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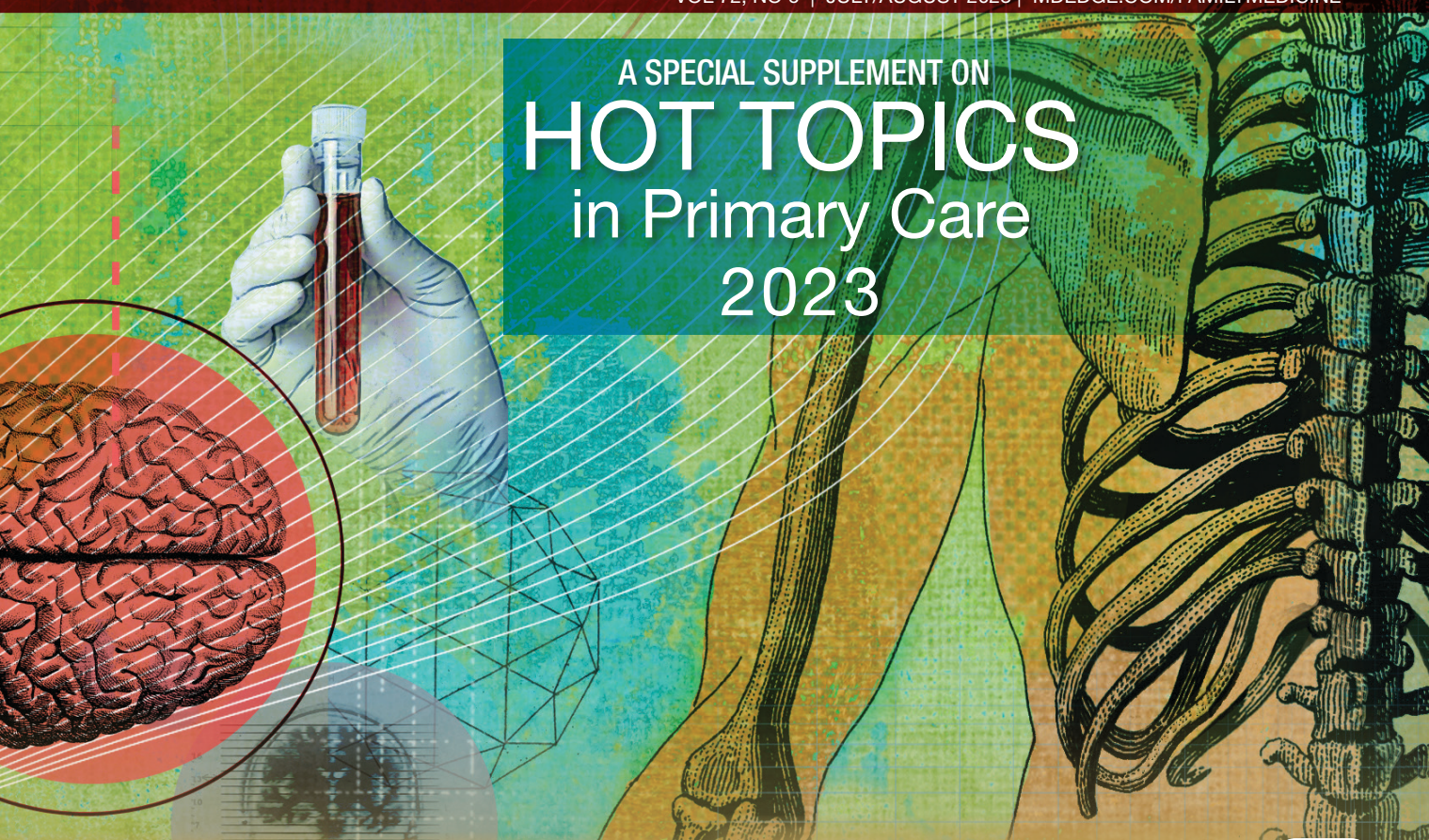
A SPECIAL SUPPLEMENT ON

HOT TOPICS in Primary Care 2023



Introduction

The scope of primary care is so large that keeping up with advances and state-of-the-art approaches to management is a challenge. To address this, *Hot Topics in Primary Care 2023* includes subjects that are important and practice changing. Discussions of cardiovascular disease and its concomitant comorbidities and relationships are featured in several articles, including management of cardio-renal-metabolic conditions in patients with T2D, the role of glucagon-like peptide 1 receptor agonists in reducing ischemic stroke, and reducing cardiopulmonary risk and exacerbations in chronic obstructive pulmonary disease (COPD).

Chronic respiratory diseases are a frequent concern in our practices and the articles on COPD and asthma provide updated guideline treatment recommendations, along with strategies to promote stable disease and prevent exacerbations.

The majority of patients with diabetes in the United States are managed in primary care settings, and several articles address various aspects of diabetes care, including new paradigms for CKD management, the practical use of continuous glucose monitoring, and early intervention to delay the onset of type 1 diabetes.

Other important clinical issues addressed in this supplement include acute pain management, early life nutrition and the developing brain, insomnia management, and a patient-centered approach to managing irritable bowel syndrome with constipation and chronic idiopathic constipation.

These articles all provide cutting-edge information and strategies to assist primary care clinicians in improving overall patient outcomes.

You may wish to start by checking out the short videos about each article. They offer the opportunity to meet the lead author and learn the key takeaways; they are a good way to "thumb through" this special supplement before reading the articles in detail (scan the QR code below).

We trust that you will find this special supplement of *Hot Topics in Primary Care 2023* helpful and keep it as a resource to refer to as needed.

Wishing good health to you and your patients.

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

COVER IMAGE: STEPHANIE DALTON COWAN/THE ISPOT

A Patient-Centered Approach to Managing IBS-C and CIC

Brian E. Lacy, MD, PhD, FACG

doi: 10.12788/jfp.0514

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

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

- Implement a staged strategy for the diagnostic evaluation of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) based on history and physical examination, including the Rome IV criteria.
- Discuss the evidence and guideline recommendations for self-care as well as over-the-counter (OTC) and prescription therapies to treat IBS-C and CIC,
- Individualize treatment for IBS-C and CIC emphasizing patient-centered care to address patient concerns, improve outcomes, and enhance quality of life.

KEY TAKEAWAYS

- Most patients with IBS-C or CIC do not seek medical care and few patients use appropriate therapies to control symptoms.
- By establishing a positive patient-provider relationship, primary care practitioners can encourage a more open discussion of bowel symptoms.
- The diagnosis of IBS-C and CIC is based on the Rome IV criteria, which differentiates the 2 conditions by small variations in symptom presentation.
- Effective treatment of IBS-C and CIC, can involve nonpharmacologic interventions, OTC medications, and prescription medications.
- For treating IBS-C, the American Gastroenterological Association (AGA) strongly recommends linaclotide and conditionally suggests tenapanor, plecanatide, lubiprostone, tricyclic antidepressants, polyethylene glycol laxatives, and antispasmodics.
- Treatment selection should address the patient's primary complaints and help them achieve their treatment goals.

TARGET AUDIENCE

Family physicians (FPs), general internal medicine physicians, and other primary care practitioners.

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SUPPORTER

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INTRODUCTION

Irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) are similar, but distinct, gut-brain disorders with overlapping symptoms. IBS-C can be defined as recurrent abdominal pain accompanied by a change in defecation, with constipation as the prevailing stool pattern.[1] CIC, also known as functional constipation, is generally diagnosed after excluding IBS-C.[1] CIC can be described as the presence of straining or incomplete evacuation, which can be accompanied by bloating or abdominal pain or discomfort, in patients who do not meet criteria for IBS-C.[1] Both IBS-C and CIC are defined by the Rome IV criteria (**TABLE 1**).[1,2]

IBS-C and CIC both cause a significant health burden to individuals and society. Approximately 4.1% of the global population is affected by irritable bowel syndrome (IBS), and about one-third of IBS patients are classified as having IBS-C.[3] Notably, this may underestimate the true prevalence, since the Rome IV criteria likely define a more severe population of patients with IBS than previous definitions.[1] The estimated global prevalence of IBS-C is 1.3%, and CIC is estimated to affect 11.7% patients worldwide.[3] These conditions pose a significant economic impact to the healthcare system, as patients with IBS-C and CIC have a significantly higher use of outpatient services, diagnostics, and imaging.[4] The total annual constipation-related healthcare costs in the United States are estimated to be more than $230 million per year.[5]

Both disorders of chronic constipation disrupt normal physiologic functioning of the gut. IBS-C can have multiple possible mechanisms, including altered motility, abnormal gut-brain interaction, bacterial overgrowth, carbohydrate malabsorption, and intestinal inflammation.[6] The pathophysiology of CIC remains unclear, but disruption of peristaltic activity and fluid secretion play a role in some patients.[7] IBS-C and CIC significantly impair patients' quality of life; the most bothersome symptoms are difficult bowel movements, bloating, and abdominal discomfort and pain.[5]

THE ROLE OF THE PRIMARY CARE PRACTITIONER

Despite the significant health burden of IBS-C and CIC, few patients use appropriate medications to control symptoms, though about 48% take medications to manage constipation.[8] Additionally, most patients with constipation do not seek medical care. Of those who do report using medication to help with constipation, 94% take over-the-counter (OTC) treatments, 1% take prescription medications, and 5% take a combination of OTC and prescription therapies.[8] Primary care practitioners (PCPs) are well positioned to establish a healthy patient-provider relationship that can be instrumental in effectively treating IBS-C and CIC.

TABLE 1. Rome IV diagnostic criteria for IBS-C and CIC[1,2]

IBS-C	Recurrent abdominal pain, on average, ≥1 day per week in the last 3 months, associated with ≥2 of the following: • Related to defecation • Change in frequency of stool • Change in form (appearance of stool) Hard/lumpy stools ≥25% Loose/watery stools <25%
CIC	Must include ≥2 of the following: • Straining • Lumpy or hard stools (Bristol Stool Form Scale 1-2) • Sensation of incomplete evacuation • Sensation of anorectal obstruction/ blockage • Manual maneuvers to facilitate >25% of defecations <3 spontaneous bowel movements per week

Self-reporting of history and symptoms is essential to a correct diagnosis and determining a therapeutic response for IBS-C and CIC.[9] Symptom reporting is influenced by age, sex, and health literacy level, and a negative patient-clinician relationship and dissatisfaction with the care plan can result in worse outcomes.[9] As PCPs build relationships with their patients over time, it is natural to adopt an individualized, patient-centered communication style that ultimately benefits disease management of both IBS-C and CIC. Additionally, implementing a personalized approach to treatment allows the patient to help choose a treatment that aligns with their preferences and goals and addresses their concerns.

As part of a patient-centered approach, clinicians should be aware of potential differences in perceptions about symptom control. The BURDEN IBS-C and BURDEN-CIC studies evaluated differences between patients' and clinicians' perceptions about disorders of chronic constipation.[10,11] Overall, these studies found that, compared to clinicians, patients reported greater acceptance, less frustration and obsession, and better control of IBS-C or CIC symptoms. This may indicate that patients tend to have a more positive outlook on their constipation symptoms than clinicians, and clinicians should recognize this possibility when managing patients with IBS-C or CIC.

It is also important to consider differences in emotional burden and symptoms; women are more likely to report shame and embarrassment associated with their bowel habits than men.[5] Additionally, women report more abdominal

bloating and distension than men.[5] Concomitantly managing comorbid conditions can be challenging and highlights the need for individualized therapy. In IBS-C, functional dyspepsia and depression are common comorbidities.[12] In CIC, functional dyspepsia, diabetes, and depression are commonly comorbid.[12] Overall, clinicians should utilize a patient-centered approach for managing IBS-C and CIC while accounting for demographic and cultural differences, comorbidities, and available therapies.[5]

CASE SCENARIO

LY is a 38-year-old female being seen for routine follow-up in her PCP's office for migraine headaches. History and physical examination show her migraines are infrequent and generally well controlled with a triptan. During her visit, she appears to be in some abdominal distress and mentions she's had trouble with constipation lately.

Upon further questioning, LY reveals that she has been too embarrassed to bring up her constipation problems before. She explains that she is able to defecate about twice a week, these bowel movements only occur with straining, and the result is lumpy, hard stools. She denies significant abdominal pain.

DIAGNOSTIC EVALUATION FOR IBS-C AND CIC

Although IBS-C and CIC are separate diagnoses, they share many common symptoms, including abdominal discomfort, difficulty with defecation, bloating, and abdominal distension.[5] Symptoms of functional bowel disorders exist along a spectrum, and patients with constipation can fluctuate between IBS-C and CIC (**FIGURE 1**).[5] Due to this overlap and symptom fluctuation, it can be challenging to establish a diagnosis of either IBS-C or CIC, especially at the first visit. Ultimately, selecting a single diagnosis may be less important than initiating effective treatment to alleviate patients' symptoms, especially given the overlap of these 2 conditions.[5]

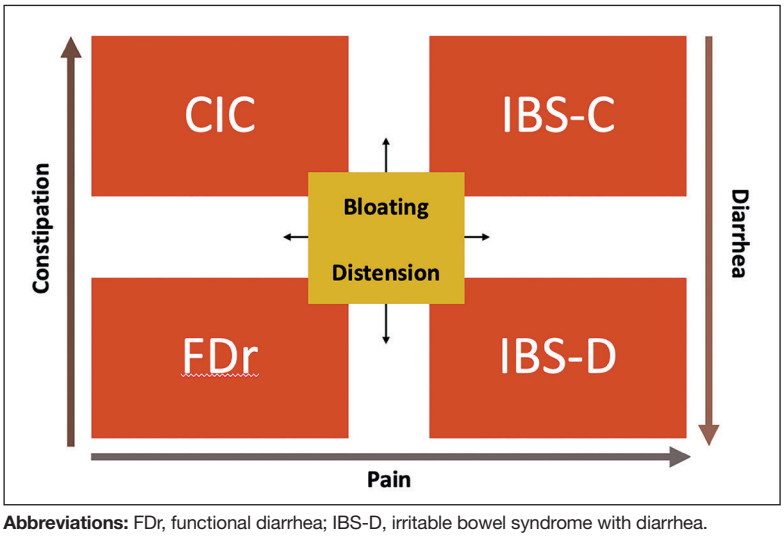
To proceed with a diagnostic workup of IBS-C and CIC, clinicians can use an algorithm incorporating components such as a thorough medical history, physical examination, and the Rome IV criteria (**FIGURE 2**).[13] The presence of abdominal or bowel symptoms can present in a variety of ways, including pain, discomfort, bloating, distension, constipation, straining, incomplete evacuation, and manual maneuvers to help defecation.[14] After discussing the presenting symptoms, a thorough patient assessment should be performed, which should include a careful symptom history, identification of comorbidities, a review of previous investigations and treatments, and a thorough physical examination.[14] A digital rectal examination can be helpful to investigate the possibility of a pelvic floor disorder contributing to constipation symptoms.[2] Routine laboratory testing such as a metabolic panel, thyroid-stimulating hormone (TSH), and complete blood count may be performed.

Once a diagnosis is suspected, PCPs should assess for alarm features, which, if present, may necessitate further diagnostic workup or referral.[14] An abnormal physical exam finding or intolerance or lack of response to standard treatment can also be indications for referral.[15] Alarm features include[13]:

- Age >45 without prior colon cancer screening
- Overt gastrointestinal bleeding
- Nocturnal stool passage
- Recent change in bowel habits
- Anemia
- Fever
- Unintentional weight loss
- Family history of celiac disease, colon cancer, or inflammatory bowel disease
- Palpable lymphadenopathy, ascites, or an abdominal mass
- Recent antibiotic use

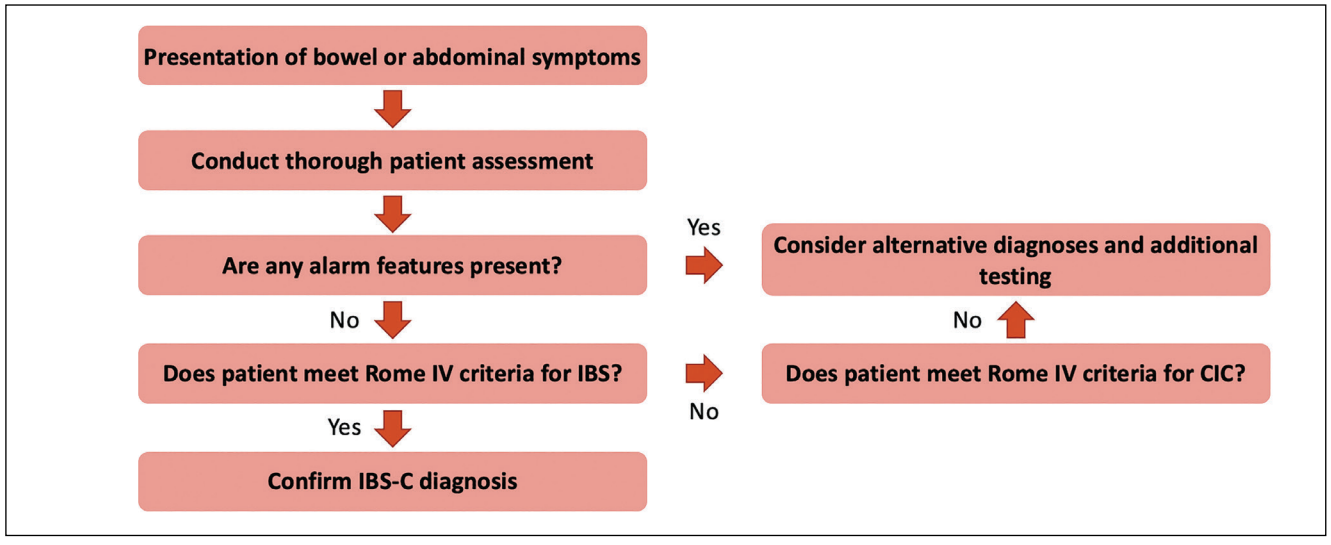
If alarm symptoms are absent, the next step is to identify whether the patient's presentation meets Rome IV criteria for IBS (**TABLE 1**). If so, and if symptomatology is consistent with constipation, a diagnosis of IBS-C can be established at the time of the first visit. If the patient's presentation does not meet Rome IV criteria for IBS, the next step is to determine whether the presentation meets Rome IV criteria for

FIGURE 1. Continuum of gut-brain disorders with primarily abdominal symptoms[1]



Abbreviations: FDr, functional diarrhea; IBS-D, irritable bowel syndrome with diarrhea.

FIGURE 2. Diagnostic algorithm for distinguishing IBS-C and CIC[14]



CIC (**TABLE 1**). If so, a CIC diagnosis can be confirmed. If not, further testing and alternative diagnosis and/or referral to a specialist may be necessary. Further testing might include celiac serologies, C-reactive protein, fecal calprotectin, thyroid-stimulating hormone (TSH), serum calcium, and colonoscopy, depending upon the patient's symptoms, history, review of symptoms, and physical exam findings.[13,14]

In the patient case scenario above, the patient meets at least 2 of the Rome IV criteria for CIC (straining, lumpy or hard stools, <3 spontaneous bowel movements per week). Her presentation is also not consistent with the Rome IV criteria for IBS-C, given the absence of recurrent abdominal pain, so the PCP should consider a diagnosis of CIC.

TREATMENT OF IBS-C AND CIC

Treatment goals for IBS-C and CIC should target improvement in global symptoms and overall severity, and individualized treatment plans should educate and encourage self-management as part of a patient-centered approach.[9] Therapeutic intervention should be selected based on the patient's primary complaints. Nonpharmacologic, OTC, and prescription treatments can be effective for treating both IBS-C and CIC (**FIGURE 3**).

Nonpharmacologic interventions

Nonpharmacologic therapy to improve symptoms in IBS-C and CIC primarily focuses on lifestyle adjustment. Effective interventions can include exercise, stress reduction, adequate hydration, improving sleep, maintaining a routine bathroom schedule, a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP), and eliminating medications that can cause or worsen constipation (opioids, iron or calcium supplements, anticholinergics, etc.).[1,14]

Implementing a low-FODMAP diet can be effective but also challenging for the patient. Multiple studies support the use of a low-FODMAP diet to treat symptoms of IBS.[16,17] However, since the diet consists primarily of excluding certain grains, fruits, and vegetables, the diet is complex and difficult to adhere to. It can also worsen constipation if fiber sources are not replaced with alternatives. Involving a nutritionist is strongly recommended to properly implement a low-FODMAP diet.[17]

OTC agents

OTC medications to treat IBS-C and CIC include fiber (psyllium, polycarbophil), stimulant laxatives (bisacodyl, sennosides), osmotic laxatives (polyethylene glycol, lactitol), and anionic surfactants (stool softeners such as docusate).[2,18] A systematic review of 41 studies identified good evidence for treating chronic constipation with polyethylene glycol and sennosides, which may be more effective than other OTC agents.[19] However, the overall quality of evidence supporting OTC agents is relatively low. Regardless, due to ease of access, many patients initially prefer to use these treatments.

OTC treatments can improve stool consistency and frequency but do not improve pain or global symptoms.[2] This is worth mentioning to patients, as abdominal pain is the most common reason patients seek medical advice. Adverse events of OTC agents include abdominal pain, diarrhea, nausea, flatulence, vomiting, and electrolyte imbalances.[2,18]

Prescription medications

US Food and Drug Administration (FDA)–approved prescription therapies for IBS-C and CIC include prosecretory agents,

serotonin 5-HT_4 receptor agonists, and a sodium-hydrogen exchanger isoform 3 (NHE3) inhibitor.[2,13,18] Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have been studied and are sometimes recommended for treatment, although this constitutes off-label use.[20] The American Gastroenterological Association (AGA) has provided recommendations for the use of certain prescription and OTC medications for IBS-C in their 2022 guideline (**TABLE 2**).[21] This guideline strongly recommends using linaclotide for IBS-C and conditionally suggests use of other agents for IBS-C such as tenapanor, plecanatide, lubiprostone, TCAs, polyethylene glycol laxatives, and antispasmodics.

Prosecretory agents. Lubiprostone, linaclotide, and plecanatide are secretagogues that act on chloride channels to increase luminal fluid content.[22] These agents have overall good evidence for use in IBS-C and CIC.[2] Lubiprostone is approved for CIC and for women with IBS-C (but not men); linaclotide and plecanatide are approved for IBS-C and CIC.[18]

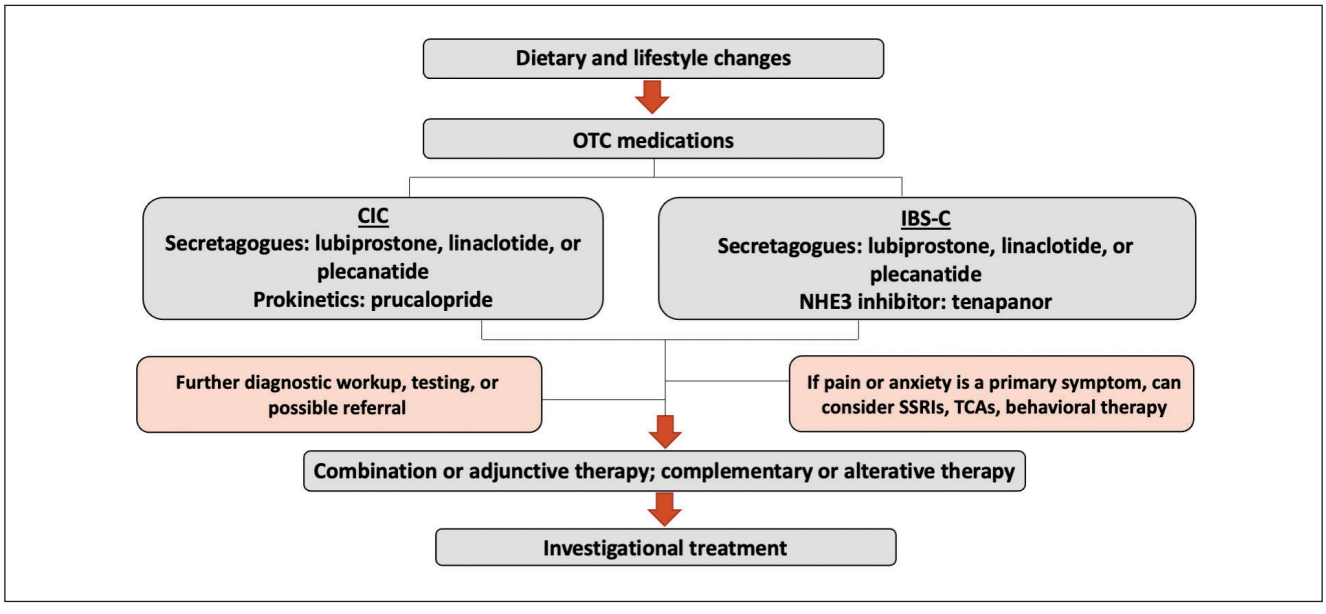
Serotonin 5-HT_4 receptor agonists. Prucalopride and tegaserod are prokinetic agents that act on 5-HT_4 receptors in the gut to help initiate peristaltic reflex, resulting in decreased colonic transit time and improved bowel movement frequency.[2,23] Prucalopride is approved for CIC and tegaserod is approved for IBS-C in women <65 years of age without a history of cardiovascular ischemic events.[18] **Note:** tegaserod was withdrawn from the market as of June 30, 2022 as a business decision and not due to concerns about efficacy, safety, or a product recall.

NHE3 inhibitors. Tenapanor is a type of secretagogue that increases luminal content by blocking the sodium-hydrogen exchanger on the epithelial surface and is approved for IBS-C.[18,24]

Clinicians considering initiating pharmacologic therapy might consider the following when making a treatment selection[25]:

- Patients often self-treat with OTC remedies prior to seeking medical care
  - Perceived failure of OTC therapies can be a turning point for patients to seek medical care and potentially escalate to prescription treatment
- Prescription agents are generally regarded by certain experts as interchangeable, with optimal treatment determined after trial and error[25]
  - No agent has demonstrated comparative superiority due to lack of head-to-head comparisons
  - However, in a meta-analysis comparing secretagogues, linaclotide 290 mcg daily was numerically superior for symptom control[26]
- Ideally, symptoms are managed with prescription agent monotherapy, but some patients may require combination therapy for complete symptom resolution
- The time course of treatment response can be variable

FIGURE 3. Treatment algorithm for IBS-C and CIC[25]



Abbreviations: NHE3, sodium-hydrogen exchanger isoform 3.

TABLE 2. AGA recommendations and strength of evidence for medications to treat IBS-C[21]

Medication	Strength of recommendation	Certainty of evidence
Tenapanor	Conditional	Moderate
Plecanatide	Conditional	Moderate
Linaclotide	Strong	High
Lubiprostone	Conditional	Moderate
Polyethylene glycol laxatives	Conditional	Low
TCAs	Conditional	Low
Antispasmodics	Conditional	Low

- Stool frequency tends to improve in hours to days, while pain, discomfort, and bloating can last many weeks before some patients notice benefit

CASE SCENARIO (CONT'D)

LY admits she's been using OTC laxatives and stool softeners "on and off" recently and she would be interested in a prescription medication "if there's one that can help."

In this scenario, the patient should be educated about lifestyle changes that can help her symptoms. The PCP might consider prescribing a secretagogue or prokinetic agent with demonstrated benefit in CIC, and the choice of agent should be consistent with the patient's treatment goals and clinical characteristics.

SUMMARY

IBS-C and CIC cause significant health burden for patients, who are frequently not appropriately treated for their symptoms. PCPs are positioned to build strong patient-provider relationships to help patients feel comfortable disclosing information related to bowel habits, which is essential to diagnosing and monitoring chronic constipation. Clinicians should implement a systematic approach for diagnosis and treatment that incorporates patients' characteristics, needs, and treatment goals. ●

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Acute Pain in Perspective

Bill McCarberg, MD

doi: 10.12788/jfp.0617

KEY TAKEAWAYS

- Acute pain is a common and nearly universal experience that usually has a sudden onset and is limited in duration. It is a normal physiologic response to a noxious stimulus that can become pathologic if untreated or not treated effectively.
- Acute pain has a limited duration (<1 month) and often is caused by injury, trauma, or medical treatments such as surgery.
- Primary care practitioners (PCPs) who encounter patients with acute pain can help preserve function and quality of life and prevent progression to chronic pain by implementing appropriate management strategies. PCPs in rural settings may bear greater responsibility for acute pain management because of the lack of accessible specialists.
- All current guidelines support using a multimodal approach to pain management and reserving use of opioids for patients with severe pain that cannot be managed with other agents.
- There are several new agents and formulations recently approved or in development for the treatment of acute pain.
- The recently approved co-crystal formulation of celecoxib and tramadol hydrochloride provides an additional option for acute pain management and utilizes a single-medication multimodal approach.

FACULTY

Bill McCarberg, MD, is a hospice and palliative medicine specialist in San Diego, CA.

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INTRODUCTION TO ACUTE PAIN

Acute pain is a nearly universal experience that usually has a sudden onset and is limited in duration. It is a normal physiologic response to a noxious stimulus that can become pathologic if untreated or not treated effectively.[1] The definition of acute pain is focused primarily on distinguishing it from chronic pain based on duration of symptoms. Acute pain is usually sudden in onset and time limited (duration of <1 month) and often is caused by injury, trauma, or medical treatments such as surgery.[1] Unresolved acute pain or subacute pain (defined as pain that has been present for 1-3 months) can evolve into chronic pain, which typically has a duration >3 months and may emerge as the result of an underlying disease, injury, response to medication, inflammation, or undetermined cause.[1] While acute and chronic pain are defined as distinct entities, chronic pain may begin as acute pain.[2-4] Ineffective treatment of acute pain increases the risk for development of chronic pain.[5]

Acute pain is very common and has significant adverse consequences. Estimates of the frequency of acute pain depend substantially on the setting in which data are collected, but it is very common in most healthcare settings. Many specialists and primary care practitioners (PCPs) are responsible for managing patients presenting with pain.[6-8] Pain is one of the most common complaints encountered in primary care practice; for example, back pain is the fourth most common reason for primary care visits in the United States (US).[9,10] PCPs may need to treat various types of acute pain, ranging from headaches and joint sprains to rotator cuff injuries and back pain.[11] Notably, patients in rural areas may rely more heavily on PCPs for management of acute pain because of lack of access to pain and surgical specialists.[12]

While acute pain might be considered adaptive, it does have significant negative outcomes when treated inappropriately or ineffectively.[13] In the surgical setting, ineffectively managed acute postoperative pain has been shown to be associated with negative consequences that include increased morbidity, impaired function, slower recovery, and increased medical costs.[14] A large prospective, multicenter study reported the proportion of patients who transitioned from acute to chronic low back pain in primary care was 32%.[15] The risk of transition was linearly associated with early care that was not concordant with current practice guidelines.[15] Inappropriate management of acute pain, including overprescribing opioids and failure to follow a multimodal approach to treatment, is a potential contributor to poor outcomes in patients treated for fractures.[16]

Acute pain also adversely affects quality of life.[17] Patients who had undergone radical prostatectomy, total hip replacement, or total knee replacement were assessed for pain, health-related quality of life, and physical and social function 1 month following discharge from the hospital using the Short Form-36

(SF-36) quality-of-life questionnaire and the Treatment Outcomes of Pain Survey.[17] Patients in the study demonstrated worse mean scores vs normal values of people in the US for bodily pain, physical functioning, and social functioning. Acute pain also interfered with sleep, sexual function, and physical function.[17]

Similar results were observed in a prospective cohort study of patients who underwent total hip or knee replacement surgery, in which a significant, inverse relationship was demonstrated between severity of acute postoperative pain and patients' health-related quality of life in the immediate postoperative period.[18]

Acute pain: Causes and mechanisms

Acute pain may be the result of many different events, including trauma, broken bones, surgery, dental procedures, childbirth, cuts and infections, burns, muscle strains, and ligament damage (sprains).[19] The pathways that convey pain signals from the periphery to the central nervous system (CNS) and central pain pathways have been well described.[20-23]

Peripheral nociceptors

The perception of acute pain begins with activation of specific sensory nerves (nociceptors), which are unmyelinated or thinly myelinated nerve fibers present in the skin, deep somatic tissue, and viscera.[23] These primary afferent neurons convey pain signals to the CNS.[23] Medications aimed at addressing acute pain often target the peripheral events that activate or change the sensitivity of nociceptors.[24]

Tissue damage can also cause the release of inflammatory mediators that can bind to peripheral receptors and recruit more inflammatory cells, amplifying pain. The actions of inflammatory molecules that contribute to pain can be addressed with anti-inflammatory therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs).[25,26]

Multiple parts of the CNS facilitate the transmission, modulation, and perception of noxious stimuli.[22,23] Processing pain in the CNS is strongly influenced by additional ascending and descending pathways. In addition, the serotonergic (5-HT) system plays a critical role in the modulation of nociception, primarily through descending pathways. Some antidepressants, including tricyclics, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors, can also impact pain perception through the 5-HT system.[27] Another means of pain modulation is the release of noradrenaline in the dorsal horn of the spinal cord. The axons of noradrenergic neurons in the brainstem inhibit nociceptive transmission in the spinal cord via activation of specific receptors on peripheral nociceptors and spinal neurons.[28] The response to peripheral nociceptive stimuli also can be modified in the spinal cord by the release of local endogenous modulators. Opioids can decrease the response to nociception, while glutamate, substance P, and prostaglandins can increase it.[29]

Treatment of acute pain

Goals

The primary aim of acute pain management is to provide treatment that reduces patients' pain levels, with minimal adverse effects, while allowing them to remain functional.[30,31] A secondary, but very important, aim is to prevent acute pain from progressing to chronic pain by interrupting the pain cycle.[32,33] Persistent nociceptive stimulation may cause changes in pain processing that result in sensitization (an increase in the response of nerve cells to input from peripheral signals or other neurons). Pathologic changes in the function of peripheral and central neurons may stimulate cerebral reorganization and a hyper-excitable state.[33] There is agreement across guidelines that pain treatment goals are best met by a multimodal approach incorporating around-the-clock nonopioid analgesics and nonpharmacologic interventions.[1,30,31]

Developing a strategy to meet acute pain treatment goals

Acute pain treatment should use a multimodal approach that addresses different aspects of the pain condition, including functionality. The treatment plan should include consideration of the risks and benefits of all interventions and should avoid unnecessary opioid exposure. Close patient monitoring and as-needed treatment adjustment are both essential. Analgesics should be used for the for the shortest time necessary while also ensuring restoration of mobility and function. Planning should include consideration of initiating or changing pain management strategies, particularly when considering initiating, increasing, tapering, or discontinuing opioids.[1,30,31]

The Centers for Disease Control and Prevention (CDC) has set forth guiding principles for the treatment of acute pain.[1] The guideline emphasizes that acute, subacute, and chronic pain should be appropriately assessed and treated using a multimodal and multidisciplinary approach that addresses the physical and psychological health and well-being of the patient and includes long-term services to acheive the patient's expected health outcomes. Importantly, these principles recognize that some patients with acute pain may require opioids as part of their treatment regimen after maximizing nonopioid therapies and carefully considering of the risks of opioid therapy, including opioid use disorder, overdose, and death.[1]

Specific treatments for acute pain

The CDC guideline also summarizes evidence supporting their recommendations.[1] Many nonpharmacologic treatments and nonopioid medications are associated with

improvements in pain and function, comparable to what can be achieved with regimens including opioids.[1] Additionally, some noninvasive, nonpharmacologic interventions have small-to-moderate effects in specific acute pain conditions and have a low risk for serious adverse events.[1] Topical lidocaine or capsaicin may be effective for the treatment of neuropathic pain.[1] Short-term (1 to <6 months) opioid administration may have efficacy similar to or less than that of NSAIDs for many frequently encountered pain conditions.[1] The CDC guideline (**TABLE**) also emphasizes that opioid use may result in significant harm and advises use of these agents only after maximizing nonopioid therapies for acute pain.[1]

Other guidelines also support first-line use of nonopioids but recognize that opioids may be required for pain management in some patients. The American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP) have published guidelines on acute musculoskeletal pain.[31,34,35] Their recommendations note that topical NSAIDs are safe and effective for treating acute pain and that oral NSAIDs, acetaminophen, or a combination are also effective for the initial treatment of acute pain syndromes. Like the CDC guideline, AAFP/ACP also emphasize that treatment selection should minimize patient risk.[31,34] Prescribing opioids should be reserved for patients with severe or refractory acute pain, and opioids should be used only in combination with other medications (eg, agents that work on opioid and monoamine receptors or acetaminophen/opioid or NSAID/opioid combinations).[31,34]

For medications that act on opioid receptors and also influence descending pathways, it is important to differentiate between the agents' potential for dependence, misuse, and abuse. To illustrate, a schedule IV drug has less potential for abuse, by definition, than a schedule II or III opioid.[36] The AAFP/ACP guidelines also recommend use of acupressure to reduce pain and improve physical function and transcutaneous electrical nerve stimulation to reduce pain. They also note that muscle relaxants are effective adjunctive medications for acute low back pain and neck pain.[31,34] Importantly, gabapentinoids, antidepressants, and cannabinoids used to treat chronic neuropathic pain ***are not recommended*** to treat acute pain.[31]

Differentiating risk across opioids used to treat acute pain

In the US, controlled substances are under strict regulation by both federal and state laws that guide their manufacture and distribution. The Controlled Substances Act established 5 drug schedules and classified drugs with the aim of controlling their manufacture and distribution.[36] As the schedules descend from I to V, the drugs listed within each category have a lower potential to cause a substance use or addiction disorder.[36]

Unmet needs in the management of patients with acute pain

Effective analgesic medications for acute pain that have lower risk for adverse events are needed.[37] There is also a need for more efficacious treatments for acute pain. Results from a recent survey of trauma patients at a US hospital indicated that only 20% achieved adequate pain control.[38] Similarly, a survey of adult postoperative patients indicated that 31% were not satisfied with their pain control.[39] The CDC guideline also notes that pain control is often inadequate in older patients.[1]

Newer approaches to the pharmacologic management of acute pain

New combinations

All treatment guidelines for acute pain support the use of multimodal treatment for acute pain.[1,30,31,40] This is consistent with observations that acute pain has multiple causes, and combining drugs from different classes with complementary mechanism(s) of action may permit dose reductions for individual medications, reducing the risk for dose-related side effects while still providing desired pain control.[41]

New combinations/formulations: *Celecoxib-tramadol hydrochloride co-crystal*

Celecoxib-tramadol hydrochloride (Seglentis; CTC) is the first and only co-crystal, multimodal analgesic for acute pain. CTC was FDA approved in October 2021 for management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.[42-44] This unique, single crystaline entity combines celecoxib and the schedule IV opioid tramadol hydrochloride via a complex scheme of hydrogen bonds in a 1:1 molecular ratio and a 1.27:1 weight ratio.[44,45] Tramadol hydrochloride is a centrally acting mu-opioid receptor agonist, and the dextro- and levorotary isomers of this drug inhibit 5-HT and norepinephrine uptake, respectively. Celecoxib is an NSAID that selectively inhibits cyclooxygenase-2 (COX-2). The CTC co-crystal yields peripheral anti-inflammatory and centrally mediated analgesia that may improve efficacy and safety compared to tramadol hydrochloride or celecoxib alone.[43]

The single, crystalline CTC combination demonstrates consistently observed differences in pharmacokinetics and solubility not achieved with simple co-administration or to individual active pharmaceutical ingredients (APIs) alone (**FIGURE**).[46,47] The observed rate and extent of absorption are different compared to the individual agents as well as the open combination or coadministration of each API. Compared with the open combination the celecoxib component of CTC demonstrates an earlier time to peak concentration (Tmax), and a greater maximum concentration (Cmax).

TABLE. CDC recommendations for the treatment of acute pain[1]

1	Nonopioid therapies are at least as effective as opioids for many common types of acute pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient.
2	Nonopioid therapies are preferred for subacute and chronic pain.
3	When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long-acting (ER/LA) opioids.
4	When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage.
5	Use opioids at the lowest effect dose for the shortest duration and for no longer than the expected duration of pain severe enough to require opioids.
6	Many patients do not experience benefit in pain or function from increasing opioid dosages to 50 MME/day or greater and are exposed to progressive increases in risk as dosage increases. Additional dosage beyond this threshold are progressively more likely to yield diminishing returns in benefits for pain and function relative to risks to patients.
7	Opioid dosages 50-90 MME/day were associated with a minimally greater improvement in mean pain intensity compared with dosages of <50 MME/day with no mean improvement in function.
8	For patients already receiving opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage.
9	When opioids are needed for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.
10	Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss risk with patients.
11	When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose.
12	Clinicians should use particular caution when prescribing opioid pain medication and benzodiazepines concurrently.
13	Clinicians should offer or arrange treatment with evidence-based medications to treat patients with opioid use disorder.

Abbreviation: MME, morphine milligram equivalents.

Data from Dowell D, Ragan KR, Jones CM, et al. CDC Clinical Practice Guideline for Prescribing Opioids for Pain—United States, 2022. *MMWR Recomm Rep*. 2022;71(3):1-95. doi:10.15585/mmwr.rr7103a1

Importantly, the tramadol hydrochloride component of CTC demonstrates a longer time to Tmax and a more gradual absorption at a lower Cmax compared with the open combination or tramadol hydrochloride alone.[46,47] This helps minimize the overall daily opioid exposure, thus aligning with the recent CDC 2022 update on acute pain management.[1]

The clinical development of CTC for US approval included 5 phase 1 studies, a phase 2 dental acute pain study, and a phase 3 post-bunionectomy with osteotomy and internal fixation study.

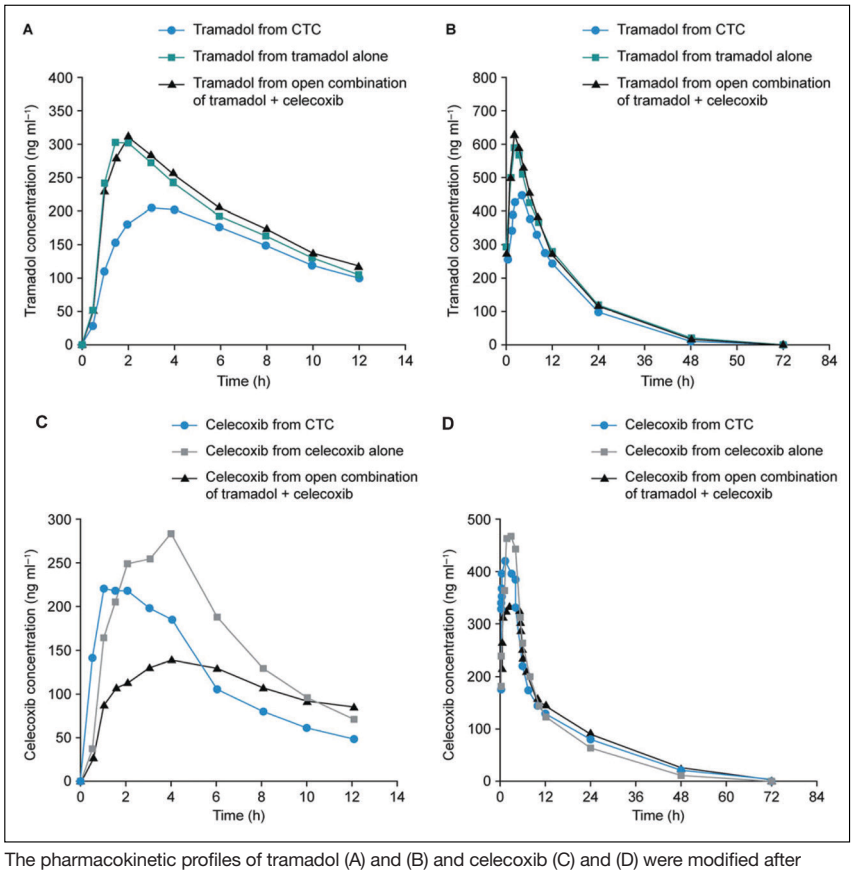
The randomized, double-blind, phase 2 clinical trial evaluated CTC versus tramadol hydrochloride alone versus placebo in 334 patients with moderate-to-severe acute dental pain following ≥2 impacted third molars requiring bone removal.[48] All doses of CTC were associated with decreased pain; effect was dose dependent. There was significantly greater decrease in sum of pain intensity differences from 0-8 hours (SPID0-8) for CTC 100 mg, 150 mg, and 200 mg compared to placebo ($P < .05$ for all) and tramadol hydrochloride ($P < .05$ for all).[48]

The randomized, double-blind, factorial, active- and placebo-controlled phase 3 trial included 637 patients with severe pain following bunionectomy with osteotomy.[44] Patients were randomized to CTC 200 mg every 12 hours (2 tablets of 56 mg celexcoxib/44 mg tramadol hydrochloride every 12 hours, n=184), tramadol 50 mg every 6 hours (n=183), celecoxib 100 mg every 12 hours (n=181), or placebo every 6 hours (n=89). Patients could receive rescue medication after discontinuation of anesthetic and initiation of study medication. Pain was measured by the 0 to 48 hour sum of pain intensity differences (SPID0-48) least squares mean.[44]

The CTC co-crystal provided superior analgesia than similar daily doses of tramadol or celecoxib (CTC: –139.1 [95% CI: –151.8, –126.5]; tramadol: –109.1 [–121.7, –96.4]; $P < .001$; and celecoxib: –103.7 [–116.4, –91.0]; $P < .001$). Onset of analgesia was 1.08 hours for CTC compared to 6.5 hours for tramadol (HR 1.293, 95% CI: 0.959, 1.743), and median onset of analgesia was not reached for celecoxib or placebo since fewer than half of patients achieved analgesia.[44]

Most patients used first-line rescue pain medication (intravenous acetaminophen), and about half used second-line rescue pain medication (oxycodone). Median time to first

FIGURE. Pharmacokinetics of the tramadol-celecoxib co-crystal vs agent alone or in a conventional fixed combination[44-46]



The pharmacokinetic profiles of tramadol (A) and (B) and celecoxib (C) and (D) were modified after administration of the co-crystal, compared with administration of the commercially available, single-entity reference products alone or in open combination.

Reproduced with minor modifications (minor changes to the size of individual points, axis title fonts, format of units on y-axes, and minor changes to the key) from Videla S, et al. Pharmacokinetics of multiple doses of co-crystal of tramadol–celecoxib: findings from a four-way randomized open-label phase I clinical trial. *Br J Clin Pharmacol*. 2018;84(1):64-78 under Creative Commons license CC BY-NC-ND. https://creativecommons.org/licenses/by-nc-nd/4.0/legalcode

rescue medication was 4.2 hours for CTC compared to 2.2, 2.1, and 1.6 hours for tramadol, celecoxib, and placebo, respectively ($P < .001$ for all).[44]

The most common adverse events reported were nausea, dizziness, vomiting, and headache across groups. Adverse events were reported by 63.4% of patients in the CTC and tramadol groups, 52.5% in the celecoxib group, and 57.3% in the placebo group.[44]

Of note, the approved CTC dose of 200 mg by mouth every 12 hours delivers a total morphine milligram equivalents (MME) per day of 35.2, below the CDC's 50 MME threshold.[1,43]

Pregabalin/tramadol

This combination is currently being evaluated in a phase 3b, multicenter, randomized, double-blind study involving patients with acute pain of neuropathic origin.[49,50] While results for this combination in patients with acute pain have not yet been reported, it has been shown to be safe and effective for the treatment of pain in patients receiving taxane chemotherapy.[51]

CASE SCENARIO

A 42-year-old male living in a rural area presents to his PCP with complaints of worsening left ankle pain following a fall from a ladder at his home yesterday. The patient also states that he had surgery on this ankle 2 weeks ago at a surgical center about 2 hours away. He reports that the pain seemed to be manageable at first but became unbearable overnight. He has been taking ibuprofen 400 mg every 8 hours with minimal pain relief. His pain is now severe, rated 9 out of 10 on a visual analog scale.

After thorough evaluation, the PCP diagnoses a severe left ankle sprain (no fracture or ligament tears), complicated by recent surgery. The patient has a history of high cholesterol and takes atorvastatin 40 mg daily. He has no history of opioid use disorder.

In this case scenario, the PCP should address the patient's acute pain to improve function and quality of life. A multimodal regimen, including nonpharmacologic methods, should be considered. The PCP might consider recommending applying ice to the affected area and elevating the leg. Because of the suboptimal results of the patient's home ibuprofen use, the PCP is considering addition of an opioid or switching to an opioid-NSAID combination but is concerned about prescribing a schedule II or III agent because of the associated risk for misuse. The PCP might consider adding a short, 3- to 5-day course of celecoxib-tramadol hydrochloride in the co-crystal formulation to the multimodal regimen since tramadol is a schedule IV agent with lower risk for physical or psychological dependence. The PCP should also recommend that the patient follow up with his surgeon to minimize the risk of long-term complications and to further address his acute pain.

CONCLUSIONS

PCPs encounter a variety of patients presenting with different types of pain in their daily practice. Although acute pain management in primary care may receive less focus than

chronic pain management, addressing acute pain is essential to preserving or restoring function and quality of life and preventing progression to chronic pain. Additionally, PCPs in rural settings may have increased responsibility for treating acute pain because of lack of access to pain and surgical specialists.

All current guidelines support using a multimodal approach to pain management and reserving use of opioids forpatients with severe pain that cannot be managed with other agents. There are several new agents/formulations recently approved or in development for the treatment of acute pain. The recently approved co-crystal formulation of celecoxib and tramadol hydrochloride (a single-medication multimodal approach) provides an additional option for acute pain management in primary care. ●

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Continuous Glucose Monitoring in Practice

Eden M. Miller, DO

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading this review article, participants should be able to:

- Prepare the practice for continuous glucose monitoring (CGM).
- Understand options available to the practice for professional (practice-owned) and personal (patient-owned) CGM.
- Locate and interpret CGM data, using the ambulatory glucose profile (AGP), to determine if the patient is achieving targets established by the International Consensus on Time in Range.
- Modify a patient's treatment plan based on CGM data to improve patient outcomes.

KEY TAKEAWAYS

- CGM is a valuable therapeutic tool for shared patient and clinician decision-making about diabetes management.
- CGM allows your patients to see in real time the impacts of behavior and medications on their glucose levels.
- You can take steps now to empower yourself, your practice, and your patients by implementing CGM.
- CGM may be a way to get your patients excited, perhaps for the first time, about their diabetes care.
- The AGP is a useful tool that can help ease patients' burden of managing their disease.

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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Visit https://www.pcmg-us.org/toolkit/cgm for a resource toolkit and an archived webinar (for additional CME). All the links noted in the article are available from the toolkit webpage.

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INCORPORATING CGM IN YOUR PRIMARY CARE SETTING

Medical technology is rapidly evolving, so it can be challenging for primary care physicians to stay current with every advancement and innovation. This is especially true in the field of diabetes, where the evolution of continuous glucose monitoring (CGM) is having an enormous impact on diabetes management and treatment. Prior to the devel-

opment of CGM, managing diabetes involved making meaningful decisions based on limited self-monitoring data, which provided mere snapshots rather than a big-picture view of patient health. CGM provides healthcare practitioners access to much more comprehensive data on their patients' glycemic control and thus better enables clinicians to evaluate the effect of various lifestyle choices and therapeutic interventions.

The large amount of data provided by CGM, summarized in the ambulatory glucose profile (AGP), has cultivated a better understanding of the individualized nature of diabetes. Access to these data increases patient engagement by illuminating the glycemic effects of lifestyle choices, stress, illness, and medication adherence. The prescriber can benefit immensely from seeing the impacts of these personal individual choices, as well as how a particular medication intervention impacts a patient's glycemic control. As CGM becomes the standard of care for monitoring glycemic control, further clinician and patient education is necessary to effectively implement this technology in clinical practice.

For decades, the sporadic nature of monitoring has limited physicians' ability to manage diabetes care effectively.[1] Glycemic control traditionally has been viewed through the lens of glycated hemoglobin (A1c), which is a 3-month average of glucose levels that does not provide insight into glucose variability, time in range (TIR), or time below and above range.[2] The real-time data provided by CGM empower each person with diabetes to personally engage in monitoring and learn about their own disease. For the prescriber, CGM reveals glycemic control details and the effectiveness of treatment interventions and patient choices, allowing for more individualized treatment.[2] CGM moves diabetes management from a limited understanding of the past via A1c to real-time data in the present and may even predict future glucose levels. CGM is distinctive in that it provides data that are meaningful to both the physician and the patient, which can be used immediately to make decisions to ease patient burden.

Some essential steps must be completed to prepare your practice effectively and create a workflow for initiating CGM. First is becoming aware of CGM devices that are approved by the US Food and Drug Administration (FDA). CGM devices are available for both professional (practice-owned) (**TABLE 1**) and personal (patient-owned) (**TABLE 2**) use.[3] Knowledge of the features of each device will assist in prescribing the right device for each patient.[2,3]

TABLE 1. FDA-approved professional CGM devices[3]

	Abbott FreeStyle Libre PRO	Dexcom G6 Pro[a] (expected G7 in 2023)	Medtronic iPro 2
Blinded or unblinded[a]	Blinded	Either	Blinded
Wear time	14 d	10 d	6 d
Calibration	0	0	3-4 times daily
Care between use	Disposable sensor/transmitter	Disposable sensor/transmitter	Sensor must be cleaned and disinfected
Insertion	Single-step process with auto-inserter	Two-step process includes inserting sensor and attaching transmitter	Multi-step process includes inserting and taping both the sensor and transmitter
Site	Upper arm	Abdomen	Abdomen
Downloading/ data reports	LibreView (download in office)	Blinded: Clarity (download in office) Unblinded: reader/apps	Carelink (download in office)

[a] Blinded devices keep glucose data hidden from the patient.

WHO WILL BENEFIT FROM CGM?

Many clinicians assume that only those with type 1 diabetes (T1D) or those who receive multiple daily injections will benefit from CGM.[4] Other clinicians primarily consider the patient's insurance coverage. The American Diabetes Association (ADA) clarified the directive with its *Standards of Medical Care in Diabetes*: CGM is recommended for all patients with T1D, patients with type 2 diabetes (T2D) on multiple daily doses of insulin, and/or those at risk for hypoglycemia.[5] On October 6, 2022, the Centers for Medicaid & Medicare Services proposed a local coverage determination that modifies the current criteria for CGM to include those with diabetes who have a history of problematic hypoglycemia.[6] These individuals tend to have other chronic diseases, experience hypoglycemic events that result in emergency care, and/or are subject to interventional therapies that can increase the risk of hypoglycemia. However, this author believes that every person with diabetes could benefit in some way from the information provided by CGM. Any individual with diabetes who desires to be more engaged in the management of their disease and wants to see how lifestyle, stress, diet, exercise, and medication affect their glucose levels should be provided with an opportunity for CGM.

Once the question of utility has been answered, clinicians should consider accessibility and affordability. First, determine if your patient has insurance coverage for CGM or is able to afford it by other means (such as cash payment and/or intermittent use). For patients who must pay for their own CGM, a recent examination of the cost of the various devices found the least expensive option is provided by Abbott, followed by Medtronic, Dexcom, and Senseonics.[7] Discounts and giveaways may also be available. Professional CGM should be considered for patients with limited

TABLE 2. FDA-approved personal CGM devices

	Abbott FreeStyle Libre 14-day/2/3	Dexcom G6 G7 approved by FDA 12/8/22	Medtronic Guardian Sensor 3 (pump integrated) and Guardian Connect (stand-alone)	Senseonics Eversense
Approved labeling	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/≥2 y/≥2 y	≥2 y	≥14y	≥18 y
Medicare coverage	Yes/Yes/No	Yes	Sensor 3: Yes; Connect: No	Yes
Wear length	14 d/2 & 3: Up to 15 days	10 d	7 d	90/180 d
Alarms	No/Yes/Yes	Yes	Yes	Yes
Data display/ Integration	Reader; Android/iPhone apps; 2 & 3 approved for integration with automatic insulin delivery systems	Reader; Android/iPhone apps; smartphone; Tandem T: slim X2 pump	630G, 670G or 770G pump; Guardian Connect	
Form	Disposable transmitter integrated with sensor patch	G6:Transmitter (3-month use) separate from sensor/G7: integrated	Transmitter (rechargeable) separate from sensor	Transmitter (rechargeable) separate from sensor
Accuracy[a]	11.4%/9.3%/7.9%	9%/8.2%	9.6%/9-11%	8.5-9.5%

[a] Accuracy figures provided by manufacturers. Accuracy is measured by mean absolute relative difference (MARD) relative to venous glucose. Lower numbers indicate greater accuracy.

financial resources, as all payors cover the application of this service and data interpretation without prior authorization. Keep checking for coverage: CGM coverage continues to expand in commercial, federal, and state insurance programs and is becoming easier to qualify for.

Medicare recently indicated that in 2023, patients on basal insulin would be considered for CGM coverage. Medicare has also removed the requirement for documentation of multiple finger sticks and added other approval indications for those with problematic hypoglycemia or at risk for hypoglycemia or chronic diseases that lead to complications when hypoglycemia occurs.[6] Finally, discuss with your patient whether they are willing to wear the sensor and engage with the data that are provided.

SETTING UP CLINICAL WORKFLOW

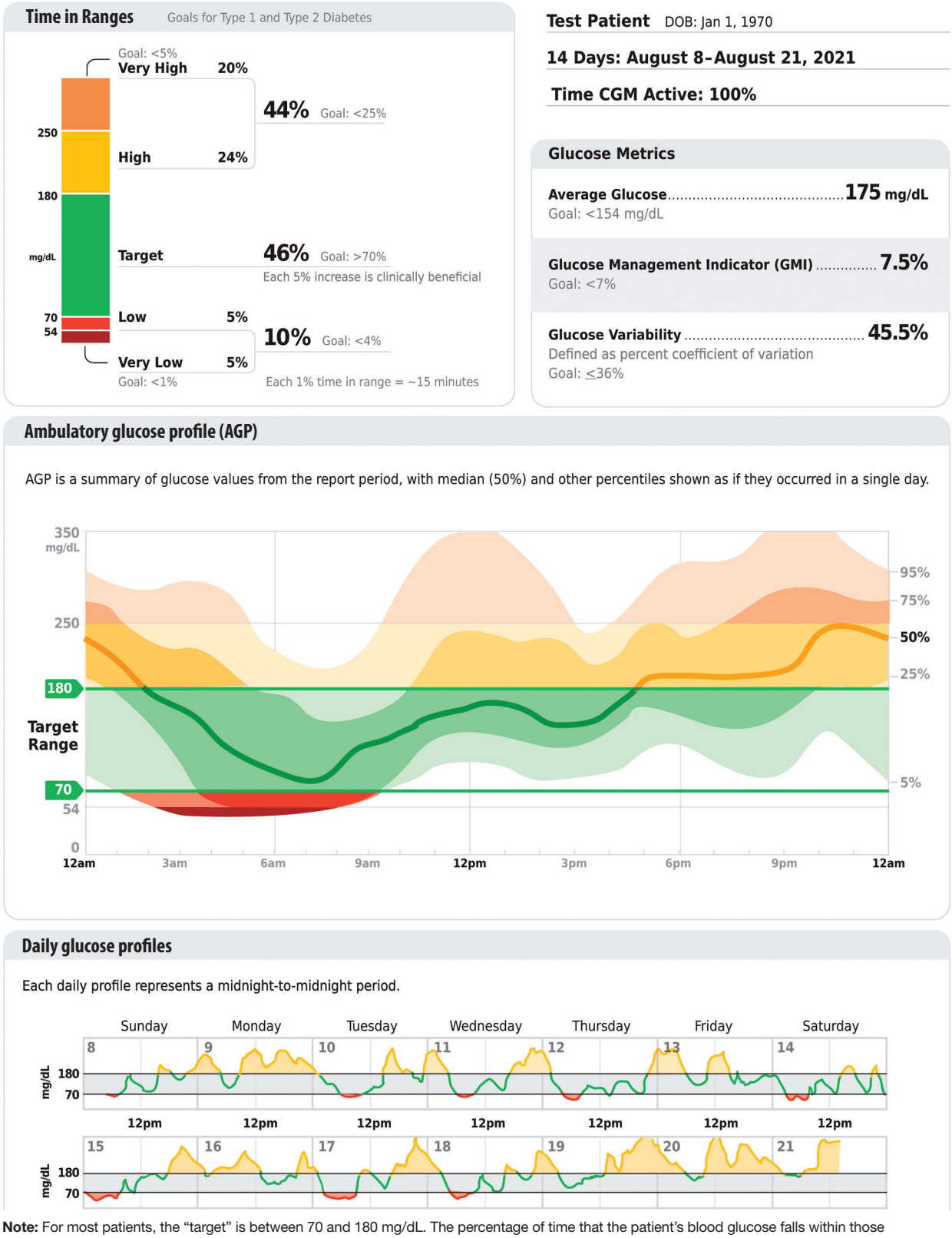
At the practice level, the physician must decide whether offering all CGM devices or only a selection works best with the clinic workflow and the needs of their patients.[3] Within the practice, the most essential and challenging aspect of CGM utilization is the creation of a clinical workflow that allows the physician to effectively identify and prescribe the appropriate device for each patient, provide training and support for the patient, download and interpret data, use that data to guide shared treatment decision-making, and bill for these services.

Multiple staff in the clinic will have a responsibility in the CGM workflow. The front office will need to make reminder calls prior to appointments, gain access to CGM data, or, for patients who only provide data at the time of their visit, encourage individuals to bring their diabetes-related technology to their visit. They must then collect those devices at check-in and start the process of data acquisition. In the back office, medically trained personnel who are familiar with the devices will download the data and prepare it for the physician.[3] Each clinic will accomplish this uniquely, depending on the responsibilities and capabilities of individual employees.

The medical assistant responsible for the AGP data download will need access to each relevant CGM manufacturer's data platform and should have a working knowledge of how to download the data. In many cases, when the patient is using a cell phone app for CGM readings, the AGP PDF can be downloaded ahead of the appointment, allowing for pre-appointment review. This is necessary for virtual/telemedicine visits.[3] Only individuals who use CGM readers will require an in-person appointment, as the data must be manually downloaded from the reader. Most devices offer online access to data without the need for manual downloading.

Each device's AGP report is slightly different, but all contain standardized, essential components, much like those

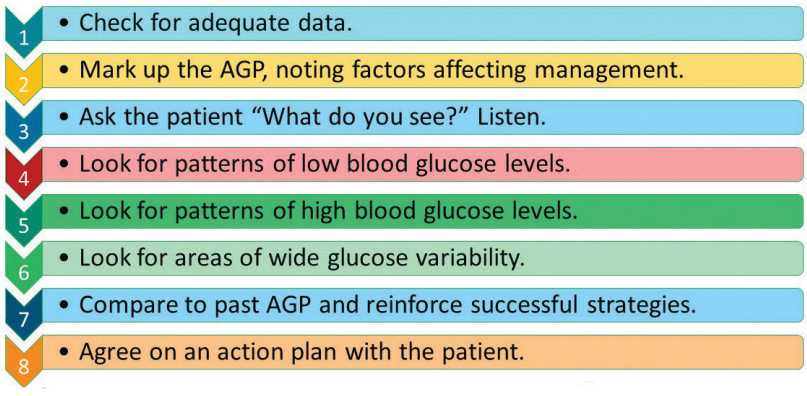
FIGURE 1. Sample ambulatory glucose profile[1]



Note: For most patients, the "target" is between 70 and 180 mg/dL. The percentage of time that the patient's blood glucose falls within those parameters is defined as TIR. (Figure 1 reprinted with the permission of the American Diabetes Association, Inc., Copyright 2022.)

shown in **FIGURE 1**; the report displays data as if occurring in a single 24-hour period.[8] Clinicians should review the report in the series of steps described in **FIGURE 2**.[9] It is vitally important that the physician become familiar with the AGP review and use the AGP with the goal of increasing the patient's TIR as established by the International Consensus on Time in Range.[10] The online resource toolkit referenced below, accessible through the QR code in **FIGURE 3**, offers a number of additional AGP examples for review as well as a detailed explanation of the components of the AGP.

FIGURE 2. Steps in AGP analysis[9]



The 14 days of data included in the AGP provide clinicians an opportunity to consider glycemic patterns. For example, in **FIGURE 1**, the hypoglycemia occurring between 1 am and 10 am is of immediate concern and should be the first item addressed. The physician may choose to proceed conservatively and wait for subsequent AGP data before suggesting additional treatment changes, keeping in mind the AGP also revealed 3 periods of very high blood sugars and high glucose variability. If those hyperglycemic episodes persist in the second AGP and the hypoglycemia issue has been resolved, the hyperglycemia should be the next priority. The AGP is currently the best tool available for offering insights that inform evidence-based treatment decisions in partnership with the patient to increase the patient's TIR. To optimize use of CGM and provide safe, effective care for patients with diabetes, it is critical that clinicians take time to learn more about the data points included in the AGP and how to interpret them.

BILLING

Billing is the last element needed for successful integration of CGM into clinical practice. Billing codes vary depending upon whether the CGM is personal or professional and which aspects of clinical workflow are being billed; for example, in some instances, device insertion and instruction require different codes than data interpretation. Some codes are device specific (such as Senseonics Eversense),

TABLE 3. Billing codes for CGM[11,12]

CPT® Code and Description
95249: Personal CGM – Startup/Training: Ambulatory continuous glucose monitoring of interstitial 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: 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 fluid via a subcutaneous sensor for a minimum of 72 hours; interpretation and report. (Do not report more than once per month.)
Evaluation and management (E/M) codes 99212-99215: Established patient visit or G0463 (Medicare outpatient clinic visits)
Eversense-only codes 0446T-0448T: 0446T (creation of subcutaneous pocket with insertion of implantable sensor, including system activation and patient education), 0447T (removal of implantable sensor from subcutaneous pocket via incision), 0448T (removal of sensor with creation of new pocket for new sensor at a different location, including system activation)

while most are appropriate for all devices (**TABLE 3**).[11,12] The patient must wear the device for at least 72 hours to be eligible for reimbursement. CGM data should be documented in the encounter note along with any additional time spent in clinical decision-making and analysis.

Face-to-face encounters are not required for Current Procedural Terminology (CPT) coding and can take place in combination with evaluation and management (E/M) or stand alone coding. Ensure that the patient has regular follow-up visits at least every 6 months. Clinical notes should demonstrate that the patient is using the CGM system to monitor their diabetes. Only those who can prescribe CGM can bill for CGM application and interpretation of data.[4]

CGM IN PRACTICE

Integrating CGM into your practice is vital for your patients with diabetes. More information is available; a resource toolkit page can be found at https://www.pcmg-us.org/toolkit/cgm, which offers an array of links to help clinicians establish an effective CGM practice workflow (see **FIGURE 3**). The toolkit also includes a webinar (offering additional CME credit), links to every source cited in this article, additional case studies, and explanations of AGPs, as well as specific information about device insertion, accessing data, and details on each device currently approved by the FDA.

CGM is not only an extremely valuable therapeutic tool for evidence-based, shared decision-making, it is doable. CGM enables patients to see firsthand and in real time the impact of their behaviors on their glucose levels and allows clinicians to treat patients more accurately and effectively. ●

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Early Intervention by Family Physicians to Delay Type 1 Diabetes

By Steven Edelman, MD

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KEY TAKEAWAYS

- Type 1 diabetes (T1D) is an autoimmune disease mediated by T cells that target and destroy insulin-producing beta cells. Individuals with genetic risk of T1D will progress at variable rates through 3 stages of immune activation and development of islet autoimmunity. Measuring pancreatic islet cell autoantibodies predicts risk for progression that can take weeks to years before the onset of T1D.
- Screening options available to family physicians can identify persons at risk or in the early stages of T1D, such as first- and second-degree relatives or those with a family history of autoimmune disorders, to ultimately offer proven interventions that may delay or prevent the condition. Screening can reduce emergency room visits, hospitalizations, and intensive care unit admissions for diabetic ketoacidosis, which can be fatal, and can educate and prepare individuals and families for a smoother transition to insulin therapy when necessary.
- Recent advances in technology and understanding of the immune pathogenesis of T1D has resulted in emerging disease-modifying therapies that are changing how family physicians approach delaying and potentially preventing or reversing the disease.

FACULTY

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INTRODUCTION

Lauren, a 30-year-old patient, expresses concern that her 34-year-old brother was recently diagnosed with type 1 diabetes (T1D). She is aware that diabetes can be genetic and is concerned not only about her own risk, but also that of her 9- and 11-year-old children.

As recently as 5 years ago, this would have been a short discussion. T1D is an autoimmune disease with a genetic origin triggered by environmental stimuli such as viruses (eg, Coxsackie B, rubella, enterovirus).[1] A blood glucose and C-peptide test would be the best a family physician could offer—to diagnose, but not predict, her or her children's risk. Additionally, there were no disease-modifying therapies (DMTs) approved for human use at that time.

For the first time, family physicians can offer to detect risk for T1D through a simple blood test.[2] Because T1D is an autoimmune disorder characterized by beta-cell destruction, measuring islet cell autoantibodies provides information that correlates to disease risk. If ≥2 autoantibodies are present, the 5-year and 10-year risk are approximately 44% and 70%, respectively, and if glucose intolerance has already developed, the risk is 75% at 5 years, with a lifetime risk of nearly 100%.[2] The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends both general population and targeted screening.[3] The American Diabetes Association (ADA) recommends screening first- and second-degree relatives.[4] Both recommend following with education and monitoring.

Adopting screening protocols provides an opportunity to identify who is likely to develop T1D and, most importantly, offers a therapeutic option to delay or prevent the onset of clinical diabetes. The recent development of new and emerging treatments may potentially change an individual's autoimmune response and delay the onset of T1D for months to years.[1,5] Lauren knows the diagnosis of T1D is life-changing for the entire family; therefore, it is beneficial to delay beta-cell loss as long as possible and maintain normal blood glucose levels to delay a lifestyle of daily insulin therapy and blood-glucose monitoring, diet and exercise restrictions, and adverse effects on education and/or work.

More than 1.45 million Americans are living with T1D. Nearly 64,000 people are diagnosed each year in the United States (US), and it is estimated that 300,000 people in the US are at risk for T1D. In addition, 2.1 million people in the US

are expected to have T1D by 2040.[6] T1D is one of the most common chronic diseases of childhood and two-thirds of cases are diagnosed by age 30 years.[3] Yet anyone at any age can develop T1D. A combination of genetic susceptibility and environmental exposure is thought to determine lifetime risk of developing T1D.[1,5] While genetic susceptibility contributes to the destruction of insulin-producing beta cells, 85% of individuals who develop T1D do not have a family history.[2] This latter fact has implications for determining who to screen for T1D risk.

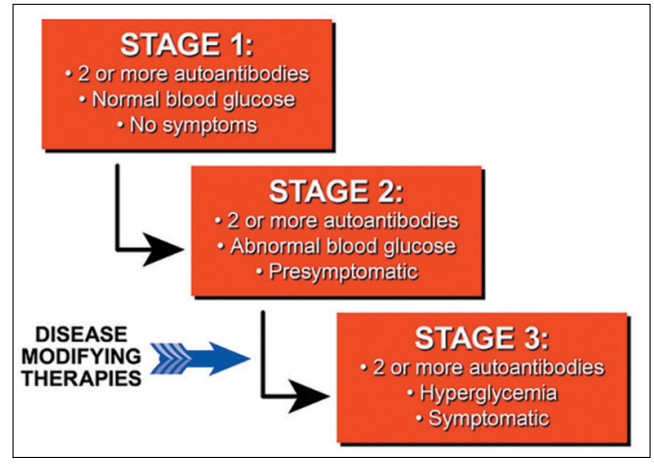
Immune pathogenesis and time course of T1D

T1D is an autoimmune disease conventionally believed to be caused by "killer" or "auto-reactive" T cell-mediated selective destruction of pancreatic insulin-producing beta cells.[7,8] While T cell-mediated autoimmunity is likely triggered by an unknown insult to the beta cells, leading to the eventual production of beta cell-destructive T cells, innate immunity and islet inflammation may be involved as well.[2,6-8] Regardless, destruction leads to a loss of beta-cell mass, with no current evidence that beta cells can regenerate after death. Three key factors are thought to be involved in the progressive development of T1D: the beta-cell mass present early in life (ages 1 to 2 years), which indicates risk and time to onset; the aggressiveness of the self-directed immune response that destroys beta cells; and the loss of beta-cell mass required for T1D onset (85% to 95% loss, with a wide range).[7]

Islet autoimmunity in T1D generally progresses slowly, taking months to years before established clinical onset.[8] The rate of beta-cell destruction varies but is typically more rapid in children than in adults.[3] If the body is unable to stop or slow the T cell destruction of beta cells, then insulin deficiency, hyperglycemia, and T1D results. Understanding the immune processes and the time course of the disease allows us to identify people currently experiencing beta-cell destruction. Knowing how far the autoimmune destruction has progressed can predict the time of onset of clinical T1D.[2]

In 2015, an international community developed a staging system that considers preclinical stages, beginning with autoimmunity and progressing through normoglycemia (Stage 1) and dysglycemia (Stage 2), and culminating in clinical T1D (Stage 3) (**FIGURE 1**).[2] Staging T1D using predictive biomarkers alters the therapeutic approach to T1D, providing opportunities to delay or prevent further disease progression. Indeed, disease-modifying therapies (DMTs) for T1D are now available, and more are being developed.[1] Just as DMTs have transformed treatment options in other autoimmune diseases, multiple DMTs may soon transform how we approach T1D in at-risk and newly diagnosed patients.[5]

FIGURE 1. Early stages of type 1 diabetes[7]



Importance of screening for T1D

Islet autoantibody screening aims to identify whether an individual is presymptomatic, that is, in Stage 1 or Stage 2. After discussing with Lauren the progressive risk for developing T1D for first- and second-degree relatives, the next step is to discuss the benefits and risks of screening or not screening for islet autoantibodies. If desired, she should be offered screening options.

Islet cell autoantibodies serve as the primary biomarkers of T1D risk and can be measured using ultra-low volumes of blood, including capillary samples and dried blood spots.[5,6,9] Insulin autoantibodies (IAA) and glutamic acid decarboxylase (GAD), islet antigen 2 (1A-2A), and zinc transporter 8 (Znt8) antibodies are currently used in the staging system. Stage 1 is defined as the beginning of beta-cell autoimmunity (≥2 islet autoantibodies), where individuals are presymptomatic and normoglycemic. Stage 2 is characterized by beta-cell autoimmunity (≥2 islet autoantibodies) with abnormal blood sugar (dysglycemia) but no symptoms. Stage 3 is beta-cell autoimmunity (≥2 islet autoantibodies), overt hyperglycemia, and symptomatic disease.[2]

The ADA and ISPAD recommend screening for T1D risk in first-degree family members of people with T1D or for research trials.[3,4] The ISPAD further recommends general population screening for all newborns.[3] Indeed, screening strategies are gaining momentum worldwide and believed to be the future standard of care.[3]

The goal of screening is to offer interventions that delay and prevent T1D—a goal we are closer to achieving than ever before. Yet, there are other clinical benefits that drive the need for active screening in clinical practice:

- Prevent diabetic ketoacidosis (DKA) and its morbidity and mortality. DKA is present at diagnosis in 30%

to 60% of US children, with a significantly higher incidence in African American and Hispanic children.[10,11] DKA is associated with increased mortality, longer hospitalizations, higher insulin requirements, shorter remission periods, and worse long-term glycemic control. Population screening and follow-up is associated with significantly less DKA and hospitalizations at diagnosis.[12]

- Preserve C-peptide secretion, a marker of insulin production, that yields better long-term metabolic control and reduced risk for complications.[13]
- Allow children, parents, and individuals time to adjust to the diagnosis, learn about diabetes management, and make a smoother transition to insulin therapy. Diabetes education and counseling can reduce the anxiety that may accompany multiple islet autoantibody test results.[14]
- Allow more time for the advancement of better devices, such as hybrid and fully closed loop systems and other adjunctive therapies.[3]
- Advance preventive and treatment therapies through clinical trial recruitment.[3,4]

Screening process, frequency, and monitoring

Autoantibody screening for T1D risk is available now to family physicians and their patients through 2 programs supported by the JDRF (formerly the Juvenile Diabetes Research Foundation): TrialNet (for relatives aged 2–45 years) or T1Detect (for those with no family history), as well as through regional screening programs. These programs use the recommended panel of autoantibodies so as not to miss a predictive biomarker: IAA, GDA, islet 1A-2A, and Znt8 antibodies. Average clinical sensitivity and specificity of assays are 96% and 97%, respectively, and correctly identify 95% of high-risk individuals with ≥2 autoantibodies.[8]

Clinicians can also order this screening panel from commercial laboratories (Mayo Laboratories, LabCorp, Quest Diagnostics), remembering that cost to the patient depends on insurance coverage. Interpretation and patient discussion guidance is available at JDRF.org.

The optimal frequency of testing in genetically high-risk individuals such as Lauren and her children is continuously under evaluation. The JDRF provides an ASK THE EXPERT resource for the latest information. Current monitoring guidelines for individuals who have been screened are based on antibody test results[5]:

- A negative autoantibody test. Rescreen if the individual becomes symptomatic. Since children are at greatest risk, screening at 2 to 3 years and 5 to 7 years can be valuable.[5] If the individual is older than 18 years of age, risk of developing T1D is low but not absent. Consider future rescreening if a family member has a history of another autoimmune disorder.
- One positive antibody test. Rescreen while monitoring for T1D symptoms. Check glycated hemoglobin (A1c) for normality (<5.7%) and perform a metabolic test within 6 months to exclude clinical T1D diabetes (eg, oral glucose tolerance test [OGTT], fasting plasma glucose [FPG], random blood glucose [BG]).
- Positive for ≥2 autoantibodies. Rescreen. Discuss disease staging and monitoring. Counsel about risk and timeline for moving through Stage 2 (abnormal glycemia) to Stage 3 T1D (symptomatic disease). Educate on signs and symptoms of T1D and DKA.
    - Stage 1: Normal glycemia. Check A1c for normality (<5.7%) and perform a metabolic test within 6 months to exclude clinical T1D diabetes (eg, OGTT, FPG, random BG).
    - Stage 2: Confirm dysglycemia with 1 or more of the following:
        - –FPG 100-125 mg/dL
        - –2-hour plasma glucose 140-199 mg/dL
        - –A1c 5.7%-6.4%
        - –An OGTT is required for staging individuals into clinical trials
        - –Perform ongoing monitoring: 6 to 12 monthly A1c tests and 2-hour postprandial or random glucose testing in children. Continuous glucose monitoring (CGM) or self-monitoring of blood glucose data can provide real-time data for early detection
    - Stage 3: Diagnose clinical diabetes using ADA criteria. Refer for diabetes self-management education, mental health professional counseling, and diabetes clinical specialist (see Diabetes.org)[4]

New era of disease-modifying interventions

Actions to prevent, delay, or even reverse the progressive beta-cell destruction in T1D can maintain beta-cell volume and function to reduce lifelong exogenous insulin dependency and associated acute and long-term complications. Recent discoveries and improvements in immunotherapy development may change our approach to T1D, just as refined therapies to treat autoimmune and inflammatory diseases like rheumatoid arthritis are now common in family practice.[1] Several newer DMTs targeting islet-specific immune pathways are being investigated in ongoing clinical trials.[3]

If a therapeutic intervention is to preserve beta-cell volume and function, it needs to be used as early as possible in the course of the disease. The majority of agents use

single immunosuppressive drugs such as methotrexate and cyclosporin, targeting T cells or B cells in new-onset T1D.[15,16] Treatment with cyclosporin A produced remission in children with T1D, but clinical remission was lost once cyclosporin was stopped.[16] A single course of low-dose antithymocyte globulin slowed decline of C-peptide and lowered A1c in new-onset T1D for at least a year.[17] Short-course rituximab, an anti-CD20 monoclonal antibody targeting B cells, slowed the fall of C-peptide by 8.2 months in new-onset T1D, but the C-peptide decline was the same as controls at 2 years.[18]

In addition to research in immunosuppressive therapy, trials of agents targeting the general inflammatory process, such as the TNF-a blocker golimumab, are ongoing in adults and children with newly diagnosed T1D and Stage 2 T1D (phase 2 trial, NCT02846545).[1] Targeting specific inflammatory pathways is thought to be the best anti-inflammatory approach, but so far there has been little success in restoring immune tolerance in T1D.

Studies in non-obese diabetic (NOD) mice demonstrated that early treatment with anti-CD3 monoclonal antibodies targeting T cells induced remission if used around the time of disease onset.[19] Anti-CD3 monoclonal antibodies are currently the most extensively studied immunologic approach to T1D as more specific and less toxic T cell–directed therapies show promise.[1]

The anti-CD3 monoclonal antibody teplizumab modifies CD8+ T lymphocytes, which are thought to kill beta cells.[20,21] Early phase 2 studies in young adults and children with T1D using a short course of teplizumab for 6 to 14 days within the first 6 weeks of diagnosis showed improvements in C-peptide responses for at least 2 years after treatment.[22] Furthermore, the average area under the curve (AUC) for C-peptide was significantly greater in the drug-treated group at each 6-month time interval. Improved clinical parameters included significantly reduced A1c and insulin requirements when compared to untreated controls.

A follow-up study examined whether 2 courses of teplizumab administered 1 year apart reduced the decline in C-peptide at 2 years.[23] Because the effects of treatment varied and were not permanent in the previous study, the investigators also set out to identify individuals as responders (for whom the effect lasted 3 years) or nonresponders. Teplizumab reduced loss of C-peptide 2 years later and C-peptide AUC at year 2 was 75% greater compared with controls. The strongest differentiator between responders and nonresponders was in metabolic features—responders had lower A1cs and insulin use at baseline. In addition, responders had fewer numbers of T cell subsets. Results of these and other studies have shown that teplizumab therapy reduces loss of beta-cell function in recent-onset T1D for as long as 5 years.[24]

Teplizumab for preventing/delaying T1D

These earlier studies led to the recognition that intervening early in Stage 2 T1D with anti-CD3 monoclonal antibodies—specifically teplizumab—could possibly prevent or delay the onset of T1D (Stage 3). In a landmark study published in 2019, teplizumab delayed the onset of T1D by an average of 3 years in nondiabetic at-risk relatives aged 8 to 45 years.[25] Relatives of people with T1D had at least 2 autoantibodies and abnormal results on an OGTT—in other words, they were in Stage 2. The percentage of diabetes-free persons in the teplizumab group was double (57%) that of the placebo group (28%). Treatment with teplizumab delayed the time to diagnosis of T1D; 19 (43%) of 44 participants on teplizumab and 23 (72%) of the 32 who received placebo were diagnosed with T1D. Median time to diagnosis was 48.4 months in the teplizumab group and 24.4 months in the placebo group (HR: 0.41; 95% CI: 0.22-0.78, P=0.006). The greatest effect of teplizumab treatment occurred in the first year, as only 3 of 44 (7%) in the treatment group were diagnosed compared with 14 of 32 (44%) in the placebo group. In a subgroup analysis, the presence of HLA-DR4 and absence of HLA-DR3 were associated with more robust responses to teplizumab. Additionally, participants who did not have Znt8 antibodies responded better.

Treatment involved a 14-day outpatient course of teplizumab delivered intravenously with dosing based on body surface area. Safety analysis revealed spontaneous rash (36% of participants) and transient lymphopenia as the 2 primary adverse events. As in previous trials in individuals with T1D, lymphocyte count decreased to a nadir on the fifth day. Lymphopenia resolved by day 45 in all but one participant, for whom it resolved on day 105. Rates of infection were similar in the 2 groups.

Teplizumab was approved by the US Food and Drug Administration in November 2022. Teplizumab is a CD3-directed antibody indicated to delay the onset of Stage 3 T1D in adults and pediatric patients aged ≥ 8 years with Stage 2 T1D.[26] This approval represents the beginning of the use of DMTs to delay or possibly prevent T1D diabetes.

DMTs to slow, stop, or reverse T1D

A growing body of evidence suggests that many patients with T1D retain beta cells long after diagnosis and likewise retain the ability to produce C-peptide.[27] DMTs can change the course of newly diagnosed T1D by preserving and/or restoring beta-cell mass; reducing insulin need; and subsequently reducing mortality, morbidity, and the burden of diabetes management. Finding clinically effective single or combination DMT that can rebalance the immune system and preserve or regenerate beta cells can change the way clinicians

approach and treat T1D. Several promising clinical trials in new-onset T1D include:

- The PROTECT trial, which is determining whether 2 courses of teplizumab administered 6 months apart slows the loss of beta cells and preserves beta-cell function in children and adolescents 8 to 17 years who have been diagnosed with Stage 3 T1D in the previous 6 weeks. Recruitment is complete and results are expected in 2023 (Identifier: NCT03875729)
- The CLVer trial, which uses hybrid closed-loop therapy and verapamil for beta-cell preservation in new-onset T1D. Verapamil has been shown to protect and strengthen beta cells and slow their destruction in T1D. Children and adolescents 7 to 17 years with diagnosis in the past 4 weeks are being enrolled (Identifier: NCT04233034)
- The Ver-A-T1D trial, which is designed to determine C-peptide response to 360 mg verapamil sustained release added to an insulin regimen in newly diagnosed adults (Identifier: NCT04545151)
- The TOPPLE study, which is testing the safety of a plasmid vector to stop beta-cell destruction in adults with T1D diagnosed in the last 4 years (NCT04279613)
- The BANDIT trial, which examines the potential for JAK inhibitors, currently approved for other autoimmune diseases, to stop beta-cell destruction in T1D. Trial results are expected in 2023 (Identifier: NCT04774224)

Practice implications

The nature of family practice means that the family physician is on the frontline of changing the paradigm for approaching those at risk for and treating T1D. Just as Lauren's example implies, identifying individuals at risk for T1D and coordinating a treatment and follow-up care plan for families will become common in family practice. Currently, this rapidly expanding field involves being prepared to:

- Inform at-risk patients of the current state of research and opportunities for screening, staging, and treating if necessary. JDRF.org contains materials for distribution and review
- Determine who should be screened
  - First- and second-degree relatives of a person with T1D
  - Individuals who have family members with autoimmune disorders associated with T1D such as celiac disease, Crohn's disease, thyroiditis, rheumatoid arthritis, and systemic lupus
  - Individuals with type 2 diabetes who appear to be misdiagnosed. Measure the presence of glutamic acid decarboxylase (GAD) antibodies if the patient is normal weight for an adult. Elevated GAD can indicate late autoimmune diabetes of adults (LADA). Decide on the screening options you feel comfortable with recommending/performing using recommended laboratories or screening programs[28]
- Stage patients using laboratory results. Discuss the meaning and value of staging and follow-up steps, if any. Monitor using suggested tests if ≥2 autoantibodies are detected
- Discuss options to treat or not treat. Direct family members to organizations with important educational information (**TABLE 1**)
- Decide on practice capacity to administer a 14-day course of teplizumab infusions or refer patients to a specialty practice for treatment and follow-up

Rapidly changing and innovative technology, along with advances in DMTs, will soon provide more options for individuals at risk for and with early-onset T1D. This is an incredibly exciting and hopeful time for families and family physicians. ●

TABLE 1. Type 1 diabetes resources

Patient information:

- JDRF.org
  - T1Detect (screening for relatives age 2–45)
  - TrialNet.org (screening with no family history)
- Diabetes.org: camps for children with diabetes
- TCOYD.org
- diaTribe.org
- Type1tested.com
- Healthcare professional information: jdrf.org/t1d-resources/hcp/?. Includes: ask the expert, screening guidelines, education; TCOYD.org/cme-enduring
  - tzieldhcp.com

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Early Life Nutrition and the Developing Brain

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KEY TAKEAWAYS

- The developmental origins of health and disease (DOHaD) hypothesis suggests prenatal nutrition sets the stage for the developing brain, with effects that last into adulthood.
- Macronutrient and micronutrient requirements increase in pregnancy and deficiencies can influence fetal neurodevelopment and cognition.
- Foods such as eggs, meat, and seafood contain many of the nutrients needed for healthy neurodevelopment and intake should be encouraged among women of reproductive age.
- Family practice clinicians play an important role in providing nutrition recommendations surrounding food and prenatal supplements to consume before, during, and after pregnancy.

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INTRODUCTION TO DOHaD

At the end of the 20th century, David Barker first suggested that the intrauterine environment influences offspring health and susceptibility to disease later in life.[1] The Developmental Origins of Health and Disease (DOHaD), also referred to as fetal programming, is a relatively new science with the goal of harnessing the prenatal period to improve the course of human health and disease.[2] Some of the first studies conceptualizing DOHaD were conducted as a result of the Dutch famine in 1944. In these studies, maternal malnutrition affected not only infant growth, but also risk of obesity and cardiovascular disease later in life.[3] Long-term effects of these epigenetic changes are likely, with studies linking early life malnutrition to schizophrenia[4] and even late-onset Alzheimer's disease.[5]

Nutrition is an important vein of DOHaD research that plays a vital role in the health and development of an individual, from preconception through adulthood. Macronutrients and micronutrients provide the building blocks for every organ system and function in the body, including the nervous system and brain. While the influence of nutrition on neurodevelopment is well studied, with several systematic reviews and metanalyses published on the topic,[6-10] this paper aims to provide a high-level summary of the current literature on prenatal nutrition and neurodevelopment. It includes practical information on nutrients and foods that should be incorporated in the diet and offers insight into how primary care physicians might play a role in sharing preconception and prenatal nutrition information.

NUTRIENTS AND NEURODEVELOPMENT

The developing brain is sensitive to the availability of nutrients during critical periods of pregnancy and infancy, after which neurodevelopmental damage is irreversible.[11] The brain and nervous system grow at a remarkable rate, achieving about 30% of adult brain weight at birth and 80% by age 2.[12] This rapid growth necessitates high levels of energy, with the fetal brain demanding up to 60% of the basal metabolic needs,[12] as well as macronutrients and micronutrients sufficient to meet the energy demands and optimize growth. Nutrition support during these periods can confer lifelong neurodevelopmental benefits and, if ignored, can increase the risk of poor neurological function into adulthood. As such, prenatal nutrition offers a crucial window of opportunity for intervention for clinicians.

All macro- and micronutrients are necessary for growth and development of the fetus, but the nutrients contained in **TABLE 1** have particularly important implications in neurodevelopmental processes. Macro- and micronutrient needs increase beyond what is needed in a pre-pregnant state to

TABLE 1. Nutrients important for the developing brain

Nutrient	Recommended intake in pregnancy[43,44]	Role in neurodevelopment	Food sources[45]
Protein	RDA: 1.1 g/kg/day First trimester: 1.2 g/kg/day Third trimester: 1.5 g/kg/day[14]	Supplies amino acids for fetal growth and neurotransmitters[14]	Poultry, meat, fish, seafood, dairy, eggs, beans, legumes, nuts
DHA	200–250 mg DHA/day[47,48]	Important for vision, psychomotor development, and infant attention and cognition[17,49,50]	Seafood, fish, liver, eggs
Iron	RDA: 27 mg/day	Neuronal metabolism, myelination, and gene regulation[51]	Heme (better absorption than non-heme): seafood, liver, meat Non-heme: fortified grains, beans, tofu, green leafy vegetables, dark chocolate
Folate	RDA: 600 mcg DFE/day DFE = dietary folate equivalents	Important for early brain formation, neural tube development, and 1-carbon metabolism[52]	Liver, leafy greens, fortified cereals, eggs, beans, seafood, meat
Iodine	RDA: 220 mcg/day	Plays an important role in thyroid function and subsequent neurodevelopment[28]	Seafood, dairy, iodized table salt, eggs, liver
Choline	AI: 450 mg/day 930 mg/day[53, 56]	Cell proliferation, neural tube formation, DHA transfer[35]	Liver, eggs, meat, seafood, beans
Zinc	RDA: 11 mg/day	Formation of neurons, hormones, and enzymes responsible for stem cell differentiation and growth[36]	Meat, seafood, seeds, nuts, seafood
Vitamin B12	RDA: 2.6 mcg/day	Neuronal growth and metabolism and myelin synthesis[30]	Meat, seafood, dairy, eggs, poultry
Vitamin A	RDA: Vitamin A: 770 mcg RAE/day RAE = retinoic acid equivalents	Organogenesis, including construction of the nervous system and neural tube development[31]	Liver, orange/red/green vegetables, eggs, fish, dairy
Vitamin D	AI: 600 IU/day Up to 4000 IU/day[54]	Neurotransmitter synthesis, structural development[38]	Sunlight, cod liver oil, seafood, fortified milk,[a] eggs

[a]Fortified milk is nutritionally enriched with nutrients like vitamin D; fortification will be indicated on the food label.

account for the growth and development of the fetus. Much of the existing research and subsequent recommendations surrounding nutrition in pregnancy are derived from studies showing the effects of dramatic nutrient deficiencies. Specific macronutrients (eg, protein, long-chain polyunsaturated fatty acids [LC-PUFA]) and micronutrients (eg, iron, iodine, choline, folate, vitamin B12, vitamin D, vitamin A) have been studied with respect to neurodevelopmental outcomes in the fetus and infant.

Protein and fat are vital due to their role in both structure and function of the cells in the brain and nervous system. Meeting protein needs in pregnancy is crucial to supply the necessary amino acids for both fetal growth and maternal homeostasis.[13] In the fetal nervous system, protein is the major building block for growth factors and neurotransmitters, which have a direct influence on cell metabolism and fetal programming.[14] Several studies have demonstrated the implications of protein deficiency, including miscarriage, intrauterine growth restriction, and slow postnatal growth velocity.[13] Neurodevelopmental and cognitive outcomes are also affected in cases of protein deficiency, as evidenced by lower intellectual quotient (IQ) at 2 years[15] and 9 years.[16] Fat, specifically the LC-PUFA known as docosahexaenoic acid (DHA), makes up the majority of the cells within the nervous system.[17] Adequate maternal DHA intake is associated with improved birth outcomes (eg, lower risk of preterm birth[18,19])

and improved infant outcomes (eg, visual and psychomotor development[20] and attention[21,22]). A recent systematic review suggests omega 3 supplementation in pregnancy may result in improved cognition in childhood, but more studies are needed to determine the proper dose and timing of supplementation strategies.[23]

A summary of the effects of micronutrient deficiencies and neurodevelopmental outcomes are briefly described here. Iron deficiency is the most common nutrient deficiency worldwide, affecting 42% of pregnancies in high-income countries[24] and up to 60% of pregnancies in low- and middle-income countries.[25] Thus, iron is one of the most well-studied micronutrients in terms of cognitive and developmental delays in children caused by deficiencies.[26] Folate deficiency was first linked to neural tube defects (NTD) in 1965, and subsequent studies showed folate supplementation significantly reduced the rate of NTD, leading to a grain fortification program in 1998.[27] Iodine deficiency in pregnancy is also well studied due to its role in thyroid function[28] and subsequent neurodevelopmental delays caused by deficiency, such as congenital hypothyroidism.[29] Vitamin B12 is important for neuronal growth, and studies of deficiency have been linked to brain atrophy and compromised function of the cerebral cortex.[30] Retinoic acid, produced by vitamin A in the body, is an essential nutrient responsible for organogenesis, including the construction of the nervous system.[31] Vitamin A deficiency during pregnancy can result in fetal death or neural cord defects, as well as other non-neurological issues.[31] Carotenoids, including beta carotene, lutein, and zeaxanthin, are also implicated in cognitive outcomes throughout the lifespan,[32] with some observational research pointing to a role in cognition in children.[33]

The research on nutrients such as choline, zinc, and vitamin D intake in pregnancy has blossomed in the last 20 to 30 years. Choline makes up the neurotransmitter acetylcholine, and prenatal deficiency can lead to neural tube defects and cognitive delays in offspring.[34] A 2020 systematic review highlighted 3 important roles of choline, including supporting normal brain development, neuronal protection when the fetus is exposed to alcohol, and improved cognitive function.[35] Zinc is the second-most abundant mineral in the body after iron and is required for the formation of neurons.[36] The effects of zinc deficiency in infancy and childhood have been associated with impaired cognitive function; however, there is insufficient evidence that supplementation with zinc during critical periods of infancy and childhood has beneficial effects on mental development of children.[37] Vitamin D is important for structural brain development and neurotransmitter synthesis[38] and recent studies have shown prenatal vitamin D deficiency is associated with poor cognitive and language function in infants.[39]

The Dietary Reference Intakes (DRIs) include the Recommended Dietary Allowance (RDAs), defined as the average amount of a nutrient required to meet the needs of 97.5% of healthy individuals. The Estimated Average Requirements (EAR) are defined as the average daily nutrient intake estimated to meet the needs of 50% of healthy individuals. In cases where an EAR or RDA cannot be established, an Adequate Intake (AI) value is set. Upper limits (UL) are also set for each nutrient and are defined as the highest daily amount that can be consumed with no adverse health effects. For pregnant women, the DRIs are calculated based on requirements for non-pregnant individuals but include an adjustment for increased energy needs for the fetus.[40] In some cases (eg, DHA), a DRI has not yet been established but nutrient needs have been studied and subsequent recommendations have been made by reputable agencies.[41] In other cases (eg, protein), research indicates levels higher than the RDA are necessary for neurodevelopment.[14] **TABLE 1** includes the DRIs as well as other recommendations when necessary or indicated, roles of each nutrient in neurodevelopment, food sources, and approximate serving sizes of specific foods required to meet the recommended intakes. Beyond the prenatal period, the foods consumed during infancy and childhood also have influence on the health and cognition of children.[42] While breast milk, formula, and complementary foods play an important role in shaping the brain and nervous system of an individual,[10] this paper focuses on the preconception and prenatal periods of intake.

Beyond single nutrients: The influence of food

Nutrients do not exist in isolation but instead come bundled together as whole foods. Foods that are high in protein and LC-PUFA are also frequently high in neuroprotective nutrients. Eggs are an example of a nutrient-dense food containing several nutrients important for neurodevelopment, including protein, fatty acids, choline, carotenoids, vitamin A, and vitamin B12. Recent evidence has shown a synergistic effect of nutrients such as DHA, choline, and carotenoids both within the maternal diet on fetal neurodevelopment,[55] and within human breast milk on cognition in infants.[56] Further, maternal egg intake alone is related to markers of fetal neurodevelopment in the third trimester.[55] Shellfish and seafood are another example of a food group containing all of the nutrients required for healthy brain development, including protein, DHA, iron, iodine, zinc, vitamin A, and vitamin B12. A systematic review found seafood intake in pregnancy is associated with improved offspring neurodevelopment, including cognitive metrics such as IQ.[57] Importantly, the

benefits to neurodevelopment have consistently been found to outweigh the potential detrimental effects of exposure to heavy metals through seafood consumption.[57]

A comprehensive assessment of the effect of diet as a whole should include diet quality and dietary patterns rather than a mere tally of individual nutrients. A 2017 systematic review concluded that better maternal diet quality during pregnancy was associated with better child neurodevelopment and cognition.[6] In general, healthy diet patterns in these studies include higher intakes of fruits, vegetables, fish, legumes, whole grains, and vegetable oils.[6] In a large cohort from the Norwegian Mother, Father and Child Cohort Study, better maternal diet quality during pregnancy was associated with lower rates of depression and anxiety at age 8 years.[58] It is worth noting the majority of studies assessing diet quality in pregnancy have been observational in nature and heterogenous in methodology; thus, recommendations surrounding specific diet patterns in pregnancy are inconclusive.

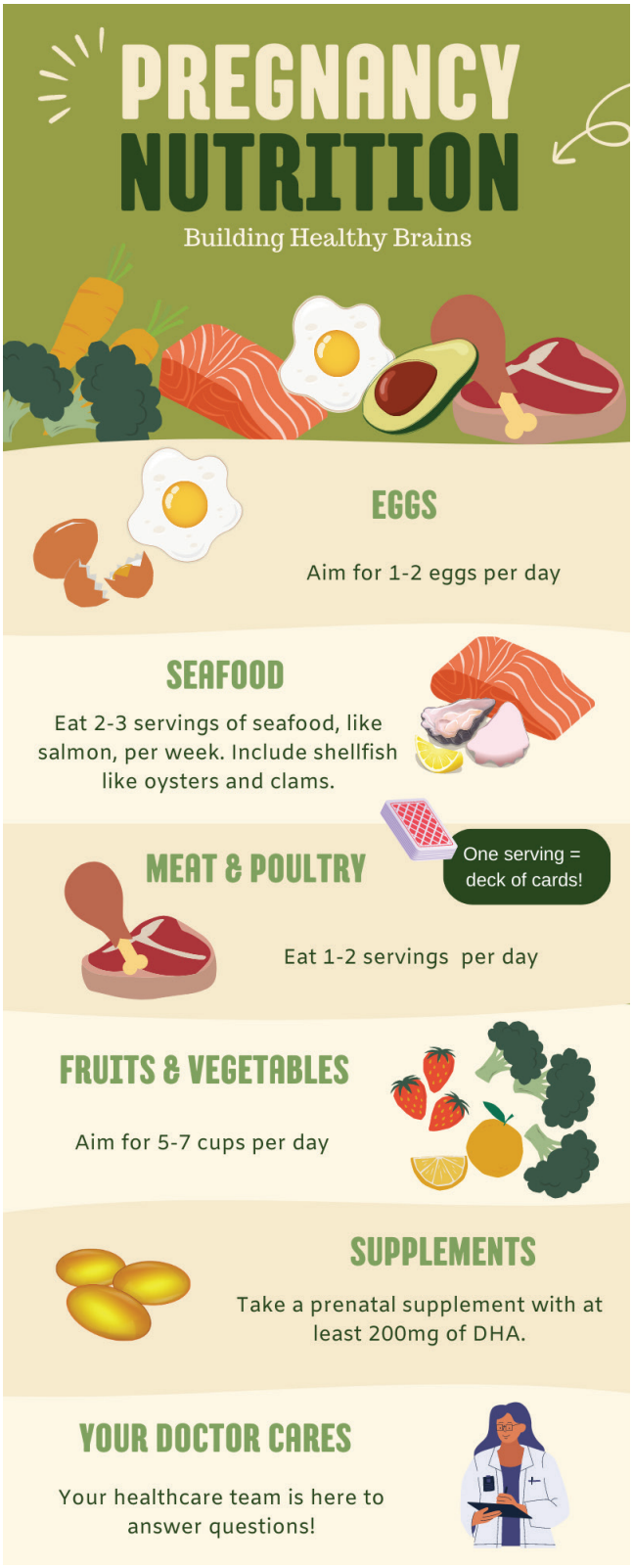
What your patients should know about early life nutrition

More than 50% of pregnancies in the United States are unplanned,[59] creating an important role for preconception health and nutrition counseling in primary care settings. Screening for pregnancy intention and providing preconception care in primary care is recommended by the Center for Disease Control (CDC) and American College of Gynecologists (ACOG).[60] According to the American Academy of Family Physicians (AAFP) and the US Preventive Services Task Force (USPSTF), women of reproductive age should maintain adequate nutrient status, maintain a healthy weight, be physically active, quit smoking, limit alcohol, and manage chronic disease states.[60]

Prenatal vitamins can be thought of as a safety net for when the diet is lacking in key nutrients required for optimal fetal growth and development. However, most prenatal vitamins lack adequate amounts of nutrients, including choline and DHA, and a separate supplement might be indicated when food consumption does not meet nutrient needs.[61] Additionally, foods such as seafood, meat, and eggs are good sources of choline and DHA and should be recommended during preconception and pregnancy. Eggs, even with recent price increases, remain one of the most affordable and accessible food sources of high-quality protein and essential nutrients. Electronic resources are commonly cited as a primary source of health information rather than healthcare providers, and this holds true for prenatal nutrition recommendations.[62] Women commonly report they are taking prenatal supplements, but few are taking them correctly.[62] Furthermore, most women report hearing more about what they cannot eat from their provider than they do regarding what they *can* eat.[63] Seafood is one food group that is nutrient dense and recommended in pregnancy by all major health agencies, but many women still report avoiding it while pregnant.[57] The specific recommendation from ACOG is for women who are pregnant or wish to become pregnant to consume 2 to 3 servings of a variety of fish per week.[64] However, patient-facing information tends to emphasize the risks of mercury consumption without also mentioning the benefits of seafood.[65] While the seafood highest in mercury (eg, shark, swordfish, tilefish, mackerel) should be avoided in pregnancy; these fish are not among the most commonly consumed seafoods in the US.[66] In a focus group study, women stated that receiving information about healthy seafood consumption during pregnancy was the most important factor contributing to an increase in consumption.[67] Women also reported wanting more constructive engagement from their healthcare team regarding nutrition during pregnancy.[63]

The National Institutes of Health (NIH) has a new initiative to advance the field of precision medicine and nutrition to create clinically relevant dietary solutions for individuals and populations, including during pregnancy.[19] While assessing nutrient status by determining nutrient levels in blood or tissues is not pragmatic in the clinic, simple questionnaires could be used as a tool to guide clinical recommendations. As such, short dietary intake questionnaires have been developed specifically for healthcare professionals not trained in nutrition to assess nutrient intake.[68] Additional tools have been studied to assess specific nutrients such as DHA that are ubiquitously low in pregnant populations. One such tool is a 7-question DHA food frequency questionnaire that asks about seafood and egg intake, correlates well with blood DHA levels, and can predict who might benefit from a higher dose supplement (eg, 1000 mg DHA/day) and who might not need a supplement due to adequate dietary intake.[69,70] A simple patient handout (see **FIGURE 1**) could also be used in clinical practice to supplement a verbal recommendation to maintain a nutrient-rich diet and take prenatal vitamins. For providers who are looking for in-depth prenatal nutrition information, there are several comprehensive resources available, including an *UpToDate* article "Nutrition in Pregnancy: Dietary Requirements and Supplements,"[71] Dietary Guidelines for Americans 2020–2025,[72] The Food and Drug Administration: Advice about Eating Fish,[73] and books such as *Real Food for Pregnancy* by Lily Nichols, RDN, CDE.[74] The role of nutrition in neurodevelopment cannot be understated, and physicians are an important conduit for providing education and empowering patients to optimize the health of the next generation. ●

FIGURE. Nutrition in pregnancy: Building healthy brains



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Insomnia Management: A Review and Update

By David P. Shaha, MD

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KEY TAKEAWAYS

- Insomnia is a distinct disorder that is common, yet underrecognized and undertreated in primary care.
- Treating insomnia has been shown to improve outcomes, including reduced risk of developing cardiovascular and mental health disorders.
- Insomnia is influenced by the brain's regulation of sleep and wake, which are mutually exclusive events.
- Insomnia should be treated as a distinct condition, even when occurring with a comorbid diagnosis such as depression or anxiety.
- Clinicians should implement a multimodal approach to insomnia management, including nonpharmacologic interventions and pharmacologic therapy (when indicated).
- Pharmacologic agents that are approved by the US Food and Drug Administration for insomnia include benzodiazepine receptor agonists (zolpidem, eszopiclone, and zaleplon), low-dose doxepin (tricyclic antidepressant), ramelteon (melatonin receptor agonist), and dual orexin receptor agonists (DORAs, daridorexant, lemborexant, and suvorexant).
- Unlike other pharmacologic agents, DORAs inhibit wakefulness rather than induce sedation. Additionally, these medications have no evidence of rebound insomnia or withdrawal, and little to no abuse potential.
- Daridorexant is the newest DORA, has an ideal half-life of 8 hours, and has demonstrated continued efficacy over a 12-month period.
- Selection of pharmacologic agent should be based on the patient's comorbid conditions, treatment goals and preferences, and other clinical characteristics.

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INTRODUCTION

Insomnia is a disorder involving trouble initiating or maintaining sleep; it leads to substantial daytime consequences, such as difficulty functioning, poor work performance, social isolation, and fatigue.[1-3] Those with insomnia have difficulty sleeping even with ample opportunity in an environment conducive to sleep.[1] Sleep disturbances that occur several times a week and persist for longer than 3 months are classified as chronic insomnia.[1] Insomnia frequently presents with comorbid conditions such as depression and other neurologic disorders, cardiovascular disease, diabetes, respiratory disorders, gastrointestinal disorders, and cancer.[4] However, insomnia is considered a distinct condition and should be treated as such, not as a secondary condition to other comorbidities.[4,5] Furthermore, insomnia increases the risk of developing conditions such as psychiatric disorders and cardiovascular disease, and adequate treatment of insomnia improves cardiovascular and mental health outcomes.[6,7]

Estimates suggest that about 10% of adults have insomnia, and up to 20% of patients seen in primary care settings report problems with insomnia symptoms that cause functional impairment and reduced productivity.[3,8] Furthermore, the direct and indirect costs of insomnia in the United States (US) amount to approximately $100 billion, primarily due to lost productivity, health care resource use, and accidents.[9] Even so, insomnia is underrecognized and undertreated, leading to a significant health burden characterized by decreased quality of life and increased morbidity and mortality.[5]

Although insomnia is frequently encountered by primary care practitioners (PCPs), many patients (approximately 70%) state that their clinicians do not ask them about sleep issues.[10] While there are no specific guidelines for universal screening for insomnia, PCPs should be sensitive to this issue and consider screening for insomnia[11] by asking patients a simple question such as, "Are you having any problems with sleep?"[12] Alternatively, the Patient Health Questionnaire-9 (PHQ-9), a screening tool for depression, includes a question asking if the patient has "trouble falling or staying asleep, or sleeping too much."[13] This could initiate further investigation, which may include the Insomnia Severity Index (ISI), a com-

monly used and relatively rapid assessment for insomnia.[14] Following diagnosis, treatment of insomnia often involves a multimodal approach, consisting of both nonpharmacologic and pharmacologic therapy, to achieve best outcomes.[4] The goals of treating insomnia are to improve sleep quality and duration and to resolve daytime consequences.[15]

CASE SCENARIO

A 57-year-old man reports to his PCP that he has had trouble sleeping for the past 6 months. Specifically, he has problems staying asleep through the night. He recently moved to the area and states that he has been taking trazodone "for a few months now." The medication seemed to work at first but now has not been helping, so he is seeking more effective treatment today. He states that he has good sleep hygiene and keeps a consistent bedtime routine.

His self-reported sleep issues are confirmed by his responses to the brief ISI, and he is given a diagnosis of chronic insomnia. The patient notes that he's concerned about being too "hung over" from taking sleeping medications the next day because he needs to get up and go to work in the morning. He also notes that he's become more anxious and depressed with the lack of sleep.

This patient is experiencing significant symptoms of insomnia despite healthy sleep habits and should receive treatment. In addition to optimizing nonpharmacologic therapy, his treatment plan should include an adjustment in his pharmacologic therapy to an agent that is effective for sleep maintenance, does not inhibit daytime activities, and does not worsen comorbidities.

PHYSIOLOGY OF SLEEP AND PATHOPHYSIOLOGY OF INSOMNIA

Sleep is a complex process with involvement from multiple brain regions.[16] Currently there is no accepted model for the insomnia disease process.[17] Proposed descriptions of insomnia include models that focus on neurobiologic, behavioral, cognitive, and emotional factors.[16] Despite the lack of clear, detailed pathophysiology, insomnia is thought to result from dysregulation of homeostatic processes and circadian rhythms that govern wakefulness and sleep.[18]

Regulation of sleep and wake

A brief review of certain components of the neuroanatomy of insomnia is helpful to understand the rationale for pharmacologic therapy. Insomnia involves primarily the ascending reticular activation system (ARAS), which drives wakefulness, and the ventrolateral preoptic (VLPO) nucleus, which influences sleep.[16] The alternating activation and suppression of the ARAS and the VLPO indicate that wakefulness and sleep are normally mutually exclusive.[17,19]

Specifically, the ARAS is responsible for stimulating various cortical regions, such as the orexin system, which blocks the VLPO to sustain wakefulness.[16] The VLPO works by inhibiting the ARAS, primarily via 2 neurotransmitters: ψ-aminobutyric acid (GABA) and galanin.[16] Many pharmacologic agents used for insomnia management target one or more of these regions and neurotransmitters.

Symptoms and manifestations of insomnia

Symptoms of insomnia (other than difficulty initiating or maintaining sleep) include both sleep-related sequelae as well as next-day impairment. Patients with insomnia may experience racing thoughts, excessive worrying, higher blood pressure and metabolic rate, high cortisol levels, and an increased risk of falls and injuries, which have both medical and economic consequences.[20,21] Next-day impairment due to insomnia can include poor functioning, fatigue, reduced alertness, and exacerbation of comorbidities, resulting in an overall reduction in the patient's quality of life.[5] Insomnia is often a clinical diagnosis, and use of validated tools can assist in confirming the diagnosis.[4]

Patients with insomnia also demonstrate increased electroencephalographic activity while asleep.[16] Although polysomnography is not necessary nor recommended for initial evaluation of insomnia, this and other tools may be useful for additional workup to rule out other conditions that may disrupt sleep, such as restless leg syndrome, mood disorders, obstructive sleep apnea, or pain disorders.[22]

PHARMACOLOGIC OPTIONS FOR INSOMNIA

Many medications have been used for insomnia (**TABLE 1**). While some are approved by the US Food and Drug Administration (FDA) and have demonstrated safety and efficacy, many are not approved for insomnia and are used off-label. Over-the-counter (OTC) medications are often used for insomnia, but they lack efficacy data, and some have substantial risks of adverse effects; therefore, they are not recommended.

Drugs used for insomnia are often limited by treatment-associated risks, such as falls, next-day drowsiness, and risk for dependence; many are listed in the Beers Criteria® as medications that should be avoided in older adults.[23] These include benzodiazepines, tricyclic antidepressants, antihistamines, mirtazapine, and benzodiazepine receptor agonists.[23] Among prescription agents, trazodone and benzodiazepines have been associated with a higher risk of falls.[24,25] Additionally, patients with insomnia and depression treated with zolpidem, trazodone, or benzodiazepines have higher health care resource use than individuals with depression but no sleep disorder.[24,26]

TABLE 1. Selected medications used for insomnia treatment

Class/drug	FDA approval for insomnia	Special considerations	Mechanism
Antidepressant			
Doxepin	Yes	• Lower concern for adverse events in older adults	Serotonin-norepinephrine reuptake inhibitor; H^1 receptor blocker
Amitriptyline	Off-label	• Lack safety and efficacy data	
Trazodone	Off-label		Serotonin antagonist and reuptake inhibitor; H_1 receptor blocker
Mirtazapine	Off-label		Serotonin-norepinephrine transmission blocker; H_1 receptor blocker
Benzodiazepine			
Alprazolam	Off-label	• Controlled substances with risk for dependence and misuse • Associated with significant adverse effects like cognitive impairment, car accidents, falls, and rebound insomnia	$GABA_A$-receptor agonist
Clonazepam	Off-label		
Flurazepam	Yes		
Lorazepam	Off-label		
Temazepam	Yes		
Triazolam	Yes		
Benzodiazepine receptor agonist			
Eszopiclone	Yes	• Shorter duration than benzodiazepines • Boxed warning for complex sleep-related behaviors	$GABA_A$-receptor agonist
Zaleplon	Yes		
Zolpidem	Yes		
Melatonin agonist			
Ramelteon	Yes	• Lower concern for adverse events in older adults • Lack of substantial effectiveness	Highly selective melatonin-receptor agonist
Dual orexin receptor agonist			
Daridorexant	Yes	• 8-hour half-life • Lower concern for adverse events in older adults	Block OX_1 and OX_2 to inhibit wakefulness
Lemborexant	Yes	• 18-hour half-life • Lower concern for adverse events in older adults	
Suvorexant	Yes	• 12-hour half-life • Lower concern for adverse events in older adults	

Abbreviations: $GABA_A$, γ-aminobutyric acid-A; H_1, histamine 1; OX_1, orexin receptor type 1; OX_2, orexin receptor type 2.
Adapted from Rosenberg RP et al, 2023.[4]

OTC and off-label agents

OTC and off-label agents are frequently used and/or recommended by clinicians for treating insomnia, despite the safety concerns and lack of evidence. For example, trazodone is the most commonly prescribed insomnia treatment in primary care, even though it is not FDA approved and safety and efficacy have not been proven in trials.[4,27,28] Additionally, the American Academy of Sleep Medicine and Department of Defense/Veterans Affairs clinical practice guidelines recommend against using trazodone for insomnia, given its poor risk-benefit profile.[29,30]

Common OTC sleep aids include products that contain diphenhydramine or doxylamine, which have anticholinergic effects that may raise the risk of falls, hangover effects, dizziness, and cognitive impairment.[31] Melatonin use for insomnia is also common, and while there are safety data for sustained-release melatonin, evidence demonstrating efficacy is lacking.[4,32]

FDA-approved prescription agents

Benzodiazepines. These agents activate $GABA_A$ receptors in the brain and are now infrequently prescribed for insomnia due to the potential for significant adverse effects. All agents in this class are controlled substances and have increased

risk for abuse, misuse, and dependence. Meta-analyses of randomized trials for chronic insomnia treatment found that several benzodiazepines are associated with faster sleep onset, improved sleep time, and better sleep quality.[33,34]

Use of benzodiazepines for insomnia is limited by abuse and misuse potential, as well as commonly occurring adverse effects such as next-day somnolence, rebound insomnia, and complex sleep behaviors.[4]

Benzodiazepine receptor agonists. Benzodiazepine receptor agonists (zolpidem, eszopiclone, zaleplon) were designed with the intent to be safer than benzodiazepines due to shorter duration and slight differences in mechanism of action. Studies have reported that benzodiazepine receptor agonists have a higher affinity for the $GABA_A$ receptors and a shorter half-life than benzodiazepines.[35] Meta-analyses of randomized trials evaluating benzodiazepine receptor agonists have showed that these agents improve sleep onset, sleep time, and sleep quality compared with other drugs used for insomnia.[33,34]

While these medications do offer a somewhat safer alternative to benzodiazepines, they have other limitations, including adverse effects such as next-day somnolence, rebound insomnia, and complex sleep behaviors.[4]

Ramelteon. Ramelteon is a melatonin receptor agonist approved in 2005 for insomnia. In randomized trials, ramelteon demonstrated modest short-term improvements in latency to persistent sleep (13-minute reduction compared to placebo), and it was well tolerated.[36,37] While ramelteon is safer than many other prescription agents due to an improved adverse effect profile, it tends to be less effective for insomnia overall than other treatments.

Doxepin. Doxepin is a tricyclic antidepressant that received an indication for insomnia in 2010 at low doses based on several phase 3 trials that demonstrated improvements in total sleep time, sleep efficiency, wake time after sleep onset, and patient-reported sleep quality compared to placebo.[38] Doxepin did not decrease sleep-onset latency significantly, and its benefit in younger adults was not as pronounced as in older adults.[39]

Dual orexin receptor antagonists (DORAs). While most medications used to aid sleep cause sedation or drowsiness as an intended effect or side effect, DORAs block the binding of wake-promoting orexin neuropeptides and thereby prevent wakefulness. They have been shown to improve both sleep onset and sleep maintenance insomnia with reduced next-day impairment. Notably, DORAs have no evidence of rebound insomnia or withdrawal and little to no abuse potential.

Daridorexant. Approved in January 2022, this agent is the most recent DORA on the market. Daridorexant demonstrated improvement in sleep and next-day function in adults at months 1 and 3 compared to placebo, with a favorable safety profile.[40] A secondary analysis of the pivotal clinical trials indicated that daridorexant is effective for older adults as well as younger, without increased risk of adverse events.[41] Long-term studies of daridorexant have demonstrated durable efficacy and safety throughout 12 months of therapy; additionally, there was no waning in efficacy and no risk of withdrawal or rebound insomnia.[42] This medication also has the shortest terminal half-life of the approved DORAs (8 hours), and the 50-mg dose has been demonstrated to improve daytime function.[4]

Lemborexant. Lemborexant was approved in 2019 and has demonstrated improved sleep onset and maintenance compared to zolpidem and placebo.[43] Furthermore, a meta-analysis of several agents used for insomnia (lemborexant, suvorexant, benzodiazepines, benzodiazepine receptor agonists, trazodone, and ramelteon) suggested that lemborexant may be preferred for sleep efficiency, latency, and total sleep time.[44] Of note, patients who are sensitive to effects of lemborexant may require a lower dose to reduce the risk of next-morning driving impairment.[45] Lemborexant has the longest half-life, 18 hours, of the DORAs.[4] This is not ideal since the long half-life can negatively impact next-day function.

Suvorexant. This drug was FDA approved in 2014 and was the first DORA approved for insomnia treatment. In clinical trials, suvorexant demonstrated improvements in total sleep time, sleep-onset latency, and wake after sleep compared to placebo.[46] Guideline recommendations regarding suvorexant are equivocal due to lack of strong evidence.[15,29,30] It has a half-life of 12 hours.[4]

MANAGING INSOMNIA IN PRIMARY CARE

To effectively manage insomnia, clinicians should implement a multimodal strategy that incorporates sleep hygiene, cognitive behavioral therapy for insomnia (CBT-I) or brief behavioral therapy for insomnia (BBT-I), and the appropriate use of medications.[4] The treatment plan should address patient preferences and treatment goals, as well as accomplish the overarching goals of insomnia treatment to improve sleep and reduce next-day impairment.[15] Using shared decision-making when developing treatment plans is also emphasized in clinical guidelines.[45]

Treatment guidelines

Several US-based treatment guidelines are available to inform clinicians regarding optimal approaches for insomnia management:

- Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians (ACP), 2016[15]
- Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline, 2017[29]

TABLE 2. Matching insomnia treatments to patient characteristics[4]

		PATIENT PRESENTATION					
		Sleep-onset insomnia	Sleep-maintenance insomnia	Treatment-resistant insomnia	Vulnerability to substance use disorder	Comorbid depression or anxiety	Need for normal next-day function
Suggested pharmacologic intervention	DORAs	X	X		X		X
	Benzodiazepines or benzodiazepine receptor agonists	X				X	
	Doxepin		X		X		X
	Ramelteon	X			X		
	Antidepressants (off-label)			X		X	
	Antipsychotics (off-label)			X		X[a]	

Abbreviation: DORAs, dual orexin receptor agonists.
[a] Comorbid depression or psychosis.

- Department of Veterans Affairs/Department of Defense Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea (2019)[30]

CBT-I and BBT-I help patients identify habits and behaviors that contribute to or perpetuate insomnia and then replace those with habits and behaviors that promote sleep. Core principles of these methods include conditioning patients to associate the bed with sleep (stimulus control), learning to create a relaxed state when attempting sleep (relaxation therapy), the controlled restriction of sleep opportunity to improve sleep efficiency (restriction therapy), and challenging negative thought patterns surrounding sleep (cognitive therapy). Trained clinicians and mental health professionals can administer these therapies in the clinical setting.[15] In addition to CBT-I and BBT-I, recommended nonpharmacologic interventions include lifestyle strategies and improving sleep hygiene. Lifestyle strategies involve eating a healthy diet, exercising adequately, and limiting alcohol and caffeine intake.[4,47] Sleep hygiene involves creating a quiet, calm environment in the bedroom and adopting daily routines that promote sleep.[4]

Because the DORAs daridorexant and lemborexant are relatively new, neither was included in any of these guidelines and may warrant additional consideration. All of the existing guidelines recommend a short duration of medication therapy, as few studies have evaluated the use of medications for more than 4 weeks.[15] As referenced above, 1 multicenter study demonstrated continued efficacy over an entire year with daridorexant and no significant withdrawal symptoms.[42] The favorable safety profile of DORAs makes them a potentially safer alternative than many prescription agents for the management of chronic insomnia.

Selecting pharmacologic treatment for insomnia

Treatment selection should be guided by patient preference as well as clinical presentation, and Rosenberg and colleagues have suggested conditions in which certain interventions might be recommended (**TABLE 2**).[4] Clinicians should consider treatments that address both insomnia as well as any applicable comorbid conditions. For example, if a patient has a history of substance use, treatments without evidence of misuse in patients with insomnia may be considered. Additionally, therapeutic regimens should seek to maximize benefit while minimizing treatment risks, such as risks for falls and next-day impairment.

Once therapy is selected and initiated, regular monitoring should assess response to, and tolerability of, the treatment.[48] If the response is suboptimal, clinicians should consider increasing the dose; if unwanted adverse effects occur, clinicians may consider lowering the dose or switching medications.[4] Notably, patients should avoid abruptly stopping prescription insomnia medications because of the risk for withdrawal or rebound insomnia, especially with benzodiazepines and benzodiazepine receptor agonists.[5]

SUMMARY

Insomnia is a commonly encountered disorder in primary care, but it is underdiagnosed and undertreated, leading to substantial healthcare burden. Insomnia is a distinct condition often associated with comorbidities. The pathophysiology of insomnia is complex and not fully understood, but the prevailing theory is that sleep is regulated by balancing inputs from wake-promoting regions and sleep-promoting regions in the brain. Optimal therapy for insomnia involves a multimodal approach using nonpharmacologic and pharmacologic interventions that align with the patient's goals and preferences.

Nonpharmacologic therapies include CBT-I, BBT-I, sleep hygiene, and lifestyle changes. (To learn more about sleep hygiene and healthy sleep habits, see the American Academy of Sleep Medicine website: https://sleepeducation.org/healthy-sleep/healthy-sleep-habits/.) Pharmacologic therapies include OTC therapies, benzodiazepines, benzodiazepine receptor agonists, ramelteon, doxepin, and DORAs. DORAs are a newer class of medications for treating insomnia that inhibit wakefulness rather than inducing sedation. Their safety profile and novel mechanism of action make them appealing options for chronic insomnia patients. They have been shown to improve both sleep onset and sleep maintenance insomnia with reduced next-day impairment. DORAs have no evidence of rebound insomnia or withdrawal and little to no abuse potential. Daridorexant is the newest DORA, has a desirable half-life of 8 hours, and has demonstrated efficacy over a 12-month period in one longitudinal study. ●

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New Paradigms for CKD Management in Patients With T2D

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

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

- Identify the risks of kidney disease and their consequences in patients with type 2 diabetes (T2D).
- Appropriately screen for the presence of chronic kidney disease (CKD) in patients with T2D.
- Initiate evidence-based therapy to slow the progression of kidney disease in patients with T2D and CKD.
- Become familiar with the novel nonsteroidal mineralocorticoid receptor antagonist finerenone and its role in the treatment of patients with T2D and CKD.

KEY TAKEAWAYS

- Chronic kidney disease (CKD) is defined by persistent abnormalities in urinary albumin excretion, estimated glomerular filtration rate (eGFR), or both. Unfortunately, CKD is widely underrecognized by clinicians and patients.
- Guideline-directed management of CKD in type 2 diabetes (T2D) involves lifestyle modifications, optimized control of modifiable risk factors, and use of therapies with evidence of cardiorenal benefit, including renin-angiotensin system (RAS) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, finerenone, and long-acting glucagon-like peptide-1 receptor agonists (GLP-1 RAs).
- Finerenone is a novel, nonsteroidal mineralocorticoid receptor antagonist (MRA), which is pharmacologically and clinically distinct from steroidal MRAs and can be used as recommended in current guidelines to improve cardiorenal outcomes in patients with T2D and CKD.

TARGET AUDIENCE

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

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CHRONIC KIDNEY DISEASE IN TYPE 2 DIABETES

Chronic kidney disease (CKD) is an important diabetes-related complication.[1] CKD in diabetes can progress to kidney failure, and the need for kidney replacement therapy (dialysis or transplant) markedly amplifies cardiovascular risk and is costly to the healthcare system.[1] CKD additionally increases mortality risk, with one analysis reporting an approximate 10-fold increase in 10-year mortality risk for patients with type 2 diabetes (T2D), albuminuria, and impaired glomerular filtration rate (GFR) when compared to people with T2D without kidney disease.[2]

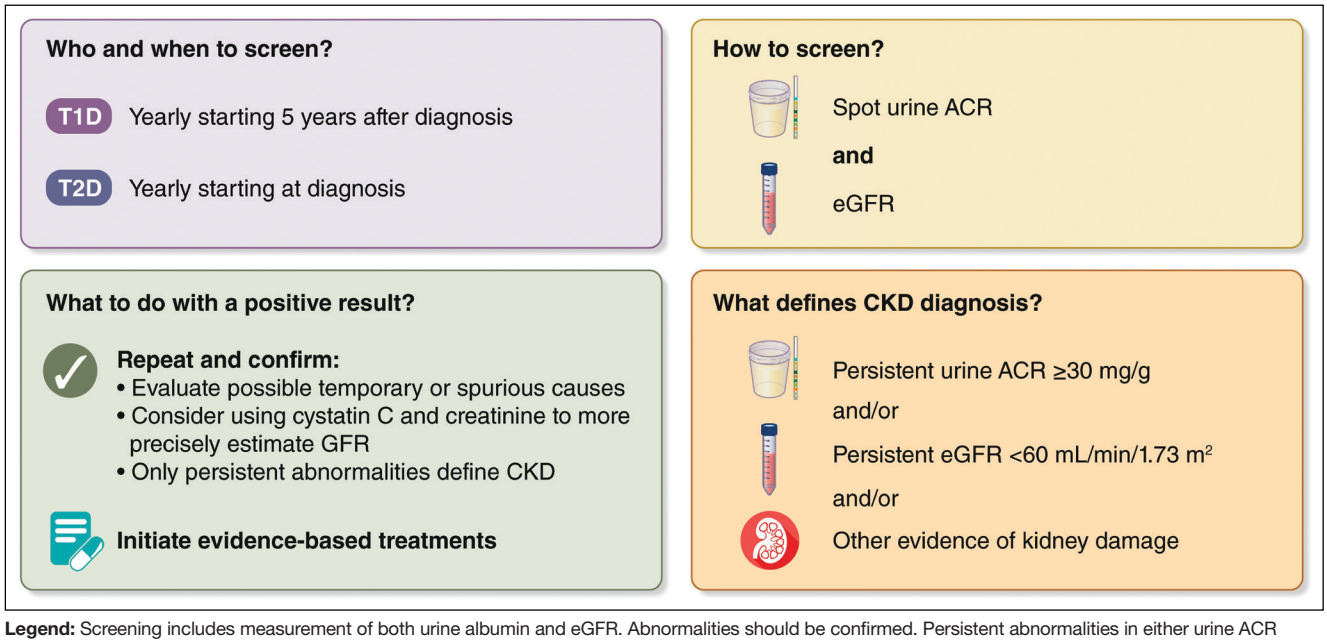
The prevalence of CKD in the United States continues to increase in parallel with the prevalence of diabetes.[3] According to estimates from the Centers for Disease Control and Prevention (CDC), approximately one-third of the estimated 37 million people living with diabetes in the United States may have CKD.[4] In most cases, CKD is initially asymptomatic and is identified and diagnosed through recommended annual laboratory screening.[5] Unfortunately, CKD awareness is quite low among clinicians and patients alike, with an estimated 90% of people with CKD unaware of their condition.[6] Early identification and management is essential, however, to slow CKD progression, mitigate cardiovascular risk, and prevent premature mortality.[1] Fortunately, recent important therapeutic advancements now provide clinicians and patients with additional therapeutic options to mitigate cardiorenal risk. Because the vast majority of people with T2D are managed in primary care settings, primary care clinicians play a critical role in the early identification and treatment of CKD in T2D.[7] Recognizing and overcoming key barriers to optimized CKD care in the primary care setting, such as suboptimal screening, lack of clinician and patient awareness, limited clinician time and resources, and suboptimal use of guideline-directed therapies, are critical to improve patient care and outcomes.[8]

DIAGNOSIS AND CLASSIFICATION OF CKD

CKD is defined by a persistent estimated GFR (eGFR) <60 mL/min/1.73 m^2, persistently elevated urine albumin excretion (albumin-to-creatinine ratio [ACR] ≥30 mg/g), or both, for >3 months.[9] Annual screening is recommended in people with T2D starting at the time of diagnosis and beginning 5 years after a diagnosis of type 1 diabetes (T1D) (**FIGURE 1**).[5] Screening for both low eGFR and albuminuria is important to identify at-risk individuals, yet evidence indicates that less than half of people with T2D are screened for albuminuria annually in the primary care setting.[10]

Kidney Disease: Improving Global Outcomes (KDIGO), a consensus recommendation from an international group of experts, has developed a "heat map" for CKD staging, which also guides decisions related to frequency of monitoring, treatment, and nephrology referral, which can be accessed here: https://pubmed.ncbi.nlm.nih.gov/36189689/#&gid=article-figures&pid=figure-2-uid-1.[5] The American Diabetes Association[1] (ADA) recommends referral to nephrology for patients with rapidly progressing CKD and/or in those with an eGFR

FIGURE 1. CKD screening and diagnosis for people living with diabetes[5]



Legend: Screening includes measurement of both urine albumin and eGFR. Abnormalities should be confirmed. Persistent abnormalities in either urine ACR or EGFR (or both) diagnose CKD and should lead to immediate initiation of evidence-based treatments.

<30 mL/min/1.73 m^2. Likewise, referral to nephrology is recommended when there is uncertainty about kidney disease etiology or when difficult management issues arise (eg, anemia, metabolic bone disease, secondary hyperparathyroidism).[1]

CKD risk factors and pathophysiology

The 2 most important risk factors for CKD in diabetes are uncontrolled hyperglycemia and/or blood pressure, with the ADA noting that optimization of glycemic and blood pressure control is the only proven strategy for the primary prevention of CKD in diabetes.[1] The CDC notes a family history of CKD, hyperlipidemia, obesity, and smoking as additional risk factors for the development of CKD in diabetes.[4] As discussed in the text that follows, proactive management of modifiable risk factors is considered a foundation of CKD management in T2D.

The pathophysiology of CKD in diabetes is complex and involves a combination of metabolic, hemodynamic, inflammatory, and fibrotic changes associated with the diabetic state.[11] These factors lead to structural and functional changes in the kidney characteristic of diabetic kidney disease.[11] Notably, overactivation of the mineralocorticoid receptor (MR) is now recognized as an important driver of inflammation and fibrosis in the kidney.[12]

Guideline-directed therapy in patients with T2D and CKD

Guideline-directed management of CKD in T2D involves a holistic approach that includes lifestyle interventions, optimized management of key modifiable risk factors (eg, lack of glycemic control, high blood pressure, elevated lipid levels), and use of therapies with evidence of cardiorenal benefit that address key pathophysiologic drivers of CKD.[1,5,13] A "4-pillars" approach for the management of CKD in patients with T2D has been proposed in the literature: treatment with a renin-angiotensin system (RAS) inhibitor, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, finerenone, and a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA), all built on a foundation of key lifestyle interventions and metabolic management.[14] This approach is supported by the current ADA/KDIGO algorithm for management of patients with diabetes and CKD, which recommends intensification of these and other therapies to reduce cardiorenal and metabolic risk. A holistic approach for improving outcomes in patients with diabetes and CKD can be accessed here: https://pubmed.ncbi.nlm.nih.gov/36189689/#&gid=article-figures&pid=figure-3-uid-2.5[5]

Lifestyle modifications and management of key modifiable risk factors

Cardiorenal risk reduction in T2D begins with implementation of healthy behaviors and optimized metabolic management.[1,5,13] ADA and KDIGO stress the importance of medical nutrition therapy (MNT) and consumption of balanced diets low in refined carbohydrates and sodium. A summary of key dietary recommendations from KDIGO is provided in **TABLE 1**.[5] Weight loss is encouraged for individuals with overweight or obesity, and these patients should avoid sedentary lifestyles by engaging in the recommended ≥150 minutes/week of moderate to intense/rigorous physical activity.[5] Optimized glycemic control (achievement of an individualized glycated hemoglobin [A1c] target ranging from 6.5% to <8.0%), treatment to a blood pressure of <130/80 mm Hg (if it can be safely attained), initiation of moderate- to high-intensity statin therapy, and smoking cessation support (if applicable) are all recommended components of a holistic cardiorenal risk reduction strategy.[5]

TABLE 1. Key dietary recommendations from KDIGO for patients with diabetes and CKD[5]

- Protein intake of 0.8 g protein/kg body weight/day for those not treated with dialysis
- Sodium intake <2 g per day
- Diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts and lower in processed meats, refined carbohydrates, and sweetened beverages

RAS INHIBITORS

Glomerular hyperfiltration occurs in up to 40% of people with T2D and has long been recognized as a driver of CKD development and progression.[11] Glomerular hyperfiltration is driven in part by systemic hypertension and obesity, thus highlighting the importance of weight and blood pressure management in the setting of T2D and CKD.[11] RAS inhibitors directly target glomerular hyperfiltration and were the first agents approved to slow CKD progression in diabetes.[15] ADA and KDIGO recommend treatment with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) at the highest tolerated dose in patients with diabetes who have hypertension and albuminuria.[5] Additionally, ADA and KDIGO note that patients with albuminuria rarely have normal blood pressure and that the evidence for treatment with RAS inhibitors in such patients is less strong.[5] RAS inhibitor therapy does increase risk for hyperkalemia and, therefore, electrolyte monitoring is recommended. Despite being a standard of care for more than 3 decades, RAS inhibitors unfortunately remain underutilized in patients with T2D and CKD.[16] Even in patients receiving RAS inhibitor therapy, considerable residual kidney and cardiovascular risk remain due to the complex pathophysiology of diabetic kidney disease.[17]

SGLT2 INHIBITORS

SGLT2 inhibitors, originally developed and approved as glucose-lowering agents for the treatment of T2D, are now recognized as standard of care cardiorenal risk-reducing medications.[18] Large cardiovascular outcome trials (CVOTs) with SGLT2 inhibitors initially established the cardiovascular benefits of several agents within the class, in addition to reporting secondary outcome findings suggesting CKD and heart failure benefits with treatment.[19-21] Dedicated kidney outcome trials were subsequently conducted with canagliflozin, dapagliflozin, and empagliflozin.[22-24] All 3 kidney outcome trials were stopped early during planned interim analyses because of overwhelming efficacy for the primary kidney composite outcome. Notably, the benefits of SGLT2 inhibitor therapy reported in these trials were realized on top of background optimized RAS inhibitor therapy.[22-24] A recently published systematic review and meta-analysis of large placebo-controlled SGLT2 inhibitor trials reported a 37% risk reduction for kidney disease progression in participants randomized to SGLT2 inhibitor therapy (relative risk [RR] 0.63; 95% CI: 0.58-0.69).[25]

SGLT2 inhibitors are believed to mitigate cardiorenal risk through several mechanisms.[18] SGLT2 inhibitors improve multiple metabolic risk factors by lowering glucose levels, weight, and blood pressure. Because the cardiorenal benefits of SGLT2 inhibition are preserved in patients with low eGFR (in whom the glucose-lowering, weight loss, and blood pressure-lowering effects of SGLT2 inhibitors are negligible), the kidney and heart benefits of SGLT2 inhibitor therapy are not dependent solely on their beneficial effects on traditional metabolic risk factors.[18] Indeed, SGLT2 inhibition normalizes glomerular hemodynamics through restoration of tubuloglomerular feedback in the kidney, and evolving evidence suggests SGLT2 inhibitors may also have anti-inflammatory and antifibrotic effects in the kidney and heart.[18]

Based on the established cardiorenal benefits of SGLT2 inhibitors in patients with T2D and CKD, they are considered first-line therapy in combination with metformin.[5] Specifically, ADA and KDIGO recommend use of an SGLT2 inhibitor with proven cardiorenal benefit in patients with an eGFR ≥20 mL/min/1.73 m^2, which is recommended for continuation (if tolerated) until initiation of dialysis or transplant.[5] In addition to being contraindicated in patients on dialysis, SGLT2 inhibitors do not carry indications for use in people with type 1 diabetes (T1D) because of an increased risk for ketoacidosis.[5] The most common adverse effect of SGLT2 inhibitor therapy is female genital mycotic infections. It is recommended that patients be counseled about the importance of hygiene and keeping the genital area clean and dry to minimize risk.[5]

GLP-1 RAs

ADA and KDIGO preferentially recommend use of a long-acting GLP-1 RA with proven cardiovascular benefit in patients with T2D and CKD who do not achieve their individualized glycemic targets despite recommended first-line treatment with metformin plus an SGLT2 inhibitor, or in patients unable to take these drugs.[5] This recommendation is supported by the preserved glucose-lowering efficacy of long-acting GLP-1 RAs in advanced CKD, their established cardiovascular benefits, and preliminary evidence of kidney benefit from secondary CVOTs with liraglutide, dulaglutide, and injectable semaglutide.[26] The most common adverse effects with GLP-1 RA therapy are nausea and vomiting, which can be minimized with careful dose titration.[5] Long-acting GLP-1 RAs are not recommended for use in patients at risk for thyroid C-cell tumors (eg, multiple endocrine neoplasia) or in people with a history of pancreatic cancer because of the theoretical risks extrapolated from preclinical trials.[5] GLP-1 RAs should also be used with caution in people with a history of pancreatitis.[5] While the kidney benefits of agents from the GLP-1 RA class are less well established when compared with RAS inhibitors, SGLT2 inhibitors, and finerenone (discussed later), an ongoing dedicated kidney outcomes trial with injectable semaglutide in patients with T2D and CKD is specifically testing the impact of GLP-1 RA therapy on CKD progression.[27] The trial is expected to be completed in 2024.[27]

MRAs

As previously noted, overstimulation of the MR promotes inflammation and fibrosis in the kidney and thus has emerged as an important therapeutic target in patients with T2D and CKD.[12] Indeed, use of MRAs alone or as an add-on to RAS inhibitor therapy has been associated with antiproteinuric effects in patients with CKD.[28] Use of traditional steroidal MRAs (eg, spironolactone, eplerenone) in the setting of T2D and CKD has been limited, however, because of concerns about treatment-related hyperkalemia, GFR decline, and antiandrogenic side effects (eg, gynecomastia).[12,29]

Unlike traditional steroidal MRAs that have not demonstrated cardiorenal benefits in patients with T2D and CKD, the novel nonsteroidal MRA finerenone has recently emerged as a guideline-directed therapy in this population.[5] Finerenone was approved by the US Food and Drug Administration (FDA) in 2021 specifically to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure in adults with T2D and CKD.[30] Finerenone uniquely binds to the MR, acting as a bulky, passive antagonist, and has unique pharmacokinetic and pharmacodynamic properties that likely account for its unique clinical effects when compared to steroidal MRAs (**TABLE 2**).[30-34] Two large outcome trials supported the approval

TABLE 2. Comparison and contrast of mineralocorticoid receptor antagonists (MRAs)[30-34]

Agent	MRA type[a]	Pharmacokinetics	Potency/ selectivity	Key adverse effects[b]	FDA-approved indications
Spironolactone	Steroidal	• Prodrug • Half-life: 1.4 h • Multiple active metabolites with long half-lives	Potent/unselective	• Hyperkalemia • Hypotension • Electrolyte and metabolic abnormalities • Gynecomastia	• Hypertension • HFrEF • Edema • Primary hyperaldosteronism
Eplerenone	Steroidal	• Half-life: 4-6 h • No active metabolites	Less potent/more selective than spironolactone	• Hyperkalemia • Dizziness • Electrolyte abnormalities	• Hypertension • HFrEF post-MI
Finerenone	Nonsteroidal	• Half-life: 2-3 h • No active metabolites	Potent/selective	• Hyperkalemia[c] • Hypotension • Hyponatremia	• To improve kidney and CV outcomes in T2D and CKD

[a]Nonsteroidal MRAs are associated with fewer antiandrogenic side effects (eg, gynecomastia) when compared with steroidal MRAs.

[b]Occurring more frequently than placebo.

[c]Mean increases in potassium with treatment were less with finerenone when compared with spironolactone (0.04-0.30 vs 0.45 mEq/L, respectively; $P < .01$) in the phase II minerAlocorticoid Receptor Antagonist Tolerability Study (ARTS).

Abbreviations: CV, cardiovascular; h, hours; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction.

of finerenone to improve cardiorenal outcomes in patients with T2D and CKD.[35,36] In the FIDELIO-DKD trial, finerenone treatment was associated with a reduced risk for the primary composite outcome that included progression to kidney failure, sustained eGFR decline of ≥40% from baseline, or death from kidney-related causes when compared with placebo (hazard ratio [HR]: 0.82; 95% CI: 0.73-0.93; $P = .001$).[35] The primary outcome in the FIGARO-DKD trial was a cardiovascular composite outcome that included nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or cardiovascular-related death.[36] When compared with placebo, finerenone treatment resulted in a 13% risk reduction for the primary outcome (HR: 0.87; 95% CI: 0.76-0.98; $P = .03$).[36] As was true for kidney outcomes trials with agents from the SGLT2 inhibitor class, these benefits were observed on top of maximum tolerated background RAS inhibitor therapy.[35,36] In consideration of these data, ADA and KDIGO recommend finerenone for patients with T2D, an eGFR ≥25 mL/min/1.73 m^2, normal serum potassium concentration, and albuminuria (albumin-creatinine ratio [ACR] ≥30 mg/g) despite treatment with a maximum tolerated dose of RAS inhibitor.[5] Key finerenone product information is summarized in **TABLE 3**.[30]

CONCLUSION

Recent advancements in the management of CKD in T2D now offer clinicians and patients additional tools to slow kidney disease progression and mitigate cardiovascular risk. Use of ancillary medications to further mitigate risk, such as statins, antiplatelet agents, and additional therapies to manage comorbidities and other CKD complications (eg, anemia, metabolic bone disease, metabolic acidosis), is also crucial to the holistic care of patients with T2D and CKD. Primary care clinicians will play a critical role in addressing current gaps in patient care through improved screening and identification of CKD and early optimization of guideline-directed therapies. ●

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TABLE 3. Key finerenone product information[29]

Indication		To reduce the risk of sustained eGFR decline, ESKD, CV death, nonfatal MI, and hospitalization for HF in adult patients with CKD associated with T2D
Availability		• 10-mg tablets • 20-mg tablets
Recommended dosing	**Starting dose**[a]	• eGFR ≥60 mL/min/1.73 m^2: 20 mg once daily • eGFR ≥25 to <60 mL/min/1.73 m^2: 10 mg once daily • eGFR <25 mL/min/1.73 m^2: Initiation not recommended
	Dose adjustments	If current dose is 10 mg once daily • Serum potassium ≤4.8 mEq/L: Increase dose to 20 mg once daily[b] • Serum potassium >4.8 to 5.5 mEq/L: Maintain at 10 mg once daily • Serum potassium >5.5 mEq/L: Hold finerenone; consider restarting at 10 mg daily once serum potassium ≤5.0 mEq/L If current dose is 20 mg once daily • Serum potassium ≤4.8 mEq/L: Maintain at 20 mg once daily • Serum potassium >4.8 to 5.5 mEq/L: Maintain at 20 mg once daily • Serum potassium >5.5 mEq/L: Hold finerenone; restart at 10 mg daily once serum potassium ≤5.0 mEq/L
Common adverse effects[c]		• Hyperkalemia • Hypotension • Hyponatremia
Contraindications		• Concomitant use with strong CYP3A4 inhibitors (eg, itraconazole) • Patients with adrenal insufficiency

[a]Finerenone not recommended for initiation if serum potassium >5.0 mEq/L.

[b]If eGFR has decreased by >30% compared with previous measurement, maintain at 10 mg once daily.

[c]Occurring in ≥1% of participants and more frequently than placebo.

Abbreviations: ESKD, end-stage kidney disease.

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Optimized Management of Cardio-Renal-Metabolic (CRM) Conditions in Patients With T2D

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Describe cardio-renal-metabolic (CRM) conditions and their impact on health and patient-centered outcomes.
- Recognize current gaps in screening, risk factor management, and utilization of guideline-directed therapies in patients with CRM conditions.
- Select appropriate guideline-directed therapies for patients with type 2 diabetes, atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease based on current guidelines and clinical evidence.
- Recognize the importance of multidisciplinary care when managing patients with CRM conditions.

KEY TAKEAWAYS

- People with type 2 diabetes (T2D) are at increased risk for cardiovascular and kidney comorbidities, which dramatically increase morbidity and mortality risk.
- Chronic kidney disease (CKD) is largely underrecognized and undertreated in the primary care setting due to suboptimal screening and lack of awareness by both clinicians and patients.
- Agents from the sodium-glucose cotransporter-2 (SGLT2) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, and mineralocorticoid receptor antagonist (MRA) classes are now considered standard-of-care therapies to mitigate risk in patients with cardio-renal-metabolic (CRM) conditions.
- Primary care providers play an important role in multidisciplinary CRM management teams to address key barriers to optimized care of patients with CRM conditions.

TARGET AUDIENCE

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

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INTRODUCTION

CASE SCENARIO

AW is a 65-year-old cisgender female presenting to the primary care clinic to establish care after moving to the area to be closer to family. AW's medical records indicate a history of type 2 diabetes (T2D), hypertension, dyslipidemia, obesity, and myocardial infarction. AW reports taking all of her medications as prescribed but can't remember the last time she saw a healthcare provider.

Vitals: Body mass index: 34 kg/m^2, blood pressure: 138/90 mm Hg (average of 3 seated measurements in clinic today)

Current Medications: Metformin 1000 mg twice daily, linagliptin 5 mg once daily, lisinopril 40 mg once daily, atorvastatin 40 mg once daily, aspirin 81 mg once daily

Key Lab Values: Glycated hemoglobin (A1c): 7.5%; estimated glomerular filtration rate (eGFR): 52 mL/min/1.73 m^2; urinary albumin-to-creatinine ratio (UACR): 220 mg/g; lipid panel and electrolytes all within normal ranges. Medical records indicate an eGFR of 58 mL/min/1.73 m^2 measured 13 months prior.

This patient has T2D, established atherosclerotic cardiovascular disease (ASCVD), and, as identified via recommended screening of eGFR and UACR, chronic kidney disease (CKD). AW represents a relatively common patient encountered in the primary care setting: a patient with T2D and multiple cardiorenal comorbidities. It is long established that cardiovascular and kidney disease are important diabetes-related complications and a highly interdependent relationship exists between heart and kidney health.[1,2] Optimized metabolic risk factor management to prevent and/or delay progression of heart and kidney disease in patients with diabetes is stressed within major guidelines due to the substantial increased risk for morbidity, decreased quality of life, and premature mortality observed in patients with cardiorenal comorbidities.[1]

Fortunately for patients with cardio-renal-metabolic (CRM) conditions (and the clinicians caring for them), a number of evidence-based therapies are now available to target key cardiorenal risk factors and to improve ASCVD, CKD, and/or heart failure (HF) outcomes.[1] While recent advancements provide options for patients with CRM conditions, important gaps in screening, treatment, and optimized use of guideline-directed therapies persist.[3] Indeed, screening and identification rates of CKD in people with diabetes are low, with estimates suggesting that less than 50% of patients with T2D receive recommended annual albuminuria screening in the primary care setting.[4] Evidence further illustrates that improvements are needed in management of traditional diabetes risk factors. Although promoting smoking cessation and optimization of glucose, blood pressure, and lipid management have been foundational components of diabetes management for decades, current estimates from the Centers for Disease Control and Prevention (CDC) indicate that less than 20% of adults achieve all general A1c, blood pressure, cholesterol, and smoking cessation goals.[5]

While optimization of glycemic control is a central component of diabetes management, some glucose-lowering agents are now recognized for their robust heart and kidney benefits. Specifically, major guidelines recommend agents from the sodium-glucose cotransporter-2 (SGLT2) inhibitor and glucagon-like peptide-1 (GLP-1) receptor agonist classes to reduce cardiorenal risk.[1,6-8] Many patients who could benefit from use of these agents, however, do not receive them. For example, recent data suggest that less than 8% of older adults with diabetes and CKD were receiving SGLT2 inhibitors in 2020, and fewer than 14% of people with diabetes and cardiovascular disease received a GLP-1 receptor agonist between 2018 and 2020.[9]

Suboptimal use of evidence-based therapies in T2D is not new. Underutilization of renin-angiotensin system (RAS) inhibitors continues to persist in patients with T2D and CKD despite being a standard of care for more than 3 decades.[10] Factors contributing to these and other gaps in CRM care are numerous and often complicated by clinician time constraints, patient preferences and priorities, and/or access/cost limitations.[3] Indeed, cost is a notable barrier to use of newer agents—including SGLT2 inhibitors and GLP-1 receptor agonists. According to cost information provided in the American Diabetes Association's (ADA's) 2023 Standards of Care in Diabetes, the monthly average wholesale price (AWP) for SGLT2 inhibitors and GLP-1 receptor agonists ranges from $390 to $685 and $814 to $1278, respectively, depending on the agent selected.[1] Although AWP prices do not account for insurance, discounts, rebates, or other price adjustments that impact the actual cost incurred by the patient, patient cost share for these newer agents represents an important barrier often necessitating cost-reduction strategies to improve access.[1]

Guidelines from organizations including, but not limited to, the ADA, Kidney Disease: Improving Global Outcomes (KDIGO), American Heart Association (AHA), American College of Cardiology (ACC), and the Heart Failure Society of America (HFSA) stress the importance of multidisciplinary approaches to CRM care, with primary care clinicians playing a critical role within the multidisciplinary team to improving outcomes by optimizing recommended screening, risk factor management, and initiation of agents with proven cardiorenal benefit (**TABLE 1**).[1,6,7]

TABLE 1. Recommendations for multidisciplinary/team-based approaches to optimize management of CRM conditions[1,6,7]

Organization/guideline	Recommendations
ADA 2023 Standards of Care in Diabetes	• People with diabetes can benefit from a coordinated multidisciplinary team that may include and is not limited to diabetes care and education specialists (DCESs), primary care and specialty clinicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals.
KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease	• Policymakers and institutional decision-makers should implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD.
AHA/ACC/HFSA 2022 Guideline for the Management of Heart Failure	• Patients with HF should receive care from multidisciplinary teams to facilitate the implementation of guideline-directed medical therapy, address potential barriers to self-care, reduce the risk of subsequent rehospitalization for HF, and improve survival. • Patients with HF should receive specific education and support to facilitate HF self-care in a multidisciplinary manner.

EVIDENCE REVIEW: GUIDELINE-DIRECTED THERAPIES TO IMPROVE OUTCOMES FOR CRM CONDITIONS

A discussion of evidence supporting use of current guideline-directed therapies to improve ASCVD, CKD, and HF outcomes follows.

Atherosclerotic cardiovascular disease (ASCVD)

Owing in part to the 2008 US Food and Drug Administration (FDA) guidance for industry requiring manufacturers of new glucose-lowering medications to demonstrate cardiovascular safety through conduct of large cardiovascular outcome trials (CVOTs), treatment with most SGLT2 inhibitors and GLP-1 receptor agonists on the US market have been evaluated in large CVOTs for risk of major adverse cardiovascular events (MACE).[11]

SGLT2 inhibitors

The EMPA-REG OUTCOME trial with empagliflozin was the first CVOT published, not only establishing cardiovascular safety but also demonstrating a 14% relative risk reduction in 3-point MACE with empagliflozin treatment (hazard ratio [HR]: 0.86; 95% confidence interval [CI]: 0.74-0.99) in people with T2D and established ASCVD.[12] CVOTs with canagliflozin and dapagliflozin shortly thereafter reported benefits of SGLT2 inhibition on MACE and on a composite of cardiovascular death or HF hospitalization, respectively.[13,14] The VERTIS CV outcome trial with ertugliflozin, however, did not report a benefit of treatment on the primary MACE outcome (HR: 0.97; 95% CI: 0.85-1.11) but did report benefit on a key secondary outcome of HF hospitalization.[15] These findings resulted in the FDA granting expanded cardiovascular indications for empagliflozin, canagliflozin, and dapagliflozin. Importantly, these CVOTs also reported consistent benefits on secondary kidney and HF outcomes, thus supporting the need for subsequent dedicated kidney and HF outcome trials.

GLP-1 receptor agonists

All GLP-1 receptor agonists evaluated in large CVOTs have demonstrated cardiovascular safety.[11] However, a recent meta-analysis of 8 GLP-1 CVOTs, reported a statistically significant class benefit of 14% reduction in MACE (HR: 0.86; 95% CI: 0.79-0.94; $P = 0.006$).[16] GLP-1 receptor agonists that have demonstrated MACE benefit within individual CVOTs and have subsequently received expanded ASCVD indications include liraglutide, injectable semaglutide, and dulaglutide.[11,17-19]

Chronic kidney disease (CKD)

SGLT2 inhibitors

In follow-up to consistently positive secondary kidney outcomes observed in CVOTs, 3 SGLT2 inhibitors available in the US have been studied prospectively in dedicated kidney outcome trials (**TABLE 2**).[20-22] All 3 trials were stopped early during planned interim analyses due to overwhelming benefit, with median durations of follow-up ranging from 2.0 to 2.6 years. Of note, all 3 trials evaluated SGLT2 inhibitor therapy in patients with CKD as add-on to background optimized RAS inhibitor therapy.[20-22] While the CREDENCE trial with canagliflozin specifically enrolled participants with T2D and CKD,[20] the DAPA-CKD and EMPA-KIDNEY trials with dapagliflozin and empagliflozin, respectively, included patients with CKD with and without T2D.[21,22] Notably, the kidney benefits observed within these trials were consistent among patients with and without diabetes and without regard to baseline eGFR. Observed benefits in both people without T2D and in those with relatively low eGFRs indicate that the cardiorenal benefits of SGLT2 inhibitors are not entirely attributable to their beneficial effects on traditional metabolic risk factors (eg, glycemia).[23] Indeed, multiple putative mechanisms of cardiorenal benefit have been proposed with SGLT2 inhibition, highlighting the interrelatedness of heart and kidney disease pathophysiology. An illustra-

TABLE 2. Summary of key SGLT2 inhibitor kidney outcome trials[20-22]

Trial	CREDENCE (n = 4401)	DAPA-CKD (n = 4304)	EMPA-KIDNEY (n = 6609)
Treatment	Canagliflozin vs Placebo	Dapagliflozin vs Placebo	Empagliflozin vs Placebo
Key inclusion criteria	• T2D • A1c 6.5 to 12.0% • eGFR 30 to <90 mL/min/1.73 m^2 • UACR >300 to 5000 mg/g • Treated with RAS inhibitor	• eGFR 25 to 75 mL/min/1.73 m^2 • UACR of 200 to 5000 mg/g • Treated with RAS inhibitor	• eGFR 20 to <45 mL/min/1.73 m^2 OR eGFR ≤45 to <90 mL/min/1.73 m^2 with UACR ≥200 mg/g • Treated with RAS inhibitor
Baseline diagnosis of T2D (%)	100	67	46
Median follow-up (years)	2.6	2.4	2.0
Primary outcome			
Primary outcome; HR (95% CI)	**ESKD, doubling of SCr, or renal or CV death** 0.70 (0.59-0.82)	**≥50% decline in eGFR, ESKD, or renal or CV death** 0.61 (0.51-0.72)	**≥40% decline in eGFR, sustained decrease in eGFR to <10 mL/min/1.73 m^2, ESKD, or renal or CV death** 0.72 (0.64-0.82)

Abbreviations: CV, cardiovascular; ESKD, end-stage kidney disease; SCr, serum creatinine.

tion of SGLT2 inhibitor-mediated kidney and heart protection can be accessed here: https://pubmed.ncbi.nlm.nih.gov/36506243/#&gid=article-figures&pid=figure-4-uid-3.[23]

Finerenone

Finerenone is a nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) FDA approved to improve cardiorenal outcomes in people with CKD associated with T2D.[24] The approval of finerenone was based primarily on findings from 2 large outcome trials studying finerenone as add-on to optimized RAS inhibitor therapy: FIDELIO-DKD and FIGARO-DKD.[25,26] In the FIDELIO-DKD trial, finerenone treatment reduced the risk for its primary kidney disease composite outcome by 18% (HR: 0.82; 95% CI: 0.73-0.93; P = .001).[25] The complimentary FIGARO-DKD trial reported a 13% risk reduction for its primary cardiovascular outcome (HR: 0.87; 95% CI: 0.76-0.98; P = .03).[26]

GLP-1 receptor agonists

CVOTs with liraglutide, injectable semaglutide, and dulaglutide included secondary outcomes for "worsening nephropathy."[17-19] While the definitions utilized within the 3 trials varied, all 3 studies reported a benefit on this exploratory outcome, thus suggesting a potential kidney benefit with GLP-1 receptor agonist therapy. Indeed, multiple potential mechanisms by which GLP-1 receptor agonists may prevent CKD progression have been proposed, including improvements in traditional metabolic risk factors and reductions in kidney inflammation, oxidative stress, and fibrosis.[27] Unlike SGLT2 inhibitors, primary evidence of kidney benefit with GLP-1 receptor agonists is not currently available. The ongoing FLOW trial (NCT03819153), however, is a dedicated kidney outcome trial with injectable semaglutide; this trial is expected to be completed in 2024, which will help further define the role of GLP-1 receptor agonists in the setting of CKD.

Heart failure

Four dedicated HF outcome trials have been completed to date with dapagliflozin and empagliflozin (**TABLE 3**).[28-31] Collectively, these trials included patients ranging from those with reduced ejection fraction HF (HFrEF) to preserved ejection fraction HF (HFpEF). The DAPA-HF trial with dapagliflozin was the first major SGLT2 inhibitor HF outcome trial published, which reported a 26% risk reduction for worsening HF or cardiovascular-related death (HR: 0.74; 95% CI: 0.65-0.85) in participants with HFrEF.[28] The DELIVER trial subsequently reported an 18% risk reduction for worsening HF or cardiovascular death with dapagliflozin in patients with mildly reduced ejection fraction HF (HFmrEF) or HFpEF.[29] The EMPEROR-Reduced and EMPEROR-Preserved trials with empagliflozin similarly reported benefits in patients with HFrEF and HFpEF, respectively (**TABLE 3**).[30,31] Importantly, these trials enrolled patients with HF with or without diabetes, with overall benefits observed regardless of diabetes status or ejection fraction.

Brief review: Guideline recommendations for management of CRM conditions in T2D

Based on the outcome trial evidence just reviewed, multiple

TABLE 3. Summary of key SGLT2 inhibitor heart failure outcome trials[28-31]

	DAPA-HF (n = 4744)	DELIVER (n = 6263)	EMPEROR-Reduced (n = 3730)	EMPEROR-Preserved (n = 5988)
Treatment	Dapagliflozin vs Placebo	Dapagliflozin vs Placebo	Empagliflozin vs Placebo	Empagliflozin vs Placebo
Key inclusion criteria	• NYHA class II, III, or IV HF • EF ≤ 40%	• Stabilized HF • EF > 40%	• NYHA class II, III, or IV HF • EF ≤ 40%	• NYHA class II, III, or IV HF • EF > 40%
Baseline diagnosis of T2D (%)	42	45	50	49
Median follow-up (years)	1.5	2.3	1.3	2.2
Primary outcome				
Primary outcome; HR (95% CI)	**Worsening HF or CV death** 0.74 (0.65-0.85)	**Worsening HF, CV death, or urgent visit for HF** 0.82 (0.73-0.92)	**CV death or HF hospitalization** 0.75 (0.65-0.86)	**CV death or HF hospitalization** 0.79 (0.69-0.90)
Key secondary outcome				
HF hospitalization; HR (95% CI)	0.70 (0.59-0.83)	0.77 (0.67-0.89)	0.69 (0.59-0.81)	0.71 (0.60-0.83)

Abbreviations: CV, cardiovascular; NYHA, New York Heart Association.

guidelines now recommend SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone as standard-of-care therapies to mitigate cardiorenal risk.[1,6-8] Contemporary recommendations offered by various organizations largely align, with use of these medications recommended without regard to A1c or the need for additional glucose lowering. Importantly, guidelines increasingly stress the importance of multidisciplinary CRM management teams to meet the numerous management and education needs of these patients by leveraging the strengths and abilities of all physician and non-physician team members.

2023 ADA Standards of Care in Diabetes

A primary goal stated within the 2023 ADA Standards of Care is to achieve cardiorenal risk reduction in high-risk patients with T2D. To achieve this goal, the ADA offers the following key recommendations[1]:

- **Patients with ASCVD or indicators of high risk:** Initiation of an SGLT2 inhibitor or GLP-1 receptor agonist with proven cardiovascular benefit is recommended. If additional glucose lowering is required after initiation of an agent from one of these classes, the ADA recommends considering the addition of an agent from the other class.
- **Patients with HF:** Initiate an SGLT2 inhibitor with proven HF benefit.
- **Patients with CKD:** It is preferably recommended to initiate an SGLT2 inhibitor with primary evidence of reducing CKD progression in patients with an eGFR ≥20 mL/min/1.73 m^2. A GLP-1 receptor agonist with proven cardiovascular benefit is recommended in patients unable to take an SGLT2 inhibitor. The ns-MRA finerenone is additionally recommended for consideration in patients with T2D, CKD, and albuminuria to reduce CKD progression and cardiovascular events.

2022 KDIGO Guideline for Diabetes Management in CKD

Recommendations from KDIGO largely align with recommendations from the ADA for patients with T2D and CKD.[6] First-line SGLT2 inhibitor and RAS inhibitor therapy are recommended in patients with T2D and CKD. SGLT2 inhibitor initiation is recommended in patients with an eGFR ≥20 mL/min/1.73 m^2, to be continued until kidney transplant or initiation of dialysis, provided the SGLT2 inhibitor continues to be well tolerated. For patients requiring additional glucose lowering to meet individualized glycemic targets, a long-acting GLP-1 receptor agonist is preferentially recommended based on established cardiovascular benefits, preserved glucose-lowering effect at low eGFR, and potential benefits of GLP-1 receptor agonist therapy on CKD progression. KDIGO also recommends finerenone as an option in patients with T2D and CKD with persistent albuminuria (≥30 mg/g) despite RAS inhibitor therapy.[6]

2022 AHA/ACC/HFSA Guideline for the Management of HF

Based on the robust benefits observed in dedicated HF outcome trials (**TABLE 3**), the 2022 AHA/ACC/HFSA guideline for the management of HF includes several recommenda-

tions regarding use of SGLT2 inhibitors in patients with or at risk for HF.[7] The guideline recommends SGLT2 inhibitor use in patients with T2D with either established cardiovascular disease or high cardiovascular risk to prevent HF hospitalization. In individuals with established HF, the guideline provides the following additional recommendations[7]:

- **Symptomatic chronic HFrEF:** SGLT2 inhibitor therapy is recommended to reduce HF hospitalization and cardiovascular mortality, irrespective of the presence of T2D.
- **HFmrEF and HFpEF:** SGLT2 inhibitor therapy can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.

2022 Diabetes Cardiorenal and Metabolism (DCRM) Multispecialty Practice Recommendations

The 2022 DCRM Multispecialty Practice Recommendations provide clinicians with a succinct set of recommendations and algorithms to guide treatment of CRM conditions.[8] The figure found here: https://pubmed.ncbi.nlm.nih.gov/34922811/ provides a summary of recommendations for use of glucose-lowering agents based on comorbidities in patients with T2D to reduce cardiorenal risk. The recommendations presented within the algorithm largely align with key recommendations from other major guidelines that address CRM management.

CASE SCENARIO: MANAGEMENT PLAN

Returning to the patient AW, through recommended screening she is now recognized as having CKD in addition to T2D and established ASCVD. Based on her past medical history, physical, and laboratory findings, she is at high risk for kidney disease progression, cardiovascular events, and cardiovascular-related mortality. AW is an ideal candidate for initiation of additional agents to mitigate her cardiorenal risk. To work toward optimal management of her CRM conditions, initial management goals include (1) improved A1c and blood pressure management to slow CKD progression, (2) initiation of SGLT2 inhibitor therapy to slow CKD progression and mitigate cardiovascular risk, and (3) referral for diabetes self-management education to reinforce a healthy lifestyle and to receive education regarding her CKD diagnosis and management options. After addressing these initial goals, her healthcare providers can consider additional interventions to reduce cardiorenal risk, including addition of a GLP-1 receptor agonist and/or finerenone as informed by patient preferences, priorities, and resources.

CONCLUSION

Patients with T2D and cardiorenal comorbidities are frequently encountered in the primary care setting. Findings from recent cardiovascular, kidney, and HF outcome trials have quickly changed the standard of care for patients with CRM conditions. Current guidelines stress the importance of screening patients for CRM conditions (eg, CKD) and promptly initiating guideline-directed therapies. Primary care providers will continue to play a critical role within the multidisciplinary CRM management team to optimize patient-centered care and outcomes. ●

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Reducing Cardiopulmonary Risk and Exacerbations in COPD

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KEY TAKEAWAYS

- New updates in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 report include major changes to initial disease assessment and pharmacologic therapy, highlighting the clinical relevance of exacerbations.
- The updated GOLD 2023 algorithms offer a shorter path to consideration of triple therapy, including both initial and follow-up treatment.
- Most mild- or moderate-severity chronic obstructive pulmonary disease (COPD) exacerbations can be successfully managed in outpatient settings; primary care clinicians have many opportunities to identify, diagnose, and treat patients with COPD earlier to reduce lung damage and disease progression.
- COPD and cardiovascular disease share common mechanisms and risk factors that influence COPD management.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is among the top 3 causes of mortality worldwide, with high economic and social costs.[1,2] Despite continual advancements in the diagnosis and management of COPD, the global COPD burden continues to increase.[3] However, disease prevalence in the United States has remained fairly steady in the past decade. A slight decrease in overall age-adjusted prevalence may be due to continued failure to recognize early COPD as well as enhanced awareness and decreased exposure to COPD risk factors such as tobacco smoke and environmental factors.[3,4]

COPD is a preventable and treatable disease, and implementing best practices can improve outcomes.[5] The substantial ongoing burden of COPD demands greater implementation of evidence-based therapies and prompts a need for continual updates and improvement in COPD management. This article highlights key practice updates recommended in the GOLD 2023 report, focusing on reducing cardiopulmonary risk and managing exacerbations in COPD.

Updates in the GOLD 2023 report

The GOLD 2023 report provided an updated definition of COPD (**BOX 1**).[3,6] This definition emphasizes the progressive nature and varied presentation of COPD, compared to prior definitions. Awareness of COPD variability and progression may help clinicians reduce diagnostic delays and incorporate individualized therapeutic strategies.[6]

BOX 1. GOLD 2023 COPD definition[3,6]

"COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airway (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction."

The definition of a COPD exacerbation has also been updated in the GOLD 2023 report (**BOX 2**).[3] Adjustments to the previous "ABCD tool," now called the "ABE tool," where groups C and D are now combined into group E, were also made.[3] Additionally, the role of eosinophils in determining the favorability of treatment with inhaled corticosteroids (ICS) has been further clarified.[3] These updates are discussed in more detail below.

BOX 2. GOLD 2023 COPD exacerbation definition[3]

"An exacerbation of COPD is defined as an event characterized by dyspnea and/or cough and sputum that worsen over <14 days. Exacerbations of COPD are often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insults to the lungs."

The primary care clinician's role

Primary care clinicians (PCCs) manage most patients with COPD and play a pivotal role in diagnosing and treating COPD.[7] Unfortunately, individualized recommendation-concordant COPD management in the PCC setting is not always accomplished.[5] When not managed to goal, COPD can lead to exacerbations associated with disease progression and lung and cardiovascular system damage.[3,8]

COPD PHYSIOLOGY: IMPACT ON CARDIOPULMONARY RISK

COPD and cardiovascular disease (CVD) are frequently associated with the pathophysiology and treatment of each being interrelated and both affecting overall health outcomes.[9-14] COPD is an independent risk factor for CVD, with the presence of COPD increasing the odds of having CVD by a factor of 2.7 compared with individuals without COPD.[15] Patients with comorbid COPD and CVD have worse quality of life, reduced exercise tolerance, increased dyspnea, and increased mortality.[9] Notably, effective prevention and management of COPD exacerbations may reduce the risk of cardiovascular events.[16]

Potential pathophysiologic mechanisms for cardiopulmonary disease

While the pathophysiologic associations between COPD and CVD are not fully understood, certain mechanisms are thought to interact and influence both conditions.[9] The potential physiologic links between COPD and CVD include lung hyperinflation, systemic inflammation, and dyspnea.[9] Risk factors contributing to COPD and CVD outcomes include age, smoking, air pollution, unhealthy diet, physical inactivity, genetic background, hypertension, hyperlipidemia, diabetes mellitus, and infections.[8,11]

Co-managing COPD and CVD to improve outcomes

Patients with COPD experience worse CVD outcomes.[9] In the days following the onset of a COPD exacerbation, patients have approximately a 4-fold increased risk of myocardial infarction within 5 days and about a 3-fold increased risk of stroke within 10 days.[8,17-20] Better awareness, evaluation, and diagnosis of coexisting COPD and CVD with adequate assessment of disease severities and co-managed CVD/COPD treatment could improve outcomes for both diseases.[8,9]

Better management of CVD has demonstrated improved survival after discharge following COPD exacerbations,[21] and treatment to prevent or reduce COPD exacerbations decreases the risk of CVD events.[16] In addition to disease-specific care, the benefits of smoking cessation for both COPD and CVD should not be overlooked or minimized. Smoking cessation has been shown to improve lung function in people with COPD and reduce the risk of both COPD exacerbations and cardiovascular events.[8]

IMPORTANCE OF EXACERBATION MANAGEMENT

When COPD exacerbations do occur, their treatment remains a key component of COPD care due to the negative impacts of exacerbations on disease progression, health status, quality of life, hospitalization, and readmission.[3,22] The GOLD 2023 report emphasizes that an exacerbation is a short-term worsening of symptoms.[3]

COPD exacerbation severity has historically been determined after the event, based on which treatment was used or whether treatment was provided within, or outside of, the hospital. This approach does not help guide or determine treatment when faced with an exacerbation.[3] The in-office assessment of exacerbation severity can begin with assessing[3]:

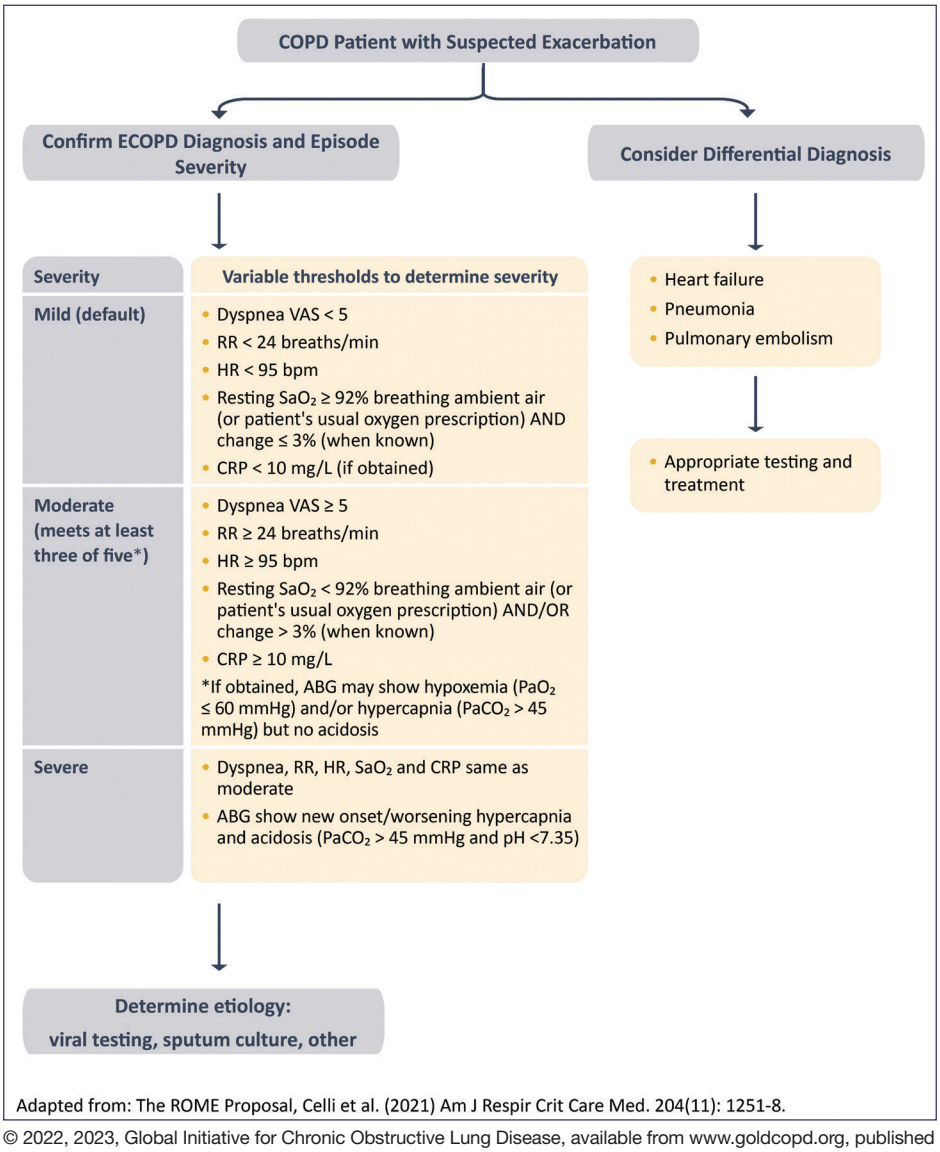
- Dyspnea intensity
  - Use a scale of 0 to 10, where 0 is "not short of breath at all" and 10 is the "worst shortness of breath you have ever experienced," to have the patient describe their dyspnea; a visual analog or simple verbal scale can be used
- Respiratory rate
- Heart rate
- Oxygen saturation level
- Rapid C-reactive protein via finger stick assessment if available

Arterial blood gases are rarely available outside of the hospital or emergency department (ED).[3] Severity is then determined based on classification using these measurements (**FIGURE 1**).[3] Differential diagnoses and assessment of co-existing problems such as heart failure, pulmonary embolism, and pneumonia should also be considered.[3]

Practical approaches for managing COPD exacerbations

Treatment must address the acute symptoms and impact of the exacerbation while considering how to prevent future exacerbations.[3,23] Patients should be educated to recognize exacerbations earlier and seek appropriate and timely treatment, which may be most easily accomplished by providing a written action plan detailing guidance on self-management of breathlessness and when to seek medical care.[3,24] An example COPD action plan can be found on the American Lung Association website (https://www.lung.org/getmedia/c7657648-a30f-4465-af92-fc762411922e/copd-action-plan.pdf.pdf). Attempting to identify exacerbation triggers may also highlight ways to limit future events.

FIGURE 1. GOLD 2023 classification of COPD exacerbation severity[3]



Adapted from: The ROME Proposal, Celli et al. (2021) Am J Respir Crit Care Med. 204(11): 1251-8.

Abbreviations: ABG, arterial blood gases; CRP, C-reactive protein; HR, heart rate; PaO_2, arterial pressure of oxygen; RR, respiratory rate; SaO_2, oxygen saturation; VAS, visual analog scale.

Most exacerbations are managed in an outpatient setting using pharmacologic therapy, but some exacerbations require hospital assessment.[3] Hospital assessment should be recommended for patients who don't respond to initial medical management and for those with severe symptoms, acute respiratory failure, severe comorbidities, lack of adequate home support, and presence of physical signs such as new peripheral edema.[3] For patients who require hospitalization, follow-up within 1 week to 10 days of discharge with an outpatient clinician helps reduce exacerbation-related readmissions.[3,25]

Outpatient therapy for COPD exacerbations may include the following[3]:

- Short-acting beta$_2$-agonists as the initial bronchodilator treatment
- Oral systemic corticosteroids for up to 5 days' duration
- Oral antibiotics for up to 5 days' duration

Hospitalization will usually include consultation with a pulmonologist for collaborative management of the exacerbation and follow-up care. When implementing short- or long-term oxygen therapy, consultation with a respiratory therapist is also helpful to educate the patient and the PCC on the appropriate device and type of oxygen.

GOLD 2023 REPORT: IMPLICATIONS FOR PRIMARY CARE

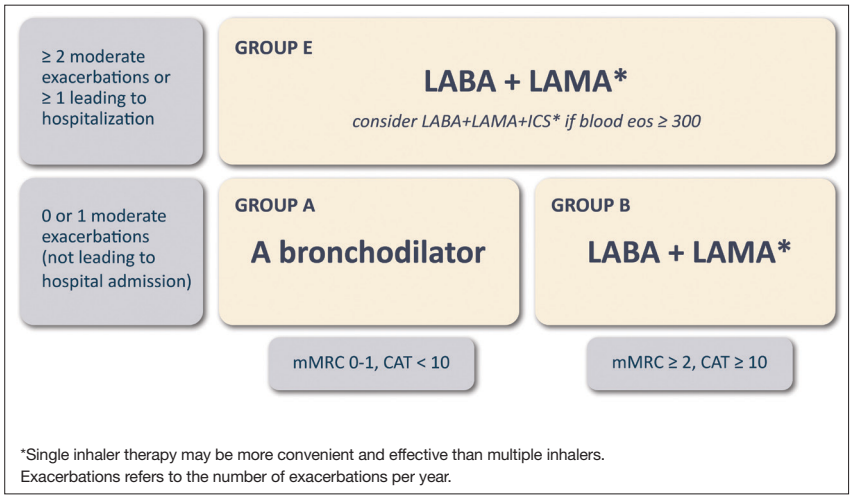
The updates in the GOLD 2023 report include significant changes in the approach to initial classification and treatment of COPD (**FIGURES 2 AND 3**). Staying abreast of these new approaches will help ensure best practices when managing COPD and preventing exacerbations.

COPD classifications for earlier stages of disease

Recent advances in understanding earlier presentations of COPD offer clinicians novel opportunities for prevention, timely diagnosis, and early intervention to preserve lung function.[26,27] It is important to note that COPD can occur in earlier adulthood due to accelerated lung function decline in childhood and adolescence and reduced peak lung function in early adulthood.[3]

Many of the newer subclassifications for COPD in the GOLD 2023 report are likely most important for research efforts because there is limited evidence for specific therapies.[3] However, PCCs often see people with these concerns. These terms include early COPD, mild COPD, young COPD, pre-COPD, and preserved ratio impaired spirometry (PRISm), described

FIGURE 2. GOLD 2023 ABE algorithm for initial pharmacologic management of COPD[3]



Abbreviations: CAT, COPD Assessment Test; eos, blood eosinophil count in cells/mcL; ICS, inhaled corticosteroids; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council dyspnea questionnaire.

Note: The mMRC is a questionnaire developed to measure breathlessness in COPD and is scored as grade 0 to grade 4, with higher grades indicating more severe breathlessness. The CAT is an 8-item questionnaire that assesses health status in patients with COPD. Scores range from 0 to 40, with higher scores indicating more symptomatic disease.

in more detail in **TABLE 1**. The current definitions of pre-COPD and PRISm are vague, can frustrate patients and healthcare professionals, and often lack utility in clinical practice because no specific therapies have been shown to alter progression.[3,28]

Opportunity for early intervention in COPD

With the recent increased emphasis on early COPD disease processes, PCCs may have opportunities to identify patients at risk for COPD earlier and incorporate prevention, early diagnosis, and prompt pharmacologic treatment.[7,29,30] Risk factors that can predict the development of COPD include prematurity, poorly controlled asthma, recurrent lung infections, and heavy smoking beginning at an early age.[3] Although there is no current standard for early screening in COPD, PCCs can reduce diagnostic and treatment delays by identifying people with these risk factors and symptoms and managing both ongoing risk factors and symptoms earlier in the disease process.

Treatment selection in COPD

The goals of pharmacologic treatment in COPD include relieving symptoms, reducing the risk for and severity of exacerbations, improving exercise tolerance, health status, and quality of life, and potentially prolonging survival.[3] The new initial pharmacologic treatment algorithm in the GOLD 2023 report emphasizes the clinical importance of exacerbations by making a group E, which combines groups C (low symptom burden) and D (high symptom burden)—both with frequent or severe exacerbations (**FIGURE 1**).[3]

With this approach, most patients are recommended to start with dual bronchodilator therapy. Additionally, even some maintenance therapy-naïve patients may be eligible for triple therapy as initial treatment—long-acting beta$_2$-agonist (LABA) + long-acting muscarinic antagonist (LAMA) + ICS—if they are in group E and have high eosinophil counts (≥300 cells/mcL).[3]

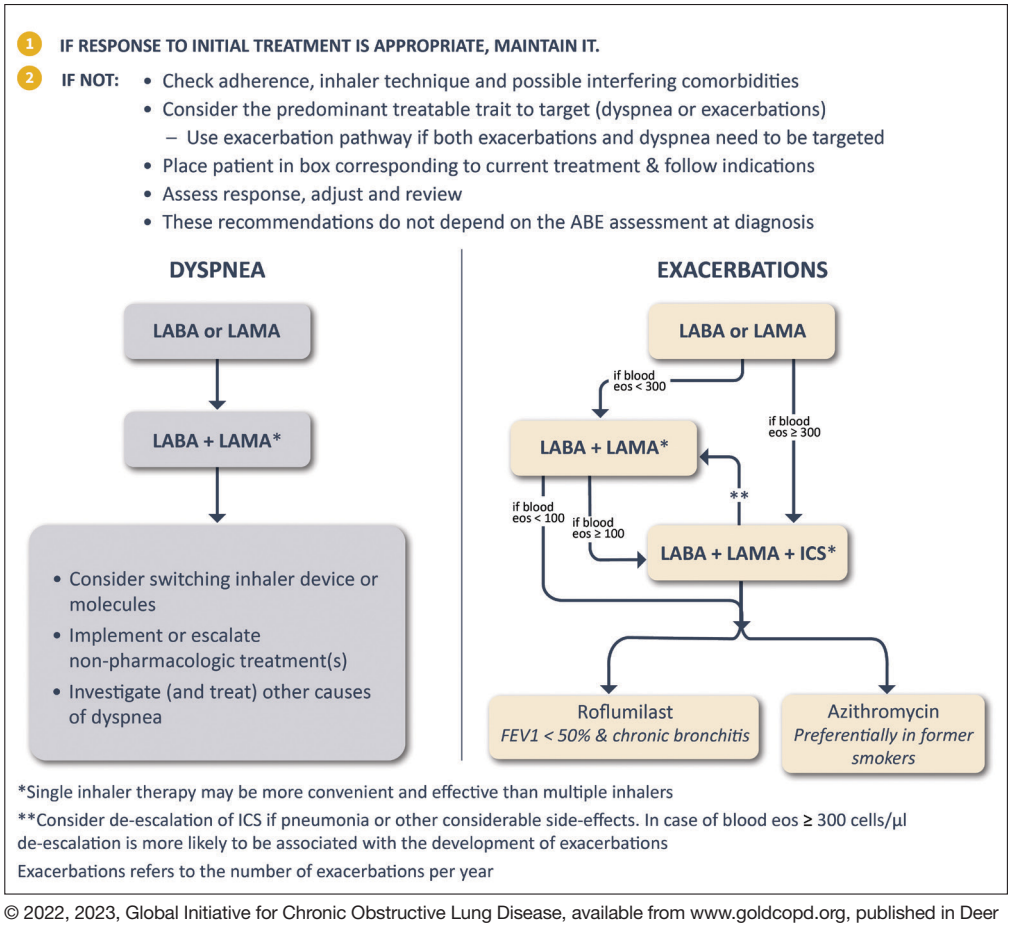
The GOLD follow-up or pharmacologic adjustment algorithm remains divided into dyspnea- or exacerbations-predominant treatable traits sections.[3] LABA+ICS has been removed completely as a recommendation for treatment of COPD, with triple therapy (LABA+LAMA+ICS) preferred for patients requiring ICS therapy as initial treatment (**FIGURE 1**) or follow-up treatment (**FIGURE 2**) of COPD.[3]

The new shorter path to triple therapy is based on studies such as PRIMUS, ETHOS, and IMPACT.[31–33] In PRIMUS, early triple therapy was associated with decreased morbidity and lower economic burden in patients who had at least 2 moderate or 1 severe COPD exacerbation in the prior year.[31] The study also found an 11% increased odds of a subsequent exacerbation with every 30-day delay of triple therapy after an exacerbation.[31]

Prior to initiating triple therapy, clinicians need to consider the role of eosinophils and weigh the risks and benefits of ICS therapy. Blood eosinophil counts are well recognized to predict the magnitude of ICS effects in preventing future exacerbations.[34] Little effect is observed in patients with eosinophil counts < 100 cells/mcL, but incremental benefits are observed as eosinophils increase.[35] Some evidence suggests that LAMA+LABA+ICS is associated with reduced exacerbations in patients with eosinophils ≥150 cells/mcL, compared to LAMA+LABA.[32] Possible adverse effects of ICS include pneumonia, voice hoarseness, skin bruising, osteoporosis, and oral candidiasis,[36] and should be weighed against the risk of exacerbations and repeated bursts of systemic corticosteroids.

When selecting inhaled therapy, consideration of an inhaler device and overcoming treatment barriers are important factors to address. Suboptimal adherence and inadequate inhaler technique are commonly associated with poor symptom control and increased exacerbations.[37,38] Selection of a

FIGURE 3. GOLD 2023 follow-up pharmacologic treatment algorithm[3]



Abbreviations: eos, blood eosinophil count in cells/mcL; ICS, inhaled corticosteroids; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist.

combination inhaler device (if multiple types of inhaled medications are indicated) may improve adherence by simplifying the medication regimen and potentially improving health status and lung function.[3,39] To further address barriers to successful COPD therapy, clinicians should also engage patients in shared decision-making and goal setting, and have other members of the care team help them navigate cost and insurance coverage concerns.[3] By implementing optimal therapy for COPD and reducing barriers to successful treatment, PCCs can help patients achieve treatment goals, reduce symptoms and exacerbations, and improve quality of life.

CASE SCENARIO

A 55-year-old man with a recent COPD exacerbation and a recent diagnosis of heart failure (elevated B-type natriuretic peptide [BNP], edema, increased shortness of breath) presents for a follow-up visit after finishing treatment for a recent COPD exacerbation. He has had 2 COPD exacerbations managed in the outpatient setting within the past year. He is currently using a LAMA maintenance inhaler and a SABA rescue inhaler. His eosinophil count is 450 cells/mcL.

Recommended interventions in this case scenario include focusing on exacerbation prevention to lower risk of both COPD and cardiovascular adverse outcomes, considering his new heart failure diagnosis. The PCC should also consider optimizing his inhaled therapy to a triple combination inhaler based on eosinophils to improve disease control, lower exacerbation risk, and decrease morbidity and economic burden (**BOX 3**).[3] Further evaluation of his CVD is also indicated to optimize CVD therapy.

SUMMARY

Updated guidance from the most recent GOLD report may change clinicians' selection of the most appropriate and optimal therapy for individual patients, with enhanced focus on exacerbation prevention. PCCs are well-suited to identify, diagnose, and treat COPD earlier in the disease course and improve overall outcomes,

BOX 3. Case scenario clinical decision-making[3]

- Inflammatory mediators in the circulation from COPD can worsen heart failure, so anti-inflammatory therapies such as ICS may have additional benefit in these patients
- Based on the GOLD 2023 algorithm for follow-up pharmacologic therapy, patients who have exacerbations while taking a LABA or LAMA with eosinophils ≥300 cells/mcL may be escalated to LABA+LAMA+ICS, depending on the clinical situation
- Patients who have exacerbations while taking LABA+ LAMA therapy with eosinophils ≥100 cells/mcL may be escalated to LABA+LAMA+ICS, depending on the clinical situation

TABLE 1. Definitions of terms proposed by the GOLD 2023 report to classify earlier COPD presentations[3]

Term	Definition
Early COPD	• Used to identify the biological first steps of COPD in an experimental setting, prior to the appearance of symptoms
Mild COPD	• Used to describe the severity of airflow obstruction measured via spirometry – when airflow obstruction becomes measurable
Young COPD	• Used to describe patients with COPD aged 20–50 years • Can include those who never reached normal peak lung function in early adulthood or with early lung function decline • May be associated with structural and functional lung abnormalities • Frequently goes undiagnosed and untreated
Pre-COPD	• Used to identify individuals of any age who have detectable functional and/or structural abnormalities and/or respiratory symptoms • However, they have no airflow obstruction observed on spirometry
PRISm	• Used to designate patients with FEV_1/FVC ≥0.7 after bronchodilation but impaired FEV_1 (<80% of reference) after bronchodilation on spirometry • High prevalence in current and former smokers • Associated with higher all-cause mortality

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

including lower risk for CVD comorbidity and reduced exacerbations. ●

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Reducing Ischemic Stroke in Diabetes: The Role of GLP-1 RAs

John E. Anderson, MD; Javed Butler, MD, MPH, MBA; Andrei V. Alexandrov, MD

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KEY TAKEAWAYS

- Stroke is a significant cause of mortality worldwide, and diabetes is an independent risk factor for ischemic stroke occurrence and recurrence.
- Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) lower the risk of ischemic stroke through beneficial effects on traditional stroke risk factors such as hyperglycemia, hypertension, and dyslipidemia.
- Primary care practitioners (PCPs) can play a substantial role in reducing ischemic stroke; studies have indicated that patients who have a PCP at the time of first stroke have a lower risk of stroke recurrence.
- Clinical practice guidelines recommend treating type 2 diabetes in patients with or at risk for cardiovascular (CV) disease with glucose-lowering agents with proven CV benefit, such as GLP-1 RAs and sodium-glucose cotransporter-2 (SGLT2) inhibitors.
- Based on meta-analyses of CV outcomes trials, GLP-1 RAs have a substantial and statistically significant benefit on ischemic stroke risk reduction, whereas SGLT2 inhibitors have a nonsignificant effect.
- The use of GLP-1 RAs, in addition to nonpharmacologic and pharmacologic management of traditional stroke risk factors, is a key component of complex therapy for ischemic stroke risk reduction.

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INTRODUCTION

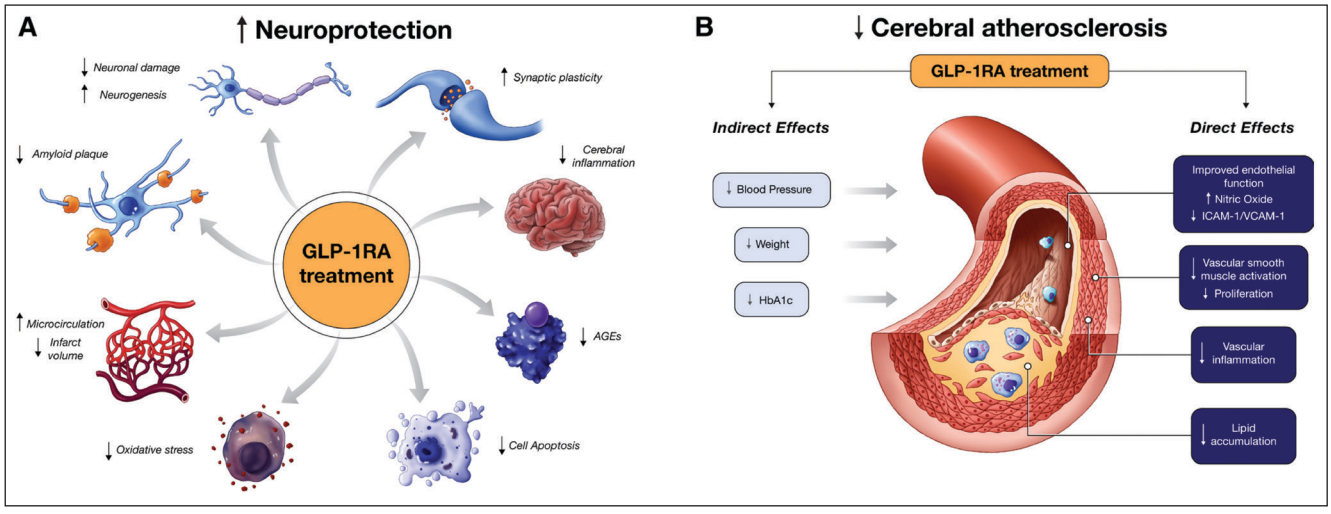
Stroke is a substantial cause of disability and mortality worldwide, with an estimated 80.1 million stroke cases each year.[1,2] In the United States (US), about 1 in 6 deaths from cardiovascular (CV) disease is due to stroke, and about every 3.5 minutes, someone in the US dies from a stroke.[3] Ischemic strokes account for approximately 84% of strokes.[1] Transient ischemic attacks (TIAs) are episodes of cerebral ischemia without resulting permanent infarction; some definitions of TIA assign a time frame that effects must fall within.[4] TIAs are often grouped with ischemic stroke for management recommendations and trial outcomes.[5] Hemorrhagic strokes occur when a weakened blood vessel in the brain ruptures.[6] They are less common than ischemic strokes and have different risk and treatment profiles.[6] The focus of this article is ischemic stroke.

Patients who have experienced a stroke are at high risk of having another stroke, especially within the first 30 days following a first stroke.[7] Additionally, recurrent strokes have a higher chance of disabling or fatal outcomes.[1]

Diabetes is an independent risk factor for ischemic stroke occurrence and recurrence and is a risk factor for neurovascular disease.[1,8] Accordingly, about one-third of individuals who have experienced stroke have diabetes.[9] Although ischemic and hemorrhagic strokes have different risk factor profiles, uncontrolled diabetes raises the risk for both ischemic and hemorrhagic strokes.[10,11] As such, reducing the risk of stroke in patients with diabetes highlights a critical need in clinical practice.

Stroke risk for patients with type 2 diabetes (T2D) can be substantially reduced with targeted intervention. For

FIGURE 1. Possible mechanisms for ischemic stroke risk reduction with GLP-1 RAs



Abbreviations: AGEs, advanced glycation end products; HbA1c, hemoglobin A1c; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular adhesion molecule-1.

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example, the Steno-2 study demonstrated a 69% reduction in the risk of stroke in patients with T2D with implementation of a multifaceted intervention that targeted multiple risk factors of CV disease.[12] Interventions included a low-fat diet, exercise regimen (90–150 minutes of light to moderate physical activity per week), angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker therapy, a daily vitamin-mineral supplement, daily low-dose aspirin, and stepwise therapy for treatment of T2D, hypertension, and dyslipidemia.[13]

Several glucose-lowering medications have demonstrated benefit in reducing risk of major adverse CV events, primarily glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors.[14]

The PCP's role in reducing ischemic stroke risk

Since primary care practitioners (PCPs) manage most patients with T2D and concurrently address other vascular risk factors such as lipids and hypertension across the disease continuum, they are typically aware of patients' stroke risk factors. Studies have demonstrated that patients who have a PCP at the time of first stroke have a lower risk of stroke recurrence.[15]

CASE SCENARIO 1

A 57-year-old man with T2D and dyslipidemia was recently hospitalized for a TIA. He is seeing his PCP for a post-hospitalization follow-up visit. His glycated hemoglobin (A1c) today is 7.4%. The patient's current medications include metformin 1000 mg twice daily, glipizide XL 10 mg daily, atorvastatin 80 mg daily, lisinopril 10 mg daily, and aspirin 81 mg daily.

The patient in case scenario 1 is at risk for ischemic stroke due to his recent TIA, along with T2D and dyslipidemia comorbidities. The PCP should evaluate his medication regimen for adjustments to reduce the risk of recurrent stroke.

POTENTIAL MECHANISMS OF GLP-1–MEDIATED STROKE RISK REDUCTION

Cardiovascular and cerebral effects of GLP-1

Several mechanisms have been proposed for the actions of GLP-1 on cardiac physiology to reduce atherosclerotic CV disease (ASCVD) risk, including stroke (**FIGURE 1**).[16-18] Based on experimental data, GLP-1 receptors are present in various components of the CV and central nervous systems, leading to beneficial effects on stroke prevention due to stimulation of these receptors from GLP-1 RAs.[17] Notably, all GLP-1 RAs cross the blood-brain barrier, enabling them to activate GLP-1 receptors in the brain.[19] Examples of antiatherosclerotic CV and cerebral effects of GLP-1 activation include improved endothelial function, enhanced plaque stability, reduced vascular smooth muscle proliferation, higher nitric oxide levels, decreased cerebral inflammation and cell apoptosis, and reduced oxidative stress.[17,18]

Improvement in traditional stroke risk factors

GLP-1 RAs have beneficial effects on hyperglycemia, dyslipidemia, blood pressure, body weight, and inflammation, which are recognized stroke risk factors.[17] Although the benefit of GLP-1 RAs on some factors is more established than on others, all may contribute to the lower risk of stroke observed with GLP-1 RAs in patients with T2D (**FIGURE 1**).[17,18]

Hyperglycemia is noted to have a causal relationship with increased risk of ischemic stroke, and reductions in A1c in CV outcomes trials (CVOTs) of GLP-1 RAs were associated with lower risk of nonfatal stroke.[17,20,21] Lipid abnormalities and hypertension heighten the risk of ischemic stroke in patients with T2D.[22,23] GLP-1 RAs have demonstrated improvements in lipid levels, specifically through mitigating postprandial increases in triglycerides and apolipoproteins and modulating lipoprotein metabolism.[17] The mechanisms of blood pressure reduction by GLP-1 activation are not yet fully elucidated.[17]

GUIDELINE RECOMMENDATIONS FOR USE OF GLP-1 RECEPTOR AGONISTS TO PREVENT STROKE IN PATIENTS WITH DIABETES

American Diabetes Association (ADA) standards of medical care

To reduce the risk of ASCVD events such as stroke, the 2023 ADA Standards of Medical Care recommend individualizing antihyperglycemic therapy based on comorbidities and risk factors, in addition to optimizing risk reduction through blood pressure and lipid management.[14,24] For patients with diabetes and ASCVD or indicators of high risk, a GLP-1 RA or SGLT2 inhibitor with proven CV benefit is preferred.[24]

AHA/ASA stroke prevention guidelines

The American Heart Association/American Stroke Association (AHA/ASA) Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack also recommends treating T2D with glucose-lowering agents such as GLP-1 RAs, which have proven to reduce the risk of future major adverse CV events.[5]

CLINICAL EVIDENCE FOR GLP-1 RECEPTOR AGONISTS IN STROKE RISK REDUCTION

Starting in 2008, the FDA mandated cardiovascular outcome trials (CVOTs) comparing the drug to placebo for CV safety to be conducted on antihyperglycemic agents submitted for approval in the US.[25] These data form the basis of CV risk assessment for GLP-1 RAs and other T2D medications.

The GLP-1 RAs evaluated in CVOTs include semaglutide, dulaglutide, liraglutide, lixisenatide, and exenatide. A summary of CVOT data can be helpful to compare specific CV outcomes of each agent, including for ischemic stroke, and can inform prescribing decisions (**TABLE 1**). Of note, the only GLP-1 RAs to demonstrate statistically significant benefit for stroke risk reduction in CVOTs are semaglutide injection and dulaglutide. The GLP-1 RAs with indications for reducing major CV events in adults with T2D who have established CV disease are semaglutide injection, dulaglutide, and liraglutide.[32-34]

TABLE 1. CVOTs of GLP-1 RAs in T2D and key outcomes related to ASCVD and stroke

Trial (drug)	Patients (n)	Inclusion criteria	Primary outcome HR (95% CI)[a]	Stroke HR (95% CI)[a]
SUSTAIN-6[26] (semaglutide injection)	3297	T2D and preexisting CV disease, CKD, or HF at ≥50 years of age or CV risk at ≥60 years of age	3-point MACE **0.74 (0.58-0.95)**	**0.61 (0.38-0.99)**
PIONEER-6[27] (semaglutide oral)	3183	T2D and high CV risk (age ≥50 years with established CV disease or CKD, or age ≥60 years with CV risk factors only)	3-point MACE 0.79 (0.57-1.11)	0.74 (0.35-1.57)
REWIND[28] (dulaglutide)	9901	T2D and prior ASCVD event or risk factors for ASCVD	3-point MACE **0.88 (0.79-0.99)**	**0.76 (0.61-0.95)**
LEADER[29] (liraglutide)	9340	T2D and preexisting CV disease, CKD, or HF at ≥50 years of age or CV risk at ≥60 years of age	3-point MACE **0.87 (0.78-0.97)**	**0.86 (0.73-1.00)**
ELIXA[30] (lixisenatide)	6068	T2D and history of ACS (<180 days)	4-point MACE 1.02 (0.89-1.17)	1.12 (0.79-1.58)
EXSCEL[31] (exenatide)	14,752	T2D with or without preexisting CV disease	3-point MACE 0.91 (0.83-1.00)	0.85 (0.70-1.03)

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular event; T2D, type 2 diabetes.

[a]Note: Boldface text indicates statistically significant results.

Of note, tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist, did not have a significantly higher or lower risk of stroke based on a meta-analysis of 7 SURPASS phase 3 trials (HR = 0.81, 95% CI, 0.39–1.68).[35]

Meta-analyses of GLP-1 RAs and stroke risk reduction

Several meta-analyses of GLP-1 RAs, including CVOTs, have been conducted to detect class benefit on ASCVD events, including stroke. One analysis of the Taiwan Health Insurance Database from 2011 to 2017 matched 4,460 individuals with T2D taking GLP-1 RAs with 13,380 patients taking dipeptidyl peptidase-4 (DPP-4) inhibitors.[36] Those taking GLP-1 RAs had a lower risk of nonfatal stroke than those taking DPP-4 inhibitors.[36]

Another meta-analysis of 8 trials and 60,080 patients with T2D found that GLP-1 RAs were associated with a statistically significant 17% reduction in fatal or nonfatal stroke compared to placebo.[37] A third meta-analysis of the same 8 trials found that GLP-1 RAs significantly reduced nonfatal stroke by 15% and fatal stroke by 16%.[38] Notably, the ELIXA trial, evaluating lixisenatide, showed a higher risk of stroke in the overall patient population, likely because patients enrolled in ELIXA had recent coronary syndrome.[38] A sensitivity analysis in one of the meta-analyses excluded patients from ELIXA and found marginally increased benefits of GLP-1 RAs.[37] Of note, both of these meta-analyses included ELIXA and PIONEER-6 in the 8 trials, indicating that results may be applicable to lixisenatide and oral semaglutide.

Other T2D medications and stroke risk reduction

SGLT2 inhibitors. One meta-analysis of 4 SGLT2 inhibitor CVOTs found no overall effect on stroke risk.[39] Another meta-analysis evaluated 6 CVOTs of SGLT2 inhibitors and found no statistically significant benefit in several stroke subanalyses.[40] A third meta-analysis of the same 6 SGLT2 inhibitor CVOTs did not find a significant association with lower stroke risk.[38]

Analysis of 19 randomized trials of DPP-4 inhibitors, including a total of 9,278 patients, showed a nonsignificant trend toward benefit for stroke (OR 0.639, 95% CI: 0.336–1.212; P = .170).[41] Pioglitazone has been associated with lower risk of recurrent stroke in patients with insulin resistance or T2D, but its unfavorable CV side effect profile limits use in patients at high CV risk.[42] Sulfonylureas have a neutral effect on stroke risk.[42]

Key message. Meta-analyses of CVOTs for GLP-1 RAs indicate that these therapies demonstrate substantial reduction of ischemic stroke versus placebo in patients with T2D.[5,37,43] In contrast, other T2D medications do not have significant ischemic stroke benefit in patients with T2D, except for pioglitazone, which is limited by CV side effects.[5,40] Therefore, of agents recommended by guidelines to mitigate CV risk in patients with diabetes (GLP-1 RAs and SGLT2 inhibitors), GLP-1 RAs are the preferred therapies for reducing risk of ischemic stroke.

REDUCING STROKE RISK IN PRIMARY CARE—PRACTICAL APPLICATION

As a primary point of care for patients with T2D who have experienced or are at risk of ischemic stroke, PCPs should be familiar with implementing evidence-based complex therapy to reduce stroke risk.

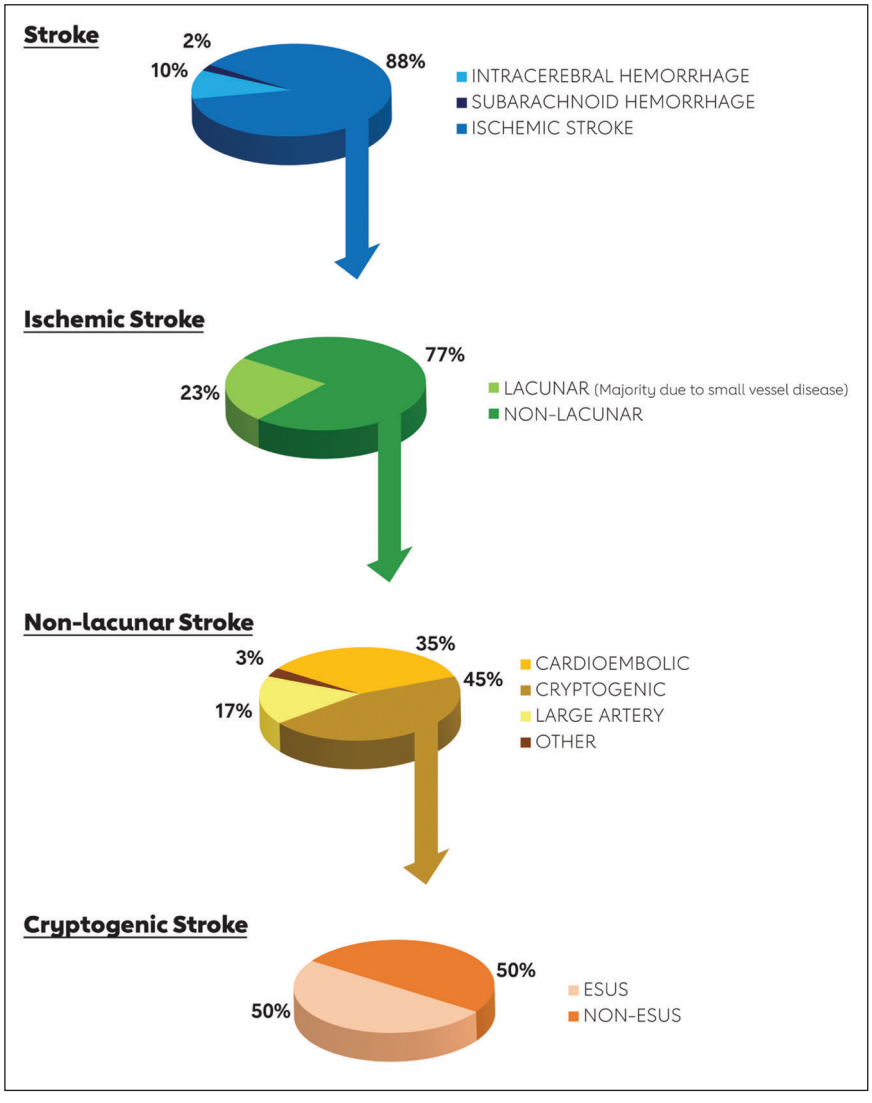
Primary prevention. Highlights of mainly primary-prevention approaches to ASCVD and stroke risk reduction, based on the ADA Standards of Medical Care, are discussed below.

- Antihyperglycemic therapy should be selected based on clinical characteristics such as ASCVD, high CV risk, heart failure, and chronic kidney disease (CKD).[24]
- GLP-1 RAs and SGLT2 inhibitors are recommended for ASCVD or high CV risk, but GLP-1 RAs are noted to have benefit in stroke prevention and SGLT2 inhibitors are not.[24]
- Hypertension is managed by targeting a blood pressure of <130/80 mm Hg, if it can be safely attained, and selection of antihypertensive agent depending on the patient's clinical characteristics.[14]
- Lipid management and primary prevention of ASCVD with moderate-intensity statin therapy is indicated for patients aged 40 to 75 years with diabetes, with high-intensity statins indicated in certain high-risk situations (including patients with ASCVD).[14]
- Lifestyle adjustments to diet and physical activity are suggested for improving and maintaining optimal levels of blood glucose, blood pressure, and lipids.[14,24]

Secondary prevention. Since management strategies for ischemic stroke depend on the subtype, defining ischemic stroke etiology, when possible, can help guide therapy (**FIGURE 2**). Topline recommendations from the AHA/ASA guidelines on secondary stroke prevention include the following[5]:

- Generally, managing vascular factors such as hypertension, diabetes, and lipids is a priority, as well as encouraging smoking cessation and engaging in multidisciplinary management.
- For patients with T2D and ASCVD, including ischemic stroke, GLP-1 RA therapy is recommended, regardless of baseline A1c.
- A healthy diet, specifically a low-sodium or Mediterranean diet, is suggested for stroke risk reduction.
- For nearly all patients who have experienced a stroke,

FIGURE 2. AHA/ASA conceptual representation of ischemic stroke subtypes



Abbreviation: ESUS, embolic stroke of undetermined source.

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barring any contraindications, antithrombotic treatment with antiplatelet or anticoagulant drugs is recommended.

The reader is referred to the full AHA/ASA guideline (https://www.ahajournals.org/doi/10.1161/STR.0000000000000375) for further discussion and detailed therapeutic strategy for secondary ischemic stroke prevention by subtype.

Revisiting case scenario 1, the PCP should consider optimizing the patient's T2D regimen to include an antihyperglycemic agent with additional A1c-lowering effects, as well as ASCVD risk reduction. Specifically, adding a GLP-1 RA would likely improve the patient's A1c and reduce the risk of ischemic stroke.

CASE SCENARIO 2

A 67-year-old female with T2D, atrial fibrillation, and CKD presents to her PCP for her annual visit. She has a family history of stroke but has been stroke free. Her medications include metformin 1000 mg daily, apixaban 2.5 mg twice daily, rosuvastatin 20 mg daily, and irbesartan 300 mg daily. Her A1c is 6.8%. At today's visit, her estimated glomerular filtration rate has declined to 21 mL/min/1.73 m^2, down from 30 mL/min/1.73 m^2 6 months ago.

In case scenario 2, the patient is at risk for ischemic stroke and would benefit from therapies that reduce stroke risk, in addition to further workup of her kidney impairment. Her kidney function has deteriorated to the point where clinicians may consider discontinuing metformin in favor of a safer agent. The degree of kidney impairment also precludes use of SGLT2 inhibitors. Discontinuing metformin and initiating a GLP-1 RA would reduce the patient's risk of ischemic stroke and improve the safety of her medication regimen, given her CV risk factors and decreased kidney function.

SUMMARY

Patients with diabetes are at increased risk for ASCVD events and should receive therapy with beneficial effects on CV outcomes—especially patients with additional CV risk factors. GLP-1 RAs have demonstrated a reduced risk of ischemic stroke in patients with T2D compared to other T2D medications, and several mechanisms have been proposed. PCPs treating patients with T2D who are at risk for occurrence or recurrence of ischemic stroke should consider incorporating GLP-1 RAs as an important component of stroke risk reduction, consistent with current evidence and clinical practice guidelines. ●

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Use of ICS and Fast-Acting Bronchodilators in Asthma: Past, Present, and Future

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KEY TAKEAWAYS

- Primary care practitioners (PCPs) play a key role in asthma management since most patients with asthma are treated in primary care settings.
- Despite continual advances in asthma care, important practice gaps remain, and the high burden of asthma exacerbations persists, with 43% of children with asthma and 41% of adults with asthma in the United States experiencing an asthma exacerbation in 2020.
- Uncontrolled asthma, incomplete assessment of exacerbation and asthma control history, reliance on systemic corticosteroids (SCS) or short-acting beta$_2$-agonist (SABA)-only therapy, and lack of patient adherence to anti-inflammatory maintenance therapies are challenges clinicians face today with asthma care.
- Inhaled corticosteroids (ICS) have been thought to have slow onset of action; however, recent data indicate that ICS onset of action on bronchial tissue is seconds to minutes through nongenomic effects.
- A large body of evidence supports the use of ICS + fast-acting bronchodilator treatments when used as needed in response to symptoms to improve asthma control and reduce rates of exacerbations.
- The symptoms that occur leading up to an asthma exacerbation provide a window of opportunity to intervene with ICS + fast-acting bronchodilators, potentially preventing the exacerbation and reducing the need for SCS.
- Incorporating patient perspectives and preferences when designing asthma regimens will help patients be more engaged in their therapy and may contribute to improved outcomes.
- In January 2023, a SABA-ICS combination rescue inhaler was approved by the US Food and Drug Administration (FDA) as the first asthma rescue inhaler for as-needed use to reduce the risk of exacerbations.

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INTRODUCTION

Asthma is a chronic lung disease that causes substantial health and economic burden in the United States (US) and worldwide. In the US, more than 25 million people were living with asthma in 2020.[1] Asthma affects approximately 8% of the US population and has several clinical phenotypes.[1-3] Common asthma phenotypes include allergic and nonallergic asthma, adult-onset (late-onset) asthma, asthma with persistent airflow limitation, and asthma with obesity.[4,5] According to the 2023 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention, asthma is defined as "a heterogeneous disease, usually characterized by chronic inflammation…defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness, and cough, that vary over time and in intensity, together with variable expiratory airflow limitation."[2]

Asthma often leads to adverse lung outcomes, including decline in lung function, persistent airflow limitation, increased dyspnea and other symptoms, and exacerbations that can lead to hospitalization and asthma-related death.[2] In the US, about 10.3 million asthma exacerbations occurred in 2020. Each year in the US, there are approximately 1.8 million emergency department visits, 170,000 hospitalizations (2019 data), and more than 4000 deaths (2020 data) due to asthma.[1]

A small portion of patients (up to 16% of adults in one study) diagnosed with asthma may experience clinical remission within 5 years.[6] The majority of patients with asthma require pharmacologic treatment to alleviate symptoms and reduce the risk of adverse outcomes.

The PCP's role in asthma management

Patients with asthma are often managed in the primary care setting.[7,8] Those who have an unclear asthma diagnosis or who have severe, persistently uncontrolled asthma may be referred for specialist care.[2,9] Since more than 60% of patients with asthma receive care from a primary care practitioner (PCP), implementing best practices for asthma management is essential.[7,8,10] Recent changes in the treatment landscape highlight a need for education on emerging data and recommended therapies.

CASE SCENARIO

A 34-year-old man presents to his PCP for an asthma follow-up visit. He is a busy professional and is currently taking a medium-dose inhaled corticosteroid (ICS) maintenance inhaler (2 doses per day) along with an albuterol rescue inhaler. He has had 2 urgent care visits in the last year for asthma exacerbations, one of which was during a concomitant upper respiratory infection.

He initially states that he is adherent to his medications, but upon further questioning, he acknowledges that he often skips 1 of the 2 doses of his maintenance inhaler, and sometimes misses using the inhaler all together. However, he says that the albuterol inhaler seems to really help him breathe better, so he carries this inhaler with him and uses it most days of the week when he feels short of breath.

The patient in the case scenario above is at risk for severe asthma exacerbations, even though his asthma is not currently classified as severe. He is especially at increased risk due to his frequent use of a SABA without concurrent ICS and his past history of exacerbations.[2] Adherence issues need to be addressed, and new approaches to treatment will soon be available to allow use of an as-needed albuterol-ICS fixed-dose combination inhaler to relieve symptoms in a manner similar to the way that albuterol does and to also lower his risk of exacerbation compared with using albuterol alone as rescue therapy.

To better understand the current, shifting paradigm of asthma care and the evolving role of ICS fast-acting bronchodilator combination therapy in asthma, it is beneficial to review the history of asthma assessment and management through the years. This review will focus on the evolution of ICS and fast-acting bronchodilator combinations and a new paradigm of SABA + ICS rescue therapy.

HISTORICAL CONTEXT OF ASTHMA

Asthma was first described by Hippocrates, the Greek physician; the term "asthma" is derived from the Greek word "asthmaino," which indicates "panting or gasping."[11] Several hundred years later, Galen linked these symptoms to bronchospasm.[11] Similar descriptions of asthma have been recognized in other ancient cultures, including Chinese, Hebrew, and Roman civilizations.[11]

As time passed, various causes of asthma were explored, including environmental and allergenic factors. Although successful treatments for asthma symptoms were still lacking, preventative strategies such as protective masks for miners and avoidance of allergens were used.[11] In the 20th century, asthma was firmly established as an inflammatory disorder, and interventional randomized trials began to shape asthma care.[11]

The advent of inhaled anti-inflammatory therapy

Early asthma therapies were focused primarily on symptom relief, and included plant extracts, surgery, and hypnosis.[11] Inhaled treatments began as rudimentary "asthma cigarettes" where the patient inhaled components such as menthol, belladonna, atropine, morphine, or cocaine. Efficacy of these early treatments was lacking, and the treatments often proved hazardous. As the understanding of the inflammatory nature of asthma physiology grew, rational and more effective treatments including xanthine derivatives (such as theophylline), beta agonists, and systemic corticosteroids (SCS) began to be introduced.[11]

In the 1970s, the first corticosteroid inhaler, beclomethasone, became available, demonstrating beneficial effects in asthma and an improvement in the frequency and severity of adverse events compared to systemic corticosteroids.[11] Widespread use of ICS did not occur until a few decades later, when the Expert Panel Report-2 in the US recommended ICS as maintenance anti-inflammatory therapy in 1997.[12] In 2001, the aggregate use of maintenance therapies, particularly ICS, exceeded that of rescue/reliever medications.[13] These trends have continued to the present day, where ICS-based therapies are the mainstay of maintenance treatment for asthma.[2] Moreover, over the last 2 decades, substantial evidence has accumulated across asthma severities about the benefits of as-needed strategies that provide ICS whenever patients use their rescue inhaler.[14]

THE CURRENT STATE OF ASTHMA CARE

Evidence-based care and treatment goals

Current recommendations for asthma care in the US are based on the 2020 Focused Update of the National Asthma Education and Prevention Program (NAEPP) and the 2007 Expert Panel Report-3 (EPR-3) guidelines.[9,12] Global asthma recommendations are based on the 2023 GINA report.[2] Suggested approaches for applying these recommendations in primary care, highlighting the importance of concurrent ICS use with bronchodilators, have been discussed previously.[15]

In brief, both NAEPP and GINA recommend initial therapy based on asthma severity and other patient characteristics, as well as a stepwise approach to intensifying therapy based on control.[2,9] GINA advocates use of a combination inhaler containing both the fast-acting (and long-acting) bronchodilator formoterol and an ICS as the preferred rescue treatment strategy for all disease severities in patients ≥12 years, based on evidence of greater efficacy in reducing severe exacerbation risk compared with SABA-only rescue therapy.[2] A SABA-ICS combination inhaler is now included in the GINA report as an alternative rescue option for patients ≥12 years across disease severities.[2] The 2020 NAEPP recommendations suggest using daily and as-needed ICS-formoterol for patients aged ≥4 years only for Steps 3 and 4 of therapy.[9] Notably, ICS-formoterol is not approved for rescue therapy in the US. For patients ≥12 years who are treated for mild persistent asthma with Step 2 therapy, 2020 NAEPP recommendations also suggest (as one of 2 preferred regimens) an ICS to be used concomitantly with SABA for symptoms.[9]

Treatment goals suggested by EPR-3 and GINA are closely aligned. Both recommend that achieving good symptom control; maintaining normal activity levels; and reducing negative asthma outcomes such as exacerbations, asthma-related death, persistent airflow limitation, and adverse effects are important clinical goals for asthma management.[2,12]

Gaps in asthma care

Although asthma care continues to improve, multiple practice gaps highlight the need for clinicians to better align management approaches with the evidence. Current gaps in asthma care include a substantial burden of uncontrolled asthma, lack of clinical assessment of exacerbation history and of asthma control, overuse of SCS, potentially inappropriate SABA-only use, and poor patient adherence to anti-inflammatory maintenance therapies.[16–22]

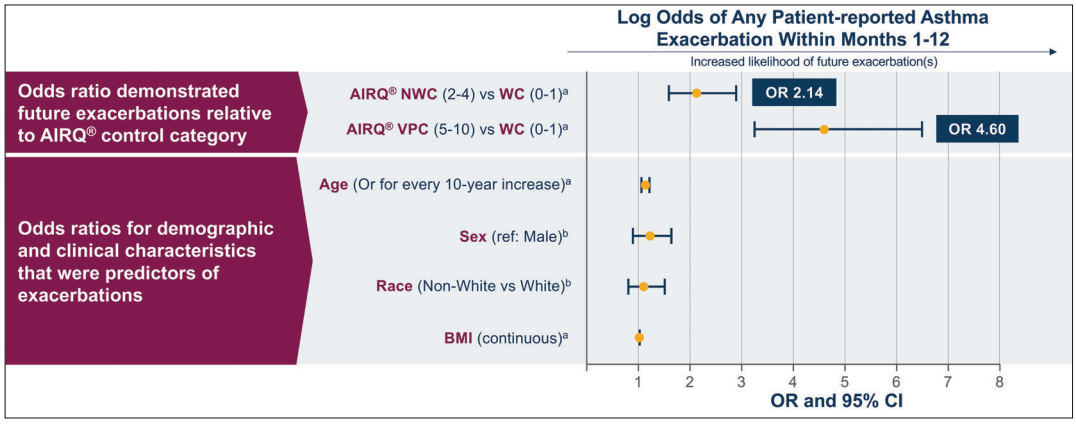
Uncontrolled asthma. Uncontrolled asthma is associated with several adverse consequences, such as higher rates of exacerbations, lower quality of life, and increased healthcare utilization, compared to controlled asthma. Approximately 60% of adults with asthma in 2019 and 44% of children with asthma in 2018 to 2020 in the US had uncontrolled asthma.[23,24] Overall, more than 80% of patients in the US with uncontrolled asthma are those treated for mild or moderate asthma.[17] The data are inconsistent on the degree to which, or even whether, asthma exacerbations, particularly severe exacerbations, have improved over the last 20 years. There has been very little change in the rate of number of emergency room visits and in the number of people dying with asthma each year since the 1990s.[1,25] Although rates of asthma exacerbations have improved since 2007, consistent with continued advances in asthma care, [26] a high burden of exacerbations remains—in the US in 2020, 41% of adults and 43% of children diagnosed with asthma experienced asthma exacerbations.[27]

Clinical assessment of asthma control. Determining degree of asthma control is critical for optimal ongoing management of asthma and achieving treatment goals.[2,9] However, most asthma assessment tools such as the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ) only incorporate questions about recent asthma symptoms.[28–30] Additionally, clinician and patient impressions also tend to overestimate asthma control.[31] Thus, clinicians often fail to address the importance of exacerbation history and poor asthma control in selecting therapy.

The Asthma Impairment and Risk Questionnaire (AIRQ) is a newer assessment tool developed and validated to incorporate assessment of both impairment and risk—automatically addressing prior exacerbations and more accurately detecting patients who may need educational interventions and/or an adjustment in their asthma therapy.[18] Asthma control measured by the AIRQ can predict the risk of future asthma exacerbations over the following 12 months.[32] Compared with patients whose AIRQ score fell in the "well-controlled" category, patients in the "not well-controlled" category were 2.14 times more likely to experience an exacerbation, and those in the "very poorly controlled" category had a 4.6-times increased risk of exacerbation in the subsequent year (**FIGURE 1**).[32] A follow-up version of the AIRQ is also available to assess disease stability and impact of interventions between annual visits.[33]

Overuse of SCS. While SCS are an essential tool for managing acute exacerbations, they have both short-term and long-term adverse effects.[2,9] Adverse effects resulting from short-term (<30 day) SCS use include increases in risk of fracture, venous thromboembolism, and sepsis.[19] Adverse effects resulting from long-term use occur based on cumulative lifetime SCS dose, starting at 0.5 g of prednisone or equivalent, with a clear risk threshold of 1 g prednisone or equivalent.[20] A common regimen for exacerbation management is prednisone

FIGURE 1. AIRQ control level predicts future patient-reported exacerbations over a 12-month period[32]



[a]Significant predictors of ≥1 exacerbation.

[b]Not a significant predictor of ≥1 exacerbation.

Abbreviations: AIRQ®, Asthma Impairment and Risk Questionnaire; BMI, body mass index; CI, confidence interval; OR, odds ratio; NWC, not well controlled; WC, well controlled; VPC, very poorly controlled.

40 to 60 mg for 5 to 10 days, adding up to a cumulative dose of 200 to 600 mg per exacerbation. Patients may approach the long-term effect risk threshold after just 2 or 3 steroid bursts.[2,9] Higher cumulative SCS doses are associated with increases in pneumonia, osteoporosis, kidney impairment, cataracts, cerebrovascular disease, cardiovascular disease, depression, anxiety, sleep apnea, weight gain, and type 2 diabetes.[20,34]

Potentially inappropriate SABA-only use. Increased SABA-only use as rescue therapy has been associated with increased risk of asthma exacerbations. Beginning around the second annual SABA fill, patients who filled at least 1 prescription for a SABA inhaler (over a 12-month period) experienced increased exacerbations.[21] Mean SABA fills were greater for patients who experienced exacerbations compared to those who did not, and for patients with multiple exacerbations compared to those with only 1 exacerbation.[21] Increasing annual SABA fills were also associated with high-cost healthcare resource utilization such as emergency department visits and hospitalizations for asthma.[21]

Poor adherence to anti-inflammatory maintenance therapies. Despite the effectiveness of ICS in treating asthma, patients often demonstrate poor adherence to prescribed ICS-containing maintenance regimens.[22,35] Suboptimal adherence to pharmacologic therapy worsens asthma control, and patients with poorly controlled asthma who are non-adherent are at the greatest risk for adverse outcomes.[36] Although patients may prefer use of SABA-only inhalers to receive symptomatic relief, a strategy of providing an ICS + fast-acting bronchodilator may allow patients to use their rescue inhaler and at the same time receive ICS, providing a benefit of decreased exacerbations compared to the use of albuterol alone, as discussed below.

The window of opportunity to intervene and prevent exacerbations

About 10 to 14 days before an asthma exacerbation, symptoms and SABA use increase and peak expiratory flow begins to decrease due to airway inflammation, foretelling a coming exacerbation (**FIGURE 2**).[37–39] Although it provides symptomatic relief, SABA-only use does not improve the underlying inflammation.[37,40] Increased ICS use, during this window of opportunity, decreases the likelihood of an exacerbation.

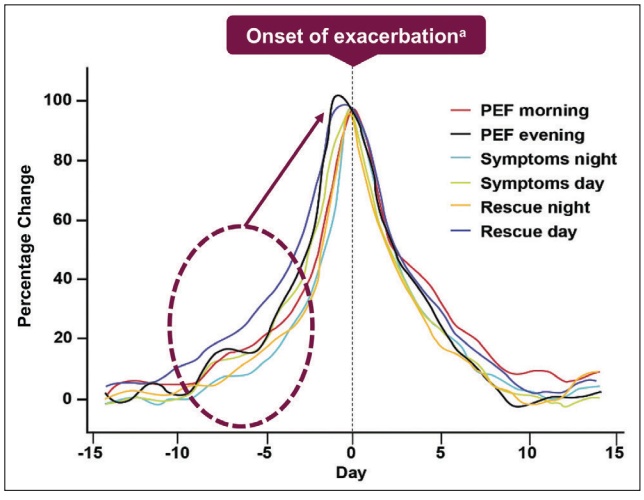
Traditionally, ICS were thought to have a slow onset of action, but recent evidence supports a more rapid onset, mediated by their nongenomic effects.[41,42] Genomic and nongenomic effects of ICS exert complementary mechanisms for reducing inflammation and potentially lowering the risk of asthma exacerbations.

Nongenomic corticosteroid effects have an onset of action occurring in seconds to minutes, and include modulation of immune cell activity, decreased airway edema and mucosal blood flow, and potentiation of bronchodilator effects.[41,42] Genomic corticosteroid effects can take 4 to 24 hours before onset of action, and include decreased transcription of inflammatory genes and increased transcription of anti-inflammatory genes.[42] Additionally, ICS prevent down-regulation of beta$_2$-receptors as well as increase their expression.[43,44] ICS also lower proinflammatory markers, potentially offsetting the increase in proinflammatory markers associated with bronchodilator use.[45,46]

PATIENT PERCEPTIONS OF ASTHMA TREATMENT

GINA and NAEPP both emphasize the importance of clinician-patient collaboration for optimal asthma management.[2,9] Patients who are educated and engaged in self-management of their disease have reduced asthma morbidity.[47,48] Additionally, shared decision-making in asthma manage-

FIGURE 2. Peak expiratory flow, daytime and nighttime symptoms, rescue inhaler use during an asthma exacerbation, and the potential window of opportunity for intervention[37]



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.

Adapted from Tattersfield AE, Postma DS, Barnes PJ, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. *Am J Respir Crit Care Med*. 1999;160(2):594-599. doi:10.1164/ajrccm.160.2.9811100. Used with permission.

ment is associated with improved adherence and asthma outcomes.[49] Clinicians should consider patients' perceptions, preferences, and goals when designing individualized asthma treatment regimens.[2,9]

The International Asthma Patient Insight Research (INSPIRE) study asked 3415 adults with asthma taking an ICS or ICS + bronchodilator maintenance therapy about asthma control, ability to recognize and self-manage worsening asthma, and medication adherence.[50] Most patients (90%) wanted treatments that work quickly and about 74% used a SABA daily despite being prescribed maintenance therapy.[50] Furthermore, 38% of patients thought they did not need to take asthma medication daily when they were feeling well.[50]

The PRACTICAL study surveyed 306 patients with mild asthma regarding their experience and preferences for symptom-driven budesonide-formoterol therapy and budesonide plus as-needed terbutaline.[51] The patients had previously been randomized to these regimens and the survey was conducted at the final study visit. A total of 135 patients (90%) randomized to as-needed budesonide-formoterol responded that they preferred a combination maintenance and rescue therapy, and 93 (60%) of patients randomized to maintenance budesonide preferred twice-daily maintenance therapy with a rescue inhaler.[51] While most patients preferred the regimen to which they were randomized, the association with budesonide-formoterol as needed was stronger.[51]

Another study evaluated patient preferences for asthma treatments using an online discrete choice experiment survey.[52] A total of 1134 adult patients completed the survey. Fewer asthma exacerbations requiring urgent medical care, fewer exacerbations requiring SCS, and lower risk of oral thrush were the most valued concepts.[52] Additionally, patients were willing to increase use of rescue medication if it meant fewer exacerbations, and they preferred a single inhaler for rescue and maintenance therapy.[52]

Overall, many patients prefer symptom-driven treatment, which has historically been focused on as-needed SABA-only rescue therapy.[50,51] This has created a paradox of asthma management, as patients increasingly seem to prefer SABA use but when used alone it does not actually help to decrease exacerbations. Clinicians may consider engaging patients in shared decision-making discussions to determine how they might best incorporate ICS into the rescue therapy portion of asthma treatment. This may include a rescue or maintenance and rescue therapy with a combination ICS + fast-acting bronchodilator inhaler.

COMBINATION ICS AND FAST-ACTING BRONCHODILATORS

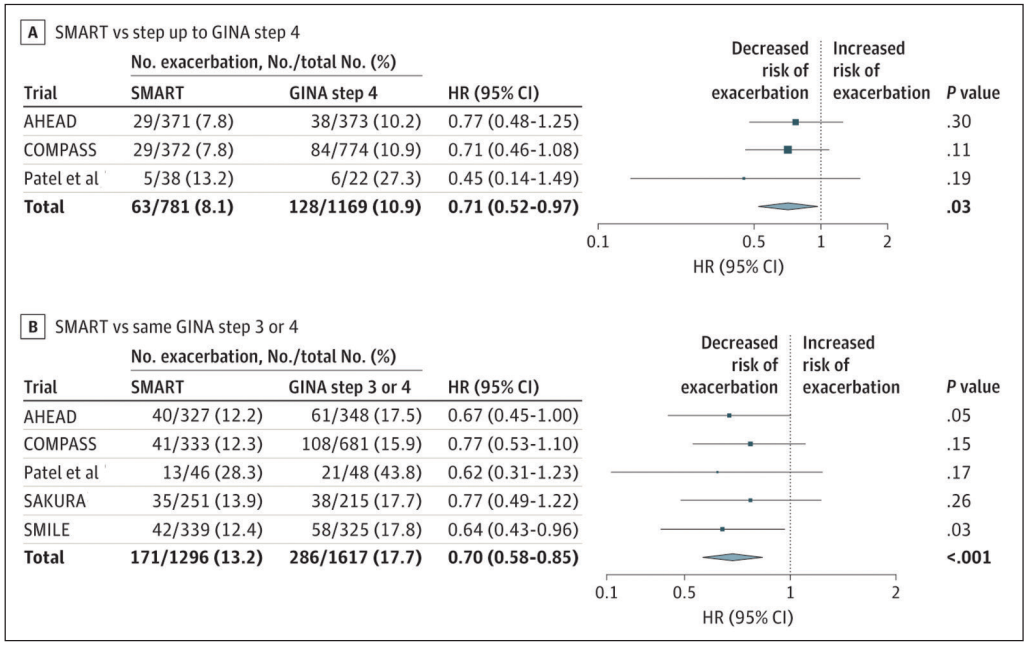
ICS + fast-acting bronchodilator combinations administered for rescue therapy in asthma care have been evaluated as 3 distinct strategies: 1) ICS-formoterol in a single inhaler, 2) ICS and SABA in separate inhalers, and 3) albuterol-ICS in a single inhaler.

Data on the use of ICS and fast-acting bronchodilators in asthma

Formoterol is a long-acting bronchodilator with rapid onset. Budesonide-formoterol has been extensively studied as maintenance and rescue therapy in patients with moderate-to-severe asthma[53–60] (**FIGURE 3**) and as rescue therapy (**TABLE 1**) in patients with mild and mild-to-moderate asthma.[61–64] These trials highlight the effectiveness of ICS + fast-acting bronchodilator in managing asthma and preventing exacerbations.

In studies evaluating as-needed budesonide-formoterol as rescue/reliever in patients with mild asthma, as-needed budesonide-formoterol was superior to as-needed SABA in reducing the rate of annual severe exacerbations (by 51–64%). Patients receiving as-needed budesonide-formoterol rescue had annualized severe exacerbation rates that were similar to those for patients receiving maintenance budesonide

FIGURE 3. Meta-analysis of budesonide-formoterol studies evaluating use as maintenance and rescue therapy in asthma in patients with uncontrolled moderate-to-severe asthma[60]



Abbreviations: GINA, Global Initiative for Asthma; SMART, single maintenance and reliever therapy.

Note: Studies mentioned in this figure used a dry powder inhaler device of budesonide-formoterol, which is not approved or available in the US; no ICS-formoterol product is approved by the FDA for as-needed use.

plus as-needed SABA in 2 of the studies, while the real-world PRACTICAL study reported a 31% reduction in rate of severe asthma exacerbations compared with maintenance budesonide plus as-needed SABA.[61–64] While these studies provide the evidence for the effectiveness of as-needed ICS + fast-acting bronchodilator, they used a dry powder inhaler device of budesonide-formoterol that is not approved in the US; no ICS-formoterol product is currently approved by the FDA for as-needed use.

Studies of other as-needed ICS-based regimens have also demonstrated efficacy in patients with varying degrees of asthma severity, even when treatment adjustments are patient-managed, based on symptoms. Proof-of-concept for a SABA-ICS rescue was provided in the BEST study in patients with mild asthma (N=455), in which as-needed albuterol-beclomethasone was associated with improvements in morning peak expiratory flow rate (8.31 liters/min improvement, *P*=.04) and a lower mean annual exacerbation rate (0.74 vs 1.63, *P*<.001) than as-needed albuterol and similar efficacy to maintenance beclomethasone therapy.[65]

The effectiveness of symptom-based adjustment of ICS, in which patients are instructed to adjust the dose of their ICS inhaler based on their symptoms and rescue inhaler needs, has been compared with physician-based adjustment of maintenance ICS in the Best Adjustment Strategy for Asthma in the Long Term (BASALT) study in adults with mild-to-moderate asthma (N=342) and in the Asthma Symptom-based adjustment of Inhaled Steroid Therapy in African American children (ASIST) study in children with mild asthma (N=206).[66,67] In these studies, the symptom-based ICS adjustment strategy was found to be as effective as the physician-directed maintenance ICS adjustment strategy, as assessed by episodes of clinical worsening of asthma (in BASALT), or asthma control and exacerbation rates (in ASIST), with lower overall ICS exposures.[66,67]

Recently, as-needed ICS plus SABA, delivered via 2 separate inhalers, vs SABA alone has been evaluated in the Person Empowered Asthma Relief (PREPARE) trial, which included 1201 US Black and Latinx adults with moderate-to-severe asthma. Patients were randomized to patient-activated symptom-driven ICS plus separate SABA for rescue therapy or SABA alone for rescue therapy; patients continued their usual maintenance therapy throughout the study.[68] Those in the patient-activated ICS + SABA group had a 15% lower annualized severe exacerbation rate than the SABA alone group (0.69 vs 0.82, HR 0.85; 95% CI 0.72 to 0.999; *P*=.048).[68]

In summary, these studies showed that: 1) use of an ICS + fast-acting bronchodilator combination as maintenance and rescue/reliever or as rescue/reliever therapy alone leads to decreased exacerbations compared to either the same or higher dose of maintenance ICS plus SABA, and 2) patient-driven decision-making can lead to outcomes that are similar to or better than clinician-driven decisions with regard to asthma treatment.

TABLE 1. Effect of budesonide-formoterol as needed on exacerbation outcomes in patients with mild or mild-to-moderate asthma

Study	Patients	Intervention/comparators	Exacerbation outcomes
SYGMA 1[61]	N=3836 ≥12 years Mild asthma	Budesonide-formoterol DPI PRN Terbutaline DPI as needed Budesonide DPI twice daily + terbutaline DPI PRN	PRN budesonide-formoterol was superior to PRN terbutaline, improving the annual rate of severe exacerbations (rate ratio, 0.36; 95% CI, 0.27-0.49; *P*<.001)
SYGMA 2[62]	N=4176 ≥12 years Mild asthma	Budesonide-formoterol DPI PRN Budesonide DPI twice daily + terbutaline DPI PRN	PRN budesonide-formoterol was noninferior to maintenance budesonide for annual severe exacerbation rates (rate ratio, 0.97; one-sided 95% upper confidence limit, 1.16)
Novel START[63]	N=668 18–75 years Mild asthma	Budesonide-formoterol DPI PRN Albuterol MDI PRN Budesonide DPI twice daily + albuterol MDI PRN	Patients taking PRN budesonide-formoterol had a significantly reduced annualized rate of asthma exacerbations compared to PRN albuterol (relative rate 0.49; 95% CI, 0.33-0.72; *P*< .001)
PRACTICAL[64]	N=885 18–75 years Mild to moderate asthma	Budesonide-formoterol DPI PRN Budesonide DPI twice daily + terbutaline DPI PRN	The budesonide-formoterol group had a lower rate of severe asthma exacerbations compared to budesonide maintenance + terbutaline (relative rate 0.69; 95% CI, 0.48-1.00; *P*=.049)

Abbreviations: PRN, as needed; DPI, dry powder inhaler; MDI, metered-dose inhaler.

Note: Studies mentioned in this table used a dry powder inhaler device of budesonide-formoterol, which is not approved or available in the US; no ICS-formoterol product is approved by the FDA for as-needed use.

EMERGING DIRECTIONS FOR INHALED COMBINATION THERAPY IN ASTHMA CARE

Despite the breadth of data indicating benefit from combined ICS + fast-acting bronchodilator therapy, the US has lacked a Food and Drug Administration (FDA)-approved inhaler regimen that includes both components until recently. In January 2023, the FDA granted approval for the as-needed use of a SABA-ICS (albuterol 180 µg and budesonide 160 µg) fixed-dose combination pressurized metered dose inhaler to treat and prevent bronchoconstriction and to reduce the risk of exacerbations for patients with asthma ≥ 18 years.[46]

Albuterol-budesonide for as-needed treatment of patients with asthma

The FDA approval of albuterol-budesonide as rescue therapy for patients with asthma ≥ 18 years was largely based on results of the MANDALA trial.[69]

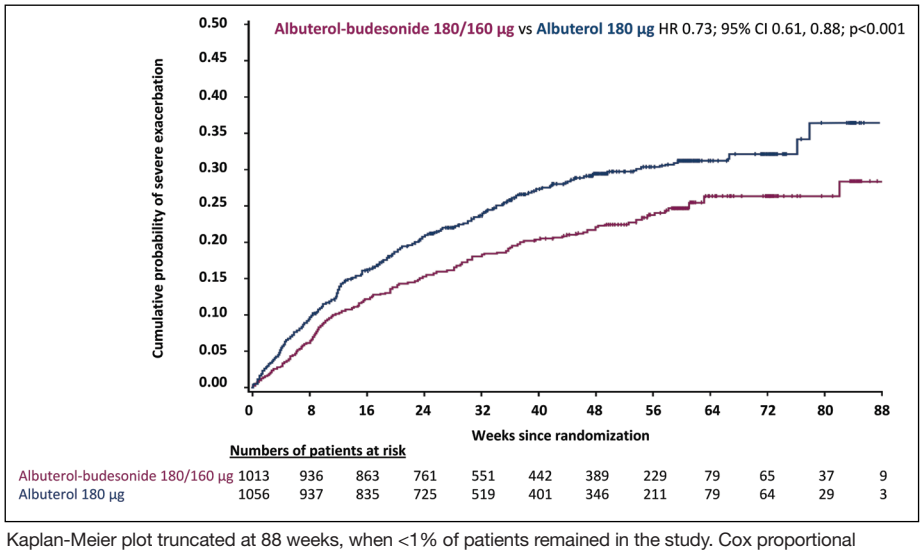
The MANDALA phase 3 randomized trial evaluated the efficacy and safety of an albuterol-budesonide fixed dose combination inhaler as rescue therapy compared with albuterol alone in 3132 patients with moderate-to-severe uncontrolled asthma receiving ICS-containing maintenance therapies. Patients ≥ 12 years were randomized 1:1:1 to 1 of 3 study arms of as-needed therapy on top of their stable study-entry maintenance medication: albuterol-budesonide 180/160 µg, albuterol-budesonide 180/80 µg, or albuterol 180 µg. In adolescent and adult patients with moderate-to-severe asthma, the fixed-dose combination of albuterol-budesonide 180/160 µg (2 inhalations of albuterol 90 µg and budesonide 80 µg), used as needed on top of their 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; *P*<.001; pre-planned efficacy analysis) compared with as-needed albuterol 180 µg (**FIGURE 4**).[70,71]

Additionally, the fixed-dose combination of albuterol-budesonide 180/160 µg compared to albuterol alone (pre-planned efficacy analysis) demonstrated the following (**TABLE 2**)[70]:

- 24% 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)
- 33% lower mean annualized total dose of SCS (86.2 ± 262.9 mg prednisone equivalents vs 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)

The investigators concluded that severe asthma exacerbation risk was "significantly lower with as-needed use of a

FIGURE 4. Time-to-event analysis of the first event of severe asthma exacerbation in MANDALA (preplanned on-treatment efficacy analysis)[70]



Kaplan-Meier plot truncated at 88 weeks, when <1% of patients remained in the study. Cox proportional hazards regression model adjusted for age group, region and number of severe exacerbations in the 12 months before screening. Data are for all patients.

Note: Children ages 4 to 11 years were excluded in the comparison between the higher-dose combination group and the albuterol-alone group.

From Papi A, Chipps BE, Beasley R, et al. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma. *N Engl J Med*. 2022;386(22):2071-2083. doi:10.1056/NEJMoa2203163. Copyright 2022 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide than with as-needed use of albuterol alone" for patients with uncontrolled moderate-to-severe asthma taking a range of ICS-containing maintenance therapies.[70]

In an additional analysis of MANDALA, the effect of as-needed albuterol-budesonide 180/160 µg on progression from symptomatic deterioration to severe exacerbation (during the "window of opportunity") was explored.[72] In MANDALA, symptomatic deteriorations were experienced by 73.7% of patients receiving albuterol-budesonide 180/160 µg and 79.4% receiving albuterol 180 µg (HR 0.83; 95% CI 0.75, 0.92; *P*<.001). Among those patients who experienced a symptomatic deterioration, albuterol-budesonide 180/160 µg significantly reduced the risk of progressing to a severe exacerbation within the next 21 days by 41% compared to albuterol 180 µg alone (HR 0.59; 95% CI 0.41-0.84; *P*=.004).[72]

The incidence of adverse events in MANDALA was similar between the albuterol-budesonide and albuterol groups, the most common being nasopharyngitis, headache, and upper respiratory tract infections in both groups.[70] The percentage of patients with adverse events associated with the use of ICS was similar between arms (2.0% with albuterol-budesonide 180/160 µg; 1.3% with albuterol 180 µg alone).[70]

DENALI was a phase 3 study evaluating the contribution of both albuterol and budesonide to the lung function efficacy of albuterol-budesonide in patients ≥12 years with mild-to-moderate asthma.[73] In the trial, albuterol-budesonide showed significant improvement in lung function measured by forced expiratory volume in one second (FEV_1), compared to the individual components albuterol and budesonide and compared to placebo. Onset of action and duration of lung function effect were similar for albuterol-budesonide and albuterol.[73]

The totality of the clinical trials data included in the FDA approval of albuterol-budesonide 180/160 µg showed that for patients ≥12 years, the common adverse reactions at an incidence ≥1% were headache, oral candidiasis, cough, and dysphonia.[74] It should be noted that because a limited number of pediatric patients (4–17 years of age) were enrolled in the MANDALA trial, the FDA concluded that the safety and effectiveness of albuterol-budesonide has not been established in pediatric patients and is currently approved only for patients with asthma ≥18 years.[74] Although albuterol-budesonide is FDA-approved, the product is not yet commercially available.

Closing the gaps in asthma care

As clinicians become more familiar with the current evidence and shifting paradigm of asthma care and implement updated approaches to asthma management, the current practice gaps should begin to close. Reducing rates of uncontrolled asthma, avoiding unnecessary SCS use, using ICS with fast-acting bronchodilators as part of a rescue strategy, incorporating asthma control and exacerbation history in clinical assessment, and enhancing patient adherence to anti-inflammatory maintenance therapy will hopefully result in improved overall patient outcomes for asthma.

Referring to the case scenario above, this patient could benefit from a combination of an ICS + fast-acting bronchodilator used as needed. This change in rescue therapy approach could more adequately address the variability in airway inflammation that is characteristic of asthma and allow for shared decision-making between the patient and clinician on maintenance therapy goals.

TABLE 2. Efficacy of as-needed albuterol-budesonide vs albuterol in the MANDALA study (pre-planned efficacy analysis)[70]

Group			Comparison with albuterol 180 µg	
Time to first severe exacerbation	**n**		**Hazard ratio (95% CI)**	***P* value**
Albuterol-budesonide 180/160 µg	1013		0.73 (0.61, 0.88)	*P*<0.001
Albuterol 180 µg	1014			
Annualized severe exacerbation rate		Annualized rate (95% CI)	Rate ratio (95% CI)	
Albuterol-budesonide 180/160 µg	1013	0.45 (0.34, 0.60)	0.76 (0.62, 0.93)	0.008
Albuterol 180 µg	1014	0.59 (0.44, 0.78)		
Annualized total SCS dose (mg/year)		Mean (SD)	% Reduction in mean	
Albuterol-budesonide 180/160 µg	1012	86.2 (262.9)	33.4%	0.002
Albuterol 180 µg	1011	129.3 (657.2)		
Asthma control: ACQ-5 response at Week 24		No. (%) of responders[a]	Odds ratio (95% CI)	
Albuterol-budesonide 180/160 µg	1013	677 (66.8)	1.22 (1.02, 1.47)	0.03
Albuterol 180 µg	1014	630 (62.1)		
Asthma quality of life: AQLQ+12 response at Week 24		No. (%) of responders[a]	Odds ratio (95% CI)	
Albuterol-budesonide 180/160 µg	994	508 (51.1)	1.23 (1.02, 1.48)	0.028
Albuterol 180 µg	993	461 (46.4)		

[a]Responders were defined as patients with a decline (ACQ-5) or increase (AQLQ+12) from baseline score of at least 0.5. ACQ-5 is scored on a scale from 0 to 6 with lower numbers indicating better asthma control; minimum clinically important difference, 0.5 point. AQLQ(S)+12 is scored on a scale from 1 to 7, with higher scores indicating better asthma-related quality of life; minimum clinically important difference, 0.5 point.

Abbreviations: ACQ-5, Asthma Control Questionnaire-5; AQLQ+12, Asthma Quality of Life Questionnaire; CI, confidence interval; SD, standard deviation.

Papi A, Chipps BE, Beasley R, et al. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma. *N Engl J Med*. 2022;386(22):2071-2083. doi:10.1056/NEJMoa2203163

SUMMARY

As our understanding of the physiology of asthma has evolved, so have the recommended treatment approaches. Despite recent advances in our understanding of the importance of ICS in managing asthma, significant practice gaps remain. The recent FDA approval for as-needed use of fixed-dose combination of albuterol-budesonide in a pressurized metered-dose inhaler in the US offers clinicians a new option to deliver ICS in a manner consistent with the way that patients most reliably take their medications, opening the potential to decrease exacerbation risk for patients across asthma severity levels. ●

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