CLINICAL PRACTICE

Glycemic Management of Type 2 Diabetes Mellitus

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 39-year-old man with a 2-year history of type 2 diabetes mellitus presents for care. He has no microvascular or macrovascular complications. His family history is positive for type 2 diabetes and cardiovascular disease in his mother and older brother. On examination, his weight is 99.8 kg (220 lb), with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 37, and his blood pressure is 125/85 mm Hg. His glycated hemoglobin level is 8.9%, serum creatinine level 1.0 mg per deciliter (88.4 μmol per liter), low-density lipoprotein (LDL) cholesterol 88 mg per deciliter (2.3 mmol per liter), high-density lipoprotein (HDL) cholesterol 45 mg per deciliter (1.2 mmol per liter), and triglyceride level 130 mg per deciliter (1.5 mmol per liter); he does not have microalbuminuria. His medications include metformin (500 mg twice daily), glipizide (5 mg twice daily), simvastatin (20 mg daily), and lisinopril (10 mg daily). What would you recommend to improve his glycemic control?

THE CLINICAL PROBLEM

Type 2 diabetes is the leading cause of blindness, nontraumatic lower-limb amputation, and chronic kidney disease in the United States. It is a major cause of cardiovascular disease, leading to early death.[1] According to the Centers for Disease Control and Prevention, the number of persons with type 2 diabetes in the United States will more than triple by 2050 from the current estimate of 26 million.[2] The increasing incidence of type 2 diabetes is largely attributable to changes in lifestyle (diet and activity levels) and obesity.[1,2] The problem is global, affects affluent and lower-income societies,[3] has substantial adverse effects on health status and life span, and carries high societal costs. Commonly associated metabolic abnormalities include hypertension, dyslipidemia, inflammation, hypercoagulation, and endothelial-cell dysfunction.[4,5]

Type 2 diabetes is a chronic, progressive, and incompletely understood metabolic disease defined by the presence of chronic hyperglycemia.[6] Although resistance to some actions of insulin and inadequate secretion of insulin for the given metabolic state are the critical abnormalities in type 2 diabetes, several other factors contribute to the hyperglycemic state (Fig. 1). Insulin resistance is typically present for some years before diagnosis, manifested as diminished stimulation of glucose transport in muscle and adipose tissue and inadequate suppression of glucose production in the liver in response to insulin. However, euglycemia is maintained as long as beta cells secrete higher amounts of insulin.[5] Over time, insulin levels decline because of the decreased number of beta cells and their diminished secretory capacity.[5,7,8] Longitudinal studies involving Pima Indians[9] and other populations[10] have shown a 50% or greater decrease in maximal beta-cell function at diagnosis.[5] Abnormal

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KEY CLINICAL POINTS

GLYCEMIC CONTROL IN TYPE 2 DIABETES MELLITUS

- Intensive glycemic control reduces the risk of microvascular complications of type 2 diabetes, but the effect of strict glycemic control on the risk of macrovascular disease (especially in well-established type 2 diabetes) is less certain.
- Psychosocial factors (e.g., motivation and capacity for self-care) and clinical factors (e.g., age, presence or absence of coexisting conditions, and presence or absence of a tendency toward hypoglycemia) should be considered in setting a target range of glycated hemoglobin for an individual patient.
- A near-normal glycemic target range (6.0 to 6.5%), if implemented safely, could be considered for otherwise healthy patients with recently diagnosed type 2 diabetes and a long life expectancy; more relaxed goals for the glycated hemoglobin level may be preferable in older patients with long-standing type 2 diabetes and cardiovascular disease.
- Lifestyle modification and metformin are recommended as initial therapies for most patients with type 2 diabetes.
- Several therapeutic agents are available when therapy in addition to metformin is needed to control glycemia, but evidence is lacking to support the choice of any one agent over another. Decisions should take into account cost, side effects, and long-term safety and effects on complications of diabetes.

postprandial suppression of glucagon secretion also occurs. Beta-cell failure is mediated by genetic factors and exposure to chronically elevated levels of blood glucose (glucotoxicity) and free fatty acids (lipotoxicity). Older age, amyloid fibrils in islets, and chronically high rates of insulin secretion also play mechanistic roles. The majority of genetic abnormalities that have been identified in patients with type 2 diabetes are related to beta-cell function.[11]

According to the American Diabetes Association, the diagnosis of type 2 diabetes is based on a glycated hemoglobin level of 6.5% or more, a fasting plasma glucose level of 126 mg per deciliter (7.0 mmol per liter) or more, or a 2-hour plasma glucose level of 200 mg per deciliter (11.1 mmol per liter) or more during an oral glucose-tolerance test.[6] The diagnosis can also be established by classic symptoms of hyperglycemia and a random plasma glucose level of 200 mg per deciliter or more. Test results require confirmation with the use of the above criteria, unless the diagnosis is obvious on the basis of the symptoms.[6]

STRATEGIES AND EVIDENCE

This article focuses on glycemic management in type 2 diabetes. However, glycemic control is only one facet of the multifactorial approach required for attempted control of all known risk factors for the development of cardiovascular and microvascular disease.[12]

GOALS OF GLYCEMIC CONTROL AND TARGET RANGE FOR GLYCATED HEMOGLOBIN

The overall aim of glycemic management is to minimize long-term complications while avoiding severe hypoglycemic events. Results of large randomized trials involving patients with type 1 diabetes or newly recognized or established type 2 diabetes show that control of glycemia delays the onset and slows the progression of microvascular complications, including nephropathy, retinopathy, and neuropathy.[13-18] Long-term follow-up of patients with newly diagnosed type 2 diabetes enrolled in the U.K. Prospective Diabetes Study (Current Controlled Trials number, ISRCTN75451837) showed a reduced risk of cardiovascular disease events 10 years after the end of the trial among patients who were initially randomly assigned to intensive glycemic management, as compared with conventional therapy (average glycated hemoglobin level, 7.0% vs. 7.9%).[19] Results of three trials involving older patients with established type 2 diabetes and a history of or risk factors for cardiovascular disease showed no reduction in total mortality or cardiovascular disease–related mortality associated with intensive lowering of glucose levels to near-normal levels with the use of multiple agents, as compared with standard glycemic control[15,16,20]; one of the studies showed increased mortality.[20] Moreover, intensive glycemic control was associated with higher rates of hypoglycemia and weight gain. Thus, the microvascular benefits that are derived from intensive glycemic control must be balanced against the risks.

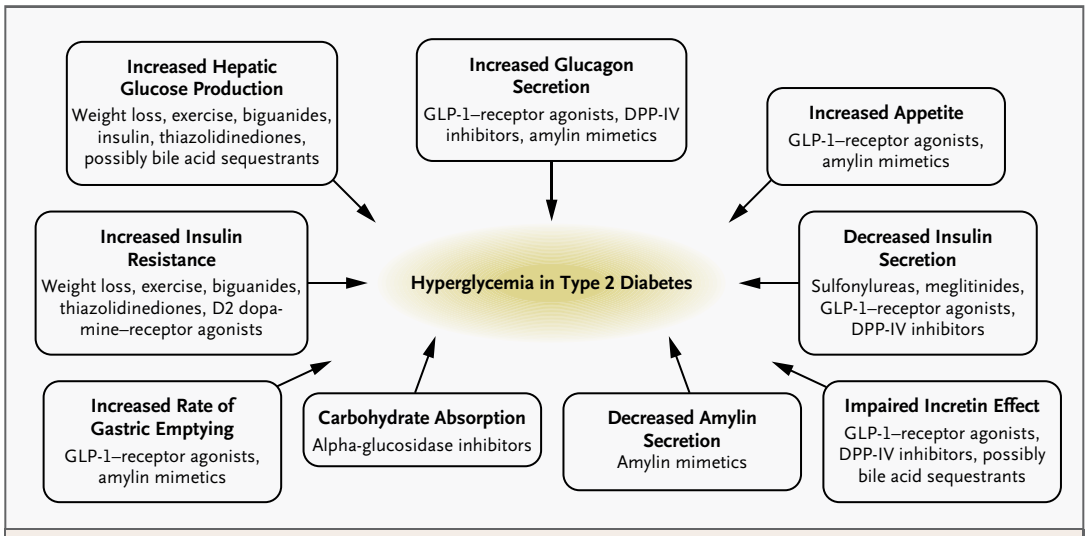

Figure 1. Pathophysiological Alterations Leading to Hyperglycemia in Type 2 Diabetes and Specific Types of Treatment.
Increased insulin resistance and decreased insulin secretion for the given metabolic state of the individual patient constitute major underlying causes of the hyperglycemic state in type 2 diabetes. However, several pathophysiological derangements contribute to hyperglycemia. Various treatment approaches that counteract the underlying disturbances are listed under each alteration. A specific agent or treatment approach may exert a beneficial effect in more than one category. DPP-IV denotes dipeptidyl peptidase IV, and GLP-1 glucagon-like peptide 1.

The first step in glycemic management is setting an appropriate glycemic target in each individual patient. Current guidelines specify glycated hemoglobin targets of less than 7.0% or less than 6.5%.[21,22] However, the appropriateness of these goals varies according to clinical characteristics and psychosocial factors, including the patient's capacity for self-care and home support systems. Intensive glycemic control often requires a greater number and larger dosages of medications, resulting in an increase in adverse events and costs.

Figure 2 shows the influence of various patient-specific features on the selection of glycated hemoglobin targets.[28] In general, in patients with recently recognized type 2 diabetes and few or no complications (especially younger patients), a near-normal glycemic target aimed at prevention of complications over many years of life can be suggested. In contrast, in older persons with cardiovascular disease or multiple risk factors for cardiovascular diseases, higher targets are often appropriate.[15,16,28]

GENERAL TREATMENT CONSIDERATIONS

Whenever possible, patients should be involved in decision making regarding glycemic targets[29,30] and should be informed that the targets may require adjustment over time with changes in clinical or personal factors, such as the patient's experience with and acceptance of frequent self-monitoring of blood glucose levels and his or her ability to identify and prevent hypoglycemic events. In general, the glycated hemoglobin level should be checked at least twice yearly.

Long-term maintenance of glycemic control ideally should involve a multidisciplinary approach, including nutrition counseling and visits with a diabetes nurse, certified diabetes educator, or both.[6] Educational programs that empower patients to become involved in their day-to-day glycemic management and education of health care providers are helpful.[6] Successful glycemic control at a reasonable cost has been reported with the use of telecommunication and computer-based information-transfer systems.[31,32]

LIFESTYLE APPROACHES

Weight loss and exercise are important nonpharmacologic approaches to improving glycemic control (Fig. 1). The American Diabetes Association recommends a balanced diet that is rich in fiber, whole grains, and legumes; contains less than 7% saturated fat and reduced trans fats; and is limited in calories and foods with a high glycemic index.[6,33] Exercise has an additive effect when combined with caloric restriction for glycemic

Glycated Hemoglobin Range

Most Intensive Level, Approximately 6.0%	Factors	Least Intensive Level, Approximately 8.0%
Highly motivated, adherent, knowledgeable, strong self-care capability	Psychosocial considerations	Less motivated, nonadherent, less knowledge, weak self-care capability
Adequate	Resources or support systems	Inadequate
Low	Risk of hypoglycemia	High
Short	Duration of type 2 diabetes	Long
Long	Life expectancy	Short
None	Microvascular disease	Advanced
None	Cardiovascular disease	Established
None	Coexisting conditions	Multiple, severe, or both

Figure 2. Suggested Goals for Glycemic Treatment in Patients with Type 2 Diabetes.

Factors that should be considered in determining glycemic goals, including psychosocial limitations (e.g., depression, which is common in patients with type 2 diabetes[23]) and clinical factors, are shown. Characteristics listed in the column at the right warrant the most attention. Despite the strong positive correlation between glycated hemoglobin levels and mean blood glucose levels in populations, blood glucose levels vary at any given level of glycated hemoglobin and glycated hemoglobin values vary at any given blood glucose level.[24] Severe hypoglycemia in patients with type 2 diabetes and cardiovascular disease may lead to myocardial ischemia and may increase the risk of myocardial infarction, cardiac arrhythmias, or sudden death.[25] The intensity of glucose control should be immediately relaxed by an average of approximately 45 to 60 mg per deciliter (glycated hemoglobin by approximately 1.5 to 2.0%)[25] for several weeks after an unexplained severe hypoglycemic episode. More prolonged relaxation of glycemic goals should be considered after two or more episodes. Glycemic targets in patients with "hypoglycemia unawareness" should be relaxed for prolonged periods, pending the potential reversal of the condition.[6] Older patients with impaired cognitive function are prone to severe hypoglycemia, and such episodes may increase the risk of dementia.[26,27] In general, the older the patient and the longer the duration of the disease, the more established the atherosclerotic process and microvascular derangements, which usually signify less benefit from intensive glycemic treatment. In patients with severe coexisting conditions that could interfere with implementation of the management strategy, the goal is prevention of clinically significant glycosuria, water and electrolyte loss, infections, and the development of nonketotic hyperosmolar coma. Adapted from Ismail-Beigi.[28]

control.[6] Patients should be encouraged to engage in at least 150 minutes of moderate-intensity aerobic exercise per week.[6]

PHARMACOTHERAPY

Medications that are available for glycemic management of type 2 diabetes,[4,5,21,34-46] their usual effects on the glycated hemoglobin level, and their major advantages and disadvantages are summarized in Table 1. Treatment options have greatly expanded in the past two decades. Available agents reduce glucose levels, often through a variety of mechanisms (Fig. 1).

Agents That Improve Insulin Sensitivity

Metformin is the cornerstone of type 2 diabetes treatment.[4,21,34,40] By stimulating AMP-activated protein kinase, metformin reduces hepatic glucose production. It does not cause weight gain and may result in a slight weight loss, and it rarely causes hypoglycemia; gastrointestinal side effects may occur, especially if therapy is initiated at higher doses.

Thiazolidinediones (pioglitazone and rosiglitazone) are peroxisome proliferator–activated receptor γ activators that enhance insulin sensitivity in peripheral tissues and reduce hepatic glucose production.[5,21] Although a randomized trial showed that rosiglitazone, as compared with metformin or a sulfonylurea as the only initial therapy, maintained glycemic control for a longer period,[35] the use of rosiglitazone is highly restricted in the United States (and was discontinued in Europe) owing to concern about an increased risk of myocardial infarction. This concern was based mostly on a meta-analysis of observational studies.[44] In a randomized study, pioglitazone was associated with a reduction in the secondary composite cardiovascular disease outcome but also with increased risks of edema and heart failure.[43]

Agents That Increase Circulating Insulin Levels

Insulin is the most potent agent for reducing glycemia. By activating plasma-membrane receptors, it stimulates glucose uptake by responsive tissues and decreases hepatic glucose production. The use of insulin causes weight gain and may cause severe hypoglycemia.[21] Long-acting (basal) and short- and rapid-acting insulin formulations and combined formulations are available.

Sulfonylureas (e.g., glipizide) stimulate insulin release by closure of specific potassium channels on beta cells. Their use is associated with modest weight gain and hypoglycemia. Meglitinides (e.g., repaglinide) have actions similar to those of sulfonylureas but have a short duration of action (hours) and are most effective preprandially.

The Food and Drug Administration (FDA) has approved agents that increase blood glucagon-like peptide 1 (GLP-1) activity or levels and stimulate insulin secretion (in a glucose-dependent manner)

while inhibiting glucagon secretion. GLP-1–receptor agonists (e.g., exenatide and liraglutide) are injectable agents that are structurally similar to endogenous GLP-1 and activate GLP-1 receptors in many tissues. Other effects include delayed gastric emptying and appetite suppression, typically resulting in a weight loss of approximately 2 to 4 kg (4.4 to 8.8 lb).[21] Dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin) are oral agents that inhibit the degradation of GLP-1 and result in modest elevations of circulating GLP-1 levels; they do not affect weight. Either class of agent may cause hypoglycemia if used with insulin or sulfonylureas. The long-term safety of these agents (including their potential for causing pancreatitis), as well as their effects on the risk of cardiovascular disease, are unknown.

Other Agents

Other FDA-approved agents are used less frequently because of the smaller reductions in glycated hemoglobin levels (typically, approximately 0.6%) and, in some cases, side effects (Table 1).[21] Alpha-glucosidase inhibitors (e.g., acarbose) interfere with the digestion of glucose polymers, thereby decreasing carbohydrate absorption; a high frequency of gastrointestinal side effects limits their use. The bile acid sequestrant colesevelam reduces hepatic glucose production and increases incretin levels by unknown mechanisms; it also reduces LDL cholesterol levels. The dopamine agonist bromocriptine activates D2 dopamine receptors and increases insulin sensitivity by unknown mechanisms; a rapid-release form was approved by the FDA for this indication. Pramlintide, an amylin mimetic, is an injectable agent that stimulates receptors for amylin. It suppresses glucagon secretion, delays gastric emptying, and decreases appetite.

STRATEGIES FOR IMPLEMENTATION

Of the various strategies for glycemic control, lifestyle modification and metformin are preferred and are cost-effective.[21,34,38,40] Patients with chronically high levels of glycated hemoglobin (approximately 9.0%) are unlikely to have adequate glycemic control with metformin alone, and in patients with clinically significant hyperglycemia (blood glucose level, >300 mg per deciliter [>16.7 mmol per liter]; glycated hemoglobin level, >10%), initial insulin therapy should be considered. If metformin monotherapy cannot be used, other oral agents (e.g., a sulfonylurea, a DPP-IV inhibitor, or pioglitazone) or a GLP-1–receptor agonist can be administered. Over time, additional medications become necessary for glycemic control. A logical strategy is to consider agents with complementary mechanisms of action (Fig. 1).[5,21] Combinations that are effective in reducing glycemia include metformin plus another oral agent, a GLP-1–receptor agonist, or long-acting insulin.[21,34,38,46] However, strong evidence is lacking to support any one particular second agent over another.

Perhaps because of the reluctance of patients and providers, insulin is generally added much later than medically indicated.[21] The recent introduction of disposable pen devices may make insulin therapy more acceptable to patients.[42] Initiation of insulin therapy with the use of a single dose of basal (long-acting) insulin, preferably at bedtime (starting with approximately 10 units and increasing by 2 to 3 units every several days) can reduce the glycated hemoglobin level by 1.5 to 2.0% or more.[21,36] If glycemia is not controlled, a dose of rapid-acting insulin can be added at the largest meal. Premixed "biphasic insulin" preparations, typically administered before breakfast and dinner, or basal insulin plus rapid-acting insulin ("basal-bolus") therapy before a meal can also be considered. Lower glycated hemoglobin levels are obtained with the use of biphasic or basal-bolus regimens but at the expense of a greater likelihood of hypoglycemia and weight gain.[36,39]

SURGICAL APPROACHES TO GLYCEMIC CONTROL

Long-term observational studies have shown considerable improvements in glycemic control, as well as improvements in associated cardiovascular risk factors and a reduced risk of cardiovascular disease,[47] among patients who have undergone bariatric surgery (laparoscopic adjustable gastric banding or Roux-en-Y gastric bypass), as compared with obese patients who have not undergone surgery. Benefits have been noted particularly among very obese persons with a shorter duration of type 2 diabetes and in association with procedures that limit the absorptive surface (bypass surgery).[48] Bariatric surgery is increasingly used in patients with type 2 diabetes who are obese but not morbidly obese. The results of two recently published randomized trials of bariatric surgery involving patients with type 2 diabetes (one of which included patients with a BMI of <35) showed significant improvement in glyce-

Table 1. Pharmacologic Agents for Glycemic Control in Patients with Type 2 Diabetes.*

Class	Agent (Brand Name)	Expected Reduction in Glycated Hemoglobin Level	Advantages	Disadvantages	Cost
		%			
Oral					
Biguanide	Metformin (Glucophage)	1.0–2.0	Extensive clinical experience; hypoglycemia rare; improved lipid profile; decreased cardiovascular disease events†; some weight loss in most patients	Gastrointestinal intolerance; lactic acidosis rare (avoid in patients at increased risk, such as men with a serum creatinine level of ≥1.5 mg/dl and women with a serum creatinine level of ≥1.4 mg/dl); vitamin B_{12} deficiency	Low (generic)
Sulfonylurea‡	Glyburide (Diabeta), glipizide (Glucotrol),§ gliclazide (Diamicron),§ glimepiride (Amaryl)	1.0–1.5	Extensive clinical experience	Hypoglycemia; less durability; weight gain	Low (generic)
Meglitinide	Nateglinide (Starlix), repaglinide (Prandin)	0.5–1.0	Short duration of action, hepatic clearance, glucose-dependent postprandial action	Low efficacy, hypoglycemia in some patients, weight gain	High
Thiazolidinedione	Rosiglitazone (Avandia), pioglitazone (Actos)	0.5–1.4	Hypoglycemia rare, more durable effect than that of metformin or sulfonylurea, improved lipid profile, some evidence of beneficial effect on coronary atherosclerosis (with pioglitazone)¶	Edema, heart failure, weight gain, increased risk of long-bone fractures and potential risk of bladder cancer and cardiovascular events (with rosiglitazone)‖; use of rosiglitazone highly restricted	High
DPP-IV inhibitor	Saxagliptin (Onglyza), linagliptin (Tradjenta), vildagliptin (Galvus),§ sitagliptin (Januvia)	0.5–0.8	Hypoglycemia rare, infrequent side effects	Less efficacy than GLP-1–receptor agonists, angioedema, unknown long-term safety, risk of pancreatitis	High
Alpha-glucosidase inhibitor	Miglitol (Glycet), voglibose (Volix),§ acarbose (Precose)	0.5–0.9	Decreased level of postprandial glucose, hypoglycemia rare, possible decrease in risk of cardiovascular disease events**	Flatulence, diarrhea	Moderate
Bile acid sequestrant	Colesevelam (Welchol)	0.5	Lowering of LDL cholesterol level; hypoglycemia rare	Gastrointestinal side effects, including constipation; low efficacy; only approved agent in class	High
D2 dopamine–receptor agonist	Bromocriptine, rapid release (Cycloset)	0.5	Hypoglycemia rare	Low efficacy; gastrointestinal side effects, including nausea; fatigue; dizziness; rhinitis; only rapid-release agent approved	High
Injectable					
GLP-1–receptor agonist	Exenatide (Byetta), exenatide once weekly (Bydureon), liraglutide (Victoza)	0.5–1.5	Hypoglycemia rare, weight loss in most patients; possible protective cardiovascular effects	Nausea and vomiting; risks of pancreatitis, thyroid C-cell hyperplasia, and tumors (with liraglutide and weekly exenatide); unknown long-term safety	High

Amylin analogue	Pramlintide (Symlin)	0.5–1.0	Weight loss in most patients, control of postprandial glycemia	Nausea and vomiting, modest effect, hypoglycemia with insulin use, unknown long-term safety	High
Insulin	Short-acting: human insulin (Novolin R or Humulin R), aspart (Novolog), glulisine (Apidra), lispro (Humalog); long-acting: neutral protamine Hagedorn (Novolin N or Humulin N), detemir (Levemir), glargine (Lantus); mixed insulin preparations	1.0–2.5	Large effect in all patients	Hypoglycemia, weight gain	Moderate to high

* Data are from Tahrani et al.,[4] DeFronzo,[5] Nathan et al.,[21] Bolen et al.,[34] and Gerstein et al.[46] DPP-IV denotes dipeptidyl peptidase IV, GLP-1 glucagon-like-peptide-1, and LDL low-density lipoprotein.

† The use of metformin in a trial involving obese patients with newly recognized type 2 diabetes was associated with a reduction in cardiovascular disease events.[14]

‡ In an observational study, the use of sulfonylureas was associated with decreased renal function.[41]

§ This agent is not available in the United States.

¶ In randomized studies, pioglitazone, as compared with glimepiride, was associated with a reduction in cardiovascular disease outcomes[43] and a decrease in the progression of coronary atherosclerosis.[37]

‖ The use of rosiglitazone is highly restricted in the United States (and has been discontinued in Europe), predominantly on the basis of a meta-analysis.[44]

** The use of this agent in patients with impaired glucose tolerance has been associated with reduced cardiovascular disease events.[45]

mia at follow-up 1 to 2 years postoperatively.[49,50] Weight loss in some patients is minimal and may not be sustained; data on the long-term effects of these procedures are lacking.

AREAS OF UNCERTAINTY

The underlying cause or causes of accelerated cardiovascular disease in type 2 diabetes and the effects of glycemic control on this process remain incompletely understood. Whereas intensive glycemic control clearly reduces the risk of microvascular complications, its effect (measured as the glycated hemoglobin level, a surrogate marker) on outcomes of cardiovascular disease is less certain. A better understanding of the factors underlying the large variations in insulin resistance and beta-cell number and function in healthy persons is needed for the development of strategies to prevent and treat type 2 diabetes; data are lacking on treatments that preserve beta-cell function.[51,52] Although there is general agreement on the first-line use of metformin in most patients with type 2 diabetes, evidence is lacking to inform the most appropriate choice of second-line agents. Devices such as continuous glucose-monitoring systems (to ascertain glycemic patterns over a period of a few days) and insulin pumps are increasingly used in patients with type 2 diabetes who require insulin, but data on the benefits and risks of these devices are lacking. Mechanisms underlying the impressive effects of bariatric surgery on glycemic control warrant further exploration. Finally, the long-term safety of GLP-1–receptor agonists, DPP-IV inhibitors, and other newer agents and their effects on diabetic complications, including cardiovascular disease, need to be determined.

GUIDELINES

The American Diabetes Association, the European Association for the Study of Diabetes, and other organizations have published guidelines for glycemic control in patients with type 2 diabetes.[6,21,29,30,53,54] All these guidelines specify that glycemic goals should be individualized (with some placing particular emphasis on psychosocial factors in setting goals),[29,30] and all advocate lifestyle modifications and metformin as first-line therapy, though they differ in their subsequent recommendations. A joint statement by the American Diabetes Association and the European Association

for the Study of Diabetes recommends that for patients with glycemia that is not adequately controlled with lifestyle changes and metformin, "well-validated" therapies, including sulfonylureas or basal insulin, should be used, followed by more intensive insulin therapy, as needed[21]; pioglitazone, GLP-1 agonists, and other medications discussed above are considered "less-well-validated" options. The recommendations in this article are generally concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette is relatively young and has a recent diagnosis of type 2 diabetes with inadequately controlled glycemia and a family history of type 2 diabetes and cardiovascular disease. The major goals of treatment should be to prevent microvascular and macrovascular complications over a period of many years, given his long life expectancy. His blood pressure and lipid levels are well controlled. I would discuss with him the risks associated with hyperglycemia and the benefits of glycemic control, and I would assess his capacity and willingness to self-monitor his blood glucose levels. In the absence of any apparent contraindications to targeting a normal or near-normal glycemic range, I would recommend a target glycated hemoglobin level of 6.0 to 6.5% (if it can be implemented safely). I would also recommend an exercise program (preferably at least 150 minutes per week) and encourage him to follow a diet that is low in fat, carbohydrates, and salt and high in grains and fiber, with the aim of gradual weight loss (perhaps 4.5 to 6.8 kg [10 to 15 lb] over the next year). I would increase the dose of metformin to 2000 mg daily while diet and exercise are actively pursued.

If these approaches are effective, it may be possible to decrease or discontinue glipizide. If the glycated hemoglobin level remains high, it is unlikely that the addition of another oral agent would reduce the glycated hemoglobin level from approximately 9% to near-normal levels. Although data are currently insufficient to guide the most appropriate choice among additional therapies, I would recommend adding long-acting insulin at bedtime or a GLP-1–receptor agonist to his regimen. Although some clinicians would consider the discontinuation of glipizide, I favor its continuation, at least initially. Basal insulin is effective and less expensive, but it is associated with hypoglycemia and weight gain. GLP-1–receptor agonists have the advantage of causing weight loss in most patients. They rarely cause hypoglycemia but are more costly than basal insulin, and data are lacking on their long-term safety.

Dr. Ismail-Beigi reports receiving consulting fees from Eli Lilly and owning stock in Thermalin Diabetes. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

1. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215-22. [Erratum, Lancet 2010;376:958.]
2. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta: Department of Health and Human Services, Centers for Disease Control and Prevention, 2011 (http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf).
3. Narayan KM, Ali MK, Koplan JP. Global noncommunicable disease — where worlds meet. N Engl J Med 2010;363:1196-8.
4. Tahrani AA, Bailey CJ, Del Prato S, Barnett AH. Management of type 2 diabetes: new and future developments in treatment. Lancet 2011;378:182-97.
5. DeFronzo R. From the triumvirate to the ominous octet: a new paradigm for the treatment of type diabetes mellitus. Diabetes 2009;58:773-95.
6. American Diabetes Association. Standards of medical care in diabetes — 2012. Diabetes Care 2012;35:Suppl 1:S11-S63.
7. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 2003;52:102-10.
8. Rahier J, Guiot Y, Goebbels RM, Sempoux C, Henquin JC. Pancreatic beta-cell mass in European subjects with type 2 diabetes. Diabetes Obes Metab 2008;10:Suppl 4:32-42.
9. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999;104:787-94.
10. U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16: overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995;44:1249-58. [Erratum, Diabetes 1996;45:1655.]
11. Voight BF, Scott LJ, Steinthorsdottir V, et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat Genet 2010;42:579-89.
12. Gaede P, Lund-Anderson H, Parving HH, Pedersen O. Effect of multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580-91.
13. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
14. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
15. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular compli-

cations in veterans with type 2 diabetes. N Engl J Med 2009;360:129-39.
16. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.
17. Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med 2010;363:233-44.
18. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010; 376:419-30.
19. Holman RR, Paul SK, Bethel M, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
20. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358:2545-59.
21. Nathan DM, Buse JB, Davidson MB, Holman RR, Sherwin R, Zinman B. 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.
22. Handelsman Y, Mechanick JI, Blonde L, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan: executive summary. Endocr Pract 2011;17:287-302.
23. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a metaanalysis. Diabetes Care 2008;31:2383-90.
24. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. Translating the A1c assay into estimated average glucose values. Diabetes Care 2008;31:1473-8.
25. Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. Diabetes Care 2003;26:1485-9.
26. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 2009;301:1565-72.
27. de Galan BE, Zoungas S, Chalmers J, et al. Cognitive function and risks of cardiovascular disease in hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Diabetologia 2009;52:2328-36.
28. Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. Ann Intern Med 2011;154: 554-9.
29. Management of diabetes mellitus in primary care. Washington, DC: Department of Veterans Affairs, 2010 (http://www.healthquality.va.gov/diabetes_mellitus.asp).
30. Qaseem A, Vijan S, Snow V, Cross JT, Weiss KB, Owens DK. Glycemic control and type 2 diabetes mellitus: the optimal hemoglobin A1c targets: a guidance statement from the American College of Physicians. Ann Intern Med 2007;147:417-22.
31. Ralston JD, Hirsch IB, Hoath J, Mullen M, Cheadle A, Goldberg HI. Web-based collaborative care for type 2 diabetes: a pilot randomized trial. Diabetes Care 2009;32:234-9.
32. Wennberg DE, Marr A, Lang L, O'Malley S, Bennett G. A randomized trial of a telephone care-management strategy. N Engl J Med 2010;363:1245-55.
33. Wolfram T, Ismail-Beigi F. Efficacy of high-fiber diets in the management of type 2 diabetes. Endocr Pract 2011;17:132-42.
34. Bolen S, Feldman L, Vassy J, et al. Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007;147:386-99.
35. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427-43.
36. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med 2009;361:1736-47.
37. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008;299:1561-73.
38. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;154: 602-13.
39. Giugliano D, Maiorino MI, Bellastella G, Chiodini P, Esposito K. Treatment regimens with insulin analogues and haemoglobin A1c target of <7% in type 2 diabetes: a systematic review. Diabetes Res Clin Pract 2011;92:1-10.
40. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2012;156:218-31.
41. Hung AM, Roumie CL, Greevy RA, et al. Comparative effectiveness of incident oral antidiabetic drugs on kidney function. Kidney Int 2012 January 18 (Epub ahead of print).
42. Davis SN, Wei W, Garg S. Clinical impact of initiating insulin glargine therapy with disposable pen versus vial in patients with type 2 diabetes mellitus in a managed care setting. Endocr Pract 2011;17: 845-52.
43. Wilcox R, Kupfer S, Erdmann E. Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: results from PROspective pioglitAzone Clinical Trial In macro Vascular Events (PROactive 10). Am Heart J 2008;155:712-7.
44. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457-71.
45. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for the prevention of type 2 diabetes, hypertension and cardiovascular disease in subjects with impaired glucose tolerance: facts and interpretations concerning the critical analysis of the STOP-NIDDM Trial data. Diabetologia 2004;47:969-75.
46. Gerstein HC, Yale JF, Harris SB, Issa M, Stewart JA, Dempsey E. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. Diabet Med 2006;23:736-42.
47. Sjostrom L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. JAMA 2012;307:56-65.
48. Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med 2009;122:248-56.
49. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery vs. conventional medical therapy for type 2 diabetes. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200111.
50. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery vs. medical therapy in obese patients with diabetes. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200225.
51. Nyalakonda K, Sharma T, Ismail-Beigi F. Preservation of beta-cell function in type 2 diabetes. Endocr Pract 2010;16: 1038-55.
52. Leahy JL, Hirsch IB, Peterson KA, Schneider D. Targeting beta-cell function early in the course of therapy for type 2 diabetes mellitus. J Clin Endocrinol Metab 2010;95:4206-16.
53. Bennett WL, Odelola OA, Wilson LM, et al. Evaluation of guideline recommendations on oral medication for type 2 diabetes mellitus: a systematic review. Ann Intern Med 2012;156:27-36.
54. Rodbard HW, Blonde L, Braithwaite SS, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 2007;13: Suppl 1:1-68.