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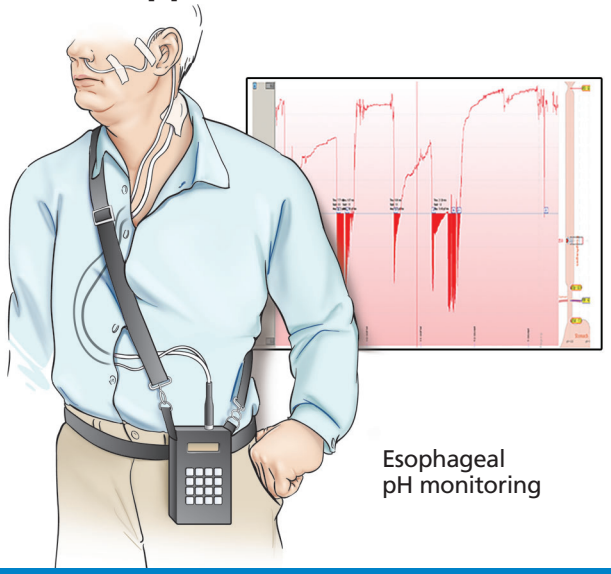

Esophageal pH monitoring

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CLEVELAND CLINIC JOURNAL OF MEDICINE

The under- and overrecognized, and the elephant in the room

In this issue of the *Journal* we have a paper reminding readers of an uncommon clinical syndrome that is underrecognized, and a second paper discussing a very common clinical syndrome that is likely overdiagnosed and overreated.

Those of you who regularly read CCJM know of my preoccupation with the value of the patient's history and the physical examination in directing the diagnostic evaluation as well as my enormous respect for clinicians who have honed those skills. The "Clinical Picture" section was born from my desire to remind us all of the power of observation by highlighting images from clinical and sometimes radiographic and other examinations.

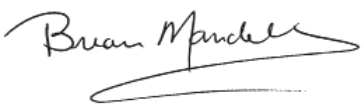
In this issue, Van Twist et al (page 194) present a picture of a patient with recurrent palmar surface finger hematomas (Achenbach syndrome). While I have seen and descriptively diagnosed this in 1 friend and several patients, ending the evaluation of their previously suspected vasculitis or Raynaud syndrome, I was not aware of its eponymous designation or of any literature describing small case series. I suspect that I may not be alone in this regard, and I thus appreciate the authors' submission.

At the other end of the spectrum, Young et al (page 223) discuss gastroesophageal reflux disease (GERD), an entity diagnosed by all of us in the clinic and at home and social gatherings. The disease is so common that we will usually be diagnosing it correctly even without taking a careful history and pointedly revisiting the diagnosis after a pre-defined therapeutic trial with a proton pump inhibitor (PPI). But as the authors point out, there are specific features of the history that should direct us to considering an alternative approach to long-term PPI therapy or to recognizing when PPI therapy has failed, and why (eg, when exactly is the patient taking the medication).

As we are all in the midst of the amazingly jarring and outright scary COVID-19 pandemic, I realize how mundane a discussion of heartburn is. Yet in a way, it is the ability to recognize the pine cones without losing our vision of the forest that characterizes us as internists and keeps us professionally on course.

Hopefully, this pandemic will pass relatively soon, and our health systems and global connections will be stronger.

Be safe.



BRIAN F. MANDELL, MD, PhD
Editor in Chief

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2020

APRIL

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Infective endocarditis: Don't forget the ICE

AUGUST 2019

To the Editor: We read with great interest the article by Mgbokikwe et al about newer and more sophisticated imaging modalities for the evaluation of infective endocarditis.[1] As outlined in Table 1 of the article, each imaging method has its advantages and limitations. One further imaging modality that should not be overlooked in select patients, however, is intracardiac echocardiography (ICE).

ICE is performed in the cardiac catheterization laboratory and requires an 8- to 10-Fr sheath in the femoral or jugular vein. Through this, the ICE catheter is advanced to the right heart, where imaging can be performed, not only of the right-sided valves, but also of the aortic and mitral valves.[2,3]

In certain cases, ICE avoids the use of sedation or general anesthesia and is an option for those with oropharyngeal or esophageal structural abnormalities for which transesophageal echocardiography (TEE) is contraindicated. ICE has been shown to be helpful in the evaluation of cardiac device and prosthetic valve endocarditis where TEE was unrevealing (**Figure 1**). Acoustic shadowing and artifacts from leads and prosthetic valves, in addition to the distance of the esophageal echo probe to the anterior right heart structures, limit the diagnostic capability of TEE compared with ICE. ICE is also useful for planning lead extraction and for monitoring for intraprocedural complications.[4]

Overall, risks of ICE are low and include transient atrial arrhythmias, cardiac chamber injury, and access site bleeding. Lastly, net procedural costs are not excessively higher than those of TEE.

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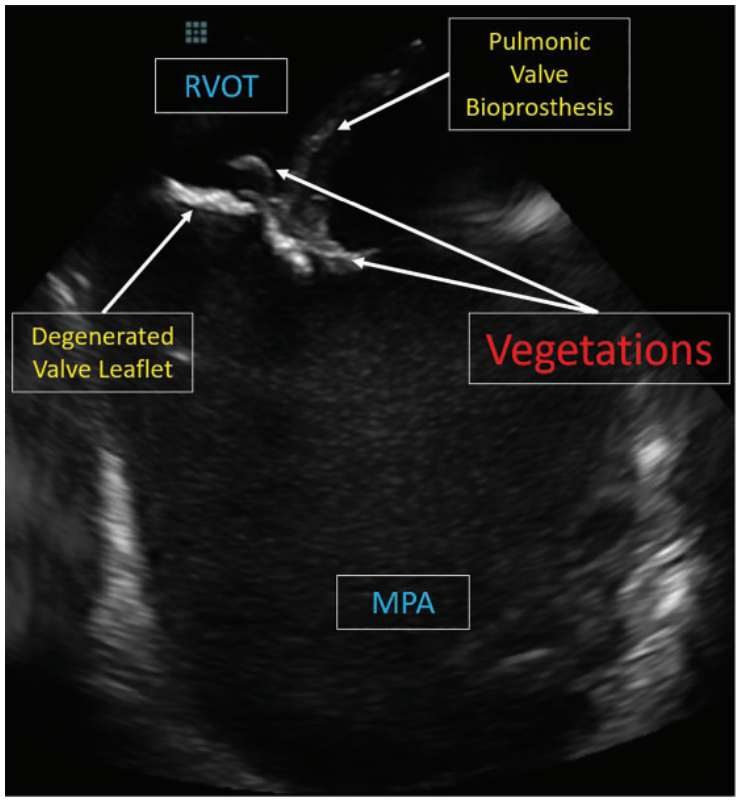

Figure 1. Intracardiac echocardiographic view of a pulmonic valve bioprosthesis in a 34-year-old man with repaired tetralogy of Fallot who presented with *Streptococcus mitis* bacteremia. Neither transthoracic nor transesophageal echocardiography could visualize valvular vegetations.

MPA = main pulmonary artery; RVOT = right ventricular outflow tract

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In reply: The letter from Drs. Araj and Luna regarding the utilization of intracardiac echocardiography (ICE) raises several interesting points. Indeed, for patients with infective endocarditis with inconclusive findings on transthoracic echocardiography (TTE) and contraindications to use of contrast-mediated studies or transesophageal echocardiography (TEE), ICE does present another potentially useful diagnostic modality. However, it is an invasive procedure, and as such, the clinical team would need to weigh the risk of complications. Further, while the authors suggest that the cost is comparable to that of TEE, the likely higher cost relative to positron emission tomography (PET) and other advanced imaging methodologies, as well as availability of institutional expertise, experience, and availability, should also be considered.

ICE, similar to TTE and TEE, relies upon the finding of an anatomic abnormality, in this case, the demonstration of a vegetation, for the diagnosis of infectious endocarditis. ^{18}FDG-PET does not rely on anatomic identification of vegetations but is a functional examination detecting inflammation, which can be helpful in detecting microscopic vegetations not identifiable by echocardiography.

Since the absence of an anatomically detected vegetation does not exclude infectious endocarditis, PET has potentially complementary additive value to the various modalities based on demonstration of vegetation for the diagnosis of infectious endocarditis.

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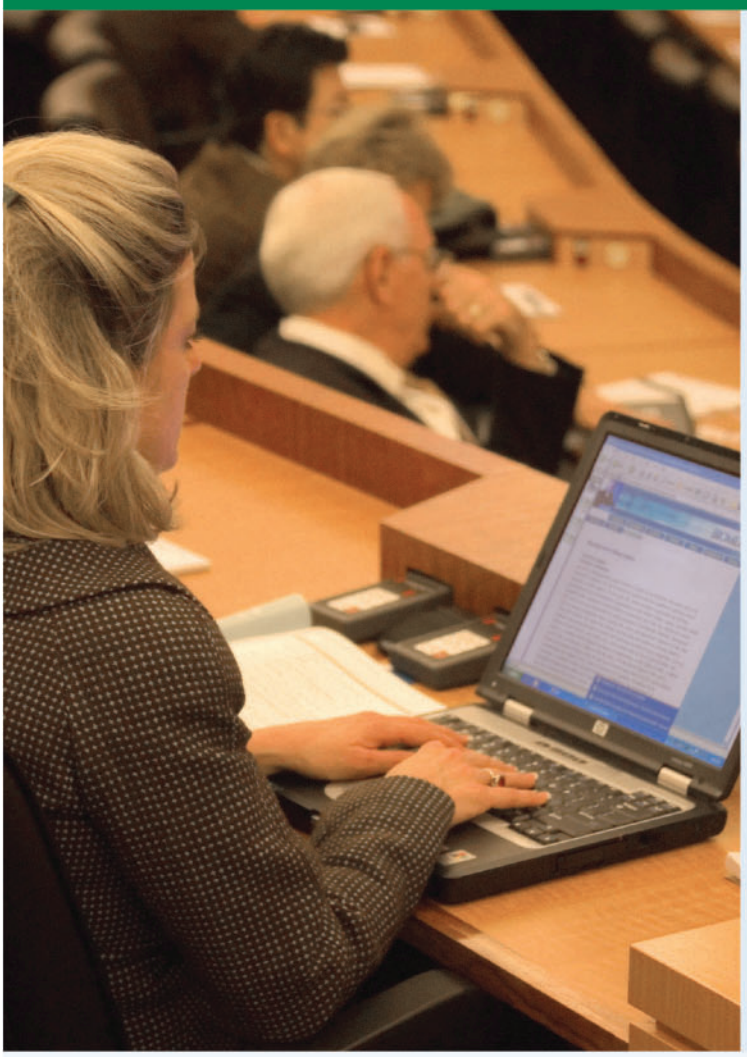

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Paroxysmal finger hematoma

A previously healthy 51-year-old woman reported recurrent episodes of blue discoloration of one or more fingers associated with pain and swelling and mainly affecting the intermediate phalanges of the fourth finger of each hand. During some episodes, the second and third fingers were also involved. Each time, the symptoms resolved spontaneously within 3 days.

She reported no other complaints and no recurrent trauma, spontaneous bleeding, palpitations, or discoloration of the fingers when exposed to cold. She was a nonsmoker.

Results of the physical examination were normal, including brachial and finger blood pressures, measured at the proximal phalanx of each finger, and Doppler studies of the brachial, radial, ulnar, and digital arteries. Other laboratory tests showed no signs of underlying inflammatory, hematologic, or coagulation disorder.

Based on the results of the evaluation, the patient's condition was diagnosed as paroxysmal finger hematoma.

PAROXYSMAL FINGER HEMATOMA

Paroxysmal finger hematoma, also known as Achenbach syndrome, is a benign, self-limiting condition that predominantly affects middle-aged women.[1] It is characterized by recurrent spontaneous subcutaneous bleeding in the fingers, typically on the palmar surface, mainly around the proximal interphalangeal joint creases. The cause is unknown, but local vascular fragility has been suggested.

Although relapses may frequently occur, no treatment is indicated, as the symptoms resolve spontaneously within a few days.

The diagnosis is based on the typical clinical presentation, as results of routine laboratory testing and Doppler studies of the arteries of the arm are usually normal.[2] Therefore, it does not require further testing if the clinical presentation is typical and there are no clinical clues for an underlying disease such as Raynaud phenomenon, autoinflammatory disease, or thromboembolism.

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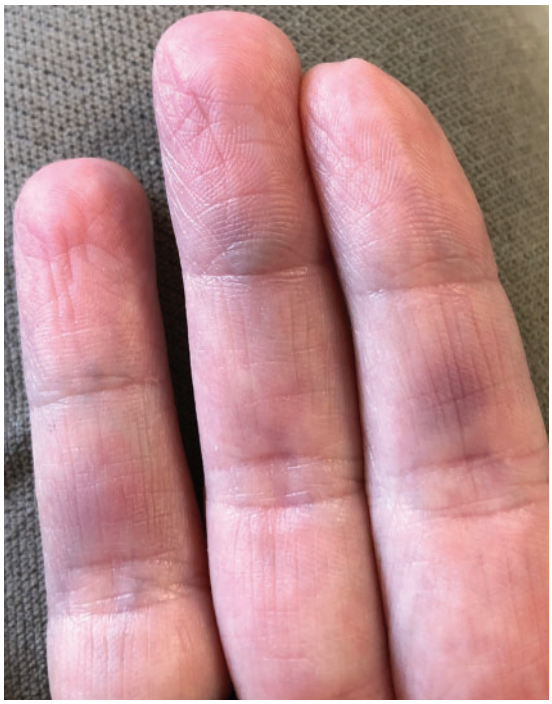

Figure 1. The patient reported recurrent episodes of blue discoloration of the palmar surface of the fingers, associated with pain and swelling. The symptoms usually resolved within 3 days.

Unfortunately, the typical symptoms are often not recognized, resulting in unnecessary and potentially harmful diagnostic procedures such as tissue biopsy and catheter-based angiography. Hence, awareness of this benign, self-limiting syndrome is important.

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Constitutional symptoms, pathologic PET-CT

A 74-year-old woman presented with a 6-month history of malaise, generalized fatigue, significant unintentional weight loss, and night sweats, as well as pain, weakness, and stiffness in the shoulder girdle most severe in the morning. She reported no headache, visual disturbances, or jaw claudication.

On examination, blood pressure in both arms was within normal limits, and cardiovascular examination including peripheral pulses was normal without bruits.

Laboratory testing results showed erythrocyte sedimentation rate 142 mm/hour (reference range for age < 30), C-reactive protein 15.80 mg/dL (0–1), hemoglobin 9.9 g/dL (12.0–15.5), and creatine kinase 55 U/L (22–198); other results were unremarkable.

Initially, malignancy was high on the differential diagnosis, in view of the patient's advanced age, weight loss, and elevated levels of inflammatory biomarkers. However, computed tomography of the chest, abdomen, and pelvis were unremarkable, and upper endoscopy and colonoscopy showed no abnormalities. Thus, an autoimmune cause was considered.

The patient underwent whole-body fluorine-18 fluorodeoxyglucose positron emission tomography and computed tomography (PET-CT), which showed diffuse hypermetabolism of the great vessel walls, including the aorta and major branches, axillary arteries, common carotid artery, and common iliac artery, consistent with large-vessel giant cell arteritis (GCA) (**Figure 1**).

Prednisone 50 mg/day (1 mg/kg/day) was started. This dosing was maintained for 4 weeks, after which it was gradually reduced

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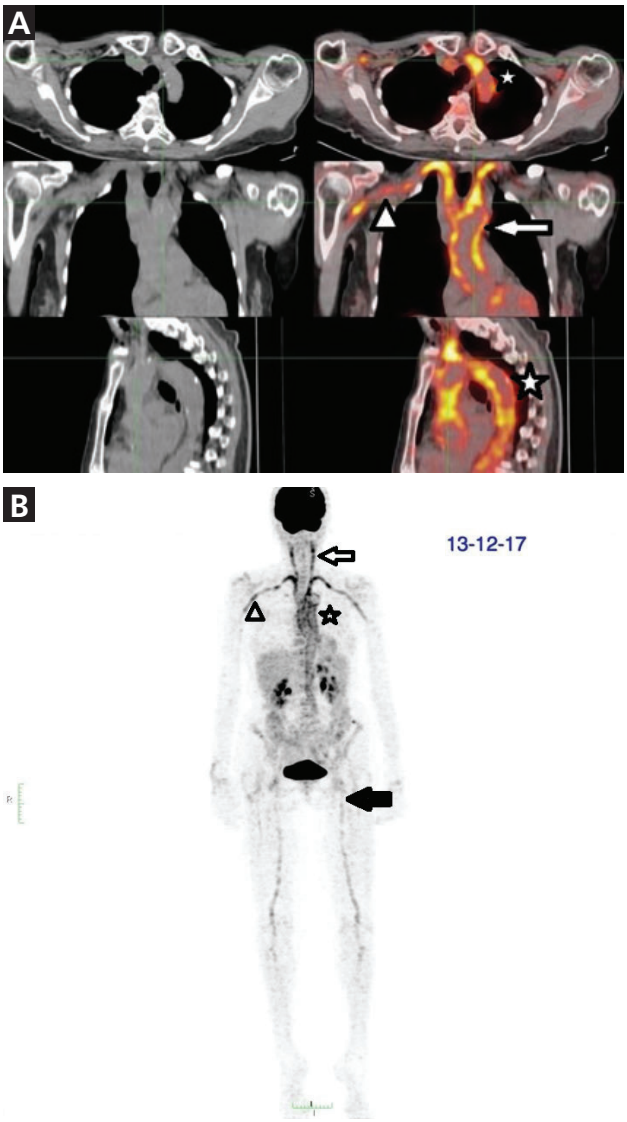

Figure 1. (A) Axial, coronal, sagittal, and (B) frontal positron emission tomography showed highly increased uptake of ^{18}F-fluorodeoxyglucose in the aorta and major branches (star), axillary arteries (arrowheads), carotid arteries (arrows), and femoral arteries (black arrow).

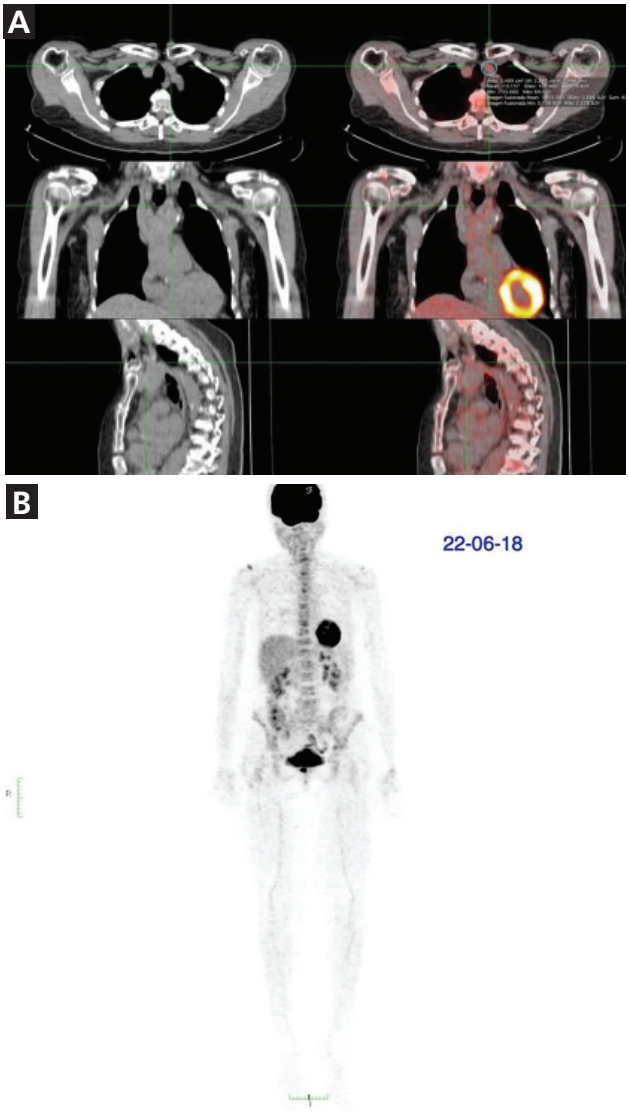

Figure 2. After 6 months of treatment, (A) axial, coronal, sagittal and (B) frontal positron emission tomography showed improvement of uptake in all arterial territories.

10% every 2 weeks. At this time, tocilizumab was not approved by the Argentine regulatory agency for the treatment of GCA, so methotrexate 15 mg weekly was added as a corticosteroid-sparing agent.

After 6 months of treatment, the patient was free of symptoms and her levels of inflammatory biomarkers had returned to normal; her erythrocyte sedimentation rate was 11 mm/hour and C-reactive protein 0.48 mg/dL. Repeat PET-CT showed significant improvement in vascular hypermetabolism, principally in the aorta and supra-aortic vessels, without metabolic activity in the subclavian arteries or extravascular metabolic hyperactivity (**Figure 2**).

LARGE-VESSEL GIANT CELL ARTERITIS

GCA is a granulomatous vasculitis that compromises medium and large arteries. The spectrum encompasses overlapping phenotypes including classic cranial arteritis and large-vessel (extracranial) GCA.[1]

Like cranial GCA, large-vessel GCA may present with constitutional symptoms such as fever of unknown origin, anorexia, weight loss, symptoms of polymyalgia rheumatica, or elevated inflammatory markers.[2]

In large-vessel GCA, especially if cranial symptoms are lacking, cross-sectional imaging such as magnetic resonance angiography, CT angiography, or PET-CT may be useful, because biopsy of the extracranial arteries is not feasible. In the Tocilizumab in Giant Cell Arteritis trial (GiACTA), the largest prospective study evaluating treatment in patients with GCA, 119 (86%) of a total of 138 patients who underwent cross-sectional imaging had findings consistent with large-vessel involvement.[3]

According to the European League Against Rheumatism recommendations for imaging in large-vessel vasculitis, the major advantage of PET in patients with suspected large-vessel vasculitis is the ability to identify GCA along with other serious pathology such as infection or tumor.[4] This may be particularly relevant in elderly patients with constitutional symptoms without specific clinical features of GCA or polymyalgia rheumatica.

High cost, limited availability, and radiation exposure limit the use of PET. But combining PET with CT permits the evaluation of wall thickness and luminal changes.[4]

High doses of glucocorticoids (40–60 mg/day prednisone-equivalent) with gradual tapering are the mainstay of treatment. In patients with refractory disease or at increased risk of glucocorticoid-related adverse effects, methotrexate may be an alternative, glucocorticoid-sparing agent.[5]

In GiACTA, sustained remission rates at week 52 were 53% with tocilizumab treatment vs 17% with glucocorticoid monotherapy,

while the cumulative glucocorticoid dose was reduced by 50% in tocilizumab-treated patients with fewer adverse events than those on glucocorticoids alone.[6] These strikingly positive results led to tocilizumab's approval by the US Food and Drug Administration.

Encouraging results have also been reported with ustekinumab, an interleukin 12 and interleukin 23 antagonist, and with abatacept, a selective T cell costimulation modulator.[2] A new era in the treatment of an old disease is coming.

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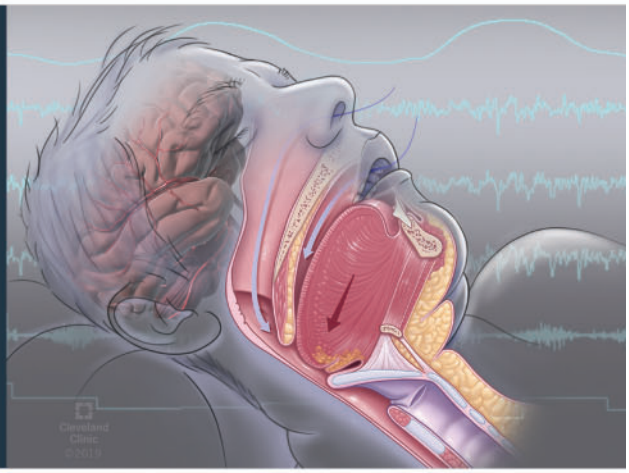

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Trousseau syndrome

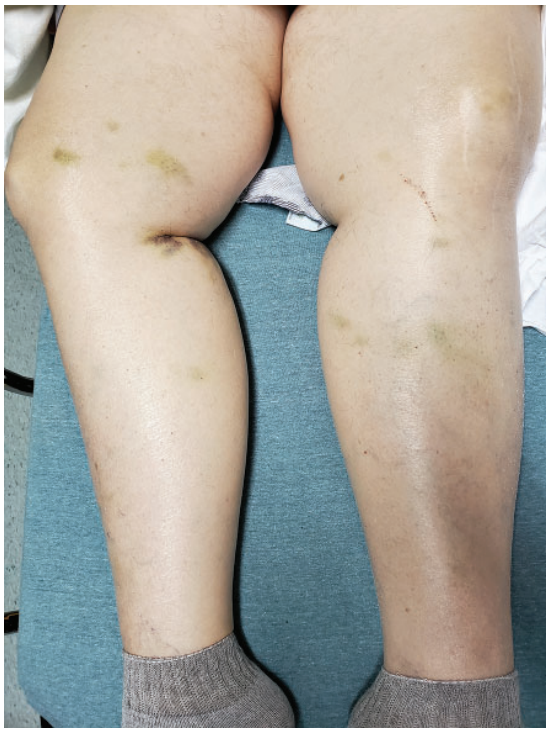

Figure 1. Multiple bluish macules were scattered on both legs, the sequelae of migratory thrombophlebitis.

A previously healthy 75-year-old man presented to the clinic with memory loss, lightheadedness, and new-onset headaches. He also reported fatigue, anorexia, and epigastric abdominal pain, but no slurred speech or focal weakness.

Physical examination confirmed he had no focal neurologic deficit, but examination of the skin revealed multiple bluish macules scattered over both legs (**Figure 1**). Closer inspection revealed extensive discoloration in the right popliteal fossa, with 2 palpable thrombosed superficial veins (**Figure 2**). With these findings suggesting Trousseau syndrome, anticoagulation was started immediately and imaging was ordered to look for deep vein thrombosis and an underlying malignancy.

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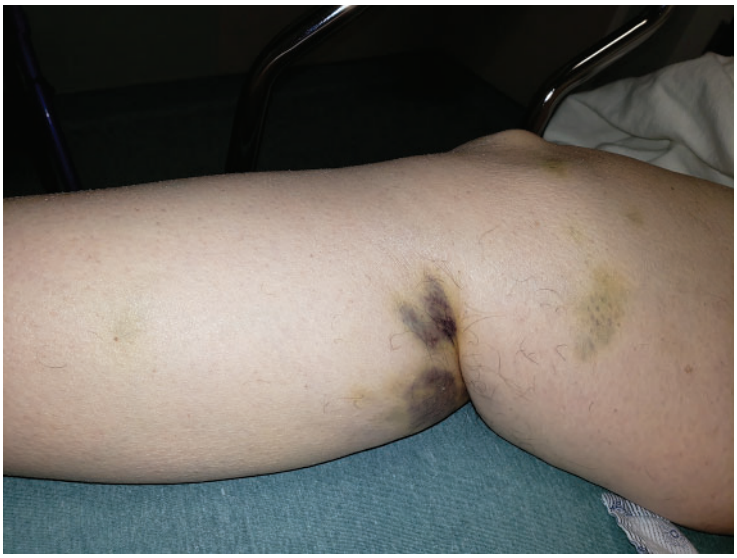

Figure 2. Closer inspection revealed extensive discoloration in the right popliteal fossa, with two palpable thrombosed superficial veins.

IMAGING GIVES A FULLER PICTURE

Although the patient had no leg pain or tenderness, Doppler ultrasonography confirmed deep vein thrombosis bilaterally, extending from the common femoral veins through the popliteal veins. Abdominal computed tomography showed a 2.8-cm pancreatic body mass, and endoscopic biopsy confirmed pancreatic adenocarcinoma.

Magnetic resonance imaging of the brain revealed multifocal acute infarcts that raised the concern for embolic disease. However, transthoracic echocardiography revealed no vegetations, valvular disease, or patent foramen ovale that could have been the source of embolism. Computed tomographic angiogra-

phy of the head and neck showed no evidence of vascular disease.

The patient was discharged on extended anticoagulation with low-molecular-weight heparin (LMWH) and was referred for palliative chemotherapy.

THE SPECTRUM OF THROMBOEMBOLIC DISEASE

The syndrome of migratory thrombophlebitis as a sign of malignancy bears the name of Armand Trousseau, who in 1865 published the first clinical record associating undiagnosed visceral malignancy and unexpected thrombosis. In a twist of fate, Trousseau diagnosed the syndrome in himself 2 years later and died of gastric cancer.[1,2]

Today, Trousseau syndrome covers a spectrum of disease including chronic disseminated intravascular coagulation, microangiopathic hemolytic anemia, nonbacterial thrombotic endocarditis, and arterial thrombosis.

Thrombosis in malignancy is complicated and represents an intersection of hematology and oncology. Mucin-producing carcinomas are commonly linked with the syndrome,[3] but this is not an exclusive association. The pathophysiology is complex, and tissue factor, tumor hypoxia, tumor-associated cysteine proteinase, and most recently, oncogene activation have been implicated.[4,5]

MANAGEMENT

Intuitively, one would think that the clinical focus should be on diagnosing and treating the underlying malignancy. However, thrombosis is an uncommon presentation of cancer, and if provoking factors are present, thrombosis should not routinely trigger a search for cancer beyond age-appropriate screening. Nevertheless, Trousseau syndrome is not a benign thrombophlebitis, and when diagnosed it requires immediate treatment.

Until recently, LMWH was the only anticoagulant recommended for cancer-associated thrombosis, based on comparisons with vitamin K antagonists. Now, with data from recent clinical trials, guidelines have been updated and the direct-acting oral anticoagulants edoxaban and rivaroxaban have been added to LMWH as preferred options because they have better efficacy than vitamin K antagonists.[6] On the other hand, a higher risk of major bleeding was seen with direct-acting oral anticoagulants, mainly in patients with luminal gastrointestinal malignancies, which have a high risk of mucosal bleeding.[6]

Therefore, when recommending therapy, clinicians should consider bleeding risk, renal function (edoxaban and rivaroxaban should be given in lower doses or not at all in patients with renal impairment), drug interactions (which are common with vitamin K antagonists), and patient preference.

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Can I use direct oral anticoagulants to treat cancer-associated venous thromboembolism?

A: Yes. The direct oral anticoagulants rivaroxaban, edoxaban, and apixaban have been studied in cancer-associated venous thromboembolism and are increasingly replacing low-molecular-weight heparins such as dalteparin and enoxaparin for this purpose. Individualizing care by balancing risks and benefits for each patient will help in choosing the right anticoagulant.

LOW-MOLECULAR-WEIGHT HEPARINS

The National Comprehensive Cancer Network guidelines previously recommended low-molecular-weight heparins as the preferred anticoagulants for cancer-associated venous thromboembolism, but now they are one of several first-line options.[1]

Before the advent of direct oral anticoagulants, low-molecular-weight heparins were recommended over vitamin K antagonists such as warfarin because they were more effective. This recommendation was supported by a large randomized trial,[2] in which the recurrence rate was significantly lower in patients treated with dalteparin than in those receiving vitamin K antagonists, with no significant difference in major bleeding between the 2 treatment groups. The number needed to treat to prevent 1 recurrence of venous thromboembolism was 13.[2]

An important advantage of low-molecular-weight heparins over vitamin K antagonists is that their anticoagulant effect does not routinely need to be monitored, whereas vitamin K antagonists require monitoring of the international normalized ratio. Low-molecular-weight heparins are, however, contraindicated in patients with severe kidney disease because these drugs are cleared renally.

RIVAROXABAN

Rivaroxaban, a direct-acting factor Xa inhibitor, is given twice daily for the first 3 weeks and then once daily thereafter when used to treat venous thromboembolism.[3] In this situation, it should be taken with food, which improves its absorption.[3]

In a randomized clinical trial,[4] rivaroxaban was more effective than dalteparin at reducing the recurrence of venous thromboembolism in cancer patients but was associated with higher rates of major bleeding and clinically relevant nonmajor bleeding. The number needed to treat to prevent 1 recurrence was 20, while the number needed to harm to cause 1 major bleed was 50.[4]

The risk of bleeding is higher with gastrointestinal and genitourinary tract cancer, and this increased risk should be borne in mind when choosing a direct oral anticoagulant for venous thromboembolism.[1]

EDOXABAN

Edoxaban is an oral direct factor Xa inhibitor that has been studied for the treatment of cancer-associated venous thromboembolism. When initiating edoxaban therapy, a parenteral anticoagulant should be given for at least 5 days before transitioning to edoxaban.[5] It is given as a once-daily dose and offers the convenience of oral route of administration.[5]

Rivaroxaban, edoxaban, and apixaban are increasingly replacing low-molecular-weight heparins

Dr. Emiloju has disclosed consulting for GlaxoSmithKline.

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In the Hokusai trial,[6] edoxaban was found to be noninferior to dalteparin for the composite end point of recurrent cancer-associated venous thromboembolism (hazard ratio 0.97, 95% confidence interval 0.70–1.36, calculated number needed to treat 29). There was, however, a higher rate of major bleeding, especially from the upper gastrointestinal tract, with edoxaban than with dalteparin (calculated number needed to harm 34). Patients with gastrointestinal cancers were more likely to experience major gastrointestinal bleeding in the study. Thus, edoxaban should be used with caution in this patient group.

APIXABAN

Apixaban, another oral direct factor Xa inhibitor, is taken twice a day when used to treat venous thromboembolism.[7] It also offers the advantage of an oral route of administration. But its twice-a-day dosing makes it less convenient than rivaroxaban or edoxaban.

A pilot randomized controlled trial compared apixaban with dalteparin in the treatment of cancer-associated venous thromboembolism and found that rates of recurrence and major bleeding were lower with apixaban.[8]

Gastrointestinal lesions are relative contraindications to the use of direct oral anticoagulants

A larger trial called CARAVAGGIO (NCT03045406) comparing apixaban with dalteparin in cancer-associated venous thromboembolism is under way, and trial results are awaited.

The National Comprehensive Cancer Network guidelines already recommend apixaban for cancer-associated venous thromboembolism,[1] but other societies such as the American Society for Clinical Oncology do not.[9] It will be important to assess the safety of apixaban in patients with gastrointestinal and genitourinary cancers in light of what we already know from trials of other direct factor Xa inhibitors such as edoxaban and rivaroxaban.

DABIGATRAN

Dabigatran is a direct thrombin (factor IIa) inhibitor that has not been specifically studied in cancer patients. There was, however, a subgroup analysis of cancer patients enrolled in a larger venous thromboembolism trial.[10] Initial parenteral anticoagulation for at least 5 days was followed by either dabigatran or warfarin. In the analysis of the cancer population within the study, there was no significant difference in recurrence and major bleeding rates between the dabigatran and warfarin groups.[10]

Major limitations of this study were that dabigatran was not compared with a low-molecular-weight heparin, which is the standard of care, and the study was not prospectively designed to study cancer-associated venous thromboembolism.

CONTRAINDICATIONS TO DIRECT ORAL ANTICOAGULANTS

Renal impairment

The direct factor Xa inhibitors are partially cleared by the kidneys, so renal function is important.

Edoxaban requires a dose reduction in patients with creatinine clearance 15 to 50 mL/min and is contraindicated in patients with creatinine clearance below 15 mL/min.[5]

Rivaroxaban is contraindicated if creatinine clearance is less than 30 mL/min, and the manufacturer recommends caution if creatinine clearance is 30 to 50 mL/min.[3]

Apixaban's manufacturer does not recommend any dose reduction with renal impairment, but patients with creatinine clearance below 15 mL/min were not included in the randomized controlled trial of this drug.[7]

Liver impairment

Given that coagulopathy is frequently associated with liver disease and that some direct oral anticoagulants are partially cleared in the liver, hepatic impairment is an important contraindication to their use.

Apixaban requires no dose adjustment in mild hepatic impairment (Child-Pugh class A) and is contraindicated in severe hepatic impairment (Child-Pugh class C).[7]

Edoxaban and rivaroxaban are contraindicated in moderate and severe hepatic dysfunction (Child-Pugh classes B and C).[3,5] The guidelines recommend not giving apixaban and edoxaban if aminotransferase levels are more than twice the upper limit of normal, while rivaroxaban is contraindicated if they are more than 3 times the upper limit of normal.[1]

Other contraindications

Gastrointestinal lesions such as cancers, ulcers, and varices and recent instrumentation

are relative contraindications to direct oral anticoagulants in cancer-associated venous thromboembolism because of an increased risk of bleeding.[4,6]

Current guidelines do not recommend direct oral anticoagulants in patients whose body mass index is above 40 kg/m^2 because the initial pharmacokinetic studies of these drugs did not include patients in this category.[9]

Other important considerations in the use of direct oral anticoagulants include potential drug interactions, especially with inducers and inhibitors of the cytochrome P450 3A4 enzymes and the potential nephrotoxicity and hepatotoxicity of concurrent anticancer agents.[1] More frequent monitoring for adverse effects and organ dysfunction is warranted in these instances.

BLEEDING RATES

Compared with low-molecular-weight heparins, rivaroxaban and edoxaban are associated with higher rates of bleeding.[4,6] The risk of bleeding is higher in patients with genitourinary or gastrointestinal abnormalities (eg, cancers, ulcers, varices) and recent instrumentation.[4,6] In these scenarios, the International Society on Thrombosis and Hemostasis recommends low-molecular-weight heparins instead of direct oral anticoagulants, and the choice of anticoagulant should be a shared one between the clinician and the patient.[11]

If life-threatening or uncontrollable bleeding develops in a patient on rivaroxaban or apixaban, andexanet alfa can potentially be used as an antidote, although it has not been studied specifically in patients with cancer-associated venous thromboembolism.[12]

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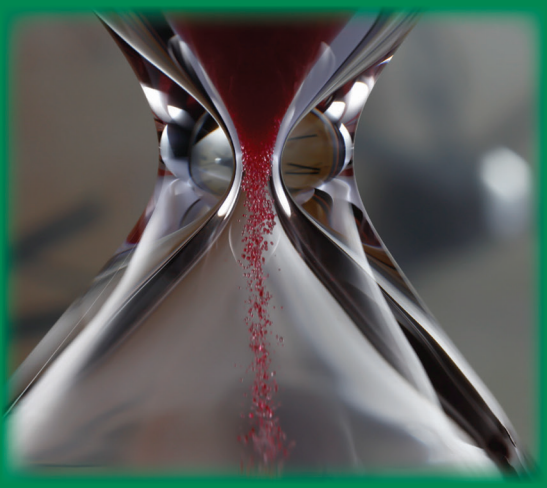

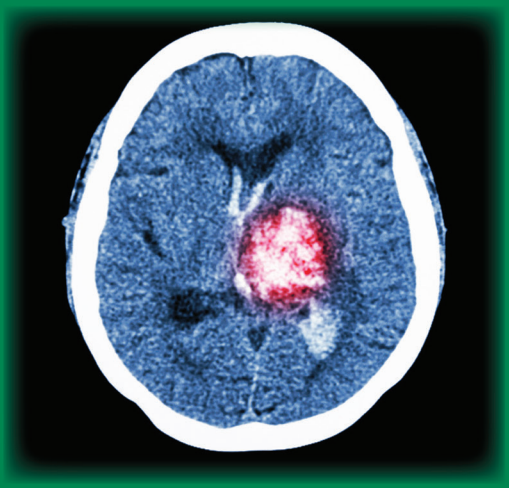

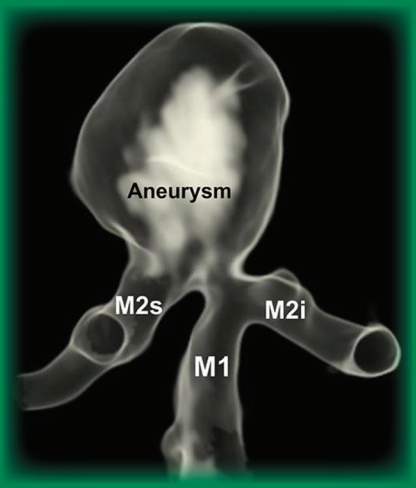

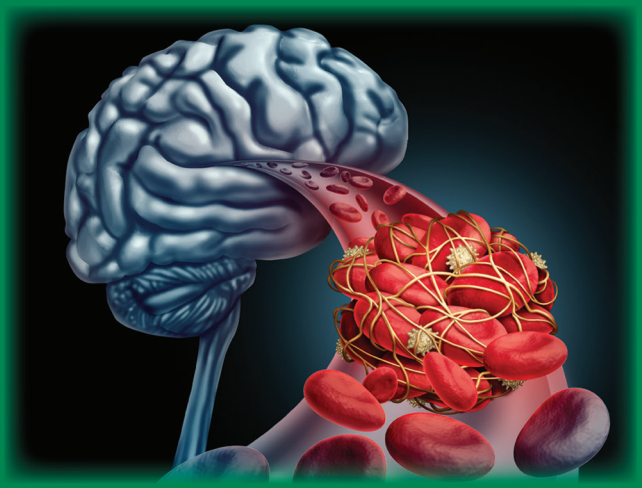

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REVIEW

CME MOC

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To scan or not to scan? DXA in postmenopausal women

ABSTRACT

Fracture is a major cause of morbidity and death in postmenopausal women. Dual-energy x-ray absorptiometry (DXA) measures bone mineral density, which helps in estimating fracture risk and in identifying those who may benefit from treatment. Although screening guidelines differ somewhat for postmenopausal women under age 65, in general, DXA is indicated if the patient has a high risk for fracture.

KEY POINTS

Bone is lost with aging and declining estrogen and testosterone levels, particularly after menopause.

Advanced age, prior fragility fracture, and low T scores (< –3.0) are the greatest risks factors for fracture.

DXA is considered the therapeutic standard for measuring bone mineral density.

In younger postmenopausal women, guidelines recommend DXA only in those who have a substantial risk of fracture based on clinical factors.

Dr. Tough DeSapri has disclosed membership on advisory committees or review panels and teaching and speaking for Amgen, and consulting for Radius Health, Inc.

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A 56-year-old woman presents for a routine physical examination. Her last menstrual period was at age 51. She takes hydrochlorothiazide for hypertension and a multivitamin containing 400 mg of calcium carbonate plus 1,000 IU vitamin D_3 daily. On most days, she eats 2 servings of calcium-rich foods (6 oz yogurt and 1 or 2 servings of cheese). She has no personal or family history of osteoporosis or fracture. She exercises 3 times a week and has had no falls or imbalance. She drinks about 5 alcoholic beverages per week. Her weight is 140 lb (63.5 kg) and height is 5 ft 2 in (157.5 cm), giving her a body mass index of 25.6 kg/m^2, stable from last year. She asks whether she should get a dual-energy x-ray absorptiometry (DXA) scan to check her bone mineral density (BMD) because many of her postmenopausal friends have done so.

Is DXA screening indicated in this patient?

BONE MINERAL DENSITY DECLINES WITH AGE AND MENOPAUSE

Most women achieve peak bone mass in their second or third decade of life, depending on skeletal site, with the most active bone formation occurring during childhood, adolescence, and young adulthood. Bone is lost with age and with declining levels of estrogen and testosterone, particularly after menopause, and low bone mineral density is associated with an increased risk of fracture.

Estrogen plays a key role in maintaining the balance between bone formation and resorption. Estrogen deficiency disrupts this balance, resulting in decreased bone formation and increased bone resorption.

The Study of Women Across Nations found that women may lose 5% to 10% of

bone mineral density in both cortical and trabecular bones during late perimenopause and the first postmenopausal years.[1] As women age, this bone loss slows but continues at an average rate of about 0.5% to 1% per year.

Women with premature ovarian insufficiency or early menopause from natural or surgical causes experience more profound bone loss and are at higher risk of fracture during their life.[2]

Several other medical, genetic, and surgical conditions also either decrease peak bone mass or accelerate bone loss. These include medications such as glucocorticoids (> 5 mg for > 3 months) and lifestyle factors such as smoking and being underweight (ie, body mass index < 18 kg/m^2). Rheumatoid arthritis and diabetes, particularly type 1 diabetes, also contribute to bone loss and increase the risk of fracture.[3]

The National Osteoporosis Foundation has published an extensive list of risk factors that can be shared with patients.[4] Advancing age, prior fragility fracture, and a T score below –3.0 are the strongest risk factors predicting future fracture.

Most women achieve peak bone mass in their second or third decade of life

OSTEOPOROSIS IS COMMON

According to data from the third National Health and Nutrition Examination Survey, more than 9.9 million Americans have osteoporosis (defined as a T score ≤ −2.5), and an additional 43.1 million have osteopenia (a T score between −1.0 and −2.5), leading to more than 2 million fractures per year.[5,6] These osteoporosis-related fractures are a major cause of morbidity and death in postmenopausal women.

DXA SCREENING

DXA measures a patient's bone mineral density. Other screening tools exist, but DXA is considered the technical standard. Results are reported in absolute terms in g/cm^2 and also as a T score (the difference, in standard deviations, between the patient's value and the mean value for healthy 30-year-olds of the same sex) and a Z score (the difference between the patient's value and the mean value of people the same age, race, and sex).

The clinical purpose of a DXA scan is to screen patients for low bone mass and osteoporosis. It also provides a surrogate measure of bone strength to help estimate fracture risk.

For example, a 10% loss of bone mass (equivalent to a 1 standard deviation decrease in the T score) in the vertebrae can double the risk of vertebral fractures. In the hip, a 10% loss of bone mass can cause a 2.5 times greater risk of hip fracture.[7,8]

For DXA to be an appropriate screening test, it must be able to detect disease (osteoporosis or osteopenia) at a stage when treatment (medication or lifestyle modification) can effectively reduce the serious consequences of the disease (eg, fracture). It must also be safe (this applies to both the test and the treatment), widely available, and inexpensive.

RECOMMENDATIONS FOR DXA SCREENING IN POSTMENOPAUSAL WOMEN

Several major medical societies strongly recommend DXA testing for women age 65 and older,[3,9,10] but the recommendations are not as clear for younger postmenopausal women, such as our patient. In general, however, women under age 65 should be screened if they have clinical risk factors for bone loss or fracture.

The US Preventive Services Task Force (USPSTF)[9] recommends DXA of the hip and spine if the 10-year predicted risk of major osteoporotic fracture according to the Fracture Risk Assessment Tool (FRAX)[11] without bone mineral density is 8.4% or greater. This is equal to the fracture risk of a 65-year-old white woman of mean height and weight without major risk factors for fracture.

The National Osteoporosis Foundation[4] and the International Society of Clinical Densitometry[10] both recommend DXA for postmenopausal women under age 65 and those in the menopausal transition who have clinical risk factors for fracture such as:

- Low body weight
- Prior fracture
- A disease or condition associated with bone loss
- Use of medications that cause bone loss, such as glucocorticoids.

DXA is also recommended in women being considered for pharmacologic treatment and to monitor treatment response.

TABLE 1

Osteoporosis risk assessment calculators

Risk factors used	FRAX[12]	Garvan[23]	OST[24]	SCORE[25]
Age	X	X	X	X
Sex	X	X	X	X[b]
Weight	X		X	X
Height	X			
Steroid use	X			
Prior fracture	X	X		X
Secondary osteoporosis	X			
BMD data	X[a]	X		
Race				X
Rheumatoid arthritis	X			X
Prior hormone therapy				X
Current smoking	X			
Hip fracture in parent	X			
Alcohol use	X			
Falls		X		

BMD = bone mineral density; FRAX = Fracture Risk Assessment Tool; HT = hormone therapy; OST = Osteoporosis Self-assessment Tool; SCORE = Simple Calculated Osteoporosis Risk Estimation

[a]Femoral bone (can calculate score without BMD); [b]Women only

WHY NOT SCREEN ALL YOUNGER POSTMENOPAUSAL WOMEN?

Because recommendations differ regarding DXA screening of postmenopausal women under age 65, patients are selected on the basis of their clinical risk factors other than bone mineral density. The USPSTF, as noted above, recommends basing the decision on the FRAX score without bone mineral density.

If a postmenopausal woman has a low clinical risk of fracture based on the FRAX score and the clinician's determination, DXA will not add any information to determine if she needs treatment. Therefore, women who recently went through menopause who are at low risk do not need DXA screening.

In addition, anyone who has already had a fragility or low-trauma fracture (eg, fracture from falling from a standing height or less) as an adult should be evaluated for treatment of clinical osteoporosis. These patients do not need DXA screening because their risk of a subsequent fracture is 85%, regardless of bone mineral density.[12]

Age, prior fragility fracture, and T scores below –3.0 are the strongest risk factors for future fracture

Does DXA have side effects?

The USPSTF found only minimal harms from DXA screening.[9] They reported that patients had no increased anxiety or decreased quality of life associated with screening.

Radiation exposure from a DXA scan is low (typically 0.001 mSv, equivalent to 3 hours of background radiation). In comparison, a mammogram releases 0.4 mSv.[13]

Overall, DXA is a low-cost screening test

for those who meet the criteria to be screened, but it should not be done in all early postmenopausal women.

FRAX IS A VALIDATED TOOL

FRAX[11] is a computer-based equation that uses clinical risk factors (and, if available, bone mineral density information) to estimate a patient's 10-year fracture probability. Although it has been validated in the general population, it has some limitations that may cause it to underestimate the fracture risk in postmenopausal women. Its use of yes-or-no responses can limit its clinical application. For example, a patient who smoked cigarettes for 10 years but has quit is considered a nonsmoker in FRAX, even though their smoking history could have a substantial effect on their peak bone deposition and rate of bone loss.

Some experts suggest using one of the alternate risk calculators that include other variables to determine the risk of fracture.[14] **Table 1** lists the risk variables used in each tool.

The Simple Calculated Osteoporosis Risk Estimate (SCORE) tool, for example, accounts for hormone therapy and race in its calculation, whereas FRAX does not. In addition, FRAX does not account for falls, which are a major contributor to fractures. Of note, except for FRAX, most of these risk calculators have not been validated in diverse populations and are not in widespread use. We recommend FRAX because it is an easy-to-use clinical tool and is used around the world, but with caveats, as mentioned above.

If a woman is at low risk based on clinical factors, DXA will not add relevant information

SHOULD OUR PATIENT UNDERGO DXA?

Our patient is a postmenopausal woman who went through menopause at an average age, does not smoke, has a normal body mass index, and has no personal or family history of osteoporosis or fracture. She consumes adequate calcium and vitamin D through supplements and diet. Based on her history and physical examination, we assume she achieved a normal peak bone mass before menopause and, thus, has a low risk for fracture. Her FRAX score, calculated without DXA screening, shows a 6% 10-year risk of major osteoporotic fracture, which does not meet the 8.4% threshold for DXA screening.

If she continues to get enough calcium, vitamin D, and exercise, and without any offending agents or conditions that accelerate bone loss, she has a low risk of fracture and a very low probability of needing treatment. If her clinical situation remains the same, she should undergo DXA screening at age 65.

In summary, clinicians can accurately assess the fracture risk in younger postmenopausal women (ie, before age 65) by performing a comprehensive history and physical examination and combining it with the FRAX tool without a DXA scan.

MANAGING LOW BONE MASS

More fractures occur in women with osteopenia than in those with osteoporosis because many more women have osteopenia, even though their fracture rate is lower.[15] Therefore, it is important to judiciously treat low bone mass in patients who meet the criteria for treatment based on their FRAX score and the practitioners' clinical judgment.

The trabecular bone score is an indirect measure of trabecular microarchitecture derived from DXA images of the lumbar spine. It provides information about bone quality. A score below 1.200 indicates degraded microarchitecture.

Using a trabecular bone score independently or in conjunction with a DXA scan or FRAX score can improve fracture prediction.[16,17] Also, FRAX can be adjusted for this score. More accurate evaluations of bone density and bone quality can help determine which patients with low bone mineral density need treatment.

The efficacy of treatment to reduce fracture rates in women at high risk of fracture but without a low T score (−2.5 or below) has not been established. Most FDA-approved therapies are indicated for treatment based on bone mineral density.

EFFECTIVE AND EMERGING THERAPIES

For postmenopausal women who are candidates for pharmacologic treatment based on their fracture risk assessment, there are safe and effective FDA-approved options.

Hormone therapy

Hormone therapy has been proven in the large Women's Health Initiative[18] and the Postmenopausal Estrogen/Progestone Interventions trial[19] to both prevent osteoporosis and reduce the incidence of fractures (such as vertebral and hip) compared with placebo. In the Million Women Study,[20] women who received hormone therapy had a significantly lower risk of any fracture than women who did not. Despite those results, hormone therapy is FDA-approved only for prevention of osteoporosis, not treatment. It is also recommended for menopause-related vasomotor symptoms and the genitourinary syndrome of menopause.

Candidates for hormone therapy are primarily women under age 60 who are fewer than 10 years past menopause; the risk-benefit ratio for older women is less favorable because of higher risks of heart disease and stroke.[21] It is important to engage the patient in an accurate, evidence-based discussion of the risks and benefits of hormone therapy.

Tissue-selective estrogen complexes can be appropriate options to reduce the fracture risk and prevent osteoporosis. These pair estrogens with selective estrogen-receptor antagonists or agonists, such as conjugated estrogen and bazedoxifene.

Selective estrogen-receptor modulators, such as raloxifene, are available in generic form. They may play a dual role of reducing risk of breast cancer and preventing or treating osteoporosis.

Antiresorptives

The antiresorptive class of medications includes bisphosphonates (oral or intravenous) and denosumab, a subcutaneous monoclonal antibody; both are considered first-line treatment for women with osteoporosis. Denosumab is indicated for women (and men) with a history of fracture or who are at increased risk of fracture and cannot tolerate other therapies.

Although effective at reducing the incidence of fractures, antiresorptive therapies may increase the risk of osteonecrosis of the jaw and atypical femoral fractures, especially with prolonged use. Fortunately, these are rare: the incidence rate with 10 years of denosumab use is 0.05%,[22] and only 0.001% to 0.01% with more than 4 years of oral bisphosphonate use.[23,24]

Anabolic drugs

The anabolic drugs such as teriparatide, abaloparatide, and romosozumab build bone mass by stimulating osteoblasts more than osteoclasts. Abaloparatide was studied head-to-head against placebo and teriparatide for 18 months, after which patients received alendronate for 2 years; sequential treatment with abaloparatide followed by alendronate reduced the risk of vertebral, nonvertrbral, clinical, and major osteoporotic fractures and increased bone mineral density.[25] Romosozumab, a humanized monoclonal antibody to sclerostin, is FDA-approved to treat women at high risk of fracture. It has a dual effect, stimulating bone formation and reducing bone resorption.

CLINICAL BOTTOM LINE

Osteoporosis and osteopenia leading to fracture are major causes of morbidity and mortality in postmenopausal women. A DXA scan is considered the best tool to measure bone mass, which can be used to determine the risk of fracture and who may benefit from treatment.

For younger postmenopausal women (age 50 to 65), the need for a DXA scan is determined by a thorough history and physical examination, noting any risk factors that contribute to bone loss. A DXA scan is indicated if their fracture risk is high (ie, equivalent to that of a woman age 65 or older) based on a FRAX calculation without a bone mineral density measurement. If DXA is not indicated, clinicians should counsel women on ways to prevent bone loss and reduce fracture risks.

Conversely, women at the highest risk of fracture are those with a prior adult fragility fracture, regardless of T score. Evaluation and pharmacologic therapy should be strongly recommended in these cases. ■

Antiresorptive drugs may increase the risk of osteonecrosis of the jaw and atypical femoral fractures, especially with prolonged use, but these are rare

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CGRP antagonists for decreasing migraine frequency: New options, long overdue

ABSTRACT

The cornerstone of preventive migraine treatment has long been drugs developed for other diseases such as epilepsy, depression, and hypertension. But a new set of drugs is available for preventing migraine attacks: erenumab, galcanezumab, fremanezumab, and eptinezumab. These monoclonal antibodies target calcitonin gene-related peptide (CGRP) or its receptors, each a key molecule in the pathophysiology of migraine.

KEY POINTS

Migraine is common, affecting nearly 40 million people in the United States.

In clinical trials, CGRP antagonists have been superior to placebo and similar in efficacy to current prophylactic treatments in terms of reducing the frequency of headaches.

These agents have long half-lives, permitting monthly or even quarterly dosing, and favorable side effect profiles compared with currently available oral therapies. This may improve adherence.

The new drugs are an exciting new frontier in headache medicine that is long overdue. However, the approach to migraine management must remain a combination of finding effective treatment and implementing patient-specific lifestyle changes for the best possible outcome.

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THE CORNERSTONE OF PREVENTIVE migraine treatment has long been drugs intended for other diseases—epilepsy, depression, and hypertension. But in 2018, the US Food and Drug Administration (FDA) approved 3 new drugs—erenumab, galcanezumab, and fremanezumab—specifically for decreasing the frequency of migraine attacks. A fourth, eptinezumab, was approved February 22, 2020. These monoclonal antibodies against calcitonin gene-related peptide (CGRP) or its receptors are the first preventive medications to target the pathophysiology of migraine.

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The new drugs represent an exciting new frontier in headache medicine that is long overdue. Although they don't seem to be more effective than current drugs, they have long half-lives, permitting monthly or even quarterly dosing, and fewer adverse effects, which may improve adherence. In addition, they carry no contraindications for patients with liver disease, kidney disease, stroke, or coronary artery disease. They also have no known significant drug-drug interactions. Their primary disadvantage is cost (about $700 per month), although insurance may pay for them, and the manufacturers have assistance programs (**Table 1**).

NEED FOR MORE OPTIONS

Headache disorders, treated as early as 1200 BCE by the ancient Egyptians, affect nearly half of the world's adult population.[1,2] In the United States alone, migraine affects nearly 40 million people and is one of the most common complaints ad-

TABLE 1

Current calcitonin gene-related peptide (CGRP) antagonists

Drug	Mechanism	Dosing and frequency[a]	Most common adverse effects[a]	Average wholesale price and Pharmaceutical Assistance Program[a]
Erenumab	CGRP receptor antagonist	Migraine: 70 or 140 mg subcutaneously, monthly	Injection site erythema or pain, 5%–6% Constipation, 3%	$690 per month (regardless of dose) If commercial insurance plan does not cover or requires prior authorization, patients are eligible for 12 doses over 24 months with a $5 copay card per month; maximum benefit $2,700 annually
Fremanezumab	CGRP ligand antagonist	Migraine: 225 mg monthly or 675 mg every 3 months subcutaneously	Injection site reaction, 45%	$690 per 225-mg syringe Patients with commercial insurance plan are eligible for 12 months of treatment with a $0 copay card; there is no annual maximum benefit; with electronic coupon, copay is $20
Galcanezumab	CGRP ligand antagonist	Migraine: 240 mg, then 120 mg per month subcutaneously Cluster headache: 300 mg at onset of cluster period, then monthly until end of cluster headache	Injection site reaction, 18%	$690 per 120-mg autoinjector If commercial insurance plan does not cover or requires prior authorization, patients are eligible for a $0 copay card; maximum coverage is $4,900 annually As of 2020, this benefit is available only after prior authorization is approved by insurance
Eptinezumab	CGRP ligand antagonist	100 mg/mL or 300 mg/mL via infusion every 90 days	Nausea, 1.6% Fatigue, 1.4%	$1,495 per infusion ($5,980 per year)

[a] Information from product package inserts and personal communication with Cleveland Clinic Adherence Specialty Pharmacy.

dressed by primary care physicians, emergency physicians, and neurologists. It is associated with decreased function in an otherwise healthy and productive demographic group[3–5] and is the leading cause of healthy life-years lost as a result of disability from ages 15 to 49.[6]

Drugs that have long been used in migraine prophylaxis[7] have many adverse effects and need to be taken daily, which can lead to nonadherence; more than 80% of patients stop taking them within 1 year.[8]

CGRP IS A KEY MOLECULE IN MIGRAINE

Migraine is a multifactorial disorder with complex interactions between multiple predisposing genetic and modulating nongenetic factors.[9]

The current understanding of migraine is that a wave of neuronal and glial depolarization activates meningeal nociceptors innervated by the trigeminovascular system. When these perivascular afferent fibers are activated, the signal travels through the trigeminal ganglion to neurons in the trigeminocervical complex, using CGRP as the prominent neurotransmitter. This leads to symptoms such as cutaneous allodynia, neck pain, photophobia, phonophobia, and osmophobia. Once this signal reaches the visual cortex, it alters visual perception, resulting in double vision, change in color saturation, and blurred vision.[9]

The discovery that using a peripherally active biologic, onabotulinumtoxinA, could be effective in migraine prophylaxis led to further investigation of the mechanism of action.[10] It

is now understood that onabotulinumtoxinA inhibits CGRP release from peripheral neuronal C fibers and does not cross the blood-brain barrier.[11]

CGRP, discovered in 1982, is a large molecule.[8] It binds 2 major receptors: calcitonin receptor-like receptor and receptor activity-modifying protein 1.[12] This leads to signaling that can cause vasodilation or release of neurotransmitters or cytokines, in turn causing neurogenic inflammation and increased neuronal excitability.[12]

CGRP receptors are found at all of the known central and peripheral sites involved in migraine pathogenesis, including the hypothalamus and parabrachial nucleus, and CGRP levels are elevated during migraine attacks and lower between attacks.[12] Studies in animals first showed that stimulation of the trigeminal ganglion was associated with increased blood flow and release of CGRP, which could be inhibited by sumatriptan or dihydroergotamine.[11] Studies in humans showed that sumatriptan, in addition to relieving migraine, lowered CGRP levels in the internal jugular vein.[13] CGRP has also been shown to induce migraine-like symptoms after intravenous infusion.[14]

These observations led researchers to develop drugs that target and block either the CGRP ligand itself or the receptors upon which it acts.

CGRP ANTAGONISTS: A NEW CLASS OF DRUGS

The first CGRP antagonists to be studied were small molecules, with names ending in the suffix "-gepant." These so-called gepants block CGRP receptors, and 6 were found to be effective in acute treatment of episodic migraine.[15–20] However, their development was discontinued due to reports of hepatotoxicity.

Next to be developed were monoclonal antibodies targeting CGRP. These agents are metabolized by the reticuloendothelial system and, as a result, bypass hepatic metabolism; to date, no adverse effects on the liver have been reported.[10,21] Further, the current injectable antibodies are not thought to be contraindicated in patients with coronary artery, cerebrovascular, peripheral vascular, or kidney disease.[10]

DEFINITIONS

Episodic migraine is defined as having fewer than 15 headache days per month fulfilling diagnostic criteria for migraine.[22]

Chronic migraine is defined as headaches on 15 or more days per month for 3 months or more in a patient with a preexisting diagnosis of migraine. Of the total headache days, at least 8 days per month should meet migraine criteria.[22]

EFFICACY OF CGRP ANTAGONISTS

Clinical trials of the monoclonal antibodies (**Table 2**)[23–33] have found them to be superior to placebo and similar in efficacy to current prophylactic treatments for episodic and chronic migraine.[34] Roughly half of patients receiving these drugs achieved at least a 50% reduction in the number of headache days per month, compared with roughly one-fourth of patients receiving placebo. The new drugs have also been shown to be tolerable and safe, with no significant effects on blood pressure or peripheral vasoconstriction.[35]

Erenumab

Unlike galcanezumab and fremanezumab, erenumab targets the canonical CGRP receptor rather than the CGRP ligand itself.

There are 2 available doses, 70 mg and 140 mg, which patients give themselves once a month at home using a preloaded subcutaneous autoinjector.[10]

In episodic migraine. Three trials looked at 50% responder rates and mean decrease in monthly migraine days with use of erenumab in patients with episodic migraine (**Table 2**).[23–25] Results were reliably better with erenumab than with placebo, including in groups with so-called refractory migraine for whom 2 to 4 oral preventive therapies had failed.[25]

In chronic migraine, the results were similar.[26] Adverse effects noted included injection site pain (reported by 4% of patients receiving active treatment), constipation (4% of those on 140 mg), and muscle spasm (4% of those on 140 mg).[26]

Erenumab received FDA approval for prevention of migraine on May 17, 2018.

Fremanezumab

Fremanezumab targets the CGRP ligand rather than the receptor. It can be taken as a

The CGRP antagonists are an exciting new frontier in headache medicine

TABLE 2

Efficacy of calcitonin gene-related peptide antagonists in clinical trials of migraine prevention

Authors	Treatment	No. of patients	Baseline migraine days per month	Decrease in migraine days from baseline	50% response rate
Tepper et al[26]	Erenumab 70 mg monthly	191	17.9	6.6	40%
	Erenumab 140 mg monthly	190	17.8	6.6	41%
	Placebo	286	18.2	4.2	23%
Dodick et al[24]	Erenumab 70 mg monthly	282	8.1	2.9	40%
	Placebo	288	8.4	1.8	30%
Reuter et al[25]	Erenumab 140 mg monthly	121	9.2	1.8	30%
	Placebo	125	9.3	0.2	14%
Goadsby et al[23]	Erenumab 70 mg monthly	317	8.3	3.2	43%
	Erenumab 140 mg monthly	319	8.3	3.7	50%
	Placebo	319	8.2	1.8	27%
Dodick et al[27]	Fremanezumab 225 mg monthly	290	8.9	4.0	48%
	Fremanezumab 675 mg quarterly	291	9.2	3.0	44%
	Placebo	294	9.1	2.6	28%
Silberstein et al[28]	Fremanezumab 675 mg, then 225 mg monthly	379	12.8	4.6	41%
	Fremanezumab 675 mg quarterly	376	13.2	4.3	38%
	Placebo	375	13.3	2.5	18%
Stauffer et al[29]	Galcanezumab 120 mg monthly	213	5.6	4.7	62%
	Galcanezumab 240 mg monthly	212	5.7	4.6	61%
	Placebo	433	5.8	2.8	39%
Skljarevski et al[30]	Galcanezumab 120 mg monthly	231	9.1	4.1	59%
	Galcanezumab 240 mg monthly	223	9.1	4.2	57%
	Placebo	461	9.2	2.3	36%
Detke et al[31]	Galcanezumab 240 mg, then 120 mg monthly	278	19.2	4.8	28%
	Galcanezumab 240 mg monthly	277	19.4	4.6	28%
	Placebo	558	19.6	2.7	15%
PROMISE-1[32]	Eptinezumab 30 mg every 12 weeks	219	8.7	4.0	50.2%
	Eptinezumab 100 mg every 12 weeks	223	8.7	3.9	49.8%
	Eptinezumab 300 mg every 12 weeks	224	8.6	4.3	56.3%
	Placebo	222	8.4	5.4	37.4%
PROMISE-2[33]	Eptinezumab 100 mg every 12 weeks	356	16.1	7.7	57.6%
	Eptinezumab 300 mg every 12 weeks	350	16.1	8.2	61.4%
	Placebo	366	16.2	5.6	39.3%

monthly subcutaneous injection of 225 mg or as a quarterly injection of 675 mg.

In episodic migraine. A phase 3 trial in episodic migraine showed a decrease in mean monthly headache days and increases in the 50% responder rate and 75% responder rate with either dose compared with placebo ($P < .0001$).[27]

In chronic migraine. The same trial also compared fremanezumab and placebo in patients with chronic migraine.[36] The number of days with headache of moderate to severe intensity was reduced by 4.2 days in the placebo group and by 6 days in both a group receiving 225 mg monthly and a group receiving 675 mg quarterly.[28] In a separate study,[37] investigators found that patients noted an improvement as early as 1 week from initiation of therapy in both dose regimens.

Fremanezumab received FDA approval for prevention of migraine on September 14, 2018.

Galcanezumab

Galcanezumab also targets the CGRP ligand. It is given subcutaneously once a month with an autoinjector or prefilled syringe in a recommended monthly dose of 120 mg after an initial loading dose of 240 mg.

In episodic migraine. Two 6-month trials compared galcanezumab monthly injections of galcanezumab 120 mg, galcanezumab 240 mg, and placebo.[29,30] Both studies demonstrated a reduction of migraine days and an increase in 50% responder rate superior to placebo.[36] Interestingly, about 17% of patients had a 100% reduction in mean migraine days. This was seen most commonly in the last 3 months of the trials and was statistically significant compared with placebo ($P < .001$).[10]

In chronic migraine. In a phase 3 trial, galcanezumab showed a significant decrease in mean monthly migraine days compared with placebo. Also, differences in the 50% and 75% responder rates were statistically significant in each treatment group compared with placebo ($P < .001$). Similar to the episodic migraine trial, 11.5% of galcanezumab recipients in the chronic migraine trial also noted 100% reduction in mean migraine days, again noted most commonly in the last 3 months of the clinical trial ($P < .001$).[31]

This drug received FDA approval for prevention of migraine on September 27, 2018.

Eptinezumab

Eptinezumab, a monoclonal antibody against the CGRP ligand, is given intravenously, whereas the other CGRP monoclonal antibodies are given subcutaneously,

In episodic migraine. In a 3-month phase 3 trial,[32] quarterly infusions of eptinezumab 300 mg significantly reduced the number of mean monthly migraine days. Secondary end points included the 75% responder rate at week 12 (49.8% in the 100-mg arm, $P = .0085$; and 56.3% in the 300-mg arm, $P < .0001$). The clinical trial also demonstrated rapid onset of effect with a reduction in the likelihood of migraine within 24 hours of infusion. Before treatment, 58% of the participants were likely to have a migraine on any given day. This declined by 27% in the placebo group, 51% in those who received 100 mg, and 53% in those who received 300 mg ($P < .0001$ for both doses). At a 300-mg dose given quarterly, the 75% responder rate was maintained for up to 1 year.[10]

In chronic migraine, a phase 3 clinical trial showed a significant reduction in mean monthly migraine days compared with placebo at doses of 100 mg and 300 mg.[33]

This drug received FDA approval February 22, 2020.

The first CGRP antagonists to be studied were small molecules, termed gepants

A PRAGMATIC APPROACH TO ANTI-CGRP DRUG THERAPY

The approach to migraine management must remain a combination of cost-effective first- and second-line treatments, generally reserving CGRP monoclonal antibodies for patients for whom these options fail. All pharmacologic treatments should be accompanied by education and specific lifestyle changes for the best possible outcome.

The Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society[7] in 2012 reviewed the evidence and ranked the migraine preventive therapies available in the United States at that time according to the evidence of their efficacy. **Level A medications**, ie, those rated as having "established efficacy," were:

- The antiepileptic drugs divalproex sodium, sodium valproate, and topiramate

- The beta-blockers metoprolol, propranolol, and timolol
- The tripan frovatriptan (for short-term prophylaxis).

Level B medications, ie, those that are "probably effective," were:

- The antidepressants amitriptyline and vanlafaxine
- The beta-blockers atenolol and nadolol
- The triptans naratriptan and zolmitriptan.

Level C medications, ie, "possibly effective," were:

- The angiotensin-converting enzyme inhibitor lisinopril
- The angiotensin II receptor blocker candesartan
- The alpha-agonists clonidine and guanfacine
- The antiepileptic drug carbamazepine
- The beta-blockers nebivolol and pindolol
- The antihistamine cryptoheptadine.

While no formal guidelines exist for deciding whether anti-CGRP drugs would be appropriate for specific patients, the American Headache Society has offered general recommendations[38,39] based on the frequency of migraine.

All drug treatments should be accompanied by education and specific lifestyle changes

Patients in whom CGRP antagonists can be considered

- **Those with 4 to 7 migraine days per month** who have been unable to tolerate a 6-week trial of at least 2 oral preventive medications with level A or B evidence (see above).[7,38,39] In addition, patients should also have at least moderate disability on the Migraine Disability Assessment Scale or the Headache Impact Test 6, both of which are used to assess functional impairment secondary to migraine.
- **Those with 8 to 14 headaches per month** who cannot tolerate a 6-week trial of at least 2 oral preventive drugs with level A or B evidence (no need to demonstrate functional impairment).
- **Those with 15 or more headaches per month** (ie, chronic migraine) if at least 2 preventive medications with level A or B evidence have failed or if onabotulinumtoxinA has produced an inadequate response after at least 2 administrations or has caused adverse effects precluding further use.

At this time, not enough data exist on the safety of this class of medications in pregnant patients or children.

The findings from clinical trials suggest that if a patient is going to respond to CGRP monoclonal antibody therapy, it should happen within the first 3 months, often as early as 1 month after starting. If migraines continue unabated in this period, it is reasonable to discontinue the medication.

GEPANTS REVISITED

Gepants have been revisited in clinical trials over the past 5 years for both abortive and preventive treatment.[40]

Ubrogepant for acute migraine treatment

A multicenter, randomized, double-blind, placebo-controlled clinical trial of ubrogepant for the acute treatment of migraine showed a statistically significant improvement in rates of pain freedom 2 hours post-dose at 25 mg (P = .013), 50 mg (P = .020), and 100 mg (P = .003).[41] Adverse effects were similar to those with placebo and included dry mouth, nausea, fatigue, dizziness, and somnolence. There were no observed liver function test elevations as were seen with previous gepant trials.

Ubrogepant received FDA approval on December 23, 2019.

Rimegepant

Rimegepant has also been studied for the acute treatment of migraine in a double-blind, randomized, placebo-controlled trial.[20,21] Patients were randomized to receive placebo, sumatriptan, or rimegepant. The primary outcome was percentage of patients who were free of pain 2 hours post-dose.

Sumatriptan 100 mg and rimegepant 75 mg, 150 mg, and 300 mg were all significantly more effective than placebo (P < .007). Rimegepant was as effective as sumatriptan. No chest discomfort or paresthesias were reported with rimegepant as they were with sumatriptan.

A prospective multicenter, open-label, long-term safety study is under way.

Atogepant

Atogepant, another oral gepant, has been evaluated for prevention of episodic migraine. Mean headache days were reduced by 4.23 days per

month with atogepant 40 mg twice daily, compared with 2.85 days with placebo (P = .0034). There was no evidence of hepatotoxicity.[42]

OTHER TYPES OF HEADACHE

Cluster headache

Episodic cluster headache is defined as cluster headache attacks occurring in periods lasting from 7 days to 1 year, separated by pain-free periods lasting at least 3 months. Chronic cluster headache, in contrast, is defined as cluster headache attacks occurring for 1 year or longer without remission, or with remission periods lasting less than 3 months.

In June 2019, galcanezumab received FDA approval for treatment of episodic cluster headaches. For treatment, galcanezumab 300 mg is administered as 3 consecutive injections of 100 mg at the onset of a cluster period and then monthly until the end of the cluster period.

In clinical trials,[43–46] galcanezumab significantly reduced mean cluster attack frequency compared with placebo, with more than 70% of patients experiencing at least a 50% reduction in weekly cluster headache attack frequency by week 3. However, while trials showed galcanezumab to be effective in episodic cluster, this was not true for chronic cluster.

Fremanezumab was also not effective in the prevention of chronic cluster headache compared with placebo.[10]

Persistent posttraumatic headache

Data from rodent models of concussion suggest that cephalic tactile pain hypersensitivity improves with administration of murine CGRP antagonists.[47] Fremanezumab is currently being studied for the prevention of persistent posttraumatic headache.[48]

Medication-overuse headache

Patients with medication-overuse headache may also benefit from anti-CGRP monoclonal antibodies. Both erenumab and fremanezumab have shown efficacy in treating the subgroup of chronic migraine patients with medication-overuse headache.[49–51] Erenumab 70 mg led to a reduction of 5.2 migraine days per month, and 140 mg had a reduction of 5.4 days, compared with a reduction of 3.5 days with placebo in patients with medication-overuse headache (P < .001).[48]

Erenumab is also being considered for evaluation in pediatric patients with chronic migraine.[52]

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EDITORIAL

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Preventing migraine: The old and the new

Migraine is a highly prevalent and debilitating condition that significantly impairs quality of life. It affects people during their childbearing and most economically productive years.[1] Preventing migraine by pharmacologic means has long been a goal of both physicians and the pharmaceutical industry.

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The ideal preventive (prophylactic) migraine treatment will be effective, safe, and well tolerated, will have few or no contraindications and few or no drug interactions, will not be teratogenic, and will be dosed in a manner to ease adherence. Our attempts to meet these goals have so far been unsuccessful.

The efficacy of preventive medications for migraine has been consistent across all drug classes. Roughly half of patients taking a preventive medication have a 50% reduction in migraine frequency. Whether in placebo-controlled trials or head-to-head studies, no medication has shown significant superiority in efficacy.

THE OLD

Methysergide was introduced into practice in the early 1960s.[2] Its use was limited by both contraindications and safety issues. Contraindications included pregnancy, peripheral vascular disorders, severe arteriosclerosis, coronary artery disease, severe hypertension, thrombophlebitis or cellulitis of the legs, peptic ulcer disease, fibrotic disorders, lung diseases, collagen disease, liver or renal function impairment, valvular heart disease, debilitation, and serious infection. Methysergide can induce retroperitoneal fibrosis and pleural and heart valve fibrosis, with an estimated incidence of 1 in 5,000 treated patients. Sale of methysergide in the United States was discontinued in 2002.[3]

Antidepressants have long been used for migraine prophylaxis. Monoamine oxidase inhibitors were studied in the late 1960s, but their use was limited by drug and food interactions that could lead to hypertensive crises. Amitriptyline was shown to reduce migraine frequency in the mid-1970s.[2] Side effects including weight gain and sedation limit its usefulness. While selective serotonin reuptake inhibitors have not been shown to be effective migraine preventives, serotonin-norepinephrine reuptake inhibitors such as duloxetine and venlafaxine appear to provide benefit. Side effects include nausea, fatigue, and insomnia.

Antihypertensive medications have been a mainstay of migraine prophylaxis.

Beta-blockers such as propranolol and timolol are approved by the US Food and Drug Administration (FDA) for migraine prophylaxis. Propranolol was initially studied for migraine in the late 1960s after the discovery that a patient with cardiac disease treated with the drug had an improvement in his migraines.[2] The use of beta-blockers is limited by side effects including nausea, vomiting, diarrhea, decreased sex drive, impotence, difficulty having an orgasm, insomnia, and fatigue. Relative contraindications include asthma, heart failure, sinus bradycardia, Wolff-Parkinson-White syndrome, second- or third-degree atrioventricular block, hyperthyroidism, kidney disease, liver disease, Raynaud disease, pheochromocytoma, depression, and myasthenia gravis.

Roughly half of patients taking any preventive medication have a 50% reduction in migraine frequency

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Verapamil, a calcium channel blocker, was first studied for migraine in the early 1980s.[4] Its use is limited by drug interactions, constipation as a common side effect, and contraindications including second- or third-degree atrioventricular block, sick sinus syndrome, Wolff-Parkinson-White syndrome, Lown-Ganong-Levine syndrome, heart failure, muscular dystrophy, myasthenia gravis, liver disease, and kidney disease.

Antiepileptic agents including valproic acid and topiramate are FDA-approved for migraine prophylaxis. Valproic acid has been used for migraine since 1983 and topiramate since 2004. Use of these agents is limited by teratogenicity and adverse effects: cognitive impairment, weight loss, paresthesia, and nephrolithiasis with topiramate, and weight gain, alopecia, and hepatic dysfunction with valproic acid.

THE NEW: CGRP ANTAGONISTS

The newest options for migraine prophylaxis are the calcitonin gene-related peptide (CGRP) antagonists. The first 3 of these drugs entered the market in 2018 and are monoclonal antibodies to either the CGRP receptor (erenumab) or the CGRP ligand (galcanezumab, fremanezumab). They are given by subcutaneous injection. A fourth CGRP antagonist (eptinezumab), given by infusion, and several oral CGRP antagonists (gepants) are likely to be approved soon; ubrogepant was approved on December 23, 2019. Unlike the drugs discussed earlier, these drugs were specifically designed to treat migraine based on the currently proposed pathophysiology.

CGRP antagonists have some clear advantages over existing therapies, but also present some new challenges

That these drugs were specifically designed to treat migraine may be a valuable marketing slogan, but it has no clinical meaning. Drugs such as aspirin, a critical drug for acute coronary syndromes, was developed as an anti-inflammatory agent for arthritis, and sildenafil, the drug that revolutionized erectile dysfunction treatment, was initially developed as an antihypertensive drug. Designing a drug specifically for migraine has not improved the efficacy of this class of drugs compared with our older agents.

The CGRP antagonists have some clear advantages over existing therapies but also present new challenges for the prescribing clinician. These drugs have many of the characteristics of an ideal prophylactic migraine treatment. While they are only as effective as our current drugs, they are well tolerated, have few contraindications, have no drug interactions, and can be dosed either monthly or quarterly to improve adherence.

Concerns about safety, especially in pregnancy

The safety of blocking CGRP remains a concern. CGRP and its receptor are present throughout the vasculature and in the peripheral and central nervous system. In addition to its role in cranial nociception, CGRP is a potent arterial vasodilator. Potential safety concerns include loss of vasodilation during ischemic events, difficulties with wound healing, problems with gastrointestinal motility and mucosal integrity, and dysregulation of pituitary function.[5] While these issues have not been demonstrated in clinical trials, long-term use of these drugs and use in patients with significant medical comorbidities have not yet been studied.

There are no data on the safety of CGRP blockade in pregnancy. In pregnancy, levels of CGRP increase. CGRP levels are lower in women with preeclampsia than in women with normotensive pregnancies, suggesting that CGRP blockade during pregnancy might be harmful.[6] This is a concern for a therapy aimed at a disease most prevalent in women during childbearing years. With many pregnancies unplanned, the long half-life of these drugs may prove to be a disadvantage. Preclinical data[7] have not shown fetal abnormalities or problems with organogenesis when CGRP antagonists were given during pregnancy in animal models. Data on humans are not yet available.

With these concerns, clinicians will need to determine the appropriate place for CGRP antagonists in practice. These medications should be avoided in pregnant women or in women of childbearing potential not using contraception. They should be used with caution in patients with significant risk of ischemic cardiovascular or cerebrovascular disease. Patients should be advised of the potential risks of CGRP block-

ade if they have gastrointestinal disease or are planning surgery.

The CGRP antagonists are a welcome addition, having many of the properties that we desire for migraine prophylaxis. But as with any new class of medication, we need to be mindful of the potential safety risks and risks to the developing fetus.

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GERD: A practical approach

ABSTRACT

Gastroesophageal reflux disease (GERD) is mainly a clinical diagnosis based on typical symptoms of heartburn and acid regurgitation. Current guidelines indicate that patients with typical symptoms should first try a proton pump inhibitor (PPI). If reflux symptoms persist after 8 weeks on a PPI, endoscopy of the esophagus is recommended, with biopsies taken to rule out eosinophilic esophagitis. This review discusses the evidence for different medical, endoscopic, and surgical therapies and presents a management algorithm.

KEY POINTS

The diagnosis of GERD is mainly symptom-based and often does not require endoscopic confirmation.

Endoscopy is warranted in patients with red-flag symptoms such as dysphagia, anemia, weight loss, bleeding, and recurrent vomiting.

PPIs are the first-line medical therapy. Histamine 2 receptor antagonists are mainly used to treat breakthrough nocturnal symptoms.

Endoscopic and surgical options exist but are pursued only if medical therapy fails.

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Gastroesophageal reflux disease (GERD) is common, accounting for more than 5.6 million physician visits each year.[1] From 10% to 20% of adults in Western countries and nearly 5% of those in Asia experience GERD symptoms at least weekly.[2] The prevalence of GERD symptoms is increasing by about 4% per year, in parallel with increases in obesity rates and reduction in prevalence of *Helicobacter pylori* over the past several decades.[3] However, patients may not have symptoms of GERD even if they have objective evidence of it such as erosive esophagitis or Barrett esophagus.[4]

In 2015, the total direct economic impact of GERD and its complications was estimated to be over $18 billion, with use of proton pump inhibitors (PPIs) accounting for $12.4 billion, while the indirect costs driven by decreased work productivity were as much as $75 billion.[1,5]

TROUBLESOME SYMPTOMS, COMPLICATIONS

An international consensus group has defined GERD as a condition that develops when reflux of stomach contents causes troublesome symptoms with or without complications.[6] Typical symptoms that lead to the diagnosis of GERD are regurgitation and heartburn. As much as 16% of the US population complains of regurgitation, and 6% report clinically troublesome heartburn.[7] However, while these symptoms are specific for the disease, they are insensitive markers of reflux.

GERD symptoms can worsen with lying recumbent, especially after meals.

Of note, dysphagia can be a symptom of uncomplicated GERD, but its presence warrants more intensive examination and potential in-

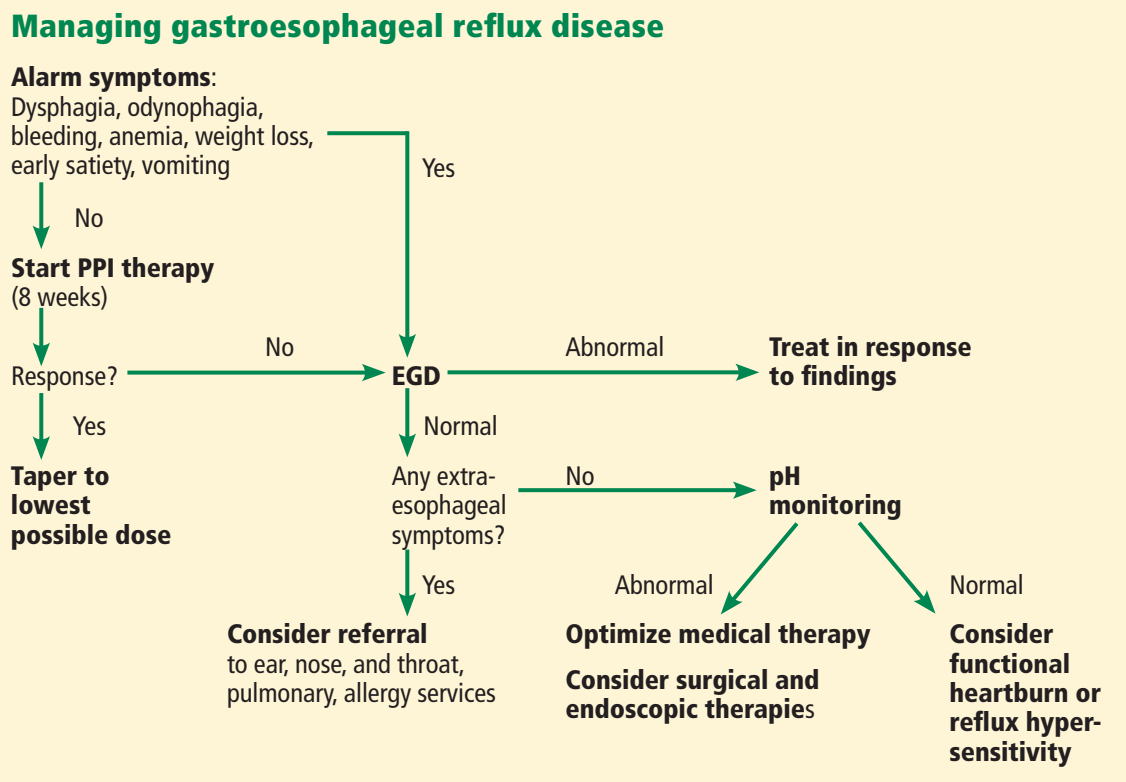


Figure 1. Approach to gastroesophageal reflux disease (PPI = proton pump inhibitor, EGD = esophagogastroduodenoscopy).

In patients with chest pain, rule out heart disease before considering a diagnosis of GERD

tervention, as it can be caused by strictures, rings, malignancy, or esophageal dysmotility.

Chest pain is another symptom often associated with GERD, but a cardiac cause should be considered and ruled out before GERD is considered.

Other symptoms of GERD include dyspepsia, nausea, bloating, sore throat, globus sensation, and epigastric pain.

A systematic review discovered that symptoms of GERD are less frequent in the elderly.[8] However, on average, the severity of disease in the elderly was found to be greater than that in younger patients. Therefore, it was concluded that while the prevalence of documented GERD in older patients is less than that in younger patients, the actual rate of GERD is likely similar.

A subset of patients has extraesophageal symptoms of GERD such as asthma, laryngitis, pharyngitis, chronic cough, sinusitis, idiopathic pulmonary fibrosis, dental erosions, and recurrent otitis media.[6]

PATHOPHYSIOLOGY

Since GERD was first described in 1879 by Heinrich Quincke, our understanding of its pathophysiology has slowly expanded and evolved.[9] Factors now known to contribute to GERD include:

- Transient lower esophageal sphincter (LES) relaxation
- Sliding hiatal hernia
- Low LES pressure
- Acid pocket development due to poor mixing of acid with chyme in the proximal stomach
- Increased gastroesophageal junction distensibility
- Obesity
- Delayed gastric emptying.[9]

Most symptoms are caused by acid reflux, but if symptoms persist on PPI therapy, they are likely due to either weakly acidic or weakly alkaline secretions.[10,11]

The distance up the esophagus that the reflux travels also plays a role in the symptoms of GERD. Acid reflux episodes that extend

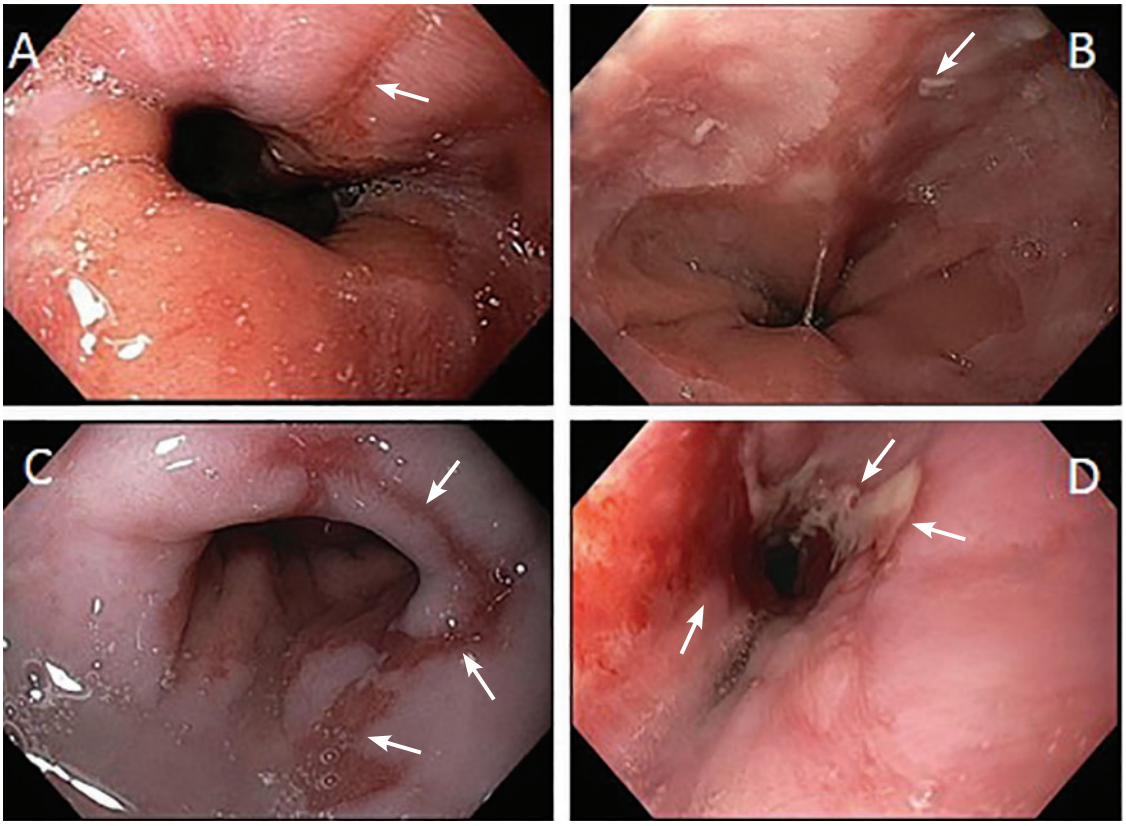


Figure 2. Endoscopic views of esophagitis grades. (A) Grade A—1 or more mucosal breaks (arrow) no longer than 5 mm that do not extend between the tops of two mucosal folds. (B) Grade B—1 or more mucosal breaks (arrow) longer than 5 mm that do not extend between the tops of two mucosal folds. (C) Grade C—1 or more mucosal breaks (arrows) that are continuous between the tops of 2 or more mucosal folds, but involve less than 75% of the circumference. (D) Grade D—1 or more mucosal breaks (arrows) that involve at least 75% of the esophageal circumference.

higher into the esophagus are associated with worse symptoms, regardless of the acidity of the bolus.[12,13]

Trimble et al[13] found that patients with GERD have enhanced esophageal sensation and likely have heightened perceptions of normal nonacidic reflux events due to lower sensory thresholds. Another hypothesis is that sustained esophageal longitudinal muscle contractions may lead to transient ischemia of the esophageal wall, resulting in GERD symptoms in some patients.[14]

DIAGNOSIS AND MANAGEMENT

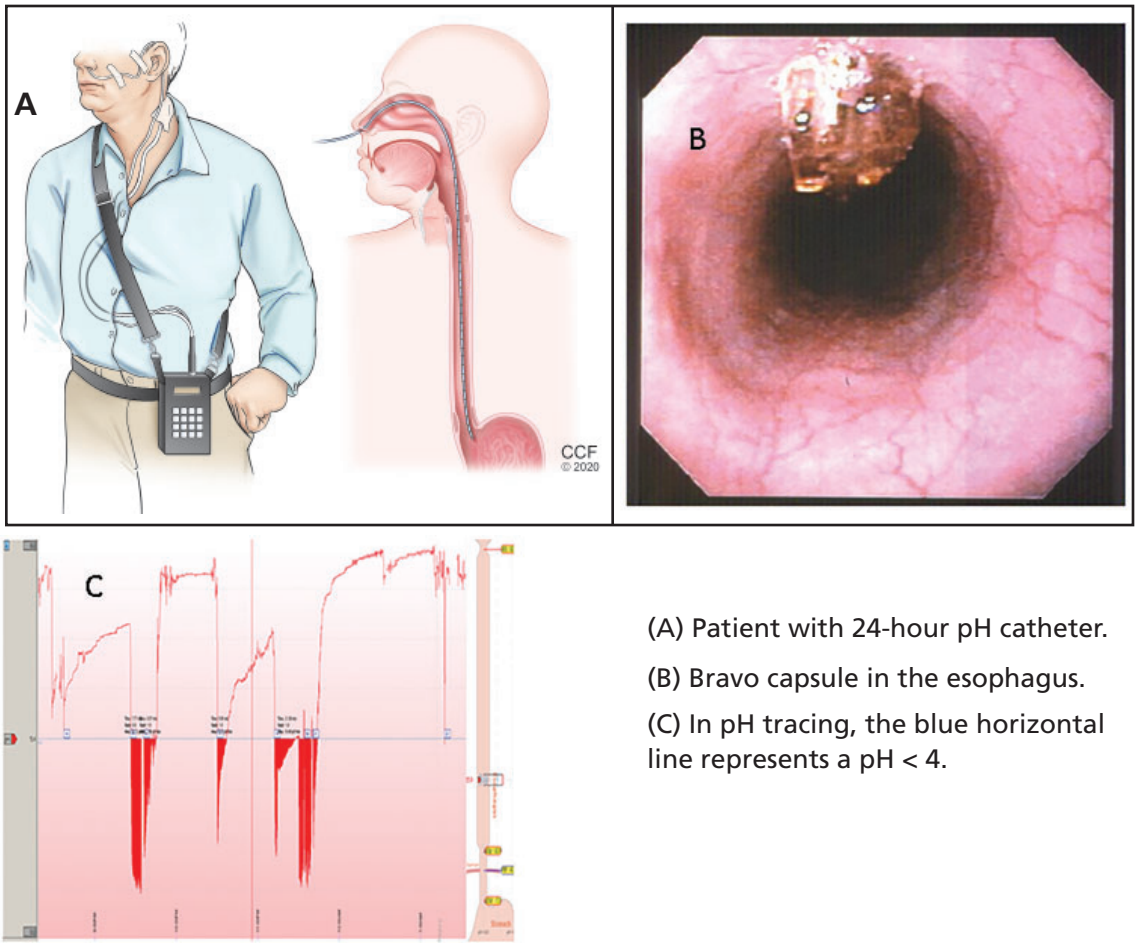
GERD is mainly a clinical diagnosis based on typical symptoms. Its diagnosis and management are summarized in **Figure 1**.

If no alarm symptoms, first try a PPI

Current guidelines indicate that patients with typical symptoms should first be given a trial of PPI treatment.[15] However, patients with alarm symptoms including dysphagia, anemia, weight loss, bleeding, and recurrent vomiting should proceed directly to upper endoscopy.

Alarm symptoms include dysphagia, anemia, weight loss, bleeding, and recurrent vomiting

There are limitations to this approach: a meta-analysis showed that a short course of PPI therapy has a 78% sensitivity and 54% specificity in accurately diagnosing GERD.[16] In general, if typical symptoms resolve with an initial trial of a PPI, GERD should be diagnosed and the patient should continue taking a PPI daily.



(A) Patient with 24-hour pH catheter.

(B) Bravo capsule in the esophagus.

(C) In pH tracing, the blue horizontal line represents a pH < 4.

Figure 3.

Give PPIs 30–60 minutes before a meal for optimal pH control

Heartburn? Or heart attack?

In patients with chest pain, a cardiac condition should be ruled out before considering GERD. In one study,[17] patients with noncardiac chest pain and endoscopic evidence of GERD had a significant response to PPI therapy, while those without endoscopic evidence had little or no response to therapy.[17]

Upper endoscopy

Endoscopy should be performed in any patient with the alarm symptoms described above, and also in patients whose symptoms do not respond to a PPI.

Abnormal endoscopic findings in GERD may include erosive esophagitis, strictures, and Barrett esophagus. However, many patients with GERD have normal findings on endoscopy. In 1999, the Los Angeles classification system was published and is now the standard method for classifying esophagitis (**Figure 2**).[18,19] In addition, during endoscopy, biopsy samples from the esophagus should be obtained to rule out eosinophilic esophagitis.

Esophageal pH monitoring

Esophageal pH monitoring is indicated in patients with persistent symptoms and normal findings on endoscopy before surgical or endoscopic interventions are considered. Esophageal pH monitoring can be done using a 24-hour transnasal pH or pH-impedance catheter or a 48-hour Bravo wireless capsule.

In clinical practice, pH testing is performed with the patient off PPI therapy when there is low clinical suspicion for GERD, whereas pH-impedance testing is performed while the patient is still on PPI therapy when there is higher likelihood of GERD, to evaluate refractory symptoms (**Figure 3**).[20]

Barium esophagography is not indicated in the workup of reflux disease as it has poor sensitivity and specificity for GERD.

TREATMENT: LIFESTYLE, DRUG THERAPY, SURGERY

Lifestyle modifications

Lifestyle modifications are the first option for most patients.

Weight loss can help reduce and eliminate GERD symptoms. A prospective cohort study found that 81% of obese patients who completed a structured weight loss program had a reduction in symptoms, and 65% had complete resolution of symptoms.[21] Another large retrospective study, with more than 15,000 patients, showed an association between improvement in GERD symptoms and reduction in body mass index (BMI) in obese patients who lost at least 2 kg/m^2 in BMI (odds ratio 2.34).[22]

Diet, smoking cessation, alcohol moderation. Numerous studies have aimed to find foods that exacerbate reflux symptoms. Historically, patients have been advised to avoid smoking, chocolate, carbonated beverages, spicy food, fatty food, alcohol, and large meals. Thus far, no study has found improvement in GERD symptoms with cessation of either smoking or alcohol. In terms of food consumption, no food has been conclusively linked with increased GERD symptoms. No consistent associations have been established between GERD symptoms and fatty food, spicy food, coffee, carbonated beverages, chocolate, citrus, or mint.

Sleep position. Other studies have promoted elevating the head of the bed, sleeping in the left decubitus position, and, in those with nocturnal GERD symptoms, avoiding meals in the 2 to 3 hours before bedtime.[23,24] A sleep positional therapy device has been shown to reduce acid exposure times and improve nocturnal reflux symptoms.[25,26] This device places the user in the left decubitus position at an incline and has been an effective tool for those with nocturnal symptoms.

Drug therapy

If lifestyle interventions fail, drug treatment options are PPIs, histamine 2 receptor antagonists (H2RAs), and antacids.

PPIs are considered the therapy of choice for symptomatic relief and healing of erosive esophagitis. Compared with H2RAs, PPIs have been shown to provide improved healing rates and fewer relapses in patients with erosive esophagitis.[27] To date, no study has shown a major difference in symptom control between the multiple PPIs. However, esomeprazole was shown, in a meta-analysis comparing it with other PPIs, to increase the probability of healing erosive esophagitis at 4 and 8 weeks.[28]

PPIs inhibit gastric acid secretion by inactivating the hydrogen potassium ATPase molecules of the parietal cell. Optimal acid suppression occurs when the proton pumps are activated as the parietal cell is maximally stimulated after a meal.

All PPIs should be taken 30 to 60 minutes before a meal for optimal pH control except dexlansoprazole, which employs dual delayed-release technology leading to sustained plasma drug concentrations; it can therefore be taken at any time of day. For patients with daytime symptoms, a PPI should be taken once daily in the morning, and for nighttime symptoms, the dose should be taken in the evening.

After the initial 8-week course of therapy, most patients with GERD should attempt to take the lowest dose required to manage their symptoms. For some, this could mean only taking the medication when symptoms arise. However, patients with severe erosive esophagitis (grade C or D), Barrett esophagus, and peptic strictures need long-term PPI treatment.

If lifestyle interventions fail, drug treatment options are PPIs, H2RAs, and antacids

Adverse effects of PPIs. All patients need to be counseled about possible long-term adverse effects of PPIs.[29] However, a recent randomized controlled trial found no association of PPIs with any adverse event when used for 3 years, with the possible exception of an increased risk of enteric infections.[30]

Vaezi et al[29] reviewed the complications of PPI therapy and listed the relative risk and absolute excess risk in randomized controlled trials. From their data, we have calculated the number needed to harm, ie, the number of patients who would need to be treated for 1 year to observe 1 adverse effect:

- Chronic kidney disease, 333–1,000
- Dementia, 67–1,429

- Bone fracture, 200–1,000
- *Campylobacter* or *Salmonella* infection, 500–3,333
- Spontaneous bacterial peritonitis (in patients with cirrhosis and ascites), 6–33
- *Clostridioides difficile* infection, 1,111–no association
- Micronutrient deficiencies, 250–333.

The authors found no association between long-term PPI use and the following:

- Myocardial infarction
- Small intestinal bacterial overgrowth
- Pneumonia
- Gastrointestinal malignancies.

Compared with earlier drugs, PPIs have been consistently shown to be superior at healing erosive esophagitis and relieving symptoms. PPIs can maintain intragastric pH higher than 4 for 15 to 21 hours daily, compared with the 8 hours that H2RAs can achieve.[31] In a randomized trial, endoscopic remission of erosive esophagitis was found in 80.2% of those taking omeprazole 20 mg daily vs 39.4% in those taking ranitidine 150 mg daily.[27]

H2RAs appear useful in GERD for controlling nocturnal acid breakthrough. However, tachyphylaxis to these drugs develops rapidly, and they may therefore have a role only if used intermittently.[32]

Antacids, especially when combined with alginate preparations, are effective for reducing postprandial esophageal acid exposure.[33]

If first-line therapy fails

PPIs have immensely changed the landscape of treatment for GERD since their introduction, but up to 40% of patients with GERD find partial or no symptom relief with first-line therapies.[34] In these nonresponders, it is important to determine compliance with PPIs, specifically the timing in relation to meals.

An 8-week course of PPI is needed to allow for healing; patients should not be considered nonresponders until after this, unless alarm symptoms are present

An 8-week course of therapy is needed to allow for healing, and patients should not be considered nonresponders until after this period unless alarm symptoms are present. For these patients, upper endoscopy should be performed within 2 weeks. For those without alarm symptoms but continued reflux in spite of therapy, endoscopy should be performed after 8 weeks, with biopsies of the esophagus to evaluate for eosinophilic esophagitis.

Esophageal impedance and pH testing are performed on these non- and partial responders while off PPIs to determine if there is persistent acidic or nonacidic reflux.

If results of pH and impedance testing are normal, the most common causes of continued symptoms are reflux hypersensitivity and functional heartburn. Reflux hypersensitivity is a heightened response to nonpathologic reflux, while functional heartburn is the presence of symptoms without any evidence of abnormal exposure. These patients should be reassured that their condition is benign, and they can be started on a pain modulator such as a selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant.

If PPIs give partial relief, they should be continued, but they can be stopped for patients who have no response to them.

In patients found to have nonacid reflux, a trial of baclofen should be offered, as it has been shown to reduce the rate of lower esophageal sphincter transient relaxations.[35]

Alternative and investigational therapies

Alternative therapies are being investigated, but none have consistently shown significant benefits over placebo.

Therapies under investigation include reflux inhibitors, prokinetics, acupuncture, and hypnotherapy. Prokinetics, including metoclopramide and domperidone, have shown benefit in select patients with GERD but have been limited in their use due to associated central nervous system side effects and QT prolongation. New medical treatments for GERD on the horizon include potassium competitive acid blockers (vonaprazan) and bile acid sequestrant (IW3718) that binds to bile in the refluxate.

SURGICAL THERAPIES

Nissen fundoplication, first performed by Dr. Rudolph Nissen in 1955, gained popularity in the 1970s and is now the most widely performed antireflux surgery. It involves reducing the hiatal hernia and wrapping the gastric fundus partially or completely around the lower esophagus to restore the LES barrier.

Indications for the procedure are presence of a large hiatal hernia, reflux esophagitis or GERD symptoms refractory to medical therapy, or adverse effects of medical therapy.

A trial comparing laparoscopic fundoplication with esomeprazole therapy found similar remission rates after 3 years and a higher rate with esomeprazole after 5 years.[36] While esomeprazole was associated with more symptoms of reflux compared with fundoplication, patients who underwent this surgery reported higher rates of dysphagia, flatulence, and bloating.

Antireflux surgery should be recommended with caution, as it can have severe side effects such as dysphagia, gas bloat syndrome, and flatulence and the intended effect may only be temporary, as up to 60% of patients will require antireflux medications regularly in the decade afterward.[37] Esophageal manometry should be obtained before surgery to screen for esophageal aperistalsis, as this is an absolute contraindication to the procedure. Furthermore, manometry will exclude other motility disorders that can present similarly to GERD as discussed. Of note, antireflux surgery is not recommended in PPI nonresponders.[15]

The Linx procedure (magnetic sphincter augmentation; Torax Medical Inc., Shoreview, MN) is a minimally invasive alternative. It involves laparoscopic insertion of a band of magnetic beads around the LES, which allows passage of food and then closes to prevent acid reflux. The procedure is associated with improvement in symptom scores and reduced need for PPI therapy but not with consistent reduction in esophageal acid exposure.[38]

Roux-en-Y gastric bypass is a surgical option for morbidly obese patients. A prospective study with 53 patients showed an improvement in GERD symptoms, reflux esophagitis, and esophageal acid exposure for more than 3 years following bypass.[39]

ENDOSCOPIC THERAPIES

Alternatively, several endoscopic treatments for GERD have been developed over the last 2 decades.[40] These include:

- Transoral incisionless fundoplication (TIF) using the Esophyx device (EndoGastric Solutions, Redmond, WA)
- Radiofrequency energy delivery to the LES (the Stretta procedure; Respiratory Technology Corporation, Houston, TX)
- Endoscopic anterior fundoplication using the Medigus ultrasonic surgical endostapler (Medigus, Omer, Israel).

Of these, the first 2 have the most evidence.

TIF involves creation of a partial gastric wrap around the lower esophagus with an Esophyx device mounted on the endoscope. TIF is associated with symptom control and PPI reduction or cessation for at least 6 years and is a viable option for a select group of GERD patients with small hiatal hernias and preserved esophageal function.

A large randomized trial comparing TIF with PPIs showed symptomatic control in 67% vs 45% patients. TIF was associated with a reduction in esophageal acid exposure time from 9.3% to 6.4% and DeMeester score reduction from 33.6 to 23.9.[41]

In 2018, a meta-analysis was performed to compare TIF with Nissen fundoplication, a sham procedure, and PPIs.[42] TIF was associated with a larger increase in quality of life measures, while Nissen fundoplication had a greater ability to improve physiologic parameters associated with GERD including LES pressure and the percentage of time the pH was less than 4.

The Stretta device was developed in 2000 and works by delivering thermal energy to the LES, which is postulated to increase sphincter thickness through scar tissue deposition, thereby reducing reflux. However in a meta-analysis of randomized controlled trials, Stretta treatment did not reduce percentage of time when pH is less than 4 or increase LES pressure or ability to stop PPIs.[43]

Antireflux surgery should be recommended with caution, as it can have severe side effects

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ACC/AHA lipid guidelines: Personalized care to prevent cardiovascular disease

ABSTRACT

The 2018 and 2019 guidelines from the American College of Cardiology and American Heart Association reflect the complexity of individualized cholesterol management. The documents address more detailed risk assessment, newer nonstatin cholesterol-lowering drugs, special attention to patient subgroups, and consideration of the value of therapy, all with the aim of creating personalized treatment plans for each patient. Overall, the guidelines recommend shared decision-making to meet the individual needs of each patient.

KEY POINTS

- Emphasize a heart-healthy lifestyle for all patients across their life span.
- A discussion with the patient is the cornerstone of shared decision-making and should include the patient's 10-year risk of atherosclerotic cardiovascular disease according to the Pooled Cohort Equations, as well as risk-enhancing factors.
- Statins are the foundation of pharmacologic therapy, to which ezetimibe and, if necessary, a proprotein convertase subtilisin/kexin type 9 inhibitor can be added to achieve lipid goals.
- Special treatment algorithms are outlined for certain patient subgroups, such as certain ethnic groups, adults with chronic kidney disease, those with human immunodeficiency virus infection, and women.

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The American College of Cardiology (ACC) and American Heart Association (AHA) Task Force on Clinical Practice Guidelines published its most recent guidelines for cholesterol management in 2018,[1] and followed it with guidelines for primary prevention of cardiovascular disease in 2019.[2]

The new guidelines have updated patient risk assessment and treatment options in primary and secondary prevention. In primary prevention, the guidelines provide clarity regarding decision-making in patients at intermediate risk of atherosclerotic cardiovascular disease ("intermediate" meaning a 7.5%–20% 10-year risk).

In secondary prevention, the guidelines group patients according to their risk (high risk vs very high risk) and incorporate new nonstatin therapies as add-on, evidence-based treatment options when low-density lipoprotein (LDL-C) remains above the 70 mg/dL threshold. The guidelines also discuss the cost and value of each treatment option for each treatment group.

Here, we review the recent guidelines and discuss the most important changes for clinical practice.[1–3]

CLASSES OF RECOMMENDATION, LEVELS OF EVIDENCE

The guidelines award classes of recommendations, signifying the certainty of benefit compared with the estimated risk and the strength of the recommendation.

- Class I (strong)—benefit greatly exceeds risk; treatment is recommended
- Class IIa (moderate)—benefit exceeds risk; treatment is reasonable
- Class IIb (weak)—benefit equals or exceeds risk; treatment might be reasonable
- Class III: No benefit (moderate)—benefit equals risk; treatment is not recommended
- Class III: Harm (strong)—risk exceeds benefit.

The guidelines also award levels of evidence to their recommendations:

- Level A—high-quality evidence
- Level B-R—moderate-quality evidence from randomized controlled trials
- Level B-NR—moderate quality evidence from nonrandomized trials
- Level C-LD—limited data
- Level C-EO—expert opinion.

STATINS AND OTHER OPTIONS

In addition to a heart-healthy lifestyle, statins are the foundation of lipid management

In addition to a heart-healthy lifestyle (which should be encouraged for all patients across their life course), statins are the foundation of lipid management. Statin therapy is divided into 3 categories of intensity:

High-intensity, aiming for at least a 50% reduction in LDL-C. Examples:

- Atorvastatin 40–80 mg daily
- Rosuvastatin 20–40 mg daily.

Moderate-intensity, aiming at a 30% to 49% reduction in LDL-C. Examples:

- Atorvastatin 10–20 mg
- Fluvastatin 80 mg daily
- Lovastatin 40–80 mg
- Pitavastatin 1–4 mg daily
- Pravastatin 40–80 mg daily
- Rosuvastatin 5–10 mg
- Simvastatin 20–40 mg daily.

Low-intensity, aiming at a LDL-C reduction of less than 30%. Examples:

- Fluvastatin 20–40 mg daily
- Lovastatin 20 mg daily
- Pravastatin 10–20 mg daily
- Simvastatin 10 mg daily.

Nonstatin drugs

The nonstatin LDL-lowering drugs such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can be added to statin therapy, as recent randomized clinical trials found them to improve cardiovascular outcomes in patients with atherosclerotic cardiovascular disease.[4–7]

Ezetimibe decreases cholesterol absorption and consequently lowers LDL-C levels by about 20%. A large randomized trial in patients who recently had acute coronary syndromes showed that ezetimibe modestly reduced cardiovascular risk over 7 years of follow-up when added to their regimen of moderate-intensity statin therapy.[4,5]

PCSK9 inhibitors lower LDL-C by 50% to 60% by binding to PCSK9, inhibiting labeling of LDL receptors for degradation, thus prolonging LDL receptor activity at the cell membrane. Several trials showed that PCSK9 inhibitors reduce cardiovascular risk in patients with stable atherosclerotic cardiovascular disease or recent acute coronary syndromes who are already on moderate- or high-intensity statin therapy.[4,6,7]

PRIMARY PREVENTION

The new guidelines advocate a multifaceted approach to primary prevention of atherosclerotic cardiovascular disease through cholesterol management. As the risk due to high cholesterol levels is cumulative over the life span, the guidelines encourage lifestyle therapy for primary prevention at all ages and in all patient categories. Additionally, they outline decision algorithms to create a therapy that suits the individual needs of each patient (**Table 1**).

Statin benefit groups

The new guidelines keep the same statin benefit groups defined in the previous (2013) ACC/AHA guidelines.[8] Statin therapy recommendations are specifically given for the following groups:

Adults with severe hypercholesterolemia

If a patient age 20 to 75 has LDL-C levels of 190 mg/dL or higher, you do not need to cal-

TABLE 1

Primary preventive therapy in different patient subgroups

Severe hypercholesterolemia

Initiate high-intensity statin therapy immediately, irrespective of 10-year risk of atherosclerotic cardiovascular disease (ASCVD)

Adding ezetimibe is reasonable if low-density lipoprotein cholesterol (LDL-C) is ≥ 190 mg/dL or there is less than 50% reduction in LDL-C levels with maximal tolerated statins

Consider adding a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor in patients with heterozygous familial hypercholesterolemia or with LDL-C ≥ 220 mg/dL with maximally tolerated statins and ezetimibe

Diabetes mellitus in adults

Irrespective of 10-year ASCVD risk, initiate moderate-intensity statin therapy immediately

Aim for reduction of LDL-C by at least 50%

Adults age 40–75 with LDL-C levels 70–189 mg/dL

Before starting statins, engage in clinician-patient risk discussion, evaluating risk factors, 10-year ASCVD risk, risk enhancers (Table 2), patient's preference, costs, and adverse effects of statins

Use coronary artery calcium score to guide decision if risk is still unclear

Children and young adults

Assess risk factors in children age 0–19 years

Initiate statin therapy if patients have severely abnormal lipid profiles or clinical presentation of familial hypercholesterolemia and cannot be treated by 3 months lifestyle therapy

Ethnicity

Review racial and ethnic features that can influence ASCVD risk and intensity of treatment (Table 3)

Adults with chronic kidney disease

Starting moderate-intensity statin alone or in combination with ezetimibe can be useful

Adults with chronic inflammatory disorders and HIV

In adults age 40–75 with LDL-C 70–189 mg/dL with a 10-year ASCVD risk of over 5%, discuss moderate- or high-intensity statin therapy

Women

History of premature menopause (before age 40) or history of pregnancy-related disorders (hypertension, preeclampsia, gestational diabetes, small-for-gestational-age infants, and preterm deliveries) are risk-enhancing factors and should influence lifestyle and pharmacologic therapy decisions

Based on information in references 1 and 2.

culate the 10-year risk. Rather, high-intensity statin therapy should be started right away to lower LDL-C by at least 50%.

If the LDL-C level remains higher than 100 mg/dL with maximal tolerated statin therapy, ezetimibe can be added (class IIb recommendation, ie, weak recommendation, but benefit exceeds risk).

If the patient has a risk factor for atherosclerotic cardiovascular disease and his or her LDL-C level remains higher than 100 mg/dL even after adding ezetimibe to the statin, a PCSK9 inhibitor may be considered.

Adults with diabetes mellitus

Moderate-intensity statin therapy is indicated in adults with diabetes, regardless of their 10-

If a patient age 20 to 75 has LDL-C ≥ 190 mg/dL, start high-intensity statin therapy right away

TABLE 2

Risk enhancers

Family history of premature atherosclerotic cardiovascular disease (in men age < 55 or in women age < 65)

Primary hypercholesterolemia
- Low-density lipoprotein cholesterol 160–180 mg/dL
- Non-high-density lipoprotein cholesterol 190–219 mg/dL

Metabolic syndrome: 3 or more of the following:
- Increased waist circumference by ethnically appropriate cut points
- Fasting triglyceride level > 150 mg/dL
- High blood pressure
- Elevated glucose
- Low high-density lipoprotein cholesterol (< 40 mg/dL in men, < 50 mg/dL in women)
- Chronic kidney disease (estimated glomerular filtration rate 15–59 mL/min/1.73 m^2)

Chronic inflammatory conditions (eg, psoriasis, rheumatoid arthritis, lupus, human immunodeficiency virus infection, acquired immunodeficiency syndrome)

History of premature menopause (age < 40) and history of pregnancy-associated conditions that increase later risk of atherosclerotic cardiovascular disease such as preeclampsia

High-risk ethnicity or race (eg, South Asian)

Lipids or biomarkers associated with elevated risk
- Persistently elevated hypertriglyceridemia (≥ 175 mg/dL nonfasting)
- Elevated high-sensitivity C-reactive protein (≥ 2.0 mg/L)
- Elevated lipoprotein (a) (≥ 50 mg/dL or ≥ 125 nmol/L)
  (relative indication for measurement: family history of premature atherosclerotic cardiovascular disease)
- Elevated apolipoprotein B (≥ 130 mg/dL)
  (relative indication for measurement: triglycerides ≥ 200 mg/dL)
- Ankle-brachial index < 0.9

Reprinted from Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019; 73(24):3168–3209. doi:10.1016/j.jacc.2018.11.002, with permission from Elsevier.

year risk. However, it is reasonable to start high-intensity statin treatment if the patient also has multiple risk factors. Similarly, the 2019 guidelines of the American Diabetes Association advocate high-intensity statin therapy in patients who have additional risk factors or a 10-year risk of an atherosclerotic cardiovascular disease event higher than 20%.[9]

Adults age 40–75, without diabetes, with LDL-C levels 70–189 mg/dL

In this group, the guidelines say to use a risk calculator to determine if the patient needs lipid-lowering medication.

Use the Pooled Cohort Equations, which are based on age, sex, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and whether the patient is receiving treatment for high blood pressure, has diabetes, or smokes (class I recommendation). This tool gives an estimate of the patient's risk of a cardiovascular event within the next 10 years, which the guidelines categorize as follows:

- Low risk: < 5%
- Borderline risk: 5%–7.5%
- Intermediate risk: 7.5%–20%
- High risk: > 20%.

The addition of the "borderline" group (only the 2018 guidelines specifically mention and explain primary preventive treatment in the "borderline" risk category) reflects the uncertainty of treatment strategies for patients at intermediate risk, while treatment recommendations for high- and low-risk groups are well established.[10]

The US Preventive Services Task Force[11] recommends statins as primary preventive therapy for adults age 40 to 75 with no history of cardiovascular disease, 1 or more risk factors, and a calculated 10-year risk of 10% or greater (grade A recommendation—there is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial). However, it gives a lower recommendation for low-intensity statin therapy for people with a lower 10-year risk, ie, between 7.5% and 10%. (grade C—they recommend selectively offering or providing it to individual patients based on professional judgment and patient preferences; there is at least moderate certainty that the net benefit is small).

Discuss the risk with the patient. After evaluating 10-year risk, clinicians should discuss it with the patient before initiating statin therapy. Risk discussions are the cornerstone of the shared decision-making process.

Review risk-enhancing factors. During the risk discussion, one should review not only the patient's 10-year risk according to the Pooled Cohort Equations, but also risk factors not included in the Pooled Cohort Equations. The guidelines describe these as "risk-enhancing factors" (**Table 2**).

TABLE 3

Racial and ethnic differences in atherosclerotic cardiovascular disease risk and coronary artery calcium scores

	Asian	Hispanic and Latino	Black, Native American, and Alaskan
ASCVD risk	South Asians[a] have higher ASCVD risk than East Asians[b]	Individuals from Puerto Rico have the highest ASCVD risk[15] CVD mortality is higher in Hispanics than whites	Increased ASCVD risk[14] Greater rates of CHD events compared with non-Hispanic white populations[17]
CAC score	South Asian men have similar CAC burden to non-Hispanic white men, but higher CAC compared with blacks and Latinos[18] South Asian women have similar CAC scores compared with other ethnic and racial groups[18]	Lower CAC burden compared with Asian-Americans and non-Hispanic whites[16]	Lower CAC scores compared with whites and Hispanics[16]

[a]Individuals from Bangladesh, India, Nepal, Pakistan, and Sri Lanka make up most of the South Asian group.
[b]Individuals from Japan, Korea, and China make up most of of the East Asian group.

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease

For patients at borderline or intermediate risk, risk-enhancing factors are particularly useful to review during the risk discussion, and the guidelines give especially detailed instructions in the decision algorithm for patients in these groups. This acknowledges the criticisms of the previous 2013 guidelines that they led to overprescription of statins due to many patients fitting the intermediate-risk category, and called for additional risk stratification tools.[12]

By evaluating risk-enhancing factors, patients' risk can be revised and preventive treatment prescribed only to those at higher risk, while avoiding overprescription for those at low risk. The guidelines give a class IIA recommendation to starting or intensifying statin therapy if risk-enhancing factors are present in borderline- and intermediate-risk adults.

In unclear cases, consider coronary artery calcium measurement. If, in view of this evidence, the patient and clinician favor statin therapy, statins should be initiated at a moderate intensity to lower LDL-C by 30% to 49%. However, if the risk decision is still unclear even after reviewing the Pooled Cohort Equations and risk enhancers, the coronary artery calcium score can be added to guide decisions.

A great body of research indicates that the coronary artery calcium score is an effective tool to stratify risk and improve risk estimation.[13] If the score is 1 to 99, statin therapy is suggested, especially in patients older than 55. If the score is 100 or higher or patients are in the 75th percentile or higher for coronary artery calcium, statin therapy is clearly indicated. If the score is 0, statin therapy may be safely withheld unless the patient smokes or has premature cardiovascular disease.

Therapy recommendations for patients on either extreme of 10-year risk are more straightforward.

For patients at low risk (< 5%), clinicians should still emphasize lifestyle changes to reduce risk modifiable factors.

For patients at high risk (> 20%), clinicians should clearly recommend statin therapy aimed at lowering LDL-C by at least 50%.

Physicians should use additional risk-stratification tools for patients at borderline and intermediate risk

Primary prevention in children and young adults

The guidelines pay special attention to cholesterol management in subgroups. The most important updates are specific recommenda-

tions for children and young adults.

The guidelines acknowledge that atherosclerosis is a lifelong process and that the effects of high cholesterol levels accumulate across an entire lifetime. This is why, unlike previous guidelines, the 2018/2019 guidelines recommend primary preventive therapy for children and young adults.

Risk factor assessment and identification of family history of hypercholesterolemia or inherited dyslipidemia should already occur for children age 0 to 19 years. Also, if children have severely elevated lipid levels related to obesity, intensive lifestyle therapy should be implemented.

Primary prevention for other populations at risk

The current recommendations also make specific recommendations for cholesterol treatment algorithms for specific patient subgroups, in which treatment decisions were previously unclear.

Primary prevention: Ethnicity

The ACC/AHA guidelines state in a class IIA recommendation that race and ethnicity influence the risk of atherosclerotic cardiovascular disease and the choice of treatment. Risk varies widely among and within ethnic groups, affecting treatment decisions (**Table 3**).[14–18] In particular, the guidelines point out that South Asian individuals have higher risk, as do those who identify as Native American or Alaskan native compared with non-Hispanic white populations.[14]

Black populations have higher rates of coronary heart disease even though they have lower coronary artery calcium scores

Socioeconomic status and acculturation level (extent of assimilation to the dominant culture—in this case American culture) can affect the burden of atherosclerotic cardiovascular disease. For instance, a cross-sectional study showed that acculturation was associated with higher cardiovascular risk in Hispanic participants.[15]

Moreover, ethnicity also affects other aspects of risk classification, such as coronary artery calcium scores. Studies suggest that ethnicity influences the pathobiologic processes of vessel atherogenesis.[19] Hispanic patients have a lower coronary artery calcium burden than Asian-Americans and non-Hispanic whites.[16] However, cardiovascular mortality rates are higher in Hispanics than in whites and Asians. Black populations also have higher rates of coronary heart disease even though they have lower coronary artery calcium scores compared with whites.[14,17] Variabilities in risk of atherosclerotic cardiovascular disease in different populations call for different clinical management of cholesterol levels.

The guidelines remark specifically on the heightened statin sensitivity of East Asian populations,[20] and suggest that Japanese patients might benefit from similar risk reductions with lower statin doses instead of the higher dosages used for other ethnic groups. A secondary prevention trial showed that moderate-intensity pitavastatin therapy was beneficial for Japanese individuals with clinically stable coronary artery disease.[21]

Metabolism of statins also seems to be affected by ethnicity. Higher rosuvastatin plasma levels were observed in Asian Indian, Chinese, Malay, and Japanese people than in white patients.[22] Thus, lower starting doses of rosuvastatin are recommended for these populations, and clinicians should be cautious when up-titrating rosuvastatin.

Primary prevention in adults with chronic kidney disease

Chronic kidney disease is a risk-enhancing factor. Moderate-intensity statin therapy in combination with ezetimibe can be useful in adults age 40 to 75 with chronic kidney disease who have greater than a 7.5% risk of atherosclerotic cardiovascular disease risk and are not treated with dialysis or kidney transplant (class of recommendation IIa). If patients are currently undergoing dialysis and already receiving a statin, it is reasonable to continue statin therapy despite potential decreased efficacy in this population.

Primary prevention in adults with chronic inflammatory disorders and HIV

Human immunodeficiency virus infection and other chronic inflammatory disorders are risk-enhancing factors. In a class IIA recommendation, the guidelines state that in this subgroup of patients, adults age 40 to 75 with LDL-C 70 to 189 mg/dL with a 10-year atherosclerotic cardiovascular disease risk of over 7.5%, moderate or high-intensity statin therapy should be discussed. In addition to evaluating risk factors, a fasting lipid profile

can be used to guide statin therapy. Before and 4 to 12 weeks after starting anti-inflammatory or antiretroviral therapy, fasting lipid profiles and atherosclerotic cardiovascular disease risk factors can be used to monitor lipid-lowering medications.

Primary prevention issues specific to women

The new guidelines identify the following conditions specific to women as risk-enhancing factors:

- Premature menopause (before age 40)
- Pregnancy-associated disorders such as hypertension, preeclampsia, gestational diabetes, and diabetes mellitus
- Infants small for gestational age
- Preterm deliveries.

The guidelines give a class I recommendation to intensively discussing lifestyle intervention and potential benefit of statin therapy in case of these conditions.

Women with these conditions could also benefit from additional risk-stratification tools like coronary artery calcium scoring to guide decisions about statin therapy. A cross-sectional study in 446 women suggest that earlier cardiovascular risk screening including coronary artery calcium scoring might benefit women with preterm deliveries.[23] Other studies showed that women with hypertensive disorders of pregnancy could benefit from earlier risk stratification through the coronary artery calcium score.[24]

Pregnant women should not take statins, however, even if they have severe hypercholesterolemia. This recommendation is based on animal data, in which teratogenic effects of statins in high doses and disruption of the cholesterol synthesis in the fetus were observed. However, recent evidence has not confirmed the teratogenic potential of statins.[25] Nevertheless, while new safety data are reassuring, suspension of statins is still advisable.[26]

The guidelines also give specific recommendations regarding statin therapy when planning or during pregnancy. Sexually active women on statin therapy are advised to use effective forms of contraception (class I recommendation). Women planning to become pregnant should stop statin therapy 1 to 2 months before pregnancy is attempted. If women become pregnant while using a statin, they should stop taking it as soon as pregnancy is discovered.

TABLE 4

Key points on secondary prevention[a]

Patient subgroup	Guideline recommendation
At very high risk[b]	If low-density lipoprotein cholesterol (LDL-C) levels are ≥ 70 mg/dL with the maximal tolerated statin therapy, it is reasonable to add ezetimibe
	If LDL-C level is ≥ 70 mg/dL on maximal tolerated statin and ezetimibe, it is reasonable to add a PCSK9 inhibitor
Not at very high risk	
Age ≤ 75	Goal is LDL-C reduction by 50%
	Use moderate-intensity statins if high-intensity statins are not tolerated
	If LDL-C ≥ 70 mg/dL on high-intensity statins, it is reasonable to add ezetimibe
Age > 75	Starting or continuing either moderate- or high-intensity statins is reasonable

[a]Secondary prevention refers to patients with clinical atherosclerotic cardiovascular disease (ASCVD), ie, those with a history of acute coronary syndrome, myocardial infarction, stable or unstable angina, arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease.
[b]Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (age ≥ 65, heterozygous familial hypercholesterolemia, history of coronary artery bypass surgery or percutaneous coronary intervention, diabetes mellitus, hypertension, chronic kidney disease, current smoking, persistently elevated LDL-C, or history of heart failure).

Based on information in reference 1.

SECONDARY PREVENTION: ATHEROSCLEROTIC DISEASE

High-intensity statin therapy is recommended for all patients with atherosclerotic cardiovascular disease, including acute coronary syndromes, myocardial infarction, stable or unstable angina, or with a history of coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease including aortic aneurysm, all of atherosclerotic origin.

The new guidelines recognize 2 phenotypes in secondary prevention: high risk and very high risk (**Table 4**). Very high risk in-

cludes a history of multiple major atherosclerotic cardiovascular disease events or 1 major event and multiple high-risk conditions.

The reduction in risk is proportional to the decrease of LDL-C levels. The authors also provide instructions on the use of nonstatin medications as part of secondary prevention. In patients with a very high risk and LDL-C levels higher than 70 mg/dL on maximal tolerated statin therapy, it is reasonable to add ezetimibe. Further, in patients at very high risk whose LDL-C level remains higher than 70 mg/dL on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable.

MONITORING RESPONSE TO LDL-C-LOWERING THERAPY

As in the last guidelines, the current ones suggest assessing adherence and percentage response after initiating or changing the dose of LDL-C-lowering medications and lifestyle changes, with repeat lipid measurements 4 to 12 weeks after therapy is started. This can be repeated every 3 to 12 months as needed.

Sexually active women on statin therapy should use effective forms of contraception

COST AND VALUE CONSIDERATIONS

The 2018 guidelines comment on the importance of considering the value of treatment in therapy decisions.[1]

The authors reviewed the cost-effectiveness of PCSK9 inhibitors using simulation models. These revealed that, to be cost-effective, the prices of PCSK9 inhibitors will have to be reduced by at least 70% in the United States from 2018 levels. However, since PCSK9 inhibitors have an incremental cost-effective ratio of $141,800 to $450,000 per quality-adjusted life-year added, the cost-effectiveness of these drugs improves only if used for very high-risk patients. This is reflected in the current guidelines, which suggest adding PCSK9 inhibitors only after maximal tolerated doses of statins and ezetimibe have not improved LDL-C levels significantly in very high-risk atherosclerotic cardiovascular disease patients or those with a family history of premature atherosclerotic cardiovascular disease. However, in mid-2018, when the 2018 guidelines were written, the US list prices of PCSK9 inhibitors were roughly $14,000 a year; now (in 2019) costs have been reduced to a little more than $6,000 a year.

STATIN ADVERSE EFFECTS

The new guidelines additionally address patients' and clinicians' fears of adverse effects of statins. They specifically recommend that the clinician-patient risk discussion also review possible adverse events and how these can be managed.

The guidelines advocate reviewing the net clinical benefit of statins and comparing the potential for reduction in risk of atherosclerotic cardiovascular disease with the risk of statin-associated side effects and drug interactions (class I recommendation, level of evidence A). Observed adverse effects include myalgias, elevation of creatine kinase, and transaminitis.[8]

When adverse effects occur, clinicians should lower the dose or dosing frequency, prescribe an alternate statin, or combine statin with nonstatin therapy. If symptoms persist despite these measures, nonstatin therapies with proven efficacy in randomized controlled trials are recommended. In recent clinical trials, evolocumab[27] as well as alirocumab[28] performed well in lowering LDL-C in statin-intolerant patients.

Muscle symptoms are the most common statin-related adverse effects. Subjective myalgia occurred in 1% to 15% of participants in randomized controlled trials but in 5% to 20% of patients in observational studies. In a class I recommendation, the authors write that patients with statin-associated muscle symptoms should undergo a detailed assessment of symptoms, and nonstatin causes and predisposing factors should be taken into consideration.

Further, statins slightly increase the risk of diabetes mellitus in patients with prediabetes. However, the guidelines clearly state that therapy should not be discontinued because of this, as the advantages of statins are much greater than the risk of diabetes mellitus.[29,30]

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