

Diagnosis and Management of Diabetes: Synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes

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Description: The American Diabetes Association (ADA) published the 2016 Standards of Medical Care in Diabetes (Standards) to provide clinicians, patients, researchers, payers, and other interested parties with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care.

Methods: The ADA Professional Practice Committee performed a systematic search on MEDLINE to revise or clarify recommendations based on new evidence. The committee assigns the recommendations a rating of A, B, or C, depending on the quality of evidence. The E rating for expert opinion is assigned to recommendations based on expert consensus or clinical experience. The Standards were reviewed and approved by the Executive

Committee of the ADA Board of Directors, which includes health care professionals, scientists, and laypersons. Feedback from the larger clinical community was incorporated into the 2016 revision.

Recommendations: The synopsis focuses on 8 key areas that are important to primary care providers. The recommendations highlight individualized care to manage the disease, prevent or delay complications, and improve outcomes.

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Since 1989, the American Diabetes Association (ADA) Standards of Medical Care in Diabetes (Standards) have provided the framework for evidence-based recommendations to treat patients with diabetes. This synopsis of the 2016 ADA Standards highlights 8 areas that are important to primary care providers: diagnosis, glycemic targets, medical management, hypoglycemia, cardiovascular risk factor management, microvascular disease screening and management, and inpatient diabetes management.

GUIDELINE DEVELOPMENT AND EVIDENCE GRADING

The ADA Professional Practice Committee (PPC), which comprises physicians, diabetes educators, registered dietitians, and public health experts, developed the Standards. All PPC members disclosed potential conflicts of interest in accordance with the Institute of Medicine standards. For the 2016 Standards, the PPC systematically searched from 1 January to 7 December 2015 on MEDLINE to find and grade new evidence. As a larger body of evidence becomes available, recommendations and their grading levels are updated.

The recommendations are assigned ratings of A, B, or C, depending on the quality of evidence. The E rating for expert opinion is a separate category for recommendations in which there is no evidence from clinical trials, clinical trials may be impractical, or evidence is conflicting. Recommendations with an A rating are based on large, well-designed clinical trials or high-quality meta-analyses. Recommendations with lower

levels of evidence may be equally important but are not as well-supported.

The PPC receives feedback from the larger clinical community throughout the year. Public comments are submitted on the Standards Web site.

The ADA funds development of the Standards out of its general revenues and does not use industry support for these purposes. The complete Standards can be downloaded at professional.diabetes.org/annals.

RECOMMENDATIONS FOR DIAGNOSIS OF DIABETES

Table 1 shows diagnostic criteria (1, 2). Classifying a patient with type 1 or type 2 diabetes mellitus (T1DM or T2DM, respectively) is important because medical management will be affected. Type 1 diabetes mellitus accounts for approximately 5% of diagnosed diabetes cases and is defined by the presence of 1 or more auto-immune markers.

During pregnancy, women with risk factors should be tested for undiagnosed T2DM using standard diagnostic criteria at the first prenatal visit (B rating). Testing for gestational diabetes should be done at 24 to 28 weeks of gestation in pregnant women not previously known to have diabetes by using the "1-step" strategy with a 75-g oral glucose tolerance test or the "2-step" approach with a 50-g (nonfasting) screen followed by a 100-g oral glucose tolerance test for those who screen positive (3, 4) (A rating). Women with gestational diabetes should be screened for persistent diabetes at 6 to 12 weeks after delivery by using nonpregnancy diagnostic criteria (E rating). Women with a history of gestational diabetes should be screened for diabetes or prediabetes at least every 3 years (B rating).

Maturity-onset diabetes of the young, which is caused by a defect in insulin secretion inherited in an autosomal dominant pattern, should be considered in patients with mild stable fasting hyperglycemia and

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multiple family members with diabetes that is not typical of T1DM or T2DM (E rating). All children diagnosed with diabetes in the first 6 months of life should have genetic testing (B rating). Clinicians should consider referring these patients to a specialist.

Certain medications, such as glucocorticoids, thiazide diuretics, and atypical antipsychotics, may increase the risk for diabetes (5).

RECOMMENDATIONS FOR GLYCEMIC TARGETS

Assessment of Glycemic Control

Glycemic control is assessed by patient self-monitoring of blood glucose (SMBG) and hemoglobin A_{1c} (HbA_{1c}) levels. Continuous monitoring of interstitial glucose may be a useful adjunct to SMBG in selected patients on intensive insulin regimens.

Self-Monitoring of Blood Glucose

Self-monitoring of blood glucose is integral to effective therapy (6), allowing patients to evaluate their individual response and assess whether glycemic targets are being achieved. Specific treatments, needs, and goals should dictate SMBG frequency and timing.

Most patients receiving intensive insulin regimens, either multiple-dose insulin injections (3 to 4 injections of basal and prandial insulin per day) or continuous subcutaneous insulin infusion (insulin pump therapy), should consider SMBG before meals and snacks; postprandially (occasionally); at bedtime; before exercise; when they suspect low blood glucose levels; and before critical tasks, such as driving.

Evidence is insufficient to determine when to prescribe SMBG and the frequency of SMBG for patients not receiving an intensive insulin regimen. Performing SMBG alone does not decrease blood glucose levels. To be useful, the information must be integrated into clinical and self-management plans.

Hemoglobin A_{1c} Testing

Hemoglobin A_{1c} level reflects average glycemia over several months and has strong predictive value for

Table 1. Criteria for the Diagnosis of Prediabetes and Diabetes

| Variable | Prediabetes | Diabetes |
|--------------------------------------|-------------|----------|
| Hemoglobin A _{1c} level, % | 5.7-6.4 | ≥6.5 |
| Fasting plasma glucose level | | |
| mmol/L | 5.6-6.9 | 7.0 |
| mg/dL | 100-125 | ≥126 |
| Oral glucose tolerance test results* | | |
| mmol/L | 7.8-11.0 | 11.1† |
| mg/dL | 140-199 | ≥200† |
| Random plasma glucose level | | |
| mmol/L | - | 11.1 |
| mg/dL | - | ≥200‡ |

* 2-h plasma glucose level after a 75-g oral glucose tolerance test.

† In the absence of unequivocal hyperglycemia, results should be confirmed by repeated testing.

‡ Only diagnostic in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

diabetes complications (7, 8). The frequency of HbA_{1c} testing should depend on the clinical situation, the treatment regimen, and the clinician's judgment. The HbA_{1c} test should be performed at least twice a year in patients who meet treatment goals and who have stable glycemic control (E rating). The HbA_{1c} test should be done quarterly in patients whose therapy has changed or who are not meeting glycemic goals (E rating). Table 2 shows the correlation between HbA_{1c} levels and mean glucose levels (9, 10).

Hemoglobin A_{1c} Limitations

Hemoglobin A_{1c} testing has limitations. Conditions that affect erythrocyte turnover (hemolysis or blood loss) and hemoglobin variants must be considered (sickle cell anemia), particularly when the HbA_{1c} result does not correlate with the patient's blood glucose levels.

Hemoglobin A_{1c} testing alone does not provide a measure of glycemic variability or hypoglycemia. Glycemic control is best evaluated by the combination of results from SMBG and HbA_{1c} testing.

Table 2. Mean Glucose Levels for Specified Hemoglobin A_{1c} Levels*

| Hemoglobin A _{1c} Level, % | Mean Plasma Glucose Level† | | Mean Fasting Glucose Level | | Mean Preprandial Glucose Level | | Mean Postprandial Glucose Level | | Mean Bedtime Glucose Level | |
|-------------------------------------|----------------------------|-------|----------------------------|-------|--------------------------------|-------|---------------------------------|-------|----------------------------|-------|
| | mmol/L | mg/dL | mmol/L | mg/dL | mmol/L | mg/dL | mmol/L | mg/dL | mmol/L | mg/dL |
| 6 | 7.0 | 126 | - | - | - | - | - | - | - | - |
| <6.5 | - | - | 6.8 | 122 | 6.5 | 118 | 8.0 | 144 | 7.5 | 136 |
| 6.50-6.99 | - | - | 7.9 | 142 | 7.7 | 139 | 9.1 | 164 | 8.5 | 153 |
| 7 | 8.6 | 154 | - | - | - | - | - | - | - | - |
| >7.00-7.49 | - | - | 8.4 | 152 | 8.4 | 152 | 9.8 | 176 | 9.8 | 177 |
| 7.50-7.99 | - | - | 9.3 | 167 | 8.6 | 155 | 10.5 | 189 | 9.7 | 175 |
| 8 | 10.2 | 183 | - | - | - | - | - | - | - | - |
| >8.0-8.5 | - | - | 9.9 | 178 | 9.9 | 179 | 11.4 | 206 | 12.3 | 222 |
| 9 | 11.8 | 212 | - | - | - | - | - | - | - | - |
| 10 | 13.4 | 240 | - | - | - | - | - | - | - | - |
| 11 | 14.9 | 269 | - | - | - | - | - | - | - | - |
| 12 | 16.5 | 298 | - | - | - | - | - | - | - | - |

* Data from references 6 and 7. A calculator for converting hemoglobin A_{1c} results into estimated average glucose levels in either mg/dL or mmol/L is available at <http://professional.diabetes.org/eAG>.

† These estimates are based on A_{1c}-Derived Average Glucose (ADAG) data of about 2700 glucose measurements over 3 months, which were correlated with hemoglobin A_{1c} measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between hemoglobin A_{1c} level and average glucose level was 0.92 (7).

Hemoglobin A_{1c} Goals in Nonpregnant Adults

The HbA_{1c} goal for most nonpregnant adults is less than 7% (Appendix Table, available at www.annals.org). Glycemic control has been shown to reduce microvascular complications of diabetes in persons with T1DM and T2DM and mortality in those with T1DM (11, 12). If implemented soon after the diagnosis of diabetes, this target is associated with long-term reduction in macrovascular disease (A rating). Providers might suggest more stringent HbA_{1c} goals (such as <6.5%) for selected patients (such as those with short duration of diabetes, T2DM treated with lifestyle or metformin, long life expectancy, or no cardiovascular disease) (C rating). More stringent goals are associated with increased hypoglycemia, and studies have shown no further improvement in cardiovascular disease or mortality (13–15). Less stringent HbA_{1c} goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia (plasma glucose level <2.22 mmol/L [<40 mg/dL]), limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes. The general goal is difficult to attain in such patients despite diabetes self-management education; appropriate glucose monitoring; and effective doses of multiple glucose-lowering agents, including insulin (16, 17) (B rating).

When individualizing a patient's goals, many factors, including patient preferences and disease factors, should be considered (Appendix Figure, available at www.annals.org) (18).

HYPOLYCEMIA

Hypoglycemia (plasma glucose level <3.9 mmol/L [<70 mg/dL]) is the major limiting factor in the glycemic management of T1DM and insulin-treated T2DM. Severe hypoglycemia, characterized by cognitive impairment, is defined as that in which the patient requires assistance from another person. Patients at risk for severe hypoglycemia should be prescribed glucagon, and their close contacts should be instructed on how to administer it (E rating). Hypoglycemia may be reversed with administration of rapid-acting glucose (15 to 20 g). Pure glucose is the preferred treatment; however, any form of carbohydrate that contains glucose will increase blood glucose level. Added fat and protein may delay the acute glycemic response. Blood glucose reversal should be confirmed with SMBG after 15 minutes; if hypoglycemia persists, the process should be repeated. Patients should be educated on situations that increase their risk for hypoglycemia, such as fasting for tests or procedures, during or after exercise, and during sleep.

Hypoglycemia unawareness is characterized by deficient counterregulatory hormone release and a diminished autonomic response, both of which are risk factors for and caused by hypoglycemia. Patients with hypoglycemia unawareness should be advised to increase their glycemic targets for at least several weeks

to partially reverse hypoglycemia unawareness and reduce the risk for future episodes.

Providers should be vigilant in preventing hypoglycemia in patients with advanced disease and should not aggressively attempt to achieve near-normal HbA_{1c} levels in patients in whom such targets cannot be safely and reasonably reached. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment regimens.

MEDICAL MANAGEMENT OF DIABETES

Foundations of Care

Optimal diabetes care addresses behavioral, dietary, lifestyle, and pharmaceutical interventions. All patients should participate in diabetes self-management education and support (B rating). An individualized medical nutrition therapy program, preferably provided by a registered dietitian, is recommended for all persons with diabetes (A rating). A physical activity plan should include at least 150 minutes of moderate-intensity aerobic activity per week, reduced sedentary time, and resistance training at least twice per week for most adults with diabetes.

Type 1 Diabetes

Most patients with T1DM should be treated with multiple-dose insulin injections or continuous subcutaneous insulin injection (19) (A rating). Studies have shown clear improvements in the risk for or progression of microvascular complications and cardiovascular disease with intensive insulin therapy (≥ 3 injections of insulin per day) or continuous subcutaneous insulin infusion compared with 1 or 2 injections per day (6, 20).

Patients should be offered education on matching prandial insulin doses to carbohydrate intake, preprandial blood glucose levels, and anticipated activity level (E rating). Patients with T1DM should use insulin analogues to reduce hypoglycemia risk (21, 22) (A rating).

Continuous glucose monitoring systems have recently been shown to significantly reduce severe hypoglycemia risk in patients with T1DM (23). Insulin pump therapy with a low blood glucose level “suspend” feature, augmented by continuous glucose monitoring, reduced nocturnal hypoglycemia without increasing HbA_{1c} levels (24).

Type 2 Diabetes

A patient-centered approach should guide the choice of pharmacologic agents (18). Providers should include efficacy; cost; potential side effects, including effects on weight, comorbidities, and risk for hypoglycemia; and patient preferences when considering different agents (E rating).

Initial Therapy

Newly diagnosed patients who are overweight or obese should begin lifestyle modifications, including physical activity, and be counseled to lose at least 5% of their body weight.

If lifestyle efforts are not sufficient to maintain or achieve glycemic goals, metformin therapy (if tolerated or not contraindicated) should be added at or soon after diagnosis. Metformin is the preferred initial pharmacologic agent (A rating). It is inexpensive, has a long-established evidence base for efficacy and safety, and may reduce risk for cardiovascular events and death (25, 26). Accumulating data suggest that metformin therapy can be continued in patients with declining renal function down to a glomerular filtration rate (GFR) of 30 to 45 mL/min, although the dose should be reduced (27).

Combination Therapy

When monotherapy with a noninsulin agent at the maximum tolerated dose does not achieve or maintain the HbA_{1c} target over 3 months, a second agent should be added (A rating). Providers should consider a combination of metformin and 1 of these 6 treatment options: sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors (28), sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, or basal insulin (Figure). The drug should be based on the patient, disease, drug characteristics, and patient preferences (17). Rapid-acting secretagogues (meglitinides) can be used in place of sulfonylureas in patients with erratic meal schedules or those who have late postprandial hypoglycemia while receiving sulfonylurea therapy. Other drugs, such as α -glucosidase inhibitors, bromocriptine, colesevelam, and pramlintide, can be used in specific situations. Initial dual-regimen combination therapy should be used when the HbA_{1c} level is 9% or greater to more quickly achieve glycemic control.

Insulin Therapy

Insulin should be used with any combination regimen in newly diagnosed patients when severe hyperglycemia causes ketosis or unintentional weight loss (E rating). Insulin therapy should not be delayed in patients not achieving glycemic goals (B rating). Once insulin therapy is initiated, timely dose titration is important. Adjustment of both basal and prandial insulins should be based on SMBG levels.

Basal Insulin

Basal insulin may be initiated at 10 units or 0.1 to 0.2 units/kg of body weight. Basal insulin is typically used with metformin and perhaps 1 additional noninsulin agent.

When basal insulin has been titrated to appropriate fasting blood glucose levels but the HbA_{1c} level remains above target, combination injectable therapy should be considered to reduce postprandial glucose excursions. A GLP-1 receptor agonist (29) or prandial insulin, such as 1 to 3 injections of a rapid-acting insulin (lispro, aspart, or glulisine) administered immediately before meals, may be used. Twice-daily premixed insulin analogues (70/30 aspart mix or 75/25 or 50/50 lis-

pro mix) may also be considered; their pharmacodynamic profiles make them suboptimal for covering postprandial glucose excursions.

Bolus Insulin

When bolus insulin is needed, insulin analogues are preferred because they are faster-acting. Inhaled insulin is available for prandial use but has a limited dosing range. It is contraindicated in patients with chronic lung disease. Lung function testing before and after initiation of therapy is required (30).

A common conundrum for providers is whether to continue oral and injectable agents when insulin therapy is initiated. Sulfonylureas, dipeptidyl peptidase-4 inhibitors, and GLP-1 receptor agonists are usually withdrawn when more complicated insulin regimens (beyond basal insulin) are used. Thiazolidinediones (usually pioglitazone) or SGLT2 inhibitors may be used to improve glucose control and reduce total daily insulin dose. Thiazolidinediones should be used with caution in patients with or at risk for congestive heart failure and have been associated with fractures and weight gain. The U.S. Food and Drug Administration recently issued a warning about the risk for ketoacidosis with SGLT2 inhibitors. Patients should stop taking their SGLT2 inhibitor and seek medical attention immediately if they have symptoms of ketoacidosis (31).

CARDIOVASCULAR RISK FACTOR MANAGEMENT

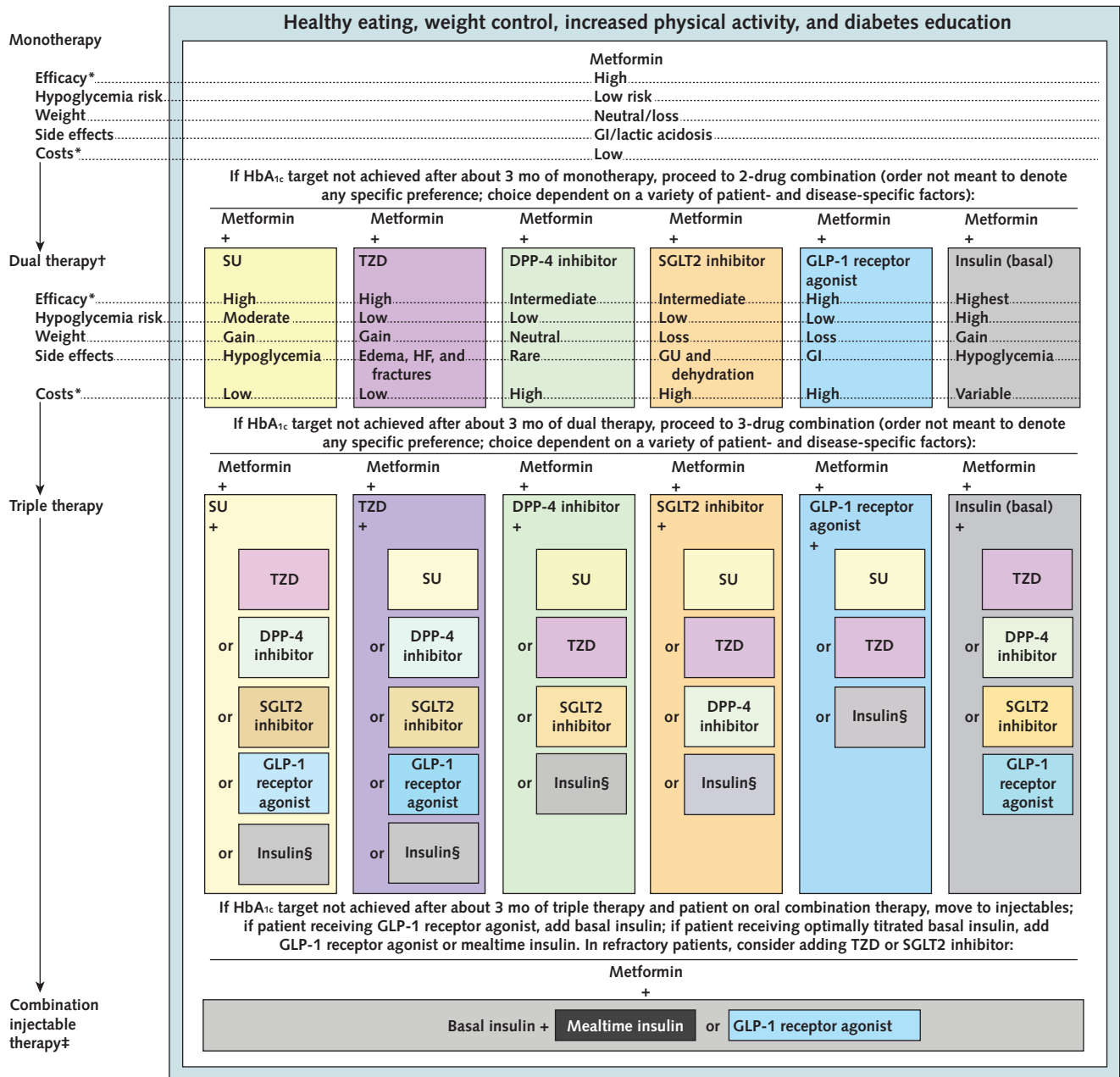
Atherosclerotic cardiovascular disease (ASCVD)—defined as an acute coronary syndrome, a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease (PAD)—is the leading cause of morbidity and mortality for persons with diabetes. In all patients with diabetes, cardiovascular risk factors should be systematically assessed at least annually. These risk factors include dyslipidemia, hypertension, smoking, a family history of premature coronary disease, and the presence of albuminuria.

Controlling individual cardiovascular risk factors can prevent or slow ASCVD in persons with diabetes. Large benefits are seen when multiple risk factors are addressed simultaneously. Measures of 10-year coronary heart disease risk among U.S. adults with diabetes have improved significantly over the past decade, and ASCVD morbidity and mortality have decreased (32–34).

Hypertension

Blood pressure should be measured at every routine visit. An elevated blood pressure should be confirmed on a separate day (B rating). Persons with diabetes and hypertension should have a blood pressure treatment goal of less than 140/90 mm Hg (35) (A rating). In older adults, pharmacologic therapy to a treatment goal of less than 130/70 mm Hg is not recommended; treatment to a systolic blood pressure goal of less than 130 mm Hg has not been shown to

Figure 1. Antihyperglycemic therapy for type 2 diabetes mellitus: general recommendations.



The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes mellitus are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). Adapted with permission from Inzucchi and colleagues (18) and the American Diabetes Association. DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; GU = genitourinary; HbA_{1c} = hemoglobin A_{1c}; HF = heart failure; SGLT2 = sodium-glucose cotransporter 2; SU = sulfonylurea; TZD = thiazolidinedione.

* See reference 18 for description of efficacy categorization.
 † Consider starting at this stage when the HbA_{1c} level is 9% or greater.
 ‡ Consider starting at this stage when blood glucose levels are 16.7 to 19.4 mmol/L (300 to 350 mg/dL) or greater and/or HbA_{1c} levels are 10% to 12%, especially if symptomatic or catabolic features are present (in which case basal insulin plus mealtime insulin is the preferred initial regimen).
 § Usually a basal insulin (neutral protamine Hagedorn, glargine, detemir, or degludec).

improve cardiovascular outcomes, and treatment to a diastolic blood pressure goal of less than 70 mm Hg has been associated with higher mortality (36) (C rating).

Lifestyle therapy for patients with diabetes and hypertension should consist of weight loss, a reduced-sodium diet, moderate alcohol intake, and increased physical activity. Pharmacologic therapy should com-

prise a regimen that includes either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB) but not both (37-39) (B rating). If one class is not tolerated, the other should be substituted (40) (C rating). Multidrug therapy is generally required to achieve blood pressure targets. During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated because they may cause fetal damage. If ACE inhibitors, ARBs, or diuretics are used, serum creatinine levels or estimated GFR (eGFR) and serum potassium levels should be monitored (E rating).

Lipid Management

In adults not receiving statins, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter (or more frequently if indicated) (E rating). A lipid profile should be obtained at initiation of statin therapy and periodically thereafter because it may help to monitor the response to therapy and inform adherence (E rating). Lifestyle modification should be recommended to improve the lipid profile. This includes focusing on weight loss (if indicated); reducing intake of saturated fat, trans fat, and cholesterol; increasing intake of ω -3 fatty acids, viscous fiber, and plant stanols or sterols; and increasing physical activity (A rating).

Lifestyle therapy should be intensified and glycaemic control optimized for patients with elevated triglyceride levels (≥ 1.7 mmol/L [≥ 150 mg/dL]) and/or low high-density lipoprotein cholesterol levels (< 1.0 mmol/L [< 40 mg/dL] for men and < 1.3 mmol/L [< 50 mg/dL] for women) (C rating). For patients with fasting triglyceride levels of 5.7 mmol/L (500 mg/dL) or greater, evaluation for secondary causes of hypertriglyceridemia should be done and medical therapy should be considered to reduce the risk for pancreatitis (C rating).

In addition to intensive lifestyle therapy, statin use is recommended for most persons with diabetes aged 40 years or older (Table 3). Table 4 provides guidance on statin use and intensity. The addition of ezetimibe to moderate-intensity statin therapy has been shown to provide additional cardiovascular benefit compared with moderate-intensity statin therapy alone, and it may be considered for patients with a recent acute coronary syndrome and a low-density lipoprotein cholesterol level of 1.3 mmol/L (50 mg/dL) or greater or for those who cannot tolerate high-intensity statin therapy (41) (A rating).

Combination therapy with a statin and a fibrate has not been shown to improve ASCVD outcomes and is generally not recommended (A rating). However, therapy with a statin and fenofibrate may be considered for men with a triglyceride level of 2.3 mmol/L (204 mg/dL) or greater and a high-density lipoprotein cholesterol level of 0.9 mmol/L (34 mg/dL) or lower (B rating). Combination therapy with a statin and niacin has not been shown to increase cardiovascular benefit more than statin therapy alone. This therapy may increase the risk for stroke and is generally not recommended (A rating).

Table 3. Recommendations for Statin and Combination Treatment in Persons With Diabetes

| Risk Factors, by Age | Recommended Statin Intensity* |
|---|------------------------------------|
| <40 y | |
| None | None |
| ASCVD risk factors† | Moderate or high (C rating) |
| ASCVD | High |
| 40-75 y | |
| None | Moderate (A rating) |
| ASCVD risk factors | High (B rating) |
| ASCVD | High |
| ACS, LDL cholesterol level > 1.3 mmol/L (> 50 mg/dL), and inability to tolerate high-dose statin therapy | Moderate plus ezetimibe (A rating) |
| <75 y | |
| None | Moderate (B rating) |
| ASCVD risk factors | Moderate or high (B rating) |
| ASCVD | High |
| ACS, LDL cholesterol level > 1.3 mmol/L (> 50 mg/dL), and inability to tolerate high-dose statin therapy | Moderate plus ezetimibe (A rating) |

ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; LDL = low-density lipoprotein.

* In addition to lifestyle therapy.

† LDL cholesterol level ≥ 2.6 mmol/L (≥ 100 mg/dL), high blood pressure, smoking, overweight or obesity, and family history of premature ASCVD.

Antiplatelet Agents

Aspirin therapy (75 to 162 mg/d) is recommended as a primary prevention strategy in patients with T1DM and T2DM who are at increased cardiovascular risk (10-year risk $> 10\%$) (C rating). Aspirin should not be recommended for ASCVD prevention in adults with diabetes who are at low ASCVD risk (10-year risk $< 5\%$) (C rating). Clinical judgment is necessary for patients with diabetes who are younger than 50 years and have several other risk factors (for example, 10-year ASCVD risk of 5% to 10%). Aspirin therapy is well-established as a secondary prevention strategy in patients with diabetes and a history of ASCVD. In patients with ASCVD and a documented aspirin allergy, clopidogrel (75 mg/d) should be used. Dual-antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome.

MICROVASCULAR DISEASE SCREENING AND MANAGEMENT

Diabetic Kidney Disease

Diabetic kidney disease is the leading cause of end-stage renal disease (42). Intensive diabetes management, with the goal of achieving near-normoglycemia, may delay the onset and progression of albuminuria and reduced eGFR (43, 44). Annual diabetic kidney disease screening should be performed via urine albumin-creatinine ratio on a spot urine sample and eGFR in patients who have had T1DM for at least 5 years, in all patients with T2DM, and in all patients with comorbid hypertension (B rating). Two of three urine albumin-creatinine ratio specimens collected over 3 to 6 months should be abnormal (> 30 mg/g) before a pa-

Table 4. High- and Moderate-Intensity Statin Therapy*

| |
|------------------------|
| High-intensity† |
| Atorvastatin, 40–80 mg |
| Rosuvastatin, 20–40 mg |
| Moderate-intensity‡ |
| Atorvastatin, 10–20 mg |
| Rosuvastatin, 5–10 mg |
| Simvastatin, 20–40 mg |
| Pravastatin, 40–80 mg |
| Lovastatin, 40 mg |
| Fluvastatin XL, 80 mg |
| Pitavastatin, 2–4 mg |

* Once-daily dosing.

† Decreases low-density lipoprotein cholesterol level by ≥ 1.3 mmol/L (≥ 50 mg/dL).

‡ Decreases low-density lipoprotein cholesterol level by 30% to <50%.

tient can be considered to have albuminuria. Patients with persistent and severely increased levels of albuminuria (≥ 300 mg/g) are more likely to develop end-stage renal disease (45, 46). Referral to a nephrologist should be considered when there is uncertainty about the cause of kidney disease or advanced kidney disease (B rating).

Use of ACE inhibitors or ARBs helps to slow the progression of kidney disease in hypertensive patients with diabetes with an eGFR less than 60 mL/min/1.73 m² and a urine albumin-creatinine ratio greater than 300 mg/g (47, 48).

Retinopathy

Optimizing glycemic control (A rating), blood pressure, and serum lipid control (A rating) is key to reducing the risk for and slowing the progression of diabetic retinopathy. Annual comprehensive eye examination by an ophthalmologist or optometrist should begin for patients who have had T1DM for more than 5 years and for those with T2DM at diagnosis (49) (B rating). Retinal photographs are not a substitute for a comprehensive eye examination.

Neuropathy

Achieving glycemic control can effectively prevent or delay diabetic peripheral neuropathy (A rating) and cardiovascular autonomic neuropathy in T1DM (50, 51) and may slow their progression in T2DM (52) (B rating), but it does not reverse neuronal loss. Manifestations of diabetic autonomic neuropathy include hypoglycemia unawareness, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction. Cardiovascular autonomic neuropathy is associated with mortality independent of other cardiovascular risk factors (13, 53). Manifestations include resting tachycardia and orthostatic hypotension.

Diabetic peripheral neuropathy can be severe and can affect quality of life (54). Symptoms may include dysesthesias and numbness. The U.S. Food and Drug Administration has approved pregabalin, duloxetine, and tapentadol for treatment of diabetic peripheral neuropathy. Tricyclic antidepressants, gabapentin, venlafaxine, carbamazepine, topical capsaicin, and tramadol may be considered as additional treatment options.

Foot Care

All patients who have had T1DM for more than 5 years and all patients with T2DM should have a foot examination annually using 10-g monofilament testing plus pinprick sensation, vibration perception, or ankle reflexes (55) (B rating). At least 2 normal test results rule out loss of protective sensation. In addition, foot examinations should include inspection of skin integrity, identification of bony deformities, and assessment of pedal pulses.

Patients with a history of foot ulceration or amputation, foot deformities, peripheral neuropathy, PAD, poor glycemic control, visual impairment, and cigarette smoking are considered to be at high risk (56). High-risk patients should be educated on proper foot care and the importance of daily foot monitoring. Patients with advanced foot disease may require custom-fitted shoes. Diabetic foot wounds without evidence of soft tissue or bone infection do not require antibiotic therapy. Foot ulcers and wounds may require care from a multidisciplinary team (57) (B rating).

Screening for PAD should include a history of claudication and assessment of pedal pulses. Ankle-brachial index testing should be considered in patients aged 50 years or older and in those younger than 50 years with PAD risk factors (including smoking, hypertension, and dyslipidemia) or a diabetes duration greater than 10 years (58).

DIABETES CARE IN THE HOSPITAL

Inpatient hyperglycemia and hypoglycemia are associated with adverse outcomes, including death (59, 60). Therefore, hospital glucose goals include preventing hyperglycemia and hypoglycemia, promoting the shortest safe hospital stay, and providing an effective transition out of the hospital that prevents complications and readmission.

Glycemic Targets in Hospitalized Patients

Inpatient glucose targets of 7.8 to 10 mmol/L (140 to 180 mg/dL) are recommended for most noncritical (C rating) and critically ill (A rating) patients (60). However, glucose targets of 6.1 to 7.8 mmol/L (110 to 140 mg/dL) may be appropriate for some patients (C rating), such as cardiac surgery patients (61, 62) and those with acute ischemic cardiac (63) or neurologic events, if the targets can be achieved without significant hypoglycemia. Conversely, higher glucose ranges may be acceptable in certain populations, such as terminally ill patients.

Antihyperglycemic Agents in Hospitalized Patients

In the critical care setting, continuous intravenous insulin infusion is the best method for achieving glycemic targets. Intravenous insulin infusions should be administered on the basis of validated written or computerized protocols that allow for predefined adjustments in the infusion rate, accounting for glycemic fluctuations and insulin dose (60, 64) (E rating).

Insulin is the preferred therapy for persistent hyperglycemia (plasma blood glucose level >10 mmol/L [>180 mg/dL]). Outside critical care units, scheduled subcutaneous insulin injections should align with meals and bedtime or should be administered every 4 to 6 hours if no meals are consumed or continuous enteral or parenteral therapy is used (60). An insulin regimen with basal, nutritional, and correction components (basal-bolus) is the preferred treatment for patients with good nutritional intake (65) (A rating). In such instances, point-of-care glucose testing should be performed immediately before meals. Consistent carbohydrate meal plans are preferred because they facilitate matching the prandial insulin dose to the amount of carbohydrate consumed (66). A basal-plus-correction insulin regimen is the preferred treatment for patients with poor oral intake or those who are receiving nothing by mouth (64) (A rating). The sole use of sliding-scale insulin in the inpatient hospital setting is strongly discouraged (60, 67) (A rating).

When intravenous insulin therapy is discontinued, a transition protocol to a subcutaneous insulin regimen is associated with lower morbidity and costs of care (68). Subcutaneous insulin should be given 1 to 2 hours before intravenous insulin therapy is discontinued. Converting to basal insulin at 60% to 80% of the daily infusion dose has been shown to be effective (60, 68, 69).

Hypoglycemia in the Hospital

Hospital-related hypoglycemia is associated with higher mortality. Iatrogenic hypoglycemia triggers include sudden reduction of corticosteroid dose; altered ability of the patient to report symptoms; reduced oral intake; emesis; new nothing-by-mouth status; inappropriate timing of short-acting insulin in relation to meals; reduced infusion rate of intravenous dextrose; and unexpected interruption of oral, enteral, or parenteral feedings. A standardized hospital-wide and nurse-initiated hypoglycemia treatment protocol should be in place to immediately address hypoglycemia (60).

Transition From the Acute Care Setting

A structured discharge plan should be tailored to the individual patient (B rating), which may reduce length of hospital stay and readmission rates and increase patient satisfaction (70). To help guide treatment decisions at the time of transition, admission orders should include an HbA_{1c} level if none is available within the prior 3 months (60). Discharge planning should begin at admission and should be updated as patient needs change. An outpatient follow-up visit within 1 month of discharge is advised.

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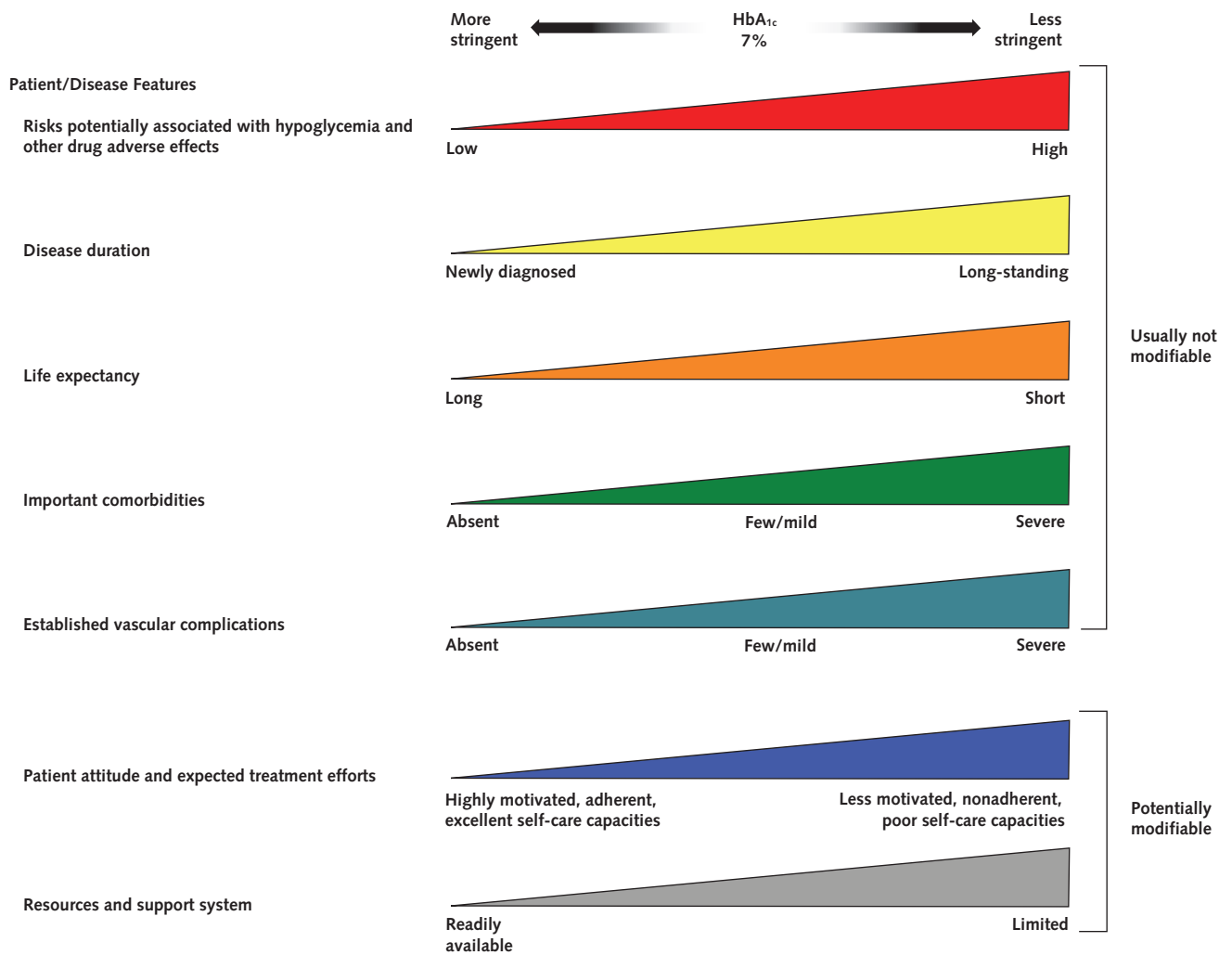
Appendix Table. Summary of Glycemic Recommendations for Nonpregnant Adults With Diabetes

| Variable | Value* |
|---|-------------------------------|
| Hemoglobin A _{1c} level | <7.0% |
| Preprandial capillary plasma glucose level | 4.4-7.2 mmol/L (80-130 mg/dL) |
| Peak postprandial capillary plasma glucose level† | <10.0 mmol/L (<180 mg/dL) |

* More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized on the basis of duration of diabetes, age/life expectancy, comorbid conditions, known cardiovascular disease or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

† Postprandial glucose level may be targeted if hemoglobin A_{1c} goals are not met but preprandial glucose goals are. Postprandial glucose measurements should be made 1-2 h after the beginning of the meal (generally peak levels in patients with diabetes).

Appendix Figure. Approach to the management of hyperglycemia.



Depicted are patient and disease factors used to determine optimal HbA_{1c} targets. Characteristics and predicaments toward the left justify more stringent efforts to lower HbA_{1c} level, and those toward the right suggest less stringent efforts. Adapted with permission from Inzucchi and colleagues (18) and the American Diabetes Association. HbA_{1c} = hemoglobin A_{1c}.