The Rx Consultant
Improving patient care through drug education

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# Diabetes Update

## Introduction

The prevalence of diabetes mellitus (DM) in U.S. adults nearly doubled between 1995 and 2010, increasing from 4.5% to 8.2%.[1] While researchers note that this dramatic increase is partly accounted for by people living longer with diabetes, the high prevalence is a significant public health issue. An estimated 11% of adults aged 20 years or older have diabetes. Among those aged 65 years or older, the prevalence is much higher – an estimated 27%.[2] Perhaps most alarming is the rise among U.S. adolescents: the prevalence of prediabetes and diabetes in the 12 - 19 year age group increased from 9% in 1999 to 23% in 2008.[3]

A boom in diabetes research over the last decade has generated new insights and considerations in diabetes management. The number of available medications with different mechanisms of action, while welcome, has complicated treatment choices. And more medications are sure to follow – a 2012 pharmaceutical manufacturer report listed 221 drugs in the pipeline for diabetes and diabetes-related conditions.[4]

This issue will discuss recent developments in diabetes, including significant changes in adult practice guidelines, the establishment of pediatric guidelines, and medication updates: angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) for the management of diabetic kidney disease, a new DPP-4 inhibitor (alogliptin), a first-in-class sodium-glucose co-transporter 2 (SGLT2) inhibitor (canagliflozin [*Invokana*™]), and an investigational, ultra-long-acting insulin.

### Continuing Education Objectives

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1. Outline the current American Diabetes Association recommendations for blood pressure goals and self-monitoring of blood glucose. Discuss current recommendations for patient-centered glycemic goals and therapy selection in type 2 diabetes.
2. Review the National Kidney Foundation's current guidelines on ACE inhibitor and ARB use in diabetic kidney disease.
3. Discuss the increasing prevalence of type 2 diabetes in children and adolescents, and the recommended treatment approach.
4. Identify the differences between alogliptin and other FDA-approved DPP-4 inhibitors. Discuss the potential benefits and adverse effects of canagliflozin.

### The Bottom Line

- The systolic blood pressure (BP) goal for most people with diabetes has been increased to < 140 mmHg.
- For most people on multiple daily insulin doses, self-monitoring of blood glucose (SMBG) is recommended at event-specific times such as before & after eating, at bedtime, before exercise, and when low BG is suspected or has been treated.
- For most people with diabetes who do not use insulin or take oral drugs that cause hypoglycemia, SMBG may be unnecessary.
- Experts recommend patient-centered diabetes care, with individualized glucose goals based on factors such as attitude/motivation, adherence, self-care capacity, disease duration and coexisting conditions.
- Current recommendations for ACEI or ARB use in patients with diabetes include:
  - In patients with hypertension, an ACEI or ARB is the preferred agent to reduce BP and prevent or slow kidney disease.
  - In patients with normal BP and abnormal urine albumin levels who have a high risk for kidney disease or its progression, an ACEI or ARB is suggested.
  - An ACEI or ARB is not recommended to prevent kidney disease in patients with normal BP and normal urine albumin levels.
  - Combined use of an ACEI plus an ARB is not recommended.
- The first pediatric guideline for type 2 diabetes recommends metformin as first-line oral drug therapy.
- New drugs include: 1) alogliptin (*Nesina*®), a DPP-4 inhibitor similar to other drugs in its class, and 2) canagliflozin (*Invokana*™), a first-in-class sodium glucose co-transporter 2 inhibitor that reduces BG by increasing urinary glucose excretion.

**Disclosure:** *Dr. Farnen and Dr. Mausner report no financial or personal relationship with any commercial interest producing, marketing, reselling, or distributing a product or service that appears in this issue.*

## American Diabetes Association (ADA) Guideline Update

The ADA publishes *Standards of Medical Care in Diabetes* to guide clinicians, patients, researchers, payers, and other individuals interested in the management of DM.[5] The standards are reviewed and revised each year, based on the most current scientific evidence. The latest edition (2013) includes major changes in blood pressure (BP) goals and recommendations for self-monitoring of blood glucose (SMBG).[5]

### New Blood Pressure Goals

Patients with diabetes often have high BP, which is a major risk factor for both cardiovascular (CV) disease and microvascular diabetes complications. Observational studies have suggested that individuals with DM who have BP consistently above 115/75 mmHg have an increased risk of CV events and death.[5] However, there is a lack of strong clinical evidence to support the ADA's historical recommendation for a systolic blood pressure (SBP) goal of less than 130 mmHg in patients with diabetes.

The 2013 practice guideline raises the target for SBP from less than 130 mmHg to less than 140 mmHg.[5] The change is based on recent research that shows the lower BP goal provides little clinical benefit – and possibly causes harm. A landmark clinical trial (the 2007 *Action to Control Cardiovascular Risk in Diabetes* [ACCORD] study) investigated whether intensive lowering of SBP to an average of less than 120 mmHg reduced major CV events more effectively than lowering SBP to less than 140 mmHg. Specifically, the trial compared a composite outcome of nonfatal heart attacks, nonfatal strokes, and CV deaths in the 2 groups.[6] After attainment of the BP goals and an average follow-up period of almost 5 years, there was no significant difference between the lower BP group and the higher BP group with respect to the composite outcome, nonfatal heart attack, nonfatal stroke, or CV death. More intensive BP control resulted in a nominally significant reduction only in the rate of nonfatal and total strokes. However, patients in the group with the lower BP goal also had higher rates of serious side effects – including hypotension, bradycardia, and hyperkalemia – attributed to antihypertensive medication.[6]

An analysis of 5 studies, which included ACCORD, had similar results: when compared with standard BP targets (SBP ≤ 140-160 mmHg and diastolic BP ≤ 85-100 mmHg), intensive BP targets (SBP ≤ 130 mmHg and diastolic BP ≤ 80 mmHg) resulted in a slightly lower risk of stroke, but no fewer deaths or heart attacks.[7]

A second analysis of studies comparing BP goals found that intensive BP control (SBP ≤ 135 mmHg) was linked with a 10% reduction in deaths due to any cause and a 17% reduction in stroke compared with less intensive BP control (SBP < 140 mmHg). However, there was a 20% increase in serious adverse events. With SBPs less than 130 mmHg, further stroke reduction occurred; however, there was no benefit for cardiac, renal, or retinal outcomes, and serious adverse events increased by 40%.[8]

Results from a large observational study further support the guideline change. Among newly diagnosed DM patients (with or without CV disease), achieving a BP of less than 130/80 mmHg did not lower the risk of death from any cause. In fact, a SBP less than 110 mmHg and a diastolic BP less than 75 mmHg were linked with a significantly increased risk of death – in patients with or without CV disease.[9]

The preponderance of evidence supports the new standard goal of SBP less than 140 mmHg and a DBP less than 80 mmHg in most patients with longstanding DM. The ADA stresses, however, that the adjusted goal is not meant to downplay the importance of treating high BP in patients with DM.[5] A target SBP of less than 130 mmHg may be appropriate for younger patients (long-term BP control may protect against kidney complications) and patients with a higher risk of stroke – if the goal can be achieved without a substantial increase in adverse effects from antihypertensive medications.[5] See Table 1 for a summary of the current ADA recommendations for managing high BP in patients with diabetes.

### Self-Monitoring of Blood Glucose (SMBG)

The ADA standard regarding SMBG in patients who use multiple daily insulin injections has been revised to highlight the need for testing based on patient needs and goals.[5] Previously, the recommendations called for SMBG "3 or more times a day." The 2013 revised standard for SMBG is more detailed, recommending testing at event-specific times and as often as needed to avoid hypo- or hyperglycemia. This includes testing before meals and snacks, occasionally after meals, at bedtime, before exercise, when low BG is suspected, after treating low BG (until a normal value is achieved), and before performing critical tasks (eg, driving).[5] According to the ADA, this amounts to 6 to 8 times a day for many patients, but could be more depending on individual needs.[5] The recommendation is partly based on a study of almost 27,000 children and adolescents with type 1 diabetes (T1DM) that showed improved metabolic control with an increase in SMBG.[10] An A1C reduction of 0.20% resulted from each additional SMBG test, up to 5 per day. The frequency of diabetic ketoacidosis also decreased steeply and significantly with increased SMBG.[10]

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**Table 1. Recommendations for Managing Hypertension in Patients with Diabetes [5]**

- People with diabetes and hypertension should be treated to a SBP goal of < 140 mmHg. A lower goal of < 130 mmHg may be appropriate for certain individuals.
  Patients with diabetes should be treated to a DBP goal of < 80 mmHg.
- Patients with a BP > 120/80 mmHg should be advised on lifestyle changes to reduce blood pressure:
  - Weight loss, if overweight
  - Dietary Approaches to Stop Hypertension (DASH)-style diet
  - Limit alcohol to moderate intake
  - Increased physical activity
- Patients with confirmed BP ≥ 140/80 mmHg should, in addition to the lifestyle advice above, begin drug therapy to achieve BP goals. An ACEI or an ARB is preferred. If one class is not tolerated, the other should be substituted.
- Combination drug therapy (2 or more agents at maximal doses) is generally required to achieve BP goals.
- Administer 1 or more antihypertensive medications at bedtime. Growing evidence suggests CV events and mortality are reduced if at least 1 antihypertensive medication is taken at bedtime.
- If ACEIs, ARBs, or diuretics are used, serum creatinine/eGFR and serum potassium levels should be monitored.
- During pregnancy, the BP target goal is 110–129 / 65– 79 mmHg (for long-term maternal health and to minimize impaired fetal growth); ACEIs and ARBs are contraindicated.

*Abbreviations: ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure*

Evidence to support SMBG in patients with type 2 diabetes (T2DM) who do not use insulin or oral hypoglycemic agents is lacking, with few studies showing a clinically meaningful benefit.[11] A recent review of 12 controlled trials of patients with T2DM who were not using insulin showed that a minor improvement in glucose control (a decrease of 0.3% in A1C) occurred after about 6 months of SMBG. However, even this small improvement subsided after 12 months of follow-up.[12] Another analysis had similar findings: 6 months of SMBG reduced A1C levels by only 0.25% in patients with non-insulin-treated T2DM. At 12 months, the reduction was 0.23%. While the small reductions in A1C demonstrated with SMBG testing were statistically significant, they were not considered clinically significant.[13] Furthermore, studies of patients with T2DM have not clearly identified specific patient characteristics that indicate a higher likelihood of benefit from SMBG.[12] It may be most appropriate for patients who are prone to hypoglycemia, or those taking medications linked with hypoglycemia (eg, sulfonylureas or meglitinides). SMBG may also be more beneficial for motivated T2DM patients who would follow through with changes in lifestyle habits and medication regimens indicated by SMBG results.[11] The ADA standards specify that all patients who undertake SMBG should be taught how to use the results to adjust food intake, exercise, and drug therapy to achieve specific goals. The ongoing need for and frequency of SMBG should be re-evaluated at each follow-up visit.[5]

## Patient-Centered Approach to T2DM Management

A joint position statement, *Management of Hyperglycemia in Type 2 Diabetes: A Patient Centered Approach*, was issued in 2012 by the ADA and the European Association for the Study of Diabetes (EASD). The joint statement takes a strong stance in recommending patient-centered care that places the patient's preferences, tolerances, needs, and values at the forefront of clinical decision making and glycemic goal setting.[14] The ADA recommendation of an A1C goal of less than 7% – with higher or lower goals based on patient-specific factors – is in alignment with the joint recommendations. However, the ADA-EASD takes the patient-centered approach further – recommending that patient-specific factors (including attitude/motivation, adherence, self-care capacity, disease duration, life expectancy, significant coexisting conditions, resources and support system) should be considered for the purpose of setting highly individualized glycemic goals. Ranges of A1C goals are provided for consideration, depending on the strength or weakness of various patient factors. For example, a stringent A1C target (eg, 6%-6.5%) may be indicated for a motivated patient with new-onset diabetes and a long life expectancy, while less stringent A1C goals (eg, 7.5%-8% or even slightly higher) are more suited to less-motivated patients with long-standing diabetes, many coexisting medical conditions, limited resources and support, or a higher risk for hypoglycemia.[14]

The joint statement also offers guidance for the use of medications to lower BG levels. Unless there are contraindications, metformin remains the recommended first-line agent, along with lifestyle changes. If the A1C target is not achieved after 3 months, the statement recommends combination therapy with metformin plus one of the following agents: a sulfonylurea, thiazolidinedione, DPP-4 inhibitor, GLP-1 receptor agonist, or (usually basal) insulin.[14] Similarly, the ADA guideline recommends a second oral agent, a GLP-1 receptor agonist (exenatide, liraglutide), or insulin – after 3 to 6 months of unsuccessful monotherapy.[5] Assuming similar efficacy among add-on agents (which typically provide a further reduction in A1C of about 1%), the ADA-EASD statement endorses patient preference and characteristics playing a major role in drug selection. However, it does say, "insulin is likely

to be more effective than most other agents as a third-line therapy, especially when A1C is very high (eg, ≥ 9.0%)."[14]

## ACEIs and ARBs in Diabetes

Chronic kidney disease (CKD) is defined as kidney damage or a glomerular filtration rate (GFR) less than 60 mL/min/1.73 $m^2$ for at least 3 months.[15] The stages of CKD are shown in Table 2. In diabetic kidney disease (DKD), the presence of protein (principally albumin) in the urine, termed "albuminuria," is a marker of kidney damage. "Microalbuminuria," an early marker of kidney damage, is defined as a urinary albumin-creatinine ratio (ACR) of 30-300 mg/g. An ACR greater than 300 mg/g is termed "macroalbuminuria" and is linked with progressive decline in GFR, an increase in blood pressure, and a high risk of kidney failure. Because urinary albumin excretion can vary within individuals, an elevated ACR should be confirmed by at least 2 additional urine specimens (in the absence of urinary tract infection) over 3-6 months.[16] In 2012, the National Kidney Foundation's *Kidney Disease Outcomes Quality Initiative* (KDOQI) issued an updated guideline for the management of albuminuria in DKD.[17]

### KDOQI Guideline Update

#### Patients with Hypertension

Most patients with DKD have hypertension (defined as a BP ≥ 130/80 mmHg).[18] In patients with DM and hypertension, ACEIs or ARBs have been shown to prevent the development of macroalbuminuria, and (where macroalbuminuria and moderately reduced GFR are already present) to slow GFR decline and help prevent end-stage kidney disease.[17] The previous KDOQI guideline recommended either an ACEI or an ARB (usually in combination with a diuretic) as the preferred antihypertensive agent in patients with diabetes and CKD.[17] For slowing the progression of macroalbuminuric kidney disease, the evidence is strongest for the use of ACEIs in T1DM and for ARBs in T2DM.[18] The guideline update does not change these recommendations.[17]

#### Patients without Hypertension

In DM without hypertension, the previous guideline recommended the use of an ACEI or ARB for patients with macroalbuminuria, and allowed for the consideration of an ACEI or ARB for patients with microalbuminuria.[19] The guideline update differs slightly, suggesting use of an ACEI or ARB in patients with normal BP and either micro- or macroalbuminuria who are at high risk for DKD or its progression.[17] Risk factors for DKD or its progression are listed in Table 3. The optimal ACEI or ARB dose in normotensive patients has not been established. The guideline update suggests titrating up to the maximum approved dose for the treatment of hypertension, as tolerated.[17]

**Table 2. Stages of CKD [15]**

| Stage | GFR (mL/min/1.73 $m^2$) |
|---|---|
| 1: Kidney damage[a] with normal or ↑ GFR | ≥ 90 |
| 2: Kidney damage[a] with mildly ↓ GFR[b] | 60 - 89 |
| 3: Moderately decreased GFR | 30 - 59 |
| 4: Severely decreased GFR | 15 - 29 |
| 5: Kidney failure | < 15 or on dialysis |

[a] *Kidney damage is defined as either pathological abnormalities (ie, on biopsy) or markers of damage (eg, abnormal urine or blood tests or imaging studies).*

[b] *In the absence of kidney damage, GFR of 60 to 89 may be normal in elderly patients.*

*Abbreviations: CKD = chronic kidney disease; GFR = glomerular filtration rate*

The update recommends against ACEI or ARB use for the primary prevention of DKD in patients with normal BP and normal urinary albumin levels (ACR < 30 mg/g).[17]

#### Albuminuria as a Treatment Target

The previous guideline states that albuminuria reduction may be considered a treatment target in DKD.[19] In contrast, the guideline update notes that the use of changes in albuminuria as a surrogate marker for treatment benefit (eg, preventing end-stage kidney disease) is increasingly being questioned because of inadequate evidence that such changes predict long-term kidney outcomes. The guideline update suggests using changes in both estimated GFR (eGFR; calculated using a formula) and albuminuria to monitor kidney status.[17]

#### ACEI/ARB Combination Therapy

The guideline update states that combined use of an ACEI plus an ARB is currently not recommended. Although such combination therapy decreases albuminuria compared with either medication alone, at least one large trial (called ONTARGET, discussed below) has shown that it increases the risk of adverse effects, including impaired kidney function and hyperkalemia.[17]

The guideline update also recommends against combined use of the direct renin inhibitor, aliskiren (*Tekturna*®), with an ACEI or ARB in patients with DM. This recommendation was prompted by a clinical trial of aliskiren plus an ACEI or ARB in participants with T2DM and either kidney impairment or cardiovascular (CV) disease. The trial was stopped early because of a lack of benefit and an increased risk of stroke, hyperkalemia, hypotension,

**Table 3. Risk Factors for Diabetic Kidney Disease or Its Progression [17]**

- Increasing albuminuria within the microalbuminuria range (urinary ACR 30-300 mg/g)
- Macroalbuminuria (urinary ACR > 300 mg/g)
- Decreasing GFR
- Increasing BP
- Retinopathy
- Elevated blood lipid and/or uric acid concentrations
- Family history of hypertension, macrovascular disease, or DKD

*Abbreviations: ACR = albumin-creatinine ratio; BP = blood pressure; DKD = diabetic kidney disease; GFR = glomerular filtration rate*

and kidney impairment.[17] Based on the same trial, the aliskiren package insert contraindicates use of aliskiren with an ACEI or ARB in patients with DM.[20] Additionally, a combination pill containing aliskiren and valsartan (*Valturna*®) has been withdrawn from the U.S. market.[21]

### The ONTARGET Trial

A landmark clinical trial (ONTARGET) compared the effects of an ACEI (ramipril), an ARB (telmisartan) and their combination on CV and kidney outcomes in participants with either vascular disease or DM and end-organ damage.[22,23] Overall, combination ACEI/ARB therapy resulted in more adverse effects than single-drug therapy, without increasing CV benefit;[23] it also resulted in worse kidney outcomes, despite a greater reduction in albuminuria.[22]

Recently, an analysis of only the ONTARGET participants with DM was published.[24] About one-third had significant CKD; the rest had normal or mildly decreased eGFR and either normal urine albumin or microalbuminuria. Patients who took an ACEI or ARB were analyzed as one, single-drug group for comparison with the combination therapy group.

Rates of CV events (a composite of CV death, nonfatal heart attack, nonfatal stroke, or hospitalization for heart failure), stroke, and all-cause death were similar in both treatment groups. Rates of a composite outcome related to kidney function (chronic dialysis for more than 2 months or doubling of baseline creatinine) were also similar in both treatment groups.[24] These results were similar whether or not participants had significant CKD when the trial started. Combination therapy increased the risk of hyperkalemia in patients with or without CKD. While combination therapy decreased systolic BP more than did single-drug therapy, it also led to more cases of hypotension; however, the difference in hypotension was statistically significant only in the group without significant CKD. The investigators concluded that combination therapy did not provide greater clinical benefit than single-drug therapy, but did increase the risk of adverse effects.[24]

### Other Combination Therapy Investigations

It has been noted that ONTARGET excluded participants with severe hypertension. The results of a prospective, observational study suggested that the benefits of combination ACEI and ARB therapy may outweigh the risks in patients with T2DM and severe hypertension.[25]

Combined ACEI/ARB use is still being studied. At least 3 ongoing clinical trials are comparing the effects of ACEI/ARB combinations and monotherapy on CV and/or renal outcomes in participants with DM who have or are at high risk for DKD.[26-28]

## A New Guideline for Pediatric T2DM

Childhood DM is usually assumed to be T1DM (juvenile-onset), while T2DM was previously called adult-onset because it typically did not occur until later in life. During the past few decades, however, the increasing prevalence of childhood obesity has been linked to the emergence of pediatric T2DM. As many as one-third of new DM cases among individuals under age 18 are T2DM. This trend is occurring not only in the U.S., but worldwide.[29]

Pediatric T2DM is most common between ages 10 and 19 years, and in ethnic minorities.[29] From 2002 to 2005, the annual incidence of new-onset T2DM among U.S. children under age 10 was 0.4 per 100,000 (about 2% of new DM cases in this age group). For individuals aged 10 through 19, the annual incidence of new-onset T2DM was 8.5 per 100,000 (more than 30% of new DM cases in that age group), with the highest rates among U.S. minorities (Asians/Pacific Islanders, non-Hispanic blacks, Hispanics, and American Indians).[30]

A new clinical practice guideline on childhood T2DM, developed by the American Academy of Pediatrics (AAP), was published in 2013.[29] Recommendations include the following:

- Initial insulin treatment is indicated for children and adolescents with ketosis or ketoacidosis, regardless of whether the diagnosis is T1DM or T2DM. Diabetic ketoacidosis requires hospital admission for immediate insulin and fluid replacement. Patients with a random BG level greater than or equal to 250 mg/dL or A1C greater than 9% may also benefit from insulin, at least initially. Insulin provides rapid glycemic control and may help preserve beta-cell function.[29]
- In less severe cases, the recommended first-line

therapy for pediatric T2DM is metformin, along with lifestyle modification. Metformin should be started at a low dose (eg, 500 mg/day) and titrated upward by 500 mg every 1-2 weeks, to a maximum of 2000 mg/day in divided doses. Insulin, or a combination of insulin and metformin, are also reasonable options. Lifestyle modification alone is generally not recommended. There is no conclusive evidence of success with lifestyle modification alone; however, expert consensus is that less than 10% of patients achieve their BG goals with this approach.[29]

- Before starting metformin, it is essential to determine that the diagnosis is T2DM, not T1DM. If there is any uncertainty, insulin should be used.[29] (See Table 4.)

- Many patients with T2DM who initially need insulin can be gradually weaned off insulin and managed with metformin and lifestyle modifications.[29]

Insulin and metformin are the only DM medications that are FDA approved for pediatric use; most others have not been studied in children or adolescents under age 19.[29] Although the guideline recommends metformin as first-line therapy, it notes the results of a recent trial showing that metformin alone does not provide sustained glycemic control in most young people with T2DM.[29] In that trial, participants aged 10 to 17 years received either metformin alone, metformin plus lifestyle intervention, or metformin plus rosiglitazone. After an average follow-up of nearly 4 years, failure rates were 52%, 47%, and 39% in the 3 treatment arms, respectively. (Failure was defined as A1C persistently ≥ 8 or persistent/repeated need for insulin.) The difference between metformin alone and metformin plus rosiglitazone was statistically significant.[31] However, the use of rosiglitazone has been restricted by the FDA because of serious adverse effects in adults, and it is unknown whether other drugs would be similarly effective.[29] The guideline suggests that, if first-line metformin therapy fails, treatment can generally be intensified in the same manner as for adults; clinicians are encouraged to consult experts in pediatric T2DM.[29]

Lifestyle modifications recommended by the AAP include diet (using the Academy of Nutrition and Dietetics' *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines*); moderate to vigorous exercise for at least 1 hour daily; and limitation of nonacademic screen (television/computer) time to less than 2 hours a day. Initial and ongoing education of the patient and family are crucial for adherence; this should include setting realistic goals and taking into account the family's perceptions of diabetes and overweight.[29]

The AAP guideline recommends monitoring of A1C every 3 months. SMBG is recommended for patients who are taking insulin or other drugs that can cause hypoglycemia. SMBG is also recommended when starting or changing treatment; during other illnesses that might affect BG levels; and when treatment goals have not been met.[29]

**Table 4. Typical Characteristics* of Childhood T2DM[29]**

- Overweight (BMI ≥ 85th and ≤ 94th percentile for age and gender) or obese (BMI > 95th percentile for age and gender)
- Strong family history of T2DM
- Gradual disease progression with few or no symptoms (with hyperglycemia but usually not ketosis or ketoacidosis) at the time of diagnosis
- Normal or elevated insulin and C-peptide levels at diagnosis (indicating that the pancreas is able to secrete insulin)
- Demonstrates insulin resistance
- No evidence of diabetic autoimmunity (negative for autoantibodies typically associated with T1DM)

* *Not every case has all of the typical characteristics. In some cases, the diagnosis of T2DM vs T1DM may not be clear at first: for example, in an obese child with ketoacidosis. Children with T2DM are more likely than those with T1DM to have hypertension and dyslipidemia.*

*Abbreviations: T2DM = type 2 diabetes mellitus; BMI = body mass index; T1DM = type 1 diabetes mellitus*

## New and Investigational Drugs

### Alogliptin

Alogliptin (*Nesina*®), a new dipeptidyl peptidase-4 (DPP-4) inhibitor, was approved by the FDA on January 25, 2013. Also approved were 2 fixed-dose combinations: alogliptin plus metformin (*Kazano*®) and alogliptin plus pioglitazone (*Oseni*®).[32] Alogliptin is the fourth DPP-4 inhibitor to enter the U.S. market, after sitagliptin (*Januvia*®), saxagliptin (*Onglyza*®), and linagliptin (*Tradjenta*®).[33]

Incretin hormones such as glucagon-like peptide-1 (GLP-1), released from the small intestine in response to a meal, stimulate pancreatic beta cells to secrete insulin. However, incretins are rapidly inactivated. DPP-4 inhibitors work by slowing incretin inactivation, thus enhancing insulin secretion and reducing BG levels in a glucose-dependent manner.[20]

Like the other DPP-4 inhibitors, alogliptin is indicated as an add-on to diet and exercise in adults with T2DM.[20] When used alone, alogliptin reduces A1C by 0.4% to 0.6%.[20,32,34] Combination therapy with alogliptin plus either metformin or pioglitazone produces greater A1C reductions than does alogliptin alone.[20,32] There have been no head-to-head comparisons of alogliptin with other DPP-4 inhibitors; however, indirect comparison suggests similar efficacy and safety.[33,35,36]

The alogliptin package insert carries a warning about postmarketing reports of pancreatitis.[20] Pancreatitis has also been reported with other DPP-4 inhibitors, and is likely a class effect.[33] There have also been postmarketing reports of liver failure in patients taking alogliptin (but not other DPP-4 inhibitors). Although a causal relationship has not been established, caution is recommended in patients with abnormal liver tests.[20] The FDA is requiring 5 postmarketing studies, including one focusing on CV outcomes; 3 pediatric trials; and a program to monitor for liver problems, pancreatitis, and severe hypersensitivity.[32,34]

The main differences among the DPP-4 inhibitors may be related to their metabolism and elimination. Alogliptin, sitagliptin, and saxagliptin require dose adjustment for kidney dysfunction, while linagliptin does not. Neither alogliptin nor sitagliptin are expected to have drug interactions related to cytochrome P450 (CYP). In contrast, saxagliptin should be given at the lowest dose if used concurrently with strong CYP3A4/5 inhibitors (eg, ketoconazole, clarithromycin, ritonavir); and linagliptin should not be used with strong CYP3A4 or P-glycoprotein inducers (eg, rifampin).[20]

Another consideration that may influence the choice of DPP-4 inhibitor is the availability of fixed-dose combination pills. When more than one oral diabetes drug is needed, combination pills reduce patients' pill burden and have been shown to improve adherence.[37,38] All the FDA-approved DPP-4 inhibitors are available in combination with metformin. Alogliptin is the only DPP-4 inhibitor available in combination with pioglitazone.[20]

### Drugs with a Novel Mechanism: Sodium Glucose Co-transporter 2 inhibitors

The first sodium glucose co-transporter 2 (SGLT2) inhibitor, canaglifozin (*Invokana*™), was approved by the FDA in March 2013 for treatment of adults with T2DM. SGLT2, a protein found in the kidney tubules, is responsible for about 90% of renal glucose reabsorption. SGLT2 inhibitors reduce glucose reabsorption in the kidneys, thus increasing urinary glucose excretion and decreasing BG levels.[39] Both fasting and postprandial glucose levels, as well as A1C, are decreased.[40,41] This novel mechanism is independent of insulin secretion or resistance and, therefore, should be effective in both newly diagnosed and long-standing DM.[40] The risk of hypoglycemia is low because SGLT2 inhibitors do not directly stimulate insulin secretion, and glucose excretion depends partially on BG levels.[39-41] SGLT2 inhibitors cause weight loss due to a net loss of calories,[39-41] and BP reduction,[41] probably from osmotic diuresis.[40] However, little evidence on long-term CV outcomes is available.[40]

Canaglifozin has been studied as monotherapy and in combination with other diabetes medications including metformin, sulfonylureas, pioglitazone, and insulin.[42] When taken as monotherapy for 6 months, canagliflozin 100 mg daily and 300 mg daily significantly lowered A1C by 0.91% and 1.16%, respectively, compared with placebo. In addition, body weight decreased 2.2% (100 mg dose) and 3.3% (300 mg dose). As add-on therapy, canagliflozin also consistently reduced A1C and body weight, compared with either placebo or active comparators.[20]

Canagliflozin should not be used in patients with diabetic ketoacidosis or with severe kidney impairment.[42] Because glucose excretion in the urine depends on the amount of glucose filtered by the kidney, SGLT2 inhibitors are less effective in patients with impaired kidney function.[39,40] The most frequent side effects are vaginal yeast infection and urinary tract infection. Postural hypotension (which may result in dizziness or fainting) may also occur, and is most common during the first 3 months of therapy.[42] Currently available evidence does not suggest a cancer concern with canaglifozin;[43,44] but other concerns include CV safety[43] and, possibly, an increased risk of fractures.[44] The FDA is requiring 5 postmarketing studies: a CV outcomes trial; a program to monitor for cancers, serious cases of pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, liver abnormalities, and adverse pregnancy outcomes; a bone safety study; and 2 pediatric studies.[42]

### Insulin Degludec

Insulin degludec (*Tresiba*®) is an investigational ultralong-acting basal insulin. Its duration of action exceeds 24 to 42 hours,[45,46] compared with 16 to 24 hours for insulins glargine and detemir.[45] This allows for flexible dosing – degludec is dosed once daily, but does not have to be taken at the same time every day[46] – and could result in less fluctuation of glycemic control and a lower risk of hypoglycemia.[47]

Clinical trial results suggest that the overall efficacy of degludec in reducing A1C is similar to that of glargine or detemir.[45,46] Some trials have found similar hypoglycemia rates with degludec compared with glargine, while others have shown lower rates with degludec.[45,46]

In 2012, an FDA panel recommended approval of insulin degludec,[48,49] with the requirement of a postmarketing study to address concerns about a possible increase in CV events.[48-50] However, the FDA rejected the drug in February 2013 and will require a CV outcomes trial before reconsidering its approval.[51,52] This will likely result in a delay – at least until 2015 – to complete the review process.[51,53]

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• ***My blood pressure goal isn't as low as it used to be – does that mean blood pressure control is not as important in my diabetes care?***

The new guidelines from the American Diabetes Association (ADA) changed the goal for the systolic (top number) blood pressure from less than 130 mmHg to less than 140 mmHg. The change was based on research showing that, for many people with diabetes, having a systolic blood pressure of less than 140 may be good enough to help protect against heart attacks, stroke, and kidney disease while possibly lowering the risk of side effects from blood pressure medications. Most people with high blood pressure need to take more than 1 medication to bring their blood pressure down to an adequate blood pressure goal; the new goal may allow patients to take fewer medications.

Controlling blood pressure is still as important as ever for preventing complications from diabetes. In fact, a systolic blood pressure of less than 130 mmHg may still be the goal for certain people, such as younger patients. Talk with your health care provider about your personal blood pressure goal and how you can reach it.

• ***I have type 1 diabetes and use insulin. My wife has type 2 diabetes and takes oral metformin. How often do we really need to check our blood sugars?***

How often really depends on a number of factors, including the type of medication you take and whether your doses are changed. The ADA recently came out with new guidelines to help you and your healthcare provider decide the right amount of testing for you.

Some people taking insulin should test before each meal and snack in order to help determine their dose. They may also need to check their sugar levels at other times; see the inset to the right for the current recommendations. Many patients on insulin will need to test 6 to 8 times per day. On the other hand, someone taking an oral medication may not need to test as often, or at all, if their medication dose is not based on their blood sugar number.

Talk with your healthcare provider about your personal testing plan. Know what to do if your numbers are above or below your targets (for example, adjust your food intake, exercise, or medication to reach your goals).

• ***Is it true that more children are getting diabetes?***

As we see more obesity in children and teenagers, more are developing diabetes and prediabetes (a higher than normal fasting blood sugar but not yet to the diabetes level). Noticing when a child is gaining too much weight and taking steps to keep him/her at a healthy weight helps prevent prediabetes. In the past when children were diagnosed with diabetes, it was nearly always type 1. Now, more children are getting type 2 diabetes – mostly in the 10 to 19 year old age group and more commonly in minority groups.

The American Academy of Pediatrics (AAP) has developed guidelines for the treatment of type 2 diabetes in children and teens. The AAP guideline includes the following recommendations:

- If it is not clear if the child has type 1 DM or type 2 DM, treatment should begin with insulin. If it is decided that child has type 2 DM, it may be possible to switch from insulin to pills.
- Treatment for children/teens with confirmed type 2 DM: metformin plus lifestyle changes (see 5th bullet)
- Get a blood test called A1C every 3 months
- How often you should check the child's blood sugar depends on many things, including the type of medicine, whether the child is starting or changing treatment, whether the child has an acute illness, and whether treatment goals are being met.
- The treatment plan should include nutrition counseling, moderate to vigorous exercise at least 60 minutes daily, and limiting nonacademic screen time (TV, computer, video games) to less than 2 hours per day.

• ***Are there any new drugs for diabetes?***

Alogliptin (*Nesina®*) was approved by the Food and Drug Administration (FDA) in January 2013 for the treatment

## Recommended Times and Conditions for Testing Blood Sugar

*The 2013 American Diabetes Association standards do not specify the number of times per day that blood sugar testing should occur, but instead focus on the conditions under which testing should occur.*

***If you use insulin, blood sugar testing is recommended:***

- Before meals and snacks
- Occasionally after eating
- At bedtime
- Before exercise
- When low blood glucose is suspected
- After treating low blood glucose, until normal blood sugar is achieved
- Before starting critical tasks such as driving

of diabetes. It helps the body release more insulin after a meal. Alogliptin works similarly to 3 other drugs that have been available: sitagliptin (*Januvia®*), saxagliptin (*Onglyza®*), and linagliptin (*Tradjenta®*). The makers of alogliptin have also combined it with other diabetes medications that are already in use. *Kazano®* is a combination of alogliptin and metformin. *Oseni®* is a combination of alogliptin and pioglitazone.

Canagliflozin (*Invokana®*) is the first in a new class of diabetes medications that lower blood sugar by letting the kidneys put more sugar out into the urine rather than returning it to the blood. In addition to improving blood sugar, this medication may help some patients lose weight and lower their blood pressure. It should not be used by patients with severe kidney disease.

Note that "newer" does not necessarily mean "better" than older drugs; sometimes, new drugs have side effects that only become apparent after broad use in a population. There are many older medications for diabetes that have been proven to be effective and safe.

- ***Why do people with diabetes have to worry about their kidneys? What can I do to keep my kidneys healthy?***

People with diabetes are more likely to get kidney disease than people who do not have diabetes. In fact, in the U.S. today, diabetes is the leading cause of kidney failure: the condition in which the kidneys are so damaged that to stay alive, the person needs either dialysis ("kidney machine") or a kidney transplant. Good blood pressure and blood sugar control not only help prevent kidney disease from occurring in the first place, they also help prevent kidney disease from getting worse.

Finding kidney damage at the earliest possible stage can make a difference. Kidney health is measured by a combination of blood and urine tests. If you have signs of kidney disease, your health care provider may prescribe either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). These medicines are also used to treat high blood pressure. They are not recommended for preventing kidney disease in patients with diabetes who have normal blood pressure and no signs of kidney damage. They also should not be used together. See inset below for ways to keep your kidneys healthy.

- ***It's too hard to do everything I am supposed to do for my diabetes care. So I just do what I can-is that okay?***

Self-management of diabetes is difficult. However, it is well known that people who are successful in keeping their blood sugar, blood pressure, and cholesterol within target ranges end up doing better in the long run, with fewer complications such as heart disease, stroke, or kidney disease. Success is largely up to you. When given a recommendation by your healthcare provider, have an honest conversation with yourself, and then with your provider, about the following:

- Am I ready to make this change? If I cannot, is there a smaller or different change I can make now instead?
- Do I understand why I am being asked to do this?
- Do I think that doing it will make a difference?
- Does the medication give me side effects? Are there alternatives?
- Does the recommendation conflict with how I or my family live?

## Keeping Kidneys Healthy

- Work with your healthcare provider to keep your blood sugars in your target range using diet, exercise and medications as prescribed.
- Work with your healthcare provider to keep your blood pressure and cholesterol levels in your target ranges.
- Ask your healthcare provider whether you should be taking an ACE inhibitor or an ARB.
- Make sure your healthcare provider is using blood and urine tests at least yearly to screen for, or to monitor, kidney disease.
- If you smoke, quit.
- Talk to your healthcare provider about other kidney protection measures, such as limiting use of NSAIDs (a group of pain relievers such as ibuprofen [eg, Advil®] that are available by prescription or over-the counter).

## Resources for More Information

- **American Diabetes Association**
  1701 North Beauregard Street, Alexandria, VA 22311
  internet: http://www.diabetes.org/
  email: askADA@diabetes.org
  phone: (800) 342-2383.
- **National Diabetes Education Program**
  One Diabetes Way, Bethesda, MD 20814-9692
  internet: http://ndep.nih.gov/
  email: http://ndep.nih.gov/ContactUs.aspx (submit question)
  phone: (888) 693-NDEP (6337)
- **National Diabetes Information Clearinghouse**
  1 Information Way, Bethesda, MD 20892-3560
  internet: http://diabetes.niddk.nih.gov/
  email: ndic@info.niddk.nih.gov
  phone: (800) 860–8747

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## Test Questions

*Write your answers on the Credit Request/answer form provided or take the test online: www.rxconsultant.com*

**Questions are based on information provided in the text, tables, and Patient Connection insert.**

*ACPE Universal program #0428-0000-13-005-H01-P*

**1. Which of the following is the current standard blood pressure (BP) goal for most patients with diabetes (DM)?**

a. < 140/90 mmHg
b. < 130/80 mmHg
c. < 140/80 mmHg
d. < 120/80 mmHg

**2. How often should self-monitoring of blood glucose (SMBG) be performed in patients with DM?**

a. As often as needed to avoid hyper- or hypoglycemia.
b. 3-4 times per day for most patients with DM.
c. When A1C needs to be lowered by 25-30%.
d. SMBG is not indicated for patients with T2DM.

**3. Which of the following DM patients may be best suited to a A1C goal of > 7.5 - 8%?**

a. A young patient with strong motivation to improve his/her condition.
b. A young patient who takes metformin and has a healthy diet.
c. An older, motivated patient who is not prone to hypoglycemic episodes.
d. An older patient with many coexisting diseases and limited resources.

**4. If glycemic goals are not met after 3-6 months of metformin plus lifestyle changes, what is currently endorsed as a next step?**

a. Switch from metformin therapy to basal insulin therapy.
b. Use patient preferences/characteristics to select an add-on medication.
c. Add either a sulfonylurea or a thiazolidinedione to metformin.
d. Enforce mandatory SMBG testing 4-6 times per day.

**5. Which of the following diabetes medications is FDA approved for pediatric use?**

a. Metformin
b. Glipizide
c. Pioglitazone
d. Sitagliptin

**6. Which of the following is a likely presentation of pediatric T2DM?**

a. Ketoacidosis in an underweight teen
b. Asymptomatic hyperglycemia & obesity
c. Recent weight loss, polyuria
d. Ketosis in a child < 10 yrs old

**7. An ACE inhibitor or ARB should NOT be used in DM patients with which of the following characteristics?**

a. Normal BP & macroalbuminuria
b. Normal BP & microalbuminuria
c. Normal BP & normal urinary albumin
d. High BP & normal urinary albumin

**8. Which statement is true of combined ACE inhibitor/ARB use, compared with monotherapy?**

a. Combination therapy reduces the risk of heart attack and stroke.
b. Combination therapy reduces all-cause mortality.
c. Combination therapy slows the decline of kidney function.
d. Combination therapy increases adverse effects without proven benefit .

**9. Current guidelines suggest which of the following for monitoring kidney status in patients with DM?**

a. Urinary albumin-creatinine ratio (ACR)
b. Glomerular filtration rate (GFR)
c. Both ACR and GFR
d. Serum creatinine

**10. Which DPP-4 inhibitor is available in a fixed-dose combination with pioglitazone?**

a. Alogliptin (*Nesina*®)
b. Saxagliptin (*Onglyza*®)
c. Linagliptin (*Tradjenta*®)
d. Sitagliptin (*Januvia*®)

**11. Which statement is true of sodium glucose co-transporter 2 (SGLT2) inhibitors such as canaglifozin *(Invokana™)*?**

a. SGLT2 inhibitors increase insulin release and cause weight gain.
b. Increased urinary glucose excretion may cause urinary tract infection.
c. Hypoglycemia is a common side effect.
d. Efficacy increases with declining kidney function.

**12. Which statement is true of alogliptin *(Nesina®)*?**

a. It is the most effective of the DPP-4 inhibitors.
b. It has many cytochrome P450-based drug interactions.
c. Caution is recommended in patients with liver disease or dementia.
d. It requires dose adjustment for kidney impairment.

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