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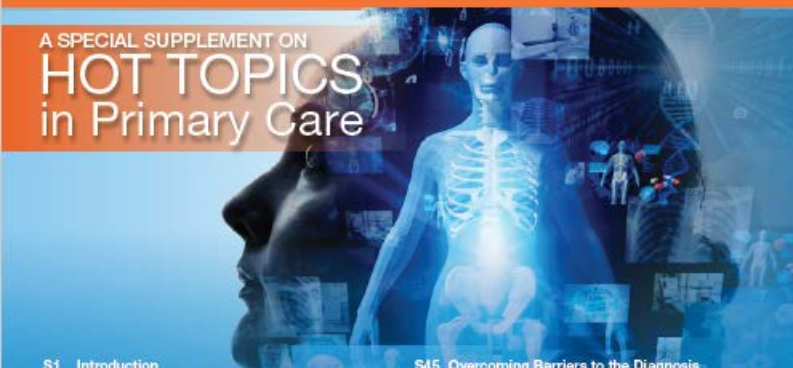

Addressing Nutritional Gaps: Simple Steps for the Primary Care Provider

Martin Quan, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Identify common shortfalls in the typical American diet.
- Address the link between poor diet quality and chronic disease.
- Identify patients at risk for vitamin deficiency and potential vitamin–drug interactions.
- Recognize patients with vitamin and mineral deficiencies.
- Partner with patients regarding selection and appropriate use of vitamin and mineral supplements to achieve recommended dietary allowances.

TARGET AUDIENCE

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

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NUTRITIONAL STATUS IN THE UNITED STATES

Although nutrition experts often advise that individuals consuming the standard American diet with 3 square meals a day do not need vitamins or nutritional supplements, it appears the American public disagrees. In fact, in 2019 the Council for Responsible Nutrition reported in its Consumer Survey on Dietary Supplements that 79% of adult females and 74% of adult males used dietary supplements with usage rates highest among those age 35 to 54 (81%) and those age >55 (79%).[1] A multivitamin was found to be the most popular supplement (58%) followed by vitamin D (31%), vitamin C (28%), and protein (21%). The top reason for taking a dietary supplement was to improve overall health and wellness. Notably, supplement users were more likely to practice healthy lifestyle habits than non-users and less than one-quarter of supplements taken by adults were recommended by their physician or other health care provider.[1]

The failure of the American diet to ensure micronutri-

ent intake adequacy was evident in a secondary analysis of nationally representative data from the National Health and Nutrition Examination Survey (NHANES).[2] Using data from the 2003–2004 and 2005–2006 data cycles, one-third of Americans were found to be at risk for 1 or more vitamin deficiency or anemia with significantly higher risk seen in non-Hispanic blacks (55%), individuals from low income households (42%), those without a high school diploma (42%), as well as underweight (42%) or obese individuals (39%). Consumption of an adequate diet based on estimated average requirements offered no guarantee of nutritional adequacy, with a 16% risk of 1 or more nutritional deficiency among those consuming an "adequate" diet compared with 57% in those with an inadequate diet.[2]

The adequacy of the American diet was further called into question by the 2012 US Centers for Disease Control and Prevention *Second National Report on Biochemical Indicators of Diet and Nutrition*.[3] Based on laboratory analysis of 58 biochemical indicators in specimens from a representative sample of the US population during a 4-year period from 2003 through 2006, the report stated that 10.5% of Americans had a vitamin B_6 deficiency (<20 nmol/L), 8.1% had a severe vitamin D deficiency (<30 nmol/L), 9.5% of women age 12 to 49 years had low body iron status (<0 mg/kg), and one-third of pregnant women were marginally iodine deficient.[3] The percentage of those who met recommended levels varied by age, sex, ethnicity, and/or geographic location.

Although *Dietary Guidelines for Americans 2015-2020* released by the US Department of Health and Human Services and the US Department of Agriculture noted that deficiencies of essential nutrients dramatically decreased over the past century, the report also noted that about one-half of all US adults have 1 or more preventable, diet-related chronic diseases.[4] Many of these, such as obesity and type 2 diabetes mellitus, were attributed to unhealthy eating patterns associated with low intakes of vegetables, fruits, whole grains, and dairy products, excess consumption of processed, calorie-dense foods, and lack of physical activity. The report identified potassium, dietary fiber, choline, magnesium, calcium, and vitamins A, D, E, and C as underconsumed nutrients and identified underconsumption of iron to be a particular concern in females age 19 to 50.

Although balanced consumption of unprocessed, nutrient-dense foods (eg, fruits, vegetables, legumes, whole grains, low-fat dairy, and lean meats) remains the preferred means of attaining recommended intakes of micronutrients, the dietary shortcomings of diets consumed by a large segment of the American public supports a role for vitamin and mineral supplementation. In the NHANES analysis,[2] users of multivitamin/mineral supplements (MVMS) were found to have the lowest risk of micronutrient deficiency (14%) compared with non-users (40%).[2] Similarly, based on data from NHANES 2007-2008 and 2009-2010, MVMS use contributed to a greater number of individuals meeting recommended intakes of almost all micronutrients measured.[5]

In addition to helping prevent micronutrient deficiency, dietary supplement use also could have a role in preventing micronutrient inadequacies, which could lead to development of chronic disease as hypothesized in the "triage theory".[6,7] According to this theory, when the availability of a micronutrient is inadequate, the body ensures that micronutrient-dependent functions required for short-term survival takes priority over more constitutive functions, the lack of which can have long-term consequences.[8] Current recommended daily vitamin intakes are based primarily on the dosage required to ensure that immediate clinical consequences associated with deficiency do not occur; for example, vitamin K to prevent bleeding, vitamin C to prevent scurvy, thiamine to prevent beriberi, and vitamin D to prevent rickets. Whether or not the current intake of micronutrients—which generally is less than the currently recommended intake—is sufficient to optimize their more subtle, long-term health effects has been questioned and remains an area of investigation. For example, although the adequacy of current vitamin K intake recommendations for coagulation function has been well established, it might not be high enough to optimize vitamin K-dependent constitutive functions important to maintain long-term health. Evidence forming the basis of the "triage theory" is presented in a perspective by McCann and Ames that supports the theory that vitamin K "inadequacy" might play a role in the development of age-related diseases such as osteoporosis, cardiovascular disease, and cancer.[8]

AT-RISK GROUPS

When taking a medical history, it is important to identify groups of patients at risk for nutritional deficiency, which can include those who are otherwise healthy, such as pregnant women,[9-11] children and adolescents,[12,13] and geriatric patients.[14,15] Individuals at particular risk for nutritional deficiency include those who are obese,[6,16-18] non-Hispanic black,[19,20] and low income or food insecure.[21,22] Other at-risk groups include individuals with inflammatory bowel disease, cancer, alcohol use disorder, HIV, chronic obstructive pulmonary disease,[23] diabetes,[24] substance use disorder, age-related macular degeneration or other vision impairment, a restricted or suboptimal eating pattern, a gastrointestinal malabsorption syndrome, those who have undergone bariatric surgery, or who have difficulty with manual dexterity such as arthritis.[2,25,26]

Drug-nutrient interactions can contribute to micronutrient deficiencies and should not be overlooked.[27] For example, metformin use has been linked to reduced intestinal absorption of vitamin B_{12} and the American Diabetes Association has recommended periodic measurement of vitamin B_{12} levels in metformin-treated patients.[28] Similarly, vitamin B_{12} deficiency has been reported with use of histamine-2 receptor antagonists.[29] Chronic proton pump inhibitor use has been linked with vitamin B_{12} deficiency and possibly with deficiencies of vitamin C, iron, calcium, and magnesium.[30,31]

Nutritional gaps are common among overweight and obese individuals and might stem from overconsumption of calorie-rich, micronutrient-poor, processed foods. Studies support these individuals being at increased risk for several micronutrient inadequacies/deficiencies, including vitamins A, C, D and E, as well as calcium and magnesium.[6] A history of bariatric surgery has been linked to deficiencies of thiamine, vitamin B_{12}, vitamin E, vitamin D, and copper.[32]

A patient's dentition can impact nutrition. In a small cross-sectional study of older adults, loss of posterior teeth on both sides was associated with less consumption of meat, nut, egg, fish, and dairy products resulting in less than adequate intake of protein, iron, and vitamin B_{12}.[33]

Whether a patient's diet includes animals or animal products also influences nutritional risk. In a Swiss study by Schupbach et al,[34] the intake and status of selected vitamins and nutrients was assessed among adults following vegetarian (n=53), vegan (n=53), or omnivore (n=100) diets for 1 or more year(s). Most participants in all 3 groups were iodine deficient. Other common deficiencies in all 3 groups included folic acid, vitamin B_6, vitamin B_2, niacin, iron, and zinc.

Finally, micronutrient deficiencies are common among patients who follow weight-loss diets, such as Dietary Approaches to Stop Hypertension (DASH), Atkins, Ornish, and Weight Watchers.[35-38] For example, high-fat, low-carbohydrate diets provide lower than recommended intakes of vitamin E, vitamin A, thiamine, vitamin B_6, folate, calcium, magnesium, iron, potassium, and dietary fiber. Very low-fat diets (eg, Ornish diet, Pritikin diet) generally are low in vitamin E, vitamin B_{12}, and zinc. Although moderate-fat, balanced nutrition diets (eg, Weight Watchers, Jenny Craig, NutriSystem) can be nutritionally sound provided appropriate and correct food choices are made, patients may be at risk for inadequate intake of several micronutrients. A recent study by Pascual et al found that subjects who lost an average of 29.7 kg over 3.4 years (body mass index 36.5 kg/m^2 at baseline) on Weight Watchers exhibited a healthier dietary pattern, including consumption of foods with higher micronutrient density, than a control group of weight-stable adults with obesity (body mass index 41.1 kg/m^2).[39] Nonetheless, one-quarter or more of the Weight Watchers group remained deficient in calcium, magnesium, zinc, vitamin A, vitamin B1, and folate, and nearly all were deficient in potassium, and vitamins D and E. Recent investigations have shown multiple deficiencies in the hypocaloric vegan Eat to Live-Vegan/Aggressive Weight Loss, high-animal protein low-carbohydrate Fast Metabolism, and weight-maintenance Eat, Drink and Be Healthy diets, particularly vitamin D, calcium, and vitamin B_{12}.[40]

VITAMIN AND MINERAL SUPPLEMENTATION

Micronutrients have distinct biologic functions essential to metabolic functioning, growth and development, and many cellular and organ system functions. It generally is agreed that achieving micronutrient intake levels on a population-wide and individual basis consistent with established reference values is a worthwhile public health goal.[4,41]

In 2018, a panel of 14 international experts in nutritional science and health was convened to clarify the role of multivitamin and mineral supplements in supporting human health.[42] Unsurprisingly, the panel's systematic review found that, on a population basis, the use of MVMS reduced the prevalence of inadequate intake of micronutrients. In addition, the panel concluded that using a daily MVMS with micronutrient amounts not exceeding tolerable upper intake levels was one way to provide the recommended levels of many micronutrients needed for maintaining health without posing a safety risk. However, the panel concluded there was insufficient evidence to indicate that MVMS are effective for primary prevention of chronic medical conditions including cardiovascular disease and cancer, and additional research was necessary to fully define the benefits of MVMS on health promotion and disease prevention.

PREVENTING CHRONIC DISEASE

The 2018 international panel also found insufficient evidence to support the long-term use of MVMS to lower the risk of some chronic diseases, such as cardiovascular disease and some types of cancer.[42] Moreover, the use of supra-dietary dosages of individual micronutrients has demonstrated potential for harm. For example, a meta-analysis by Miller et al reported a higher risk of all-cause mortality associated with dosages of vitamin E ≥400 mg/d.[43] In addition, a higher risk of lung cancer has been reported with beta-carotene supplementation, particularly in heavy smokers.[44]

Other investigators have found no benefit of micronutrient supplementation in reducing risk of chronic diseases. A systematic review and meta-analysis of 18 studies with

18.4 million person-years of follow-up found no association between MVMS use and cardiovascular disease or coronary heart disease mortality.[45] Similarly, a prospective cohort study of 30,899 US adults followed over a median of 6.1 years found dietary supplement use was not associated with a mortality benefit.[46]

In its 2013 systematic evidence review, the US Preventive Services Task Force (USPSTF) found limited evidence supporting any benefit from MVMS for preventing cardiovascular disease or cancer and no evidence supporting a benefit or harm of multivitamin use on cardiovascular disease, cancer, or mortality in healthy individuals without known nutritional deficiencies.[47] For cancer, after pooling findings of 2 randomized controlled trials, the USPSTF noted a 7% reduction (unadjusted pooled relative risk, 0.93 [confidence interval, 0.87 to 0.99]) of all cancer incidence among men who took a multivitamin for ≥10 years but no protective benefit among women.

A lack of cognitive benefit has been reported with use of some over-the-counter supplements. A systematic review of 38 trials evaluated the efficacy of omega-3 fatty acids, soy, ginkgo biloba, B vitamins, vitamin D plus calcium, vitamin C, or β-carotene, and multi-ingredient supplements in preventing cognitive decline, mild cognitive impairment, and Alzheimer-type dementia.[48] The investigators found insufficient evidence to recommend use of any over-the-counter supplement for cognitive protection in adults with normal cognition or mild cognitive impairment.

Although useful for preventing and treating micronutrient deficiencies, it is unclear whether supplement use by itself offers direct health benefits comparable to nutrients sourced from foods. Chen et al[40] found that supplement use was not associated with mortality benefits among US adults in a recent prospective cohort study of more than 27,000 adults using NHANES data from 1999 to 2010 linked to National Death Index mortality data. Although the study found adequate intake of vitamin K, vitamin A, magnesium, zinc, and copper was associated with reduced all-cause or cardiovascular disease mortality, the associations were restricted to nutrient intake from foods rather than supplements. In addition, the study found evidence of an increased risk of cancer death associated with excess calcium intake in participants who took supplemental dosages of at least 1000 mg/d and no association between cancer risk and calcium intake from foods. The bottom line: Although supplement use contributes to an increased level of total nutrient intake, there appears to be beneficial associations with nutrients from foods that aren't seen with supplements. This underscores the importance of encouraging patients to achieve adequate nutrient intake from eating nutrient-dense, whole, fresh, unprocessed foods within the framework of a healthy, balanced diet rather than relying solely on nutritional supplements to make up for the deficits associated with a poor diet.

SUPPLEMENTS IN CLINICAL PRACTICE

Choosing a supplement

The US Food and Drug Administration (FDA) regulates dietary supplements, but unlike prescription and non-prescription medications, the FDA is not authorized to review dietary supplements for safety and effectiveness before they are sold.[49] Only after a dietary supplement enters the marketplace can the FDA take action against adulterated or misbranded dietary supplements.

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Under the terms of the Dietary Supplement Health and Education Act of 1994, manufacturers of dietary supplements are not required to receive FDA approval before marketing dietary supplements that were sold in the United States prior to 1994. However, they are required to submit a safety-focused new dietary ingredient notification for any ingredient not falling under this clause. Manufacturers are required to ensure that the product label is truthful and not misleading, but for most claims made in labeling dietary supplements, the manufacturer or seller is not required to prove to the FDA that the claim is accurate or truthful before it appears on the product label. It is illegal for a manufacturer to market a dietary supplement product as a treatment or cure for a specific disease or to alleviate symptoms of a disease. Advertising of dietary supplements is under the Federal Trade Commission's jurisdiction.

To assist and inform consumers, the National Institutes of Health has launched an online Dietary Supplement Label Database at https://dsld.od.nih.gov/dsld. This database lists

the ingredients of thousands of dietary supplements and includes information from the label on dosage, health claims, and cautions.

Because the FDA does not validate the quality of supplements, a number of third-party groups have taken on this role, including the nonprofits US Pharmacopeia (USP) and National Science Foundation International, as well as the for-profit ConsumerLab.com and UL (formerly Underwriters Laboratory). Among these, the standards for supplements established by USP are the most widely accepted. USP also sets mandatory standards for pharmaceuticals.

PROVIDING NUTRITIONAL CARE IN PRIMARY CARE

The foundation for providing effective nutritional care in the outpatient setting is grounded in good communication with the patient, including the use of online tools and resources as well as involving a multidisciplinary care team.[50] Because nutrition is heavily influenced by behaviors that occur outside the provider-patient encounter, it is paramount to identify and address behaviors, as well as patient values and concerns, that contribute to nutritional deficiencies.[51] This process is directed toward fostering and supporting patients' motivation and sense of control, thereby boosting patient empowerment.

Because a goal of dietary counseling is for patients to take greater responsibility for and a more active role in decision making referable to their health, structuring the patient encounter using the 5 As construct might be helpful. Applying this framework to dietary counseling calls for: 1) Assessing the patient's diet and associated comorbidities, 2) Advising on the nutritional soundness of their diet and the benefits of selected changes, 3) Assessing readiness for change, 4) Assisting the patient in deciding where to begin making changes and behaviors to focus on, and 5) Arranging for follow-up and/or referral to available resources, as appropriate.[50]

Shared decision making is a key component of patient counseling and engagement to ensure that medical care better aligns with a patient's preferences and values. This approach requires the provider to explore treatment options with the patient to clarify the patient's values and concerns. This might entail discussing various options such as eating a healthy diet, taking 1 or more vitamin and mineral supplement(s), or doing nothing. It is important to keep in mind that the patient must be willing and able to implement the agreed upon treatment and the provider's role is to coach and support the patient.

RESOURCE TOOLKIT

A list of resources that might be helpful in learning about micronutrient-related issues, including those for patient education, is at http://www.pcmg-us.org/nutrition. ●

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An Individualized, Case-Based Approach to the Management of Irritable Bowel Syndrome

Brian E. Lacy, MD, PhD, FACG

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- Describe the multiple symptoms of irritable bowel syndrome (IBS) and their impact on quality of life
- Use a staged strategy for the diagnostic evaluation of IBS based on history and physical examination, including Rome IV criteria
- Individualize treatment for IBS based on an evolving understanding of pathophysiologic mechanisms using evidence-based therapies to address patient concerns and improve quality of life

TARGET AUDIENCE

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

DISCLOSURES

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BURDEN OF DISEASE

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder that affects 10% to 15% of the US population.[1] IBS is more prevalent in women and in persons younger than 50 years.[2] IBS is characterized by recurrent abdominal pain and altered bowel habits; bloating and distention frequently coexist. Based on the predominant bowel habit pattern, IBS is classified as constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), or a mixed pattern of constipation and diarrhea (IBS-M).[3]

Patients with IBS-D have significantly lower self-esteem than healthy controls[4] and patients with IBS-C.[5] Regardless of which type of IBS a patient may have, IBS sufferers report significantly greater symptom severity than patients with

inflammatory bowel disease (IBD).[6] Approximately one-third of people with IBS-D experience mild symptoms, one-half have moderate symptoms, and 1 in 8 have severe symptoms.[7] The IBS in America survey showed that three-quarters of persons with IBS symptoms tried an average of 3.6 nonprescription products before seeking medical care.[8,9] Abdominal pain was the most common reason people sought medical care.

CASE STUDY 1

SC is a 25-year-old woman with symptoms of constipation that began in high school, persisted through college, and worsened over the last 3 years. She reports skipping 1 to 2 days without having a bowel movement; she has significant straining at stool. Her stool is often hard and difficult to evacuate. She describes pressure and pain in her lower abdomen that is present more days than not. The abdominal pain generally improves after having a bowel movement. She frequently feels bloated and jokes that her boyfriend says that she sometimes looks "pregnant" because of the gas.

Adding more fiber to her normal fiber diet (25 g/d) made her more bloated, while stool softeners provided no benefit. SC has taken large amounts of magnesium citrate, which only caused urgent diarrhea and did not help with the abdominal pain or bloating. A trial of polyethylene glycol helped the constipation, but did not improve the abdominal pain or bloating.

She reports that her weight has been stable over the last few years (body mass index [BMI] 22). Her recent gynecologic exam, including a pregnancy test and complete blood count (CBC), was normal. Her only medication is an oral contraceptive. SC has not had any abdominal surgeries and she is otherwise healthy. No family member has IBD, celiac disease, or any type of GI malignancy. Her physical exam in the office is normal other than mild discomfort in the left lower quadrant. A rectal examination, with a chaperone present, is normal.

SC asks what her diagnosis is, whether she needs a colonoscopy, and whether other treatment options are available.

"What do you think I have? Do I need a colonoscopy?"

The diagnosis of IBS can be made by taking a careful history (medical, surgical, dietary, psychological) and asking about potential warning signs or "red flags." These signs include unexplained anemia, evidence of GI bleeding, unintentional weight loss, age >45 years without prior colon cancer screening, and family history of colorectal cancer or IBD. In addition to the history, the diagnosis is also based on a careful physical examination, ideally based on the Rome IV criteria (https://theromefoundation.org/rome-iv/whats-new-for-rome-iv/).[3] In addition to facilitating making a positive diagnosis instead of a diagnosis of exclusion, the Rome IV criteria are also useful to categorize IBS as IBS-C, IBS-D, or IBS-M.[3]

The Rome IV criteria are clinically useful for the accurate diagnosis of IBS. The criteria state that patients should have abdominal pain ≥1 day per week on average associated with ≥2 of the following symptoms: pain related to defecation, pain associated with a change in stool frequency, or pain associated with a change in stool form.[3] Symptoms should be active within the prior 3 months and should have developed at least 6 months earlier. Unlike previous Rome criteria, Rome IV criteria now suggest limited testing. This testing includes (1) a CBC to ensure the absence of anemia; (2) C-reactive protein (CRP) and/or fecal calprotectin to lower the suspicion for IBD and to prevent indiscriminate use of colonoscopy; and (3) serologic testing to rule out celiac disease.[3,10] In patients without red flag symptoms, further testing does not increase the sensitivity of the diagnosis.[11,12] Patients who may benefit from colonoscopy have warning signs or persistent symptoms, despite appropriate therapy, especially women age >60 years with persistent diarrhea, in whom microscopic colitis is a concern.

"What is the treatment for IBS-C?"

In 2018, the American College of Gastroenterology (ACG) published updated recommendations for the treatment of IBS based on a systematic review.[13] Nonpharmacologic therapy such as fiber, nonprescription laxatives, and stool softeners generally comprise initial therapy, but treatment satisfaction is low.[8,9] Three prosecretory medications are approved in the United States for IBS-C: linaclotide and plecanatide, both of which are guanylate cyclase C agonists, and lubiprostone, a chloride channel activator. All 3 are strongly recommended by the ACG for overall symptom improvement for IBS-C based on prospective, randomized controlled trials (RCTs). The use of lubiprostone is limited to women age ≥18 years. Patients treated with a prosecretory medication should be educated about the possible occurrence of severe diarrhea requiring treatment discontinuation and rehydration.

The efficacy and safety of linaclotide are supported by 4 RCTs involving 2867 patients with IBS-C.[13] Patients treated with linaclotide were less likely to remain symptomatic compared with placebo (relative risk [RR] 0.81; 95% confidence interval [CI], 0.77-0.85). Reduction in abdominal pain was significantly greater with linaclotide.

The use of lubiprostone and plecanatide is supported by 3 RCTs for each medication involving 1366 and 2612 patients with IBS-C, respectively.[13] Patients treated with lubiprostone (RR 0.91; 95% CI, 0.87-0.95) or plecanatide (RR 0.88; 95% CI, 0.84-0.92) were less likely to remain symptomatic compared with placebo.

CASE STUDY 1 (CONTINUED)

SC was told that, based on her history and examination, she had IBS-C. A colonoscopy was not recommended given her age and the absence of warning signs. She was started on once-daily linaclotide 290 µg. During a follow-up telephone call 2 weeks later, she reported that she was having a bowel movement each day and that her bloating and discomfort were better.

CASE STUDY 2

HP is a 51-year-old man with an 8-year history of loose, watery, bowel movements and lower abdominal pain. Symptoms occurred after he took antibiotics for a dental procedure and developed *Clostridium difficile* colitis. He has been tested multiple times for *C. difficile* and all studies have been negative. Laboratory studies (CBC, basic metabolic panel, CRP) have been normal on multiple occasions and a recent fecal calprotectin was also normal. A screening colonoscopy, including random biopsies throughout the colon, at age 50 years was normal.

On an average day, he has 5 to 6 loose, urgent bowel movements. His lower abdominal pain improves temporarily after having a bowel movement but then returns. He describes intermittent bloating and a feeling of "gassiness." He has eliminated dairy and caffeine from his diet without benefit. Loperamide helps the diarrhea to some degree, but does not help the abdominal pain or bloating. Despite these symptoms, he has gained weight over the past 5 years and is now overweight, with a BMI of 27.

The physical examination is normal other than mild tenderness in the left lower quadrant. He is worried because a cousin had similar symptoms and was diagnosed with Crohn's disease. No first-degree family member has had colorectal cancer or IBD, although his aunt has celiac disease.

HP is frustrated and has several questions.

"Why are my test results normal?"

This patient has had diarrhea and other symptoms for many years, but does not have any warning signs on history or physical examination (he is not anemic, has no weight loss, no history of colorectal cancer or IBD in a first-degree family member, and no serious findings on physical examination). In addition, laboratory tests and stool studies have been normal. These findings all increase the likelihood that his symptoms represent a functional GI disorder, such as IBS, rather than an organic disorder. Further evidence supporting the diagnosis of IBS are a normal CBC and CRP.

In patients with chronic diarrhea, it is also recommended that fecal calprotectin be measured to help distinguish IBS from IBD.[14] A fecal calprotectin level ≤40 µg/g combined with a normal CRP essentially excludes IBD in patients with IBS symptoms. In this patient, both a fecal calprotectin and a CRP were normal. Finally, serologic testing for celiac disease should be performed in patients with persistent diarrhea symptoms.[15] This was performed at the time of the office visit (with assurance that the patient had been ingesting some wheat-containing products within the past 2 weeks) and the results were normal, effectively excluding the diagnosis of celiac disease.

"Why did my symptoms develop?"

The etiology and pathophysiology of IBS are complex and incompletely understood. In addition to genetics, insults to the GI tract (eg, infections, inflammation, surgery, ischemia, medications, stress) may alter the gut microbiome, disrupt the immune system, and change both GI motility and sensation.[15,16] Identification of these factors and their interaction with the brain suggest that IBS is a disorder of gut-brain interactions.[17,18]

In HP's case, the prior GI infection (*C difficile* colitis) likely led to the development of his IBS symptoms. In fact, considerable evidence indicates that a prior acute infectious gastroenteritis is the strongest risk factor for IBS, occurring in 4% to 36% of patients.[19-21] Microbial factors may exert effects on the immune system and gut barrier function, as well as the gut-brain axis.[18,22] The prevailing theory is that IBS-D is associated in some patients with bacterial overgrowth in the small intestine that impairs gut motility, whereas IBS-C is associated in some patients with increased levels of archaea that slow intestinal contractility.[22]

"What is the role of diet in treating my symptoms?"

Many patients with IBS associate symptoms of abdominal pain, bloating, or diarrhea with eating a meal. Thus, dietary interventions appear to be a reasonable treatment approach. The addition of a soluble fiber product to the diet that has a low rate of fermentation (eg, psyllium) may improve IBS symptoms in some patients.[13] However, fiber products, especially insoluble fiber, may worsen bloating and abdominal pain. No large prospective studies have assessed the utility of soluble fiber in patients with IBS-D.[13]

The 2 diets most commonly used for the treatment of IBS are a low/no gluten diet and a low FODMAP (fermentable oligo-, di-, monosaccharide, and polyol) diet.[13,23] Routine use of a gluten-free diet is not recommended due to the low-quality evidence supporting its use.[23] Patients who note improvement on a low/no gluten diet likely improve not because they are allergic to wheat or have celiac disease, but rather because gluten contains a large amount of fructan, a short-chain carbohydrate that can cause gas, bloating, distension, and diarrhea.[24]

An analysis of 7 RCTs evaluating the efficacy of a low

FODMAP diet to treat IBS symptoms showed improvement in overall IBS symptoms compared with control diets.[23] The ACG recommends this diet as a reasonable approach, recognizing that the quality of evidence is very low.[13] It is important to remember that the elimination phase of the low FODMAP diet should be carried out for only 4 to 6 weeks, to minimize the likelihood of micronutrient deficiencies. Foods should then be reintroduced slowly.

"What about using a probiotic to improve my symptoms?"

Because alterations in the gut microbiome can lead to symptoms of IBS, modulating the gut microbiome with a probiotic appears to make sense. Probiotics, defined as ". . . live microorganisms that, when administered in adequate amounts, confer a health benefit on the host,"[25] come in a wide array of formulations and doses. A recent meta-analysis of 53 RCTs showed that probiotics were more likely to improve symptoms of IBS compared with placebo, although the results were not overwhelming.[26] Probiotics containing a mixture of different organisms, especially those with *Lactobacillus* and *Bifidobacteria*, appear to be better than probiotics that contain only a single organism.[13,26] Based on low-quality evidence, the ACG gave probiotics, as a class, a weak recommendation.[13]

"Will an antibiotic improve my IBS-D symptoms?"

Treating patients with IBS-D with a course of antibiotics has been shown to be effective.[27] The most commonly studied antibiotic for the treatment of IBS without constipation (both IBS-D and IBS-M) is rifaximin, a nonabsorbable antibiotic. Although its mechanism for improving IBS symptoms is unclear, several large, prospective RCTs have demonstrated that a dose of 550 mg 3 times daily for 14 days is both safe and effective (number needed to treat [NNT] = 9).[13,26,27] In contrast to other medications or diets, which need to be used chronically, a 2-week course of rifaximin may improve symptoms for up to 12 weeks.

Recognizing that IBS is a chronic condition for most patients, authors of a recent study demonstrated that repeated dosing with rifaximin was both safe and effective.[28] Because a validated treatment algorithm for the treatment of IBS-D does not exist, a precise answer of when to use rifaximin for the treatment of IBS-D symptoms cannot be provided. However, if a patient has not had symptom improvement after trying dietary therapy and over-the-counter agents, then rifaximin is a reasonable choice.

"Are other treatment options available?"

Loperamide is often used for IBS-D, but there is little evidence to support its use and it does not improve either the cardinal symptom of IBS—abdominal pain—or bloating. Consequently, the ACG recommends against the use of loperamide to treat overall IBS symptoms.[13]

Eluxadoline acts as an agonist on the mu- and kappa-opioid receptors, while it is an antagonist on the delta-opioid receptor.[29] Three large RCTs showed that eluxadoline, at either the 75- or 100-mg dose, was more likely to improve overall IBS-D symptoms (both diarrhea and abdominal pain) than placebo (NNT=9-10).[29] Consequently, eluxadoline is recommended by the ACG to treat overall IBS-D symptoms, although the recommendation is weak because of some heterogeneity in the published studies.[13] This medication should not be used in patients who have undergone cholecystectomy or in patients who abuse alcohol, as these 2 factors are associated with the development of pancreatitis.[30] However, eluxadoline would be a reasonable treatment option for HP.

Another treatment option for IBS-D is alosetron, a serotonin antagonist. Several large, randomized placebo-controlled studies have demonstrated that alosetron can improve symptoms of abdominal pain, diarrhea, and urgency in women with symptoms of IBS-D in whom standard therapy has failed (NNT=7.5).[13,31] A more recent, real-world, dose-titration study, using the lower dose of 0.5 mg twice daily with dose escalation as needed, found an overall response rate of 45% with few adverse effects.[32] Alosetron has been associated with rare events of ischemic colitis. Alosetron is not approved for men and, thus, would not be an appropriate treatment option for this patient.

A review of the safety profile of all medications used to treat IBS-D symptoms was recently published.[33]

CASE STUDY 3

RE is a 57-year-old woman with symptoms of alternating constipation and diarrhea. Symptoms began in her mid-40s, primarily characterized by lower abdominal pain and symptoms of constipation (skipping days without a bowel movement, hard to evacuate stool, harder stool). As there was no evidence of an organic disorder, she was diagnosed with IBS-C at the time. She was treated with polyethylene glycol and as-needed use of smooth muscle antispasmodic agents, which provided some relief of her constipation symptoms, but not much relief of her abdominal pain.

Approximately 18 months ago, RE noted that she began having 1 or 2 days per week with loose, urgent bowel movements. The other days were characterized by stool that was harder and somewhat difficult to evacuate. She increased her use of polyethylene glycol, resulting in stool that was often loose and unpredictable.

She finds that daily loperamide controls the diarrhea, but worsens the constipation and accompanying abdominal pain. Bloating is present most days and she frequently feels distended. She has not changed her diet, exercise routine, or prescription medications (levothyroxine for hypothyroidism, loratadine for mild seasonal allergies, and paroxetine for mild anxiety). She has gained approximately 1 pound per year for the past 10 years (BMI 28).

A recent gynecologic exam was normal. Because her bowel habits had changed, her gynecologist referred her for a colonoscopy, which was normal. A CBC, thyroid-stimulating hormone level, and serum tissue transglutaminase antibody with serum immunoglobulin A (IgA) also were normal. Her physical exam in the office is normal other than mild discomfort in the left lower quadrant. A rectal examination, with a chaperone present, is normal. No family member has colorectal cancer, celiac disease, or IBD.

RE is particularly bothered by bloating, and the urgent diarrhea makes it difficult to attend meetings at work and participate in social events. She is worried that the change in bowel habits represents something serious such as a hidden cancer.

Treatment plan for this patient

The natural history of IBS and how bowel habits frequently change over time (from IBS-C to IBS-M or IBS-M to IBS-D or IBS-D to IBS-M; less commonly directly from IBS-C to IBS-D) was reviewed with RE. IBS-M occurs in approximately one-quarter of patients with IBS, while IBS-D occurs in 40% and IBS-C in 35%.[2] This patient did not have any red flags on history or exam. Recent laboratory findings, gynecologic examination, and colonoscopy were all normal. As no medication is US Food and Drug Administration approved for IBS-M, and because bloating was a predominant symptom, we decided to institute a low FODMAP diet. She did this for 4 weeks and noted a significant improvement in general IBS symptoms, although her constipation became a bit worse. Improvement of 1 symptom and worsening of another with treatment is not unusual.

RE slowly reintroduced foods per the low FODMAP protocol to identify trigger foods. We decided that she should take a little more polyethylene glycol each day for the constipation symptoms. To help with visceral pain and bowel urgency, we added a neuromodulator at a low dose, ie, amitriptyline 10 mg at bedtime. Tricyclic antidepressants have been shown to improve symptoms of abdominal pain in patients with IBS (NNT = 4.5).[13] We discussed routine scheduled bathroom time in the morning to help empty her lower colon, with the goal of minimizing symptoms of urgent diarrhea later in the day. To prevent urgent diarrhea, RE began to use one-half of a 1-mg loperamide tablet 1 hour before a business meeting or social event. After 4 weeks, she reported feeling 50% better and a bit less anxious about urgent diarrhea. This latter point underscored the importance of addressing the patient's fears and concerns as such support can dramatically improve a patient's quality of life. Having identified several foods that made her bloating much worse, she continued on the low FODMAP diet. With the goal of reducing her symptoms further, she continued on low-dose amitriptyline, but we increased the dose to 20 mg at bedtime. At her visit 4 weeks later, she reported not using any loperamide since her last visit and that she felt 80% better. Because she was generally satisfied with her symptoms, we decided to make no further changes. ●

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A New Era in Asthma Management: Assessment of Asthma Control

Kevin R. Murphy, MD; Joel Solis, MD

BURDEN OF DISEASE

Asthma is recognized as a chronic, heterogenous disease characterized by airway inflammation and a history of respiratory symptoms (eg, wheeze, shortness of breath, chest tightness, or cough) that vary over time and in intensity.[1] Variations are often triggered by factors such as exercise, allergen or irritant exposure, change in weather, or viral respiratory tract infections. Asthma symptoms and airflow limitation may resolve spontaneously or in response to treatment. Symptoms may be absent for weeks or months, yet airway hyperresponsiveness related to chronic airway inflammation usually persists.[1]

Asthma is a common disease in children, adolescents, and adults that results in substantial morbidity and utilization of health care resources.[2] In 2018, there were an estimated 5.5 million children and 19.2 million adults in the United States with asthma, of whom 45% had ≥1 asthma attack.[2] In 2016, there were nearly 10 million office visits with asthma as a primary diagnosis.[2] One-third (33.1%) of adults with asthma report their health as fair or poor.[3] Anxiety, depression, and asthma control are independent predictors of diminished health-related quality of life in people with asthma.[4]

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The economic burden of asthma, including costs incurred by absenteeism and mortality, was estimated at $82 billion in 2013.[5] By comparison, the total economic burden – including lost productivity – has been estimated at $330 billion for heart disease and stroke and $327 billion for diabetes.[6] The 20-year estimated burden of direct and indirect costs associated with asthma is $964 billion, with a loss of 15.5 million quality-adjusted life-years in adolescents and adults.[7]

A key factor contributing to the burden of disease associated with asthma is poor adherence to treatment by patients.[8-10] A variety of additional factors contribute, including limited understanding among patients about asthma and its treatment, as well as poor patient-clinician communication.[11-13] Discordance regarding asthma control is common between patients and clinicians.[14] Patients often overestimate their asthma control[15] or may tolerate symptoms indicative of poor control based on the belief that the symptoms are part of living with asthma.[16] Collectively, these factors contribute to suboptimal asthma control.

ASSESSING ASTHMA CONTROL

Asthma control means the extent to which the effects of asthma either can be seen in the patient or have been reduced or resolved by treatment. Asthma control has 2 domains: symptom control and risk factors for future poor outcomes, particularly flare-ups (exacerbations). It is important to assess the patient's future risk for exacerbations, even when symptom control is good. Risk factors for exacerbations that are independent of symptom control include a history of ≥1 exacerbation in the previous year, socioeconomic disadvantages, poor treatment adherence, incorrect inhaler technique, low lung function, smoking, and blood eosinophilia.[1]

Many tools are available to assess asthma control and are listed in the **TABLE**.[17-26] Of those tools, the Asthma Impairment and Risk Questionnaire (AIRQ) and Asthma Control Test (ACT) are validated for patients age ≥12 years and have numerically scored questions providing total scores and cut points for varying levels of asthma control. The ACT (**FIGURE 1**) is limited to assessing symptom control with no direct measure of future risk.[19,20,23]

TABLE. **Tools for assessing asthma control**

Tool	Focus		Target patient age (y)	Administered by	No. of items	Recall time
	Symptoms	Risk				
Asthma APGAR[17,18]	✓	✓	5-45	Self	6	2 wk (symptoms and risk)
Asthma Control Questionnaire[19]	✓		≥11	Self	7	1 wk
	✓		6-10	HCP	7	1 wk
Asthma Control Test[20]	✓		≥12	Self	5	4 wk
Asthma Control and Communication Instrument[21]	✓	✓	≥12	Self	12	Since last visit (symptoms and risk)
Asthma Impairment and Risk Questionnaire[22]	✓	✓	≥12	Self/HCP	10	2 wk (symptoms); 1 year (risk)
Childhood Asthma Control Test[23]	✓		4-11	Self/parent	7	4 wk (symptoms); 1 year (risk)
Composite Asthma Severity Index[24]	✓	✓	6-17	HCP	8	2 wk (symptoms); 2 mo (risk)
Pediatric Asthma Control and Communication Instrument[25]	✓	✓	≤21	Self/parent	12	2 wk (symptoms); since last visit/2 mo (risk)
Test for Respiratory and Asthma Control in Kids[26]	✓	✓	<5	Parent	5	4 wk (symptoms); 12 mo (risk)

Abbreviations: HCP, health care professional.

ASTHMA IMPAIRMENT AND RISK QUESTIONNAIRE

To address the gaps in commonly used tools for assessing asthma control, the Asthma Impairment and Risk Questionnaire (AIRQ) was recently developed.[22] The AIRQ was devised using a modified Delphi process by a network of 190 US scientific experts and primary and specialty care clinicians with diverse practice experiences in geographic areas representing a high burden of disease. The AIRQ was validated using patients (N=442) from geographically diverse US allergy/immunology and pulmonology clinics. The symptom control domain of the AIRQ was validated against the ACT, whereas the future risk domain was validated against the patient's prior-year exacerbations as documented in their medical record. From the initial 15 questions that assessed symptom control and risk, the final questionnaire includes 10 dichotomous (yes or no) questions, 7 focusing on symptom control and 3 on future risk (**FIGURE 2**).[49] The 10 questions evaluate symptoms, social and physical activities, exacerbations, related health care resource utilization, perception of asthma control, and use of rescue medications. The AIRQ score ranges from 0 to 10. A score of 0 or 1 indicates asthma is well-controlled, whereas a score of 2 to 4 indicates asthma is not well-controlled. A score of 5 to 10 indicates asthma is very poorly controlled.

The AIRQ performed exceptionally well, including a superior comparison to the ACT.[20,22] Importantly, as shown in the AIRQ validation study, 31% of patients classified as well-controlled by ACT score (≥20) had suffered ≥1 exacerbation in the previous year, suggesting limitations in using ACT as a sole measure of asthma control.[22] Inclusion of the wide array of items in AIRQ to assess both symptom control and future risk identified many patients with exercise limitations and exacerbations that were characterized by acute treatment with oral corticosteroids or emergency department/unplanned office visits, events that are not assessed by the ACT or many other asthma control tools for patients age ≥12 years.

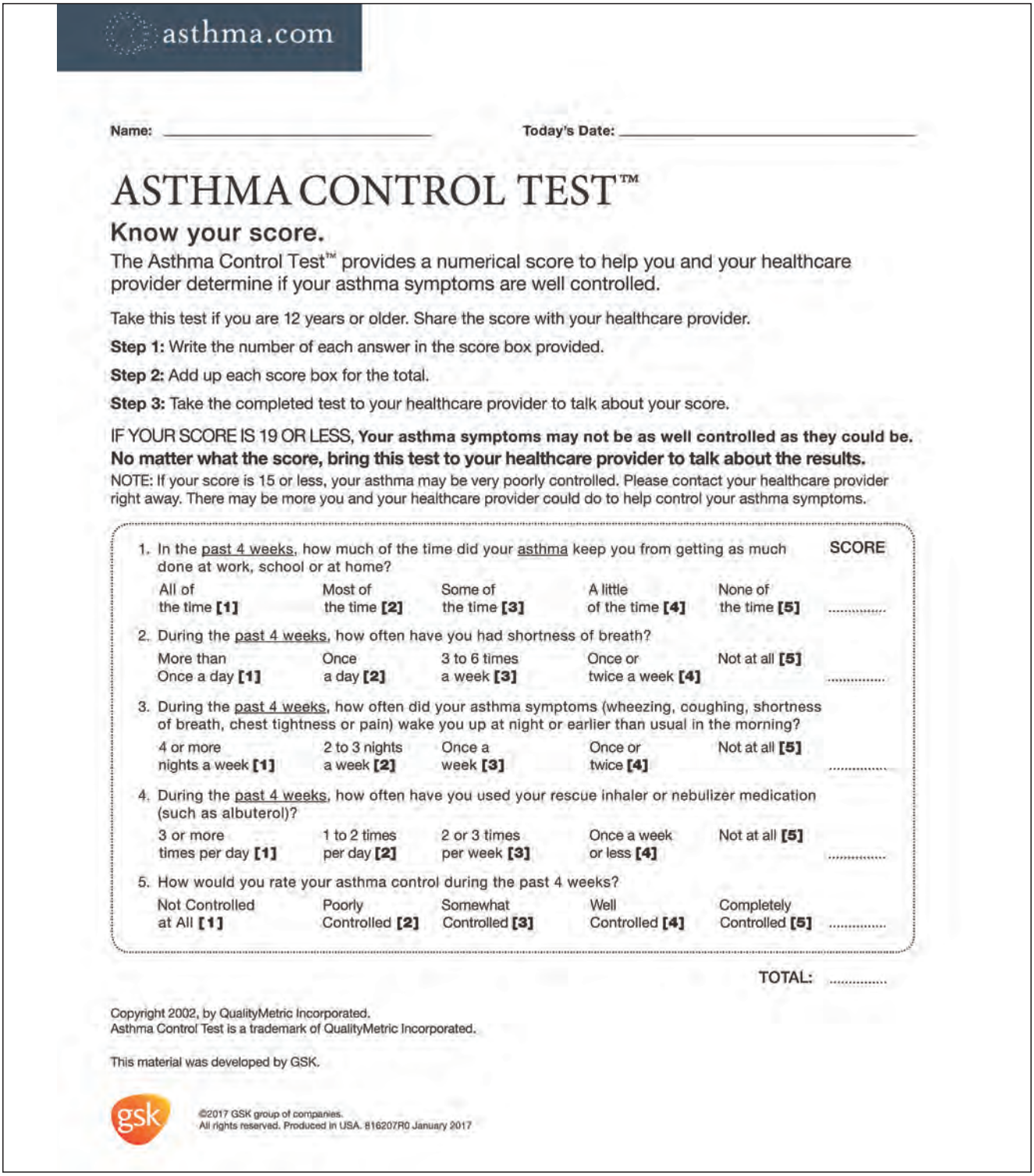
MANAGEMENT OF PATIENTS WITH UNCONTROLLED ASTHMA

The most up-to-date recommendations for managing patients with uncontrolled asthma (discussed below) were released by Global Initiative for Asthma (GINA) in 2020.[1] Updated recommendations by the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report-4 (EPR-4) have been circulated in draft form and are currently being finalized.

Patients found to have uncontrolled asthma should continue to receive care that meets their clinical and personal needs and capabilities. A key step in managing a patient with uncontrolled asthma is to confirm the asthma diagnosis. If not done as part of assessing asthma control, lung function should be measured. In addition, reevaluation of asthma control is appropriate to ensure that the treatment plan is consistent with recommended evidence-based therapy.

Attention should be paid to verify that all modifiable

FIGURE 1. **Asthma Control Test**[48]



asthma.com

Name: _____ Today's Date: _____

ASTHMA CONTROL TEST™

Know your score.

The Asthma Control Test™ provides a numerical score to help you and your healthcare provider determine if your asthma symptoms are well controlled.

Take this test if you are 12 years or older. Share the score with your healthcare provider.

Step 1: Write the number of each answer in the score box provided.

Step 2: Add up each score box for the total.

Step 3: Take the completed test to your healthcare provider to talk about your score.

IF YOUR SCORE IS 19 OR LESS, **Your asthma symptoms may not be as well controlled as they could be. No matter what the score, bring this test to your healthcare provider to talk about the results.**

NOTE: If your score is 15 or less, your asthma may be very poorly controlled. Please contact your healthcare provider right away. There may be more you and your healthcare provider could do to help control your asthma symptoms.

					SCORE
1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?	All of the time **[1]**	Most of the time **[2]**	Some of the time **[3]**	A little of the time **[4]**	None of the time **[5]**	.....
2. During the past 4 weeks, how often have you had shortness of breath?	More than Once a day **[1]**	Once a day **[2]**	3 to 6 times a week **[3]**	Once or twice a week **[4]**	Not at all **[5]**	.....
3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?	4 or more nights a week **[1]**	2 to 3 nights a week **[2]**	Once a week **[3]**	Once or twice **[4]**	Not at all **[5]**	.....
4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?	3 or more times per day **[1]**	1 to 2 times per day **[2]**	2 or 3 times per week **[3]**	Once a week or less **[4]**	Not at all **[5]**	.....
5. How would you rate your asthma control during the past 4 weeks?	Not Controlled at All **[1]**	Poorly Controlled **[2]**	Somewhat Controlled **[3]**	Well Controlled **[4]**	Completely Controlled **[5]**	.....

TOTAL: .....

This material was developed by GSK.

[https://www.asthma.com/additional-resources/asthma-control-test.html]

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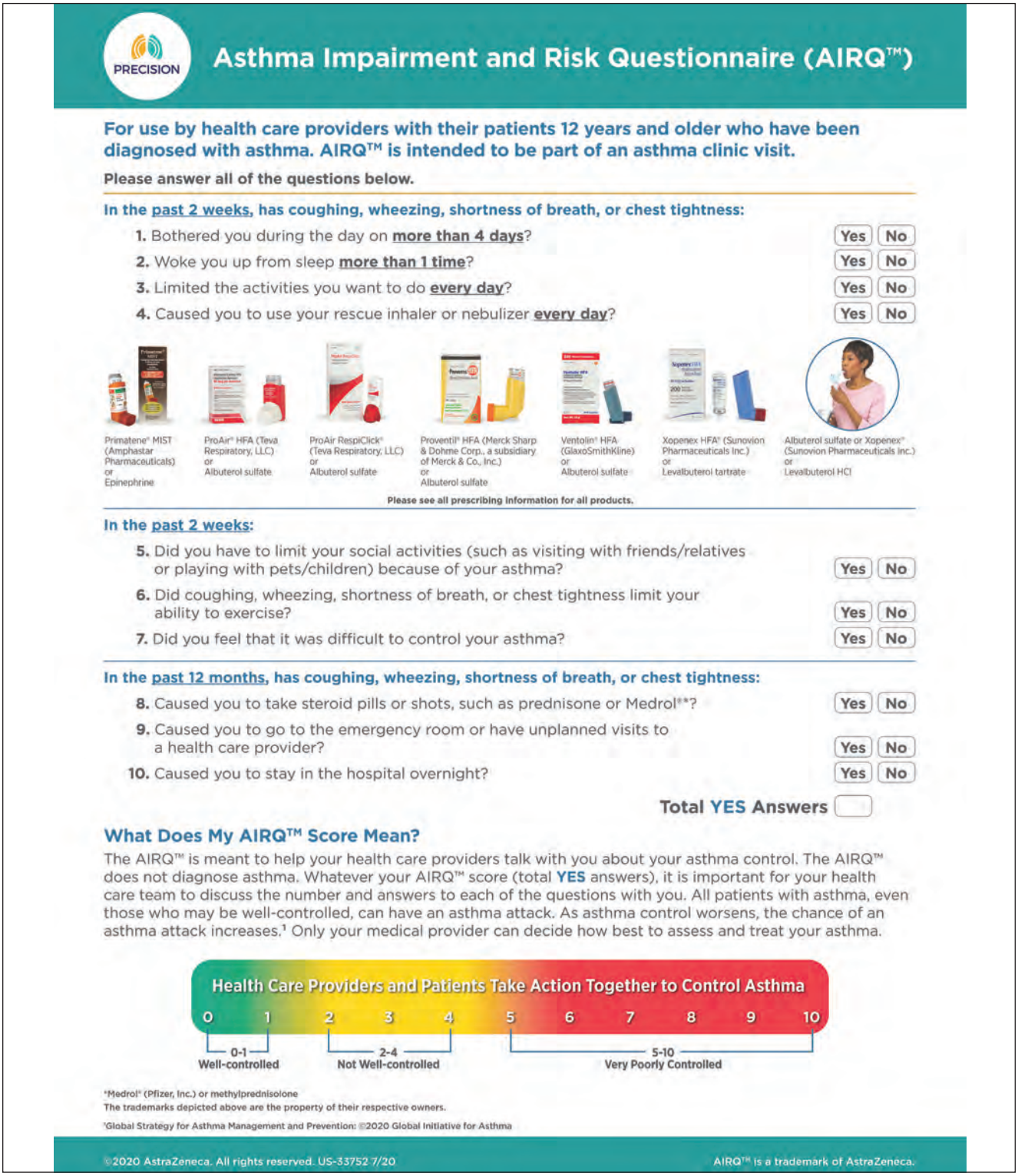
FIGURE 2. **Asthma Impairment and Risk Questionnaire**[49]



PRECISION

Asthma Impairment and Risk Questionnaire (AIRQ™)

For use by health care providers with their patients 12 years and older who have been diagnosed with asthma. AIRQ™ is intended to be part of an asthma clinic visit.

Please answer all of the questions below.

In the past 2 weeks, has coughing, wheezing, shortness of breath, or chest tightness:

1. Bothered you during the day on **more than 4 days**? Yes No
2. Woke you up from sleep **more than 1 time**? Yes No
3. Limited the activities you want to do **every day**? Yes No
4. Caused you to use your rescue inhaler or nebulizer **every day**? Yes No

Primatene® MIST (Amphastar Pharmaceuticals) or Epinephrine

ProAir® HFA (Teva Respiratory, LLC) or Albuterol sulfate

ProAir RespiClick® (Teva Respiratory, LLC) or Albuterol sulfate

Proventil® HFA (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.) or Albuterol sulfate

Ventolin® HFA (GlaxoSmithKline) or Albuterol sulfate

Xopenex HFA® (Sunovion Pharmaceuticals Inc.) or Levalbuterol tartrate

Albuterol sulfate or Xopenex® (Sunovion Pharmaceuticals Inc.) or Levalbuterol HCl

Please see all prescribing information for all products.

In the past 2 weeks:

5. Did you have to limit your social activities (such as visiting with friends/relatives or playing with pets/children) because of your asthma? Yes No
6. Did coughing, wheezing, shortness of breath, or chest tightness limit your ability to exercise? Yes No
7. Did you feel that it was difficult to control your asthma? Yes No

In the past 12 months, has coughing, wheezing, shortness of breath, or chest tightness:

8. Caused you to take steroid pills or shots, such as prednisone or Medrol®*? Yes No
9. Caused you to go to the emergency room or have unplanned visits to a health care provider? Yes No
10. Caused you to stay in the hospital overnight? Yes No

Total YES Answers ☐

What Does My AIRQ™ Score Mean?

The AIRQ™ is meant to help your health care providers talk with you about your asthma control. The AIRQ™ does not diagnose asthma. Whatever your AIRQ™ score (total **YES** answers), it is important for your health care team to discuss the number and answers to each of the questions with you. All patients with asthma, even those who may be well-controlled, can have an asthma attack. As asthma control worsens, the chance of an asthma attack increases.† Only your medical provider can decide how best to assess and treat your asthma.

Health Care Providers and Patients Take Action Together to Control Asthma

0 1 2 3 4 5 6 7 8 9 10

0-1 Well-controlled

2-4 Not Well-controlled

5-10 Very Poorly Controlled

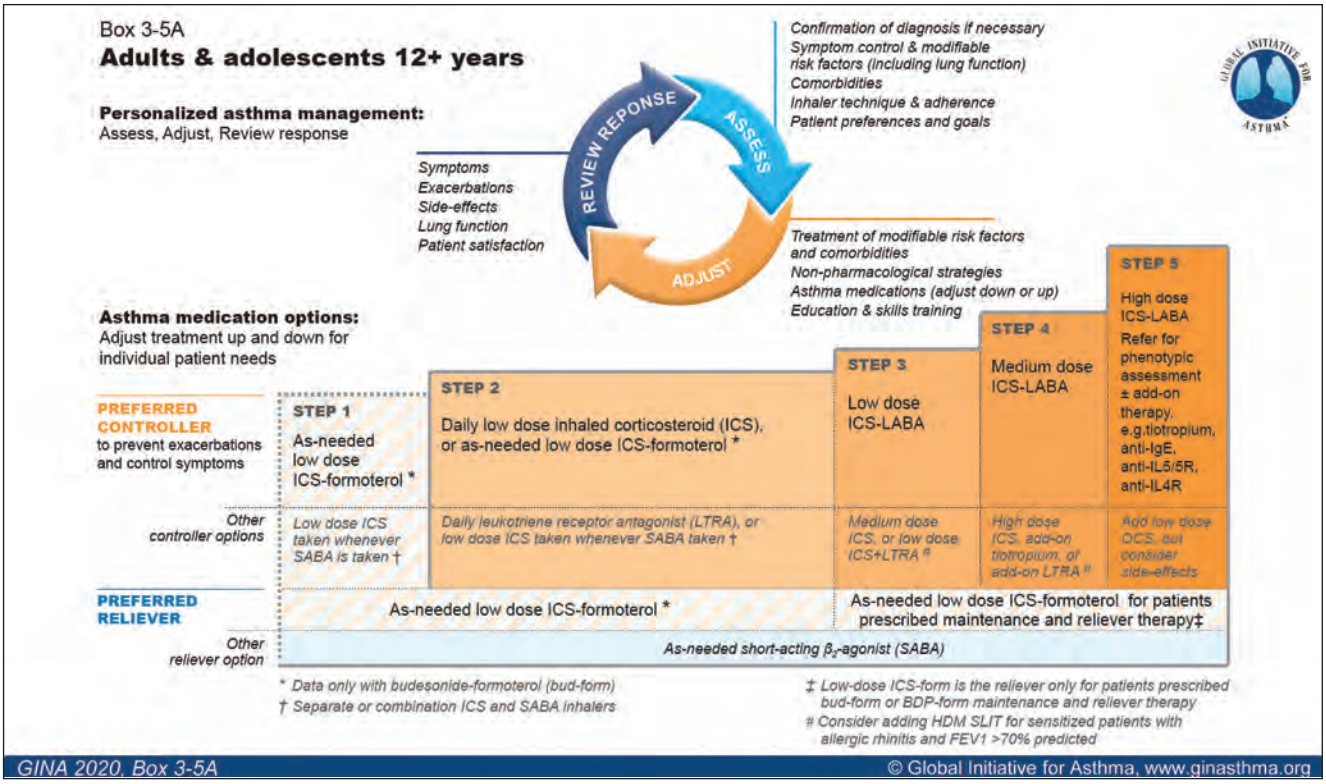
*Medrol® (Pfizer, Inc.) or methylprednisolone

The trademarks depicted above are the property of their respective owners.

†Global Strategy for Asthma Management and Prevention: ©2020 Global Initiative for Asthma

[http://www.airqscore.com]

FIGURE 3. **Modifying treatment in adults and adolescents with uncontrolled asthma**[1]



Abbreviations: BDP, beclomethasone dipropionate; FEV1, forced expiratory volume in 1 second; HDM SLIT, house dust mite sublingual immunotherapy; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL5, interleukin-5; IL5R, interleukin-5 receptor; LABA, long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting beta$_2$-agonist.

risk factors have been identified and appropriate treatment instituted. This strategy is particularly important for risk factors that do not require or respond to a step-up in controller treatment. Examples include poor inhaler technique, suboptimal treatment adherence, home and workplace atopic and irritant triggers, tobacco use or exposure, and comorbidities such as gastroesophageal reflux disease, nasal polyposis, obesity, and sleep apnea.

Patient understanding of asthma, treatment goals, and treatment options should be assessed and reinforced with further education. A guide for patients and families is available from the National Heart, Lung, and Blood Institute (https://www.nhlbi.nih.gov/files/docs/public/lung/SoYouHaveAsthma_PRINT-reduced-filesize.pdf). Patients should be educated about the importance of the use of anti-inflammatory medications, because only 39% of adults and 40% of children with asthma use a long-term control medication.[27] In addition, patient education should include the importance of reducing the risk of exposure to allergens or other sensitizing agents.[1]

The patient's familiarity with their written asthma action plan should be assessed routinely, as this is an indicator of the patient's ability to self-manage their asthma. Patients should be invited to share difficulties they may be having with the action plan or any other issues that may affect treatment adherence. If difficulties are identified, focus a collaborative discussion on finding a solution that is acceptable to the patient and that they are able and willing to implement. Sample written action plans are available from the National Heart, Lung, and Blood Institute (https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/asthma-action-plan) and GINA (https://ginasthma.org/wp-content/uploads/2019/01/GINA-Implementation-Toolbox-2019.pdf).

Objective assessment of inhaler technique is especially important because proper technique has a direct impact on patient health outcomes and treatment tolerability.[28] Because administration errors with inhaled medications by patients are common, and clinicians are often unfamiliar with proper administration technique,[29-33] the use of authoritative patient education resources demonstrating proper inhaler technique – such as those by the Centers for

Disease Control and Prevention – is recommended (https://www.cdc.gov/asthma/inhaler_video/default.htm).

PHENOTYPES AND BIOMARKERS

The heterogeneous nature of asthma and the many clusters of demographic, clinical, and/or pathophysiologic characteristics point to the importance of recognizing asthma phenotypes and endotypes in patients with uncontrolled asthma.[1,34] Identifying the asthma phenotype is especially important for patients with moderate or severe uncontrolled asthma because some phenotype-specific treatments are available. For example, omalizumab is indicated for allergic asthma, whereas benralizumab, dupilumab, mepolizumab, and reslizumab are indicated for the eosinophilic phenotype.

Two peripheral biomarkers (Immunoglobulin E [IgE] and eosinophils) are particularly helpful in identifying asthma phenotype and guiding treatment. IgE is the predominant biomarker for allergic asthma that is produced early in the allergic cascade.[35] The serum IgE level correlates closely with the presence and severity of asthma in adults, adolescents, and children.[36,37]

Owing to the inflammatory nature of asthma, eosinophils are recruited through the complex interaction of cytokines and other inflammatory mediators.[38,39] The blood eosinophil count is more closely correlated with risk of asthma exacerbations.[40] Symptom severity is increased in eosinophilic asthma, although symptom severity is not identified exclusively with eosinophilia.[35,41-43]

KEY ASTHMA TREATMENT RECOMMENDATIONS

Global Initiative for Asthma

GINA was implemented in 1993 to develop a network of individuals, organizations, and public health officials for the dissemination of information related to the care of patients with asthma.[44] Another key purpose of GINA was to provide a mechanism to incorporate the results of scientific evidence into asthma care, leading to the first GINA report in 1995, developed in collaboration with the National Heart, Lung, and Blood Institute. The report has been updated several times, and recently on a yearly basis, to reflect the totality of the evolving evidence. Consequently, the GINA report provides comprehensive recommendations for the diagnosis and treatment of patients with asthma.[1] Key recent changes include the recommendations that all adults and adolescents should be treated with an inhaled corticosteroid (ICS) to reduce the risk of severe exacerbations. In addition, treatment with only a short-acting beta$_2$-agonist is no longer recommended.

Specific recommendations for step-up therapy are beyond the scope of this article, as recommendations depend on the patient's current therapy and asthma control. Nonetheless, step-up therapy involves either increasing the dose of the current controller therapy or adding another controller medication. For example, a patient aged ≥12 years whose asthma is uncontrolled with the combination of a low-dose ICS plus a long-acting beta$_2$-agonist may benefit from increasing to a medium-dose ICS plus a long-acting beta$_2$-agonist (**FIGURE 3**).[1] Discussions with a patient about step-up therapy should consider affordability, as asthma care in the United States is associated with high rates of cost-related underuse of medications. Although the reason is unclear, suboptimal adherence to asthma medications does not appear to be directly related to income.[45] Any step-up should be regarded as a therapeutic trial, and the response reviewed after 2 to 3 months.[1] In some cases, for example, during viral infection or seasonal allergen exposure, the duration of step-up therapy may be only 1 to 2 weeks.

National Asthma Education and Prevention Program

The NAEPP was initiated in 1989 to address the growing health problem of asthma in the United States.[46] From the beginning, the NAEPP has involved a wide variety of stakeholder groups and organizations with the general goals to raise awareness among all asthma stakeholders about the importance of asthma, as well as to promote effective, evidence-based treatment so as to reduce the disease burden. The first guideline report was published in 1991, with subsequent updates and comprehensive revisions. The last comprehensive revision was the Expert Panel Report-3 in 2007. The EPR-4, which is a limited revision that focuses on 6 topics, is being finalized.[47]

SUMMARY

Asthma is often uncontrolled in patients of all ages and is frequently unrecognized, resulting in a significant burden of disease. Consequently, assessing asthma control at every opportunity is critical. A wide variety of tools to assess asthma control are available; however, many have clinically important limitations to their use. The AIRQ was developed recently to be more widely applicable, by assessing both symptom control and future risk domains. In patients with uncontrolled asthma, step-up therapy is generally required using evidence-based recommendations for treatment provided in the GINA 2020 report and soon-to-be-released NAEPP EPR-4 report. ●

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Case Studies in Hyperlipidemia

Michael Cobble, MD, FNLA

INTRODUCTION

I had a conversation with a cardiologist 15 years ago at the American College of Cardiology annual meeting during which he asked a simple question regarding patients at intermediate risk for atherosclerotic cardiovascular disease (ASCVD) – "Why wait until they see me in the cath lab after a heart attack to treat their lipids?" The point that resonated with me was to target patients at intermediate risk before they have a life-changing event or even develop angina. This simple question changed my approach to managing patients with dyslipidemia, particularly those at intermediate risk for ASCVD who make up a large subgroup of the US population.[1] In fact, because we have 2 more decades of favorable evidence from statin outcome trials including safety data, my resolve to assess and treat patients at intermediate risk for ASCVD is stronger today.[2,3] Moreover, we have learned to better risk-stratify patients with various assessment tools and incorporation of epidemiologic data supporting use of risk-enhancing factors to identify those at higher CV risk because of comorbid conditions.[3]

In this article, I provide suggestions for identifying patients classified as "intermediate risk" for preventive care. According to the American College of Cardiology (ACC)/American Heart Association (AHA), these patients have a 10-year ASCVD risk score of ≥7.5% to <20%, but because of the presence of risk-enhancing factors, have a higher overall ASCVD risk.[3] Such factors are intended to guide the clinician and influence therapy initiation and degree of lowering low-density lipoprotein cholesterol (LDL-C). Further, I provide recommendations to help navigate common clinical dilemmas when proper statin selection is imperative to avoid major drug interactions (DIs), prevent recurrence of adverse effects (AEs), and not aggravate coexisting conditions. Finally, I provide some thoughts about shared decision-making because it is essential to limit patient apprehension and achieve the individual's maximum tolerated statin and dosage.[2,3] These lessons are applicable in clinical practice as primary prevention.

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CASE SCENARIO 1

ML is a 63-year-old Hispanic female, BP 142/86 mm Hg, on amlodipine 5 mg/d, mixed dyslipidemia with an LDL-C of 110 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 49 mg/dL, and triglycerides of 185 mg/dL, while taking pravastatin, 20 mg/d. She reports that she "didn't feel good" on atorvastatin, 40 mg/d, and is hesitant to try a 3rd statin. She also states, "they can cause diabetes," and is concerned the statin is putting her at a higher risk of diabetes because of her family history.

Other labs: *fasting blood glucose (FBG) 101 mg/dL, A1C 5.9%, serum creatinine (SCr) 1 mg/dL; urinary analysis and hepatic transaminases are within normal limits.*

Body mass index (BMI) *31 kg/m², waist circumference: 91.5 cm (36 inches), (-) tobacco, (-) EtOH, walks 3x/week.*

Her ACC/AHA *10-year ASCVD risk score is 7.8%.*

Family history: *both parents developed type 2 diabetes mellitus (T2DM) and ASCVD in their early 60s.*

According to the 2018 ACC/AHA Guideline on the Management of Blood Cholesterol, ML is considered "intermediate risk" because her 10-year ASCVD risk score is ≥7.5%.[3] This likely is underestimated because of factors not accounted for by the ASCVD risk calculator, including her family history of ASCVD and presence of metabolic syndrome (MetS), both of which are risk-enhancing factors.[3] Her risk score and the presence of risk enhancers indicate the need for moderate-intensity statin therapy to reduce LDL-C by 30% to 49%.

RISK-ENHANCING FACTORS FOR FURTHER RISK STRATIFICATION

To improve risk-stratification and guide initiation and

intensity of statin therapy, the 2018 ACC/AHA Cholesterol Guideline introduced risk-enhancing factors (**TABLE**).[3] The risk-enhancing factors have been identified primarily from epidemiologic data. When present, risk-enhancing factors indicate a greater overall ASCVD risk and are often proportional to the degree and duration of the specific condition. For example, the associated relative risk (RR) of ASCVD for diabetes mellitus (DM) with MetS is 2.35,[4,5] chronic kidney disease (CKD) ranges from approximately 1.4 to 3.3 depending on severity,[6,7] while systemic lupus erythematosus carries a RR of 6.4 for major cardiometabolic disease.[8] In ML's case, MetS increases her RR of ASCVD by 1.78, compared with no MetS.[4] Similarly, her family history of ASCVD, especially her mother experiencing a premature CV event (age <65), further increases ML's risk by approximately 2-fold. Therefore, her 10-year risk of a CV event is much higher than suggested by the 10-year ASCVD risk score alone.

STATIN-ASSOCIATED DIABETES MELLITUS

One component of MetS in ML is her impaired glycemic indices indicating prediabetes.[9] Her family history also is significant because both parents developed T2DM in their 60s. Understandably, ML expresses concern about statin-associated DM and does not want to further worsen her glucose parameters. Is her concern justified?

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) each released statements in 2012 about the association between statin therapy and elevated A1C and FBG,[10] and increased risk of new-onset diabetes (NOD) among those predisposed to DM.[11]

Numerous studies have solidified these statements, but with mixed results. Findings from meta-analyses of randomized-controlled trials (RCTs) have demonstrated significant but modest increases in glucose parameters.[12,13] An analysis evaluating data from 13 major RCTs noted a 9% increase in incident DM with statin therapy.[12] Conversely, a meta-analysis of observational studies reported a more robust association with statins (RR, 1.44; 95% confidence interval [CI] 1.31 to 1.58).[14] Differences among individual agents also have been evaluated, and most data indicate that statin potency and dosage play a role.[15] Specific statins appear less diabetogenic with no dose dependency.[16] Atorvastatin, rosuvastatin, and simvastatin have the strongest associations compared with minimal or no association with fluvastatin, lovastatin, pitavastatin, and pravastatin.[15] These findings are consistent with a study analyzing rates of NOD among Asian patients recently hospitalized for acute myocardial infarction and no DM at baseline.[17] During the approximately 3-year follow up, patients receiving rosuvastatin (10.4%) and atorvastatin (8.4%) reported significantly more instances of NOD compared with pitavastatin (3%).

Given the inconclusive data, the FDA and EMA indicate the risk/benefit ratio favors the use of statin therapy among patients at risk for DM.[10,11] Nonetheless, monitoring glycemic indices at baseline and during statin therapy is recommended.[13]

CASE SCENARIO 1 (CONTINUED)

Overall, ML's evaluation suggests a 10-year ASCVD risk above the 7.8% calculated by the ACC/AHA risk estimator and, therefore, the need to intensify therapy. The clinical challenge is to balance the need for more intensive therapy without reintroducing previously experienced statin AEs or aggravating the patient's already impaired glucose. If unsuccessful, medication nonadherence commonly manifests, resulting in elevated LDL-C and poor clinical outcomes.[18] ML's current lipid therapy is pravastatin, 20 mg/d, and although she reports no AEs, the agent is classified as a low-intensity statin with LDL-C reduction of <30%.[3] Because of her ASCVD risk, consider a safe, moderate-intensity statin that provides a 30% to 49% reduction in LDL-C and does not predispose her to a higher risk of NOD should be considered. Reasonable options include titrating to pravastatin 80 mg/d, or switching to pitavastatin, 2 to 4 mg/d, or rosuvastatin, 5 to 10 mg/d. To maintain adherence, shared decision-making and counseling regarding the risk/benefit ratio of statin therapy, including that the new statin is unlikely to worsen her glycemia, is essential.

CASE SCENARIO 2

RJ is a 56-year-old white male with human immunodeficiency virus (HIV) on antiretroviral therapy (ART).

BP 148/88 mm Hg, repeat 146/86 mm Hg (hypertension not treated).

Labs/procedures: *FBG 99 mg/dL, A1C 5.8%, SCr 1.2; hepatic transaminases, urinary analysis, prostate-specific antigen, and colonoscopy – all WNL.*

Lipid panel: *total cholesterol (TC) 192 mg/dL, HDL-C 46 mg/dL, triglycerides 180 mg/dL, LDL-C 110 mg/dL, non-HDL-C 146 mg/dL (all values similar to last 2 lipid profiles).*

BMI *29 kg/m^2, waist circumference 101.6 cm (40 inches), (-) tobacco (quit last year – 60-pack-year history), (+) EtOH 2 drinks/week, no formal exercise.*

Patient reports taking simvastatin in his 40s but discontinued because of fatigue and myalgias.

ACC/AHA *10-year ASCVD risk score 7.7%.*

Family history *is complicated by tobacco and alcohol abuse. He is aware of DM and ASCVD in the family, although details are limited.*

RJ has a mixed dyslipidemic pattern and is at intermediate risk of a primary event. His ASCVD risk score of 7.7% likely underrepresents his true risk because of the presence of numerous

TABLE. **General risk-enhancing factors for additional risk stratification[2]**

- **Family history of premature ASCVD** (males, age <55; females, age <65)
- **Primary hypercholesterolemia** (LDL-C 160-189 mg/dL; non-HDL 190-219 mg/dL)
  - **Metabolic syndrome** (increased waist circumference, elevated triglycerides (≥150 mg/dL), elevated blood pressure, elevated fasting blood glucose, and low HDL-C (<40 mg/dL in men; <50 mg/dL in women) are factors; >3 makes the diagnosis
- **Chronic kidney disease** (eGFR 15 to 59 mL/min/1.73 m_2, with or without albuminuria; not treated with dialysis or kidney transplant)
- **Chronic inflammatory conditions** such as psoriasis, RA, HIV/AIDs
- **History of premature menopause (age <40) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia**
- **High-risk race/ethnicities** (eg, South Asian ancestry)
- **Lipid/biomarkers:** associated with increased ASCVD risk
  - **Persistently* elevated, primary hypertriglyceridemia** (≥175 mg/dL)
  - **If measured:**
    - **Elevated high-sensitivity C-reactive protein** (≥2 mg/L)
    - **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL constitutes a risk-enhancing factor especially at higher levels of Lp(a)
    - **Elevated apolipoprotein B** ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
    - **Ankle-brachial index** <0.9

Abbreviations: AIDS, acquired immunodeficiency syndrome; ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; RA, rheumatoid arthritis.

*Optimally, 3 determinations

[a]Or on drug treatment for noted condition is also an indication

risk-enhancing factors including HIV, MetS, persistently elevated triglycerides, and possible family history of premature ASCVD.[3] According to the 2018 ACC/AHA Cholesterol Guideline, initiation of a moderate-intensity statin for an LDL-C reduction of 30% to 49% is favored because of his ASCVD risk score and multiple risk-enhancing factors.[3] For example, his HIV status elevates his ASCVD risk by nearly 3-fold compared to non-infected individuals, secondary to chronic inflammation and comorbid (mixed) dyslipidemia.[19] In addition, persistently elevated triglycerides are associated with a 1.37 RR increase in ASCVD.[20] As noted in case 1, a family history of premature ASCVD and MetS also increases RR of ASCVD by approximately 2.0 and 1.78, respectively.

DRUG INTERACTIONS

Statin-related AEs generally are not idiosyncratic in nature, but are caused by increased serum concentrations often resulting from a drug interaction.[21] Statin metabolism is a complex, multi-step process. The cytochrome P450 (CYP450) system plays a major role in metabolism as it does for several other drugs.[22] Approximately 75% of all medications are metabolized via CYP450, with 50% of such agents having affinity for the common CYP3A4 isoenzyme.[23] Current FDA labeling indicates lovastatin, simvastatin, and, to a lesser degree, atorvastatin most subject to DIs because of their high affinity for the CYP3A4 isoenzyme.[24-26] The remaining statins have less risk of major DIs.[22] Clinically relevant CYP3A4 inhibitors include azole antifungals, amiodarone, clarithromycin, erythromycin, HIV protease inhibitors (eg, boceprevir, telaprevir), diltiazem, verapamil, and grapefruit juice.[21,22,27]

Statin metabolism involves more than the CYP450 system. Other common drug transporters that may be involved include breast cancer-resistant protein (BCRP), P-glycoprotein (P-gp), organic anion-transporting polypeptides (OATPs), and multi-drug-resistant protein.[21,22] Inhibition of drug transporters, such as OATP1B1 and P-gp can also increase statin exposure. All statins are substrates for OATP transporters, especially OATP1B1, and common inhibitors include cyclosporine, erythromycin, and gemfibrozil. Importantly, cyclosporine inhibits multiple steps (eg, BCRP, OATP1B1, CYP3A4) in statin metabolism and can markedly elevate statin serum concentrations.[21,22] Further, cyclosporine has been implicated in many cases of rhabdomyolysis when co-administered with a statin.[28] Of all agents, cyclosporine may carry the most risk for major statin DIs and related AEs.[22]

In the case of RJ, his HIV status should alert the clinician to the importance of individualizing therapy due to the potential for major DIs and statin-related AEs.[22] The HIV population is especially prone to DIs because of complex medi-

cation regimens including the use of protease inhibitors. The FDA published a Drug Safety Communication in 2012 advising that the concomitant use of statins and protease inhibitors, which are commonly used for treating patients with HIV and hepatitis C virus, increases the risk of myopathy and rhabdomyolysis.[27] These cautions are included in current statin labeling.[24-27,29-32]

Similar to previously discussed CYP3A4 interactions, certain statins are contraindicated (lovastatin, simvastatin) with concomitant HIV protease inhibitors, while others have dose limitations and/or should be avoided depending on the interacting protease inhibitor (rosuvastatin, atorvastatin).[27] Information for fluvastatin is not available. Alternatively, pitavastatin and pravastatin have no limitations, precautions, or contraindications with HIV protease inhibitors.[22,27]

The HIV population is understudied with limited statin options, but are at significant risk for ASCVD because of risk-enhancing factors (eg, chronic inflammation, MetS).[19] The National Institute of Allergy and Infectious Disease is conducting a landmark outcome trial (REPRIEVE) involving 7770 patients that compares the effects of pitavastatin with placebo on composite CV events; results are expected in 2023.[33]

Because of the complexities of statin metabolism, there are 2 key areas to help the clinician recognize common DI pitfalls: 1) medications that are commonly used and have the most potential to inhibit statin metabolism, and 2) differences among individual statins regarding metabolic pathways. Using this practical approach should alert the clinician to high-risk medications, in hopes of preventing the negative outcomes associated with major statin DIs. To help guide prescribing and limit the risk of muscle injury, the FDA published 2 additional Drug Safety Communications involving restrictions on simvastatin and lovastatin.[10,34] For a more comprehensive discussion on clinically important statin DIs, see Kellick et al.[22]

CASE SCENARIO 2 (CONTINUED)

The risk of ASCVD for RJ is likely greater than the 7.7% determined from the ACC/AHA 10-year risk estimator. In addition to his noted risk-enhancing factors, MJ has an extensive smoking history, probable hypertension, and prediabetes. A structured lifestyle program could potentially improve the latter 2 risk factors.[2] The Diabetes Prevention Program demonstrated the benefits of exercise and modest weight loss on glucose metabolism. Those with prediabetes who adopted a structured lifestyle program have been shown to be nearly 60% less likely to develop T2DM.[35] Such findings emphasize the importance of diet and exercise for cardiometabolic conditions and the likelihood of limiting NOD with statin therapy.[2,3]

Given RJ's ASCVD risk, a moderate-intensity statin or maximally tolerated statin would be primary prevention to reduce the risk of a major CV event.[3] Being aware of potential DIs with his ART and previous intolerance is important. Appropriate choices from the FDA to safely reduce LDL-C by 30% to 49% include pitavastatin, 1 to 4 mg/d, or pravastatin, 40 to 80 mg/d, or limiting rosuvastatin to 5 to 10 mg/d.[27] It is possible that his previously reported statin AE might have been secondary to coadministration of simvastatin and ART, and markedly elevated simvastatin levels. Because RJ has a history of statin intolerance, consider starting with a lower dosage and gradually increasing. Other options to manage statin intolerance include initiating a long half-life agent (eg, atorvastatin, rosuvastatin) with an alternative dosing schedule such as twice weekly with gradual increase as tolerated. Adding ezetimibe would provide additional LDL-C reduction and generally does not worsen statin-related AEs.[36]

CASE SCENARIO 3

FF is a 59-year-old African American female with a family history of premature ASCVD (her father had a myocardial infarction at age 48). She is taking hydrochlorothiazide, 25 mg/d, for hypertension (average BP at home 138/68 mm Hg). Since her early 40s, she also has taken methotrexate, 12.5 mg once weekly, and glucosamine/chondroitin daily for rheumatoid arthritis (RA).
She follows a low-sodium diet; exercise involves daily stretching and walking for 20 minutes most days.
***BMI** 28 kg/m², (-) EtOH, (-) tobacco.*
***Labs:** hepatic transaminases, SCr, thyroid stimulating hormone and A1C - all WNL, high-sensitivity C-reactive protein (hsCRP) 3.8 mg/L, lipids: TC 194 mg/dL, HDL-C 53 mg/dL, triglycerides 135 mg/dL, LDL-C 114 mg/dL, non-HDL-C 141 mg/dL, lipoprotein (a) [Lp(a)] 56 mg/dL.*
***ACC/AHA** 10-year ASCVD risk score 8.0%.*

Once again, we have a patient at intermediate risk of a CV event with ASCVD risk greater than indicated by her ASCVD risk score of 8.0%.[3] Her notable risk-enhancing factors include a family history of premature ASCVD, chronic inflammation from RA, elevated hsCRP, and elevated Lp(a). The presence of RA elevates the RR of major cardiometabolic disease by 1.7.[8] Lp(a) is not routinely drawn and RR is variable, but measuring can be considered in those with a family history of premature ASCVD.[3] Further, her overall lipid profile is fairly unremarkable, possibly providing a false sense of limited ASCVD risk. Nonetheless, this is a patient that would benefit from statin therapy and LDL-C reduction of 30% to 49%.[3]

A common clinical challenge in patients such as FF is a hesitation to start a statin because her "cholesterol is fine." In such cases, measuring coronary artery calcium (CAC) or carotid intima-

Pearls and Pitfalls: Key Take-Home Messages

- Don't wait to start statin therapy until after a patient at intermediate risk has had a CV event.
- Most females age >55 or age males >45 years with ≥2 CV risk factors are at intermediate risk.
- The 10-year ACC/AHA risk estimator alone could underestimate an individual patient's CV risk.
- Including risk-enhancing factors provides a more accurate assessment of overall CV risk.
- The case scenarios demonstrate patients at "intermediate risk" with a wide range of 10-year ASCVD risk scores ≥7.5% to <20%, and how risk factors and enhancers are intended to guide therapy and intensity.
- The presence of 1 risk-enhancing factor can elevate the RR of ASCVD by approximately 1.25 to >6-fold.
- Patients at intermediate risk with unremarkable lipid profiles, but risk-enhancing factors, commonly "fall through the cracks" for ASCVD prevention.
- Individually risk-stratifying patients and individualizing statin selection are imperative for safe and effective LDL-C reduction.
- Some patient populations (eg, HIV) have elevated ASCVD risk, are prone to major DIs because of complex medication regimens, and have limited statin options.
- Be cognizant of statins metabolized by CYP3A4 (lovastatin, simvastatin, atorvastatin) and the potential for major DIs and significant statin-related AEs. Similarly, note other commonly prescribed agents (eg, cyclosporine, gemfibrozil, erythromycin) that are implicated in major statin DIs.
- Measure CAC or CIMT to further refine assessment if the risk decision is uncertain or issues surrounding statin therapy are present.
- We now have 3-plus decades of favorable statin outcome trials, including safety data. This is useful information when discussing the risk/benefit of statin therapy with patients.
- Engaging the patient in shared decision-making is especially helpful in patients who "feel fine" but are at increased CV risk or have experienced a statin-related AE and resist statin therapy.

media thickness (CIMT) to determine degree of atherosclerosis can help inform the decision.[3,37] The presence of substantial atherosclerotic burden with either measure favors initiation of statin therapy and the visualization of disease often resonates with patients.[37] Additionally, the inherent musculoskeletal complaints from her RA can be misinterpreted as statin associated myalgia. Patient counseling noting the presence of baseline myalgias and arthralgias can be helpful if the patient subsequently reports muscle-related symptoms thought to be from statin therapy.[18]

A frank clinician-patient risk discussion and shared decision-making when initiating statin therapy cannot be overemphasized. As part of this process, it is important to invite the patient to share their understanding of the disease and concerns they may have. FF is an example of a patient with an intermediate risk and significant risk-enhancing factors who would likely benefit from this type of discussion. Since she believes her "cholesterol is fine," informing her of the factors beyond cholesterol that elevate ASCVD risk, including her father's myocardial infarction at age 48 years, the chronic inflammation from her RA, and elevated Lp(a), would provide key insight and allow for a more informed decision. Finally, it is important to stress that the higher the ASCVD risk, the greater the benefit from statin therapy.[3] An informed patient who feels she has been part of the decision-making process is more likely to be adherent to therapy, resulting in improved clinical outcomes.[3] ●

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Current and Emerging Issues in the Management of Heart Failure in Primary Care

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LEARNING OBJECTIVES

- Describe the epidemiology of heart failure in people with diabetes mellitus.
- Implement evidence-based nonpharmacologic and pharmacologic therapies for heart failure with preserved ejection fraction and heart failure with reduced ejection fraction as recommended in current guidelines.
- Characterize the role of glucose-lowering medications, focusing on the sodium glucose cotransporter-2 inhibitors, for the treatment of people with type 2 diabetes mellitus.

EPIDEMIOLOGY

Heart failure (HF) is a debilitating, often fatal disease that results in major health and socioeconomic consequences. The 5-year mortality rate for HF is similar to many types of cancer, eg, prostate, bladder, and colorectal cancers in men, and breast, colorectal, and ovarian cancers in women.[1] Far exceeding hospitalizations for heart attack, coronary artery disease, or atrial fibrillation, HF was the primary diagnosis for 978,135 hospitalizations in the United States in 2014.[2] Estimates are that the prevalence of HF will increase 46% from 2012, reaching >8 million adults in 2030.[3] A major factor contributing to this rising prevalence of HF is the increasing prevalence of obesity,[4] which serves as an independent risk factor for HF, as well as many other common risk factors for HF, such as coronary heart disease, diabetes mellitus, and hypertension.[5-8] In fact, people with type 2 diabetes mellitus (T2DM) have more than twice the risk of HF than people without T2DM.[3,9-12] Despite this strong association, the mechanism(s) for the increased risk of HF in people with T2DM is unclear, as some evidence indicates that lowering the blood glucose concentration does not necessarily result in improved cardiovascular (CV) outcomes.[13-16]

HF is the most common CV complication in people with T2DM[3] and is a common initial presentation of CV disease in T2DM.[11] While the median age at HF diagnosis in the general US adult population is 59 years, it is 56 years in people with diabetes and 55 years in people with obesity.[17] The onset of changes in the myocardium in people with T2DM generally precedes HF symptoms by several years, as shown by the SHORTWAVE trial.[18] The trial involved 386 people with T2DM (median duration ~5 years), of whom 68% had echocardiographic evidence of systolic and/or diastolic left ventricular dysfunction despite being clinically asymptomatic.

TYPES OF HEART FAILURE

Chronic HF has 2 distinct phenotypes. One is HF with reduced ejection fraction (HF*r*EF), or systolic HF, and the other is HF with preserved ejection fraction (HF*p*EF), primarily diastolic HF (**FIGURE 1**).[8] HF*r*EF is defined as a left ventricular ejection fraction ≤40%, while HF*p*EF is defined as an ejection fraction ≥50%. Approximately half of people with HF have HF*r*EF and the other half HF*p*EF.[19,20] A small subset of people have a midrange ejection fraction between 40% and 50%, with many similarities to HF*p*EF, and may also benefit from treatment.

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DISCLOSURES

Dr. Chilton discloses that he is a consultant for MSD, Pfizer, Boston Scientific, Boehringer Ingelheim, Lilly, AstraZeneca, and Novo Nordisk.

Dr. Brunton discloses that he serves on the advisory boards of Abbott Diabetes, Sanofi, Xeris, Novo Nordisk, Janssen, Bayer, and AstraZeneca and on the speakers' bureau for Lilly, Novo Nordisk, AstraZeneca, Bayer, and Janssen.

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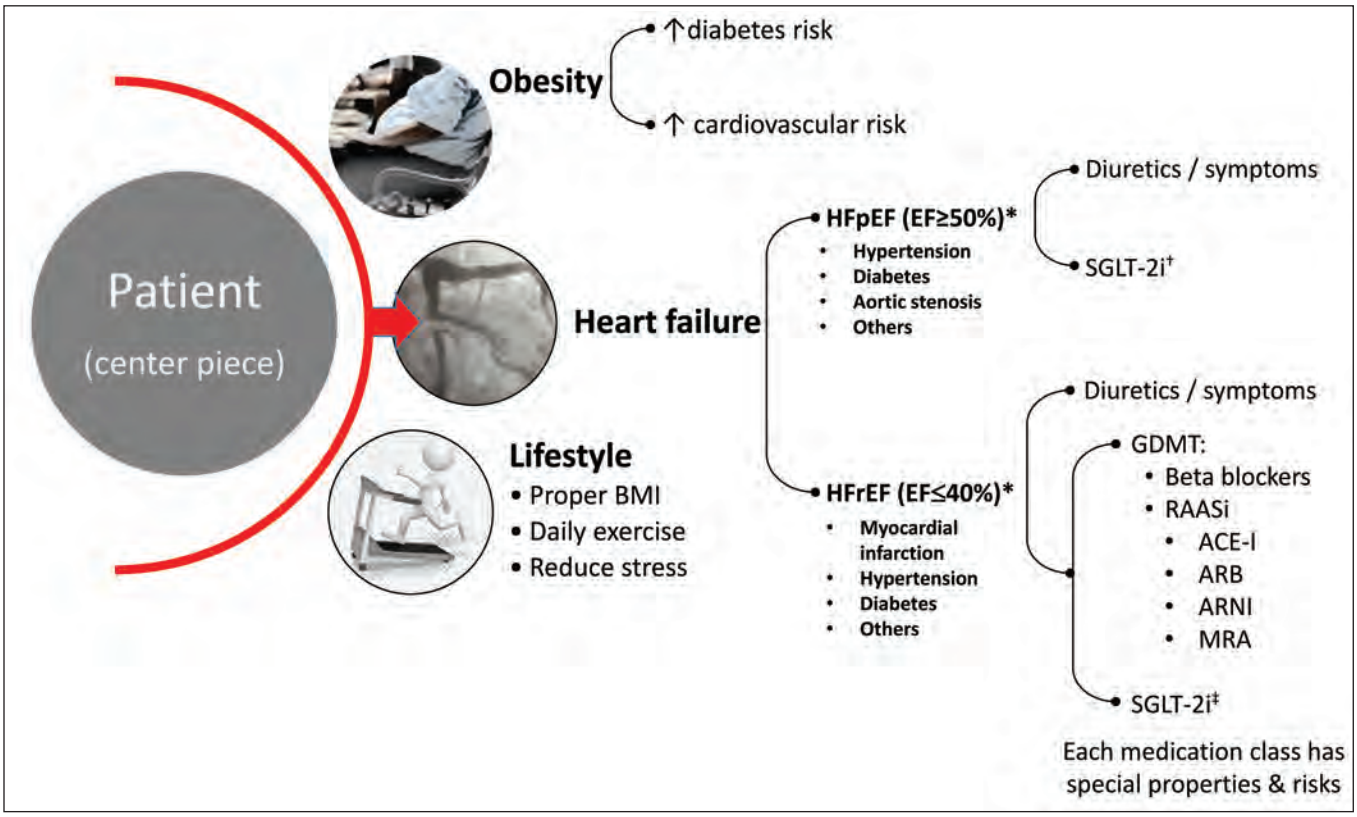
FIGURE 1. **Phenotypes of heart failure and key treatment options**



Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin/neprilysin inhibitor; BMI, body mass index; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF*p*EF, heart failure with preserved ejection fraction; HF*r*EF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT-2i, sodium glucose cotransporter-2 inhibitor.

* Patients with EF >40% to <50% are identified as either HF*p*EF borderline or HF*p*EF improved.

† Preliminary evidence suggests possible benefit with canagliflozin, dapagliflozin in HF*p*EF.

‡ Evidence indicates benefit with canagliflozin, dapagliflozin, empagliflozin in HF*r*EF, with greatest benefit with dapagliflozin.

HF*r*EF is most often caused by ischemic heart disease (myocardial infarction [MI]) and is characterized by the loss, function, and stretch of cardiomyocytes resulting in marked left ventricular enlargement and large increases in circulating natriuretic peptides, eg, brain natriuretic peptide (BNP).[21] Consequently, drugs that interfere with neurohormonal systems (eg, angiotensin-converting enzyme inhibitors [ACE-Is], angiotensin receptor blockers [ARBs], beta-blockers, mineralocorticoid receptor antagonists [MRAs], and neprilysin inhibitors) have been used to treat people with HF*r*EF. More recently a new class of agents, sodium glucose cotransporter-2 inhibitors (SGLT-2is), has shown clinical benefit in reducing hospitalization for HF in patients with or without diabetes. In addition, both SGLT-2is and glucagon-like-receptor agonists (GLP-1RAs) currently used for the treatment of diabetes were found to reduce CV events with important kidney protection.[22,23] Patients with HF in general have systemic and adipose tissue inflammation that results in microvascular dysfunction and myocardial fibrosis. Patients with HF*p*EF frequently have a small stroke volume with thick ventricular walls, in contrast to patients with HF*r*EF, who have a large stroke volume and thin ventricular walls. Treatment of HF with a diuretic is recommended acutely for symptomatic relief of shortness of breath due to pulmonary edema, while beta-blockers and neurohormonal antagonists have ongoing effects of improved ventricular remodeling and reduction of cardiac events. SGLT-2is have been found to have acute benefits of reduction in CV events and improved kidney function. Studies with GLP-1RAs have not found significant benefit in reducing hospitalizations for HF.[21]

The New York Heart Association (NYHA) classifies HF in 4 stages based on exercise capacity and symptomatic status.[24] The stages of HF are as follows:

1. Class I: No symptoms and no limitation in ordinary physical activity, eg, no shortness of breath when walking, climbing stairs, etc.

2. Class II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
3. Class III: Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20–100 m). Comfortable only at rest.
4. Class IV: Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Although the NYHA classification is based on subjective assessment, it is an independent predictor of mortality.

DIAGNOSIS

The history and physical examination remain the cornerstones of the clinical evaluation of HF, in addition to new biomarkers (eg, BNP) in patients with unclear shortness of breath.[8] A key objective of the diagnostic evaluation is to stratify the patient's CV risk so as to guide therapeutic decision making. The difficulty in patients with diabetes is the inherent risk of ischemic heart disease. Patients also often have metabolic syndrome features with hypertension.

Patients with HF*p*EF classically present with shortness of breath and a hypertension history. Certainly, they also can present with other features such as electrocardiogram (ECG) findings indicating left ventricular hypertrophy, small stroke volume, and atrial enlargement. The echocardiogram frequently is reported to have findings compatible with diastolic dysfunction with normal ejection fraction. The BNP level can be elevated; however, in obese individuals it can be normal. Clinical evaluation with wet lungs, pretibial pitting edema, and distended neck veins can be helpful signs of HF.

Patients with HF*r*EF usually present with a history of ischemic heart disease, eg, MI or coronary artery bypass graft surgery. They also will have shortness of breath with edema and elevated BNP level. Moreover, many have a history of diabetes and hypertension, which increases their CV risks.

Laboratory evaluation includes complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, nonfasting lipids, liver function tests, and thyroid-stimulating hormone.[8] The N-terminal pro BNP (NT-proBNP) level is useful to establish prognosis and disease severity, particularly in people with obesity, because findings from the clinical evaluation may be equivocal. Also included in the initial evaluation are a 12-lead electrocardiogram, chest x-ray, and 2-dimensional echocardiograph with Doppler to assess heart size and function, pulmonary congestion, and to rule out other disorders. Noninvasive evaluation is warranted due to the high suspicion for obstructive coronary artery disease. Help from a cardiologist in directing the next best option is often important. Noninvasive imaging also can be considered to detect myocardial ischemia and viability in people presenting with new-onset HF who have known coronary heart disease and no angina.

CARDIOVASCULAR OUTCOME TRIALS

In 2008, the US Food and Drug Administration (FDA) began requiring manufacturers of new medications for T2DM to conduct clinical trials to compare the CV safety of the new medication vs placebo as part of standard care.[25] This includes the dipeptidyl peptidase-4 inhibitor, GLP-1RA, and SGLT-2i classes of medications. Since then, more than 20 CV outcome trials (CVOTs) have been completed, with nearly all demonstrating that the CV safety of each of these medications is noninferior to placebo as part of standard care. Noninferiority was assessed based on the composite outcome of CV death, nonfatal MI, and nonfatal stroke.

The methods and patient populations in the CVOTs varied; thus, comparing the results is not possible. All CVOTs investigated the use of the glucose-lowering medication in people who had had a CV event, ie, secondary prevention. Most CVOTs also included people who were at high CV risk, but who had not had a CV event, ie, primary prevention.

Beyond CV safety, several of these medications have shown a significant reduction in CV risk vs placebo. These medications are the GLP-1RAs dulaglutide, liraglutide, and semaglutide, and the SGLT-2is canagliflozin, dapagliflozin, and empagliflozin. Ertugliflozin showed noninferiority, but not superiority, compared with placebo for the composite of major CV events.[26] With respect to HF, the GLP-1RAs did not significantly reduce HF hospitalization.[27] In contrast, the SGLT-2is canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin were associated with a reduction in HF hospitalization, although the trials were not designed to look at this outcome in all cases and in different populations.[26-35]

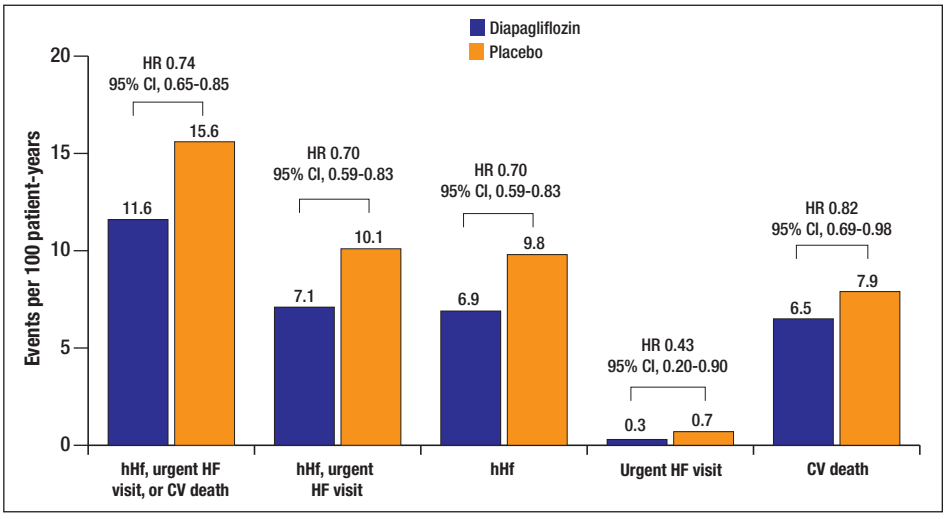
In patients with T2DM, the HF hospitalization benefit with canagliflozin was observed in those with a history of HF, but not in patients with no history of HF.[36] For dapagliflozin and empagliflozin, the HF hospitalization benefit was observed in patients with and without a history of HF.[37,38]

In these CVOTs involving an SGLT-2i in patients with T2DM, the proportion of people with established atherosclerotic CV disease (ASCVD) was 66% for canagliflozin, 41% for dapagliflozin, and 100% for empagliflozin. The proportion of people with a history of HF was 14.4% for canagliflozin, 10.0% for dapagliflozin, 10.1% for empagliflozin, and 23.7% for ertugliflozin, thus making it clear that only a small minority of people with T2DM in the SGLT-2i CVOTs had HF at baseline.

Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure (DAPA-HF) trial

The phase 3 DAPA-HF trial is the only CVOT that has prospectively evaluated the efficacy and safety of a glucose-lowering medication only in subjects meeting standard criteria for HF*r*EF, including elevated NT-proBNP.[39] All subjects received standard therapy for HF*r*EF. Forty-two percent of subjects in both the dapagliflozin and placebo groups had T2DM at baseline, all of whom received standard therapy for T2DM.

FIGURE 2. **Cardiovascular outcomes observed in the DAPA-HF trial**[40]



Abbreviations: CI, confidence interval; CV, cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure; HF, heart failure; hHF, hospitalization for heart failure; HR, hazard ratio.

Subjects (N=4744) were randomized 1:1 to treatment with dapagliflozin or placebo. The primary outcome was a composite of CV death or hospitalization/urgent visit for HF resulting in the initiation of intravenous therapy. After a median of 18.2 months, the primary outcome occurred in 16.3% and 21.2% of dapagliflozin and placebo subjects, respectively (hazard ratio [HR] 0.74; 95% confidence interval [CI], 0.65-0.85; *P*<.001) (**FIGURE 2**).[40] Fewer subjects treated with dapagliflozin were hospitalized for HF (9.7% vs 13.4%, respectively; HR 0.70; 95% CI, 0.59-0.83) or had an urgent HF visit (0.4% vs 1.0%, respectively; HR 0.43; 95% CI, 0.20-0.90). Additionally, CV death occurred in 9.6% in the dapagliflozin group and 11.5% in the placebo group (HR 0.82; 95% CI, 0.69-0.98).

The effect of dapagliflozin on the primary outcome was generally consistent across prespecified subgroups, including subjects with or without diabetes at baseline. This latter finding not only suggests that the benefits of dapagliflozin in subjects with preexisting HF involve nonglycemic mechanisms, it has led some to recommend inclusion of dapagliflozin as standard therapy for patients with HF*r*EF regardless of diabetes history.[21,41] The trial also showed that subjects in NYHA functional class III or IV experienced less benefit than subjects in class II. The occurrence of a serious adverse event related to volume depletion or renal adverse event was similar in the dapagliflozin and placebo groups.

Significantly more subjects in the dapagliflozin group than in the placebo group experienced significant improvement in symptoms based on the Kansas City Cardiomyopathy Questionnaire.[40,42] Similarly, significantly fewer subjects in the dapagliflozin group experienced significant symptom deterioration.

Additional analyses of DAPA-HF have shown improved outcomes with dapagliflozin vs placebo across various subgroups. Age group (<55, 55–64, 65–74, and ≥75 years) had no significant effect on the rate of the primary outcome, adverse events, or study drug discontinuation.[43] Another analysis found that the benefit of dapagliflozin over placebo on the primary outcome was consistent regardless of background guideline-recommended pharmacotherapy or device therapy for HF*r*EF,[44] thus suggesting that the effects of dapagliflozin are incremental and complementary to conventional therapies for HF*r*EF.[45] Further analysis showed a similar reduction in the risk of the primary composite endpoint with dapagliflozin in subjects treated with a neprilysin inhibitor, ie, sacubitril/valsartan, or not treated with a neprilysin inhibitor.[40] Finally, significantly fewer patients without T2DM at baseline developed T2DM on trial. Subjects in whom T2DM developed generally had a higher mean baseline A1C, body mass index, and lower estimated glomerular filtration rate.[46]

Ongoing CVOTs

Additional clinical trials involving SGLT-2i therapy in people with HF are underway. In people with HF*r*EF, these include the DETERMINE-Reduced (NCT03877237) with dapagliflozin and EMPEROR-Reduced (NCT03057977) with empagliflozin. In people with HF*p*EF, these include the DETERMINE-Preserved (NCT03877224) and DELIVER (NCT03619213) trials with dapagliflozin and EMPEROR-Preserved (NCT03057951) with empagliflozin.

Implications for patient care

The results of the CVOTs have reshaped recommendations regarding the treatment of people with HF and T2DM. For secondary prevention, the American Diabetes Association *Standards of Medical Care in Diabetes–2020* recommends an SGLT-2i in people with T2DM and HF who do not achieve adequate glycemic control with the combination of lifestyle management plus metformin.[22] Among the SGLT-2i agents, dapagliflozin is preferred based on the results of the DAPA-HF trial. The American Association of Clinical Endocrinologists/American College of Endocrinology provides similar recommendations.[23]

For the treatment of patients with T2DM for primary prevention, the American College of Cardiology/American Heart Association recommends considering an SGLT-2i or a GLP-1RA in people with T2DM and additional ASCVD risk factors who do not achieve glycemic control with the combination of lifestyle management plus metformin.[47]

Finally, the product labeling approved by the FDA reflects key results from CVOTs.[48-51] Of the 4 SGLT-2i agents, the labeling for canagliflozin reflects a benefit in reducing the risk of hospitalization for HF in patients with T2DM and chronic kidney disease, while the benefit with dapagliflozin is in patients with T2DM and established CV disease or multiple CV risk factors. Dapagliflozin is also indicated to reduce the risk of CV death and hospitalization for HF in adults with HF*r*EF (NYHA class II-IV).

BOTTOM LINE

Several points are key regarding the management of people with T2DM. First, HF, as well as ASCVD, is common in people with T2DM. For people with T2DM, treatment is shifting beyond a glucocentric focus to include CV risk reduction. Therefore, it is critical that glycemia, CV disease, and other risk factors be managed as recommended in evolving guidelines and consistent with FDA-approved labeling. Because guidelines and product labeling are rapidly changing to reflect data from clinical trials, it is important to check this information frequently. Finally, while the benefits of lifestyle management are established, the pharmacotherapeutic management with SGLT-2is in patients with HF with or without T2DM is a rapidly evolving field. Therefore, it is important to educate and support people with T2DM – in fact, all people – to adopt and maintain a healthy lifestyle with normal body weight, good nutrition, and daily physical activity. ●

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