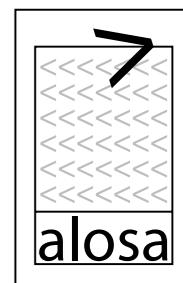


**Just a spoonful of medicine
helps the sugar go down:**

**IMPROVING THE MANAGEMENT
OF TYPE 2 DIABETES**

A PRACTICAL REVIEW OF CURRENT DATA



The Alosa Foundation



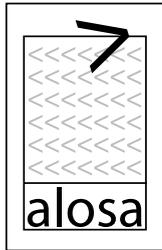
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March 2009

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Balanced data about medications

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March 2009

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▲ INTRODUCTION

Diabetes presently affects over 20 million Americans, and rates of type 2 diabetes in older adults are rapidly increasing.¹ Successful management of diabetes requires multiple steps, including:

- Patient education, lifestyle modification, and self-monitoring
- Ongoing clinical contact to determine whether glucose and cardiovascular risk factors are controlled, and if medication adjustment is necessary
- Detection and prevention of complications
- Treatment of related conditions such as hypertension and hypercholesterolemia.

Accomplishing all of these tasks can be complex and time-consuming, requiring significant effort by physicians, nurses, and diabetes educators, and a major commitment by patients.

There is abundant evidence that many patients with diabetes do not control their blood sugar well enough to reduce the risk of complications.²⁻⁴ Many factors contribute to this problem. Patients find it difficult to make the lifestyle adjustments required for better glycemic control. 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.

This monograph provides practical information to help physicians manage diabetes more successfully. Although it focuses largely on medication therapy, it also addresses diagnostic, monitoring, and other practice-relevant areas. The Independent Drug Information Service (iDiS) has also produced educational materials for patients to make it easier for them to adhere to their physicians' recommendations, available at www.RxFacts.org.

▲ MAKING THE DIAGNOSIS

Diabetes is sometimes diagnosed when a patient presents with symptoms of uncontrolled hyperglycemia such as polyuria or polydipsia, and elevated blood glucose is found. In such patients, a single random blood glucose >200 mg/dL is often adequate to diagnose diabetes.⁵ 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. The diagnostic criteria for diabetes in non-pregnant adults are summarized in Table 1.

A substantial number of people, currently over 50 million in America, may not fulfill the diagnostic criteria for diabetes but may have “pre-diabetes,” which is defined by impaired fasting glucose or impaired glucose tolerance.¹ This condition is a risk factor for the future development of diabetes, and increases the risk of developing cardiovascular disease.⁵ At present, however, most authorities recommend managing “pre-diabetes” with diet and exercise alone, rather than with drugs.

Table 1. Diagnosis of diabetes.⁵

Patient presentation	Test and threshold	Notes
Symptomatic: e.g., polyuria, polydipsia, weight loss	Random plasma glucose ≥ 200 mg/dL	
Asymptomatic	Fasting plasma glucose ≥ 126 mg/dL	Repeat on a second day to confirm; ⁶ Fasting glucose 100-125 mg/dL indicates pre-diabetes ⁷
	Oral glucose tolerance test (OGTT); ⁸ plasma glucose ≥ 200 mg/dL 2 hrs after 75 gm glucose load	Used less often due to inconvenience; Glucose 140-199 mg/dL indicates pre-diabetes ⁸ ; repeat test recommended for clinical confirmation

Current evidence does not support screening all asymptomatic patients for diabetes. Screening is most appropriate in the specific groups noted below:

Table 2. Screening for diabetes. Population wide-screening for diabetes is not currently recommended, but should be considered in patients meeting these criteria.⁵

Age	BMI	Other Risk	Notes
≥ 45	Any	None required	Repeat at 3 year intervals
< 45	≥ 25	<ul style="list-style-type: none"> • Family history of diabetes • Physically inactive • High-risk ethnic group • History of gestational diabetes • Hypertension • Polycystic ovary syndrome • Low HDL/high triglycerides • Vascular disease • Pre-diabetes on previous testing 	For patients with multiple risk factors, consider screening more frequently (every 1-2 years)

Screening is best done under fasting conditions (no caloric intake for at least 8 hours), and results interpreted as in Table 1. The oral glucose tolerance test is a traditional option for screening, but because of its inconvenience, it is generally not used routinely. Although the hemoglobin A1c (A1c) level is used to monitor glycemic control for patients with diabetes (see “Overall goals of care,” below), it is currently not recommended for use as a screening or diagnostic test due to inadequate sensitivity.^{5, 9 10, 11}

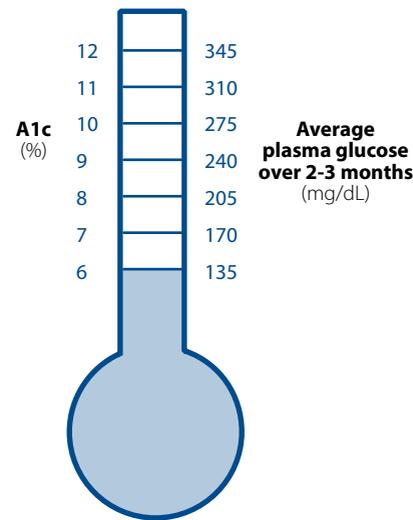
▲ OVERALL GOALS OF CARE

The goal of diabetes treatment is to optimize the plasma glucose level and reduce the risk of macrovascular (e.g., cardiac) and microvascular (e.g., ophthalmologic and renal) disease.

Figure 1. Correlation between A1c level and average plasma glucose.

Derived from Rohlfing et al.¹²

Glycosylated hemoglobin (A1c) provides an indication of a patient's average blood sugar levels in the preceding 2-3 months (see Figure 1).¹² A1c levels should be measured at least twice per year, but checking every 3 months is warranted in patients who are not meeting their goals or with ongoing adjustments in the medication regimen.⁵ In general, an A1c level close to 7% is considered adequate control, and some recently published trials have raised questions about the most appropriate A1c target and whether the level should be pushed below 7%.



These trials are discussed in more detail on pages 24-26. In general, the benefits of lowering A1c more aggressively must be balanced against the increased risk of hypoglycemic episodes;¹³ the decision to pursue more aggressive control (such as a A1c below 7%) should be made on a patient-by-patient basis.

In addition to periodic A1c measurement, patients' monitoring of their own blood glucose is an important part of diabetes management.¹⁴⁻¹⁶ The goal for blood glucose is a level between 70 and 130 mg/dL when fasting, with postprandial (1-2 hours after meal) glucose levels below 180 mg/dL.⁵ 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 A1c, less frequent monitoring (once per day or occasionally less often) may be acceptable.¹⁷ 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.⁵

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

▲ WEIGHT MANAGEMENT, DIET AND EXERCISE

Much of the steady increase in the prevalence of diabetes in recent years has been attributed to the increasing rates of overweight and obesity in the United States. Correspondingly, there is good evidence from studies of patients with pre-diabetes that weight loss can reduce insulin resistance and reduce the risk of developing frank diabetes.¹⁸ Although many physicians despair about the effectiveness of such lifestyle approaches to management, in one large trial an aggressive program of diet and exercise actually performed better than drug therapy in containing serum glucose.¹⁹ Aggressive weight management is also beneficial for other conditions associated with diabetes, such as hypertension and dyslipidemia. Working with patients on a structured program to reduce overall caloric intake, and especially to reduce the calories from fat and saturated fat, can help promote weight reduction, although sustained weight loss remains challenging for many patients.¹⁸ The current evidence is insufficient to recommend diets featuring carbohydrate restriction or diets based on dietary glycemic index/load, but patients should be encouraged to choose “healthy” carbohydrates.⁵

Structured exercise programs can improve the control of diabetes, even if patients do not lose weight in the process.^{20,21} Most guidelines recommend at least 2.5 hours per week of moderate aerobic exercise or 1.5 hours of strenuous aerobic exercise, if possible and clinically appropriate.⁵ Resistance training can also help, and combined aerobic-resistance programs are the most effective.²⁰ For patients with diabetes who have been physically inactive, review cardiac risk factors before recommending an exercise regimen. If the 10-year risk of a coronary event is below 10%, most patients can be encouraged to begin an exercise program; if the risk is above 10%, an exercise test should be considered prior to beginning any program of training.²² (To determine the 10-year risk for any given patient, a calculator is available at <http://hp2010.nhlbihin.net/atp/iii/calculator.asp>.) Patients prone to hypoglycemia or who have developed symptoms of retinopathy or neuropathy will require extra caution in devising an exercise regimen.⁵

Lifestyle modification, diet change, and increased exercise can improve glycemic control in patients with diabetes and can slow progression from pre-diabetes to diabetes while offering multiple other health benefits. A recent systematic review suggests that programs combining diet and exercise are especially effective.²³ Unfortunately, sustained success with these approaches is relatively uncommon, due both to patient difficulty in maintaining new habits and the progressive nature of diabetes. Most patients diagnosed with diabetes and treated with lifestyle interventions will eventually reach A1c levels above 7% and will require pharmacological intervention. As the following section will review, some patients may require treatment before the A1c level reaches 7%.

▲ PREVENTION OR DELAY OF DIABETES

The concept of pre-diabetes has focused attention on the possibility of preventing diabetes from developing in the millions of patients found each year to have mildly abnormal glucose metabolism. Lifestyle interventions can delay the development of diabetes significantly, though many pre-diabetics will eventually go on to develop the full-blown disease in any case.

Trials of lifestyle intervention

The first large trial of lifestyle modification was **the Finnish Diabetes Prevention Study**¹⁸ in which overweight pre-diabetic patients were randomized to usual care or a program of lifestyle modification including weight loss, reduced dietary saturated fat, and substantial amounts of exercise (30 minutes 5 times weekly). 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). At three-year follow-up, lifestyle modification reduced the incidence of diabetes by 43%.²⁴

The Diabetes Prevention Program (DPP) also studied overweight pre-diabetic patients, randomizing them to placebo, lifestyle modification, or metformin.¹⁹ As in the Finnish study, the incidence of diabetes was reduced by 58% in lifestyle modification patients 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 DPP were more overweight than patients in the Finnish study, which may account for the higher rates of diabetes.

Strikingly, while patients in the metformin group fared better than controls, the lifestyle-modification group actually had the lowest rate of diabetes development (4.8 cases of diabetes per 100 patient-years with lifestyle modification, vs. 7.8 cases with metformin and 11.0 cases in the control group).¹⁹

Other medication trials in pre-diabetes

The **STOP-NIDDM** trial found that treatment with acarbose reduced the development of diabetes in pre-diabetics by 25%, but gastrointestinal symptoms limited adherence.²⁵ In the **DREAM** trial, pre-diabetic patients treated with rosiglitazone were 62% less likely to develop diabetes (10.6% vs. 25% in placebo),²⁶ but more recent concerns about the cardiovascular toxicity of rosiglitazone outweigh the benefits of preventive treatment in this population.

Table 3. Treatment to prevent development of diabetes.

Treatment	Reduction in diabetes (compared to placebo)	Notes
Lifestyle modification • weight loss • decreased saturated fat • exercise	58% ^{18, 19}	Results over 3-4 years; at 3-year follow-up reduction was 43% ²⁴
metformin 850 mg b.i.d.	31% ¹⁹	Cost-effectiveness of treatment unclear
acarbose 100 mg t.i.d.	25% ²⁵	GI side effects limit acceptability to patients
rosiglitazone 8 mg q.i.d.	62% ²⁶	Cardiac toxicity/CHF limits use ²⁷⁻²⁹

NOTE: None of the listed medications have an FDA-labeled indication for prevention/delay of diabetes

▼ ▼ BOTTOM LINE ▼ ▼

Intensive lifestyle modification, including weight loss (5% or more), reduced saturated fat intake, and increased exercise (30 minutes 5 times weekly) can reduce the incidence of diabetes in pre-diabetic patients by over 50%. Oral medication can also reduce the incidence of diabetes, but the benefits must be weighed carefully against side effects and costs.

▲ NON-INSULIN TREATMENT OF DIABETES

Six major classes of oral hypoglycemic agents and several non-insulin injectables are now available to treat patients who have developed type 2 diabetes (see Table 4).

Table 4. Classes and mechanisms of action of hypoglycemic agents.

Class	Examples (brand names)	Principal mechanisms of action
sulfonylureas*	glyburide (Diabeta, Micronase), glipizide (Glucotrol), glimepiride (Amaryl)	Increase insulin secretion
biguanides	metformin (Glucophage)	Decrease hepatic glucose production (major), increase uptake of glucose from blood into the tissues (minor)
glitazones (thiazolidinediones)	pioglitazone (Actos), rosiglitazone (Avandia)	Increase insulin-mediated glucose uptake into adipose tissues and skeletal muscles (major), decrease hepatic glucose production (minor)
α -glucosidase inhibitors	acarbose (Precose), miglitol (Glyset)	Reduce rate of glucose production from dietary carbohydrates in the intestine
meglitinides	repaglinide (Prandin), nateglinide (Starlix)	Increase insulin secretion
dipeptidyl peptidase 4 inhibitors (DPP4)	sitagliptin (Januvia)	Increase incretin hormones, which augment glucose-dependent insulin secretion and decrease glucagon release
incretin mimetics	exenatide (Byetta)	Mimic naturally occurring incretin hormones which stimulate insulin production and the response to elevated blood glucose; inhibit release of glucagons after meals, slows nutrient absorption.

*For the purpose of this monograph, "sulfonylureas" refers only to second generation agents and not older agents such as chlorpropamide, which are seldom used in current practice.

In addition to differences in their mechanisms of action, these medications differ in their ability to lower A1c and fasting glucose, their side effects, and their cost. Some agents have been carefully evaluated in clinical trials that measured actual clinical outcomes, while others have only been shown to improve laboratory glucose measurements.

Comparison of oral hypoglycemic agents

The comparative effectiveness of various oral hypoglycemic agents was extensively reviewed in a 2007 meta-analysis performed by researchers at Johns Hopkins University.^{30, 31} Below is a summary of the results of this analysis along with findings from several other recently published studies.

Impact of oral hypoglycemic agents on major clinical outcomes

The fundamental goal of diabetes medications is to reduce clinically important outcomes such as diabetes-related complications (cardiovascular disease, nephropathy, neuropathy and retinopathy), death and disability. 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.

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, and were followed up for 10 years.³² Intensive drug therapy with either regimen was substantially more effective than diet for lowering A1c and reducing the risk of microvascular complications, but resulted in only a small reduction in the risk of myocardial infarction (relative risk 0.84, 95% confidence interval 0.74 to 1.0).³² No differences were found in patients treated with sulfonylurea versus insulin. This trial refuted earlier evidence from an older trial conducted by the University Group Diabetes Program, in which patients treated with sulfonylureas had a higher incidence of myocardial infarction than patients receiving diet alone.⁹

In a second component of **UKPDS**, overweight patients (>120% ideal body weight) were randomized to receive conventional therapy (primarily diet alone), or intensive therapy with metformin, or intensive therapy with insulin or a sulfonylurea (glibenclamide or chlorpropamide).³³ In contrast to the results in normal-weight patients, metformin significantly reduced the risk of diabetes-related death and death from all causes, compared to diet alone.³³ Metformin did not reduce the rate of microvascular complications.

More recently, 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.³⁴ 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 non-significantly 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.

Trials directly comparing different agents

In addition to comparing different oral hypoglycemic agents to placebo, the UKPDS study directly compared different antidiabetic medications. In the study component involving overweight patients, metformin resulted in lower rates of all-cause mortality and stroke (but not myocardial infarction) compared to sulfonylurea or insulin.³³ The benefits of metformin observed in the UKPDS have not been tested in other randomized trials.

In a supplementary randomized trial of UKPDS, 537 overweight and non-overweight patients who were already on maximal doses of sulfonylurea were randomized to continued sulfonylurea monotherapy or the addition of metformin.³³ Surprisingly, patients in the metformin-plus-sulfonylurea group had significantly increased risk of diabetes-related death and all-cause mortality compared to patients continued on sulfonylurea monotherapy. However, in subsequent analysis in which data from this study was pooled with data from the rest of the UKPDS trial, patients who received combined metformin and sulfonylurea were no more likely to die than patients treated with all other treatment regimens.³³

In 2006, results from the **ADOPT** study (**A Diabetes Outcome Progression Trial**) were published. This trial randomized 4,360 untreated patients with diabetes to monotherapy with rosiglitazone, metformin, or glyburide.² 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.

The glitazone controversy

In mid-2007, a meta-analysis of 42 randomized controlled trials was published in *The New England Journal of Medicine* and immediately set off a wave of concern among physicians, patients, and regulators. It evaluated a large number of randomized controlled clinical trials that had allocated patients to rosiglitazone (Avandia) vs. placebo or another oral hypoglycemic regimen. The analysis found that across all the studies, 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 This analysis and other studies such as **ADOPT** gave rise to concerns that the glitazones may not protect patients with diabetes from myocardial infarction and death, and may in fact increase these risks.

A subsequent meta-analysis published in *JAMA* of four large, longer-term trials that prospectively collected information on cardiovascular events confirmed the findings of the original meta-analysis.^{27, 28} However, an interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study did not.³⁵ In this trial, which will not be completed for several more years, 4,447 overweight patients with poorly controlled diabetes despite maximum doses of metformin or a sulfonylurea were randomized to have rosiglitazone added to their regimen or to receive combined metformin and sulfonylurea therapy. After a mean follow-up of 3.75 years, no significant differences in the rate of the primary study end-point (hospitalization or death from cardiovascular causes) were seen. Unfortunately, as pointed out by the study authors, this interim analysis was under-powered to rule out an increased risk of myocardial infarction from rosiglitazone.

Based on these and other data, the U.S. Food and Drug Administration (FDA) placed a black box warning on the rosiglitazone prescription label warning of the potential increased risk of myocardial ischemia. For further information, see: <http://www.fda.gov/cder/foi/label/2008/021071s034lbl.pdf>.

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% ($p=0.005$).³⁶

As discussed in further detail below, both rosiglitazone and pioglitazone increase the risk of heart failure and fracture. It is unclear why rosiglitazone and pioglitazone appear to differ with regard to their risk of myocardial infarction, but if substantiated, this would be another example of how similar drugs in the same class can have markedly different risk profiles.

▼ ▼ BOTTOM LINE ▼ ▼

The existing data does not clearly demonstrate that any one class of oral hypoglycemic agents is more effective in reducing cardiovascular events. Trials have found benefits from metformin, sulfonylureas and pioglitazone. However, both of the available glitazones can cause congestive heart failure, and there is evidence that rosiglitazone increases the risk of major cardiovascular events.

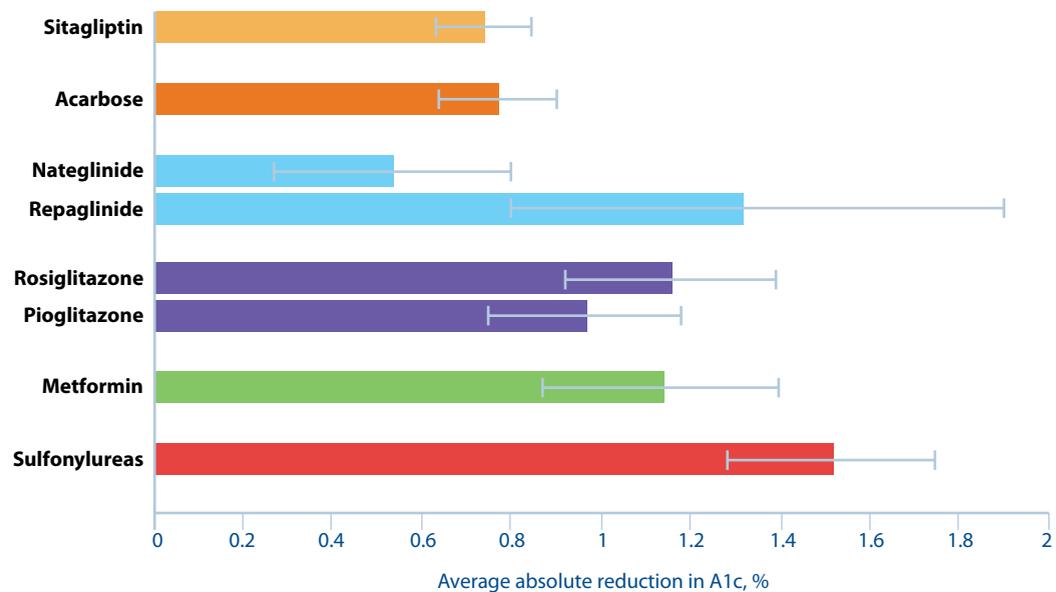
Reductions in hemoglobin A1c

Many studies have compared the ability of oral hypoglycemic agents to reduce hemoglobin A1c – a validated surrogate for long-term glycemic control in patients with diabetes. However, the recent findings concerning rosiglitazone, which was effective in lowering A1c but also increased the risk of congestive heart failure and myocardial infarction, have prompted questions about whether this surrogate marker in isolation can provide a complete picture of a drug's clinical worth. Nevertheless, understanding how different agents lower A1c 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 A1c compared to placebo. Sulfonylureas, metformin, and repaglinide all lower A1c to similar extents – by about one percentage point (see Figure 2).³¹ Glitazones are about as effective.

Figure 2. Expected reductions in A1c from indirect comparisons of different oral hypoglycemic agents. Derived from Bolen et al.³¹, Amori et al.³⁷



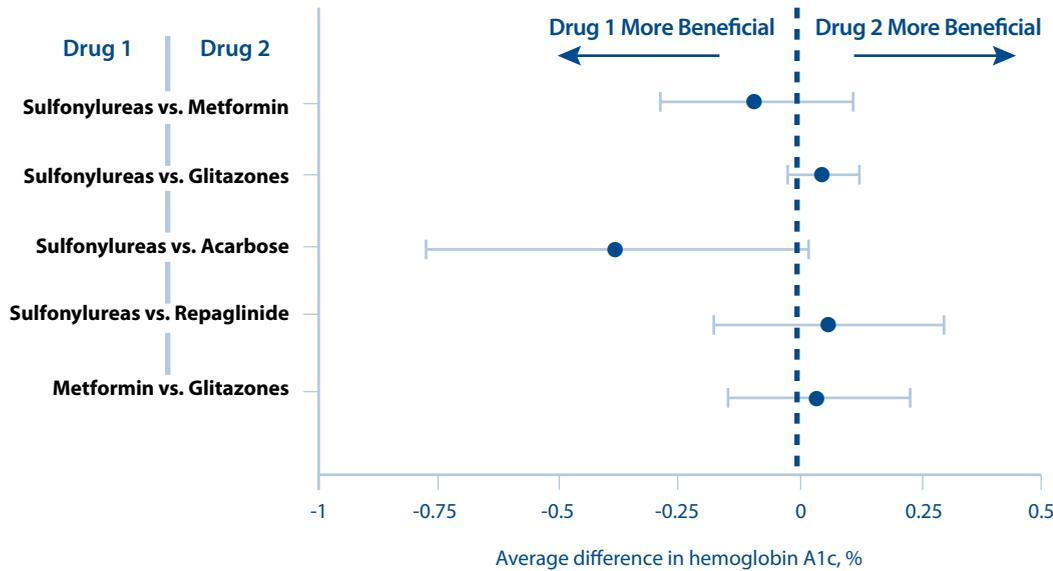
Acarbose and nateglinide appear to have less effect on A1c. Similarly, dipeptidyl peptidase 4 (DPP4) inhibitors lower A1c by an average of 0.7%³⁷; only one drug in this class, sitagliptin (Januvia), has been approved by the FDA. A second agent with equivalent A1c lowering effects, vildagliptin (Galvus), is awaiting approval.

Direct comparisons of oral hypoglycemic agents

A number of head-to-head trials have directly compared the capacity of various oral agents to lower A1c. A recently published meta-analysis of these trials confirms the observation that most drug classes produce similar reductions in A1c (see Figure 3).³⁰

Figure 3. Direct comparisons of different oral hypoglycemic agents.

Derived from Bolen et al.³¹ Differences were modest across all drug classes.



The ADOPT trial was not included in the results in Figure 3. In that study (also described above), patients randomized to rosiglitazone achieved A1c levels that were 0.13% lower than patients treated with metformin and 0.42% lower than patients treated with glyburide.² Similarly, rosiglitazone-treated patients were significantly less likely to have persistently elevated blood sugars on their assigned therapy, although the comparison drug was not given at maximum dosage.² The results of this trial must also be interpreted in light of the cardiovascular risks associated with rosiglitazone.

Several studies have compared A1c lowering with DPP4 inhibitors (sitagliptin and vildagliptin) and other oral agents (sulfonylureas, metformin and the glitazones). When the results of these studies were pooled in a recent meta-analysis, DPP4 inhibitors achieved reductions in A1c that were 0.21% (95% confidence interval 0.02% to 0.39%) smaller than those achieved by other oral hypoglycemic agents (i.e., DPP4 inhibitors were less effective than the agents to which they were compared).³⁷

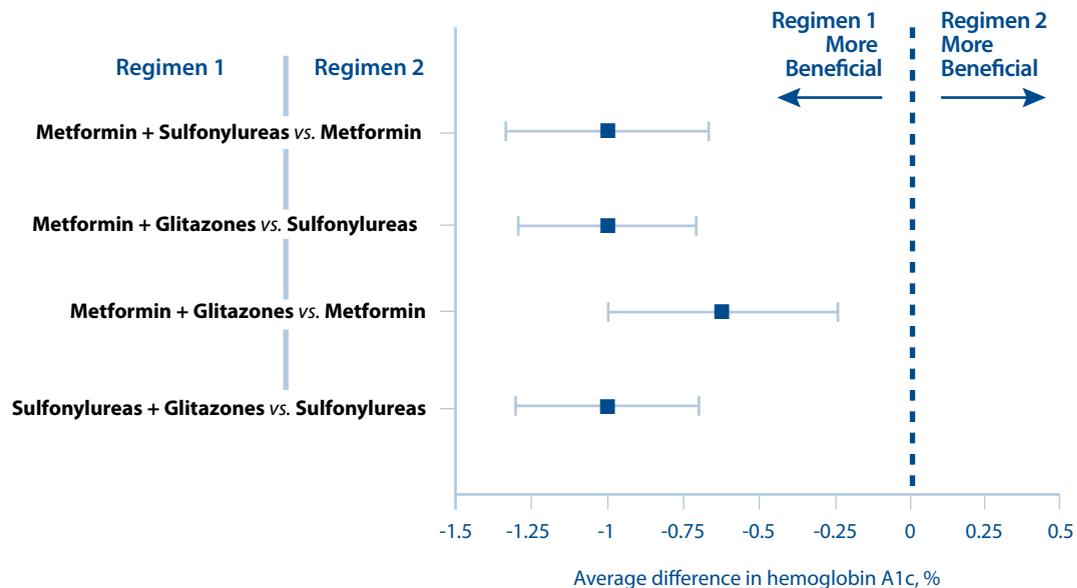
Combination therapy

A number of trials have evaluated whether adding a second non-insulin agent to an existing treatment regimen achieves better glycemic control. These trials have consistently shown an additive effect, probably because these drugs act by different and complementary mechanisms. In general, the addition of a second oral agent from a different class lowers A1c by an additional 1% over treatment with maximum doses of a single agent (see Figure 4).³⁰

Several randomized studies have directly compared different add-on regimens (metformin-sulfonylurea vs. metformin-rosiglitazone). Despite slight under-dosing of the sulfonylurea in these trials, both treatment arms resulted in equivalent reductions in A1c.^{10, 11, 31} The DPP4 inhibitors appear to be as effective as other oral hypoglycemic agents when used as add-on therapy, although the data supporting their use is thus far very limited.^{38, 39}

Figure 4. Comparisons of combined versus monotherapy.

Derived from Bolen et al.³¹



▼ ▼ BOTTOM LINE ▼ ▼

Sulfonylureas, metformin, and repaglinide all appear to lower A1c by roughly equivalent amounts. Glitazones may be about as effective in lowering A1c. Combining oral hypoglycemic agents from different classes has an additive effect on glycemic control.

Other clinical outcomes

Oral hypoglycemic agents differ in their impact on other clinically important outcomes as well. Metformin appears to have the most beneficial effect on LDL cholesterol levels, resulting in average reductions of 10 mg/dL.³⁰ In contrast, sulfonylureas, repaglinide, and acarbose have little effect on LDL levels, while the glitazones increase LDL by an average of 10 mg/dL. Rosiglitazone also appears to elevate triglyceride levels, whereas pioglitazone and all other major classes of oral agents appear to reduce triglycerides.³⁰ The glitazones increase HDL levels, whereas other agents appear to have no effect on HDL.

Metformin has the most favorable effects on body weight. Sulfonylureas, the glitazones, and repaglinide generally cause equivalent amounts of weight gain, whereas patients taking metformin consistently lose weight or remain weight-neutral.³⁰ Nateglinide may result in less weight gain than repaglinide and acarbose appears to have similar effects on weight as metformin.³¹

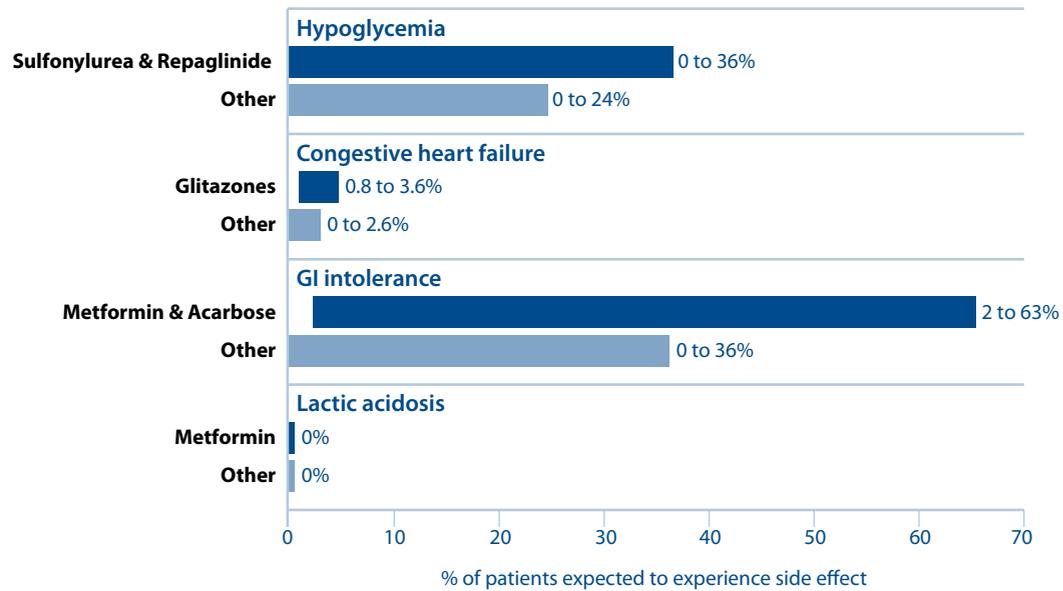
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Metformin appears to have the most beneficial effects on LDL, triglycerides, and body weight, whereas rosiglitazone adversely affects these parameters.

Are these agents all equally safe?

Oral hypoglycemic agents produce a variety of adverse effects because of their different mechanisms of action. Figure 5 summarizes the comparative safety of the different agents; additional detail is provided on the next page.

Figure 5. Adverse events associated with different oral hypoglycemic agents.



Hypoglycemia

Many patients with diabetes experience episodes of hypoglycemia, even those who are not on drug therapy. The risks of hypoglycemic 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).³³

Metformin and the glitazones do not appear to increase the risk of hypoglycemia compared to placebo.³¹ By 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.³⁰ This is particularly relevant for patients whose A1c is close to 7%, and in the elderly. There is limited data about the risks of hypoglycemia from nateglinide, glucosidase inhibitors, and DPP4 inhibitors, although the risks from these agents appears to be low.³⁷

Longer-acting sulfonylureas such as glyburide increase the absolute risk of hypoglycemia by 2% (95% confidence interval 0.5% to 5%) compared to shorter-acting agents such as glipizide and glimepiride.³¹ Accordingly, the latter agents can be used more safely in patients with renal insufficiency and in the elderly.

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Sulfonylureas and repaglinide increase the risk of hypoglycemia while other classes of agents appear not to. Longer-acting sulfonylureas (e.g., glyburide) are more likely to cause hypoglycemia than short-acting agents (e.g., glipizide).

Congestive heart failure and peripheral edema

In contrast to the documented risk of myocardial infarction caused by rosiglitazone, the risk of congestive heart failure caused by both glitazones has been well known for some time. For example, in the PROactive trial of patients with diabetes with known vascular disease, pioglitazone increased the risk of hospitalization for congestive heart failure by about 50% over placebo (from 4% to 6% of study subjects).³⁴ Even in lower risk populations, both pioglitazone and rosiglitazone substantially elevate the risk of heart failure.^{27, 28, 36}

In head-to-head trials, the glitazones increased the risk of heart failure by 1-2 percentage points compared to sulfonylureas.³⁰ Similar results were seen in the **ADOPT** trial.² Surprisingly, in this study, the risk of heart failure in patients treated with metformin was roughly equivalent to that seen in rosiglitazone-treated patients – a finding usually not seen in other trials. In contrast, in the **UKPDS** metformin was associated with a non-significant decrease in heart failure events.³³ Few other studies provide data to evaluate relative risks of heart failure from different oral hypoglycemic agents.

Two recent meta-analyses published in the *Journal of the American Medical Association* suggest that the glitazones increase the risk of congestive heart failure by between 40% and 100%.^{27, 28, 36} In light of the mounting evidence, the U.S. Food and Drug Administration (FDA) issued a “black box” warning about the risk of heart failure associated with rosiglitazone and pioglitazone.^{29, 40}

Rates of peripheral edema are also substantially elevated with the glitazones as compared to either metformin, sulfonylureas and repaglinide. Randomized controlled trials comparing glitazones to sulfonylureas show absolute differences in the rate of peripheral edema ranging from 4 to 21%.³¹

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The glitazones substantially increase the risk of congestive heart failure and peripheral edema compared with sulfonylureas and metformin. There is less information about CHF risk for many of the newest classes of oral hypoglycemic agents.

Other side effects

Although an older biguanide no longer available in the U.S. (phenformin) caused lactic acidosis, a recent systematic review found no cases of lactic acidosis in clinical trials of metformin.⁴¹ 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 this drug quotes the risk of metformin-induced lactic acidosis at 3 cases per 100,000 treated.

Gastrointestinal intolerance is a frequent side effect for metformin, occurring in up to 60% of patients.³⁰ It occurs very frequently with acarbose, but is substantially lower in patients receiving sulfonylureas, glitazones and 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.

The glitazones appear to increase the risk of fracture in women. In the **PROactive** trial, 5.1% of pioglitazone-treated women had a fracture as compared with 2.5% of patients who received placebo.³³ In the ADOPT trial, the incidence of fracture in women was 9.3% in patients treated with rosiglitazone as compared with 3.5% and 5.1% in patients who received glyburide or metformin, respectively.² No increased risk of fracture was observed in men.

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Metformin 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 appear to increase the risk of fracture.

Incretin mimetics (exenatide)

Exenatide, marketed as Byetta, was approved for use in the U.S. in 2005. The drug potentiates glucose-mediated insulin secretion, suppresses glucagon secretion, and slows gastric motility. It is administered twice a day by subcutaneous injection.

Several short-term randomized controlled trials have shown that exenatide reduces hemoglobin A1c by 0.5% – 1.0% when added to treatment with sulfonylureas and/or metformin in patients whose glucose was poorly controlled.⁴²⁻⁴⁵ Gastrointestinal side effects were frequent. More than half of patients complained of nausea; vomiting and diarrhea were also common. Recent evidence suggests that exenatide is also associated with a significant increase in the risk of pancreatitis, causing the FDA to request a labeling change to warn patients about this side effect.⁴⁶ In trials, patients lost approximately 2 – 3 kg over 6 months on the drug, some of which may be due to its gastrointestinal side effects. Exenatide has been approved for use in combination with sulfonylureas or metformin, but not with insulin, and cannot be used in patients with severe renal impairment.

The role of exenatide in the management of type 2 diabetes is not well defined at this point. Due to its high rates of side effects, high cost (about \$230 per month), and relatively scant long-term evidence, exenatide is not included in the treatment algorithm recommended by the American Diabetes Association. It may be considered as an adjunct to oral therapy in some patients who are within 0.5% of their A1c target on maximum oral therapy and who are obese. It may also be useful in patients who remain uncontrolled on oral therapies, but who have occupational restrictions that prohibit insulin use (e.g., pilots, truck-drivers).

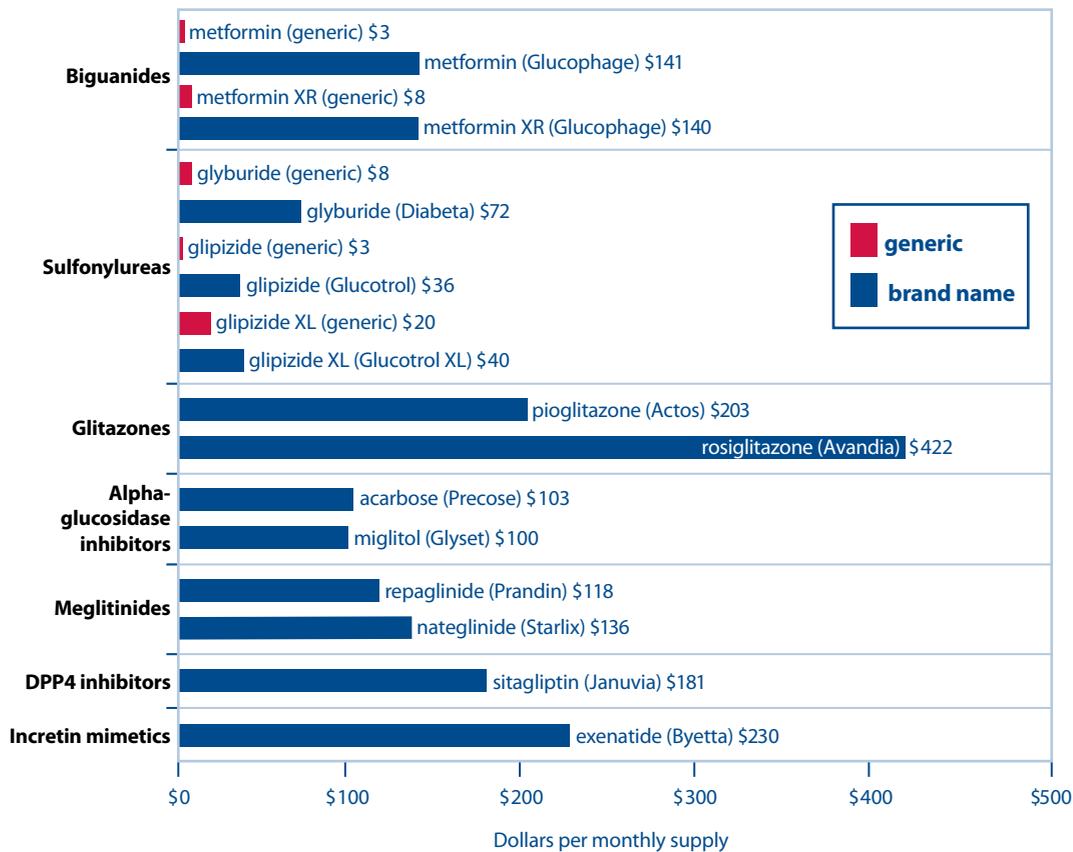
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Due to high rates of side effects, the need for daily injections, high costs, and scant long-term data, exenatide was not included in the ADA treatment algorithm for type 2 diabetes management. Its use should be limited to carefully selected obese patients who are nearly controlled on maximum oral therapy.

Cost

Non-insulin agents vary widely in cost (see Figure 6).

Figure 6. Costs for monthly supplies of equivalent doses of non-insulin agents.



The lowest daily costs for these medications are based on several websites, including www.drugstore.com, www.target.com, and www.samsclub.com. Prices obtained January 2009.

Because sulfonylureas and metformin have been on the market for many years, generic versions exist, and their monthly cost is extremely low. In contrast, all of the newer diabetic agents are protected by patents and cost 20 to 100 times those of generic sulfonylureas and metformin.

Putting it all together: optimal use of oral hypoglycemic and non-insulin injectable agents

Table 5 summarizes the comparative efficacy, safety and cost of the available classes of oral hypoglycemic agents. Green boxes indicate the best outcome, yellow boxes indicate intermediate outcomes, and red boxes indicate an important problem.

Table 5. Summary of comparative efficacy, safety, and cost of non-insulin agents.

Drug	Risk of death, and/or major CV events	Control of A1c	Weight gain or loss	Hypo-glycemia	Heart failure and edema	LDL	GI	Cost	Overall
metformin	Green	Green	Green	Green	Green	Green	Red	Green	Green
sulfonylureas	Yellow	Green	Red	Red	Green	Yellow	Yellow	Green	Yellow
glitazones	pioglitazone	Yellow	Red	Green	Red	Yellow	Yellow	Red	Yellow
	rosiglitazone	Red	Green	Green	Red	Red	Yellow	Red	Red
α-glucosidase inhibitors		Yellow	Green			Yellow	Red	Yellow	
meglitinides	repaglinide	Green	Red	Red		Yellow	Yellow	Yellow	
	nateglinide		Yellow	Yellow		Yellow	Yellow	Yellow	
DPP4 inhibitors		Yellow						Red	
exenatide		Yellow	Green	Yellow			Red	Red	

GI = gastrointestinal intolerance; LDL = LDL cholesterol level

Best outcome	Intermediate	Problem	Unknown
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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 in keeping with the 2009 **American Diabetes Association (ADA) and European Association for the Study of Diabetes guidelines** for the management of type 2 diabetes.⁴⁷ These guidelines, which recommended initial therapy with metformin, were largely supported by results from **UKPDS**. **The data supporting the use of other classes of agents (i.e., glucosidase inhibitors, meglitinides, and the DPP4 inhibitors) is insufficient to recommend their routine use at present for most patients.**

Of course, because of contraindications or intolerances, these guidelines may not apply to all patients. Table 6 summarizes situations in which metformin and other oral agents may be contraindicated.

Table 6. Contraindications and required dose-adjustments for various agents as indicated on the FDA-approved product labels.

Class	Examples	Contraindications and warnings*
sulfonylureas*	glyburide, glipizide	<ul style="list-style-type: none"> • Glyburide generally not recommended for patients with CrCl < 50 mL/min • Glipizide generally not recommended for patients with CrCl < 10 mL/min
biguanides	metformin	<ul style="list-style-type: none"> • 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
glitazones (thiazolidinediones)	pioglitazone, rosiglitazone	<ul style="list-style-type: none"> • Symptomatic heart failure including established Class III or IV heart failure; rosiglitazone associated with increased MI risk
α-glucosidase inhibitors	acarbose, miglitol	<ul style="list-style-type: none"> • Cirrhosis • Inflammatory bowel disease, colonic ulceration, partial intestinal obstruction (or predisposition to obstruction), chronic intestinal disease associated with disorders of digestion or absorption
meglitinides	repaglinide, nateglinide	<ul style="list-style-type: none"> • Patients with severe renal insufficiency should initiate therapy with reduced doses; use with caution in patients with impaired liver function
dipeptidyl peptidase 4 inhibitors (DPP4)	sitagliptin	<ul style="list-style-type: none"> • Patients with severe renal insufficiency should initiate therapy with reduced doses
incretin mimetics	exenatide (Byetta)	<ul style="list-style-type: none"> • Monitor for hypoglycemia when used with sulfonylureas • Not tested in patients with gastroparesis or severe gastrointestinal disease • Acute pancreatitis can occur • Not recommended in patients with severe renal impairment

*CrCl = creatinine clearance; *In addition to known hypersensitivity, type 1 diabetes, and diabetic ketoacidosis (which should be treated with insulin); #Label material for glyburide not available on the FDA website; information derived from Micromedex® Healthcare Series.⁴⁸ Full prescribing information is provided on the FDA-approved label for each drug.

What is the most appropriate therapeutic goal?

Large trials such as UKPDS have found that intensive glucose control for patients newly diagnosed with diabetes can reduce diabetes-related outcomes, supporting the idea that the lower the HbA1c, the better. **Ten-year follow-up data from the UKPDS study** was published recently.⁴⁹ It revealed that although the between-group differences in HbA1c levels did not persist after the first year, patients in 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 MI (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%, $P = 0.01$), MI (33%, $P = 0.005$), and death from any cause (27%, $P = 0.002$).

Other trials published in 2008, however, have raised questions about this “lowest is best” approach. Three trials of patients with long-standing diabetes, the **Action to Control Cardiovascular Risk in Diabetes (ACCORD)**,⁵⁰ **Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)**⁵¹ and the **Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes (VADT)** study,⁵² found no significant reduction in macrovascular events with intensive glycemic control. These trials are summarized on the next page.

	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 randomized patients with type 2 diabetes and either known heart disease or at least 2 risk factors to receive either intensive medical treatment (A1c goal < 6%) or standard medical treatment (HbA1c 7 to 7.9%).⁵⁰ Surprisingly, patients assigned to a target HbA1c level under 6% were found to have an increased risk of mortality. By contrast, there was no increase in mortality with intensive glycemic control in the **ADVANCE**⁵¹ or **VADT**⁵² studies. It is unclear why intensive glycemic control (i.e., targeting HbA1c levels well below 7%) increased mortality in **ACCORD**. Although patients in the intensive A1c 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. Other possible causes of the higher death rate in the intensive treatment group of **ACCORD** as compared to **ADVANCE** and **VADT** include:

- large magnitude of the reduction in HbA1c (under 6%)
- speed of the reduction in HbA1c (reductions of approximately 1.4% in the intensive therapy group and 0.6% in the standard-therapy group within the first 4 months after randomization)
- differences in drug regimens
- rates of hypoglycemia
- undetected adverse interactions among the various drug classes used at high doses.

Of note, 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 getting intensive glycemic control in the **VADT** study.

Following publication of these recent studies, the **American Diabetes Association**, the **American College of Cardiology Foundation**, and the **American Heart Association** addressed the implications of the **ACCORD**, **ADVANCE**, and **VADT** studies for glycemic control goals.⁵³ The main recommendations were:

- **The lack of significant reduction in CVD events with intensive glycemic control in these studies should not lead to an abandonment of the general target of an HbA1c < 7.0%, because of the well-established benefit of good glucose control on microvascular (renal, retinal) complications.**
- **Lowering HbA1c to approximately 7% or less reduces the microvascular complications of diabetes. Thus, the goal for most non-pregnant adults in general is an HbA1c of 7%.**
- **Although randomized controlled trials of intensive versus standard glycemic control have not shown a significant reduction in cardiovascular disease outcomes, long-term follow-up of the UKPDS trial suggests that treating to a target HbA1c of 7% or less soon after diabetes is diagnosed may cause long-term reduction in risk of cardiovascular disease.**

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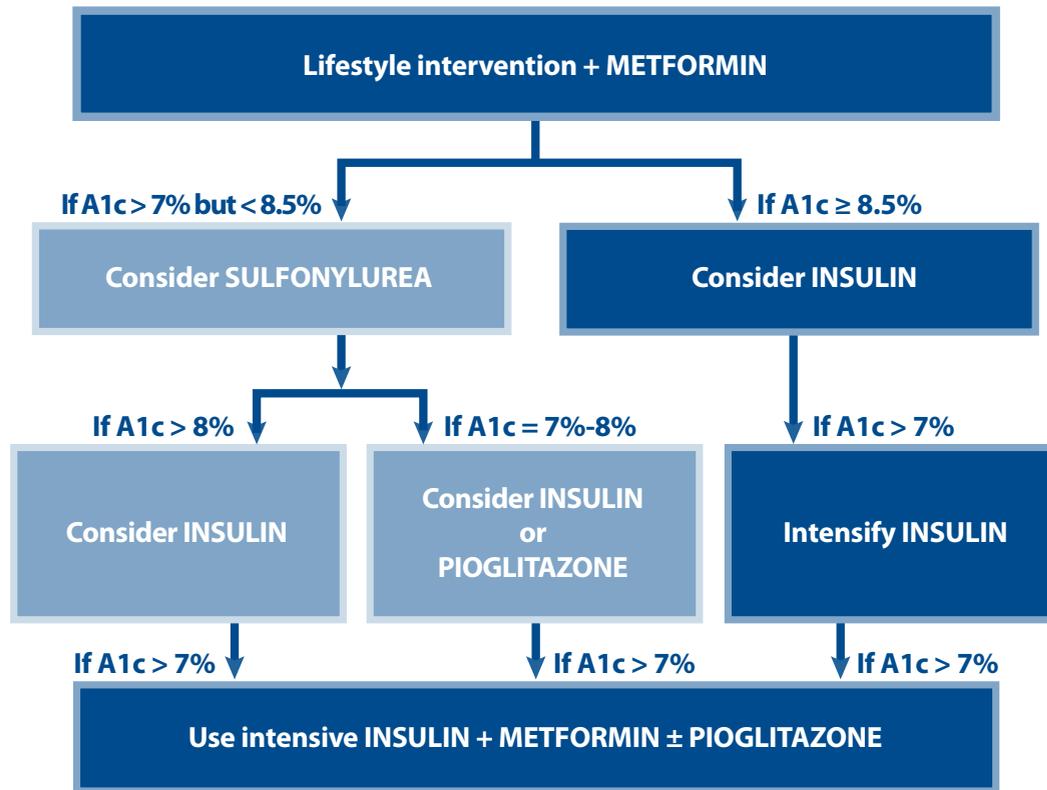
It is important to treat elevated HbA1c, and the greatest clinical benefit of good glycemic control may occur early in the course of the disease. A reasonable HbA1c target is 7% for most patients. This goal should be individualized in selected patients such as the frail elderly and pregnant women.

Monitoring and dose intensification

After initiation of therapy, the ADA recommends measuring hemoglobin A1c every 3 months until a level of 7% is achieved, and at least every 6 months thereafter.⁴⁷

As outlined in Figure 7, there are many therapeutic options for patients who are poorly controlled on monotherapy. Given the risks of death and myocardial infarction associated with rosiglitazone and the risks of heart failure from both rosiglitazone and pioglitazone, a combined regimen of metformin and sulfonylurea is a very reasonable next step when multi-drug therapy is needed (see Figure 7).

Figure 7. Treatment algorithm for the management of type 2 diabetes.*



*Based on the American Diabetes Association and European Association for the Study of Diabetes Consensus Statements for the Medical Management of Hyperglycemia in Type 2 Diabetes^{47,54}

- Reinforce lifestyle intervention at every visit.
- Check A1c every 3 months until 7%, and then at least every 6 months.
- Although three oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense.

▲ OPTIMIZING THE USE OF INSULIN

Over time, many patients with diabetes cannot be adequately managed with oral medications, and will require insulin therapy. After a successful initial response, patients in the UKPDS trial failed oral therapy at a rate of 5-10% 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 the target A1c value.⁴ Data from the National Health and Nutrition Examination Survey reveal that only about a third (37%) of patients with diabetes reach a goal of A1c < 7%.⁵⁵

Despite convincing evidence demonstrating the importance of careful management of blood glucose in diabetes, delays in initiation of insulin therapy are common in practice. A number of observational studies of diabetes care have found delays in intensification of oral medical therapy as well as in initiation of insulin therapy to improve glycemic control. This delay often occurs even when physicians and patients are aware that blood sugars are poorly controlled.⁵⁶⁻⁵⁸ A number of studies have investigated the reasons for this patient and physician reluctance to begin insulin therapy. Patients report fear of injections and its associated 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.^{59, 60} Physicians express concerns 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.”^{59, 60}

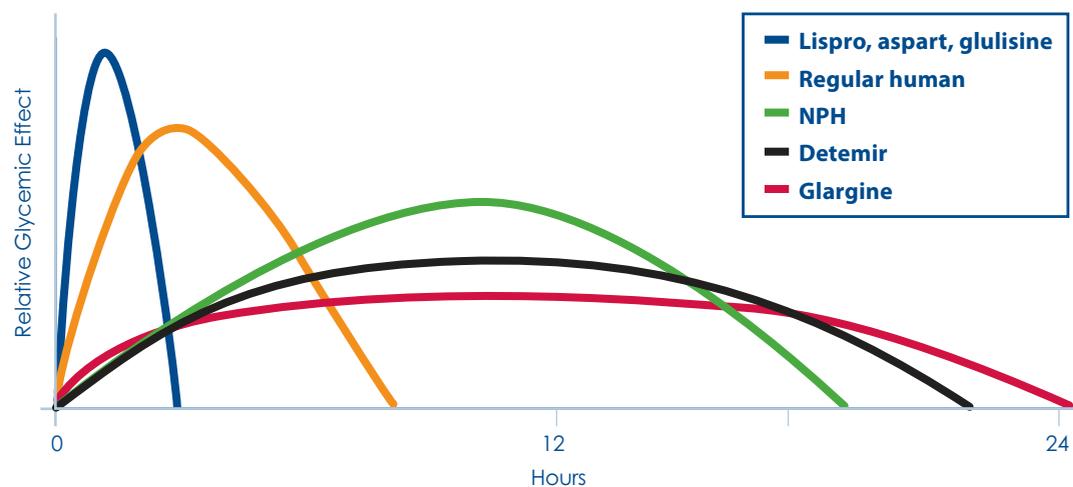
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Hyperglycemia is often under-treated in diabetes, and physicians often delay initiation of insulin therapy when it is indicated.

Insulin preparations

Figure 8 describes the currently available insulin preparations; they are described in more detail below.^{61, 62}

Figure 8. Comparison of Human Insulin Preparations and Insulin Analogs. Reproduced with permission from McMahon and Dluhy, *NEJM*, 2007.⁶³



Used with permission, McMahon GT, Dluhy RG. Intention to treat - initiating insulin and the 4-T study. *NEJM* 2007;357(17):1759-61.¹⁵

Short-acting insulin (regular insulin)

Regular insulin, a short-acting insulin, was the first insulin used to manage the rapid glucose increase that occurs after meals. Once injected, it must dissociate before binding to its receptor, so that onset of action occurs 30-60 minutes after injection, with a peak at 2-3 hours. As a result, the timing of activity of regular insulin does not closely mimic that of the physiologic postprandial insulin burst. Therefore, 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 (3-4 hours). 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 alternative than regular insulin in type 1 diabetes.⁶⁴ However, in type 2 diabetes, **a meta-analysis of 42 randomized controlled trials found no benefit of rapid acting insulin over regular insulin in managing A1c or in reducing hypoglycemic episodes.**⁶⁴

Intermediate-acting insulin (neutral protamine hagedorn [NPH])

NPH is absorbed more slowly than regular insulin (onset of action 2-4 hours) and has longer duration due to the addition of a protamine molecule, resulting in slower absorption and 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 daily or twice daily.

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

Insulin glargine is a long-acting insulin analog that is soluble in a mildly acidic medium, but precipitates after injection at the physiologic pH of subcutaneous tissue. The onset of action of insulin glargine 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. 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 recent trial suggests that morning glargine may provide better glucose control than bedtime glargine.⁶⁵

Insulin detemir also has the favorable characteristics of prolonged action, primarily by slowing absorption. It is also soluble in a neutral pH and binds to albumin in the circulation, leading to stable plasma glucose levels. The duration of action is approximately 20 hours (shorter than glargine), and it can be used once or twice daily. Both long-acting insulins have a half-life that is dose-dependent.

Premixed (biphasic) insulin combinations

Premixed insulin combinations contain a fixed ratio of faster and slower acting insulins, and are available with conventional and analog preparations. 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 that a patient will require, while providing both basal and postprandial coverage. As a result, these agents may be a better option for patients whose adherence requires simplification of the regimen. However, the fixed ratios 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.

When should insulin therapy be initiated?

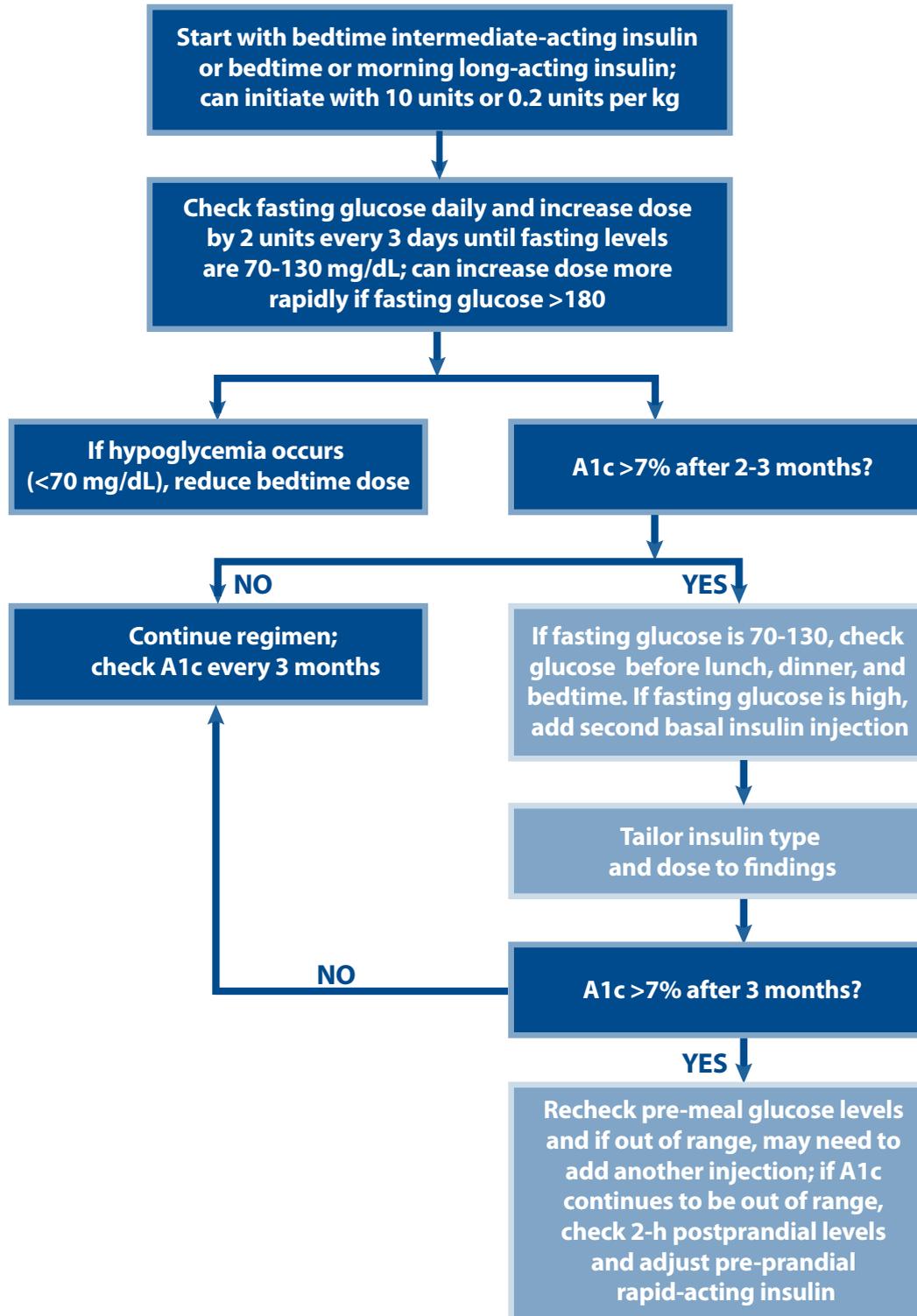
Generally, insulin is required for patients who do not respond adequately to oral hypoglycemic therapy (see Figures 6 and 7). The ADA guidelines suggest that if A1c > 8.5% on one oral hypoglycemic medication, or > 8.0% on two oral medications, clinicians should initiate insulin rather than another oral medication to provide better glucose control. One randomized controlled trial of patients poorly controlled on two oral hypoglycemic agents found that treatment with 70/30 premixed insulin twice a day in combination with metformin was as effective and substantially less expensive than addition of a third oral hypoglycemic agent.⁶⁶ As a result, the ADA guidelines suggest that **if A1c is 7.0 – 8.0% with two maximally dosed oral hypoglycemic agents, addition of insulin is preferred to addition of a third oral medication**, and should be considered.⁴⁷

In some patients with severely elevated glucose at the time of diagnosis, initiation on insulin therapy, at least for a period, is appropriate. Use of insulin is also indicated for patients who are pregnant, require high-dose glucocorticoid therapy, or are intolerant of oral hypoglycemic agents,⁴⁷ as well as for patients hospitalized with an acute myocardial infarction or another acute illness, or in a perioperative/intensive care setting.⁴¹

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If a diabetic patient has an A1c > 8.5% on maximal dose oral hypoglycemic monotherapy, or an A1c > 8.0% on two oral hypoglycemic agents, insulin therapy should be initiated. Also consider insulin if A1c is from 7.0 – 8.0% on two oral hypoglycemics.

Figure 9. ADA consensus algorithm for initiating and intensifying insulin.⁴⁷



Choosing an insulin regimen

Studies comparing different insulin regimens have not clearly demonstrated any one treatment regimen to be superior. The 2009 ADA consensus statement recommends starting with bedtime intermediate-acting (NPH) insulin or bedtime or morning long-acting (glargine or detemir) insulin.⁴⁷ At initiation, the dosage should be either 10 units or 0.2 units per kg, or higher if hyperglycemia is severe. Fasting glucose should be checked daily and insulin dose increased by 2 units every 3 days if not in the 70-130 mg/dL range, or by larger increments if glucose is >180 mg/dL. A1c should be checked every 2-3 months. If A1c is > 7%, insulin should be intensified, with tailored intensification strategies described in the algorithm below.

Treating to target

A commonly used algorithm for insulin intensification comes from the **Treat-to Target** study.¹⁷ This randomized controlled trial demonstrated that most patients inadequately controlled on one or two oral agents could achieve an A1c < 7% by following this simple algorithm:

Table 7. Insulin initiation and titration.

<ul style="list-style-type: none">• Start with 10 units per day of bedtime basal insulin.• Adjust insulin every week. To adjust, calculate the mean self-monitored fasting blood glucose (FBG) values from the previous 2 days.	
Mean FBG	Increase insulin by
100-120 mg/dL	2 units
120-140 mg/dL	4 units
140-180 mg/dL	6 units
≥ 180 mg/dL	8 units

Current clinical evidence does not clearly favor either intermediate-acting (NPH) or long-acting (glargine or detemir) insulins. The Treat-to-Target Trial randomized 756 overweight subjects with type 2 diabetes and inadequate glycemic control (A1c 7.5% to 10%) while using one or two oral agents to receive bedtime glargine or NPH insulin.¹⁷ At

the end of the 24-week study, the mean fasting blood glucose levels and A1c levels achieved were similar. NPH and glargine were equally effective in achieving target levels of glycemic control (A1c levels of $\leq 7\%$), with about 60% of patients reaching this goal in each group. More nocturnal hypoglycemic events occurred in the NPH group (33% vs. 27%). 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.⁶⁷ A1c 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 A1c of 7%. Patients treated with detemir had significantly fewer hypoglycemic events than patients treated with NPH (26% vs. 16%; $p=.008$).

The **LANMET** study compared treatment with glargine and metformin to treatment with NPH and metformin in type 2 diabetes.⁶⁸ 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.

There appears to be no benefit of long-acting versus intermediate-acting insulin in managing hyperglycemia in type 2 diabetes, but intermediate-acting preparations confer a greater risk of hypoglycemia, at least in the short term. However, rates of severe hypoglycemic episodes with NPH are low (only 1-3 events per 100 person years),⁴⁷ and intermediate-acting insulin is far less expensive. The choice should be based on the relative costs and benefits to a particular patient.

▼ ▼ **BOTTOM LINE** ▼ ▼

Long-acting insulin (e.g., glargine) and intermediate-acting insulin (NPH) have equivalent effects on glucose control in type 2 diabetes. Long-acting insulins may be associated with modest reductions in overnight hypoglycemic events. Treatment choices should be tailored to the needs of individual patients.

More recently, several studies have suggested that treatment with biphasic (mixed-preparations) and prandial (ultra-fast acting) regimens offer improved glucose control, although they increase the risk of hypoglycemia and cause more weight gain.⁶⁹⁻⁷¹ In the 4-T trial, patients poorly controlled with oral hypoglycemic agents were randomized to receive biphasic insulin, prandial insulin, or detemir.⁶⁹ The authors found a greater likelihood of reaching the goal of A1c <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 occurred only in patients with a starting A1c >8.5%. On the other hand, the recently published 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 HgbA1c, 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.⁷²

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Recent studies raise questions about whether biphasic or prandial insulin preparations are more effective as initial therapy, compared to basal insulin alone. Biphasic and prandial formulations produce more side effects and are more difficult for patients to manage. This evidence is not currently definitive. Recommendations are still to start with intermediate or long-acting insulin at night and titrate as needed, based on individual response.

Inhaled insulin: no longer in use

Inhaled insulin was a fast-acting insulin approved by the FDA in 2006, but recently was removed from the marketplace by its manufacturer.⁷³ Given as monotherapy or in combination with long-acting insulin, inhaled insulin was not shown in published trials to decrease A1c to < 7%.^{74,75} Inhaled insulin was also very expensive and contraindicated in patients who smoke or have pulmonary disease. The ADA guidelines never included inhaled insulin in their treatment algorithms,⁴⁷ and the drug should no longer be used.

Combining insulin with oral hypoglycemic agents

In initiating insulin, the ADA guidelines recommend adding it to existing oral therapy. Meta-analyses have demonstrated significant reductions in fasting serum glucose and A1c requiring a smaller daily insulin dose (11 units less a day) when insulin is added to oral therapy compared to using insulin alone.^{76,77} 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.⁷⁸ As a result, it is often recommended that sulfonylureas should be stopped when insulin therapy is initiated, but other oral hypoglycemics which are not secretagogues should be continued. The **ADA guidelines** recommend metformin and insulin as first-line combination therapy in type 2 diabetics who require insulin therapy (see Figures 7 and 9),⁴⁷ and propose combining insulin with a medication that works via a different mechanism (i.e., metformin or glitazones rather than sulfonylureas). Despite evidence suggesting that insulin-glitazone combinations effectively reduce glucose,⁷⁹ the **ADA guidelines** warn about fluid retention from glitazones, and recommend metformin first⁴⁷ recent safety concerns with the glitazones reinforce this point.

▼ ▼ BOTTOM LINE ▼ ▼

Combination therapy with oral hypoglycemic agents and insulin can produce improved glucose control and less weight gain than therapy with insulin alone. Insulin combined with metformin offers the greatest synergy for clinical effect and the lowest risk of adverse events.

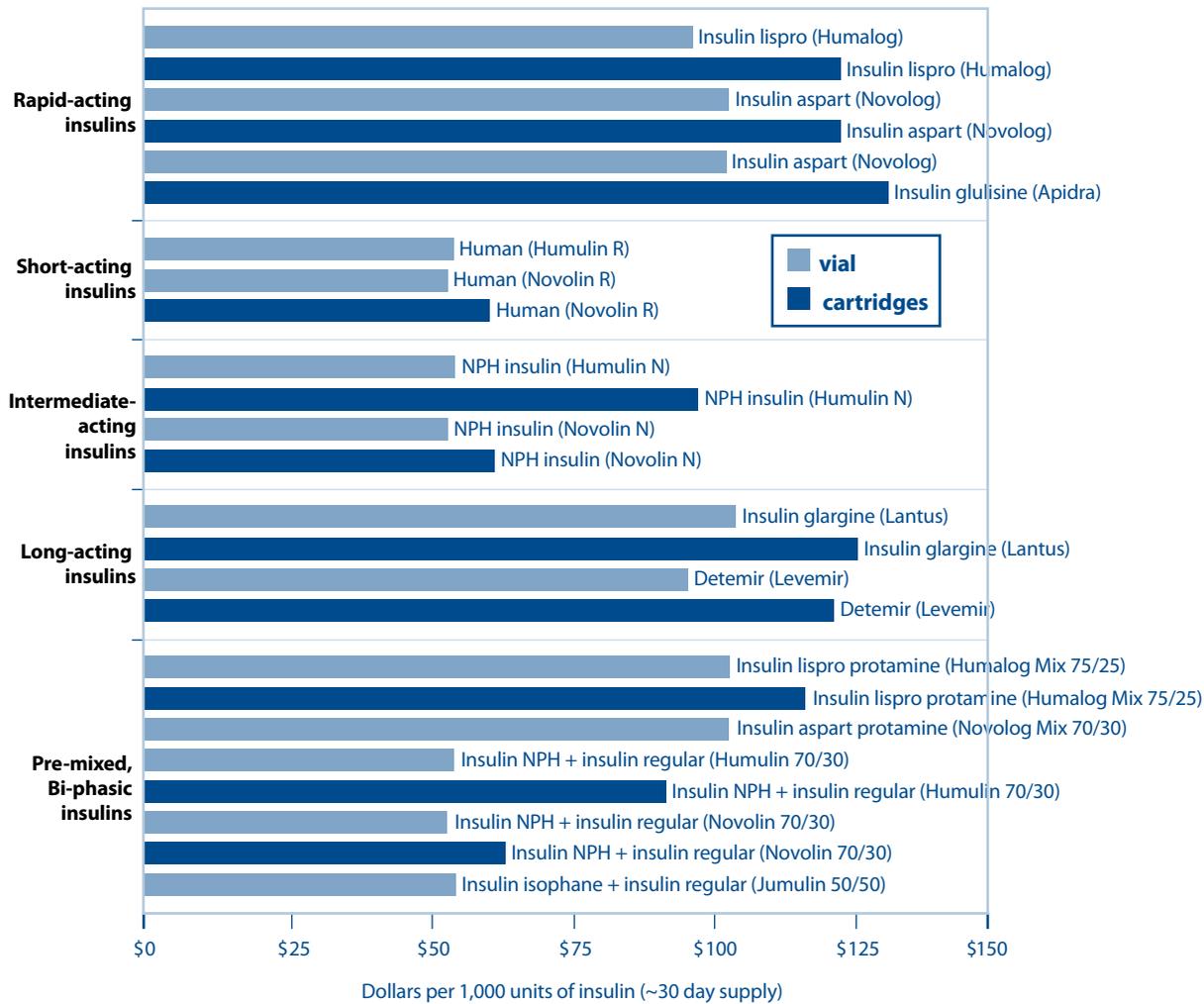
Amylin analogs

One additional class of medications can potentially serve as an adjunct to insulin therapy. Pramlintide (Symlin) is an analog of amylin, a naturally occurring hormone co-secreted by the pancreas along with insulin, and must be injected subcutaneously. Pramlintide has a limited use – it can only be used as an adjunct with prandial insulin when adequate control cannot otherwise be achieved. Pramlintide has been shown to modestly improve glucose control while reducing insulin doses required.⁸⁰ Frequent monitoring of blood glucose is needed to reduce the risk of hypoglycemia.

Costs of insulin preparations

Insulin preparations vary widely in cost (see Figure 10). Regular insulin and NPH cost less than half the newer insulin analogues, and costs increase dramatically for preparations that can be used with prefilled devices (pens). While there are several qualitative studies that show that some patients prefer the pen, no high-quality studies have been published demonstrating any improvements in medication adherence or health outcomes associated with use of the pen.

Figure 10. Costs* of insulin preparations per 5,000 units.



*Prices obtained from www.drugstore.com or www.cvs.com, January 2009.

Considering the lack of evidence of benefit for the newer analog rapid-acting insulin preparations compared with regular insulin, the difference in cost can be important when selecting a rapid-acting preparation. Similarly, there is no evidence of better glucose control with long-acting analogs compared to NPH insulin, but a marginally improved side effect profile is seen in some studies. Decisions to initiate a patient on long-acting analogs versus NPH should be based on an individual patient's needs.

▼ ▼ BOTTOM LINE ▼ ▼

The new insulin analogs differ substantially in price from conventional insulins but not necessarily in efficacy. Preparations that are used with insulin pens add significant additional costs.

▲ SPECIAL CONSIDERATIONS

Setting blood glucose goals in the elderly

The incidence of diabetes increases with age, and management of blood glucose is extremely important in the elderly in order to avoid micro- and macro-vascular complications. However, many elderly are frail and/or cognitively impaired, and therapeutic regimens must account for individual characteristics. The risks of hypoglycemia, polypharmacy, and drug interactions may outweigh the value of intensive therapy in some frail patients.

The American Geriatrics Society convened an expert panel to address this and other issues related to the management of elderly patients with diabetes. It recommended that for elderly patients in relatively good health and with good functional status, the target A1c should be < 7%. But for frail older adults, patients with a life expectancy of less than 5 years, and others for whom risks outweigh the benefits of treatment, a less stringent target (e.g., A1c < 8%) is more appropriate.⁸¹ In light of the recent evidence of possible adverse consequences with aggressive glycemic control (see “Therapeutic Goals” section), concern about selecting an appropriate A1c target for elderly patients is especially important.

▼ ▼ BOTTOM LINE ▼ ▼

In frail elderly patients, glycemic goals should be tailored to balance the risks and benefits of treatment.

Potential complications of diabetes

While diabetes can 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. Preventing the complications of diabetes can be just as important as managing the blood glucose level.

This effort should begin at the first evaluation after a patient is diagnosed with careful monitoring of the eyes, heart, and kidneys.⁵ This should include:

- A fundoscopic exam and referral to an ophthalmologist for periodic dilated eye exams
- 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
- Management of cholesterol levels
- 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
- Good foot care, including patient education about foot care and referral to a podiatrist as needed.

▲ RELATED CONDITIONS AND TREATMENT RECOMMENDATIONS

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 adjustment of therapy where appropriate (see Table 8). Many components of medical management for patients with diabetes with these conditions have been covered in previous iDiS monographs on hypertension (*Controlling the Hypertension Epidemic*), hyperlipidemia (*Pushing Down Cholesterol*), and antiplatelet drugs (*Sticking to the Evidence for Antiplatelet Drugs*), all available at www.RxFacts.org.

Table 8. Treatment of related conditions.

Condition	Identification	Goal of therapy	Recommended Interventions
Hypertension	Check BP at all visits	SBP \leq 130 mmHg DBP \leq 80 mmHg	<ul style="list-style-type: none"> • Begin with lifestyle modification • Drug therapy should include ACE-I (ARB if ACE-I not tolerated) • Thiazide-type diuretic if second agent is needed
Hyperlipidemia	Check fasting lipids	LDL $<$ 100 mg/dL (LDL $<$ 70 mg/dL if CAD)	<ul style="list-style-type: none"> • Treat with statins for elevated LDL
Antiplatelet therapy	Assess for cardiac risk factors	Risk reduction	<ul style="list-style-type: none"> • Aspirin for patients with coronary artery disease
Smoking	Inquire about tobacco use	Smoking cessation	<ul style="list-style-type: none"> • Nicotine replacement • Bupropion/varenicline • Counseling programs

Hypertension

The targets for blood pressure in patients with diabetes are lower than those for other patients. Systolic blood pressure should be below 130 mmHg and diastolic blood pressure should be below 80 mmHg.^{5,82} Patients with modest elevation of blood pressure (systolic BP 130-139 mmHg or diastolic BP 80-89 mmHg) can be treated initially with lifestyle modification, including weight reduction, salt restriction, and exercise. Many of these interventions will also be helpful for improving control

of diabetes. If lifestyle intervention is not successful, or if initial blood pressure is more than modestly elevated, patients should be started on medication.

Virtually all patients with diabetes treated for hypertension should receive a drug that blocks the renin-angiotensin axis.^{83, 84} The initial choice should be an angiotensin-converting enzyme inhibitor (ACE-I), many of which are available in low-cost generic forms that can be given once per day.⁸² About 10% of patients may experience side effects when treated with ACE-I (most often cough), and these patients can be effectively treated with an angiotensin-receptor blocker (ARB).⁸⁵ Many patients with diabetes will require treatment with multiple drugs to achieve target blood pressures. For patients who need a second drug in addition to an ACE-I or ARB, a thiazide-type diuretic is the recommended choice.^{82, 86}

The central importance of blood pressure control for reducing morbidity and mortality in patients with diabetes was demonstrated in the recently-published **UKPDS** 10-year follow-up study. Researchers followed patients in this trial for ten years in order to determine whether the micro- and macro-vascular risk reductions initially achieved with good blood pressure control would be sustained over 10 years.⁸⁷

As with glycemic control (see “Therapeutic Goals” section), 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, for patients receiving tight blood pressure control the risk reductions found during the trial for diabetes-related endpoints, diabetes-related death, microvascular disease, and stroke were not sustained during the post-trial follow-up.

The finding that the benefits of tight blood pressure control were not maintained once the differences in blood pressure seen during the trial were lost suggests that good control of hypertension must be continued if its benefits are to be maintained. Accordingly, antihypertensive medications should be adjusted aggressively to maintain blood pressure below target levels. Physicians should beware of “clinical inertia,” the reluctance of both patients and physicians to add new medications, even when the potential benefits are large.⁸⁸

Some patients with diabetes and hypertension require special consideration. Pregnant women should have hypertension aggressively controlled, but ACE-I and ARB 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 physicians should still attempt to treat to the target levels unless contraindicated.⁵

▼ ▼ BOTTOM LINE ▼ ▼

Blood pressure >130/80 mm/Hg should be treated aggressively in patients with diabetes, and control should be maintained over time. ACE-inhibitors should be first-line treatment, with ARBs reserved for patients who cannot tolerate ACE-I. Multi-drug therapy is often needed, and thiazide-type diuretics should be added when needed.

Hyperlipidemia

All patients with diabetes should have their cholesterol checked at least once per year.⁵ Recommended target cholesterol levels include LDL cholesterol <100 mg/dL, triglycerides <150 mg/dL, HDL cholesterol >40 mg/dL (men), and HDL > 50 mg/dL (women).⁵ For patients not meeting these thresholds, a trial of lifestyle intervention including diet modification and exercise is warranted. If this does not succeed in lowering LDL adequately, medication should be started (in patients with co-existing cardiac disease, medication should be started immediately). For high-risk patients, recent studies have shown that more aggressive treatment to drive the LDL cholesterol below 70 mg/dL can further reduce the risk of cardiovascular events.^{89, 90}

Most patients with diabetes requiring cholesterol reduction should be treated with a statin. Many drugs within this class can reduce the risk of cardiovascular events in such patients.⁹¹⁻⁹³ With multiple statins now available generically, most patients can use an affordable, generic statin that will lower their LDL to target levels. If the LDL level must be lowered to a greater extent (50% or more), high-dose treatment with atorvastatin or rosuvastatin may be required.⁹⁴

▼ ▼ BOTTOM LINE ▼ ▼

Elevated cholesterol (LDL>100 mg/dL) should be treated aggressively in all patients with diabetes, and the LDL goal may be lowered to 70 mg/dL for high-risk patients. Generic statins are an effective and affordable choice for most patients with diabetes.

Antiplatelet medication

Antiplatelet treatment, specifically with aspirin, has traditionally been recommended for most adults with diabetes.⁹⁵ Randomized controlled trials have clearly shown 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.⁹⁶ Clopidogrel also has a role in the management of patients with recent acute coronary syndromes, coronary stent insertions or peripheral vascular disease.⁹⁷ Diabetes is generally considered a coronary artery disease “risk equivalent,” and thus aspirin has generally been suggested for most patients with diabetes, including those without known vascular disease. However, two recent large trials have raised new questions about the role of aspirin in primary prevention.

The **POPADAD study**⁹⁸ evaluated whether 100 mg of aspirin daily is effective in preventing cardiovascular events in patients with diabetes and asymptomatic peripheral arterial disease but no symptomatic cardiovascular disease. It enrolled 1,276 adults (mean age 60) with type 1 or type 2 diabetes and followed them for a median of almost seven years. Approximately 10% of participants were using insulin.

In this trial, aspirin produced no significant reduction of either death from cardiovascular causes or a composite end-point of fatal and non-fatal cardiovascular events. The rate of death from any cause was 14.7% in patients randomized to aspirin and 15.8% in controls, a non-significant difference. The rate of gastrointestinal bleeding was 4.4% with aspirin and 4.9% in controls, also non-significant.

Like **POPADAD**, the **JPAD study**⁹⁹ 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.

The primary outcome measure was any fatal or nonfatal cardiovascular event. Secondary endpoints studied included each primary endpoint and combinations of primary endpoints, as well as death from any cause. Median follow-up was 4 years.

In this study, 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 (p value not stated). There was no significant difference in the composite outcome of hemorrhagic stroke and severe gastrointestinal bleeding.

Prior guidelines advocate 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.⁵ The **POPADAD** and **JPAD** trials have forced a re-evaluation of that approach, since they indicate that using aspirin for primary prevention of cardiovascular disease in patients with diabetes offers little or no benefit with a possible increase in the risk of adverse events. Patients with multiple cardiac risk factors or with symptomatic peripheral vascular disease may benefit from aspirin therapy, but careful clinical judgment must be exercised regarding the expected risks and benefits.

▼ ▼ 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.

Smoking

All patients with diabetes should be encouraged not to smoke. 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), varenicline (Chantix), and counseling programs.⁵

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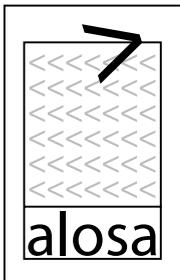
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