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A SPECIAL SUPPLEMENT ON

HOT TOPICS in Primary Care 2022

Introduction

The scope of primary care is so large that it can create challenges trying to keep up with advances and "state-of-the-art" approaches to management. In an effort to address some of these issues, *Hot Topics in Primary Care 2022* includes topics that are important—and practice changing. Discussions of cardiovascular disease are featured in several articles, including ones that focus on reducing the risk of thrombotic disease in polyvascular disease, the role of eggs in a healthy diet, and issues related to atherosclerotic vascular disease in women and people with HIV. The increasing realization of the important role that primary care can play in addressing renal disease is addressed in 2 articles, including the role of SGLT-2 inhibitors and the management of anemia in chronic kidney disease. The recognition of the pandemic of opioid abuse is covered with practical suggestions about over-the-counter alternatives in pain management; recent developments in the treatment of adolescent and pre-adolescent acne is the focus of another article.

Primary care clinicians see an increasing number of patients with mild cognitive impairment and Alzheimer disease, so it is incumbent upon us to recognize and manage these conditions in order to help patients and their families. Chronic respiratory diseases are a frequent concern in our practices, and the articles on chronic obstructive pulmonary disease and asthma provide updated guideline-recommended treatment options, particularly strategies to maintain stable disease and prevent exacerbations. Diabetes remains a significant and increasing problem in our practices and society in general. Several articles provide insights to assist in the management of this disease: one article discusses how continuous glucose management can make us more effective in achieving glycemic goals, and another reviews the role of fixed-ratio combinations of insulin and GLP-1 agonists. The article on screening for type 1 diabetes mellitus provides insight into its emerging role in the diagnosis of the disease, and the article on the role of the microbiome addresses an issue that is becoming increasingly prominent and deserving of our attention. These articles all provide important information and strategies to assist in our management to improve overall patient outcomes.

If you can't decide which articles to read first, you may want to check out the short video segment for each article. The videos offer the opportunity to meet the author and learn the key takeaways from each article. They are a nice way to "thumb through" the supplement before reading the articles in detail.

As always, any comments you wish to make about the quality and relevance of the articles in this special issue will be greatly appreciated. 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

The Hot Topics in Primary Care 2022 supplement, including short videos about each article, can be found at **mdedge.com/familymedicine/HotTopics2022.**

Cover image: Roy Scott/ScienceSource

A Paradigm Shift for Asthma Care

Njira Lugogo, MD; Neil Skolnik, MD; and Yihui Jiang, DO

doi: 10.12788/jfp.0437

KEY TAKEAWAYS

- Asthma remains a substantial health burden, despite continued treatment advances.
- Patients with mild or moderate asthma, even those with intermittent symptoms, are at risk for severe or fatal exacerbations.
- Use of short-acting beta$_2$-agonist (SABA)-only rescue therapy is associated with an increased risk of exacerbations, beginning at about the second fill annually.
- Systemic corticosteroids have short-term and long-term adverse effects, and long-term adverse effects are driven by cumulative lifetime doses starting at 0.5 to 1.0 g.
- Expert opinion on the use of SABA only for rescue therapy differs, but recent evidence suggests that a fast-acting bronchodilator combined with inhaled corticosteroids (ICS) is more effective at reducing the risk of exacerbations than SABA alone.
- There is a window of opportunity just prior to an asthma exacerbation during which use of fast-acting bronchodilator + ICS may play a significant role in mitigating the risk of exacerbation.
- Patients may respond better to a combination inhaler of a fast-acting bronchodilator and an ICS as needed for rescue therapy or as part of a maintenance and rescue therapy paradigm, rather than attempting to use separate inhalers. However, there is currently no fixed-dose, fast-acting bronchodilator + ICS approved in the United States for as-needed use.

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DISCLOSURES

Dr. Lugogo serves on the advisory board for Amgen, AstraZeneca, Genentech, GSK, Novartis, Regeneron, Sanofi, and Teva and has received honoraria from AstraZeneca and GSK. Dr. Skolnik serves on the advisory board or as a consultant to AstraZeneca, Teva, Lilly, Boehringer Ingelheim, Sanofi, Sanofi Pasteur, GSK, Bayer, Abbott, and Genentech, and on the speakers bureau for AstraZeneca, Boehringer Ingelheim, Lilly, GSK, and Bayer. He also receives research support from Sanofi, AstraZeneca, Boehringer Ingelheim, GSK, Bayer, and Novo Nordisk. Dr. Jiang and Austin Ulrich, PharmD, have no disclosures to report.

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INTRODUCTION

CASE SCENARIO

A 33-year-old woman with asthma presents to her primary care practitioner (PCP) in November for a routine visit. She is currently treated as a patient with mild persistent asthma and is adherent to her inhaler regimen—low-dose inhaled corticosteroids (ICS) daily—with good inhaler technique. She notes that she's feeling great and has had no trouble with her breathing recently. Her Asthma Impairment and Risk Questionnaire (AIRQ) score today is 2 (steroids in the past 12 months and emergency room visit for breathing symptoms), indicating "not well-controlled" asthma. Upon further discussion, she adds that she gets "asthma attacks" when she exercises during allergy seasons (fall and spring) and so she always uses her albuterol inhaler before jogging (5 times/week) during these times of the year.

Despite substantial advances in asthma treatment and increased availability of therapies and guidance to manage disease, asthma remains a substantial public health burden.[1] As in the case scenario, patients with mild or moderate asthma with intermittent symptoms are still at risk for adverse outcomes.[2] Primary care providers (PCPs) are essential to the optimal care of patients with asthma, as approximately 60% of patients with mild or moderate asthma are cared for by PCPs.[1,3]

In the United States, an estimated 25.1 million individuals (7.8% of the population) were living with asthma

as of 2019.[4] Of those with asthma, about 41% experience at least 1 asthma attack per year; the total number of individuals in the United States reporting an asthma attack in 2019 was ~10.3 million.[4] Approximately 1.6 million emergency department visits and 178,000 hospitalizations per year are due to asthma, with 3524 deaths nationwide in 2019.[4] Additionally, more than 7.9 million school days and about 10.9 million work days are missed yearly due to asthma in the United States, as of 2018.[5]

Asthma is a chronic, heterogeneous respiratory disease affecting adults and children of all ages[6] that is characterized by airway inflammation and symptoms that include shortness of breath, wheeze, chest tightness, and cough.[6] Symptoms and severity can change over time, often based on triggering factors such as exposure to allergens or irritants, viral infections, weather change, and exercise.[6] Although symptoms may be episodic, resolving either spontaneously or with medication use, underlying chronic airway inflammation and hyperresponsiveness may persist and vary over time to increase the risk of exacerbations.[6]

Role of PCPs in asthma care

Most patients with asthma are managed by PCPs, while some patients with severe, persistently uncontrolled asthma or in whom the asthma diagnosis is unclear are referred for specialist care.[6–8] Although the majority of patients achieve successful asthma control in primary care, there are underrecognized symptoms and risk factors, such as multiple aeroallergen sensitivities in children as well as obesity and sinus disease in adults that increase the likelihood of severe adverse outcomes in those with mild or moderate asthma.[6–9]

UNMET ASTHMA NEEDS IN PRIMARY CARE

Uncontrolled asthma

Consensus guidelines for asthma address symptom management as well as ways to decrease the risk of future exacerbations. In addition, attention is paid to lung function impairment, loss of lung function over time, and adverse effects of therapies.[6,8,10,11] Uncontrolled asthma is associated with a lower quality of life, increased rate of exacerbations, and increased healthcare utilization when compared with controlled asthma.[12,13] Improving asthma control could potentially prevent over $900 billion in direct and indirect costs over 20 years.[14,15] The Centers for Disease Control and Prevention estimated the prevalence of uncontrolled asthma at about 60% for adults in 2016 and 50% for children from 2012 to 2014, based on definitions in the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report (EPR) 3 Guidelines.[10,16,17]

In a study using a national claims database of about 4.5 million patients with asthma, 3.2% were found to have severe uncontrolled asthma as defined by maintenance treatment with medium- to high-dose ICS/long-acting beta-agonist (LABA) and ≥2 claims for systemic corticosteroids (SCS) within a 12-month period.[18] Another analysis using the same database defined uncontrolled asthma as ≥3 short-acting beta$_2$-agonist (SABA) prescription fills or ≥2 SCS claims in 12 months. In this analysis, 7% of patients with severe asthma had uncontrolled disease, and 30% of patients with mild or moderate asthma had uncontrolled disease.[19]

These recent estimates reflect that the number of patients with mild or moderate asthma who are uncontrolled is about 4 times the number of patients with severe asthma who are uncontrolled (**FIGURE 1**).[18,19] Overall, approximately 81% of patients who are uncontrolled have mild or moderate asthma and 19% have severe asthma.[18] Historically, a major focus of asthma care has been on patients with severe uncontrolled asthma, but this only represents about 3% of all patients with asthma, and targeted therapies are available to treat these patients.[18,20]

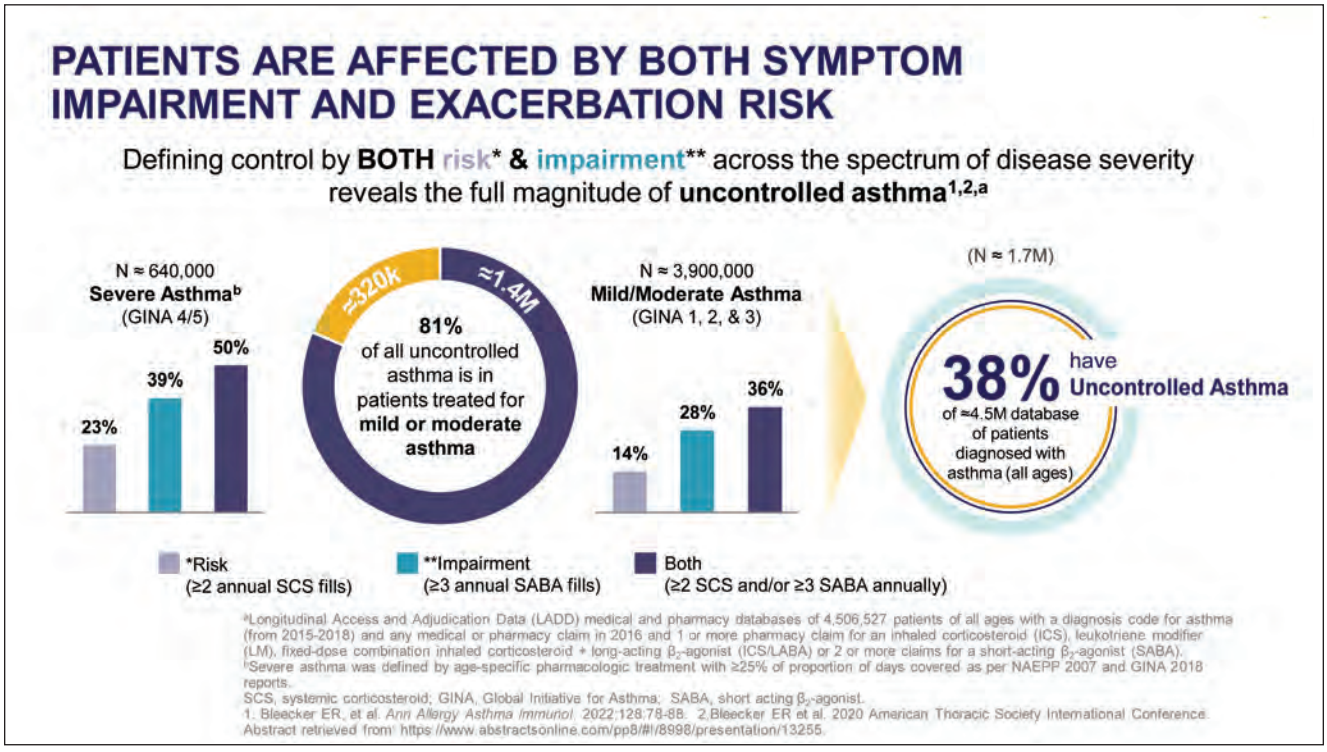
A significant challenge remains how to address patients with mild or moderate asthma who are at risk for exacerbations. It can often be difficult to identify patients with uncontrolled mild or moderate asthma due to the seasonal or intermittent nature of exacerbations; during an appointment patients may not discuss exacerbations if they are feeling well, and clinicians may think that the patient's asthma is controlled if a rescue inhaler is filled only 1 or 2 times during the prior year. To improve detection of uncontrolled mild or moderate asthma, clinicians can raise patients' awareness of what constitutes lack of control and may choose to assess asthma control and future risk of exacerbations using validated tools (see *Assessment of Asthma Control and Risk of Exacerbations* section below).[6,8]

Overuse of SCS

Use of SCS is associated with acute, as well as long-term, adverse effects. Adults aged 18 to 64 years, who received SCS for <30 days, demonstrated an increase in sepsis, venous thromboembolism, and fracture within 30 days of drug initiation.[21]

Long-term adverse effects of SCS begin to occur at approximately 0.5 g of prednisone or equivalent cumulative lifetime dose, with a clear threshold of a 1 g prednisone or equivalent cumulative dose increasing the risk of comorbidities.[22] An increased risk of osteoporosis, cataracts, pneumonia, cardiovascular diseases, cerebrovascular disease, sleep apnea, kidney impairment, depression/anxiety, type 2 diabetes, and weight gain have been associated with higher

FIGURE 1. **Percentages of patients with mild or moderate uncontrolled asthma vs severe uncontrolled asthma**



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cumulative SCS doses (**FIGURE 2**).[22] The median time period for observation and cumulative SCS dose observed was 7.4 years for the SCS group, indicating that long-term adverse effects can result from additive cumulative SCS exposure over at least 7 consecutive years.[22]

A common regimen for exacerbations is prednisone 40 to 60 mg for 5 to 10 days, for a cumulative dose of approximately 300 mg of prednisone per exacerbation. This means that patients may approach the risk threshold for long-term side effects after receiving only 2 to 3 steroid bursts.[6,10] Despite the risks of SCS, these treatments are indicated in some patients; for example, in those with severely uncontrolled asthma or in those who are experiencing an acute asthma exacerbation.[6,8]

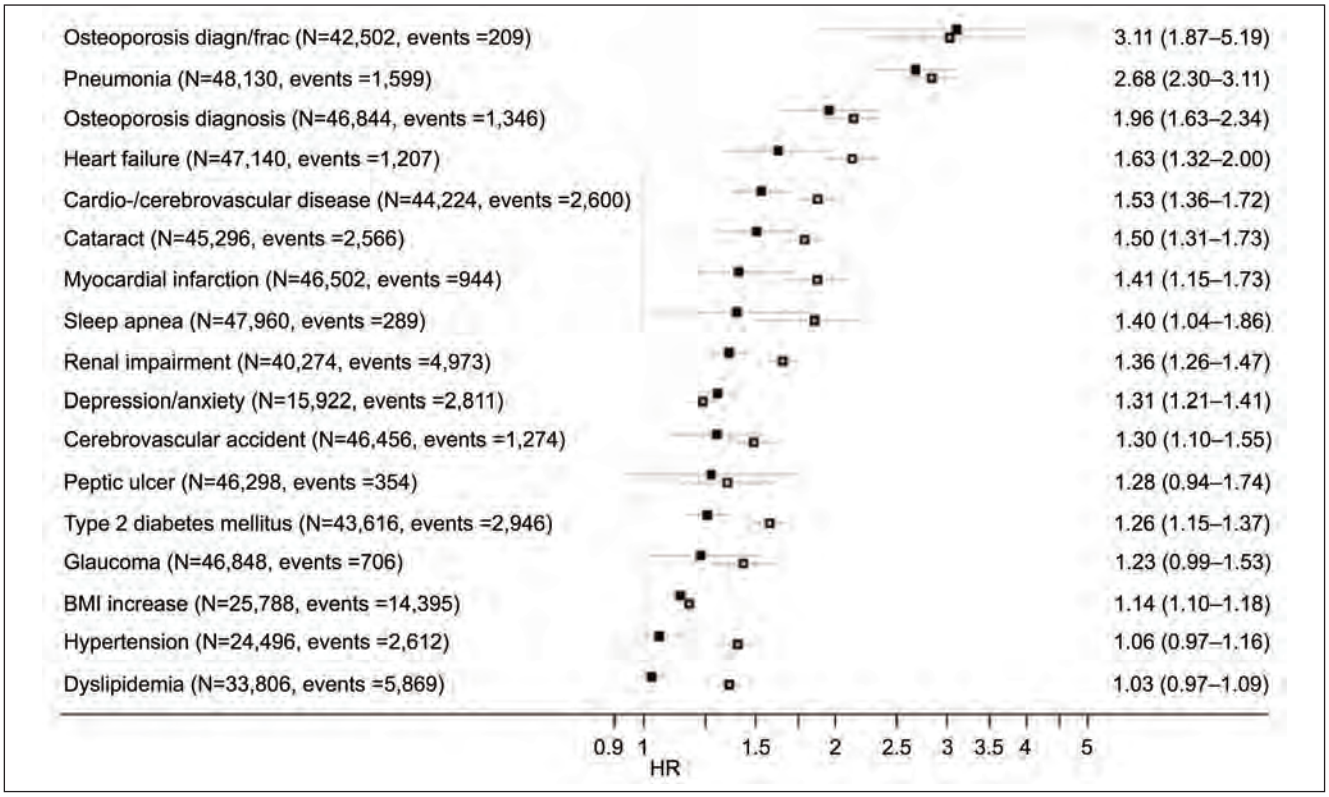
Use of SABA

Increasing SABA use is associated with an increased risk of exacerbations. A recent study demonstrated an increased risk of exacerbation associated with increasing SABA fills beginning at about the second fill, based on claims data for 135,540 patients who filled at least 1 prescription for a SABA inhaler over a 12-month period.[23] Regardless of disease severity and maintenance medication adherence, severe exacerbations occurred across cohorts, and mean SABA fills were greater for those who had exacerbations vs those who did not and for those who experienced multiple exacerbations vs those who experienced only 1 exacerbation. Moreover, as annual SABA fills increased, so did high-cost healthcare resource utilization such as emergency department and unscheduled outpatient visits and inpatient hospitalizations for asthma (**FIGURE 3**).[23]

Proposed mechanisms for increased exacerbation risk with regular or frequent use of SABA include downregulation of beta-receptors, rebound hyperresponsiveness, decreased bronchoprotection, decreased bronchodilator response, increased allergic response, and increased eosinophilic airway inflammation.[24,25] The Global Initiative for Asthma (GINA) expert report emphasizes that the risk of severe exacerbations is increased from use of SABA without concomitant ICS. SABA-only use can increase airway hyperresponsiveness and inflammation, increase exercise-induced bronchoconstriction, and reduce bronchodilator response.[6]

The International Asthma Patient Insight Research (INSPIRE) study surveyed 3415 adults with asthma being treated with ICS or ICS + LABA as maintenance therapy in 11 countries about their asthma control, medication use, and

FIGURE 2. **Hazard ratios for long-term adverse outcomes from SCS use compared with no SCS use in asthma**



Abbreviations: BMI, body mass index; HR, hazard ratio.

HR (95%) confidence interval (CI) for each adverse outcome for the SCS group vs the no SCS group.

The open squares represent unadjusted results and the closed squares, adjusted results. The adjusted HRs (95% CIs) are shown on the right.

Source: Price et al. *J Asthma Allergy*. 2018;11:193-204. Originally published by and used with permission from Dove Medical Press Ltd.[22]

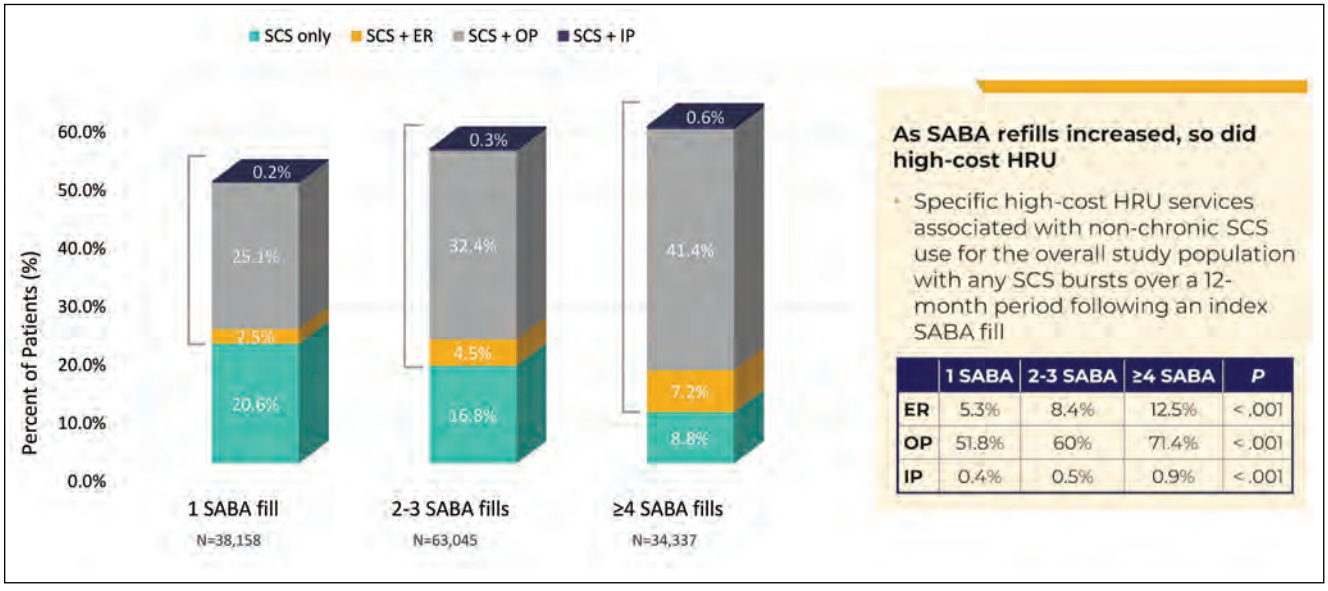
ability to recognize and self-manage worsening asthma.[26] About 74% of these patients used SABA daily despite being prescribed maintenance therapy; 38% believed there was no need to take medication daily when they felt well, and 90% of patients wanted treatments that work quickly.[26] Additionally, 51% were classified as having uncontrolled asthma based on the Asthma Control Questionnaire (ACQ).[26]

Patients often self-manage worsening asthma symptoms by increasing SABA use, aiming for immediate rescue. However, concomitant use of an as-needed fast-acting bronchodilator and ICS can both provide rapid relief and address the variability of the underlying inflammation.[27] Combination inhalers containing ICS + a fast-acting bronchodilator as maintenance and rescue therapy are more effective than higher doses of maintenance ICS and LABA.[27] This is why some have suggested using ICS alongside a fast-acting bronchodilator for treatment of escalating or increasing asthma symptoms.[27]

Budesonide-formoterol is an ICS + long-acting (and fast-acting) bronchodilator combination inhaler, and it has been studied for use as rescue and rescue and maintenance therapy for mild, moderate, and severe asthma.[28-35] Results of studies in patients aged ≥12 years showed budesonide-formoterol as rescue and as rescue and maintenance therapy reduced ICS exposure, resulted in better symptom control, and improved lung function.[28, 30-35] Collectively, trials demonstrate reductions in asthma exacerbations when budesonide-formoterol is used as needed for symptoms compared with as-needed SABA alone across all asthma severity treatment steps.[28-35] However, inhaled budesonide-formoterol in the fixed-dose combination device used in these studies is not approved and not available for rescue therapy or for maintenance and rescue therapy in the United States.

Based on US drug labeling, there is also no currently approved formulation of ICS + SABA for rescue therapy in

FIGURE 3. **Annual healthcare resource utilization associated with patients with ≥1 SCS burst**



	1 SABA	2-3 SABA	≥4 SABA	*P*
ER	5.3%	8.4%	12.5%	<.001
OP	51.8%	60%	71.4%	<.001
IP	0.4%	0.5%	0.9%	<.001

Abbreviations: ER, emergency room; HRU, healthcare resource utilization; IP, inpatient visit (hospitalization); OP, outpatient visit.

Left: Of patients in the study population, percentage of patients in each SABA fill group with ≥1 exacerbation over a 12-month period. Right: HRU assessed only for patients in the study population with ICS exposures.

Source: Adapted from Lugogo et al. *Ann Allergy Asthma Immunol*. 2021;126(6):681-689.e1. Adaptation used with permission from AstraZeneca.

asthma in the United States. Patients can take ICS + SABA for rescue therapy in separate inhalers, based on US drug labeling, but this is not common in current practice and is cumbersome for patients because it would require the use of two inhalers each time a rescue dose is needed.

Use of as-needed ICS alongside a SABA can reduce exacerbations compared with SABA use alone. In the Person Empowered Asthma Relief (PREPARE) trial, adults with moderate-to-severe asthma were assigned randomly to patient-activated ICS along with SABA for rescue therapy and their usual maintenance therapy or SABA for rescue therapy and their usual maintenance therapy.[36] Patients who were instructed to take ICS every time they used rescue therapy had a lower annualized rate of severe exacerbations than the comparator group (0.69 vs 0.82, HR 0.85; 95% CI 0.72 to 0.999; *P* = .048). Patients in the intervention group also had better asthma control and fewer missed days of work, school, and usual activities than the comparator group.[36]

Three phase 3 trials looking at the efficacy and safety of a fixed-dose combination of a SABA and an ICS in a pressurized metered dose inhaler (albuterol-budesonide) have been completed.[37-40] The combination of albuterol and budesonide has been shown to protect against exercise-induced asthma in adolescents and adults with mild asthma compared with placebo.[40] This combination also results in better lung function compared with the individual components alone in patients with mild-to-moderate asthma.[37]

The MANDALA phase 3 randomized study evaluated the efficacy and safety of an albuterol-budesonide fixed-dose combination inhaler as rescue therapy compared with albuterol alone in 3132 patients with moderate-to-severe uncontrolled asthma. In adolescent and adult patients, the fixed-dose combination of albuterol 180 µg and budesonide 160 µg used for symptoms on top of the routine maintenance therapy demonstrated a 27% reduction in the risk of severe asthma exacerbations in a time-to-event analysis (HR, 0.73; 95% CI, 0.61 to 0.88; pre-planned efficacy analysis) compared with as-needed albuterol 180 µg.[38,39,41] Additionally, the fixed dose combination compared to albuterol alone (pre-planned efficacy analysis) demonstrated the following:

- Decrease in the annualized rate of severe asthma exacerbations (0.45 vs 0.59; rate ratio, 0.76; 95% CI 0.62 to 0.93)
- Lower mean annualized total dose of SCS (86.2 ± 262.9 mg prednisone equivalents versus 129.3 ± 657.2 mg)
- Improvement in asthma control, measured by a 24-week response on the Asthma Control Questionnaire-5 (ACQ-5; decrease of at least 0.5 points from baseline score; 66.8% vs 62.1% ; OR 1.22; 95% CI, 1.02 to 1.47)
- Improved asthma-related quality of life, as accessed

by the Asthma Quality of Life Questionnaire at week 24 (AQLQ+12, validated for persons ≥12 years of age; increase of at least 0.5 points from baseline; 51.1% vs 46.4%; OR, 1.23; 95% CI, 1.02 to 1.48).

While expert opinion differs regarding the use of SABA alone for rescue treatment in asthma, an increasing body of evidence supports administration of as-needed anti-inflammatory therapy with SABA for symptoms and to prevent exacerbations.[6,23]

MANAGING ASTHMA IN PRIMARY CARE

Use of single maintenance and reliever therapy has been recognized for years as an important part of asthma care globally.[6,8] Now, a paradigm shift in asthma care is slowly emerging for patients with asthma of mild-to-moderate severity due to the recognition that a significant proportion of asthma exacerbations occur in these patients. The shift will continue as clinicians recognize the consequences of SCS overuse and carefully consider whether rescue therapy should include an ICS, rather than SABA alone.

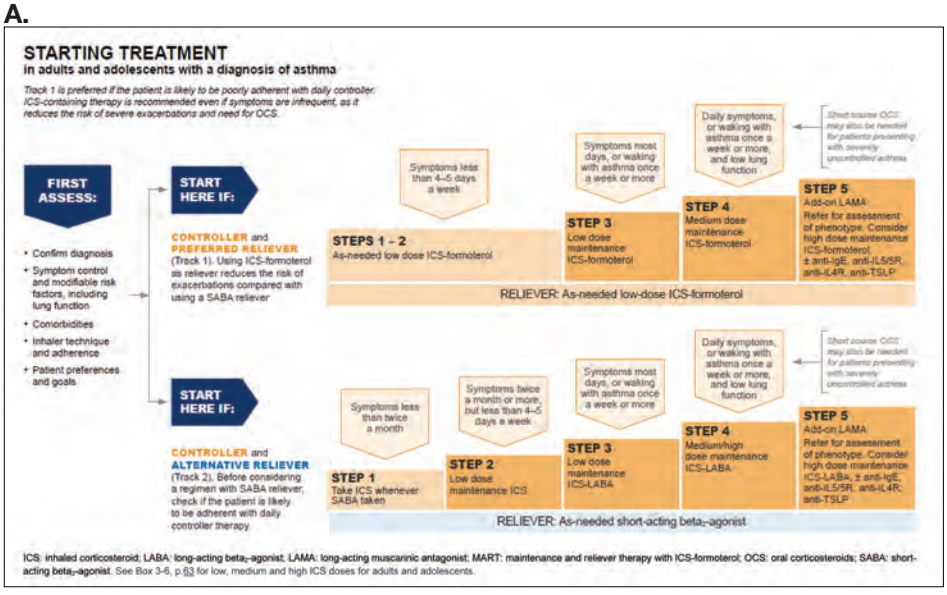
Asthma expert reports and guidelines

The most recent expert asthma reports and guideline updates are from GINA (2022) and the NAEPP (2020), respectively. The NAEPP 2020 is a focused update of the NAEPP EPR-3 guidelines (2007).[6,8,10,11]

Initial therapy. The GINA report recommends 1 of 2 "tracks" based on patient char-

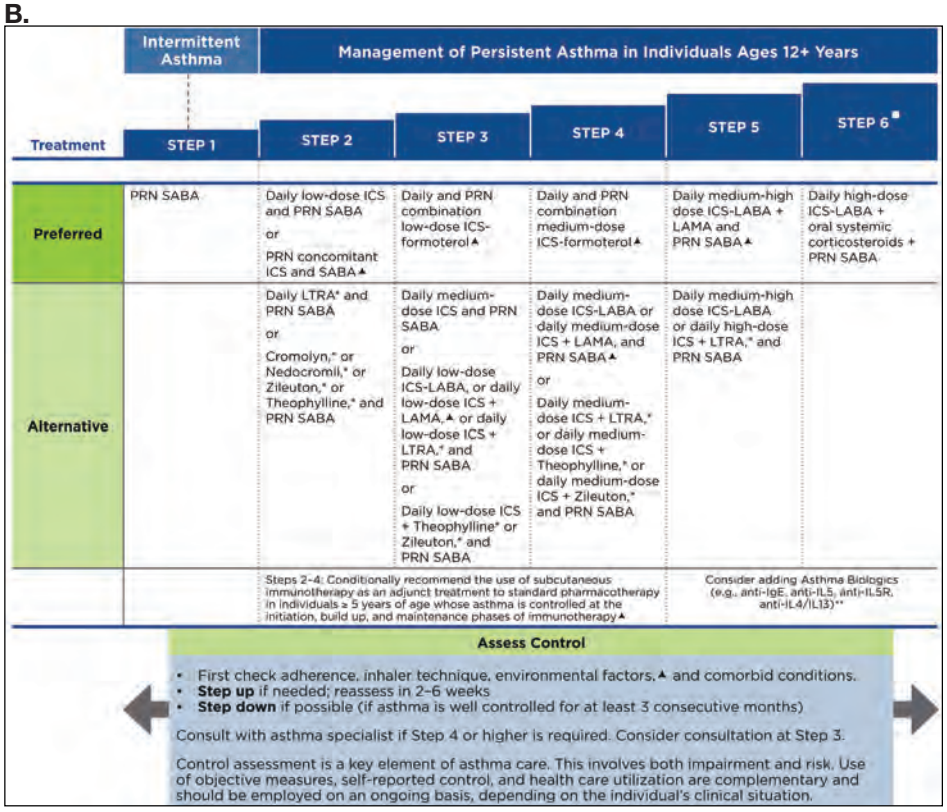
FIGURE 4. **Selecting initial controller treatment in patients aged 12 and older, according to (A) GINA reports and (B) NAEPP guidelines**

A.



Source: From GINA ©2022 Global Initiative for Asthma, reprinted with permission. Available from www.ginasthma.org.

B.



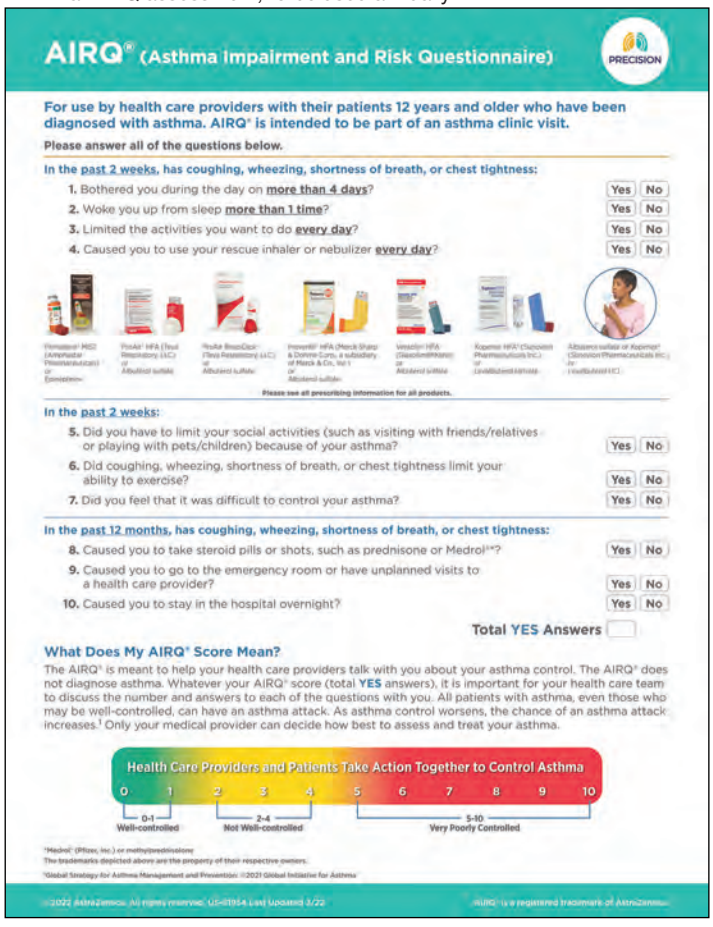
Abbreviations: LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MART, maintenance and reliever therapy with ICS-formoterol; OCS, oral corticosteroids; PRN, as needed.

Note: The use of ICS-formoterol is not approved for rescue therapy or for maintenance and rescue therapy in the United States. The recommendations for ICS-formoterol are based on clinical data evaluating the use of ICS-formoterol formulations and strengths not approved and not available in the United States.

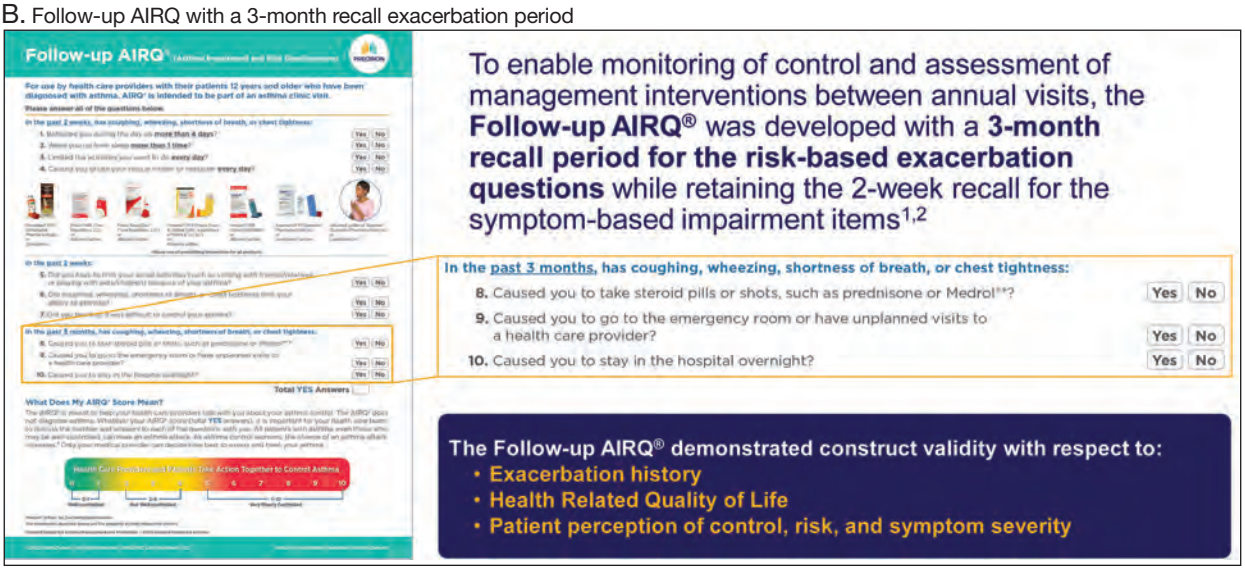
Source: Republished with permission of Elsevier, from 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group, Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier et al. 2020;146(6):1217-1270. Permission conveyed through Copyright Clearance Center, Inc.

FIGURE 5. **The Asthma Impairment and Risk Questionnaire (AIRQ)**

A. Initial AIRQ assessment, to be used annually



B. Follow-up AIRQ with a 3-month recall exacerbation period



acteristics including symptom control, adherence, and preferences and goals (**FIGURE 4**).[6] Selecting initial therapy is based on assessment of asthma severity and implementation of the corresponding level of step therapy (**FIGURE 4**).[10]

Assessment of asthma control and risk of exacerbations. Determining the degree of asthma control is essential for the ongoing management of asthma to optimize medication therapy and achieve treatment goals.[6,10] According to GINA, asthma symptom control "should be assessed at every opportunity," and NAEPP recommends periodic assessments at 1- to 6-month intervals as well as "ongoing monitoring" of asthma control.[6,10] Both expert reports acknowledge the utility of questionnaires and assessment tools to evaluate asthma control, although both also suggest a set of questions to assess control. Available asthma assessment tools include the following:

- Asthma Control Test (ACT): Scores range from 5 to 25, with higher scores indicating better control.[42] A score of 20 to 25 indicates well-controlled asthma, and the maximum clinically important difference is 3 points.[43]
- Asthma Therapy Assessment Questionnaire (ATAQ): This is a 4-question assessment, with scores ranging from 0 to 4; a higher score indicates worse asthma control.[44]
- Asthma Control Questionnaire (ACQ): This assessment includes 5 symptom questions, with SABA rescue use included in ACQ-6 and pre-bronchodilator forced expiratory volume in

1 second (FEV_1) included in ACQ-7.[6,45] Scores range from 0 to 6, with higher scores indicating worse asthma control; the total score is an average of individual items.[6]

- AIRQ: The AIRQ is a validated assessment developed in recent years to incorporate both impairment and risk assessment, the 2 key domains of asthma control (**FIGURE 5**).[46] The 7 symptom impairment questions reflect a 2-week recall period, and the 3 risk questions assess exacerbations over the prior 12 months. Scores range from 0 to 10, with a score of 0 to 1 indicating well-controlled asthma and higher scores representing worsening asthma control.[46] AIRQ control level has been found to predict risk of future exacerbations over the following 12 months.[47] Between annual visits, a follow-up version of AIRQ using the same 10 items, but with exacerbation questions having a 3-month recall period, can be used to assess disease stability and the impact of management interventions.[48]

Step therapy. Both GINA and NAEPP recommend a stepwise approach to intensifying therapy in asthma based on control.[6,8] The primary difference is that in GINA, there is a clear indication that a rescue bronchodilator should always be used with ICS for all patients aged ≥12 years, whether as formoterol + ICS or by taking ICS with each dose of SABA.[6]

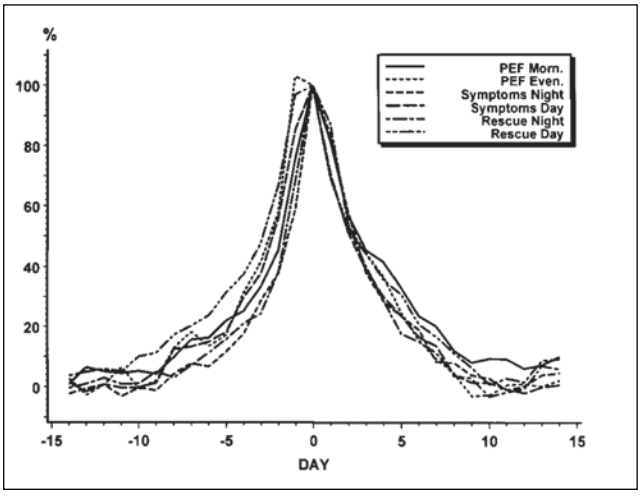
PREVENTING EXACERBATIONS: THE WINDOW OF OPPORTUNITY

Preventing exacerbations is important to decrease emergency department visits, hospitalizations, and mortality as well as for improvement in quality of life. Regular use of ICS as controller therapy leads to decreases in exacerbations, hospitalizations, and mortality, even at low doses, and the benefits of regular ICS as controller therapy are evident across asthma severity levels.[49,50] When a fast-acting bronchodilator + ICS as rescue is added to maintenance therapy, further reductions in exacerbations and improvements in asthma control and health-related quality of life have been found compared with maintenance therapy with a SABA as rescue.[30,36,41,50] Evidence is accumulating to suggest that there may be a "window of opportunity" that exists prior to an asthma exacerbation during which rescue therapy that includes ICS may prevent progression to a more severe exacerbation.[36,41,51]

Time window prior to exacerbation

Approximately 10 to 14 days prior to an exacerbation, peak expiratory flow begins to decrease, and there is an increase in symptoms and SABA utilization (**FIGURE 6**).[52-54] During this time, rising inflammation underlies the decrease in lung function that results in airway symptoms and need for SABA.[25,52] Although SABA use can bring symptomatic relief, it does not address flare-ups in airway inflammation.[25,52] This timeframe leading up to an exacerbation may represent a "window of opportunity" during which intervention with anti-inflammatory therapy can be implemented. If recognized early, prompt treatment might mitigate the rise in airway inflammation and prevent or reduce exacerbations.

FIGURE 6. **Changes in peak expiratory flow, daytime and nighttime symptoms, and rescue inhaler use during an asthma exacerbation**



Abbreviation: PEF, peak expiratory flow.

Data are standardized (Day 14 = 0%, maximum change = 100%) to allow comparison of changes with time between different endpoints. Due to the data standardization, PEF curves demonstrate an inverse relationship on the graph, where 0% indicates baseline PEF and 100% indicates worst PEF during an exacerbation. Day 0 indicates the point of exacerbation.

Source: Tattersfield AE, et al. *Am J Respir Crit Care Med*. 1999;160(2):594-599. Used with permission.

The role of ICS

Traditional teaching is that the anti-inflammatory effects of ICS take days to occur. More recent evidence supports a more rapid onset of action. ICS exert nongenomic and genomic effects that are complementary mechanisms that reduce inflammation and so may decrease the likelihood of an asthma exacerbation.[55,56] Nongenomic effects of corticosteroids have a rapid (seconds to minutes) onset of action and include decreased airway mucosal blood flow and airway edema, immune cell activity modulation, and potentiation of bronchodilator effects.[55,56] Genomic effects of corticosteroids have a delayed (4 to 24 hours) onset of action, and these effects cause increased transcription

of anti-inflammatory genes and decreased transcription of inflammatory genes.[56] Additionally, ICS decreases pro-inflammatory markers, which may offset the increase in proinflammatory markers that occurs with bronchodilators.[57,58]

Clinical evidence for ICS + fast-acting bronchodilators

The rationale for recommending a combination of ICS and fast-acting bronchodilators in the GINA expert reports is based on the increased risk of severe or fatal exacerbations as SABA is increasingly used alone, as well as evidence showing a decrease in exacerbation frequency with ICS + formoterol as controller and rescue therapy.[6,28–33,59] Several studies now provide data supporting benefits of as-needed ICS + SABA, either as a fixed-dose combination or delivered by 2 separate inhalation devices.[27,36,59,60] Thus, this indicates a clinical need for an approved ICS + SABA combination inhaler in the United States.

THE ROLE OF SHARED DECISION-MAKING AND PATIENT VOICE IN ASTHMA CARE

Incorporating patient preferences into clinical decisions is recommended for optimal asthma care.[6,10] As the focus on reducing exacerbation risk increases in patients with mild or moderate uncontrolled asthma through ICS use with rescue therapy, proper education and communication is needed to help patients understand the change in approach.

The results of the INSPIRE study highlight the tendency of patients to want treatment that seems to provide immediate relief, as well as to downplay the need for daily maintenance inhalers. The use of as-needed ICS + a fast-acting bronchodilator rescue therapy fits established patient preferences.

Revisiting the patient case scenario presented previously, the PCP might discuss with the patient how to recognize and treat pre-exacerbation symptoms due to seasonal triggers, such as rising inflammation that narrows the airways and produces shortness of breath or wheezing. The PCP could also review with the patient how to monitor her asthma with a peak flow meter as part of an asthma action plan. The action plan could also include a follow-up plan for when to speak with the PCP to optimize treatment based on clinical evidence and the patient's preferences.

SUMMARY

A large unmet need currently exists in asthma care, with over 60% of patients having uncontrolled asthma and 40% having ≥1 asthma exacerbations per year. The need for better care is not just for patients with severe asthma, as 30% to 40% of asthma exacerbations that lead to emergency care occur in patients with mild asthma. Reliance on SABA for symptom relief without using an ICS to treat underlying inflammation is associated with an increased risk of exacerbations. Adverse effects of SCS occur at much lower cumulative doses than are generally appreciated, with 500 to 1000 mg of prednisone or equivalent cumulative dose increasing the risk of comorbidities including osteoporosis, cataracts, pneumonia, and type 2 diabetes. Asthma exacerbations and need for SCS may be decreased by the use of ICS as a component of rescue therapy whenever SABA is needed. ●

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Common Questions on Continuous Glucose Monitoring in Primary Care

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Identify patients who are good candidates for a continuous glucose monitor (CGM) vs fingerstick self-monitoring of blood glucose (SMBG)
- Discuss the information provided by CGM systems
- Generate and interpret patient CGM data using the ambulatory glucose profile (AGP) to assess time targets established by the International Consensus on Time in Range
- Modify the treatment plan based on CGM data to improve patient outcomes

KEY TAKEAWAYS

- CGM overcomes some of the limitations of glycated hemoglobin and fingerstick SMBG.
- The standardized AGP and time in range (TIR) have been established to serve as an actionable format for presenting and interpreting CGM data.
- For most healthy adults with type 1 (T1D) or type 2 diabetes (T2D), the desired target for TIR (70-180 mg/dL) 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 the benefits of CGM and AGP are not limited to individuals using insulin.
- The AGP provides an excellent opportunity for shared decision-making and increased patient engagement.

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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RESOURCE TOOLKIT

WHAT IS CONTINUOUS GLUCOSE MONITORING AND WHICH PATIENTS WILL BENEFIT FROM ITS USE?

Continuous glucose monitoring (CGM) is a method of measuring glucose by means of a small medical device that measures interstitial glucose continuously over time, unlike fingerstick self-monitoring, which only provides the blood glucose at the time of the testing by measuring capillary plasma glucose concentrations.[1] The venous or capillary glycated hemoglobin level (A1c) shows an aggregate measure of blood glucose levels over a period of approximately 3 months.[2] Real-time CGM shows how various activities (like eating or exercise) impact glucose over time, and allows the patient and the clinician to see treatment issues not otherwise revealed by either fingerstick testing or A1c, such as glycemic variability.

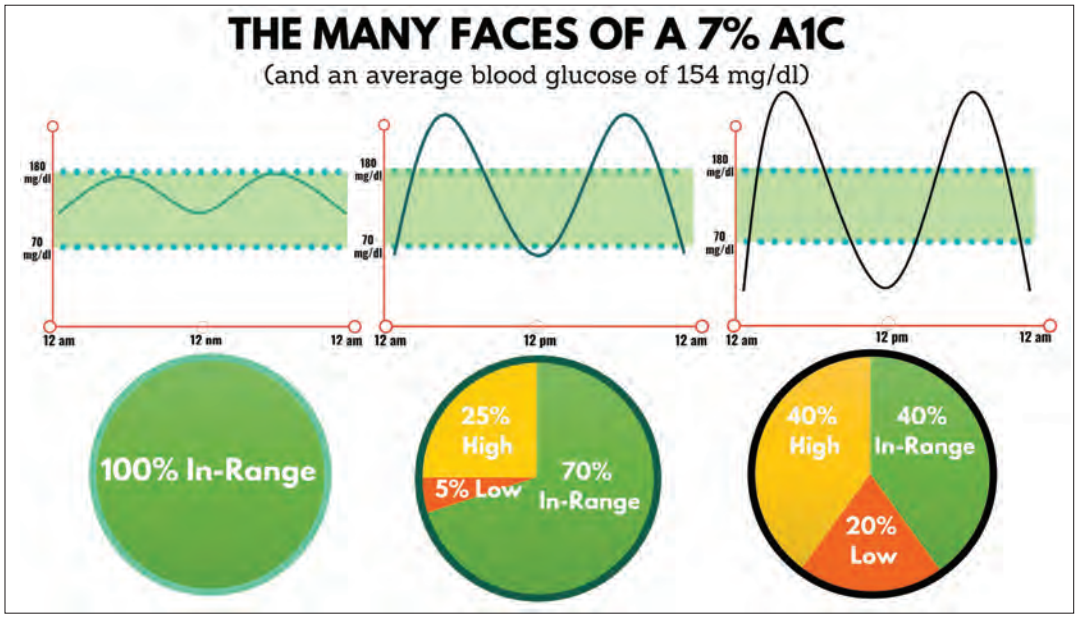
The limitations of the A1c are readily apparent. Because it is an aggregate measure, a patient with a constant glucose value of 154 mg/dL (no glycemic variability) is likely to have the same A1c result as a patient with glucose values of 64 mg/dL half of the time, and 244 mg/dL the other half of the time: 7.0%. In this hypothetical situation, one of these patients is well controlled and the other is not, although their A1c results may be precisely the same (**FIGURE 1**).

CGM offers a host of real-world benefits, including improved glycemic control. The control of 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 disease, as demonstrated in clinical studies.[3-10] CGM is recommended by the American Diabetes Association for individuals with diabetes who are receiving multiple daily injections, continuous subcutaneous insulin infusions, and other forms of insulin therapy.[11] Other candidates for CGM include individuals who are not at goal and those with frequent hypoglycemia or hypoglycemia unawareness, taking other medications that cause low blood glucose, with kidney disease, and with varying and/or intensive activity, as well as those who have a desire to improve glycemic control and are willing and able to use CGM.[12-14] Key benefits of CGM use include early warnings of high, low, and/or rapidly changing glucose levels, and CGM clearly shows the results of patient actions and subsequent consequences. This author does not feel there are any poor candidates for CGM as all people with diabetes could benefit on some level from the data and insight it provides. CGM use must take into consideration the cost/benefit ratio, which may vary between individuals as to the frequency of use, professional or personal CGM device used, and objectives for use (eg, modification of treatment intervention, determination of the impact that diet and activities of daily living are having on glycemia, identification of glucose variability, or prevention of hypoglycemic events). Additional background information about CGM may be found at https://pro.aace.com/pdfs/diabetes/AACE-DRC-CGM-Slides.pdf.[15]

WHAT ARE THE AVAILABLE US FOOD AND DRUG ADMINISTRATION (FDA)–APPROVED OPTIONS FOR CGM?

There are currently 5 CGM devices approved for use in the United States (**TABLE 1**). Clinicians should be aware that, for their patients on an insulin pump, some of these devices may offer pump integration.

FIGURE 1. **Examples of a 7.0% A1c**



Source: The diaTribe Foundation. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. 2021. https://diatribe.org/foundation/beyonda1c. Copyright and all rights reserved. Used with the permission of the diaTribe Foundation.

TABLE 1. **FDA-approved CGM devices**

	Abbott FreeStyle Libre 14-Day	Abbott FreeStyle Libre 2 (FreeStyle Libre 3 recently received FDA approval)	Dexcom G6 (G7 awaiting FDA approval)	Medtronic Guardian Sensor 3 (pump integrated) and Guardian Connect (stand-alone)	Senseonics Eversense (subcutaneous insertion by clinician)
Approved labeling	Replaces fingersticks for treatment decisions; no fingerstick calibration required	Replaces fingersticks for treatment decisions; no fingerstick calibration required	Replaces fingersticks for treatment decisions; no fingerstick calibration required	Requires ≥2 fingerstick calibrations/d	Replaces fingersticks for treatment decisions; requires ≥2 fingerstick calibrations/d
Age	≥18 y	≥4 y	≥2 y	≥14 y	≥18 y
Medicare coverage	Yes	Yes	Yes	Sensor 3: Yes Connect: No	Yes
Wear length	14 d	14 d	10 d	7 d	180 d
Warmup	1 h	1 h	2 h	2 h	24 h after insertion
Alarms for lows, highs	No	Yes	Yes	Yes	Yes
Data display	Reader; Andriod, iPhone app	Reader; Android, iPhone app	Reader; Android, iPhone app; smartwatches; Tandem pump	Android, iPhone app; 630G, 670G or 770G pump; Guardian Connect	Android, iPhone app
Form	Disposable transmitter integrated with sensor patch	Disposable transmitter integrated with sensor patch	Transmitter (3-month use) separate from sensor	Transmitter (rechargeable) separate from sensor	Transmitter (rechargeable) separate from sensor

HOW DO I ACCESS THE CGM DATA?

The ambulatory glucose profile (AGP) is produced by a software application that aggregates CGM data to characterize glycemic exposure, variability, and stability, overlaying all data from the survey period as if it were a single day. While every AGP has a similar format, every brand of CGM offers a different mechanism for accessing the data (**TABLE 2**).

ONCE I HAVE THE AGP, HOW DO I USE THE DATA TO INTERVENE CLINICALLY?

An adequate time period is needed for pattern recognition. The time period covered by the AGP is determined by the user, and the length allowed varies by 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.[15] For individuals with greater glycemic variability, exhibited by wide fluctuations or variability in the glucose level (eg, coefficient of variation ≥36%), longer CGM collection periods may be required.

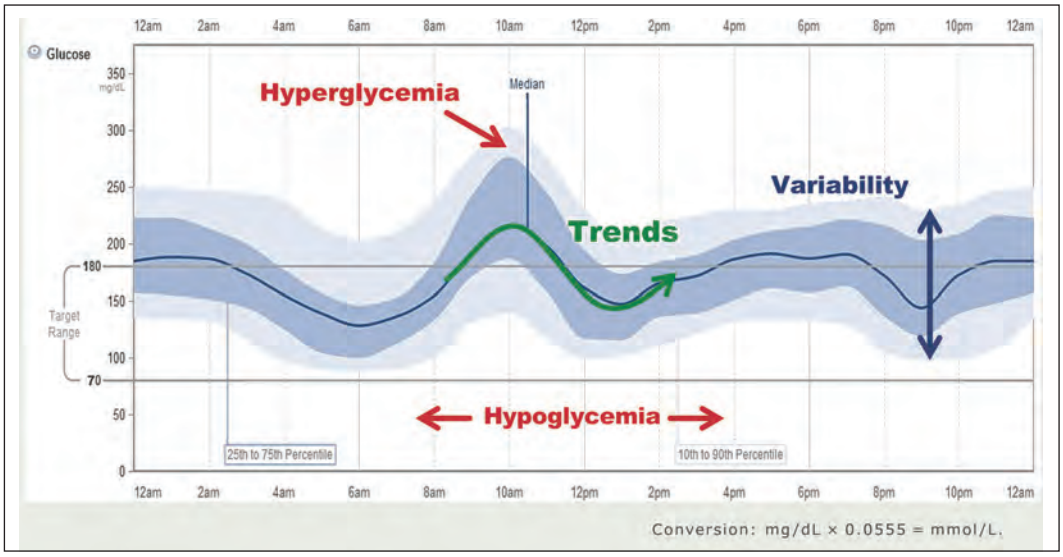
For ease of interpretation, the AGP is presented visually as a modal day plot according to time as if the data points collected over 7, 10, or 14 days occurred over 24 hours

TABLE 2. **Accessing CGM data**

Device	URL	Details
Abbott FreeStyle Libre	https://www.freestyleprovider.abbott/	LibreView or FreeStyle Libre Pro
Dexcom G6	https://provider.dexcom.com/products	Dexcom Clarity for Professional Data Analysis
Medtronic Guardian Sensor 3	https://www.medtronic.com/us-en/healthcare-professionals/products/diabetes/data-management-software/carelink.html	Carelink
Senseonics Eversense	https://www.ascensiadiabetes.com/eversense/hcp/	Eversense Data Management System (DMS) Pro

(**FIGURE 2**). The AGP includes 3 key CGM measurements: time within target range (TIR), time above target range (TAR), and time below target range (**FIGURE 3**).[16] Other helpful metrics include the average glucose, which is used to calculate the glucose management indicator (GMI), an approximate A1c if levels remained here for 2 to 3 months.

FIGURE 2. **Ambulatory glucose profile**



Increasing TIR is the primary goal, with the added benefit of reducing glycemic variability, and, particularly, hypoglycemia. 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.[14] It is recommended that pregnant woman should aim for a TIR of >70% (16 h, 48 m) and a TAR of <25% (6 h), from as early as possible during the pregnancy for optimal neonatal outcomes.[17] Glycemic targets differ in pregnancy compared to the general population.

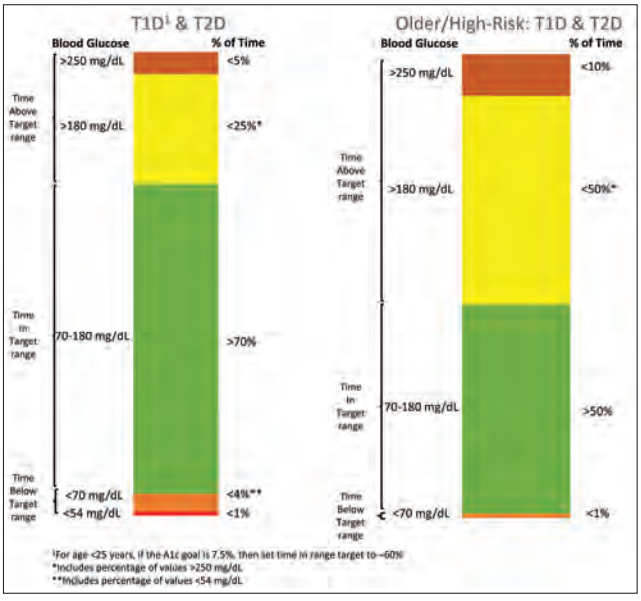
Interpreting the AGP provides an opportunity for shared decision-making and collaborating with the patient to identify situations where the glucose level is and is not well controlled. Discussion may then focus on reinforcing behaviors contributing to good glycemic control, as well as overcoming challenges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

CASE STUDY

- 77-year-old male with T2D (11 years)
- History of hypertension, hyperlipidemia, high blood pressure (now controlled), and coronary artery disease
- A1c = 7.8%
- Current Medications:
  - Metformin extended-release tablets (500 mg), 2 in AM
  - Losartan 50 mg daily
  - Atorvastatin 40 mg daily
  - Amlodipine 10 mg daily
  - Clopidogrel 75 mg daily
  - Lantus 12 units in the PM and 10 units in the AM

Sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists have been suggested but were declined due to cost. Patient tests his glucose once per day

FIGURE 3. **CGM targets for different populations with diabetes[16]**



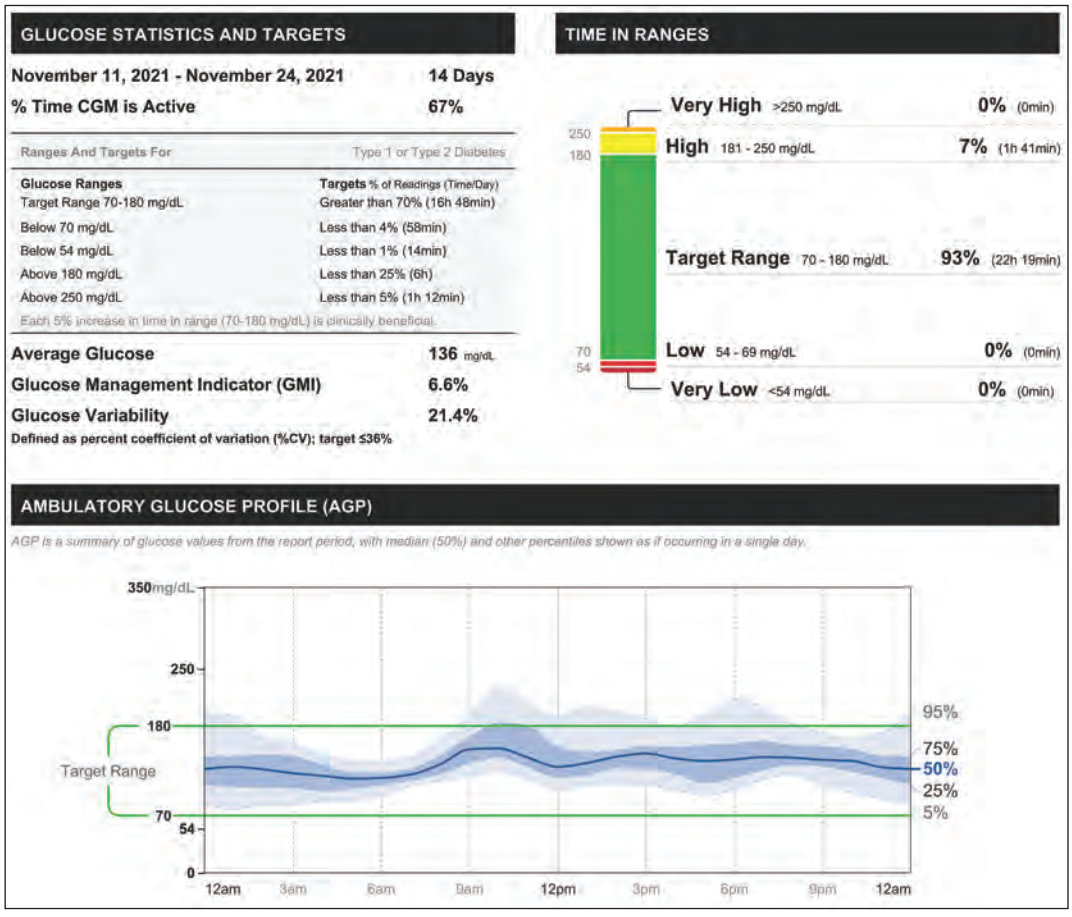
Source: American Diabetes Association. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. 2019. Copyright and all rights reserved. Material from this publication has been used with the permission of the American Diabetes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

in the morning and he notes high blood glucose readings and great variability.

The patient agreed to wear a CGM for 2 weeks and was provided instruction on keeping a meal and activity log. He was also asked not to split the dose of his long-acting insulin, but rather to take it one time per day as approved, starting with 25 units in the evening and adding 1 unit every day until his fasting morning glucose falls below 140 mg/dL.

In the follow-up appointment, the patient was asked what he had learned from the experience of wearing a CGM for 2 weeks. He indicated that logging his diet, activity, sleep, and stress level combined with the real-time glucose data the CGM provided offered enormous insight into the impact his activities had on his overall glycemic control. He changed his breakfast from oatmeal to egg whites and sauteed vegetables. He up-titrated his insulin to achieve his target fasting blood sugar of <140 mg/dL, and within a week's time was able to be consistently at target (with 28 units). He realized that he was not experiencing any hypoglycemic episodes and noted that exercising in the afternoon helped maintain his control through dinner. He chuckled over the impact that some Thanksgiving cheesecake had on his numbers. He asked to continue using a CGM. If he maintains the excellent control he achieved with his CGM, the GMI shown on his AGP suggests that his next A1c would likely be about 6.6% (**FIGURE 4**).

FIGURE 4: **Case study**



WHAT ARE THE KEY ELEMENTS TO OBTAINING MEDICARE, MEDICAID, AND PRIVATE INSURANCE COVERAGE?

Medicare coverage criteria for CGM were updated in 2021 to eliminate extensive blood glucose log data, making obtaining coverage less daunting.[18] The prescribing clinician must provide supporting clinical indications for CGM. Coverage can be expected if the patient is insulin-treated with ≥3 daily injections of insulin or is using a pump, and the patient's insulin treatment regimen requires frequent adjustments on the basis of glucose readings. In addition, the patient must have been seen by the clinician within 6 months of the order to evaluate diabetes mellitus (DM) control and determine that the above criteria are met. Following the initial prescription, the patient must have in-person visits with the clinician every 6 months to assess adherence to the CGM regimen and the DM treatment plan. The CGM must be ordered through durable medical equipment (DME), not the pharmacy.

Medicaid coverage varies from state to state, and states with expanded Medicaid usually offer more coverage options. Information for each state's Medicaid program can be found at the diatribechange.org website: https://bit.ly/3okAdUg. What is covered, who is covered, and at what cost also varies among private insurance policies. Patients with T1D and those with T2D who are on an insulin regimen are likely to

TABLE 3. **Codes for billing for CGM**

Code	Description
95249	Personal CGM – Startup/Training: Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; patient-provided equipment, sensor placement, hook-up, calibration of monitor, patient training and printout of recording. (Do not report more than once while patient owns device.)
95250	Professional CGM – Ambulatory continuous glucose monitoring of interstitial fluid via a subcutaneous sensor for a minimum of 72 hours; clinician-provided equipment, sensor placement, hook-up, calibration of monitor, patient training removal of sensor, and printout of recording. (Do not report more than once per month.)
95251	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; interpretation and report. (Do not report more than once per month.)
99212-99215	Evaluation and Management (E/M) Codes: Established Patient Visit or G0463 (Medicare Outpatient Clinic Visits).
0446T, 0447T, and 0448T	Eversense codes only: for insertion (including system activation and patient training) and removal of implantable interstitial glucose sensor. (Do not report any in conjunction with others of this set of codes; do not report 0446T in conjunction with 95251.)

have coverage. Detailed patient notes, describing the reasons CGM is needed, are helpful. Shared decision-making should also play a role here, with the patient able to take the lead and determine which CGM options are available by way of their insurance coverage.

In a recent comparison of retail costs, Abbott's FreeStyle Libre had the lowest monthly cost, followed by Medtronic, Dexcom, and Eversense.[19] Patient out-of-pocket costs will vary based on numerous factors, including location, discounts, insurance coverage, changing price structures, and manufacturing coupons and incentives at the time of purchase.

HOW DO I DOCUMENT AND BILL FOR CGM?

Relevant billing codes cover all FDA-approved CGM devices (**TABLE 3**). There are additional Senseonic Eversense-specific codes for the insertion and removal of the unique implantable subcutaneous CGM.

SUMMARY

CGM is an important tool for improving care of patients with T1D and T2D. AGP data create the opportunity for more informed clinical decisions and empower the patient to understand the impact of their actions on their glucose more clearly and address issues of glycemic variability. Gaining coverage for CGM is easier now than it has been in the past and is likely to become easier still in the future. CGM is quickly emerging as a standard of care for many patients with diabetes.[20] ●

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Detecting and Managing ASCVD in Women: A Focus on Statins

Pam Kushner, MD

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LEARNING OBJECTIVES

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

- Summarize important findings and trends involving women and atherosclerotic cardiovascular disease (ASCVD).
- Characterize the multiple cardiometabolic changes that occur during menopause and the associated ASCVD risk.
- Discuss the challenges of assessing ASCVD risk and dyslipidemia management in women.
- Identify women with elevated ASCVD risk and implement guideline-recommended statin therapy.

KEY TAKEAWAYS

- ASCVD remains the leading cause of death among women, with a stagnation in downward ASCVD trends noted over the past decade.[1]
- ASCVD has traditionally been viewed as a "male disease," with research gaps in our knowledge of ASCVD in women resulting in underdiagnosis and undertreatment.[1]
- Risk stratification in primary prevention in women is more challenging than in men because of unique risk factors and underestimation of ASCVD risk with 10-year risk scoring.[1-4]
- No clinically relevant differences appear between sexes regarding safety, efficacy, and outcomes with statin therapy.[1,3]
- Guideline-recommended therapy to manage low-density lipoprotein cholesterol (LDL-C) in women is similar to that for men, but consideration of sex-specific risk factors and common risk-enhancing factors, to better inform risk, is imperative.[3-5]

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CASE SCENARIO

A 52-year-old white female with a history of gestational diabetes mellitus (GDM), fibromyalgia, post-traumatic stress disorder, and major depression presents to the clinic. Her lipid panel has previously been unremarkable with low-density lipoprotein cholesterol (LDL-C) levels of <100 mg/dL, but since menopause she has gained 30 pounds and "lacks the energy to exercise." To better risk stratify and due to premature cardiovascular (CV) events in both parents, a coronary artery calcium (CAC) scan is performed.

Key information

- **Cholesterol (mg/dL):** total cholesterol 215, LDL-C 135, high-density lipoprotein cholesterol (HDL-C) 57, triglycerides 115, non-HDL-C 158
- Blood pressure 116/72 mm Hg, glycated hemoglobin (HbA1c) 6.2%, C-reactive protein (CRP) 4.5 mg/L (<3 mg/L)
- Body mass index 26.8 kg/m^2, negative for tobacco or alcohol use
- **Current medications:** gabapentin, tramadol, estradiol patch, fluoxetine
- American College of Cardiology (ACC)/American Heart Association (AHA) 10-year atherosclerotic cardiovascular disease (ASCVD) risk=1.3%
- CAC score=73 (>90th percentile for age)

INTRODUCTION

Despite manifesting approximately 10 years later in women than in men, ASCVD remains the leading cause of mortality among women.[1,6] As a relative comparison, ASCVD accounts for 35% of all deaths, compared to 2.6% for breast cancer,[7] with ischemic heart disease and stroke being the most common subtypes of ASCVD.[1] Although ASCVD usually manifests later in women, one-third of CV events occur among those <65 years of age.[6]

Currently, ASCVD in women is understudied, underdiagnosed, and undertreated. The traditional view of ASCVD as primarily a "disease of men" has led to decades of poor representation of women in ASCVD research, including clinical trials.[1] As a result, there is now a limited understanding of sex differences (eg, in mechanisms and pathophysiology), ultimately resulting in higher rates of hospitalizations and mortality among women compared to men.[1,2,8] Overall, ASCVD mortality has dropped markedly since the 1970s in both sexes.[6] However, among women, ASCVD mortality has stagnated over the past decade and is even increasing in certain populations, including younger women.[9,10] A major

concern is whether these disturbing trends will continue to uptick due to the rise in obesity and diabetes mellitus (DM) and the frequent utilization of e-cigarettes (ie, vaping) among young females.[1] These statistics prompted the formation of multiple initiatives to better understand and prevent ASCVD in women. Such programs include a state-of-the art review on women and ASCVD from the ACC's CVD in Women Committee,[11] the "Follow YOUR Heart" campaign to empower older women with human immunodeficiency virus (HIV) to participate in ASCVD research,[12] and formation of the *Lancet* women and cardiovascular disease Commission.[1] Collectively, these initiatives focus on the unmet need to reduce the global burden of ASCVD among women.[1] The existing knowledge gaps, sex-specific differences, and trends present concerns and unique challenges for practitioners.

The goal of this article is to provide a guide for primary care clinicians to identify women at elevated ASCVD risk, with an end goal of reducing CV events and mortality with appropriate statin therapy.

DYSLIPIDEMIA ACROSS THE FEMALE LIFESPAN

Premenopausal women typically have favorable lipid profiles compared to men. Overall values of major lipoproteins including total cholesterol and LDL-C are usually lower, while HDL-C levels are ~10 mg/dL higher.[13] However, menopause is a transitional period that often results in multiple negative metabolic changes that increase ASCVD risk. For example, a sharp increase in LDL-C levels coupled with a shift to the more atherogenic small, dense LDL-C results in an increase in LDL particle number.[14,15] Other ASVCD risk factors often worsen or manifest during menopause, including weight gain, usually involving a pattern of central obesity, hypertension, and metabolic syndrome.[2] The utilization of estrogen replacement therapy reverses some of the lipoprotein changes and is unique in that it is one of only a few treatments effective at lowering lipoprotein(a).[3] Nonetheless, randomized controlled trials involving hormone replacement therapy (HRT) have not confirmed CV benefit,[1] and a major study demonstrated a small but significant increase in ASCVD.[16] Accordingly, HRT is not indicated for primary or secondary prevention of ASCVD and should be discontinued among women with existing ASCVD.[1,5]

OUTCOME DATA—AVAILABLE EVIDENCE IN WOMEN

Early cardiovascular outcome trials (CVOTs) failed to enroll a substantial proportion of women, resulting in underrepresentation[1] and the inability to demonstrate sex-specific benefits. This fueled the idea that statins do not reduce CV events when used in primary prevention among women. Presently, a host of outcome data are available that are specific to women.[3,5,15] Numerous analyses indicate that women experience similar LDL-C reductions with statin therapy to those of men.[2,17] More importantly, a 2013 Cochrane analysis reported that statins reduce ASCVD, total mortality, and the need for revascularization in primary prevention among women, similar to their male counterparts.[18] These findings are further supported by the more comprehensive 2015 Cholesterol Treatment Trialists' Collaboration, which involved nearly 50,000 women.[17] This meta-analysis evaluated statin vs placebo and more intensive compared to less intensive statin therapy among primary and secondary prevention patients. Overall, the investigators concluded that for every 1-mmol/L (39-mg/dL) reduction in LDL-C, proportional reductions in major adverse cardiovascular events and total mortality, and occurrence of adverse events (AEs), did not differ by sex.

In summary, despite early CVOT shortcomings, current data indicate that no clinically relevant differences exist between sexes regarding safety, efficacy, and outcomes with statin therapy.

CLINICAL ASSESSMENT AND CHALLENGES

In the clinical world, statins are underutilized and underdosed in women, creating disparities in the quality of CV care.[1] This is supported by findings indicating that women are less often treated with guideline-recommended therapies, including statins.[19,20] These differences may be explained by challenges with ASCVD risk estimation, including assessment models that underestimate ASCVD risk in women.[21,22] For example, risk stratification is arguably more complicated in females because of unique and sex-specific risk factors. These factors are not incorporated in common risk assessment models such as the Framingham Risk Score, resulting in ASCVD underestimation by the assessment tool, and possibly the clinician.

Major CV risk factors are critical for risk stratification in women (**TABLE 1**).[1,2,23-26] Importantly, hypertension, dyslipidemia, DM, and smoking are all associated with higher CV event rates in women compared to men.[1,2] Similarly, obesity and insufficient physical activity are more prevalent among women,[1] making them more likely to develop metabolic syndrome. A history of sex-specific factors associated with elevated ASCVD risk, including premature menopause or pregnancy-related complications, further confounds risk assessment. In addition, underrecognized CV risk factors or risk-enhancing factors may disproportionately affect women. Inflammatory-driven autoimmune disorders, such as rheumatoid arthritis and systemic lupus erythemato-

TABLE 1. **ASCVD risk factors in women**[1-3,23-26]

Category	Risk factor	Comments
Traditional	• Hypertension • Dyslipidemia • DM • Smoking	• Major risk factors all associated with increased CV event rates compared to men; DM also associated with higher mortality • The prevalence of smoking, including e-cigs, is high among young women
Risk-enhancing[a]	• Autoimmune disorders (RA, SLE) • Increased systemic inflammation • Race/ethnicity (eg, South Asian) • Elevated lipoprotein(a) • Chronic kidney disease • Family history of premature ASCVD • Metabolic syndrome • Human immunodeficiency virus	• Females account for nearly 80% of all autoimmune disorders • Chronic inflammation = increased ASCVD
Sex-specific	• Premature menopause (<40 years old) • Preeclampsia or preterm labor • Gestational DM • Low-birthweight infant	• Premature menopause and preeclampsia are also classified as "risk-enhancing" factors
Underrecognized	• Psychosocial - Mood disorders, stress • Environmental/social factors	• Women have increased rates of depression, anxiety, and perceived stress and are more likely to be victims of abuse and intimate partner violence • ASCVD risk and mortality are inversely related to socioeconomic status

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DM, diabetes mellitus; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

[a]Defined as a clinical condition or factor that is associated with ASCVD used to inform therapy decisions.

sus, have demonstrated accelerated atherosclerosis and increased ASCVD risk,[3,5,27] while several psychosocial and environmental factors linked to ASCVD are more common among women.[1] A key message to emphasize among primary care clinicians is to utilize other tools when ASCVD risk is uncertain. Imaging modalities such as measuring carotid intima media thickness or, more commonly, CAC can provide substantial insight (eg, visualization of atherosclerosis) for risk stratification to further guide treatment.[3,5]

Sex differences also exist regarding medication adherence and AEs. Women are more likely to be nonadherent with statin therapy while experiencing higher rates of medication-related side effects.[2,28] Statin-associated myalgia (SAM) is the most commonly reported AE,[3,5] and the agents have also demonstrated a negative impact on energy and fatigue.[29] Factors that may influence predisposition to SAMs or other side effects compared to men include females having more concern regarding drug-related AEs,[28] potentially higher susceptibility to statin-associated fatigue and reduced energy,[2] and also a higher prevalence of hypothyroidism, in which the associated muscle symptoms may be misinterpreted as SAMs.[30] Another important factor to consider when prescribing drug therapy to women for managing dyslipidemia is childbearing potential. Recently, the Food and Drug Administration has softened the language surrounding statins and pregnancy.[31] In essence, statins should generally be avoided during pregnancy, unless the patient is

TABLE 2. **2018 ACC/AHA Guideline on the Management of Cholesterol (women)**[3]

Risk category	Recommendations
Clinical ASCVD or FH (LDL-C of ≥190 mg/dL)	• High-intensity statin ± ezetimibe to achieve LDL-C reduction of ≥50% • LDL-C goals (*ideal*) - (+) ASCVD: <70 mg/dL - (+) FH: <100 mg/dL
DM (40-75 years old)	• Moderate-intensity statin *regardless* of 10-year ASCVD risk • If DM + multiple risk factors: high-intensity statin to achieve LDL-C reduction of ≥50%
Primary prevention (40-75 years old)	*Most challenging group for risk estimation/stratification* • Use 10-year ASCVD risk calculator (*often underestimated in women*) - 5% to 7.5%: *consider* moderate-intensity statin - 7.5% to <20%: *favors* moderate-intensity statin - ≥20%: *initiate* statin to reduce LDL-C ≥50% • Factor in ASCVD risk enhancers* (*to better inform risk*) - Specific to women: preeclampsia, premature menopause - Family history of premature ASCVD, inflammatory diseases, CKD, HIV, metabolic syndrome, certain race/ethnicity (eg, South Asian) • If risk decision is uncertain: consider CAC in certain adults - CAC 0: statin *not indicated* unless: (+) tobacco, (+) DM, or strong family history of premature ASCVD - CAC 1 to 99: *favors* statin - CAC ≥100 and/or 75th percentile: *initiate* statin
TLCs including smoking cessation, moderate-intensity physical activity, and achieving and maintaining desired body weight are considered initial treatment for *all* women with dyslipidemia.	

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CKD, chronic kidney disease; DM, diabetes mellitus; FH, familial hypercholesterolemia; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; TLC, therapeutic lifestyle change.

*Defined as a clinical condition or factor that is associated with ASCVD used to inform therapy decisions.

at very high risk for ASCVD (eg, previous CV event). The agency also communicated that statins are safe in women who are not pregnant but could become pregnant, noting that unintended exposure to statins during early pregnancy is unlikely to harm the fetus. Breastfeeding is not recommended while on statin therapy.

GUIDELINE-RECOMMENDED THERAPY

Early detection and management of dyslipidemia and other common cardiometabolic comorbidities is critical for preventing premature CV events and mortality in women.[1] An initial emphasis on therapeutic lifestyle changes (TLCs) is recommended for all women with dyslipidemia, regardless of ASCVD risk category.[3,5] Women are more prone to physical inactivity compared to men,[1] and TLCs can address many of the common cardiometabolic conditions strongly associated with menopause. Implementing components of the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets along with 150 minutes of physical activity per week can provide moderate improvements in numerous CV markers and reduce overall ASCVD risk.[3,5]

Major cholesterol guidelines recommend similar approaches to managing dyslipidemia regardless of sex.[3,5] **TABLE 2** provides treatment recommendations from the 2018

ACC/AHA Guideline on the Management of Blood Cholesterol, with recommendations specific to women incorporated.[3] Major risk categories include those with clinical ASCVD or familial hypercholesterolemia (FH), adults with DM, and—the most challenging to risk stratify—primary prevention. The importance of treating women with a history of ASCVD with high-intensity statin therapy is widely recognized.[3,5] The inherent ASCVD risk associated with FH and DM and the benefit of statin treatment are also established.[3,5] Particularly challenging is identifying female patients who fall outside these categories and have unremarkable 10-year ASCVD risk scores. Tools available to improve risk stratification and guide therapy include utilizing risk-enhancing factors to better inform ASCVD risk and measuring CAC to visualize atherosclerosis in this population.[3]

CASE SCENARIO (CONT'D)

This case illustrates the numerous cardiometabolic changes (eg, weight gain, elevation in LDL-C, prediabetes) that can occur with menopause. It shows how sex-specific and underrecognized risk factors and risk-enhancing factors (eg, GDM, psychosocial stressors, family history of premature ASCVD) can contribute to atherosclerosis and ASCVD risk. The 10-year ASCVD risk score fails to capture her actual CV risk, as the elevated CAC indicates significant subclinical atherosclerosis and elevated risk for a CV event.[3,5] Guideline recommendations would include aggressive TLCs to improve lipoproteins and limit additional weight gain and the development of type 2 DM. Moderate- to high-intensity statin therapy should be strongly considered given her risk factors and evidence of subclinical disease.

SUMMARY

ASCVD remains the primary cause of death among women. Additional concern stems from disturbing trends displaying a plateau in mortality and even an increase in CV events among younger women. These factors prompted the formation of multiple initiatives aimed at reducing ASCVD in women. Statins are the drugs of choice for managing LDL-C in women because data indicate that the agents are safe, effective, and reduce vascular events and mortality, similar to the agents' effect in men. Clinicians must be cognizant of the unique and sex-specific risk factors in women and the numerous negative cardiometabolic effects that manifest or worsen with menopause. Such awareness will identify women with elevated ASCVD risk, resulting in enhanced lipid management and, ultimately, reductions in premature CV morbidity and mortality.

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Improving Detection and Management of Anemia in CKD

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

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

- **Describe** approaches to improve recognition of chronic kidney disease (CKD) and anemia in primary care.
- **Explain** the importance of early management of anemia in CKD to reduce adverse outcomes and improve symptoms.
- **Prescribe** evidence-based treatment for patients with anemia in CKD who can be managed in the primary care setting.
- **Discuss** emerging evidence for new agents being studied for treating anemia in CKD.

KEY TAKEAWAYS

- Test hemoglobin (Hb) at least once a year, or more frequently if needed, in patients with CKD to screen for anemia.
- Test Hb at least every 3 months, or more frequently if needed, in patients with CKD and anemia not being treated with an erythropoiesis-stimulating agent (ESA).
- Initial treatment of anemia in CKD can be with oral or intravenous iron if iron deficiency is present; ESAs can be used if the response is inadequate or if Hb remains <10 g/dL.
- Deciding on treatment with ESAs requires balancing risks such as cardiovascular events, and benefits, which include improved symptoms and reduced blood transfusion risk.
- Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) are a novel, investigational class of drugs that increase production of erythropoietin and improve iron utilization.

TARGET AUDIENCE

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

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INTRODUCTION

Anemia in patients with chronic kidney disease (CKD) is primarily a result of decreased secretion of erythropoietin (EPO).[1] As CKD progresses, anemia is more likely to occur; based on data from the National Health and Nutrition Examination Survey (NHANES) 2007-2010, anemia is least common in stage 1 CKD and most common in stage 5 CKD (**FIGURE 1**).[2] Patients with CKD and anemia have a reduced quality of life due to symptoms such as fatigue and reduced exercise capacity. Anemia in CKD is also marked by increased ventricular mass and a higher incidence of heart failure and myocardial infarction.[3] Identifying anemia in primary care is crucial because primary care practitioners (PCPs) are often the first to encounter this condition and can intervene early.

Despite the prevalence of anemia in CKD, it tends to be underrecognized in clinical settings due to its often asymptomatic presentation and attention directed toward other comorbidities in CKD.[4,5] PCPs may be hesitant to manage anemia in patients with CKD and may refer to nephrology, sometimes unnecessarily.[4,5] As PCPs are more aware of this condition and recommended management, they can help detect and treat anemia earlier.

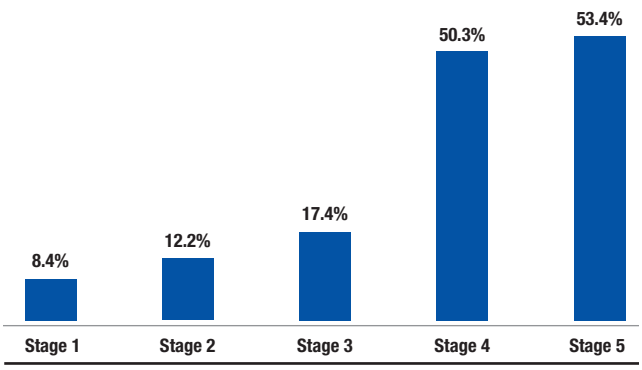
CASE SCENARIO

A 57-year-old man with a history of hypertension, hyperlipidemia, hypothyroidism, and CKD presents to his PCP for an annual office visit. He has not had lab work for the past 6 months. His hemoglobin (Hb) is 9.9 g/dL today, down from 12.2 g/dL 6 months ago. His estimated glomerular filtration rate is 51 mL/min/m^2 today, worsened from 59 mL/min/m^2 6 months ago. He is managed appropriately for his other conditions, and he notes that he takes aspirin 81 mg daily.

IDENTIFICATION OF ANEMIA IN CKD

In this case scenario, the patient can be diagnosed with anemia based on his Hb level and is likely indicated for treatment. Guidelines from Kidney Disease Improving Global Outcomes (KDIGO) represent the current standard of care for identifying and treating anemia in CKD in the United States.[6] However, since the publication of this guideline in 2012, more data are available to help guide clinicians in managing anemia in CKD; some experts have suggested a guideline update is underway and may be published in the near future.[7] Guidelines for anemia in CKD used globally include those from the National Institute for Health and Care Excellence (NICE), as well as those from The Renal Association.[8,9]

FIGURE 1. **Proportion of patients with anemia by CKD stage[2]**



Source: Data from the National Health and Nutrition Examination Survey (NHANES) 2007-2010.

TESTING AND DIAGNOSIS

For patients without anemia, KDIGO recommends testing Hb at specific frequencies depending on the patient population and clinical conditions[6]:

- For CKD patients without anemia, measure Hb:
  - At least annually if stage 3 CKD or higher
  - At least twice per year if stage 4-5 CKD
  - At least every 3 months if on dialysis
- For patients with CKD and anemia not being treated with an erythropoiesis-stimulating agent (ESA):
  - At least every 3 months if stage 3-5 CKD
  - At least monthly if receiving hemodialysis

Diagnosis of anemia occurs at certain Hb thresholds[6]:

- Diagnose in adults and children >15 years with CKD when Hb is <13.0 g/dL (males) and <12.0 g/dL (females)
- Diagnose anemia in children with CKD if Hb concentration is <11.0 g/dL (0.5-5 years), <11.5 g/dL (5-12 years), and <12.0 g/dL (12-15 years)

Furthermore, KDIGO recommends including other laboratory tests for initial evaluation of anemia: complete blood count, absolute reticulocyte count, serum ferritin level, serum transferrin saturation (TSAT), serum vitamin B_{12}, and folate.

MANAGING ANEMIA IN CKD

After establishing a diagnosis of anemia, the next step is to rule out contributing causes. Treatment of anemia in CKD can be accomplished with iron replacement, ESAs, and/or red blood cell (RBC) transfusion.[6] In selecting a treatment for anemia, clinicians should consider the severity of anemia, iron test results, Hb levels, and the patient's symptoms. For all treatments, the risks and benefits to patients should be

TABLE. **Available ESAs and initial dosing**[12,13,15,20]

Drug	Brand name	Approval date	Initial dosing
Epoetin alfa	Epogen/Procrit	6/1/1989	50-100 units/kg IV or SC 3 times a week
	Retacrit	5/18/2018	
Darbepoetin alfa	Aranesp	9/17/2001	0.45-0.75 mg/kg IV or SC every 1-4 weeks, depending on CKD status
Methoxy polyethylene glycol-epoetin beta	MIRCERA	11/15/2007	0.6 mg/kg IV or SC every 2 weeks

Abbreviations: ESA, erythropoiesis-stimulating agents; SC, subcutaneous.

considered, and generally the lowest effective dose is recommended to correct anemia.

Prior to initiating treatment for anemia, clinicians should address any reversible factors, including medications, that can lower Hb. In 1 study, for example, patients with anemia in CKD were often prescribed agents that increase the risk of bleeding.[10] In this study of over 1 million patients, of those with anemia and CKD, 73.0% of patients were prescribed nonsteroidal anti-inflammatory drugs, 61.0% were prescribed aspirin, 14.1% were prescribed warfarin, and 12.4% were prescribed clopidogrel.[10]

In the case scenario described previously, the patient is taking aspirin 81 mg daily, which could be contributing to anemia. If not precluded by other indications, this medication could be stopped to see if it is a primary cause of the anemia.

IRON THERAPY

Oral iron therapy is easily accessible and often is well tolerated; it can be used first to treat a patient with mild anemia with minimal symptoms. KDIGO recommends 65-200 mg of elemental iron taken orally once a day for 1-3 months.[6] Alternatively, intravenous (IV) iron should be considered either as first-line treatment or if oral iron is ineffective.[6]

IV iron is administered as a 1000 mg dose initially, either as a single large dose or repeated smaller doses, depending on the product. This dosage form is often preferred in patients receiving dialysis since IV access is easily attainable and IV iron is more effective at improving anemia.[6] The dose should be repeated if Hb does not increase or if TSAT remains ≤30% and ferritin remains ≤500 mg/dL.[6]

TREATMENT WITH ESAs

ESAs have been used to improve production of erythropoietin in patients with anemia and CKD since the 1980s, with the introduction of epoetin alfa.[11-13] Initially, ESAs were primarily used in patients on dialysis, but their use has expanded to other stages of CKD over time. Newer ESAs have been developed over the years, with longer durations of action and less frequent dosing requirements (**TABLE**).[14,15]

Available ESAs include epoetin alfa, darbepoetin alfa, and methoxy polyethylene-glycol epoetin beta.[12-15] A biosimilar of epoetin alfa is also available in the United States.[16] ESAs have recognized benefits in treating anemia, such as increasing Hb levels, correcting the anemia, improving symptoms, reducing the need for blood transfusion, and improving quality of life.[17] However, ESAs also have risks, primarily cardiovascular (CV) risks related to thrombosis. Several key studies have highlighted the importance of avoiding overtreatment of anemia and that Hb levels that are too high increase risk of CV events (increased cardiovascular risk has only been seen with treatment to Hb targets of ≥13 g/dL).[18-21] In studies with full anemia correction (Hb >13 g/dL), adverse events have included higher rates of vascular access thrombosis, cerebrovascular and CV events, earlier requirement for kidney replacement therapy, and higher mortality.[17] ESAs can be initiated when Hb is <10.0 g/dL, and ESA therapy is recommended for patients on dialysis whose Hb is at risk of dropping below 9.0 g/dL.[6]

Once patients are initiated on ESA therapy, it is essential to monitor Hb and clinical symptoms to ensure adequate response. Dose adjustment for ESAs is based on degree of Hb increase, current ESA dose, and clinical circumstances.[6] KDIGO recommends a target ceiling of 11.5 g/dL for Hb, with an absolute ceiling of 13.0 g/dL.[6] Hb monitoring should occur every month during ESA initiation and at least every 3 months thereafter; patients receiving dialysis and treated with an ESA should have Hb checked every month for the duration of therapy.[6] The dose should be lowered rather than withheld if downward adjustment of Hb is needed.[6]

SPECIALIST REFERRAL

While many patients with anemia in CKD can be managed in the primary care setting, some scenarios warrant referral to a nephrologist or hematologist. For a PCP without experience with ESAs or IV iron, a nephrologist could help manage treatment. For patients with more symptomatic anemia,

acutely worsening CKD, or low Hb despite standard treatment, a referral to nephrology is appropriate.[22] Additionally, patients with causes of anemia other than CKD who do not improve after addressing the cause should be referred to a hematologist.

In the patient case scenario, the patient could be treated with iron therapy or ESAs, based on the clinician's judgment. If the anemia did not improve after an adequate trial of standard treatment, or if his CKD was acutely worsening, he could be referred to a specialist.

EMERGING THERAPIES FOR ANEMIA IN CKD

In recent years, research has focused on developing new agents to treat anemia in CKD; it has been over a decade since the last US Food and Drug Administration (FDA)–approved treatment for anemia in CKD was brought to market. The need for additional therapies is highlighted by challenges and shortcomings of current treatments.[10,17] For example, oral iron is often ineffective for treating anemia, IV iron has a relatively high rate of infusion reactions, ESAs have a risk of CV adverse events, and there are risks associated with RBC transfusions.[10,17]

Hypoxia-inducible factor prolyl hydrolase inhibitors (HIF-PHIs) are a new class of agents being developed for anemia in CKD. They work by enhancing the effects of hypoxia-inducible factor (HIF) through inhibiting prolyl hydrolase.[17] Enhancing the effects of HIF promotes increased production of erythropoietin and improved iron utilization through a variety of mechanisms within RBCs and bone marrow (**FIGURE 2**).[17] If approved, these oral agents could provide treatment options that offer a more convenient dosage form to many patients.

At present, several investigational HIF-PHIs are being studied in late-stage clinical trials for anemia in CKD, including daprodustat, roxadustat, vadadustat, molidustat, and enarodustat.[23] Daprodustat, roxadustat, and vadadustat are all under review by the FDA. Each agent is generally studied in 2 different populations: those with CKD and anemia not receiving dialysis and those with CKD and anemia receiving dialysis.

Daprodustat. In the Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydrase Inhibitor Daprodustat-Non-Dialysis (ASCEND-ND) trial, daprodustat was compared with subcutaneous (SC) darbepoetin alfa in 3872 adults with CKD and anemia not on dialysis.[24] This was an open-label, phase 3 randomized trial, and patients had baseline Hb ranging from 8.0-11.0 g/dL, with a target Hb of 10.0-11.0 g/dL. The mean change in Hb was 0.74 g/dL in the daprodustat group and 0.66 g/dL in the darbepoetin alfa group, meeting prespecified noninferiority criteria. After a median of 1.9 years of follow up, major adverse cardiovascular events (MACE) occurred in 19.5% of the daprodustat group and 19.2% of the darbepoetin alfa group, which met the definition of noninferiority.

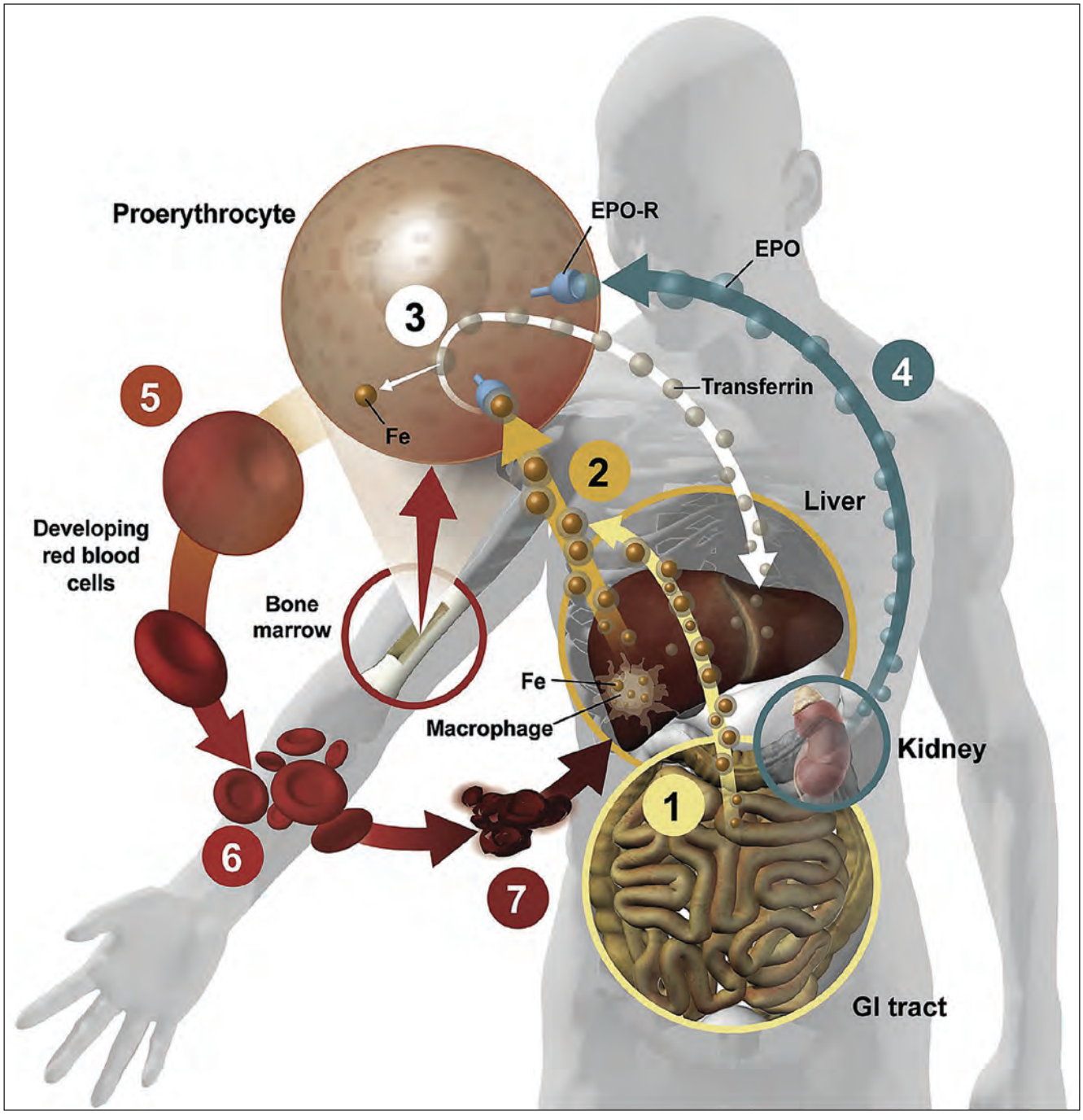
The Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat–Dialysis (ASCEND-D) trial evaluated daprodustat compared with epoetin alfa (for patients receiving hemodialysis) or darbepoetin alfa (for patients receiving peritoneal dialysis) in 2964 adults with CKD and anemia.[25] In this open-label, phase 3 randomized trial, patients had Hb ranging from 8.0-11.5 g/dL, with a goal to maintain Hb at 10.0-11.0 g/dL. The mean change in Hb was 0.28 g/dL in the daprodustat group and 0.10 g/dL in the ESA group, which met prespecified noninferiority criteria. After a median of 2.5 years of follow up, MACE occurred in 25.2% of the daprodustat group and 26.7% of the darbepoetin alfa group, meeting noninferiority.

Roxadustat. In the Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients, Not on Dialysis, in Comparison to Darbepoetin Alfa (DOLOMITES) trial, roxadustat was compared with darbepoetin alfa in 616 adults with CKD and anemia not on dialysis.[26] This was an open-label, phase 3 randomized trial, with a target Hb of 10.0-12.0 g/dL. An Hb response was defined as Hb ≥11.0 g/dL and a change from baseline ≥1.0 g/dL if baseline Hb was >8.0 g/dL or change from baseline ≥2.0 g/dL if baseline Hb was ≤8.0 g/dL. There was an Hb response in 89.5% of the roxadustat group and 78.0% of the darbepoetin alfa group, which met prespecified noninferiority criteria. Treatment-emergent adverse events occurred in 91.6% of the roxadustat group and 92.5% of the darbepoetin alfa group; more frequent treatment withdrawal was observed with roxadustat (7.7% vs 3.8%).

The Study to Evaluate the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Participants With ESRD on Stable Dialysis (SIERRAS) trial evaluated roxadustat compared with epoetin alfa in 741 adults with CKD and anemia receiving dialysis and treated with an ESA.[27] In this open-label, phase 3 randomized trial, patients had a mean Hb of 10.3 g/dL (range 9.0-12.0 g/dL) and the goal was to achieve and maintain Hb of 11.0 g/dL. The mean change in Hb was 0.39 g/dL in the roxadustat group and –0.09 in the epoetin alfa group, which met prespecified noninferiority criteria. Treatment-emergent adverse events occurred in 91.6% of the roxadustat group and 91.4% of the epoetin alfa group.

Vadadustat. The PRO_2TECT analysis encompasses 2 clinical trials for vadadustat: 1) the Efficacy and Safety Study to Evaluate Vadadustat for the Correction of Anemia in Subjects With Non-dialysis-dependent Chronic Kidney Disease and 2) the Efficacy and Safety Study to Evaluate Vadadustat for the Maintenance Treatment of Anemia in Subjects With

FIGURE 2. **Erythropoietic effects of HIF**[16]



(1) HIF upregulates divalent metal transporter 1 (DMT1) and duodenal cytochrome B (DcytB) to increase intestinal iron (Fe) absorption; (2) transferrin transports Fe to transferrin receptors in the bone marrow; (3) Fe is released from transferrin into the developing erythrocyte; (4) HIF upregulates the erythropoietin (EPO) receptor (EPO-R) and endogenous EPO production; (5) HIF upregulates transferrin receptor, increasing iron uptake by proerythrocytes; (6) HIF promotes the formation of fully functional mature erythrocytes replete with Hb; (7) after a lifespan averaging approximately 120 days, exhausted erythrocytes are scavenged in the liver and the Fe is returned for reuse.

Abbreviation: GI, gastrointestinal.

Source: Reprinted from *American Journal of Kidney Diseases*, Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: a potential new treatment for anemia in patients with CKD, 69(6):815-826, Copyright 2017, with permission from Elsevier.

Non-dialysis-dependent Chronic Kidney Disease trials.[28] These trials evaluated vadadustat compared with darbepoetin alfa in a total of 3476 adults with CKD and anemia not receiving dialysis. The trials were open-label, phase 3 randomized trials, and patients had baseline Hb of 8.0-12.0 g/dL in both study arms (eg, those not taking an ESA and those taking an ESA). The mean change in Hb between the 2 groups was 0.05 g/dL (not taking ESA) and –0.01 g/dL (taking ESA) and both met prespecified noninferiority criteria. The MACE hazard ratio between groups for both arms was 1.17 (95% CI 1.01-1.36) and it did not meet the prespecified noninferiority margin of 1.25 for vadadustat.

The INNO$_2$VATE analysis also encompasses 2 clinical trials for vadadustat: 1) the Efficacy and Safety Study to Evaluate Vadadustat for the Correction or Maintenance Treatment of Anemia in Subjects With Incident Dialysis-dependent Chronic Kidney Disease and 2) the Efficacy and Safety Study to Evaluate Vadadustat for the Maintenance Treatment of Anemia in Subjects With Dialysis-dependent Chronic Kidney Disease.[29] These trials compared vadadustat with darbepoetin alfa in a total of 3923 adults with CKD and anemia receiving dialysis. These were open-label, phase 3 randomized trials, and patients had baseline Hb of 8.0-12.0 g/dL, with a goal to achieve and maintain Hb 10.0-12.0 g/dL. There were 2 study arms in each trial, those with incident dialysis-dependent CKD (DD-CKD) and those with prevalent DD-CKD. The mean change in Hb between both groups was –0.31 g/dL (incident DD-CKD) and –0.17 (prevalent DD-CKD), and both arms met prespecified noninferiority criteria. MACE occurred in 18.2% of the vadadustat group and 19.3% of the darbepoetin alfa group; both arms met noninferiority criteria.

SUMMARY

Anemia in CKD is a common condition encountered in primary care that can be successfully managed by PCPs. KDIGO guidelines recommend standards for testing to identify anemia and for treatment with iron, ESAs, and blood transfusions. HIF-PHIs are investigational agents on the horizon that, if approved, will offer patients an oral option to treat anemia in CKD. ●

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OTC Analgesics vs Opioids for Pain Management

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KEY TAKEAWAYS

- The use of opioids in acute pain may be appropriate in some situations, but there are opportunities to reduce exposure to opioids with equally effective monotherapy and combination therapy over-the-counter (OTC) medications.
- There are a number of OTC analgesics that are readily accessible and cost-effective options to treat pain.
- The American College of Rheumatology Osteoarthritis Guideline "strongly" recommends the use of topical nonsteroidal antiinflammatory drugs (NSAIDs) and oral NSAIDs to treat arthritis pain, and it conditionally recommends against the use of opioids (other than tramadol).
- The American Headache Society suggests that OTC NSAIDs and combination medications such as acetaminophen, aspirin, and caffeine are Level A recommendations for reducing migraine pain and other symptoms.
- Nonopioid OTC analgesics, such as NSAIDs and the NSAID/acetaminophen combination, are safe and effective first-line options for managing acute dental pain according to the American Dental Association.
- The American College of Physicians supports the use of NSAIDs as first-line therapy for the treatment of low back pain.

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INTRODUCTION

In 2012, healthcare professionals in the United States wrote approximately 259 million opioid prescriptions to manage pain nationwide.[1] Using opioids for pain management on this scale has led to prescription misuse and the potential for diversion, as outlined by the National Institute on Drug Abuse.[2,3] From 2010 to 2014, the prevalence of diagnosed opioid abuse doubled.[4] The national economic burden of opioid misuse on an annual basis is staggering: in 2017 it was calculated at over $1 trillion.[5,6]

Emergency rooms, as well as primary care settings, have been identified as primary locations where patients may receive opioids for acute pain management, setting the stage for potential misuse.[7,8] To protect the patient's best interest, while still appropriately managing their acute and chronic pain, recommendations for safe alternatives to opioids have coalesced into a number of evidence-based treatment guidelines. Over-the-counter (OTC) medications, such as nonsteroidal antiinflammatory drugs (NSAIDs), combination analgesics, and acetaminophen, have well-established safety profiles, without the same dependence potential as opioids.[9] NSAIDs have some associated risks and sides effects, such as gastrointestinal issues, renal toxicity, and blood pressure elevation. They are also cost-effective and readily available in the pharmacy setting. An observed reduction in opioid prescriptions within the emergency department (ED) occurred from 2009 to 2018, due to increasing awareness of the opioid crisis.[10] These trends are reassuring, with an increased focus on alternatives like OTC and prescription nonopioid pain relievers, as well as nonpharmacologic approaches as viable options for managing pain.

The World Health Organization (WHO) suggests addressing pain using an analgesic ladder, starting with NSAIDs and combination therapy, escalating to combination therapy with the use of weak opioids, and ending with the use of combination therapy with more potent opioids.[11] Frameworks such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) can assist in determining responsible opioid-prescribing practices for patients experiencing chronic pain lasting over 3 months.[12] This approach takes into consideration the scientific evidence, potential for positive and negative patient outcomes, and patient prefer-

ences. The concerning side effects of opioids include physiologic dependence, sedation, respiratory depression, and constipation. Even though opioids can be used appropriately and offer proven benefits, there are stereotypes and stigmas associated with their use.[13,14]

The opioid epidemic has caused a shift toward equally effective classes of medication for pain reduction, and OTC analgesics are one of the clear options.[15] Even in the case of acute pain, ED opioid treatment should only be prescribed in the short term.[16,17] An abundance of expert guideline recommendations and clinical data support the effectiveness of OTC analgesics for acute pain management of arthritis, migraines, dental pain, and back pain. Additionally, these products are first-line options in the WHO analgesic ladder.[15,18-21] These pain states are among the most commonly seen by healthcare professionals, and targeted patient education on reasonable clinical interventions will assist in reducing opioid misuse. This review summarizes the clinical study data supporting OTC analgesics as first-line options for the previously mentioned pain states.

OSTEOARTHRITIS

The American College of Rheumatology (ACR) 2019 guidelines strongly recommend oral NSAIDs for the treatment of osteoarthritis (OA) of the hand, knee, or hip.[18] ACR guidelines further recommend the use of oral NSAIDs over other oral medications, regardless of the affected body area. The panel for OA of the knee strongly recommends topical NSAIDs, even before considering oral NSAIDs, due to their low systemic exposure. A conditional recommendation for topical NSAID use was determined by the panel for hand OA. The use of acetaminophen was conditionally recommended for hand, hip, and knee OA. Capsaicin (conditional recommendation for knee) and chondroitin sulfate (conditional recommendation for hand) were the only other OTC analgesics recommended.

In contrast to NSAIDs, ACR conditionally recommended against the use of opioids, with the exception of tramadol. This recommendation is mainly based on the high risk of toxicity and dependence associated with long-term opioid therapy coupled with very modest benefit. The ACR panel does conditionally recommend the use of tramadol in hand, hip, and knee OA because there is support for its use when contraindications to NSAIDs exist or other agents fail. ACR notes that opioids may be appropriate in some circumstances, particularly in patients who have exhausted other treatment options.

A recent meta-analysis comparing the effectiveness and safety of NSAIDs and opioids concluded that the clinical benefit from opioid treatment does not outweigh the potential harm to patients with OA, underscoring the importance of oral and topical NSAIDs in the treatment of OA.[19] The authors also concluded that topical diclofenac, which is available OTC, could be effective and is generally safer because of reduced systemic exposure and lower dose and could be considered as first-line pharmacologic treatment for knee OA.

The SPACE randomized clinical trial compared the effectiveness of nonopioid vs opioid therapies for the treatment of OA.[15,20] The results further support the use of NSAIDs as a first-line treatment over opioids due to similar effectiveness and fewer medication-related symptoms over a 12-month period. This trial demonstrated no significant difference between opioid and nonopioid therapy groups regarding pain-related function.

Based on the clinical evidence and recommendations of guidelines from the ACR, nonopioid options such as oral and topical NSAIDs should be considered for managing OA pain before opioids. Opioids play a role in OA pain management when other options have failed and risks can be managed.

MIGRAINES

Migraine headaches are the most common primary headache disorder that cause patients to seek treatment in the ED, accounting for approximately 1.2 million visits to the ED yearly.[20] Migraines are often debilitating, and pain management efforts need to be enacted swiftly. Opioids are prescribed often, despite guidelines recommending nonopioid pain treatment.[22] One study suggested that ED visit times were significantly longer for patients who were treated with opioids vs nonopioids.[21] The noted difference in visit times averaged 142 minutes (95% CI: 124, 160) for opioids vs 111 minutes (95% CI: 93, 129) for nonopioids (P = .015). Opioid misuse is a strong reason to consider other nonopioid medications.

In 2015, the American Headache Society (AHS) conducted an updated assessment of evidence for acute migraine medications.[23] The AHS guidelines concluded that oral NSAIDs and the acetaminophen, aspirin, and caffeine (AAC) combination are effective for acute migraine treatment based on available evidence (Level A). It is recommended that NSAIDs should not be used >10 to 15 days per month. The guidelines also recommend a number of nonopioid prescription medications, particularly in the triptan class.[23] Butorphanol nasal spray was the only opioid considered effective for acute migraine treatment. However, the guidelines point out that it is commonly avoided due to concerns about dependence, addiction, and the development of medication-overuse headache, and it is not recommended for regular use.

Ibuprofen and the AAC combination are the only Food and Drug Administration–approved OTC treatments for migraine in the United States. Strong clinical trial data support their use in the treatment of migraine. Lipton et al published a review of the use of caffeine in the management of headache, including a review of randomized trials of OTC analgesics combined with caffeine.[24] Based on the clinical trials reviewed, they concluded that combining caffeine with OTC analgesic medications, such as acetaminophen and aspirin, significantly improves efficacy over analgesics alone. However, they also address the potential for caffeine-containing analgesics to cause medication-overuse headache. The daily use of AACs for migraines is not recommended due to the possible occurrence of "rebound" headaches.[25] The use of ibuprofen is also associated with significant efficacy in migraine. Codispoti et al evaluated the efficacy and safety of ibuprofen, 200 mg and 400 mg, compared with placebo and each dosage separately for the treatment of migraine pain.[26] Significantly ($P \leq .006$) more patients treated with ibuprofen, 200 mg or 400 mg, reported mild to no pain after 2 hours (41.7% and 40.8%, respectively), compared with those treated with placebo (28.1%). Another randomized, double-blind placebo-controlled dose-finding study evaluated a single 200 mg, 400 mg, or 600 mg dose of a liquigel formulation of ibuprofen over 8 hours.[27] This study demonstrated a superior response to ibuprofen vs placebo for pain reduced to mild or none from 0.5 hour (600 mg) or 1 hour (200 and 400 mg) to 8 hours. All 3 ibuprofen doses were also significantly superior to placebo for pain relief and for mild or no limitation of activity.

In summary, nonopioid options, such as ibuprofen and the AAC combination, should be considered for acute migraine treatment prior to opioids based on clinical efficacy and guidelines such as the AHS recommendations.

DENTAL PAIN

The use of analgesics in patients with dental pain is common, yet selecting the appropriate agent to manage this pain has its own complexities. Dentists in the United States prescribe 12% of immediate-release opioids.[28] Although opioids do have their place in therapy, evidence suggests that adverse events associated with acute dental pain are most common among children and adults utilizing opioid treatment.[29] The American Dental Association (ADA) suggests that effective management of acute pain can be safely achieved with nonopioid pain medications.[30] Effective and well-tolerated alternate options for acute dental pain include oral NSAIDs, acetaminophen, and the ibuprofen/acetaminophen combination due to their ability to manage dental pain and their well-defined safety profiles.[30-33]

While dental pain is most commonly addressed with the use of NSAIDs such as ibuprofen, acetaminophen, or oral opioid combinations, the fixed-dose combination of ibuprofen and acetaminophen has been extensively studied and proven effective in dental pain. A study investigating the efficacy and safety of single and multiple doses of a fixed-dose combination of ibuprofen and acetaminophen (single-dose fixed-dose combination ibuprofen/acetaminophen 250/500 mg) in the treatment of postsurgical dental pain demonstrated that the combination was significantly more effective than ibuprofen 250 mg or acetaminophen 650 mg on a number of efficacy endpoints.[31]

Moore and Hersch conducted an analysis to evaluate the scientific evidence for using the ibuprofen/acetaminophen combination and its effectiveness in managing acute postoperative pain in dentistry.[32] The results suggested the ibuprofen/acetaminophen combination may be more effective, with fewer side effects than opioid-containing formulations. The results also indicated that the combination provided greater pain relief than monotherapy with either drug after third-molar extractions. They used the results of this analysis to suggest a stepwise approach to acute postoperative pain management in dentistry (**TABLE**).

Moore et al assessed the benefits and harms associated with analgesic medications used in the management of acute dental pain.[29] The ibuprofen/acetaminophen combination had the highest association with treatment benefit and the highest proportion of adult patients who experienced maximum pain relief. Opioids were associated most frequently with adverse events, and pain relief from opioids has been difficult to quantify due to variability in patient dosage and trial design.[33] Overall, the use of NSAIDs, with or without acetaminophen, offered the most favorable balance between benefits and harms.

While opioids remain an important option for consideration with dental pain, clinical evidence and ADA guidelines suggest that nonopioid options, such as ibuprofen, acetaminophen, and the ibuprofen/acetaminophen combination should be considered for managing dental pain over opioids.

BACK PAIN

Low back pain (LBP) is a leading cause of disability in the United States. In 2017, the American College of Physicians (ACP) Clinical Practice Guidelines for Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain were updated.[34] For acute and subacute LBP, nonpharmacologic treatment is recommended, but the updated guidelines strongly recommended NSAIDs or skeletal muscle relaxants if pharmacologic treatment is desired. Acetaminophen is no longer recommended. For patients with chronic LBP

TABLE. **Analgesic use for dental pain according to pain level**[32]

Pain level	Oral analgesic options
Mild	Ibuprofen 200-400 mg as needed for pain every 4-6 hours
Mild to moderate	Ibuprofen 400-600 mg fixed interval every 6 hours for 24 hours then Ibuprofen 400 mg as needed for pain every 4-6 hours
Moderate to severe	Ibuprofen 400-600 mg plus acetaminophen 500 mg fixed interval every 6 hours for 24 hours then Ibuprofen 400 mg plus acetaminophen 500 mg as needed for pain every 6 hours
Severe	Ibuprofen 400-600 mg plus acetaminophen 650 mg with hydrocodone 10 mg fixed interval every 6 hours for 24-48 hours then Ibuprofen 400-600 mg plus acetaminophen 500 mg as needed for pain every 6 hours

Source: Adapted from Moore PA, Hersh EV. Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions: translating clinical research to dental practice. *J Am Dent Assoc*. 2013;144(8):898-908. Copyright 2013, with permission from Elsevier.

who have had an inadequate response to nonpharmacologic therapy, treatment with NSAIDs as first-line therapy should be considered. Opioids should only be considered in patients who have failed other treatments and only if the potential benefits outweigh the risks for individual patients.

ACP guideline updates were based on a systematic review of randomized, controlled trials (or systematic reviews) of pharmacologic and nonpharmacologic treatments for LBP.[35] Pharmacologic treatments evaluated included NSAIDs, antidepressants, opioids, benzodiazepines, anticonvulsants, corticosteroids, and muscle relaxants, and parameters such as pain, function, and risk were assessed. Several trials demonstrated improvement of LBP in both acute and chronic cases when treated with NSAID therapy vs placebo. A placebo-controlled trial of acetaminophen in acute LBP found acetaminophen was no more effective than placebo.[36] For acute LBP, 1 trial made direct comparisons of opioid therapy vs NSAID therapy (oxycodone vs acetaminophen and naproxen), and no significant difference was found between groups with regard to pain control and patient function.[35] For chronic LBP, 3 trials in the systematic review reported inconsistent effects of opioids vs NSAIDs for pain relief, and 1 trial found no difference in function.[35] The review found that opioids had a higher risk for nausea, dizziness, constipation, vomiting, somnolence, and dry mouth than placebo. However, the trials assessed were not designed to assess long-term harms or the risk for overdose, abuse, or addiction.

Ultimately, opioids may offer benefit in some patients, but clinical evidence and guidelines recommendations, such as those from the ACP, suggest oral NSAIDs should be considered for LBP over opioids.

CONCLUSION

Pain management remains a challenge for clinicians, who are increasingly looking for alternatives to opioids. A number of nonpharmacologic options can help with pain management, but there remains a need for pharmacologic options when nonpharmacologic options alone are inadequate. Numerous evidence-based treatment guidelines issued by medical societies currently recommend OTC analgesics as initial treatment for arthritis pain, migraine headaches, dental pain, and back pain. These guideline recommendations are based on an abundance of clinical data supporting the efficacy and safety of OTC analgesics. Additionally, mounting evidence suggests that not only are OTC analgesic options safer and better tolerated than opioids, but they are just as effective in many pain states.

Through education and the use of peer-reviewed guidelines, healthcare professionals can minimize the potential for opioid misuse while effectively managing a patient's pain with alternate nonopioid pharmacologic options. ●

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Practical Considerations for Use of Insulin/Glucagon-Like Peptide 1 Receptor Agonist Combinations in Older Adults With Type 2 Diabetes

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KEY TAKEAWAYS

- Over 25% of adults ≥65 years of age have type 2 diabetes (T2D).
- Individualization of care is important in older adults with T2D, with treatment targets and therapeutic approaches informed by patient-specific medical, psychosocial, functional, and social considerations.
- Fixed-ratio combination injectable products offer unique benefits in older adults, including reduction of both fasting and postprandial glucose, low hypoglycemia risk, lack of weight gain, fewer gastrointestinal side effects, strong durability of effect, and the potential for medication regimen simplification.

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INTRODUCTION

According to most recent estimates, more than 37 million individuals currently live with diabetes mellitus (DM) in the United States.[1] The large majority (90%-95%) of these individuals have type 2 diabetes (T2D).[1] T2D is particularly common in older adults. Data indicate that more than 25% of adults ≥65 years of age have DM.[1] The American Diabetes Association (ADA) stresses the importance of patient-centered care, inclusive of establishing individualized glycemic targets and treatment approaches developed in partnership with patients through a process of shared decision-making.[2] Individualized care is of particular importance in older adults who often have medical, psychological, functional, and/or unique social factors that can impact care decisions and priorities.[2] While glycated hemoglobin A1C (A1C) remains a gold standard measure of glycemic control, the ADA stresses the importance of additional glycemic metrics including fasting plasma glucose (FPG), postprandial glucose (PPG), time in range, and measures of glycemic variability when evaluating and optimizing glycemic targets and management.[2] The importance of hypoglycemia prevention is stressed, as is the prevention and treatment of diabetes-related complications through optimized risk-factor management and use of glucose-lowering agents with proven cardiovascular and renal benefits in at-risk individuals.[2]

Avoidance of therapeutic inertia is important in T2D to maintain optimized, patient-centered care. Therapeutic inertia is not limited to situations of delayed initiation or intensification of therapy, but also includes delays or failure to de-intensify and/or simplify treatment when clinically appropriate.[2,3] Indeed, the ADA stresses the importance of re-evaluating patient-centered treatment goals and considering de-intensification and/or simplification of medication regimens when clinically indicated, particularly in older adults.[2] One potential strategy to achieve regimen simplification while maintaining glycemic control is through the use of

fixed-ratio combination (FRC) injectable glucose-lowering products.[4] This brief review will discuss practical considerations for use of basal insulin/glucagon-like peptide-1 receptor agonist (GLP-1 RA) FRC products and their potential advantages in older adults with T2D.

CASE SCENARIO: PART 1

RJ is a 72-year-old man with T2D presenting to the primary care clinic. RJ was diagnosed with T2D 12 years ago and has a history of hypertension, hypercholesterolemia, and obesity. RJ is currently managed on basal-bolus insulin (BBI) therapy, and reports difficulty managing his insulin regimen, including occasionally forgetting to inject his mealtime insulin. A review of RJ's blood glucose data reveals 4 hypoglycemic events in the previous 14 days, ranging from 51 to 67 mg/dL. RJ reports no hypoglycemia symptoms until his blood glucose is in the "low 50s." RJ additionally experiences frequent PPG spikes >250 mg/dL. In addition to forgetting to administer his mealtime insulin on occasion, RJ also notes difficulty affording his insulin, resulting in insulin rationing at the end of the month.

Lab work: A1C 8.2%, estimated glomerular filtration rate 63 mL/min/1.73m^2, urinary albumin-to-creatinine ratio 5 mg/g, low-density lipoprotein cholesterol 89 mg/dL, high-density lipoprotein cholesterol 42 mg/dL, and total cholesterol 170 mg/dL

Vitals: Body mass index 34 kg/m^2, blood pressure 132/88 mmHg in clinic today

Current medications: metformin 1000 mg twice daily, insulin glargine (U-100) 22 units once daily in the morning, insulin lispro (U-100) 6 units three times daily before meals, lisinopril 20 mg once daily, amlodipine 10 mg once daily, atorvastatin 40 mg once daily

Question: What are your goals of therapy for RJ given his presentation and current medication regimen?

2022 ADA STANDARDS OF MEDICAL CARE IN DIABETES UPDATES

The 2022 ADA *Standards of Medical Care in Diabetes* provide multiple recommendations supporting use of GLP-1 RAs in persons with T2D.[2] First, GLP-1 RAs with proven benefit are preferentially recommended as an option for patients with, or considered at high risk for, atherosclerotic cardiovascular disease independent of baseline A1C, individualized A1C target, or background glucose-lowering therapy.[2] For persons with T2D not meeting individualized glycemic targets, use of a GLP-1 RA is recommended as an option when minimization of hypoglycemia and/or promotion of weight loss is desired.[2] As emphasized within the intensification of injectable therapies algorithm (**FIGURE**), the ADA preferentially recommends a GLP-1 RA as the first injectable over insulin when possible. Additionally, the ADA recommends insulin use in combination with a GLP-1 RA for greater efficacy and durability of treatment effect when insulin is required to meet individualized treatment goals.[2] In older adults with longstanding T2D, however, insulin is often required when oral glucose-lowering therapies are deemed ineffective to maintain individualized glycemic goals.

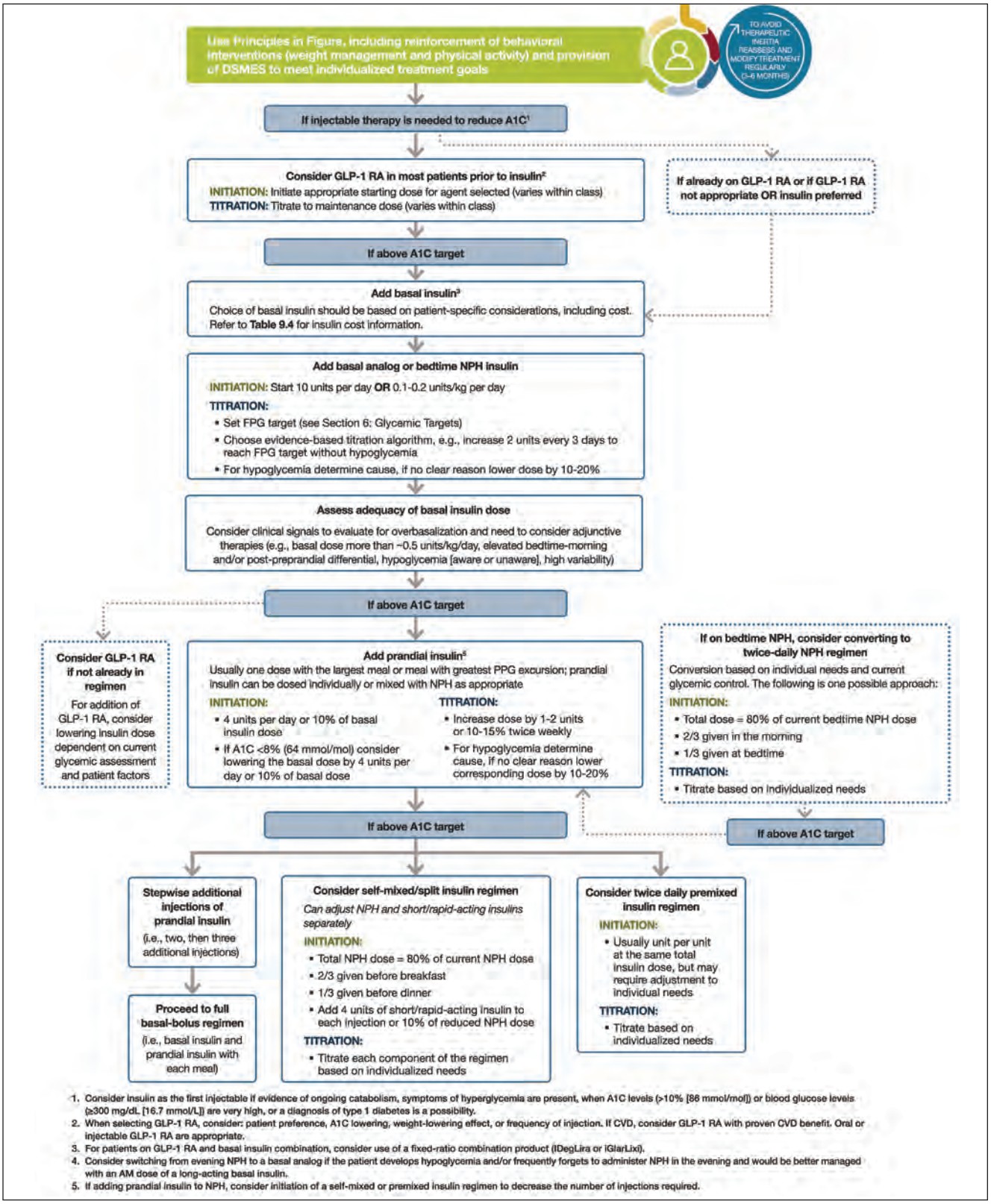
The ADA also provides considerations for management of T2D in older adults and emphasizes the importance of individualized glycemic targets and treatment approaches.[2] Key factors noted for consideration include assessment of medical, psychological, functional, and social (eg, presence of caregiver, support system) domains, as well as multiple geriatric syndromes that may impact patient care and outcomes.[2] These factors additionally inform the selection of glucose-lowering therapies and application of general treatment recommendations offered by the ADA. Avoidance of "overtreatment" and hypoglycemia is stressed. Key recommendations regarding individualization of glycemic goals and treatment approaches for older adults with T2D are summarized in **TABLE 1**.[2] Overall, based on patient-specific considerations, liberalization of treatment goals, de-intensification of therapy, and/or simplification of the medication regimen may be appropriate to optimize care, minimize hypoglycemia risk, and reduce treatment burden.[5,6]

BRIEF REVIEW OF CLINICAL EVIDENCE AND POTENTIAL BENEFITS OF FRC THERAPIES

While basal insulin may be sufficient to achieve FPG targets, additional agents are often needed to manage PPG excursions when the A1C remains above goal (**FIGURE**),[2] especially in older adults who often experience significant postprandial hyperglycemia.[7] While the addition of prandial insulin is one approach, FRC agents offer an alternative strategy with potential advantages (**TABLE 2**).[8-14]

Treatment with FRC agents has demonstrated greater A1C reductions when compared to intensification of basal insulin or GLP-1 RAs alone in persons with T2D that is inadequately controlled on their current glucose-lowering regimen.[4] Participants randomized to FRC agents characteristically achieve greater A1C reductions without an increase in hypoglycemia or weight gain when compared to basal insulin alone, and with fewer gastrointestinal adverse events when compared to GLP-1 RA treatment alone.[4] A post hoc analysis of data from 2 trials with the insulin glargine/lixisenatide FRC product reported that enrolled participants ≥65 years of age derived similar benefit as participants <65 years of age.[8] Importantly, data show that treatment with the FRC agent iDegLira results in longer durability of treatment effect (defined as time after medication initiation until treat-

FIGURE. **Intensifying injectable therapies in T2D[2]**



Abbreviations: DSMES, diabetes self-management education and support; NPH, neutral protamine hagedorn insulin.

Source: American Diabetes Association Standards of Care - 2022, Figure 9.3, American Diabetes Association, 2021. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

TABLE 1. **Key ADA recommendations related to treatment of older adults with T2D[2]**

- Consider the assessment of medical, psychological, functional (self-management abilities), and social domains in older adults to provide a framework to determine targets and therapeutic approaches for DM management
- Screen for geriatric syndromes (ie, polypharmacy, cognitive impairment, depression, urinary incontinence, falls, persistent pain, and frailty) in older adults, as they may affect diabetes self-management and diminish quality of life
- In older adults with T2D at increased risk for hypoglycemia, medication classes with a low risk of hypoglycemia are preferred
- Overtreatment of DM is common in older adults and should be avoided
- Deintensification (or simplification) of complex regimens is recommended to reduce the risk of hypoglycemia and polypharmacy, if it can be achieved within the individualized A1C target
- Consider costs of care and insurance coverage rules when developing treatment plans to reduce risk of cost-related nonadherence

TABLE 2. **Potential advantages of FRC agents in older adults with T2D**

- Regimen simplification (basal insulin + GLP-1RA in single injection) to improve medication compliance/persistence[8,13,14]
- Reductions in both FPG and PPG[12]
- Lack of weight gain[10,11]
- Decreased gastrointestinal side effects when compared to GLP-1 receptor agonists alone[8]
- Low hypoglycemia risk when compared to basal-bolus insulin therapy[10]
- Non-ß-cell reliance with preserved efficacy in patients with longstanding T2D[8]
- Durability of glycemic benefit[9]

TABLE 3. **Currently available FRC agents[15,16]**

	Insulin glargine/lixisenatide FRC	Insulin degludec/liraglutide FRC
Indication	Adjunct to diet and exercise to improve glycemic control in adults with T2D	Adjunct to diet and exercise to improve glycemic control in adults with T2D
Initial recommended dosing	*Naïve to basal insulin or to a GLP-1 RA, currently on a GLP-1 RA, or currently on <30 units of basal insulin daily:* • Discontinue therapy with current basal insulin or GLP-1 RA • Initiate at 15 units (15 units of insulin glargine/5 mcg lixisenatide) subcutaneously once daily *Currently on 30-60 units of basal insulin daily, with or without a GLP-1 RA:* • Discontinue therapy with current basal insulin or GLP-1 RA • Initiate at 30 units (30 units of insulin glargine/10 mcg lixisenatide) subcutaneously once daily	*Naïve to basal insulin or a GLP-1 RA:* • Initiate at 10 units (10 units of insulin degludec/0.36 mg liraglutide) subcutaneously once daily *Currently on basal insulin or a GLP-1 RA:* • Discontinue therapy with current basal insulin or GLP-1 RA • Initiate at 16 units (16 units of insulin degludec/0.58 mg liraglutide) subcutaneously once daily
Recommended titration	Titrate based on FPG: • ***Above target range:*** Increase dose by 2 to 4 units • ***Within target range:*** No change • ***Below target range:*** Decrease dose by 2 to 4 units	Titrate based on FPG: • ***Above target range:*** Increase dose by 2 units • ***Within target range:*** No change • ***Below target range:*** Decrease dose by 2 units
Maximum dose[a]	60 units	50 units

[a] Dosing of FRC agents is based on units of the basal insulin component.

ment intensification is required to maintain glycemic targets) when compared with basal optimization alone.[9]

In persons with T2D that is inadequately controlled on basal insulin, switching to IDegLira therapy is associated with comparable glycemic efficacy to intensification with BBI therapy, with more favorable effects on hypoglycemia rates and body weight.[10] Likewise, intensification to a once-daily insulin glargine/lixisenatide product has also been shown to be at least as effective as intensification to a twice-daily premixed insulin (70/30) regimen in basal insulin–treated T2D, with the FRC treatment resulting in weight benefit and less hypoglycemia.[11]

Trials evaluating the benefits of a GLP-1 RA added on to BBI and transitioning from a BBI to an FRC regimen highlight the potential benefits of FRC therapies. First, the addition of a GLP-1 RA (albiglutide) in persons with T2D on background BBI therapy resulted in decreased prandial insulin needs while also facilitating medication regimen simplification, promoting weight loss, and reducing hypoglycemia events.[12] Similarly, trials transitioning persons with T2D from BBI to a once-daily FRC agent reported similar or better glycemic control, a need for fewer injections, and less hypoglycemia following transition to the FRC agent.[13,14] Notably, Taybani and colleagues tested this approach in an older population of persons with T2D (mean baseline age = 64 years) and a mean baseline A1C of 6.42%.[14] In this trial, transitioning participants from BBI to FRC resulted in reductions in A1C (mean, -0.3%; P <0.0001) and body weight (mean, 3.11 kg; P <0.0001), indicating that clinical benefits can be realized even in persons with T2D with "good" glycemic control by transitioning from BBI to an FRC agent.[14]

CURRENTLY AVAILABLE INSULIN/GLP-1 RA FRC PRODUCTS

Based on the evidence discussed above supporting the efficacy of FRC agents in the treatment of T2D, 2 products have received US Food and Drug Administration approval and are currently available in the United States.[15,16] A summary of key product information is provided in **TABLE 3**.[15,16]

CASE SCENARIO: PART 2

Question: Based on the information just covered, what changes would you consider for RJ? How would you work with RJ to implement these changes and maximize his success? As previously presented, RJ is a 72-year-old man with T2D, hypercholesterolemia, and obesity. RJ has voiced challenges managing a complex regimen that includes BBI therapy in addition to financial challenges affording his medications. RJ's A1C (8.2%) is above his individualized goal of 7.0% (**TABLE 4**). He is experiencing notable glycemic variability, including frequent hypoglycemic events and postprandial hyperglycemia.

TABLE 4. **Framework for considering treatment goals for glycemia**

Patient Characteristics/ Health Status	Rationale	Reasonable A1C Goal, % (mmol/mol)‡
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.0–7.5 (53-58)
Complex/ intermediate (multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0 (64)
Very complex/poor health (LTC or end-stage chronic illnesses or moderate-to-severe cognitive impairment or 2+ ADL impairments)	Limited remaining life expectancy makes benefit uncertain	Avoid reliance on A1C; glucose control decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia

Abbreviations: ADL, activities of daily living; LTC, long-term care.

Source: American Diabetes Association Standards of Care - 2022, Table 3.1, American Diabetes Association, 2021. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

While there are many issues that would need to be addressed with RJ, his current glucose-lowering regimen is not meeting his needs. To reach his glycemic goal, minimize his hypoglycemia risk, and simplify his regimen, RJ's BBI regimen was discontinued, and he was transitioned to treatment with an insulin/GLP-1 RA FRC product. Given RJ's financial challenges, he was assisted in taking advantage of the Medicare Part D Senior Savings Model where he was able to obtain his FRC product at a maximum copay of $35/month.[17] De-intensification of therapy from a BBI regimen to an insulin/GLP-1 RA FRC product resulted in reduced glycemic variability, elimination of his hypoglycemic events, improvements in his PPG and A1C levels, and simplification of his regimen.

SUMMARY AND CONCLUSIONS

It is important to consider the unique needs of older adults with T2D when determining patient-centered glycemic goals

and treatment plans. Insulin/GLP-1 RA FRC products offer key advantages that may allow for regimen simplification while maintaining glycemic control and minimizing hypoglycemia risk. ●

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Practical Screening for Islet Autoantibodies: The Time Has Come

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KEY TAKEAWAYS

- The increasing prevalence of type 1 diabetes (T1D) suggests family physicians will regularly see first-degree relatives of patients with T1D with the genetic propensity for developing T1D.
- T1D autoantibody screening by family clinicians addresses an important need to identify at-risk individuals early and achieve short- and long-term health benefits.
- Multiple T1D screening options and programs are available to clinicians that provide patient education, testing, result analysis, follow-up, and opportunity for participation in T1D prevention trials.
- The provider-patient relationship in family medicine places clinicians in a unique position to provide monitoring and follow-up crucial to family members with positive autoantibody results.

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Dr. Reid discloses that he serves on the advisory board for Pendulum Therapeutics. Christine Beebe has no disclosures to report.

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According to the Centers for Disease Control and Prevention's (CDC) National Diabetes Statistics Report (2020), 1.6 million adults and 244,000 youth under 20 years of age have type 1 diabetes (T1D).[1] Estimated prevalence per 1000 youth has increased from 1.48 in 2001 to 2.15 in 2017.[2] During the COVID-19 pandemic, the incidence increased significantly in individuals <18 years, suggesting an associated risk requiring ongoing evaluation.[3] Combined with the fact that T1D is a common chronic disease in children, it is highly probable that at-risk individuals, particularly relatives, are present in nearly every primary care practice. Autoantibody screening and monitoring in relatives has potential short- and long-term health benefits to these at-risk relatives.[4] Benefits include early diagnosis, reducing the risk of life-threatening diabetic ketoacidosis (DKA), and reducing short- and long-term complications of clinical diabetes.[4-6] In addition, the future holds promise of therapies that may delay or even prevent clinical T1D.

The progression of beta-cell destruction to the eventual development of clinical T1D is a continuum that progresses over months to years.[7-9] Long before the manifestation of symptoms, the disease is present in 3 well-defined stages corresponding to beta-cell loss.[10] In stage 1, ≥2 islet autoantibodies are present, indicating T1D, but normoglycemia is maintained. Stage 2 is characterized by ≥2 autoantibodies and progression to dysglycemia (impaired glucose tolerance). Stage 3 represents the onset of clinical T1D and overt hyperglycemia, requiring exogenous insulin.

The rate of progression varies between individuals and is influenced by variables including the age islet autoantibodies develop and number of autoantibodies.[11,12] Young children are more likely to experience rapid beta-cell destruction than adolescents or adults and are at the greatest risk of developing life-threatening DKA at diagnosis.[8,11,12] Destruction can be gradual, as adults may retain enough beta-cell function to slow progression to clinical T1D for years.[9]

BENEFITS OF SCREENING

Measuring autoantibodies in relatives represents targeted screening to identify who may eventually develop T1D.[9,10] The presence of ≥2 islet autoantibodies is a near certain predictor of clinical T1D; 69.7% of children develop T1D by 10

years and nearly all (84.2%) by 15 years of follow-up.[9,10] Progression is most rapid in children with multiple autoantibodies before age 3.[9]

Clinical T1D presents with life-threatening DKA 40% to 60% of the time at diagnosis and results in longer and more burdensome hospitalizations.[13,14] Since the mortality rate from DKA is 0.2% to 2.0%, preventing DKA is an important goal. During the COVID-19 pandemic, the increased incidence of T1D among US children was accompanied by an increase in DKA.[3,15] Two US medical claims databases reported a significant increase in new T1D diagnoses (166% and 31%) among patients with COVID-19, and nearly half had DKA at diagnosis.[3]

Early risk identification coupled with monitoring, counseling, and diabetes education enables earlier diagnosis and lowers the risk of DKA. In the Diabetes Prevention Trial (DPT-1), 63.3% of asymptomatic participants were diagnosed early based on laboratory parameters, including autoantibody testing, and only 3.67% developed DKA.[16] In the Diabetes Autoimmunity Study in the Young (DAISY), only 3% of children were hospitalized with DKA at diagnosis compared with 44% from the age- and-sex-matched community.[17] Children in The Environmental Determinants of Diabetes in the Young (TEDDY) study were also significantly less likely to experience DKA at diagnosis compared with a comparable population.[18]

Preventing DKA has more than short-term clinical benefits. Preventing DKA at diagnosis increases the likelihood of partial remission (the honeymoon phase) of T1D, characterized by dramatically reduced insulin requirements, and is associated with better long-term metabolic control and lower insulin requirements.[4,5,19] Thus, preventing or delaying individuals moving from stage 1 to stage 3 T1D would have enormous health benefits. Furthermore, ongoing clinical trials examining disease-modifying methods of treating autoantibody-positive individuals in stage 2 have the potential to prevent or delay the diagnosis of stage 3 clinical T1D.[20-22] For these reasons, the American Diabetes Association (ADA) offers this recommendation:

> *Screening for presymptomatic type 1 diabetes using screening tests that detect autoantibodies to insulin (IAA), glutamic acid decarboxylase (GAD), islet antigen 2 (IA-2A), and zinc transporter 8 (Znt8A) is currently recommended in the setting of a research study or can be considered an option for first-degree family members of a proband with type 1 diabetes.*[21]

SCREENING CONVERSATIONS

While genetics play a key role in the pathogenesis of T1D, only 10% to 20% of cases occur in individuals with a family history.[23,24] Nevertheless, targeted screening of at-risk family members is practical and beneficial. Family members of patients with T1D have approximately a 15-fold increased risk (1:20), compared with the general population risk of 1:300.[9,21]

The CDC advocates for increased surveillance for T1D in US youth, particularly minority populations, as steeper increases were observed from 2002 to 2015 among blacks (2.7%/year), Hispanics (4%/year), and Pacific Islanders (4.4%/year) than among whites (0.7%/year).[2] The peak incidence for development of islet autoantibodies occurs in the first few years of life, generally between 3 and 5 years of age, with sensitivity peaking at 4 years.[23-25] Age 3 to 4 years has been suggested as the best time to screen children using islet autoantibody testing.[24,25] Yet concern exists that this would miss the youngest children. Vigilance in monitoring youth in at-risk families is important as diagnosis can occur at any age but is most often in youth 10 to 14 years of age.[26,27]

Family physicians are trusted sources of information for their patients and families. Shared decision-making occurs at every step of the T1D screening journey, beginning with the discussion of whether an individual wants to know their own or a loved one's risk of developing T1D. The psychological impact of a positive result can be a source of stress and anxiety that may offset the benefit of an early diagnosis.[28-30] Parents could impair family well-being by treating a child differently in an attempt to control environmental risk factors.

Parents of children receiving positive autoantibody test results exhibit high anxiety scores.[28-30] Mothers have higher anxiety than fathers, and mothers from families with T1D exhibit significantly greater anxiety (P = .002) than mothers from the screened general population. This implies that knowing the burden of T1D may increase anxiety. Uncertainty about when stage 3 T1D will develop in children with multiple autoantibodies, along with the feeling that parents cannot do anything to prevent it, can lead to high anxiety. While anxiety declines over the years, parents of children with multiple autoantibodies continue to experience long-term high anxiety.[29]

Fortunately, integrating basic diabetes education, counseling, and access to mental health professionals in families with multiple positive islet autoantibody results yields long-term positive effects on anxiety.[28-30] This is encouraging as it reinforces that clinicians who adequately prepare individuals, as suggested in **TABLE 1,** can lower anxiety risk in families.[31]

AUTOANTIBODY SCREENING OPTIONS

A panel of islet autoantibodies is recommended over individual tests to ensure that an autoantibody that may be predic-

TABLE 1. **Autoantibody screening process**

Initial discussion
Risk of developing T1D
Benefits and risks of testing: early diagnosis, prevent DKA, reduce risk for clinical disease, potential to participate in prevention trials or therapeutic options
Psychological impact of screening results
Refer to JDRF T1Detect, TrialNet, or askhealth.org for resources
Screening
Commercial laboratory (physician order required)
TrialNet (no prescription, screen families of T1D patients)
JDRF, T1Detect (no prescription, screens regardless of family history)
Regional programs (ASK, PLEDGE, CASCADE)
Follow-up/monitoring
Results and risk implications
Confirming autoantibody tests
Metabolic testing
Diabetes education
Evaluation and follow-up
Emotional support/resources
Clinical trials and therapy options
Endocrinologist consult

Source: Adapted from Type 1 Diabetes TrialNet. TrialNet Recommendations for clinicians. Accessed Arpil 15, 2022. https://www.trialnet.org/healthcare-providers

tive is not missed: autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA), islet antigen 2 (IA-2A), and zinc transporter 8 (Znt8A).[22] Average clinical sensitivity and specificity of assays are 96% and 97%, respectively, and have been reported to correctly identify 95% of high-risk individuals with ≥2 autoantibodies.[32]

Clinicians can screen at-risk relatives in their clinical practice by ordering screening panels from commercial laboratories (the cost of which is dependent on insurance availability and coverage). Laboratories offering autoantibody screening panels include Mayo Laboratories, LabCorp, and Quest Diagnostics.[33] Interpretation and next steps are determined by the prescribing practitioner. A useful guideline is suggested by the JDRF (formerly Juvenile Diabetes Research Foundation) in **TABLE 2.**[33]

T1Detect (JDRF.org) offers patients autoantibody screening, education before and after testing, and guidelines for follow-up. Access is available to anyone, regardless of family history. A physician order is not required to obtain a test kit. The test uses a finger-prick blood sample. Three markers are measured: IAA, GADA, and IA-2A. Results and interpretation are returned to the patient with suggestions for discussing results with their clinician.[33]

TrialNet (https://trialnet.org/), a National Institutes of Health–funded network of researchers, clinicians, and academic institutions, is dedicated to understanding the natural history of T1D and preventing or delaying the disease.[21,34] TrialNet provides free autoantibody screening kits to relatives for in-home testing or taking to their local laboratory. TrialNet testing sites are also available. Results and interpretation are returned in 4 to 6 weeks. Autoantibody-positive individuals can participate in follow-up and clinical trials, including prevention trials. TrialNet and T1Detect offer resources for both healthcare professionals and participants.

Free regional screening programs that do not require a physician order are presented here:

- **ASK,** Autoimmunity Screening for Kids, open to Colorado children ages 1 to 17 years, with or without a family history: https://www.askhealth.org/childhood-diabetes
- **PLEDGE,** a screening program available to children under 6 years of age at Sanford Health System, South Dakota: https://www.sanfordhealth.org/medical-services/pediatrics/pediatrics-specialized-care/pledge
- **CASCADE,** screening for T1D in children from birth to 8 months and 4 to 8 years in Washington state: https://cascadekids.org/

FOLLOW-UP

Explaining results to patients and families involves correlating the number of autoantibodies with approximate risk for developing T1D. Participants will present with either no autoantibodies, 1 detected autoantibody, or ≥2 autoantibodies.

Individuals with no antibodies are at low risk for developing T1D. While this does not mean they will not develop T1D, data from TrialNet suggest it is uncommon. Testing positive for a single autoantibody is associated with a 14.5% risk of progressing to T1D in 10 years.[8-11] However, some children <5 years of age may progress faster if the single autoantibody is IA-2A.[10]

Individuals in stage 1 T1D have a 44% risk of progressing to clinical T1D within 5 years and 70% within 10 years.[9] If the disease has progressed to include dysglycemia (stage 2), individuals have a 60% risk in 2 years and a 75% risk in 4 to 5 years.

MONITORING

Currently, there are no evidence-based guidelines for

TABLE 2. **Monitoring after T1D autoantibody screening**

Results	Monitoring
Autoantibody negative	Rescreen • If symptomatic • At age 5 years, if previously screened • 11 years if screened between 5 and 10 years of age
1 autoantibody positive	• Rescreen • HbA1C for normality (<5.7%) • Metabolic testing in 6 months to exclude clinical T1D (OGTT, FPG, random BG) • If single autoantibody-positive for 2 years, rescreen annually
≥2 autoantibodies positive	Stage 1: Normoglycemia (HbA1C <5.7%) • Rescreen • Exclude clinical (stage 3) T1D diagnosis • Follow up in 6 months to exclude clinical T1D diagnosis (OGTT, FBG, random BG) • Educate regarding signs and symptoms Stage 2: Dysglycemia confirmed – Fasting plasma glucose 100-125 mg/dL – 2-hour plasma glucose 140-199 mg/dL – HbA1C 5.7%-6.4% • Rescreen • Fasting blood glucose and 2-hour post largest meal BG once weekly (CGM or test strips) • BG >200 mg/dL consult endocrinologist • At 3 months, repeat autoantibodies, exclude T1D diagnosis with metabolic testing • T1D education Stage 3: Symptomatic diabetes • Assess: polyuria, polydipsia, weight loss, DKA • Exogenous insulin treatment • Consult endocrinologist

Abbreviations: BG, blood glucose; CGM, continuous glucose monitoring; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.
Source: Adapted from JDRF.org. T1Detect: learn why you should be screened. Accessed April 24, 2022. https://www.jdrf.org/t1d-resources/t1detect/

monitoring individuals with islet autoantibodies. However, based on published T1D screening studies, practical stage-specific recommendations are available at https://www.askhealth.org/experts. Next steps for patients and families after screening for T1D autoantibodies can be found here: https://1x5o5mujiug388ttap1p8s17-wpengine.netdna-ssl.com/wp-content/uploads/2021/07/TalkingtoPatientsandFamiliesAboutT1DRiskandScreeningTests-.pdf?_ga=2.256589835.1689151409.1647704787-2006460947.1628718247.[33]

Any positive autoantibody screening test result should be confirmed within 2 to 6 weeks.[8,27] Monitoring for symptoms of T1D is recommended in all at-risk individuals. In addition to stage-specific recommendations, a diagnosis of T1D is excluded with metabolic testing (**TABLE 2**).[35]

Metabolic testing criteria are used to identify the gradual metabolic deterioration in beta-cell function.[34,35] Tests include:

- **Glycated hemoglobin (HbA1C):** Recommended for all at-risk patients. Increasing levels of HbA1C above baseline (≥10%) or A1C of 5.7% to 6.4% serve as a biomarker of progression to T1D.
- **Oral glucose tolerance test (OGTT):** The 2-hour

glucose value in an OGTT predicts progression as early as 1.45 years prior to T1D.[36] However, in the TEDDY study, only 6% of children under 3 years were diagnosed by an OGTT.[23]

- **Fasting plasma glucose (FPG):** FPG and a 2-hour plasma glucose identify impaired glucose tolerance and diagnose diabetes. The 2-hour plasma glucose is optimal.[36]
- **Random plasma glucose:** A random plasma glucose >200 mg/dL is diagnostic of diabetes in symptomatic individuals and used in stage 2 as a call to action if asymptomatic.
- **C-peptide levels:** Fasting C-peptide and stimulated levels are not recommended in screening as they lag behind changes in the OGTT.

Recently, a composite screening measure known as Index60 using fasting C-peptide, 60-minute C-peptide, and a 60-minute serum glucose has been proposed as an option in stage 2 to identify individuals with declining beta-cell function who would otherwise be missed on an OGTT.[37] The premise is that if dysglycemia is the only criterion for stage 2, a substantial group with normoglycemia would lose the opportunity for intervention.

In the DAISY study, time spent with glucose values >140 mg/dL (time above 140 [TA140]; 7.8 mmol/L) predicted progression to diabetes in autoantibody-positive children.[38,39] Continuous glucose monitoring reports time above target blood glucose levels. The ASK study found TA140 >10% was associated with a high risk of progression to clinical diabetes within 1 year in autoantibody-positive children.[38] Continuous glucose monitoring has the potential to provide easier monitoring of at-risk individuals if more studies confirm these data.

While monitoring (particularly OGTT) can be burdensome, the patient-primary care clinician relationship can enhance follow-up. Children are more likely to maintain monitoring than adults (70.4% vs 58.2%) as are individuals with a proband with T1D.[34] Enrollment in a clinical trial with the possibility of therapeutic benefit is also considered motivating.[34]

CONCLUSION

The prevalence of T1D is increasing in the United States, with cases in youth of diverse populations growing at the fastest rate. Identifying the progression of T1D early is an important part of primary prevention strategies. Given that the disease process can be detected through autoantibody testing, family physicians have an opportunity to initiate screening of relatives, particularly children, of individuals with T1D and potentially impact the course of the disease. Once staged, monitoring and follow-up can lead to early detection, reduce likelihood of DKA, and reduce long-term metabolic complications of the disease. If preventative therapies are approved in the future, primary care clinicians will be able to guide treatment of autoantibody-positive relatives as well. ●

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Reducing Thrombotic Risk From Polyvascular Disease in Primary Care

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

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

- Describe the burden of disease and risk of atherothrombotic events in patients with polyvascular disease—peripheral arterial disease (PAD) and coronary artery disease (CAD).
- Implement screening and diagnostic procedures to improve detection of polyvascular disease and accurately assess overall atherothrombotic risk.
- Select evidence-based treatment to reduce cardiovascular and limb events in patients with polyvascular disease.

KEY TAKEAWAYS

- Polyvascular disease is classified as atherosclerosis in multiple arterial beds, and common presentations include a combination of CAD, PAD, and/or cerebrovascular disease (CVD).
- Patients with polyvascular disease are at a significantly increased risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE) compared to patients with atherosclerosis in only 1 vascular bed.
- Routine screening for polyvascular disease after diagnosis of an initial atherosclerotic disease is controversial, but clinicians can detect disease in additional vascular beds with a careful history and physical examination.
- Antithrombotic agents such as clopidogrel, rivaroxaban, ticagrelor, vorapaxar, and aspirin can reduce thrombotic events in patients with polyvascular disease; the only antithrombotic agent approved for both CAD and PAD is rivaroxaban.

TARGET AUDIENCE

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

FACULTY

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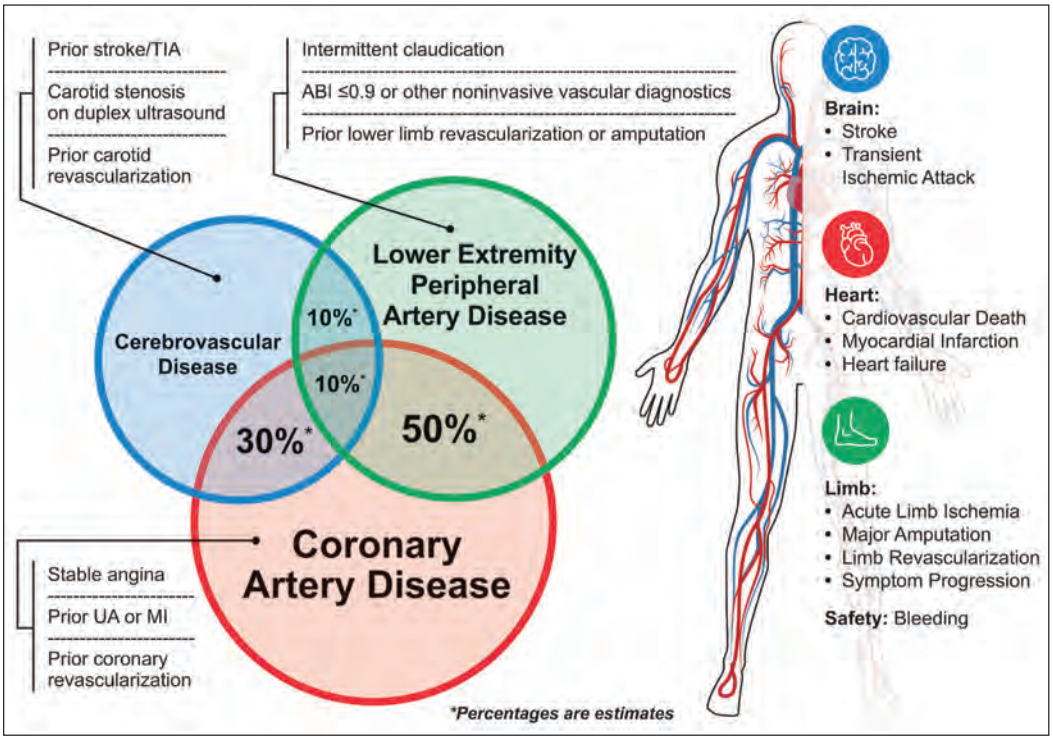
INTRODUCTION

Polyvascular disease is defined as the presence of atherosclerosis in 2 or more arterial beds, and is most commonly described as a combination of coronary artery disease (CAD) and peripheral arterial disease (PAD), though it can also include cerebrovascular disease (CVD) (**FIGURE**).[1-3] The atherosclerosis in these diseases comprises low-grade inflammation, plaque formation, and diseased endothelium in the

FIGURE. **Relative frequencies of polyvascular subtypes, broad diagnostic criteria for the vascular territories, and ischemic outcomes related to each territory[3]**



Approximate relative frequencies of each polyvascular disease subtype within the overall absolute polyvascular disease frequency of 15%–25% in patients with known atherosclerosis in 1 disease territory with related diagnostic criteria. Ischemic outcomes associated with atherosclerosis in each included arterial territory.

Abbreviations: ABI, ankle-brachial index; MI, myocardial infarction; TIA, transient ischemic attack; UA, unstable angina.

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vasculature, which leads to vessel occlusion.[4,5] Progression of atherosclerosis increases the risk of occlusion and subsequent cardiovascular, limb, and neurologic events including stroke, myocardial infarction (MI), heart failure, limb ischemia, and amputation.[3,5,6] Historically, polyvascular disease has been underrecognized, but clinical and research efforts to address noncoronary atherosclerosis has increased awareness of this condition.[1] The relevance for polyvascular disease centers on an increased risk of adverse cardiovascular and limb events in patients with this condition.[1]

Worldwide, prevalence of CAD is estimated at 5%-8% and prevalence of PAD is estimated at 10%-20% of the general population.[5] To better characterize atherothrombotic diseases, an international prospective cohort was established in 2003-2004.[7] The Reduction of Atherothrombosis for Continued Health (REACH) registry evaluated patients in 44 countries with CAD, PAD, and CVD, as well as those with at least 3 risk factors for atherothrombosis.[7] In the REACH cohort, approximately 18%-35% of patients with CAD and 46%-68% of patients with PAD had disease in more than 1 vascular bed.[5,8]

Despite the significant risks of polyvascular disease, patients with PAD are often underdiagnosed, leading to underdiagnosis of polyvascular disease overall.[9,10] Since patients with PAD usually first present to their primary care practitioner (PCP), clinicians in the primary care setting can improve detection of PAD and polyvascular disease and assist with early intervention to reduce atherothrombotic risk.[11,12]

THROMBOTIC RISK IN POLYVASCULAR DISEASE

Observational studies of patients with polyvascular disease have demonstrated that patients with both PAD and CAD experienced up to 60% higher rates of atherothrombotic risk compared to patients with either disease alone.[7,13] Additionally, as the number of symptomatic arterial disease locations increased in a 1-year analysis of the REACH registry, so too did the event rates significantly increase.[7] The REACH registry also identified that polyvascular disease was the strongest predictor of future ischemic events, with a 99% increase in major adverse cardiovascular events (MACE) after 4 years of follow-up.[14]

In patients with polyvascular disease, the risk of major adverse limb events (MALE) is also increased, primarily driven by the presence of PAD.[15] MALE represents a significant burden for patients with PAD, and it includes acute limb ischemia, critical limb ischemia, lower-extremity revascularization, and major amputation.[16] Patients at the highest risk for limb ischemia include those with prior peripheral revascularization, current smokers, and those with an ankle-brachial index (ABI) of ≤0.5 or ≥1.3.[16] In the primary care setting,

presentation with acute or limb-threatening ischemia represents a medical emergency that necessitates urgent referral to a vascular surgeon.[12]

Since patients with polyvascular disease, especially those with CAD and PAD, experience significant increases in the risk of thrombotic events, they can benefit from proper implementation of antithrombotic and cholesterol-lowering therapies.[1] Several studies indicate that patients with polyvascular disease have reductions in MACE and MALE with intensive antithrombotic and/or cholesterol-lowering treatment.[17-21]

CASE SCENARIO

A 59-year-old woman presents to her PCP with complaints of leg pain she's been having on and off for about a year. She notices the pain mostly when she's walking, and it is not alleviated by over-the-counter pain medication. She has a history of CAD, medically managed by her cardiologist for the past 7 years. Her ABI today is 0.4, she is a former smoker (quit 20 years ago), and she has not had any prior revascularization.

DETECTION OF POLYVASCULAR DISEASE AND RISK STRATIFICATION

In the case scenario above, the patient's complaints of leg pain should be addressed with medical therapy; upon further discussion, this pain might be identified as intermittent claudication, a hallmark symptom of PAD.[12] Additionally, the increased risk of thrombosis due to potential for polyvascular disease should also be realized, based on a likely new diagnosis of PAD, in addition to her history of CAD.

ESTABLISHING THE PRESENCE OF POLYVASCULAR DISEASE

While screening and diagnostic techniques for PAD and CAD have been thoroughly explored and described in published literature, routine screening for polyvascular disease after initial detection of atherosclerosis in a single arterial bed is controversial.[1,22,23] Possible reasons for the lack of guidance on follow-up screening for polyvascular disease include a lack of cost-effectiveness analyses; no difference in recommended treatment (in some guidelines); and difference in risk perception between CAD, PAD, and CVD.[1]

PAD. Screening for and diagnosing PAD involves a comprehensive medical history, physical exam, and ABI testing. The US Preventive Services Task Force (USPSTF) has stated that there is insufficient evidence to recommend for or against the use of the ABI to screen for PAD in asymptomatic adults, primarily due to the lack of studies evaluating benefits and harms of screening with ABI.[24] However, in patients with suspected PAD based on risk factors or symptoms, the ABI is considered a core diagnostic test, and the only one required to establish a diagnosis of PAD.[22] The 2016 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of lower-extremity PAD suggest an algorithm to aid clinicians in using a systematic approach to diagnostic testing for PAD.[22]

CAD. Despite substantial research and countless publications, the optimal approach to diagnosis of CAD remains unclear and poses a major challenge to healthcare systems in the United States.[23] Identifying stable CAD via functional or stress testing to detect ischemia is the most common noninvasive diagnostic test.[23,25] However, newer diagnostic tests such as coronary computed tomography angiography (CCTA) and simple, low-cost tests such as electrocardiogram (ECG) stress testing are also considered options for diagnosing CAD.[23,25-28] For patients with unacceptable ischemic symptoms or whose clinical characteristics indicate a high likelihood of severe ischemic cardiovascular disease, invasive testing via coronary angiography may be indicated.[29]

To enhance detection of polyvascular disease, PCPs should be attentive to signs and symptoms of atherosclerosis in other vascular beds for patients with established atherosclerotic disease.[1] A careful history and physical examination can often reveal noncardiac symptoms including amaurosis fugax and claudication.[1] The presence of polyvascular disease designates higher risk for MACE and MALE due to atherothrombotic events, and may indicate a need for aggressive antithrombotic therapy or even revascularization.[1]

MANAGING THROMBOTIC RISK FROM POLYVASCULAR DISEASE IN PRIMARY CARE

Pharmacologic treatment for polyvascular disease involves antithrombotic agents, comprising a variety of antiplatelet and anticoagulant drugs. Several guidelines can aid PCPs in selecting antithrombotic treatment, but not all guidelines have incorporated the most recent data.[12,22,30] US Food and Drug Administration (FDA)-approved agents for reducing thrombotic risk in PAD include clopidogrel, rivaroxaban, ticagrelor, and vorapaxar; aspirin has also been used.[31-34] Of note, rivaroxaban is the only agent indicated for reducing events in both PAD and CAD, including patients who have undergone lower-extremity revascularization.[32]

CURRENT RECOMMENDATIONS FOR ANTITHROMBOTIC THERAPY IN PAD/CAD

PAD. Current recommendations for antithrombotic therapy in PAD are informed by several clinical guidelines.[12,22,30,35,36] Overall, the guidelines recommend the following principles to reduce atherothrombotic risk in PAD:

- In patients with symptomatic PAD, antiplatelet agents are recommended to reduce MI, vascular death, and stroke.[22]

- Combination treatment with aspirin and low-dose rivaroxaban for prevention of cardiovascular events and MALE should be considered for patients with PAD and/or stable coronary artery disease.[30,36]
- Following revascularization, statins and antiplatelet drugs are recommended to decrease cardiovascular complications.[35]
- Rivaroxaban plus aspirin may also be an option for decreasing amputations and mortality after revascularization.[20,35]

CAD. For patients with established atherosclerotic CAD, antiplatelet agents are commonly used to prevent secondary events.[37,38] Historically, aspirin has been a cornerstone for secondary prevention, though studies of other antiplatelet agents as well as anticoagulants have demonstrated improvement in ischemic outcomes, usually at the expense of increased bleeding.[30,38] Clinicians are encouraged to balance the risk of recurrent ischemic and bleeding events when considering antithrombotic therapy in patients with CAD.[38] In regard to lipid therapy, high-intensity statin treatment is indicated for patients with atherosclerotic CAD, with a low-density lipoprotein (LDL) target of <70 mg/dL.[39]

CLINICAL TRIALS WITH DATA IN PATIENTS WHO HAVE POLYVASCULAR DISEASE

As noted previously, the risk of ischemic outcomes increases with the number of vascular beds with atherosclerosis, but so also does the potential benefit of antithrombotic agents. Since recent clinical trials have included data on atherosclerosis in noncardiac vascular beds, there are many trials that have at least 1 subgroup of patients that can be classified as having polyvascular disease and give insight for clinical management (**TABLE**).

CAPRIE. The Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial was one of the first to incorporate patients with atherosclerotic disease in noncoronary vascular territories.[40] This trial randomized patients with symptomatic PAD, recent ischemic stroke, or recent MI to clopidogrel or aspirin and found high rates of MACE (20%) in patients with polyvascular disease randomized to aspirin. The clopidogrel group demonstrated a relative risk reduction of 8.7% in MACE (95% confidence interval [CI], 0.3-16.5; *P*=0.043).[40]

TRA2°P-TIMI 50. The Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis–Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50) included patients with PAD, ischemic stroke, or stable prior MI and randomized them to vorapaxar or placebo.[41] After 3 years of follow-up, the vorapaxar group experienced a lower rate of MACE than the placebo group (9.3% vs 10.5%; hazard ratio [HR] 0.87; *P*<0.001). Additionally, the rates of MACE increased across groups with the number of atherosclerotic vascular beds (1 bed, 7.8%; 2 beds, 14.7%; and 3 beds, 21.7%).[42]

PEGASUS-TIMI 54. In the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS-TIMI 54) trial, patients with prior MI were treated with low-dose aspirin and were randomized to ticagrelor or placebo.[18] At 3 years of follow-up, ticagrelor reduced MACE compared to placebo for patients with PAD (absolute risk reduction 4.1% [95% CI, -1.07% - 9.29%]) and without PAD (absolute risk reduction 1.0% [95% CI, 0.14%-1.9%]). Patients with CAD and PAD combined had higher rates of MACE than those with CAD only (19.3% vs 8.4%).[18]

EUCLID. The Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease (EUCLID) trial included patients with PAD who were randomized to ticagrelor or clopidogrel.[43] There was no difference between the 2 treatment groups in rates of MACE (10.8% for ticagrelor vs 10.6% for clopidogrel; *P*=0.65).[44] Patients with PAD and CAD had higher rates of MACE than those with PAD only (15.3% vs 8.9%; HR 1.28 [95% CI, 1.13-1.99]). Additionally, in this cohort, polyvascular disease was independently associated with a higher risk of lower-extremity revascularization.[15]

SAVOR-TIMI 53, LEADER, and IMPROVE-IT. These 3 trials included patients with type 2 diabetes (T2D) and polyvascular disease since these conditions are closely related. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus (SAVOR-TIMI 53) trial, patients with T2D at risk for cardiovascular disease randomized to saxagliptin or placebo experienced similar rates of MACE, but those rates increased with additional vascular bed involvement.[45] In Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Results (LEADER), patients with T2D and high cardiovascular disease risk took liraglutide or placebo with no significant difference in MACE between groups; however, those with polyvascular disease were at higher risk of MACE than those with single-bed disease (22.2% vs 15.3%; HR 1.52 [95% CI, 1.33-1.72]).[46] The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) included patients with and without T2D and polyvascular disease, and found an increased rate of MACE in those with polyvascular disease compared to those without polyvascular disease (37.8% vs 19.5%; HR 1.55 [95% CI, 1.41-1.70]).[47] In the IMPROVE-IT trial, the simvastatin-ezetimibe group demonstrated lower rates of MACE than the simvastatin monotherapy group (32.7% vs 34.7%; HR 0.936; *P*=0.016).[48]

FOURIER. The Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial included participants with high-risk cardiovascular

TABLE. **Clinical trials evaluating risks of polyvascular disease and benefits of antithrombotic therapy**[1]

Study	Risks of polyvascular disease	Benefits of therapy
CAPRIE[40]	Increased CV death, MI, or stroke	Clopidogrel vs aspirin; lower CV death, MI, or stroke overall; no separate polyvascular analysis
TRA2°P-TIMI 50[41,42]	Increased CV death, MI, or stroke	Vorapaxar vs placebo; lower CV death, MI, or stroke; lower peripheral revascularization
PEGASUS-TIMI 54[18]	Increased CV death, MI, or stroke; composite and individual	Ticagrelor + aspirin vs aspirin alone; lower CV death, MI, or stroke; lower MALE
EUCLID[15,43]	Increased CV death, MI, or stroke; increased LE revascularization	Ticagrelor vs clopidogrel; no difference in CV death, MI, or stroke
SAVOR-TIMI 53[45]	Increased CV death, MI, or stroke	Saxagliptin vs placebo; lower CV death, MI, or stroke overall; no additional benefit in polyvascular subgroups
LEADER[46]	Increased CV death, MI, or stroke	Liraglutide vs placebo; no difference in CV death, MI, or stroke
IMPROVE-IT[47]	Increased CV death, MI, or stroke	Ezetimibe vs placebo; lower CV death, MI, or stroke overall; no additional benefit in polyvascular subgroups
FOURIER[17,49]	Increased CV death, MI, or stroke	Evolocumab vs placebo; lower CV death, MI, or stroke; lower MALE
COMPASS[20,50]	Increased CV death, MI, or stroke	Low-dose rivaroxaban + aspirin vs aspirin + placebo; lower CV death, MI, or stroke; lower MALE
VOYAGER-PAD[21]	Higher CV death, MI, stroke, acute limb ischemia, or major amputation for vascular causes	Low-dose rivaroxaban + aspirin vs aspirin + placebo; lower CV death, MI, stroke, acute limb ischemia, or major amputation for vascular causes

Source: Adapted from: Gutierrez JA, Aday AW, Patel MR, Jones WS. Polyvascular disease: reappraisal of the current clinical landscape. *Circ Cardiovasc Interv*. 2019;12(12):e007385.

disease or symptomatic PAD receiving appropriate statin therapy and randomized them to evolocumab or placebo.[49] There was a significant reduction in MACE with evolocumab (5.9% vs 7.4%; HR 0.80 [95% CI, 0.73-0.88]) in the overall study population, but not in the subgroup with polyvascular disease.[17]

COMPASS. In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, patients with stable atherosclerotic disease were randomized to rivaroxaban 2.5 mg twice daily plus aspirin, rivaroxaban 5 mg daily, or aspirin 100 mg daily.[20] In patients with polyvascular disease, rivaroxaban 2.5 mg twice daily plus aspirin demonstrated fewer net clinical benefit adverse outcomes (incorporating adverse efficacy events as well as safety bleeding events) vs aspirin (HR 0.80 [95% CI, 0.70-0.91]), primarily through reduction of adverse efficacy events.[50]

VOYAGER PAD. The Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER PAD) study enrolled patients with PAD (about one-third of whom had symptomatic CAD) who had undergone revascularization to rivaroxaban 2.5 mg twice daily plus aspirin or aspirin alone.[21] The rivaroxaban group experienced a lower rate of the composite efficacy outcome (acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from cardiovascular causes) at 3 years (17.3% vs 19.9%; HR 0.85 [95% CI, 0.76-0.96]; P=0.009).[21]

Although data are now emerging about the benefits of antithrombotic therapy in polyvascular disease, clinical evidence does not support specific antithrombotic therapy based on polyvascular disease phenotype.[1] Once polyvascular disease is identified, clinicians must decide whether to intensify therapy based on balance between reduction in the risk of ischemic events and the risk of bleeding.[1] Additionally, high-intensity statin therapy targeting an LDL of <70 mg/dL for patients with polyvascular disease is consistent with current guideline recommendations.[39]

CASE SCENARIO (CONT'D)

The 59-year-old woman is given a diagnosis of PAD, in addition to CAD, and thus has polyvascular disease. Due to the increased risk of MACE and MALE, she should be prescribed a high-intensity statin (if she's not taking one already). She should also be prescribed antithrombotic therapy, either with one of the antiplatelet agents with proven reduction in MACE (clopidogrel, ticagrelor, or vorapaxar), or with rivaroxaban 2.5 mg twice daily plus aspirin.

SUMMARY

Polyvascular disease is an underrecognized condition with significant clinical consequences. Patients with atherosclerosis in multiple vascular beds were consistently at higher risk for thrombotic events compared to those without polyvascu-

lar disease. PCPs can help initiate and monitor adequate antithrombotic and statin therapy in these patients and refer to specialists when necessary.

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Strategies to Improve Outcomes in COPD

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Dr. Yawn discloses that she serves on the advisory board of Boehringer Ingelheim, AstraZeneca, and GlaxoSmithKline. She also serves as a consultant to Boehringer Ingelheim and GlaxoSmithKline. Julie Akers, PharmD, discloses that she is on an advisory board for AstraZeneca.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease with no cure.[1] Despite being preventable and treatable, COPD is in the top 3 causes of mortality worldwide,[2] is the sixth leading cause of death in the United States,[1] and is a major cause of morbidity and healthcare expenditures.

COPD is expected to become more prevalent due to an aging population and risk factors such as smoking and air pollution.[3] While there are several risk factors for COPD, such as air pollution, exposure to fuel, and genetic or developmental abnormalities, smoking tobacco is the most common contributing factor in the United States[4] and is rapidly becoming a major risk factor in developing countries.[5,6]

COPD is estimated to contribute to nearly $40 billion in annual US healthcare expenditures.[7] The largest contributing factor to the economic burden of COPD is exacerbations, especially those frequent or severe enough to require emergency department visits or hospitalizations. In addition, cost of care directly correlates with disease progression and worsening symptoms with higher rates of comorbidities, polypharmacy, hospitalizations, and oxygen therapy.

This economic burden is also directly related to treatment for comorbidities, their impact on COPD progression, as well as the impact of COPD exacerbations on the comorbidities. Common comorbidities include diabetes, cardiovascular disease (CVD), lung cancer, gastroesophageal reflux disease, osteoporosis, depression, and anxiety.

According to the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) 2022 Report, several comorbid conditions can negatively impact COPD patient outcomes and vice versa.[8] Data spanning 35 years found that patients with COPD had a 2 to 5 times higher risk of ischemic heart disease than those without COPD.[9] In another study, the risk for a cardiovascular event was 10 times greater during the first 30 days following a COPD exacerbation that required hospitalization.[10] Therefore, the goals of management have shifted toward reducing symptoms, preventing exacerbations, and decreasing the risk of premature death.

DIAGNOSING AND ASSESSING THE SEVERITY OF COPD

Along with CVD, COPD has been shown to be an important primary consideration in the differential diagnosis of shortness of breath, frequent coughing or wheezing, sputum production, fatigue, and difficulty with deep inhalation.[8] While these symptoms plus smoking or other inhalation exposures, premature birth, age >40 years, and family history are key indicators, they are not diagnostic without spirometry confirmation.[8] The differential diagnoses include asthma, CVD, congestive heart failure, bronchiectasis, tuberculosis, lung cancer, cystic fibrosis, chronic allergic rhinitis, and gastroesophageal reflux disease.[8] Spirometry is the primary diagnostic tool to confirm COPD, with a postbronchodilator ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) of <0.7 indicative of COPD.[11] Spirometry will not rule out other comorbidities but is necessary to "rule in" COPD.

Patient-reported symptoms can be assessed using the modified Medical Research Council (mMRC) questionnaire, which measures breathlessness and assigns a grade of 0 to

4.[12] The COPD Assessment Test (CAT) is a comprehensive health status questionnaire that incorporates additional factors beyond breathlessness, such as frequency of cough and symptom impact on daily activities. CAT scores range from 0 to 40.[13] An mMRC grade of ≥2 or a CAT score of ≥10 indicates that the patient has a significant symptom burden. The mMRC is shorter but not as responsive to change as the CAT, but both are included in the GOLD 2022 ABCD Assessment Tool to guide treatment decisions.

GOLD recommendations are reviewed and updated annually based on emerging evidence; they recommend assessment of a patient's COPD status including airflow limitation, patient-reported symptoms, and exacerbation history to help predict patient outcomes and guide treatment decision-making.[8] Severity of airflow limitation is divided into 4 grades based on FEV_1: GOLD 1 (mild), an FEV_1 ≥80% predicted; GOLD 2 (moderate), an FEV_1 ≥50% and <80% predicted; GOLD 3 (severe), an FEV_1 ≥30% and <50% predicted; and GOLD 4 (very severe), an FEV_1 <30% predicted. These grades can be helpful in guiding timing for oxygen therapy evaluation.

THE IMPORTANCE OF REDUCING COPD EXACERBATIONS

Exacerbations are defined as an acute worsening of respiratory symptoms, including dyspnea, cough, and wheeze, and increased sputum purulence and volume, which necessitate additional therapy. Exacerbations have a negative effect on lung function and mortality,[14-16] and a history of exacerbations is a strong predictor of future exacerbations.[8]

Exacerbation assessment is grouped into low and high risk of future events based primarily on history of previous exacerbations, with lower risk indicated by 0 to 1 exacerbations not requiring hospitalization in the prior 12 months. Higher risk is indicated by the occurrence of ≥2 exacerbations not requiring hospitalization in the prior 12 months or ≥1 exacerbation that led to a hospital admission. The results of patient-reported symptoms and exacerbation history are combined to determine placement into groups A, B, C, or D; the resultant grouping is then used to guide initial pharmacologic treatment decisions (**FIGURE 1**).[8]

Exacerbation severity is classified by the treatments used to manage them. Mild exacerbations require only short-acting

FIGURE 1: **The refined ABCD assessment tool**

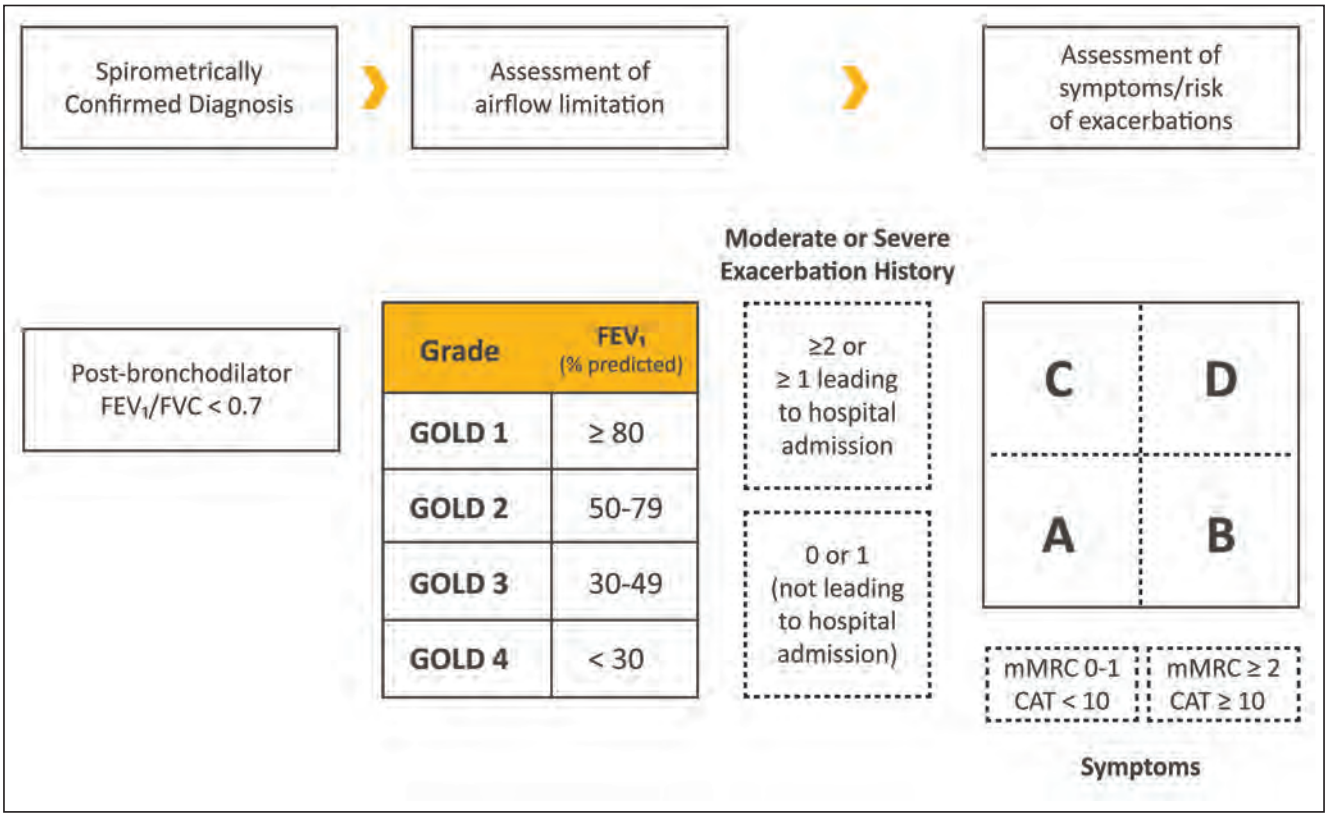

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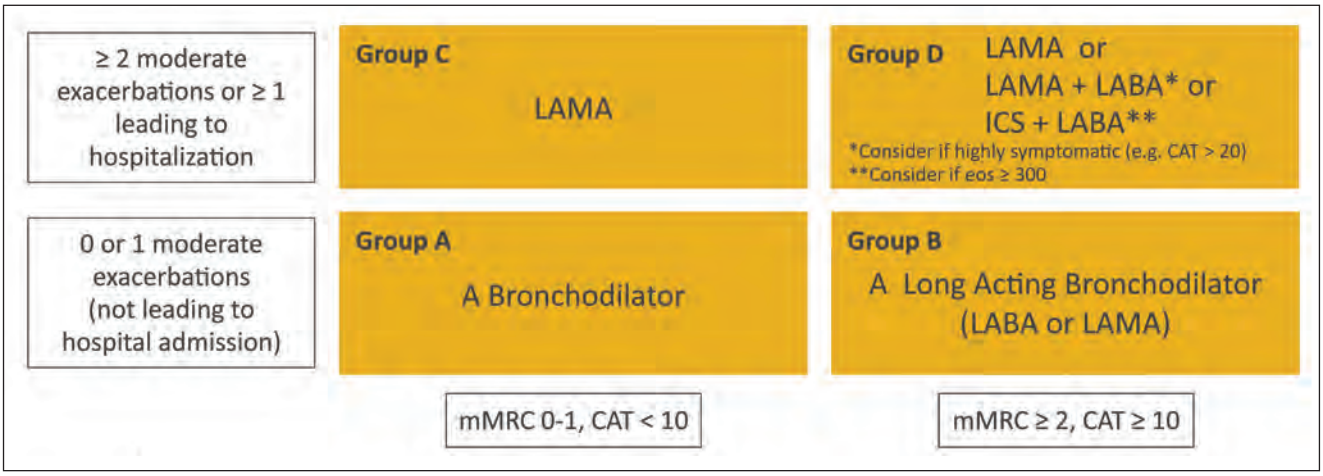
FIGURE 2. **Initial pharmacologic treatment**



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beta agonist (SABA) or short-acting muscarinic antagonist (SAMA) therapy. Moderate exacerbations require oral corticosteroid and/or antibiotic therapy. Severe exacerbations require an emergency department (ED) visit or hospitalization.[8]

Both moderate and severe exacerbations reduce lung function in patients with COPD of all groups, with the greatest losses in those with milder disease.[14] Additionally, increasing frequency and severity of exacerbations is tied to an increased risk of death.[15] In 1 study, 43% of patients with 1 severe exacerbation died within 6 years posthospitalization, and that death rate increased to 56% for patients who experienced ≥2 severe exacerbations.[16]

MANAGING COPD EXACERBATIONS

COPD exacerbations can be brought on by several factors, with respiratory tract infections being the most common.[8] While management of acute exacerbations focuses on immediate symptom resolution, the long-term goal is to prevent future exacerbations and mortality. That prevention starts by ensuring a follow-up appointment within about 1 week of an exacerbation, especially a severe exacerbation, to reduce rehospitalization and ED visits. Those patients not seen within 30 days of an exacerbation have an increased 90-day mortality rate.[17]

The postexacerbation visits should address exacerbation prevention measures, such as reassessing inhaler technique, adherence, smoking status, and irritant exposures as well as monitoring patient-reported symptoms (mMRC/CAT).

This is also an excellent opportunity to discuss pulmonary rehabilitation and evaluate comorbid conditions. Studies report that only 20% to 30% of patients are adherent to their prescribed COPD regimen,[18,19] and inhaler technique errors may occur in >50% of cases.[20] For some people, medication therapy management and counseling or adherence coaching have been shown to be helpful.[21] This may also be a good time to schedule repeat spirometry testing to assess COPD progression.

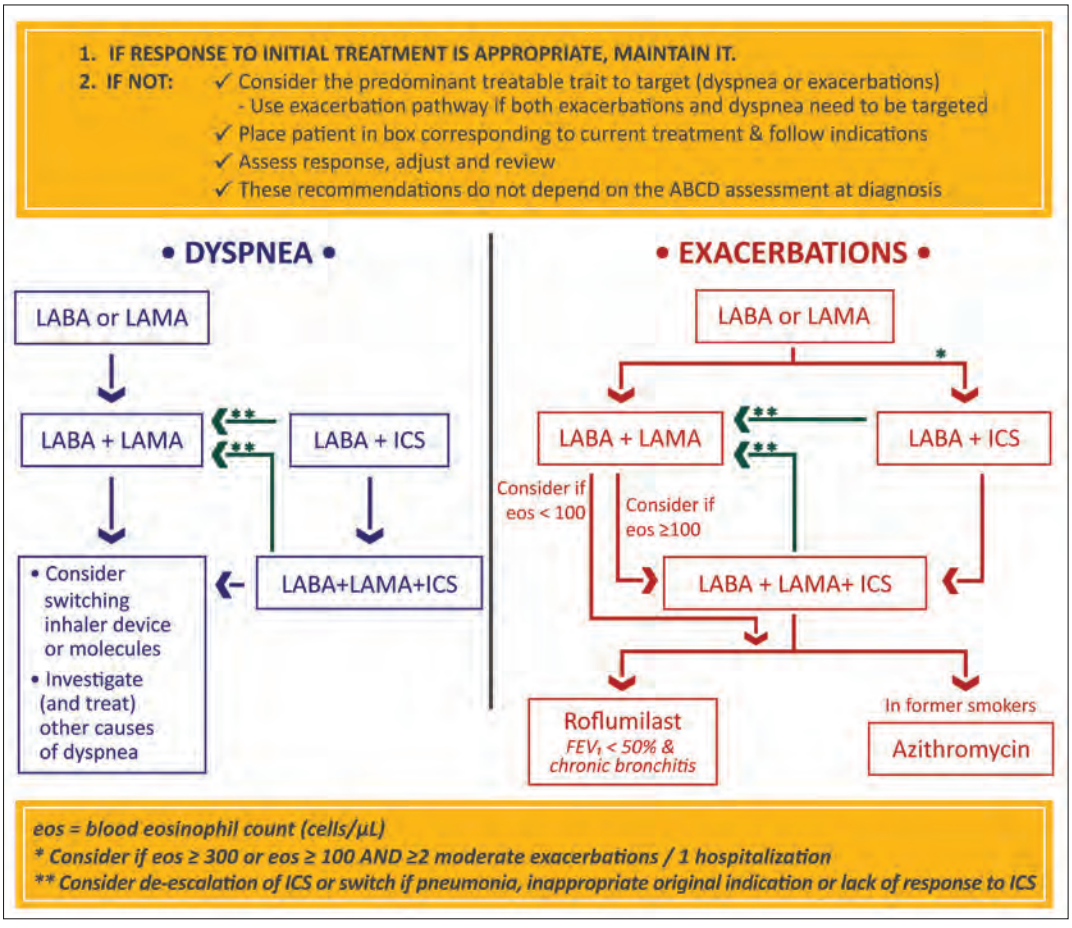
PHARMACOLOGIC TREATMENT OPTIONS

The goal of maintenance therapy is to reduce symptoms and exacerbations. The cornerstone of maintenance therapy is a pharmacologic approach based on symptoms, exacerbations, patient preference, side effects, costs, access, and patient ability to use the drug delivery device.

The GOLD ABCD Assessment Tool guides initial pharmacologic therapy choices (**FIGURE 2**).[8] All patients diagnosed with COPD should be prescribed a short-acting bronchodilator, such as a SABA or SAMA, for quick relief of increased shortness of breath or cough. For patients in group A, this can be the only therapy, but few people are diagnosed at this level of COPD. Patients in group B should be prescribed a long-acting bronchodilator, either a long-acting beta agonist (LABA) or long-acting muscarinic antagonist (LAMA) initially or in combination for those with greater breathlessness.

Patients in groups C and D have a greater risk of exacerbations, which guides their initial pharmacotherapy. Those in group C are recommended to begin therapy with a LAMA preferred over a LABA since LAMAs may be more effective in preventing exacerbations. Those in group D can be initiated on a LAMA, with dual therapy with LAMA + LABA if the CAT is >20 and adding an inhaled corticosteroid (ICS) if the blood eosinophil count is ≥300 cells/μL. ICS is used to prevent exacerbations, with recent recommendations noting that ICS is more effective in individuals with higher blood eosinophil counts.[22] Therefore, the choice to initiate ICS therapy is based on exacer-

FIGURE 3. **Follow-up pharmacologic treatment**



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bation prevention, treatment of coexisting asthma, and blood eosinophilia, balanced against risks in those with repeated pneumonia events or mycobacterial infection. Depending on response to initial pharmacologic therapy, adjustments to the patient's regimen may be warranted. **FIGURE 3**[8] provides follow-up treatment guidance and is separated into 2 sections—one for patients presenting with continued or worsening dyspnea, and the other for those presenting with frequent new or continuing exacerbations. If the patient presents with both exacerbations and dyspnea, the exacerbation pathway is used. Additional therapies may include moving to 2 bronchodilators or adding ICS or a phosphodiesterase-4 inhibitor or long-term antibiotic therapy. The figure includes recommendations for de-escalating therapy, such as discontinuation of ICS in those without exacerbations.

The timing of pharmacologic adjustments may play an important role in reducing future risk. In the PRIMUS study published in 2022,[23] researchers evaluated exacerbation frequency, all-cause and COPD-related healthcare utilization, and costs among patients who had experienced ≥2 moderate or ≥1 severe exacerbation and who started triple therapy within 30 days of the exacerbation (prompt), between 31 and 180 days postexacerbation (delayed), and 181 and 365 days postexacerbation (very delayed). Results showed 11% increased odds for any exacerbation and 7% increased odds of a hospitalization for every 30-day delay in triple therapy. Additionally, both all-cause and COPD-related costs increased as a result of delayed triple therapy.

The PRIMUS study results reinforce the need for prompt patient-clinician communication regarding increased symptoms and follow-up visits within days after an ED visit or hospitalization for an exacerbation to ensure therapy is appropriately and promptly modified.

Two single-inhaler triple therapies (SITT) are available in the United States, making it easier to prescribe ICS + LAMA + LABA in a single inhaler. Two large, 52-week, phase 3 studies (IMPACT and ETHOS) evaluated the effect of SITT vs LABA + ICS or LAMA + LABA on exacerbations, lung function, quality of life, and all-cause mortality. In these studies of symptomatic patients with a history of frequent and/or severe exacerbations, triple therapies reduced the rate of moderate or severe exacerbations and COPD-related hospitalizations. Additionally, a beneficial effect on all-cause mortality was observed with triple therapies vs LAMA + LABA.[24,25]

NONPHARMACOLOGIC RECOMMENDATIONS FOR COPD

To address COPD holistically requires assessment of the

impact of COPD on patients' current and desired activity capabilities, exacerbations, and patient and family preferences, as well as comorbidities. Management includes prevention and maintenance interventions, which range from lifestyle modifications to prescription therapies.

A 2020 survey noted that the smoking rate among US patients with COPD was >45%, which is higher than among patients with other chronic diseases (23%), asthma (20%), and no chronic disease (18.9%).[26] Smoking cessation can greatly improve disease prognosis. Successful smoking cessation programs include a multimodal approach incorporating counseling, nicotine replacement therapy, and other prescription pharmacologic products. Electronic cigarettes are not recommended for nicotine replacement therapy, as several studies indicate a link to lung injury and death.[27-30]

While smoking abstinence is the primary preventative measure to reduce exacerbations and slow disease progression, other measures to avoid irritants and infections including COVID-19 (masking, hand washing, distancing) and vaccination against influenza, pneumonia, COVID-19, pertussis (Tdap), and shingles are important.[8]

Additionally, patients in GOLD ABCD groups B to D should be considered for pulmonary rehabilitation, which formalizes a physical activity plan with goal setting, supervised exercise, smoking cessation, nutrition education, and tools for self-management. When pulmonary rehabilitation is not available, activity goal setting can increase exercise and activities.

EDUCATION AND FOLLOW-UP

Patient education and routine follow-up are important elements of a COPD care plan. Rapid COPD assessment tools such as the CAT or mMRC can provide a quick assessment of continuing or new disease burden and can be done while the patient is waiting in the examination room. Developing a written action plan to address daily therapy and increase patient awareness of early symptom exacerbation are cornerstones of COPD self-management. At every visit it is important to assess the patient's ability to adhere to therapy by asking nonjudgmental questions such as, "How often are you able to take all of your medicines?" "Do you have any problems getting or paying for your medicines?" Reviewing and observing inhaler technique repeatedly is beneficial since technique adequacy often declines 3 to 6 months after the initial instructions. Ask patients to bring their inhalers to each visit since the exact type or brand of inhaler may vary from what was prescribed due to insurance or cost requirements. For people with low adherence, motivational interviewing techniques may help address issues. A quick assessment of adequate sleep, a healthy diet, and regular exercise can identify areas for future support and emphasize the importance of a more in-depth program such as pulmonary rehabilitation.

Discuss avoiding exacerbation triggers like upper respiratory infections and continually reinforce the importance of smoking abstinence and avoidance if the patient continues to smoke or is around others who smoke. Review vaccination history and make appropriate recommendations based on the Advisory Committee on Immunization Practices vaccine schedule, the GOLD 2022 Report, and Centers for Disease Control and Prevention recommentations.[31] Patients with COPD should be seen every 3 to 6 months, depending on disease severity and frequency of exacerbations. The schedule for repeating spirometry varies based on initial results and the course of the COPD. Those with a greater symptom burden and more frequent exacerbations should have more frequent spirometry testing, which may guide therapy and timing of referral to a pulmonologist or allergist.

CASE SCENARIO PART 1

A 67-year-old woman is new to your practice. She reports she was diagnosed with COPD 2 years prior, when she was experiencing dyspnea and a chronic cough. She had a CAT score of 12 and no exacerbation history, was categorized in group B, and was prescribed a SABA and a LAMA. Six months after diagnosis, she experienced an exacerbation that was treated with oral steroid therapy. At that time, her daily maintenance therapy was not changed—she says she was told to remain on the LAMA, which she says she uses most days. She presents today with a chief complaint of increased breathlessness and cough for approximately 2 weeks that is not manageable with the SABA, used as needed, in addition to her daily LAMA. Her past medical history includes hypertension (controlled with an angiotensin-converting enzyme inhibitor for the past 10 years) and osteoporosis (treated with bisphosphonate). She smoked for 30 years, quitting 2 years ago when diagnosed with COPD. She states she receives an annual influenza vaccination and has had her COVID-19 vaccines and a booster as well as recent Tdap and shingles vaccine series.

Spirometry: postbronchodilator FEV_1 = 47%
CAT = 24
Eosinophil = 150 cells/μL
Oxygen saturation = 91% at rest
CT = no infiltrates, no signs of bronchiectasis, significant emphysema, or lung masses. Cardiac size is not increased

CASE SCENARIO PART 2: CLINICAL RESPONSE

It is important to consider alternative reasons for her increased dyspnea, such as COVID-19 or new cardiovascular symptoms vs a COPD exacerbation. She reports getting a COVID test at the drug store last week and again yesterday and both were nega-

tive. She has no current arrhythmias or complaints of chest pains, weight gain, or edema. Since she complains primarily of dyspnea, this could be the start of an exacerbation. This is especially important to consider since her FEV_1 is lower than anticipated. Her pulse oxygen level falls in the 88% to 92% range targeted for most COPD patients[32] and does not suggest that immediate hospitalization is necessary.

Because this may be an exacerbation, therapy will be both short-term use of an oral corticosteroid burst and consideration of modifying her current therapy. Since she is already on pharmacotherapy, it is appropriate to use the follow-up therapy flow diagram (**FIGURE 3**) to decide on modifications. The next step would be to move to dual bronchodilator therapy with LAMA + LABA and continue the SABA as needed.

She may soon become a candidate for triple therapy by adding an ICS to her LAMA + LABA if she experiences another exacerbation and her eosinophil count remains >100 cells/μL. Triple therapy has been shown to improve lung function and patient-reported outcomes and reduce exacerbations when compared with LAMA, LABA + LAMA, and LABA + ICS. Azithromycin may also be considered as add-on therapy as the patient is a former smoker and does not have chronic bronchitis.

The patient needs to have a follow-up visit in 7 to 10 days and receive details on how to contact the physician's office if her dyspnea progresses. It would also be appropriate to retest her spirometry in 6 to 8 weeks to see if the values reflect an exacerbation or disease progression. The follow-up visit is an excellent time to discuss pulmonary rehabilitation opportunities, to develop a COPD action plan, and to provide additional education and support. ●

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The Evolving Landscape of ASCVD Risk Among Patients With HIV

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LEARNING OBJECTIVES

- Summarize the multiple atherosclerotic cardiovascular disease (ASCVD) risk factors commonly present in persons living with human immunodeficiency virus (HIV).
- Identify factors for clinical assessment and risk stratification in persons with HIV (PWH).
- Discuss the clinical challenges of dyslipidemia management among the HIV population, including avoidance of major drug-drug interactions (DDIs).
- Implement appropriate and safe statin therapy in PWH and elevated ASCVD risk.

KEY TAKEAWAYS

- PWH are living longer and developing high rates of cardiometabolic abnormalities, placing this population at elevated risk of ASCVD.
- Antiretroviral therapy (ART) is responsible for reducing opportunistic infections and extending life. However, some ART regimens may be associated with increased incidence of cardiometabolic conditions and significant DDIs with some commonly used statins.
- ASCVD risk is underestimated in PWH, including among routinely used 10-year ASCVD risk calculators.
- Guideline-recommended therapy to manage increased ASCVD risk and low-density lipoprotein cholesterol (LDL-C) in PWH includes the use of statins.

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CASE SCENARIO

A 48-year-old white man with HIV, metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), and hypertension presents to clinic. He denies current alcohol, tobacco, or illicit drug use, but has a 50-pack-year smoking history. To help guide therapy, a coronary artery calcium (CAC) scan was performed.

Key Information

Laboratory: Lipid panel (mg/dL): total cholesterol 191; LDL-C 118; high-density lipoprotein cholesterol (HDL) 37; triglycerides 180; non-HDL 154

Hepatic enzymes slightly increased; high-sensitivity C-reactive protein 5 mg/dL (<3); glycated hemoglobin (HbA1c) 6.2%

Other: BP 124/78 mm Hg; 10-year ASCVD risk score 4.1%; CAC – 103 (moderate calcium deposits)

Medications: lisinopril, escitalopram, darunavir/cobicistat + tenofovir alafenamide + emtricitabine

INTRODUCTION

The introduction of potent antiretroviral therapy (ART) in the mid-1990s has markedly reduced mortality among persons with human immunodeficiency virus (PWH).[1,2] Currently, life expectancy for PWH is approaching that of the general population. As a result, care for PWH has evolved to also manage age-related comorbidities including dyslipidemia, hypertension, and glucose impairment.[1,3] While traditional risk factors such as smoking,[4,5] hypertension,[6,7] and diabetes[8] are more prevalent among PWH than in the general population, such conditions are further exacerbated by chronic human immunodeficiency virus (HIV) infection.[3] Transgender individuals with HIV also have increased atherosclerotic disease (ASCVD) risk due, in part, to the use of hormone therapy in gender-affirming treatment.[9]

As of 2022, approximately 50% of PWH in the United States were >50 years of age, and 80% of that group were men,[10] which further magnifies the overall burden of ASCVD

in PWH since heart disease manifests a decade earlier in men compared with women.[11] Even though the proportion of PWH who are virally suppressed has increased as ART regimens have become more potent and better tolerated, chronic HIV infection is associated with increased ASCVD risk, even in the setting of complete viral suppression. In the last decade, the incidence of myocardial infarction and strokes has continued to increase, and ASCVD has emerged as a leading cause of death among PWH.[12,13]

Polypharmacy is common among older PWH.[1] Some ART drug classes, including protease inhibitors (PIs) and, to a lesser extent, non-nucleoside reverse transcriptase inhibitors, are associated with significant drug-drug interactions (DDIs) and possible severe drug toxicities.[14] Therefore, treatment of comorbidities requires careful selection of medications by the clinician. The intent of this discussion is to guide practitioners in assessing ASCVD risk in PWH and safely and effectively managing dyslipidemia.

ELEVATED ASCVD RISK AMONG PWH

PWH are 50% to 100% more likely to have an ASCVD event compared with uninfected individuals across all age groups.[15,16] Increased ASCVD risk in PWH can be partly attributed to higher rates of common risk factors.[15] However, HIV infection is an independent enhancer of ASCVD risk due to residual immune activation that results in chronic inflammation, increased dyslipidemia, thrombosis, endothelial dysfunction, and vascular inflammation, even in the setting of viral suppression.[17] Furthermore, after adjustment for traditional risk factors, a clear gradient of ASCVD risk exists among PWH that increases with lower CD4 counts and higher viral loads, indicating the importance of viral control and immune reconstitution with ART.[18]

Further, it is estimated that up to ~20% of transgender women are living with HIV. Viral suppression rates are lower in this population, possibly due to poor treatment adherence and socioeconomic factors,[19] resulting in prolonged periods of increased chronic inflammation, which is associated with higher rates of ASCVD.[9] As noted, hormone therapy as part of gender-affirming treatment in this population is also associated with increased ASCVD risk. Other risk factors associated with HIV and ART are also commonly present in this population (**TABLE 1**).[11,20,21]

An important challenge in assessing ASCVD risk in PWH is that widely used risk calculators such as the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations and the Framingham Risk Score may underestimate ASCVD risk in PWH.[22-24]

PIs have been associated with significant cardiometabolic toxicities, with the possible exception of atazanavir.[25,26] Other contemporary ART classes, including integrase strand transfer inhibitors (INSTIs), may not directly increase cardiovascular (CV) risk, although significant weight gain has been observed with the use of INSTIs and with the nucleoside reverse transcriptase inhibitor tenofovir alafenamide.[14,27,28]

Insulin resistance drives metabolic changes in PWH, including mixed dyslipidemia.[3,11,20] PWH often present with low levels of high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and normal to moderately elevated low-density lipoprotein cholesterol (LDL-C). Approximately 14% of PWH in North America are co-infected with the hepatitis C virus (HCV).[29] Liver fibrosis due to untreated viral hepatitis or NAFLD in PWH further increases ASCVD risk.[30] Smoking rates in PWH are 2- to 3-fold higher compared with the general population, while physical activity is lower.[3,31,32] Higher rates of substance abuse (eg, alcohol, illicit drugs) and mood disorders also contribute to ASCVD risk, while gender-based discrimination and violence are more widespread and associated with poor health outcomes.[9,32]

Inflammation and immune activation negatively impact atherosclerosis and elevate ASCVD risk in PWH.[10,11,21] Compared with those without HIV, PWH have increased high-risk noncalcified carotid plaque, which is even observed in young PWH with few traditional CV risk factors.[33] CAC has also been shown to progress more rapidly in PWH compared with people without HIV.[34] In addition to their lipid-lowering properties, statins may also help to reverse atherosclerosis caused by chronic inflammation in PWH. Rosuvastatin has been shown to reduce ASCVD events in patients without HIV with increased inflammatory markers but normal LDL-C, as well as to decrease markers of immune activation and vascular inflammation, compared with placebo in a small trial of PWH.[10,35] Another trial in PWH demonstrated improvements in biomarkers of immune activity and inflammation with pitavastatin, which produced significantly greater reductions of soluble CD14, oxidized LDL-C, and lipoprotein-associated phospholipase 2 compared with pravastatin.[36] Collectively, statins appear to mitigate some of the unique risk factors that accelerate atherosclerosis and predispose PWH to CV events.

STATIN THERAPY IN HIV POPULATIONS AND THE IMPACT ON ASCVD AND MORTALITY

Statin therapy remains the foundation for lowering LDL-C and managing CV risk factors observed in PWH.[3,11,21] Challenges persist, however, including the avoidance of major DDIs and addressing disparities in access to care and inconsistencies in management of traditional risk factors in different populations. Critical questions are still being answered including, do statins reduce ASCVD events in

TABLE 1. **Common cardiometabolic abnormalities and ASCVD risk factors among PWH**[3,11,20,21]

• Mixed dyslipidemia	• Thrombosis
• Hypertension	• Immune activation
• Insulin resistance/glucose impairment	• Hepatic steatosis
• Systemic inflammation	• Gut dysbiosis
• Endothelial dysfunction	• ↑↑ behavioral/lifestyle factors
• Weight gain, ↑ central obesity	• Gender-affirming treatments

PWH? Further, it is widely reported that statins are underused and underdosed in PWH.[37] Studies indicate that clinicians are less likely to prescribe statin therapy to high-risk PWH,[38] while those who receive a statin are more likely to receive less-intensive therapy.[39]

Prior studies suggested ASCVD event reductions with statins in HIV-infected cohorts are similar to those in the general population.[40-42] The need for a large primary prevention, randomized, placebo-controlled statin trial to assess the effect of statins beyond lipid-lowering in PWH was recognized by the National Institutes of Health, with the development of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE).[43] This trial has enrolled >7700 PWH in 12 countries between the ages of 40 and 75 years, randomized to either pitavastatin 4 mg daily or matching placebo. The REPRIEVE trial is primarily designed to measure the impact of statin therapy on ASCVD outcomes in PWH, but also includes an important substudy evaluating the relationship between immune and inflammatory biomarkers and coronary plaque.[33] The trial is scheduled to be completed in 2023, with results expected shortly thereafter.

CLINICAL CHALLENGES AND CONCERNS

ASCVD risk assessment and management of dyslipidemia among PWH is essential.[3,21] Comorbidities in PWH may include NAFLD and coinfection with chronic viral hepatitis B or HCV.[37] Importantly, most statins can be safely used in patients with NAFLD and/or HCV or with mildly elevated hepatic transaminases.[11,32] In fact, drug-induced liver injury and overall mortality were each significantly less frequent among statin users compared with statin nonusers with HIV/HCV or HIV alone.[44] Although liver function monitoring after starting statins is not recommended by the Food and Drug Administration, clinicians may consider checking liver enzymes 1 month after initiating statins in patients who may have preexisting conditions or who take other medications that could increase the risk of liver toxicity. Persistently elevated hepatic transaminases exceeding 3 times the upper limit of normal is the threshold for dose reduction or discontinuing statin therapy.[3,11]

Major DDIs between statins and ART primarily involve the PIs (**TABLE 2**).[3,42] Importantly, the PI boosters ritonavir and cobicistat, designed to specifically inhibit the metabolism of PIs (and of the INSTI elvitegravir) to achieve higher serum levels, also inhibit cytochrome P450 3A4 enzyme-dependent statins (ie, lovastatin, simvastatin), markedly increasing statin serum levels and potentially resulting in myotoxicity.[11,14,32] Consequently, statin selection should be based on the potential for DDIs with ART (**TABLE 2**).[3,11,21]

CLINICAL ASSESSMENT AND RISK STRATIFICATION

All adult PWH require ASCVD risk assessment. Statins are underprescribed and underdosed in PWH, resulting in lower LDL-C reduction.[37-39] Lipid panels are recommended initially and again with ART modification.[10] Unfortunately, ASCVD risk calculators (ACC/AHA Pooled Cohort Equation, Framingham Risk Score) may underestimate risk in PWH.[3,24] A CAC can be considered in selected individuals when the decision about whether to initiate a statin is uncertain.[11,21]

GUIDELINE REVIEW: TREATMENT

Specific ASCVD risk management recommendations for PWH are evolving from major guideline organizations (**TABLE 3**).[3,11,21] After ASCVD risk assessment, an initial emphasis on therapeutic lifestyle changes cannot be overstated. Increasing physical activity, smoking cessation, and maintaining mental health wellness are a few components that reduce ASCVD risk and improve quality of life for PWH. Early initiation of ART and maintenance of viral suppression are critical to limit ASCVD events and overall mortality for all PWH. Interrupted ART is strongly associated with an increase in acute ASCVD events and death.[45] Second, comprehensive management of modifiable risk factors is important.[3,11,21] Lastly, statins should be considered for all adult PWH with established ASCVD, untreated dyslipidemia, diabetes mellitus, or a high calculated ASCVD risk. Statin therapy should also be considered for PWH with moderate calculated ASCVD risk or with HIV-related risk-enhancing factors such as prolonged viremia, low CD4 nadir, metabolic syndrome, history of NAFLD, or HCV

TABLE 2. **Statin dose recommendations with HIV protease inhibitors**[3,10]

Statin	Effect of PIs and cobicistat on statin	Statin dose recommendations
Atorvastatin	Moderate AUC ↑↑	Avoid TPV/RTV Use lowest starting dose: LPV/RTV Dose limit 20 mg: DRV/RTV, FPV/RTV, SQV/RTV, or FPV alone Dose limit 40 mg: NLV
Fluvastatin	No data with most PIs except NLV	Appropriate dosing and monitoring, except not recommended with NLV[a]
Pitavastatin	Minor/modest AUC changes	No dose adjustments needed
Pravastatin	Mostly minor/modest AUC changes, except with DRV AUC ↑ 81%	No dose adjustments needed except use lower starting dose: DRV
Rosuvastatin	Some moderate AUC ↑↑; others only minor AUC changes	Dose limit 10 mg: ATV/RTV, LPV/RTV Use lowest effective dose: DRV/RTV
Lovastatin	All PIs and cobicistat: AUC ↑↑↑	**Contraindicated**
Simvastatin	All PIs and cobicistat: AUC ↑↑↑	**Contraindicated**

Abbreviations: ATV, atorvastatin; AUC, area under the curve; DRV, darunavir; FPV, fosamprenavir; LPV, lopinavir; NLV, nelfinavir; RTV, ritonavir; SQV, saquinavir; TPV, tipranavir.

[a]Limited data, based on known metabolism of fluvastatin.

TABLE 3. **Key cholesterol guideline recommendations for primary prevention in adults with HIV**[3,11,21]

	ACC/AHA 2018	ESC/EAS 2019	NLA 2015
HIV CV risk status	Risk enhancer[a]	Confers↑ risk	Independent risk factor
Lipid goals and treatment	Optimize TLC including smoking cessation • 40-75 years old with LDL-C 70-189 mg/dL • 10-year ASCVD risk ≥7.5% ○ Favors moderate- to high-intensity statin • 10-year ASCVD risk ≥5% ○ Consider moderate-intensity statin	Many HIV patients qualify as high risk • Goal: LDL-C reduction >50% and LDL-C <70 mg/dL	Emphasize TLC • Diet/exercise • Smoking cessation HIV + 2 other risk factors • Goal: LDL-C <100 mg/dL and non-HDL <130 mg/dL
Preferred statins (based on potential for major DDIs)	None specified	Fluvastatin, pravastatin, pitavastatin, rosuvastatin	Pitavastatin (no dose limits) Atorvastatin or rosuvastatin (with dose limitations)
Other	Consider CAC to further risk stratify Obtain a fasting lipid panel to: • Evaluate ASCVD risk • Monitor and adjust lipid-altering therapy, before and 4-12 weeks after initiating ART	Consider CV imaging (eg, CAC) as a risk modifier in primary prevention patients	Obtain a fasting lipid panel before and after initiating ART

Abbreviations: ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; NLA, National Lipid Association; TLC, therapeutic lifestyle changes.

[a]Defined as a clinical condition or factor that is associated with ASCVD and used to inform therapy decisions.

coinfection.[32] Statins may also be indicated for PWH without dyslipidemia with low to moderate calculated ASCVD risk as they improve underlying abnormalities (eg, inflammation, immune activation, endothelial dysfunction) beyond LDL-C.[3] The results of the REPRIEVE trial will help to determine the role of statins in this population.

CASE SCENARIO (CONT'D)

This PWH has multiple cardiometabolic issues and underestimated ASCVD risk, as the CAC indicates significant subclinical disease. Guidelines would favor prescribing a moderate-intensity statin and carefully selecting an agent based on potential for DDIs (noting that cobicistat inhibits CYP3A4). A statin is not contraindicated due to the NAFLD and slightly elevated hepatic transaminases.

SUMMARY

PWH are living longer and commonly develop cardiometabolic conditions and accelerated atherosclerosis because of traditional risk factors and underlying chronic inflammation. ASCVD risk in PWH is often underestimated, and dyslipidemia management can pose challenges for the clinician, including the avoidance of major DDIs. Guidelines suggest ASCVD risk should be assessed for all adult PWH and appropriate and safe statin therapy implemented among those with elevated ASCVD risk. ●

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The New Face of Preadolescent and Adolescent Acne: Beyond the Guidelines

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DISCLOSURES

Dr. Eichenfield discloses that he serves as an investigator or consultant for Allergan, Almirall, Cassiopea, Dermata, Galderma, L'Oreal, Ortho Dermatologics, and RBC Consultants. Dr. Hebert discloses that research funds are paid to UTHealth McGovern Medical School – Houston by Cassiopea, Galderma, Allergan, Pfizer, and Novan, and honoraria are received from Verrica, Pierre Fabre, and Relife. She serves on the Data Safety Monitoring Board for Sanofi-Regeneron, Ortho Dermatologics, and GlaxoSmithKline. Dr. Desai serves as a consultant for or on the speakers bureau for Galderma, Almirall, Cassiopeia, Foamix, Scientis, Ortho Dermatologics, Dermira, and Pfizer; and as a principal investigator of research grants for AbbVie, Watson, SymBio, and Novan. Dr. Levy discloses that he serves as an investigator and/or advisor for Cassiopea, Regeneron, Janssen, Abeona, Castle Creek, and Krystal; and as an author and section editor for UpToDate. Dr. Mancini discloses that he serves on the advisory board and has received an honorarium from Cassiopea. Dr. Rice serves on the advisory board for Cassiopea, Pfizer, and Medscape; as a consultant for Brickell Bio, Cassiopeia, Dermira, and Pfizer; as a principal investigator of research grant for Anacor, Celgene, Galderma, Regeneron/Sanofi-Genzyme, Merck, and AbbVie; and on the speakers bureau for Dermira, International Hyperhidrosis Society, Pfizer, and PRIME. Dr. Sugarman discloses that he serves on the advisory board or as a consultant for Cassiopea, Bausch, Galderma, and Solgel. Dr. Zaenglein discloses that she serves on the advisory board or as a consultant for Cassiopea, Pierre Fabre, and Pfizer; as a researcher for Incyte and AbbVie; and as an editor for *Pediatric Dermatology*.

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ABSTRACT

Acne is a highly prevalent condition, affecting the majority of people at some point in their lifetimes, most often during adolescence. Acne has also become increasingly common among preadolescents (aged ≥7 to ≤12 years old).

Acne is often treated in primary care settings by nondermatologists. The most recent acne guidelines were published in 2016; since then, there have been important developments in the acne treatment landscape. Familiarity with these options is important for physicians who manage patients with acne.

The Preadolescent Acne Roundtable group of dermatologists was convened in July 2019 to support discussion around modernizing the approach to treatment and evalua-

tion of preadolescent acne. During a face-to-face meeting, 5 key areas requiring careful communication emerged: acne pathophysiology, specifically the role of hormones; psychological aspects of acne; management of acne in younger patients; acne in skin of color; and evaluation of clinical success.

This roundtable report describes these 5 focus areas, with the aim of empowering primary care physicians to refine the care they provide for patients with acne. This report can help bridge the information gap until new acne treatment guidelines are published.

INTRODUCTION

Acne is estimated to affect >90% of adolescents (aged 12 to 20 years) in some populations.[1,2] Globally, as of 2017, nearly 120 million people were affected by acne.[3] While typically associated with mid- to late adolescence, acne can also affect preadolescents,[4] and its prevalence in this population may be increasing.[5]

The last American Academy of Dermatology (AAD) guidelines on acne treatment were published in 2016,[6] and the American Academy of Pediatrics–endorsed evidence-based clinical guidelines for the management of pediatric acne were published in 2012.[7] As consensus reports have noted, practice guidelines may become outdated before new ones are published.[8] Therefore, it is important for practicing physicians to stay up to date on recent advances in the acne field.

The Preadolescent Acne Roundtable group of dermatologists was convened in 2019 to support discussion around modernizing the approach to the treatment and evaluation of preadolescent acne. During the meeting, 5 key areas were discussed: acne pathophysiology, specifically the role of hormones; psychological aspects; acne management in younger patients; acne in skin of color; and evaluation of clinical success.

The group also discussed that not all patients with acne are managed by a dermatologist; a survey reported that 26% of preadolescent patients with acne were managed by a general or family practitioner.[9] This report, therefore, was developed to provide the latest updates and information to primary care professionals before new guidelines are published. For each topic, "clinical pearls" from the authors are included.

This report follows the terminology used in the American Academy of Pediatrics/American Acne and Rosacea Society Evidence-Based Recommendations for the Diagnosis and Treatment of Pediatric Acne; preadolescent acne refers to patients aged ≥7 to ≤12 years old, or before menarche in female patients.[7]

PATHOPHYSIOLOGY OF ACNE

Androgens in acne pathogenesis

Acne pathophysiology involves 4 main components: increased production of sebum, follicular hyperkeratinization, colonization with *Cutibacterium* (formerly *Propionibacterium*) *acnes* (*C. acnes*), and inflammation.[10-12] Androgens, such as testosterone and dihydrotestosterone, enhance sebaceous gland activity and stimulate sebum production.[10,11,13] The **FIGURE** shows an overview of the role of androgens in acne pathophysiology.[11,13,14]

Systemic treatments targeting hormones have become a mainstay of treatment for moderate to severe acne in adolescent girls and older women, usually in combination with other therapies.[6] Combined oral contraceptives (COCs) and spironolactone are commonly used hormonal treatments.[6] However, spironolactone is not approved by the US Food and Drug Administration (FDA) for this indication, and limited safety data exist in adolescents.[6,15] Furthermore, some adolescents and their parents are not comfortable with COC use.[16] The use of topical hormonal therapy such as clascoterone cream 1% can target androgen-stimulated sebaceous gland activity and decrease acne in both male and female patients, with a favorable safety profile.[17]

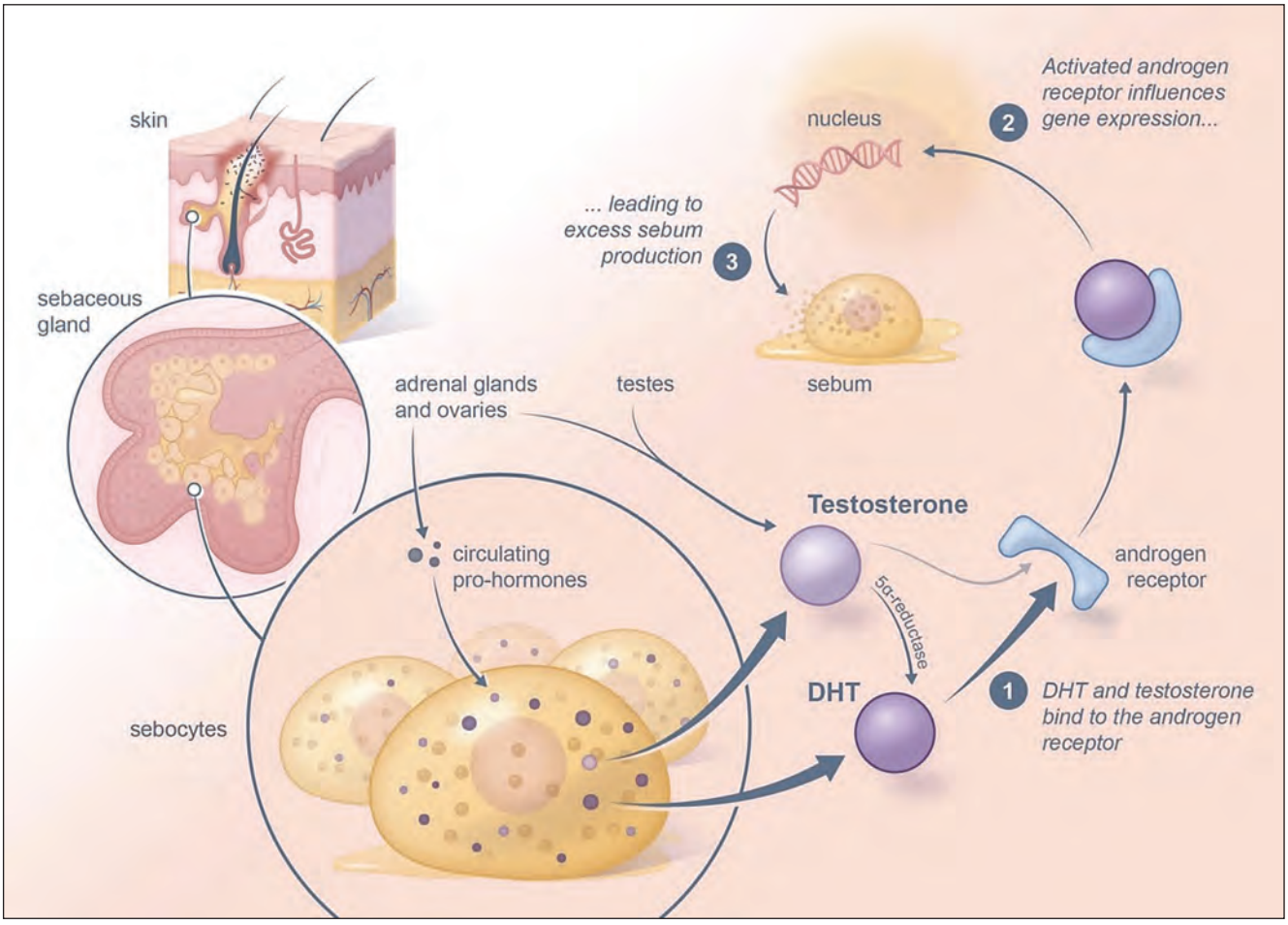
Clinical pearl: *Teach patients and families some of the basics of acne pathophysiology so that they can better understand the rationale behind management decisions.*

Preadolescent acne microbiome

The skin microbiome changes with age and is known to influence skin conditions,[18] but limited information is available on the microbiome of preadolescents with acne. A pilot study found a greater diversity of cutaneous bacteria in preadolescents with acne than without acne.[19] In pretreatment observations, the relative abundance of bacterial species differed between the groups: those with acne had more *Staphylococcus* and *Cutibacterium* species than controls. All participants had a relatively high amount of *Streptococcus*.[19] Following treatment with benzoyl peroxide (BP) or tretinoin, diversity of the skin microbiome was reduced to levels similar to those of control subjects.[19]

A larger study with 51 girls aged 7 to 12 years old found that changes in microbiome diversity were associated with increasing age and acne lesion number. *Streptococcus mitis* was more abundant in younger individuals and those with fewer lesions, and *C. acnes* was more abundant in older individuals and those with higher numbers of acne lesions. *C. acnes* was more prevalent in sebaceous vs less sebaceous sites (forehead/nose vs cheeks/chin), consistent with these being areas of early sebaceous gland activity.[20] The num-

FIGURE. **The role of androgens in acne pathophysiology**



Circulating pro-hormones produced by the adrenal glands and ovaries can be converted within sebaceous glands in the skin into testosterone and dihydrotestosterone (DHT).[13] Circulating testosterone is produced by adrenal glands, testes, and ovaries. Sebocytes express 5α-reductase, which converts testosterone into the more potent dihydrotestosterone.[13,14] Dihydrotestosterone and testosterone bind to the androgen receptor within sebocytes, causing it to translocate to the nucleus and act as a transcription factor.[14] This can lead to the excess sebum production seen in acne, which can result in inflammation and influence keratinocyte proliferation and differentiation, leading to follicular hyperkeratinization.[11]

ber of acne lesions decreased after BP treatment (average 7 weeks), but changes in the microbiome were not observed.[20]

PSYCHOLOGICAL ASPECTS OF ACNE

Acne can have a significant adverse impact on quality of life (QOL),[7,8] and even mild acne may be troubling for patients.[7] A cross-sectional study of 1531 respondents aged 11 to 19 years reported the adverse effects of acne on QOL and psychological health.[21] Nearly half of respondents with mild acne reported embarrassment and reduced self-esteem, while nearly one-third reported feelings of unworthiness and teasing due to their acne.[21] Results of questionnaires sent to a national acne dermatologic support group found a likely correlation between respondents with higher levels of skin-related social anxiety and reports of lower self-esteem and less intention to participate in sports and exercise.[22]

While some QOL impairments may be short-term or easily managed, patients may experience more serious problems. A questionnaire-based study of 3775 adolescents in Norway found that 24.1% of respondents with substantial acne vs 9.5% with no to little acne reported suicidal ideation in the previous week.[23] Other recent studies have further confirmed the serious impact of acne on QOL.[24-26]

The psychological aspects of acne focusing on preadolescent patients have not been reported; with increasing numbers of younger patients presenting with acne, the authors encourage research into this important area.

Numerous measures to assess the impact of dermato-

logic conditions on QOL exist.[8] In the authors' experience, completing a detailed, formal QOL assessment in clinical practice can be challenging due to time constraints. However, simple questions about how the patient is feeling can yield information about their emotional well-being and indicate whether further investigation or intervention is required. The high risk for anxiety and depression among patients with acne warrants aggressive treatment and consideration of routine psychiatric screening.[27]

Previous consensus recommendations have noted the importance of physician counseling for patients with acne, setting expectations for when treatment effects can be seen and understanding the causes of acne.[8] It is important that treating physicians show empathy for their patients' emotional distress due to acne.[8]

Clinical pearl: *Ask the patient how acne is impacting daily life. This can elicit valuable information about the patient's emotional well-being.*

SOCIAL MEDIA

Over the last decade, the environment for adolescents has changed considerably with the widespread use of smartphones and the impact of social media. Social media can be a valuable source of easily accessible information and support from others with similar conditions.[28] Discussions on acne treatment can be found on numerous social media platforms.[29] Healthcare professionals should be aware of the benefits and risks of social media use by acne patients.

A systematic review of social media use in healthcare categorized the reasons patients use social media for health-related purposes as emotional support, esteem support, information support, network support, emotional expression, and social comparison.[28] These may represent unmet needs for patients, although the results were not specific to dermatology or acne. The review reported that patients typically use social media as a complement to their interactions with healthcare professional services.[28] Better informed and more confident patients may be able to communicate on a more equal footing with healthcare professionals.[28]

Risks of social media include possible dissemination of imbalanced information or incorrect and even dangerous healthcare myths.[30] For example, only a small portion of English tweets regarding mask-related acne posted in September 2020 were from healthcare providers and organizations (1.7%) or dermatologists (0.1%), while the majority (68.8%) were from patients. Of tweets from commercial business sources, 83.7% promoted acne treatments or encouraged online shopping.[31] The top 50 TikTok videos categorized as "Accutane Check" focused on improvement in acne severity before and after isotretinoin treatment, with minimal discussion of side effects,[32] and a cross-sectional study evaluating acne-related medical information on TikTok raised serious concerns regarding the low quality of such information.[33]

Use of social media has also been associated with diminished subjective well-being. A data analysis from nationally representative surveys reported that adolescents who spent more time on screen activities were more likely to have high depressive symptoms or a suicide-related outcome vs those who spent more time on nonscreen activities.[34] Furthermore, adolescents who used social media sites every day were 13% more likely to have high levels of depressive symptoms than those who used social media less often.[34]

Healthcare professionals should be aware that patients may access inaccurate information online and should directly address this to avoid misunderstanding. However, optimal utilization of social media for its beneficial aspects could be encouraged to empower patients and make them stakeholders in their treatment.

Clinical pearl: *Suggest reliable online resources to help prevent the spread of misinformation. Remember that patient use of social media should complement, not replace, interactions with healthcare professionals.*

ACNE IN YOUNGER PATIENTS

Epidemiology of acne in younger patients

While typically associated with puberty, acne is not rare in preadolescent children.[4] A prospective observational study from Italy reported acne prevalence of 34.3% in children aged 9 to 14 years and 6% in 9-year-old children.[4] Results from 2 retrospective multicenter studies in Korea found that patients aged <13 years accounted for 11% of the total non-adult acne patients, and that the number of children <10 years old with acne had increased by 73% over the past 10 years.[5] A survey in the United States showed similar results: 4.8% of acne visits among patients 18 years of age and younger were for preadolescent patients (aged 7 to 11 years).[9]

EARLIER ACNE ONSET

Studies have noted a trend toward younger age at first acne presentation, possibly due to earlier onset of puberty.[7,35] In the authors' experience, additional factors pertaining to both patients and healthcare professionals may lead to earlier acne presentation. For example, increased media coverage and direct-to-consumer advertising have improved awareness of treatment options among patients and their families. Family history may play a role; parents may advo-

cate for treatment earlier if they experienced successful treatment themselves. Finally, as discussed previously, social media has increased pressure for clear skin, meaning patients may be more likely to seek acne treatment.

Regarding physicians, improved messaging and education has led to increased referrals to dermatologists from primary care physicians and pediatricians. The recognition of the importance of early treatment to reduce sequelae such as scarring has also increased among physicians.

Treatments for preadolescent patients with acne

The treatment of uncomplicated acne in preadolescent patients is typically comparable with that in older patients, although some agents are used off label.[7] As guiding principles, the treatment of preadolescent acne should be the least aggressive regimen that is effective, while avoiding development of antibiotic resistance and targeting the greatest number of pathogenic factors.[7] Over-the-counter products containing ingredients such as salicylic acid or BP may be effective for preadolescent patients with mild acne, as in older patients.[7]

While a growing number of FDA-approved acne medications such as topical retinoids and a fixed combination of adapalene and BP are available for preadolescent acne patients ≥9 or ≥10 years old,[6,36-40] the safety and effectiveness of the majority of acne treatments have not been established in pediatric patients <12 years of age (**TABLE**).[6]

COCs are useful treatment options for older adolescents when indicated; however, there is some concern regarding bone mass accrual in younger adolescent patients.[6,7] The FDA has approved 4 COCs for the treatment of acne in female patients who desire contraception: norgestimate/ethinyl estradiol, norethindrone acetate/ethinyl estradiol/ferrous fumarate, drospirenone/ethinyl estradiol, and drospirenone/ethinyl estradiol/levomefolate.[6,7] However, none are approved for patients <14 years old,[6] and the pediatric acne recommendations suggest withholding oral contraceptives for acne unassociated with endocrinologic pathology until 1 year after onset of menstruation.[7] The safety and efficacy of spironolactone in preadolescent patients with acne have not been well studied.

An analysis of prescribed acne treatment for preadolescents and adolescents found that the top 3 most commonly prescribed medications for preadolescent acne were all topical: adapalene, BP, and tretinoin.[9] There was some disparity in treatments prescribed by different specialists, with primary care physicians preferring antibiotics (topical and oral) and dermatologists preferring topical retinoids. The findings of this study highlighted a potential knowledge gap among primary care providers based on their prescribing behaviors.[9] It should be noted that off-label prescribing for acne in preadolescent patients is common,[9] possibly due to the limited number of approved therapies.[7]

Considerations for managing younger patients with acne

In the authors' experience, adherence can be challenging with all patients, including adolescent and younger patients. For preadolescent patients, parents are often involved in treatment and are crucial for maintaining adherence. For all patients, streamlined regimens with combination products or fewer medications should be considered to maximize treatment adherence.

Earlier onset of comedonal acne is associated with more severe disease later on.[41,42] Recognition of early significant acne should encourage close monitoring to ensure prompt treatment for more severe disease, if indicated, with more aggressive therapy considered when needed.

Clinical pearl: *Appropriately treat patients—regardless of their age—according to the severity of their acne.*

ACNE IN SKIN OF COLOR

Despite similar etiology, the clinical presentation of and therapeutic approach to acne can differ in patients with Fitzpatrick skin types IV to VI.[43] Adolescents with darker skin types have increased risk of post-acne keloid formation and are more likely to develop postinflammatory pigmentary changes, such as postinflammatory hyperpigmentation (PIH), compared with lighter-skinned adolescents.[44,45] In a study of photographs from 2895 women and girls (aged 10 to 70 years), clinical acne and hyperpigmentation were more prevalent in African American (37% and 65%) and Hispanic subjects (23% and 48%) relative to continental Indian (23% and 10%), Caucasian (24% and 25%), and Asian (30% and 18%) subjects.[46] In a survey of 208 adult women 25 to 45 years of age with facial acne (49% non-white/Caucasian [Black/African American, Hispanic/Latina, Asian, and other], 51% white/Caucasian), PIH incidence was greater in non-white/Caucasian women compared with Caucasian women.[47]

PIH can be very concerning for patients, who may be worried about long-term appearance. Often interpreted as scarring, PIH is reversible, although long lasting. Treatment counseling for patients with skin of color should therefore include discussion of PIH, with reassurance that these are surface changes—which are usually temporary and fade over time—in contrast to true scars. For physicians, PIH can be difficult to assess. A study reported significant variability among dermatologists reviewing potential PIH cases, with

TABLE. **Management of pediatric acne: Selected recommendations from the 2016 AAD guidelines[6]**

Product	Indication/pediatric use
Topical treatments	
BP	Safety and effectiveness have not been established in pediatric patients <12 years of age
Salicylic acid	Salicylic acid 6% cream, lotion, and gel and 15% plaster are not recommended in children <2 years of age. Increased risk of toxicity with prolonged use in pediatric patients <12 years of age
Azelaic acid	Safety and efficacy have not been established in pediatric patients <12 years of age
Antibiotics	
Erythromycin	Safety and efficacy of single-entity topical gel or solution have not been established in children
Erythromycin/BP	Safety and effectiveness have not been established in pediatric patients <12 years of age
Clindamycin	Safety and effectiveness have not been established in pediatric patients <12 years of age
Clindamycin/BP	Safety and effectiveness have not been established in pediatric patients <12 years of age
Clindamycin/tretinoin	Safety and effectiveness have not been established in pediatric patients <12 years of age; clindamycin phosphate 1.2%/tretinoin 0.025% gel is approved for patients ≥12 years
Minocycline foam[54]	Approved for use in patients ≥9 years
Retinoids	
Adapalene	Safety and effectiveness have not been established in pediatric patients <12 years of age
Adapalene 0.1%/BP 2.5%	Approved for use in patients ≥9 years
5% dapsone	Safety and effectiveness have not been established in pediatric patients <12 years of age
Tretinoin	Safety and effectiveness have not been established in pediatric patients <10 years of age; 0.05% micronized tretinoin gel is approved for patients >10 years of age
Systemic treatments	
Antibiotics	
Tetracycline	Should not be used in children <8 years of age
Minocycline	Should not be used in children <8 years of age
Doxycycline	Safety or efficacy not established for pediatric use
Hormonal agents	
Estradiol/drospirenone	Safety and efficacy established if started after menarche
Spironolactone	Safety or efficacy not established for pediatric use; used off-label for acne treatment
Isotretinoin	Safety and effectiveness have not been established in pediatric patients <12 years of age

Source: Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74(5):945-973 e933. Used with permission.

highest variability when acne was also present.[48] Clear and simple criteria to assess PIH are an unmet need in the management of acne in skin of color.

Given their proven efficacy in clearing acne and improving PIH, topical retinoids are the first-line therapy in patients with dark skin.[43] Antimicrobial agents are also particularly important to minimize inflammation in these patients.[43] Azelaic acid, topical tretinoin 0.05% lotion, and topical dapsone 7.5% improve both acne and PIH and are considered safe in adolescents with darker skin types. Topical adapalene and tazarotene as well as clindamycin/BP can also ameliorate hyperpigmentation and acne lesions in adolescents with dark Fitzpatrick skin types.[44] Bleaching creams, such as hydroquinone, should be carefully evaluated when planning a skin-color–tailored treatment strategy for acne and used appropriately as advised by a dermatologist due to their potential for skin irritation.[49] The underlying inflammation (ie, acne) should be addressed first; initiating treatment early may prevent further darkening.[50] However, there is a balance to strike, as irritation from acne treat-

ments could cause or exacerbate PIH.[49,51] The importance of sun protection should be emphasized.[45,49,50]

There are no reports focusing on preadolescent acne in skin of color; this is an area of research that requires further attention.

Clinical pearl: *Address PIH with patients. Thoroughly discuss the differences between active acne, PIH, and scarring, as well as the expected duration of these findings.*

EVALUATING CLINICAL SUCCESS

Although numerous acne grading scales are used in clinical research and practice, the AAD guidelines identified tools to better characterize acne as a research/knowledge gap.[6,11] The FDA's Investigator's/Physician's Global Assessment (IGA/PGA) for acne has been proposed as a simple, intuitive measure of disease severity that could be used in everyday clinical practice, with reports of high initial physician compliance.[11,52]

While it is important to assess if treatments reduce acne symptoms, the authors emphasize that individual patients determine clinical success. One patient may be satisfied with an IGA score of 2 (mild), while another will only be happy with a score of 0 (clear). Therefore, it is important to practice shared decision-making and identify what is most important to each patient.

Clinical pearl: *Recognize that treatment success is ultimately determined by each patient's expectations.*

EVOLVING THERAPIES

The treatment landscape for preadolescent acne has evolved since the previous guidelines,[6] with a number of treatments investigated and/or FDA approved. For existing modes of action, 2 tetracycline antibiotics were recently approved by the FDA to treat moderate to severe acne in patients aged ≥9 years old: sarecycline (oral) and minocycline (topical foam).[53,54] Novel formulations of retinoid medications also approved for the topical treatment of acne vulgaris in patients aged ≥9 years include tretinoin lotion 0.05%[36]; tazarotene lotion 0.045%[39]; and trifarotene cream 0.005%.[40]

Additionally, 1% clascoterone topical cream is an androgen receptor inhibitor recently approved by the FDA for the treatment of acne vulgaris in patients 12 years of age and older.[55] Results from in vitro studies suggest that clascoterone competes with dihydrotestosterone for binding to the androgen receptor.[56,57] This results in inhibition of downstream signaling and therefore reduced sebum production, reduced secretion of inflammatory cytokines, and inhibition of inflammatory pathways.[56,57] Systemic hormonal therapy, while effective for managing acne, is limited to treatment of girls and women aged ≥14 years.[6,10,11] However, clascoterone has limited systemic activity,[56] meaning it is suitable for male and female patients.

Results of 2 phase 3 studies demonstrated that clascoterone cream 1% was significantly more effective than vehicle at achieving IGA success ($P < .001$) in patients aged ≥9 years with facial acne vulgaris.[17] Nineteen patients in the trials were ≥9 to <12 years of age.[58] Results indicated a favorable safety profile and improvement in efficacy measures in pediatric patients with moderate to severe acne, although patient numbers for the 9- to 11-year age group were small, and further study is needed in this subpopulation.[58]

Clinical pearl: *Maximize the care provided to patients by staying abreast of recent advances in the treatment of acne and being alert to evolving therapies on the horizon.*

CONCLUSION

This roundtable report covers expert opinions on the current state of acne treatment in preadolescent and adolescent patients. Before new guidelines are published, it is important that experts communicate the latest updates to all physicians who treat patients with acne to ensure optimized patient care. ●

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The Role of Eggs in Healthy Diets

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KEY TAKEWAYS

- Eggs can be part of a healthy diet.
- Epidemiologic evidence and clinical trials have found no links between egg intake and increased risk for heart disease.
- Eggs are a good source of high-quality protein.
- Eggs, in addition to numerous vitamins and minerals, contain compounds including choline, lutein, and zeaxanthin with functions that go beyond nutrition as they protect against chronic disease.

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HISTORICAL OVERVIEW OF THE ROLE OF EGGS IN DIETARY RECOMMENDATIONS

Dietary cholesterol has been a controversial issue since the 1960s when the upper limit for cholesterol intake was set at no more than 300 mg/day. It is now recognized that this arbitrary number was not based on data derived from epidemiologic studies or clinical interventions but more on limited information that existed at the time.[1] The 2015 Dietary Guidelines for Americans have now changed that historical perspective by removing the upper limit of dietary cholesterol among healthy populations[2] following the conclusions reached by numerous other countries, which had long ago realized that cholesterol from the diet does not increase the risk for cardiovascular disease (CVD).[3] Because of these early recommendations in the United States, eggs, with their high content of dietary cholesterol (about 180 mg in a large egg), have been regarded as the icon that exemplifies dietary cholesterol and hence, by association, heart disease risk. Despite new dietary guidelines, the perception of the dangers of egg consumption are, for many people, still based on outdated information. More recent data suggest that eggs do not increase the risk for heart disease and should be considered a valuable component of a healthy diet.

EFFECTS OF EGGS ON CARDIOVASCULAR RISK: EPIDEMIOLOGIC FINDINGS

There are a number of epidemiologic studies that have shown a lack of association between eggs and cardiovascular risk.[3-7] In a recent updated cohort comprised of a number of individuals including 83,349 women from the Nurses' Health Study (NHS), 90,214 women from NHS II, and 42,055 men from the Health Professional Follow-Up who were free of CVD, type 2 diabetes, and cancer at baseline, it was found that moderate egg consumption was not associated with increased cardiovascular risk (pooled relative risk 0.98, 95% confidence interval [CI] 0.93 to 1.03, heterogeneity test [I2] = 62.3%).[4] Similarly, a current meta-analysis of 39 studies that included 2 million individuals arrived at the same conclusion: intake of 2 eggs per day is not associated with cardiovascular risk (relative risk = 0.96, 95% CI: 0.91 to 1.00).[5] More importantly, a recent publication on 3 large international prospective studies that included 177,000 individuals from 50 countries and 6 continents showed a statistical trend that egg intake was not related to plasma lipids, mortality (hazard ratio [HR]: 1.04; 95% CI: 0.94 to 1.15; *P*-trend = 0.38), or CVD events (HR: 0.92; 95% CI: 0.83 to 1.01; *P*-trend = 0.20),[6] A meta-analysis of randomized clinical trials, with some limitations, has further confirmed the lack of association between biomarkers of heart disease and egg intake by showing no association between egg consumption and inflammatory markers including C-reactive protein (CRP) (95% CI: -0.43 to 0.90; *P* = 0.48), interleukin-6 (IL-6) (95% CI: -0.71, 1.11; *P* = 0.50), and tumor necrosis factor alpha (TNF-α) (CI: -0.87 to 0.10; *P* = 0.12).[7] Interestingly, egg intake has been associated with lower cardiovascular risk in Asian populations[3,8] and with lower mortality among patients with hypertension.[9] Although controversy exists in the literature related to egg consumption and risk for diabetes, a recent epidemiologic analysis conducted by Harvard investigators reported no correlation between egg intake and risk of diabetes (95% CI: 0.99 to 1.15; I2= 69.8%),[10] an

important finding due to the strong correlation between diabetes and risk for heart diseases. Thus, from an epidemiologic point of view, recent cohort studies and a large meta-analysis have not reported an association between egg intake and cardiovascular risk.

EFFECTS OF EGGS ON PLASMA LIPIDS, LIPOPROTEINS, AND INFLAMMATORY BIOMARKERS IN DIVERSE POPULATIONS

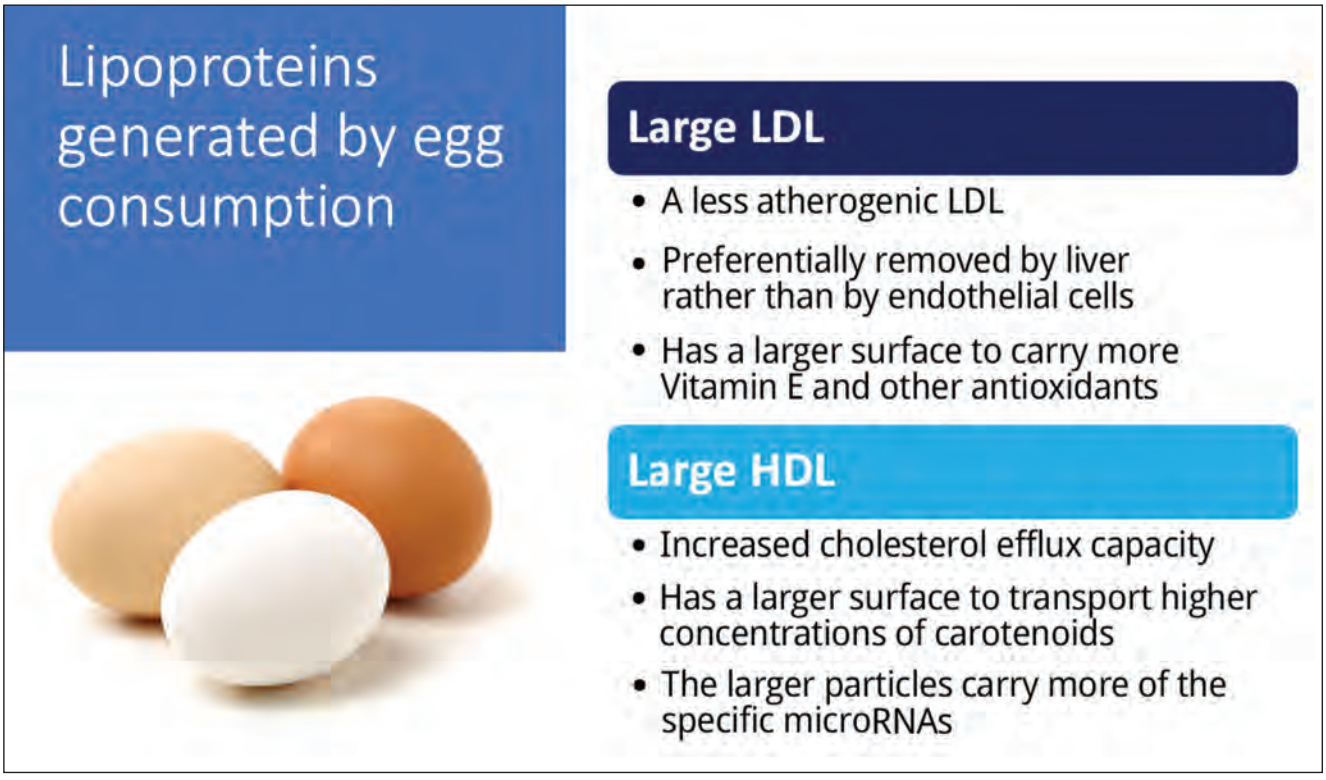
The low-density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio has been recognized as a key biomarker of coronary heart disease risk.[11] Clinical interventions conducted in the last 20 years have unequivocally shown that egg intake consistently results in increases in HDL cholesterol and either maintenance or decreases in the LDL/HDL ratio.[12-28] **TABLE 1** illustrates different clinical interventions with diverse populations including children, young adults, elderly people, overweight-obese adults, individuals with metabolic syndrome, and patients with diabetes, which clearly demonstrate that consumption of 2-3 eggs per day for extended periods results in no effects or an improvement in the LDL/HDL ratio.

Another important metabolic alteration induced by eggs is the reduction of concentrations of atherogenic lipoproteins. Eggs have been shown to contribute to the formation of large LDL,[12] a less atherogenic lipoprotein compared to small LDL. Small LDL has been recognized as more atherogenic because of its limited ability to transport sufficient antioxidants and its capability to penetrate the arterial wall where it becomes oxidized. At that point, the

TABLE 1. **Changes in LDL cholesterol, HDL cholesterol, and LDL/HDL ratio compared to alternative treatment (egg substitute [sub], oatmeal [OM], 0 eggs or a choline supplement [CholS]) either in crossover- or parallel-design studies**

Type of study	Populations and comparisons	Number of eggs and time	LDL	HDL	LDL/HDL
Crossover[19]	Children	2 eggs/d 4 wk	Increased	Increased	No change
Crossover[20]	Young women compared to sub	3 eggs/d 4 wk	Increased	Increased	No change
Crossover[21]	College students compared to OM	2 eggs/d 4 wk	Increased	Increased	No change
Crossover[22]	Elderly compared to sub	3 eggs/d 4 wk	Increased	Increased	No change
Crossover[23]	Patients > 60 years	4 eggs/wk 4 wk	No change	Increased	Decreased
Parallel[24]	College students compared to 0 eggs	3 eggs/d 4 wk	No change	Increased	Decreased
Parallel[25]	Adult men and women compared to bagel	2 eggs/d 8 wk	No change	No change	No change
Parallel[26]	Obese/overweight men compared to sub	3 eggs/d 12 wk	No change	Increased	Decreased
Parallel[15]	Metabolic syndrome compared to sub	3 eggs/d 12 wk	No change	Increased	Decreased
Parallel[27]	Metabolic syndrome compared to CholS	2 eggs/d 12 wk	No change	No change	No change
Parallel[18]	Diabetic patients compared to OM	1 egg/d 5 wk	No change	No change	No change
Parallel[28]	Diabetic patients compared to low cholesterol	2 eggs/d 12 wk	No change	Increased	Decreased

FIGURE 1. **Lipoproteins generated by egg consumption and their benefits**



The large LDL is considered a less atherogenic lipoprotein than small LDL[12] since it is removed from circulation by the liver rather than by macrophages.[29] By being a larger particle, it has the ability to carry more Vitamin E and other antioxidants.[29] The large HDL has been shown to have increased cholesterol efflux capacity[13,14] and being a larger particle, it has the ability to carry more lutein and zeaxanthin,[15] carotenoids that have been shown to have antioxidant properties and to protect against age-related macular degeneration.[23] The large HDL also carries more specific microRNAs with hormonal properties.

Abbreviations: LDL = low-density lipoprotein; HDL = high-density lipoprotein, RNAs = ribonucleic acids.

oxidized LDL is taken up by the macrophages in an unregulated manner leading to foam cell formation and the beginning of the atherosclerotic process.[29] The elevation in the number of large LDLs induced by eggs also leads to higher plasma antioxidants characteristically transported by this lipoprotein.

Recent evidence has been presented that HDL functionality may be more important than circulating concentrations of HDL cholesterol.[30] Functionality of HDL refers to its cholesterol efflux capacity, a major function in reverse cholesterol transport, specific micro ribonucleic acids (microRNAs) in HDL that provide hormonal properties, and the antioxidants transported by this lipoprotein.[30] Larger HDL particles have been identified as biomarkers of cholesterol efflux capacity while high concentrations of small HDL particles have been identified as a marker of diabetes.[31] Consumption of eggs leads to the formation of large HDL particles with increased phosphatidyl choline content, which has been demonstrated to enhance reverse cholesterol transport in cell studies[13,14] and to be a better carrier for lutein and zeaxanthin, carotenoids present in eggs.[15] **FIGURE 1** illustrates the lipoproteins that are increased by egg intake and their properties. Egg intake generates large LDL that is not easily oxidized because it carries more antioxidants and will most likely be removed by the liver via apoB-100. Eggs also generate large HDL that is involved in a more efficient HDL efflux. Large HDL also transports more carotenoids and microRNAs with hormonal properties in plasma.

Other studies have demonstrated that eggs reduce inflammatory markers including IL-6, CRP, serum amyloid A, TNF-α, and liver enzymes in patients with metabolic syndrome[16,17] or those with diabetes.[18] This reduction is possibly due to the high number of antioxidants present in eggs.

BENEFITS OF EGGS ACROSS THE LIFESPAN

Eggs do not increase the biomarkers of heart disease including LDL cholesterol, the LDL/HDL ratio, or inflammatory

TABLE 2. **Protective effects of eggs against chronic disease**

Disease	Protective effects
Coronary heart disease[13-16,28]	• Generation of HDL particles with efficient cholesterol efflux capacity • Lowering of systemic inflammation
Age-related macular degeneration (AMD)[23,36]	• Eggs contain highly bioavailable lutein and zeaxanthin, 2 carotenoids selectively captured by the eye that protect against AMD
Cognitive failure[33]	• Eggs are a good source of choline, which has been shown to improve cognitive function
Protein malnutrition[40,41]	• Highly bioavailable protein

markers[14-16]; in contrast, there are numerous benefits associated with egg consumption. Eggs are a source of highly bioavailable protein that has all essential amino acids and can be utilized by individuals across the life spectrum.[32] Eggs are a major source of choline, which is a metabolite that plays an important role in liver health, is an intrinsic part of cell membranes and lipoproteins, and is a precursor of the neurotransmitter acetylcholine. Evidence also suggests that choline can protect against decline in cognitive function.[33] Further, dietary choline from eggs does not increase the chronic concentrations of trimethylamine oxide (TMAO)[30,34] a metabolite recognized as a biomarker of heart disease.[35] Eggs contain highly bioavailable lutein and zeaxanthin,[14,30] carotenoids that accumulate in the retina and protect against age-related macular degeneration.[36] Lutein and zeaxanthin are also potent carotenoids that are mainly transported by HDL[14] and that have been shown to exert antioxidant and anti-inflammatory effects in various organs.[37,38] Further, a role of lutein in cognitive function has been recently recognized.[39] A brief description of the protective role of eggs against chronic disease is presented in **TABLE 2.**

SUMMARY AND CONCLUSIONS

Eggs have been historically considered as food with a high cholesterol content. Strong evidence from rigorously conducted epidemiologic analyses[4,10] and from well-controlled clinical trials[16-31] indicates that eggs do not increase the biomarkers for heart disease or negatively alter the lipoprotein profile, when consumed in moderation (ie, <3 eggs daily). Eggs are, in fact, worthy of consideration as a component of a healthy diet due to their high concentrations of vitamins E and D and selenium[40] and their high-quality protein.[41,42] Additionally, they are a good source of choline[24,34] and of the highly bioavailable carotenoids, lutein and zeaxanthin,[15,23] shown to be protective antioxidants against age-related macular degeneration,[23,38] fatty liver, and the development of atherosclerosis in animal studies.[43] ●

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Update on the Gut Microbiome for the Primary Care Clinician

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KEY TAKEAWAYS

- The gut microbiome, sometimes referred to as the "organ" we do not know we have, is a dynamic ecosystem that plays an important role in human health and disease.
- Alterations in the gut microbiome (dysbiosis) are associated with wide-ranging disease states, including metabolic diseases like type 2 diabetes mellitus (T2D).
- Growing evidence suggests improved gut microbiome composition from targeted microbiome interventions leads to improvement in glycemic control in patients with T2D.

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DISCLOSURES

Dr. Miller discloses that she serves on the advisory board and speakers bureau for Abbott Diabetes, Boehringer Ingelheim, Eli Lilly, and Novo Nordisk; on the advisory board for AstraZeneca, Merck, Plenity, and Sanofi-Aventis; and does research for Abbott Diabetes and Pendulum Therapeutics. Dr. Neumiller discloses that he serves as a consultant to Bayer and is on the speakers bureau for Dexcom and on advisory boards for Novo Nordisk and Sanofi-Aventis.

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THE GUT MICROBIOME: A DYNAMIC "MICROBIAL ORGAN"

The understanding of the role of the gut microbiome in health and disease continues to evolve rapidly.[1] Within the gut resides a complex ecosystem composed of trillions of microorganisms.[2] While microbiota research extends at least back to the 19th century (providing the foundation for our modern understanding of microbiology and infectious disease),[3] microbiome science has advanced dramatically over the past several decades with the advent of high throughput DNA sequencing coupled with enhanced computational capabilities.[4] It is now recognized that commensal gut bacteria provide multiple benefits to the host, including serving an important role by competing with pathogenic organisms, thus preventing colonization and associated illness.[5] This vast gut ecosystem, primarily residing in the colon but with contributions coming from the entire alimentary canal, impacts multiple aspects of human physiology and metabolism both within the gut and systemically, leading some to refer to the gut microbiome as an underappreciated "organ."[2,6] The microbiome is important in immune system development, especially as it relates to the recognition of self vs non-self host cell proliferation, energy biogenesis, biosynthesis of vitamins, steroid hormones, neurotransmitters, and metabolism of amino acids, dietary nutrients, bile salts, drugs, and other xenobiotics.[1] Notably, gut bacteria generate short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, through anaerobic fermentation of dietary fiber.[7] SCFAs serve as a primary energy source for the intestinal epithelium. Butyrate is also an important signaling molecule for the immune system, as well as lipid metabolism, glucose homeostasis, and neurogenesis.[1,8,9]

While the microbiome is clearly important in maintaining human health, numerous factors can influence the composition and function of the microbiome. Key factors include host genetics, geography, birth mode (cesarean vs vaginal delivery), nutrition during infancy (breast vs formula feeding), dietary practices, age, exercise, exposure to antibiotics, childhood immunizations, and other medications, as discussed below.[10]

Medication use: Medication use can have a significant impact on microbiome diversity and function. Antibiotics are well known to interfere with the balance of the gut microbiome.[1] Use of potent, broad-spectrum antibiotics reduces gut microbial diversity, including loss of important species of gut bacteria.[11] Disruption of the gut ecosystem increases susceptibility to colonization by pathogenic

microorganisms, with broad-spectrum antibiotic use typically preceding *Clostridioides difficile* infection and increasing the risk for colonization by other antibiotic-resistant organisms such as vancomycin-resistant *Enterococcus*.[11] Restoration of the gut microbiome is an important treatment strategy for recurrent *C difficile* infection, with fecal microbial transplantation from normal-weight, healthy individuals serving as an effective strategy to resolve the infection in resistant cases and/or in cases refractory to other treatment approaches.[1] Beyond the increased risk for gut colonization by pathogenic bacteria, perturbation of the gut microbiome promotes dysbiosis and risk for associated disease, as discussed in more detail later.[11] Other medications also impact the gut ecosystem. Multiple glucose-lowering medications, including metformin and incretin-based therapies, have been noted to influence the composition of the gut microbiome.[12] In fact, an increase in beneficial gut bacteria observed with metformin treatment has been suggested as a supporting mechanism in the treatment of type 2 diabetes mellitus (T2D).[13]

Dietary practices: Diet impacts the composition and diversity of the gut microbial community.[14] The Western diet (high in protein and fat; low in fiber) is associated with reductions in key beneficial bacteria species, including SCFA producers as well as *Akkermansia muciniphila,* which is integral in maintenance of the gut mucin layer.[15] SCFAs carry out important physiologic functions, and decreased SCFA production is associated with disease development.[6] Furthermore, the composition and size of the bile acid pool are impacted by microbial metabolism of bile acids in the gut.[16] Dietary impacts on microbiome composition can result in alterations in bile salt metabolism. Conversion of primary bile salts to secondary bile acids, which are integral to lipid and glucose metabolism, is facilitated by microbiota in the colon.[17]

Geography and environment: Interindividual differences in gut microbiome composition are highly associated with an individual's geographic location.[18] Geographical differences in eating patterns also affect the gut microbiome. Environmental influences such as gardening and having pets can also contribute to the overall gut biome population.

Physical activity: Exercise not only improves body composition, but also contributes to gut microbial diversity.[8] Notably, elite athletes appear to have greater microbiome diversity, including enriched bacterial species, including *A muciniphila,* adept at producing SCFAs.[8] The maintenance of appropriate SCFA production has been hypothesized as 1 mechanism by which physical activity promotes health and enhancement of gut barrier integrity.[19]

Birth mode and nutrition during infancy: The developing infant microbiome is highly influenced by the mother's microbiome.[20] Mode of delivery at birth is an important variable, with infants born by cesarean delivery having low bacterial diversity compared with vaginally delivered infants.[21] In addition to mode of delivery, formula feeding (vs breastfeeding) has an important impact on the composition and diversity of the microbiota of infants.[22] While current evidence demonstrates differences in the development of the gut microbiome between breast- and formula-fed infants, additional research is needed to better understand the long-term impact of these differences.

Host genetics: While environmental influences have a large impact on microbiome composition, host genetics also play a role. Twin studies have demonstrated that microbiomes of monozygotic siblings have greater similarity compared with those of dizygotic siblings.[23]

Age: As discussed previously, multiple factors can impact the developing gut ecosystem during childhood, and microbiome composition remains dynamic until the age of 3 to 4 years, when it becomes fully mature.[24] Microbiome diversity is decreased in the elderly and may contribute to important physiologic, neurologic, and immunologic changes observed in older adults.[1]

Stress and anxiety: The microbiome-gut-brain relationship is emerging as an important connection. Lower microbiome diversity has been associated with increased stress and anxiety levels, with consumption of foods containing naturally occurring probiotics or prebiotics associated with lower stress and anxiety levels in 1 study.[25]

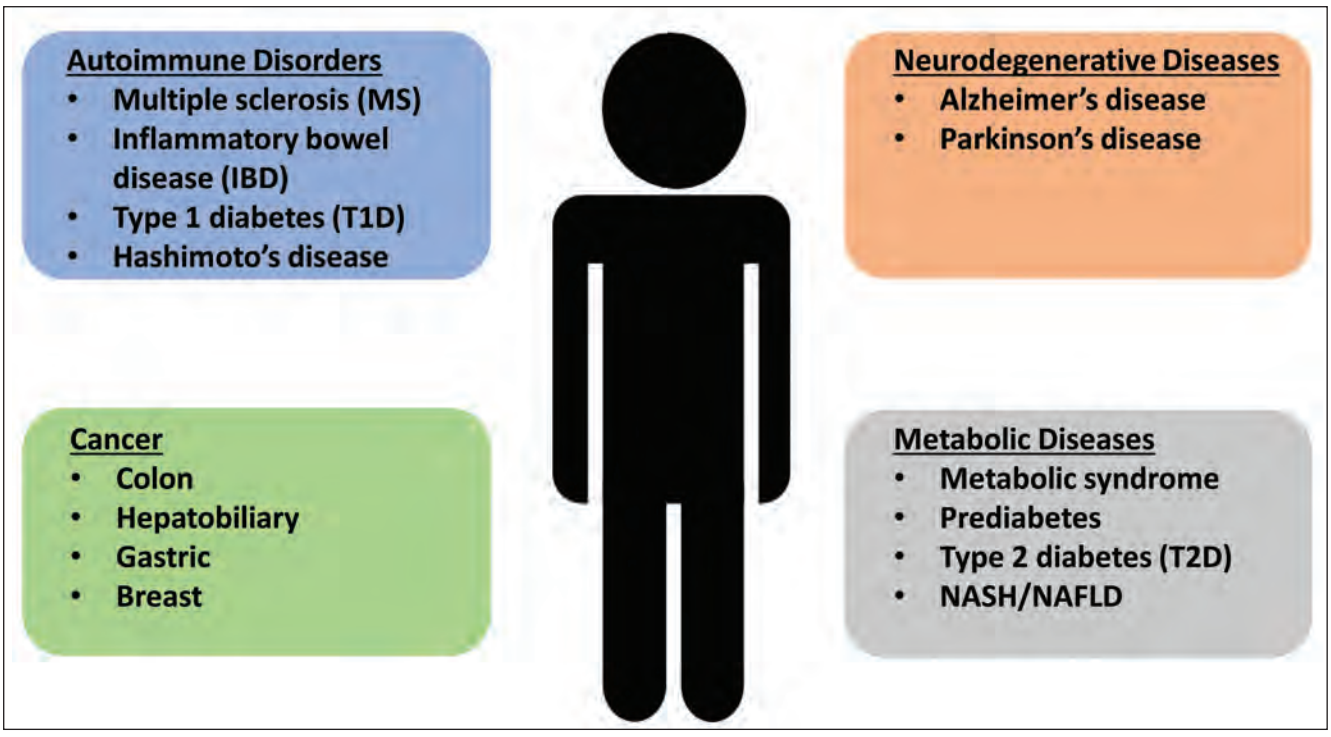
DYSBIOSIS IS ASSOCIATED WITH MULTIPLE DISEASE STATES

Rapid development of analytical techniques to quantify gut bacteria and analyze their genes and metabolic products has expanded our understanding of the relationships between the microbiome and disease.[1] Alterations in gut microbiome composition (dysbiosis) is associated with risk for a variety of diseases (**FIGURE 1**).[1,4,10,20,26] While dysbiosis is associated with multiple diseases, additional work is necessary to determine whether dysbiotic ecosystems are a consequence or cause of disease.[1] Nonetheless, there is great interest in leveraging the microbiome to help guide the diagnosis, prognosis, and treatment of associated diseases.[10]

T2D, OBESITY, AND THE GUT MICROBIOME

Gut microbiome composition is predictive of incident T2D,[27] and obesity is associated with diminished diversity and richness of the gut microbiome, which can be reversed through dietary intervention.[28] Discordant twin studies

FIGURE 1. **Dysbiosis is associated with multiple chronic disease states**[1,4,10,20,27]



Abbreviations: NASH/NAFLD, non-alcoholic steatohepatitis/non-alcoholic fatty liver disease.

showing that fecal transplants modulate metabolism in mice provide additional direct evidence that dysbiosis contributes to the pathophysiology of obesity and metabolic disorders.[29] A study with human subjects showed that a transfer of intestinal microbiota increased insulin sensitivity in subjects with metabolic syndrome.[30] **FIGURE 2** provides a summary and discussion of key alterations in gut microbiota observed in people with obesity and T2D,[3,10] including the observation that T2D patients have less SCFA-producing gut bacteria.[6] Further contributing to gut dysbiosis is an inadequate population of *A muciniphila*.[31] By maintaining the gut barrier, *A muciniphila* helps prevent systemic inflammation that can contribute to the development of insulin resistance, other metabolic abnormalities (eg, nonalcoholic steatohepatitis/nonalcoholic fatty liver disease, atherosclerosis), and cancers.[1,6,32] As previously discussed, SCFAs are important in glucose metabolism and are theorized to affect glucose metabolism through multiple mechanisms, including stimulation of glucagon-like peptide 1 (GLP-1) release (**FIGURE 3**).[24]

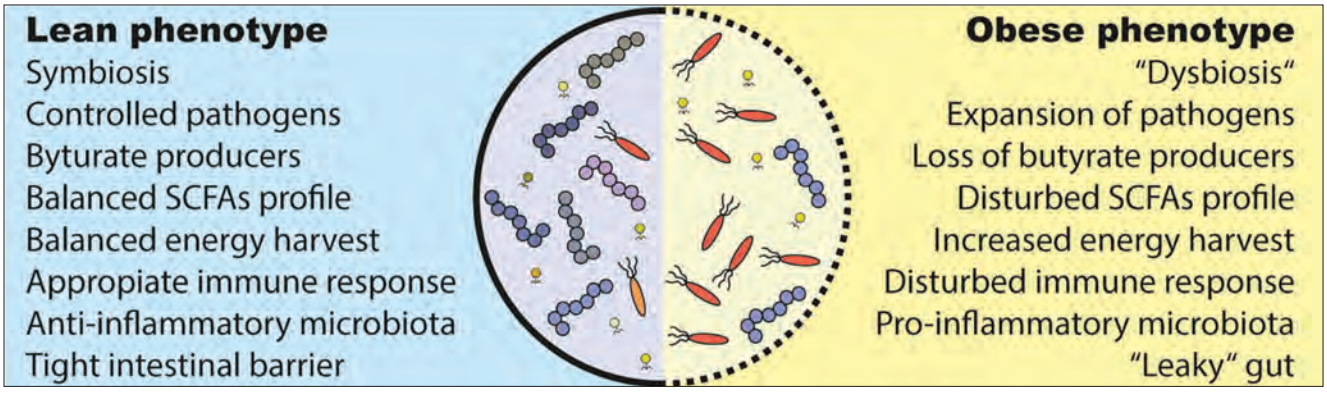
LEVERAGING THE GUT MICROBIOME TO TREAT T2D: OPPORTUNITIES AND CHALLENGES

For the reasons detailed previously, there is great interest in leveraging the gut microbiome to improve health and/or treat disease. Many are seeking targeted microbiome approaches with clinically validated strains that produce the key signaling molecules. Specifically, people with T2D have multiple deficiencies that can be potentially ameliorated through improved microbiome function, including 1) deficient butyrate (SCFA) production; 2) reduced production of secondary bile acids; and 3) thinning of the mucin layer and loosening of tight junctions in the epithelial layer of the gut.[18] Of particular note, the genus *Akkermansia* is known to play an important role in maintaining mucin layer integrity and reducing inflammation, with significantly lower levels of gut *A muciniphila* noted in T2D.[18]

EVIDENCE SUPPORTING PROBIOTIC USE IN T2D

Evidence supporting probiotic use to improve glycemic control in T2D continues to expand.[17] A recently published, multicenter, double-blind, placebo-controlled, randomized trial reported by Perraudeau et al enrolled 78 participants with T2D managed with diet and exercise alone, or in combination with metformin and/or a sulfonylurea.[13] The clinical trial was designed to test the hypothesis that oral supplementation with a probiotic formulation would improve metabolic health, including improvements in mea-

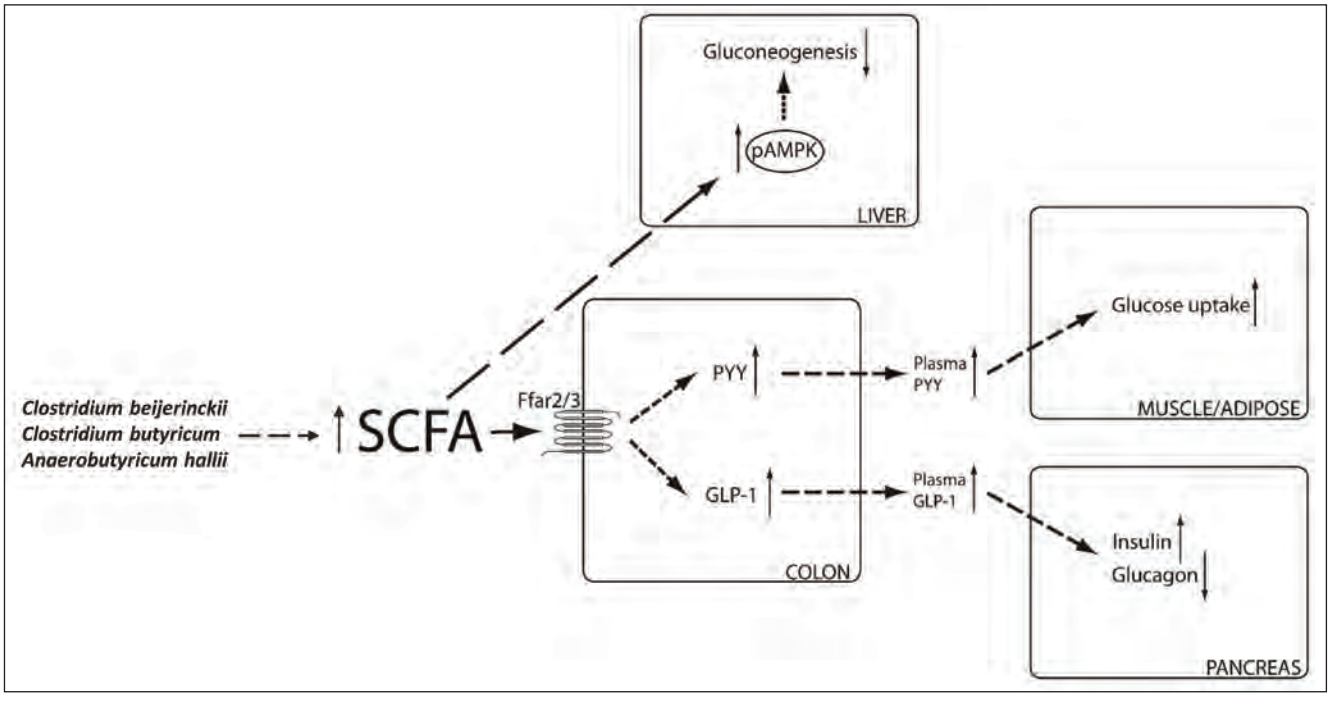
FIGURE 2. **Alterations in the gut microbiota of people with obesity and diabetes**



Under healthy conditions, the gut microbiota live in symbiosis and provide the host with several beneficial functions. For example, gut microbiota produce SCFAs that are used as an energy source and facilitate multiple important metabolic processes in the host. The gut microbiota observed in individuals with obesity and other metabolic diseases is often described as "dysbiotic," meaning that there is an expansion of normally underrepresented bacteria and diminished microbial diversity. A disturbed intestinal immune response and a Western diet are discussed as causes. Further, a Western diet induces a "leakiness" of the gut, which allows bacteria to cross the intestinal barrier and induce a pro-inflammatory response in the host. Finally, people with obesity show an increased energy harvest by the gut microbiota and a different SCFA profile when compared with lean individuals.

Source: Modified and reprinted from Vrieze A, Van Nood E, Holleman F, et al. *Gastroenterology*. 2012;143(4):913-916.e7 in accordance with the terms of the Creative Commons Attribution License (CC BY).

FIGURE 3. **Schematic overview of the proposed mechanisms by which targeted SCFA-producing microbes affect glucose metabolism**



In the colon, SCFAs can increase PYY and GLP-1 expression. PYY has been shown to increase glucose uptake in muscle and adipose tissue, whereas GLP-1 increases insulin and decreases glucagon production in the pancreas. In addition, SCFAs have been shown to decrease hepatic gluconeogenesis.

Abbreviations: pAMPK, phosphorylated AMP-activated protein kinase; PYY, peptide YY.

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TABLE. **Leveraging the gut microbiome through use of probiotics to treat T2D**

Opportunities
• Improvement of key derangements associated with dysbiosis
○ Increased butyrate production
○ Increased production of secondary bile acids
○ Thickening of mucin layer and tightening of junctions in the epithelial lining of the gut
Challenges
• Validation of safety for human consumption
• Manufacturing challenges
○ Cultivation of anaerobic bacteria of interest
○ Production without exposure to animal products
○ Capacity for large-scale production

sures of glycemia. The proprietary probiotic formulation was designed to increase butyrate (eg, SCFA) production through inclusion of the butyrate-producing strains *Clostridium beijerinckii, C butyricum, Bifidobacterium infantis*, and *Anaerobutyricum hallii*, in addition to promoting health of the colonic mucin layer through supplementation with *A muciniphila*.[13] All bacterial strains included within the study formulations were commensal organisms grown under controlled conditions (consistent with Good Manufacturing Practices) and in the absence of animal-derived products to ensure safe human use.[13] Further, the product was formulated with food-grade ingredients and qualified as generally recognized as safe. Participants were randomized to twice-daily administration of the probiotic formulation or placebo for a duration of 12 weeks.

Use of the probiotic formulation was associated with a reduction in both the glucose total area under the curve (AUC) (-36.1 mg/dL/180 min; P = .05) and the incremental glucose AUC during a standardized meal tolerance test (-28.6 mg/dL/180 min; P = .0066), representing a significant improvement in postprandial glucose control. A trend toward an improvement in glycated hemoglobin (A1c) was also noted with the probiotic when compared with placebo (-0.6%; P = .054).[13] Fecal analysis revealed an increase in stool butyrate with treatment, and plasma metabolomic analysis demonstrated increases in plasma butyrate and ursodeoxycholic acid (a secondary bile acid).[13] Overall, findings from this trial provide additional evidence supporting the safety and glycemic efficacy of the studied probiotic formulation in patients with T2D.

Leveraging the gut microbiome through the use of innovative probiotics with the potential to restore these deficits presents both opportunities to improve health and challenges related to production and manufacturing of probiotic formulations for human use (**TABLE**). Notably, probiotic preparations capable of delivering these benefits to patients are composed almost exclusively of anaerobic bacteria species that must be cultivated in the absence of oxygen, which presents manufacturing challenges.

SUMMARY

The gut microbiome clearly plays an important role in human health and disease, with dysbiosis associated with multiple disease states. A particularly strong association exists between dysbiosis and metabolic disorders, including T2D. An expanding literature base supports the use of evidence-based, disease-relevant probiotics, such as that studied by Perraudeau et al,[13] to improve gut microbiome composition and glycemic control in patients with T2D. Future trials including larger populations with longer-term follow-up will further explore the role of specific probiotics in the treatment of T2D and other diseases associated with dysbiosis. Given the importance of probiotic bacterial composition on outcomes, healthcare providers may wish to consider recommending products with evidence of benefit. ●

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Updates in the Management of Mild Cognitive Impairment and Alzheimer Disease

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

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

- Implement evidence-based methods for cognitive impairment screening in primary care.
- Identify correct diagnostic criteria for mild cognitive impairment (MCI) and Alzheimer disease (AD) based on current guideline recommendations.
- Design appropriate and effective treatment plans for patients with MCI and AD and refer to a specialist when necessary.
- Describe advances in testing and treatment for AD that may impact dementia care.

KEY TAKEAWAYS

- Due to the expanding older population and an increased burden of MCI and AD, the shortage of dementia care specialists is expected to worsen, prompting a need for primary care practitioners (PCPs) in managing MCI and AD.
- PCPs should routinely screen patients at risk for AD with a validated cognitive assessment tool to help detect early disease.
- MCI and AD are diagnosed clinically, but newer imaging and biomarker tests can confirm an AD diagnosis. Such tests, however, are not always accessible and are usually only used by specialists and in clinical trials.
- The approved therapies for AD provide only symptomatic benefit and are not indicated in patients with MCI. Research is currently being directed at disease-modifying treatments, including an agent that recently received accelerated approval for AD, pending confirmatory studies for continued approval.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of mild cognitive impairment and Alzheimer disease.

FACULTY

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DISCLOSURES

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INTRODUCTION

Alzheimer disease (AD) is a progressive neurodegenerative disease often present decades before symptoms are evident.[1] As of 2021, approximately 6.2 million patients in the United States aged 65 and older had AD with dementia, and estimates predict this number to double by the year 2050.[1] AD and other dementias represent a significant cost burden in the US, with an estimated $305 billion spent on healthcare, long-term and hospice care for patients, as well as lost patient and caregiver productivity.[2]

AD is characterized by the progressive dysfunction and loss of synapses and neurons associated with neurotoxic protein aggregates—neurofibrillary tangles (composed primarily of phosphorylated tau) and beta-amyloid plaques—resulting in cognitive, behavioral, and functional changes in affected individuals.[3] AD is the most common cause of dementia, accounting for approximately 60% to 80% of dementia cases.[4] Notably, about 50% of patients with AD have a "mixed" etiology, exhibiting pathology and symptoms related to other dementia types in addition to AD.[2]

AD progresses along a continuum that begins with preclinical or asymptomatic AD and progresses to mild cognitive impairment (MCI), mild dementia, and eventually moderate and severe AD (**FIGURE**).[5] Several different staging systems describe the progression of AD, with variations in nomenclature but overall similarities with regard to pathophysiology and neurologic deficits.[5,6] Symptoms become evident in the MCI phase of the AD continuum, characterized by subtle cognitive changes that may only be noticeable to the patient, family members, friends, and caregivers.[1] Biomarkers of AD can be detected much earlier than symptoms; for example, plaque deposition can occur up to 20 years prior to onset of cognitive symptoms.[6,7]

THE PCP'S ROLE IN DEMENTIA CARE

The aging population and increase in older patients overall creates an urgent need for better management and treatment of AD. Due to a shortage of dementia care specialists, and since primary care practitioners (PCPs) are capable of managing cognitive impairment and dementia, it often falls to PCPs to care for patients with MCI and AD.[2] Patients with early signs of dementia or AD often present first to their PCP, who can help detect, diagnose, and manage early-stage AD.[8]

2020 Alzheimer's Association primary care surveys

In 2020, the Alzheimer's Association published a series of surveys including approximately 1400 PCPs in the US.[2] About half of the survey respondents believed that the medical profession is unprepared to meet the expected increase in demand for providing care for AD and other dementias, and that there are not enough specialists to receive referrals for all patients with AD.[2] However, about 32% of PCPs reported referring patients with dementia to specialists at least once a month.[2] Most PCPs reported answering questions about AD or dementia every few days, and about 1 in 5 PCPs reported responding to these questions daily.[2] Approximately 82% of survey respondents answered that they feel they are on the front lines of providing dementia care.[2]

In addition to spending time during annual wellness visits (AWVs) or other appointments dedicated to cognitive evaluation, PCPs may detect cognitive or behavioral changes as part of routine visits, prompting follow-up cognitive testing.[8] Once a diagnosis of MCI or AD is established, PCPs can treat many of the patients in primary care, and those who are not candidates for treatment by the PCP can be referred to a specialist.[5]

CASE SCENARIO

An 82-year-old woman presented to her PCP for a routine AWV. She had a history of hypertension and a family history of dementia. Her routine labs were within normal limits, and her blood pressure was 118/70 mm Hg. She had been treated with amlodipine 10 mg daily. She presented with her husband, who usually accompanies her to appointments. She did not have any specific complaints and was "just here for the yearly check-up."

COGNITIVE ASSESSMENT IN PRIMARY CARE

Despite cognitive assessment as a standard component of AWVs for patients with Medicare, only 16% of patients aged 65 years and older report receiving a regular, brief cognitive assessment.[9] PCPs should routinely screen patients at risk for AD with one of several validated tools used in primary care settings.[5] Many of the tools are available online and easily implemented in clinical practice (**TABLE**).

SELECT METHODS FOR COGNITIVE ASSESSMENT BY PCPs

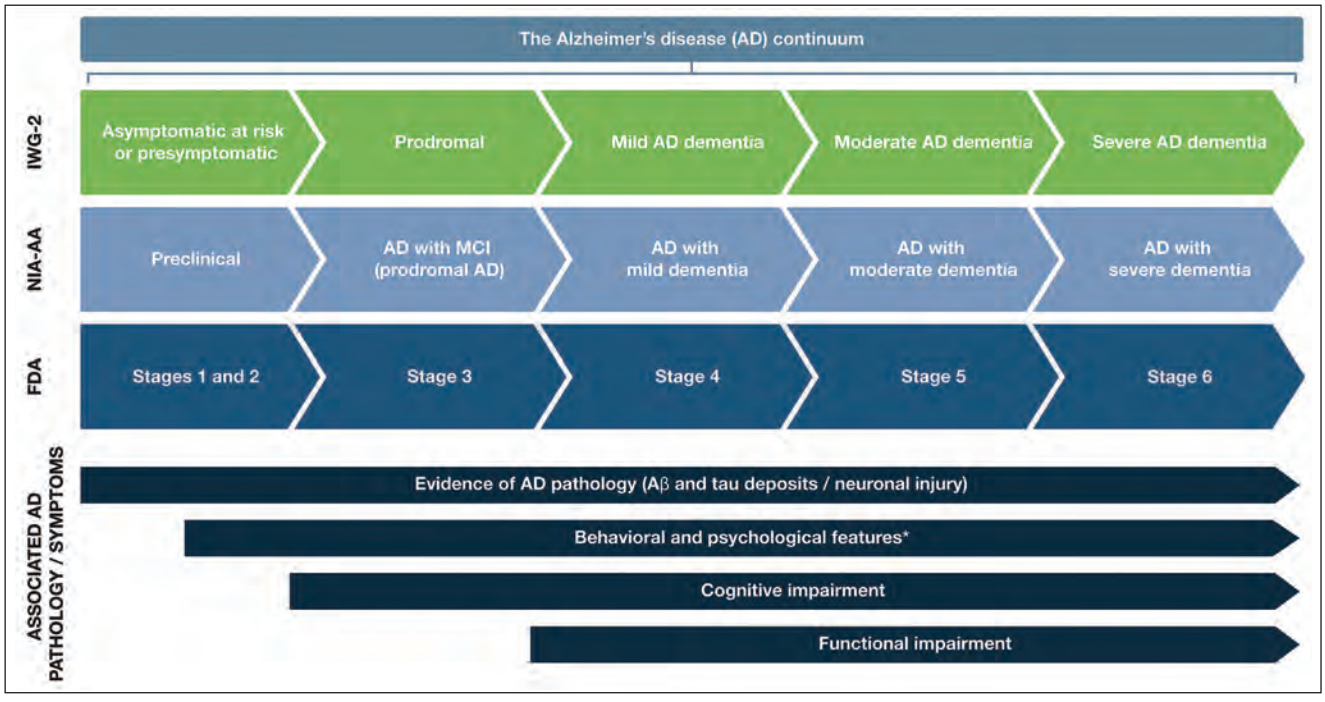
Mini Mental State Examination (MMSE). The MMSE is a 30-item instrument administered to the patient, which takes about 5-10 minutes to complete.[10] This tool is sensitive and reliable for detection of memory and language deficits, but may not capture impaired executive functioning.[11]

Montreal cognitive assessment (MoCA). The MoCA is a 12-item assessment that takes about 10 minutes to complete.[5] This tool was originally developed to improve detection of MCI, and thus is more sensitive than the MMSE for evaluating visuospatial, language, memory, and executive function.[11,12] Clinicians who use the MoCA are mandated to undergo a certification that takes approximately 1 hour to complete.[12]

Mini cognitive assessment instrument (Mini-Cog). This brief evaluation consists of a 3-item recall and clock

FIGURE. **The continuum of Alzheimer disease[5]**

The AD continuum can be classified into different stages from preclinical AD to severe AD dementia; the nomenclature associated with each stage varies between the different clinical and research classifications. This figure provides a summary of the different naming conventions that are used within the AD community and the symptoms associated with each stage of the continuum; *Mild behavioral impairment is a construct that describes the emergence of sustained and impactful neuropsychiatric symptoms that may occur in patients ≥50 years old prior to cognitive decline and dementia (112).



Abbreviations: Aβ, amyloid beta. AD, Alzheimer's disease. FDA, Food and Drug Administration. IWG, International Working Group. MCI, mild cognitive impairment. NIA-AA, National Institute on Aging—Alzheimer's Association.

Source: Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of early Alzheimer's disease: clinical practice in 2021. *J Prev Alzheimers Dis*. 2021;8(3):371-386.

A numeric reference from the original article was removed from this figure prior to its reproduction in this article.

drawing that is administered to the patient and takes about 2-3 minutes to complete.[5] This assessment requires no training, and the results are easy to interpret.[5]

AD8 dementia screening interview (AD8). This short, 2-to-3-minute, 8-item tool is usually administered to an informant to help detect dementia in patients, based on the informant's responses.[5] Some experts suggest that the AD8 may be administered to patients in the absence of an informant, with similar results, especially in patients with mild dementia.[13]

Informant questionnaire on cognitive decline in the elderly (IQCODE). The IQCODE is another questionnaire designed to be administered to an informant, and it takes about 10 minutes to complete.[5,14]

Exclusion of reversible causes of cognitive impairment

The PCP's initial assessment needs to exclude reversible causes of cognitive impairment, such as hormone imbalances, depression, electrolyte or vitamin deficiencies, and medications that can cause cognitive impairment.[5,15] Reversible causes of impairment need to be identified, addressed, and corrected, if possible, prior to continuing AD evaluation.

Laboratory testing. Vitamin B12 deficiency, vitamin D deficiency, and thyroid disorders are common causes of cognitive impairment that can be ruled out with laboratory tests.[15,16] The following blood analyses are recommended for the initial assessment of AD: complete blood count, blood glucose, electrolytes, liver function, kidney function, thyroid-stimulating hormone, vitamin B12, vitamin D, and folate.[8,16]

Comorbidities. Behavioral symptoms and sleep disturbances are common in patients with MCI or AD.[17] Depression can have similar presenting symptoms as cognitive impairment and can often be a comorbidity for patients with dementia, so

TABLE. **Open-access assessment tools for Alzheimer disease**

MMSE	https://www.psychdb.com/cognitive-testing/mmse
MoCA	https://www.parkinsons.va.gov/resources/MOCA-Test-English.pdf
Mini-Cog	https://www.alz.org/getmedia/9687d51e-641a-43a1-a96b-b29eb00e72bb/cognitive-assessment-toolkit (page 9)
AD8	https://www.alz.org/getmedia/9687d51e-641a-43a1-a96b-b29eb00e72bb/cognitive-assessment-toolkit (page 14)
IQCODE	https://www.alz.org/getmedia/9687d51e-641a-43a1-a96b-b29eb00e72bb/cognitive-assessment-toolkit (page 11)
QDRS	http://med.fau.edu/research/The%20Quick%20Dementia%20Rating%20System%20Instructions%20and%20Form.pdf
FAQ	https://www.alz.org/careplanning/downloads/functional-activities-questionnaire.pdf
FAST	https://alzprogression.com/scales/fast/
GDS	https://wwwoundcare.ca/Uploads/ContentDocuments/Geriatric%20Depression%20Scale.pdf
NPI-Q	https://www.alz.org/media/documents/npiq-questionnaire.pdf

Abbreviations: MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; Mini-Cog, Mini Cognitive Assessment Instrument; AD8, AD8 Dementia Screening Interview; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; QDRS, Quick Dementia Rating System; FAQ, Functional Activities Questionnaire; FAST, Functional Analysis Screening Tool; GDS, Geriatric Depression Scale; NPI-Q, Neuropsychiatric Inventory Questionnaire.

screening for depression using a validated tool such as the Patient Health Questionnaire-9 (PHQ-9) is recommended.[18] Therapeutic interventions for depression, anxiety, and sleep disorders can alleviate cognitive symptoms associated with these comorbidities and provide a clearer picture of cognitive impairment due to neurologic degeneration.[19,20]

In the case scenario above, it would be prudent for the PCP to include cognitive assessment as part of the AWV due to the patient's multiple risk factors for cognitive impairment, including older age and a family history of dementia. Too often, these screening opportunities may be missed or overlooked.

BEST PRACTICES FOR DIAGNOSIS OF MCI AND AD

Underdiagnosis of AD and other dementias is common in primary care, and a substantial number of Medicare patients meeting AD criteria are undiagnosed.[1] The diagnostic process for AD includes initial detection or suspicion of disease, assessment, diagnosis, and treatment, with various tests and possible specialist referral considered along the way.[5] Additionally, the National Institute on Aging–Alzheimer's Association (NIA-AA) workgroup has established core clinical diagnostic criteria for MCI and AD that can facilitate clinical diagnosis.[21,22] Notably, these criteria can help distinguish AD from other major forms of dementia.[23]

After the initial screening and workup for MCI or AD, a full evaluation can be conducted to establish a clinical diagnosis, which should include the following:

- Medical history
- Physical examination
  - o Blood pressure, temperature, pulse, lung auscultation
- Cognitive, functional, and behavioral examinations
  - o Functional examinations include the Functional Activities Questionnaire (FAQ), the Functional Analysis Screening Tool (FAST), and the Quick Dementia Rating System (QDRS)
  - o Behavioral examinations include the Geriatric Depression Scale (GDS) and the Neuropsychiatric Inventory Questionnaire (NPI-Q)
- Laboratory tests
- Interview of a knowledgeable informant
- Medication profile review to assess for drugs that can cause cognitive impairment
- Analysis of risk factors for AD: family history of dementia, older age, female sex, physical inactivity, obesity, diabetes, low education, and apolipoprotein E (ApoE) ε4 carrier status

Historically, confirming a diagnosis of AD was possible only postmortem, but recent advances in imaging and fluid biomarkers for AD allow for diagnostic confirmation. However, these tests are not yet widely used due to lack of access and reimbursement; use of imaging and fluid biomarkers is more common in specialist settings and clinical trials.[24]

While many patients with MCI or AD can be managed in the primary care setting, a specialist referral may be warranted for patients presenting with any of the following characteristics[5,25]:

- Less than 65 years old (ie, early disease onset)
- Presence of parkinsonian features

- Presence of hallucinations or delusions
- Rapid progression or fluctuations of cognitive impairment
- Unexplained visual impairment
- Severe depression

TREATING MCI AND AD IN PRIMARY CARE

For patients managed in the primary care setting, PCPs should consider how best to disclose the diagnosis to the patient, family members, and caregivers, as well as discuss treatment options and support resources.[5,15] PCPs can encourage patients and family members to have conversations about care planning, in the event the patient is no longer able to make informed decisions for themselves.[5] Monitoring for worsening cognitive function should include cognitive and functional assessments at routine follow-up appointments about every 6-12 months.[5]

Nonpharmacologic therapy for MCI and AD

Nonpharmacologic therapies can have a positive impact on the quality of life for patients with MCI and AD and are relatively safe and inexpensive.[10,26] Possible nonpharmacologic interventions include dietary changes, physical exercise, cognitive training, social interactions with others, adequate sleep, and proper personal hygiene.[10,26]

Pharmacologic therapy for AD

Several agents are Food and Drug Administration (FDA)-approved for AD, but no pharmacologic therapy is indicated for patients with MCI. These agents can provide symptomatic benefit but are not disease-modifying treatments.[5,27] The approved acetylcholinesterase inhibitors for AD are rivastigmine, galantamine, and donepezil.[27] Memantine, an *N*-methyl-D-aspartate receptor antagonist, is also approved for use for moderate or severe AD.[27] A complete discussion regarding the benefits, risks, initiation, titration, and side effects of these medications is beyond the scope of this article. Additional information can be found in published review articles.[27] While some patients may be interested in using alternative treatments for AD such as natural products or supplements, there is no clear clinical benefit from these therapies.[28]

RECENT ADVANCES IN AD MANAGEMENT

Emerging diagnostics and therapeutics have the potential for practice-changing advances in diagnosing, treating, and preventing AD in the coming years. Laboratory testing and/or imaging biomarkers can help detect AD much earlier in the disease process, and research is under way to evaluate potential disease-modifying agents for early AD.[5]

Advances in imaging

Structural magnetic resonance imaging (MRI) can assess atrophy and tissue changes in the brain, and functional MRI provides a measure of neuronal activity.[29] Structural brain MRI is readily accessible, but both structural and functional MRI lack the ability to detect amyloid plaques and tau tangles specific to the AD disease process.[29] Fluorodeoxyglucose (FDG) positron emission tomography (PET) uses FDG as a marker of brain glucose metabolism, which reflects neuronal function. Regional metabolic patterns help distinguish AD from frontotemporal dementia, and Medicare will reimburse for such scans.[29] Amyloid-PET imaging identifies amyloid plaques in the brain and can be helpful to confirm the diagnosis of AD for inconclusive cases; however, its clinical use is limited due to cost and concerns for variation in protocols and cutoffs for interpreting results.[29,30] Tau-PET can distinguish AD dementia from other neurodegenerative disorders and potentially predict cognitive change, but it is expensive and has limited availability.[31]

Advances in biomarkers

In 2018, the NIA proposed a research framework for biomarkers in AD, intended to separate biomarkers specific for pathologic tau from nonspecific neurodegeneration that can occur in non-AD conditions.[6] Currently, biomarkers are not used in clinical care protocols, but they are used in research.[6] The NIA uses an AT(N) biomarker grouping as follows[6]:

- A: Aggregated amyloid beta; measured using cerebrospinal fluid (CSF) amyloid beta (also amyloid-PET)
- T: Aggregated tau; measured using CSF phosphorylated tau (also tau-PET)
- (N): Neurodegeneration or neuronal injury; measured using CSF total tau (also anatomic MRI, FDG-PET)

Advances in treatment

Aducanumab was FDA-approved in June 2021, the first new agent for AD in almost 20 years.[32] It was approved under the accelerated pathway, and confirmatory trials are needed for continued approval.[32] The approval was based on 2 phase 3 studies that showed a statistically significant reduction in brain amyloid plaques for the aducanumab groups compared to placebo.[33,34] Notably, there has been controversy in the scientific community regarding the accelerated approval of aducanumab, as well as its safety and costs, in consideration of its observed clinical benefit.[35]

In the EMERGE study (NCT02484547), the 1643 participants, aged 50-85 years, met criteria for MCI or mild AD, and had a positive amyloid-PET scan.[33] Patients were randomized 1:1:1 to placebo, low-dose aducanumab, and high-dose

aducanumab groups. Results demonstrated a 22%, statistically significant reduction (P=0.012) in clinical decline in the amyloid-PET and CSF biomarker substudies (total of 302 patients evaluated).[33]

The ENGAGE trial (NCT02477800) enrolled 1647 patients aged 50-85 years with MCI or mild AD and a positive amyloid-PET scan.[34] Similar to EMERGE, patients were randomized 1:1:1 to placebo, low-dose aducanumab, and high-dose aducanumab. In the amyloid-PET and CSF biomarker substudies (374 patients), no statistically significant difference was observed in the rate of clinical decline.[34]

Aducanumab is indicated for AD in patients with MCI or mild dementia and is administered as an intravenous infusion given over 60 minutes, every 4 weeks.[36] The dose of aducanumab starts at 1 mg/kg for infusions 1 and 2, then increases to 3 mg/kg (infusions 3 and 4), then increases to 6 mg/kg (infusions 5 and 6), and the maintenance dose is 10 mg/kg starting with infusion 7. Doses should be administered at least 21 days apart.[36]

SUMMARY

MCI and AD are frequently encountered in primary care. As the population continues to age and these diseases become more prevalent, the role of PCPs in early diagnosis and management will become increasingly important, especially considering the shortage of dementia care specialists. PCPs should implement protocols for routine cognitive evaluation (such as AWVs) that involve use of validated tools to screen for cognitive impairment. Diagnosis and management of MCI and AD can be accomplished in primary care, but patients with atypical or complex presentations may require referral to specialists. Emerging diagnostics and therapeutics may prompt changes in practice for managing MCI and AD in the coming years. ●

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Use of SGLT-2 Inhibitors to Treat Chronic Kidney Disease in Primary Care

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KEY TAKEAWAYS

- Chronic kidney disease (CKD) remains underrecognized by patients and clinicians in the primary care setting, largely due to its asymptomatic presentation in early stages.
- Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have demonstrated kidney-protective effects in clinical trials—including in patients with and without type 2 diabetes (T2D)—and there are several proposed mechanisms for these benefits.
- Dapagliflozin and canagliflozin are SGLT-2 inhibitors with indications for CKD, and only dapagliflozin is indicated for CKD in patients without T2D.
- Clinically relevant adverse events associated with SGLT-2 inhibitors include volume depletion, diabetic ketoacidosis, and genital mycotic infections.

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INTRODUCTION

CASE SCENARIO

BT is a 59-year-old man who presents to a primary care clinic to establish care after moving to a new area. BT's medical records indicate diagnoses of hypertension, dyslipidemia, prediabetes, obesity, osteoarthritis, and gout. He states that he feels that his current medications are working well for him, and he "just needs an annual check-up" because his wife told him he needs one.

Lab work: glycated hemoglobin (A1c) 6.0%, estimated glomerular filtration rate (eGFR) 54 mL/min/1.73 m^2, urinary albumin-to-creatinine ratio (UACR) 140 mg/g, and lipid panel within normal limits; from 6 months ago at an outside clinic, the patient's eGFR was 50 mL/min/1.73 m^2

Vitals: Body mass index 32.4 kg/m^2, blood pressure 144/72 mmHg in clinic today

Current medications: losartan 50 mg daily, atorvastatin 10 mg daily, allopurinol 300 mg daily, and ibuprofen 200 mg 1-2 tablets twice daily as needed (uses once monthly)

The patient in this case scenario has chronic kidney disease (CKD), although this appears to be a new diagnosis based on his past medical records. He has several risk factors for CKD due to comorbidities and medications that can worsen kidney function. Although he is still in the earlier, and likely asymptomatic, stages of CKD, intervention is needed to address modifiable risk factors, prevent progression, and reduce the risk of adverse clinical outcomes from CKD.

CKD is defined as abnormality in kidney function or structure persistent for longer than 3 months.[1-3] It is commonly encountered in primary care, yet it remains underrecognized and underappreciated by many clinicians and patients.[2,4] CKD is thought to affect 8%-16% of the population globally, with a prevalence of 37 million (15%) adults in the United States.[5,6] Due to its often asymptomatic presentation, many patients with early CKD are unaware of the disease, underscoring the need for routine screening and awareness. Primary care practitioners (PCPs) can play a key role in reducing the burden of CKD by identifying and managing CKD, especially in earlier stages.

TABLE 1. **Risk factors for chronic kidney disease**

Clinical risk factors	
• Diabetes	• Kidney stones
• Hypertension	• Recurrent urinary tract infections
• Smoking	• Urinary tract obstruction
• Obesity	• Malignancy
• Autoimmune diseases	• Reduced kidney mass (low birth weight, nephrectomy, etc)
• Systemic infections (such as hepatitis B, hepatitis C, HIV)	• History of acute kidney injury
• Nephrotoxic drugs (such as NSAIDs, herbal products, lithium)	• Intravenous drug use
	• Family history of kidney disease
Sociodemographic risk factors	
• Older than 60 years of age	• Low education
• Non-white race	• Low income
Genetic risk factors	
• Polycystic kidney disease	• Sickle cell trait and disease
• Congenital anomalies of the kidney and urinary tract	• APOL1 risk alleles
• Other familial causes	• Alport syndrome

Abbreviations: APOL1, apolipoprotein L1; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs.

Source: Adapted from: Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. *JAMA*. 2019;322(13):1294-1304. doi:10.1001/jama.2019.14745

CKD is characterized by a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, UACR ≥30 mg/g, or by other markers of kidney damage such as hematuria or structural abnormalities.[1,3] In the United States, estimates suggest that >50% of individuals will develop a GFR <60 mL/min/1.73 m^2 during their lifetime. Notably, GFR declines with age, with a loss of about 1 mL/min/1.73 m^2 per year of life beginning around age 60.[7] Thus, there is a need for early detection and treatment to avoid adverse outcomes from progressive CKD, such as atherosclerotic cardiovascular disease (ASCVD), end-stage kidney disease (ESKD), and death.[8-10] Risk factors for CKD include many clinical, sociodemographic, and genetic characteristics (**TABLE 1**).[2,11]

Historically, sodium-glucose cotransporter-2 (SGLT-2) inhibitors have been studied and approved by the US Food and Drug Administration as antihyperglycemic drugs to treat type 2 diabetes mellitus (T2D).[12] However, in recent years, clinical evidence has confirmed cardiovascular and kidney benefits for certain SGLT-2 inhibitors, leading to added indications for heart failure with reduced ejection fraction (dapagliflozin), heart failure regardless of ejection fraction (empagliflozin) and kidney disease for patients with (dapagliflozin and canagliflozin) and without (dapagliflozin) T2D.[13-15]

Managing CKD in primary care should include reducing cardiovascular risk; managing hypertension, diabetes, and other comorbidities; avoiding nephrotoxins; ensuring correct medication dosing; and monitoring kidney function and other pertinent laboratory tests.[2] Drug therapy that is often considered includes statin therapy, renin-angiotensin-aldosterone system (RAAS) blockade with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) and/or an aldosterone receptor antagonist; and antihyperglycemic agents in patients with T2D.[2] Based on recent evidence, as noted subsequently in this article, SGLT-2 inhibitors may become standard therapy for reducing the risk of adverse clinical outcomes from CKD, including diabetic kidney disease (DKD).

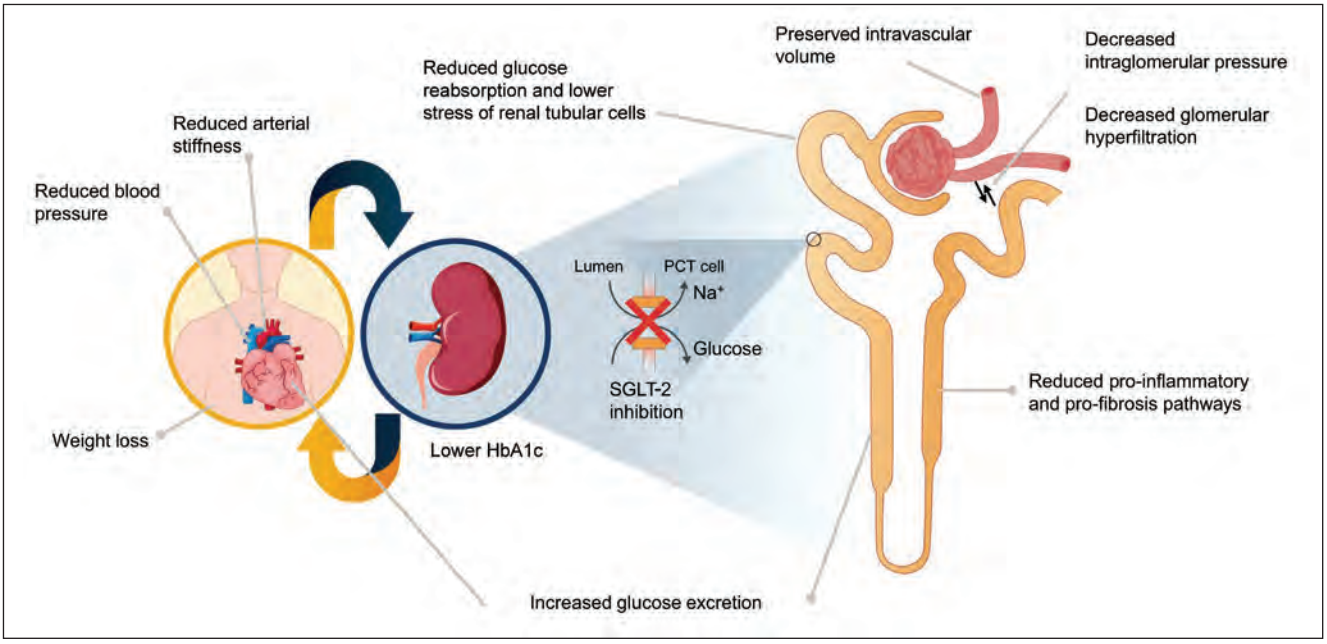
KIDNEY-PROTECTIVE MECHANISMS OF SGLT-2 INHIBITORS

There are several proposed mechanisms for the kidney benefits observed from SGLT-2 inhibitor therapy; most are independent of effects on blood glucose (**FIGURE**).[16] Based on results from trials of dapagliflozin and canagliflozin, SGLT-2 inhibitors can provide kidney benefits in patients with CKD. Specifically, the benefits are evident in those with T2D, an eGFR of 25 mL/min/1.73 m^2 (dapagliflozin) to 30 mL/min/1.73 m^2 (canagliflozin) or greater, and coadministration of an ACE inhibitor or ARB.[17-20] Only dapagliflozin has shown kidney benefits in patients without T2D.[20]

SGLT-2 inhibitors are thought to exert the following effects directly on the kidneys as well as effects on body systems interconnected with the kidneys[12]:

- *Improvement in tubuloglomerular feedback;* however,

FIGURE. **Proposed kidney-protective pathways for SGLT-2 inhibitors**[16]



Source: Giorgino F, Vora J, Fenici P, Solini A. Renoprotection with SGLT2 inhibitors in type 2 diabetes over a spectrum of cardiovascular and renal risk. *Cardiovasc Diabetol*. 2020;19(1):196. doi:10.1186/s12933-020-01163-9

The figure text was simplified and original superscript references from the source publication were removed prior to its reproduction in this article.

effects on glomerular hemodynamics are unclear

- *Reduction of tubular workload and hypoxia* by reducing sodium and glucose reabsorption
- *Reduction in glucose metabolic fluxes,* improving mitochondrial function
- *Enhancement of diuresis and natriuresis* leading to reductions in interstitial fluid in the kidneys and alleviating kidney hypoxia
- *Limiting inflammation and fibrosis* through reductions in various inflammatory components, including uric acid

Overwhelmingly, more research is needed to elucidate mechanisms of kidney protection clearly, but trial data affirm the benefits of SGLT-2 inhibitors in patients with CKD, including DKD.[12] Notably, SGLT-2 inhibitors also provide kidney protection through less direct mechanisms by simply improving risk factors for CKD and ASCVD, including reducing blood glucose levels and blood pressure.

ROLE OF SGLT-2 INHIBITORS IN DIABETIC AND NON-DIABETIC CKD

Guideline recommendations for SGLT-2 inhibitors in CKD

Society clinical guidelines have recognized the kidney benefits of SGLT-2 inhibitors in patients with diabetes, and to a lesser extent, those without diabetes. The American Diabetes Association recommends the use of SGLT-2 inhibitors in patients with stage 3 CKD or higher and T2D, regardless of glycemic control, to slow CKD progression and reduce the risk of heart failure.[21]

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend using SGLT-2 inhibitors as a first-line therapy, along with metformin, in patients with T2D and CKD with eGFR ≥ 30 mL/min/1.73 m^2.[22] KDIGO also suggests reducing doses of other antihyperglycemic drugs, if needed, to accommodate initiation of an SGLT-2 inhibitor. The guidelines recommend prioritizing SGLT-2 inhibitors with documented kidney or cardiovascular benefits and obtaining a baseline eGFR. Additionally, KDIGO suggests that once an SGLT-2 inhibitor is started, it can be continued even if the eGFR drops below 30 mL/min/1.73 m^2, unless it is not tolerated or dialysis is needed.[22]

The American Heart Association recognized the beneficial effects of SGLT-2 inhibitors on cardiovascular and kidney outcomes in a scientific statement that recommends use of SGLT-2 inhibitors in patients with T2D and CKD based on adequate eGFR per drug labeling.[23] Lastly, a joint guideline from the European Society of Cardiology and the European Association for the Study of Diabetes acknowledges the kidney-protective effects of SGLT-2 inhibitors and recommends

their use in patients with T2D who are already on metformin or who are treatment naïve.[24]

Evidence and indications for SGLT-2 inhibitors in CKD

Several cardiovascular and renal outcomes trials form the evidence base for using SGLT-2 inhibitors in patients with CKD. Patients in each trial had varying levels of kidney disease, and although many outcomes are similar between the agents, there are a few key inter-drug differences.[16]

Dapagliflozin: indicated for adults with CKD at risk of progression to reduce the risk of sustained eGFR decline, ESKD, cardiovascular death, and hospitalization for heart failure.[13] In the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, patients with T2D who had or were at risk for ASCVD received dapagliflozin or placebo.[25] Results demonstrated a reduction in a secondary renal composite endpoint (≥40% reduction in eGFR to <60 mL/min/1.73 m^2, kidney failure, or death due to kidney disease), as well as lower rates of progression to a higher category of albuminuria and prevention of new-onset albuminuria. In a kidney-specific analysis from DECLARE-TIMI 58, dapagliflozin was found to prevent and reduce progression of kidney disease in a population where about 93% of patients had an eGFR >60 mL/min/1.73 m^2.[26]

In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial, patients with or without T2D, an eGFR of 25-75 mL/min/1.73 m^2 and a UACR of 200-5000 mg/g received dapagliflozin or placebo.[20,27,28] The dapagliflozin group experienced a reduction in the primary cardio-renal composite endpoint (sustained decline in eGFR of at least 50%, ESKD, or death from kidney disease or cardiovascular causes), a slower mean rate of eGFR decline, and a reduction in albuminuria. These benefits were observed regardless of diabetes or glycemic status.

Canagliflozin: indicated to reduce the risk of ESKD, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with T2D and diabetic nephropathy with albuminuria.[14] The Canagliflozin Cardiovascular Assessment Study (CANVAS) program enrolled patients with T2D and high cardiovascular risk.[29] The canagliflozin group showed a reduction in a secondary renal composite endpoint (sustained 40% reduction in eGFR, need for kidney replacement therapy, or death from kidney disease) and prevention of new-onset albuminuria.

In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, patients with T2D and albuminuric CKD (eGFR of 30-90 mL/min/1.73 m^2 and a UACR of >300-5000 mg/g) received canagliflozin or placebo.[17] Trial results indicated a reduction in the primary cardio-renal composite endpoint (serum creatinine doubling, kidney failure treated by kidney replacement therapy, or death from kidney disease or cardiovascular causes). Kidney benefits also included a slower mean rate of eGFR decline and reduction in mean UACR.

Empagliflozin: not currently indicated for patients with CKD or DKD.[15] The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial enrolled patients with T2D and established ASCVD, and assigned them to either empagliflozin or placebo.[30,31] The empagliflozin group experienced a reduction in a secondary renal composite endpoint (incident or worsening nephropathy or cardiovascular death), progression to macroalbuminuria, doubling of serum creatinine, and initiation of renal-replacement therapy.[31]

The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) clinical trial to evaluate the effect of empagliflozin in patients with CKD, was stopped early due to evidence of positive efficacy, with published results expected later in 2022.[32]

Ertugliflozin: not currently indicated for patients with CKD or DKD.[33] In the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes (VERTIS CV) trial, patients with T2D and ASCVD received ertugliflozin or placebo.[34] The ertugliflozin group demonstrated a nonsignificant reduction in a secondary renal composite outcome (doubling of serum creatinine, renal replacement therapy, and death from renal causes) as well as a significant reduction in an exploratory renal composite outcome (sustained 40% reduction from baseline in eGFR, chronic dialysis/kidney transplant, or renal death).[34,35]

Evidence-based treatment of CKD with SGLT-2 inhibitors in primary care

When considering initiating an SGLT-2 inhibitor for patients with CKD, PCPs should consider patient-specific factors in light of trial data and guideline recommendations to select an agent (**TABLE 2**). Of note, SGLT-2 inhibitors can safely and effectively be combined with ACE inhibitors and ARBs for treatment of kidney disease, and the vast majority of patients with CKD in the trials mentioned earlier were receiving concurrent treatment with an ACE inhibitor or ARB.[36] Patients' eGFR, albuminuria status, CKD stage, and diabetes status may render them ineligible for certain SGLT-2 inhibitors. Notably, dapagliflozin is the only SGLT-2 inhibitor with a renal-specific indication including patients with and without T2D and spanning CKD stages (including earlier stages of CKD such as eGFR >60 mL/min/m^2 and UACR >30 mg/g).

ADVERSE EVENTS OF SGLT-2 INHIBITORS

Clinically relevant adverse events of SGLT-2 inhibitors include volume depletion (1.2%-1.5%), genital mycotic infections

TABLE 2. **SGLT-2 inhibitors, their eGFR criteria, and their indications**

Drug	CV/renal outcomes clinical trial(s)	Selected trial outcomes	eGFR criteria[a] and relevant indications
Dapagliflozin[13]	DECLARE-TIMI 58[25]	Incidence of secondary renal composite: 4.3% in dapagliflozin group vs 5.6% in placebo group (HR 0.76; 95% CI: 0.67, 0.87) Reduction in eGFR decline by at least 40% to <60 mL/min/1.73 m^2 by 46% with dapagliflozin compared to placebo (HR 0.54; 95% CI: 0.43, 0.67)	≥25 CKD (with or without T2D) and T2D
	DAPA-CKD[20,28]	Incidence of primary cardio-renal composite: 9.2% in dapagliflozin group vs 14.5% in placebo group (HR 0.61; 95% CI: 0.51, 0.72) Reduction in mean UACR by 29.3% with dapagliflozin compared with placebo (95% CI: -33.1, -25.2; *P* <.0001)	
Canagliflozin[14]	CANVAS[29]	Incidence of secondary renal composite: 5.5 vs 9.0 participants per 1000 patient-years for canagliflozin vs placebo (HR 0.60; 95% CI: 0.47, 0.77) Albuminuria progression occurred in 89.4 vs 128.7 per 1000 patient-years with canagliflozin compared to placebo (HR 0.73; 95% CI: 0.67, 0.79)	≥30 DKD, T2D
	CREDENCE[17]	Incidence of primary cardio-renal composite: 43.2 vs 61.2 events per 1000 patient-years for canagliflozin vs placebo (HR 0.70; 95% CI: 0.59, 0.82) Reduction in mean UACR by 31% with canagliflozin compared to placebo (95% CI: -25, -35)	
Empagliflozin[15]	EMPA-REG OUTCOME[30]	Incidence of secondary renal composite: 12.7% in empagliflozin group vs 18.8% in placebo group (HR 0.54; 95% CI: 0.40, 0.75) Progression to macroalbuminuria: 11.2% in empagliflozin group vs 16.2% in placebo group (HR 0.62; 95% CI: 0.54, 0.72) Doubling of serum creatinine: 1.5% in empagliflozin group vs 2.6% in placebo group (HR 0.56; 95% CI: 0.39, 0.79) Initiation of renal-replacement therapy: 0.3% in empagliflozin group vs 0.6% in placebo group (HR 0.45; 95% CI: 0.21, 0.97)	≥30 T2D
Ertugliflozin[33]	VERTIS CV[34,35]	Incidence of secondary renal composite: 3.2% in ertugliflozin group vs 3.9% in placebo group (HR 0.81; 95% CI: 0.63, 1.04) Incidence of exploratory renal composite: 6.0 vs 9.0 events per 1000 person-years for ertugliflozin vs placebo (HR 0.66; 95% CI: 0.50, 0.88)	≥45 T2D

[a]eGFR measured in mL/min/1.73 m^2

Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

(2%-4% in men, 3%-7% in women), and diabetic ketoacidosis (DKA).[12] One study estimates that DKA occurs in about 1 in 800 patients with diabetes receiving an SGLT-2 inhibitor, about twice as often as those not taking an SGLT-2 inhibitor.[37] For patients with a history of these adverse events, especially severe or recurrent events, clinicians should carefully consider whether pursuing therapy with an SGLT-2 inhibitor is the most appropriate clinical decision. PCPs should engage patients in shared decision-making when discussing SGLT-2 inhibitors and provide a clear, simple discussion of their risks and benefits.

Although there may be an initial, acute decrease in eGFR (≥10% decrease in about half of patients) when starting an SGLT-2 inhibitor, the eGFR tends to stabilize thereafter and can ultimately be reversed with discontinuation of therapy.[38] Additionally, the small initial eGFR drop is not associated with progressive long-term kidney injury or loss of function and should not be a reason for discontinuation.[39] Initial drop in eGFR >30% occurred in 0.5% of patients and was associated with a slightly increased risk of kidney-related adverse events.[39] Since volume depletion can occur with SGLT-2 inhibitors, monitoring volume status and kidney function can help identify this trend. However, adjusting diuretic or antihypertensive therapy is usually not necessary when starting an SGLT-2 inhibitor.[12]

Although DKA is rare, SGLT-2 inhibitors have a warning for DKA, which may be euglycemic.[12] Factors that may increase the risk of DKA include insulin use, surgery, and acute illness. Clinicians should consider holding SGLT-2 inhibitors for 3 days prior to surgery or during acute illness.[12]

Women are more likely than men to experience genital mycotic infections when taking an SGLT-2 inhibitor, and the risk of these infections can be improved by proper personal hygiene (such as rinsing the genital area with water after voiding and before bed and wearing cotton underwear) and optimized T2D management.[40]

SUMMARY

CKD is a common condition encountered in primary care, and PCPs are well positioned for early identification and treatment of the disease to slow progression and prevent adverse outcomes. SGLT-2 inhibitors now have data and indications to support use in kidney disease in patients with T2D (dapagliflozin and canagliflozin) and without T2D (dapagliflozin). Clinicians should consider treating patients with CKD with an SGLT-2 inhibitor consistent with clinical evidence and guideline recommendations, based on eGFR, albuminuria, and diabetes status. Engaging patients in shared decision-making discussions can help them accurately weigh the benefits and risks of treatment with an SGLT-2 inhibitor. ●

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