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What's new in type 2 diabetes?

The "ABCD IS diabetes" mnemonic can help you follow the latest recommendations from the American Diabetes Association.

In April 2012, the American Diabetes Association (ADA) updated its guidelines for evaluating and treating type 2 diabetes mellitus (T2DM). In particular, the ADA acknowledges the value of an individualized, patient-centered approach that is less formulaic than its earlier guidelines. In this article, we highlight these and other recently published developments in the context of a case study. To help ensure follow-through on these newest recommendations, we also frame our review with the mnemonic, "ABCD IS diabetes."

CASE ▶ JR is a 57-year-old man being seen for a regular follow-up appointment. His medical history includes T2DM, hypertension, and obesity. He is taking metformin 1000 mg twice daily, lisinopril 40 mg each morning, and amlodipine 10 mg each morning. He is current on his influenza and pneumococcal vaccinations. He does not smoke cigarettes. His physical exam and lab results reveal the following:

- blood pressure (BP), 132/70 mm Hg
- body mass index (BMI), 33 kg/m^2
- glycosylated hemoglobin (A1C), 7.6%
- lipid profile: Total cholesterol, 185 mg/dL; high-density lipoprotein (HDL), 40 mg/dL; triglycerides (TG), 145 mg/dL; low-density lipoprotein (LDL), 90 mg/dL

Applying the "ABCD IS diabetes" mnemonic leads us through the following assessments.

Antiplatelets

In the past, guidelines have recommended that most patients with diabetes be placed on aspirin therapy. However, 2 trials published in 2008 failed to demonstrate significant reduction in cardiovascular disease (CVD) end points with aspirin use, raising questions about its effectiveness for primary CVD prevention in patients with diabetes.[1,2] In 2010, the ADA, American Heart Association, and American College of Cardiology Foundation modified their recommendations for primary prevention,[3] which remain unchanged in the 2012 ADA guidelines.[4]

Antiplatelet agents continue to play a role in primary prevention of CVD for patients with T2DM, but only after appropriate risk stratification.[4] Consider low-dose aspirin therapy (75-162 mg/d) for patients with diabetes who have a 10-year Framingham risk >10%.[4] (To calculate a patient's 10-year risk, go to http://hp2010.nhlbihin.net/atpiii/calculator.asp.)

Many patients with T2DM seen in the primary care setting will reach this risk level and qualify for aspirin—in particular, men older than 50 years and women older than 60 with a family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria.[4] Aspirin therapy is not recommended for primary prevention in adults with diabetes at low risk for CVD (10-year Framingham risk <5%)—eg, men <50 and women <60 years without additional CVD risk factors.[4] For patients with a 10-year Framingham risk between 5% and 10%, a decision to treat rests with the physician.

CASE ▶ Should JR be started on aspirin therapy for primary prevention of CVD? Initiating low-dose aspirin is recommended, assuming no contraindications, because his 10-year Framingham risk assessment is 11%.

"ABCD IS diabetes" at-a-glance practice recommendations[4,16,28]

- **A** **(antiplatelets):** Consider low-dose aspirin therapy (75-162 mg/d) for diabetes patients with a 10-year Framingham risk >10%.
- **B** **(blood pressure):** Individualize a patient's goal for systolic blood pressure, aiming higher or lower than the customary systolic target of <130 mm Hg, as appropriate.
- **C** **(cholesterol):** Recommend lifestyle changes and prescribe a statin, as needed, to achieve LDL goals in T2DM patients.
- **D** **(drug management):** Use a patient-centered approach to achieve an individualized A1C goal. Metformin is the initial medication of choice. Select additional drug classes to balance adverse effects, cost, and effectiveness.
- **I** **(immunizations):** Ensure that each T2DM patient receives influenza and pneumococcal vaccines, and the hepatitis B vaccine if <60 years.
- **S** **(surveillance):** Confirm at each visit that annual surveillance testing for nephropathy, retinopathy, and peripheral neuropathy has been completed.

Blood pressure

The benefits of lowering BP in diabetes to <140 mm Hg systolic and <80 mm Hg diastolic have been established in randomized control trials.[5-8] However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial demonstrated that, in patients with T2DM, intensive BP lowering to <120 mm Hg systolic yielded no significant differences in fatal and nonfatal cardiovascular events compared with BP maintained between 130 and 140 mm Hg.[9] Moreover, aggressive BP lowering may be associated with serious adverse events.[10] The 2012 ADA guidelines state that a systolic BP goal of <130 mm Hg is appropriate for most patients; however, higher or lower BP targets may be individualized.[4]

Recommendations for adding a second antihypertensive agent and timing medication administration. For T2DM patients with hypertension, the 2012 guidelines recommend that you treat initially with either an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), if tolerated.[4] When adding a second agent, the Avoiding Cardiovascular Events through COMbination therapy in Patients LIving with Systolic Hypertension (ACCOMPLISH) trial demonstrated reduced morbidity and mortality in patients receiving benazepril and amlodipine compared with those receiving benazepril and hydrochlorothiazide.[11] As a result, amlodipine has joined diuretics as a preferred second oral antihypertensive agent after an ACEI or ARB.

If a patient is taking multiple BP medications, one or more should be taken at bedtime.[4] Administering an antihypertensive at night results in better ambulatory BP control and reduces cardiovascular mortality.[12]

CASE ▶ JR is on maximal doses of 2 antihypertensive agents, and his BP is 132/70 mm Hg. His physician must individualize care and decide if adding a third agent is worth the risk of another medication when clear benefit has not been demonstrated. It is reasonable to continue his current regimen with the exception of changing his lisinopril dose to the evening and reassessing his BP control at his next visit.

Cholesterol

Controlling LDL remains the top priority of T2DM lipid management. In addition to lifestyle changes, statins are the primary means of achieving LDL goals. All patients with overt CVD should receive a statin.[4] Also prescribe a statin for patients with diabetes who do not have CVD but who are older than 40 and have one or more cardiac risk factors, regardless of their baseline LDL cholesterol.[4] The recommended LDL goal in T2DM patients continues to be <100 mg/dL. However, <70 mg/dL is a reasonable goal for those with known CVD.[13]

CONTINUED

Patients with diabetes taking multiple blood pressure medications should take one or more of them at bedtime.

Using additional lipid-lowering agents besides a statin may improve cholesterol numbers, but not CVD outcomes.

Using additional lipid-lowering agents besides a statin may improve cholesterol numbers, but not CVD outcomes. In the ACCORD study, adding fenofibrate to simvastatin did not decrease fatal cardiovascular events or nonfatal myocardial infarction and stroke compared with simvastatin given alone.[14] The AIM-High study showed no difference in cardiovascular outcomes and a possible increase in ischemic stroke with combination niacin and statin compared with statin therapy alone.[15] For now, lifestyle changes and statins remain the ideal modalities to achieve LDL goals.

CASE ▶ Should a statin be initiated for our patient? Since JR is over 40 without known CVD and has a cardiac risk factor of hypertension, he should be started on statin therapy regardless of his baseline LDL (90 mg/dL), which is already at goal (<100 mg/dL).

Drug management

Let the glycemic goal for each patient guide your medication management. The 2012 ADA recommendation for most adults is an A1C of <7%.[4] More strict control (A1C <6.5%) may be appropriate for certain individuals with a long life expectancy, short duration of diabetes, and no significant micro- or macrovascular disease.[4] Less strict control (A1C <8%) may be appropriate for individuals with significant comorbidities, shorter life expectancy, severe hypoglycemia, or long-standing T2DM that's been difficult to control despite multiple medications, including insulin.[4]

Individualize treatment. In April 2012, the ADA released a position statement encouraging a patient-centered approach to managing hyperglycemia in T2DM.[16] This statement contains a new treatment algorithm (available at: http://care.diabetesjournals.org/content/early/2012/04/17/dc12-0413.full.pdf+html; see page 8) that is less prescriptive than the previous 2009 algorithm and balances provider judgment, patient preference, and susceptibility to adverse effects in order to attain an individualized A1C target.[16] Although a comprehensive review of T2DM pharmacotherapy is beyond the scope of this article, we will discuss the importance of metformin, familiarize prescribers with incretin-based therapy, and highlight recent safety concerns regarding thiazolidinediones (TZDs).

Metformin is first line. The 2012 ADA guidelines recommend prescribing metformin at the time of diagnosis of T2DM, in addition to advising lifestyle changes.[4,16] The American College of Physicians (ACP) also recommends metformin as the first agent in diabetes management, citing the benefits of weight loss, improved lipid profiles, and decreased cardiovascular mortality.[17] Adding a second medication to metformin at the time of diagnosis may be considered if the initial A1C value is >9%.[16] Because robust comparative trials are lacking, the selection of additional medications beyond metformin depends on a patient-centered approach, with consideration of efficacy, adverse effect profile, and cost.[16] The **TABLE** provides a succinct review of the key properties of diabetic medications that clinicians may discuss with their patients. All of the listed agents are valid second-line treatments, and you should select one based on the individual's needs.

Incretin-based therapy. Among newer antihyperglycemic agents, incretins have drawn much attention and thus warrant special focus. The emphasis on these agents should not be interpreted as an implied endorsement for their second-line use. There are 2 main classes: dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists. Both act on the gut peptide GLP-1 to enhance glucose-stimulated insulin secretion and glucagon suppression.[16]

DPP-4 inhibitors promote the effects of endogenous GLP-1 by inhibiting its breakdown by the enzyme DPP-4. By increasing GLP-1, these agents achieve mild glucose lowering while remaining weight neutral.[16] DPP-4 inhibitors can be combined with metformin and other oral agents and are not associated with hypoglycemia.[16]

Injectable GLP-1 receptor agonists provide supraphysiologic levels of GLP-1, resulting in increased insulin secretion, reduced glucagon secretion, delayed gastric emptying, increased satiety, and weight loss.[16] Research has shown that exenatide can de-

TABLE

Matching diabetic medication attributes to patient needs

Class	Medications	Actions	Benefits	Possible adverse effects and disadvantages	A1C-lowering (%)	Cost*
Biguanides	Metformin	↓ Hepatic glucose production	Weight neutral or loss No hypoglycemia ↓ CV mortality	GI side effects Lactic acidosis Impaired B_{12} absorption Use caution or avoid in renal dysfunction	1-2	$
Sulfonylureas	Gliclazide Glimepiride Glipizide Glyburide	↑ Insulin secretion	Fast-onset glucose lowering	Hypoglycemia Lack of durable glycemic control Weight gain	1-2	$
Meglitinides	Repaglinide Nateglinide	↑ Insulin secretion	Improve meal-related insulin release and postprandial glucose	Hypoglycemia Weight gain	0.1-2.1	$$-$$$
Thiazolidinediones	Pioglitazone	↑ Insulin sensitivity	No hypoglycemia ↑ HDL ↓ Triglycerides	Bladder cancer concerns Edema Fracture risk Heart failure Weight gain	0.5-1.4	$$$
GLP-1 receptor agonists	Exenatide Liraglutide	↑ Insulin secretion ↓ Glucagon secretion Delayed gastric emptying Early satiety	Possible beta-cell preservation Weight loss	GI (nausea, vomiting, diarrhea) Injectable Medullary thyroid tumors in rodents Pancreatitis	0.5-1.5	$$$
DPP-4 inhibitors	Linagliptin Saxagliptin Sitagliptin Vildagliptin	↓ Glucagon secretion ↑ Insulin secretion	No hypoglycemia Weight neutral	Angioedema Pancreatitis	0.5-0.8	$$$
Alpha-glucosidase inhibitors	Acarbose Miglitol	Delays carbohydrate absorption	Nonsystemic medication Reduces postprandial glucose	Frequent dosing GI side effects (abdominal cramping, flatulence)	0.5-0.8	$$
Insulin	Aspart Detemir Glargine Lispro NPH Regular	Replaces endogenous insulin	Mimics physiology Rapidly effective	Hypoglycemia Weight gain	1.5-3.5	$-$$$

CV, cardiovascular; DPP, dipeptidyl peptidase; GI, gastrointestinal; GLP, glucagon-like peptide, HDL, high-density lipoprotein.

*Monthly cost of an average daily maintenance dose of available products: $, <$50; $$, $50.01-$100; $$$, >$100. **Source:** www.drugstore.com; accessed October 10, 2012.

Adapted from: Reid TS. Options for intensifying diabetes treatment. *J Fam Pract.* 2011;9(suppl 1):S7-S10; American Diabetes Association Position Statement. Standards of Medical Care in Type 2 Diabetes-2012. *Diabetes Care.* 2012;35(suppl 1):S11-S63.

crease mean weight by 7 kg over 2.4 years.[18,19] Exenatide is dosed subcutaneously twice daily, while liraglutide is administered once daily. Once-weekly exenatide was approved by the US Food and Drug Administration (FDA) in February 2012. A recent study showed once-weekly exenatide lowered A1C levels, reduced weight, and caused fewer episodes of hypoglycemia compared with adding insulin glargine to the regimen when diabetes was uncontrolled on metformin (with or without a sulfonylurea).[20] Patients may experience nausea, vomiting, and diarrhea at the onset of use of GLP-1 agonists.[21] Slow titration and forewarning the patient of these adverse effects will help with compliance.

In October 2011, the FDA approved the use of exenatide with basal insulin. For patients already taking basal insulin with or without metformin or pioglitazone, adding exenatide resulted in improved A1C values and weight loss over a 30-week period.[22] Reducing the dose of basal insulin at the initiation of exenatide helps decrease the incidence of hypoglycemia when considering this combination.[22] Basal insulin lowers fasting glucose levels, while exenatide reduces postprandial glucose.

Although gaining in popularity, incretin therapy is being monitored for long-term safety. Cases of pancreatitis have been reported in both classes of medicines.[4] Liraglutide has been associated with medullary thyroid cancer (MTC) in rodents.[23,24] The FDA has recommended against using liraglutide and extended-release exenatide in patients with a personal or family history of MTC.[16] Although the long-term safety of GLP-1 agonists and DPP-4 inhibitors is unknown, their novel mechanisms of action can prove useful for the right patient.

Concerns over TZDs. In addition to the FDA recommendation to avoid TZDs in patients with symptomatic heart failure, 2 studies have recently found that pioglitazone may be associated with an increased risk of bladder cancer.[25,26] The FDA recommends avoiding use of pioglitazone in patients with *active* bladder cancer, and that it should be used with caution in patients with a history of *cured* bladder cancer. The European Medicines Agency also recommends against pioglitazone use in patients with uninvestigated macroscopic hematuria.[27] The potential association between pioglitazone and bladder cancer requires further study. At this point, TZDs remain a valid second- or third-line treatment option in patients only after they are made aware of the potential risks and benefits.

CASE ▶ JR's A1C of 7.6% is above his individualized goal of 7%. He feels he has maximized his efforts in the realm of lifestyle changes and is interested in another medication. Using the recommended patient-centered approach, we discuss with him the risks and benefits of each medication in the **TABLE** and we select the medication best suited to him based on adverse-effect profile.

Adding a second medication to metformin at the time of diagnosis may be considered if the initial A1C value is >9%.

Immunizations

An often overlooked but important part of the diabetes visit is reviewing the patient's immunization history. Unless there are contraindications, all individuals with diabetes should receive the pneumococcal and annual influenza vaccines.[4] In addition, the Advisory Committee on Immunization Practices now recommends hepatitis B virus (HBV) vaccine for unvaccinated adults with diabetes from ages 19 to 59.[28] Unvaccinated adults with diabetes over age 60 should be vaccinated at the discretion of the provider after risk assessment.[28] Patients may be at risk of contracting HBV in long-term care facilities where assisted blood sugar monitoring commonly occurs.[28] Studies have shown that patients with diabetes may progress to chronic hepatitis B infection more often than patients without diabetes, and are at higher risk for nonalcoholic liver disease and hepatocellular carcinoma.[29]

CASE ▶ JR's history shows that he is current on his influenza and pneumococcal vaccines. However, he doesn't recall whether he's been vaccinated against HBV. Serum testing reveals no previous immunization, and recommending HBV vaccine is appropriate.

Surveillance

The 2012 ADA recommendations do not

include any new surveillance practices for microvascular disease. Providers should continue to offer the following screening to T2DM patients annually: urine albumin excretion testing and serum creatinine to assess for nephropathy, a comprehensive dilated eye exam to assess for retinopathy, and a foot exam to assess for distal symmetric polyneuropathy.[4]

CASE ▶ Each of these tests were performed (or ordered) for JR. We'll see him again in 2 to 3 months for diabetes follow-up. JFP

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