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Initial management of blood glucose in type 2 diabetes mellitus

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INTRODUCTION — Treatment of patients with type 2 diabetes mellitus includes education, evaluation for microvascular and macrovascular complications, normalization of glycemia, minimization of cardiovascular and other long-term risk factors, and avoidance of drugs that can aggravate abnormalities of insulin or lipid metabolism. 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 secretion, responsiveness, or both, or decreasing the rate of carbohydrate absorption.

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 — Achieving near normal blood glucose concentrations markedly reduces the risk of microvascular and macrovascular complications in type 1 diabetes. (See "Glycemic control and vascular complications in type 1 diabetes mellitus".)

Improved glycemic control also improves the risk of microvascular complications in patients with type 2 diabetes (graph 1) [1]. Every 1 percent drop in A1C is associated with improved outcomes with no threshold effect. To date, no randomized clinical trial has convincingly demonstrated a beneficial effect of intensive therapy on macrovascular outcomes in type 2 diabetes. 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 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 "Overview of medical care in adults with diabetes mellitus", section on 'Monitoring and degree of control' and "Glycemic control and vascular complications in type 2 diabetes mellitus", section on 'Glycemic goals'.)

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. (See "Choice of antihypertensive drug and blood pressure goal in patients at increased risk for a cardiovascular event", section on 'Choice of therapy'.) However, in spite of evidence that aggressive risk factor reduction lowers the risk of both micro- and macrovascular complications in patients with diabetes, the vast majority of 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", section on 'Adequacy of care' and "Prevalence

of and risk factors for coronary heart disease in diabetes mellitus".)

NONPHARMACOLOGIC THERAPY — Besides contributing to microvascular and macrovascular disease, hyperglycemia adversely and reversibly affects both insulin resistance and insulin secretion [2,3]. Diet, weight reduction, and exercise 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 [4].

Diet — Dietary modification can improve many aspects of type 2 diabetes, including obesity, hypertension, and insulin release and responsiveness. The improvement in glycemic control is related both to the degree of caloric restriction and weight reduction [5,6]. Modest weight reduction may also improve liver function in nonalcoholic steatohepatitis, which is associated with insulin resistance and type 2 diabetes. (See "Nonalcoholic steatohepatitis", section on 'Weight loss'.)

The immediate effect of caloric restriction 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.

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 UKPDS, for example, all patients were given a low calorie, low fat, high complex carbohydrate diet [7]. 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 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) (graph 2). Of note, any degree of weight loss is likely to improve glycemia and/or decrease the need for medications.

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 [5,8,9]. This difficulty results from both limited success in long-term adherence to calorie-restricted diets, plus an apparent effect of weight loss in lowering the metabolic rate, thereby retarding further weight loss. (See "Obesity and weight reduction in hypertension", section on 'Limitation to maintenance of weight reduction'.) There are, however, impressive successes reported with intensive dietary intervention [10,11].

Pharmacotherapy for weight loss may be effective in patients with type 2 diabetes, but generally is associated with high dropout rates due to medication side effects and is not recommended as primary therapy for diabetes [4]. (See "Drug therapy of obesity".)

Surgical treatment of obesity — Surgical treatment of obese patients with diabetes results in the largest degree of sustained weight loss and, in parallel, the largest improvements in blood glucose control. In a two-year study of 60 obese patients (BMI 30 to 40), with a history of type 2 diabetes diagnosed within the previous two years, subjects randomly assigned to laparoscopic banding with conventional therapy versus conventional therapy alone (education, lifestyle modification, pharmacologic therapy) experienced greater weight loss (20 versus 1.4 percent, respectively) and remission rates of diabetes (73 versus 13 percent, respectively) [12]. Despite these impressive results, concerns remain about the rigorousness of the lifestyle modification (see 'Intensive lifestyle modification' below, long-term success rates in maintaining weight loss, and reproducibility of the results in patients with an extensive history of diabetes or with a different surgical team. Thus, longer-term follow-up is required before laparoscopic banding surgery can be routinely recommended for the treatment of recent onset, obesity-

related type 2 diabetes.

Another bariatric surgery procedure, the Roux-en-Y gastric bypass (RYGB), which has been previously recommended for persons with a BMI >40 kg/m2 (or >35 kg/m2 if obesity-related complications such as diabetes have developed) has also been associated with significant weight loss and remission of diabetes. However, unlike the banding procedure, RYGB is associated with rapid resolution of diabetes, occurring within a few days to weeks following the procedure, prior to substantial weight loss. The mechanisms mediating this effect are uncertain, but likely are related to changes in gastrointestinal hormones (the incretins, glucagon-like peptide and glucose-dependent insulinotrophic polypeptide) following surgery. (See "Surgical management of severe obesity", section on 'Effectiveness of bariatric surgery'.)

Exercise — Regular exercise is also 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 [13]. These effects are directly due to exercise but concurrent weight reduction can play a contributory role. (See "Effects of exercise in diabetes mellitus in adults".) However, only a fraction of patients with type 2 diabetes are able to maintain a regular exercise regimen. In one 10-year study, for example, compliance with regular exercise fell from 80 percent at six weeks to less than 50 percent at three months and to less than 20 percent at one year [13].

Intensive lifestyle modification — Intensive lifestyle intervention programs involving weight loss, physical activity, and behavior modification are more likely to be successful in improving long-term glycemic control than traditional diabetes support and education programs. In the Look AHEAD trial, which will continue for 11.5 years, 5145 individuals with type 2 diabetes were randomly assigned to an intensive lifestyle intervention or standard diabetes education [14]. The intensive intervention includes 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 dieticians, 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.

After one year, the intensive group lost an average of 8.6 percent of their initial weight, and mean A1C decreased from 7.3 to 6.6 percent, whereas the control group lost 0.7 percent and A1C decreased from 7.3 to 7.2 percent. In addition, the use of glucose lowering medications decreased in the intensive group and blood pressure, HDL, and triglyceride concentrations improved more than in the control group. Whether individuals maintain the initial weight loss and experience subsequent cardiovascular benefits will be determined over the next decade.

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) [15]. Concurrent depression may also interfere with self-care. Psychotherapy reduces psychological distress and improves glycemic control in some [16], but not all [17] 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]) [16]. Measures of psychological distress were also significantly lower in the intervention group, but there were no differences in weight control.

MEDICATIONS FOR INITIAL THERAPY — 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 significantly elevated, is associated with improved glycemic control over time and decreased long-term complications [18]. Pharmacologic therapy is often not initiated soon enough, resulting in poor glycemic control. A consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends that metformin therapy (in the absence of

contraindications) be initiated, concurrent with lifestyle intervention, at the time of diabetes diagnosis [19]. Metformin was chosen for initial therapy because of glycemic efficacy, absence of weight gain and hypoglycemia, general tolerability, and favorable cost. (See 'Metformin' below.)

Other options for initial therapy in those with contraindications to metformin are available (table 1). A consensus algorithm for initiating medication in type 2 diabetes by the American Diabetes Association and the European Association for the Study of Diabetes was developed in 2006 and updated in 2009 (algorithm 1) [19,20]. The selection of drugs in the ADA/EASD consensus guideline was based upon clinical trial evidence and clinical experience in achieving glycemic targets, with the recognition that there is a paucity of many high-quality head to head drug comparison trials and trials with important clinical endpoints, such as effects on complications. In addition, the guidelines emphasize the importance of individualizing the choice of medications for the treatment of diabetes.

In patients with contraindications to metformin, the ADA/EASD consensus guideline suggests either insulin or a sulfonylurea [19,20]. The 2009 algorithm has recommended against the use of rosiglitazone, owing to concern regarding safety and the availability of alternative therapies, including pioglitazone, that don't have the same concerns [19].

In patients with contraindications to metformin, we suggest a shorter acting sulfonylurea, such as glipizide. Insulin is also a reasonable option for initial therapy in patients who present with symptomatic or poorly controlled diabetes or in patients in whom it is difficult to distinguish type 1 from type 2 diabetes. (See 'Insulin' below and "Classification of diabetes mellitus and genetic diabetic syndromes", section on 'DKA in type 2 diabetes'.)

Pioglitazone may be considered in patients with lower initial A1C values or if there are specific contraindications to sulfonylureas. If a thiazolidinedione is to be used as initial therapy, pioglitazone is recommended because of the greater concern about atherogenic lipid profiles and a potential increased risk for cardiovascular events with rosiglitazone. (See "Thiazolidinediones in the treatment of diabetes mellitus", section on 'cardiovascular effects'.)

Other oral and injectable agents, such as meglitinides, alpha-glucosidase inhibitors, DPP-IV inhibitors, or GLP-1 agonists may be appropriate initial therapy for some patients [20]. However, limited clinical experience, lower or overall equivalent effectiveness compared with metformin, insulin, and sulfonylureas, higher cost, and/or side effects reduce their appeal as initial agents.

Combinations of these drugs are often 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".)

A discussion of the individual medications considered in the algorithm follows below.

Metformin — In the absence of contraindications, metformin is the first choice for oral treatment of type 2 diabetes. It generally reduces A1C by 1.5 percentage points [21,22]. In contrast with most other antidiabetic drugs, metformin often leads to modest weight reduction or weight stabilization (graph 3) [7,23,24]. Furthermore, obese patients in the UKPDS who were assigned initially to receive metformin rather than sulfonylurea or insulin therapy had a decreased risk of the aggregate diabetes-related endpoint and all-cause mortality [25]. During the post-interventional observation period of the UKPDS, reductions in the risk of macrovascular complications were maintained in the metformin group. (See "Glycemic control and vascular complications in type 2 diabetes mellitus", section on 'UKPDS'.) The cardiovascular benefits of metformin in the UKPDS need to be confirmed before metformin can be recommended to reduce cardiovascular disease.

Gastrointestinal side effects are common, but metformin monotherapy does not usually cause hypoglycemia. Metformin can rarely cause lactic acidosis, and because of the potentially fatal outcome of this side effect, metformin should not be administered when conditions predisposing to lactic acidosis are present. Such conditions include impaired renal function (creatinine above 1.4 mg/dL [124 mmol/L] in women and 1.5 mg/dL [133 mmol/L] in men), decreased tissue perfusion or hemodynamic instability due to infection or other causes, concurrent liver disease or alcohol abuse, and heart failure. Factors predisposing to lactic acidosis are discussed in detail elsewhere. (See "Metformin in the treatment of diabetes mellitus", section on 'Predisposing factors'.)

Patients who are about to receive intravenous iodinated contrast material (with potential for contrast-induced renal failure) or undergo a surgical procedure (with potential compromise of circulation) should have metformin held until renal function and circulation can be established (normal urine output, normal serum creatinine, and no physical exam evidence of fluid overload or circulatory compromise). Serum creatinine is typically assessed two to three days after contrast administration. (See "Metformin in the treatment of diabetes mellitus", section on 'Lactic acidosis'.)

Sulfonylureas — Sulfonylureas are the oldest class of oral hypoglycemic agents. They are moderately effective, lowering blood glucose concentrations by 20 percent and A1C by 1 to 2 percent. However, their effectiveness decreases over time. (See "Sulfonylureas and meglitinides in the treatment of diabetes mellitus".)

The major adverse effect of sulfonylureas is hypoglycemia. Before beginning a sulfonylurea, the patient should be instructed about the symptoms and treatment of hypoglycemia. Hypoglycemia induced by long-acting sulfonylureas may be severe and is often prolonged in the absence of appropriate therapy. Risk factors for hypoglycemia include increasing age, alcohol abuse, poor nutrition, and renal insufficiency. Shorter acting sulfonylureas, such as glipizide and gliclazide, are less likely to cause hypoglycemia than the older, long-acting sulfonylureas (table 2), and therefore are the preferred sulfonylureas, especially in older patients. Initiation of sulfonylurea therapy is also associated with weight gain. (See "Sulfonylureas and meglitinides in the treatment of diabetes mellitus", section on 'Side effects'.)

The choice of sulfonylurea is primarily dependent upon cost, risk of hypoglycemia, and local availability, since the efficacy of the available drugs is similar. In a patient who is not a candidate for metformin or who cannot tolerate metformin, we suggest a shorter-duration sulfonylurea, such as glipizide.

Meglitinides — Repaglinide and nateglinide are short-acting glucose-lowering drugs that act similarly to the sulfonylureas and have similar or slightly less efficacy in decreasing glycemia. Meglitinides are pharmacologically distinct from sulfonylureas and may be used in patients who have allergy to sulfonylurea medications. They have a similar risk for weight gain as sulfonylureas but possibly less risk of hypoglycemia. However, they are considerably more expensive than sulfonylureas, and have no therapeutic advantage over these other drugs that warrant the added cost. (See "Sulfonylureas and meglitinides in the treatment of diabetes mellitus".)

Nateglinide is hepatically metabolized, with renal excretion of active metabolites. With decreased renal function, the accumulation of active metabolites and hypoglycemia has occurred. This drug must therefore be used cautiously in this setting, if at all. Repaglinide is principally metabolized by the liver, with less than 10 percent renally excreted. Dose adjustments with this agent do not appear to be necessary in patients with renal insufficiency. (See "Management of hyperglycemia in diabetics with end-stage renal disease", section on 'Meglitinides'.) In addition, repaglinide is somewhat more effective in lowering A1C than nateglinide. Thus, repaglinide could be considered as initial therapy in a patient with chronic kidney disease who is intolerant of sulfonylureas.

Thiazolidinediones — The thiazolidinediones, rosiglitazone and pioglitazone, lower blood glucose concentrations by increasing insulin sensitivity. The first drug in this class, troglitazone, was removed

from the market in the United Kingdom and the United States because of relatively rare, but severe idiosyncratic hepatic injury that was either fatal or necessitated liver transplantation. Hepatotoxicity does not appear to occur with rosiglitazone and pioglitazone. (See "Thiazolidinediones in the treatment of diabetes mellitus".)

The United States Food and Drug Administration has approved pioglitazone and rosiglitazone for monotherapy. As monotherapy, thiazolidinediones are probably somewhat less effective in lowering glycemia than metformin, lowering A1C by 0.5 to 1.4 percentage points [26]. They are also associated with more weight gain and fluid retention than metformin, and are considerably more expensive than generic sulfonylureas and metformin. In addition, the cardiovascular benefit-risk ratio of individual thiazolidinediones is not entirely clear. Drugs in this class are not recommended in patients with symptomatic heart failure and are contraindicated in patients with New York Heart Association class III or IV heart failure. Furthermore, some meta-analyses have questioned the safety of rosiglitazone with regard to the risk of myocardial infarction. (See "Thiazolidinediones in the treatment of diabetes mellitus", section on 'cardiovascular effects'.)

As a result, we do not generally choose thiazolidinediones for initial therapy and reserve their use for second-line treatment in combination with other anti-diabetic medications where synergistic effects can lower A1C substantially. If a thiazolidinedione is used, pioglitazone is recommended because of the greater concern about atherogenic lipid profiles and a potential increased risk for cardiovascular events with rosiglitazone. (See "Thiazolidinediones in the treatment of diabetes mellitus", section on 'cardiovascular effects'.)

DPP-IV inhibitors — Sitagliptin is a DPP-IV inhibitor that is approved as initial pharmacologic therapy for the treatment of type 2 diabetes. However, because of modest glucose lowering effectiveness, expense, and limited clinical experience, sitagliptin is more commonly used as a second agent in those who do not respond to a single agent, such as a sulfonylurea, metformin or a thiazolidinedione; or as a third agent when dual therapy with metformin and a sulfonylurea does not provide adequate glycemic control. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'DPP-IV inhibitors'.)

Sitagliptin can be considered as monotherapy in patients who are intolerant of or have contraindications to metformin, sulfonylureas, or thiazolidinediones. As an example, sitagliptin might be a good choice as initial therapy in a patient with chronic kidney disease at risk for hypoglycemia. However, given the unknown consequences of long-term DPP-IV inhibition, we prefer to use repaglinide in this situation. (See "GLP-1-based therapies for the treatment of type 2 diabetes mellitus", section on 'DPP-IV inhibitors'.)

Although sitagliptin is currently the only DPP-IV inhibitor available for the treatment of type 2 diabetes in the United States, vildagliptin is available in several countries, and other DPP-IV inhibitors (saxagliptin, alogliptin) are in clinical trials. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'DPP-IV inhibitors'.)

Glucagon-like peptide 1 agonists — Exenatide is a glucagon-like peptide 1 (GLP-1) analog that is administered subcutaneously. It is approved in the United States by the FDA for the treatment of type 2 diabetes in patients not sufficiently controlled with oral agents. Exenatide requires two daily injections and could be considered as an add-on drug for patients with type 2 diabetes who are poorly controlled on maximal doses of one or two oral agents. There are inadequate data to support the use of exenatide as monotherapy. (See "GLP-1-based therapies for the treatment of type 2 diabetes mellitus" and "Management of persistent hyperglycemia in type 2 diabetes mellitus".)

Alpha-glucosidase inhibitors — Because they act by a different mechanism, the alpha-glucosidase inhibitors, acarbose and miglitol, have additive hypoglycemic effects in patients receiving diet, sulfonylurea, metformin, or insulin therapy [1]. This class of drugs is less potent than the sulfonylureas or metformin, lowering A1C by only 0.5 to 0.8 percentage points.

The main side effects, which may limit their acceptance, are flatulence and diarrhea. Although these drugs have been studied as monotherapy for initial treatment of diabetes, we do not consider them to be usual first-line therapy because of reduced efficacy, expense, and poor tolerance. (See "Alpha-glucosidase inhibitors and lipase inhibitors for treatment of diabetes mellitus".)

Insulin — 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".)

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".)

Comparison of initial therapies — There are few high quality head-to-head comparison trials of the available oral agents.

In A Diabetes Outcome Progression Trial (ADOPT), 4360 recently diagnosed patients with type 2 diabetes were randomly assigned to monotherapy with rosiglitazone, metformin, or glyburide [27].

- 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

- At the four year evaluation, insulin sensitivity was significantly better in the rosiglitazone group compared to the other two groups, whereas insulin secretion was slightly but significantly better in the rosiglitazone and glyburide groups compared with the metformin group

- Rosiglitazone caused greater increases in weight, peripheral edema, and concentrations of LDL cholesterol. There was also an unexpected increase in fractures in women taking rosiglitazone. (See "Thiazolidinediones in the treatment of diabetes mellitus", section on 'safety'.)

- Glyburide caused weight gain and a greater incidence of hypoglycemia and metformin more gastrointestinal side effects

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 [28].

The use of metformin as initial therapy is supported by a meta-analysis of 216 trials and two systematic reviews evaluating the effects of oral hypoglycemic agents on intermediate outcomes, such as A1C, and adverse events [29]. Older agents (metformin and second generation sulfonylureas) (table 2) had similar efficacy in reducing A1C values (approximately one percentage point) and other cardiovascular risk factors (blood pressure, lipids, body weight) compared with newer agents (thiazolidinediones, meglitinides, alpha-glucosidase inhibitors). Although each oral hypoglycemic agent is associated with adverse events, metformin was associated with fewer episodes of hypoglycemia compared with sulfonylureas and less edema, congestive heart failure, and weight gain compared with thiazolidinediones. In addition, metformin is less expensive and has more clinical practice experience than thiazolidinediones.

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. (See "Patient information: Diabetes mellitus type 2: Overview" and "Patient information: Diabetes mellitus type 2: Treatment" and "Patient information: Self-blood glucose monitoring in diabetes mellitus".) We encourage you to print or e-mail this topic review, or to refer patients to our public web site, www.uptodate.com/patients, which includes this and other topics.

SUMMARY AND RECOMMENDATIONS

- In the absence of specific contraindications, we suggest metformin as initial therapy in most patients (**Grade 2B**). (See 'Medications for initial therapy' above.) Insulin can also be considered a first-line therapy for all patients with type 2 diabetes, particularly patients presenting with A1C >10 percent, fasting plasma glucose >250 mg/dL (13.9 mmol/l), random glucose consistently >300 mg/dL (16.7 mmol/l), or ketonuria. (See 'Insulin' above and "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**). 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' above and "Metformin in the treatment of diabetes mellitus", section on 'Lactic acidosis'.)

- In the presence of contraindications to metformin, we suggest a shorter-duration sulfonylurea (glipizide) for initial therapy (**Grade 2B**). (See 'Sulfonylureas' 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 'Meglitinides' above and "Management of hyperglycemia in diabetics with end-stage renal disease", section on 'Meglitinides'.)

Another alternative is a thiazolidinedione, which may be considered in patients with lower initial A1C values or if there are specific contraindications to sulfonylureas. If a thiazolidinedione is to be used as initial therapy, pioglitazone is preferred because of the greater concern about atherogenic lipid profiles and a potential increased risk for cardiovascular events with rosiglitazone. (See 'Thiazolidinediones' above and "Thiazolidinediones in the treatment of diabetes mellitus", section on 'cardiovascular effects'.)

Sitagliptin can be considered as monotherapy in patients who are intolerant of or have contraindications to metformin, sulfonylureas, or thiazolidinediones. As an example, sitagliptin might be a good choice as initial therapy in a patient with chronic kidney disease at risk for hypoglycemia. It is however, more expensive and less potent in lowering glycemia than the glinides, such as repaglinide, which can also be used safely in patients with chronic kidney disease.

- 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'.)

- Further adjustments of therapy, which should usually be made no less frequently than every three months, are based upon the A1C result (and the results of home glucose monitoring), aiming for levels as close to the nondiabetic range as possible, and with A1C values >7 percent suggesting need for further adjustments in the diabetic regimen.

- If inadequate control is achieved (A1C remains >7 percent), 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".)

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REFERENCES

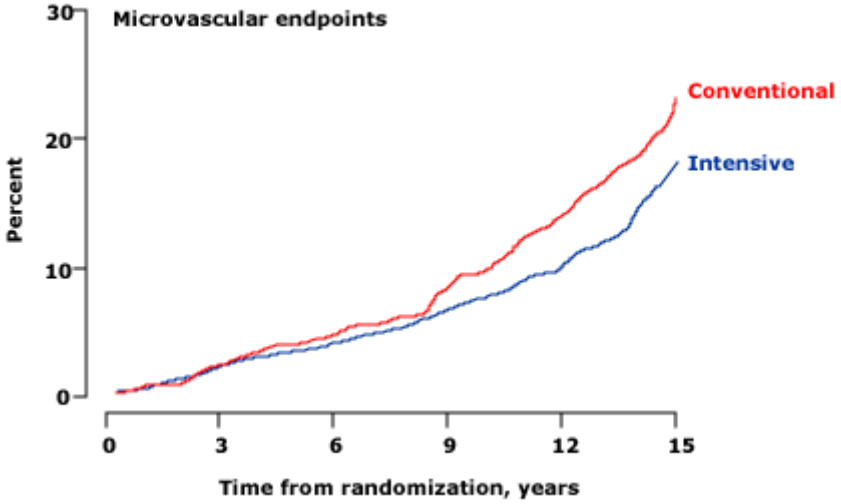
1. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:837.
2. Yki-Järvinen, H. Glucose toxicity. Endocr Rev 1992; 13:415.
3. Kosaka, K, Kuzuya, T, Akanuma, Y, Hagura, R. Increase in insulin response after treatment of overt maturity-onset diabetes is independent of the mode of treatment. Diabetologia 1980; 18:23.
4. 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.
5. Henry, RR, Schaeffer, L, Olefsky, JM. Glycemic effects of intensive caloric restriction and isocaloric refeeding in non-insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1985; 61:917.
6. 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.
7. United Kingdom Prospective Diabetes Study Group. United Kingdom prospective diabetes study group (UKPDS) 13: relative efficacy of randomly allocated diet, sulfonylureas, insulin, or metformin in patients with newly diagnosed non-insulin-dependent diabetes followed for three years. BMJ 1995; 310:83.
8. 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.
9. 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.
10. Hadden, DR, Blair, AL, Wilson, EA, et al. Natural history of diabetes presenting age 40-69 years: a prospective study of the influence of intensive dietary therapy. Q J Med 1986; 59:579.
11. Uusitupa, M, Laitinen, J, Siitonen, O, et al. The maintenance of improved metabolic control after intensified diet therapy in recent type 2 diabetes. Diabetes Res Clin Pract 1993; 19:227.
12. Dixon, JB, O'Brien, PE, Playfair, J, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA 2008; 299:316.
13. Schneider, SH, Khachadurian, AK, Amorosa, LF, et al. Ten-year experience with exercise-based outpatient life-style modification program in the treatment of diabetes mellitus. Diabetes Care 1992; 15:1800.
14. Pi-Sunyer, X, Blackburn, G, Brancati, FL, 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.
15. 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.
16. 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.

17. 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.
18. Colagiuri, S, Cull, CA, Holman, RR. 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.
19. 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. Diabetes Care 2009; 32:193.
20. 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.
21. Bailey, CJ, Turner, RC. Metformin. N Engl J Med 1996; 334:574.
22. Defronzo, R, Goodman, AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med 1995; 333:541.
23. Hermann, LS, Schersten, B, Bitzen, PO, et al. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. Diabetes Care 1994; 17:1100.
24. United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 24: A 6-year randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. Ann Intern Med 1998; 128:165.
25. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:854.
26. Schernthaner, G, Matthews, DR, Charbonnel, B, et al. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. J Clin Endocrinol Metab 2004; 89:6068.
27. Kahn, SE, Haffner, SM, Heise, MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355:2427.
28. Nathan, DM. Thiazolidinediones for initial treatment of type 2 diabetes?. N Engl J Med 2006; 355:2477.
29. Bolen, S, Feldman, L, Vassy, J, et al. Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus. Ann Intern Med 2007; 147:386.

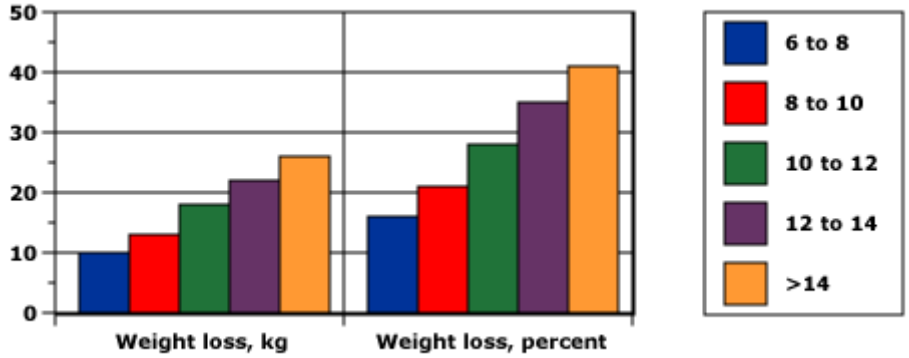
GRAPHICS

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 UK Prospective Diabetes Study, Lancet 1998; 352:837.

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, Metabolism 1990; 39:905.

Summary of glucose-lowering interventions

Intervention	Expected decrease in A1C with monotherapy, percent	Advantages	Disadvantages
Tier 1: well-validated core			
Step 1: initial therapy			
Lifestyle to decrease weight and increase activity	1.0-2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0-2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: additional therapy			
Insulin	1.5-3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Sulfonylurea	1.0-2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
Tier 2: less well validated			
TZDs	0.5-1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5-1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established, expensive
Other therapy			
α-Glucosidase inhibitor	0.5-0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5-1.5*	Rapidly effective	Weight gain, three times/day dosing, hypoglycemia,

			expensive
Pramlintide	0.5-1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
DPP-4 inhibitor	0.5-0.8	Weight neutral	Long-term safety not established, expensive

CHF: congestive heart failure; GI: gastrointestinal; MI: myocardial infarction.
* Repaglinide more effective in lowering A1C than nateglinide.

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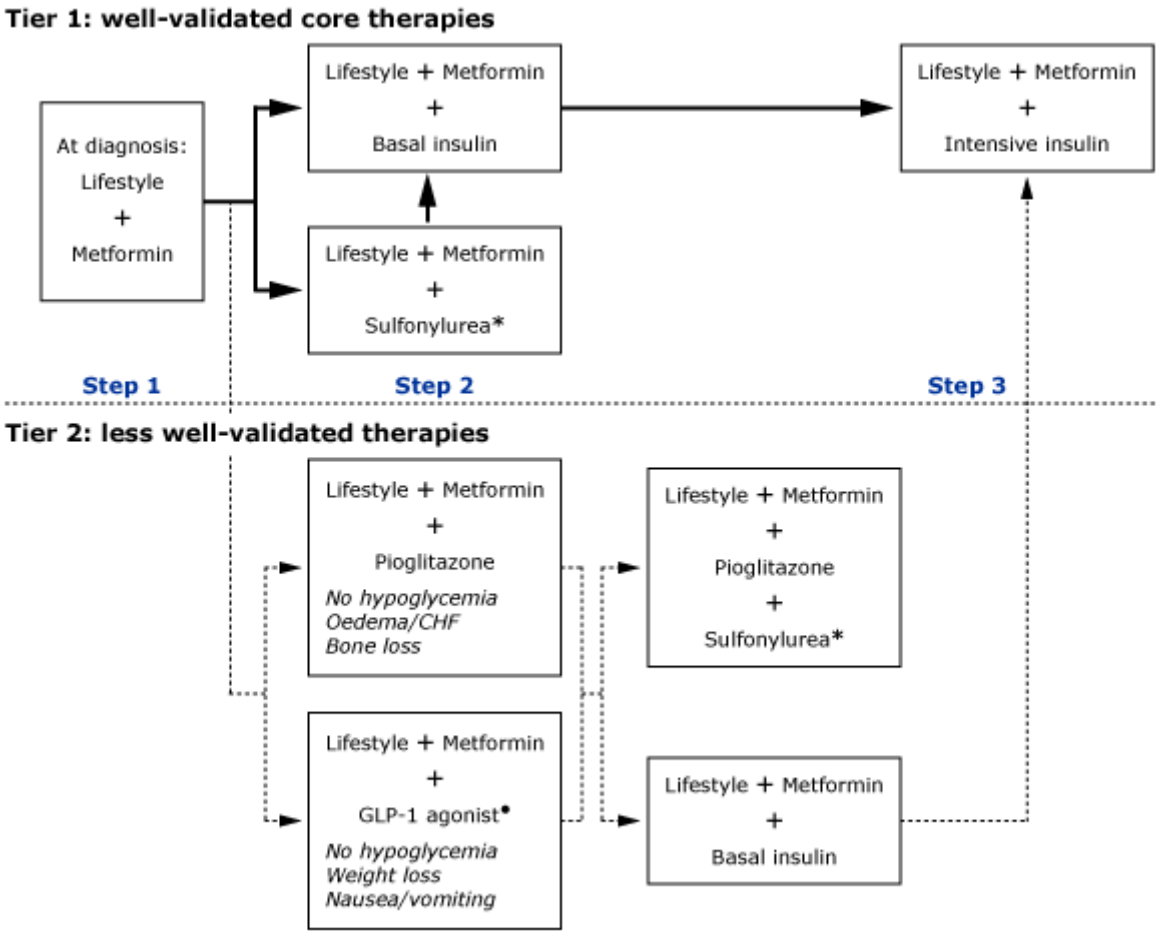
Management type 2 diabetes



Algorithm for the metabolic management of type 2 diabetes; Reinforce lifestyle interventions at every visit and check A1C every 3 months until A1C is <7 percent and then at least every 6 months. The interventions should be changed if A1C is ≥7 percent.

* Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide.

• Insufficient clinical use to be confident regarding safety.

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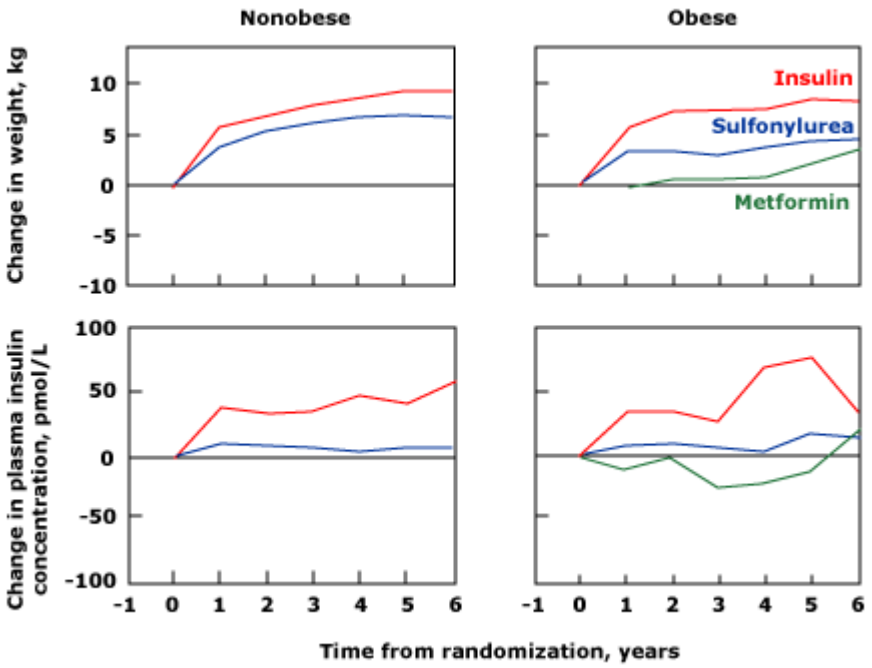
Metabolic effects of drug therapy in type 2 diabetes

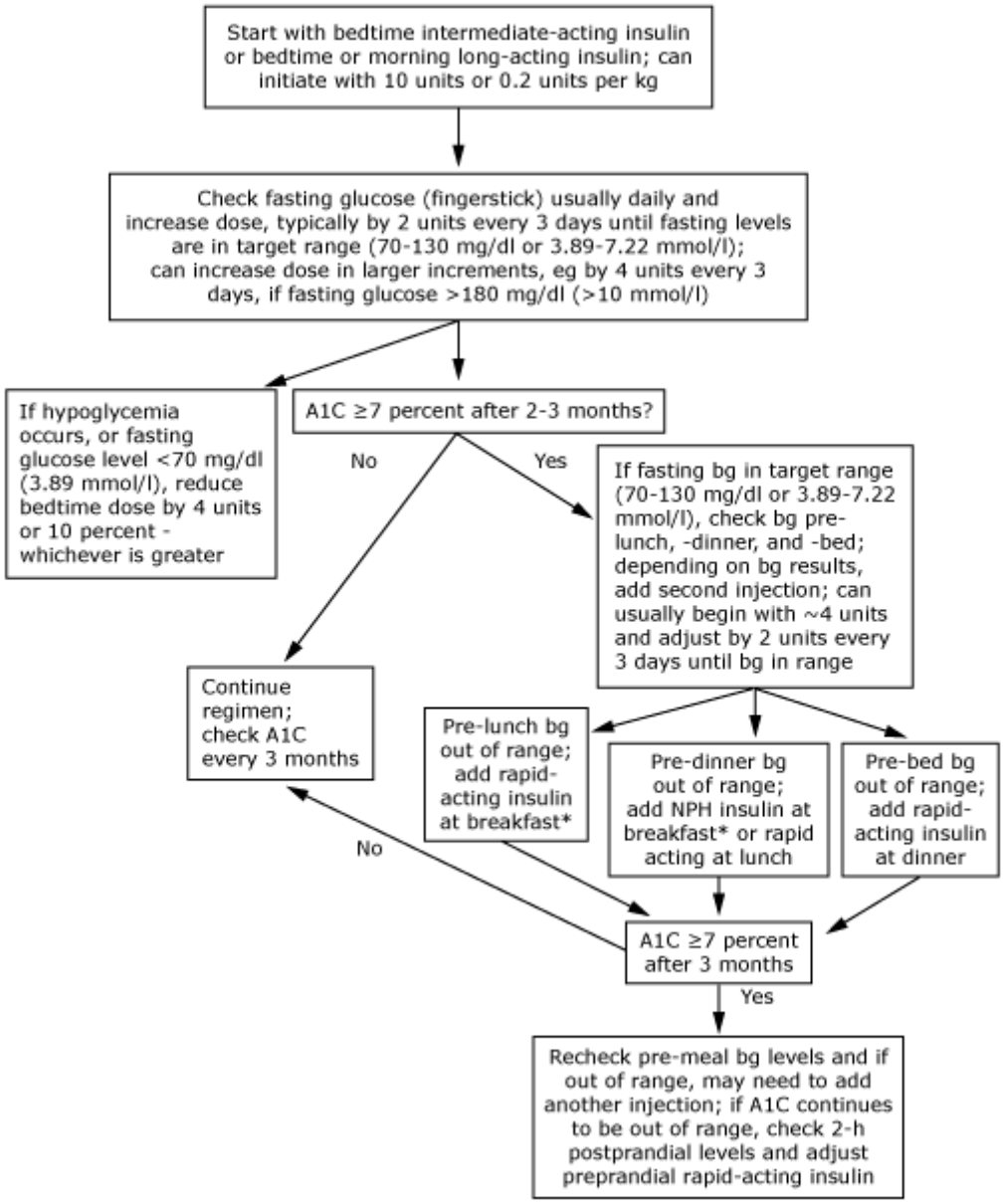


Mean changes in body weight (top) and fasting plasma insulin concentrations (bottom) over six years in patients with type 2 diabetes mellitus in the primary diet failure group who were allocated to therapy with insulin (red), sulfonylurea (blue), or, only in obese subjects, metformin (green). Left panels show data from nonobese patients, right panels show data from obese patients. Metformin did not increase weight or raise plasma insulin. To convert plasma insulin values to µU/mL divide by 6.
Data from United Kingdom Prospective Diabetes Study Group, Ann Intern Med 1998; 128:165.

Sulfonylureas

Drug	Duration of biologic effect, h	Usual daily dose, mg	Dosing per day
First-generation sulfonylureas			
Acetohexamide	12 to 18	500 to 750	Once or divided
Chlorpropamide (Diabinese)	24 to 72	250 to 500	Once
Tolbutamide (Orinase)	14 to 16	1000 to 2000	Once or divided
Second-generation sulfonylureas			
Glipizide	14 to 16	2.5 to 10	Once or divided
(Glucotrol)			
(Glucotrol XL)		5 to 10	Once
Gliclazide	24	40 to 240	Once
(Diamicron R)			
(Diamicron MR)			
Glyburide (Glibenclamide)	20 to 24+	2.5 to 10	Once
(Diabeta)			
(Micronase)			
(Glynase)			
Glimepiride (Amaryl)	24+	2 to 4	Once

Initiation and adjustment of insulin regimens



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.

bg: blood glucose.

* 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.

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