Initial management of blood glucose in adults with type 2 diabetes mellitus

Author: David K McCulloch, MD
Section Editor: David M Nathan, MD
Deputy Editor: Jean E Mulder, MD

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INTRODUCTION — Treatment of patients with type 2 diabetes mellitus includes education, evaluation for microvascular and macrovascular complications, attempts to achieve near-normal glycemia, minimization of cardiovascular and other long-term risk factors, and avoidance of drugs that can aggravate abnormalities of insulin or lipid metabolism. All of these treatments need to be tempered based on individual factors, such as age, life expectancy, and comorbidities. Although several studies have noted remissions of type 2 diabetes mellitus that may last several years, most patients require continuous treatment in order to maintain normal or near-normal glycemia. Treatments to achieve normoglycemia focus on increasing insulin availability (either through direct insulin administration or through agents that promote insulin secretion), improving sensitivity to insulin, delaying the delivery and absorption of carbohydrate from the gastrointestinal tract, or increasing urinary glucose excretion.

Methods used to control blood glucose in patients with newly diagnosed type 2 diabetes are reviewed here. Further management of persistent hyperglycemia and other therapeutic issues, such as the frequency of monitoring and evaluation for microvascular and macrovascular complications, are discussed separately. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus" and "Overview of medical care in adults with diabetes mellitus".)

TREATMENT GOALS

Degree of glycemic control — Improved glycemic control improves the risk of microvascular complications in patients with type 2 diabetes (figure 1) [1]. Every 1 percent drop in glycated hemoglobin (A1C) is associated with improved outcomes with no threshold effect. To date, only one randomized clinical trial has demonstrated a beneficial effect of intensive therapy on macrovascular outcomes in type 2 diabetes [2], with several trials not supporting a beneficial effect [3,4] and one trial suggesting harm [5]. A reasonable goal of therapy might be an A1C value of ≤7.0 percent (53.0 mmol/mol) (calculator 1) for most patients. However, target A1C goals in patients with type 2 diabetes should be tailored to the individual, balancing the improvement in microvascular complications with the risk of hypoglycemia. Glycemic targets are generally set somewhat higher for older adult patients and those with comorbidities or a limited life expectancy and little likelihood of benefit from intensive therapy. Glycemic goals are discussed in more detail separately. (See "Glycemic control and vascular complications in type 2 diabetes mellitus", section on 'Glycemic targets' and "Overview of medical care in adults with diabetes mellitus", section on 'Glycemic control' and "Treatment of type 2 diabetes mellitus in the older patient", section on 'Glycemic targets'.)

Cardiovascular risk factor management — In addition to glycemic control, vigorous cardiac risk reduction (smoking cessation, aspirin, blood pressure control, reduction in serum lipids, diet, and exercise) should be a top priority for all patients with type 2 diabetes. However, in spite of evidence that aggressive risk factor reduction lowers the risk of both micro- and macrovascular complications in patients with diabetes, many patients do not achieve recommended goals for A1C, blood pressure control, and management of dyslipidemia. (See "Overview of medical care in adults with diabetes mellitus" and "Treatment of hypertension in patients with diabetes mellitus" and "Management of elevated low density lipoprotein-cholesterol (LDL-C) in primary prevention of cardiovascular disease" and "Management of low density lipoprotein cholesterol (LDL-C) in secondary prevention of cardiovascular disease".)

DIABETES EDUCATION — Patients with newly diagnosed diabetes should participate in a comprehensive diabetes self-management education program, which includes instruction on nutrition, physical activity, optimizing metabolic control, and preventing complications. In clinical trials comparing diabetes education with usual care, there was a small but statistically significant reduction in A1C in patients receiving the diabetes education intervention [6]. There

was no difference in quality of life. In two meta-analyses, use of mobile phone interventions for diabetes education was successful in significantly reducing A1C (-0.5 percentage points) [7,8].

Medical nutrition therapy (MNT) is the process by which the dietary plan is tailored for people with diabetes, based on medical, lifestyle, and personal factors. It is an integral component of diabetes management and diabetes self-management education. For patients with type 2 diabetes who are overweight (body mass index [BMI] ≥25 to 29.9 kg/m^2) and obese (BMI ≥30 kg/m^2), major emphasis should be placed on lowering caloric intake and increasing physical activity to achieve weight loss. Improved glycemic control induced by weight loss is associated with partial correction of the two major metabolic abnormalities in type 2 diabetes: insulin resistance and impaired insulin secretion [9]. For patients who are not overweight, the goal of MNT is weight management, consistency in day-to-day carbohydrate intake at meals and snacks, and overall nutritional content. MNT is reviewed in detail elsewhere. (See "Nutritional considerations in type 2 diabetes mellitus".)

Weight reduction — For patients with type 2 diabetes who are overweight (BMI ≥25 to 29.9 kg/m^2) and obese (BMI ≥30 kg/m^2), major emphasis should be placed on lowering caloric intake, increasing physical activity, and behavior modification to achieve weight loss (see 'Intensive lifestyle modification' below). Pharmacologic therapy for weight loss and weight loss surgery can be effective but are not considered initial therapy. (See "Obesity in adults: Overview of management", section on 'Approach to therapy'.)

Diet — Weight loss through dietary modification can improve many aspects of type 2 diabetes, including glycemic control and hypertension. The improvement in glycemic control is related both to the degree of caloric restriction and weight reduction [9,10]. Modest weight reduction may also improve liver function in nonalcoholic steatohepatitis, which is associated with insulin resistance and type 2 diabetes. (See "Natural history and management of nonalcoholic fatty liver disease in adults", section on 'Weight loss'.)

The immediate effect of caloric restriction on blood glucose levels is not well understood but may be related to depletion of hepatic glycogen stores, thereby reducing hepatic glucose output, the main determinant of fasting blood glucose. However, this benefit will persist only if negative calorie balance and weight reduction are continued.

Despite the clear benefit of weight loss, only a small percentage of patients with type 2 diabetes are able to attain and maintain substantial weight loss [9,11,12]. Several studies have evaluated the long-term efficacy of diet (alone or with exercise) in patients with newly diagnosed type 2 diabetes (see "Nutritional considerations in type 2 diabetes mellitus"). In the United Kingdom Prospective Diabetes Study (UKPDS), for example, all patients were given a low-calorie, low-fat, high complex carbohydrate diet [13]. Although the initial results of the dietary intervention were substantial, after three years, only 3 percent of those treated with diet alone had achieved and maintained the desired fasting blood glucose concentration below 108 mg/dL (6 mmol/L). Furthermore, the mean glucose value was substantially higher with diet alone than with diet plus an oral hypoglycemic drug or insulin.

The likelihood of a successful glycemic response to diet is determined in large part by the initial fasting blood glucose. In the UKPDS, the degree of weight loss required to normalize the fasting blood glucose was 10 kg (16 percent of initial body weight) if the initial value was 108 to 144 mg/dL (6 to 8 mmol/L) versus 22 kg (35 percent) if the initial value was 216 to 252 mg/dL (12 to 14 mmol/L) (figure 2).

Pharmacologic therapy — Pharmacotherapy for weight loss may be effective in patients with type 2 diabetes, but it is generally associated with high dropout rates due to medication side effects and is not recommended as primary therapy for diabetes [14]. (See "Obesity in adults: Drug therapy".)

Surgical therapy — Weight loss surgery in obese patients with diabetes results in the largest degree of sustained weight loss and, in parallel, improvements in blood glucose control. However, longer-term follow-up is required before bariatric surgery procedures can be routinely recommended for the treatment of obesity-related type 2 diabetes. This topic is reviewed in detail separately. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Surgical treatment of obesity'.)

Exercise — Adults with diabetes are encouraged to perform 30 to 60 minutes of moderate-intensity aerobic activity (40 to 60 percent VO_2 max) on most days of the week (at least 150 minutes of moderate-intensity aerobic exercise per week). In the absence of contraindications (eg, moderate to severe proliferative retinopathy, severe coronary artery disease), people with type 2 diabetes should also be encouraged to perform resistance training (exercise with free weights or weight machines) at least twice per week. Regular exercise is beneficial in type 2 diabetes, independent of weight loss. It leads to improved glycemic control due to increased responsiveness to insulin; it can

also delay the progression of impaired glucose tolerance to overt diabetes [15,16]. These beneficial effects are directly due to exercise, but concurrent weight reduction can play a contributory role (see "Effects of exercise in adults with diabetes mellitus"). In one study, however, only 50 percent of patients with type 2 diabetes were able to maintain a regular exercise regimen [17].

Intensive lifestyle modification — In patients with established type 2 diabetes, intensive behavioral modification interventions focusing on weight reduction and increasing activity levels are successful in reducing weight and improving glycemic control while, at the same time, reducing the need for glucose-lowering and other medications [3,18-20]. However, intensive lifestyle modification has not been shown to reduce macrovascular complications. In the Look AHEAD (Action for Health in Diabetes) trial, 5145 individuals with type 2 diabetes and BMI >25 kg/m^2 were randomly assigned to an intensive lifestyle intervention or standard diabetes education [21]. The intensive intervention included caloric restriction (maximum 30 percent calories from fat, minimum 15 percent protein, and the remainder from carbohydrates, in the form of liquid meal replacements, frozen food entrees, or structured meal plans), moderate-intensity physical activity (goal 175 minutes weekly), and weekly group or individual sessions with registered dietitians, behavioral psychologists, and exercise specialists. If weight loss goals were not achieved in the first six months, a weight loss medication (orlistat) and/or advanced behavioral strategies were initiated.

The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for angina. Although the anticipated follow-up period was 13.5 years, the trial was stopped early due to lack of cardiovascular benefit [3]. After a median follow-up of 9.6 years, the composite primary outcome occurred in a similar number of patients in the intervention and control groups (403 and 418 individuals, 1.83 and 1.92 events per 100 person-years, respectively; [hazard ratio (HR) 0.95, 95% CI 0.82-1.09]) [3].

The following summarizes other major observations [3,21-28]:

- Weight loss was greater in the intervention than control group, with the largest difference noted at one year (mean weight loss 8.6 versus 0.7 percent of initial body weight). The difference was attenuated but remained significant throughout the trial (6.0 versus 3.5 percent at study end). Changes in waist circumference and physical fitness were also significantly better in the intervention group throughout the study.
- Glycemic control was significantly better in the intervention group during the first year (mean A1C decreased from 7.3 to 6.6 percent, compared with 7.3 to 7.2 percent in the control group). By study end, mean A1C was significantly lower in the intervention group (7.33 versus 7.44 percent), but the small difference is of uncertain clinical significance.
- Low-density lipoprotein (LDL) cholesterol was slightly lower in the control group than in the intervention group (mean difference 1.6 mg/dL [0.04 mmol/L]). The use of antihypertensive medications, statins, and insulin was lower in the intervention group.
- The intensive lifestyle intervention reduced microalbuminuria.
- Noncardiac benefits of the lifestyle intervention included reductions in urinary incontinence, sleep apnea, and depression, and improvements in quality of life, physical functioning, sexual functioning, and mobility.

The improvement in weight and glycemia did not reduce the occurrence of cardiovascular events. Possible reasons for this finding include the lower than expected rates of cardiovascular events in both groups, improved overall cardiovascular risk factor treatment with medical therapy (antihypertensives, statins), enrollment of a relatively healthy patient population, and gradual weight loss in the control group such that the differential weight loss between the two groups was only 2.5 percent at study end [29]. A sustained weight loss of greater than that achieved in the trial may be required to reduce the risk of cardiovascular disease (CVD). However, this degree of weight loss is difficult to maintain through lifestyle intervention alone. Weight loss and exercise remain an important component of diabetes management due to overall health benefits.

Psychological interventions — Patients with type 2 diabetes often experience significant stress related to the many self-care responsibilities to optimize glycemic control (lifestyle modifications, medication, and self-monitoring of blood glucose [SMBG]) [30]. Concurrent depression may also interfere with self-care. Psychotherapy reduces psychological distress and improves glycemic control in some [31,32], but not all [33], studies. In a meta-analysis of 12 trials of patients with type 2 diabetes randomly assigned to psychological intervention or usual care, mean A1C was lower in the intervention group (pooled mean difference -0.32, 95% CI -0.57 to -0.07; absolute decrease in A1C was 0.76

percent [-1.32 to -0.18]) [31]. Measures of psychological distress were also significantly lower in the intervention group, but there were no differences in weight control.

INITIAL PHARMACOLOGIC THERAPY

When to start — The metabolic abnormalities that characterize type 2 diabetes worsen with age. Early institution of treatment for diabetes, at a time when the A1C is not substantially elevated, is associated with improved glycemic control over time and decreased long-term complications [34]. Pharmacologic therapy is often not initiated soon enough, resulting in poor glycemic control.

- For most patients presenting with A1C at or above target level (ie, >7.5 to 8 percent), pharmacologic therapy should be initiated at the time of diabetes diagnosis.
- For highly motivated patients with A1C near target (ie, <7.5 percent), a three- to six-month trial of lifestyle modification before initiating pharmacologic therapy is reasonable.

Choice of initial therapy — Our suggestions are based upon clinical trial evidence and clinical experience in achieving glycemic targets and minimizing adverse effects (table 1), with the recognition that there is a paucity of many high-quality, head-to-head drug comparison trials and long-duration trials or ones with important clinical endpoints, such as effects on complications. The long-term benefits and risks of using one approach over another are unknown.

In selecting initial therapy, we consider patient presentation (eg, presence or absence of symptoms of hyperglycemia and comorbidities, baseline A1C level), individualized treatment goal, and the glucose-lowering efficacy of individual drugs.

Asymptomatic — The majority of patients with newly diagnosed type 2 diabetes are asymptomatic, and hyperglycemia is noted on routine laboratory evaluation.

A1C at (<7.6 percent) or close to (>0.5 to 1.5 percent above, eg, 7.6 to 8.5 percent) treatment goal — In the absence of specific contraindications, we suggest metformin as initial therapy in most patients with glycated hemoglobin (A1C) at or close to target. For most patients, we suggest initiating metformin at the time of diabetes diagnosis, along with consultation for lifestyle intervention (algorithm 1). We begin with 500 mg once daily with the evening meal and, if tolerated, add a second 500 mg dose with breakfast. The dose can be increased slowly (one tablet every one to two weeks) as necessary. (See 'When to start' above and "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Dosing and monitoring'.)

Metformin was chosen for initial therapy because of glycemic efficacy, absence of weight gain and hypoglycemia, general tolerability, and favorable cost. Although virtually all recommendations for initial pharmacologic therapy (outside of China, where alpha-glucosidase inhibitors are used frequently) endorse use of metformin, there are, in fact, relatively few relevant direct comparative effectiveness data available. (See 'Glycemic efficacy' below.)

A1C relatively far from goal (eg, 8.5 to 9.5 percent) — For asymptomatic patients whose glycated hemoglobin (A1C) levels are substantially higher than the goal, we also suggest metformin. Insulin is an alternative option for initial therapy.

Insulin can be considered a first-line therapy for all patients with type 2 diabetes, particularly patients presenting with A1C relatively far from goal (eg, >9 percent). Although historically insulin has been used for type 2 diabetes only when inadequate glycemic control persists despite oral agents and lifestyle intervention, there are increasing data to support using insulin earlier and more aggressively in type 2 diabetes. By inducing near normoglycemia with intensive insulin therapy, both endogenous insulin secretion and insulin sensitivity improve; this results in better glycemic control, which can then be maintained with diet, exercise, and oral hypoglycemics for many months thereafter. Insulin may cause weight gain and hypoglycemia. (See "Insulin therapy in type 2 diabetes mellitus", section on 'Insulin as initial therapy'.)

Contraindications to metformin — For patients with contraindications to metformin, other options for initial therapy are available (table 1). (See "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Contraindications'.)

- For patients with contraindications to metformin, we suggest a shorter-acting sulfonylurea, such as glipizide. The choice of sulfonylurea balances glucose-lowering efficacy, universal local availability, and low cost with risk of hypoglycemia and weight gain.

  For patients who are initiating sulfonylureas, we suggest initiating lifestyle intervention first, at the time of diagnosis, since the weight gain that often accompanies a sulfonylurea will presumably be less if lifestyle efforts are underway. However, if lifestyle intervention has not produced a significant reduction in symptoms of hyperglycemia or in glucose values after one or two weeks, then the sulfonylurea should be added. (See "Sulfonylureas and meglitinides in the treatment of diabetes mellitus".)

- For patients who are intolerant of or are not candidates for metformin or sulfonylureas, repaglinide is a reasonable alternative, particularly in a patient with chronic kidney disease at risk for hypoglycemia. (See "Sulfonylureas and meglitinides in the treatment of diabetes mellitus".)

- Pioglitazone, which is now available as a generic and is another relatively low-cost oral agent, may also be considered in patients with specific contraindications to metformin and sulfonylureas. However, the risk of heart failure, fractures, and the potential increased risk of bladder cancer raise the concern that the overall risks and cost of pioglitazone may exceed its benefits. (See "Thiazolidinediones in the treatment of diabetes mellitus", section on 'Safety'.)

- Other oral and injectable agents, such as glucagon-like peptide-1 (GLP-1) agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 (SGLT2) inhibitors, or dipeptidyl peptidase-4 (DPP-4) inhibitors, may be appropriate initial therapy for some patients [35,36]. However, limited clinical experience; lower or overall equivalent effectiveness compared with metformin, insulin, and sulfonylurea; higher cost; and/or side effects reduce their appeal as initial agents [37]. (See "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus" and "Alpha-glucosidase inhibitors and lipase inhibitors for treatment of diabetes mellitus" and "Dipeptidyl peptidase-4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus" and "Management of persistent hyperglycemia in type 2 diabetes mellitus".)

Symptomatic or severe hyperglycemia — The frequency of symptomatic or severe diabetes has been decreasing in parallel with improved efforts to diagnose diabetes earlier through screening. Insulin, rather than oral hypoglycemic agents, is often indicated for initial treatment of symptomatic or severe hyperglycemia (fasting plasma glucose >250 mg/dL [13.9 mmol/L], random glucose consistently >300 mg/dL [16.7 mmol/L], A1C >9.5 [80.3 mmol/mol]), depending on the severity of the baseline metabolic disturbance.

- **Ketonuria and/or weight loss present** – For patients presenting with symptomatic (eg, weight loss) or severe hyperglycemia with ketonuria, insulin is indicated for initial treatment. (See "Insulin therapy in type 2 diabetes mellitus", section on 'Indications for insulin'.)

- **Ketonuria and/or weight loss absent** – For patients presenting with severe hyperglycemia (fasting plasma glucose >250 mg/dL [13.9 mmol/L], random glucose consistently >300 mg/dL [16.7 mmol/L], A1C >9.5 [80.3 mmol/mol]) but without ketonuria or spontaneous weight loss, insulin remains the preferred initial therapy.

  However, for patients who are insulin averse, initial therapy with high-dose sulfonylurea is an alternative option, particularly for patients who have been quenching their thirst with sugar-sweetened beverages, in whom elimination of carbohydrates will cause a reduction in glucose within a couple of days. High-dose sulfonylureas are effective in rapidly reducing hyperglycemia in patients with severe hyperglycemia [38]. Metformin monotherapy is not helpful in improving symptoms in this setting, because the initial dose is low and increased over several weeks. However, metformin can be started at the same time as the sulfonylurea, slowly titrating the dose upward. Once the diet has been adequately modified and the metformin dose increased, the dose of sulfonylurea can be reduced and sometimes even discontinued.

  On the other hand, if adequate control is not achieved with metformin and high-dose sulfonylurea, it is preferable to start bedtime insulin. When insulin is started, some clinicians discontinue sulfonylureas while others will continue it, particularly for patients whose main problem is fasting hyperglycemia.

- **Dosing**

  - Insulin therapy in type 2 diabetes is initially aimed at increasing basal insulin concentrations (algorithm 2). Patients with type 2 diabetes require relatively large doses of insulin, compared with those needed for type 1

diabetes. Insulin preparations, insulin regimens, and timing of dosing are discussed in detail elsewhere. (See "Insulin therapy in type 2 diabetes mellitus".)

- The dose of sulfonylureas to treat severe or symptomatic hyperglycemia is higher than initial therapy for mild to moderate hyperglycemia. We typically use glimepiride 4 or 8 mg once daily. An alternative option is immediate-release glipizide 10 mg twice daily. (See "Sulfonylureas and meglitinides in the treatment of diabetes mellitus", section on 'Sulfonylureas'.)

Difficult to distinguish type 1 from type 2 — In patients in whom it is difficult to distinguish type 1 from type 2 diabetes (patients who are underweight, are losing weight, or are ketotic), initial treatment with insulin is required. (See "Classification of diabetes mellitus and genetic diabetic syndromes", section on 'Distinguishing type 1 from type 2 diabetes' and "Insulin therapy in type 2 diabetes mellitus", section on 'Adult-onset type 1 diabetes'.)

Glycemic efficacy — The use of metformin as initial therapy is supported by a meta-analysis of 179 trials and 25 observational studies evaluating the effects of oral or injectable diabetes medications as monotherapy and in combination with other oral agents or insulin on intermediate outcomes (A1C, body weight, lipid profiles) and adverse events [39,40]. Most medications used as monotherapy (metformin, second-generation sulfonylureas, thiazolidinediones [TZDs]) had similar efficacy in reducing A1C values (approximately 1 percentage point). In this and other meta-analyses, metformin reduced A1C levels more than DPP-4 inhibitor monotherapy [39-42].

Although each diabetes medication is associated with adverse events, metformin was associated with fewer episodes of hypoglycemia compared with sulfonylureas and with less edema, congestive heart failure, and weight gain compared with TZDs. In addition, metformin is far less expensive and has more clinical practice experience than TZDs.

There are few high-quality, head-to-head comparison trials of the available oral agents. In one such trial, A Diabetes Outcome Progression Trial (ADOPT), 4360 recently diagnosed patients with type 2 diabetes were randomly assigned to monotherapy with rosiglitazone, metformin, or glyburide [43]. At the four-year evaluation, 40 percent of the subjects in the rosiglitazone group had an A1C value less than 7 percent, as compared with 36 percent in the metformin group and 26 percent in the glyburide group. Glyburide resulted in more rapid glycemic improvement during the first six months but caused weight gain and a greater incidence of hypoglycemia, and metformin caused more gastrointestinal side effects. Rosiglitazone caused greater increases in weight, peripheral edema, and concentrations of low-density lipoprotein (LDL) cholesterol. There was also an unexpected increase in fractures in women taking rosiglitazone. The study was limited by a high rate of withdrawal of study participants. Although rosiglitazone had greater durability as monotherapy than glyburide, its benefit over metformin was fairly small and of uncertain clinical significance [44]. (See "Thiazolidinediones in the treatment of diabetes mellitus", section on 'Safety'.)

Cardiovascular outcomes — The long-term benefits and risks of using one agent over another are unknown. There is a paucity of high-quality, head-to-head drug comparison trials and trials with important clinical endpoints, such as effects on microvascular and macrovascular complications and mortality. Metformin does not have adverse cardiovascular effects, and it appears to decrease cardiovascular events in certain populations [40,45,46]. (See "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Cardiovascular effects'.)

Many of the recently approved diabetes drugs are now being required by the US Food and Drug Administration (FDA) to prove cardiovascular disease (CVD) safety with large trials. On the basis of these trials and other data, there does not appear to be an increased risk of adverse coronary heart disease outcomes with insulin glargine or short-term use of DPP-4 inhibitors (used in combination with another oral agent). However, DPP-4 inhibitors may be associated with an increased risk of hospitalization for heart failure. TZDs are associated with an increased risk of fluid retention and heart failure, and the use of rosiglitazone in particular is not recommended, because of the greater concern about its atherogenic lipid profiles and a potential increased risk for cardiovascular events. The cardiovascular effects of diabetes drugs (when data are available) are reviewed in the individual topics. (See "Insulin therapy in type 2 diabetes mellitus", section on 'Cardiovascular effects' and "Sulfonylureas and meglitinides in the treatment of diabetes mellitus", section on 'Cardiovascular effects' and "Thiazolidinediones in the treatment of diabetes mellitus", section on 'Cardiovascular effects' and "Dipeptidyl peptidase-4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus", section on 'Cardiovascular effects'.)

Guidelines — Our approach is largely consistent with American and European guidelines [35,36,47-49]. A consensus statement regarding the management of hyperglycemia in type 2 diabetes by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) was developed in 2006 and has been updated

regularly [35,36,47]. The guidelines emphasize the importance of individualizing the choice of medications for the treatment of diabetes, encouraging clinicians to integrate the current evidence in the context of patient-specific factors (including patient preferences, needs, and values) [36]. The ADA/EASD recommends metformin (in the absence of contraindications) as initial therapy in most patients. In patients with contraindications to metformin, the ADA/EASD consensus guideline suggests either a sulfonylurea/glinide, pioglitazone, a DPP-4 inhibitor, an SGLT2 inhibitor, a GLP-1 receptor agonist, or basal insulin [35,36,47].

MONITORING — We obtain A1C at least twice yearly in patients meeting glycemic goals and more frequently (quarterly) in patients whose therapy has changed or who are not meeting goals. Self-monitoring of blood glucose (SMBG) is not necessary for most patients with type 2 diabetes who are on a stable regimen of diet or oral agents and who are not experiencing hypoglycemia. SMBG may be useful for some type 2 diabetic patients who would take action to modify eating patterns or exercise, as well as be willing to intensify pharmacotherapy, based on SMBG results. (See "Self-monitoring of blood glucose in management of adults with diabetes mellitus", section on 'Indications'.)

PERSISTENT HYPERGLYCEMIA — For patients who are not meeting glycemic targets despite diet, exercise, and metformin, combination therapy is necessary to achieve optimal results. The balance among efficacy in lowering A1C, side effects, and costs must be carefully weighed in considering which drugs or combinations to choose. Avoiding insulin, the most potent of all hypoglycemic medications, at the expense of poorer glucose control and greater side effects and cost, is not likely to benefit the patient in the long term. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Treatment options'.)

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diabetes mellitus in adults".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Type 2 diabetes (The Basics)" and "Patient education: Treatment for type 2 diabetes (The Basics)")
- Beyond the Basics topics (see "Patient education: Diabetes mellitus type 2: Overview (Beyond the Basics)" and "Patient education: Diabetes mellitus type 2: Treatment (Beyond the Basics)" and "Patient education: Self-monitoring of blood glucose in diabetes mellitus (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Patients with newly diagnosed diabetes should participate in a comprehensive diabetes self-management education program, which includes instruction on nutrition, physical activity, optimizing metabolic control, and preventing complications. Weight reduction through diet, exercise, and behavioral modification can all be used to improve glycemic control, although the majority of patients with type 2 diabetes will require medication over the course of their diabetes. (See 'Diabetes education' above.)
- Target glycated hemoglobin (A1C) levels in patients with type 2 diabetes should be tailored to the individual, balancing the improvement in microvascular complications with the risk of hypoglycemia. A reasonable goal of therapy might be an A1C value of ≤7.0 percent (53.0 mmol/mol) (calculator 1) for most patients. Glycemic targets are generally set somewhat higher for older adult patients and for those with comorbidities or a limited life expectancy and little likelihood of benefit from intensive therapy. (See 'Degree of glycemic control' above and "Glycemic control and vascular complications in type 2 diabetes mellitus", section on 'Glycemic targets'.)

- In the absence of specific contraindications, we suggest metformin as initial therapy in most patients (**Grade 2B**). (See 'A1C at (<7.6 percent) or close to (>0.5 to 1.5 percent above, eg, 7.6 to 8.5 percent) treatment goal' above and 'A1C relatively far from goal (eg, 8.5 to 9.5 percent)' above.)

  Insulin can also be considered a first-line therapy for all patients with type 2 diabetes, particularly patients presenting with A1C >9 percent (74.9 mmol/mol). (See "Insulin therapy in type 2 diabetes mellitus".)

  We suggest initiating metformin at the time of diabetes diagnosis, along with consultation for lifestyle intervention (**Grade 2C**). For highly motivated patients with A1C near target (ie, <7.5 percent), however, a three- to six-month trial of lifestyle modification before initiating pharmacologic therapy is reasonable. (See 'When to start' above.)

  The dose of metformin should be titrated to its maximally effective dose (usually 2000 to 2500 mg per day in divided doses) over one to two months, as tolerated. Metformin should not be administered when conditions predisposing to lactic acidosis are present. (See "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Contraindications'.)

- In the presence of contraindications to metformin, we suggest a shorter-duration sulfonylurea (glipizide) for initial therapy (**Grade 2B**). (See 'Contraindications to metformin' above.)

  We suggest initiating lifestyle intervention first, at the time of diagnosis, since the weight gain that often accompanies a sulfonylurea will presumably be less if lifestyle efforts are underway (**Grade 2C**). However, if lifestyle intervention has not produced a significant reduction in symptoms of hyperglycemia or in glucose values after one or two weeks, then the sulfonylurea should be added.

- In patients who are intolerant of or are not candidates for metformin or sulfonylureas, repaglinide is a reasonable alternative, particularly in a patient with chronic kidney disease at risk for hypoglycemia. (See 'Contraindications to metformin' above and "Management of hyperglycemia in patients with type 2 diabetes and pre-dialysis chronic kidney disease or end-stage renal disease", section on 'Meglitinides'.)

  Other oral and injectable agents, such as glucagon-like peptide-1 (GLP-1) agonists, alpha-glucosidase inhibitors, sodium-glucose co-transporter 2 (SGLT2) inhibitors, or dipeptidyl peptidase-4 (DPP-4) inhibitors may be appropriate initial therapy for some patients. However, limited clinical experience; lower or overall equivalent effectiveness compared with metformin, insulin, and sulfonylurea; higher cost; and/or side effects reduce their appeal as initial agents. (See 'Choice of initial therapy' above.)

  Pioglitazone, which is now available as a generic and is another relatively low-cost oral agent, may also be considered in patients with specific contraindications to metformin and sulfonylureas. However, the risk of heart failure, fractures, and the potential increased risk of bladder cancer raise the concern that the overall risks and cost of pioglitazone may exceed its benefits. (See 'Contraindications to metformin' above and "Thiazolidinediones in the treatment of diabetes mellitus", section on 'Cardiovascular effects'.)

- For patients presenting with symptomatic (eg, weight loss) or severe hyperglycemia (fasting plasma glucose >250 mg/dL [13.9 mmol/L], random glucose consistently >300 mg/dL [16.7 mmol/L], A1C >9.5 [80.3 mmol/mol]) with ketonuria, insulin is indicated for initial treatment. For patients presenting with severe hyperglycemia but without ketonuria or spontaneous weight loss, insulin remains the preferred initial therapy. However, for patients who are insulin averse, initial therapy with high-dose sulfonylurea is an alternative option, particularly for patients who have been quenching their thirst with sugar-sweetened beverages, in whom elimination of carbohydrates will cause a reduction in glucose within a couple of days. (See 'Symptomatic or severe hyperglycemia' above and "Insulin therapy in type 2 diabetes mellitus".)

- A potential problem is that patients who are initially thought to have type 2 diabetes may actually have type 1 diabetes and, therefore, require insulin as initial therapy. In patients in whom it is difficult to distinguish type 1 from type 2 diabetes, initial treatment with insulin is required. (See "Insulin therapy in type 2 diabetes mellitus", section on 'Insulin as initial therapy'.)

- We obtain an A1C at least twice yearly in patients meeting glycemic goals and more frequently (quarterly) in patients whose therapy has changed or who are not meeting goals. Further adjustments of therapy, which should usually be made no less frequently than every three months, are based upon the A1C result (and in some settings, the results of home glucose monitoring). (See 'Monitoring' above.)

- If inadequate control is achieved (A1C remains >7.0 percent [53.0 mmol/mol]), another medication should be added within two to three months of initiation of the lifestyle intervention and metformin. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus" and "Insulin therapy in type 2 diabetes mellitus".)

REFERENCES

1. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:837.
2. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359:1577.
3. Look AHEAD Research Group, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013; 369:145.
4. ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358:2560.
5. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358:2545.
6. Pal K, Eastwood SV, Michie S, et al. Computer-based diabetes self-management interventions for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev 2013; :CD008776.
7. Saffari M, Ghanizadeh G, Koenig HG. Health education via mobile text messaging for glycemic control in adults with type 2 diabetes: a systematic review and meta-analysis. Prim Care Diabetes 2014; 8:275.
8. Liang X, Wang Q, Yang X, et al. Effect of mobile phone intervention for diabetes on glycaemic control: a meta-analysis. Diabet Med 2011; 28:455.
9. Henry RR, Scheaffer L, Olefsky JM. Glycemic effects of intensive caloric restriction and isocaloric refeeding in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1985; 61:917.
10. Wing RR, Blair EH, Bononi P, et al. Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. Diabetes Care 1994; 17:30.
11. Niskanen LK, Uusitupa MI, Sarlund H, et al. Five-year follow-up study on plasma insulin levels in newly diagnosed NIDDM patients and nondiabetic subjects. Diabetes Care 1990; 13:41.
12. Norris SL, Zhang X, Avenell A, et al. Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with type 2 diabetes: a meta-analysis. Am J Med 2004; 117:762.
13. United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 1995; 310:83.
14. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006; 29:1963.
15. Umpierre D, Ribeiro PA, Kramer CK, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. JAMA 2011; 305:1790.
16. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. Diabetes Care 2007; 30:744.
17. Egan AM, Mahmood WA, Fenton R, et al. Barriers to exercise in obese patients with type 2 diabetes. QJM 2013; 106:635.
18. Pillay J, Armstrong MJ, Butalia S, et al. Behavioral Programs for Type 2 Diabetes Mellitus: A Systematic Review and Network Meta-analysis. Ann Intern Med 2015; 163:848.
19. Johansen MY, MacDonald CS, Hansen KB, et al. Effect of an Intensive Lifestyle Intervention on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. JAMA 2017; 318:637.

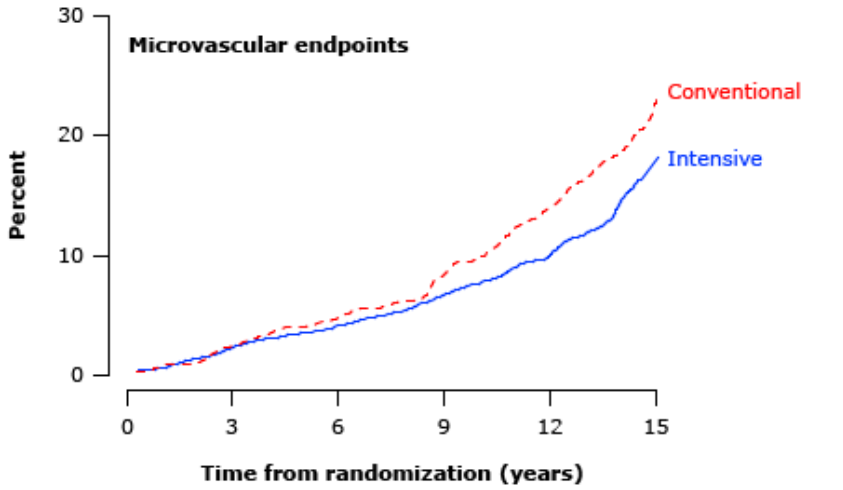
20. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2017.
21. Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care 2007; 30:1374.
22. Look AHEAD Research Group, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med 2010; 170:1566.
23. Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012; 308:2489.
24. Jakicic JM, Egan CM, Fabricatore AN, et al. Four-year change in cardiorespiratory fitness and influence on glycemic control in adults with type 2 diabetes in a randomized trial: the Look AHEAD Trial. Diabetes Care 2013; 36:1297.
25. Kuna ST, Reboussin DM, Borradaile KE, et al. Long-term effect of weight loss on obstructive sleep apnea severity in obese patients with type 2 diabetes. Sleep 2013; 36:641.
26. Wing RR, Bond DS, Gendrano IN 3rd, et al. Effect of intensive lifestyle intervention on sexual dysfunction in women with type 2 diabetes: results from an ancillary Look AHEAD study. Diabetes Care 2013; 36:2937.
27. http://www.diabetes.org/for-media/2013/sci-sessions-look-ahead.html (Accessed on July 18, 2013).
28. Look AHEAD Research Group. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol 2014; 2:801.
29. Arterburn DE, O'Connor PJ. A look ahead at the future of diabetes prevention and treatment. JAMA 2012; 308:2517.
30. Surwit RS, van Tilburg MA, Zucker N, et al. Stress management improves long-term glycemic control in type 2 diabetes. Diabetes Care 2002; 25:30.
31. Ismail K, Winkley K, Rabe-Hesketh S. Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. Lancet 2004; 363:1589.
32. Safren SA, Gonzalez JS, Wexler DJ, et al. A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in patients with uncontrolled type 2 diabetes. Diabetes Care 2014; 37:625.
33. Williams JW Jr, Katon W, Lin EH, et al. The effectiveness of depression care management on diabetes-related outcomes in older patients. Ann Intern Med 2004; 140:1015.
34. Colagiuri S, Cull CA, Holman RR, UKPDS Group. Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcomes?: U.K. prospective diabetes study 61. Diabetes Care 2002; 25:1410.
35. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy. Update regarding the thiazolidinediones. Diabetologia 2008; 51:8.
36. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38:140.
37. Desai NR, Shrank WH, Fischer MA, et al. Patterns of medication initiation in newly diagnosed diabetes mellitus: quality and cost implications. Am J Med 2012; 125:302.e1.
38. Davidson MB. Successful treatment of markedly symptomatic patients with type II diabetes mellitus using high doses of sulfonylurea agents. West J Med 1992; 157:199.
39. https://effectivehealthcare.ahrq.gov/ehc/products/607/2215/diabetes-update-2016-report.pdf (Accessed on April 21, 2016).
40. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. Ann Intern Med 2016; 164:740.

41. Karagiannis T, Paschos P, Paletas K, et al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012; 344:e1369.
42. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes: A Meta-analysis. JAMA 2016; 316:313.
43. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355:2427.
44. Nathan DM. Thiazolidinediones for initial treatment of type 2 diabetes? N Engl J Med 2006; 355:2477.
45. Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care 2013; 36:1304.
46. Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med 2009; 169:616.
47. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; 32:193.
48. Qaseem A, Barry MJ, Humphrey LL, et al. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med 2017; 166:279.
49. American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care 2017; 40:S64.

Topic 1779 Version 46.0

GRAPHICS

Intensive glycemic control prevents microvascular disease in patients with type 2 diabetes



Kaplan-Meier plots of aggregate endpoints of microvascular disease in patients with type 2 diabetes mellitus in the United Kingdom Prospective Diabetes Study who were randomly assigned to receive either intensive therapy with a sulfonylurea or insulin or to conventional treatment with diet; drugs were added if the patients had hyperglycemic symptoms or fasting blood glucose concentrations greater than 270 mg/dL (15 mmol/L). Intensive therapy was associated with a 25 percent reduction (p = 0.01) in the development of microvascular disease, which was defined as renal failure, death from renal failure, retinal photocoagulation, or vitreous hemorrhage.

Data from: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:837.

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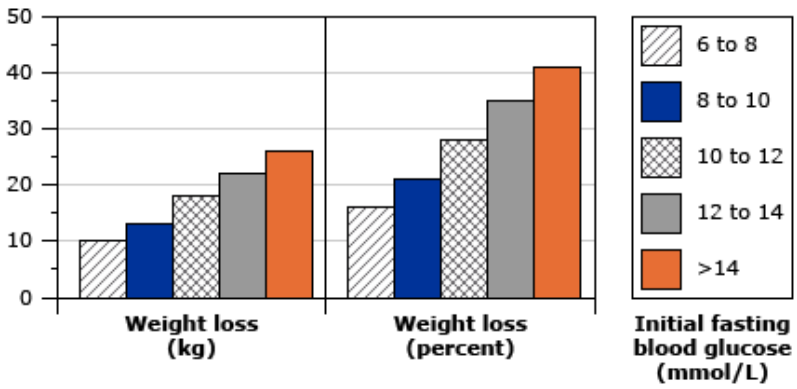
Initial fasting blood glucose concentration determines degree of weight loss required to achieve normoglycemia in type 2 diabetes



Glycemic response to weight reduction according to initial fasting blood glucose (in mmol/L) in type 2 diabetes. Patients who had mildly elevated fasting blood glucose concentrations of 6 to 8 mmol/L (108 to 144 mg/dL) initially had to lose 10 kg (16 percent of initial body weight) to achieve a value below 6 mmol/L (<108 mg/dL). Greater degrees of weight loss were required in patients with higher initial values, rising to 26 kg and 41 percent, respectively, in patients with an initial value above 14 mmol/L (>252 mg/dL).

Data from: United Kingdom Prospective Diabetes Study Group. UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients, UKPDS Group. Metabolism 1990; 39:905.

Graphic 78027 Version 3.0

Summary of glucose-lowering interventions

Intervention	Expected decrease in A1C with monotherapy (%)	Advantages	Disadvantages
Step 1: Initial therapy			
Lifestyle change to decrease weight and increase activity	1.0 to 2.0	Broad benefits	Insufficient for most within first year owing to inadequate weight loss and weight regain
Metformin (usually 1700 to 2000 mg per day)	1.0 to 2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency (eGFR <30 mL/min)*
Step 2: Additional therapy			
Insulin (usually with a single daily injection of intermediate- or long-acting insulin initially)	1.5 to 3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Sulfonylurea (shorter-acting agents preferred)	1.0 to 2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
GLP-1 agonist (daily to weekly injections)	0.5 to 1.0	Weight loss, reduced cardiovascular mortality (liraglutide, semaglutide) in patients with established CVD	Requires injection, frequent GI side effects, long-term safety not established, expensive
Thiazolidinedione	0.5 to 1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, HF, weight gain, bone fractures, potential increase in MI (rosiglitazone) and bladder cancer (pioglitazone)
Glinide	0.5 to 1.5¶	Rapidly effective	Weight gain, three times/day dosing, hypoglycemia
SGLT2 inhibitor	0.5 to 0.7	Weight loss, reduction in systolic blood pressure, reduced cardiovascular mortality in patients with established CVD	Vulvovaginal candidiasis, urinary tract infections, bone fractures, lower limb amputations, acute kidney injury, DKA, long-term safety not established
DPP-4 inhibitor	0.5 to 0.8	Weight neutral	Long-term safety not established, expensive, possible increased risk of HF with saxagliptin
Alpha-glucosidase inhibitor	0.5 to 0.8	Weight neutral	Frequent GI side effects, three times/day dosing
Pramlintide	0.5 to 1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive

A1C: glycated hemoglobin; GI: gastrointestinal; eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like protein-1; CVD: cardiovascular disease; MI: myocardial infarction; HF: heart failure; SGLT2: sodium-glucose co-transporter 2; DKA: diabetic ketoacidosis; DPP-4: dipeptidyl peptidase-4.

* Initiation is contraindicated with eGFR <30 mL/min and not recommended with eGFR 30 to 45 mL/min.

¶ Repaglinide is more effective in lowering A1C than nateglinide.

Modified with permission from: Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; 32:193-203. Copyright © 2009 American Diabetes.

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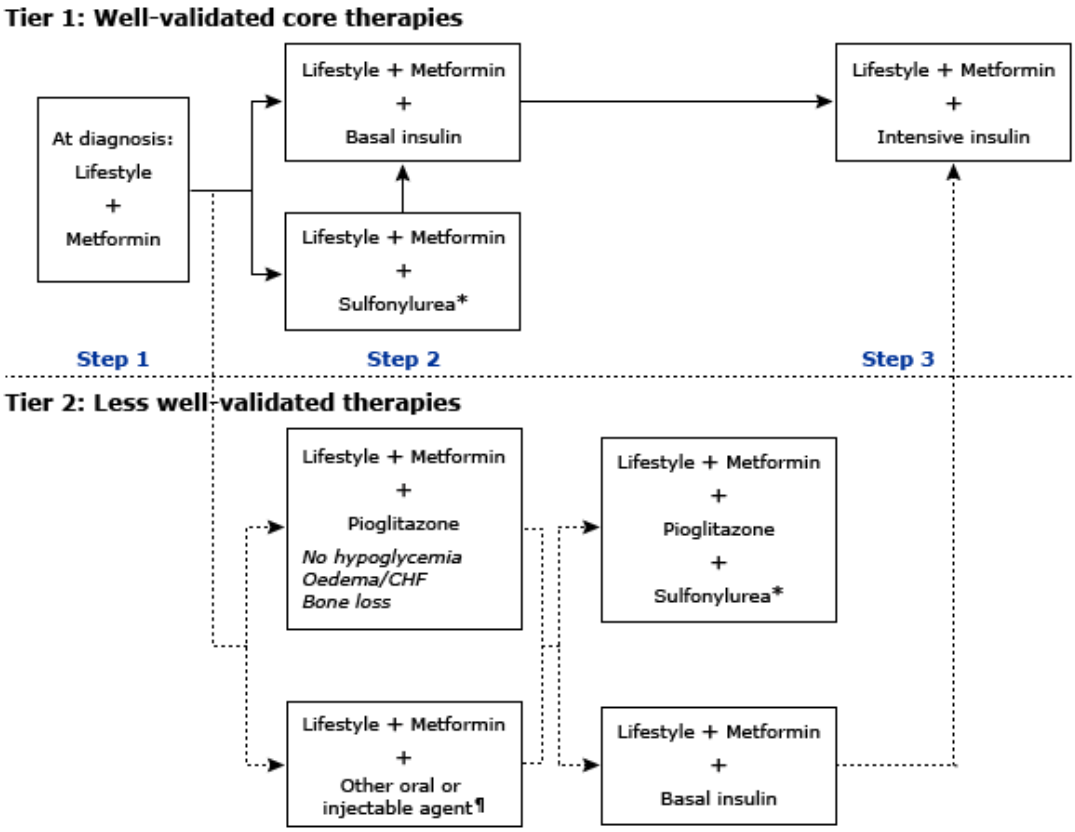
Management of type 2 diabetes



Algorithm for the metabolic management of type 2 diabetes; reinforce lifestyle interventions at every visit and check A1C every three months until A1C is <7% and then at least every six months. The interventions should be changed if A1C is ≥7%.

CHF: congestive heart failure; A1C: glycated hemoglobin; GLP-1: glucagon-like peptide-1; DPP-4: dipeptidyl peptidase-4; SGLT2: sodium-glucose co-transporter 2.
* Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide.
¶ Alternative agents include: GLP-1 agonists, DPP-4 inhibitors, alpha-glucosidase inhibitors, SGLT2 inhibitors.

Modified with permission from: Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; 32:193-203. Copyright © 2009 American Diabetes.

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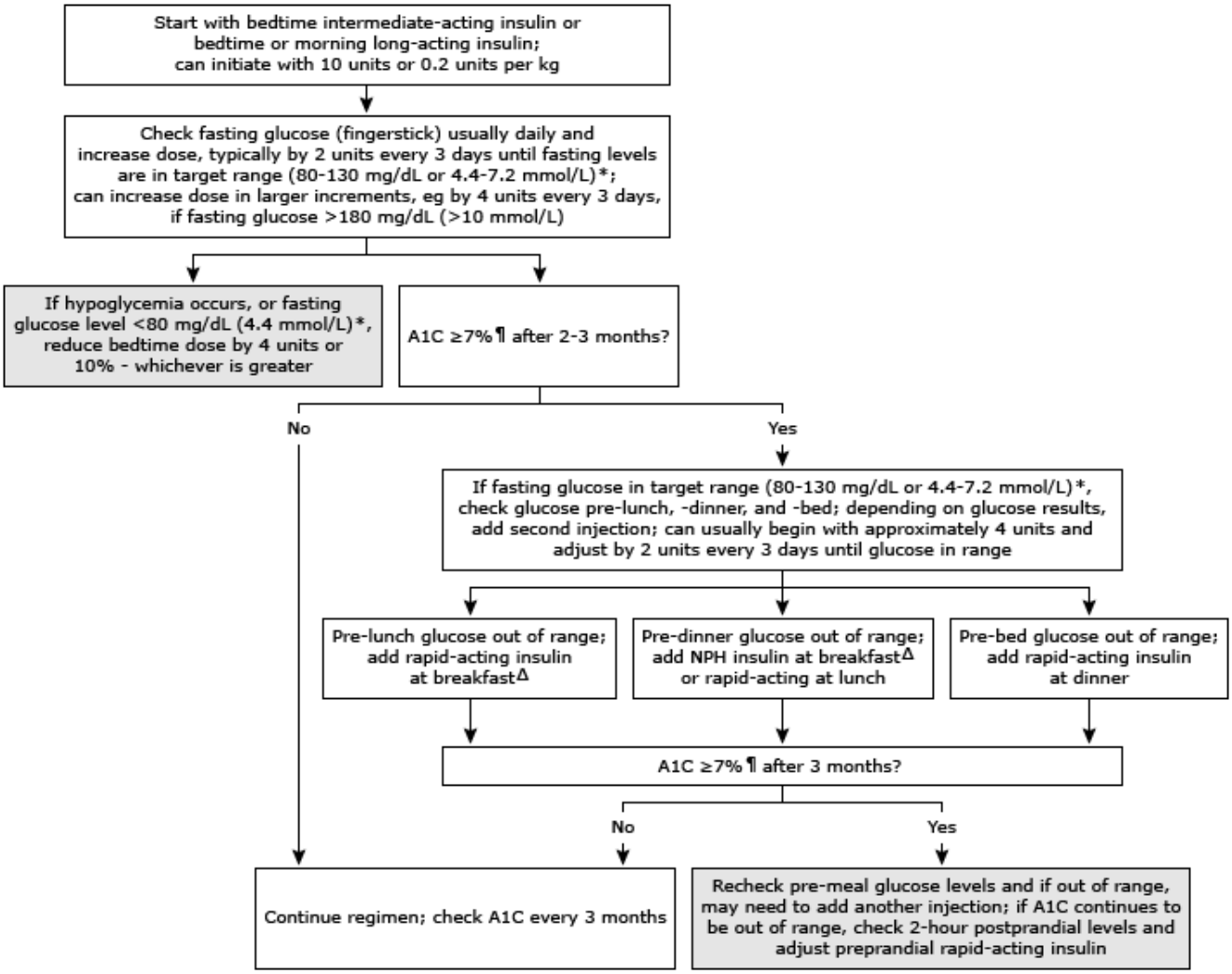
Initiation and adjustment of insulin regimens in type 2 diabetes mellitus



Insulin regimens should be designed taking lifestyle and meal schedule into account. The algorithm can only provide basic guidelines for initiation and adjustment of insulin.

A1C: glycated hemoglobin.

* Glucose levels updated with data from: American Diabetes Association. Glycemic Targets. Diabetes Care 2016; 39 Suppl 1:S39.

¶ The A1C goal should be individualized in accordance with patient age, comorbidities, and life expectancy.

Δ Premixed insulins are not recommended during adjustment of doses; however, they can be used conveniently, usually before breakfast and/or dinner if proportion of rapid- and intermediate-acting insulins is similar to the fixed proportions available.

Adapted with permission from: Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; 32:193. Copyright © 2009 American Diabetes Association.

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Contributor Disclosures

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