increased risk of lactic acidosis in clinical trials. The glitazones increase the risk of fracture and bladder cancer.

Cost

The various non-insulin agents vary widely in cost.

Figure 9: Price for a 30-day supply of non-insulin agents



Source: Prices are from goodrx.com as of January 2016. Doses defined by the World Health Organization Defined Daily Dose table.

Because sulfonylureas and metformin have been on the market for many years, generic versions exist, and their monthly cost is extremely low. In contrast, the newer diabetic agents are protected by patents and cost 25 to 65 times more than generic sulfonylureas and metformin.

Putting it all together: optimal use of non-insulin hypoglycemic drugs

Table 9 summarizes the comparative CV efficacy, other outcomes and key precautions of the available classes of non-insulin hypoglycemic agents.

Table 9: Cardiovascular outcomes and adverse effects of hypoglycemic drugs

Class	CV outcomes	Weight change	Hypoglycemia	LDL	Precautions
biguanide metformin (Glucophage)	**32% reduction**	**loss**	**low risk**	**lowers**	avoid in renal disease or insufficiency
sulfonylureas chlorpropamide (Diabinese) glyburide (DiaBeta, Glynase)	**16% reduction**	**gain**	**high risk**	*	hypoglycemia
glipizide (Glucotrol)	*				
glitazones rosiglitazone (Avandia)	**64% increase**	**gain**	**low risk**	**raises**	heart failure, fracture
pioglitazone (Actos)	**18% reduction**				
meglitinides nateglinide (Starlix)	*	**gain**	**high risk**	*	caution with impaired liver function
repaglinide (Prandin)					
gliptins (DPP-4 inhibitors) alogliptin (Nesina) saxagliptin (Onglyza) sitagliptin (Januvia)	**neutral**	*	*	*	? pancreatitis
linagliptin (Tradjenta)	*				
GLP-1 receptor agonists liraglutide (Victoza)†	**neutral**	**loss**	*	*	? pancreatitis
albiglutide (Tanzeum) dulaglutide (Trulicity) exenatide (Byetta, Bydureon)	*				
flozins (SGLT-2 inhibitors) empagliflozin (Jardiance)	**24% reduction**	**loss**	**low risk**	**raises**	UTI, ketoacidosis, genital infections, hypotension
canagliflozin (Invokana) dapagliflozin (Farxiga)	*				

* No data available.

† New CV outcome data on liraglutide pending.

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[13] as well as the 2016 AACE-ACE consensus statement on type 2 diabetes management.[42] 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) the diagnosis is made, particularly when lifestyle interventions alone are unlikely to achieve HbA1c goals. This recommendation is supported by results from UKPDS and other studies. **Actual clinical outcome data supporting the use of other classes of agents (i.e., α-glucosidase inhibitors, meglitinides, DPP4 inhibitors, most GLP-1 receptor agonists, and most SGLT-2 inhibitors) are insufficient to recommend their routine use as initial therapy at present for most patients.**

These guidelines may not apply to all patients, of course, due to contraindications or intolerances. Table 10 summarizes situations in which metformin and other oral agents may be contraindicated. To avoid gastrointestinal side effects, metformin should be started at a low dose and gradually titrated upwards.[44]

Table 10. Non-insulin hypoglycemic agents contraindications and warnings

Class	Contraindications and warnings
Metformin	**renal disease or dysfunction** Cr ≥1.5 mg/dL in males, 1.4 mg/dl in females or abnormal CrCl acute or chronic metabolic acidosis
Sulfonylureas	**hypoglycemia** renal impariment: 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
Glitazone	**heart failure** **fracture in women with osteoporosis** **MI** (rosiglitazone)
α-glucosidase inhibitors	**cirrhosis;** inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or predisposition to it, chronic intestinal disease with marked disorders of digestion or absorption, and patients who have conditions that may deteriorate as a result of increased gas formation in the intestine
Meglitinides	Patients with several renal insufficiency should initiate therapy with reduced doses; the drug should be used with caution in patients with impaired liver function
Gliptins (DPP-4 inhibitors)	**? pancreatitis** No adjustment needed for renal insufficiency, except sitagliptin
GLP-1 receptor agonists	**? pancreatitis** 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
Flozins (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)
Sources: Garber AJ et al. *Endocr Pract.* Jan 2016;22(1):84-113; package inserts for metformin, glyburide, glipizide, alph-glucosidase inihibitors, meglitinides, DPP-4, GLP-1, SLGT-2; and FDA safety information for glitazones and SGLT-2 inhibitors.	

BOTTOM LINE: Metformin remains the drug of first choice for the treatment of type 2 diabetes unless contraindicated (especially by renal insufficiency). 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 American Diabetes Association recommends repeating an HbA1c every 3 months until a target HbA1c is achieved (typically <7%) and at least every 6 months thereafter.[8]

There are many therapeutic options for patients who are poorly controlled on monotherapy such as the recommended first-line agent 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 g/day, titrated up slowly to enhance tolerance and therefore adherence.) Which agent is chosen next can be based on a patient's risk of hypoglycemia (see Figure 10 on the following page). The algorithm in Figure 10 has been developed in light of the availability of evidence concerning a drug's impact on clinical outcomes such as cardiovascular risk.

If HbA1c is above 9% at diagnosis and the patient is symptomatic (e.g., polydipsia, polyuria), start metformin and basal insulin therapy. If the HbA1c goal is still not met, intensify the insulin therapy until the goal is met. On the other hand, if the patient's HbA1c level is below 9% at diagnosis, one can start metformin and then add a second non-insulin agent if HbA1c goals are not met in 3 months. Before advancing the regimen, titrate the existing medication(s) to their optimal doses and inquire about adherence. Many seemingly 'inadequate' regimens are actually the result of patients' not taking their prescriptions as directed.

For patients who are not having acute symptoms of hyperglycemia, if the risk of hypoglycemia is a major clinical concern (e.g. in a frail older patient or one prone to falls), an appropriate second agent can be a flozin or gliptin. In the former category, the evidence is strongest for empagliflozin (Jardiance), which has been shown to prevent cardiac complications.[66,92] An older SGLT-2 inhibitor, canagliflozin (Invokana) has not demonstrated comparable cardiovascular protection, and has been associated with rare ketoacidosis. All flozins can cause UTI, dehydration, potential urosepsis, and genital infection.

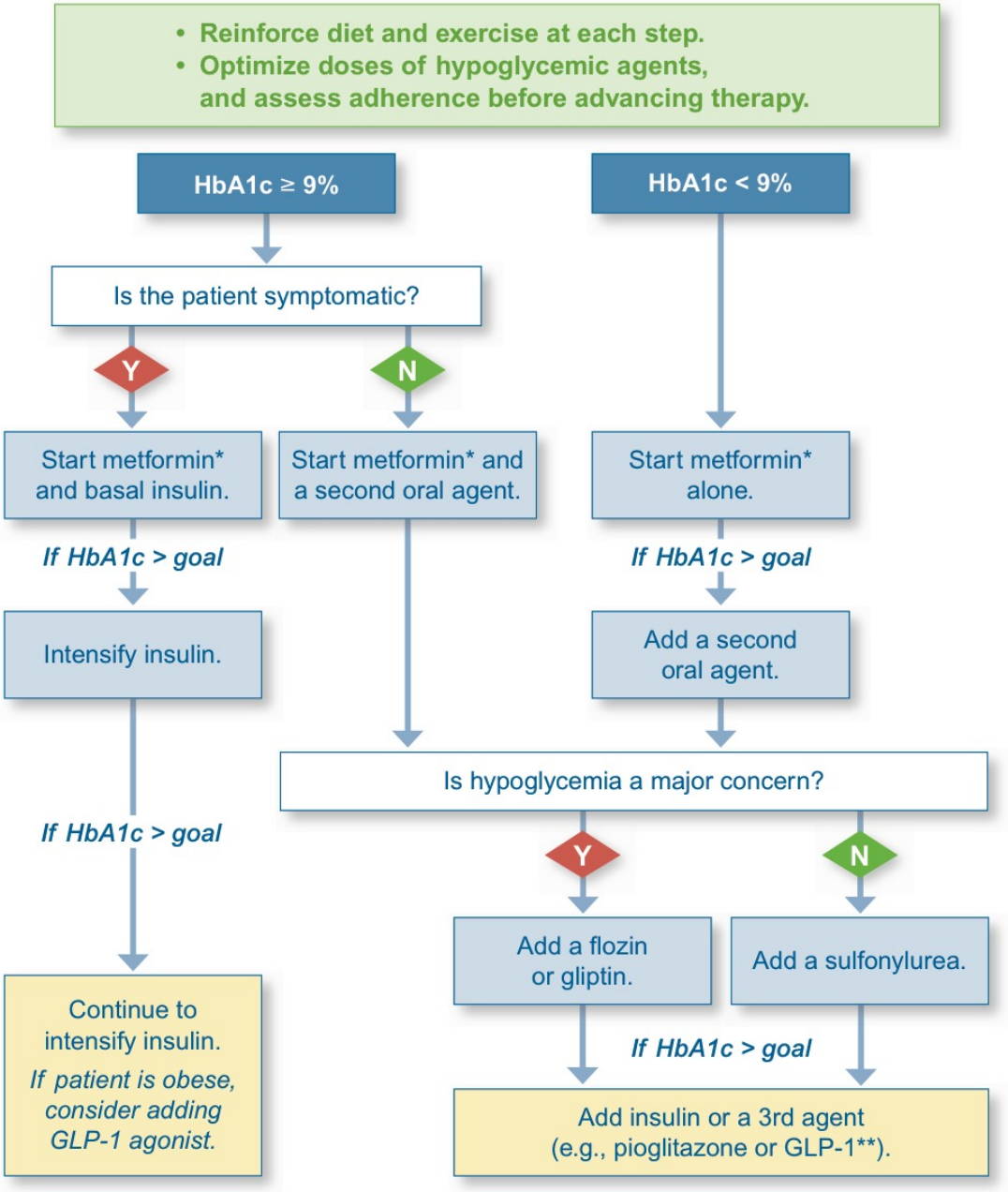
On the other hand, if there is less concern about the risks associated with hypoglycemia in a given patient, a good second-line agent is a sulfonylurea, which has evidence for prevention of end-organ complications. In this category, use a shorter half-life agent, such as glipizide, especially in older patients. Avoid longer-acting sulfonylureas such as glyburide and chlorpropamide. If the patient still cannot reach the target HbA1c goal with either dual-therapy mode, add insulin or a 3rd non-insulin agent.

Whenever possible, treatment decisions should involve the patient, addressing his or her preferences, needs, and values. Ultimately, many patients will require insulin therapy (usually in combination with other agents) to maintain good glucose control.[44]

Monitor patients regularly for side effects, and continue education and motivation to achieve lifestyle changes. For appropriate patients who are very obese, bariatric surgery can have impressive effects on serum glucose, sometimes even eliminating the need for medications.

For all patients, reinforce weight control and exercise recommendations at every visit, even after mediations have been started. Check HbA1c every 3 months until at goal, and then at least every 6 months.

Figure 10: Treatment algorithm for the management of type 2 diabetes*



* If contraindicated or not tolerated, go to the next step.
** GLP-1 can be added when a gliptin is not selected as the second agent.

* 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. All existing hypoglycemic agents reduce HbA1c, but most do not bring about microvascular or macrovascular benefits except metformin, sulfonylureas, and SGLT-2 inhibitors.

2. Some agents carry significant risk (e.g., glitazones for CHF, myocardial infarction, fractures, and flozins for ketoacidosis).

3. There are substantial price differences among these drugs.

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

5. When a second agent is needed, the selection should be made based on patient characteristics.

6. Individualize HbA1C targets as required. The target for most patients is 7%, but a higher goal (e.g. 8%) may be best for frail elderly patients, and a lower target may be preferable for younger patients and pregnant women.

Insulin therapy

Over time, a very large proportion of patients with type 2 diabetes cannot be adequately managed with non-insulin medications, and will require insulin therapy.[44] After a successful initial response, patients in the UKPDS trial failed oral therapy at a rate of 5 to 10% per year. Among patients initially controlled with a single drug, 50% required the addition of a second drug after three years, and 75% needed multiple therapies by nine years to achieve their HbA1c targets.[6] Data from the National Health and Nutrition Examination Survey indicate that only about a third (37%) of patients with diabetes reach a goal of HbA1c <7%.[97] Nonetheless, evidence clearly shows that early initiation of insulin can help improve glycemic control and help patients reach their HbA1c goals.

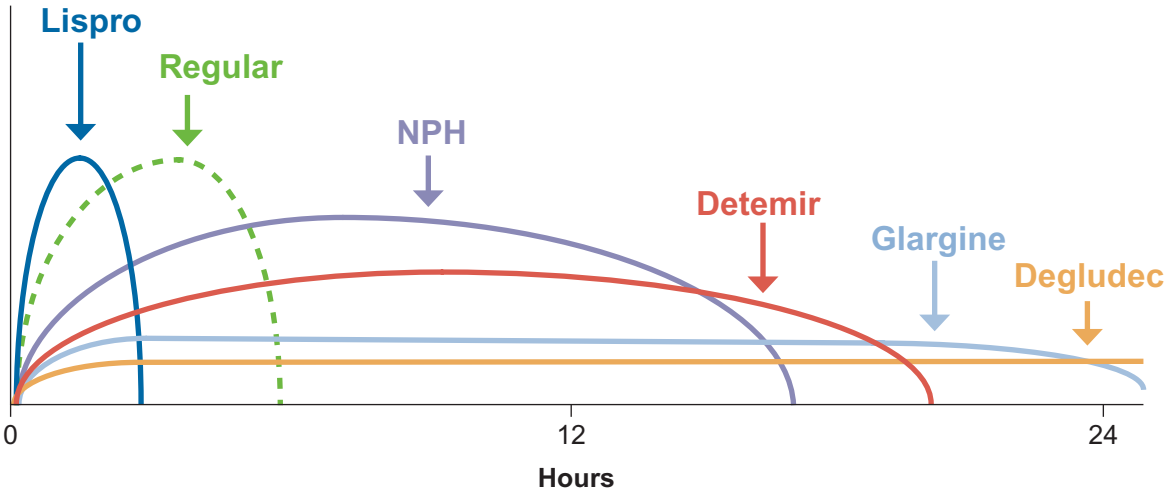
Unfortunately, despite convincing evidence, insulin often is not started even when clinicians and patients are aware of poor glucose control. [98-100] Patients' fear of injections and their discomfort as a major barrier to use, as well as low perceived efficacy and a belief that adding insulin therapy is a sign of treatment and lifestyle failure.[101,102] 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 oral medications, and the belief that insulin should only be started when "absolutely essential."[101,102]

BOTTOM LINE: Hyperglycemia is often under-treated in diabetes, and physicians and patients often delay initiation of insulin therapy when it is indicated. Early initiation of insulin can help improve glycemic control and achieve HbA1c goals.

Insulin preparations

Figure 11 depicts currently available insulin preparations; they are described in more detail below.[103,104]

Figure 11: Comparison of human insulin preparations and insulin analogs[105]



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 improved 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. These analogs 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.[106] For patients with type 2 diabetes, however, 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.[106]

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 approximately 6-7 hours to reach peak effectiveness. When used as basal insulin, it can be given once or twice daily.

Long-acting (basal) insulin (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 long duration of action of up to 24 hours (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.[107]

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 hrs), and it can be used once or twice daily. Both long-acting insulins have a half-life that is dose-dependent.

"Ultra" long-acting insulin

Insulin degludec is marketed as an ultra-long acting insulin. The onset of action is 2-4 hours after subcutaneous injection. It has a half-life of 25 hours, but 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.[108] Degludec dosing is more flexible than glargine, and may be beneficial for patients in whom compliance is a concern.[109]

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 be a better option for patients for whom a simpler regimen might 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 have been developed for most insulin types. Regular U500 is available in a vial and requires extensive patient education to ensure that the correct number of units is drawn up for each dose. A tuberculin syringe is recommended to reduce confusion. By contrast, the other concentrated insulins are available only in 'pen' administration devices. These products include: lispro U200 (Humalog), glargine U300 (Basaglar and Toujeo, and degludec U200 (Tresiba). These can be easy and safer for patients to use because they do not require any calculations - the patient simply dials in the prescribed dose in units before injecting subcutaneously.

Insulin patches

One type of insulin delivered by a patch-like device is currently on the market (Valeritas V-Go) and two more are poised to enter the market as of February 2016 (Calibra Finess and CeQur PaQ), but this method of administration has not achieved widespread use.

Figure 12. Insulin patch-like devices

	Valerirtas V-Gou 	Calibra Finesse 	CeQur PaQ 
Days of us	1	Up to 3	Up to 3
Bolus	2 units increments	2 units increments	2 units increments
Basal	Yes, 20, 30, & 40 units per day	No	Yes, 16, 20, 24, 32, 40, 50, 60 units per day
Cannula	Metal	Soft	Soft
FDA Approval	Yes	Yes	No
Marketed	Yes	No	No

When should insulin therapy be initiated?

Generally, insulin is required for patients who do not respond adequately to non-insulin hypoglycemic therapy or who have high baseline blood glucose. The ADA/EASD guidelines suggest that:

- Patients with a high baseline HbA1c (e.g., ≥9.0%) have a low probability of achieving target HbA1c with monotherapy. Insulin (with metformin), or 2 non-insulin agents, should be considered in this circumstance.
- If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations (e.g., >300-350 mg/dL or HbA1c ≥10.0-12.0%), insulin therapy should be strongly considered from the outset.
- Insulin should be used when the HbA1c level is high despite two optimally dosed non-insulin agents, since it is unlikely that another non-insulin agent will be of sufficient benefit.[44]

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.[44] 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.[44] 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.

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.[44]

Insulin is also indicated for patients who are pregnant, require high-dose glucocorticoid therapy, or are intolerant of oral hypoglycemic agents,[110] as well as for hospitalized patients.[93]

BOTTOM LINE: Insulin may be necessary in a patient with HbA1c >1% above goal on an optimal dose of a non-insulin monotherapy, or HbA1c >0.5% above goal on two non-insulin agents. 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 study.[53] 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 11.

Table 11. 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:
100-200 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 between 7.5% and 10%) while receiving bedtime glargine or NPH insulin.[53] At the end of the 24-week study, NPH and glargine were equally effective in achieving target levels of glycemic control (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.[111] HbA1c reductions were similar in both groups (an 8.6% to 6.8% decrease in the detemir group and an 8.5% to 6.6% decrease in the NPH group). 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 are equally effective in reducing HbA1c, but long-acting insulins may be preferred in patients at higher risk for hypoglycemic events.

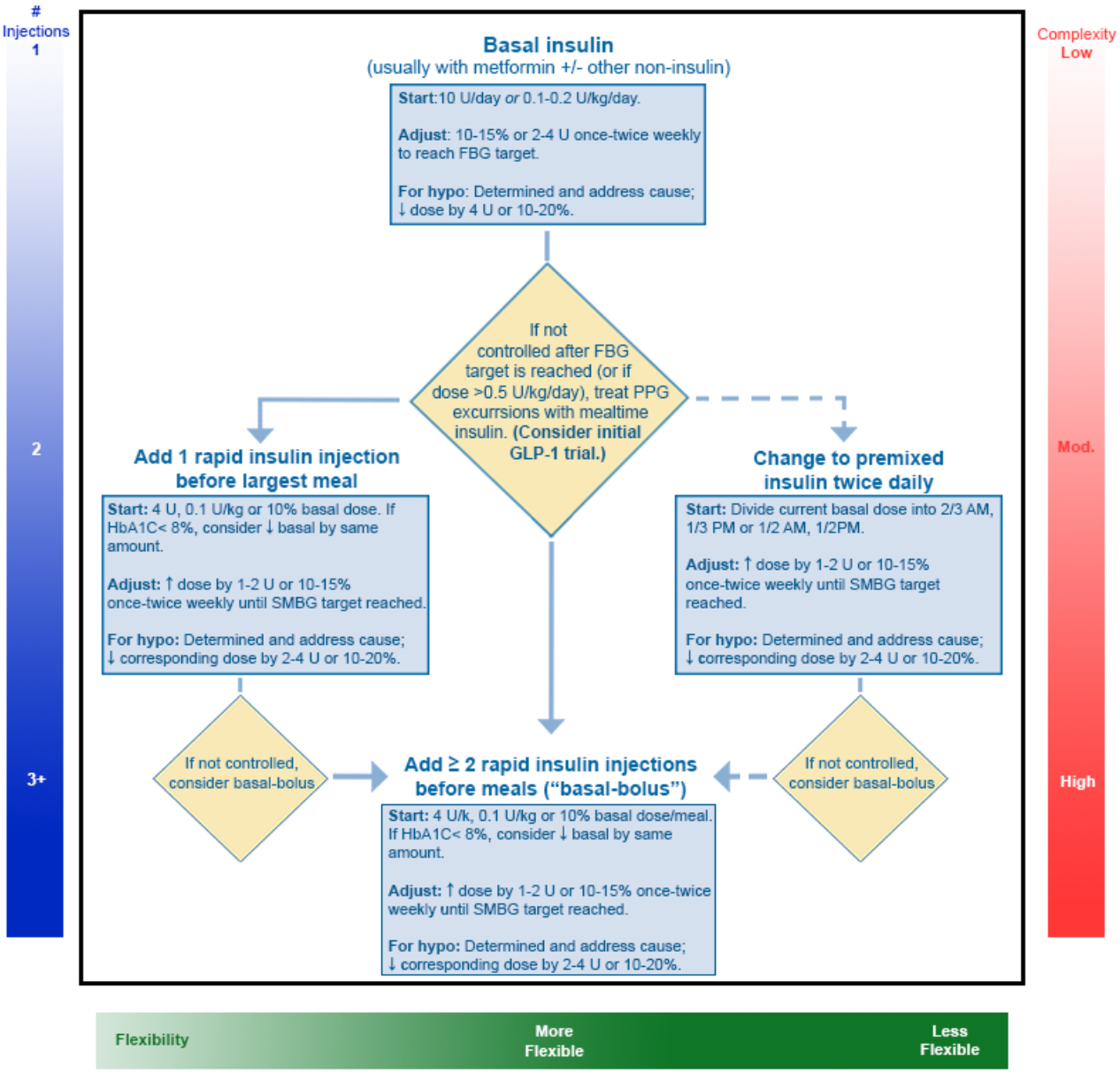
The LANMET study compared treatment with glargine and metformin to treatment with NPH and metformin in type 2 diabetes.[112] It found glucose control was similar in both groups, but there were fewer hypoglycemic events in the first 12 weeks in the glargine group. However, at 36 weeks, the investigators 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 starting treatment.

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.[113-115] In the 4-T trial, patients poorly controlled with oral hypoglycemic agents were randomized to receive biphasic insulin, prandial insulin, or detemir.[113] The study found a greater likelihood of reaching the goal of 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 patients receiving glargine once daily compared to those receiving fast-acting lispro three times a day. In that study, investigators randomized 418 patients with inadequately controlled diabetes to one of the two active treatment arms. 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.[116]

In summary, studies comparing different insulin regimens have not clearly demonstrated any one treatment regimen to be superior 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 13 provides some strategies for tailoring the initiation and intensification of insulin therapy.

Figure 13: ADA consensus algorithm for initiating and intensifying insulin[44,110]



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.

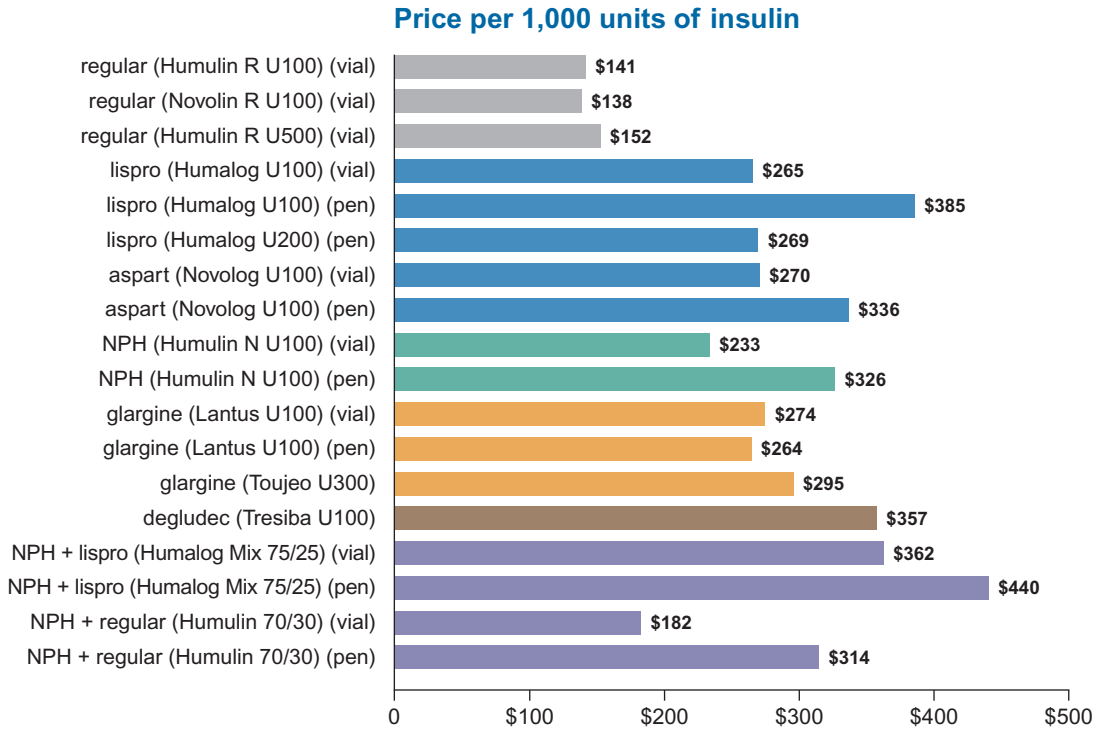
Combining insulin with other hypoglycemic agents

In 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 requiring daily insulin dose (11 units less a day) when insulin is added to existing therapy compared to using insulin alone.[117-119] 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.[120] As a result, it is often recommend that secretagogues (sulfonylureas, meglitinides) should be stopped when insulin therapy is initiated or intensified, but other oral agents that are not secretagogues can be continued.[44] The ADA guidelines recommend metformin and insulin as first-line combination therapy in people with type 2 diabetes who require insulin therapy.[44] Despite evidence suggesting that insulin-glitazone combinations effectively reduce glucose,[121] fluid retention and other safety concerns about the glitazones make metformin-insulin a better first-line choice.[122]

BOTTOM LINE: Combination therapy with other hypoglycemic agents and insulin can produce improved glucose control and greater weight loss 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 14: Costs of selected insulin preparations per 1,000 units



Source: Prices from goodrx.com as of January 2016. Prices are standardized to 1,000 units, however this may not reflect package size. For example, Humulin R U500 is available only in a 20 mL vial (10,000 units) and costs over $1,500.

Bariatric surgery

Gastric bypass and biliopancreatic diversion in morbidly obese patients can often result in remission of type 2 diabetes. A 2012 trial randomized 60 patients between the ages of 30 and 60 years with a BMI ≥35, a history of at least 5 years of type 2 diabetes, and an HbA1c ≥ 7.0% to receive conventional medical therapy or undergo either gastric bypass or biliopancreatic diversion.[123] 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).[123] 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 (average HbA1c=7.7% in the medical-therapy group, 6.4% in the gastric-bypass group, and 5.0% in the biliopancreatic-diversion group.[123]

Another study compared the efficacy of intensive medical therapy alone versus medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy in 150 obese patients with uncontrolled type 2 diabetes.[124] Baseline average HbA1c was 9.2%. After 12 months, glycemic control significantly improved in all three groups, although with lower levels in the two surgery arms: mean HbA1c of 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 ($p=0.003$).[124]

Bariatric surgery may be a useful therapeutic alternative for very obese adults with BMI >35 kg/m^2 and 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 that there is a mortality benefit after 10 years.[8]

End-organ damage

While diabetes can sometimes cause morbidity or mortality through acute events such as ketoacidosis or hyperosmolar coma, most complications develop slowly as end-organ damage caused by prolonged hyperglycemia. This damage can result in myocardial infarction, stroke, peripheral vascular disease, renal failure, damage to peripheral nerves, and retinopathy. Diabetes is the leading cause of renal failure, non-traumatic lower limb amputations, and new cases of blindness in the United States.[1] Preventing the complications of diabetes is just as important as managing the blood glucose level, and aggressive management of all cardiovascular 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.[8] This should include:

- A fundoscopic exam and referral to an ophthalmologist for periodic dilated eye exams
- Control of blood pressure, generally with an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin-receptor blocker (ARB) if an ACE-I cannot be tolerated (see below)
- Careful management of cholesterol levels (see below)
- Annual screening for microalbuminuria, and serum creatinine measurement to estimate glomerular filtration rate (GFR) 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.[125] Microalbumiuria and low GFR are both indicators of compromised renal function, and very strong predictors of cardiovascular disease as well as end stage renal disease
- Good foot care, including patient education about foot care 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 (see Table 12 on following page). (Many components of medical management for patients with diabetes with these conditions have been covered in previous IDIS monographs and are available at AlosaHealth.org.

Table 12. 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)	Begin with lifestyle modification. Drug therapy should include ACE-I (ARB, if ACE-I is not tolerated)
Hyperlipidemia	Check fasting lipids	Adherence to appropriate statin therapy	Treat with statins for all diabetes patients >40 Treat with moderate-intensity statins for patients 40-75 years without risk factors Treat with high-intensity statin for patients with CV disease or risk factors
Atherosclerotic cardiovascular disease	Assess for cardiac risk factors	Risk reduction	Aspirin for patients with high CV risk (e.g., existing coronary artery disease or 10-year CV risk >10%)
Smoking	Inquire about tobacco use	Smoking cessation	nicotine replacement bupropion 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 type 2 diabetes.[126] 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 ACE-I/ARB and aspirin in addition to a range of antihyperglycemic agents to treat their diabetes. The mean treatment period was 7.8 years, with follow-up for a further 5.5 years.

Results of the study are provided in Tables 13 and 14 below. In summary, intensive multifactorial interventions for patients with type 2 diabetes resulted in substantially reduced rates of cardiovascular events, microvascular complications, and death. 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 13: 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

Table 14: Clinical outcomes of the Steno-2 study

Outcome	Risk reduction (intensive compared with conventional therapy) after 13.3 years
All-cause mortality	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

The recommended systolic blood pressure target for people with diabetes is <140 mmHg, and the target diastolic blood pressure is <80 mmHg. Lower systolic targets, such as <130 mmHg, may sometimes be appropriate, such as in younger patients, if this can be achieved without undue adverse effects.[8]

All patients with a blood pressure of >120/80 should be advised about lifestyle modifications that can help reduce blood pressure, including weight reduction, salt restriction, a DASH diet, and exercise. Many of these interventions will also be helpful for improving control of diabetes. Patients with confirmed blood pressure >140/80 mmHg should (in addition to lifestyle therapy) have prompt initiation and titration of drug therapy to achieve blood pressure targets.

ACEIs, angiotensin receptor blockers (ARBs), thiazide diuretics, beta blockers, and calcium channel blockers have been shown to help reduce cardiovascular risk in patients with diabetes.[127] ACEI- or ARB-based treatments can also slow the progression of nephropathy and reduce albuminuria.[127] Virtually all patients with diabetes treated for hypertension should receive a drug that blocks the renin-angiotensin axis.[22,128] The initial choice should be an ACE-I, many of which are available in low-cost generic forms that can be given once per day.[127] About 10% of patients may have side effects when treated with ACE-I (most often cough), and these patients can be switched to an ARB.[23] Many patients with diabetes will

require treatment with multiple drugs to achieve target blood pressures.[8] For patients who need a second drug in addition to an ACE-I or ARB, a thiazide-type diuretic is recommended.[127,129] If ACE-Is, ARBs, or diuretics are used, monitor the estimated glomerular filtration rate (eGFR) and serum potassium levels.[8]

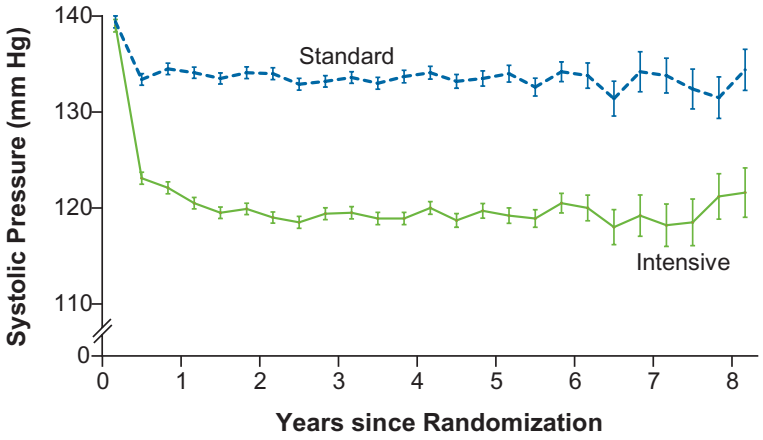
The central importance of blood pressure control for reducing morbidity and mortality in patients with diabetes was demonstrated in the UKPDS 10-year follow-up study. Researchers followed patients in this trial for ten years to determine whether the micro- and macro-vascular risk reductions initially achieved with good blood pressure control would be sustained over 10 years.[130]

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 after 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 beware of “clinical inertia,” the reluctance of both patients and prescribers to add new medications, even when the potential benefits are large.[131]

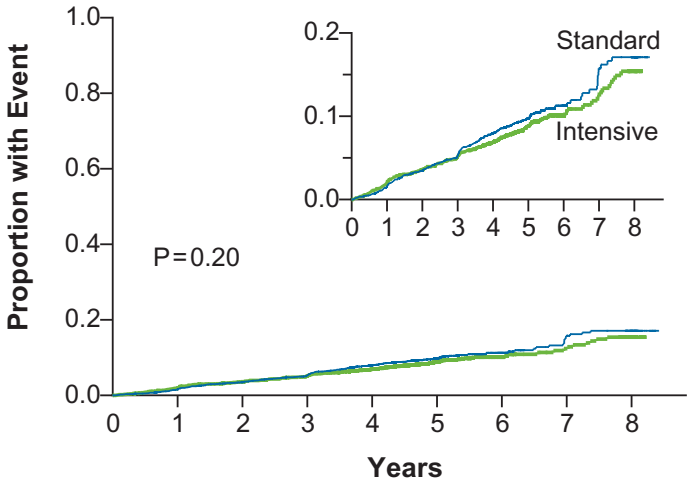
A sub-study (ACCORD-BP) of the ACCORD trial compared intensive vs. standard BP control (<120 mm vs. <140 mm systolic) in 4,733 patients with diabetes at high risk for CV events.[132] Patients in the intensive group had an average systolic blood pressure of 119 mmHg, compared to an average systolic blood pressure of 134 mmHg in the control group (see Figure 15). After a mean follow up of 4.7 years, patients assigned to intensive BP reduction did not have a significant benefit in the composite CV events (1.9% in the intensive group versus 2.1% in the usual care group; p=0.20; 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 explained.

Figure 15: Between-group differences in systolic blood pressure in the ACCORD-BP study[132]



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

Figure 16: Primary outcome in the ACCORD-BP study[132]



No. at Risk									
Intensive	2362	2273	2182	2117	1770	1080	298	175	80
Standard	2371	2274	2196	2120	1793	1127	358	195	108

Some patients with diabetes and hypertension require special consideration. Pregnant women should have hypertension aggressively controlled, but ACE-Is and ARBs are contraindicated in pregnancy. 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, but usually it's important to try and treat to the target levels unless contraindicated or if such an approach produces intolerable hypotensive episodes.

BOTTOM LINE: Treat blood pressure >140/80 mmHg aggressively in patients with diabetes, and maintain BP control over time. ACE-Is are first-line treatment, with ARBs reserved for patients who cannot tolerate ACE-Is. Multi-drug therapy is often needed to reach target, adding thiazide-type diuretics as appropriate. A systolic BP target of <140 mmHg appears to be as effective as more intensive therapy with a target of <120 mmHg.

Hyperlipidemia

All patients with diabetes should have their cholesterol checked upon diagnosis, and then every five years if not started on statin therapy.[133] Lifestyle intervention including diet modification and exercise is 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 14. Recommendations for statin treatment

Age	Risk factors	Recommended statin intensity*
<40 years	None ASCVD risk factors** ASCVD	None Moderate or high High
40–75 years	None ASCVD risk factors ASCVD	Moderate High High
>75 years	None ASCVD risk factors ASCVD	Moderate Moderate or high High

* Lifestyle interventions are continued with statin therapy
** ASCVD risk factors include: LDL cholesterol ≥100 mg/dL, high blood pressure, smoking, overweight or obese, and family history of premature ASCVD.

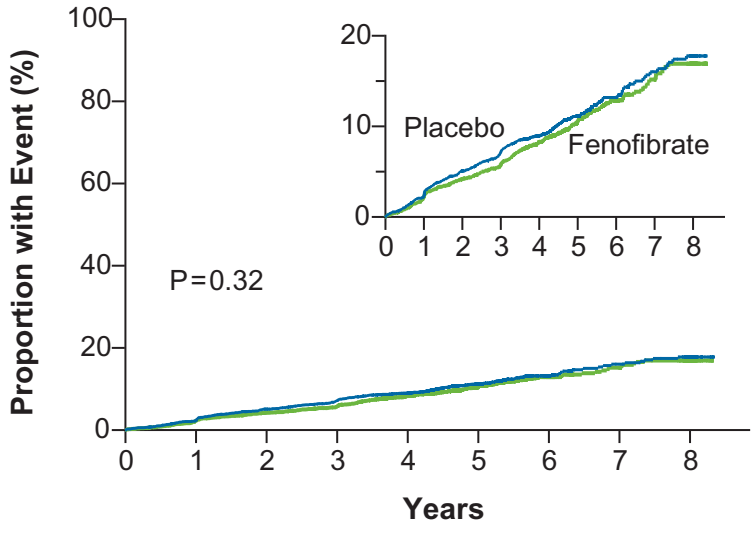
Intensity of statins is defined both by the drug and dose (Table 15). Treat most patients with diabetes requiring cholesterol reduction with a statin that has been shown to reduce the risk of cardiovascular events.[134-136] With multiple statins now available generically, most patients can use an affordable, generic statin that will lower their LDL to target levels.[137] Atorvastatin is preferred for high-intensity therapy due to its generic availability (vs. rosuvastatin). A 30-day supply of atorvastatin 80 mg is $78 while rosuvastatin 40 mg (Crestor) is currently about $290 according to goodrx.com.

Table 15. 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. 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) (see Figure 17) or all-cause mortality (1.5% versus 1.6%; p=0.33).[138]

Figure 17: Primary outcome in the ACCORD-LIPID study[138]



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

There appears to be a modest increase in the development of diabetes in patients given statins, though the effect is quite small. 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.[139] The well-demonstrated benefit of statins in preventing cardiovascular events is far greater in magnitude and of more clinical consequence than the small increase in risk of 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. Generic statins are an effective and affordable choice for most patients with diabetes. 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.[140] 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.[141] Clopidogrel also has a role in the management of many patients with recent acute coronary syndromes, coronary stent insertions, or peripheral vascular disease.[142]

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.[143] Despite limitations of the sentinel study suggesting risk equivalence,[143] 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.[144]

Two large trials and several subsequent meta-analyses have raised new questions about the role of aspirin in primary prevention. The POPADAD study[145] looked at whether 100 mg of aspirin daily is effective in preventing cardiovascular events in 1,276 patients (mean age 60 years) with type 1 or 2 diabetes and asymptomatic peripheral arterial disease but no symptomatic cardiovascular disease. Aspirin produced no significant reduction of cardiovascular or all-cause deaths or a composite end-point of fatal and non-fatal cardiovascular events. The rate of gastrointestinal bleeding was similar (4.4% with aspirin and 4.9% in controls).

Like POPADAD, the JPAD study[146] examined the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in patients with type 2 diabetes. It randomized 2,539 patients with type 2 diabetes and no history of atherosclerotic disease to receive either 81 or 100 mg aspirin per day, or placebo. Over the median follow-up of four years, low-dose aspirin did not reduce the incidence of total atherosclerotic events (coronary, cerebrovascular, and peripheral vascular) compared to placebo. However, deaths from MI or stroke were significantly reduced in the low-dose aspirin group (1 death vs. 10 deaths, p=0.0037), though all-cause mortality was not significantly reduced. Gastrointestinal bleeding occurred in 12 patients in the aspirin group and 4 patients in the placebo group. There was no difference in the composite outcome of hemorrhagic stroke and severe gastrointestinal bleeding.

A 2009 meta-analysis of six studies (including POPADAD and JPAD) of aspirin in the primary prevention of major vascular events in people with diabetes found that aspirin resulted in no statistically significant reduction in the risk of major CV events, CV mortality, or all cause mortality. There was a significant reduction in the risk of myocardial infarction in men, but not in women.[147]

A 2011 meta-analysis of seven primary and secondary prevention trials of aspirin in diabetes found no significant reduction in all-cause mortality from aspirin used in primary prevention (RR 1.01; 95% CI: 0.85-1.19).[148] Similarly, another 2011 meta-analysis of seven studies of aspirin for primary prevention of major cardiovascular events in patients with diabetes found no significant reduction in major CV events (RR 0.91; 95% CI: 0.82-1.00) or mortality from CV-related or all causes.[149]

Prior guidelines have advocated that most patients with diabetes over age 40 or who have other cardiovascular risk factors such as family history, smoking, hypertension, hyperlipidemia, or proteinuria should be treated with aspirin.[150] The POPADAD and JPAD trials and several subsequent meta-analyses have forced a re-evaluation of that approach, since they indicate that using aspirin for *primary prevention* of CV disease in patients with diabetes offers little or no benefit, with a possible increase in adverse events. Patients with multiple cardiac risk factors or with symptomatic peripheral vascular disease are more likely to benefit from aspirin therapy, but careful clinical judgment must be exercised regarding the expected risks and benefits.

Two trials in progress are examining the effect of aspirin for primary prevention of cardiovascular events in patients with diabetes (**ASCEND** and **ACCEPT-D**) and may provide a clearer answer**.**

The 2013 American Diabetes Association standards of medical care for diabetes recommend the following for *primary* prevention:[8]

- Consider aspirin if 10-year risk of a CV event is >10%.
- Aspirin is not recommended if 10-year risk of a CV event is <5%.
- Clinical judgment is required if 10-year risk of a CV event is 5–10%.

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 there is a compelling contraindication.

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. Although tobacco addiction 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), and counseling programs. The addition of pharmacological therapy to counseling is more effective than either therapy alone.[8] A recent study has raised questions concerning the value of varenicline (Chantix) in promoting smoking cessation.[151]

Conclusions

- Diet and exercise have a major impact on glucose control, and can slow the progression of prediabetes to diabetes.
- Target a hemoglobin A1C of 7% for most patients with diabetes. But modify the goal (e.g., 8% or higher) for 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; tailor the second-line treatment based on patient characteristics.
- Add insulin promptly when oral agents are not sufficient to achieve A1C the goal.
- Manage hypertension and hyperlipidemia aggressively to prevent diabetes-related complications.
- Continuously promote healthy diet, exercise and adherence to medications.

Appendix 1. Results of the Look AHEAD study

The Look AHEAD study examined the CV effects of intensive lifestyle interventions (ILI) compared with diabetes support and education (DSE) in obese adults with type 2 diabetes. Some interim results of clinical outcomes are provided in the following table (next page). Further information on the trial can be found at lookaheadtrial.org/public/home.cfm.

Table 15: Summary of Look AHEAD trial results to date

Outcome measure	Results
Weight loss averaged across at 4 years	Significantly greater loss in ILI group (6.5% of initial weight versus 0.9%).[55] More ILI than DSE participants lost ≥5% (46% vs. 25%; p<0.0001) and ≥10% (23% vs. 10%; p<0.0001) of initial weight.[152]
Fitness at 4 years[153]	Significantly higher in ILI group
Physical activity at 4 years[153]	Significantly higher in ILI group
HbA1c averaged across 4 years[55,153]	Significantly reduced in ILI group (-0.36% versus -0.09%; p<0.001), and associated with change in fitness
C-reactive protein at 1 year[154]	Significantly reduced in ILI group (-44% versus -17%; p<0.001)
Blood pressure averaged across 4 years[55]	Systolic: significantly reduced in the ILI group (-5.33 vs. -2.97 mmHg; p<0.001) Diastolic: significantly reduced in the ILI group (-2.92 vs. -2.48 mmHg; p=0.01)
Lipids averaged across 4 years[55]	HDL: significantly higher in ILI group (3.67 vs. 1.97 mg/dL; p<0.001) Triglycerides: significantly reduced in the ILI group (-25.56 vs. -19.75 mg/dL; p<0.001) LDL: significantly reduced in the DSE group (-12.84 versus -11.27 mg/dL; p=0.009)
Bone loss at 1 year[155]	Bone loss over 1 year was greater in ILI at the total hip (-1.4% versus -0.4%; p<0.001) and femoral neck (-1.5% versus -0.8%; p=0.009), but change in BMD for the lumbar spine and whole body did not differ between groups. In ILI, bone loss at the total hip was independently associated with weight loss in men and women and with poorer glycemic control in men, but was not associated with changes in fitness.
Urinary incontinence at 1 Urinary incontinence at 1 year[156]	Fewer women in the ILI group reported urinary incontinence (25.3% vs. 28.6% in the DSE group, p=0.05) In participants without urinary incontinence at baseline, 10.5% of ILI and 14.0% of DSE patients experienced urinary incontinence after 1 year (p=0.02) No significant between-group differences in the resolution of existing urinary incontinence (p>0.17) Each kilogram of weight lost was associated with a 3% reduction in the odds of urinary incontinence developing (p=0.01), and weight losses of 5% to 10% reduced these odds by 47% (p=0.002)
Depression at 1 year[157]	The incidence of potentially significant symptoms of depression was significantly lower in the ILI than DSE group (6.3% vs. 9.6%; RR 0.66; 95% CI: 0.5-0.8; p<0.001)

Appendix 2. Dipeptidyl peptidase-4 (DPP-4) inhibitors (Gliptins)

alogliptin (Nesina)

linagliptin (Tradjenta)

saxagliptin (Onglyza)

sitagliptin (Januvia)

Mechanism of action

DPP-4 inhibitors increase incretin hormones, increasing glucose-dependent insulin secretion and decreasing glucagon production.

Macro/micro-vascular risk

There are no prospective clinical studies providing conclusive evidence of reduced risk of microvascular or macrovascular complications or mortality with the DPP-4 inhibitors. Clinical trials to date have focused on surrogate markers such as HbA1c.

Pooled analyses of randomized clinical trials have found that treatment with sitagliptin is not associated with an increased risk of adverse cardiovascular events in patients with type 2 diabetes mellitus.[158,159]

A meta-analysis of 8 phase II and phase III trials found no evidence that saxagliptin increases CV risk in patients with type 2 diabetes.[84,160]

A number of studies in progress (EXAMINE, SAVOR-TIMI 53) are examining macrovascular outcomes with the DPP-4 inhibitors.

HbA1c

DPP-4 inhibitors as monotherapy lower HbA1c by an average of about 0.7%.

Short-term trials of combination therapy with a placebo control (i.e. DPP4 inhibitor+drug X vs. placebo+drug X) have shown significant reductions in HbA1c as follows:

- alogliptin compared with placebo when added to metformin, glyburide, pioglitazone+/-metformin+/-sulfonylurea, or insulin+/-metformin
- linagliptin compared with placebo when added to metformin, a sulfonylurea, pioglitazone, metformin+sulfonylurea, or insulin.
- saxagliptin compared with placebo when added to metformin, glyburide, a thiazolidinedione, or insulin+/-metformin.
- sitagliptin compared with placebo when added to metformin, glimepiride, pioglitazone, metformin+glimepiride, metformin+rosiglitazone, or insulin+/-metformin.

Other short-term trials have shown the following in relation to HbA1c:

- no significant difference between alogliptin and pioglitazone
- greater reduction with alogliptin+metformin than with alogliptin alone
- greater reduction with alogliptin+pioglitazone than with alogliptin alone

- greater reduction with linagliptin+metformin than with linagliptin alone
- less reduction with linagliptin+glimepiride than with metformin+glimepiride
- linagliptin non-inferior to metformin[161]
- linagliptin+metformin non-inferior to glimepride+metformin[162]

- greater reduction with saxagliptin+metformin than with saxagliptin alone
- no significant difference between saxagliptin+metformin and glipizide+metformin

- greater reduction with sitagliptin+metformin than with sitagliptin alone
- no significant difference between sitagliptin+metformin and glipizide+metformin

In patients taking metformin, saxagliptin has been shown to be non-inferior to glipizide and sitagliptin in reducing HbA1c.[163]

Weight and lipid profile

The DPP-4 inhibitors have generally been reported as being weight neutral, although some studies have reported small weight gains/losses.

Studies on lipid profiles 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.[83] Alogliptin, linagliptin, and saxagliptin have been reported as being lipid neutral.[84-86] A 2012 meta-analysis found that the DPP-4 inhibitors reduced total cholesterol and triglycerides.[87]

Serious adverse effects

There is an increased risk of hypoglycemia when DPP-4 inhibitors are used with insulin or an insulin secretagogue such as sulfonylureas or repaglinide.

DPP-4 is found in many tissues including the immune system. An increased risk of upper respiratory tract infections, nasopharyngitis, and urinary tract infections with DPP-4 inhibitors compared with placebo has been reported in clinical trials.

There have been reports of acute pancreatitis with the DPP-4 inhibitors in clinical trials and post-marketing.

Hepatic failure has been reported with alogliptin. Use with caution in hepatic impairment.

Renal impairment

Dosage adjustments of alogliptin, sitagliptin and saxagliptin are recommended in patients with moderate or severe renal insufficiency and in patients with end-stage renal disease. No dose adjustment of linagliptin is needed in renal impairment.

Summary

The DPP-4 inhibitors lower HbA1c by about 0.7% as monotherapy. In combination with another hypoglycemic agent, they consistently reduce HbA1c more than either agent alone. The DPP-4 inhibitors are expensive, and more outcome data on microvascular and macrovascular complications are needed to better define the role of these medications in the management of type 2 diabetes.

Appendix 3. Glucagon-like peptide-1 (GLP-1) receptor agonists

exenatide (Byetta)

exenatide XR (Bydureon)

liraglutide (Victoza)

albiglutide (Tanzeum)

dulaglutide (Trulicity)

NOTE: Some of the following material summarizes results of clinical trials and other information reported by the FDA. Other material is referenced as appropriate.

Mechanism of action

GLP-1 agonists mimic naturally occurring incretin hormones that stimulate insulin production, inhibit release of glucagon, and slow nutrient absorption.

Macro/micro-vascular risk

There are no prospective clinical studies providing conclusive evidence of reduced risk of microvascular or macrovascular complications or mortality with the GLP-1 agonists. Clinical trials to date have focused on surrogate markers such as HbA1c.

The results of a retrospective pooled analysis of 12 clinical trials suggested that exenatide did not increase the risk of major CV events compared to placebo or insulin.[164]

HbA1c

GLP-1 agonists as monotherapy lower HbA1c by about 1.0%.

Short-term trials of combination therapy have shown the following in relation to HbA1c:

- greater reduction with exenatide+metformin than with metformin alone
- greater reduction with exenatide+metformin than with sitagliptin+metformin[165]
- greater reduction with exenatide+metformin than with pioglitazone+metformin[165]
- greater reduction with exenatide+sulfonylurea than with sulfonylurea alone
- greater reduction with exenatide+metformin+sulfonylurea than with metformin+sulfonylurea alone
- greater reduction with exenatide+thiazolidinedione than with thiazolidinedione alone
- greater reduction with exenatide+insulin than with insulin alone
- similar reductions with exenatide and insulin glargine, and weight loss with exenatide, in patients with poor glycemic control with metformin+sulfonylurea.[166]
- greater reduction at 26 weeks and at 84 weeks with exenatide than with insulin glargine in patients with poor glycemic control with metformin or metformin+sulfonylurea; at 84 weeks,

patients taking exenatide had lost 2.1 kg of body weight, whereas those taking insulin glargine gained 2.4 kg[167,168]

- greater reduction with exenatide XR (Bydureon) than with exenatide (Byetta)
- greater reduction with liraglutide than with glimepiride
- greater reduction with liraglutide+metformin than with metformin alone
- no difference between liraglutide+metformin and glimepiride+metformin
- greater reduction with liraglutide+metformin than with sitagliptin+metformin
- greater reduction with liraglutide+glimepiride than with glimepiride alone
- greater reduction with liraglutide+metformin+insulin than with liraglutide+metformin
- greater reduction with liraglutide+metformin+glimepiride than with metformin+glimepiride
- greater reduction with liraglutide+metformin+/-sulfonylurea than with exenatide+metformin+/-sulfonylurea
- greater reduction with liraglutide+metformin+rosiglitazone than with liraglutide+rosiglitazone

Weight and lipid profile

Weight loss of 2-3 kg over 6-12 months has been reported with the GLP-1 agonists, some of which may be due to gastrointestinal adverse effects.

Clinical studies, pooled analyses, and a meta-analysis have reported exenatide as being lipid neutral or beneficial.[88-91]

Serious adverse effects

There is an increased risk of hypoglycemia when GLP-1 agonists are used with insulin or an insulin secretagogue such as sulfonylureas or repaglinide.

Exenatide and exenatide XR are associated with an increased risk of pancreatitis, and should be discontinued (and not restarted) if pancreatitis occurs. Other agents should be considered in patients with a history of pancreatitis. Pancreatitis has also been reported during liraglutide treatment.

Gastrointestinal side effects such as nausea, vomiting, and diarrhea occur commonly with the GLP-1 receptor agonists.

Contraindications

Bydureon and liraglutide carry black box warnings advising that the drug is contraindicated in patients with a personal or family history of medullary thyroid carcinoma, and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2).

Exenatide and exenatide XR are contraindicated in patients with severe renal impairment or end stage renal disease. Liraglutide should be used with caution in patients with renal impairment.

Exenatide and exenatide XR are contraindicated in patients with severe gastrointestinal disease (e.g. gastroparesis).

Summary

The GLP-1 agonists lower HBA1C by about 1.0% as monotherapy. In combination with another hypoglycemic agent, they consistently reduce HbA1c more than monotherapy with the comparator drug. The GLP-1 agonists are expensive, and high rates of gastrointestinal adverse effects may limit their utility. A trial of lixisenatide failed to demonstrate a cardiovascular endpoint benefit, but a more recent study of liraglutide was reported to reduce cardiovascular events. At the time of this writing, its complete data have not been made public. More outcome data on microvascular and macrovascular complications are needed to better define the role of these medications in the management of type 2 diabetes.

Appendix 4. Thioglitazones

Pioglitazone (Actos)

NOTE: Some of the following material summarizes results of clinical trials and other information reported by the FDA. Other material is referenced as appropriate. Rosiglitazone is not discussed as it is rarely used.

Mechanism of action

Pioglitazone increases insulin-mediated glucose uptake into adipose tissues and skeletal muscles (major effect), and decreases hepatic glucose production (minor effect).

Macro/micro-vascular risk reduction

In the PROactive study comparing pioglitazone with placebo in patients with type 2 diabetes and cardiovascular disease, the primary composite endpoint (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) was not significantly reduced with pioglitazone.[65]

A secondary outcome of PROactive (all-cause mortality, non-fatal myocardial infarction, or stroke) was significantly reduced by 16% in pioglitazone-treated patients.[65] In patients with prior myocardial infarction, there was a significant 28% reduction in the risk of fatal or non-fatal MI, and a 19% reduction in the composite end point of nonfatal MI (excluding silent MI), coronary revascularization, ACS, and cardiac death.[169] In patients with previous stroke, pioglitazone significantly reduced fatal or nonfatal stroke by 47% and a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke by 28%.[170]

A meta-analysis of 19 randomized controlled trials found that pioglitazone significantly reduced the relative risk of a composite end-point of death, myocardial infarction or stroke by 28%.[71]

Another meta-analysis of randomized controlled trials of pioglitazone (the analysis excluded PROactive) found a significant 70% reduction (95% CI: 37-86%) in all-cause mortality with no increase in non-fatal coronary events.[171]

A third meta-analysis of 5 randomized controlled trials found that pioglitazone did not increase the risk of myocardial infarction.[172]

HbA1c

Pioglitazone as monotherapy lowers HbA1c by about 1.0%.

Short-term trials of combination therapy have shown the following in relation to HbA1c:

- greater reduction with pioglitazone+metformin compared with metformin alone
- greater reduction with pioglitazone+sulfonylurea compared to sulfonylurea alone
- greater reduction with pioglitazone+insulin compared with insulin alone[173,174]

Weight and lipid profile

Pioglitazone causes equivalent amounts of weight gain to sulfonylureas and repaglinide.[76]

Pioglitazone increases LDL and HDL levels, and reduces triglyceride levels.[76,87]

Serious adverse effects

Pioglitazone does not appear to increase the risk of hypoglycemia compared to placebo. Hypoglycemia may occur when pioglitazone is used with insulin or insulin secretagogues (e.g., sulfonylureas, repaglinide).

Pioglitazone can cause or exacerbate congestive heart failure. Pioglitazone increases the risk of fractures in women.

The FDA has reported that use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer. Two recent meta-analyses support that finding.[175,176]

Pioglitazone may cause hepatotoxicity and macular edema.

Contraindications

Pioglitazone is contraindicated in patients with symptomatic heart failure and New York Heart Association (NYHA) Class III or IV heart failure.

Pioglitazone is contraindicated in patients with active bladder cancer.

Summary

Pioglitazone lowers HbA1c by about 1.0% as monotherapy. In combination with another hypoglycemic agent, it reduces HbA1c more than monotherapy with the comparator drug. There is evidence that pioglitazone reduces the risk of macrovascular complications in diabetes. Generic pioglitazone is inexpensive and may be added to metformin if further glycemic control is required. Serious adverse effects including heart failure and fractures may limit its utility.

Appendix 5. Meglitinides

repaglinide (Prandin)

nateglinide (Starlix)

NOTE: Some of the following material summarizes results of clinical trials and other information reported by the FDA. Other material is referenced as appropriate.

Mechanism of action

Meglitinides increase insulin secretion.

Macro/micro-vascular risk reduction

There are no clinical studies providing conclusive evidence of reduced risk of microvascular or macrovascular complications or mortality with the meglitinides. Clinical trials to date have focused on surrogate markers such as HBA1C.

A recent clinical trial found that treatment with nateglinide for 5 years did not reduce the risk of adverse cardiovascular events in patients with IGT and existing cardiovascular disease or cardiovascular risk factors.[177]

HbA1c

Repaglinide and nateglinide as monotherapy lower HbA1c by about 0.5-1.0%.

Short-term trials of combination therapy have shown the following in relation to HbA1c:

- greater reduction with repaglinide+metformin compared with either agent alone
- greater reduction with repaglinide+pioglitazone compared with either agent alone
- greater reduction with repaglinide+rosiglitazone compared with either agent alone

- lesser reduction with nateglinide than with glyburide
- lesser reduction with nateglinide than with metformin
- greater reductions with nateglinide+metformin than with either agent alone
- greater reductions with nateglinide+rosiglitazone than with rosiglitazone alone
- no difference between nateglinide+glyburide compared with glyburide alone

Weight and lipid profile

Repaglinide causes similar amounts of weight gain to sulfonylureas and the glitazones.[76] Nateglinide may cause less weight gain than repaglinide.[72]

Repaglinide has little effect on LDL and HDL levels, but reduces triglyceride levels.[76]

Adverse effects

There is an increased risk of hypoglycemia with repaglinide and nateglinide, the former by the same degree as the sulfonylureas.[76]

Other common adverse effects of meglitinides include gastrointestinal symptoms, back pain, joint pain, and upper respiratory infection symptoms (runny or stuffy nose, sneezing, cough, cold or flu symptoms).

Renal and hepatic impairment

Dosage adjustment of repaglinide is recommended in patients with severe renal impairment. Use repaglinide and nateglinide with caution in patients with moderate to severe hepatic impairment.

Summary

The meglitinides reduce HbA1c by 0.5-1.0% as monotherapy. In combination with another hypoglycemic agent, they generally lower HbA1c more than either agent alone. Meglitinides are relatively expensive, and more outcome data on microvascular and macrovascular complications are needed to better define the role of these medications in the management of type 2 diabetes.

Appendix 6. Sodium glucose cotransporter 2 (SGLT-2) inhibitors

canagliflozin (Invokana)
canagliflozin and metformin (Inokamet)
dapagliflozin (Farxiga)
dapagliflozin and metformin extended-release (Xigduo XR)
empagliflozin (Jardiance)
empagliflozin and linagliptin (Glyxambi)
empagliflozin and metformin (Synjardy)

Mechanism of action

The kidneys reabsorb glucose via sodium-glucose co-transporters. By blocking these transporters (primarily SGLT-2) SGLT-2 inhibitors reduce renal glucose reabsorption, increasing urinary glucose excretion.

Macro/micro-vascular risk reduction

In a 2015 study, empagliflozin was associated with significantly lower rates of all-cause and cardiovascular death and lower risk of hospitalization for heart failure.[66] Heart failure–related endpoints appeared to account for most of the observed benefits in this study. In the EMPA-REG OUTCOME(R) trial, empagliflozin added to standard of care reduced the risk of 3-point major adverse cardiovascular events, cardiovascular and all-cause death, and hospitalization for heart failure in patients with type 2 diabetes and high cardiovascular risk.[92] The study found that in patients with type 2 diabetes and high cardiovascular risk, empagliflozin reduced heart failure hospitalization and cardiovascular death, with a consistent benefit in patients with and without baseline heart failure.

HbA1c, weight, and blood pressure

The glucosuric effects of SGLT-2 inhibitors result in decreased HbA1c levels, weight, and systolic BP.[42]

Adverse effects

SGLT-2 inhibitors are associated with increased risk of mycotic genital infections and slightly increased low-density lipoprotein cholesterol (LDL-C) levels, and because of their mechanism of action, they have limited efficacy in patients with an eGFR <45 mL/min/1.73 m^2.[42] Dehydration due to increased diuresis may lead to hypotension. The incidence of bone fractures in patients taking canagliflozin and dapagliflozin was increased in clinical trials. The FDA has added warnings about ketoacidosis and serious urinary tract infections, including urosepsis and pyelonephritis, to the labels of SGLT2 inhibitors.

Renal and hepatic impairment

Dosage adjustment of SGLT-2 inhibitors is recommended in patients with severe renal impairment. Use SGLT-2 inhibitors with caution in patients with moderate to severe hepatic impairment.

Summary

SGLT-2 inhibitors rarely cause hypoglycemia and can decrease weight and blood pressure. These advantages are offset by the high cost of the drugs and the increased risks of genitourinary infections, polyuria, increases in LDL-C, dehydration, and the potential for ketoacidosis. Recent evidence from a large randomized trial does, however, indicate that they can reduce cardiovascular events, including heart failure hospitalization and cardiovascular death – a property not seen with many other drugs used to treat diabetes.

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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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