

# CLEVELAND CLINIC JOURNAL OF MEDICINE

**It's a new year, looking back  
and looking forward**

**Conjunctival petechiae**

**Wearable cardiac monitors:  
Where do we stand?**

**Gastric intestinal metaplasia  
and gastric cancer prevention:  
Watchful waiting**

**2023 Update in ambulatory  
general internal medicine**

**When should we consider SGLT-2  
inhibitors in patients with acute  
decompensated heart failure?**

**Nonstatin therapy to reduce  
low-density lipoprotein cholesterol  
and improve cardiovascular outcomes**

**Consumer-grade wearable cardiac  
monitors: What they do well,  
and what needs work**



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May 2  
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# It's a new year, looking back and looking forward

2023 on the world stage was not exactly an uplifting Oscar winner. But within the microcosm of medicine, we have at least for the moment weathered the worst of COVID-19. The packed ICU hallways with crumpled blue masks overflowing from trash cans and trailer morgues in our hospital parking lots are memories. And we celebrated key professional accomplishments, recognizing Drs. Katalin Karikó and Drew Weissman with the Nobel prize in medicine and physiology for their research that contributed to the creation and delivery of the successful RNA vaccines that played a major role in “flattening the curve” of the pandemic.

And in what may be the denouement to a long chain of increasingly sophisticated molecular studies devoted to understanding and treating sickle cell anemia, arguably beginning with the work of Linus Pauling and colleagues in 1949, the US Food and Drug Administration approved 2 gene therapies as potential cures of the disease. However, there is the yang to the yin. Vaccine hesitancy in the United States has grown, and these therapies are prohibitively expensive, are a physical challenge to tolerate, and require technical expertise and resources that are available in very few medical centers. Delivering the new gene therapies to the hundreds of thousands of people with sickle cell disease worldwide will be impossible.

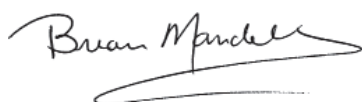
We continue to face challenges in our healthcare system that impede widespread implementation of other available life-prolonging medical treatments that are less technology-dependent. Consider the practical cost impediments to disseminating some very effective therapies discussed by Alexander et al,<sup>1</sup> Badwan et al,<sup>2</sup> and Singh and Cho<sup>3</sup> in this issue of *The Journal*. These challenges are extremely difficult to overcome for patients who are socioeconomically disadvantaged, further widening the inequity of medical care across the globe, including demographic groups in the United States. Societal evolution seemingly takes longer than scientific evolution.

Moving from these global challenges to topics much closer to home, with the march of time into 2024 we have several impending changes of note at *The Journal*. Pelin Batur, 1 of our 2 physician deputy editors (Craig Nielsen is the other), is stepping down to devote more time to pursue her other clinical and educational interests. She will be the physician lead on a new project to expand midlife women's services throughout the Cleveland Clinic and aligned communities, with a special focus on optimizing connectivity between clinicians in the various specialties providing women's healthcare. As ongoing Professor of Obstetrics and Gynecology and Reproductive Biology, Pelin will continue her clinical practice within women's health, national lecturing, and writing. She is developing a new patient-centered educational program that includes shared medical appointments focusing on menopause. This will allow patients to have 90 minutes to discuss and really digest background information and their many options. This program represents a wonderful alternative to patients simply searching “Dr. Google” to order testimonial-based supplements online, and an anticipated effective adjunct to the time patients spend with their physicians at annual “wellness visits,” which is usually insufficient to permit meaningful dialogue. The women's health community's gain is *The Journal's* loss. Pelin has managed our Guidelines to Practice series,

has personally shepherded the acquisition and editing of women's health (and many other) articles, and has been a superbly talented peer reviewer with a keen eye for identifying ways to enhance the educational value of all of the manuscripts she reviewed.

In another key transition, Dave Huddleston, our current Managing Editor, will be retiring from *The Journal*. He will be pursuing several personal interests, including continuing his musical career as an established guitarist and vocalist in the Cleveland area. Dave joined *The Journal* as Managing Editor in 1991 after more than a decade as a proofreader, general assignment reporter, and medical news magazine writer/editor. He left in 1995 for a 2-year stint in the United States Peace Corps, and he rejoined us in 1997 as Technical Writer and Editor, and then reassumed the role of Managing Editor. Dave has been an editorial rock throughout my 20 years as Editor in Chief. Dave initially worked with former long-time CCJM editors Phil Canuto and Ray Borazanian, and the 3 of them completely transformed the stylistic presentation of our articles into a consistently readable and accessible format. Dave's steady editorial hand and penchant for consistency have been evident in every piece he has touched, including my own commentaries and clinical publications, which (with I am sure a fair amount of frustration over my use of parenthetical comments) he has patiently "Englishized." Dave, thank you.

Finally, but not at all insignificantly, we welcome Robert Litchkofski as our new Managing Editor. Bob has spent more than 25 years editing peer-reviewed medical journals in both print and online formats, including the *Journal of Hospital Medicine*. He has extensive experience editing medical education materials for physicians preparing for board certification and recertification, attributes all useful in his new role with CCJM.



Brian F. Mandell, MD, PhD  
Editor in Chief

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## Late complications after allogeneic hematopoietic cell transplant

I read with interest the excellent article by Granat et al<sup>1</sup> on long-term management after allogeneic hematopoietic cell transplant. As the authors noted, most patients will experience premature ovarian insufficiency (POI) after treatment. Premature (before age 40) and early (before 45) loss of estrogen are associated with multiple negative consequences, including adverse cardiovascular, neurologic, mortality, bone, quality-of-life, and sexual-health outcomes.<sup>2</sup> There is agreement that POI management should include menopausal hormone therapy (MHT) at higher doses to correct the physiologic deficiency until at least the age of natural menopause (age 51 or 52).<sup>2</sup> The notable exceptions are the small percentage of women who would require antiestrogen therapies to treat their condition. Yet in clinical practice young individuals are frequently asked to discontinue MHT based on misinterpretation of risks that apply to women who start hormones in their 60s or later. Thus, clarification of MHT risks is critical to the care of young cancer survivors with POI.

The authors caution about endometrial cancer risk with MHT, but this is only a concern when estrogen is used unopposed (without adequate progestin) in individuals with a uterus. Appropriately dosed MHT has been associated with a neutral to decreased risk of endometrial cancer and hyperplasia.<sup>3–5</sup> To ensure endometrial safety, progestin should be offered for no less than 12 days of each month, at a dose to match the higher estrogen doses typically required to reach physiologic premenopausal ranges.

The authors also note the importance of assessing fracture risk and discuss treatment options such as bisphosphonates. MHT has been associated with preservation of bone density and fracture reduction at all sites (including the hip). In contrast to other osteoporosis therapies mentioned in the article, MHT has not been associated with risks of long-term suppression of bone turnover, such as osteonecrosis of the jaw or atypical femoral hip fractures. Given that women under age 50 have relatively lower fracture risk, MHT is an important option to postpone the need for other bone agents in those with POI, thereby limiting the duration of exposure and the rare risks of long-term bone suppression. Women who have undergone hematopoietic cell transplant and who suffer from POI should be reassured that MHT at physiologic dosing offers a favorable risk-benefit ratio, including protection from bone loss, without increased risk of endometrial cancer when correct formulations are chosen.

Pelin Batur, MD, FACP, MSCP  
Professor of Ob/Gyn and Reproductive Biology  
Cleveland Clinic, Cleveland, OH

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**Akinori Sekizawa, MD**  
Department of General Medicine,  
National Defense Medical College,  
Saitama, Japan

**Ayaka Nagano, MD**  
Department of Cardiology,  
National Defense Medical College,  
Saitama, Japan

**Kenichi Hashimoto, MD, PhD**  
Department of General Medicine,  
National Defense Medical College,  
Saitama, Japan

**Yosuke Ono, MD, PhD**  
Department of General Medicine,  
National Defense Medical College,  
Saitama, Japan

# Conjunctival petechiae in infective endocarditis



**Figure 1.** Petechial hemorrhage in the palpebral conjunctiva of the right lower eyelid.

A 75-YEAR-OLD-MAN presented with a 33-day history of intermittent nocturnal fevers of 39°C (102°F) and truncal rashes. He had a history of paroxysmal atrial fibrillation, hyperlipidemia, and benign prostatic hyperplasia. He had been taking only the alpha-1 blocker naftopidil for benign prostatic hypertrophy.

The fevers initially persisted, but temporarily resolved after the patient took clarithromycin 200 mg twice daily for 4 days early after fever onset. He finished taking the clarithromycin 7 days after fever onset. The fevers recurred the day after he finished the clarithromycin prescription and became sustained, even with acetaminophen. Acetaminophen 600 mg daily was prescribed on day 20, and, because of insufficient

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**Figure 2.** Irregular macular erythema distributed on the patient's abdomen.

antipyretic effect, the dose was increased to 1,200 mg daily, which was taken on day 30.

The truncal rashes were thumbprint-sized with pale-pink margins and without scales, pain, or itching. They appeared on the same day as the fever, and persisted for the entire period, even during the patient's afebrile periods.

The physical examination was notable for petechial hemorrhage on the right palpebral conjunctiva (**Figure 1**) and erythematous macules distributed over the abdomen to lower back (**Figure 2**). No cardiac

murmur, lymphadenopathy, mucosal ulcers, or lesions on the arms or legs were observed. There were no notable findings on the fingers or nails suggestive of infectious endocarditis, including Osler nodes, Janeway lesions, and splinter hemorrhages. The patient's oral hygiene was poor. He had 4 teeth, all with associated gum inflammation.

Results of laboratory testing were as follows:

- White blood cell count  $6.7 \times 10^9/L$  (reference range 3.3–8.6), with 79% neutrophils, 14.8% lymphocytes, 5.8% monocytes, and 0.1% eosinophils
- Hemoglobin 12.4 g/dL (13.7–16.8)
- Platelet count  $158 \times 10^9/L$  (158–348)
- Lactate dehydrogenase 218 U/L (100–225)
- Blood urea nitrogen 17 mg/dL (8–20)
- Creatinine 0.91 mg/dL (0.61–1.13; patient's baseline level was 0.72–0.81 mg/dL)
- Brain natriuretic peptide 77.8 pg/mL (< 18.4)
- Ferritin 555.7 ng/mL (23–250)
- Erythrocyte sedimentation rate 79 mm/h (1–7)
- C-reactive protein 5.4 mg/dL (< 0.3)
- Procalcitonin 0.23 ng/mL (< 0.05).

Testing for rheumatoid factor, antinuclear antibodies, and antineutrophil cytoplasmic antibodies was negative. Urinalysis revealed mild proteinuria (1+) and microscopic hematuria (30–49 blood cells per high-power field). No white cell or blood cell casts were observed. Three sets of blood cultures were positive for *Streptococcus mitis*, an oral bacterium.

Transesophageal echocardiography revealed a vegetation 9 mm by 2 mm on the right coronary cusp of the aortic valve, diagnosed as left-sided infective endocarditis. Contrast-enhanced brain magnetic res-

onance imaging revealed 3 mycotic aneurysms and multiple cerebral microhemorrhages.

The patient received intravenous penicillin G and underwent extraction of the teeth, and the rashes and petechial hemorrhage completely disappeared within 20 days.

## DIFFERENTIAL DIAGNOSIS OF CONJUNCTIVAL PETECHIAE AND ERYTHEMA MULTIFORME

Conjunctival petechiae can be caused by increased venous or capillary pressure in the head and neck, complete venous blockage, or capillary-wall damage.<sup>1</sup> Conjunctival petechiae are observed in situations such as homicidal asphyxia, head injury, asthma attack, epileptic seizure, post partum (after normal delivery), coughing, sneezing, vomiting, and the Valsalva maneuver.<sup>1</sup> The initial differential diagnosis of the conjunctival petechiae in our patient included septic microemboli, adenovirus infection, and vasculitis. Conjunctival petechiae are an uncommon sign of infective endocarditis, with a reported prevalence of 5%.<sup>2</sup>

Erythema multiforme is associated with various infections and drugs.<sup>3</sup> A rare case of erythema multiforme associated with alpha-hemolytic streptococci was reported.<sup>4</sup> Infection with *S mitis* or its proteins may induce the release of cytokines that lead to epidermal tissue damage and may explain our patient's truncal rash.

## DISCLOSURES

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**Abdilahi Mohamoud, MBBS**

Department of Internal Medicine, Hennepin County Medical Center, Minneapolis, MN

**Joseph Jensen, MD**

Department of Internal Medicine, Division of Cardiology, Hennepin County Medical Center, Minneapolis, MN; Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis, MN

**Kevin G. Buda, DO**

Department of Internal Medicine, Division of Cardiology, Hennepin County Medical Center, Minneapolis, MN; Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis, MN

# Consumer-grade wearable cardiac monitors: What they do well, and what needs work

## ABSTRACT

Consumer-grade smart devices, including smartwatches and smartphones, are potentially valuable tools in detecting cardiac arrhythmias, particularly atrial fibrillation, and their use is increasing. These devices, which use photoplethysmography, show remarkably high sensitivity and specificity for detection of atrial fibrillation, with implications for stroke prevention and management in at-risk patients. The ability of the devices to detect atrial fibrillation is being compared with single-lead electrocardiography. Physicians will increasingly be asked to interpret data from these nonmedical-grade devices as they become more common. Limitations include high false-positive rates in certain populations and disparities in access.

## KEY POINTS

Familiarity with the available devices and the data they generate will enhance patient care.

Many consumer devices have been validated against gold-standard medical-grade devices and have shown high sensitivity and specificity for heart rate and detection of atrial fibrillation.

There is a large gap between consumer-grade and medical-grade devices for detecting more complex arrhythmias.

**T**ECHNOLOGICAL ADVANCES in consumer-grade wearable devices have increased the opportunity to diagnose and manage cardiac arrhythmias, especially atrial fibrillation. Devices that provide remote and long-term cardiac monitoring, such as smartphones, smartwatches, and handheld electrocardiography (ECG) devices, allow us to monitor high-risk patients outside the hospital.

*See related editorial, page 31*

As consumer wearables become more user-friendly, less costly, and more widely available, patients will expect physicians to be familiar with data generated from their devices.<sup>1</sup> Therefore, knowledge of the available devices and their reliability compared with medical-grade devices will become increasingly important.

This article reviews common consumer-grade wearables, their accuracy compared with standard medical-grade devices, and our approach to patients with rate or rhythm abnormalities identified on at-home monitoring.

## ■ ATRIAL FIBRILLATION: A SIGNIFICANT RISK FACTOR

By 2030, an estimated 2.6 million people in the United States will have atrial fibrillation.<sup>2</sup> Often asymptomatic, atrial fibrillation may remain undetected until a thromboembolic event such as an ischemic stroke occurs. Approximately 25% of patients with transient

**TABLE 1**  
**Consumer-grade 'smart devices' for detecting cardiac arrhythmias**

Device	CE and FDA clearance	Validation	PPG monitoring frequency	Sensitivity, %	Specificity, %
FibriCheck <sup>6</sup> smartphone camera app	Atrial fibrillation	Validated vs standard 12-lead ECG	Not applicable	95.6	96.6
KardiaMobile <sup>10</sup> ECG monitor	Single-lead and 6-lead ECG to detect bradycardia, tachycardia, and atrial fibrillation	Validated vs standard 12-lead ECG	Not applicable	96.6	94.1
Apple Watch Series 6 <sup>9</sup>	Irregular heart rhythm notification and ECG monitoring	Validated vs standard 12-lead ECG <sup>a</sup>	Intermittent (every 5 minutes)	85	75
Garmin smartwatch <sup>8</sup>	Garmin Venu 2 Plus model with ECG capability	Garmin Forerunner 945 model validated vs Holter monitoring	Continuous	96.9	99.3
Samsung smartwatch <sup>7</sup>	ECG capability	Active 2 model validated vs BioTech ECG patch	Intermittent or continuous (user defined)	96.9	99.3
Fitbit <sup>9</sup>	Detecting atrial fibrillation, with ECG capability	Fitbit Sense model validated vs standard 12-lead ECG <sup>a</sup>	Continuous in some models (eg, Fitbit Charge 5)	66	79
Withings ScanWatch <sup>9</sup>	Detecting atrial fibrillation using ECG functionality and measuring blood oxygen saturation	Validated vs standard 12-lead ECG <sup>a</sup>	Intermittent (every 10 minutes)	58	75

<sup>a</sup>The BASEL Wearable Study (reference 9) also validated Samsung Galaxy Watch 3 and KardiaMobile against standard 12-lead ECG and demonstrated closely comparable sensitivity and specificity to the Apple Watch, Fitbit, and Withings ScanWatch.

CE = Conformité Européenne; ECG = electrocardiography; FDA = US Food and Drug Administration; PPG = photoplethysmography

ischemic attack or stroke are found to have atrial fibrillation, diagnosed only after the event.<sup>3</sup> In more than 25% of strokes, the stroke itself is the initial manifestation of atrial fibrillation.<sup>4</sup> Even subclinical atrial fibrillation is a significant risk factor. A recent meta-analysis found a 2.4-fold increase in annual stroke risk (95% confidence interval [CI] 1.8–3.3,  $P < .001$ ) in patients with subclinical atrial fibrillation compared to those without.<sup>5</sup> Therefore, early recognition is critical.

Consumer wearables were validated primarily for detection of atrial fibrillation because of the ease of identifying irregular intervals. Most smartphones, smartwatches, and handheld single-lead ECG consumer devices use photoplethysmography (PPG) sensor technology, which measures changes in blood flow based on the intensity of reflected light. This produces pulse intervals known as tachograms, with the “peak-

to-peak” interval representing the R-R interval, or the interval from 1 QRS complex to the next. Device-dependent algorithms can therefore be used to detect irregular rhythms based on variation in pulse intervals. **Table 1** summarizes the available devices with their regulatory clearance and validation.<sup>6–10</sup>

### CONSUMER-GRADE VS MEDICAL-GRADE DEVICES: VALIDATION COMPARISONS

Overall, the sensitivity of smart devices for atrial fibrillation detection is remarkably high. A recent meta-analysis found that smartphones detected atrial fibrillation with a sensitivity of 94% and a specificity of 96%, and there was no difference in atrial fibrillation detection between devices that use PPG and single-lead ECG.<sup>11</sup> Another meta-analysis showed that smartwatches were noninferior to medical-grade devices for detecting atrial fibrillation.<sup>12</sup>

### Camera applications

Using smartphone camera applications to detect atrial fibrillation is convenient, as it is easily accessible and requires no additional hardware. FibriCheck is the only smartphone-based application with US Food and Drug Administration (FDA) clearance for rhythm monitoring.<sup>6</sup> It uses the light-emitting diode smartphone flash reflected from the finger (the index finger is placed on the smartphone's camera) or from facial video recordings. A validation study that compared the FibriCheck atrial fibrillation algorithm with a standard 12-lead ECG found that the application's sensitivity and specificity for atrial fibrillation detection were 95.6% and 96.6%, respectively.<sup>6</sup>

A meta-analysis of 3,852 participants found that smartphone camera applications for diagnosing atrial fibrillation (Cardio Rhythm Mobile, PULSE-SMART, FibriCheck, and Preventicus) were highly successful in detecting atrial fibrillation (combined sensitivity 94.2%, specificity 95.8%). The negative predictive value was high (99.8%) in all analyses, but the positive predictive value was very low (19.3%–37.5%) in asymptomatic individuals age 65 or older.<sup>13</sup>

### Smartphone-paired devices

Handheld ECG devices are comparable in ease of use with the standard single-lead devices such as Zio patch but have the benefit of real-time monitoring. However, data from the Zio patch can be seen only after it is mailed in.

KardiaMobile is a small, portable handheld ECG device that can provide a 30-second single-lead ECG. The user places 1 finger of each hand on the electrodes and the device wirelessly transmits the ECG to a connected smartphone.<sup>14,15</sup> It has multiple forms, including a small handheld device, phone case, watchband, and card. KardiaMobile 6L has the ability to record all 6 limb leads. A single-center study examined whether KardiaBand could accurately detect atrial fibrillation. When blinded electrophysiologists compared the KardiaBand ECGs with standard 12-lead ECGs, the sensitivity and specificity of KardiaBand ECG recordings for detecting atrial fibrillation were 93% and 84%, respectively, with a K coefficient of 0.77.<sup>14</sup> In a similar study, patients with KardiaMobile were instructed to record their ECG 3 times daily or if they had palpitations. The KardiaMobile detection rate was superior to 24-hour ECG monitoring (9.5% vs 2.0%, respectively).<sup>15</sup> Monitoring with KardiaMobile also seemed to increase atrial fibrillation detection. The REHEARSE-AF study (Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation)<sup>16</sup> randomized 1,001 participants over age 65 with no history

of atrial fibrillation to standard care vs twice-weekly monitoring with AliveCor Kardia. Atrial fibrillation was noted in 3.8% of patients in the handheld ECG arm compared with less than 1% in the standard-care arm.<sup>16</sup>

### Smartwatches

The Apple Watch uses PPG technology to periodically measure heart rate and rhythm over 1-minute intervals while the user is stationary. It can also continuously monitor every 6 seconds during workout mode. Earlier models of the Apple Watch (Series 1 to 3) had only PPG technology. Newer models have incorporated single-lead 30-second ECG, which can be recorded on demand through electrodes on the back of the watch and the watch crown. Of note, the International Trade Commission recently ruled that most Apple Watch models contain technology that infringes on patents held by Masimo Corporation. A cease-and-desist order on sales of the Apple Watch is scheduled to take effect December 26, 2023.<sup>17</sup>

Similarly, Garmin watches also use PPG technology. The Garmin Venu 2 Plus has ECG capability and FDA clearance for detecting arrhythmias. The Samsung smartwatches, including the Galaxy Watch 3 and Galaxy Watch Active 2, and the Withings ScanWatch have PPG and ECG technology.

The growth of the smartwatch market makes it easier to conduct studies with large sample sizes.<sup>18</sup> The Apple Heart Study<sup>19</sup> recruited 419,297 participants without atrial fibrillation over 8 months. Participants who received a notification of irregular pulse through their smartwatch would get a telemedicine visit and have an ECG patch mailed to them to monitor for up to 7 days. More than 2,000 participants (0.52%) had irregular pulse notifications; 450 returned their ECG patches with analyzable data. The positive predictive value for irregular pulse notifications for atrial fibrillation was 84% (95% CI 0.76–0.92).<sup>19</sup>

The Fitbit device, with 37 million active users as of 2022,<sup>20</sup> is a wrist-worn device used primarily as a fitness tracker, but it is also equipped with PPG technology. Fitbit models such as Fitbit Sense and Charge 5 can also record a single-lead ECG. The Fitbit Heart Study<sup>21</sup> is a large prospective remote clinical trial that enrolled Fitbit users. Compared with the Apple Heart Study,<sup>19</sup> it showed a better positive predictive value at 98.2% (95% CI 95.5%–99.5%).

While the Apple Heart Study used smartwatch PPG technology, it only monitored 1-minute intervals every 2 hours.<sup>19</sup> Other studies assessed the ability of smartwatches using continuous PPG monitoring to detect atrial fibrillation and quantify atrial fibrillation burden



in a daily-living setting. In Avram et al,<sup>7</sup> when the Samsung Galaxy Watch Active 2 was compared with a 28-day Holter monitor, it was found to have moderate ability to detect atrial fibrillation with PPG (sensitivity 87.8%, specificity 97.4%). Sensitivity improved to 96.9% and specificity improved to 99.3% with the addition of on-demand ECG for rhythm confirmation.<sup>7</sup> In another study, the Garmin smartwatch also had high sensitivity, specificity, and positive predictive value for atrial fibrillation detection.<sup>8</sup>

Mannhart et al<sup>9</sup> assessed the accuracy of 5 wearable smart devices in detecting atrial fibrillation and found that the sensitivity and specificity for atrial fibrillation detection were comparable between devices. A manual review was required in about one-fourth of the cases due to inconclusive tracings.

## ■ CONCERNS: DURATION, RISK REDUCTION, OTHER ARRHYTHMIAS

### Duration of monitoring

Since rhythm monitoring with PPG is usually intermittent and of short duration (typically less than 5 minutes at a time), there is a theoretical concern that it may have a lower detection rate than longer-duration sampling. However, longer sampling frequency did not improve atrial fibrillation detection in the Watch AF trial (Smartwatches for the Detection of Atrial Fibrillation),<sup>22</sup> which compared a smartwatch-based algorithm using PPG signals vs a single-lead handheld ECG analyzed by 2 cardiologists. The smartwatch algorithm detected atrial fibrillation based on 1-minute PPG recordings with 96.1% accuracy, and the diagnostic accuracy did not improve significantly with 3-minute or 5-minute recording durations.<sup>22</sup>

### Does increased atrial fibrillation detection reduce stroke risk?

It is crucial to determine whether increased detection with smart devices leads to increased use of therapeutic anticoagulation and reduced stroke risk. The Heartline Study,<sup>23</sup> an ongoing randomized app-based trial with more than 26,000 participants age 65 and older, addresses this uncertainty. Patients were randomized to 2 cohorts based on the presence of atrial fibrillation and were further randomized to a digital engagement program with or without the Apple Watch. The key outcomes are the detection of atrial fibrillation in patients with no prior history of atrial fibrillation and improved adherence to direct oral anticoagulation in patients previously diagnosed with atrial fibrillation.<sup>23</sup>

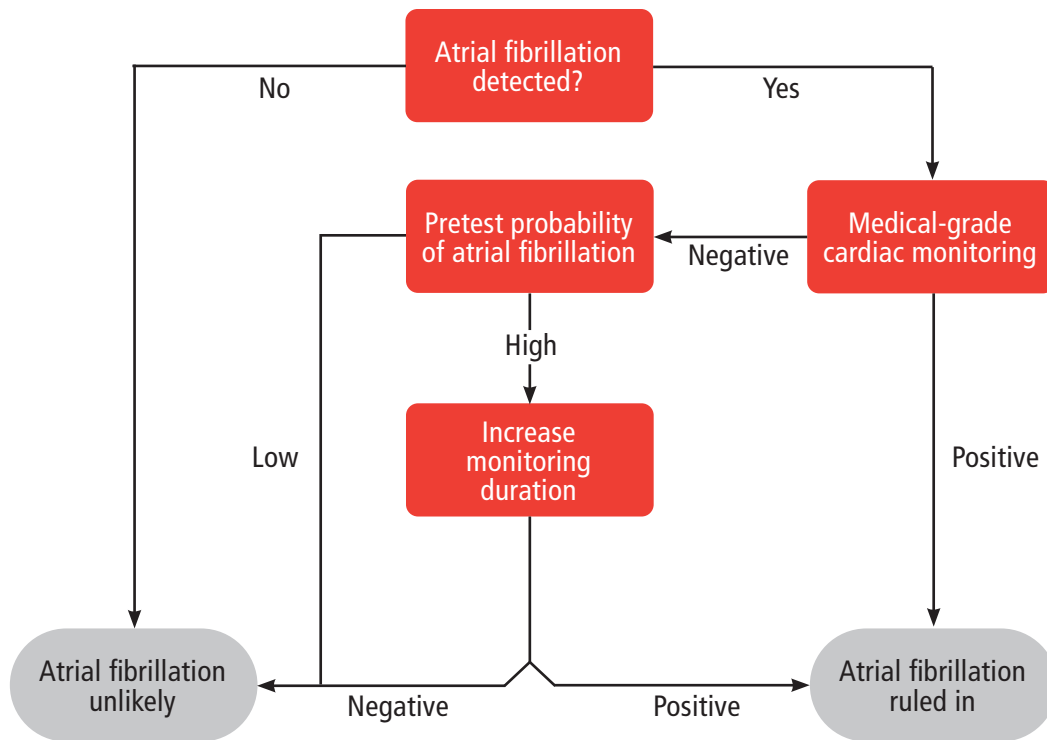
The STROKESTOP trial<sup>24</sup> (Systematic ECG Screening for Atrial Fibrillation Among 75-year-old Subjects in the Region of Stockholm and Halland, Sweden) randomly assigned 27,993 participants residing in the region of Halland and Stockholm, age 75 to 76, to a control group or to the use of a handheld single-lead Zenicor-ECG device twice daily for 2 weeks. At 6.9 years of follow-up, the screening group had a lower incidence of the combined end point of ischemic or hemorrhagic stroke, systemic embolism, bleeding leading to hospitalization, and all-cause mortality, although the effect was small (5.45 vs 5.68 events per 100 patient-years), with a hazard ratio of 0.96 (95% CI 0.92–1.00,  $P = .045$ ).<sup>24</sup>

### Detection of other rate or rhythm abnormalities

A small pilot study assessed the feasibility of measuring the corrected QT interval with KardiaMobile vs standard 12-lead ECG. The handheld single-lead ECG was noninferior to standard 12-lead ECG and was accurate within a range of plus or minus 20 ms.<sup>25</sup> The new 6-lead KardiaMobile device has interval measurements comparable to a standard 12-lead ECG.<sup>26</sup> There is currently no commercially available QT interval measurement algorithm, though preliminary data show that the Apple Watch can reliably assess the corrected QT interval.<sup>27</sup>

Validation of consumer-grade devices has been less promising in detecting supraventricular tachycardia, in part because of the regular ventricular rhythm and lack of variation of the R-R interval.<sup>8</sup> A prospective multicenter validation study of 50 patients aimed to improve the detection of atrial flutter using KardiaMobile.<sup>27</sup> After KardiaMobile recorded lead I, the device was repositioned by holding the panel in the right hand and placing the opposite electrode onto the left leg to generate a lead II. Two independent blinded electrophysiologists analyzed the recordings. The sensitivity of lead I alone for detecting atrial flutter was poor for both electrophysiologists at 27.3%, but sensitivity improved to 72.7% and 54.6% with the incorporation of the additional lead.<sup>28</sup>

Detection of other forms of supraventricular tachycardia, pathologic Q waves, and heart blocks has received limited study. One study of Apple Watch 2, Samsung Galaxy Gear S3, and Fitbit Charge 2 found excellent accuracy in diagnosing the heart rate of supraventricular tachycardia, but the rhythm was not analyzed.<sup>29</sup> The sensitivity of KardiaMobile in detecting pathologic Q waves was found to be 20.6% in a study by Koltowski et al.<sup>30</sup> Limited data suggest that Apple Watch's single-lead ECG may help recognize first- and second-degree atrioventricular block.<sup>31</sup>



**Figure 1.** Our approach to atrial fibrillation identified on consumer-grade wearable devices.

## LIMITATIONS OF CONSUMER-BASED DEVICES

The availability of consumer-grade heart rhythm monitors comes with limitations as well as potential for future research, including the following:

- A high false-positive rate
- Disparities in access
- An influx of consumer-grade data on a strained provider workforce
- Potential for improvements in technology and data.

### False-positive results and pretest probability

The high false-positive rate for detecting atrial fibrillation in young, otherwise healthy populations is a significant limitation of consumer-based devices that may lead to increased anxiety and unnecessary health-care utilization. However, although false alerts have been shown to reduce perceived physical well-being, the financial impact of false-positive detections is not well understood.<sup>32</sup>

As with all medical tests, the positive predictive value varies significantly based on the patient population. An important tenet of Bayesian reasoning is that the posttest probability depends on the pretest probability. In other words, atrial fibrillation detected

on a smartwatch in a young, healthy patient (low pretest probability) is unlikely to be atrial fibrillation. In contrast, atrial fibrillation detected in an elderly hypertensive patient with obstructive sleep apnea (high pretest probability) is highly likely to be atrial fibrillation. Atrial fibrillation incidence increases with age, from 1.5% at age 55 to 59 to 23.5% at age 80 to 89.<sup>33</sup> Both the Apple Heart Study<sup>19</sup> and the Fitbit Heart Study<sup>20</sup> noted higher rates of detection and diagnosis of atrial fibrillation in participants age 65 and older. The VITAL-AF Study (Screening for Atrial Fibrillation in Older Adults at Primary Care Visits)<sup>34</sup> evaluated more than 30,000 participants age 65 or older without atrial fibrillation. The study compared KardiaMobile vs usual care and found no difference in the incidence of atrial fibrillation diagnosis between the screening and the control groups. However, in a prespecified analysis of patients over age 85, atrial fibrillation was more likely to be detected in the screening group than in the control group (5.56% vs 3.76%).<sup>34</sup>

### Disparities

There are disparities in device access and utilization. Only one-third of US adults and 18% of patients with cardiovascular disease have smart devices. Further, patients over age 65 and those with lower education

and socioeconomic status have less access to smart devices and a higher risk of atrial fibrillation.<sup>10</sup>

### Burden to healthcare system

The influx of data from consumer-grade devices will increase the burden on an already strained healthcare system. In addition to more data, automated rhythm readings may be deemed inconclusive despite producing readable single-lead ECGs, as was shown in the BASEL Wearable Study.<sup>9</sup> However, a manual review of the tracings by a cardiologist reduced the rate of inconclusive tracings from 26% to around 1%.<sup>9</sup> There are no well-established best practices for physician notifications, documentation, reimbursement protocols, and care coordination with detection of atrial fibrillation from consumer-grade devices.

### Improved technology and security

Large, high-quality, randomized controlled trials demonstrating that wearable atrial fibrillation detection improves hard clinical outcomes are still lacking, and it is hoped that the randomized Heartline Study<sup>23</sup> will address some of these gaps. Future trials and observational studies are needed to determine whether earlier atrial fibrillation diagnosis from consumer-grade wearable devices increases adherence to appropriate anticoagulation and reduces adverse events. Further studies on cost-effectiveness are also needed.

Advances in sensors like improved PPG and multilead ECG may enhance accuracy of detection. More sophisticated algorithms that utilize deep learning on large ECG datasets could also improve performance and decrease false-positive results.

## ■ OUR APPROACH

Our approach to atrial fibrillation identified on consumer devices is summarized in **Figure 1**. Given the high sensitivity of each device, lack of detection on device interrogation makes atrial fibrillation unlikely regardless of pretest probability. We consider atrial fibrillation “unlikely” rather than “ruled out,” given that consumer-grade devices are not truly continuous (they sample PPG or ECG only intermittently), are not always worn, and may need to be removed for charging.

**If atrial fibrillation is detected, we review the tracings from the device, if available.** It is common for a manual review to demonstrate normal rhythm with

ectopy or sinus arrhythmia, in which case reassurance and continued consumer-grade monitoring are appropriate.

**If no tracings are available or the tracings suggest atrial fibrillation, we move on to medical-grade cardiac monitoring** because of a slightly higher specificity in medical-grade devices. If the medical-grade monitor also shows atrial fibrillation, we diagnose atrial fibrillation and engage in shared decision-making with the patient about the risks and benefits of treatment.

**If the consumer-grade device suggests atrial fibrillation and the medical-grade device shows none,** we assess the pretest probability of atrial fibrillation. If the pretest probability is low and there are clear alternate causes of an irregular rhythm on the medical-grade monitoring (such as sinus rhythm with frequent ectopy or sinus arrhythmia), we consider atrial fibrillation unlikely.

**If the medical-grade device shows no atrial fibrillation and we think the pretest probability is high,** we typically increase the monitoring duration via longer Holter monitoring or, if the arrhythmia is infrequent, an implantable loop recorder.

## ■ OUTLOOK: BETTER DETECTION, BETTER TREATMENT

With comparable sensitivity to medical-grade devices, wearable consumer-grade devices show promise in detecting cardiac arrhythmias, particularly atrial fibrillation. These increasingly common devices can potentially improve the detection of atrial fibrillation and the prescription of therapeutic anticoagulation in appropriate cases, leading to improved patient outcomes. Given the high sensitivity and lower specificity of these devices, absence of atrial fibrillation should be reassuring, while detected atrial fibrillation should prompt further testing with medical-grade devices and referral to an experienced ECG reader. As with any diagnostic test, the result needs to be contextualized with an understanding of the pretest probability of atrial fibrillation. Ongoing research will address the effectiveness of these devices in detecting other cardiac pathologies and their impact on long-term outcomes, such as stroke risk and therapeutic anticoagulation. ■

## ■ DISCLOSURES

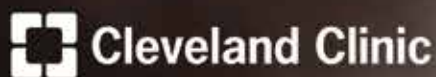
Dr. Jensen has disclosed being an advisor or review panel participant for, having ownership interest in, and being an executive level board member for Dose Health. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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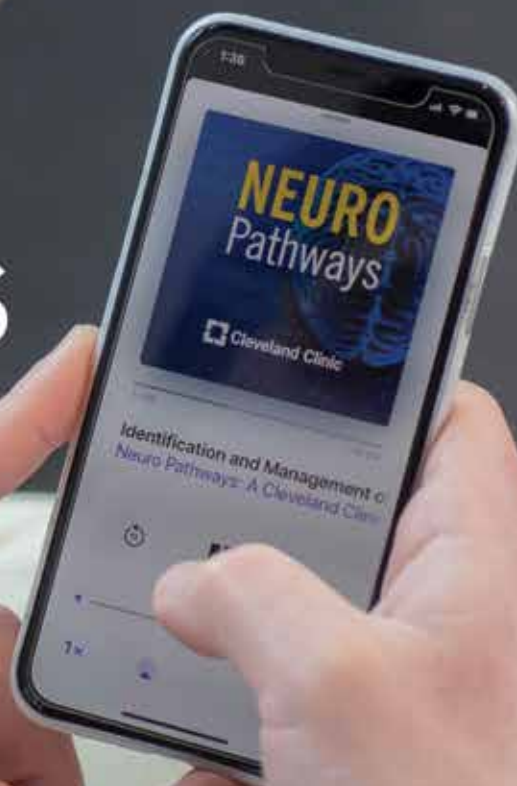
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Address: Kevin G. Buda, DO, Department of Internal Medicine, Division of Cardiology, Hennepin County Medical Center, 925 S. 8th St, G5-125, Minneapolis, MN 55415; Kevin.buda@hcmcd.org





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**Jakub Sroubek, MD, PhD**

Department of Cardiovascular Medicine and Division of Cardiac Pacing and Electrophysiology, Heart, Vascular, and Thoracic Institute, Cleveland Clinic, Cleveland, OH; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

# Wearable cardiac monitors: Where do we stand?

**O**H, HOW TIME FLIES! When I started my postgraduate training a decade ago, evaluation of (most) patients with palpitations was simple: history, physical examination, and a 48-hour Holter monitor. In those days, affordable consumer-grade cardiac monitors were based solely on photoplethysmography (PPG, akin to pulse oximetry), which in its early form rarely offered actionable diagnostic information for an electrophysiologist. Instead, a clinical-grade Holter monitor was needed. Holter monitors and the related event monitors were conceptualized in the late 1940s<sup>1</sup> and commercialized in the early 1960s, but their fundamental design, management, and interpretation has changed very little over time. While not always practical for the patient, the devices represented a tried-and-true diagnostic tool for most clinicians.

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*See related article, page 23*

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Over the past decade, marked improvement in both the quality and affordability of consumer-grade wearable monitors has changed the game completely—especially after many products acquired the ability to record single-lead electrocardiogram (ECG) tracings. This is most apparent in the outpatient electrophysiology clinic, where patients routinely hand me their phones and ask me to scroll through their ECG logs. I do this gladly, and not just to humor them. The home ECG data are incredibly helpful! Countless times, these tracings have directly affected patient management.

While Holter and event monitors continue to play a major role in patient care, the consumer-grade cardiac monitors are becoming just as important, and their value, reliability, and ubiquity will only grow. Regardless of one's technological savvy, any practicing clinician should be familiar with the most frequently used wear-

able cardiac monitors and, importantly, with the clinical evidence that supports or challenges their utility.

In this issue of the *Journal*, Mohamoud et al<sup>2</sup> provide a helpful and succinct review of the most up-to-date clinical information behind consumer-grade wearable monitors. They make it clear that the bulk of research efforts so far have focused on proving the utility of PPG-based devices as population-wide screening tools for atrial fibrillation. The 2 largest studies—the Apple Heart Study<sup>3</sup> and the Fitbit Heart Study<sup>4</sup>—together enrolled almost 1 million patients and proved that wearable monitors do indeed perform well as screening tools for atrial fibrillation.

While such information is crucial for future research efforts, it has little direct impact on the day-to-day practice of most clinicians. Indeed, Mohamoud et al<sup>2</sup> show that some nuanced but clinically crucial questions have barely been addressed. From the vantage point of a clinical electrophysiologist, I am interested in consideration of 3 dilemmas, discussed below.

## ■ DO WEARABLE CARDIAC MONITORS TRANSLATE TO STROKE PREVENTION?

The idea is simple: patients self-detect incidental atrial fibrillation on wearable cardiac monitors. After confirming the diagnosis, a physician prescribes therapeutic anticoagulation to appropriate patients (eg, after risk-stratification using the CHA<sub>2</sub>DS<sub>2</sub>-VASc<sup>5</sup> model or similar) and prevents cardioembolic events.

But we know that things are rarely so simple. For example, when patients with permanent pacemakers experience asymptomatic episodes of atrial fibrillation, their risk of stroke is indeed higher than that of the general population, but it is considerably lower than that predicted by the CHA<sub>2</sub>DS<sub>2</sub>-VASc model.<sup>6</sup> It is easy to imagine that if we extend the atrial fibrillation screening process to an even healthier population (ie,

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anyone in the general public wearing a consumer-grade monitor), the applicability of existing risk-stratification paradigms may decline even more.

In practical terms, should we start therapeutic anticoagulation in every 66-year-old man with hypertension (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2) who walks into our office and shows us an Apple watch tracing with 15 minutes of atrial fibrillation? Additional studies are needed to address this question.

### ■ WHAT IS THE ROLE OF WEARABLE CARDIAC MONITORS FOR OTHER INDICATIONS?

As shown by Mohamoud and colleagues, most evidence for wearable monitors circles around de novo screening for atrial fibrillation. Relatively less is known about using these devices to manage patients with known atrial fibrillation. In our practice, we often ask patients to send us KardiaMobile ECG tracings once a week (or whenever the patient is symptomatic) for 3 months after undergoing catheter ablation. This approach makes intuitive sense and, in our experience, has been very effective in identifying early recurrences of atrial fibrillation. But it has never been formally studied.

The utility of cardiac wearables in the diagnosis and management of suspected short-duration arrhythmias is also unknown. Patients with symptoms caused by cardiac ectopy are often managed based on the absolute burden of premature beats. Will wearable devices help with that? What about patients with syncope? Will PPG-based wearable devices ever be able to provide sufficiently granular diagnostic information, or will clinical-grade ECG Holter devices always be necessary?

### ■ CAN WE STREAMLINE CLINICAL INTERPRETATION?

As noted, in our electrophysiology practice, established patients with arrhythmias occasionally ask to have their home device ECG tracings reviewed by a physician. Patients who require frequent ECG monitoring may also subscribe to a service that enables them to send their KardiaMobile ECG tracings directly to our device clinic, where a team of nurses and technicians

can quickly review the information. This helps ensure prompt diagnosis of arrhythmias (if present), and it improves patient satisfaction and provides reassurance. In some cases, this ECG review precludes an unnecessary office or emergency room visit. Today, the volume of such information exchange is manageable, but as more patients purchase home monitors, the availability and affordability of review services may become limited unless systemic change is implemented.

The problem of scaling is even more evident when we consider population-wide screening using consumer-grade cardiac monitors. Most wearable devices provide automatic detection of atrial fibrillation, but its clinical verification remains manual. Even if we accept the high precision of the automated diagnosis of atrial fibrillation (a positive predictive value near 98% in the FitBit Heart Study<sup>4</sup>), most clinicians would be reluctant to treat new patients based only on what their home monitor app reports. Instead, physicians typically review the primary device data manually or reassess the patient with a Holter monitor or both before moving to treatment. In some cases, this may result in a specialty (cardiology) or subspecialty (electrophysiology) referral. Like the subscription services we provide in our practice, this process may be sustainable now, but increased numbers of self-screened individuals might require a more streamlined approach. What this would look like remains to be seen, but the possibilities include workforce extension (more ECG technicians in hospital and industry) and technology so precise that manual confirmation will be unnecessary.

### ■ CLOSING THOUGHTS

Technological advances have enabled us to reimagine the diagnosis and management of cardiac arrhythmias, especially atrial fibrillation. Judicious application of these enhanced tools will require continued analysis of their potential, as well as how to manage the data they generate. ■

### ■ DISCLOSURES

The author reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

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Address: Jakub Sroubek, MD, PhD, Department of Cardiovascular Medicine, J2-2, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; sroubek@ccf.org

## REVIEW

### Shrouq Khazaaleh, MD

Department of Internal Medicine,  
Cleveland Clinic Fairview Hospital,  
Cleveland, OH

### Mohammad Alomari, MD

Department of Gastroenterology  
and Hepatology, Cleveland Clinic Florida,  
Weston, FL

### Mamoon Ur Rashid, MD

Department of Gastroenterology  
and Hepatology, Cleveland Clinic Florida,  
Weston, FL

### Daniel Castaneda, MD

Department of Gastroenterology  
and Hepatology, Cone Health Annie Penn  
Hospital, Reidsville, NC

### Fernando J. Castro, MD

Department of Gastroenterology  
and Hepatology, Cleveland Clinic Florida,  
Weston, FL; Clinical Assistant Professor,  
Cleveland Clinic Lerner College of Medicine  
of Case Western Reserve University,  
Cleveland, OH

# Gastric intestinal metaplasia and gastric cancer prevention: Watchful waiting

## ABSTRACT

Gastric intestinal metaplasia (GIM), a common histologic finding, is associated with increased risk of gastric cancer, and GIM associated with *Helicobacter pylori* infection is classified as an environmental metaplastic atrophic gastritis. Patients may be asymptomatic or present with various dyspeptic symptoms. Autoimmune metaplastic atrophic gastritis is a less common but important cause of chronic gastritis. The Correa cascade describes the evolution of precancerous mucosal changes that lead to development of GIM, with differentiation of 2 histologic types of GIM (complete and incomplete) and the consequences of each type. The risk of progression to malignancy is higher with incomplete GIM. It is also higher for those who immigrate from regions with a high incidence of *H pylori* infection to areas where the incidence is low. Guidelines regarding endoscopic management of GIM vary by geographic region.

## KEY POINTS

Factors in the complex chain of events leading to malignant transformation include genetic predisposition, the anatomic extension of the metaplasia, and histologic differentiation.

Environmental risk factor control such as *H pylori* eradication, smoking cessation, and moderation in alcohol intake may halt the progression of atrophic gastritis to GIM.

Careful risk stratification is key: Patients at high risk should undergo endoscopic surveillance.

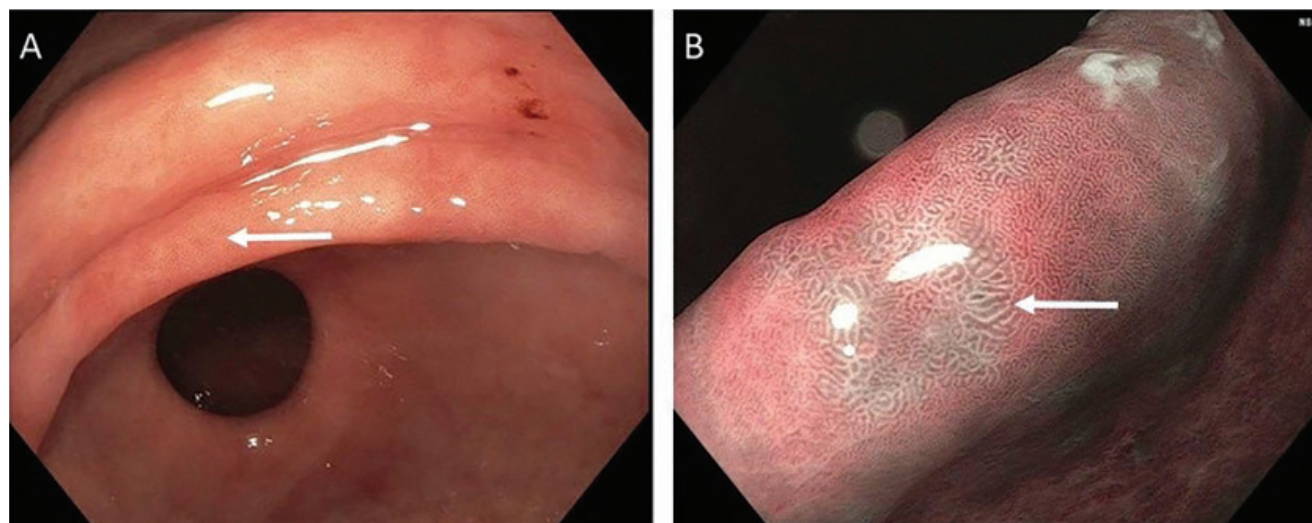
**G**ASTRIC INTESTINAL METAPLASIA (GIM), a common histologic finding in clinical practice, is the differentiation of gastric epithelium into a form that resembles intestinal epithelium (Figure 1). It often represents a repair process in response to gastric injury such as from peptic ulcer or gastritis, and therefore most cases have no clinical significance. But if the gastric injury continues without treatment, GIM may be a warning sign of progression to gastric cancer, thus warranting further assessment and risk stratification. However, despite the risk of progression, malignancy develops in only a small minority of patients. Recognition of clinical, endoscopic, and histologic features linked with cancer development is critical to identifying high-risk patients who require endoscopic surveillance.

## RISK OF CANCER PROGRESSION

Although uncommon, progression of GIM to gastric cancer is well documented. A total of 10 cohort studies, including 2 that were US-based, involving 25,912 patients with GIM, reported a pooled incidence rate of gastric cancer of more than 12 cases per 10,000 person-years.<sup>1</sup> Cancer progression is more likely in patients with GIM who develop dysplasia. In a study from the Netherlands, the annual incidence of gastric cancer was 0.25% with GIM, 0.6% with mild-to-moderate dysplasia, and 6% with severe dysplasia at baseline.<sup>2</sup>

Barrett esophagus has a similar histopathologic background and established cancer-





**Figure 1.** Endoscopic appearance of gastric intestinal metaplasia (GIM). (A) White-light endoscopy reveals macroscopic GIM, with an irregular, even surface. The arrow indicates an elongated, groove-type pit pattern. (B) Enhanced narrow-band imaging of the same surface shows multiple pale, elevated patches.

**TABLE 1**

## Autoimmune vs environmental metaplastic atrophic gastritis

	Autoimmune-mediated metaplastic atrophic gastritis	<i>Helicobacter pylori</i> -mediated metaplastic atrophic gastritis
Location	Primary involvement of the gastric body and fundus	All gastric epithelium including antrum
Acid production	Lost entirely	Decreased
Fasting gastrin level	Markedly elevated	Variable
Antibodies	Antibodies to intrinsic factor and parietal cells	Antibodies to <i>H pylori</i>
Vitamin B <sub>12</sub> deficiency	Present, often severe	May be present, usually mild
Association	Other autoimmune disorders	Peptic ulcer disease, adenocarcinoma, "MALToma"

MALToma = mucosa-associated lymphoid tissue lymphoma or MALT lymphoma

Based on information in reference 15.

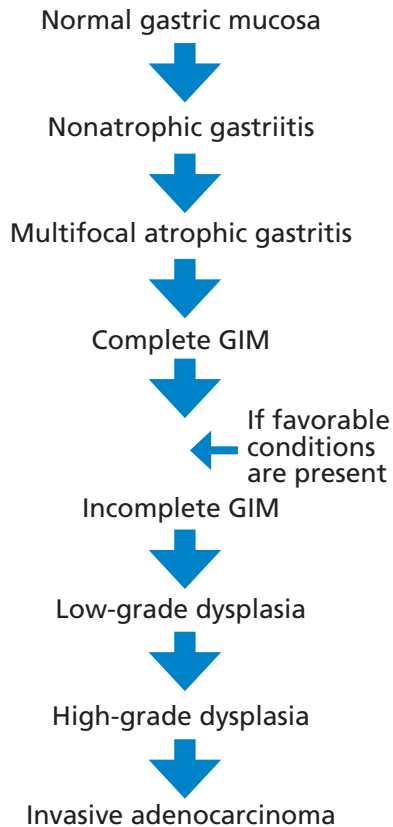
progression risk. The overall risk of progression to esophageal adenocarcinoma in Barrett esophagus is 0.22% per year.<sup>3</sup> The presence of low-grade dysplasia increases the annual cancer risk to 0.5% per year, and high-grade dysplasia increases the risk to 5% to 8% per year.<sup>4,5</sup> Although the risk of cancer progression with GIM and Barrett esophagus is similar in the United States, endoscopic surveillance only improved patient-important outcomes in Barrett esophagus, likely because of the lower prevalence of GIM compared with Barrett esophagus.<sup>1,6</sup>

## CHRONIC GASTRITIS AND GIM

Regardless of its cause, chronic gastric inflammation may lead to atrophic gastritis characterized by mucosal thinning and replacement of gastric glandular cells by intestinal epithelium (ie, GIM).

### Environmental metaplastic atrophic gastritis

*Helicobacter pylori* infection remains the leading cause of chronic gastritis, with earlier studies suggesting that it is responsible for more than 90% of cases.<sup>7</sup>



**Figure 2.** The Correa cascade illustrates the progression from precancerous histologic changes in the gastric mucosa to the development of gastric intestinal metaplasia.

GIM as a result of *H pylori* infection is classified as an environmental metaplastic atrophic gastritis (EMAG). *H pylori* is more prevalent than previously thought, based on estimates that 50% of the world population has been infected in their lifetime,<sup>8</sup> and the overall prevalence in the United States is 36%.<sup>9</sup> If not eradicated, *H pylori* infection can progress to atrophic gastritis with damage to the gastric glands. Notably, the virulence of specific *H pylori* strains can play a critical role in infection outcomes. Strains that express the cytotoxin-associated gene *CagA* or the vacuolating cytotoxin *VacA* s1m1 genotype are associated with an increased risk of precancerous lesions and progression to adenocarcinoma.<sup>10</sup>

Chronic use of proton pump inhibitors (PPIs) has not been shown to prevent or modify histologic changes of GIM. In fact, chronic PPI use often results in decreased *H pylori* densities and proximal migration of the bacteria from the antrum to the body of the stomach, factors that complicate its diagnosis and timely eradication. Unmonitored long-term use of PPIs should be avoided.<sup>11</sup>

**TABLE 2**

**Risk factors for progression to malignancy in gastric intestinal metaplasia**

	Relative risk	95% confidence interval
Incomplete gastric intestinal metaplasia <sup>1</sup>	3.33	1.96–5.64
Extensive gastric intestinal metaplasia <sup>1</sup>	2.07	0.97–4.42
Family history of a first-degree relative with gastric cancer <sup>1</sup>	4.5	1.3–15.5
Smoking <sup>26</sup>	1.57	1.24–1.98
Alcohol <sup>26</sup>	1.29	1.12–1.50

Other possible causes of EMAG include habits such as high salt intake, cigarette smoking, and alcohol use.<sup>12</sup>

Clinically, patients with EMAG may be asymptomatic or present with dyspeptic symptoms with variable severity. Autoantibodies to parietal cells and intrinsic factor are lacking, and levels of fasting gastrin tend to be low. In addition to evaluation for *H pylori* and its timely eradication, EMAG patients should be screened for coexisting conditions such as vitamin B<sub>12</sub> and iron deficiency and treated appropriately.

**Autoimmune metaplastic atrophic gastritis**

A less common but important cause of chronic gastritis is autoimmune metaplastic atrophic gastritis (AMAG). Affecting 0.15% of the adult population,<sup>13</sup> AMAG primarily involves the gastric body and fundus while sparing the antrum. Most patients are asymptomatic, but some may present with manifestations of vitamin B<sub>12</sub> deficiency or iron-deficiency anemia. In contrast to laboratory findings for EMAG, supportive laboratory findings with AMAG include positive antibodies to intrinsic factor (more specific) and parietal cells (more sensitive), fasting hypergastrinemia, and decreased serum pepsinogen I/II ratio. Screening should be considered for concomitant autoimmune conditions such as type 1 diabetes mellitus and autoimmune thyroid disease.<sup>14</sup> **Table 1** compares the features associated with EMAG and AMAG.<sup>15</sup>

**TABLE 3**  
**Variations in society recommendations for the management of gastric intestinal metaplasia**

Geographic location	Society recommendations
East Asia	Endoscopic or radiographic screening of all men and women at age 50 or older <sup>29</sup>  In patients with gastric intestinal metaplasia and high-risk features, endoscopy recommended in 1 to 3 years
Europe	Patients with extensive gastric intestinal metaplasia should undergo endoscopic surveillance every 3 years  Consider endoscopic surveillance in patients with gastric intestinal metaplasia limited to the corpus or antrum of the stomach but with a family history of gastric cancer, persistent <i>Helicobacter pylori</i> infection, incomplete gastric intestinal metaplasia, or autoimmune gastritis <sup>30</sup>
United States	AGA recommends against routine endoscopic surveillance after gastric intestinal metaplasia is detected in the general population, but if <i>H pylori</i> is detected, treatment is encouraged  Patients with gastric intestinal metaplasia and risk factors associated with progression could be considered for endoscopic surveillance every 3 to 5 years if the patient favors surveillance (which has an unclear impact on mortality risk) vs endoscopic evaluation, which has a risk of complications <sup>31</sup>  ASGE recommends endoscopic surveillance exclusively in patients with risk factors, but not in the general cohort of patients in whom gastric intestinal metaplasia is detected <sup>32</sup>

AGA = American Gastroenterological Association; ASGE = American Society for Gastrointestinal Endoscopy

## CORREA CASCADE: DIFFERENTIATING COMPLETE AND INCOMPLETE GIM

The Correa cascade describes the progression from precancerous histologic changes in the gastric mucosa to the development of GIM and its consequences, including adenocarcinoma (**Figure 2**). The process begins with development of nonatrophic gastritis and progresses to multifocal atrophic gastritis followed by GIM.

GIM can present 2 histologic types:

- The *complete* and fully intestinalized pattern has markers for intestinal mucin and absence of gastric mucin.
- The *incomplete* gastric and intestinal mixed glands pattern has both gastric mucin and intestinal mucin markers.<sup>16</sup>

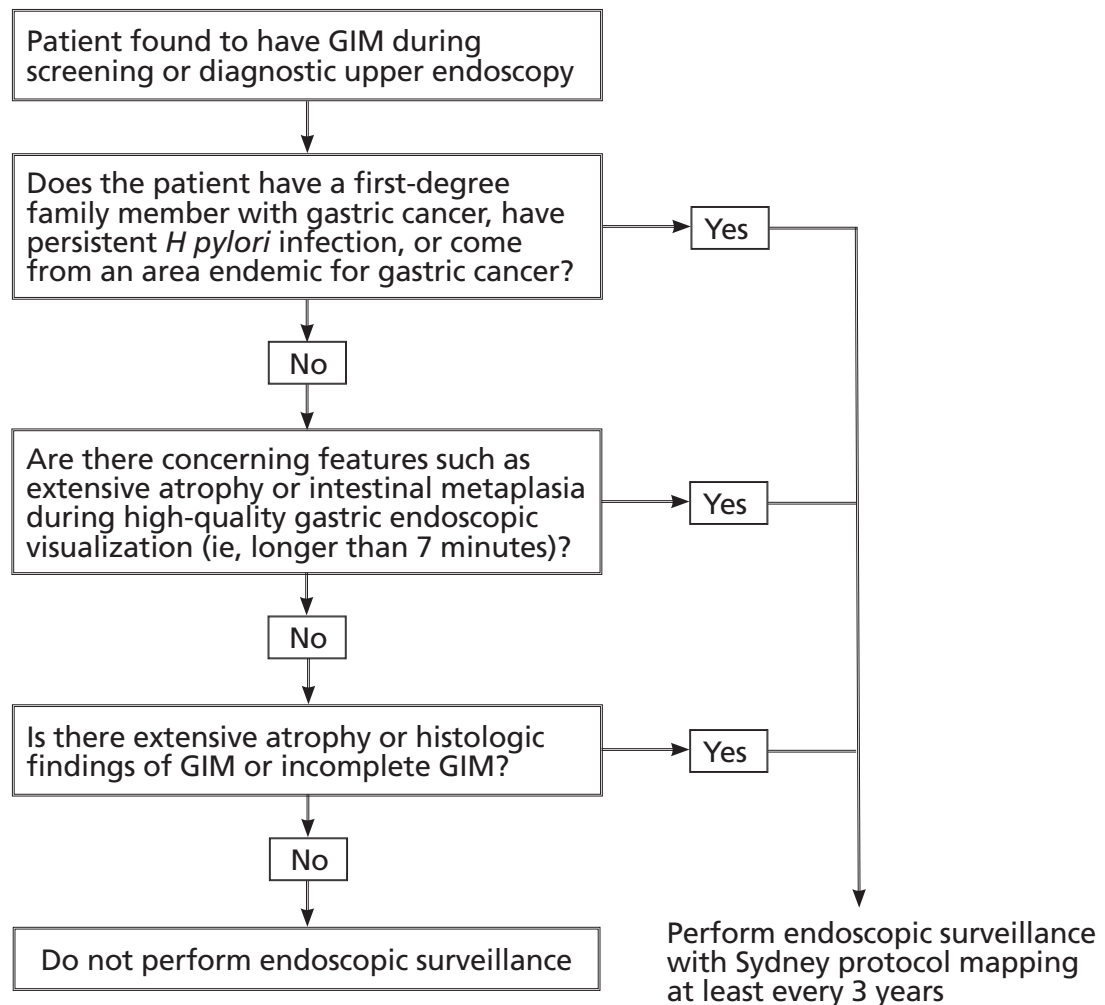
Complete GIM may progress to incomplete GIM if conditions leading to severe inflammation are present (eg, advanced atrophy or hypochlorhydria) before identifiable dysplastic changes.<sup>17</sup> Subsequently, the tissue progresses to low-grade dysplasia, followed by high-grade dysplasia, and finally invasive adenocarcinoma.<sup>18</sup>

Differentiation of the 2 types of GIM is important. Incomplete GIM has been associated with an increased risk of cancer progression, and some experts consider it a mild degree of dysplasia.<sup>19,20</sup>

## RISK FACTORS FOR PROGRESSION TO MALIGNANCY

The risk of developing gastric cancer may be higher in patients with histologic evidence of incomplete and extensive GIM (ie, involvement of the antrum and corpus) than in those with complete and limited GIM.<sup>1,21,22</sup> Some studies suggest that the topographic distribution of intestinal metaplasia may affect the risk of cancer progression. In Cassaro et al's<sup>23</sup> cohort study of 135 Colombian patients, a GIM distribution involving the lesser curvature of the stomach from the cardia to the pylorus was associated with higher cancer risk (odds ratio 5.7, 95% confidence interval 1.3–26) compared with “antrum-predominant” or “focal” patterns.<sup>23</sup>

The incidence of gastric cancer exhibits significant geographic variation worldwide due to potential environmental exposure factors and genetic predisposition. The reported rates are highest in Eastern Asia, Eastern Europe, and South America, and lowest in North America.<sup>24</sup> People who immigrate from a region of high incidence to a region of low incidence have an increased risk of gastric cancer.<sup>25</sup> **Table 2** summarizes risk factors for malignancy.<sup>1,26</sup>



**Figure 3.** An algorithmic approach to the management of gastric intestinal metaplasia (GIM).

### ■ ENDOSCOPIC MANAGEMENT

The role for endoscopy in GIM is limited to detection and surveillance, as no other methods are currently available for this. Specific recommendations for endoscopy are discussed in the various guidelines below.

### ■ NONENDOSCOPIC MANAGEMENT

GIM management should emphasize risk-factor modification, including smoking cessation and moderation in alcohol intake. In patients with *H pylori*-induced gastritis, early *H pylori* detection and eradication are crucial to halt progression to gastric cancer. In contrast, the effects of *H pylori* eradication once GIM occurs are undetermined. GIM changes may

be irreversible, and the impact of *H pylori* eradication on cancer progression once GIM is established may be minimal.<sup>27</sup>

Observational studies have reported partial GIM reversal and decreased progression to stomach cancer with use of aspirin and nonsteroidal anti-inflammatory drugs such as celecoxib.<sup>28</sup> More evidence is needed to support their use.

### ■ GLOBAL DIFFERENCES IN GUIDELINE RECOMMENDATIONS

The optimal follow-up of patients with isolated glands of GIM remains controversial, with significant differences in guidelines in the Eastern and Western regions of the world (Table 3).<sup>29–32</sup>



## Recommendations for Eastern regions

In countries such as Japan, where the incidence of gastric cancer is high, national screening programs recommend mass endoscopic or radiographic screening of all men and women at age 50 or older.<sup>29</sup> For patients found to have GIM without malignancy on initial screening, surveillance endoscopy in 1 to 3 years is recommended if they have GIM with high-risk features such as incomplete GIM, extensive GIM, family history of gastric cancer, smoking, or excessive alcohol use.

## Recommendations for Western regions

The British Society of Gastroenterology guidelines<sup>33</sup> identify patients with GIM as having increased risk for gastric malignancy and recommend endoscopic surveillance every 3 years if there is extensive GIM (ie, affecting the antrum and corpus), antral GIM with risk factors such as *H pylori*, or a family history of gastric cancer.<sup>33</sup>

A 2019 consensus guideline by 4 European organizations agreed with the British Society of Gastroenterology.<sup>30</sup> The guideline recommends that patients with GIM who are considered at high risk, including those with histologically proven GIM of the corpus and antrum, undergo endoscopic surveillance every 3 years. The guideline advises consideration of surveillance if GIM is present only in the corpus or antrum but the patient has a family history of gastric cancer, persistent *H pylori*, incomplete GIM, or autoimmune gastritis.

## US recommendations

Two US societies have published guidelines addressing the management of GIM.

The American Gastroenterological Association guidelines<sup>31</sup> recommend against routine endoscopic surveillance after GIM is detected in the general population, but if *H pylori* is detected, treatment is encouraged. Patients with GIM and risk factors associated with progression can be considered for endoscopic surveillance every 3 to 5 years if the patient favors surveillance, which has an unclear impact on mortality

risk, vs endoscopic evaluation, which has potential complications.<sup>31</sup>

The guidelines subcategorized risk factors associated with progression of gastric cancer as follows:

- Highest risk: incomplete GIM, extensive GIM, or family history of gastric cancer
- Overall increased risk: certain racial or ethnic minorities immigrating from high-incidence regions.<sup>31</sup>

The American Society for Gastrointestinal Endoscopy recommendations<sup>32</sup> are similar to those of European groups. They advise endoscopic surveillance exclusively for patients with risk factors, but not for the general cohort of patients in whom GIM is detected.

## AN ALGORITHMIC APPROACH TO DIAGNOSIS AND MANAGEMENT

Figure 3 suggests an approach to managing patients who have GIM. The updated Sydney protocol includes the collection of 5 nontargeted biopsy specimens: 2 from the antrum (at the lesser and greater curvature), 2 from the corpus (at the lesser and greater curvature), and 1 from the incisura.<sup>34</sup> It is recommended that these biopsy specimens be placed in separate jars.

Careful inspection should be carried out with high-definition white-light endoscopy rather than standard-definition endoscopy. Adequate air insufflation, use of mucolytic and defoaming agents (for improved visibility), appropriate withdrawal times, and photodocumentation are key for a quality endoscopic examination.<sup>35</sup> Additionally, use of narrow-band imaging should be encouraged because it has been shown to improve the detection of GIM.<sup>36</sup> It also allows for more targeted biopsies for GIM.

## DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Address: Mohammad Alomari, MD, Department of Gastroenterology and Hepatology, Cleveland Clinic Florida, 2950 Cleveland Clinic Boulevard, Weston, FL 33331; dr\_mohd1987@hotmail.com

## REVIEW

**Jason T. Alexander, MD**

Department of Medicine,  
University of Chicago, Chicago, IL

**Simran K. Singh, MD**

Department of Medicine, Case Western  
Reserve University, Cleveland, OH

**Sachin D. Shah, MD**

Department of Medicine,  
University of Chicago, Chicago, IL

**Brianna Lambert, MD**

Department of Medicine,  
University of Chicago, Chicago, IL

**Jeremy P. Smith, MD**

Department of Internal Medicine,  
University of Wisconsin-Madison,  
Madison, WI

# 2023 Update in ambulatory general internal medicine

## ABSTRACT

The practice of outpatient medicine is demanding, encompasses a wide scope of practice, and leaves little time for internists to stay up to date with the current literature. This article reviews 5 studies published in 2022 and 2023 that have the potential to change the practice of outpatient medicine. Topics covered include chronic kidney disease, secondary cardiovascular disease, kidney stones, obesity, and lipid management.

## KEY POINTS

Empagliflozin slowed the progression of chronic kidney disease in patients with chronic kidney disease; the benefit was most pronounced in patients with significant albuminuria.

A Mediterranean diet was superior to a low-fat diet for secondary prevention of major cardiovascular events.

Hydrochlorothiazide did not decrease symptomatic or radiologic recurrence of calcium-containing kidney stones.

Tirzepatide was effective for weight loss in patients who were obese or overweight with weight-related complications.

Ezetimibe, added to lower-intensity statin therapy, was noninferior to high-intensity statin therapy with respect to major adverse cardiovascular events.

**I**NTERNISTS WHO PRACTICE ambulatory medicine face many challenges. The time pressure of managing a patient's acute concerns, discussing their chronic medical problems, and advising on disease prevention is excessive.<sup>1</sup> Often, this leaves little time for practitioners to stay current on recently published evidence.

This review identifies and critically appraises 5 studies, each covering a different topic germane to the practice of ambulatory medicine, that have the potential to change practice. Studies were identified by reviewing abstracts from high-impact journals including the *New England Journal of Medicine*, *Journal of the American Medical Association*, *Lancet*, and *Annals of Internal Medicine*. Articles addressing topics relevant to ambulatory medicine were identified and appraised, and 5 final articles were agreed upon by all authors to critique for the current review. We discuss the role of empagliflozin in preventing progression of chronic kidney disease, diet for preventing secondary cardiovascular disease, hydrochlorothiazide for preventing kidney-stone recurrence, tirzepatide for weight loss, and ezetimibe for cholesterol management.

## ■ SLOWING THE PROGRESSION OF CHRONIC KIDNEY DISEASE

A 59-year-old woman with a history of hypertension and stage 3b chronic kidney disease with an estimated glomerular filtration rate of 40 mL/min/1.73 m<sup>2</sup> presents for clinic follow-up. Her blood pressure is well controlled with an angiotensin II receptor blocker and a thiazide diuretic. Recent laboratory results are remarkable for a normal urine albumin-to-creatinine ratio. She asks you if there

*are any other medications available that may preserve her current kidney function. What do you recommend?*

### **SGLT-2 inhibitors and chronic kidney disease**

Several large randomized trials have shown that sodium-glucose cotransporter 2 (SGLT-2) inhibitors decrease the risk of kidney-related complications for patients with or without diabetes.<sup>2,3</sup> For example, in a trial of patients with both type 2 diabetes and chronic kidney disease with albuminuria, the SGLT-2 inhibitor canagliflozin decreased the risk of kidney disease progression.<sup>2</sup> Similarly, dapagliflozin, another SGLT-2 inhibitor, decreased kidney disease progression in patients with chronic kidney disease and albuminuria, with or without diabetes.<sup>3</sup>

Whether SGLT-2 inhibitors slow the progression of kidney disease in patients with chronic kidney disease without albuminuria was unknown and is an important question, given that the global burden of chronic kidney disease is high<sup>4</sup> and most patients with it have normal urine albumin levels.<sup>5</sup>

### **Empagliflozin decreases progression of chronic kidney disease**

The EMPA-KIDNEY Collaborative Group<sup>6</sup> examined whether empagliflozin delayed kidney disease progression in patients with established chronic kidney disease in an international, randomized, placebo-controlled trial. They enrolled 6,609 participants 18 years or older who were already receiving a renin-angiotensin system inhibitor. The participants' race-adjusted estimated glomerular filtration rate had to be either in the range of at least 20 to less than 45 mL/min/1.73 m<sup>2</sup>, or at least 45 to less than 90 mL/min/1.73 m<sup>2</sup> with a urinary albumin-to-creatinine ratio of at least 200 mg/g. Exclusion criteria included a history of polycystic kidney disease, symptomatic hypotension, history of kidney transplant, or a life-limiting diagnosis.

Participants were randomized to receive either empagliflozin 10 mg once daily or placebo. The primary outcome of the trial was a composite of progression of kidney disease or death from cardiovascular causes. Progression of kidney disease was defined as end-stage kidney disease, a sustained decrease in the estimated glomerular filtration rate to less than 10 mL/min/1.73 m<sup>2</sup>, a decrease in the estimated glomerular filtration rate from baseline of at least 40%, or death from cardiovascular causes.

**Results.** During a median follow-up of 2 years, a primary outcome event occurred in 13.1% of patients in the empagliflozin group compared with 16.9% of patients in the placebo group (hazard ratio [HR] 0.72,

95% confidence interval [CI] 0.64–0.82,  $P < .001$ , number needed to treat 27). The lower rate in the empagliflozin group was mostly owing to a lower rate of progression of kidney disease (HR 0.71, 95% CI 0.62–0.81); the difference in the risk of death from cardiovascular causes was not statistically significant when analyzed independently (HR 0.84, 95% CI 0.60–1.19). Serious adverse events were uncommon and did not differ between groups.

While the effect sizes in several prespecified subgroups tended to mirror those in the overall group, a differential effect was seen when the primary outcome was stratified by baseline albuminuria. Empagliflozin made no difference in the primary outcome among patients with either a baseline urine albumin-to-creatinine ratio less than 30 mg/g (HR 1.01, 95% CI 0.66–1.55) or baseline urine albumin-to-creatinine ratio of at least 30 mg/g but no higher than 300 mg/g (HR 0.91, 95% CI 0.65–1.26). Only when the baseline urine albumin-to-creatinine ratio exceeded 300 mg/g was an effect observed favoring empagliflozin (HR 0.67, 95% CI 0.58–0.78).

### **Should our patient get an SGLT-2 inhibitor for her chronic kidney disease?**

Although the EMPA-KIDNEY trial demonstrated a reduction in the progression of kidney disease among all patients receiving empagliflozin, whether our patient, who does not have albuminuria, would stand to benefit from empagliflozin or an alternative SGLT-2 inhibitor is less clear. A discussion is warranted about the potential benefits, risks (eg, genital yeast infections,<sup>7</sup> diabetic ketoacidosis<sup>8</sup>), and cost (more than \$400 per month, and an out-of-pocket expense of about \$50 for Medicare patients in 1 analysis<sup>9</sup>) of starting an SGLT-2 inhibitor.

In clinical practice, utilization rates of SGLT-2 inhibitors are relatively low. A 2023 analysis of 105,799 patients from 130 Veterans Affairs facilities who had type 2 diabetes, heart failure, and atherosclerotic cardiovascular disease (and thus multiple indications for an SGLT-2 inhibitor) showed that only 15% were receiving an SGLT-2 inhibitor.<sup>10</sup> Whether healthier patients such as ours with fewer comorbidities and likely fewer baseline medications would be willing to start an SGLT-2 inhibitor to prevent chronic kidney disease progression will be an important area for future study.

### **DIET AS SECONDARY PREVENTION**

*A 63-year-old man presents for follow-up after undergoing coronary revascularization 6 months ago. He is currently adherent to medical therapy and is asking whether there are*



any diets to further reduce his risk of recurrent cardiovascular disease. What would you recommend?

## Diet and cardiovascular disease

Diet can be modified to reduce the incidence and recurrence of cardiovascular events.<sup>11</sup> Guidelines encourage everyone to limit dietary fats and to consume complex carbohydrates daily to replace saturated fats and increase fiber intake.<sup>12,13</sup> The Mediterranean diet—with generous portions of fruits, vegetables, legumes, cereals, nuts, and seeds, with white meat and fish as the primary sources of protein, and with olive oil as the primary source of fat—has been touted as healthy.<sup>14,15</sup> Estruch et al<sup>16</sup> demonstrated that the Mediterranean diet was more effective than a reduced-fat diet as primary prevention for patients at high risk of cardiovascular disease. However, until recently, there was little evidence on the effect of a Mediterranean diet as secondary prevention.

## A Mediterranean diet is superior to a low-fat diet for secondary prevention

Delgado-Lista et al<sup>17</sup> conducted the first large, long-term, randomized, controlled trial comparing the Mediterranean diet vs a low-fat diet in secondary prevention of major cardiovascular events, defined as myocardial infarction, revascularization, ischemic stroke, peripheral arterial disease, or cardiovascular death.

This single-center trial conducted in Spain enrolled 1,002 patients with established coronary heart disease; 83% were men, and the mean age was 60. Patients were excluded if they had heart failure with an ejection fraction of 35% or less or New York Heart Association class III or IV symptoms, could not follow a diet, or had severe liver, renal, pulmonary, or psychiatric disease.

No energy restriction was implemented, and no physical activity was promoted. Both groups came in for individual in-person visits every 6 months and group sessions every 3 months, and received telephone calls every 2 months. Participants in the Mediterranean-diet group received 1 L of extra-virgin olive oil per week at no charge, while the low-fat-diet group received a bag of healthy food rich in complex carbohydrates, worth about the same Euro amount as the olive oil.

**Results.** By the end of the 7-year study, 132 participants had abandoned their diets, 86 in the low-fat group and 46 in the Mediterranean-diet group ( $P = .0002$ ). Baseline adherence to the Mediterranean diet was 8.78 on a scale of 0 (worst) to 14 (best). As expected, participants in the Mediterranean-diet group had increased their intake of total fat, primarily from increased intake of extra-virgin olive oil, oily fish, and

nuts. In contrast, baseline adherence to the low-fat diet was 3.81 on a scale of 0 (worst) to 9 (9 best), and participants had increased their intake of carbohydrates, mainly from complex carbohydrates, and decreased their intake of total fat.

A total of 198 primary outcome events occurred, 87 in the Mediterranean-diet group (in 17.3% of this group) and 111 in the low-fat-diet group (in 22.2% of this group)—a 25% reduction in major cardiovascular events with the Mediterranean diet (unadjusted HR 0.745, 95% CI 0.563–0.986, number needed to treat 21). In men, the Mediterranean diet was even more superior, reducing the rate of major cardiovascular events by nearly 33%. The groups did not differ in their adherence with antiplatelet, antihypertensive, or lipid-lowering medications, nor in their lipid or glucose blood levels at the completion of the study.

Limitations of this study include the intense dietary interventions, the majority male population, and the study location in Spain, which has a higher acceptance of the Mediterranean diet, all of which may impact the generalizability of these results to other populations. Furthermore, the mortality rates were lower in this study than in studies in similar settings during the same time period, which might support the notion that both diets were very effective in preventing cardiovascular recurrences.

## What should we tell this patient?

The patient should be told that a Mediterranean diet rich in extra-virgin olive oil, fatty fish, and nuts lowers the risk of recurrent major cardiovascular events by roughly 25% compared with a low-fat diet. A referral to a nutritionist may lead to better adherence to the Mediterranean diet.

## PREVENTING RECURRENT KIDNEY STONES

*A 62-year-old man presents for a routine physical. You note a history of kidney stones. His last stone event was 1 year ago, and the stone passed spontaneously. The stone was mostly composed of calcium oxalate. Laboratory testing shows a normal serum calcium level and a high 24-hour level of urine calcium excretion. Do you recommend hydrochlorothiazide to try to prevent recurrent stones?*

## Data on preventing recurrent calcium stones are sparse

Roughly 80% of kidney stones contain calcium, most commonly in the form of calcium oxalate.<sup>18</sup> Small studies have suggested that dietary modifications such as taking in more potassium and calcium and less animal protein and sodium can reduce the likelihood of

recurrent calcium stones.<sup>19–22</sup> One randomized controlled trial showed that increasing water intake to achieve urine volume of more than 2 L per day significantly reduced the risk of recurrent stones compared with standard water intake.<sup>23</sup>

Thiazide diuretics reduce urine calcium excretion.<sup>24</sup> One meta-analysis found moderate-strength evidence that thiazides decrease the risk of stone recurrence but not the risk of *symptomatic* recurrence, and the included studies were small and had methodologic limitations.<sup>25</sup>

### Hydrochlorothiazide to prevent recurrent calcium stones

Dhayat et al<sup>26</sup> recently performed the largest study to date examining whether thiazide diuretics prevent recurrent stones. Patients were enrolled from 12 centers in Switzerland; eligibility criteria included age greater than 18, at least 2 kidney-stone episodes in the past 10 years, and any stone containing at least 50% calcium oxalate or calcium phosphate. Those with secondary causes of stones or who were taking medications that could interfere with stone formation were excluded. Of 1,335 patients who were screened, 416 were assigned to treatment. The median age was 49, 80% were men, and 63% had baseline hypercalciuria.

Patients were randomized in 4 equal groups to receive hydrochlorothiazide 12.5 mg, 25 mg, or 50 mg daily or placebo. They were followed for a maximum of 3 years for both radiographic and symptomatic recurrence of stones.

**Results.** There were no differences in the rate of the primary outcome between any of the groups, and no relation between hydrochlorothiazide dose and occurrence of a primary end-point event. Higher doses of hydrochlorothiazide (25 and 50 mg) were associated with a reduced risk of radiographic recurrence, a secondary study end point. Patients assigned to hydrochlorothiazide had lower urine calcium excretion, but urine relative supersaturation ratios were not different from those in patients assigned to placebo. Patients taking hydrochlorothiazide had higher rates of hypokalemia, gout, new-onset diabetes, skin allergy, and acute kidney injury.

Limitations of the trial included nonadherence to assigned treatment in 15% to 26% of patients, underrepresentation of women in the trial, and relatively short trial duration.

### What should we recommend for our patient?

The results of this trial would not support a recommendation to use hydrochlorothiazide to reduce the likelihood of recurrent stones. Our patient should be

told to increase his water intake to achieve a urine output of at least 2 L per day. Based on limited available evidence, other measures to consider would be use of citrates and allopurinol, dietary changes including more dietary calcium and potassium, and reduction in intake of soft drinks, animal protein, and sodium.

## ■ LOSING WEIGHT

*A 46-year-old woman with obesity (body mass index 34 kg/m<sup>2</sup>), prediabetes, and hypertension presents to clinic for follow-up. She takes olmesartan 20 mg daily for hypertension. She has made several unsuccessful attempts to lose weight with changes in diet and exercise. What additional pharmacotherapy might you recommend next?*

### The obesity epidemic and its treatments

Obesity is a global epidemic. Its prevalence has been increasing worldwide for several decades, and it is associated with poor health outcomes including cardiovascular disease, diabetes mellitus, malignancy, and musculoskeletal diseases.<sup>27</sup> For people who are obese, losing as little as 5% to 10% of body weight helps to improve cardiovascular risk factors, and losing more has even greater benefit.<sup>28</sup> Major guidelines continue to recommend low-calorie diets, exercise, and comprehensive lifestyle management plans as cornerstones of obesity management.<sup>29,30</sup>

However, the human body seems to have a set point for weight, with metabolic and homeostatic adaptations that make it difficult to lose weight or maintain weight loss.<sup>31</sup> Therefore, many patients regain weight after participating in lifestyle modification programs.<sup>32</sup> As a result, pharmacotherapy is an important consideration for achieving weight-loss goals. Newer drugs such as semaglutide have shown promising outcomes for weight loss and maintenance.<sup>33,34</sup>

### Tirzepatide once weekly promotes weight loss in patients without diabetes

Jastreboff et al<sup>35</sup> examined whether tirzepatide, a once-weekly subcutaneous injection drug with agonist activity at glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, was safe and effective for weight loss in people with obesity. In a double-blind, industry-sponsored, randomized clinical trial conducted in 19 countries, participants were randomized in a 1:1:1:1 ratio to receive tirzepatide 5 mg, 10 mg, or 15 mg or placebo injections for 72 weeks. All groups received dietary and physical activity intervention.

Participants were age 18 and older, had a body mass index of at least 30 kg/m<sup>2</sup>, or had a body mass index of at

least 27 kg/m<sup>2</sup> with at least 1 weight-related complication, defined as hypertension, hyperlipidemia, obstructive sleep apnea, or cardiovascular disease. Exclusion criteria included diabetes, treatment with other weight-loss medications within 90 days before screening, and planned weight-loss surgery. The coprimary outcomes were change in body weight from baseline to week 72 and weight reduction of at least 5%.

**Results.** A total of 2,539 participants were randomized, of whom 68% were women, 71% were White, and 48% were Hispanic or Latino. All of the active-treatment groups lost a significant amount of weight, and the higher the dose the more they lost: The mean change in body weight was −15% with tirzepatide 5 mg, −19.5% with tirzepatide 10 mg, −20.9% with tirzepatide 15 mg, and −3.1% with placebo. More than 85% of participants in the tirzepatide groups lost more than 5% of their body weight, compared with 35% of those in the placebo group.

Nausea, vomiting, and diarrhea were more common in patients receiving tirzepatide than in patients receiving placebo, but these adverse effects infrequently led to drug discontinuation and were clustered around drug initiation or dose increases. A higher risk of cholecystitis was seen in patients receiving tirzepatide, but the incidence was less than 0.6%.

### Should we prescribe tirzepatide for our 46-year-old patient without diabetes?

In addition to ongoing diet, exercise, and lifestyle counseling, consideration of pharmacotherapy is a reasonable option. Both tirzepatide and semaglutide are approved by the US Food and Drug Administration for weight loss, but the high cost and varying insurance coverage for each of these medications render them unobtainable for many patients.<sup>36</sup> Before patients start weight-loss therapy, clinicians and patients should discuss its possible benefits, risks, cost, availability, and duration (which is unknown at this point but may need to be lifelong to prevent weight regain).

## ■ LOWERING LDL-C

*A 60-year-old man presents to his primary care physician with concerns about his cardiovascular health. He had a myocardial infarction at age 57 for which he received a coronary artery stent. He has been taking aspirin 81 mg, irbesartan 150 mg, metoprolol succinate 50 mg, and rosuvastatin 20 mg daily with good adherence, but endorses mild, intermittent myalgias, which he attributes to his rosuvastatin. His current low-density lipoprotein cholesterol (LDL-C) level is 85 mg/dL. What changes to his medications might you advise?*

### Lower LDL-C is associated with reduced risk of major cardiovascular events

Current clinical guidelines for blood cholesterol management in people with atherosclerotic cardiovascular disease recommend starting with statin monotherapy and titrating up to the highest tolerated dose before considering additional nonstatin therapy.<sup>12</sup> This is in part based on the low cost, wide availability, and efficacy of statins with respect to lowering LDL-C and reducing major cardiovascular events compared with other lipid-lowering therapy.<sup>37,38</sup> However, adherence to high-intensity statins remains relatively low, even in high-risk groups.<sup>39</sup>

Ezetimibe has been shown to decrease the risk of major cardiovascular events when added to statin therapy in patients recently hospitalized with acute coronary syndrome.<sup>40</sup> Whether a lower-intensity statin combined with ezetimibe would provide clinical benefit similar to that of high-intensity statin monotherapy had not been previously evaluated prospectively.

### High-intensity statin monotherapy vs lower-dose statin therapy combined with ezetimibe

Kim et al<sup>41</sup> conducted a pharma-sponsored, randomized, open-label, noninferiority trial in South Korea comparing the long-term clinical outcomes of high-intensity statin monotherapy vs lower-intensity statin therapy combined with ezetimibe.

Patients were included if they were over age 18 and had a history of atherosclerotic cardiovascular disease. Exclusion criteria included active liver disease, persistent unexplained elevation of aspartate aminotransferase or alanine aminotransferase twice the upper limit of normal, and prior allergy or hypersensitivity to any statin or ezetimibe. The mean age was 64, and 75% of the patients were men.

Patients were randomly assigned in a 1:1 ratio to monotherapy with rosuvastatin 20 mg or combination therapy with both rosuvastatin 10 mg and ezetimibe 10 mg. The primary end point was a composite outcome of cardiovascular death, major cardiovascular events, and nonfatal stroke within 3 years, with a noninferiority margin of 2%.

**Results.** Combination therapy was noninferior to high-intensity statin monotherapy for the 3-year composite outcome, which occurred in 9.1% of the combination-therapy group vs 9.9% of the high-intensity statin group (absolute difference −0.78%, 90% CI −2.39 to 0.83). Additionally, the combination-therapy group had a significantly lower mean LDL-C at 3 years than the high-intensity-statin monotherapy group (58 mg/dL vs 66 mg/dL),



and more patients in the combination-therapy group achieved a target LDL-C concentration of less than 70 mg/dL (72% vs 58%).

Subjective adverse effects such as muscle pain were reported more frequently with high-intensity statin monotherapy than with combination therapy (1.9% vs 1.1%, respectively), and more patients in the high-intensity-statin monotherapy group had to discontinue or take a lower dose of the study medications than in the combination therapy group (8.2% vs 4.8%, respectively,  $P < .0001$ ).

Limitations of the study include its open-label design, lower-than-expected event rates, and lack of a study arm receiving moderate-intensity statin monotherapy (rosuvastatin 10 mg), which would have afforded a better comparison of the potential benefit of adding ezetimibe to rosuvastatin.

Overall, the study suggests that combination therapy using a moderate-intensity statin and ezetimibe is an effective and safe alternative to high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease. Given that lipid-lowering ther-

apy is not intense enough in the real world,<sup>42</sup> these findings could help usher in a shift in strategy in lipid management toward combination therapy, similar to the current standard of care in hypertension management.<sup>43</sup> Will this strategy be an acceptable alternative to statin monotherapy in real-world practice? Will it contribute to polypharmacy? These are important topics for future study.

### What should we advise our patient?

Given the patient's history of myalgias on his current high-intensity rosuvastatin dose, reducing his rosuvastatin dose to 10 mg and adding ezetimibe 10 mg daily is a reasonable option to consider to reduce his risk of future cardiovascular events and improve long-term adherence, and may carry less risk of myalgia than continuing his current rosuvastatin dose. ■

### DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Address: Jason T. Alexander, MD, Department of Medicine, University of Chicago, 5841 S. Maryland Ave, MC 3051, Chicago, IL 60637; [jalexander3@bsd.uchicago.edu](mailto:jalexander3@bsd.uchicago.edu)

## 1-MINUTE CONSULT

### Osamah Z. Badwan, MD

Department of Internal Medicine,  
Cleveland Clinic, Cleveland, OH

### Lorenzo Braghieri, MD

Department of Internal Medicine,  
Cleveland Clinic, Cleveland, OH

### Warren Skoza, MD

Department of Internal Medicine,  
Cleveland Clinic, Cleveland, OH

### Ankit Agrawal, MD

Department of Cardiovascular Medicine,  
Cleveland Clinic, Cleveland, OH

### Venu Menon, MD

Department of Cardiovascular Medicine,  
Cleveland Clinic, Cleveland, OH;  
Professor, Cleveland Clinic Lerner College  
of Medicine of Case Western Reserve  
University, Cleveland, OH

### W. H. Wilson Tang, MD

Department of Cardiovascular Medicine,  
Cleveland Clinic, Cleveland, OH;  
Professor, Cleveland Clinic Lerner College  
of Medicine of Case Western Reserve  
University, Cleveland, OH



# Q: When should we consider SGLT-2 inhibitors in patients with acute decompensated heart failure?

**A:** Sodium-glucose cotransporter 2 (SGLT-2) inhibitors should be started as early as possible in patients hospitalized with acute decompensated heart failure who do not have clear contraindications to them, and continued after discharge (**Figure 1**). These medications are well tolerated, can aid in decongestion without worsening renal function, and have multiple cardiovascular benefits.

Introduced in 2012, SGLT-2 inhibitors were developed to treat type 2 diabetes by reducing reabsorption of glucose from the renal filtrate, but they have since been found to have multiple cardiovascular benefits beyond glucose-lowering,<sup>1</sup> which may be attributed to their natriuretic and osmotic diuretic effects and other metabolic effects.<sup>2-4</sup> Of note, they lower N-terminal pro-B-type natriuretic peptide levels, which may be a key determinant of improved clinical outcomes regardless of left ventricular ejection fraction.<sup>3-5</sup>

## ■ BENEFITS OF STARTING EARLY

Acute decompensated heart failure is one of the leading reasons for hospital admissions worldwide and is associated with considerable morbidity and mortality.<sup>6</sup> As outlined below and in **Table 1**,<sup>3,4,7-11</sup> studies have suggested that patients hospitalized for acute decompensated heart failure could tolerate SGLT-2 inhibitors and derive cardiac benefit from them, especially when these drugs were started early. While most of the patients in these trials had reduced left ventricular ejection fraction, the benefits were consistent across all left-ventricular-ejection-fraction groups.

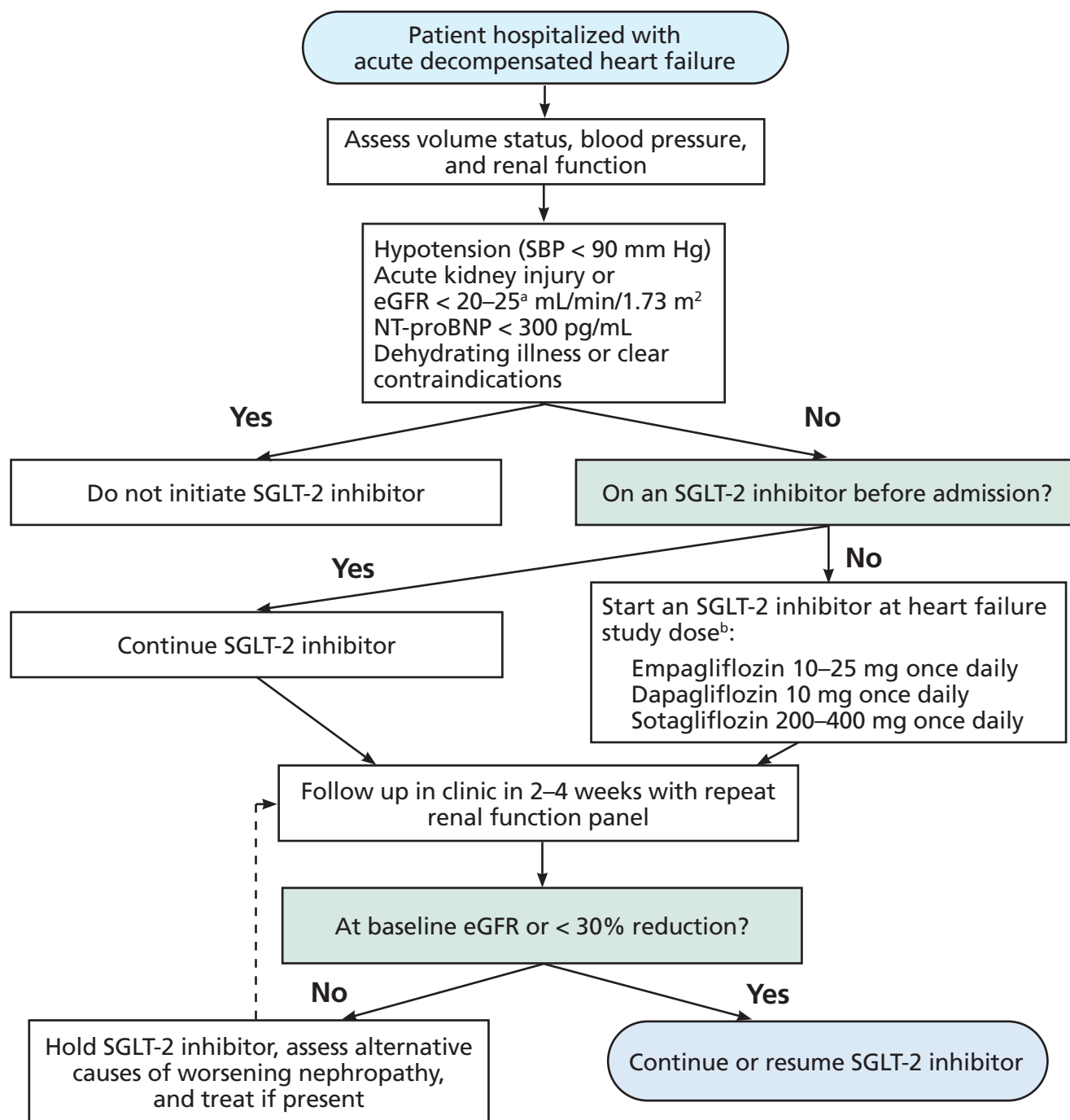
The **EMPA-RESPONSE-AHF trial** (Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure),<sup>7</sup> with 79 patients, found patients who were randomized to empagliflozin within 24 hours of admission had a significant reduction in the composite outcome of worsening heart failure, rehospitalization for heart failure, or death at 60 days compared with placebo.

The **EMPULSE trial** (Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized)<sup>3</sup> found that patients who were randomized to receive empagliflozin 10 mg daily within 5 days of admission had a significant reduction in the combined primary end point, ie, a hierarchical composite of death from any cause, number of heart failure events, and time to first heart failure event, or a 5-point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days compared with placebo.

The **DELIVER trial** (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure),<sup>12</sup> in a prespecified analysis of 654 (10.4%) of the trial patients who were randomized to receive dapagliflozin or placebo while hospitalized for heart failure or within 30 days of hospital discharge, demonstrated a reduced risk of worsening heart failure or cardiovascular death. The investigators calculated that the number needed to treat with dapagliflozin to prevent 1 primary outcome event was 28 patient-years in recently hospitalized patients and 65 patient-years in patients not recently hospitalized.

The **SOLOIST-WHF trial** (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes

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**Figure 1.** Proposed algorithm for initiating sodium-glucose cotransporter 2 inhibitors in acute decompensated heart failure.

<sup>a</sup>Dapagliflozin: No dosage adjustment for  $\text{eGFR} \geq 25 \text{ mL/min/1.73 m}^2$ . Manufacturer labeling does not recommend initiation of therapy at  $\text{eGFR} < 25 \text{ mL/min/1.73 m}^2$ . Sotagliflozin is not indicated for patients with  $\text{eGFR} < 25 \text{ mL/min/1.73 m}^2$ . For heart failure, empagliflozin is not indicated for  $\text{eGFR} < 20 \text{ mL/min/1.73 m}^2$ . For type 2 diabetes mellitus, empagliflozin is not indicated for  $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ .

<sup>b</sup>Direct evidence on the effects of canagliflozin and ertugliflozin on heart failure outcomes is available only in patients with type 2 diabetes mellitus. It remains to be determined if they have similar effects in patients without type 2 diabetes.

eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure; SGLT-2 = sodium-glucose cotransporter 2

TABLE 1

**Randomized controlled trials of sodium-glucose cotransporter 2 inhibitors in acute decompensated heart failure**

Trial	Patients	Treatment	Results
EMPULSE <sup>3</sup>	N = 530, 67% with left ventricular ejection fraction (LVEF) < 40%	Empagliflozin 10 mg/day or placebo for 90 days, started a median of 3 days after hospital admission	Early benefit, defined by a hierarchical composite that incorporated all-cause mortality, time to heart failure events, and quality of life (measured by Kansas City Cardiomyopathy Questionnaire Total Symptom Score) with empagliflozin use
EMPAG-HF <sup>4</sup>	N = 59, mean LVEF 45 ± 16%	Empagliflozin 25 mg/day or placebo for 5 days, started within 12 hours of admission	A 25% increase in cumulative urine output over 5 days without affecting markers of renal function with empagliflozin use
SOLOIST-WHF <sup>8,9</sup>	N = 1,222, 79% with LVEF < 50%	Sotagliflozin 200–400 mg/day or placebo for a median of 9 months, initiated before or shortly after hospital discharge	A 33% reduction of a composite of cardiovascular death and hospitalizations or urgent visits for heart failure and apparent improvement in quality of life as measured by the Kansas City Cardiomyopathy Questionnaire 12 score at 4 months in sotagliflozin group
EMPA-RESPONSE-AHF <sup>7</sup>	N = 79, 100% with LVEF < 50%	Empagliflozin 10 mg/day or placebo for 30 days, initiated within 24 hours of presentation while on intravenous diuretics	Significantly reduced composite outcome of worsening heart failure, rehospitalization for heart failure, or death at 60 days in empagliflozin group
DAPA-RESIST <sup>10</sup>	N = 61, 44% with LVEF ≤ 40%	Dapagliflozin 10 mg or metolazone 5–10 mg for up to 3 consecutive days, initiated within 24 hours of trial screening	Significant weight reductions at up to 96 hours of dapagliflozin use compared with metolazone group
DICTATE-AHF <sup>11</sup>	N = 240, 52% with LVEF < 40%	Dapagliflozin 10 mg/day + protocolized diuretic titration or protocolized diuretic titration alone, initiated within 24 hours of presentation	Strong signal of improved diuretic efficiency (defined as weight change divided by loop diuretic dose) until day 5 of hospitalization or discharge if sooner

DAPA-RESIST = Dapagliflozin Versus Thiazide Diuretic in Patients With Heart Failure and Diuretic Resistance, DICTATE-AHF = Efficacy and Safety of Dapagliflozin in Acute Heart Failure, EMPAG-HF = Empagliflozin in Acute Decompensated Heart Failure, EMPA-RESPONSE-AHF = Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure, EMPULSE = Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized, SOLOIST-WHF = Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure

Post Worsening Heart Failure),<sup>8</sup> in a prespecified analysis based on timing of the first dose of the SGLT-1/2 inhibitor sotagliflozin, found the degree of benefit in the primary end point (the total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure) was similar regardless of whether the drug was started during the admission (48.8% of the overall group) or within 3 days after discharge. Similarly, a post hoc analysis of this trial demonstrated that starting sotagliflozin before discharge in patients with type 2 diabetes hospitalized for acute decompensated heart failure significantly decreased cardiovascular deaths and heart

failure events through 30 and 90 days after discharge.<sup>9</sup> However, no trials to date have directly compared SGLT-2 inhibitors with combined SGLT-1/2 inhibitors.

Another advantage of starting these medications while the patient is in the hospital is the opportunity to address medication reconciliation and potential barriers to adherence, which we usually do on discharge.

### ■ SGLT-2 INHIBITORS HELP REMOVE FLUID

Congestion is thought to be the primary reason patients are hospitalized with acute decompensated heart failure.<sup>13</sup> Excreting more sodium early during decongestive



therapy is strongly associated with better postdischarge outcomes, and sodium excretion is a better prognostic indicator than urine output, net fluid balance, or weight change.<sup>14</sup>

A concern about starting SGLT-2 inhibitors as an add-on therapy (in addition to loop diuretics) is the potential for excessively rapid intravascular volume removal and renal injury. Nevertheless, empagliflozin was shown to achieve decongestion without worsening renal function in patients with type 2 diabetes hospitalized for acute decompensated heart failure.<sup>15</sup> This might be explained by the natriuresis and osmotic diuresis caused by SGLT-2 inhibition, leading to reduced plasma volume and, subsequently, reduced preload.<sup>2</sup> Furthermore, SGLT-2 inhibitors may act synergistically with loop diuretics for decongestion and have other beneficial metabolic effects.<sup>16</sup>

The 2023 DAPA-RESIST trial (Dapagliflozin Versus Thiazide Diuretic in Patients With Heart Failure and Diuretic Resistance)<sup>10</sup> showed that dapagliflozin 10 mg daily was as effective as metolazone 5 to 10 mg daily in alleviating congestion in patients with acute decompensated heart failure with resistance to loop diuretics. Although patients in the dapagliflozin group received a higher total amount of furosemide, they encountered fewer biochemical disturbances than those in the metolazone group.

### ■ PATIENTS ALREADY ON SGLT-2 INHIBITORS

Although SGLT-2 inhibitors lowered blood pressure only slightly by themselves in large heart failure clinical trials, it is important to consider volume status, especially in those receiving other heart failure agents such as angiotensin receptor-neprilysin inhibitors and loop diuretics, which can increase the risk of orthostasis and falling after the patient goes home. Nevertheless, unless patients have a clear contraindication such as severe hypotension (systolic blood pressure < 90 mm Hg), shock, acute kidney injury, estimated glomerular filtration rate (eGFR) less than 20 or 25 mL/min/1.73 m<sup>2</sup> (depending on the specific agent), or diabetic ketoacidosis (including euglycemic ketoacidosis), those who are already receiving SGLT-2 inhibitors and are admitted with acute decompensated heart failure would benefit from continuing this therapy.<sup>3,7-9,12</sup>

Of note, evidence of the beneficial effects of canagliflozin and ertugliflozin on heart failure outcomes is available only in patients with type 2 diabetes, and there is even less evidence currently for outcomes with bexagliflozin. It remains to be determined if these drugs have similar effects in patients without type 2 diabetes.

### ■ PATIENTS WITH RENAL DYSFUNCTION

While SGLT-2 inhibitors have been shown to slow the progression of chronic kidney disease, they generally are not indicated for patients whose eGFR is less than 20 or 25 mL/min/1.73 m<sup>2</sup> (depending on the particular SGLT-2 inhibitor). A reason for caution in this situation is that SGLT-2 inhibitors cause a temporary drop in eGFR and persistent reductions in plasma volume. However, this initial nadir in eGFR early after starting SGLT-2 inhibitors partially reverses over the subsequent 6 to 8 weeks. Further, continuation is associated with improved renal and cardiovascular outcomes, and new studies suggest that SGLT-2 inhibitors should not be discontinued unless the eGFR decreases by more than 30%.<sup>17</sup>

### ■ DIABETIC KETOACIDOSIS AND INFECTIONS

SGLT-2 inhibitors are not approved for patients with type 1 diabetes, since their use may promote hypoglycemia in patients without sufficient insulin secretagogue activity, a situation also posing a risk for euglycemic diabetic ketoacidosis.<sup>18</sup> Also, prescribers have been cautioned about genital mycotic infections and the rare severe complication of Fournier gangrene in patients at high risk (eg, older men and those with diabetes, alcohol use disorder, obesity, or immunocompromising conditions).

Fortunately, none of the previously mentioned trials found a higher risk of these complications in patients started on SGLT-2 inhibitors during admissions for acute decompensated heart failure.

### ■ THE BOTTOM LINE

In patients with acute decompensated heart failure without clear contraindications to these agents, an SGLT-2 inhibitor should be started as early as possible or continued if the patient is already receiving one. As an adjuvant therapy for decongestion, they have been shown to be well tolerated and can aid in decongestion without worsening renal function. Their use early during hospitalization and their continuation after discharge may translate into long-term clinical benefits. ■

### ■ DISCLOSURES

Dr. Tang has disclosed consulting for Boston Scientific, CardiaTec Biosciences, Cardiol Therapeutics, Genomics, Intellia Therapeutics, Kiniksa Pharmaceuticals, preCARDIA, Relypsa, Renovacor, Sequana Medical, WhiteSwell, and Zehna Therapeutics; board examination writing/approval committee for American Board of Internal Medicine; and editorship/authorship for Springer Nature. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Address: W. H. Wilson Tang, MD, Department of Cardiovascular Medicine, J3-4, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; tangw@ccf.org

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**Abhayjit Singh, MD**

Department of Cardiovascular Medicine,  
Cleveland Clinic, Cleveland, OH

**Leslie S. Cho, MD**

Section Head, Preventive Cardiology and Cardiac Rehabilitation, Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH; Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

# Nonstatin therapy to reduce low-density lipoprotein cholesterol and improve cardiovascular outcomes

## ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality, with low-density lipoprotein (LDL) cholesterol being a causative risk factor. Though statins have a decades-long track record of efficacy and safety, nonstatin agents may be used to reduce LDL cholesterol as an adjunct or alternative to statin therapy. Several new nonstatin medications have been approved in recent years, with robust data from clinical trials supporting their use in atherosclerotic disease. This review addresses the indications, evidence, and important prescribing considerations for using nonstatin lipid-lowering therapy and proposes a practical approach for determining when to initiate nonstatin therapy.

## KEY POINTS

The use of statins to reduce LDL cholesterol remains key to the prevention and treatment of ASCVD; target LDL cholesterol levels should be individualized based on cardiovascular risk profiles and shared decision-making.

Some patients are unwilling or unable to tolerate statin therapy, while others fail to achieve LDL cholesterol goals despite statin use. In such instances, clinicians may consider nonstatin therapy to lower LDL cholesterol.

Nonstatin lipid-lowering agents including ezetimibe, proprotein convertase subtilisin/kexin type 9 monoclonal antibodies, and bempedoic acid have been shown to reduce cardiovascular risk when given in conjunction with or in place of statins.

**A**THEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) remains the leading cause of morbidity and mortality worldwide. ASCVD is a broad term that encompasses coronary heart disease (myocardial infarction or obstructive coronary artery disease), cerebrovascular disease (stroke, transient ischemic attack, or significant carotid artery stenosis), peripheral arterial disease (claudication or limb ischemia), aortic atherosclerotic disease, and prior coronary or arterial revascularization due to atherosclerosis.

It is now indisputable that low-density lipoprotein (LDL) cholesterol has a causal relationship to atherosclerosis, the process that underpins the development of clinical ASCVD.<sup>1</sup> Lipoproteins are particles that transport fats throughout the body, and LDL specifically transports cholesterol. Standard lipid panels normally report the serum concentration of LDL cholesterol, ie, the amount of cholesterol being transported by LDL particles. In the past few decades, LDL cholesterol has emerged as a powerful predictor of cardiovascular risk and a determinant of target levels of lipid-lowering therapy. Encouragingly, a meta-analysis of 26 randomized trials found that each 1.0-mmol/L (18-mg/dL) decrease in LDL cholesterol resulted in a 22% relative risk reduction in major vascular events ( $P < .0001$ ), further supporting the notion that lower is better when it comes to LDL cholesterol.<sup>2</sup>

For decades, the cornerstone of both prevention and treatment of ASCVD has been 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, better known as statins.

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By inhibiting the rate-limiting enzyme in cholesterol synthesis, statins increase cell-surface LDL receptor expression and clearance of LDL cholesterol from the bloodstream. The Scandinavian Simvastatin Survival Study,<sup>3</sup> published in 1994, was the first to demonstrate that statins improve outcomes (reduction in cardiovascular mortality and major coronary events with simvastatin) in patients with coronary artery disease and hyperlipidemia.

Successive large-scale clinical trials over the next 3 decades added more and more supporting evidence. Today, statins are one of the most prescribed drugs in clinical practice. Given the overwhelming evidence of cardiovascular benefit conferred by these agents, clinicians should continue to prescribe statins at the maximum tolerated doses for appropriate patients.

While statin therapy has a long track record of safety and efficacy in treating ASCVD, there are instances in which nonstatin lipid-lowering therapies may be needed. These scenarios include patient unwillingness to take statins, intolerability of statin side effects, and failure to meet LDL cholesterol goals with statin therapy alone. An analysis of the Patient and Provider Assessment of Lipid Management registry found that more than 25% of adults meeting criteria for statin therapy were not taking one, largely because they were never offered a statin or because they were concerned about potential adverse effects.<sup>4</sup> Nearly 55% of former statin users in the registry cited perceived side effects, most commonly muscle-related symptoms, as the primary reason for drug discontinuation.<sup>4</sup> Similarly, a recent meta-analysis estimated between 5% and 17% of patients discontinue statins due to medication side effects, rates far higher than expected in clinical trials.<sup>5</sup> These findings emphasize the need for ongoing patient education regarding statin use and for clinician familiarity with nonstatin therapies for lipid management.

This review simplifies the guidance on when to consider the addition of nonstatin therapy for LDL-lowering based on recent clinical trial data. We also aim to provide practical strategies that clinicians can use to determine the most appropriate nonstatin therapy as an adjunct to or in place of statins. Many of the recommendations in this review are based on the 2018 American College of Cardiology/American Heart Association cholesterol guidelines<sup>6</sup> and the subsequent 2022 American College of Cardiology Expert Consensus Decision Pathway<sup>7</sup> on the role of nonstatin therapies for lowering LDL cholesterol. We also include recently published outcome data from CLEAR (Cholesterol Lowering via Bempedoic Acid [ECT1002], an ACL [adenosine triphosphate-citrate lyase]-Inhibiting

Regimen).<sup>8</sup> This large double-blind, randomized controlled trial of 13,970 patients with statin intolerance were assigned to bempedoic acid or placebo, which has provided robust evidence for another nonstatin agent in the ever-changing landscape of LDL cholesterol management.

### ■ INDICATIONS AND GOALS FOR LIPID-LOWERING THERAPY

A holistic assessment of each patient's cardiovascular risk and baseline lipid profile is essential for determining goal levels of LDL cholesterol. The 2018 American College of Cardiology/American Heart Association Task Force multisociety guideline<sup>6</sup> on the management of blood cholesterol and the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines<sup>9</sup> for the management of dyslipidemias discuss in detail the indications and treatment goals for lipid-lowering therapy. Evidence-based indications for lipid-lowering therapy are divided into primary and secondary prevention of ASCVD, and recommendations for either moderate- or high-intensity statin therapy depend on estimated cardiovascular risk.

Patients treated for primary prevention include adults with LDL cholesterol of at least 190 mg/dL or patients between ages 40 and 75 who have diabetes or an estimated 10-year risk for ASCVD of least 7.5% (taking into consideration comorbidities and risk-enhancers).<sup>6,9</sup> On the other hand, patients treated for secondary prevention have clinical manifestations of ASCVD—cardiovascular, cerebrovascular, or peripheral arterial disease—and are further subdivided into high-risk and very-high-risk categories. In patients for whom lipid-lowering therapy is indicated, the next decision is to what level the cholesterol—most commonly LDL cholesterol—should be lowered. Over the past decade, more and more data have supported the notion that lower is better regarding levels of atherogenic lipids.

The society guidelines noted indicators for efficacy and suggest that there is a relative target level of cholesterol reduction (ie, 30% to 49% reduction for moderate-intensity statins or  $\geq 50\%$  reduction for high-intensity statins from baseline LDL cholesterol) for patients treated with lipid-lowering therapy.<sup>6,7,9</sup> One concern with this strategy from a practical perspective is that many patients have been on some form of LDL-lowering therapy, and a true “baseline” LDL level may not be available. Another issue with this approach is that patients with significant hypercholesterolemia may have LDL cholesterol levels that remain

**TABLE 1**  
**Main nonstatin lipid-lowering therapies**

Agent	Mechanism	Dosing	Cost	Expected lowering of LDL cholesterol	Major prescribing considerations
Ezetimibe <sup>7,10–15</sup>	Inhibition of intestinal cholesterol absorption leads to increased synthesis of LDL receptors and increased LDL cholesterol clearance	Daily oral medication	\$	Monotherapy: 15%–19%  With statin therapy: 13%–25%	Generally well tolerated (avoid in hepatic dysfunction)  Low cost  Available in combination with simvastatin  Often first-line recommended nonstatin for lowering LDL
Alirocumab, evolocumab <sup>7,16–19</sup>	Monoclonal antibodies bind to PCSK9 protein, reducing destruction of LDL receptors and increasing LDL cholesterol clearance	Subcutaneous injection every 2–4 weeks	\$\$\$	Monotherapy: 50%  With statin therapy: 54.7%–70%	Substantially more LDL-lowering than oral options  Requires ongoing injections  Risk of site reactions  Variable insurance coverage may result in high cost
Bempedoic acid <sup>7,8,20–22</sup>	Inhibition of ATP citrate lyase leads to a reduction in cholesterol biosynthesis, leading to an increase in LDL receptors and to increased LDL cholesterol clearance	Daily oral medication	\$\$	Monotherapy: 17.2%–26.5%  With statin therapy: 16.5%–18%  With ezetimibe: 25%–35%	Generally well tolerated  No muscle-related side effects  Relatively high cost and variable coverage (may need prior authorization)  Available as combination therapy with ezetimibe
Inclisiran <sup>7,23–26</sup>	Inhibits translation of PCSK9 via RNA interference, reducing destruction of LDL receptors and increasing LDL cholesterol clearance	Subcutaneous injection every 6 months	\$\$\$	Monotherapy: limited data  With statin therapy: 39.7%–52.3%	Twice-yearly dosing may be convenient and desirable  High cost and variable coverage  Limited access (current ongoing cardiovascular outcomes trials ORION-4 and VICTORION-2P)
Bile acid sequestrants <sup>7,27</sup>	Less intestinal bile acid absorption leads to an increase in cholesterol converted to bile acid, which leads to an increase in LDL receptors and LDL cholesterol clearance	Daily oral medication	\$	Monotherapy: 15%  With statin therapy: additional 10%–16%	Unpalatable agents with gastrointestinal side effects  Cardiovascular outcome data older and weaker than other options  Not recommended by guidelines to lower LDL cholesterol

ATP = adenosine triphosphate; LDL = low-density lipoprotein; ORION = A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease; PCSK9 = proprotein convertase subtilisin/kexin type 9; VICTORION = A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial, Assessing the Impact of Inclisiran on Major Adverse Cardiovascular Events in Participants With Established Cardiovascular Disease

substantially elevated even after relative reduction. Accordingly, most experts advocate for an absolute LDL cholesterol target alongside a relative reduction and consider the addition of nonstatin therapy when patients remain above goal despite maximally tolerated statin therapy. Absolute LDL cholesterol targets range from 55 mg/dL to 100 mg/dL depending on indication for therapy, overall cardiovascular risk, and patient goals of care.<sup>7</sup>

In recent years, several new nonstatin agents have been shown in clinical trials to both lower LDL cholesterol levels and reduce cardiovascular events in select patients (**Table 1**).<sup>7,8,10–27</sup> It is worth noting that to date, no LDL-lowering nonstatin therapy has been shown to reduce all-cause or cardiovascular mortality. This may be due to underpowering, inadequate follow-up duration, or a true lack of mortality benefit in the era of goal-directed medical therapy. Regardless, reduction in rates of myocardial infarction, stroke, or coronary revascularization is very meaningful clinically. In the following section, we review nonstatin therapies that clinicians may consider as an adjunct or alternative to statins in select patients.

## SPECIFIC NONSTATIN THERAPIES

### Ezetimibe

Ezetimibe, US Food and Drug Administration (FDA)-approved in 2002, is the most prescribed nonstatin agent for the treatment of hyperlipidemia.<sup>7</sup> Ezetimibe blocks the Niemann-Pick C1-Like 1 protein and inhibits uptake of cholesterol in the small intestine, thereby reducing the absorption of dietary and biliary cholesterol.<sup>7</sup> This subsequently promotes synthesis of hepatic LDL receptors, resulting in a reduction of serum LDL cholesterol.<sup>10</sup> Ezetimibe is an oral medication and lowers serum LDL cholesterol by an additional 13% to 25% from baseline when added to statin therapy depending on statin intensity, or 15% to 19% when given as monotherapy compared with placebo.<sup>10,11</sup> Ezetimibe is affordable and generally well-tolerated, with principal side effects of headache and upper respiratory tract symptoms occurring in 4% and 8% of patients.<sup>11</sup> In addition, no dosage adjustments are required for individuals with hepatic or renal impairment.

The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial),<sup>12</sup> published in 2015, evaluated the effect of ezetimibe in combination with simvastatin, compared with simvastatin alone, in 18,144 patients with recent acute coronary syndrome. At 7 years, the rates for the primary end point (composite of death from cardiovascular disease,

major coronary event, or nonfatal stroke) were 32.7% in the simvastatin-ezetimibe group and 34.7% in the simvastatin monotherapy group, with an absolute risk reduction of 2% and number needed to treat of 50 patients over 7 years to prevent 1 event. A later analysis found a high rate of subsequent events not included in the primary analysis—thus, the cardiovascular risk reduction from ezetimibe may be even greater than the original trial suggests.<sup>13</sup>

IMPROVE-IT firmly established the utility of ezetimibe, with other trials lending further support. Published in 2011, the SHARP (Study of Heart and Renal Protection) trial<sup>13,14</sup> randomized patients with chronic kidney disease and without clinical ASCVD to receive ezetimibe with simvastatin or placebo. With a median 4.9-year follow-up, the study found that patients receiving simvastatin and ezetimibe had a lower incidence of the composite end point (myocardial infarction, coronary death, ischemic stroke, or any revascularization procedure) compared with those receiving placebo (11.3% vs 13.4%; absolute risk reduction 2.1%; number needed to treat 50),<sup>13,14</sup> though there was limited analysis of the combination compared with simvastatin alone.

The more recent RACING (Randomised Comparison of Efficacy and Safety of Lipid Lowering With Statin Monotherapy Versus Statin–Ezetimibe Combination for High-Risk Cardiovascular Disease) trial,<sup>15</sup> which enrolled 3,780 patients and was published in 2022, demonstrated that the combination of moderate-intensity rosuvastatin and ezetimibe was noninferior to high-intensity rosuvastatin therapy for the composite primary end-point events (cardiovascular death, major cardiovascular events, nonfatal stroke) over a 3-year period. Also notable was the fact that patients receiving combination therapy achieved lower levels of LDL cholesterol and a lower incidence of drug intolerance (4.8% vs 8.2%). These clinical trials have demonstrated ezetimibe's efficacy, safety, and impact on cardiovascular outcomes across a wide spectrum of patients receiving lipid-lowering therapy.

### PCSK9 monoclonal antibodies

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a protein produced primarily by hepatocytes that circulates in the plasma and binds to LDL receptors, triggering a signaling cascade resulting in lysosomal degradation of the LDL receptors and decreased LDL cholesterol clearance.<sup>16</sup> These fully human monoclonal antibodies bind free plasma PCSK9, preventing PCSK9 interaction with the LDL receptor. This results in increased LDL receptor recycling within hepatocytes

and increased clearance of circulating LDL cholesterol. PCSK9 monoclonal antibodies are administered subcutaneously, usually at 2- or 4-week intervals, and tend to lower LDL cholesterol by approximately 50% when given alone, and by approximately 70% in patients already on statin therapy.<sup>16</sup>

Two PCSK9 antibodies—alirocumab and evolocumab—were FDA-approved in 2015.<sup>7,17–19</sup> The GAUSS-3 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3) trial<sup>17</sup> randomized patients with statin-intolerance to evolocumab or ezetimibe and demonstrated a far more potent LDL cholesterol reduction in patients receiving evolocumab (52.8% vs 16.7%).

In the following years, 2 randomized placebo-controlled trials confirmed the efficacy of PCSK9 monoclonal antibodies in reducing cardiovascular events.<sup>18,19</sup> The FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial,<sup>18</sup> published in 2017, randomized 27,564 patients with clinical ASCVD and LDL cholesterol levels greater than or equal to 70 mg/dL despite statin therapy to the addition of evolocumab or placebo. At a median follow-up of 2.2 years, evolocumab reduced the risk of the primary end point (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) compared with placebo (9.8% vs 11.3%; absolute risk reduction 1.5% with number needed to treat 74). The only notable difference in adverse events between groups was a higher rate of injection-site reactions in the evolocumab group (2.1% vs 1.6%).

The ODYSSEY (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) Outcomes trial<sup>19</sup> evaluated whether alirocumab reduced the risk of recurrent ischemic cardiovascular events in 18,924 patients with recent acute coronary syndrome and cholesterol levels above goal despite maximally tolerated statin therapy. At a median follow-up of 2.8 years, the alirocumab group had a lower incidence of the composite primary end point (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) compared with placebo (9.5% vs 11.1%; absolute risk reduction 1.6% and nearly identical to the outcome observed in the FOURIER trial). The ODYSSEY trial had a similarly high rate of local injection-site reactions in the PCSK9 monoclonal antibodies group.

The advent of PCSK9 monoclonal antibodies allowed for the reduction of LDL cholesterol to levels rarely achieved with conventional lipid-lowering

therapy, along with an excellent safety profile. The corresponding impact on cardiovascular outcomes gave further credence to the notion that lowering LDL cholesterol levels beyond what is attainable with statins is possible and offers incremental cardiovascular benefit.

### Bempedoic acid

Bempedoic acid is an oral medication that inhibits adenosine triphosphate citrate lyase, an enzyme in the cholesterol biosynthesis pathway upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (the target of statins).<sup>7,8,20,21</sup> Like the effect of statins, inhibition of cholesterol synthesis results in increased LDL cholesterol receptor expression and increased clearance of serum LDL cholesterol. Notably, the enzyme required to activate bempedoic acid is present in hepatocytes but absent in skeletal muscle, resulting in far lower concern for statin-associated muscle symptoms compared with statin therapy. Bempedoic acid lowers LDL cholesterol by 17.2% to 26.5% as monotherapy, by 16.5% to 18% when added to a background of statin therapy, and by up to 50% when given as a fixed-dose combination with ezetimibe.<sup>20,21</sup>

In the recently published CLEAR Outcomes trial,<sup>8</sup> 13,970 patients with a prior cardiovascular event or at high risk for ASCVD and unable to tolerate more than a very low dose of a statin (22.7% of patients were taking a low-dose statin and 11.5% were taking ezetimibe) were randomized to receive oral bempedoic acid or placebo. In this trial, bempedoic acid lowered LDL cholesterol by about 20% from baseline, and patients receiving bempedoic acid had a 21.6% greater reduction in high-sensitivity C-reactive protein levels compared with patients receiving placebo. At a median follow-up of 40.6 months, patients receiving bempedoic acid had a lower incidence of the composite primary end point (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) compared with placebo (11.7% vs 13.3%; absolute risk reduction 1.6% with number needed to treat of approximately 63.6).<sup>8,28</sup> Bempedoic acid was well-tolerated, with rates of discontinuation in the bempedoic acid arm similar to those with placebo. Side effects occurring more frequently in patients receiving bempedoic acid compared with placebo included elevated liver aminotransferase levels (4.5% vs 3%), renal injury (11.5% vs 8.6%), gout (3.1% vs 2.1%), and cholelithiasis (2.2% vs 1.2%).<sup>8</sup>

It is important to note that in the CLEAR Outcomes trial,<sup>8</sup> bempedoic acid was given in place of statin therapy (or with a very low average daily statin dose), not as adjunct treatment. This is in contrast to



the landmark trials of other nonstatin therapies, which were generally added to a background of maximally tolerated statin therapy. This trial specifically targeted patients who could not or would not tolerate statin therapy. Patients and their physicians specifically documented the inability or refusal to take a higher dose of statin despite understanding the benefit of statins.<sup>8</sup> While bempedoic acid lacks outcomes data when given alongside high-intensity statins, it is encouraging that patients who do not tolerate statins have another available therapy that lowers LDL cholesterol and reduces cardiovascular risk.

As mentioned, bempedoic acid is also available in combination with ezetimibe (1 tablet containing 180 mg of bempedoic acid and 10 mg ezetimibe). This combination is FDA-approved to lower LDL cholesterol levels in adults with ASCVD or familial hypercholesterolemia.<sup>7,22</sup> A phase 3 clinical trial found that after 12 weeks of treatment, this combination reduced LDL cholesterol levels by 36.2%, a greater reduction than that with either bempedoic acid (17.2%) or ezetimibe (23.2%) alone.<sup>22</sup> In addition, a recent phase 2 study demonstrated that combination bempedoic acid, ezetimibe, and atorvastatin triple therapy was generally well-tolerated and lowered LDL cholesterol levels by 63.6% compared with placebo, with more than 90% of patients achieving LDL cholesterol concentrations below 70 mg/dL.<sup>29</sup> While there are as yet no cardiovascular outcome data specific to this therapy, the significant reduction in LDL levels from synergistic oral therapy is encouraging.

### Inclisiran

Beyond monoclonal antibodies for PCSK9-lowering, there have been recent advances in using small interfering RNA molecules (siRNA) to reduce PCSK9 translation at the cellular level. The siRNA molecules engage the natural pathway of RNA interference and lead to the degradation of PCSK9 mRNA, resulting in decreased production of the PCSK9 protein.<sup>23</sup> One such siRNA targeting the PCSK9 protein, inclisiran, was granted FDA approval in December 2021 as an adjunct for adults with clinical ASCVD or familial hypercholesterolemia who require lowering of LDL cholesterol beyond what is achieved with statins.<sup>7</sup>

Phase 3 clinical trials published in 2020 (A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease [ORION] 9, 10, and 11) demonstrated that inclisiran, administered twice yearly as an injection, was well-tolerated without any major adverse events.<sup>24,25</sup> Patients receiving inclisiran had a 39.7%

to 52.3% reduction of LDL cholesterol on top of statin therapy.<sup>25</sup> It is worth noting, however, that inclisiran appears to be less efficacious at lowering LDL cholesterol than PCSK9 monoclonal antibodies.<sup>26</sup>

In an extension study of ORION-1,<sup>26</sup> 92 patients originally assigned to placebo were treated with twice-monthly evolocumab for 1 year and subsequently transitioned to twice-yearly inclisiran. Treatment with evolocumab lowered LDL cholesterol by 61% followed by a time-averaged LDL cholesterol reduction of 45% over 3 years after switching to inclisiran.<sup>26</sup> Though the early data on LDL cholesterol reduction and drug safety appear promising, larger trials examining the impact of siRNA-based therapies on cardiovascular risk reduction are ongoing, and effects of inclisiran on cardiovascular outcomes remain undetermined. There are currently 2 ongoing trials—ORION-4 and VICTORION-2P Prevent (A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial, Assessing the Impact of Inclisiran on Major Adverse Cardiovascular Events in Participants With Established Cardiovascular Disease) that aim to determine whether inclisiran will impact cardiovascular morbidity or mortality for primary and secondary prevention.

## THERAPIES NOT ROUTINELY RECOMMENDED FOR LIPID MANAGEMENT

### Dietary supplements

Nearly every clinician who prescribes lipid-lowering pharmacotherapy has been asked about the use of dietary supplements to lower LDL cholesterol. Of the many available supplements, red yeast rice and plant sterols have the most data supporting lipid-lowering, with various studies reporting LDL cholesterol reductions on the order of 10% to 25%.<sup>30,31</sup> In fact, plant sterols are endorsed as an option to lower blood cholesterol levels in the 2019 revision of the European Society of Cardiology/European Atherosclerosis Society dyslipidemia guideline.<sup>9</sup> A principal problem, however, is that most supplements are not FDA-regulated, so different manufacturers or formulations may have varying efficacy. Further, there is a dearth of quality data on the effect of these supplements on cardiovascular health.

The recently published Supplements, Placebo, or Rosuvastatin Study<sup>32</sup> compared the efficacy of common supplements that have been purported to lower lipid levels on lowering the LDL cholesterol concentration.<sup>32</sup> This prospective, single-blind clinical trial randomized 190 patients without evidence of clinical ASCVD but with an increased 10-year ASCVD risk and LDL cholesterol of 70 to 189 mg/dL to receive

**TABLE 2**  
**Clinical trials of nonstatin therapy**

Trial	Intervention	Study population, prevention goal	Composite primary outcome	Major findings
IMPROVE-IT 2015 <sup>12</sup>	Simvastatin plus ezetimibe vs simvastatin only	18,144 patients with recent acute coronary syndrome and LDL cholesterol 50–125 mg/dL  Secondary prevention	Cardiovascular death, myocardial infarction, stroke, unstable angina, or coronary revascularization	Simvastatin + ezetimibe combination reduced primary end point at 7 years (32.7% vs 34.7%)  Driven primarily by myocardial infarction and stroke  No mortality effect
FOURIER 2017 <sup>18</sup>	Evolocumab plus statin vs statin alone	27,564 patients with ASCVD and LDL cholesterol $\geq$ 70 mg/dL despite statin use  Secondary prevention	Cardiovascular death, myocardial infarction, stroke, unstable angina, or coronary revascularization	Evolocumab reduced primary end point at 2.2 years (9.8% vs 11.3%)  Driven by myocardial infarction, stroke, need for revascularization  No mortality effect
ODYSSEY 2018 <sup>19</sup>	Alirocumab + statin vs statin alone	18,924 patients with recent acute coronary syndrome and elevated lipids despite statin use  Secondary prevention	Cardiovascular death, myocardial infarction, stroke, or unstable angina	Alirocumab reduced primary end point at 2.8 years (9.5% vs 11.1%)  No significant mortality benefit
CLEAR 2023 <sup>8</sup>	Bempedoic acid vs placebo	13,970 patients with ASCVD or at high risk and unable to take statins  Primary and secondary prevention	Cardiovascular death, myocardial infarction, stroke, or coronary revascularization	Bempedoic acid reduced primary end point at 40.6 months (11.7% vs 13.3%)  No significant effect on fatal or nonfatal stroke, cardiovascular death, or all-cause mortality

ASCVD = atherosclerotic cardiovascular disease; LDL = low-density lipoprotein

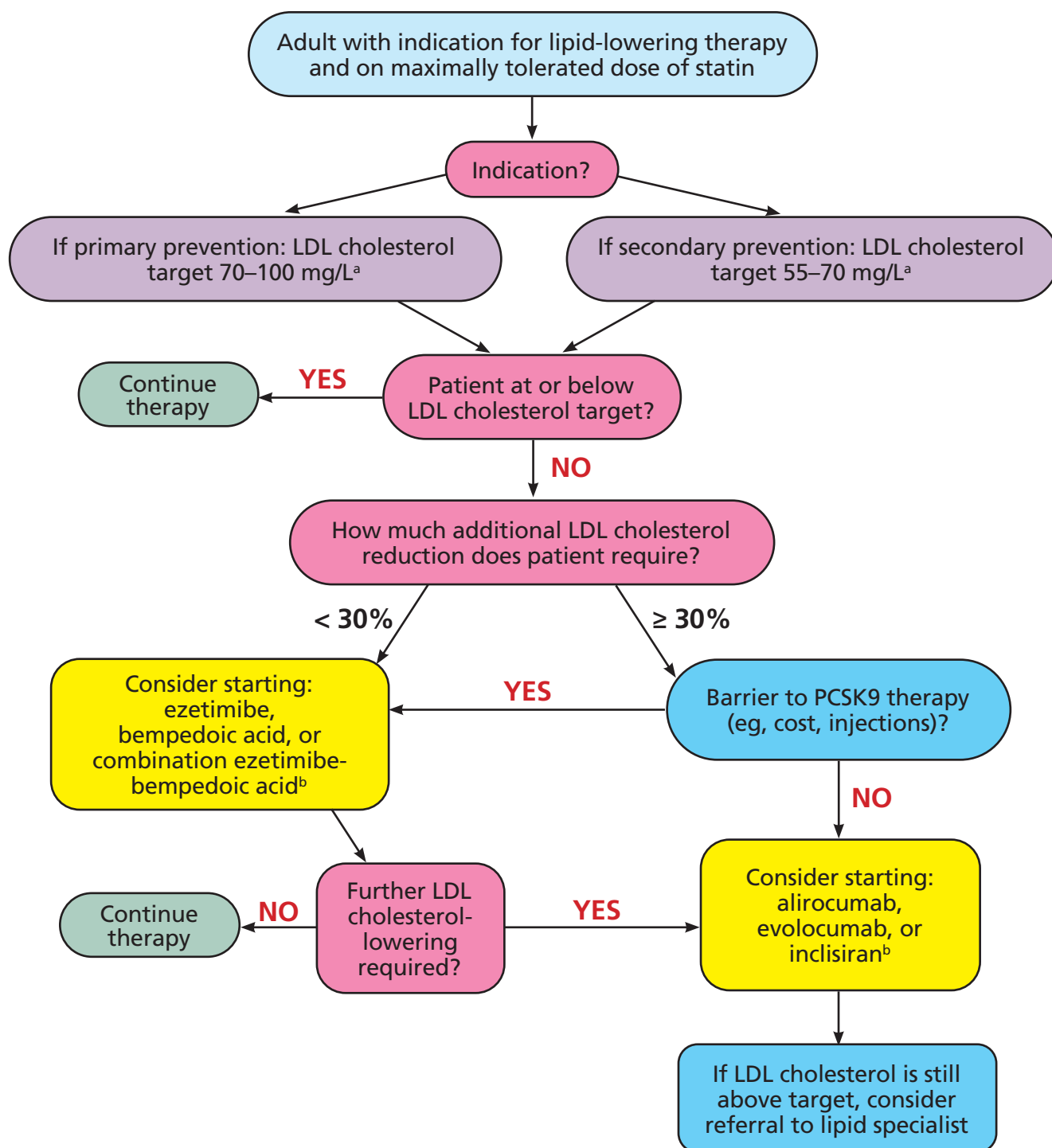
rosuvastatin 5 mg daily, placebo, fish oil, cinnamon, garlic, turmeric, plant sterols, or red yeast rice. After 28 days, rosuvastatin decreased LDL cholesterol levels by 35.2%, while none of the dietary supplements demonstrated a significant decrease in LDL cholesterol compared with placebo. Though this trial did not assess cardiovascular outcomes, it provides evidence that the studied supplements—often promoted for cholesterol-lowering benefits—do not significantly impact levels of atherogenic lipids.

### Bile acid sequestrants

Bile acid sequestrants, such as cholestyramine, colestevlam, or colestipol, were one of the first classes of lipid-lowering therapies.<sup>7,27</sup> These nonabsorbed polymers bind intestinal bile acids and impede their reab-

sorption, leading to a decrease in the bile acid pool and concurrent increase in the conversion of cholesterol to bile acids. The net effect is a modest reduction of LDL cholesterol, with possible increase in serum triglyceride concentrations. On average, bile acid sequestrants were shown to reduce LDL cholesterol by about 15% as monotherapy and an additional 10% to 16% in combination with statin therapy.

The Lipid Research Clinics Coronary Primary Prevention trial,<sup>27</sup> published in 1984, randomized 3,806 asymptomatic men with primary hypercholesterolemia to cholestyramine compared with placebo for an average of 7.4 years. Cumulative incidence of the primary end point (definite coronary heart disease death and/or definite nonfatal myocardial infarction) was 7% in the cholestyramine group compared with 8.6% in



**Figure 1.** Practical approach to the addition of nonstatin therapy.

<sup>a</sup>Individual LDL-cholesterol target based on patient risk profile.

<sup>b</sup>No current cardiovascular outcome data.

LDL = low-density lipoprotein; PCSK9 = proprotein convertase subtilisin/kexin type 9

those receiving placebo (relative risk reduction of 19% and absolute risk reduction of 1.6%).<sup>27</sup> Though this study showed an effect on cardiovascular outcomes, the use of bile acid sequestrants is limited by drug-drug interactions (often decreasing absorption of other medications) and frequently intolerable gastrointestinal side effects, including nausea, constipation, and dyspepsia. In light of the cardiovascular outcomes data for both statins and recent nonstatin therapies, the clinical utility of bile acid sequestrants continues to diminish.

### Niacin and fibrates

Niacin and fibrates (fenofibrate or gemfibrozil) are prescribed primarily as triglyceride-lowering drugs, though they may also mildly lower LDL cholesterol levels.<sup>33</sup> The effects of fibrates on LDL cholesterol are quite minimal, and more importantly, randomized trials have not reliably shown these therapies to reduce cardiovascular risk. Some older data suggested that fibrates may be beneficial in patients with high triglyceride or low high-density lipoprotein cholesterol levels, though the effect is more modest than statins, and the combination of fibrates and statins often results in significant myalgias.

Despite lowering LDL cholesterol, niacin is poorly tolerated with significant side effects, and more importantly has failed to demonstrate a benefit for cardiovascular outcomes in the era of statins.<sup>34</sup> While niacin and fibrates may have a niche in carefully selected patients with very high triglycerides, neither is currently recommended as an alternative or adjunct to statin therapy for lowering LDL cholesterol.

## ■ THERAPIES SPECIFIC TO PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

Familial hypercholesterolemia is an inherited disorder that results in very high levels of LDL cholesterol and an increased risk of premature ASCVD. Clinical features differ depending on whether one or both alleles are affected. While homozygous familial hypercholesterolemia is very rare, heterozygous familial hypercholesterolemia is the most common monogenic autosomal dominant disorder, affecting 1 in 250 individuals.<sup>24,35</sup> Patients with heterozygous familial hypercholesterolemia are nearly always treated with lipid-lowering therapy and will often require additional therapies beyond high-intensity statins to lower LDL cholesterol.<sup>36</sup> Patients with homozygous familial hypercholesterolemia will nearly always require nonstatin therapies, and there are specific therapies, such as lomitapide (a microsomal triglyceride transfer protein inhibitor, necessary for very low LDL assembly and secretion)

and evinacumab (a monoclonal antibody against angiopoietin-like protein 3, a regulator of lipoprotein metabolism), approved specifically for these patients.<sup>36</sup> These therapies are not currently approved for nonhomozygous familial hypercholesterolemia patients and are given under the direction of a lipid specialist; they are thus beyond the scope of this review.

## ■ CHOICE OF NONSTATIN THERAPY: A PRACTICAL APPROACH

Once patient and clinician have decided to initiate nonstatin therapy, there are multiple factors that should be considered when choosing the agent. First, patients should preferentially be prescribed therapies that have been shown not only to lower LDL cholesterol, but also to reduce ASCVD risk. Therapies with high-quality evidence for reducing cardiovascular events include ezetimibe, bempedoic acid, and PCSK9 monoclonal antibodies (landmark trials detailed in **Table 2**).<sup>8,12,18,19</sup>

There is also biological plausibility for ASCVD risk-reduction benefit with bempedoic acid-ezetimibe combination therapy and inclisiran, though these therapies lack outcome data currently. Other important considerations for patients may include efficacy of LDL cholesterol-lowering, route of administration (oral or subcutaneous injection), cost (insurance plan coverage, availability of assistance programs, or need for prior authorization), and attention to drug-drug interactions and side effects of each agent.<sup>37</sup> Given the number of patients requiring lipid-lowering therapy, with multiple agents to choose from and varying recommendations from major societal guidelines, a simplified approach is needed.

We propose an algorithmic approach for the addition of nonstatin therapy (**Figure 1**). From a practical standpoint, we categorize LDL cholesterol goals by whether patients are being treated for primary prevention (goal LDL cholesterol 70 to 100 mg/dL) or secondary prevention (goal LDL cholesterol 55 to 70 mg/dL), with the understanding that patients and clinicians will modify LDL cholesterol goals based on patient cardiovascular risk profile and the desire for more-aggressive rather than less-aggressive cholesterol reduction. We propose to subsequently stratify the choice of nonstatin therapy based on patient LDL cholesterol level at the time of initiation of therapy, which informs how much additional LDL cholesterol-lowering is required.

In patients who require LDL cholesterol-lowering of at least 30% from current levels, upfront therapy with a PCSK9 monoclonal antibody (alirocumab or evolocumab) is reasonable, assuming the patient does not



have financial coverage barriers and can tolerate subcutaneous injections. Inclisiran is a possible alternative for these patients, though cardiovascular outcome data are not yet available. For patients who have barriers to PCSK9-inhibiting therapies or require less than 30% LDL cholesterol-lowering, ezetimibe or bempedoic acid are evidence-based oral options with modest impact on LDL cholesterol levels, though greater reduction can be achieved with combination therapy.

## FUTURE DIRECTIONS

ASCVD remains the world's leading cause of death despite advances in our understanding of the disease process. Statin therapy has been revolutionary in improving cardiovascular outcomes, particularly for high-risk patients, but there remains a need for other forms of lipid-lowering therapy as an adjunct or alternative to statins. Landmark clinical trials have cemented ezetimibe, PCSK9 monoclonal antibodies, and bempedoic acid as nonstatin agents that both lower LDL cholesterol levels and provide cardiovascular benefit to patients, with a large-scale outcome trial currently testing the efficacy of inclisiran.

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Additional novel therapies to lower LDL cholesterol are entering clinical development, including recently completed phase 2b studies of an oral macrocyclic peptide PCSK9 inhibitor (MK-0616) and a liver-targeted antisense oligonucleotide that inhibits PCSK9 expression (AZD8233).<sup>38,39</sup> Other regulators of LDL cholesterol levels, such as angiopoietin-like protein 3, apolipoprotein C-III, and cholesteryl ester transfer protein have also emerged as promising targets for lipid-lowering drug development.<sup>40,41</sup> There is no doubt that the landscape of nonstatin therapies will continue to evolve in coming years, with each therapy having unique indications, advantages, disadvantages, and evidence base, and ultimately providing patients more therapeutic options for reducing cardiovascular risk.

## DISCLOSURES

Dr. Cho has disclosed consulting for AstraZeneca, Esperion, and Merck; research: PI for AstraZeneca and Novartis; steering committee for CLEAR outcomes for Esperion. The other author reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

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Address: Leslie S. Cho, MD, Section Head, Preventive Cardiology and Cardiac Rehabilitation, Department of Cardiovascular Medicine, JB-1, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; chol@ccf.org

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