This supplement was sponsored by Primary Care Education Consortium and Primary Care Metabolic Group. It was edited and peer reviewed by *The Journal of Family Practice*.

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SUPPLEMENT TO
THE JOURNAL OF FAMILY PRACTICE®

VOL 70, NO 6 | JULY/AUGUST 2021 | MDEDGE.COM/FAMILYMEDICINE

A SPECIAL SUPPLEMENT ON

HOT TOPICS in Primary Care 2021

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Hot Topics in Primary Care 2021

INTRODUCTION

It's understandable that the COVID-19 pandemic has dominated healthcare news and education over the past year. But in case you missed news about advances in other diseases, you will find this year's issue of *Hot Topics in Primary Care* interesting—and practice-changing. Several articles relate to cardiovascular disease, as there have been important advances in pharmacologic treatment, including wider use of "glucose-lowering" medications. These articles provide important strategies to reduce cardiovascular risk and improve overall patient management. Another article involves communication techniques and office practices, as well as individualizing long-term medications, for managing patients with obesity. The article on continuous glucose monitoring includes 4 cases that focus on interpreting the ambulatory glucose profile to make treatment decisions. The articles on asthma and chronic obstructive pulmonary disease focus on updated guideline treatment recommendations, particularly strategies to promote stable disease and prevent exacerbations. The article on statin therapy outlines considerations to optimize treatment, particularly in patients thought to be statin intolerant. Finally, the article on screening for type 1 diabetes mellitus provides insight into its emerging role.

If you can't decide which articles to read first, you may want to check out the short video segment for each article. This is a new feature in this year's *Hot Topics in Primary Care*. Each video segment describes the content and key takeaways of the article. It's a nice way to "thumb through" the special issue before reading the articles in detail. You can view the videos at mdedge.com/familymedicine/HotTopics2021.

As always, any comments you wish to make about the quality and relevance of the articles in this special issue will be greatly appreciated. And if you'd like to offer your thoughts about other clinical issues you'd like to see addressed, please let us know by using the QR code below.

Wishing you and your patients good health.

Stephen Brunton, MD, FAAFP
Executive Vice President
Primary Care Education Consortium

Cardiometabolic Risk Reduction: A Review of Clinical Guidelines and the Role of SGLT-2 Inhibitors

Timothy Reid, MD

doi: 10.12788/jfp.0216

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Identify how heart failure (HF), chronic kidney disease (CKD), and type 2 diabetes mellitus (T2DM) and associated cardiovascular (CV) risks are interconnected.
- Initiate guideline-recommended therapy to reduce CV risk in patients with HF, CKD, and/or T2DM.
- Apply evidence for sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) to clinical practice, based on recent and emerging trials.
- Review evidence suggesting increased incidence and severity of COVID-19 infection in patients with diabetes.

KEY TAKEAWAYS

- Current guideline-directed treatment algorithms for HF and diabetes both recommend SGLT-2 inhibitors based on patient-specific characteristics and comorbidities.
- In patients with HF, the SGLT-2 inhibitors canagliflozin, dapagliflozin, and empagliflozin reduced rates of cardiovascular death and hospitalization for worsening heart failure.
- The SGLT-2 inhibitors canagliflozin and dapagliflozin are associated with a lower risk of worsening kidney function and cardiovascular or renal death. A phase 3 trial evaluating kidney outcomes for empagliflozin is currently ongoing.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of cardiometabolic diseases.

DISCLOSURES

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Dr. Reid discloses that he serves on the advisory board and speakers bureau for Novo Nordisk and Sanofi. Stephen Brunton, MD, editor, serves on the advisory board and speakers bureau for AstraZeneca, Bayer, and Novo Nordisk. He serves on the speakers bureau for Lilly and on the advisory board for Abbott Diabetes, Acadia, Sanofi, and Xeris. Austin Ulrich, PharmD, editorial support, reports no conflicts of interest.

SPONSORSHIP

This article is sponsored by Primary Care Education Consortium, in collaboration with the Primary Care Metabolic Group.

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ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, of the Primary Care Education Consortium.

SUPPORTER

This article is supported by an educational grant from Boehringer Ingelheim Pharmaceuticals, Inc. and Eli Lilly and Company.

CASE SCENARIO

RW is a 56-year-old woman whose last primary care visit was more than 7 years ago. When RW was lost to follow-up, she had a history of type 2 diabetes mellitus (T2DM), obesity, and hypertension (HTN). She reports not taking any medications during this time but did quit smoking 3 years ago. She now seeks medical care because she reports feeling unwell. A thorough diagnostic evaluation confirms T2DM, obesity, and hypertension (HTN). RW

also has heart failure with reduced ejection fraction (HFrEF) and stage 2 chronic kidney disease (CKD) with moderate albuminuria.

Lab work: Glycated hemoglobin (A1c) 9.0%, estimated glomerular filtration rate (eGFR) 62 mL/min/1.73 m^2, urinary albumin-to-creatinine ratio (UACR) 120 mg/g, and left ventricular ejection fraction (LVEF) 35%

Vitals: Body mass index (BMI) 36.0 kg/m2, blood pressure 144/92 mm Hg in clinic today

Current medications: None; historically was prescribed metformin 500 mg 1 tablet twice daily, atorvastatin 10 mg daily, and lisinopril 5 mg daily

CARDIOVASCULAR DISEASE

The patient in the case scenario above is at risk for multiple medical issues, including cardiovascular (CV) complications, given her comorbidities and history. Cardiovascular diseases (CVDs) include those affecting the heart or blood vessels. Physiologically, the CV system is highly interconnected with the renal and metabolic systems.[1] The integration of the cardio-renal-metabolic system is responsible for a variety of homeostatic processes including blood pressure regulation, volume status, and glucose reabsorption and transportation.[1] Thus, CV and renal risk exist along an interconnected pathophysiologic continuum.[2,3]

Chronic heart failure. HF is a complex clinical syndrome in which structural or functional impairment of ventricular filling or ejection of blood interferes with the heart's ability to pump effectively.[4] Chronic HF can be broadly grouped into 2 categories: systolic heart failure, or heart failure with reduced ejection fraction (HFrEF), and diastolic heart failure, or heart failure with preserved ejection fraction (HFpEF). HFrEF is defined as an LVEF ≤40%, while HFpEF is an LVEF ≥50%.[4] Presence and severity of HF is further classified by the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) stages of HF and the New York Heart Association (NYHA) functional classification.[4]

Chronic kidney disease. CKD is defined as abnormalities of kidney structure or function, present for at least 3 months, with known health implications.[5,6] Staging of CKD is classified based upon cause, glomerular filtration rate (GFR) category, and albuminuria category.[5,6] GFR categories (G1-G5) are assigned along a spectrum of GFR measurements, from ≥90 mL/min/1.73 m^2 (normal) to <15 mL/min/1.73 m^2 (which is end-stage kidney disease [ESKD]).[7] Albuminuria is categorized from normal to severe as A1 (UACR <30 mg/g), A2 (UACR 30-300 mg/g), or A3 (UACR >300 mg/g).[7]

Epidemiology. The prevalence of HF in the United States is estimated at 6.5 million individuals; this number is projected to surpass 8 million by 2030.[7] Despite advances in surgical and medical therapy, HF remains a major cause of healthcare utilization and diminished health-related quality of life (HRQoL).[8,9] In 2014 alone, there were more than 1 million emergency department visits, approximately 980,000 hospitalizations, and 83,705 deaths with HF as the primary diagnosis.[10] Comparatively, the prevalence of CKD is more than 38 million individuals in the United States.[11,12]

Risk factors. Several comorbid conditions serve as independent risk factors for developing HF. Coronary artery disease, HTN, diabetes mellitus, metabolic syndrome, smoking, and obesity are among those most frequently implicated.[4,13] According to the ACCF/AHA, HTN may be the single most important modifiable risk factor for HF in the United States.[4,14] Higher levels of blood pressure and longer duration of HTN, particularly in individuals of advanced age, are associated with a greater incidence of HF.[4] Clinical trials suggest patients with T2DM are at nearly 2 times the risk of developing HF as those without diabetes.[15,16] Similarly, uncontrolled diabetes and HTN are the most common causes of CKD in adults.[12] The relationships between CKD, diabetes mellitus, and HF are bidirectional, with each disease independently increasing the risk for the others.[12,17]

GUIDELINE-RECOMMENDED MEDICAL THERAPY

Nonpharmacologic therapy for HF. Guideline-directed nonpharmacologic interventions for HF management include daily weight checks, regular physical activity, and sodium restriction. All patients with HF are encouraged to participate in regular physical activity as functional status permits.[4] Cardiac rehabilitation in the HF population has been shown to improve functional capacity, exercise duration, and HRQoL while reducing hospitalizations and mortality.[4] Due to the association between sodium intake and HTN, left ventricular hypertrophy (LVH), and CVD, the AHA recommends restricting sodium intake to ≤1500 mg/d in patients with stage A or B HFrEF.[4] While evidence for limiting dietary sodium in stage C and D HFrEF is less clear, some degree of sodium restriction (eg, <3 g/d) is likely warranted.[4]

HFrEF pharmacologic therapy. Guideline-directed medical therapy (GDMT) is the mainstay of pharmacologic therapy for HFrEF.[4] For individuals at risk of HF, or those in stage A, HTN and lipid disorders should be managed concordant with published guidelines.[4] Thus, optimal blood pressure for individuals with HFrEF is <130/80 mm Hg.[18-21] In addition to appropriate blood pressure control and statin therapy, angiotensin-converting enzyme inhibitors (ACEIs) and evidence-based beta blockers should be used in all patients with stage B HFrEF.[4] Treatment with 1 of 3 evidence-based beta blockers—bisoprolol, carvedilol, or metoprolol succinate—should be initiated at low doses in stable patients and gradually titrated up as tolerated to target doses of 10 mg/d, 50 mg/d

in 2 divided doses, and 200 mg/d, respectively.[4] In patients with HFrEF NYHA class II-IV who tolerate an ACEI or angiotensin II receptor blocker (ARB), replacement with an angiotensin receptor neprilysin inhibitor (ARNI) is recommended to further reduce morbidity and mortality.[18,21] Additionally, diuretics should be prescribed as needed for volume overload in stage C HFrEF.[4] The 2021 Update to the 2017 American College of Cardiology Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment describes the treatment algorithm for GDMT in stage C HFrEF **(FIGURE 1)**.[22] The inclusion of dapagliflozin and empagliflozin as GDMT for symptomatic HF highlights the emerging role for sodium-glucose cotransporter-2 (SGLT-2) inhibitors in HFrEF management.[22]

HFpEF pharmacologic therapy. Whereas GDMT is the standard of care for HFrEF, HFpEF pharmacotherapy is more limited and is aimed at controlling symptoms and managing comorbid conditions. Blood pressure control in accordance with existing HTN guidelines remains the most important recommendation for patients with HFpEF. Renin-angiotensin-aldosterone system (RAAS) inhibition with an ACEI, ARB, or possibly ARNI represents preferred antihypertensive therapies to attain systolic blood pressure <130 mm Hg in the setting of HFpEF.[18,20] Diuretics should be prescribed to all patients with HTN and HFpEF who have evidence of fluid retention.[4,20]

Pharmacologic approaches to glycemic treatment. The American Diabetes Association's (ADA) *Standards of Medical Care in Diabetes–2021* maintain that metformin and comprehensive lifestyle modifications, including weight management and physical activity, are first-line interventions in the management of T2DM.[23] Based on the results of CV outcomes trials (CVOTs), the ADA now recommends considering indicators of high-risk or established atherosclerotic CVD (ASCVD), CKD, or HF for all patients to help guide therapy independent of baseline A1c, A1c goals, or metformin use **(FIGURE 2)**.[23]

For patients with T2DM and HF, guidelines recommend initiation of an SGLT-2 inhibitor with proven benefit.[23,24] While empagliflozin, canagliflozin, and dapagliflozin have all shown a reduction in HF in CVOTs, empagliflozin and dapagliflozin are the 2 SGLT-2 inhibitors with primary HF outcome data.[23,25,26] For patients with diabetic kidney disease (DKD) and albuminuria, an SGLT-2 inhibitor with primary evidence supporting slowed CKD progression is preferred.[23] In the absence of albuminuria, patients with T2DM and CKD (eGFR <60 mL/min/1.73 m^2) may consider a glucagon-like peptide-1 receptor agonist (GLP-1 RA) or SGLT-2 inhibitor with proven CVD benefit.[27-33] When established ASCVD or indicators of high ASCVD risk are present, a GLP-1 RA or SGLT-2 inhibitor with proven CVD benefit is preferred.[23,24]

For T2DM patients without high-risk or established ASCVD, CKD, or HF, medication selection is based upon efficacy, side effect avoidance, cost, and patient preference.[23] If there is a compelling need to minimize hypoglycemia, such as patients who experience frequent hypoglycemic episodes or hypoglycemia unawareness, an SGLT-2 inhibitor, GLP-1 RA, dipeptidyl peptidase-4 inhibitor (DPP-4i), or thiazolidinedione (TZD) is preferred.[23] To minimize weight gain or to promote weight loss, an SGLT-2 inhibitor or GLP-1 RA is recommended.[23] Finally, if cost is a major issue, TZDs or sulfonylureas should be considered.[23]

Management of diabetes in CKD. The Kidney Disease: Improving Global Outcomes (KDIGO) 2020 Clinical Practice Guidelines for Diabetes Management in CKD recommend a comprehensive approach to kidney-heart risk factor management.[5] Treatment with an ACEI or ARB should be initiated in patients with diabetes, HTN, and albuminuria, and these medications should be titrated to the highest approved dose that is tolerated.[5] Metformin and SGLT-2 inhibitors are the preferred, first-line antihyperglycemic therapies for patients with T2DM, CKD, and an eGFR ≥30 mL/min/1.73 m^2.[5]

EMERGING ROLE OF SGLT-2 INHIBITORS

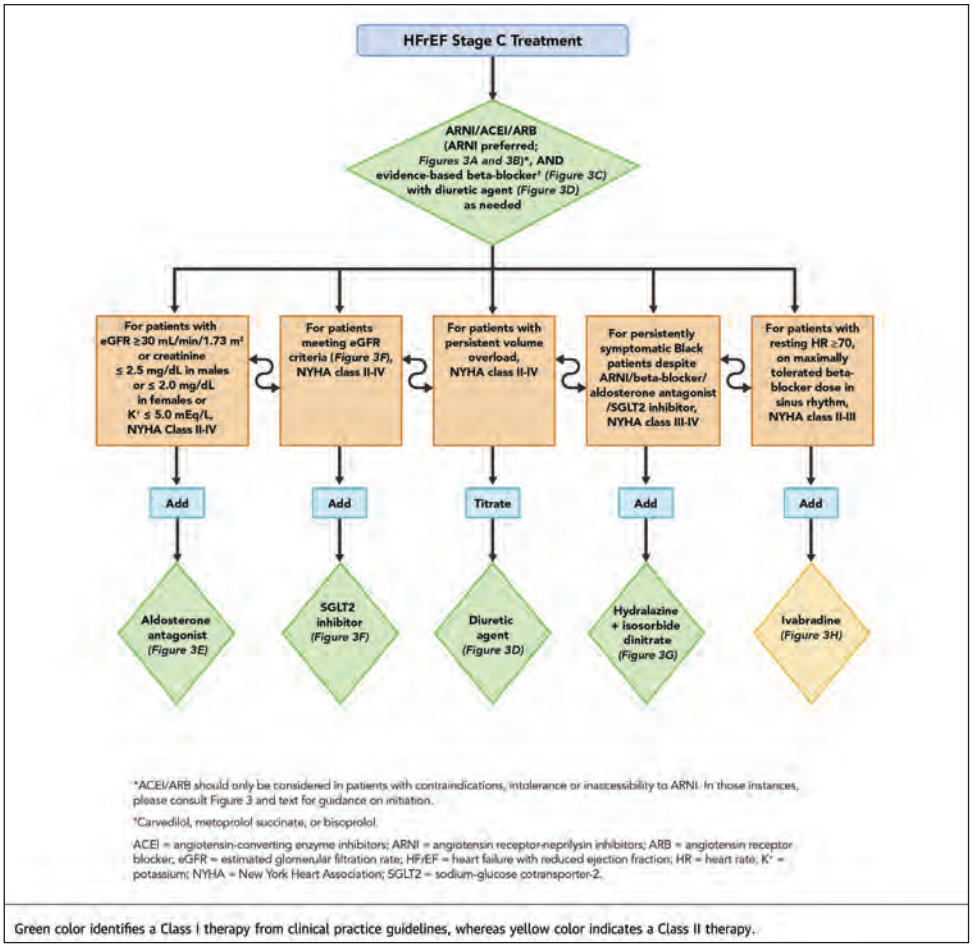
Cardiovascular outcomes trials. In 2008, the FDA issued guidance for industry requiring CVOTs for all new T2DM medications.[33] A composite of CV death, myocardial infarction, or ischemic stroke, referred to as 3-point major adverse cardiac events (MACE), often serves as the primary outcome of CVOTs. The 4 SGLT-2 inhibitors currently available in the United States have each demonstrated noninferiority to placebo as part of standard therapy with respect to CV safety.[34-40] Reduced rates of hospitalizations for HF have been observed across the class of SGLT-2 inhibitors in CVOTs.[35-37,40]

Empagliflozin was the first drug in this class to not only demonstrate CV safety but also benefit in patients with T2DM at high CV risk compared to placebo, based on results of the EMPA-REG (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) in 2015.[36] The hazard ratio for reduction in MACE with empagliflozin was 0.86 (95% confidence interval (CI): 0.74-0.99; P=0.04). Canagliflozin was studied in patients with T2DM and high CV risk, demonstrating a reduced rate of 3-point MACE compared to placebo.[35] Dapagliflozin was noninferior to placebo for reducing CV risk in patients with T2DM and ASCVD or at high CV risk.[37] Ertugliflozin was non-inferior to placebo for 3-point MACE in patients with T2DM and ASCVD.[40]

SGLT-2 inhibitors in chronic HF

Canagliflozin. In patients with T2DM and high CV risk, canagliflozin reduced HF-related fatalities and hospitalizations by 30% compared to placebo (HR 0.70; 95% CI: 0.55-0.89).[40] In subgroup analyses, the hazard ratios for HFrEF, HFpEF, and HF

FIGURE 1. **Treatment algorithm for guideline-directed medical therapy in HFrEF**[22]



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unknown EF (HFuEF) were 0.69 (95% CI: 0.48-1.00), 0.83 (95% CI: 0.55-1.25), and 0.54 (95% CI: 0.32-0.89), respectively.[40] When HFuEF events were assumed to be HFpEF, the updated HR for HFpEF was 0.71 (95% CI: 0.52-0.97), and when HFuEF events were assumed to be HFrEF, the updated HR for HFrEF was 0.64 (95% CI: 0.48-0.86).[40] Thus, further studies will be required to clarify the benefit of canagliflozin in HFrEF vs HFpEF.

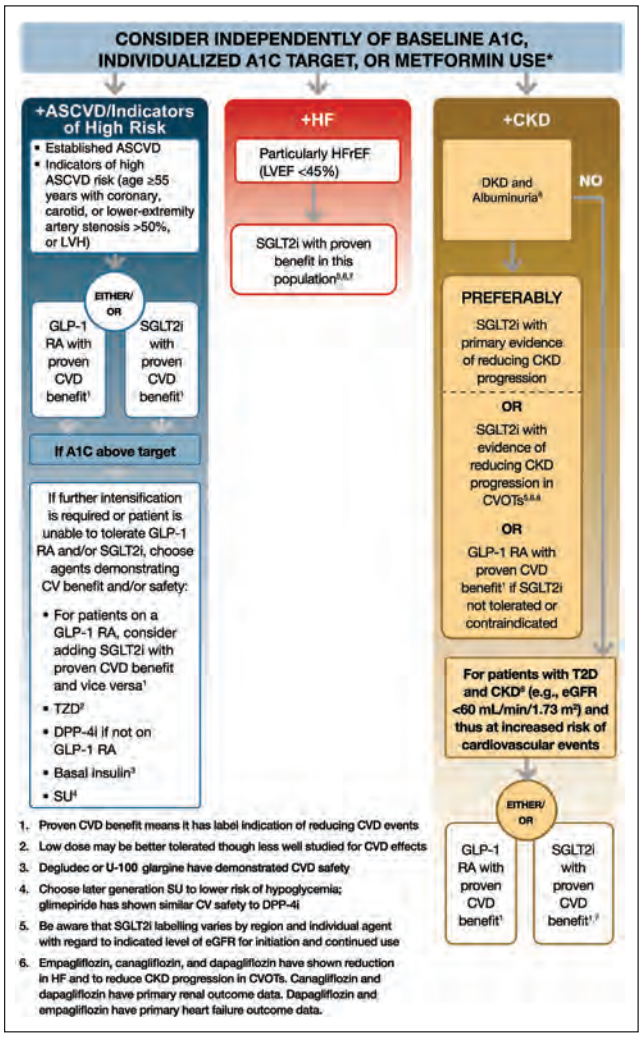
Dapagliflozin. The DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) trial compared dapagliflozin 10 mg/d to placebo, in addition to standard therapy, in patients with NYHA class II-IV HF and an LVEF ≤40% with or without T2DM. During the 18.2-month follow-up period, the composite outcome of worsening HF or CV death occurred in 16.3% of patients receiving dapagliflozin vs 21.2% of patients in the placebo group (P<0.001).[41] Additionally, individuals in the dapagliflozin group were less likely to experience CV death or hospitalization due to HF (16.1% vs 20.9%; P<0.001).[41] The use of dapagliflozin also resulted in fewer symptoms of HF, as quantified by the Kansas City Cardiomyopathy Questionnaire (P<0.001).[41] Findings of DAPA-HF were consistent in patients regardless of the presence or absence of T2DM.

DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) is an ongoing, phase 3 trial evaluating the effect of dapagliflozin in reducing the composite of CV death or HF events in patients with HFpEF NYHA class II-IV with or without T2DM.[42] Dapagliflozin 10 mg/d will be compared to placebo, in addition to the standard of care.

DETERMINE-preserved (Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Preserved Ejection Fraction) is a phase 3 trial evaluating the effect of once-daily dapagliflozin on exercise capacity in patients with HFpEF NYHA class II-IV with or without T2DM.[43] The trial was completed in July 2020; however, results are not yet available.

Empagliflozin. In the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) trial, patients with NYHA class II-IV HF and an LVEF ≤40% were randomized to empagliflozin 10 mg/d or placebo, in addition to standard therapy. Treatment with empagliflozin reduced rates of the primary composite outcome of CV death or hospitalization for worsening heart failure (19.4% vs 24.7%; P<0.001).[44] The effect of empagliflozin on the primary outcome was consistent in patients with and without T2DM. Moreover, a total of 553 patients were hospitalized for HF in the placebo group whereas only 388 patients were hospitalized for HF in the empagliflozin group (P<0.001). Uncomplicated genital tract

FIGURE 2. **2021 ADA diabetes treatment algorithm**[23]



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infections were reported more frequently with empagliflozin.

EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) is an ongoing phase 3 trial evaluating the safety and efficacy of once-daily empagliflozin compared to placebo in patients with HFpEF with or without T2DM.[45]

SGLT-2 inhibitors in CKD

Canagliflozin. In the CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) trial, patients with T2DM and albuminuric CKD were assigned to canagliflozin 100 mg/d or placebo. Eligible patients had an eGFR of 30 to <90 mL/min/1.73 m^2, a UACR of >300 to 5000 mg/g, and were treated with RAAS blockade.[46] The trial was stopped early due to the efficacy benefit of canagliflozin; this resulted in a median follow-up period of 2.62 years. The primary outcome, a composite of serum creatinine doubling, ESKD, renal death, or CV death, occurred in 11.1% of patients in the canagliflozin group and 15.5% of patients in the placebo group (P<0.001).[46] The relative risk of the renal-specific composite of ESKD, serum creatinine doubling, or renal death was 34% lower in the canagliflozin group (HR 0.66; P<0.001), while the relative risk of ESKD alone was 32% lower in the canagliflozin group (HR 0.68; P=0.002).[46] There were no differences in the rates of amputation or fracture between groups.

Dapagliflozin. DAPA-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease) compared dapagliflozin 10 mg/d to placebo in patients with an eGFR of 25 to 75 mL/min/1.73 m^2 and a UACR of 200 to 5000 mg/g with or without T2DM. The trial was stopped early due to efficacy, resulting in a median follow-up of 2.4 years.[47] The rate of the primary outcome, a composite of a sustained decline in eGFR of 50%, ESKD, or death from renal or CV causes, was lower in the dapagliflozin group (9.2%) vs the placebo group (14.5%; P<0.001).[47] Death from any cause also occurred less frequently in the dapagliflozin group (4.7% vs 6.8%; P=0.004).[47] The effects of dapagliflozin were similar in patients with and without T2DM, and the incidence of adverse events and serious adverse events were similar between groups.

Empagliflozin. EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) is an ongoing, phase 3 trial evaluating the effect of empagliflozin on kidney disease progression and CV death in patients with preexisting CKD with or without T2DM.[48]

CASE SCENARIO *(CONT'D)*

Patient RW, a 56-year-old woman seeking medical care after 7 years of minimal healthcare contact.

Pertinent medical conditions: T2DM, obesity, HTN, stage B HFrEF, and stage 2 CKD with moderate albuminuria

Though there are many issues that would need to be addressed, medical management would include prescribing medications for T2DM, HTN, HF, and CKD. Based on current evidence, a suggested approach might be to restart metformin, add an SGLT-2 inhibitor, restart an ACEI, add a GDMT beta blocker for HF (carvedilol, bisoprolol, or metoprolol succinate), and restart a moderate-intensity statin. Symptomatic treatment for fluid overload related to HF might also be indicated, which would include the use of diuretics. Her eGFR should be closely monitored with initiation of these medications.

COVID-19 AND T2DM

Diabetes is one of the most important comorbidities linked to severity of COVID-19 infection.[49] The risk of a fatal outcome from

COVID-19 is up to 50% higher in patients with diabetes than in those without diabetes.[49,50] Several hypotheses exist to explain the increased incidence and severity of COVID-19 infection in this population; in general, individuals with diabetes are at an increased risk of infection due to hyperglycemia-associated immune dysfunction.[49,51] Regardless of the exact mechanism, the risk of mortality in patients with T2DM appears significantly and independently related to hyperglycemia.[50] The relationship between improved glycemic control and improved outcomes in patients with COVID-19 and preexisting T2DM serves as a guiding principle for the provision of care.[52]

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Decision Points in the Management of Patients with Diabetic Kidney Disease

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doi: 10.12788/jfp.0217

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Identify the risks of kidney disease and their consequences in patients with type 2 diabetes (T2D).
- Appropriately screen for the presence of chronic kidney disease (CKD) in patients with T2D.
- Initiate evidence-based therapy to slow the progression of kidney disease in patients with T2D and CKD.
- Describe the benefits and limitations of the steroidal and nonsteroidal mineralocorticoid receptor antagonists in the treatment of patients with DKD.

KEY TAKEAWAYS

- Diabetes is second only to hypertension as a cause of chronic kidney disease (CKD).
- Urine albumin-to-creatinine ratio (UACR) is an independent and better predictor of cardiovascular mortality than estimated glomerular filtration rate (eGFR) across the full range of kidney function.
- In patients with diabetic kidney disease (DKD), comprehensive treatment that includes achieving blood pressure, blood glucose, blood lipid, and body weight goals, as well as smoking cessation, is critical.
- Treatment with a sodium-glucose cotransporter-2 inhibitor (SGLT-2i) should not be initiated in patients with an eGFR <60 mL/min/1.73 m^2 (ertugliflozin), <45 mL/min/1.73 m^2 (dapagliflozin or empagliflozin), or <30 mL/min/1.73 m^2 (canagliflozin).
- The addition of an SGLT-2i (ie, canagliflozin, dapagliflozin, or empagliflozin) is recommended for patients with DKD who have inadequate glycemic control with metformin.
- Finerenone is an nonsteroidal mineralocorticoid receptor antagonist shown to further improve kidney outcomes in patients with albuminuric DKD treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.
- New treatment options for cardiovascular and renal protection are becoming available for use in combination with traditional medications for blood pressure, blood glucose, and blood lipid control.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of diabetic kidney disease.

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SPONSORSHIP

This article is sponsored by Primary Care Education Consortium, in collaboration with the Primary Care Metabolic Group.

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ACKNOWLEDGMENT

Editorial support was provided by Gregory Scott, PharmD, RPh, of the Primary Care Education Consortium.

SUPPORTER

This article is supported by an educational grant from Bayer HealthCare Pharmaceuticals Inc.

OVERVIEW AND DEFINITION OF DKD

Chronic kidney disease (CKD) is common in the United States, affecting an estimated 37 million adults.[1] CKD is defined as abnormalities of kidney structure or function for more than 3 months with implications for health.[2] Two key criteria for CKD are albuminuria (ie, albumin excretion rate ≥30 mg/24 h or urine albumin-to-creatinine ratio ≥30 mg/g) and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.

Among the many risk factors for CKD, diabetes is second only to hypertension.[3] Diabetes is responsible for 35% of all cases of CKD,[4] while approximately 37% of adults with diabetes have CKD.[5] Increasing duration of diabetes increases CKD risk.[6] Other risk factors include older age, male sex, race/ethnicity (American Indian, Hispanic, Asian/Pacific Islander), family history of CKD, obesity, and smoking.[7] This article focuses on CKD in individuals with diabetes, ie, diabetic kidney disease (DKD).

CASE SCENARIO

58-year-old male diagnosed with type 2 diabetes (T2D) 7 years ago. Since diagnosis, his glycated hemoglobin (A1c) has been <7.0% for only short periods. He says he feels well but complains of puffiness in both feet.

Medical history:

- T2D, low-density lipoprotein cholesterol (LDL-C) hypercholesterolemia, obesity; former smoker (quit 4 years ago)
- 10-year atherosclerotic cardiovascular disease (ASCVD) risk is 20.7%

Cardiac: blood pressure 134/84 mm Hg; pulse 78 beats/min
Lungs: clear; respiratory rate 16 breaths/min
Eyes: mild retinopathy with occasional hemorrhages
Body mass index 33.4 kg/m^2

Laboratory:

- Electrolytes normal
- Estimated glomerular filtration rate (eGFR) 48 mL/min/1.73 m^2 (57 mL/min/1.73 m^2 11 months ago)
- A1c 8.3% (7.6% 1½ years ago)
- Cholesterol: total cholesterol 224 mg/dL, LDL-C 126 mg/dL, triglycerides 270 mg/dL, high-density lipoprotein cholesterol (HDL-C) 44 mg/dL

Current treatment:

- Metformin 1 g twice daily
- Sitagliptin 100 mg once daily
- Simvastatin 40 mg once daily
- Ramipril 10 mg once daily
- Aspirin 81 mg once daily

Should this patient be screened for CKD?

The American Diabetes Association (ADA) recommends, and the International Society of Nephrology (ISN) supports, that all children and adults with type 1 diabetes (T1D) or T2D be screened at least annually.[8-10] Children should begin screening at puberty or age >10 years, whichever is earlier, once the child has had T1D or T2D for ≥5 years. Adults with T1D should begin screening 5 years after diagnosis, while adults with T2D should begin screening at diagnosis.

How should this patient be screened for the presence of CKD?

Screening for CKD in children and adults involves measuring urinary albumin (morning preferred) with a spot urine to calculate the urine albumin-to-creatinine ratio (UACR).[9,11] Albuminuria is an independent and better predictor of cardiovascular (CV) mortality than eGFR across the full range of kidney function **(FIGURE)**.[2,12] However, the eGFR also should be measured in adults since one may become abnormal before the other. Albuminuria, for example, can occur more than a decade before a noticeable decline in eGFR,[13,14] while approximately 40% of individuals with T2D have an eGFR <60 mL/min/1.73 m^2 without detectable albuminuria.[15,16]

Should the patient be referred to a nephrologist?

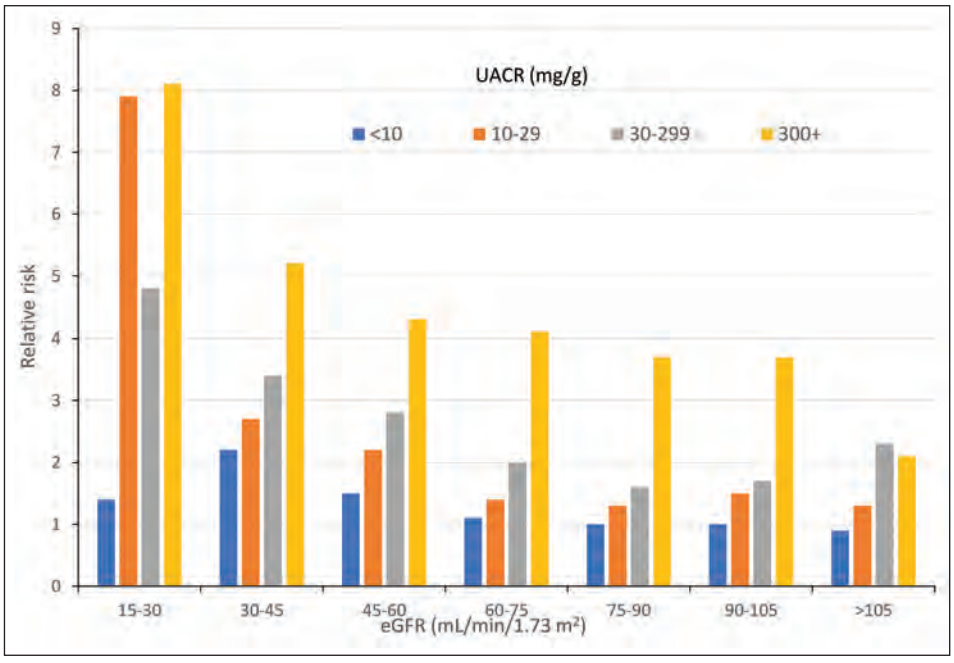
The ADA recommends that referral to a nephrologist be considered in several situations.[9] These include 1) uncertain etiology of kidney disease; 2) difficult management issues, eg, anemia, metabolic bone disease, secondary hyperparathyroidism, resistant hypertension, or electrolyte disturbance; 3) eGFR <30 mL/min/1.73 m^2; and 4) rapidly progressing kidney disease. Since this patient's eGFR has declined from 57 mL/min/1.73 m^2 to 48 mL/min/1.73 m^2—or 16%—over 11 months, nephrologist referral is appropriate. When making the referral, it is recommended to clearly state the reason, such as "I am referring this patient since his eGFR is <60 mL/min/1.73 m^2 and has declined 16% over 11 months."

What are the goals of treatment for this patient with DKD?

Following diagnosis of DKD, intervention to prevent further deterioration in kidney function or to at least slow disease progression is the primary goal. This requires achieving blood glucose, blood pressure, blood lipid, and body weight targets, as well as cessation of tobacco use, if appropriate.[9-11] Empowering individuals through ongoing education, coaching, and support provided in a coordinated manner by a mul-

tidisciplinary care team is critically important.[10,17]

FIGURE. **Cardiovascular mortality risk based on eGFR and UACR[2]**



What changes should be made to the treatment plan other than medications for T2D?

Holistic patient management is of paramount importance in individuals with chronic diseases such as diabetes mellitus and CKD to achieve the glycemic, blood pressure, and other treatment targets needed to optimize health outcomes. Currently, the patient in the case scenario does not meet several of these treatment targets. Among these, his A1c of 8.3% indicates that his glucose-lowering therapy needs to be intensified (see below). Reinforcing the importance of continuing to not smoke is advisable.

The patient's 10-year ASCVD risk of 20.7% places him at high risk for a CV event. For individuals with a 10-year ASCVD risk >15%, the target blood pressure is <130/80 mm Hg, whereas it is <140/90 mm Hg for individuals with a 10-year ASCVD risk score <15%.[18] Since his 10-year ASCVD risk is 20.7% and his blood pressure is >130/80 mm Hg, his dose of the angiotensin-converting enzyme inhibitor (ACEI) ramipril should be increased up to a maximum of 20 mg once daily, although this should be done cautiously due to his eGFR of <60 mL/min/1.73m^2.[10] His LDL-C and triglyceride levels are above recommended levels, while his HDL-C level is below recommended levels, necessitating an increase to high-intensity statin therapy.[19] If he does not tolerate an increase in statin dose, adding other LDL-C-lowering therapy, eg, ezetimibe or a proprotein convertase subtilisin/kexin type 9 inhibitor, should be considered.[18] If his triglyceride level remains elevated following intensified statin therapy, consideration may be given to initiating therapy to target triglycerides.

Weight loss for those with overweight or obesity is of demonstrated benefit in improving CV markers and glycemic control.[20] Lifestyle management is an important first step for weight loss; pharmacotherapy with medications approved for long-term use (ie, liraglutide, naltrexone/bupropion extended-release, orlistat, or phentermine/topiramate extended-release) is often needed.[21] For individuals with non–dialysis-dependent DKD, dietary intervention includes reducing dietary protein intake to 0.8 g/kg/d and dietary sodium to 2300 mg/d; dietary potassium should be closely monitored, particularly in individuals treated with an ACEI or angiotensin receptor blocker (ARB).[9]

Continuing preventive care is important. For example, hepatitis B vaccine is indicated for patients likely to progress to end-stage kidney disease.[9]

What precautions should be taken regarding the use of medications in DKD?

It is particularly important to assess the benefits and limitations of medications in individuals with DKD.[22] Some medications can cause kidney injury, while others that are principally cleared by the kidneys can rise to toxic levels as kidney function declines. Alternatives should be considered for commonly used nephrotoxic medications, eg, nonsteroidal anti-inflammatory drugs, iodinated contrast material, and aminoglycosides. Some medications may require temporary discontinuation in individuals with eGFR <60 mL/min/1.73 m^2 who have a serious intercurrent illness that increases the risk of acute kidney injury. Such medications include ACEIs, ARBs, aldosterone inhibitors, direct renin inhibitors, and diuretics.[22]

Medications that are principally cleared by the kidney should be used with caution, with dosing modification and close monitoring for associated toxicity. Examples of glucose-lowering medications principally cleared by the kidneys include insulin, metformin, glyburide, dipeptidyl pepti-

dase-4 inhibitors (eg, alogliptin, saxagliptin, and sitagliptin), glucagon-like peptide-1 receptor agonists (GLP-1 RAs; eg, exenatide and lixisenatide), and sodium-glucose cotransporter-2 inhibitors (SGLT-2is).[9,10]

What changes should be made to the treatment plan for blood glucose control?

Before modifying the treatment plan, the patient's adherence with current treatment should be assessed. Once confirmed, intensification of his glucose-lowering medications will be needed since his A1c is 8.3%. Improved glycemic control to achieve A1c <7.0% reduces the risks of sustained hyperglycemia and slows the progression of DKD.[23-26] It should be noted that less intensive control is recommended for patients with CKD who have substantial comorbidities.[9] Reducing the doses of metformin and sitagliptin will be needed in the near future since his eGFR is approaching 45 mL/min/1.73m^2.[22] Renal function is an important consideration, as this impacts the initiation and dosing of many glucose-lowering medications. While continuing metformin is reasonable due to its favorable tolerability profile, low cost, and complementary mechanism of action with other glucose-lowering medications, discontinuing the dipeptidyl peptidase-4 inhibitor sitagliptin is appropriate since its magnitude of glycemic lowering is modest and it does not promote weight loss or reduce CV risk.[10,27]

In contrast, medications within the GLP-1RA and SGLT-2i classes promote weight loss and have been shown in CV outcomes trials to reduce CV risk. In addition, both GLP-1 RAs and SGLT-2is are associated with a low incidence of hypoglycemia, which is especially important to avoid in patients with CKD.[10,27] Consequently, selected medications in both classes are recommended as second-line therapy for patients who do not achieve adequate glycemic control with metformin.[10,27] In patients with DKD, SGLT-2i medications with proven kidney benefit are preferred over a GLP-1 RAs.[10,27]

All of these CV outcomes trials had prespecified kidney endpoints. Of the GLP-1 RAs, dulaglutide,[28] liraglutide,[29] and semaglutide[30] (but not exenatide[31] or lixisenatide[32]) showed reductions in major kidney outcomes. Of the SGLT-2is, canagliflozin,[33] dapagliflozin,[34] and empagliflozin[35] (but not ertugliflozin[36]) showed reductions in major kidney outcomes, although ertugliflozin slowed the rate of decline in eGFR.[36]

Additional CV outcomes trials limited to patients with preexisting CKD were subsequently conducted with the SGLT-2is canagliflozin and dapagliflozin. These were the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation)[37] and DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease)[38] trials. A third trial involving ertugliflozin, EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin),[39] is in progress. CREDENCE and DAPA-CKD demonstrated significant reductions in kidney and CV outcomes with canagliflozin and dapagliflozin, respectively. Consequently, canagliflozin and dapagliflozin are recommended by the ADA and ISN for patients with CKD who do not achieve glycemic control with metformin.[10,27]

Of key importance in CREDENCE[37] and DAPA-CKD[38] is that there were no significant differences in rates of amputation or fracture between SGLT-2i therapy and placebo. These findings are consistent with the results of a recent meta-analysis of 10 trials reporting the incidence of CV or kidney outcomes with SGLT-2i therapy.[40] Diabetic ketoacidosis (DKA) was observed with canagliflozin in CREDENCE[37] but not with dapagliflozin in DAPA-CKD.[38] In the meta-analysis, the rate of DKA was significantly higher with SGLT-2i therapy vs placebo, although the incidence was <0.2% and it occurred only in individuals with T2D.[40] Urinary tract infection was not reported in the meta-analysis. Overall, the incidence of serious adverse events was significantly lower with SGLT-2is vs placebo (risk ratio [RR] 0.68; 95% confidence interval [CI]: 0.60-0.77), with modest heterogeneity (RR 0.93; 95% CI: 0.90-0.95).[40]

Another consideration when using SGLT-2i therapy in patients with DKD is dosing based on kidney function. Treatment should not be initiated in patients with eGFR <60 mL/min/1.73 m^2 (ertugliflozin[41]), <45 mL/min/1.73 m^2 (dapagliflozin[42] or empagliflozin[43]), or <30 mL/min/1.73 m^2 (canagliflozin[44]).

Do the mineralocorticoid receptor antagonists have a role in the treatment of patients with DKD?

Medications that inhibit the renin-angiotensin-aldosterone system (RAAS) are recommended in most patients with CKD. RAAS inhibitor therapy involving an ACEI or ARB slows the progression of albuminuria; however, the aldosterone level increases in 50% of patients within 1 year.[45] The addition of the mineralocorticoid receptor antagonist (MRA) spironolactone or eplerenone to an ACEI or ARB results in further reduction in albuminuria as well as blood pressure.[46-49] However, hyperkalemia due to the steroidal properties of spironolactone and eplerenone is common, particularly in patients with stage ≥3 CKD (ie, eGFR <60 mL/min/1.73 m^2).[50,51] In addition, acute reversible reduction in eGFR when added to background therapy with an ACEI or ARB or diuretic, particularly among patients with eGFR <45 mL/min/1.73 m^2, has limited the use of steroidal MRAs in CKD.[52]

Finerenone is an nonsteroidal MRA with the potential to cause less potassium retention than steroidal MRAs.[53] The

phase 3 randomized clinical trials FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) were recently completed. Both trials are limited to patients with T2D and albuminuric CKD treated with an ACEI or ARB.[54,55] FIGARO-DKD included more patients with earlier-stage CKD and T2D. In FIDELIO-DKD, the primary composite endpoint was time to first occurrence of kidney failure, sustained decrease ≥40% in eGFR, or renal death.[54] In FIGARO-DKD, the primary composite endpoint was time to first occurrence of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or heart failure hospitalization (hHF).

In FIDELIO-DKD, the annual rate of the primary event over a median follow-up of 2.6 years was 7.59 vs 9.08 events/100 patient-years with finerenone vs placebo, respectively (hazard ratio [HR] 0.82; 95% CI: 0.73-0.93; *P*=0.001). Finerenone also resulted in significant improvement in the secondary renal composite endpoint (sustained doubling of serum creatinine for ≥4 weeks or renal death) (HR 0.76; 95% CI: 0.65-0.90). Other key CV outcomes were reduced with finerenone as well, including CV death, nonfatal MI, nonfatal stroke, and hHF. The frequency of adverse events was generally similar in the finerenone and placebo groups, although the incidence of hyperkalemia-related treatment discontinuation was higher with finerenone than placebo (2.3% vs 0.9%). A prespecified exploratory analysis showed that the incidence of new-onset atrial fibrillation or atrial flutter was significantly lower in the finerenone vs placebo group (3.2% vs 4.5%; relative risk 0.7; 95% CI: 0.53-0.94; *P*=0.016).[56]

Preliminary results from FIGARO-DKD showed that finerenone significantly reduced the primary composite endpoint.[57]

As of July 9, 2021, the FDA has approved finerenone to reduce the risk of kidney function decline, kidney failure, CV death, non-fatal heart attacks, and hospitalization for HF in adults with DKD. ●

CASE SCENARIO (*CONT'D*)

Intensified comprehensive treatment is needed for this patient to help him achieve and maintain glycemic, blood pressure, blood lipid, and body weight targets, as well as minimize the chance that he resumes smoking. Sitagliptin should be discontinued and an SGLT-2i with demonstrated kidney benefits initiated. RAAS inhibitor therapy is essential to improve kidney outcomes. He should receive support from a multidisciplinary care team that includes coaching to improve nutrition and physical exercise.

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Improving Shingles Vaccination Rates in Family Medicine

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doi: 10.12788/jfp.0218

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Characterize the burden of herpes zoster infections.
- Recommend the recombinant zoster vaccine to patients in accordance with guidance from the Advisory Committee on Immunization Practices.
- Implement strategies to increase patient acceptance of herpes zoster and other vaccinations.
- Use available resources to increase awareness among patients about the importance and safety of recommended vaccinations.

KEY TAKEAWAYS

- Vaccines represent one of the most important public health advancements of the modern age to reduce the burden of infectious diseases.
- Despite the rigorous methods employed by the Centers for Disease Control and Prevention to ensure vaccine safety, some patients still have concerns about the safety of vaccines.
- The recombinant zoster vaccine is the only approved herpes zoster vaccine available in the United States, and it provides highly effective and durable protection against shingles and post-herpetic neuralgia.
- In addition to supporting national initiatives to increase vaccination rates for shingles and other vaccine-preventable diseases, health care providers can use a variety of strategies to help patients receive recommended vaccines.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding shingles.

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SPONSORSHIP

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ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, of the Primary Care Education Consortium.

SUPPORTER

This educational activity is supported by an educational grant from GlaxoSmithKline.

INTRODUCTION

The introduction of vaccines over the past several hundred years has been one of the most important innovations in modern society to curb the spread of infectious diseases. With the introduction of the smallpox vaccine in 1798, up through COVID-19 vaccines currently being implemented and still undergoing development, vaccination has been a significant public health success, and also a source of controversy.[1,2] In the United States, widespread vaccine use has nearly eliminated polio, diphtheria, rubella, and measles, and has significantly reduced the occurrence of other vaccine-preventable diseases.[3]

In the United States as of 2017, infectious diseases accounted for about one-fourth of physician office visits and, combined with parasitic diseases, 4.5 million hospital days.[4] Approximately $120 billion is spent on direct and indirect medical costs each year for these diseases.[4] Herpes zoster infection, commonly known as "shingles," constitutes a significant portion of the infectious disease burden, with about 1 million cases each year in the United States.[4,5] Shingles can be associated with impaired quality of life and functional disability—approximately 10% of immunocompetent adults experience complications from shingles, including ophthalmic and neurologic complications.[6] An estimated one-third of individuals will develop shingles during their lifetime, and the potential complications from shingles prompt a need for vaccination to prevent this disease.[5]

The Healthy People 2020 initiative, which began in the United States in 2010, established a shingles vaccination goal of 30%, when the shingles vaccination rate was 10% in the US population.[7] This goal was met and surpassed in the years following the initiative, starting with a 30.6% vaccination rate in 2015 and increasing to 34.5% in 2018, the most recent available data.[7,8] In October 2017, the two-dose series recombinant zoster vaccine (RZV) was approved by the Food and Drug Administration (FDA).[9] This vaccine is highly efficacious, up to 97% effective in preventing shingles, and is likely playing a role in increased vaccination rates. The Healthy People 2030 initiative is currently under development, but the target shingles vaccination rate will likely be higher than 30%, considering current rates and the recent introduction of the RZV.[10] Primary care clinicians are often faced with challenges in helping patients receive recommended vaccines, including the shingles vaccine, and employing effective strategies can help increase vaccination rates.

VACCINE SAFETY

CASE SCENARIO

A 58-year-old man is being seen for a painful skin eruption involving his upper back. Evaluation reveals that he is suffering from an episode of shingles. He is prescribed valacyclovir; instructed to take an over-the-counter analgesic as needed, apply wet compresses, and use calamine lotion; and provided instructions to minimize transmission to his family. He and his wife (who has accompanied him) have a recent history of refusing vaccinations, stating that they have concerns about the safety of vaccines.

The patient case scenario described above is not uncommon in primary care settings. Many patients express hesitancy regarding vaccines for various reasons, and though not all patients who refuse vaccines may contract a vaccine-preventable disease, this is certainly a possible outcome.[11] Concerns about vaccine safety—encompassing adverse effects, allergic reactions, and intolerance—are common objections to receiving vaccines, including the shingles vaccine, and clinicians should be aware of how to discuss vaccine safety concerns to resolve patients' misconceptions.[2]

Vaccine safety is a primary concern of the Centers for Disease Control and Prevention (CDC).[12] Starting in the 1970s, an increased focus on personal health caused some individuals to become concerned about vaccine safety, and several personal injury lawsuits were filed against vaccine manufacturers in which compensation was awarded despite a lack of supporting evidence.[13] This led to a vaccine shortage and the National Childhood Vaccine Injury Act (NCVIA) in 1986. Among other provisions, the NCVIA required healthcare providers to report vaccine adverse events to the Vaccine Adverse Event Reporting System (VAERS), which is still in use today as a primary method to monitor adverse events to vaccines.[12]

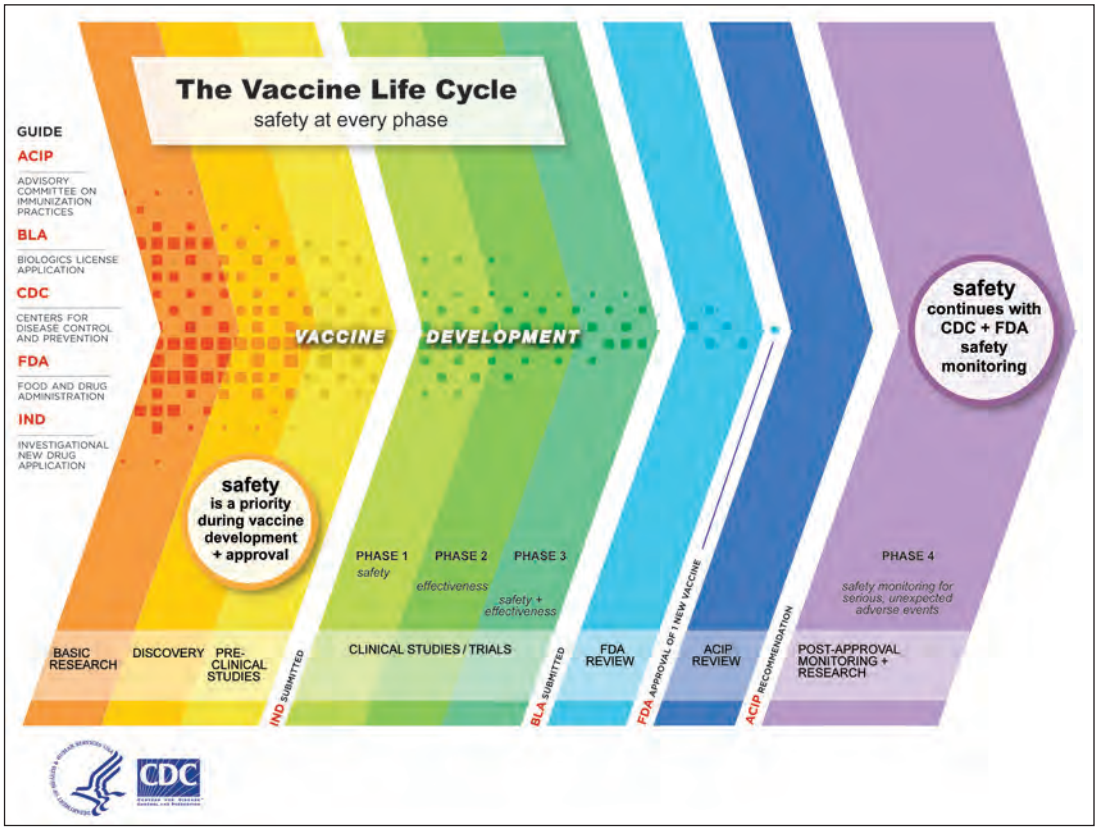
In 2009, a study published about 10 years earlier linking autism to the MMR (measles, mumps, and rubella) vaccine was retracted from the *Lancet*.[14] This is the well-known story of a physician who reported results of a biased and arguably unethical study of the correlation between autism and the MMR vaccine. Although it was eventually proven inaccurate, this misinformation is a source of many false beliefs about vaccines still held by adults and highlights the strong sensitivity individuals have to vaccine safety information.

The CDC seeks to ensure vaccine safety throughout product development by reviewing clinical trial safety data as well as inspecting manufacturing plants and protocols. Since vaccines typically go through the same approval process as prescription drugs and other biologics, there are many checkpoints where safety issues can be identified **(FIGURE)**. Once vaccines are approved, the FDA and CDC continue surveillance for safety issues and respond accordingly.

The NCVIA also created the National Vaccine Injury Compensation Program (VICP) to provide remuneration to people injured by vaccines on a no-fault basis.[12] The VICP is still active today, and it is intended to serve as a safety net for very rare cases where individuals have a severe allergic reaction or adverse event to a vaccine.[15] If the person who filed the claim is awarded compensation at the court level, the US Department of Health and Human Services pays the awarded amount.[15]

Another tool used by the CDC to monitor vaccine safety is the Vaccine Safety Datalink (VSD), which represents a collaboration between the CDC and 9 healthcare organizations.[16] This tool uses electronic health record information from the participating organizations to conduct vaccine research and

FIGURE. **The vaccine life cycle**



Source: https://www.cdc.gov/vaccinesafety/ensuringsafety/history/index.html#four

monitor safety. Data from the VSD can also inform committees that create immunization schedules and guidelines.[16]

HERPES ZOSTER VACCINE

From 2006 to 2017, the live-attenuated herpes zoster vaccine (ZVL) was the only available shingles vaccine. However, with the introduction of the RZV, the ZVL fell out of favor due to lower efficacy rates and eventually was discontinued in November 2020. RZV, administered in 2 separate doses at months 0 and 2-6, is the only shingles vaccine currently available in the United States.[9]

Since development of herpes zoster infection is likely related to a decrease in varicella zoster virus–specific immunity, RZV is targeted at increasing the varicella zoster virus–specific immune response, which is thought to be the mechanism employed by the vaccine to protect against zoster disease.[9] RZV is labeled for "prevention of herpes zoster (shingles) in adults age 50 years and older."[9]

Based on clinical trials, RZV is 97% effective at preventing shingles in adults ages 50 to 69 years and 91% effective in adults age 70 years and older.[17,18] RZV was 91% effective at preventing post-herpetic neuralgia (PHN) in adults ages 50 to 69 years and 89% effective at preventing PHN in adults age 70 and older.[17,18] Notably, in people age 70 years and older, RZV's efficacy for prevention of shingles and PHN persisted throughout 4 years in clinical trials, remaining above 85%.[19] As a comparison, ZVL had 51% efficacy preventing shingles and 67% efficacy preventing PHN, and efficacy lasted only for a maximum of 5 years.[20] In a meta-analysis comparing RZV and ZVL, RZV was statistically superior for efficacy, but also had more injection-site reactions than ZVL.[21] In clinical trials, injection-site reactions from ZVL were reported in 81.5% of adults age 50 years and older and 74.1% of adults age 70 years and older.[17,18]

The Advisory Committee on Immunization Practices (ACIP) published a guideline in 2018 that outlines recommendations for prevention of herpes zoster infection.[22] The following are recommendations for the shingles vaccine within the guideline:

- RZV is recommended for the prevention of herpes zoster and related complications for immunocompetent adults age ≥50 years.
- RZV is recommended for the prevention of herpes zoster and related complications for immunocompetent adults who previously received ZVL.

According to ACIP, RZV may be administered regardless of prior varicella vaccine history and does not require a varicella screening.[22] RZV is administered as an intramuscular injection, and 2 doses of the vaccine are needed with at least 4 weeks between doses; as mentioned above, the recommended schedule is that the second dose be received 2 to 6 months after the first dose. For patients who

previously received ZVL, there is no established time frame after which they are eligible to receive RZV; studies examined RZV administered ≥5 years after ZVL, but based on expert opinion, patients can receive RZV >2 months after ZVL.[22,23] RZV can be coadministered with other vaccines at different anatomic sites, based on CDC guidance.[24] Reactions to the first dose of RZV did not predict second-dose reactions, and patients should be encouraged to receive the second dose of RZV even if they had a mild reaction to the first dose.[22,25]

ACIP also offers guidance on administration of RZV to special populations.[22] Patients with a previous herpes zoster infection should still receive RZV because infection can recur, though if a patient has an active shingles infection, the vaccine should be postponed until symptoms resolve. Patients with chronic medical conditions, taking low-dose immunosuppressive therapy (<20 mg/day of prednisone or inhaled/topical steroid use), anticipating immunosuppression, or recovering from an immunocompromising illness should receive RZV. There is no current recommendation for patients receiving moderate to high doses of immunosuppressive therapy. In patients known to be negative for varicella based on serologic testing, ACIP suggests following recommendations for administering the varicella vaccine, and notes that RZV has not been studied in this population. In patients who are pregnant or breastfeeding, consider delaying RZV.[22]

STRATEGIES FOR INCREASING VACCINATION RATES

Many organizations have established initiatives, protocols, and recommendations that healthcare providers can use to assist with increasing vaccination rates for the shingles vaccine, as well as other recommended vaccines. These initiatives are especially prevalent at the current time, as controversy surrounding COVID-19 vaccines is widespread.

Individualize by group

One strategy that can be effective for increasing vaccination rates is targeting specific groups or populations that have similar characteristics. Generally, individuals can be placed into 1 of 3 groups based on their opinions about vaccination[26]:

1. *Vaccine Adopters*. Patients in this group understand the benefits of vaccination and seek to obtain recommended vaccines. Their support of vaccines can be leveraged to help people unsure about vaccination feel more confident.
2. *Movable Middle*. These patients may feel unsure or hesitant about receiving vaccines but can be responsive to encouragement to receive suggested vaccines. Clinicians should seek to help these individuals build trust in vaccine safety and boost motivation to accept recommended vaccines, as well as make it easy for them to receive vaccines.
3. *Vaccine Detractors*. Also termed "anti-vaxxers," individuals in this group are actively opposed to receiving vaccines due to a negative view or misunderstanding of vaccines. Their opposition to vaccines can sway others to become vaccine detractors, and this "movement" has been termed by some "a regression in modern medicine."[27]

Non-Hispanic Black patients have lower vaccination rates than other populations,[28] and particular attention to this group may help boost rates. One study reported an improvement in influenza immunization rates in a population where 41% of participants self-identified their race as Black or African American.[29] This study implemented a practice-based intervention that involved patient tracking, recall, outreach, and provider prompts, and noted a vaccination rate of 64% for the intervention group compared to 22% for the placebo group (P=0.0001).[29]

Many organizations seek to help minority and underserved communities with accurate information about and access to vaccines. The Rochester Health Community Partnership is an example of one of these organizations.[30] In response to the COVID-19 pandemic, it provided additional assistance to help disenfranchised communities overcome vaccine hesitancy and help distribute accurate information about COVID-19 vaccines in patients' native languages. Partnering with community organizations and leaders can be helpful, as minorities may respond more favorably to vaccines offered at trusted community locations, such as community centers or churches.

Another group that may benefit from improved vaccination rates is patients who are immigrants or refugees. These patients are required to have a medical examination where they must either provide proof of vaccination or begin vaccination according to approved CDC/ACIP schedules.[31] Primary care clinicians who care for immigrants or refugees can consult their state health department for support and guidelines regarding vaccine administration guidance and assistance for these patients.

Shared decision-making and other general strategies

The use of shared decision-making has been widely recognized as a successful and patient-centered approach to medicine, and this includes vaccination.[32] Clinicians should seek to consult respectfully with patients regarding vaccines and communicate with empathy. This can be especially important when resolving patients' concerns about vaccines. The **TABLE** describes several approaches that can be effective when addressing various concerns about vaccines in both children and adults.[2]

TABLE. **Strategies for communicating with patients about vaccines**

Presumptive Recommendations
• Use a presumptive statement that the patient is due for whichever vaccine(s) you are recommending
• Establish that receiving recommended vaccines is the standard choice for most patients
Motivational Interviewing
• If a patient is hesitant, use open-ended questions to determine the core objections or concerns
• Ask permission to share information
• Keep the tone conversational rather than a "lecture" about vaccine facts
Clarifying Vaccine Myths
• If a patient's concern is a vaccine-related myth, use care when clarifying the myth
• Lots of time spent talking about a myth can paradoxically strengthen it in the patient's mind
• Identify the myth as a myth and state that it is false
• Focus on the facts
• State the core facts simply; if the truth seems more complicated, it may be easier to continue accepting simple information in the myth
Disconfirmation Bias
• When presented with evidence about a belief, people more easily accept evidence that supports the existing belief and are critical of evidence that discredits the belief
• Rather than discrediting incorrect elements of existing beliefs, try to provide new information to replace those elements
• Pivot the conversation to focus on the diseases that vaccines prevent
Storytelling
• Personal stories and anecdotes are powerful communication tools

Adapted from: McClure CC, Cataldi JR, O'Leary ST. *Clin Ther*. 2017;39(8):1550-1562.[2]

Clinicians should encourage the use of health technology in helping improve vaccination rates; this can include media such as the internet, email, text messages, social media, and electronic health records.[33] Technology can be used to help communicate accurate vaccine information as well as prompt healthcare professionals to offer vaccines at the appropriate time.

Suggesting that patients can receive vaccines at their local pharmacy, in addition to primary care practices, can promote easier access and reduced costs to many patients. Many pharmacy organizations have implemented initiatives to help increase vaccine rates; one example was the Project IMPACT pilot program, conducted by the American Pharmacists Association.[34] Project IMPACT used an integrated care model in participating pharmacies that allowed pharmacists to use a point-of-care immunization information system to review a patient's vaccine history, identify unmet vaccine needs, and recommend appropriate vaccines. The pilot program resulted in a 41.4% increase in the number of vaccines administered and provided patients with additional opportunities for vaccine education.[34]

Standards for adult immunization practice

In coordination with the National Vaccine Advisory Committee, the CDC has developed "Standards for Adult Immunization Practice" that apply to all healthcare professionals.[35] These standards are based on gaps in adult vaccination, including low adult vaccination rates, unawareness of vaccine necessity, benefits of healthcare professional vaccine recommendation, and missed vaccination opportunities due to lack of routine assessment. Many organizations have adopted alerts or other tracking methods for immunization schedules within the electronic medical record, which can be an effective way to implement routine vaccine assessment.

The primary recommendations of the Standards for Adult Immunization Practice are as follows[35]:

1. Assess immunization status of all your patients at every clinical encounter.
    a. Implement protocols and policies to ensure routine review.
2. Strongly recommend vaccines that patients need.
3. Administer or refer your patients to a vaccination provider.
    a. Refer patients to other providers that offer vaccines you don't stock.
4. Document vaccines received by your patients.
    a. Participate in your state's immunization registry.

National Adult Immunization Plan

The National Adult Immunization Plan (NAIP) is yet another public health initiative in the United States to reduce the burden of preventable infectious diseases by increasing adult vaccination rates.[36,37] The focus of the NAIP is a set of recommendations intended for "federal and nonfederal partners" to assist with implementing systematic strategies to increase vaccination rates. The NAIP consists of 4 key goals, each supported by objectives and strategies.

Infrastructure goal: Strengthen the adult immunization infrastructure. Supporting objectives pertinent to primary care clinicians for this goal include monitoring and reporting trends in adult vaccine-preventable diseases and vaccination coverage, assessing vaccine safety, and increasing the use of

electronic health records to track immunization data.

Access goal: Improve access to adult vaccines. Primary care clinicians play a role in helping ensure adequate supply of vaccines at primary care clinic sites and helping to expand the adult immunization provider network.

Demand goal: Increase community demand for adult immunizations. Primary care clinicians can assist in educating and encouraging individuals and groups to be aware of and receive recommended vaccines.

Innovate goal: Foster innovation in adult vaccine development and vaccination-related technologies. NAIP objectives for vaccine innovation are primarily focused on vaccine development, distribution, storage, and delivery.

RESOURCES

For more information about helping patients receive recommended vaccines, including RZV, the following can be helpful resources for primary care clinicians:

1. American Academy of Family Physicians: Immunizations & Vaccines
2. American Geriatrics Society: Health in Aging Foundation
3. CDC: Strategies for Increasing Adult Vaccination Rates
4. National Quality Forum: Addressing Performance Measure Gaps for Adult Immunizations

SUMMARY

Shingles is a common vaccine-preventable disease in older adults and is associated with significant morbidity. RZV is a highly effective vaccine to protect against shingles and PHN in patients age 50 and older, and clinicians should recommend RZV to all eligible patients. While many individuals in the United States exhibit some degree of vaccine hesitancy, primary care clinicians are uniquely positioned to help improve vaccination rates. Implementing effective strategies to communicate accurate information about vaccines can help clinicians overcome patients' concerns and misconceptions. Partnering with organizations to improve vaccine access for minority and underserved populations can help improve patient outcomes and meet national goals for vaccination. ●

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National Asthma Education and Prevention Program 2020 Guidelines: What's Important for Primary Care

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doi: 10.12788/jfp.0219

KEY TAKEAWAYS

- The *2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group* provides updated recommendations for 6 topics related to the management of individuals with asthma.
  - For the primary care clinician, key important updated recommendations relate to the use of intermittent inhaled corticosteroids, the use of long-acting muscarinic antagonists in the treatment of patients age ≥12 years, and a more focused approach to indoor allergen mitigation.
- The classification of asthma severity and asthma control, as well as the concept of utilizing a stepwise approach to pharmacologic treatment, were not updated from the *Expert Panel Report 3*, released in 2007.
- However, important updates in preferred therapies for intermittent and persistent asthma at treatment steps 1 through 5 were suggested.
- Recommendations regarding biologic therapy were not included in the 2020 update, as only evidence and US Food and Drug Administration approvals through October 2018 were considered.
- The most recent 2021 Global Initiative for Asthma guidelines are not included in this review but can be used in a complementary manner to assist primary care clinicians to optimize decisions regarding the care of patients with asthma.

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DISCLOSURES

Dr. Murphy discloses that he serves on the advisory board and/or speakers bureau for AstraZeneca, Genentech, GlaxoSmithKline, Novartis, Regeneron, and Sanofi. Dr. Solis and Gregory Scott, PharmD, have no disclosures to report.

ACKNOWLEDGMENT

Editorial support was provided by Gregory Scott, PharmD, RPh, at the Primary Care Education Consortium.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and the Primary Care Respiratory Group and supported by funding from AstraZeneca Pharmaceuticals LP.

HISTORICAL OVERVIEW OF NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAM

The National Heart, Lung, and Blood Institute (NHLBI) created the National Asthma Education and Prevention Program (NAEPP) in 1989 to address the burgeoning health and socioeconomic consequences related to asthma in the United States. From its inception, the focus of NAEPP has been to raise awareness and ensure appropriate diagnosis and management of asthma with the goal of reducing related morbidity and mortality and to improve the quality of life of individuals with asthma. To accomplish its goals, NAEPP has involved a wide variety of stakeholder groups and organizations. The first expert panel was published in 1991, the second expert panel report was published in 1997, and the third expert panel report (EPR-3) was published in 2007.[1]

In 2014, groups within NHLBI (which included members of EPR-3) determined that a focused update on 6 high-priority topics was needed.[2] The Agency for Healthcare Research and Quality (AHRQ) was tasked with performing systematic literature reviews on these 6 priority areas. Their findings were published in 2017 and 2018.[3-7] Later in 2018, the Expert Panel Working Group was convened and charged with using the systematic reviews to make recommendations on key questions that could be implemented by clinicians and individuals with asthma.

The Expert Panel Working Group updated the AHRQ systematic review through October 2018; thus, subsequent publications and US Food and Drug Administration (FDA) medication approvals were not included. The final report, published in December 2020, focused on 6 selected topics that closely aligned with the AHRQ systematic literature review findings[2]:

1. Intermittent inhaled corticosteroids
2. Long-acting muscarinic antagonists
3. Fractional exhaled nitric oxide for diagnosis and monitoring
4. Allergen reduction strategies
5. Subcutaneous and sublingual immunotherapy
6. Bronchial thermoplasty

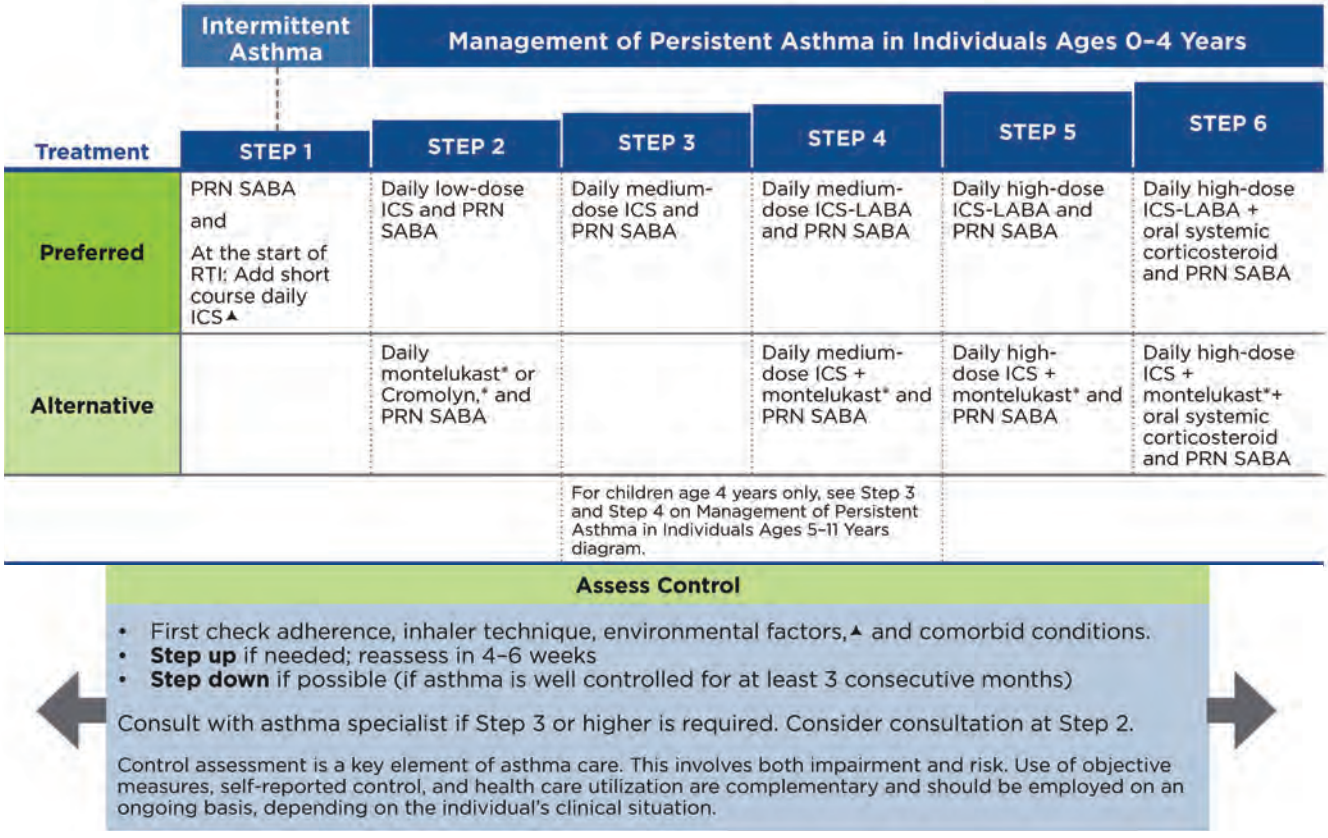
STEPWISE THERAPY

Because the *2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel* (NAEPP 2020 Focused Updates) was not a full revision of the 2007 NAEPP EPR-3,[1] many of the definitions and recommendations described in EPR-3 remain relevant for the management of patients with asthma and are discussed below. Recommendations for pharmacologic therapy continue to be based on a stepwise approach using shared decision-making to achieve and maintain asthma control at the lowest effective therapeutic regimen **(FIGURE 1)**.[2]

Within the stepwise approach to treatment, the NAEPP 2020 Focused Updates guidelines provide some new recommendations for intermittent (step 1), mild persistent (step 2), and moderate-severe persistent (steps 3-5) asthma.[2] Many of these relate to new usages for as-needed dual therapy with a fast-acting bronchodilator combined with an inhaled corticosteroid (ICS), as well as the use of long-acting muscarinic antagonists and adjunctive subcutaneous immunotherapy.

FIGURE 1. **Stepwise approach for management of asthma**

A. Age 0-4 years



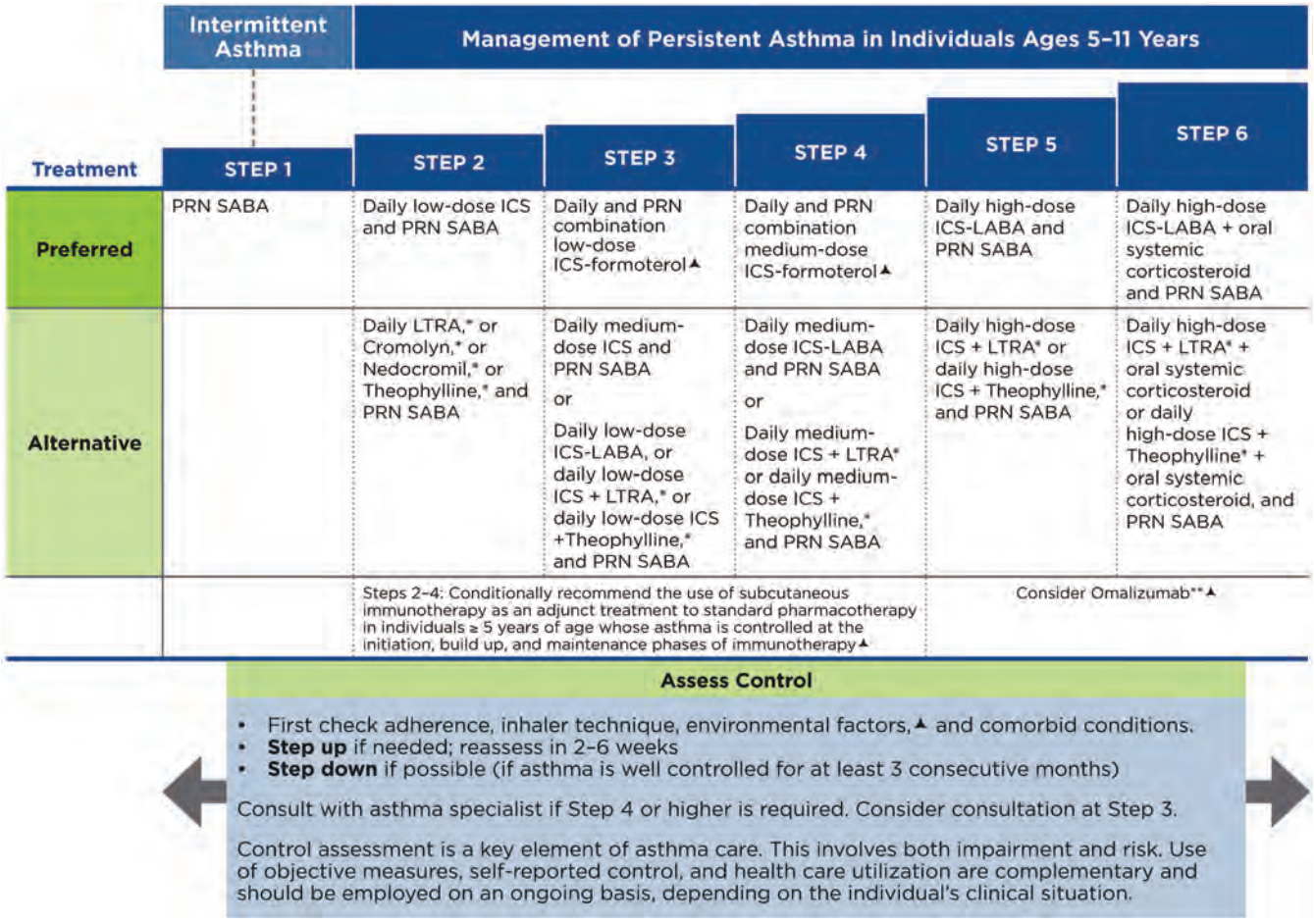
Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; PRN, as needed; SABA, inhaled short-acting β_2-agonist; RTI, respiratory tract infection

▲Updated based on the 2020 guidelines.

*Cromolyn and montelukast were not considered for this update and/or have limited availability for use in the United States. The FDA issued a boxed warning for montelukast in March 2020.

FIGURE 1. **Stepwise approach for management of asthma (cont'd)**

B. Age 5-11 years



Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting β_2-agonist.

▲Updated based on the 2020 guidelines. Recommendations supporting the use of maintenance and reliever therapy in 1 inhaler consisting of ICS/formoterol are primarily based on clinical data with an ICS/formoterol dry powder inhaler product that is not approved or available in the United States.

*Cromolyn, nedocromil, LTRAs including montelukast, and theophylline were not considered in this update and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a boxed warning for montelukast in March 2020.

**Omalizumab is the only asthma biologic currently FDA-approved for this age range. [Author's note: mepolizumab is a biologic now approved in the United States for patients with severe asthma aged 6 years and older.]

Classifying asthma severity

According to EPR-3, asthma severity is broadly categorized as intermittent or persistent. Individuals with intermittent asthma are treated with step 1 therapy, whereas individuals with persistent asthma are treated with steps 2 through 6 therapy, depending on whether they have mild, moderate, or severe persistent asthma.

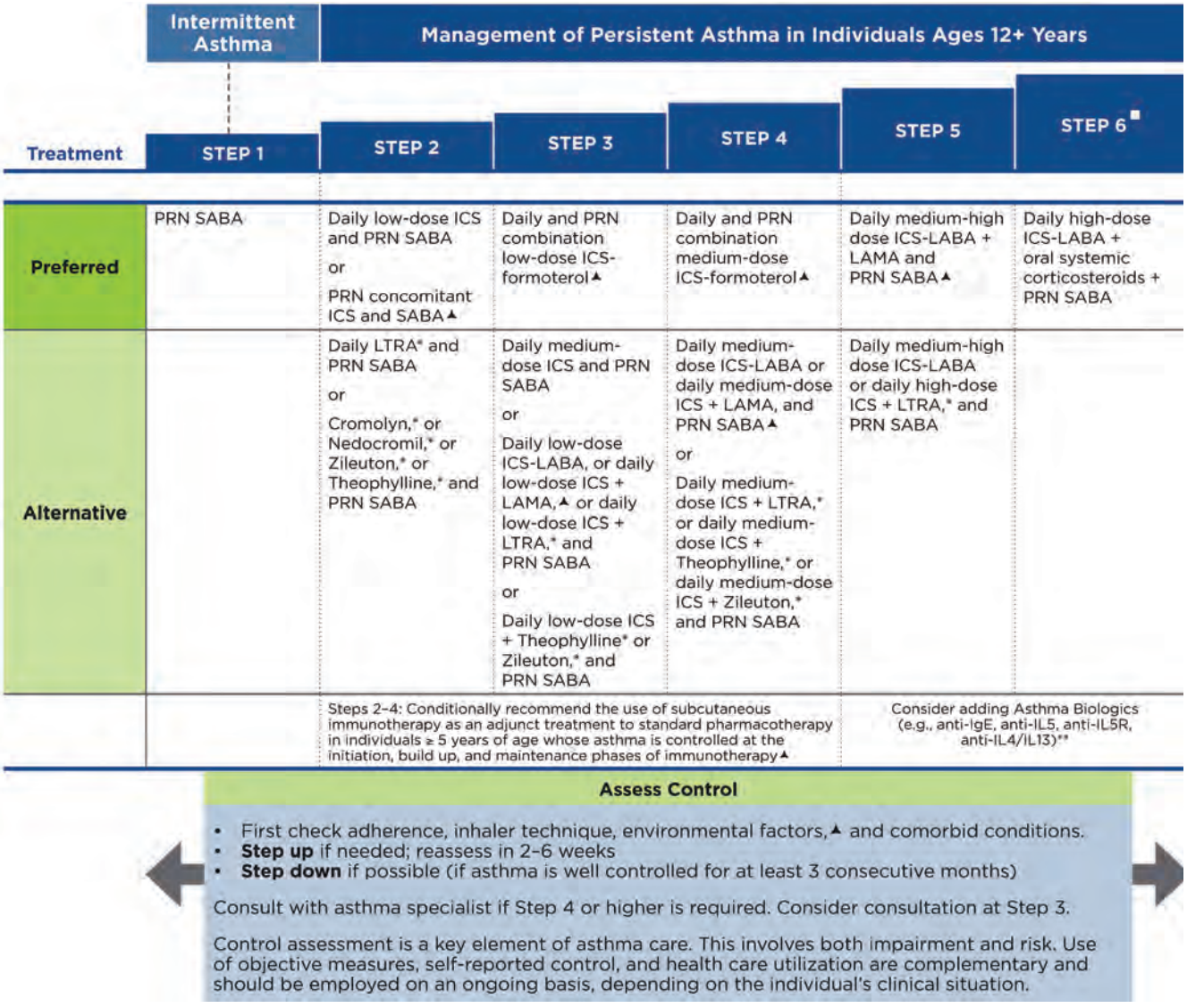
Asthma severity is the intrinsic intensity of disease and is based on the lowest level of therapy that allows the patient's asthma to remain controlled. Asthma control is based on impairment and future exacerbation risk criteria.[1] Impairment is ascertained by the patient's/caregiver's recall of symptoms and functioning during the previous 2 to 4 weeks, as well as spirometry findings. Risk is ascertained by the number and frequency of exacerbations requiring oral corticosteroids. Asthma severity is assigned to the most severe category in which any feature exists.

Assessing asthma control

Following initiation of treatment, assessing control is a key element of asthma care. EPR-3 classification of asthma control is based on similar—but not identical—impairment and risk criteria for categorizing asthma severity **(TABLE)**.[1] Clinical assessment of asthma control should be obtained through

FIGURE 1. **Stepwise approach for management of asthma (cont'd)**

C. Age ≥12 years



Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting β_2-agonist.

▲Updated based on the 2020 guidelines. Recommendations supporting the use of maintenance and reliever therapy in 1 inhaler consisting of ICS/formoterol are primarily based on clinical data with an ICS/formoterol dry powder inhaler product that is not approved or available in the United States.

*Cromolyn, nedocromil, LTRAs including zileuton and montelukast, and theophylline were not considered for this update, and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a boxed warning for montelukast in March 2020.

**The AHRQ systematic reviews that informed this report did not include studies that examined the role of asthma biologics (eg, anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13). Thus, this report does not contain specific recommendations for the use of biologics in asthma in steps 5 and 6.

▪Data on the use of LAMA therapy in individuals with severe persistent asthma (step 6) were not included in the AHRQ systematic review and thus no recommendation is made.

medical history, validated asthma control tools **(TABLE and FIGURE 2A)**, and, when appropriate, pulmonary function testing.

Many tools have been validated to assess asthma control. The Asthma Control Questionnaire (ACQ),[8] Asthma Control Test (ACT),[9,10] and Childhood Asthma Control Test[10] assess symptom control with no direct measure of future risk. Tools that assess both symptoms and future risk include the Asthma Control and Communication Instrument,[11,12] Asthma Impairment and Risk Questionnaire (AIRQ),[13] Composite Asthma Severity Index,[14] and Test for Respiratory and Asthma Control in Kids.[15]

TABLE. **Assessing asthma control in adolescents age ≥12 years and adults**[1]

Components of control		Well controlled	Not well controlled	Very poorly controlled
Impairment	Symptoms	≤2 d/wk	>2 d/wk	Throughout the day
	Nighttime awakening	≤2x/mo	1-3x/wk	≥4x/wk
	Interference with normal activity	None	Some limitation	Extremely limited
	SABA use for symptom control[a]	≤2 d/wk	>2 d/wk	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60%-80% predicted/ personal best	<60% predicted/personal best
	Validated questionnaires			
	ATAQ	0	1-2	3-4
	ACQ	≤0.75[b]	≥1.5	NA
	ACT	≥20	16-19	≤15
Risk	Exacerbations	0-1/y	≥2/y[c]	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term follow-up care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control, but should be considered in the overall assessment of risk.		

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ATAQ, Asthma Therapy Assessment Questionnaire; NA, not applicable; SABA, short-acting β_2-agonist.

[a]Not prevention of exercise-induced bronchoconstriction.

[b]ACQ values of 0.76-1.4 are indeterminate regarding well-controlled asthma.

[c]At present, there are inadequate data to correspond to frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

- Asthma Control Test: for use with adults and adolescents 12 years of age and older with asthma (https://www.asthma.com/understanding-asthma/severe-asthma/asthma-control-test/)
- Childhood Asthma Control Test (CACT) /Asthma Control Test: for use with children 4 to 11 years of age with asthma (https://www.asthma.com/understanding-asthma/severe-asthma/asthma-control-test/)
- Asthma Impairment and Risk Questionnaire **(FIGURE 2A)**: for use with adults and adolescents 12 years of age and older with asthma (http://www.airqscore.com/)
- Test for Respiratory and Asthma Control in Kids: for use with children under 5 years of age who have a history of 2 or more episodes of wheezing, shortness of breath, or cough lasting more than 24 hours and have previously been prescribed quick-relief bronchodilator medications (https://getasthmahelp.org/documents/track.pdf)

For patients age ≥12 years, only the AIRQ is validated as a single instrument assessing both impairment and control. The questionnaire has numerically scored questions providing total scores and cut points for varying levels of asthma. AIRQ includes 10 dichotomous (yes or no) questions that evaluate symptoms, social and physical activities, exacerbations, related healthcare resource utilization, perception of asthma control, and use of rescue (reliever) medications. The AIRQ score ranges from 0 to 10. A score of 0 or 1 indicates asthma is well controlled, a score of 2 to 4 indicates asthma is not well controlled, and a score of 5 to 10 indicates asthma is very poorly controlled. AIRQ identifies patients with exacerbations requiring treatment with oral corticosteroids or emergency department/unplanned office visits or hospitalizations for asthma that are not assessed by many other asthma control tools. A companion brochure for patients, "AIRQ: Asthma Control and You" **(FIGURE 2B)**, explains the purpose of assessing asthma control and encourages patients to use their AIRQ results as part of a shared decision-making conversation with their healthcare providers.

Using an asthma management assessment checklist in conjunction with an asthma control questionnaire can facilitate a thorough investigation and optimization of asthma control. The Asthma Checklist **(FIGURE 3)** is an example of an asthma management assessment tool that includes factors such as medication adherence, use of an action plan, psychological issues, vaccinations, and suggestions for specialty care referral.

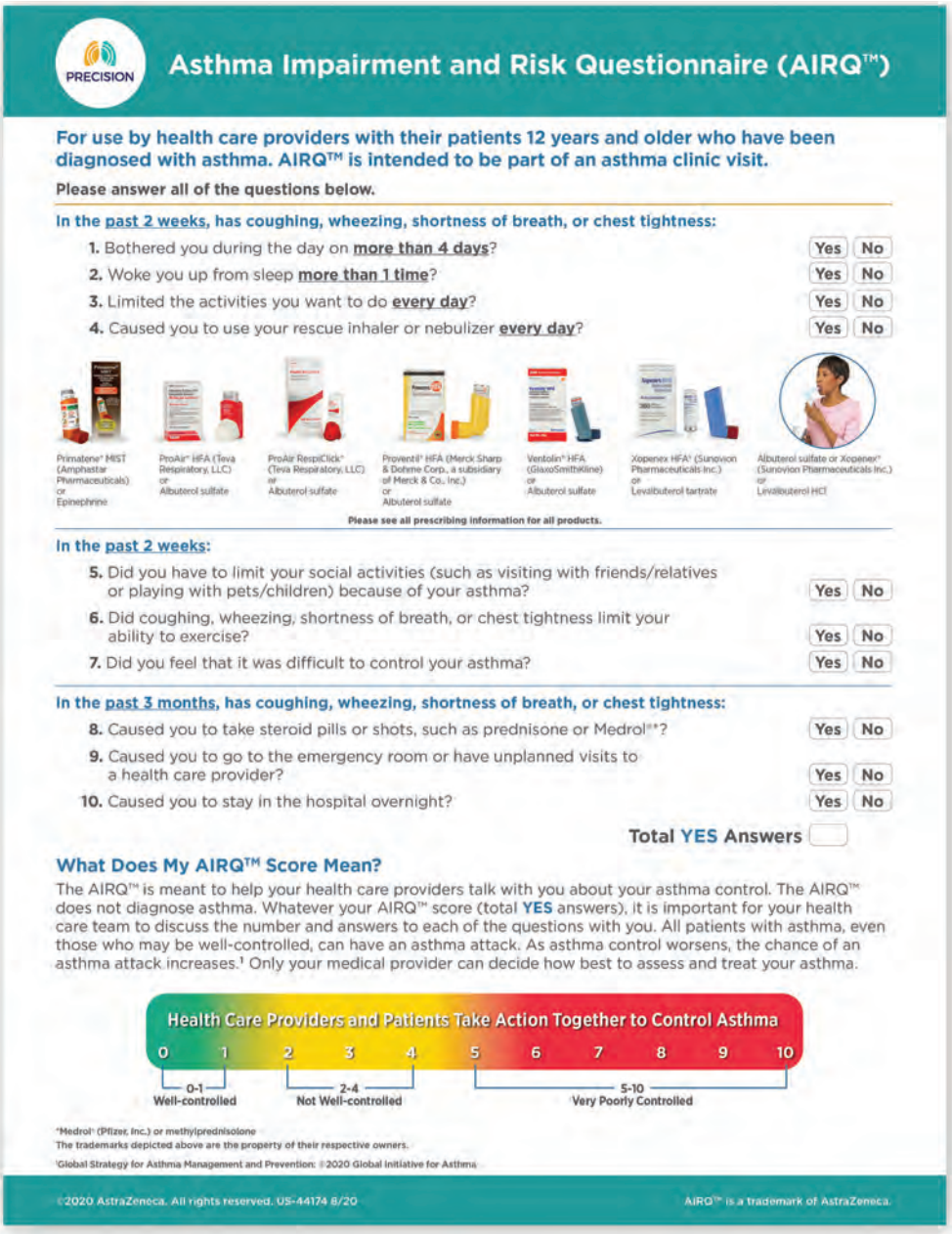
If asthma is well controlled, therapy should be maintained at the current step with regular follow-up every 1 to

6 months to maintain control. Stepping down therapy should be considered if asthma is well controlled for ≥3 months. Once asthma becomes well controlled, treatment steps are used to classify a patient's asthma severity.[1]

If asthma is not well controlled, therapy should go up a step with reevaluation in 2 to 6 weeks. If asthma is very poorly controlled, therapy should go up 1 or 2 steps, and a short course of systemic corticosteroids should be considered, with reevaluation in 2 weeks. If adverse effects occur with intensified therapy, alternative treatment appropriate for the increased step level should be considered.

Although systemic corticosteroids are recommended in certain situations as they are very effective in resolving acute asthma symptoms and exacerbations, recent evidence provides a cautionary note. Although the adverse consequences of long-term use of systemic corticosteroids are widely recognized, growing evidence indicates that even frequent, brief dosing periods, ie, 3 to 7 days, in individuals with asthma are associated with a variety of negative health outcomes. These include significant increases in the risk of pneumonia, osteoporosis and osteoporotic fracture, heart failure, sleep apnea, myocardial infarction, cataracts, type 2 diabetes, hypertension, and other disorders, as well as higher healthcare costs.[16-19] Consequently, an important new consideration is the recommendation from some experts that the cumulative dose of systemic corticosteroids should be limited to the equivalent of <500 mg to 1000 mg of prednisone per year.[20]

FIGURE 2. **(A) Asthma Impairment and Risk Questionnaire (AIRQ) to assess control**



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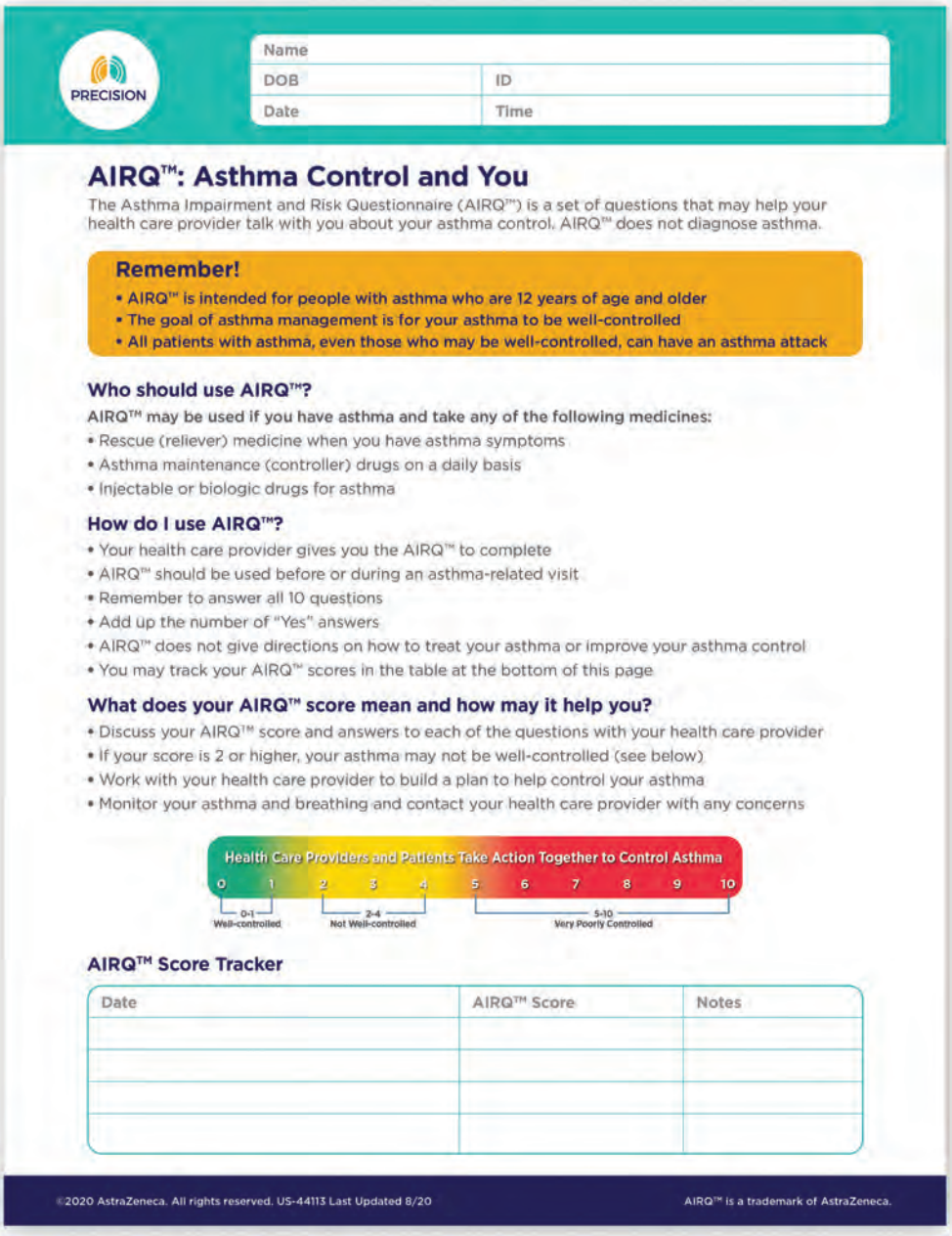
CONT'D

1: INTERMITTENT INHALED CORTICOSTEROIDS

The NAEPP 2020 Focused Updates modify some of the recommendations made by EPR-3 regarding the use of ICS. Updated preferred recommendations include the following (**FIGURE 1**)[2]:

FIGURE 2. **(B) AIRQ: Asthma Control and You for patient education on asthma control (cont'd)**



PRECISION

Name	
DOB	ID
Date	Time

AIRQ™: Asthma Control and You

The Asthma Impairment and Risk Questionnaire (AIRQ™) is a set of questions that may help your health care provider talk with you about your asthma control. AIRQ™ does not diagnose asthma.

Remember!

- AIRQ™ is intended for people with asthma who are 12 years of age and older
- The goal of asthma management is for your asthma to be well-controlled
- All patients with asthma, even those who may be well-controlled, can have an asthma attack

Who should use AIRQ™?

AIRQ™ may be used if you have asthma and take any of the following medicines:

- Rescue (reliever) medicine when you have asthma symptoms
- Asthma maintenance (controller) drugs on a daily basis
- Injectable or biologic drugs for asthma

How do I use AIRQ™?

- Your health care provider gives you the AIRQ™ to complete
- AIRQ™ should be used before or during an asthma-related visit
- Remember to answer all 10 questions
- Add up the number of "Yes" answers
- AIRQ™ does not give directions on how to treat your asthma or improve your asthma control
- You may track your AIRQ™ scores in the table at the bottom of this page

What does your AIRQ™ score mean and how may it help you?

- Discuss your AIRQ™ score and answers to each of the questions with your health care provider
- If your score is 2 or higher, your asthma may not be well-controlled (see below)
- Work with your health care provider to build a plan to help control your asthma
- Monitor your asthma and breathing and contact your health care provider with any concerns

Health Care Providers and Patients Take Action Together to Control Asthma

0 1 2 3 4 5 6 7 8 9 10

0-1 Well-controlled | 2-4 Not Well-controlled | 5-10 Very Poorly Controlled

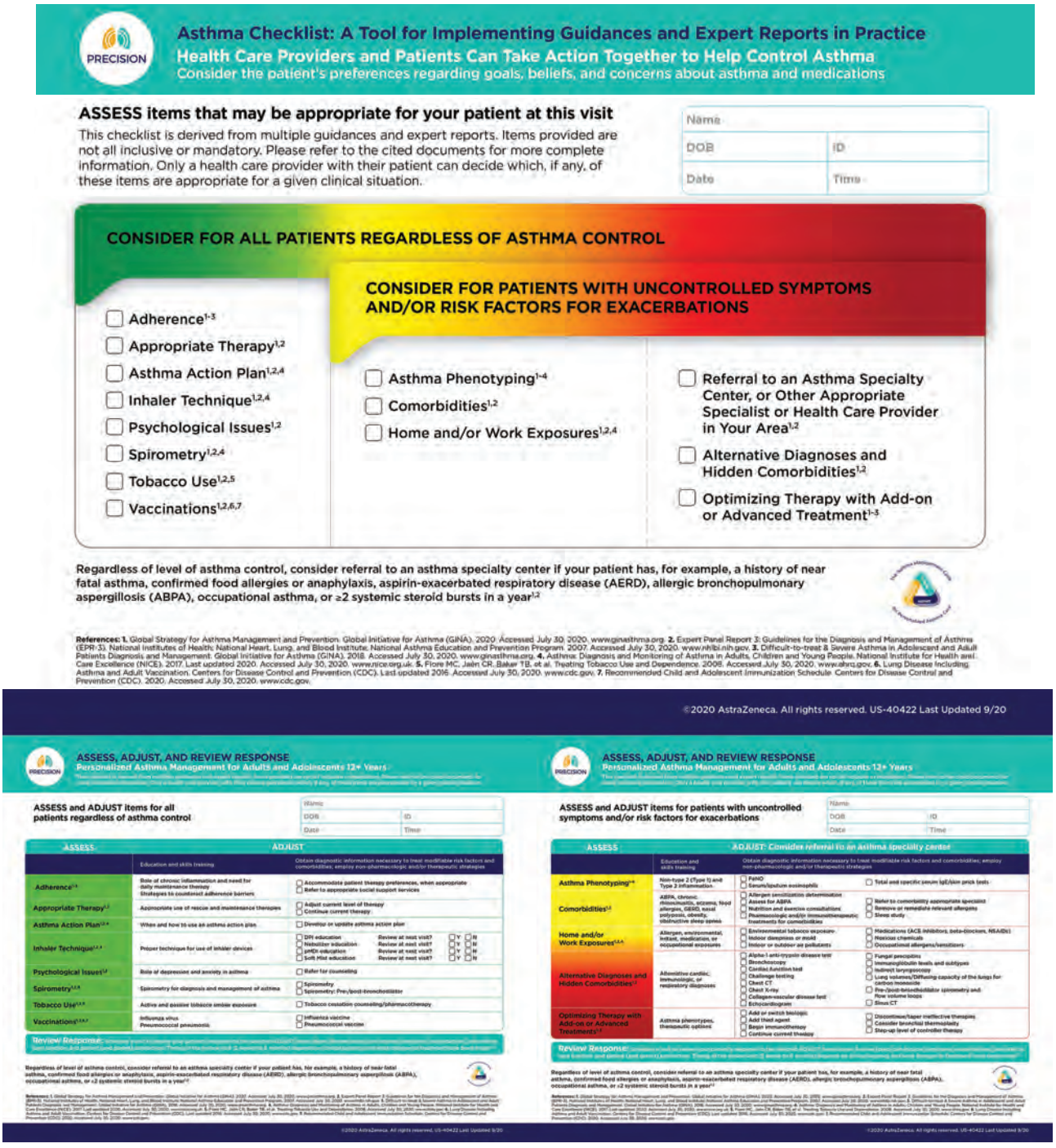
AIRQ™ Score Tracker

Date	AIRQ™ Score	Notes

other instruments without prior written approval. The 10 questions of the AIRQ® must appear verbatim, in order, and together as they are presented and not divided on separate pages. All copyright and trademark information must be maintained as it appears on the bottom of the AIRQ® and on all copies. The layout of the final authorized AIRQ® may differ slightly, but the item wording will not change.

- Individuals age 0 to 4 years:
  - Step 1: at the start of a respiratory tract infection, add a short course of ICS to as-needed short-acting β_2-agonist (SABA).
  - Step 3 or 4 for patients 4 years of age: see recommendations for patients 5 to 11 years of age below.
- Individuals age 5 to 11 years:
  - Step 3 or 4: for increased symptoms or decreased peak flow, do not treat with a short-term increase in ICS dose for patients who are already likely to be adherent to daily ICS.
  - Step 3 or 4: maintenance (medication taken daily for long-term control) and reliever (medication taken as needed for quick relief of shortness of breath) therapy in 1 inhaler consisting of low-dose ICS and formoterol (step 3) or medium-dose ICS and formoterol (step 4) given as 1 to 2 puffs once or twice daily as maintenance and 1 to 2 puffs as needed for symptoms. (Do not exceed 8 total puffs per day in children age 4 to 11 years.) [The use of ICS/formoterol in 1 inhaler for maintenance and reliever therapy is not approved in the United States for any patients.]
  - These steps 3 and 4 recommendations are preferred to either a higher-dose ICS as daily controller plus as-needed SABA for quick relief or single-inhaler dual same-dose ICS and long-acting β_2-agonist (LABA) as daily controller therapy plus SABA for quick relief.
- Individuals age ≥12 years:
  - Step 2: either a daily low-dose ICS plus as-needed SABA for quick relief or an as-needed ICS plus a SABA used concomitantly.
  - Step 3 or 4: as per children age 4 to 11 years, maintenance and reliever therapy in 1 inhaler consisting of low-dose ICS and formoterol (step 3) or medium-dose ICS and formoterol (step 4) given as 1 to 2 puffs once or

FIGURE 3. **Management Assessments (Asthma Checklist)**



The Asthma Checklist is available at www.asthmaresourcecenter.com. The Asthma Resource Center contains point-of-care and self-directed educational resources for healthcare providers and their patients that are available free of charge. These materials were developed to include a wide range of topics suggested by multiple guidelines and expert reports as pertinent to asthma care.

twice daily as maintenance and 1 to 2 puffs as needed for symptoms. (Do not exceed 12 total puffs per day in patients age ≥12 years.)

- This recommendation is preferred to single-inhaler dual higher-dose ICS and LABA as daily controller therapy plus SABA for quick relief.

- Recommendations supporting the use of maintenance and reliever therapy in 1 inhaler consisting of ICS/formoterol are

primarily based on clinical data with an ICS/formoterol dry powder inhaler product that is not approved or available in the United States. Consequently, differences in ICS/formoterol devices as well as doses must be considered when applying these recommendations in clinical practice.

2: USE OF LONG-ACTING MUSCARINIC ANTAGONISTS AS ADD-ON THERAPY

The use of long-acting muscarinic antagonist (LAMA) therapy was included for the first time in the NAEPP 2020 Focused Updates.[2] LAMAs can be used for long-term asthma control but not for quick relief to treat acute symptoms. LAMAs should not be used in individuals with or at risk of urinary retention or glaucoma.

Specific recommendations include the following in individuals age ≥12 years[2]:

- Step 3: uncontrolled on ICS maintenance therapy alone, addition of a LABA to the same dose of ICS is recommended over addition of a LAMA since adding a LAMA to ICS controller therapy provides no more benefit than adding a LABA to ICS controller therapy and may increase the risk of asthma-related hospitalization.
- Step 3: addition of a LAMA to low-dose ICS is recommended as alternative therapy if the individual cannot use a LABA.
- Step 4: addition of a LAMA to medium-dose ICS is recommended as alternative therapy for patients who cannot use a LABA.
- Step 5: for patients uncontrolled with the combination of medium-dose ICS and LABA, adding a LAMA to medium- to high-dose ICS/LABA is recommended for many individuals because its use is associated with an improvement in asthma control and quality of life with no change in exacerbations.
- Step 6: if uncontrolled on step 5 therapy that utilizes an ICS and a LABA and a LAMA, discontinue LAMA therapy.

3: FRACTIONAL EXHALED NITRIC OXIDE TESTING

Fractional exhaled nitric oxide (FeNO) testing is a biomarker for type 2, or eosinophilic, inflammation of the airway. The NAEPP 2020 Focused Updates recommend its use only in limited situations, in part because FeNO lacks specificity for asthma. FeNO is not recommended in isolation to assess asthma control, predict future exacerbations, or assess exacerbation severity, nor should it be used to predict future development of asthma.[2]

According to the NAEPP 2020 Focused Updates, FeNO testing can be used adjunctively to diagnose asthma if there is uncertainty based on history, physical examination, and spirometry, including bronchodilator responsiveness. FeNO is also recommended as part of an ongoing asthma monitoring and management strategy in individuals with persistent allergic asthma for whom there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapy. Monitoring FeNO every 2 to 3 months has the potential benefit of reducing the incidence of asthma exacerbations.

4: ALLERGEN REDUCTION STRATEGIES IN ASTHMA MANAGEMENT

The identification of environmental factors that contribute to asthma is a cornerstone of asthma management, as described in EPR-3.[1] The EPR-3 recommended that all individuals with asthma, regardless of severity, should be assessed for exposure to allergens at home and work, for symptoms on exposure, and for sensitization either by allergy skin testing or allergen-specific immunoglobulin E (IgE). This recommendation was reiterated in the NAEPP 2020 Focused Updates.[2]

The NAEPP 2020 Focused Updates recommendations for allergen mitigation are more focused than the EPR-3 recommendations, indicating that there is no need to eliminate all potential allergens.[2] Allergen mitigation interventions are not recommended in individuals who have no history of exposure and in whom there is no evidence of sensitization and/or symptoms with exposure.

For individuals who are both exposed to and either sensitized to or develop symptoms on exposure to specific allergens, single-component allergen-specific interventions are not recommended except for pests (cockroaches and rodents).[2] Multicomponent interventions are recommended for the following:

- Exposure to cockroaches and rodents: integrated pest management to block infestation and abatement, either alone or as part of a multicomponent allergen-specific mitigation intervention
- Exposure to dust mites: impermeable pillow/mattress covers; HEPA filter–equipped vacuum, carpet/curtain removal; cleaning products only as part of a multicomponent allergen mitigation intervention, not as single-component intervention
- Mold: HEPA purifiers and mold abatement

Otherwise, individuals with symptoms related to exposure to specific indoor allergens (eg, dust mites or cat dander) should be treated using multicomponent mitigation strategies because such interventions have been shown to improve symptoms (but not individual measures of exacerbations). Multicomponent mitigation strategies to be used in combination include dust mite–impermeable pillow and mattress covers, HEPA vacuums (for children), integrated pest management, and mold mitigation.[2]

5: ROLE OF SUBCUTANEOUS AND SUBLINGUAL IMMUNOTHERAPY IN TREATMENT OF ALLERGIC ASTHMA

Immunotherapy, delivered either subcutaneously or sublin-

gually, refers to treatments used to attenuate the IgE-mediated allergic clinical response associated with asthma. Before initiating immunotherapy, individuals with asthma need to demonstrate allergic sensitization by either immediate hypersensitivity testing followed by an assessment 15 to 20 minutes later for a wheal-and-flare reaction or laboratory testing to measure the blood level of antigen-specific IgE antibody.

In the NAEPP 2020 Focused Updates, subcutaneous immunotherapy (SCIT) is recommended as adjunctive treatment for individuals aged ≥5 years with mild-moderate persistent asthma who have allergic sensitization and worsening symptoms after acute exposure on a seasonal basis. The benefit of SCIT, particularly if marginal, must be weighed against the potential for systemic reactions.

Although not recommended as a treatment specifically for asthma, sublingual immunotherapy (SLIT) has the potential to reduce the symptoms of some comorbidities such as allergic rhinitis and allergic conjunctivitis.

6: BRONCHIAL THERMOPLASTY

Bronchial thermoplasty is a physical modality used as part of a bronchoscopy that uses radio waves to reduce airway smooth muscle mass. The NAEPP 2020 Focused Updates recommend against the use of bronchial thermoplasty in adults with persistent asthma.[2] Individuals with forced expiratory volume in 1 second (FEV_1) of <50% to 60% or life-threatening asthma are not candidates. Bronchial thermoplasty may be considered for adults, eg, those with poorly controlled asthma who place a high value on potential benefits and low value on potential harms. Potential benefits include improved health-related quality of life and a small reduction in number of exacerbations. Potential harms include short-term symptom worsening and unknown long-term adverse effects.

SHARED DECISION-MAKING AND SPECIALIST REFERRAL

Important in the care of patients with asthma is a shared decision-making discussion including recommending referral for specialist assessment depending on the severity step and experience and training of the healthcare provider. This is especially important in patients with uncontrolled or difficult-to-control asthma, particularly in patients with an AIRQ score of ≥5 or ACT or CACT score of ≤15.

RESOURCES

A wide variety of resources for managing individuals with asthma are available.

- Asthma Resource Center (www.AsthmaResourceCenter.com)
  - Patient education brochures and animations in English and Spanish
  - Comparisons of NAEPP 2020 Focused Updates and Global Initiative for Asthma report
  - Asthma Checklist and asthma action plans
- Centers for Disease Control and Prevention (https://www.cdc.gov/asthma/default.htm)

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New Perspectives in COPD Management

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doi: 10.12788/jfp.0220

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Collaborate with patients to inform treatment decision-making that addresses their symptoms, goals, and concerns
- Individualize guideline-recommended therapy to reduce chronic obstructive pulmonary disease (COPD) exacerbations, improve lung function, manage daily symptoms such as breathlessness, and help achieve the patient's goals
- Select an inhaler and an optimal dose of medication to best meet a patient's needs and capabilities

KEY TAKEAWAYS

- The goal of treatment is to achieve and maintain stable disease by reducing both symptoms and the future risk of exacerbations.
- Holistic management consists of addressing 5 issues: 1) risk factors; 2) individualizing treatment; 3) comorbidities; 4) preventive therapy; and 5) self-management education to address patient's goals and preferences.
- Patients with COPD most likely to experience benefit with an inhaled corticosteroid (ICS) include those with ≥2 exacerbations and/or 1 hospitalization in the previous year.
- There is a continuous relationship between blood eosinophils and ICS benefit with those with blood eosinophil count <100 cells/mL likely to achieve little or no benefit with ICS therapy.
- Single inhaler dual or triple therapy offers several advantages compared with separate inhaler dual or triple therapy, including improved symptom control, reduced rate and time to first moderate/severe exacerbation, and, for some patients, lower co-payments.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of COPD.

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SPONSORSHIP

This article is sponsored by Primary Care Education Consortium, in collaboration with the Primary Care Respiratory Group.

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ACKNOWLEDGMENT

Editorial support was provided by Gregory Scott, PharmD, RPh, of the Primary Care Education Consortium (PCEC).

SUPPORTER

This article is supported by an educational grant from AstraZeneca Pharmaceuticals LP.

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BURDEN OF DISEASE

Chronic obstructive pulmonary disease (COPD) is well established as causing extensive morbidity and mortality among the 6.6% of adults with diagnosed COPD in the United States.[1] The U.S. Burden of Disease Collaborators determined that COPD was responsible for 1.2 million years lived with disability, the eleventh leading cause, in 2016.[2] Morbidity from COPD may be affected by coexisting diseases, eg, car-

diovascular disease, musculoskeletal impairment, diabetes mellitus, gastroesophageal disease, osteoporosis, lung cancer, anxiety, and depression.[3]

Also in 2016, COPD was responsible for 2.3 million years of life lost, the third leading cause, or 501 years of life lost per 100,000 people.[2] In 2014, the death rate due to COPD in the United States was 39.1 deaths per 100,000 people and was higher in males than females (44.3 vs 35.6 deaths per 100,000 people, respectively).[4] One-quarter of adults with COPD have never smoked.[5] Geographic and sociodemographic patterns of COPD prevalence are similar among current smokers, former smokers, and adults who have never smoked.[5]

Exacerbations caused by COPD are associated with numerous negative outcomes, eg, accelerated decline in lung function, poor functional status and quality of life, and increased healthcare resource utilization. Severe exacerbations, ie, those requiring hospital admission, are associated with poor prognosis.[6]

CHANGING THE TREATMENT PARADIGM

For more than 20 years, the treatment of COPD has consisted of managing symptoms and preventing exacerbations.[3,7] However, 20 years ago, controlling daily symptoms was especially challenging because of the limited effectiveness of available medications in treating symptoms and the underlying inflammation. Moreover, the duration of action of most medications was short, which required dosing multiple times daily. Consequently, much of the treatment focus was on reducing the severity of exacerbations once they occurred.

Fortunately, medications have become available that are more effective and have a longer duration of action. This has enabled the effective reduction of daily symptoms to be a realistic goal. This is fortuitous since compelling evidence has emerged as to the negative consequences of exacerbations, including increased risk for future exacerbations and death, as well as progressive decline in lung function.[8-10]

This changing paradigm has been embraced in the past few years by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). As identified by GOLD, the broad goal of treatment is to achieve and maintain stable disease. Although GOLD 2020 does not explicitly define stable disease, the objective is to reduce both symptoms and the future risk of exacerbations.[3] This treat-to-target approach is increasingly employed in the treatment of individuals with other chronic diseases, eg, diabetes mellitus, inflammatory bowel disease, and rheumatoid arthritis. The treat-to-target approach involves employing treatment to first achieve the treatment target and then modifying treatment as needed to maintain the treatment target. In the case of COPD, the treatment target is stable disease. Therefore, when disease control begins to deteriorate and symptoms increase but an acute exacerbation has not yet occurred, the patient should be empowered to intensify treatment. Action plans have been customarily aimed at treating an acute exacerbation; however, it is important for patients to know steps to intensify treatment at the onset of deteriorating symptoms, as is done for migraine headaches. A key item for inclusion in the written action plan is a reminder for the patient to contact their primary care clinician (PCC) at the time treatment is intensified, even if symptom stability is regained.

Effective self-management requires that the patient has the knowledge, motivation, and means to implement the treatment plan.[11] Effective communication and shared decision-making that engages the patient are key steps complemented with ongoing education and coaching by the multidisciplinary care team described below.[12] Shared decision-making should be utilized at each patient visit, with a key objective to solicit and address patient barriers, goals, and concerns. The treatment plan, as well as the written action plan, should be revised as needed.

HOLISTIC MANAGEMENT

Holistic management that places the patient at the center of care is a key to achieving and maintaining stable disease.[11] Five basic components of holistic management in individuals with COPD are 1) eliminate/minimize risk factors, 2) initiate individualized nonpharmacologic and pharmacologic therapy early in the disease course and intensify as needed using a treat-to-target approach, 3) identify and treat comorbidities, 4) provide preventive therapy, and 5) provide self-management education.[3] Smoking cessation is of paramount importance, with support and treatment provided for the rest of the patient's life. The importance of a healthy diet should not be overlooked since a diet rich in antioxidants may have beneficial effects on lung function.[13] Treatment cost and affordability are also important considerations and should be discussed with the patient.

Clinicians should consider and screen for comorbidities such as diabetes, cardiovascular disease, and depression. If found, clinicians should provide treatment with evidence-based therapies. Generally, the treatment of comorbidities does not alter COPD treatment, and the presence of COPD will not alter basic treatment of comorbid conditions. Treatment of individuals with COPD, such as with pulmonary rehabilitation, may have a beneficial impact on comorbidities, such as depression, anxiety, sleep disturbance, and fatigue.[14-16] The overall treatment plan should be simplified as much as possible, including minimizing the number of medications and using combination medications, including inhalers. Assistance for smoking cessation is a key component of preventive therapy. In addition to practicing healthy

FIGURE 1. **ABCD assessment tool for selection of initial pharmacologic treatment[3]**

≥2 Moderate exacerbations or ≥1 leading to hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA[a] or ICS + LABA[b]
0 or 1 Moderate exacerbations (not leading to hospital admission)	**Group A** Bronchodilator	**Group B** Long-acting bronchodilator (LAMA or LABA)
	mMRC 0-1; CAT <10	mMRC ≥2; CAT ≥10

CAT, COPD Assessment Test; mMRC, Modified British Medical Research Council Questionnaire.

[a]Consider if highly symptomatic (eg, CAT >20).

[b]Consider if eosinophil count ≥300 cells/microliter.

lifestyle recommendations, individuals should be screened for lung cancer and should receive recommended vaccinations including pneumococcal, influenza, tetanus, diphtheria, pertussis (Tdap), shingles, and COVID-19.

Holistic management generally involves care provided by a multidisciplinary care team, with the PCC playing a key role in collaborating with the pulmonologist, chronic care managers, mental health clinician, respiratory therapist, physical therapist, and others. Collaboration among the multidisciplinary care team is especially important during any hospitalizations to ensure that transitions in care take place smoothly. Finally, although COPD is a progressive disease, a key role of the PCC is to nurture hope through close collaboration with the patient and provide assurances that treatment will be individualized to achieve treatment goals.

PHARMACOLOGIC TREATMENT

Initial

Initial pharmacologic treatment selection recommended by GOLD is guided by the revised ABCD assessment tool **(FIGURE 1)**.[3] This tool utilizes clinical parameters, ie, symptoms and history of exacerbations, but not airflow limitation as identified by spirometry. This separation acknowledges the limitations of lung function assessment in predicting symptom burden and risk of exacerbation and, therefore, pharmacologic treatment decisions, while remaining a key factor in diagnosis and prognosis assessments.

Bronchodilator therapy using a β_2-agonist or antimuscarinic or a combination of these medications is the cornerstone of pharmacologic treatment for individuals with COPD as it increases the forced expiratory volume in 1 second (FEV_1) and/or improves other spirometric variables. Although bronchodilator therapy has not been shown to impact lung function decline,[17,18] it has numerous other benefits, eg, reducing symptoms, improving health status, and reducing exacerbation rates.[19-22] Long-acting antimuscarinic (LAMA) therapy has a greater effect on reducing exacerbation rates than long-acting β_2-agonist (LABA) therapy.[23,24] Compared with monotherapy, combination LAMA/LABA therapy provides for greater improvement in lung function and patient-reported outcomes such as quality of life.[25-28]

Anti-inflammatory therapy using an inhaled corticosteroid (ICS) as monotherapy is not indicated in COPD management as it has not been shown to modify the long-term decline in FEV_1 or reduce mortality, symptom burden, or dynamic hyperinflation, the latter of which often leads to dyspnea.[29] Consequently, ICS therapy in combination with ≥1 long-acting bronchodilator(s) is recommended for patients with severe disease, eg, GOLD ABCD group D.[3] Specifically, an ICS is recommended for patients with severe disease and an elevated blood eosinophil count. The eosinophil count helps predict the magnitude of the effect of ICS (in combination with bronchodilator therapy) in preventing future exacerbations.[30-35] Patients with a blood eosinophil count >300 cells/μL are most likely to achieve treatment benefit with ICS therapy,[3] although there is a continuous relationship between blood eosinophils and ICS benefit, and those with a blood eosinophil count >100 cells/μL are likely to achieve benefit with ICS therapy.[3] Since the primary role is exacerbation prevention, patients most likely to benefit from ICS-containing therapy are those with high exacerbation risk, ie, ≥2 exacerbations and/or 1 hospitalization in the previous year.[31,33,36] Thus, treatment decisions about ICS therapy should be based on the clinical assessment of exacerbation risk and should consider blood eosinophil count.[3]

TREATMENT DECISIONS ABOUT ICS THERAPY SHOULD BE BASED ON THE CLINICAL ASSESSMENT OF EXACERBATION RISK AND SHOULD CONSIDER BLOOD EOSINOPHIL COUNT.

TABLE 1. **Checklist for the COPD follow-up office visit**

- Repeat the CAT
  - Have patient complete in waiting room or examination room[a]
  - Compare to previous CAT score to assess progressive symptoms like dyspnea
- Ask about:
  - Respiratory problems or events since last visit, particularly if they required an urgent care/emergency department visit
  - Changes in comorbidities
  - Changes in activity level (be specific)
  - Difficulties with prescription refills
  - Difficulties following the treatment plan
  - Satisfaction with treatment
- Check inhaler technique by observation
  - Can be done by trained staff
- Review medications patient is taking to be sure they are the ones prescribed
  - Requires patient to bring in actual medications instead of a list; telehealth may provide good opportunity for patient or family to bring medication to video device
  - Note brand and inhaler type may have been changed due to insurance
- Review patient's goals and action plan[a]

CAT, COPD Assessment Test.

[a]Can be facilitated by using the COPD Foundation application available at https://bit.ly/2RwrX79

Follow-up

Assessing the patient's response to treatment is essential at every visit **(TABLE 1)**. Two validated tools that can be used are the Modified British Medical Research Council Dyspnea Scale (mMRC)[37] and the COPD Assessment Test (CAT).[38] However, the mMRC is of limited use since it measures only breathlessness and changes from 1 level to the next may not be very sensitive to changes in symptom burden or lung function decline. In contrast, the CAT is a broad measure of symptoms and is more inclusive of overall health status. While neither tool categorizes patients by symptom severity for the purpose of modifying treatment, using the CAT at every visit allows the clinician to assess health changes over time.

Patient assessment should also investigate any other changes in health or difficulties with treatment adherence the individual might be experiencing. As always, clear communication using shared decision-making can help quickly identify factors that might contribute to a change in disease stability. If the individual is experiencing difficulties or has concerns, it is important that solutions be found in collaboration with the patient and complemented by education and support so that the patient is willing and able to successfully implement the revised treatment plan. This is also the opportune time to reinforce nonpharmacologic treatment and inhaler technique.

FIGURE 2 outlines the recommended pathway for intensifying maintenance treatment in an individual who is experiencing disease instability.[3] The pathway does not include consideration of GOLD ABCD group identified at treatment initiation or disease duration.[3] Treatment is modified based on whether dyspnea or exacerbations are the predominant treatable trait. The CAT is useful to identify trends and changes in symptom control. For individuals with dyspnea as the predominant trait who are treated with long-acting bronchodilator monotherapy, ie, LAMA or LABA, the addition of a second long-acting bronchodilator is appropriate. Alternatively, switching the inhaler device or molecules can be considered.

For an individual with exacerbations as the predominant trait, either dual or triple combination therapy is needed, with the choice based on current treatment as well as blood eosinophil count.[3] For example, the addition of an ICS is recommended for a patient with blood eosinophil level >100 cells/μL who experiences an exacerbation despite good adherence to combination LABA/LAMA therapy.

Orally inhaled medications

To optimize inhalation therapy, inhaler selection must be individualized **(TABLE 2)**.[39] Ease of use and convenience are factors patients consider important in the selection of an inhaler device. Therefore, selection must take into account patient capabilities and preferences, including experience with inhalers.[40,41] Patient physical and cognitive limitations are important to consider as well. Device choice may also be

dictated by insurance coverage and co-payments, which are often very important to the patient.

In addition to demonstrating and verifying correct inhaler technique by watching the patient use the inhaler initially, inhaler technique should be reviewed and observed at each visit since a decline in correct inhaler technique is common within weeks to months of initial instruction.[40,42-44]

For patients who require treatment with ≥2 inhaled medications, a single inhaler containing 2 or 3 medications, ie, single inhaler dual or triple therapy, should be used whenever possible. This not only reduces the amount of time required for medication administration, but it also simplifies the overall treatment plan. If individual inhalers must be used, the same inhaler device, eg, metered dose inhaler, dry powder inhaler, soft mist inhaler, should be used when possible to avoid patient confusion and errors in inhaler use.[45]

Single inhaler triple therapy has been shown to provide significant improvement in symptom control and severity of exacerbations vs separate triple inhaler therapy.[46] Similarly, single inhaler triple

FIGURE 2. **Follow-up pharmacologic treatment[3]**

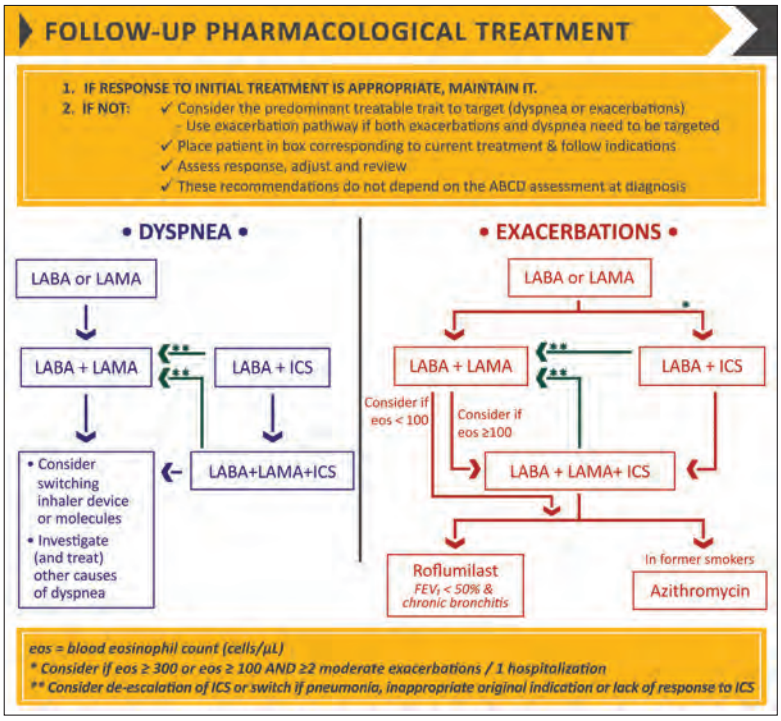

TABLE 2. **Advantages and disadvantages of inhaler devices[39]**

	Advantages	Disadvantages
Pressurized metered-dose inhaler (pMDI)	• High reproducibility between doses[48] • Independent of inspiratory flow rate[49] • Option for spacer add-on to optimize delivery[48]	• Requires coordination of actuation and inhalation[48] • Many patients cannot use it correctly[50] • High oropharyngeal deposition[50]
pMDI + spacer	• Compared with pMDI ○ Easier to coordinate[50] ○ Less oropharyngeal deposition[50] ○ Higher lung deposition	• Subject to static charge[50] • Compared with pMDI ○ More expensive ○ Less portable[50] ○ Requires additional cleaning
Dry power inhaler (DPI)	• Does not contain propellant[50] • No coordination needed[50] • Quicker time to achieve mastery in technique[51]	• Requires minimum inspiratory flow[50] • Many patients cannot use it correctly[50] • Most types are moisture sensitive[50]
Soft mist inhaler (SMI)	• Multidose device[50] • High lung deposition[50] • Does not contain propellant[50]	• May require assembly • Requires some coordination of actuation and inhalation[52] • Relatively expensive
Nebulizer	• May be used at any age[50] • No specific inhalation technique required[50] • May dispense drugs not available with pMDIs and DPIs[50]	• Treatment times can be long[50] • Performance varies among nebulizers[50] • Risk of bacterial contamination[50] • Often requires separate administration for each medication used

therapy has been shown to provide significant improvement in rate of moderate/severe exacerbations and time to first moderate/severe exacerbation over 52 weeks vs single inhaler dual therapy.[47]

The COPD Foundation provides video-based education related to the use of a wide variety of inhalers (https://www.copdfoundation.org/Learn-More/Educational-Materials-Resources/Educational-Video-Series.aspx). Additional resources include:

- American Thoracic Society/Mayo Clinic: https://www.thoracic.org/professionals/clinical-resources/video-lecture-series/obstructive-lung-disease/asthma/inhaler-device-selection-and-technique.php
- Asthma and Allergy Network: https://allergyasthmanetwork.org/what-is-asthma/how-is-asthma-treated/
- Centers for Disease Control and Prevention: https://www.cdc.gov/asthma/inhaler_video/default.htm

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Obesity 2021: Current Clinical Management of a Chronic, Serious Disease

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doi: 10.12788/jfp.0221

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Recognize obesity as a chronic, relapsing, serious disease warranting long-term management and early intervention to minimize disease burden and decrease associated morbidity and mortality.
- Destigmatize obesity to initiate and enhance patient engagement.
- Apply guideline-recommended care for screening, diagnosis, and individualized treatment of adults and others with obesity.
- Incorporate practical practice management strategies.

KEY TAKEAWAYS

- Obesity is deeply rooted in genetic, psychosocial, behavioral, and environmental factors that are intertwined with a complex pathophysiology involving persistent adaptations in numerous gut hormones and neuropeptides.
- Destigmatizing obesity in the health care environment is needed and can be accomplished through recognition that obesity is a chronic disease, improved communication facilitated by motivational interviewing, and properly equipping the office environment.
- Nonpharmacologic therapy is the foundation of comprehensive treatment for patients with obesity.
- There are 5 antiobesity medications currently approved for long-term use, and these should be considered for patients who are unable to achieve weight management goals with lifestyle treatment alone.
- Injectable semaglutide is a glucagon-like peptide-1 receptor agonist recently approved based on the results of clinical trials showing it to be safe and well tolerated in patients with obesity, enabling one-half of patients without diabetes to achieve significant weight loss.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of obesity.

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Dr. Kushner serves on the advisory board for Novo Nordisk. Gregory Scott, PharmD, editorial support; Joseph Nadglowski, reviewer; and James Zervios, reviewer, report no conflicts of interest. Dr. Stephen Brunton, editor, serves on the advisory board and speakers bureau for AstraZeneca, Bayer, and Novo Nordisk. He serves on the speaker bureau for Lilly and on the advisory board for Abbott Diabetes, Acadia, Sanofi, and Xeris.

SPONSORSHIP

This article is sponsored by IAFP and Primary Care Education Consortium, in collaboration with the Primary Care Metabolic Group and the Obesity Action Coalition.

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ACKNOWLEDGMENT

Editorial support was provided by Gregory Scott, PharmD, RPh, of the Primary Care Education Consortium.

SUPPORTER

This article is supported by an educational grant from Novo Nordisk.

In the 1950s, the prevalence of obesity (body mass index [BMI] ≥30 kg/m^2) in the United States was 10.2% for men and 13.9% for women.[1] In 2018, 43.0% of men and 41.9% of women had obesity.[2] From 1999 to 2016, mean body weight, waist circumference, and BMI increased for all adult age groups in the United States.[3] These trends over the past 7 decades are concerning since obesity serves as an independent risk factor for several of the most debilitating conditions in adults age <65 years,[4] being linked to 10% to 20% of all cancer cases,[5-7] 50% to 85% of all type 2 diabetes mellitus (T2D) cases,[8,9] and 15% to 30% of all osteoarthritis cases.[10]

Advancements in disease understanding and treatment approaches provide opportunities to implement 5 strategies aimed at curbing obesity trends and improving health outcomes. A toolbox of resources for each of the 5 strategies is available at https://www.pcmg-us.org/obesitytoolkit. Not discussed in this review is another important part of the continuum of obesity care, metabolic and bariatric surgery (MBS). Referral to qualified MBS centers should be considered for patients with BMI >40 kg/m^2 or those with BMI >35 kg/m^2 with obesity-related comorbidities.[11]

STRATEGY #1

Recognize that obesity is a chronic, relapsing, serious disease with diverse causes.

An important barrier to the management of individuals with obesity was the common belief that obesity was simply a consequence of an individual's personal decisions regarding his/her own lifestyle and behaviors. This belief began to change in 2012 when the American Association of Clinical Endocrinology designated obesity as a chronic disease.[12] The American Medical Association (AMA) followed suit in 2013,[13] with the World Health Organization, World Obesity Federation, The Obesity Society, and other organizations subsequently making similar designations.

Designation of obesity as a disease was based on an improved understanding of the complex system that integrates external and internal information throughout the initiation, procurement, consummatory, and metabolic phases of eating **(FIGURE)**.[14] The critical role of several gut hormones and neuropeptides, ie, the "gut-brain axis," was made clear by Sumithran et al, who demonstrated long-term persistence of hormonal adaptations to weight loss.[15] Their investigation in 50 patients with overweight/obesity showed that 1 year after diet-induced weight loss (mean 30 lbs), levels of circulating mediators of appetite that promote weight regain did not revert to levels prior to weight loss. Subjects reported increased hunger and less fullness driven by changes in key mediators including leptin, peptide YY, cholecystokinin, insulin, ghrelin, gastric inhibitory polypeptide, and pancreatic polypeptide. The investigators concluded that the body actively adapts numerous gut and neurohormonal mediators to protect fat mass in people with overweight/obesity.

In addition to metabolic adaptations, obesity is deeply rooted in genetic, psychosocial, behavioral, and environmental factors. Environmental factors include the ready availability of food—particularly calorie-dense, nutrient-deficient, ultra-processed food—fast-paced lifestyle making food preparation and physical activity a greater challenge, and the cultural norm of engaging in social activities that involve food.

STRATEGY #2

Destigmatize obesity by creating an office environment that is sensitive to the needs and experiences of patients with obesity.

Evidence over the past 2 decades indicates that weight bias is common within the healthcare environment with clinicians often viewing patients with obesity as lacking self-control, lazy, unintelligent, and annoying.[16-20] Moreover, as patient BMI increases, physicians report having less patience, less respect, and less desire to help the patient.[21] In turn, patients with obesity feel berated and disrespected and believe their health concerns are not taken seriously. Delaying or canceling healthcare appointments, including preventive care, is common.[22] Overall, evidence indicates that weight bias within healthcare contributes to a cycle that perpetuates obesity.

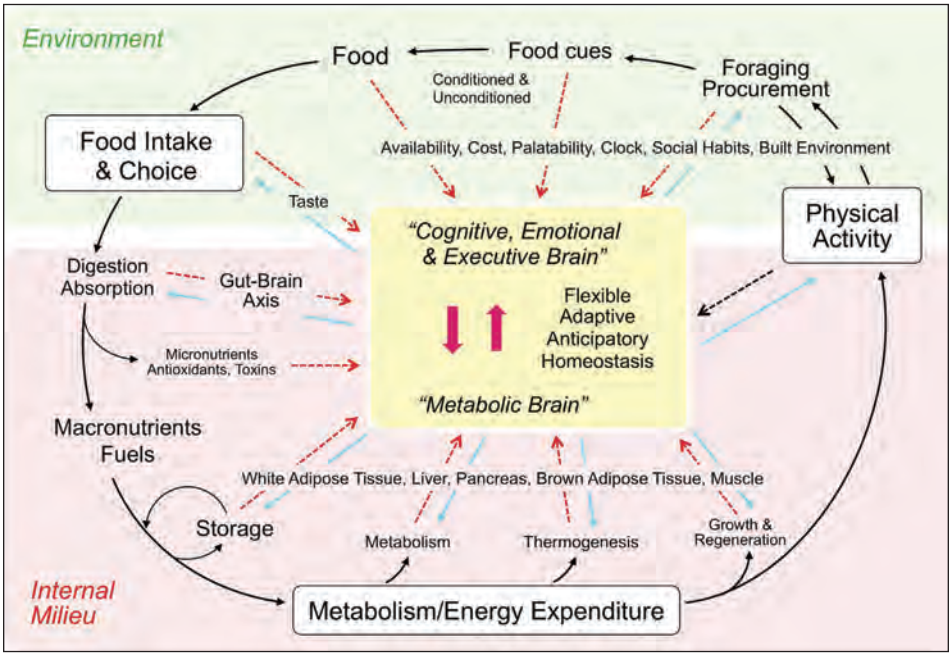
ATTITUDES AND BELIEFS

Destigmatizing obesity is of critical importance within healthcare and requires creating an office environment that is sensitive to the needs and experiences of this patient population. An important first step is to change how clinicians and staff view obesity and patients who are afflicted. This necessitates accepting that obesity is a disease just like T2D, hypertension, cancer, and coronary heart disease, and that obesity is a product of genetic and environmental factors that kindle a complex pathophysiology.

COMMUNICATION

A second step is to improve patient-clinician communication since the simple act of discussing a patient's weight is more likely to promote patient self-efficacy.[23,24] In fact, a successful conversation with patients with obesity can be 10% to 20% more effective than didactic delivery of recommendations in increasing patient motivation and encouraging action that

FIGURE. **The system that regulates eating is complex**[14]



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results in sustained changes.[25]

Good communication includes using supportive language that avoids placing blame and emphasizes health improvement. Using people-first language is helpful to avoid placing blame. Instead of referring to "the obese patient," it is more welcoming to use people-first language and refer to "the patient with obesity." The AMA adopted a resolution in 2017 that encourages the use of people-first language as an important communication strategy for patients with obesity.[26] The AMA resolution also encourages the use of preferred terms such as weight and unhealthy weight, rather than stigmatizing terms such as obese, morbidly obese, and fat.

MOTIVATIONAL INTERVIEWING

Because psychosocial, behavioral, and other environmental factors generally serve as modifiable causes of obesity, identifying targets related to the patient's lifestyle is fundamental to treatment. To do this, motivational interviewing (MI) can be very helpful. MI is a patient-centered guiding method for enhancing intrinsic motivation to change behavior by exploring and resolving ambivalence.[27] MI has much in common with shared decision-making, but relates more to behaviors in which there clearly is a healthier option.

MI is based on 4 key principles: 1) expressing empathy; 2) supporting self-efficacy; 3) rolling with resistance; and 4) developing and resolving discrepancies. The need for the clinician to roll with resistance occurs when a patient displays resistance to changing one or more behaviors despite recognizing the need to do so to achieve a goal. Instead of trying to fix or solve the problem, the clinician should sidestep the resistance, helping the patient resolve the ambivalence or discrepancy between behavior and goals or values. Helping the patient resolve the discrepancy can be facilitated by constructing a 2 by 2 matrix of the benefits/pros vs costs/cons of making the change or not making the change (this is one example of an MI technique; there are many others).

One model of MI is known by the acronym OARS: 1) open-ended questions; 2) affirmative statements; 3) reflections; and 4) summary statements.[27] By encouraging patients to talk about their goals rather than focus on their obstacles, OARS can enable patients to make behavioral changes about which they have been ambivalent or previously found difficult.

As a method of communication, MI is inherently collaborative, beginning by inviting the patient to set the agenda, often by identifying the behavior they feel most contributes to their obesity and/or the behavior they are most ready to address. For MI to be most effective, clinicians should resist finding solutions for the patient, instead helping the patient find solutions they are willing to implement. A key role for the clinician is to then educate and support the patient so that they are able to successfully change behavior. Using MI in the office setting can take time. However, with experience and skill building, it is rewarding and helps to create an improved patient-provider relationship.

Examples of MI for patients with obesity are provided in the toolbox of resources for this article.

PHYSICAL OFFICE ENVIRONMENT

Finally, the physical office environment in which care is provided is also of importance and should be welcoming to the patient with obesity. In its 2017 resolution, the AMA emphasized the importance of equipping healthcare facilities with properly sized furniture, medical equipment, and gowns for patients with obesity. The AMA also noted the importance

of weighing patients respectfully, which involves asking the patient for permission to weigh them, measuring weight in a private setting, and recording the weight silently and without judgment, reserving the discussion about weight for the privacy of the examination room.[28,29]

STRATEGY #3

Set individualized and realistic short- and long-term treatment goals in collaboration with the patient.

Most patients with obesity are not aware that modest weight loss of 5% has significant health and quality of life (QoL) benefits.[30] In fact, patients with obesity often strive to lose 15% or more of their body weight.[31] A frank discussion of realistic expectations and the importance of long-term weight management (WM) is essential. MI is helpful to establish treatment goals and can be facilitated by using the SMART strategy: 1) specific; 2) measurable; 3) attainable; 4) realistic; and 5) timely. Establishing attainable goals, particularly at the beginning, is especially important to sustain and enhance patient motivation by building on success.

In the discussion of health benefits with weight loss, it is important to consider not only the general health benefits with weight loss, but also the benefits for an individual patient. For example, all patients should be educated about the cardiovascular benefits. But talking about QoL benefits with the patient who has difficulty climbing stairs or who cannot play with their grandchildren due to shortness of breath can be very motivating.

STRATEGY #4

Identify the role of nonpharmacologic therapy.

Nonpharmacologic therapy is the foundation of comprehensive treatment for patients with obesity. There are 3 components: dietary intervention, increased physical activity, and behavioral modification, with each component affecting the others, as well as being influenced by biological, cultural, and environmental factors along with attitudes and beliefs.

Creating a negative energy balance is the key to weight loss.[30,32] A systematic review showed that among 17 dietary patterns, none was superior in terms of ability to produce and sustain weight loss.[11] Consequently, the best dietary intervention is the one that provides needed nutrients and that the patient is willing and able to follow.[33]

For weight loss, aerobic physical activity (eg, a brisk walk) >150 minutes per week is recommended.[11,34] Engaging in weekly physical activity of greater intensity and for longer duration results in greater short- and long-term weight loss.[35] Recent evidence shows that compared with a person who takes 2,000 steps per day, a person who regularly takes 10,000 steps per day has one-third the cardiovascular mortality rate and one-half the cancer mortality rate.[36] Resistance training is recommended at least 2 days per week to promote loss of fat mass and reduce health risk; it does not, however, enhance weight loss.[35] Some patients, particularly those who have led a sedentary lifestyle, may find it difficult to achieve the recommended level of physical activity initially, but should be encouraged through education that even 5 minutes of physical activity daily has real health benefits.[34]

To achieve and sustain the dietary and physical activity habits needed for WM, changing behavior is required. Successful behavioral interventions often use MI and combine education with behaviorally oriented counseling to help patients acquire the skills, motivation, and support needed to alter the targeted behavior. The Centers for Medicare & Medicaid Services has developed a program guide and reimbursement structure for behavioral therapy for obesity (https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=353).

STRATEGY #5

Individualize therapy with approved medications (liraglutide, naltrexone/bupropion, phentermine/topiramate, orlistat, semaglutide) for long-term use.

Two groups of medications are available for weight loss, those that are approved by the US Food and Drug Administration (FDA) for short-term use (8-12 weeks) and those that are FDA approved for long-term use. Medications currently approved for long-term use are liraglutide, naltrexone/bupropion extended-release (ER), orlistat, phentermine/topiramate ER, semaglutide, and setmelanotide. Setmelanotide is indicated for weight loss in a small group of children and adults with specific genetic deficiencies and will not be discussed further.[37] The glucagon-like peptide-1 receptor agonist (GLP-1 RA) semaglutide, which is approved for T2D, was approved in June 2021 by the FDA for once-weekly administration for weight loss.

APPROVED MEDICATIONS FOR LONG-TERM WEIGHT LOSS

The 5 antiobesity medications currently approved for long-term weight loss are indicated as adjunctive therapy to help patients who do not achieve health and weight targets with lifestyle management alone. Weight loss at 1 year among the 4 medications ranges from 6% to 11%.[38] Medication selec-

TABLE 1. **Key patient characteristics in selecting a medication approved for long-term weight loss**[39-42]

Patient characteristic	Recommendations[a]
Pregnancy	LIR, NB, OR, PT: C/I
Age ≥65 years	NB, PT: use with caution OR: limited experience
Moderate renal impairment	LIR: use with caution NB: do not exceed 16/180 mg daily PT: do not exceed 7.5/46 mg daily
Moderate hepatic impairment	LIR: use with caution NB: do not exceed 16/180 mg daily PT: do not exceed 7.5/46 mg daily
History of depression	NB, PT: caution
History of hypertension	NB: C/I if uncontrolled PT: monitor BP if being treated for HTN; if hypotensive symptoms develop, adjust antihypertensive drug regimen
History of seizure	NB: C/I
History of kidney stones	PT: avoid due to increased risk of calcium oxalate stones; increase fluid intake
History of pancreatitis	LIR: use with caution
Personal or family history of medullary thyroid cancer or MEN type 2	LIR: C/I
History of cognitive impairment	PT: caution about operating automobiles, hazardous machinery

BP, blood pressure; C/I, contraindicated; HTN, hypertension; LIR, liraglutide; MEN, multiple endocrine neoplasia; NB, naltrexone/bupropion extended-release; ORL, orlistat; PT, phentermine/topiramate extended-release.

[a]Information for semaglutide is not included in this table due to its approval as the article was about to go to press.

tion is based on individual patient factors, eg, comorbidities and differences among the medications, and patient preference. Individual differences include mechanism of action, route of administration, contraindications, warnings, adverse events, drug interactions, and cost **(TABLE 1)**.[39-42]

Weight loss of 5% to 10% over 6 months is the recommended weight loss target.[11] Treatment response should be evaluated after approximately 3 to 4 months. If a patient has not lost at least 4% to 5% of baseline body weight, the medication should be discontinued and alternative treatment initiated.[11] The exception is for phentermine/topira-

TABLE 2. **Topline results from the semaglutide STEP 1 through 4 clinical trial program**

	STEP			
	1[43] (N=1961) Overweight or obesity, without diabetes	**2[44] (N=1210) Overweight or obesity, with diabetes**	**3[45] (N=611) 8-week LCD and 30-week IBT**	**4[46] (N=803[a]) Overweight or obesity, without diabetes**
Treatment duration	68 wks	68 wks	68 wks	20-wk run-in[b] followed by 48-wk randomized period
Mean change in BW (placebo-corrected)	-12.7 kg	-6.2 kg	-10.6 kg	Run-in[b]: -11.1 kg Randomized: SEM: -7.1 kg PBO: 6.1 kg
Mean % change in BW (placebo-corrected)	-12.4%	-6.2%	-10.3%	Run-in[b]: -10.6% Randomized: SEM: -7.9% PBO: 6.9%
% Achieving WL ≥15% (placebo-corrected)[c]	45.6%	22.6%	42.6%	Wk 0 to 68: 54.5%

BW, body weight; IBT, intensive behavioral therapy; LCD, low-calorie diet; PBO, placebo; SEM, semaglutide; WL, weight loss.

[a]Patients who completed the 20-week run-in period and were randomized.

[b]All patients received semaglutide during the 20-week run-in period.

[c]Based on the number of participants for whom data were available at the week 68 visit (n=1212 semaglutide; n=577 placebo).

mate ER, where the dose can be increased to the maximum daily dose of 15 mg/92 mg, if tolerated.[11] As when initiating treatment, MI is helpful to inform treatment modification, including lifestyle management.

Semaglutide

The safety and efficacy of semaglutide 2.4 mg injected subcutaneously once weekly for the treatment of patients with obesity has been investigated in the STEP 1–4 clinical trial program: 1) WM[43]; 2) WM in T2D[44]; 3) WM with intensive behavioral therapy[45]; and 4) sustained WM.[46] Results of the STEP 1 through 4 trials have been published. The primary endpoint in all STEP trials is change in body weight from baseline to end of treatment at 68 weeks.

In the STEP 1 through STEP 3 trials, the mean change in placebo-corrected body weight from baseline to week 68 ranged from -6.2% to -12.4%. Weight loss ≥5% was achieved by 68.8% to 86.6% of semaglutide patients and 28.5% to 47.6% of placebo patients. Weight loss ≥15% was achieved by 25.8% to 55.8% of semaglutide patients and 3.2% to 13.2% of placebo patients **(TABLE 2)**. The STEP 4 trial showed that semaglutide resulted in substantial weight loss during the 20-week run-in dose titration phase, with further weight loss over an additional 48 weeks compared with weight gain in patients switched to placebo following the run-in phase.

In STEP 1–4, gastrointestinal events, such as mostly transient mild to moderate nausea, were observed in 49% to 83% of semaglutide patients and 26% to 63% of placebo patients. Rates of acute pancreatitis and malignant neoplasms were low and similar in the semaglutide and placebo groups. ●

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Primary Prevention of CVD with Aspirin: Benefits vs Risks

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doi: 10.12788/jfp.0222

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DISCLOSURES

Dr. Brunton discloses that he serves on the advisory board and speakers bureau for AstraZeneca, Bayer, and Novo Nordisk; on the speakers bureau for Lilly; and on the advisory board for Abbott Diabetes, Acadia, Sanofi, and Xeris.

Dr. Weisman discloses that he is Head of Clinical and Regulatory Support at Innovative Science Solutions, a consultancy to the pharmaceutical industry, and has received consultancy fees from Bayer related to the topic of this manuscript.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and the Primary Care Metabolic Group and supported by funding from Bayer.

ABSTRACT

Low-dose aspirin (acetylsalicylic acid [ASA]; 75 to 100 mg/d) is widely used in the prevention of cardiovascular (CV) events based on the results of large-scale studies supporting a benefit. However, questions remain regarding the benefit-risk relationship in certain settings since long-term use of ASA is not devoid of risk. Incontrovertible evidence supports the benefits of ASA treatment, which exceed the risks, in patients who have had a previous CV event (myocardial infarction, stroke, unstable angina, or transient ischemic attack). Nonetheless, the question remains for those patients who have not had a previous event (primary prevention), where the risk of CV events is lower and, consequently, the absolute benefit is also lower than in patients who have a history of a CV event or its equivalent (secondary prevention). Recent evidence from large-scale clinical trials shows that administration of low-dose ASA is associated with a reduced risk of CV events with a corresponding small absolute increase in the risk of major bleeding (eg, gastrointestinal bleeding and hemorrhagic stroke). Although the benefit and the risk of low-dose ASA in primary prevention are numerically similar, the clinical consequences of an increased risk of bleeding and a decreased risk of a CV event may not be equivalent. If these data are applied to patients with higher levels of CV outcome risk, more patients may potentially benefit from aspirin use in primary prevention.

BACKGROUND

Aspirin (acetylsalicylic acid [ASA]) is a well-studied and widely used drug, with a well-established safety profile. ASA has been marketed for over 120 years as an analgesic and for more than 25 years for cardiovascular (CV) prophylaxis and has a well-established risk profile that is independent of underlying CV risk. ASA is recommended and approved for use in multiple CV disease (CVD) prevention settings, including the secondary prevention of myocardial infarction (MI), fatal and nonfatal stroke following a stroke or transient ischemic attack (TIA), and for reducing the risk of death and reinfarction during an acute evolving MI.[1] In these settings the benefits of treatment have been deemed to exceed the risks, and such use is widely supported by treatment guidelines. In the primary prevention setting, ASA appears to be equally effective in reducing the risk of CV events based on the same underlying mechanism of action of preventing platelet aggregation. Though the relative risk reductions are similar across the CV risk strata, the benefit-risk relationship is less well established based on the lower rate of occurrence of CV events in the primary prevention setting, while the risks of complications (largely bleeding risks) remain largely the same.[2-4] As new data have become available, a reassessment of the overall benefit vs risk in primary prevention is now possible.

GASTROINTESTINAL BLEEDING WITH LOW-DOSE ASA

Due to the same antiplatelet mechanism of action supporting ASA's use in the prevention of CVD, one of the well-documented risks associated with long-term ASA use is

the increased risk of bleeding (minor and major), with the most common risk that of gastrointestinal (GI) bleeding.[5,6] A meta-analysis of clinical studies evaluating low-dose ASA in primary prevention of CV events reported a relative risk (RR) of major bleeding of 1.43 (95% confidence interval [CI]: 1.3-1.6), with major GI bleeding having an RR of 1.56 (95% CI: 1.4-1.8).[7] Of importance, the available data suggest a dose-dependent relationship for ASA, such that low-dose ASA regimens of 75 to 100 mg/d have been shown to be associated with a lower risk and incidence of GI bleeding compared to higher-dose ones.[8] While GI bleeding is dose-dependent, the antiplatelet effects that underlie ASA's utility in vascular disease in this dose range are not. Studies have shown similar efficacy with low-dose ASA compared with higher doses. Thus, low-dose ASA has emerged as the optimal regimen for the prevention of CVD.[8] Routine use of low doses of ASA along with potential preventive strategies including the use of proton pump inhibitors (PPIs) may further reduce the risk of GI bleeding with ASA. While long-term controlled studies haven't been conducted evaluating the benefit of combination PPI and ASA use, data suggest that eliminating *Helicobacter pylori* infection before ASA use could reduce the incidence of upper GI complications by approximately 25%.[9] Furthermore, a meta-analysis conducted by Mo et al (2015) evaluating the preventive effects of PPIs in ASA-associated upper GI injuries noted that PPIs decreased the risk of ASA-associated upper GI ulcers (odds ratio [OR] 0.16; 95% CI: 0.12-0.23) and bleeding (OR 0.27; 95% CI: 0.16-0.43) compared with control.[10,11]

ASA USE IN PRIMARY VS SECONDARY PREVENTION OF CVD

Extensive evidence from multiple clinical trials has demonstrated that daily, low-dose ASA reduces the risk of recurrent vascular events in patients who previously experienced an event or who are at high risk of CV events (secondary prevention).[12,13] While numerous clinical trials have demonstrated similar relative risk reductions in patients at low to moderate levels of risk but who have not had a previous event (primary prevention), these patients are at a lower risk of an event and thus would be expected to receive a lower absolute benefit while having a comparable risk of bleeding.[7]

The risk of CV events is impacted by a number of factors. ASA therapy (75-162 mg/d) may be considered as a primary prevention strategy in those with diabetes who are at increased CV risk, after a comprehensive discussion with the patient on the benefits vs the comparable increased risk of bleeding. Based on the large number of CV events in patients who have not had a previous event, preventive strategies that are safe and effective are desperately needed. As such, the obvious question is how to determine which patients would be candidates for ASA therapy such that the benefit-risk relationship can be optimized.

In 2013, the American College of Cardiology (ACC)/American Heart Association (AHA) developed the Arteriosclerotic Cardiovascular Disease (ASCVD) Risk Estimator to help calculate CVD risk and guide physicians in treating patients with increased risk. The ASCVD calculator is a peer-reviewed calculator that was designed to assess the 10-year primary risk of an initial CV event based on a Pooled Cohort Equation (ie, the Framingham Heart Study [FHS], the Atherosclerosis Risk in Communities [ARIC] study, the Coronary Artery Risk Development in Young Adults [CARDIA], and the Cardiovascular Health Study [CHS]), in patients without preexisting CVD. In practice, clinicians use the ASCVD Risk Estimator to help them assess risk and better treat patients who may benefit from ASA but have not had a prior CV event, with adults categorized into low (<5%), borderline (5 to <7.5%), intermediate (≥7.5 to <20%), or high (≥20%) 10-year risk categories.[14]

Additionally, the US Preventive Services Task Force (USPSTF) is in the process of updating its recommendations on ASA use for primary prevention of CVD.[15] When completed, its review of the evidence will provide additional guidance as to benefits and risks from low-dose ASA therapy in primary prevention.

RECENT TRIALS IN PRIMARY PREVENTION

A number of trials of low-dose ASA in primary prevention of CVD involving large numbers of subjects (N=47,140) have been recently completed and, when looked at with the larger overall database, provide additional safety and efficacy insight.

Meta-analysis of ASA in primary prevention of CVD

A meta-analysis conducted by Zheng et al (2019) reviewed the most up-to-date ASA studies conducted in primary prevention, including the 3 most recently completed studies (ie, Aspirin to Reduce Risk of Initial Vascular Events [ARRIVE],[16] A Study of Cardiovascular Events in Diabetes [ASCEND], and Aspirin in Reducing Events in the Elderly [ASPREE]).[7] The meta-analysis included randomized controlled trials conducted with low-dose ASA through 2018, enrolling at least 1000 participants with no known CVD and with a follow-up of at least 12 months. Included studies compared ASA use with no ASA (placebo or no treatment). The primary outcome assessed was a composite of CV mortality, nonfatal MI, and nonfatal stroke. The primary bleeding outcome was any major bleeding.[7]

The meta-analysis evaluated a total of 13 trials that randomized 164,225 participants. Participants were on average

TABLE 1. **Overview of studies**

	ARRIVE[17]	ASCEND[18]	ASPREE[19-21]	Meta-analysis[7]
N	12,546	15,480	19,114	164,225
Age, years	Men >55, women >60	>40	>70, or >65 if Hispanic or Black	>40
ASA dose, mg	100	100	100	75-500
Years of follow-up (median)	6.0	7.5	4.7	≥1
Country (year)	7 countries (2018)	United Kingdom (2018)	Australia and United States (2018)	-
Endpoints				
Efficacy analysis	Composite of time to first occurrence of CV death, MI, unstable angina, stroke, or TIA	First serious vascular event (ie, MI, stroke or TIA, or death from any vascular cause, excluding any confirmed intracranial hemorrhage)	Composite of all-cause mortality, incident dementia, and persistent physical disability	Composite of CV mortality, nonfatal MI, and nonfatal stroke
Safety analysis	GI bleeding by severity	Major bleeding	Major bleeding	Major bleeding
Special population	Older participants (average age 74)	Participants with diabetes	Participants with moderate to high estimated CV risk	Participants without known preexisting CVD

62 years of age (range, 53-74), 77,501 (47%) were men, and the median baseline risk of the primary CV outcome was 10.2% (range, 2.6%-30.9%) **(TABLE 1)**. Results of the meta-analysis show that ASA use was associated with significant reductions in the composite CV outcome compared with no ASA, with a total of 2911 (3.4%) events in the ASA arm and 3341 (4.2%) events in the no-ASA arm (HR 0.89; 95% credible interval variable [CrI]: 0.84-0.94), with an absolute risk reduction (ARR) of 0.41% (95% CrI: 0.23%-0.59%), which translated into number needed to treat (NNT) of 241 **(TABLE 2)**.

Major bleeding (defined by the individual studies) was reported in a total of 2029 (1.4%) patient events, with 1195 (1.6%) participants experiencing events in the ASA arm compared with 834 (1.1%) participants in the no-ASA arm (HR 1.43; 95% CrI: 1.30-1.56), with an absolute risk increase (ARI) of 0.47% (95% CrI: 0.34%-0.62%), translating into a number needed to harm (NNH) of 210.

The current data demonstrate that the absolute risk reduction for CV events and absolute risk increase for major bleeding associated with ASA use were of similar magnitude; the reduction in the risk of an MI or stroke is similar to the risk of a major bleeding event.

Overview of ARRIVE, ASCEND, and ASPREE safety findings

The 3 recently completed studies evaluating ASA in primary prevention, ARRIVE, ASCEND, and ASPREE, were all conducted in different settings and confirmed a consistent safety profile, as noted in earlier primary prevention studies, with no additional safety signals identified. These studies provided additional insight regarding the safety of low-dose ASA to better inform benefit-risk determination and are summarized below.

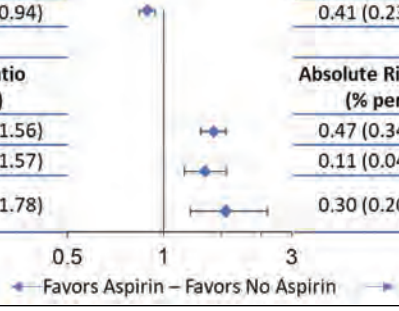
ARRIVE

ARRIVE[16] was a randomized, double-blind, placebo-controlled, multicenter study. The study enrolled 12,546 patients, who were followed for 6 years **(TABLE 1)**. The study included men older than 55 and women older than 60, who had a 10-year CV risk deemed to be moderate, ranging from 10% to 20%. The study excluded those patients at high risk of GI bleeding or other bleeding, or diabetes. Patients were assigned to receive 100 mg/d of ASA or placebo.[17]

GI bleeding events (mostly mild) occurred in 61 (0.97%) patients in the ASA group vs 29 (0.46%) in the placebo group (HR 2.11; 95% CI: 1.36-3.28; *P*=0.0007), with an ARI of 0.51%

TABLE 2. **Primary prevention in meta-analysis—CV events and major bleeding[7,a]**

Event Type	Aspirin Events (% rate)	Placebo Events (% rate)	Hazard Ratio (95% CI)	Absolute Risk Reduction (% per year)	NNT
Composite CV outcome	2911 (3.7%)	3342 (4.2%)	0.89 (0.84 – 0.94)	0.41 (0.23 to 0.59)	241
			Hazard Ratio (95% CI)	**Absolute Risk Increase (% per year)**	**NNH**
Major Bleeding	1195 (1.6 %)	834 (1.1 %)	1.43 (1.30 – 1.56)	0.47 (0.34 to 0.62)	210
Intracranial bleeding	349 (0.4 %)	257 (0.3%)	1.34 (1.14 – 1.57)	0.11 (0.04 to 0.18)	927
Major gastrointestinal bleeding	593 (0.8 %)	380 (0.5%)	1.56 (1.38 – 1.78)	0.30 (0.20 to 1.78)	334



The composite CV outcome consisted of CV mortality, nonfatal MI, and nonfatal stroke. Hazard ratios and 95% credible interval variables (CrIs) were calculated using Bayesian meta-analysis of trial-level event counts. The absolute risk reductions and increases were calculated by multiplying the control event risk by the relative risk and 95% CIs derived by frequentist meta-analysis. NNT; NNH.

[a]Adapted from Zheng et al., 2019.

(TABLE 3). Of note, although significant, GI bleeding events were infrequent and mostly mild. Furthermore, there were no increases in fatal bleeding.

ASCEND

ASCEND[18] was a randomized, double-blind, placebo-controlled study that looked at 15,480 patients with diabetes who were older than 40 years of age **(TABLE 1)**. The study was conducted in subjects who had diabetes but no evident CVD. Patients were randomly assigned to receive 100 mg/d of ASA or placebo and followed for 7.5 years.

The primary safety outcome was the first occurrence of any major bleeding event, which was defined as a composite of any confirmed intracranial hemorrhage, sight-threatening bleeding event in the eye, GI bleeding, or any other serious bleeding (ie, a bleeding event that resulted in hospitalization or transfusion or that was fatal). Major bleeding events were experienced by 314 (4.1%) patients in the ASA group vs 245 (3.2%) patients in the placebo group (rate ratio 1.29; 95% CI: 1.09-1.52; *P*=0.003), with an ARI of 1.29% **(TABLE 2)**. Most of the differences noted were GI bleeding events. ASA increased the rate of major bleeding by 29% in relative terms and 0.9% in absolute terms.

ASPREE

ASPREE[19-21] was a randomized, double-blind, placebo-controlled, multicenter study **(TABLE 1)**. The study enrolled 19,114 patients older than 70 years of age, or older than 65 if black or Hispanic (5%), from Australia and the United States. Patients did not have CVD, dementia, or disability, and were assigned to receive 100 mg/d of ASA or placebo. Patients were followed for a median of 4.7 years.

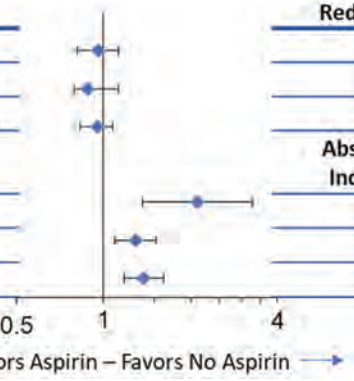
The primary endpoint was a composite of all-cause mortality, incident dementia, and persistent physical disability, with secondary endpoints including fatal and nonfatal CV events (ie, coronary heart disease death, nonfatal MI, fatal and nonfatal stroke, and any hospitalization for heart failure). Major hemorrhage was a secondary endpoint and defined as any hemorrhagic event (hemorrhagic stroke, symptomatic intracranial bleeding, or major GI bleeding or other extracranial bleeding).

In ASPREE there was a low rate of major hemorrhage, yet the rate was increased in the ASA group: 361 (3.8%) patients in the ASA group compared to 265 (3.2%) patients in the placebo group (HR 1.38; 95% CI: 1.18-1.62; *P*<0.001), with an ARI of 1.07% **(TABLE 2)**.

The ASPREE study focused on an older patient population (average age 74 years) than normally evaluated in CVD trials, with the hope of better understanding how this group of patients would benefit from low-dose ASA in a primary prevention setting. Of note, half of the excess bleeding events were GI bleeding cases, where such events could potentially have been prevented with concurrent PPIs; however, only a quarter of participants in the study actually were using PPIs.[22] Additionally, subgroup analysis demonstrated that the bleeding events were mostly driven by patients over 70 years of age, and that the 5-year absolute risk of serious bleeding was modest in younger individuals. Of note, the absolute risk of serious GI bleeding more than doubles in an 80-year-old person (5-year risk of around 0.60%) compared to a 70-year-old person (5-year risk of around 0.25%). Additionally, Mahady et al's (2018) review of the ASPREE trial noted that bleeding infrequently led to death or other long-term morbidity, with only 2 fatal bleeds in the placebo arm.[23]

TABLE 3. **Primary prevention in ARRIVE,[17] ASCEND,[18] and ASPREE[19-21] —CV events and major bleeding[a]**

Event Type	Aspirin	Placebo		
Composite CV outcome	Events (% rate)	Events (% rate)	Hazard Ratio (95% CI)	Absolute Risk Reduction (%)
ARRIVE	269 (4.3%)	281 (4.5%)	0.96 (0.81 – 1.13)	0.20
ASCEND	658 (8.5%)	743 (9.6%)	0.88 (0.79 – 0.97)	1.10
ASPREE	448 (4.7%)	474 (4.9%)	0.95 (0.83 – 1.08)	0.20
Major Bleeding			Hazard Ratio (95% CI)	Absolute Risk Increase (%)
ARRIVE	61 (0.97%)	29 (0.46%)	2.11 (1.36 – 3.28)	0.51
ASCEND	314 (4.1%)	245 (3.2%)	1.29 (1.09 – 1.52)	1.29
ASPREE	361 (3.8%)	265 (2.8%)	1.38 (1.18 – 1.62)	1.00



The composite CV outcome consisted of CV mortality, nonfatal MI, and nonfatal stroke.

[a]Adapted from: Gaziano et al. 2018[16]; The ASCEND Study Group, 2018[18]; McNeil et al., 2018.[19-21]

CONCLUSIONS

Mounting evidence, including data from 47,140 newly studied patients, shows that subjects who use low-dose ASA for the primary prevention of vascular disease reduce their relative risk of composite CV outcomes by 11%, with an absolute risk reduction of 0.41%. However, these subjects are 1.43 times more likely to experience GI bleeding than those receiving placebo. The effect is small in terms of absolute risk (0.47%; 95% CI: 0.34%-0.62%).[7]

In primary prevention it has been very difficult to clearly state the benefit and risk of extended use of low-dose ASA, where a decreased risk of CV events may be offset by an increased risk of major bleeding. The best way to enhance the overall benefit is to evaluate underlying CV risk more effectively, such that use of ASA in those at highest risk will yield the highest benefit. The routine use of risk calculators could help in this decision-making. Likewise, possible strategies for mitigating the risk of GI bleeding may help to reduce this bleeding risk. Initial research suggests that GI bleeding risk can potentially be mitigated by testing for *H. pylori* and treating it before starting ASA[9] and/or by treatment with PPIs,[10,24] with additional studies necessary to confirm benefit.

While questions remain as to how best to maximize the benefits and minimize the risks of low-dose ASA in primary prevention, the available evidence demonstrates that many vascular events could be prevented with broader appropriate use of ASA. This includes more comprehensive use in secondary prevention as well as in patients who are at higher-than-average risk of such events who have not had a previous event. Recent studies have provided additional data regarding the safety of ASA and demonstrated that, while significant, the absolute risk of a bleeding event is small, potentially leading to a favorable benefit-vs-risk discussion and determination for many more patients. ●

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Screening for Autoantibodies in Type 1 Diabetes: A Call to Action

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doi: 10.12788/jfp.0223

KEY TAKEAWAYS

- Type 1 diabetes (T1D) is an autoimmune disease that progresses through 3 distinct stages.
- T1D can be diagnosed at any age, with a peak incidence at 10-14 years of age.
- The incidence of T1D in the United States is rising.
- Screening for T1D autoantibodies has positive clinical consequences, including reduction of diabetic ketoacidosis events, improved glycemic control, and positive impact on short- and long-term complications.
- Primary care clinicians can play a critical role in promoting islet autoantibody screening.

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DISCLOSURES

Dr. Peters discloses that she serves on the advisory board for Abbott Diabetes Care, Bio-Rad, Eli Lilly and Company, MannKind, Medscape, Merck, Novo Nordisk, and Zealand; receives research support from Dexcom; received donated devices from Abbott; and has stock options in Omada Health and Teladoc. Gregory Scott, PharmD, RPh, editorial support, discloses he has no real or apparent conflicts of interests to report. Dr. Stephen Brunton, issue editor, serves on the advisory board and speakers bureau for AstraZeneca, Bayer, and Novo Nordisk. He serves on the speakers bureau for Lilly and on the advisory board for Abbott Diabetes, Acadia, Sanofi, and Xeris.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and the Primary Care Metabolic Group and supported by funding from Provention Bio.

The lack of therapeutic interventions to prevent progression of autoantibody-positive presymptomatic patients to clinical symptomatic type 1 diabetes (T1D) has meant that screening asymptomatic individuals for T1D is not commonly done. For instance, in 2015, the US Preventive Services Task Force recommended against performing routine serum islet autoantibody screening for T1D.[1] Nevertheless, results from the more recent Fr1da study[2,3] (see below) suggest that substantial health benefits may accrue from general population screening for islet autoantibodies. However, general population screening is costly, difficult to implement, and requires a significant commitment of time and resources. On the other hand, targeted screening of the at-risk population (ie, those with first- or second-degree relatives with T1D) zeroes in on a population more likely to have detectable islet autoantibodies. As such, the primary focus of this article is at-risk population screening. With the prospect of therapeutic agents that can potentially modify the autoimmune progression leading to clinical symptomatic T1D, the potential benefits of screening are mounting. Even though such therapeutic agents are not yet available, identifying the presence of islet autoantibodies has potential short- and long-term health benefits. This article will discuss the epidemiology, autoimmune basis, and natural history of T1D; the benefits of early detection; immunologic markers; and most importantly, the vital role that family and primary care clinicians can play in educating families about islet autoantibody screening.

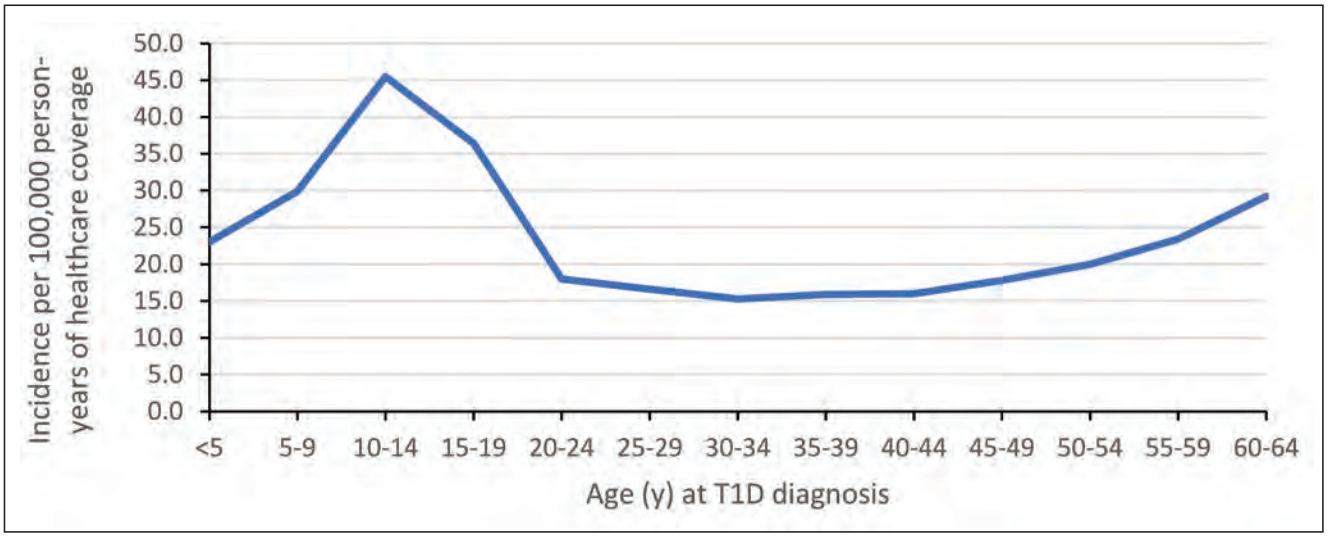
EPIDEMIOLOGY OF T1D

Nearly 190,000 children and adolescents have been diagnosed with T1D,[4] making it one of the most common chronic diseases in childhood.[5] Analyses of the SEARCH for Diabetes in Youth registry and Clinformatics Data Mart database showed that the incidence of T1D in youth (age 0 to 19 years) increased at an annual rate of 1.9% from 2001-2002 to 2015, with the incidence peaking in 10- to 14-year-olds **(FIGURE)**.[6,7] While T1D is generally thought of as a disease affecting only children, analysis of the Clinformatics Data Mart database showed that 59% of incident T1D cases were actually diagnosed in adults aged 20 to 64 years.[7]

AUTOIMMUNE BASIS OF T1D

More than 40 years ago, multiple lines of clinical evidence established an autoimmune pathogenesis for T1D leading to partial, or in many cases absolute, insulin deficiency.[8-11]

FIGURE. **Incidence of type 1 diabetes mellitus by age, 2001-2015**[7]



Although detection of serum islet autoantibodies against pancreatic B-cells is diagnostic for T1D, T1D is typically diagnosed based on clinical symptomatology associated with overt hyperglycemia, metabolic imbalance, and, in many cases, diabetic ketoacidosis (DKA).[12] Recent evidence from the SEARCH for Diabetes in Youth registry shows that the prevalence of DKA at or near T1D diagnosis increased from 35.3% in 2010 to 40.6% in 2016, representing a 2% relative annual increase.[69] In asymptomatic individuals, the development of islet autoantibodies against multiple β-cell antigens indicates a high probability of developing clinically symptomatic T1D (description of T1D disease stages to follow).

Genetics plays a key role in the pathogenesis of T1D, as demonstrated by the fact that the risk for autoimmunity and subsequent development of T1D is up to 10-fold higher in children with a first-degree relative with T1D as compared to children in the general population.[13] Some statistics worth noting are as follows. First, the prevalence of T1D at age 20 years in individuals of European descent is 2% for a child of a mother with T1D and 6% if the father has T1D.[14-16] The lifetime risk may be as high as 50% in individuals with multiple first-degree relatives with T1D.[16-18] The lifetime risk of T1D for a person with an identical twin with T1D may be as high as 60%.[19] For a non-twin sibling, the risk is 4% to 7% by age 20 years and 10% by age 60 years.[19]

Certain human leukocyte antigen (HLA) subtypes, particularly DR and DQ, can increase susceptibility or confer protection against development of T1D.[16,20] Smaller contributions are made by more than 50 non-HLA genes or loci.[12,21-28] The majority of individuals with T1D carry DR4, DQB*0302 and/or DR3, DQB*0201 and are considered genetically at risk for clinical T1D. Conversely, HLA alleles such as DQB1*0602 are associated with dominant protection from T1D.[29]

Nonetheless, only 10% to 20% of cases of T1D occur in individuals with a family history of T1D,[30,31] indicating that other factors play a key role in the pathogenesis of T1D. A wide variety of environmental factors have been proposed as being associated with the development of islet autoantibodies and subsequent T1D, but evidence is often conflicting.[32,33] Some data suggest that high birthweight for gestational age,[34] prematurity,[34] and higher rate of weight gain in early childhood may contribute.[35] Additional evidence suggests that the development of some autoantibodies may be preceded by changes in nutrition intake[36,37] or depend on the individual's metabolic profile.[38]

Notably, early childhood infections seem to play an important role in the development of islet autoimmunity.[39] These include recent respiratory infections such as common cold, influenza-like illness, sinusitis, and laryngitis/tracheitis,[40] as well as enteroviruses, particularly coxsackievirus types A and B.[41] Detection of enteroviruses in stools and circulating antivirus neutralizing antibodies precedes the appearance of islet autoantibodies by several months in children at increased genetic risk for T1D.[42-44] Furthermore, islet autoantibody-positive children with enterovirus RNA in their blood experience faster progression to T1D.[45]

NATURAL HISTORY OF T1D

Following the onset of islet autoimmunity, T1D progresses through 3 stages **(TABLE)**.[12,46] Stage 1 occurs in individuals who have developed ≥2 types of islet autoantibodies asso-

TABLE. **Metabolic stages of type 1 diabetes mellitus**[12,46]

	Stage 1	Stage 2	Stage 3
β-cell autoimmunity?	Yes	Yes	Yes
Symptoms?	No	No	Yes
Blood glucose	No IGT or IFG	• IGT and/or IFG • FPG 100-125 mg/dL • 2-h PPG 140-199 mg/dL • A1c 5.7%-6.4% or ≥10% increase in A1c	• Random glucose ≥200 mg/dL with symptoms • FPG ≥126 mg/dL • 2-h PPG ≥200 mg/dL • A1c ≥6.5%
5-y risk of symptomatic disease	44%	75%	–

IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PPG, postprandial glucose.

ciated with T1D but remain normoglycemic. As functional pancreatic β-cell mass declines, progression to stage 2 occurs. Although individuals remain asymptomatic, evidence of dysglycemia emerges. Dysglycemia is defined as fasting plasma glucose (FPG) of 110 to <126 mg/dL, 2-hour oral glucose tolerance test (OGTT) of 140-199 mg/dL, and glycated hemoglobin (A1c) of 5.7%-6.4%. Further β-cell damage results in symptomatic stage 3 T1D, which is characterized by the typical symptoms and signs of diabetes, eg, polyuria, polydipsia, weight loss, and fatigue, corresponding to an FPG >126 mg/dL, 2-hour OGTT >200 mg/dL, and A1c >6.5%. If not treated with timely administration of exogenous insulin, it can quickly progress to DKA. DKA on presentation occurs in approximately one-third of individuals[6] and is often characterized by nausea, vomiting, abdominal pain, weakness, and confusion.

Approximately 70% of individuals with ≥2 islet autoantibodies progress from stage 1 to symptomatic stage 3 within 10 years[47] and 74% from stage 2 to symptomatic stage 3 within 4 to 5 years, although progression can be as short as weeks and as long as decades. It is important to note that individuals with 1 islet autoantibody may never progress to multiple autoantibodies (stage 1 or 2) and, ultimately, symptomatic stage 3 T1D. Although there are no guidelines for monitoring individuals with only 1 islet autoantibody, annual evaluation for dysglycemia or additional islet autoantibody testing every 1 to 2 years should be considered given their increased risk. In rare cases, loss of islet autoantibody positivity is observed, also referred to as inverse seroconversion.[3]

BENEFITS OF EARLY DETECTION OF AT-RISK INDIVIDUALS

Several clinical trials have investigated the impact of early detection of T1D in at-risk individuals, as well as the general population. One of the first was the Diabetes Autoimmunity Study in the Young (DAISY), a longitudinal study that followed children with either a family history of T1D (at-risk) or who expressed high-risk HLA genotypes.[48] Children identified as multiple islet autoantibody–positive and followed to symptomatic stage 3 T1D were hospitalized significantly less often than the T1D cases from the general population (3.3% vs 44%). Additionally, they had a lower mean A1c at T1D diagnosis (7.2% vs 10.9%; $P<0.0001$) and 1 month after diagnosis (6.9% vs 8.6%; $P<0.0001$), but not 6 months or 12 months after diagnosis due to the initiation of insulin therapy in the general population cohort. A major finding of the DAISY study was a decrease in hospitalizations due to DKA, which has significant long-term sequelae.

The BABYDIAB and the Munich Family Study followed children with a first-degree family member (at-risk) with a history of T1D. Data from these German databases were analyzed by the Diabetes Prospective Documentation Initiative.[49] Among the 101 children screened and found to be positive for islet autoantibodies, the A1c at symptomatic stage 3 T1D onset was significantly lower than in non-screened children presenting with symptomatic stage 3 T1D (8.6% vs 11%). In addition, the prevalence of DKA was significantly lower in screened children (3.3% vs 29.1%) and was associated with a significantly shorter hospitalization period at onset (11.4 vs 14.9 days).

Recently, the results of the German Fr1da study demonstrated important benefits with population-based screening for islet autoantibodies.[3] Screening was offered to children ages 1.75 to 5.99 years by pediatricians during well-baby visits. Of 90,632 children screened (median age 3.1 years), 196 (0.22%) were found to be in stage 1, 17 (0.02%) in stage 2, and 26 (0.03%) in symptomatic stage 3, for an overall prevalence of 0.31%; 41 children with a family history of multiple islet autoantibodies declined metabolic staging. Over 3 years of follow-up, the risk of progressing from stage 1 to stage 2 or 3 was 28.7%. Key factors significantly associated with disease progression were obesity, presence of 4 islet autoantibodies,

and A1c ≥5.7%. The study showed that preschool screening for islet autoantibodies in the general population effectively identified young children with previously undiagnosed, symptomatic stage 3 T1D.

The Fr1da study also showed that psychological stress was significantly higher in mothers of children identified as having stage 1 or 2 T1D compared with mothers of children without islet autoantibodies. The stress level decreased to baseline within 12 months of identification. Of the 62 children with stage 1 or 2 T1D who progressed to symptomatic stage 3, only 2 presented with mild or moderate DKA, both without clinical symptoms. The decline in psychological stress and the low incidence of DKA were predicted, since >80% of children with stage 1 or 2 T1D and their families participated in the diabetes education program.

These investigations demonstrate that early identification of individuals with stage 1 and 2 T1D allows for early intervention that results in reduced morbidity and improved glycemic control. An additional possible benefit of early detection of stage 1 or 2 T1D is that it might enable earlier intervention to mitigate common chronic complications of T1D that begin to emerge within months or years of diagnosis. For example, the SEARCH for Diabetes in Youth Study showed that several complications were common in youth and young adults with T1D at a mean disease duration of 8 years. These were cardiovascular autonomic neuropathy (14.4%), arterial stiffness (11.6%), hypertension (10.1%), peripheral neuropathy (8.5%), diabetic kidney disease (5.8%), and retinopathy (5.6%).[6]

The occurrence of DKA at symptomatic stage 3 T1D diagnosis results in additional complications. One investigation showed that children ages 6 to 18 years with DKA at symptomatic stage 3 T1D diagnosis experienced a decrease in total white matter volume and an increase in gray matter over 6 months, changes that were associated with adverse neurocognitive outcomes.[50] DKA at diagnosis of symptomatic stage 3 T1D also adversely affects long-term glycemic control.[51] A prospective study of 3364 children diagnosed with symptomatic stage 3 T1D before 18 years of age and followed for 15 years found that the A1c was 1.4% higher in those with severe DKA at diagnosis compared with children without DKA at diagnosis.[51]

Finally, the cost-effectiveness of islet autoantibody screening of the general population for T1D risk has been investigated in 2 studies.[52,53] One study based cost-effectiveness on reducing the incidence of DKA at symptomatic stage 3 diagnosis in children age <5 years,[52] while the other based cost-effectiveness on reduction in DKA events and long-term glycemic control.[53] Although neither study found screening the general population for islet autoantibodies to be cost-effective, no consideration was given to other possible benefits of early detection such as reducing long-term sequalae of having DKA at time of symptomatic stage 3 T1D diagnosis (as highlighted earlier). In contrast, data from the Autoimmunity Screening for Kids (ASK) study in Colorado determined that general population screening for islet autoantibodies is feasible and well accepted by parents and providers.

METABOLIC MARKERS

A variety of genetic, immunologic, and metabolic markers may be used to predict T1D. Among metabolic markers, the first-phase insulin response to glucose during an intravenous glucose tolerance test[54] and 2-hour OGTT[55] are useful to identify autoantibody-positive individuals who are at highest risk for progressing to T1D. Recent investigation confirmed that worsening longitudinal changes in the glucose response curve during OGTT occur in individuals who progress to T1D.[56] Individuals with undiagnosed clinical T1D (stage 3) may be identified using common metabolic tests, eg, random plasma glucose >200 mg/dL and A1c ≥6.5%.

PRACTICAL CONSIDERATIONS FOR ISLET AUTOANTIBODY TESTING

Symptomatic stage 3 T1D is preceded by the development of autoantibodies against pancreatic β-cell antigens. The most commonly studied and measured islet autoantibodies are islet cell antibodies (ICAs), insulin autoantibodies (IAAs), glutamic acid decarboxylase autoantibodies (GADAs), insulinoma-associated antigen-2 autoantibodies (IA-2As), and zinc transporter 8 autoantibodies (ZnT8As).[57-59] It should be noted that ICAs are not specific for T1D and not generally used for T1D screening.[60] Children who develop islet autoantibodies before age 2 years usually exhibit ZnT8As and IAAs first, while individuals who develop autoantibodies during preschool are more likely to exhibit IA-2As and GADAs first.[61,62] At the time of T1D diagnosis, 50% to 90% of individuals are IAA-positive, 50% to 80% GAAD-positive, 50% to 70% ZnT8A-positive, and 30% to 70% IA-2A-positive.[63]

A panel of several of the most common autoantibodies, ie, IAA, GAAD, IA-2A, and ZnT8A, should be used rather than individual antibody tests.[46,64,65] This strategy is beneficial for several reasons. First, an individual may be positive for only 1 autoantibody early in the disease course and would be missed without performing the complete panel. Second, the islet autoantibody profiles of individuals who progress to symptomatic stage 3 T1D vary. A diagnosis of T1D can be made only when 2 or more autoantibodies persist.

OPTIONS FOR AUTOANTIBODY SCREENING

Panels for screening are accessible to clinicians through

commercial labs, as well as programs such as those being offered through the JDRF T1Detect program (https://www.jdrf.org/t1d-resources/t1detect/), or for research purposes through TrialNet (https://www.trialnet.org/participate). The T1Detect program is a population screening education and awareness program for early detection of people with stage 1 or stage 2 T1D launched in December 2020.[66] The intent is to decrease the incidence of DKA and help those at risk of progressing to symptomatic stage 3 and their families develop a plan for further monitoring. Reducing the risk of DKA was recently found to be of paramount importance to parents with and without children with T1D in the United States.[67]

RECOMMENDATIONS FOR SCREENING

Currently, there are no universally agreed-upon recommendations for islet autoantibody screening for T1D outside of the research setting. The guidelines of multiple professional organizations including the American Diabetes Association, International Society for Pediatric and Adolescent Diabetes, and European Society for Paediatric Endocrinology do not recommend screening for autoantibodies as standard of care, but rather call for them to be performed only within the context of a clinical trial. Although the stated rationale for this approach is the lack of approved therapeutic options to prevent progression to symptomatic stage 3, the landscape is rapidly changing, with several investigational agents currently in late-stage development or under review by the US Food and Drug Administration and other regulatory bodies. Perhaps more importantly, there are data demonstrating reduction of DKA in both population and high-risk individual screening programs. In addition to the immediate life-threatening complications of DKA, correlations exist with poorer long-term glycemic outcomes, making the argument to screen compelling. The aspirational goal of population screening is important; however, implementation provides formidable challenges. In contrast, islet autoantibody screening of those at risk, who have a 10-fold-greater risk of developing symptomatic stage 3 T1D in their lifetime, is achievable today.

ROLE OF PRIMARY CARE CLINICIANS IN SCREENING AT-RISK INDIVIDUALS

As the primary healthcare clinicians for children and adolescents, family physicians and pediatricians are the anchor of their overall healthcare. Consequently, family physicians and pediatricians are likely to be the first point of contact when a child with T1D becomes clinically symptomatic (stage 3 T1D). Given the intimacy and familiarity with the family and caregivers, the impact that these clinicians can have on promoting awareness of the option and rationale to screen is unique. Screening can be performed in a variety of different settings, including the office, commercial labs, and at home. Moreover, because family physicians provide general care to adults with T1D,[68] they are in a key position to recommend screening of children, siblings, parents, and other relatives of their adult patients with T1D. Finally, more than half of incident cases of T1D are identified as adults; thus, family physicians should consider T1D in lean adults with evidence of hyperglycemia or those diagnosed with type 2 diabetes who progress rapidly to require insulin.

CONCLUSION

T1D is an autoimmune disease with 3 stages that can be identified through islet autoantibody screening. The likelihood of developing symptomatic stage 3 T1D approaches 100% in the presence of 2 or more antibodies. Detecting the antibodies in asymptomatic, high-risk patients has potential benefits including reductions in DKA events as well as short- and long-term complications. Family physicians and other primary care clinicians can play a unique role in their ability to promote and recommend the option of screening for families who are at risk for developing symptomatic stage 3 T1D. ●

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The Challenge: Finding the Most Appropriate Statin and Dose for Each Patient

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doi: 10.12788/jfp.0224

KEY TAKEAWAYS

- Discontinuing statin therapy results in increased cardiovascular risk.
- The nocebo effect is a common reason for perceived statin intolerance.
- Statin intolerance is much less commonly reported in clinical trials than in clinical practice, suggesting that patient education and other safeguards employed in clinical trials are important to include in clinical practice.
- Several strategies are available that can enable continuation of statin therapy in patients who are truly statin-intolerant.

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DISCLOSURES

Dr. Lillo has no conflicts to disclose.

ACKNOWLEDGMENT

Editorial support was provided by Jim Backes, PharmD, and Gregory Scott, PharmD, RPh, of the Primary Care Education Consortium.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and supported by funding from Kowa Pharmaceuticals America, Inc.

CASE SCENARIO

A 68-year-old male with coronary stents, diabetes mellitus, hypertension, and statin intolerance presents to clinic. He has taken lisinopril, verapamil, metformin, and gemfibrozil for the past few years. However, he has discontinued atorvastatin and the combination of simvastatin/ezetimibe during the past several months "because it was too hard to go up steps." Symptoms appeared shortly after he started the statin and resolved within a week after discontinuation. Due to his statin intolerance, PCSK9 inhibitor therapy is being considered.

- Cardiac:
  - Systolic blood pressure 125 mm Hg
- Laboratory:
  - Cholesterol: total cholesterol 181 mg/dL, low-density lipoprotein cholesterol (LDL-C) 110 mg/dL, high-density lipoprotein cholesterol (HDL-C) 39 mg/dL, triglycerides 160 mg/dL, non-HDL-C 142 mg/dL
  - A1c 6.5%
- Thyroid and vitamin D normal

INTRODUCTION

Clinicians may believe that statin intolerance is "anything that the patient perceives it to be" because of the frequency and variety of patient-reported adverse events (AEs). The use of statin therapy is supported by decades of data demonstrating a reduction in morbidity and mortality with a safety profile similar to placebo.[1,2] Yet unlike study subjects, clinic patients struggle with adhering to statins primarily due to muscle complaints or are skeptical to initiate statin therapy because of misconceptions, which may result in the nocebo effect (inverse of the placebo effect).[3,4]

Major societies provide formalized definitions of statin intolerance. The National Lipid Association (NLA) reports, "Statin intolerance is a clinical syndrome characterized by the inability to tolerate at least two statins: one at the lowest starting daily dose AND another at any daily dose, due to objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment, and reversible upon statin discontinuation, but reproducible by rechallenge with other known determinants being excluded."[5] Other cardiovascular (CV) societies specifically highlight the importance of drug-drug interactions (DDIs), conditions known to increase statin intolerance (eg, hypothyroidism, underlying muscle disease), and that symptoms must appear within the first 12 weeks of initiation or dose increase, with symptom improvement or disappearance within 4 weeks of discontinuing statin therapy.[6,7] Even

with guidance by major societies, identifying and managing statin intolerance, whether real or perceived, while finding the maximally tolerated statin and dose to maintain therapy continues to be a challenge for clinicians.

DISCONTINUING OR NOT OPTIMIZING STATIN THERAPY

LDL-C is considered the root cause of atherosclerosis.[8] This relationship is supported by CV outcomes trials (CVOTs) dating back to 1984 with the Lipid Research Clinics Coronary Primary Prevention Trial, which utilized cholestyramine.[9] A host of other CVOTs have demonstrated that a reduction in LDL-C, whether using ileal bypass surgery, statins, ezetimibe, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors,[10-13] results in fewer CV events. Finally, CVOTs, such as the Cholesterol Treatment Trialists (CTT) study in patients at low risk of a CV event, conclude that lowering LDL-C by 1 mmol/L (39 mg/dL) lowers CV risk by 23%.[2] Lipidologists may argue that ignoring LDL-C is comparable to not acknowledging elevated blood pressure given the vast evidence from CVOTs,[14] which is further supported by accumulating data indicating that nonadherence to statin therapy is strongly associated with higher rates of CV morbidity and mortality.[15,16] Consequently, long-term use of statin therapy at the maximally tolerated dose in eligible patients is a key approach for reducing CV risk.

Because the pharmacology of statins varies within the class, it is critical to properly select the most appropriate statin and dose based on individual patient characteristics. Such guidance is provided by the American College of Cardiology/American Heart Association 2019 Guidelines (https://www.ahajournals.org/doi/epub/10.1161/CIR.0000000000000678).[17] These guidelines provide an in-depth discussion of risk stratification and appropriate therapeutic interventions. The guidelines also updated the utility of coronary artery calcium scoring to assist in shared decision-making about initiating statin therapy.

Long-term use of statin therapy can be a challenge often as a result of patient and clinician misperceptions. Once the seed of concern about a statin is planted, it can quickly become the clinical syndrome of statin intolerance as described by the NLA.[18] Further, having to initiate non-statin therapies for LDL-C reduction is associated with prescribing complexities and additional time-consuming hurdles, limited efficacy, and often higher treatment costs.[19] For example, ezetimibe is a safe and effective LDL-C-lowering agent that is generically available but has a relatively limited LDL-C reduction of ~20%. Bile acid resins have a similar limited effect on LDL-C, must be administered 1 hour before or 4 hours after other medications to prevent binding of concomitant agents, and are further limited by poor palatability and gastrointestinal (GI) AEs.[14] Bempedoic acid is a new statin alternative that lowers LDL-C by ~20%, but often requires prior approval by many third-party payers. Moreover, its impact on CV events has yet to be determined.[20] Finally, PCSK9 inhibitors are highly effective, possess a good safety profile, and have demonstrated CV event reduction in CVOTs, but prescribing barriers due to cost and the need for subcutaneous injection can be problematic.[19]

CLINICAL ASSESSMENT—WHAT WE HAVE LEARNED

Identifying patients with true statin intolerance and differentiating true intolerance from the nocebo effect are critical for managing and maintaining therapy. To help evaluate statin-associated muscle symptoms (SAMS), a clinical index score has been developed to capture objective information given that the frequently used biomarker to assess myotoxicity, creatine kinase (CK), is nonspecific and not always associated with symptoms **(TABLE 1)**.[18,21] The myalgia index closely follows the NLA's definition of statin intolerance and indicates whether the patient's symptoms are probable, possible, or unlikely to be statin-related.[22] Assessing and acknowledging underlying muscle, arthralgia, and pain disorders present at baseline is also important to discuss with the patient. Otherwise, such complaints may be attributed to the newly prescribed statin. Further, ruling out common conditions that may mimic SAMS (eg, physical exertion, low serum vitamin D) is imperative.[21]

Other patient-reported AEs and alterations in laboratory values, although less common, are also clinically observed with statins.[23] These include headache, GI disturbances, and elevations in hepatic transaminases, CK, or glycemic markers. Guidance is limited for less common statin-related AEs, but switching statins or reducing the dosage is clinically prudent. For concerns related to laboratory elevations, obtaining baseline values among patients at higher risk for such abnormalities (eg, people with prediabetes or nonalcoholic fatty liver disease) may be considered; otherwise the correlation to statin therapy will be unclear and may cause apprehension for both the patient and clinician. Marked elevations in hepatic transaminases are uncommon and dose-dependent, so if causation is linked to statin therapy, dosage reduction may be considered. A dose-dependent relationship also exists for statins and incident diabetes. Evidence suggests that atorvastatin, rosuvastatin, and simvastatin are more likely to worsen glycemic indices, while fluvastatin, lovastatin, pitavastatin, and pravastatin appear to have little or no effect.[24-26] Preexisting risk factors for diabetes mellitus appear to play a role.[27,28]

Much has been learned regarding the risk factors for statin-related myotoxicity since the first case reports of rhabdomyolysis involving lovastatin were published over 30 years ago.[29]

TABLE 1. **Proposed statin myalgia clinical index score**[18]

Clinical symptoms (new or increased unexplained muscle symptoms)	
Regional distribution/pattern	
Symmetric hip flexors/thigh aches	3
Symmetric calf aches	2
Symmetric upper proximal aches	2
Nonspecific asymmetric, intermittent	1
Temporal pattern	
Symptoms onset <4 weeks	3
Symptoms onset 4-12 weeks	2
Symptoms onset >12 weeks	1
Dechallenge	
Improves upon withdrawal (<2 weeks)	2
Improves upon withdrawal (2-4 weeks)	1
Does not improve upon withdrawal (>4 weeks)	0
Challenge	
Same symptoms reoccur upon rechallenge (<4 weeks)	3
Same symptoms reoccur upon rechallenge (4-12 weeks)	1
Statin myalgia clinical index score (total points)	
Probable	9-11
Possible	7-8
Unlikely	<7

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Severe myotoxicity is rare with statin therapy.[14] However, case reports have identified critical DDIs and other factors that predispose patients to muscle-related AEs **(TABLE 2)**.[18] In addition to DDIs, key components commonly involved with severe myotoxicity include medical complexity and advanced age. Other common clinical traits involving SAMS include chronic kidney or hepatic disease, low body mass index (BMI), and underlying musculoskeletal or metabolic conditions.[21]

Statin therapy is associated with an extensive spectrum of muscle complaints, ranging from benign symptoms to rare cases of rhabdomyolysis.[18] Thus, proper clinical assessment is important. However, emerging research demonstrates a strong connection to statins and the nocebo effect among most patients considered statin-intolerant.[30,31] The nocebo (Latin for "I shall harm") effect can occur when a patient has negative treatment expectations that result in AEs even when the treatment is benign.[4] Common scenarios may involve a negative statin news story or purported AEs in a family member, which cause a patient to note a worsening of muscle complaints with their statin or cause a candidate for statin therapy to hesitate in initiating treatment. Many patients will also commonly research medication adverse effects via the Internet; a recent Google search of "statin side effects" yielded more than 9.3 million results. Unfortunately, this may negatively impact patient care as statin adherence and CV events worsen upon patients' hearing a negative statin-related news story. Conversely, positive stories result in adherence and a reduction in CV events.[32]

Frequency of statin intolerance

Rates of reported statin intolerance are highly variable and dependent upon the setting.[33] Data from randomized controlled trials (RCTs) demonstrate discontinuation rates and AEs comparable to placebo. A meta-analysis of placebo-controlled RCTs (N > 125,000) with a mean follow-up of 4.1 years was conducted.[34] Discontinuation rates for statin users (13.3%) and placebo recipients (13.9%) were not statistically different, nor were differences noted between primary and secondary prevention subgroups. Similar observations were reported for incidence of myopathy (muscle weakness + elevated CK) between treatment and placebo groups. These findings are in sharp contrast to the statin intolerance rate of 29% reported in clinical practice.[6]

Why is there such a gap between study subjects and patients in real-world clinical practice? Differences may be attributed to the study subjects being carefully selected and monitored and willing to begin treatment, which is often not the case for clinic patients.[14,18] But it needn't be so. High tolerability among study subjects illustrates that avoidance of major DDIs and careful monitoring of clinic patients coupled with explicit counseling on the risks and benefits of statin therapy may result in improved adherence, fewer AEs, and improved clinical outcomes.

Patient education during the shared decision-making process prior to statin initiation is critically important since recent findings strongly suggest that the nocebo effect is responsible for most cases of SAMS. Two trials specifically designed to test the nocebo effect among patients classified as statin-intolerant have been conducted. The SAMSON trial was a double-blind study that evaluated severity of SAMS among patients who previously discontinued statin therapy due to intolerable AEs.[30] Subjects were given a total of 12 bottles, with 4 bottles containing atorvastatin 20 mg, 4 bottles containing matching placebo, and 4 empty bottles. Each bottle was used

for 1-month periods in random sequence, with subjects reporting symptom intensity daily. No significant difference (P=0.39) in mean symptom scores (0=no symptoms; 100=worst imaginable symptoms) between placebo months and statin months was observed; and interestingly, subjects also reported symptom scores even during the no-tablet months.

Similarly, the Statin Web-based Investigation of Side Effects (StatinWISE) study enrolled 200 subjects with a history of statin intolerance.[31] Participants were provided atorvastatin 20 mg daily or placebo for 6 double-blind, 2-month treatment periods and asked to rate their muscle symptoms. Overall muscle symptom scores did not differ between the placebo and atorvastatin treatment periods. Also, study withdrawal because of intolerable muscle AEs was similar between groups. Most of the subjects completing the trial reported restarting long-term statin therapy.

DIFFERENCES AMONG STATINS

Muscle complaints with statin therapy are considered a class effect and RCTs evaluating SAMS with individual agents are limited to small trials.[18] Nonetheless, insight regarding statin properties and communications from the US Food and Drug Administration (FDA) provide some prescribing guidance.[35,36] Statins that undergo extensive cytochrome P450 (CYP) 3A4 metabolism include lovastatin, simvastatin, and, to a lesser extent, atorvastatin.[35] Concomitantly administered inhibitors of CYP3A4 **(TABLE 2)** can cause a considerable increase in serum levels of these statins and resultant concentration-dependent AEs. Conversely, CYP metabolism, particularly CYP3A4, plays no/minimal role in the clearance of fluvastatin, pitavastatin, pravastatin, and rosuvastatin.[35] Yet like all statins, these agents are implicated in DDIs with concomitant therapies (eg, cyclosporine, gemfibrozil) via other statin metabolic pathways.[35]

Data also indicate higher rates of SAMS with the more lipophilic statins.[37,38] Agents such as atorvastatin, lovastatin, and simvastatin are considered lipophilic statins that may be more likely to diffuse into extrahepatic tissue (eg, skeletal muscle) than their hydrophilic counterparts (pravastatin, rosuvastatin).

Finally, theories have been proposed regarding the role of coenzyme Q10 (CoQ10) and the development of SAMS.[21] Statins typically lower serum levels of CoQ10, and deficiencies of CoQ10 are associated with AEs including myalgia. Theoretically, supplementation with CoQ10 should offset SAMs, or utilizing a statin (ie, pitavastatin) that does not lower serum CoQ10 may limit muscle complaints.[21,39] Clinical reports support both approaches, yet formal studies assessing the impact on SAMs are limited.

Only small studies have evaluated possible differences between individual statins and SAMS. However, findings align with the aforementioned factors. Rosuvastatin has demonstrated favorable tolerability at lower daily doses and intermittent dosing (eg, 2-3 times/week).[21] Pravastatin and fluvastatin, although less potent, appear to be alternatives when patients are unable to tolerate more-potent statins. Finally, 2 studies indicate that ~70% of patients can tolerate pitavastatin[39,40] and remain on therapy for >12 months when previously reporting statin intolerance.[40,41]

STATIN OPTIMIZATION STRATEGIES

CASE SCENARIO (CONT'D)

A review of the patient's medication profile shows that he has taken verapamil and gemfibrozil for several years. Both are metabolic inhibitors that potentially elevated serum levels of his previous statins (atorvastatin, simvastatin) severalfold. This DDI would have caused concentration-dependent AEs resulting in his limited ability to climb steps.

This case emphasizes the importance of choosing initial statin therapy carefully and/or modifying concomitant medications as appropriate to avoid major DDIs. Once patients experience SAMS, they frequently become hesitant to initiate or optimize statin therapy. Since the patient was receiving ezetimibe in combination with simvastatin, it, too, might be eliminated from future use because of perceived intolerance. Since the patient case likely illustrates valid SAMS, rechallenging with a noninteracting statin or finding alternative treatments to the interacting medications would be prudent. Counseling the patient that ezetimibe is not a statin and likely did not contribute to his AEs is also imperative. Ultimately, combining the ezetimibe with a statin free of major DDIs would likely be well tolerated and achieve significant LDL-C reduction, possibly avoiding the need for a PCSK9 inhibitor.

True intolerance or nocebo effect?

A key to optimizing statin therapy is differentiating true intolerance from the nocebo effect. Data support that most clinic patients reporting SAMS are experiencing the latter.[30,31] Utilizing such tools as the NLA's Myalgia Clinical Index Score can help guide the practitioner.[18] In our patient case, the reported symptoms, pattern, and timing associated with statin dechallenge and rechallenge reveal an index score of ~11, indicating a "probable" association. In contrast, those with the nocebo effect have lower index scores because of more-generalized complaints, nonspecific distribution, and timing of symptoms that do not align with the initiation and discontinuation of statin therapy. It is also important to note that most patients considered statin-intolerant can tolerate some level of statin intensity.[5]

Patient engagement and shared decision-making

Engaging the patient and utilizing shared decision-making are critical for managing SAMS. Working through the clinical index score and illustrating to those with the nocebo effect that the reported symptoms do not align with their statin can be an effective strategy for reintroducing or optimizing therapy. Questioning the patient regarding how bothersome their reported AEs are and addressing any concerns or hesitations that may be present further engages and allows the patient to believe their input is part of the solution. Finally, educating the patient on the benefits of statin therapy, including significantly reducing their chances of a major catastrophic vascular event such as a myocardial infarction or stroke, is often very motivational in guiding their decision to initiate or continue statin therapy. The protective effects of statins are durable and consistent across databases, extending beyond 30 years.[2,14]

Strategies for continuing the statin despite intolerance

Upon reintroduction of statin therapy or a dose increase, a few strategies can be considered to potentially elevate the statin threshold. Limited data suggest that repleting low serum vitamin D levels or initiating the ubiquinol formulation of CoQ10 may improve statin tolerability and/or possibly offset the nocebo effect.[21,42] Although the data are limited, such therapies are safe and may be clinically justified if supplementation enables patients at high CV risk to receive statin therapy.

Older data indicate that 43% of statin-intolerant patients experience no recurrent symptoms when simply switching statins.[43] Yet a more guided approach may produce better results. Instead of randomly switching to another statin, practitioners should consider choosing agents with data supporting improved tolerability and probability of fewer DDIs, including rosuvastatin and pitavastatin. If less LDL-C reduction is needed, fluvastatin and pravastatin are alternatives.[21,35,38] For patients who are highly statin-intolerant or hesitant to initiate therapy, using conservative, intermittent dosing with gradual titration can be effective. Statins possessing long half-lives (ie, atorvastatin, pitavastatin, rosuvastatin) can achieve significant LDL-C reduction when administered a few times weekly. The intermittent dosing also simplifies determining if an AE is statin-related.[21] For example, if the patient begins rosuvastatin 10 mg every Sunday and reports muscle complaints later in the week, the timing and pharmacokinetics do not support a correlation to the statin. This can be a key point when counseling patients.

Ongoing assessment

Continued monitoring and reassurance is often needed to maintain statin therapy, especially among patients who are highly statin-intolerant.[21] Critical to success is educating those experiencing the nocebo effect that reported AEs are not likely statin-related. This may require periodic statin dechallenge and rechallenge for resistant patients. Clinical follow-up of statin-intolerant patients typically follows a few scenarios. First are those patients who are managed by switching to a better-tolerated statin and/or, when able, modifying concomitant medications to avoid subsequent DDIs.[21] Such patients illustrate the importance of appropriately selecting an initial statin that avoids major DDIs and potential AEs for improved tolerability. For more-intolerant patients, a regimen of vitamin D and ubiquinol (CoQ10) may be considered (although evidence is controversial), followed by conservative and gradual titration of an extended-half-life statin.[21]

Many patients who are highly statin-intolerant can suc-

TABLE 2. **Clinical factors potentially predisposing to statin-associated muscle symptoms[21]**

Advanced age
Female gender
Asian ethnicity
Low body mass index (frailty)
Pre-existing muscle/joint/tendon conditions
Chronic pain disorders
Diabetes mellitus
Obesity
Neuromuscular conditions
Chronic renal or hepatic disease
Hypothyroidism
Vitamin D deficiency
Physical exertion
Family history of myalgia (with or without statin therapy)
DDIs via CYP3A4: potentially ↑↑ statin serum levels
Amiodarone
Azole antifungals - multiple agents
Amlodipine
Diltiazem
Verapamil
Macrolide antibiotics - clarithromycin, erythromycin
Protease inhibitors - multiple agents
Excess grapefruit/juice consumption
Other common interacting medications
Cyclosporine
Gemfibrozil

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cessfully utilize a low-dose, intermittent statin regimen with concomitant ezetimibe. Such combination therapy has few third-party payer barriers and can often achieve an LDL-C reduction of ~30% to 40%.[21] Importantly, titration for those able to tolerate statin therapy to the maximally tolerated dose is essential. A key message from clinical guidelines is to achieve and maintain the maximally tolerated statin and dose. Finally, for the <5% of patients deemed statin-intolerant,[5] the utilization of non-statin therapies, including ezetimibe, bempedoic acid, and PCSK9 inhibitors, will need to be considered to achieve the required LDL-C reduction.

SUMMARY

Although no definition of statin intolerance has been universally adopted, many major organizations provide guidance to the clinician for identifying and managing statin intolerance. Nonadherence to statin therapy or not optimizing the statin dose is associated with a higher rate of CV events. It remains imperative to involve the patient in shared decision-making, explicitly counseling on the risks and benefits of statin therapy and common misconceptions that can result in statin hesitation or the nocebo effect. Certain statins are less prone to major DDIs and are likely better tolerated. Choosing such agents when reintroducing statin therapy and implementing other strategies are critical to prevent recurrent statin intolerance and ultimately improve long-term adherence and reduce CV events. The number one cause of death in the United States remains heart disease, and statin therapy is one of our core strategies in our ongoing attempts to mitigate this disease.[14]

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Use of SGLT-2 Inhibitors in Patients with Chronic Kidney Disease

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doi: 10.12788/jfp.0225

KEY TAKEAWAYS

- Chronic kidney disease (CKD) is common, occurring in 1 of 7 adults in the United States.
- 9 out of 10 adults with CKD are unaware of it.
- People with CKD have the same risk for cardiovascular (CV) death as people with known atherosclerotic heart disease.
- The risk for CV events and death increases with worsening albuminuria and estimated glomerular filtration rate (eGFR).
- Patients with risk factors for CKD (hypertension, diabetes, family history of CKD, or advancing age) should be screened by measuring both eGFR and urinary albumin-to-creatinine ratio.
- Sodium-glucose cotransporter-2 inhibitors are first-line agents for treatment of patients with type 2 diabetes mellitus and CKD or a history of atherosclerotic CV disease.
- Dapagliflozin has demonstrated equivalent efficacy for reducing kidney events in patients with CKD irrespective of diabetes status, and a similar, ongoing trial with empagliflozin may provide potential confirmation.

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DISCLOSURES

Dr. Mottl discloses that she serves on the advisory board for Bayer. Gregory Scott, PharmD, has no disclosures to report.

ACKNOWLEDGMENT

Editorial support was provided by Gregory Scott, PharmD, RPh, at the Primary Care Education Consortium.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and the Primary Care Metabolic Group and supported by funding from AstraZeneca Pharmaceuticals LP.

INTRODUCTION

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function present for >3 months, and it carries significant risk for cardiovascular (CV) health.[1] Three criteria are used to classify CKD: etiology, glomerular filtration rate stage (G1 to G5), and albuminuria category (A1 to A3).[1] Numerous factors have been shown to independently increase the risk of CKD, including uncontrolled diabetes mellitus, uncontrolled hypertension, obesity, heart failure, age >60 years, tobacco use, family history of CKD, history of acute kidney injury, and genetic factors.[2-5] In turn, CKD increases the risk for a wide variety of CV diseases, including hypertension, myocardial infarction, stroke, chronic heart failure, peripheral vascular disease, and end-stage kidney disease (ESKD),[6-8] making clear the extensive interaction between the kidney and heart.

Of the estimated 37 million adults (15%) in the United States who have CKD, an estimated 9 out of 10 are unaware, particularly those with early-stage disease.[9] This is a concern since patients with early-stage CKD may not be receiving appropriate treatments or, worse yet, may be receiving potentially nephrotoxic medications, leading to more rapid rates of disease progression.[5,10] Diabetes and hypertension are the 2 principal causes of CKD and ESKD,[5] accounting for 47% and 29%, respectively, of the 124,500 incident ESKD cases diagnosed in 2017.[11] ESKD is defined as kidney failure treated with dialysis or kidney transplant. Fewer than half (44.9%) of individuals who develop ESKD survive 5 years.[11] Given the extensive morbidity and mortality associated with CKD, greater and earlier awareness among individuals at risk for CKD is urgently needed, with primary care clinicians (PCCs) playing a sentinel role in early diagnosis and treatment.

SCREENING FOR CKD

Routine screening of kidney function in post-pubertal children with diabetes and all individuals with type 2 diabetes mellitus has been recommended by the American Diabetes Association (ADA) since the 1990s.[12] Since that time, the ADA recommendations have become more defined, with their 2021 *Standards of Medical Care in Diabetes* providing specific screening recommendations for individuals with type 1 diabetes (T1D) or type 2 diabetes (T2D) **(TABLE 1)**.[13-15] Updated recommendations released in 2020 by Kidney Disease: Improving Global Outcomes (KDIGO) mirror the ADA's recommendations.[1]

A key point in both the ADA and KDIGO screening recommendations is that adults with T1D or T2D should be screened for kidney disease by measuring both estimated

TABLE 1. **ADA recommendations for screening for CKD in individuals with diabetes mellitus**[13-15]

	Adults[a]	Children/adolescents
Who?	T1D: Duration ≥5 years T2D: All	At puberty or age >10 years, whichever is earlier, once the child has had diabetes 5 years
How?	Urinary albumin (eg, spot urine for UACR) and eGFR	Urinary albumin with a random (morning preferred) spot urine for UACR
When?	At least annually	Annually

[a]Adults with diabetes and UACR >300 mg/g and/or eGFR 30-60 mL/min/1.73 m^2 should be monitored twice annually to guide therapy.

glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR). Annual measurement of kidney function in individuals with diabetes is a new quality care indication for public and private payers introduced in 2021. Measuring both eGFR and UACR is essential since one may become abnormal in advance of the other. Approximately 40% of patients with T2D will have an eGFR of <60 mL/min/1.73 m^2 in the absence of albuminuria.[16,17] Albuminuria can occur a decade or more before a noticeable decline in the eGFR, which typically does not occur until there is advancing glomerulosclerosis.[18,19] Thus, small changes in a patient's eGFR, such as a serum creatinine that is 0.9 to 1.1 mg/dL compared to 0.7 to 0.9 mg/dL several years ago, should be investigated to identify the cause.

Clinical evidence demonstrates that there is a graded increase in risk for all-cause and CV mortality, as well as adverse kidney outcomes, with increasing levels of albuminuria and decreasing eGFR. These effects are independent of one another, but interact in an additive fashion.[20,21] Even for individuals with an eGFR of >60 mL/min/1.73 m^2, the risks are significantly increased for a UACR of ≥30 mg/g. For example, for an individual with an eGFR of 75 to 90 mL/min/1.73 m^2, the risk of CV mortality is doubled if the UACR is 30 mg/g vs <10 mg/g.[22]

TREATMENT OVERVIEW

Once an individual is identified as having CKD, evidence-based therapy should be initiated to prevent further deterioration in kidney function.[1,14] As part of comprehensive treatment,[1,14] it is critically important to treat the underlying cause of the kidney disease. Equally important is the avoidance of nephrotoxic medications, particularly nonsteroidal anti-inflammatory drugs, which are commonly used in individuals with CKD.[5] Moreover, care must be taken to appropriately dose medications that are principally cleared by the kidneys, of which antibiotics are among the most frequent offenders.

Use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker is essential for most individuals with albuminuric CKD to reduce the risk of worsening albuminuria and progressive deterioration of eGFR.[1,14] In individuals with T1D or T2D, intensive glycemic control, ie, glycated hemoglobin (A1c) of <7.0%, to achieve near-normoglycemia delays the onset and progression of albuminuria and reduced eGFR.[1,14] Less intensive glycemic control, ie, A1c of <8.0%, may be appropriate in some individuals with advanced CKD, significant CV disease, or limited life expectancy.[1]

While early-stage or uncomplicated CKD can often be managed by the PCC, early referral to a nephrologist (eGFR of ≥30 mL/min/1.73 m^2) is advised in some situations. These include 1) uncertain etiology of kidney disease, particularly in the setting of persistent microscopic hematuria or atypically elevated UACR, eg, ≥1000 mg/g; 2) rapidly increasing albuminuria or nephrotic-range proteinuria; 3) rapidly decreasing eGFR (>3 mL/min/1.73 m^2 per year); and 4) particularly challenging management issues, eg, anemia, metabolic bone disease, secondary hyperparathyroidism, resistant hypertension, and electrolyte disturbances.[14] Additionally, the absence of retinopathy in individuals with T1D suggests alternative or additional causes of kidney disease.[14] All individuals with CKD with an eGFR of <30 mL/min/1.73 m^2 should be evaluated by a nephrologist unless life expectancy is limited (<1 year).

USE OF SGLT-2 INHIBITORS IN T2D AND CARDIOVASCULAR SAFETY AND BENEFITS

The sodium-glucose cotransporter-2 inhibitor (SGLT-2i) class of medications have several pharmacodynamic advantages for the treatment of individuals with T2D. First, they are administered orally once daily. Second, their unique glucosuric mechanism of action is complementary to all other glucose-lowering medications. Third, they do not cause hypoglycemia unless combined with sulfonylureas or insulin. Fourth, they promote modest weight loss. For these latter 2 reasons, the ADA recommends SGLT-2i therapy when hypoglycemia or overweight/obesity are a concern.[23] Lastly, SGLT-2i therapy causes modest reduction in blood pressure, which can be advantageous as hypertension is common in individuals with T2D.

TABLE 2. **Efficacy outcomes from CVOTs**

	Canagliflozin (CANVAS)[24]	Dapagliflozin (DECLARE-TIMI 58)[25]	Empagliflozin (EMPA-REG OUTCOME)[26,27]	Ertugliflozin (VERTIS-CV)[28]
N; % male	10,142; 64.2	17,160; 62.6	7020; 71.5	8246; 70.0
% with established atherosclerotic CV disease	65.6	40.6	99.2	–[a]
Primary MACE endpoint; HR (95% CI)	0.86 (0.75-0.97)[b]	0.93 (0.84-1.03)[c]	0.86 (0.74-0.99)[b]	0.97 (0.85-1.11)[b]
CV death or hospitalization for heart failure; HR (95% CI)	0.78 (0.67-0.91)	0.83 (0.73-0.95)[d]	0.66 (0.55-0.79)[e]	0.88 (0.75-1.03)
CV death; HR (95% CI)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.62 (0.49-0.77)	0.92 (0.77-1.11)
Myocardial infarction; HR (95% CI)	0.85 (0.69-1.05)[f]	0.89 (0.77-1.01)	0.87 (0.70-1.09)[f]	1.04 (0.86-1.27)[f]
Stroke; HR (95% CI)	0.90 (0.71-1.15)[f]	1.01 (0.84-1.21)[g]	1.24 (0.92-1.67)[f]	1.00 (0.76-1.32)[f]
Renal composite endpoint; HR (95% CI)	0.60 (0.47-0.77)[h]	0.53 (0.43-0.66)[i]	0.54 (0.40-0.75)[j]	0.81 (0.63-1.04)[k]
Hospitalization for heart failure; HR (95% CI)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.65 (0.50-0.85)	0.70 (0.54-0.90)

Boxes shaded in gray indicate significant benefit favoring SGLT-2 inhibitor vs placebo.

CANVAS, Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; VERTIS-CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial.

[a]Not specified, but established coronary, cerebrovascular, or peripheral atherosclerotic CV disease was a required inclusion criterion.

[b]Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

[c]Cardiovascular death, myocardial infarction, or ischemic stroke.

[d]Co-primary endpoint.

[e]Excluding fatal stroke.

[f]Nonfatal.

[g]Ischemic.

[h]40% reduction in eGFR, renal-replacement therapy, or renal death.

[i]≥40% reduction in eGFR to <60 mL/min/1.73 m^2, ESKD, or renal death.

[j]Doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m^2, renal-replacement therapy, or renal death.

[k]Renal death, renal-replacement therapy, or doubling of the serum creatinine level.

Multiple large CV outcomes trials (CVOTs) have demonstrated the CV safety of all 4 SGLT-2 inhibitors currently available in the United States **(TABLE 2)**.[24-28] CV safety was based on major adverse CV events (MACE), a composite endpoint of CV death, nonfatal myocardial infarction, or nonfatal stroke. All CVOTs involving an SGLT-2i included individuals who had suffered a CV event, ie, secondary prevention, while some included individuals who were at high CV risk but who had not suffered a CV event, ie, primary prevention.

Some but not all CVOTs showed significant reductions in CV death; however, all showed reductions in hospitalization for heart failure.[24-26,28] While reductions in CV death were restricted to those with baseline CV disease, reductions in hospitalization rates for heart failure were irrespective of baseline CV disease status.[29]

The results of these CVOTs led the ADA[23] and the American College of Cardiology/American Heart Association (ACC/AHA)[30] to recommend SGLT-2i therapy as a preferred option for secondary CV prevention. The ADA recommends the addition of an SGLT-2i as an option for individuals with T2D and established CV disease who do not achieve glycemic control with optimized metformin and lifestyle management.[23] The ACC/AHA also suggest considering combined use of an SGLT-2i and a glucagon-like peptide-1 receptor agonist for primary prevention of CV disease in patients with T2D and additional risk factors for CV disease.[30]

TABLE 3. **Baseline demographics and efficacy outcomes in kidney disease trials**

Average	Canagliflozin (CREDENCE)[32]	Dapagliflozin (DAPA-CKD)[33]
N; % male	4401; 66.1	4304; 66.9
Mean age, y	63.0	61.9
Mean eGFR, mL/min/1.73 m^2	56.2	43.1
UACR (median), mg/g	927	949
% with T2D	100	67.5
% with CV disease	50.4	37.4
% with HTN	96.8	NR
% on RAAS inhibitor	99.9	98.2
Randomized treatment	Canagliflozin 100 mg/d or placebo	Dapagliflozin 10 mg/d or placebo
Follow-up (median), y	2.6	2.4
Primary composite endpoint; HR (95% CI)	0.70 (0.59-0.82)[a]	0.61 (0.51-0.72)[b]
CV death; HR (95% CI)	0.78 (0.61-1.00)	0.81 (0.58-1.12)
All-cause death; HR (95% CI)	0.83 (0.68-1.02)	0.69 (0.53-0.88)
CV death or hospitalization for heart failure; HR (95% CI)	0.69 (0.57-0.83)	0.71 (0.55-0.92)
Doubling of SCr; HR (95% CI)	0.60 (0.48-0.76)	–
eGFR decline ≥50%; HR (95% CI)	–	0.53 (0.42-0.67)
ESKD; HR (95% CI)	0.68 (0.54-0.86)	0.64 (0.50-0.82)
eGFR <15 mL/min/1.73 m^2; HR (95% CI)	0.60 (45-0.80)	0.67 (0.51-0.88)
Dialysis or kidney transplantation; HR (95% CI)	0.74 (0.55-1.00)	0.66 (0.49-0.90)
Long-term dialysis; HR (95% CI)	–	0.66 (0.48-0.90)

Boxes shaded in gray indicate significant benefit favoring SGLT-2 inhibitor vs placebo.

HTN, hypertension; NR, not reported; SCr, serum creatinine.

Outcomes are shown as hazard ratio (95% confidence interval).

[a]Dialysis, kidney transplantation, sustained eGFR <15 mL/min/1.73 m^2, doubling of serum creatinine level, renal death, or CV death.

[b]Sustained decline in eGFR ≥50%, dialysis for ≥28 days, transplantation, sustained eGFR <15 mL/min/1.73 m^2, CV death, or renal death.

KIDNEY OUTCOMES AND SGLT-2 INHIBITORS

The CVOTs all had prespecified secondary kidney endpoints, and dapagliflozin, empagliflozin, and canagliflozin (but not ertugliflozin) showed reductions in major kidney outcomes (those being a 40% decline in eGFR and/or doubling of serum creatinine, or renal death). Despite the lack of a statistically significant reduction in these hard events, ertugliflozin was found to slow the rate of eGFR decline,[28] with results consistent with the other CVOT trials.[31] The vast majority of patients in the CVOTs had minimal or no evidence of CKD at baseline, suggesting primary or early benefit of these drugs to prevent progression of CKD in T2D.

Two kidney outcomes trials, CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation)[32] and DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease),[33] have been conducted exclusively in individuals with CKD and their results reported. A third, EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin), is in progress.[34] CREDENCE included only individuals with T2D, whereas DAPA-CKD and EMPA-KIDNEY include individuals with or without T2D. Inclusion criteria were: 1) CREDENCE, eGFR of 30 to <90 mL/min/1.73 m^2 and UACR of >300 to 5000 mg/g; 2) DAPA-CKD, eGFR of 25 to 75 mL/min/1.73 m^2 and UACR of 200 to 5000 mg/g; and 3) EMPA-KIDNEY, eGFR of 20 to <45 mL/min/1.73 m^2 or eGFR of 45 to <90 mL/min/1.73 m^2 and UACR of ≥200 mg/g.

CREDENCE and DAPA-CKD both demonstrated significant kidney and CV benefits with canagliflozin and dapagliflozin, respectively. Key baseline demographics are shown in **TABLE 3**; all of the individuals in CREDENCE and two-thirds in DAPA-CKD had T2D and nearly all were treated with a renin-angiotensin-aldosterone system (RAAS) blocker.[32,33]

TABLE 4. **Adverse events of special interest in clinical trials of SGLT-2 inhibitors focused on patients with CKD**

Adverse event	CREDENCE[32]			DAPA-CKD[33]		
	Canagliflozin, %	**Placebo, %**	**HR (95% CI)**	**Dapagliflozin, %**	**Placebo, %**	***P***
Any adverse event	81.1	84.7	0.87 (0.82-0.93)	–	–	–
Any serious adverse event	33.5	36.7	0.87 (0.79-0.97)	29.5	33.9	–
Amputation	3.2	3.9	1.11 (0.79-1.56)	1.6	1.8	0.73
DKA	0.5	<0.1	10.80 (1.39-83.65)	0	<0.1	0.50
Fracture	3.0	3.1	0.98 (0.70-1.37)	4.0	3.2	0.22
Major hypoglycemia[a]	–	–	–	0.7	1.3	0.04
Hypoglycemia[b]	10.2	10.9	0.92 (0.77-1.11)	–	–	–
Hyperkalemia	6.9	8.2	0.80 (0.65-1.00)	–	–	–
Volume depletion	6.5	5.2	1.25 (0.97-1.59)	5.9	4.2	0.01
Renal-related	13.2	17.7	(0.71 (0.61-0.82)	7.2	8.7	0.07
Acute kidney injury	3.9	4.5	0.85 (0.64-1.13)	1.8	2.4	–

[a]Characterized by symptoms of severe impairment in consciousness or behavior, need of external assistance, intervention to treat hypoglycemia, and prompt recovery from acute symptoms after the intervention.

[b]Symptomatic and asymptomatic.

In CREDENCE, canagliflozin was superior to placebo for preventing the primary renal outcome (composite of dialysis, transplantation, sustained eGFR of <15 mL/min/1.73 m^2, doubling of serum creatinine, CV death, or renal death) (hazard ratio [HR] 0.70; 95% confidence interval [CI]: 0.59-0.82).[32] The number needed to treat (NNT) for the primary renal outcome was estimated to be 22 over 2.5 years.

Similarly, DAPA-CKD demonstrated significant reductions with dapagliflozin in the primary renal outcome (composite of sustained decline in eGFR of ≥50%, dialysis, transplantation, sustained eGFR of <15 mL/min/1.73 m^2, or CV or renal death) (HR 0.61; 95% CI: 0.51-0.72), with an NNT of 19 over 2.4 years.[33] The significant reduction of the primary renal outcome was observed in individuals with T2D (HR 0.64; 95% CI: 0.52-0.79) and without T2D (HR 0.50; 95% CI: 0.35-0.72); *P* for interaction = 0.24. Treatment with dapagliflozin also resulted in a significant reduction in the primary renal outcome in individuals with an eGFR of ≥45 mL/min/1.73 m^2 (HR 0.49; 95% CI: 0.34-0.69) and an eGFR of <45 mL/min/1.73 m^2 (HR 0.63; 95% CI: 0.51-0.78), as well as a UACR of ≤1000 mg/g (HR 0.54; 95% CI: 0.37-0.77) and a UACR of >1000 mg/g (HR 0.62; 95% CI: 0.50-0.76).[33] Moreover, dapagliflozin reduced the risk of kidney failure, CV death, or hospitalization for heart failure, and prolonged survival in individuals with CKD independent of the presence of concomitant CV disease.[35]

The overwhelming evidence for SGLT-2 inhibitors as a risk mitigation strategy in diabetes and CKD led to the recent recommendation by KDIGO for an SGLT-2i as initial therapy in combination with lifestyle management and metformin in individuals with T2D and CKD with an eGFR of ≥30 mL/min/1.73 m^2.[36] Moreover, based on the results from DAPA-CKD, dapagliflozin was approved by the US Food and Drug Administration in April 2021 to reduce the risk of kidney function decline, kidney failure, CV death, and hospitaliza-

tion for heart failure in adults with CKD who are at risk of disease progression.

ADVERSE EVENTS

SGLT-2i trials have shown fairly consistently that the adverse effects of this drug class include genital mycotic infections and a small but statistically significant increased risk of euglycemic diabetic ketoacidosis (DKA).[37] Experts across disciplines generally agree that while the risk of DKA is real, it can be mitigated by instructions to hold medication during conditions that predispose to DKA, such as fasting or acute illness. The risk of amputation was a concern raised by the CANVAS study, involving canagliflozin[24]; however, the CREDENCE trial did not show a difference compared to placebo **(TABLE 4)**.[32] Notably, an increased risk of urinary tract infections has not been shown in meta-analyses.[37] Increased rates of volume depletion or hypotension have been seen, but these are infrequent adverse effects and easily avoided by decreasing concurrent diuretic medications in patients who are euvolemic at the time of initiating SGLT-2i therapy. Moreover, the risk of acute kidney injury is actually mitigated by SGLT-2i therapy.

IMPLICATIONS FOR PRIMARY CARE

Both canagliflozin and dapagliflozin significantly reduce renal events in individuals with baseline CKD, regardless of the severity of albuminuria or low eGFR. In addition, dapagliflozin provides kidney benefits in individuals with or without T2D. These findings have prompted the question: Are SGLT-2 inhibitors glucose-lowering medications with cardiorenal benefits or are they cardiorenal medications that lower glycemia?[38-40] Advances in the treatment of CKD emphasize the key role of PCCs in the early identification and diagnosis of these individuals. SGLT-2 inhibitors have become an important treatment option in individuals with T2D and established CV disease, including CKD, as recommended in current guidelines and reflected in approved product labeling.[41-44]

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Utilizing CGM Ambulatory Glucose Profiles to Optimize Diabetes Management

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doi: 10.12788/jfp.0226

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participant will be able to:

- Identify patients who could benefit from continuous glucose monitoring (CGM) vs fingerstick blood glucose monitoring.
- List the types of information provided by CGM systems.
- Interpret CGM data using the ambulatory glucose profile (AGP) to assess if the patient is achieving targets established by the International Consensus on Time in Range.
- Modify the treatment plan based on CGM data to improve patient outcomes.

KEY TAKEAWAYS

- Continuous glucose monitoring (CGM) overcomes some of the limitations of glycated hemoglobin and fingerstick self-monitoring of blood glucose.
- The standardized AGP and time in range have been established to serve as an actionable format for presenting and interpreting CGM data.
- For most healthy adults with type 1 or type 2 diabetes, the desired target for time in range is ≥70%.
- The AGP provides glycemic patterns that facilitate the identification of glucose variability, hyperglycemic episodes, and individuals at high hypoglycemic risk.
- The AGP is particularly useful for individuals treated with insulin, but benefits of CGM and AGP are not limited to individuals using insulin.
- The AGP provides an excellent opportunity for shared decision-making.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of diabetes.

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Dr. Miller serves on the advisory board and speakers bureau for Abbott Diabetes. Gregory Scott, PharmD, editorial support, reports no conflicts of interest. Dr. Stephen Brunton, editor, serves on the advisory board and speakers bureau for AstraZeneca, Bayer, and Novo Nordisk. He serves on the speakers bureau for Lilly and on the advisory board for Abbott Diabetes, Acadia, Sanofi, and Xeris.

SPONSORSHIP

This article is sponsored by Primary Care Education Consortium, in collaboration with the Primary Care Metabolic Group.

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ACKNOWLEDGMENT

Editorial support was provided by Gregory Scott, PharmD, RPh, of the Primary Care Education Consortium.

SUPPORTER

This article is supported by an educational grant from Abbott Diabetes.

BLOOD GLUCOSE MONITORING

The control of blood glucose at levels close to physiologic levels in humans is well established as conferring numerous benefits, such as weight control and reduced risk for cardiovascular events.

The glycated hemoglobin level (A1c) has been widely used as a surrogate measure of glycemic control as it is

strongly predictive for diabetes complications.[1,2] However, the A1c has many limitations that preclude its use as the sole measure of glycemic control.[3] Among these is that the A1c is an aggregate measure of the blood glucose level over approximately 3 months,[3] with no indication of fluctuations in the blood glucose level, ie, glycemic variability. It is unreliable in anemia, renal failure, and pregnancy. In contrast, fingerstick self-monitoring of blood glucose (SMBG) provides a measure of the blood glucose level at the time testing is done. However, SMBG is subject to its own limitations, including user technique and the impractical demands of performing it multiple times a day every day. In addition, SMBG does not provide a clear picture as to glycemic variability or overall control.[3-5]

A third option for monitoring the blood glucose level is continuous glucose monitoring (CGM). CGM is recommended by the American Diabetes Association for individuals with diabetes on multiple daily injections and continuous subcutaneous insulin infusions and other forms of insulin therapy.[4] Other candidates for CGM include individuals with frequent hypoglycemia, hypoglycemia unawareness, or varying and/or intensive activity, as well as those who have a desire to improve glycemic control.[6-8]

CONTINUOUS GLUCOSE MONITORING

Benefits

The use and impact of CGM have been investigated in a wide variety of clinical trials involving individuals with type 1 diabetes (T1D) or type 2 diabetes (T2D). CGM overcomes many of the shortcomings observed with A1c and SMBG, with numerous real-world benefits shown in clinical studies **(TABLE 1)**.[9-16] Of key importance is that CGM provides an early warning of high, low, and/or rapidly changing blood glucose levels, which allows for early intervention, thereby improving glycemic control and avoiding complications such as hypoglycemia. CGM has the added benefit of allowing an individual to observe a clear association between action (eg, exercise, eating) and consequence (eg, hypoglycemia, hyperglycemia), thereby enabling more appropriate adjustments in nonpharmacologic and pharmacologic treatment. In the author's experience, these benefits often help to increase patient engagement in disease management, reduce clinical inertia, reduce diabetes distress, and improve treatment adherence. To achieve the full benefits of CGM, patients and clinicians should no longer consider CGM as a different kind of glucose meter, but rather should view it as the retrospective and predictive tool that it is. Background information about CGM, including devices, may be found at https://pro.aace.com/pdfs/diabetes/AACE-DRC-CGM-Slides.pdf.

Potential barriers

Patient education is vital for success with CGM devices and must be provided on a routine basis. Individuals with diabetes, as well as family members, must learn the fundamentals of sensor insertion, calibration, and setting of alerts and alarms. It is important that the individual be educated that fingerstick SMBG can still be used as a backup to CGM to measure the blood glucose level, eg, when a CGM result does not correlate with symptoms.

By providing hundreds of blood glucose readings per day, CGM devices generate an enormous amount of data internally, and interpretation of these data may seem challenging. To overcome this situation, the ambulatory glucose profile (AGP) was developed.

TABLE 1. **Real-world benefits of continuous glucose monitoring[9-16]**

- Fewer episodes of hypoglycemia
- Reduced hospital admission for hypoglycemia and/or diabetic ketoacidosis
- Improved glycemic control
- More frequent insulin dose adjustments
- Better understanding of blood glucose level fluctuations
- Reduced treatment costs
- Fewer work absences
- Reduced treatment burden
- Increased patient satisfaction
- Reduced family worry

AMBULATORY GLUCOSE PROFILE

The AGP is a software application that aggregates CGM data to statistically characterize glycemic exposure, variability, and stability. The time period of the report is determined by the user and can be as short as 2 days and as long as 90 days (depending on the CGM device). A 14-day report is considered adequate for pattern recognition and is generally viewed as being statistically similar to a 90-day report.[17] For billing, Medicare requires a minimum of 72 hours of data. For individuals with greater glycemic variability, exhibited by wide fluctuations or variability in the blood glucose level, eg, coefficient of variation >36%, longer CGM collection periods may be required.

To facilitate interpretation and shared decision-making, the AGP is presented visually as a modal day plot according to time as if the data points collected over 7, 10, or 14 days occurred over 24 hours **(FIGURE 1)**. The AGP includes 3 key CGM measurements: time within target range (TIR), time above target range (TAR), and time below target range (TBR) **(FIGURE 2)**.[17] Other helpful metrics include the average blood glucose, which is used to calculate the glucose management indicator (GMI), or approximate A1c level.

FIGURE 1. **Ambulatory glucose profile**

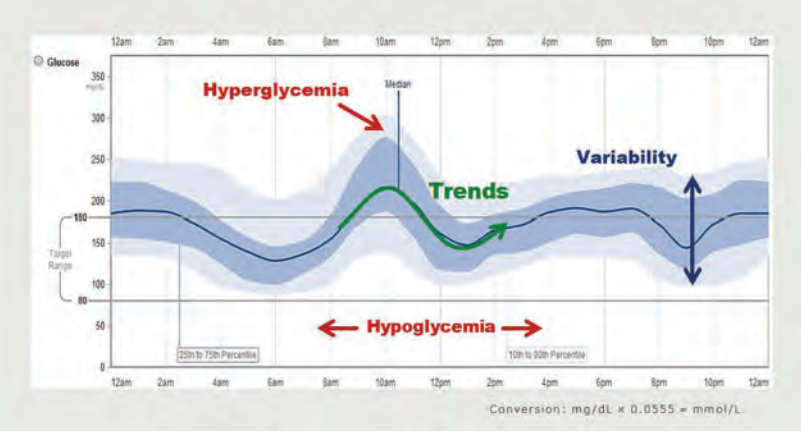
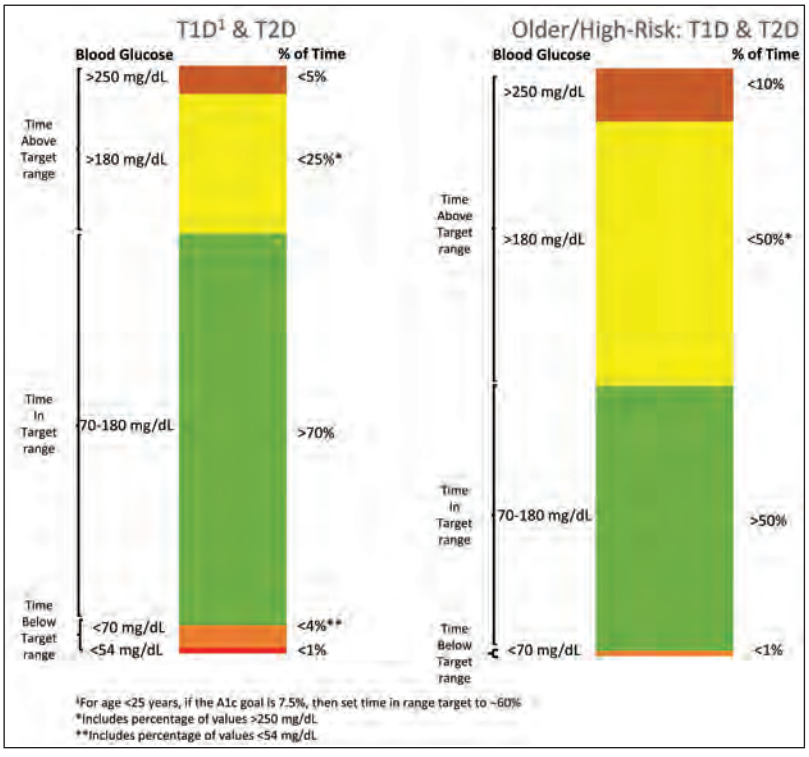


FIGURE 2. **CGM targets for different populations with diabetes[17]**



American Diabetes Association. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. American Diabetes Association. 2019. Copyright and all rights reserved. Material from this publication has been used with the permission of the American Diabetes Association.

The primary goal for effective and safe glucose control is to increase the TIR while reducing the TBR and TAR, ie, glycemic variability. For many individuals with T1D or T2D, the TIR should be ≥70%, as this correlates with better glycemic control, ie, A1c <7.0%. TIR >50% may be appropriate for individuals who are older or who have comorbidities, eg, cognitive deficit, renal disease, joint disease, osteoporosis, fracture, and/or cardiovascular disease, that place them at higher risk of complications.[17] TIR recommendations for women who are pregnant are not available due to limited experience in this population.

Interpreting the ambulatory glucose profile

Interpreting the AGP provides an opportunity to collaborate with the patient to identify situations where the blood glucose level is and is not well controlled. Discussion may then focus on reinforcing behaviors contributing to good glycemic control, as well as challenges that may contribute to poor glycemic control.

A systematic process to optimize the time spent with the patient in this process has been suggested by Richard Bergenstal, MD, of the International Diabetes Center **(TABLE 2)**. To better interpret an individual's AGP, it is helpful to mark up the AGP, noting factors such as times meals are eaten, insulin is administered, and exercise is done. This can be especially valuable to identify factors contributing to wide glycemic variability.

TABLE 2. **Key steps to interpreting the AGP**

1. Check for adequate data.
2. Mark up the AGP, noting factors affecting management.
3. Ask the patient, "What do you see?" Listen.
4. Look for patterns of low blood glucose levels.
5. Look for patterns of high blood glucose levels.
6. Look for areas of wide glycemic variability.
7. Compare current AGP to past AGPs; reinforce successful strategies.
8. Agree on an action plan with the patient.
9. Copy the AGP for the patient and place copy in the electronic medical record.

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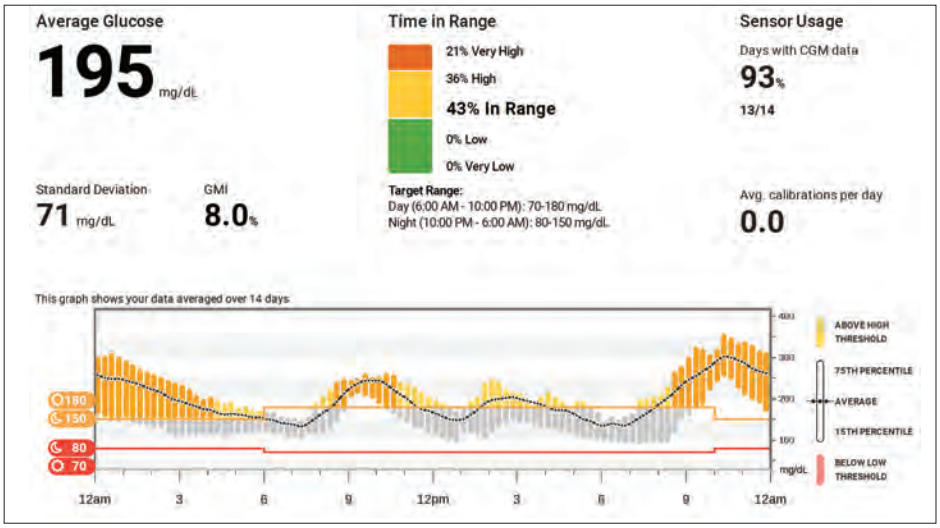
CASE STUDIES

CASE #1

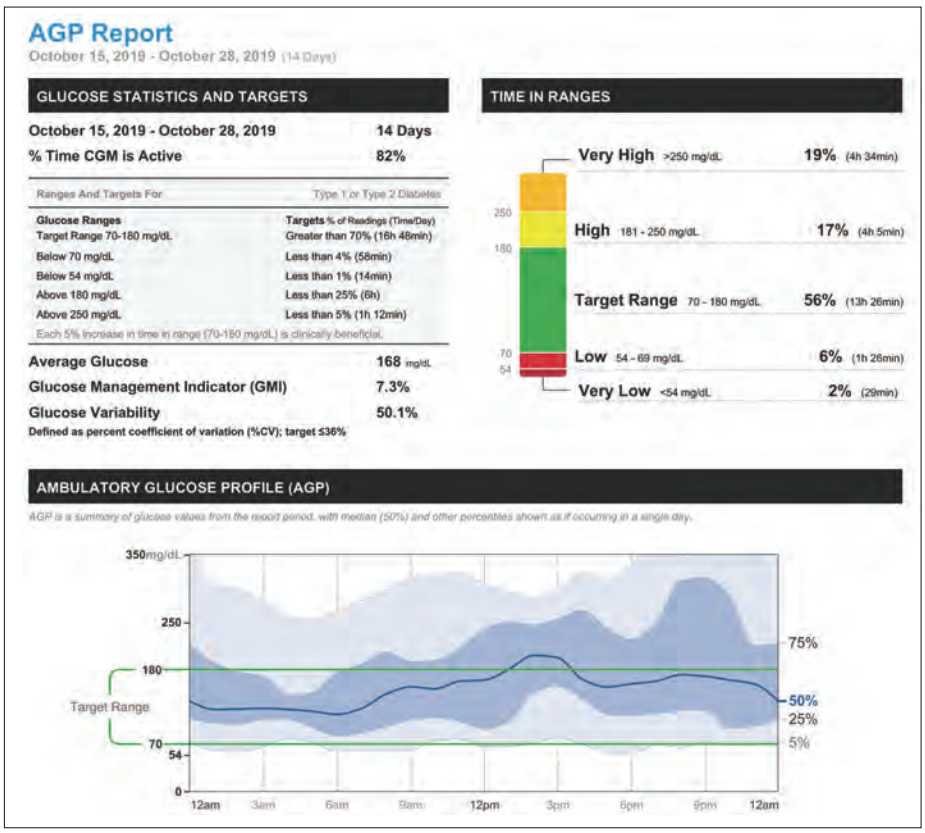
- 71-year-old man with T2D
- Current treatment:
  - Rapid-acting insulin 8 units with breakfast, 6 units with lunch, 10 units with dinner
  - Basal insulin 52 units at bedtime



Discussion. The patient's GMI, which is an approximation of A1c, is 8.0% and average blood glucose is 195 mg/dL (standard deviation, 71 mg/dL). Both indicate poor glycemic control. Moreover, 57% of his day is spent with hyperglycemia, particularly after breakfast and dinner. In addition, his TIR of 43% is below the 50% recommended for older adults. His breakfast and dinner doses of rapid-acting insulin need to be increased with appropriate monitoring. He should be reminded to take his rapid-acting insulin shortly before or at the beginning of each meal, particularly because he is at risk of hypoglycemia after lunch and dinner. Consideration may be given to reducing his dose of basal insulin since his blood glucose level is low from 3 am to 9 am.

CASE #2

- 66-year-old woman with T2D for 9 years
- Medical history:
  - Class 2 obesity body mass index [BMI], (36.9 kg/m^2)
  - Chronic obstructive pulmonary disease
  - Gastroesophageal reflux disease
- Current treatment:
  - Metformin 1000 mg twice daily
  - Basal insulin 0.64 units/kg with dinner
- A1c 7.2% 2 months ago

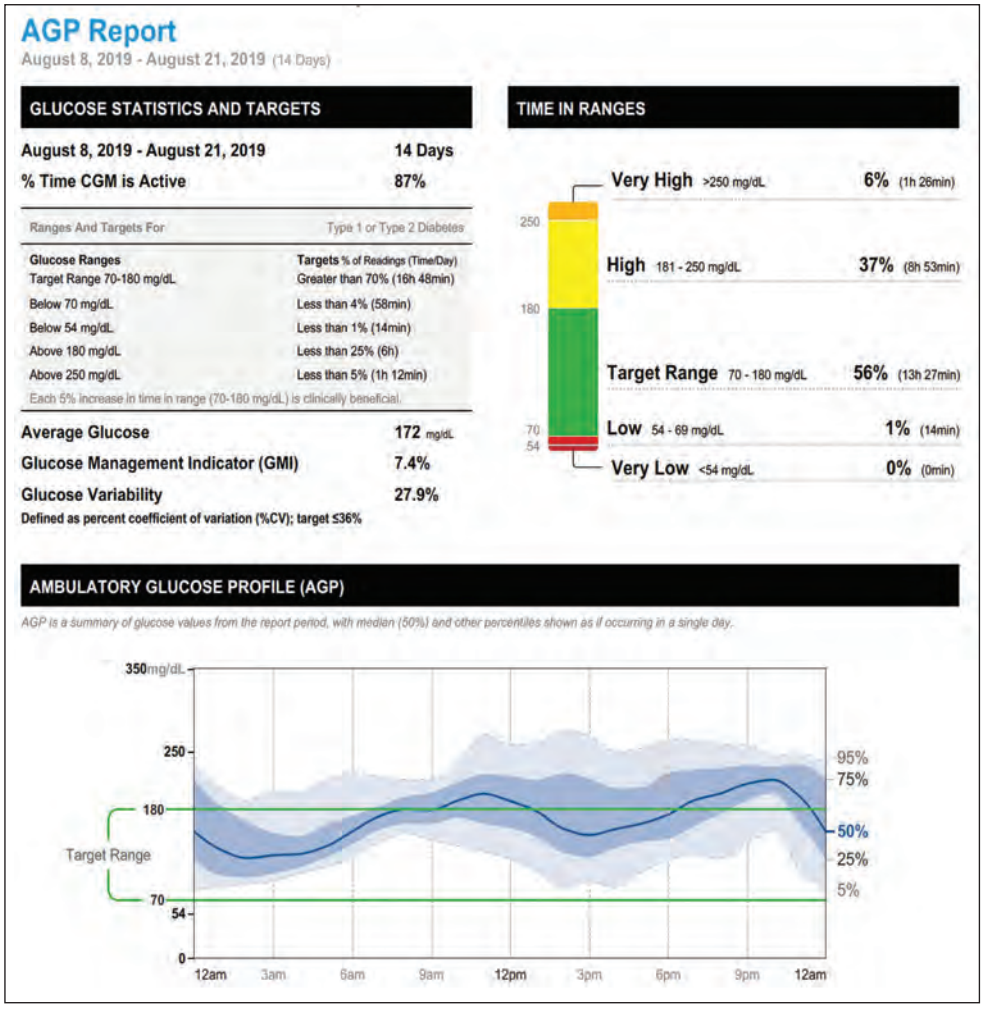


Discussion. While the patient's GMI of 7.3% suggests that her blood glucose level is close to target, her average blood glucose of 168 mg/dL, with one-third (36%) of her day spent with hyperglycemia, indicates that her blood glucose is poorly controlled. This is further

demonstrated by her glycemic variability of 50.1%, which is well above the 36% threshold recommended for good glycemic control. She experiences hypoglycemia about 2 hours over the course of a day, although she is at risk for hypoglycemia during most of the day. She needs further education about the consequences of prolonged hyperglycemia. Her treatment clearly needs to be intensified, but this must be done cautiously to avoid increasing her risk for hypoglycemia. One option is to reduce the dose of basal insulin and begin rapid-acting insulin only with dinner, which would reduce the significant glycemic spike around 9 pm. Since her blood glucose level rises after breakfast and continues to rise throughout the day, another option would be to give the basal insulin twice daily with breakfast and dinner and reduce the total daily dose by 10% so as to minimize the risk for hypoglycemia. A shared decision-making process would be helpful to develop the revised treatment plan.

CASE #3

- 45-year-old man with T2D for 13 years
- Medical history:
  - Hypertension
  - Hyperlipidemia
  - Class 3 obesity (BMI, >40 kg/m^2)
- Current treatment:
  - Metformin 1000 mg twice daily
  - NPH insulin twice daily; total daily dose >60 units
- Rarely performs fingerstick SMBG
- A1c 7.9% 6 months ago

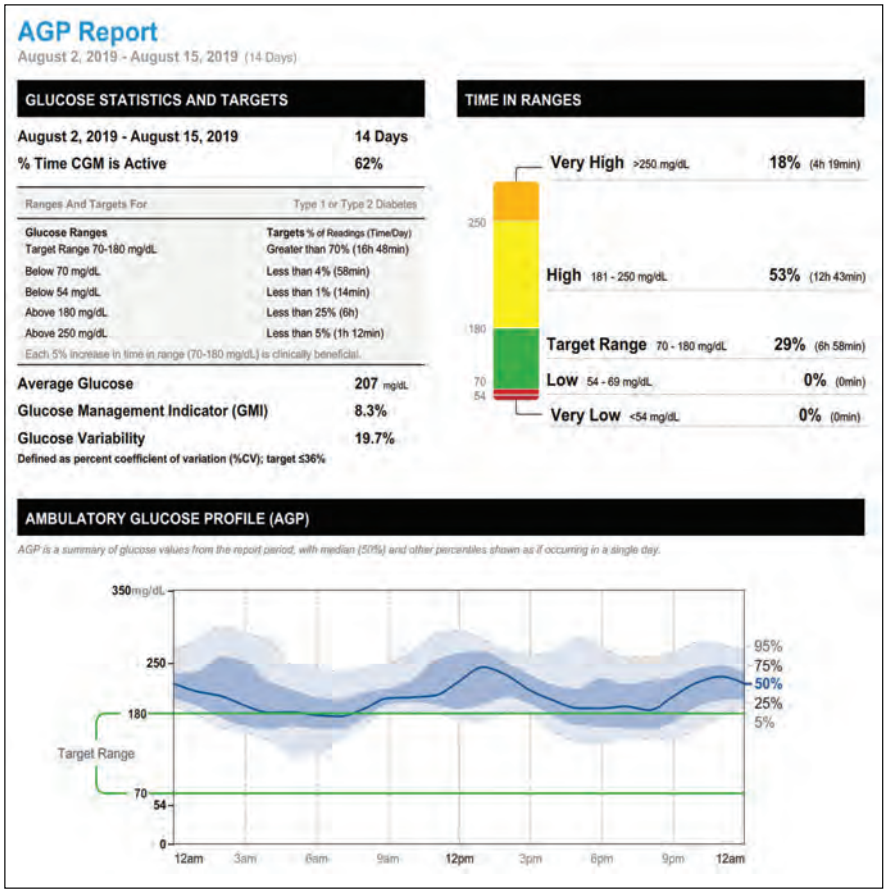


Discussion. The patient's GMI of 7.4%, average blood glucose of 172 mg/dL, and TIR of 56% all indicate suboptimal glycemic control. His glycemic variability of 27.9% is below the maximum of 36% that is recommended and reflects the fact that only 1% of his time is spent with hypoglycemia. To gain better glycemic control, a glucagon-like peptide-1 receptor agonist (GLP-1 RA) could be added with concomitant dose reduction of NPH to achieve blood glucose <140 mg/dL in the morning. A short-acting GLP-1 RA may be preferred, as it would target postprandial hyperglycemia, although this would add to treatment complexity. Asking the patient his preferences should be helpful.

CONT'D

CASE #4

- 43-year-old woman with T2D for 3 years
- Medical history:
  - Hypertension
  - Hyperlipidemia
  - Class 2 obesity (BMI, 35.4 kg/m^2)
- Current treatment:
  - Metformin 1000 mg twice daily (poor adherence)
- Personal CGM provided to increase patient engagement and create awareness of blood glucose values
- A1c 8.4% 2 months ago



Discussion. This patient has poor glycemic control, as demonstrated by her GMI of 8.3%, average blood glucose of 207 mg/dL, TIR of 29%, and 71% hyperglycemia. Her AGP reveals no hypoglycemia and low glycemic variability (19.7%). She reports that when using the CGM device, she is significantly more aware of the effect that food, stress, activities, and poor medication adherence have on her blood glucose levels. Personal CGM was prescribed because she expressed a desire to continue CGM monitoring, or, as she calls it, "her diabetes accountability partner." Upon questioning, the patient indicates that she has not taken metformin as prescribed because she often feels nauseous for a few hours after taking it. Consequently, metformin is discontinued and a long-acting GLP-1 RA is initiated. The long-acting GLP-1 RA will help lower her fasting blood glucose level and promote weight loss. At every visit, treatment adherence will be reinforced through patient education and patient concerns will be identified and worked through via shared decision-making. ●

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