Initial management of hyperglycemia in adults with type 2 diabetes mellitus

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INTRODUCTION

Treatment of patients with type 2 diabetes mellitus includes education, evaluation for micro- and macrovascular complications, attempts to achieve near normoglycemia, minimization of cardiovascular and other long-term risk factors, and avoidance of drugs that can exacerbate abnormalities of insulin or lipid metabolism. All of these treatments and goals need to be tempered based on individual factors, such as age, life expectancy, and comorbidities. Although studies of bariatric surgery, aggressive insulin therapy, and behavioral interventions to achieve weight loss have noted remissions of type 2 diabetes mellitus that may last several years, the majority of patients with type 2 diabetes require continuous treatment in order to maintain target glycemia. Treatments to improve glycemic management work by 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, increasing urinary glucose excretion, or a combination of these approaches. For patients with overweight, obesity, or a metabolically adverse pattern of adipose tissue distribution, body weight management should be considered as a therapeutic target in addition to glycemia.

Methods used to manage 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 general medical care in nonpregnant adults with diabetes mellitus".)

TREATMENT GOALS

Glycemic management — Target glycated hemoglobin (A1C) levels in patients with type 2 diabetes should be tailored to the individual, balancing the anticipated reduction in microvascular complications over time with the immediate risks of hypoglycemia and other adverse effects of therapy. A reasonable goal of therapy is an A1C value of ≤7 percent (53.0 mmol/mol) (calculator 1) for most patients. Glycemic targets are generally set somewhat higher for older adult patients and those with comorbidities or a limited life expectancy who may have little likelihood of benefit from intensive therapy.

Improved glycemic management lowers 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 over the long term with no threshold effect. However, as A1C levels decrease below 7 percent, the absolute risk for microvascular complications becomes low and the incremental benefit of lowering A1C further has diminishing returns. Several randomized clinical trials have demonstrated a beneficial effect of intensive glycemia-lowering therapy on macrovascular outcomes in type 2 diabetes [2,3], with other trials not supporting a significant beneficial effect [4] and one trial suggesting harm [5]. Glycemic goals are discussed in more detail separately. (See "Overview of general medical care in nonpregnant adults with diabetes mellitus", section on 'Glycemic management' and "Treatment of type 2 diabetes mellitus in the older patient", section on 'Controlling hyperglycemia' and "Glycemic control and vascular complications in type 2 diabetes mellitus", section on 'Choosing a glycemic target'.)

Cardiovascular risk factor management — In addition to glycemic management, vigorous cardiac risk reduction (smoking cessation; blood pressure control; reduction in serum lipids with a statin; diet, exercise, and weight loss or maintenance; and aspirin for those with established atherosclerotic cardiovascular disease [ASCVD] or after shared decision-making) should be a top priority for all patients with type 2 diabetes. However, in

spite of evidence that aggressive multifactor risk reduction lowers the risk of both micro- and macrovascular complications in patients with diabetes [6,7], a minority of adults with diabetes fully achieve recommended goals for A1C, blood pressure control, and management of dyslipidemia [8]. (See "Overview of general medical care in nonpregnant adults with diabetes mellitus", section on 'Aspirin' and "Treatment of hypertension in patients with diabetes mellitus" and "Low-density lipoprotein cholesterol-lowering therapy in the primary prevention of cardiovascular disease" and "Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease" and "Overview of general medical care in nonpregnant adults with diabetes mellitus", section on 'Multifactorial risk factor reduction'.)

DIABETES EDUCATION

Patients with newly diagnosed diabetes should participate in a comprehensive diabetes self-management education program, which includes individualized 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 [9]. In two meta-analyses, use of mobile phone interventions for diabetes education was successful in significantly reducing A1C (-0.5 percentage points) [10,11].

Medical nutrition therapy — Medical nutrition therapy (MNT) is the process by which a 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 all patients, the goals of MNT include avoidance of weight gain, consistency in day-to-day carbohydrate intake at meals and snacks, and balanced nutritional content. MNT may be customized to achieve body weight reduction and is reviewed in detail elsewhere. (See 'Diet' below and "Nutritional considerations in type 2 diabetes mellitus".)

Weight management — For patients with type 2 diabetes, body weight management should be considered as a therapeutic target in addition to glycemia. Patients should receive counseling regarding changes in diet and physical activity to achieve weight loss or to prevent weight gain. Weight loss improves glycemia through mitigation of insulin resistance and impaired beta cell function, two major metabolic perturbations evident in type 2 diabetes [12,13]. For patients who have difficulty achieving weight loss, weight

maintenance (rather than gain) is an alternative goal.

Strategies for weight management include lifestyle change, pharmacologic therapy, and metabolic surgery. Lifestyle change includes diet and physical activity, as well as behaviors that facilitate these changes, and is an essential component of any weight management plan. We emphasize lifestyle change as our initial approach to body weight reduction and reserve pharmacotherapy and metabolic surgery for patients who do not achieve targeted weight loss with lifestyle change alone. We tailor our specific recommendations to patients' goals and preferences and encourage "intensive" lifestyle modification, where available, for highly motivated patients.

Diet — Diagnosis of type 2 diabetes is often a powerful motivator for lifestyle change. Dietary modification is a highly effective strategy for weight loss and for management of glycemia and hypertension in patients who are willing to commit to it, with metabolic benefit likely outlasting the effect of weight loss per se. The improvement in glycemia is related both to the degree of caloric restriction and weight reduction [12,14,15]. Body weight loss of 5 to 10 percent may also improve nonalcoholic steatohepatitis, sleep apnea, and other comorbidities of type 2 diabetes [16]. Consumption of sugar-sweetened beverages, including natural fruit juice, should be specifically queried and strongly discouraged in order to manage glycemia, weight, and reduce risk for CVD and fatty liver [17]. (See "Nutritional considerations in type 2 diabetes mellitus", section on 'Designing a nutrition care plan' and "Management of nonalcoholic fatty liver disease in adults", section on 'Initial lifestyle interventions'.)

In the DiRECT trial, which included patients with type 2 diabetes (duration <6 years) and not treated with insulin at baseline, intensive clinician-supervised caloric restriction (carried out in the primary care setting and including total meal replacement for the first 3 to 5 months) resulted in weight loss of at least 15 kg in 24 percent of patients (compared with no patients in the control group) and diabetes remission at one year in 46 percent of patients, compared with 4 percent in the control group [15]. Remission rates were associated with the magnitude of weight loss, increasing from 7 to 86 percent as weight loss increased from <5 to >15 percent. In a two-year analysis of the DiRECT trial, only 11 percent of intervention participants had weight loss of 15 kg or more compared with 24 percent in the one-year analysis [18]. However, 36 percent of participants maintained diabetes remission, compared with 3 percent of control patients.

Despite the clear benefit of weight loss, only a small percentage of patients with type 2

diabetes are able to achieve and maintain substantial weight loss (body weight loss ≥15 percent) [12,19,20]. 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 [21]. 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 targeted solely for weight management is effective in patients with type 2 diabetes. Although metformin is usually started for the management of hyperglycemia, it is also frequently an effective medication to promote modest weight loss. When additional body weight reduction is a primary goal of therapy, we choose medications that promote weight loss and lower glucose. Glucagon-like peptide 1 (GLP-1) receptor and dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) agonist therapies promote weight loss and help prevent weight gain due to other glucose-lowering pharmacotherapies. We add these medications sequentially to metformin if additional glucose lowering or weight loss is a treatment goal. (See "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus" and "Obesity in adults: Drug therapy", section on 'GLP-1 receptor agonists'.)

Surgical therapy — Weight loss surgery in patients with obesity and type 2 diabetes results in the largest degree of sustained weight loss and, in parallel, improvements in blood glucose management and the most frequent sustained remissions of diabetes. Weight loss surgery is an option to treat poorly managed type 2 diabetes when other modalities have failed. This topic is reviewed in detail separately. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Bariatric (metabolic) surgery'.)

Exercise — Regular exercise is beneficial in type 2 diabetes, independent of weight loss. It leads to improved glycemic management due to increased responsiveness to insulin; it can also delay the progression of impaired glucose tolerance to overt diabetes [22,23]. These beneficial effects are directly due to exercise, but concurrent weight reduction plays a contributory role. In one study, however, only 50 percent of patients with type 2 diabetes were able to maintain a regular exercise regimen [24]. (See "Exercise guidance in adults with diabetes mellitus".)

- **Aerobic exercise** – Adults with diabetes are encouraged to decrease sedentary time and 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, spread over at least three days per week, with no more than two consecutive days without exercise). Shorter-duration, intensive exercise may be appropriate for physically fit individuals [25].

- **Resistance training** – 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.

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 management while, at the same time, reducing the need for glucose-lowering and other medications [15,18,26-29].

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 targeting individual weight loss goal of 10 percent or standard diabetes education [30]. 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 [26]. 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) [26].

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) in the standard diabetes education arm, enrollment of a relatively healthy patient population, 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, or the absence of a causal role of weight loss on cardiovascular disease (CVD) [31]. A sustained weight loss of greater than that achieved in the trial may be required to reduce the risk of CVD. In an observational post hoc analysis of the Look AHEAD trial, weight loss of 10 percent or greater in the first year was associated with a reduction in the primary outcome (1.43 events compared with 1.69 events per person-years in the group with stable weight, hazard ratio [HR] 0.79, 95% CI 0.64-0.98) [32]. However, this post hoc analysis is problematic. Moreover, the degree of weight loss is difficult to achieve and maintain through lifestyle intervention alone. Weight loss, weight loss maintenance, and exercise remain important components of diabetes management due to overall health benefits.

The following summarizes several other major observations from the Look AHEAD trial [26,30,33-40]:

- 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 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 management 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 medications to manage glycemia, blood pressure, and lipids (including statins) was lower in the intervention group.
- The intensive lifestyle intervention reduced albuminuria.
- 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.

Psychological interventions — Patients with type 2 diabetes often experience significant stress, a condition often called diabetes distress, related to the many self-care responsibilities required for glycemic management (lifestyle modifications, medication, and self-monitoring of blood glucose [SMBG]) [41]. Concurrent depression similarly may interfere with self-care. (See "Overview of general medical care in nonpregnant adults with diabetes mellitus", section on 'Comorbid conditions'.)

Psychotherapy reduces psychological distress and improves glycemic management in some [42,43], but not all [44], 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]) [42]. Measures of psychological distress were also significantly lower in the intervention group, but there were no differences in weight management.

Pregnancy planning — All women of childbearing age with diabetes should be counseled about the potential effects of diabetes and commonly used medications on maternal and fetal outcomes and the potential impact of pregnancy on their diabetes management and any existing complications. (See "Pregestational (preexisting) diabetes: Preconception counseling, evaluation, and management".)

INITIAL PHARMACOLOGIC THERAPY

When to start — Early institution of treatment for diabetes, at a time when the A1C is not substantially elevated, is associated with improved glycemic management over time and decreased long-term complications [45]. Pharmacologic therapy should be initiated along with consultation for lifestyle modification focusing on dietary and other lifestyle contributors to hyperglycemia. Weight loss and weight loss maintenance underpins all effective type 2 diabetes therapy, and lifestyle change reduces the risk of weight gain associated with sulfonylureas and insulin.

- 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 type 2 diabetes diagnosis (with lifestyle modification). However, for those patients who have clear and modifiable contributors to hyperglycemia and who are motivated to change them (eg, commitment to reduce consumption of sugar-sweetened beverages), a three-month trial of lifestyle modification prior to initiation of pharmacologic therapy is warranted.

- 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 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, comorbidities, baseline A1C level), individualized treatment goals and preferences, the glucose-lowering efficacy of individual drugs, and their adverse effect profile, tolerability, and cost [46]. We prefer initiating a single agent (typically metformin) and then sequentially adding additional glucose-lowering agents as needed, rather than starting with combination therapy [47].

Asymptomatic, not catabolic — The majority of patients with newly diagnosed type 2 diabetes are asymptomatic, without symptoms of catabolism (eg, without polyuria, polydipsia, or unintentional weight loss). Hyperglycemia may be noted on routine

laboratory examination or detected by screening.

Metformin — In the absence of specific contraindications, we suggest metformin as initial therapy for patients with newly diagnosed type 2 diabetes who are asymptomatic. 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 tolerated to reach a total dose of 2000 mg per day. (See 'When to start' above and "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Dosing'.)

Metformin is the preferred initial therapy because of glycemic efficacy (see 'Glycemic efficacy' below), promotion of modest weight loss, very low incidence of hypoglycemia, general tolerability, and favorable cost [46]. Metformin does not have adverse cardiovascular effects, and it appears to decrease cardiovascular events [48-50]. (See "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Cardiovascular effects'.)

Metformin is far less expensive and has more clinical practice experience than glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose co-transporter 2 (SGLT2) inhibitors. Although some guidelines and experts endorse the initial use of these alternative agents as monotherapy or in combination with metformin [47,51], we prefer initiating a single agent (typically metformin) and then sequentially adding additional glucose-lowering agents as needed, rather than starting with combination therapy. In the clinical trials that demonstrated the protective effects of GLP-1 receptor agonists and SGLT2 inhibitors, these agents were added to background metformin therapy in most participants. Further, the cardiorenal benefits of GLP-1 receptor agonists and SGLT2 inhibitors have not been demonstrated in drug-naïve patients without established CVD (or at low cardiovascular risk) or without severely increased albuminuria. Although each diabetes medication is associated with adverse events, metformin is associated with less weight gain and fewer episodes of hypoglycemia compared with sulfonylureas, and with less edema, heart failure (HF), and weight gain compared with thiazolidinediones. (See "Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus", section on 'Cardiovascular effects' and "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Cardiovascular effects'.)

Although virtually all recommendations for initial pharmacologic therapy (outside of China,

where alpha-glucosidase inhibitors are recommended as an alternate first-line monotherapy [52]) endorse use of metformin, there are, in fact, relatively few relevant direct comparative effectiveness data available.

Contraindications to or intolerance of metformin — For patients who have gastrointestinal intolerance of metformin, slower titration, ensuring that the patient is taking the medication with food, or switching to an extended-release formulation may improve tolerability.

For patients who still cannot tolerate metformin or have contraindications to it, we choose an alternative glucose-lowering medication guided initially by patient comorbidities, and in particular, the presence of atherosclerotic CVD (ASCVD) or albuminuric chronic kidney disease. (See "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Contraindications'.)

Established cardiovascular or kidney disease — Patients with cardiovascular and/or kidney comorbidities (generally a minority of new-onset type 2 diabetes) should be treated with glucose-lowering medications that have evidence of cardiac or kidney benefit. When compared with placebo, the GLP-1 receptor agonists liraglutide, semaglutide, and dulaglutide demonstrated favorable atherosclerotic cardiovascular and kidney outcomes [53-58]. The SGLT2 inhibitors empagliflozin, canagliflozin, and dapagliflozin have also demonstrated benefit, especially for HF hospitalization, risk of kidney disease progression, and mortality [58-63]. The majority of patients in cardiovascular and kidney outcome trials had established CVD or diabetic kidney disease (DKD) with severely increased albuminuria (>300 mg/gm creatinine). Patients at high CVD risk but without a prior event might benefit, but the data are less supportive. Similarly, patients without severely increased albuminuria have some benefit, but the absolute benefits are greater among those with severely increased albuminuria.

To select a medication, we use shared decision-making with a focus on beneficial and adverse effects within the context of the degree of hyperglycemia as well as a patient's comorbidities and preferences. As examples:

- **ASCVD** – For patients in whom ASCVD predominates, particularly in the setting of higher A1C or motivation to lose weight, we typically prescribe liraglutide, subcutaneous semaglutide, or dulaglutide. SGLT2 inhibitors with cardiovascular benefit (empagliflozin or canagliflozin) are good alternatives, especially in the

presence of HF. Given the high cost of these classes of medications, formulary coverage often determines the choice of the first medication within the class. (See "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Cardiovascular effects' and "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Microvascular outcomes'.)

- **HF and/or DKD** – For patients in whom HF or DKD (albuminuria [urine albumin excretion >200 mg/day] and estimated glomerular filtration rate [eGFR] <60 but ≥20 mL/min/1.73 m^2) [64] predominate, we prescribe a low dose of an SGLT2 inhibitor (empagliflozin, canagliflozin, dapagliflozin). Choice of agent is primarily dictated by provider preference, insurance formulary restrictions, eGFR, and cost. In the setting of declining eGFR, the main reason to prescribe SGLT2 inhibitors is to reduce progression of DKD. For the treatment of hyperglycemia, SGLT2 inhibitors are not recommended for initiation with eGFR <30 to 45 mL/min/1.73 m^2, as they have diminishing effects with lower eGFR, with some differences in each medication depending on the labeling. However, kidney and cardiac benefits have been shown in patients with eGFR below this threshold. Dosing in the setting of DKD is reviewed in detail elsewhere. (See "Treatment of diabetic kidney disease", section on 'Type 2 diabetes: Treat with additional kidney-protective therapy'.)

SGLT2 inhibitors generally have low efficacy in reducing A1C levels and have even **less glycemic efficacy with eGFR <45 mL/min/1.73 m^2**. An alternative (or an additional) agent may be necessary to achieve glycemic goals. GLP-1 receptor agonists are an alternative in patients with DKD as their glycemic effect is not related to eGFR. In addition, GLP-1 receptor agonists have been shown to slow the rate of decline in eGFR and prevent worsening of albuminuria. (See 'Microvascular outcomes' below and "Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus" and "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus".)

Of note, we avoid use of SGLT2 inhibitors in patients with frequent bacterial urinary tract infections or genitourinary yeast infections, low bone density and high risk for falls and fractures, foot ulceration, and factors predisposing to diabetic ketoacidosis (eg, pancreatic insufficiency, drug or alcohol abuse disorder) because of increased risk while using these agents. SLGT2 inhibitors should be held for 3 to 4 days before procedures including

colonoscopy preparation and with poor oral intake to prevent diabetic ketoacidosis. (See "Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus", section on 'Contraindications and precautions'.)

In the setting of nondialysis chronic kidney disease stage 4 (eg, eGFR <30 mL/min/1.73 m^2), we prefer a short-acting low-dose sulfonylurea (eg, glipizide), repaglinide, linagliptin, or cautious use of a GLP-1 receptor agonist or insulin. Repaglinide acts at the sulfonylurea receptor to increase insulin secretion but is much shorter acting than sulfonylureas and is principally metabolized by the liver, with less than 10 percent renally excreted. Limited data suggest that dipeptidyl peptidase 4 (DPP-4) inhibitors are effective and relatively safe in chronic kidney disease patients. However, linagliptin is the only DPP-4 inhibitor that does not require a dose adjustment in the setting of kidney failure. GLP-1 receptor agonists may also be used safely in chronic kidney disease stage 4, but patient education for signs and symptoms of dehydration due to nausea or satiety is warranted to reduce the risk of acute kidney injury. Insulin may also be used, with a greater portion of the total daily dose administered during the day due to the risk of hypoglycemia, especially overnight, in chronic kidney disease and end-stage kidney disease (ESKD). (See "Management of hyperglycemia in patients with type 2 diabetes and advanced chronic kidney disease or end-stage kidney disease", section on 'Patients not on dialysis'.)

Without established cardiovascular or kidney disease — For patients without established CVD or kidney disease who cannot take metformin, many other options for initial therapy are available (table 1). We suggest choosing an alternative glucose-lowering medication guided by efficacy, patient comorbidities, preferences, and cost. As examples:

- **A1C >9 percent (>74.9 mmol/mol)** – For patients with A1C levels relatively far from goal (eg, 9 to 10 percent [>74.9 to 85.8 mmol/mol]), we suggest insulin or a GLP-1 receptor agonist for initial therapy.

  Although historically insulin has been used for type 2 diabetes only when inadequate glycemic management 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 management, 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 'Indications for insulin'.)

If type 1 diabetes has been excluded, a GLP-1 receptor agonist is a reasonable alternative to insulin [65,66]. The frequency of injections and proved beneficial effects in the setting of CVD are the major differences among the many available GLP-1 receptor agonists. In practice, given the high cost of this class of medications, formulary coverage often determines the choice of the first medication within the class. Cost and insurance coverage may limit accessibility and adherence. (See "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Patient selection'.)

- **A1C ≤9 percent** – For patients with A1C levels ≤9 percent, options (in addition to insulin or GLP-1 receptor agonists) include sulfonylureas, SGLT2 inhibitors, DPP-4 inhibitors, repaglinide, or pioglitazone. Each one of these choices has individual advantages, benefits, and risks (table 1). (See "Sulfonylureas and meglitinides in the treatment of type 2 diabetes mellitus" and "Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus", section on 'Patient selection' and "Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus", section on 'Patient selection' and "Thiazolidinediones in the treatment of type 2 diabetes mellitus", section on 'Potential indications'.)

  - **Weight management** – If weight management is a priority, GLP-1 receptor agonists or SGLT2 inhibitors may be preferred. (See "Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus", section on 'Weight loss' and "Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus", section on 'Patient selection' and "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Weight loss'.)

  - **Cost concerns** – If cost is the predominant concern, a short- or intermediate-acting sulfonylurea, such as glipizide or glimepiride, remains a reasonable alternative. The choice of sulfonylurea balances glucose-lowering efficacy, universal availability, and low cost with risk of hypoglycemia and weight gain. Pioglitazone, which is generic and another relatively low-cost oral agent, may also be considered in patients with specific contraindications to metformin and sulfonylureas. However, the risk of weight gain, HF, fractures, and the potential

increased risk of bladder cancer raise the concern that the overall risks and cost of pioglitazone may approach or exceed its benefits. (See "Sulfonylureas and meglitinides in the treatment of type 2 diabetes mellitus" and "Thiazolidinediones in the treatment of type 2 diabetes mellitus", section on 'Potential indications'.)

For patients who are starting 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. Side effects may be minimized with diabetes self-management education focusing on medication reduction or omission with changes in diet, food accessibility, or activity that may increase the risk of hypoglycemia.

- **Risk of hypoglycemia** – If avoidance of hypoglycemia is a priority (ie, because of potentially dangerous work), GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, or pioglitazone are options as they are associated with a low hypoglycemia risk. (See "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Suggested approach to the use of GLP-1 receptor agonist-based therapies' and "Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus", section on 'Mechanism of action' and "Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus", section on 'Mechanism of action' and "Thiazolidinediones in the treatment of type 2 diabetes mellitus", section on 'Hypoglycemia'.)

Symptomatic (catabolic) 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 >10 [85.8 mmol/mol]), depending on the severity of the baseline metabolic disturbance. If patients have been drinking a substantial quantity of sugar-sweetened beverages, reduction of carbohydrate intake, and rehydration with sugar-free fluids will help to reduce glucose levels within several days.

- **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. Insulin should also be initiated whenever there is a possibility of undiagnosed type 1 diabetes, which should be suspected among those who are lean or present with marked catabolic symptoms, especially in the presence of a personal or family history of other autoimmune disease and/or the absence of a family history of type 2 diabetes. (See "Insulin therapy in type 2 diabetes mellitus", section on 'Initial treatment'.)

- **Ketonuria and 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 percent [74.9 mmol/mol]) but without ketonuria or spontaneous weight loss, in whom type 1 diabetes is not likely, insulin or GLP-1 receptor agonists may be used (with or without metformin, depending on contraindications or intolerance).

  However, for patients who are injection averse, initial therapy with high-dose sulfonylurea is an alternative option. High-dose sulfonylureas are effective in rapidly reducing hyperglycemia in patients with severe hyperglycemia [67]. 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 potentially discontinued.

- **Dosing**

  - Insulin therapy in type 2 diabetes is initially aimed at suppressing hepatic gluconeogenesis by increasing basal insulin to target morning fasting glucose levels (algorithm 1). Patients with type 2 diabetes require relatively high 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".)

  - GLP-1 receptor agonists are started at the lowest dose per product labeling and increased after several days to weeks as tolerated based on labeling and gastrointestinal symptoms. (See "Glucagon-like peptide 1-based therapies for the

treatment of type 2 diabetes mellitus", section on 'Administration'.)

- 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 (or, where available, gliclazide immediate-release 80 mg daily). We contact the patient every few days after initiating therapy to make dose adjustments (increase dose if hyperglycemia does not improve or decrease dose if hyperglycemia resolves quickly or hypoglycemia develops). (See "Sulfonylureas and meglitinides in the treatment of type 2 diabetes mellitus", section on 'Sulfonylureas'.)

Glycemic efficacy — The use of metformin as initial therapy is supported by meta-analyses of trials and observational studies evaluating the effects of oral or injectable diabetes medications as monotherapy on intermediate outcomes (A1C, body weight, lipid profiles) and adverse events [50,68-70]. In a network meta-analysis of 134 trials evaluating monotherapy in drug-naïve patients, all treatments reduced A1C compared with placebo (reductions in A1C ranged from -0.6 to -1.48 percentage points) [70]. Most medications used as monotherapy 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 [50,68-70].

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 the thiazolidinedione rosiglitazone, metformin, or glyburide [71]. 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 modest 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 [72]. (See "Thiazolidinediones in the

treatment of type 2 diabetes mellitus", section on 'Safety'.)

Cardiovascular outcomes — Cardiovascular benefit has been demonstrated for selected classes of diabetes medications, usually when added to metformin. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Monotherapy failure'.)

The cardiovascular effects of diabetes drugs are reviewed in the individual topics. (See "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Cardiovascular effects' and "Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus", section on 'Cardiovascular effects' and "Sulfonylureas and meglitinides in the treatment of type 2 diabetes mellitus", section on 'Cardiovascular effects' and "Thiazolidinediones in the treatment of type 2 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' and "Insulin therapy in type 2 diabetes mellitus", section on 'Cardiovascular effects'.)

Microvascular outcomes — In trials designed to evaluate kidney outcomes in patients with DKD and severely increased albuminuria (eg, eGFR 25 to <90 mL/min/1.73 m^2 **and** with urine albumin-to-creatinine ratio [ACR] 200 up to 5000 mg/g, median 927 to 950 mg/g]), SGLT2 inhibitors reduced the risk of kidney disease progression and death from kidney disease [59,63]. In trials of patients with type 2 diabetes with and without chronic kidney disease, GLP-1 receptor agonists slowed the rate of decline in eGFR and prevented worsening of albuminuria [53,55,57]. These trials and other trials evaluating microvascular outcomes are reviewed in the individual topics.

Guidelines — Our approach is largely consistent with American and European guidelines [51,73,74]. 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, with the most recent revision published in 2022 [74].

The guidelines emphasize the importance of individualizing the choice of medications for the treatment of diabetes, considering important comorbidities (CVD, HF, or chronic kidney disease; hypoglycemia risk; and need for weight loss) and patient-specific factors (including patient preferences, values, and cost) [74].

The ADA/EASD recommends a patient-centered approach, starting with lifestyle and

diabetes self-management education and support, shared decision-making to select medications, and letting the choice be guided by CVD, similar to the approach outlined here. We also agree with the World Health Organization (WHO) that sulfonylureas have a long-term safety profile, are inexpensive, and are highly effective, especially when used as described above, with patient education and dose adjustment to minimize side effects [75].

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 diabetes patients who use the results to modify eating patterns, exercise, or insulin doses on a regular basis. (See "Glucose monitoring in the ambulatory management of nonpregnant adults with diabetes mellitus", section on 'Type 2 diabetes'.)

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 management 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 'Our approach'.)

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: Type 2 diabetes: Overview (Beyond the Basics)" and "Patient education: Type 2 diabetes: Treatment (Beyond the Basics)" and "Patient education: Glucose monitoring in diabetes (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Comprehensive diabetes education** – All patients with newly diagnosed diabetes should participate in a comprehensive diabetes self-management education program, which includes instruction on nutrition and eating pattern, physical activity, optimizing metabolic control, and preventing complications. Weight reduction through diet, exercise, and behavioral modification can all be used to improve glycemic management, although the majority of patients with type 2 diabetes will require medication. (See 'Diabetes education' above.)
- **Glycemic goals** – Target glycated hemoglobin (A1C) levels in patients with type 2 diabetes should be tailored to the individual, balancing the anticipated reduction in microvascular complications over time with the immediate risks of hypoglycemia and other adverse effects of therapy. A reasonable goal 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 adults and for those with comorbidities or a limited life expectancy and little likelihood of benefit from intensive therapy. (See 'Glycemic management' above and "Glycemic control and vascular complications in type 2 diabetes mellitus", section on 'Choosing a glycemic target'.)

- **Asymptomatic, not catabolic** – The majority of patients with newly diagnosed type 2 diabetes are asymptomatic, without symptoms of catabolism (eg, without polyuria, polydipsia, or unintentional weight loss).

  - **Initial treatment with metformin** – There are many pharmacologic options to treat diabetes (table 1). In the absence of specific contraindications, we suggest metformin as initial therapy for most patients (**Grade 2B**). Although some guidelines and experts endorse the initial use of alternative agents as monotherapy or in combination with metformin, we prefer initiating a single agent (typically metformin) and then sequentially adding additional glucose-lowering agents as needed. (See 'Metformin' above and 'Glycemic efficacy' above.)

    We suggest initiating metformin at the time of diabetes diagnosis (**Grade 2C**), along with consultation for lifestyle intervention. However, for those patients who have clear and modifiable contributors to hyperglycemia and who are motivated to change them (eg, commitment to reduce consumption of sugar-sweetened beverages) or an A1C near target (ie, <7.5 percent), a three- to six-month trial of lifestyle modification prior to initiation of pharmacologic therapy is reasonable. (See 'When to start' above.)

    The dose of metformin should be titrated to its maximally effective dose (usually 2000 mg per day in divided doses) over one to two months, as tolerated. Metformin should not be administered when estimated glomerular filtration rate (eGFR) is <30 mL/min/1.73 m^2 or conditions otherwise predisposing to lactic acidosis are present. (See "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Contraindications'.)

  - **Contraindications to metformin** – In the presence of contraindications to metformin, we choose an alternative glucose-lowering medication guided by patient comorbidities, preferences, and cost (table 1). (See 'Contraindications to or intolerance of metformin' above.)

- **Existing cardiovascular and/or kidney comorbidities** – For patients with cardiorenal comorbidities who cannot take metformin, we suggest a glucagon-like peptide 1 (GLP-1) receptor agonist (liraglutide, subcutaneous semaglutide, or dulaglutide) or a sodium-glucose co-transporter 2 (SGLT2) inhibitor (empagliflozin, canagliflozin, dapagliflozin) that has demonstrated cardiorenal benefit (**Grade 2B**). To select a medication, we use shared decision-making with a focus on beneficial and adverse effects within the context of the degree of hyperglycemia as well as a patient's comorbidities and preferences. (See 'Established cardiovascular or kidney disease' above.)

  The majority of patients in the cardiovascular and renal outcomes trials had established cardiovascular disease (CVD) or diabetic kidney disease (DKD) with severely increased albuminuria, and therefore, these are the primary indications for one of these drugs. Patients at high CVD risk but without a prior event might benefit, but the data are less supportive. Similarly, patients without severely increased albuminuria have some benefit, but the absolute benefits are greater among those with severely increased albuminuria.

- **Absence of ASCVD, heart failure (HF), or DKD**

  For patients without cardiorenal disease, and **with A1C levels relatively far from goal (eg, >9 percent** [74.9 mmol/mol], without suspected type 1 diabetes), we suggest insulin or a GLP-1 receptor agonist for initial therapy (**Grade 2B**). (See 'Without established cardiovascular or kidney disease' above.)

  For similar patients **but with A1C levels ≤9 percent**, options (in addition to insulin or GLP-1 receptor agonists) include sulfonylureas, SGLT2 inhibitors, dipeptidyl peptidase (DPP-4) inhibitors, repaglinide, or pioglitazone. Each one of these choices has individual advantages and risks (table 1). Choice of medication is guided by efficacy, patient comorbidities, preferences, and cost. Sulfonylureas remain a highly effective treatment for hyperglycemia, particularly when cost is a barrier. Side effects of hypoglycemia and weight gain can be mitigated with careful dosing and diabetes self-management education. (See 'Without established cardiovascular or kidney disease' above.)

- **Symptomatic or severe hyperglycemia** – For patients presenting with symptomatic

(eg, weight loss) or severe hyperglycemia with ketonuria, insulin is indicated for initial treatment. 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 percent [74.9 mmol/mol]) but without ketonuria or spontaneous weight loss, in whom type 1 diabetes is not likely, we suggest insulin or a GLP-1 receptor agonist (**Grade 2B**). For patients who are injection averse, initial therapy with high-dose sulfonylurea is an alternative, particularly for patients who have been consuming large amounts of sugar-sweetened beverages, in whom elimination of carbohydrates can be anticipated to cause a reduction in glucose within several days. (See 'Symptomatic (catabolic) or severe hyperglycemia' above and "Insulin therapy in type 2 diabetes mellitus".)

- **Monitoring** – 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 self-monitoring of blood glucose [SMBG]). (See 'Monitoring' above.)

  If glycemia is not optimally managed (A1C remains >7.0 percent [53.0 mmol/mol] or an alternative patient-specific target level), 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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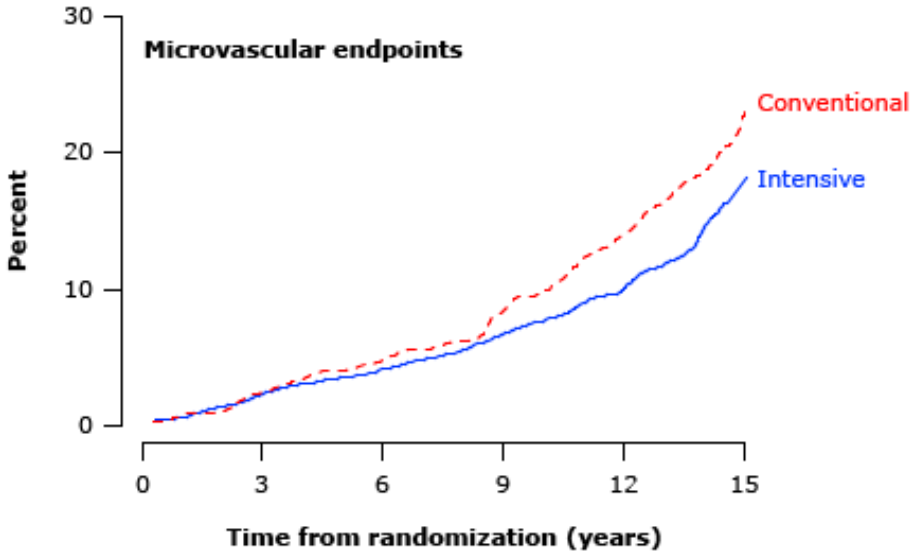
Topic 1779 Version 72.0

GRAPHICS

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

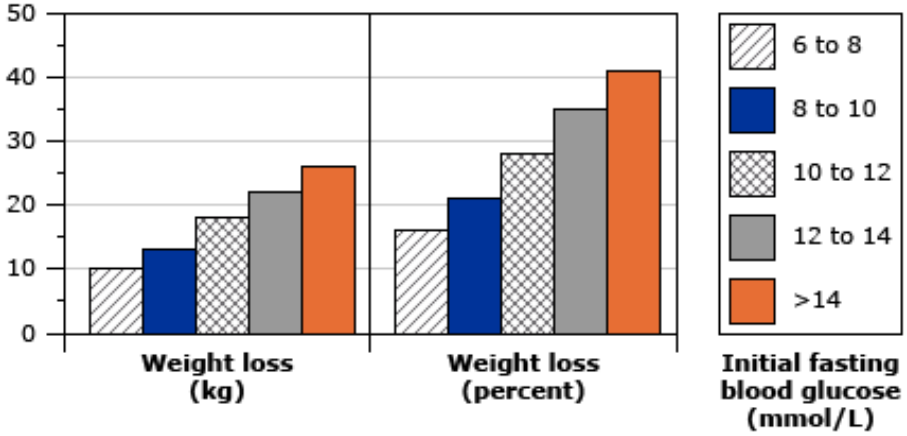


Kaplan-Meier plots of aggregate endpoints of microvascular disease in patients with type 2 diabetes mellitus in the United Kingdom Prospective Diabetes Study who were randomly assigned to receive either intensive therapy with a sulfonylurea or insulin, or to conventional treatment with diet; drugs were 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% 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.

Graphic 52273 Version 4.0

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.

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Summary of glucose-lowering interventions

Intervention	Expected decrease in A1C with monotherapy (%)	Advantages	Disadvantages
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	1.0 to 2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency (eGFR <30 mL/min/1.73 m^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	1 to 4 injections daily, monitoring, weight gain, hypoglycemia, analogs are expensive
Sulfonylurea (shorter-acting agents preferred)	1.0 to 2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
GLP-1 receptor agonist (daily to weekly injections)	0.5 to 1.5	Weight loss, reduction in major adverse cardiovascular events (liraglutide, semaglutide, dulaglutide) in patients with established CVD and	Requires injection, frequent GI side effects, expensive

		potentially for those at high risk for CVD	
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[Δ]	Rapidly effective	Weight gain, 3 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, improved renal outcomes in patients with nephropathy	Vulvovaginal candidiasis, urinary tract infections, bone fractures, lower limb amputations, DKA
DPP-4 inhibitor	0.5 to 0.8	Weight neutral	Possible increased risk of HF with saxagliptin, expensive
Alpha-glucosidase inhibitor	0.5 to 0.8	Weight neutral	Frequent GI side effects, 3 times/day dosing
Pramlintide	0.5 to 1.0	Weight loss	3 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 peptide-1; CVD: cardiovascular disease; MI: myocardial infarction; HF: heart failure; SGLT: sodium-glucose co-transporter 2; DKA: diabetic ketoacidosis; DPP-4: dipeptidyl peptidase 4.

* Initiation is contraindicated with eGFR <30 mL/min/1.73 m^2 and not recommended with

eGFR 30 to 45 mL/min/1.73 m^2.

¶ The order of listing of additional therapies does not indicate a preferred order of selection. The choice of additional therapy should be based on criteria discussed in the UpToDate topics on the management of hyperglycemia in diabetes mellitus.

Δ 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 Association.

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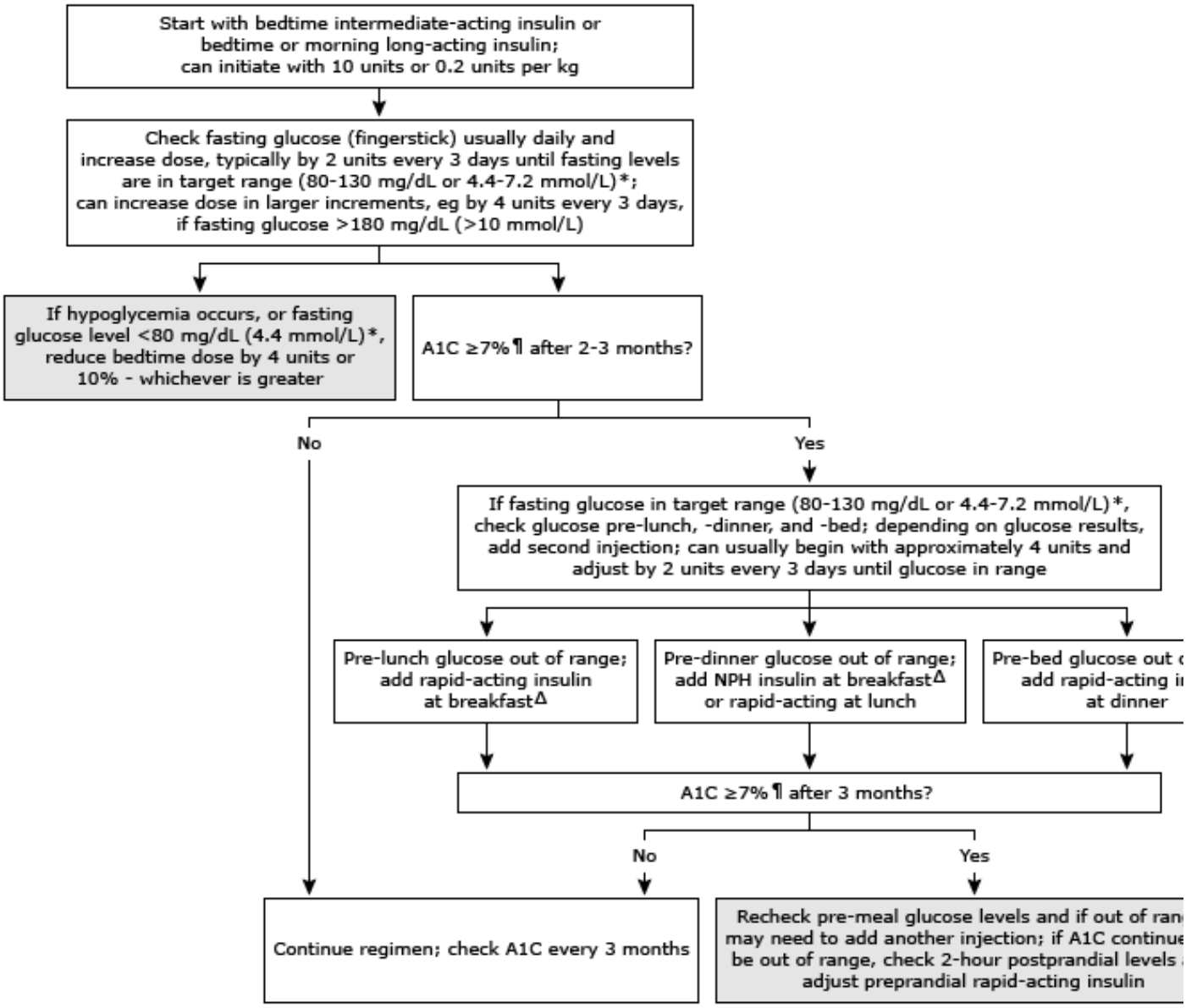
Initiation and adjustment of insulin regimens in type 2 diabetes mellitus



Insulin regimens should be designed taking lifestyle and meal schedule into account. The algorithm ca
provide basic guidelines for initiation and adjustment of insulin. Many different approaches are possib

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A1C: glycated hemoglobin.
* Glucose levels updated with data from: American Diabetes Association. Glycemic Targets. Diabetes C
2016; 39 Suppl 1:S39.
¶ The A1C goal should be individualized in accordance with patient age, comorbidities, and life expect
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-acting and intermediate-ac
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 Dia

Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Associatio the European Association for the Study of Diabetes. Diabetes Care 2009; 32:193. Copyright © 2009 American Diabetes Associat

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Contributor Disclosures

Deborah J Wexler, MD, MSc Consultant/Advisory Boards: Novo Nordisk – Data Monitoring Committee [Cardiovascular and renal outcome trials]. All of the relevant financial relationships listed have been mitigated. **David M Nathan, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Katya Rubinow, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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