

# CLEVELAND CLINIC JOURNAL OF MEDICINE

**An LDL mimic that may be only skin deep**

**Differentiating atherogenic from nonatherogenic xanthomas**

**The double-tongue sign**

**Is exercise restriction necessary in patients with pericarditis?**

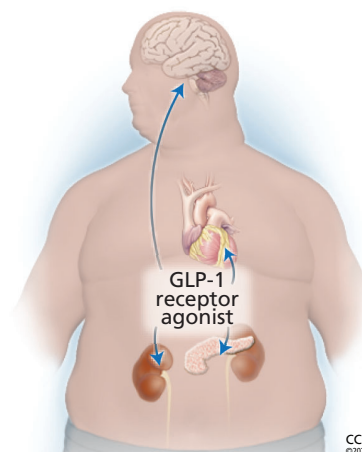
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**Unilateral atrophic kidney in a 45-year-old woman**

**The role of GLP-1 receptor agonists in managing type 2 diabetes**



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# Mapping the Breast Cancer Patient Journey: Using Health System and Patient-Facing Data Sources to Understand the Context

Tuesday, September 20, 2022 Noon – 1:00 pm | Virtual



**Maia Jacobs, PhD**

Assistant Professor  
Department of Computer Science  
Department of Preventive Medicine  
Core Faculty, Center for Human  
Computer Interaction + Design  
Northwestern University



**Zahraa AlHilli, MD, FACS, FRCSI**

Breast Surgeon  
Department of General Surgery  
Digestive Diseases and  
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## LEARNING OBJECTIVES

- › Discuss methods required to capture health system level data to map the journey of a patient diagnosed with breast cancer
- › Identify potential methods that can be utilized to capture patient-facing data to better understand patient perspectives after a breast cancer diagnosis
- › Discuss approaches and challenges to interpreting combined health system and patient-facing data sources to improve care delivery

This activity has been approved for *AMA PRA Category 1 Credit™*

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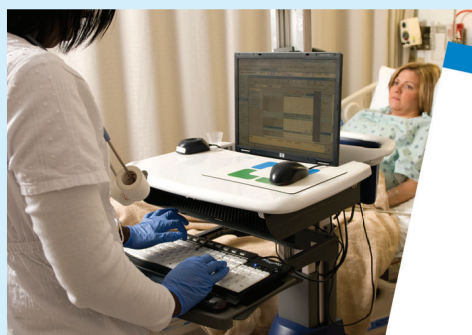
The option of risk-reducing mastectomy is for those at highest risk, and multidisciplinary conversations setting patient expectations are critical for optimal patient outcomes.

Holly J. Pederson, MD; Allison W. Kurian, MD, MSc; Zahraa Al Hilli, MD

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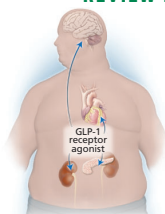
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The following article in the July 2022 issue contained an error: Ganeshan S, Kelemen B, Dhaliwal G, Zier L. An unexpected turn: A 71-year-old man with myocardial infarction. *Cleve Clin J Med.* 2022;89(7):401–407. doi:10.3949/ccjm.89a.21030

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## Circulating lipids are not all bad: An LDL mimic that may be only skin deep

Mai and Akhondi<sup>1</sup> in this issue of the *Journal* present photographs from a single patient with 4 distinct skin findings usually associated with different lipid disorders. The patient, a 42-year-old woman, seems to have fairly typical intermediate to late-stage primary biliary cholangitis (PBC). She will need to be assessed for cirrhosis and treated based on that assessment as well as on her performance on a PBC disease-severity index. She seems not to have any other associated autoimmune disease.

But what she does have, in addition to hepatic test abnormalities, is extremely elevated levels of total and low-density lipoprotein (LDL) cholesterol, a low high-density lipoprotein cholesterol (HDL), and—despite the presence of eruptive xanthomas—only a marginally increased triglyceride level. This lipid profile is not unusual for patients with PBC. But as Mai and Akhondi point out, despite this patient's strikingly elevated LDL (and low HDL), most studies<sup>2</sup> suggest that patients with PBC are not at increased risk of cardiovascular disease—even in the presence of skin deposits that would ordinarily suggest diffuse atherosclerotic disease.

Looking at the images of lipid deposition in skin and around the small hand joints, and an LDL level of  $> 400$ , it is hard to imagine that the patient's arteries are not equally laden with oxidized LDL and, in the setting of a chronic inflammatory disease (her C-reactive protein, a marker of inflammation, is likely to be elevated), that she is not at high risk for myocardial infarction or stroke.

And that apparent paradox relates to the interesting biology<sup>3,4</sup> of lipoprotein-X (LP-X). LP-X is a lipoprotein particle that appears in the sera of patients with cholestatic liver disease (particularly PBC, it seems), graft-vs-host disease, lipid infusions in parenteral nutrition, and enzymatic deficiency of cholesterol esterification. Although LP-X separates out by density in the LDL fraction and thus may appear as LDL in the laboratory report, it is biologically unique. LP-X is formed in the setting of intrahepatic or extrahepatic cholestasis by cholesterol entrance into plasma rather than by being converted into bile acid and ultimately secreted into the gut. There is no apolipoprotein B at its core. Instead, there is phospholipid, albumin, unesterified cholesterol, and some apolipoprotein C. It is not cleared by the LDL receptor, nor will its presence in the circulation provide any feedback inhibition for further cholesterol synthesis. LP-X seems to be cleared by components of the reticuloendothelial system and is concentrated in the spleen and in the skin when levels are high. Ingestion by macrophages leads to the formation of foam cells.

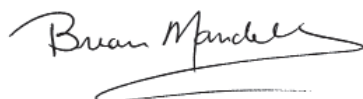
LP-X may be present in atherosclerotic plaque, but LP-X is larger than LDL and has less ability to penetrate the arterial wall. In vitro studies suggest that it suppresses LDL oxidation<sup>5</sup> and thus may exert an anti-atherogenic effect. Nonetheless, patients with PBC can and do develop clinically significant cardiovascular disease, although usually in the presence of other cardiovascular risk factors such as hypertension.

In PBC, relieving cholestasis using ursodeoxycholic acid rapidly reduces the LP-X concentration. It has been proposed that this is due to the return of some biliary function and decreased duct damage from other noxious bile acids, as opposed to a direct effect on lipid metabolism.

Recognizing that super-high LDL values in a patient with PBC may be due to LP-X and thus

doi:10.3949/cjcm.89b.08022

may not indicate the presence of elevated atherogenic LDL can avoid additional evaluation or treatment of potential cardiovascular disease. However, it is also worth noting that patients with cirrhosis who are taking statins<sup>6</sup> have a decreased occurrence of hepatic decompensation and death.



Brian F. Mandell, MD, PhD  
Editor in Chief

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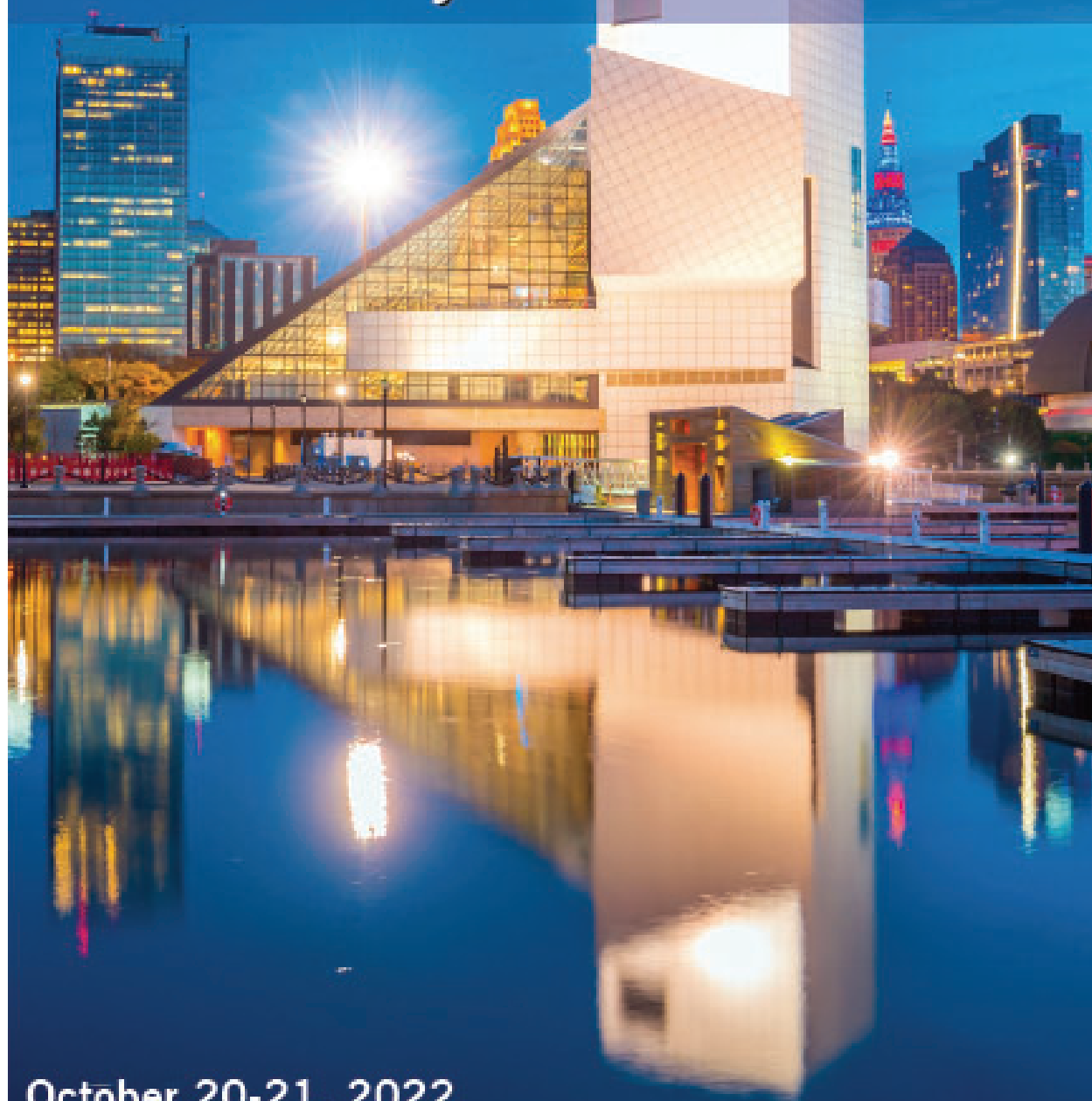
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# Cardiovascular Update for the Primary Care Provider



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# Xanthomas: Differentiating atherogenic from nonatherogenic



**Figure 1.** Coalescing plaques around both eyes (arrows). These plane xanthomas can be seen in the presence or absence of hyperlipidemia.



**Figure 2.** Xanthoma striatum palmare (arrows) on the palmar surfaces of hands is commonly seen in dysbetalipoproteinemia.

A 42-YEAR-OLD WOMAN with a known history of primary biliary cholangitis, a chronic progressive cholestatic autoimmune liver disease of uncertain etiology, presented with worsening of generalized pruritus and a gradually increasing number of yellow skin lesions. Physical examination demonstrated raised yellow coalescing plaques around both eyes (**Figure 1**), similar lesions on the palmar surfaces of the hands (**Figure 2**), cobblestone-like nodules on the dorsal joints of the hands (**Figure 3**), and pale pink lesions on the left buttock (**Figure 4**). She had mild jaundice and scleral icterus.

Laboratory testing showed the following:

- Alanine aminotransferase 265 U/L (reference range 7–55)
- Aspartate aminotransferase 191 U/L (8–48)
- Alkaline phosphatase 1,109 U/L (40–129)

This research was supported (in whole or part) by HCA Healthcare and/or an HCA Healthcare-affiliated entity. The views expressed in this publication represent those of the authors and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

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- Total bilirubin 16.8 mg/dL (0.2–1.2)
- Unconjugated bilirubin 14.6 mg/dL (0.2–1.2)
- Total cholesterol > 585 mg/dL (< 200)
- Triglycerides 179 mg/dL (< 150)
- High-density lipoprotein cholesterol 31 mg/dL (> 60)
- Low-density lipoprotein (LDL) cholesterol > 400 mg/dL (< 100).

Albumin, protein, and renal function panel results were within normal limits.

Based on the presentation and the results of laboratory testing, the lesions were diagnosed as cutaneous xanthomas.

## WORKING THROUGH THE DIFFERENTIAL DIAGNOSIS

Cutaneous xanthomas arise from oxidized lipid deposits in the dermis.<sup>1</sup> Xanthoma subtypes include plane (ie, xanthelasma), eruptive, tendinous, tuber-



**Figure 3.** Cobblestone-like nodules (arrows) on the dorsal joints of hands can be seen in underlying hypercholesterolemia.



**Figure 4.** Pale pink lesions (arrows) on the left buttock representing eruptive xanthoma are seen in hypertriglyceridemia.

ous, and verruciform,<sup>2</sup> and the morphology gives valuable hints about the underlying disease and whether it is atherogenic or nonatherogenic. For example, plane xanthoma can be seen with or without hyperlipidemia, eruptive xanthoma is seen in hypertriglyceridemia, and tuberous xanthoma in hypercholesterolemia. Tendinous xanthoma is seen in familial hyperlipidemia syndromes with elevated LDL cholesterol or familial defective apolipoprotein B-100. Verruciform xanthoma is not associated with dyslipidemia at all.<sup>2</sup>

Classically, these dyslipidemias contribute to worrisome cardiovascular complications such as myocardial infarction. However, it appears that the lipid accumulation seen in primary biliary cholangitis is a unique lipid subfraction known as lipoprotein X,<sup>3</sup> an abnormal nonatherogenic LDL particle that is not associated with increased risk of cardiovascular disease.

### Xanthoma striatum palmare

In our patient, the tendinous xanthomas on the dorsal joints of the hand and the eruptive xanthomas on the buttock would typically point the clinician toward underlying primary dyslipidemia. This is also supported by plane xanthelasmas around the eyes. However, our patient also exhibited xanthoma striatum palmare on the volar aspect of the hand, a rare finding that has been described in primary biliary cholangitis, a secondary dyslipidemia.<sup>4</sup> This type of eruption is associated with dysbetalipoproteinemia. The diffuse display of 4 different xanthoma subtypes in a single patient is rare, with only 1 other case reported in the literature.<sup>4</sup>

### Volar skin lesions

The differential diagnosis of a widespread pattern of skin lesions on the palms includes disseminated tophaceous gout, characterized by creamy white lesions consisting of monosodium urate buildup, and typically occurring in the ears, tendons, and bursas. Another condition in the differential for this generalized pattern includes pseudoxanthoma elasticum, which is characterized by elastic fibers in the dermis of flexural skin surfaces, as well as in arterial blood vessels. Lipoid proteinosis, a rare autosomal recessive disorder, also presents with this extensive distribution and appears as wart-like, cobblestone-like lesions mostly seen on mucocutaneous membranes. Our patient's cobblestone lesions were not compatible with this and were on the dorsum of the hand.

### TREATMENT OPTIONS

The definitive treatment for this patient is the same as for primary biliary cholangitis, ie, liver transplant.<sup>5</sup> Cholestyramine is the guideline-recommended first-line drug for itching in primary biliary cholangitis,<sup>6</sup> but it only relieves the pruritus and does not treat the condition. High-intensity statin therapy is not recommended in this patient, as studies have not indicated increased cardiovascular risk in patients with primary biliary cholangitis,<sup>6</sup> but it may be beneficial if the benefits outweigh the risks.

Most evidence has shown that hypercholesterolemia in primary biliary cholangitis does not increase cardiovascular risk without a concomitant metabolic syndrome.<sup>7</sup> This is due to the distinctive elevated level of cardioprotective lipoprotein X in primary biliary cholangitis.<sup>7</sup>



## ■ TAKE-HOME MESSAGE

Our patient's case highlights the importance of differentiating atherogenic from nonatherogenic causes of dyslipidemia. By recognizing that the appearance of xanthomas may help differentiate between the two, we can remember to broaden our differential and

appropriately tailor our therapies to treat dyslipidemia correctly. ■

## ■ DISCLOSURES

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

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## THE CLINICAL PICTURE

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# The double-tongue sign

**A**N 85-YEAR-OLD WOMAN WITH stage 3 chronic kidney disease presented to our hospital with dyspnea and intermittent mild fever. She had a history of significant odynophagia and dysphagia. In the previous 2 days, the submandibular area had become erythematous and swollen.

The patient's vital signs were the following:

- Glasgow coma Scale 14 out of 15 (ie, responsive)
- Blood pressure 107/60 mmHg
- Pulse rate 91 beats per minute
- Body temperature 36.8°C (98.2°F)
- Respiratory rate 20 breaths per minute
- Oxygen saturation 95% on room air.

Physical examination revealed the “double tongue” sign on the floor of the mouth (**Figure 1**), with tender, slightly erythematous swelling under the jaw. She had slight difficulty opening her mouth, but she had no dental caries or cervical lymphadenopathy.

Laboratory testing on hospital admission revealed the following:

- White blood cell count  $6.9 \times 10^9/L$  (reference range 4–11)
- Neutrophils  $5.7 \times 10^9/L$  (1.5–8.0)
- C-reactive protein 10.8 mg/dL (0–0.3)
- Blood urea nitrogen 33.5 mg/dL (8–21)
- Creatinine 1.8 mg/dL (0.58–0.96)
- Estimated glomerular filtration rate 20.9 mL/min/1.73 m<sup>2</sup> ( $\geq 60$ ).

Laboratory data showed elevated C-reactive protein induced by oral infection, elevated blood urea nitrogen and creatinine levels due to dehydration, and pre-renal acute kidney injury caused by poor oral intake for approximately 2 days.

Computed tomography showed enlarged mylohyoid and geniohyoid muscles, surrounding inflammatory findings, and small gas retentions. There were no findings suggestive of malignant neoplasms



**Figure 1.** Swelling in the submandibular space pushes the tongue upward, resulting in what resembles a double tongue (arrow).

of the neck, chest, or abdomen. The patient was diagnosed with Ludwig angina based on the physical examination and features noted on computed tomography.

## TREATMENT FOLLOWED BY A SECOND SIGN

An oral surgeon performed incision and drainage, and the patient was prescribed antibiotic therapy with intravenous ampicillin-sulbactam 1.5 g every 12 hours for 14 days in the hospital. Pus culture detected *Streptococcus parasanguinis* and *Bacteroides fragilis*.

Her recovery was uneventful, and the double-tongue sign disappeared completely at discharge on day 16 without any complications. However, 3 days later, she returned because her tongue had turned black without other symptoms. She was diagnosed with black hairy tongue caused by antibiotic therapy (**Figure 2**). Her tongue color returned to normal spontaneously after 14 days.

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**Figure 2.** Black hairy tongue sign. Although there are no subjective symptoms, the tongue's surface takes on a dark, hairy appearance (arrow) due to abnormal elongation and discoloration of the filiform papillae. The discoloration cannot be removed by brushing or scraping.

## TONGUE EXAMINATION KEY TO DIAGNOSIS

This case exemplifies how careful physical examination of the tongue can help achieve a meaningful diagnosis. Ludwig angina is a rare deep-neck infection occurring on the floor of the mouth under the tongue. Prompt treatment is needed to prevent airway obstruction.<sup>1,2</sup>

In this patient, early recognition of the double-tongue sign resulted in an accurate diagnosis. Although the sensitivity, specificity, and likelihood

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ratios for Ludwig angina were not quantified, the double-tongue sign is a valuable physical finding, characterized by elevated floor of the oropharynx caused by infection in the submandibular space.<sup>1,3</sup>

## Black hairy tongue

Black hairy tongue is characterized by abnormal elongation and discoloration of the filiform papillae, typically resulting in a carpet-like appearance on the dorsal surface of the tongue.<sup>4–6</sup> Black hairy tongue is a benign and painless condition.<sup>4–6</sup> However, its etiology and pathophysiology remain vague. Studies suggest that it occurs more commonly in men and is caused by changes in the oral flora due to aging, smoking, alcohol use, poor oral hygiene, and specific antibiotic treatments.<sup>5,6</sup> An association with beta-lactam antibiotics has been reported.<sup>6</sup> The condition resolves spontaneously when oral hygiene is maintained.

Tongue examination may not be commonly performed often in clinical practice. However, this case shows that understanding characteristic tongue findings helps achieve a meaningful diagnosis and prevent excessive examination and intervention.

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## DISCLOSURES

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## 1-MINUTE CONSULT

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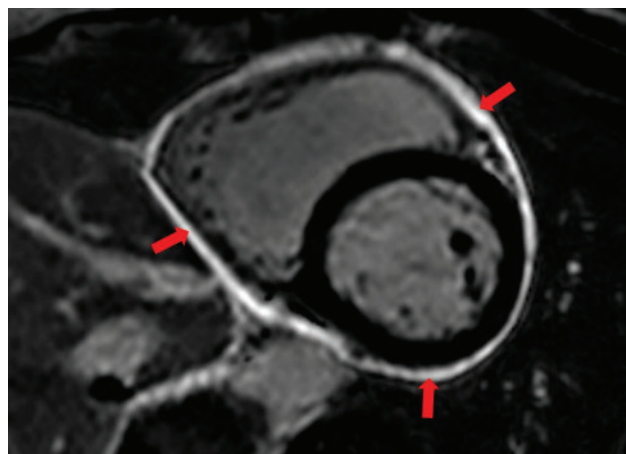
# Q: Is exercise restriction necessary in patients with pericarditis?

A 47-year-old woman presents with recurrent episodes of pleuritic chest pain. She is physically active and exercises 5 times per week on average, although recently she has had to stop after noticing worsening of her symptoms with strenuous exercise. Inflammatory markers are found to be elevated, and echocardiography reveals a new small pericardial effusion. Cardiac magnetic resonance imaging (MRI) with gadolinium contrast reveals circumferential delayed hyperenhancement of the pericardium (**Figure 1**). A diagnosis of acute pericarditis is made, and the patient is started on anti-inflammatory therapy. When is it safe to recommend resumption of her physical activity?

**A:** Although there is little published evidence, experts recommend against participation in exercise and competitive sports during episodes of acute and recurrent pericarditis and 1 to 3 months after an acute episode to ensure resolution of disease.

### ■ EXERCISE AND PERICARDITIS: TRIGGERS AND MECHANISMS

Physical exercise is thought to worsen pericardial inflammation, and it has been implicated as a trigger for inflammation in genetically predisposed patients.<sup>1,2</sup> The proposed mechanisms include a tachycardia-mediated increase in shear stress through friction of the pericardial layers and an increase in the release of free radicals causing oxidative stress through enhanced blood supply to the pericardium.<sup>1</sup> Additionally, extreme physical exercise in elite athletes can decrease the innate and adaptive immune response.<sup>3</sup> However, this interplay and its relevance to the clinical course of pericarditis in elite athletes has not been studied specifically. Exercise restriction is commonly recommended to patients with pericar-



**Figure 1.** Cardiac magnetic resonance imaging with gadolinium contrast showing delayed contrast enhancement of the pericardium on fat-suppression imaging sequences in a 47-year-old female with acute pericarditis. The arrows point to the circumferential contrast enhancement of the pericardium. Our experience suggests that complete remission may take as long as 3 to 5 years.

ditis as a means to decrease symptoms and the risk of complications, even though published evidence of a causative relationship between exercise and worsening pericarditis is limited to case reports.<sup>4</sup>

Elevations in heart rate appear to be particularly implicated in worsening pericardial inflammation, and studies have shown a correlation between C-reactive protein levels and heart rate in patients hospitalized with acute pericarditis.<sup>5</sup> Local inflammation from pericarditis has been proposed as a mechanism that worsens tachycardia, which in turn can perpetuate a vicious cycle of inflammation.<sup>6</sup> Some experts have suggested maintaining heart rates below 100 beats per minute in patients with pericarditis, and a role

**TABLE 1**

## Exercise recommendations in patients with isolated pericarditis<sup>a</sup>

### European Association of Preventive Cardiology<sup>8</sup>

Athletes with pericarditis should not participate in competitive sports during the acute phase. Athletes can return to sport activity only after complete resolution of the active disease. A period of 3 months is considered appropriate to ensure complete clinical and biologic resolution of the disease, but a shorter period (at least 1 month) may be considered in select cases with only mild clinical picture and prompt resolution (class III, level C).<sup>8</sup>

It is reasonable to return to play if the serum biomarkers have normalized, left ventricular function is normal, and there are no resting or exercise-induced frequent or complex ventricular arrhythmias detectable on 24-hr electrocardiography monitoring or exercise electrocardiography (class IIa, level C).<sup>8</sup>

### European Society of Cardiology

Return to all forms of exercise including competitive sports is recommended after 30 days to 3 months for individuals who have recovered completely from acute pericarditis, depending on clinical severity (class I, level C).<sup>9</sup>

Participation in leisure-time or competitive sports is not recommended for individuals with a probable or definitive diagnosis of recent pericarditis while active inflammation is present, regardless of age, sex, or extent of left ventricular systolic dysfunction (class III, level C).<sup>9</sup>

### American Heart Association/American College of Cardiology

Athletes with pericarditis, regardless of its pathogenesis, should not participate in competitive sports during the acute phase. Such athletes can return to full activity when there is complete absence of evidence for active disease, including effusion by echocardiography, and when serum markers of inflammation have normalized (class III, level C).<sup>10</sup>

<sup>a</sup> Explanation of recommendations. Class I recommendation: Evidence or general agreement that a given treatment or procedure is beneficial, useful, effective (ie, is recommended or is indicated). Class IIa recommendation: Weight of evidence or opinion is in favor of usefulness or efficacy (ie, should be considered). Class III recommendation: Evidence or general agreement that the given treatment or procedure is not useful or effective, and in some cases may be harmful (ie, is not recommended). Level of evidence C: Consensus of opinion of the experts or small studies, retrospective studies, registries.

has been proposed for using cardiac MRI to monitor disease activity in order to guide the resumption of exercise.<sup>4</sup>

In an observational study by Imazio et al,<sup>7</sup> beta-blockers were administered to patients with acute pericarditis targeting a heart rate of less than 70 beats per minute. Patients who received beta-blockers had a lower rate of symptom recurrence at 3 weeks (4% vs 14%,  $P = .024$ ) and a trend toward fewer recurrences at 18 months.<sup>7</sup> Although mechanisms other than heart rate reduction, such as downregulation of proinflammatory cytokines, could contribute to symptom reduction in these patients, this study indirectly supports the contention of exercise restriction to lower heart rates in patients with acute pericarditis. Of note, no randomized clinical trials using heart-rate-lowering therapies in this patient population have been conducted.

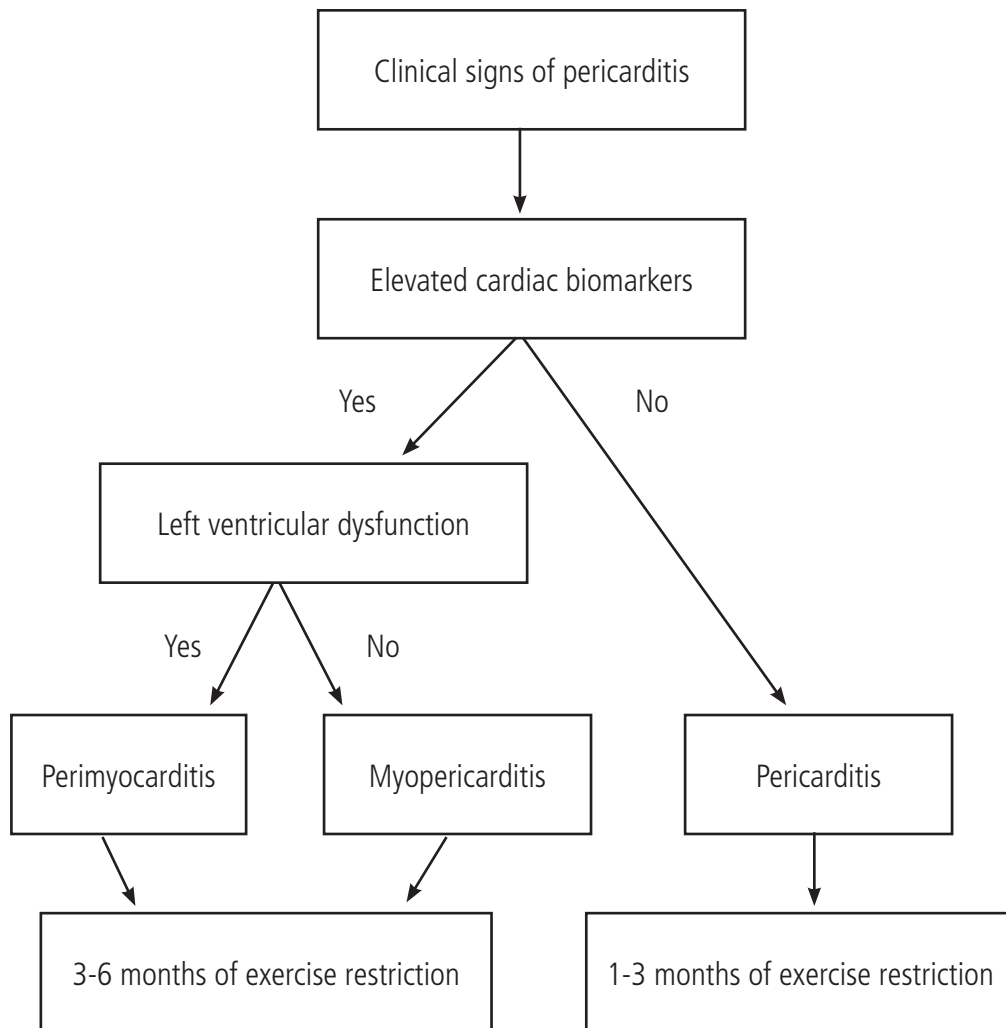
## SOCIETY GUIDELINES

Several professional societies have published recommendations on physical exercise in patients with pericarditis (Table 1),<sup>8-10</sup> but the recommendations are generally not supported by data from randomized

clinical trials and instead rely on observational data and expert opinion. Moreover, the guidelines emphasize recommendations for return to competitive sports for athletes rather than recommendations on activity levels in the general population of nonathletes.

The European Association of Preventive Cardiology (EAPC) released recommendations on return to play for athletes in 2019.<sup>8</sup> They recommend against participation in competitive sports during the acute phase of pericarditis and not resuming sports activity for 1 to 3 months after resolution of the active phase. Return to play was deemed reasonable if biomarkers had normalized, left ventricular function was normal, and no resting or exercise-induced ventricular arrhythmias could be detected on 24-hour electrocardiography monitoring or exercise electrocardiography.

The European Society of Cardiology (ESC) released guidelines on sports cardiology and exercise in patients with cardiovascular disease in 2020.<sup>9</sup> They provide more generalized recommendations for the general population of patients in terms of leisurely activity. In contrast to the EAPC recommendations, both competitive sports and leisure-time exercise are actively discouraged until complete recovery from



**Figure 2.** Proposed algorithm for exercise restriction in pericarditis with or without myocardial involvement, based on European Society of Cardiology and American Heart Association/American College of Cardiology recommendations. The detection of biomarkers of myocardial injury indicates active myocardial inflammation, which necessitates exercise restriction for 3 to 6 months regardless of left ventricular function.

pericarditis. Similar to the EAPC recommendations, return to activity is recommended after a period of 30 days to 3 months after resolution of disease, depending on severity.

The American Heart Association and American College of Cardiology (AHA/ACC) released a joint scientific statement in 2015 on disqualification and eligibility for competitive athletes with cardiovascular abnormalities.<sup>10</sup> In concordance with the ESC and EAPC recommendations, the AHA/ACC statement recommends against participation in competitive sports during the acute phase of pericarditis. Return to

full activity is recommended in the complete absence of evidence for the disease. They provide no specific guidance in terms of timing of return or stratification of physical activity for athletes and nonathletes.

## MYOPERICARDITIS

Myopericarditis is a term used to describe predominant pericarditis with concurrent myocardial involvement as defined by the detection of biomarkers of myocardial necrosis in the blood. The relative myocardial involvement can be variable and ranges from isolated inflammation of the pericardium to perimy-



carditis, a term used to describe predominant myocardial involvement typically evidenced by new focal or diffuse left ventricular systolic dysfunction. **Figure 2** shows a proposed algorithm for determining exercise restriction in patients with these conditions, based on ESC and AHA/ACC recommendations.<sup>9,10</sup>

Any evidence of myocardial involvement is considered a contraindication to exercise regardless of left ventricular systolic function, and professional societies recommend exercise electrocardiography, 24-hour Holter monitoring, and echocardiography no less than 3 to 6 months before resuming exercise.<sup>11</sup> The underlying rationale behind this recommendation is the concern that exercise can worsen the inflammatory response with potentially fatal consequences. Indeed, sudden cardiac death without prodromal symptoms has been reported in patients with myocarditis following strenuous activity, and mouse models of myocarditis have shown an association between daily exercise and sudden cardiac death.<sup>9,11</sup> Return to exercise can be guided by the use of cardiac MRI to assess for delayed hyperenhancement and myocardial edema on T2-weighted imaging, enabling clinicians to tailor their recommendations for asymptomatic patients who may or may not have active inflammation on imaging. And while there is no clear consensus about the appropriate use of MRI, the ESC guidelines recommend repeating it if edema or delayed hyperenhancement was present on the initial MRI.<sup>9,11</sup>

Recently, myocarditis has gained increased relevance given its association with COVID-19 infection. However, the overall risk is low. A 2021 study found evidence of cardiac involvement in 0.7% of athletes and 3% in athletes who underwent primary screening MRI.<sup>12</sup>

### ■ THE BOTTOM LINE

Patients with isolated pericarditis should refrain from physical exercise during acute episodes. Athletes should avoid competitive sports for 1 to 3 months after an acute episode, depending on the severity, as part of shared decision-making with their treating clinicians. It is reasonable to resume physical activity if biomarkers (C-reactive protein, erythrocyte sedimentation rate) have normalized, left ventricular function is normal, and there are no residual abnormalities on electrocardiography.

Although specific guidance is lacking for the non-athlete population, we generally recommend patients to limit their physical activity to walking and to limit their active heart rate to 100 beats per minute as long as they are receiving anti-inflammatory medications for pericarditis.

Active myocardial involvement should be considered a contraindication to exercise, given its reported association with sudden cardiac death. There is insufficient evidence to routinely recommend beta-blockers to patients with acute pericarditis. However, it is reasonable therapy in patients in whom beta-blockers can have synergistic effects (eg, those with hypertension or atrial fibrillation) or if their resting heart rate was significantly elevated at baseline. We would aim to decrease the active heart rate to below 100 beats per minute.

### ■ BACK TO THE CASE SCENARIO

In the scenario presented earlier, our patient showed delayed hyperenhancement on cardiac MRI. In our experience, these imaging findings can resolve over the course of 3 to 5 years, and anecdotally, exercise can worsen both symptoms and radiologic evidence of disease activity. In light of this, for patients such as this, we would recommend continued exercise restriction if there is ongoing neovascularization or inflammation on MRI. However, acknowledging the health benefits of exercise during a risk-benefit discussion with the patient is always warranted.

Randomized trials are needed to validate the use of imaging to tailor exercise recommendations in acute pericarditis and to determine if there is a role for the use of emerging biologic treatments, such as the anti-interleukin 1 agents anakinra and rilonacept, in enabling a timely return to exercise and competitive sports. ■

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### ■ DISCLOSURES

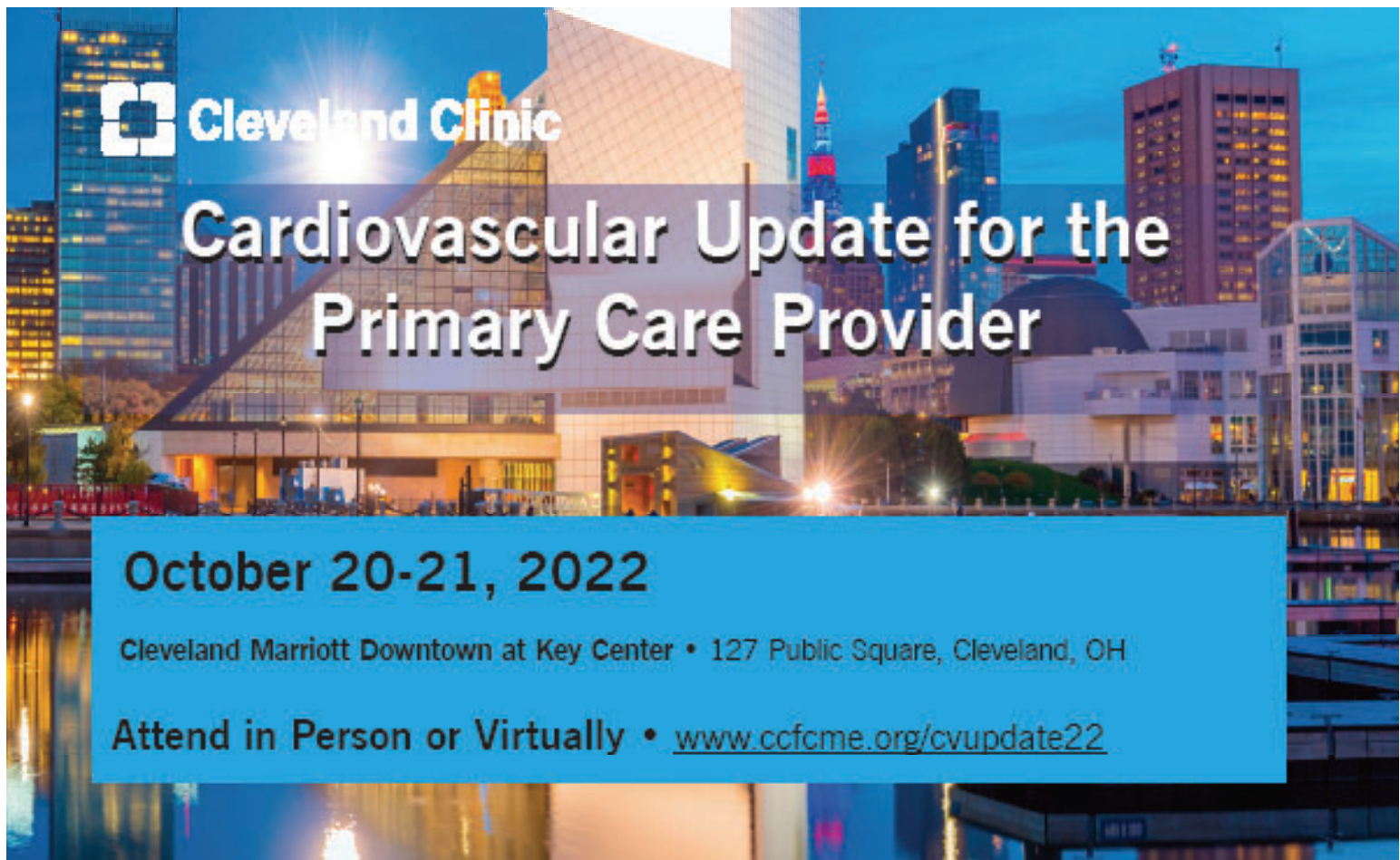
Dr. Klein reports advisor or review panel participation with Cardiol Therapeutics, Kiniksa, and Pfizer; consulting for Kiniksa Pharmaceuticals and Pfizer; and intellectual property rights with Elsevier and Wolters-Kluwer. Dr. Berglund reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.



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## 1-MINUTE CONSULT

BRIEF  
ANSWERS  
TO SPECIFIC  
CLINICAL  
QUESTIONS

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## Q: What are the considerations in patient selection and timing of risk-reducing mastectomy?

**A:** In patients with pathogenic or likely pathogenic genetic variants in high-risk genes (*BRCA1*, *BRCA2*, *PALB2*, *PTEN*, *TP53*, and *CDH1*), compelling family history, or a history of thoracic radiation therapy before age 30, risk-reducing mastectomy is an option to be discussed in addition to effective screening and risk-reducing medications. Owing to possible morbidity, impact on body image, psychological distress, and loss of chest-wall sensation, patient selection and shared decision-making are critical to determine optimal patient choices. The option of risk-reducing mastectomy is for those at the highest levels of risk, and multidisciplinary conversations setting patient expectations are critical for optimal patient outcomes.

### ■ BREAST CANCER RISK AND RISK-REDUCING MASTECTOMY

Breast cancer remains the most common solid tumor in women, making it critical to identify patients with highly penetrant germline genetic variants early, as cancers often begin to develop at age 30.<sup>1</sup> The 3 pillars of risk management for high-risk women include enhanced surveillance (the addition of contrast-enhanced magnetic resonance imaging to mammography, often alternating every 6 months), risk-reducing medication (selective estrogen-receptor modulators such as tamoxifen or raloxifene, or aromatase inhibitors such as anastrozole or exemestane), and risk-reducing mastectomy.

Patients may be over-treated with surgery; it is critical for both clinicians and patients to understand cancer risks and recommendations. That being said, most surgical patients are satisfied with their decision given the reduced risk of breast cancer of at

least 90%.<sup>2</sup> No randomized studies have compared enhanced surveillance with surgery. Modeling studies have suggested a 6% to 8% mortality reduction for patients with *BRCA1* carriers and 3% for *BRCA2* carriers.<sup>3,4</sup>

### ■ HOW TO DISCUSS WITH THE PATIENT?

The decision to undergo risk-reducing mastectomy is highly personal and should not be introduced as a clinician's recommendation. Rather, patients should be presented with the risks and benefits of each option including effective screening for high-risk patients, risk-reducing medications, and risk-reducing mastectomy to make their own informed choice. Further, risk-reducing bilateral salpingo-oophorectomy has been recommended for *BRCA1/2* carriers as screening is neither sensitive nor specific enough to detect early-stage ovarian cancer.<sup>2</sup>

### Guidelines

According to guidelines from the National Comprehensive Cancer Network, the National Cancer Institute, and the American College of Obstetrics and Gynecology, risk-reducing mastectomy should generally be considered only in individuals with a pathogenic or likely pathogenic variant (not a variant of uncertain significance) conferring a high risk for breast cancer, compelling family history, or possibly with a past history of thoracic radiation therapy under age 30 (such as mantle radiation for treatment of Hodgkin lymphoma).<sup>5</sup> The value of risk-reducing mastectomy in individuals with pathogenic or likely pathogenic variants in moderate risk genes (such as *CHEK2* or *ATM*) in the absence of a compelling family history of breast cancer is unknown.<sup>6</sup> While risk-reducing mastectomy has been previously considered for lobular carcinoma in situ, the preferred

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approach currently is risk-reducing medication given its effectiveness.<sup>5</sup>

### Gene carriers and risk

There are 6 gene carriers for which a discussion about risk-reducing mastectomy is indicated due to their absolute estimated risk of developing breast cancer: *BRCA1* (72%),<sup>1</sup> *BRCA2* (69%),<sup>1</sup> *PALB2* (up to 53%),<sup>7</sup> *PTEN* (up to 85%),<sup>8</sup> *CDH1* (43%),<sup>9</sup> and *TP53* (85%).<sup>8,10</sup> Some patients have clinical features of Cowden syndrome but test negative for a *PTEN* mutation (clinical Cowden syndrome). These patients are felt to be at lower risk for breast cancer,<sup>11</sup> and consideration of risk-reducing mastectomy should be based on family history.<sup>6</sup> Excellent long-term results have been reported for bilateral nipple-sparing mastectomy for breast cancer risk-reduction in appropriate patients.<sup>12</sup>

Genes for which evidence is insufficient for risk-reducing mastectomy and those to be managed based on family history include *CHEK2*, *NF1*, *STK11*, *ATM*, and *BARD1*. Genes for which there is insufficient data, where management (including magnetic resonance imaging screening) is based on family history include *BRIP1*, *RAD51C*, and *RAD51D*.<sup>6,13</sup>

### Treatment determination

The risk associated with many genetic variants decreases with age,<sup>1</sup> and patient selection is critical. Regarding timing, the risk of breast cancer is quite low under the age of 30, and the residual risk decreases after the age of 50.<sup>1</sup> Older women should be advised that their residual risk declines with age, informing decision-making. The benefit of risk-reducing mastectomy may be offset by operative risks and other causes for mortality.<sup>1,14</sup> There is no absolute age at which risk-reducing mastectomy is no longer recommended. However, it is important to provide age-specific cancer risk estimates to determine appropriate interventions.<sup>1,14</sup> In a recent study, the cumulative risk of invasive breast cancer in women ages 60 to 80 was 20.1% for *BRCA1* carriers and 17.3% for *BRCA2* carriers.<sup>1,14</sup>

Chemoprevention is a risk management alternative, although *BRCA1* carriers under age 50 are predisposed to triple-negative breast cancer, and preventive medication is likely to offer little benefit.<sup>1,5,13,15</sup> Older women with *BRCA1* are more commonly diagnosed with estrogen-receptor-positive disease,<sup>16</sup> and it is reasonable to offer preventive medication to *BRCA1* carriers over age 50.<sup>2</sup> *RAD51C* and *RAD51D* carriers are predisposed to estrogen-receptor-negative disease and may not benefit from preventive therapy.<sup>17</sup>

## BRCA, OVARIAN CANCER, AND BREAST CANCER

Women with *BRCA* mutations who have developed ovarian cancer, the most lethal gynecologic malignancy,<sup>18</sup> have an overall 5-year survival rate of 45.6%.<sup>19</sup> Experts suggest that women with stage I ovarian cancer who are disease-free for at least one year, are most likely to benefit from risk-reducing mastectomy.<sup>7,18,20</sup> In patients with stage II/III disease, *BRCA* mutation carriers have a relatively low risk of breast cancer and their prognosis is largely determined by their ovarian cancer diagnosis. Studies show a 2% to 6% incidence of breast cancer in the first 5 years and an approximate 10% risk in the first 10 years following epithelial ovarian cancer diagnosis.<sup>7,18,20,21</sup> The risk of breast cancer is lower in ovarian cancer survivors who carry *BRCA* mutations than that reported for *BRCA* carriers who have not developed ovarian cancer (possibly due to oophorectomy or use of chemotherapy that could eliminate microscopic breast cancer at the cellular level).

### Consideration of risk-reducing mastectomy after ovarian cancer diagnosis

In a modelling study by Gamble et al,<sup>20</sup> the added gain in survival benefit in months following risk-reducing mastectomy, if performed in the first several years after an ovarian cancer diagnosis, was small and greatest in women under 50.<sup>20</sup> The study also noted that risk-reducing mastectomy is not indicated within 5 years of an ovarian cancer diagnosis due to a high rate of ovarian cancer relapse.<sup>20</sup> It has been suggested that consideration of risk-reducing mastectomy for *BRCA* carriers be reserved for those who remain in remission for 5 years,<sup>7</sup> and possibly for women age 50 or younger at ovarian cancer diagnosis.<sup>18,22</sup> Furthermore, a study of 1,455 women who developed primary breast cancer after ovarian cancer showed mean time from ovarian cancer diagnosis to breast cancer diagnosis of 7.3 years.<sup>23</sup>

## TAKE-HOME POINTS

- Discuss the option of risk-reducing mastectomy in patients with pathogenic or likely pathogenic variants in *BRCA1*, *BRCA2*, *PALB2*, *PTEN*, *TP53* and *CDH1*.
- Consider risk-reducing mastectomy in patients with compelling family history or with a past history of thoracic radiation therapy under the age of 30.
- Discuss the option of risk-reducing mastectomy in *BRCA* carriers following an ovarian cancer diagnosis only after 5 years of remission.



## THE BOTTOM LINE

Although most women who choose to undergo risk-reducing mastectomy are generally satisfied with their decision, many report adverse impact on body image and sexual relationships, and emotional distress due to a sense of loss and abnormal chest-wall sensation. Despite constant improvements in reconstructive cosmetic outcomes, there is considerable morbidity related to the procedure, and patient selection is

critical for optimal results. Shared decision-making is key. Risk-reducing mastectomy is for patients with the highest levels of risk, and multidisciplinary conversations setting patient expectations are critical for optimal patient outcomes.

## DISCLOSURES

Dr. Pederson has disclosed consulting for Myriad Genetics. Dr. Kurian and Dr. Al Hilli report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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## SYMPTOMS TO DIAGNOSIS

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# Altered mental status in a man with metabolic syndrome

A 29-YEAR-OLD MAN WAS found by his father to be unresponsive with shallow breathing and foaming at the mouth. The man's father called emergency medical services and reported his son had a history of bipolar I disorder, posttraumatic stress disorder, hypertension, type 2 diabetes, and severe obesity (body mass index 44.5 kg/m<sup>2</sup>). The patient had been to the emergency department in the past for depression and mania, but had no past suicidal ideation or attempts. His relevant home medications are listed in Table 1. The patient was intubated and transported to the emergency department.

## ■ PHYSICAL EXAMINATION

In the emergency department, the patient's vital signs were blood pressure of 76/28 mm Hg, heart rate of 113 beats per minute, and respiration rate of 8 to 10 breaths per minute. During the physical examination, he was stuporous and had limited responsiveness to verbal and physical stimuli. Computed tomography of the head revealed mild cerebral edema with concern for global anoxic injury. Chest radiography showed consolidation suggestive of aspiration. Electroencephalography was not done at the time.

Differential diagnosis included medication overdose, stroke, central nervous system injury, sepsis, cardiogenic shock, severe electrolyte imbalances, carbon monoxide poisoning, and toxin exposures such as botulism.

Pertinent results of laboratory testing include glucose 46 mg/dL (reference range 70–100 mg/dL), creatinine 2.78 mg/dL (0.7–1.3 mg/dL), potassium 5.5 mmol/L (3.5–5 mmol/L), lactate 4.5 mmol/L (0.5–2.2 mmol/L), and creatine kinase 166 U/L (24–204 U/L). His elevated creatinine was likely due to prolonged

hypotension and his normal creatine kinase ruled out rhabdomyolysis.

Electrocardiogram showed sinus tachycardia. Initial arterial blood gases were notable for pH 7.20 (7.35–7.45), partial pressure of carbon dioxide 68 mm Hg (35–45 mm Hg), partial pressure of oxygen 95 mm Hg (75–100 mm Hg), bicarbonate 26 mEq/L (22–26 mEq/L), and a base excess of -4 mEq/L (-2 to +2 mEq/L). Urine toxicology was positive for tetrahydrocannabinol and lithium levels were within normal limits. No other serum concentrations of medications were obtained. The number of pills remaining in all medication bottles were consistent with the date of last refill and were not concerning for overdose.

The patient received intravenous fluids and broad-spectrum antibiotics for possible sepsis and aspiration pneumonia and was admitted to the intensive care unit (ICU) for hemodynamic support and mechanical ventilation. In the ICU, he received norepinephrine and vasopressin infusions due to persistent hypotension. Sepsis was ruled out by repeat negative blood cultures and his antibiotic regimen was deescalated to amoxicillin-clavulanic acid for aspiration.

## ■ POSSIBLE MEDICATION OVERDOSE

**1** With a history of substance abuse, overdose of what drug from the patient's list of medications is most consistent with the patient's symptoms?

- ☐ Aripiprazole
- ☐ Lithium
- ☐ Metoprolol
- ☐ Metformin

The patient's clinical presentation is most consistent with metoprolol overdose. Beta-blockers such as

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**TABLE 1**  
**Relevant home medications**

Medication	Dosage	Notes
Aripiprazole	400 mg intramuscularly every 4 weeks	Initiated 9 days prior to admission
Clonazepam	0.5 mg twice daily	
Fluoxetine	20 mg daily	Initiated 29 days prior to admission
Lithium extended release	600 mg in the morning, 900 mg at bedtime	
Metformin	500 mg twice daily	Initiated 2 years prior to admission
Metoprolol	50 mg twice daily	
Quetiapine	50 mg at bedtime	

metoprolol, propranolol, and labetalol are commonly used to treat a wide range of conditions including hypertension, heart failure, arrhythmias, ischemic heart disease, tremor, glaucoma, and hyperthyroidism. When ingested in excessive amounts, as competitive inhibitors of adrenergic receptors, beta-blockers disrupt the metabolic and circulatory functions of catecholamines through the decrease of intracellular cyclic adenosine monophosphate.<sup>1</sup> Although bradycardia and hypotension are most common, tachycardia had also been reported in some cases.<sup>2</sup> Severe toxicity commonly presents with altered mental status, cardiogenic shock, seizure, hypoglycemia, and bronchospasm. In most cases, symptoms develop within 2 hours of ingestion.<sup>3</sup>

Each type of beta-blocker has specific pharmacodynamic properties that may contribute to differential clinical manifestation of toxicity. Lipophilic agents including propranolol and nebivolol readily cross the blood-brain barrier to cause central nervous system effects such as seizure and delirium.<sup>1,4</sup> Beta-blockers with membrane stabilization activity, such as propranolol and carvedilol, pose higher risks of arrhythmia and QRS prolongation due to inhibition of fast sodium channels in the myocardium.<sup>4,5</sup> Co-ingestion of other cardioactive medications such as calcium channel blockers, cyclic antidepressants, and neuroleptics significantly elevates the risks of morbidity.<sup>2,5</sup> Treatment involves proactive airway management, fluid resuscitation for hypotension, atropine for bradycardia, and activated charcoal for gastrointestinal decontamination.<sup>6,7</sup> Hypoglycemia should be treated

with intravenous dextrose, and seizure should be treated with benzodiazepines.<sup>6,7</sup> Glucagon, insulin with glucose, and calcium salts are also used to reverse symptoms.<sup>8</sup> Lipid emulsion therapy is particularly useful for lipophilic beta-blockers.<sup>9</sup>

Overdose of aripiprazole is limited to mild sedation in most cases.<sup>10,11</sup> Hemodynamic instability and cardiovascular disturbances are rare.

Although lithium poisoning can cause altered mental status and central nervous system symptoms such as delirium, tremor, and seizure, it is typically associated with gastrointestinal symptoms such as nausea, vomiting, and diarrhea.<sup>12</sup> Medications that cause renal impairment or dehydration such as nonsteroidal anti-inflammatory drugs and diuretics increase the risk of lithium toxicity.<sup>13</sup>

Metformin overdose most commonly causes gastrointestinal symptoms such as nausea and abdominal pain.<sup>14</sup> Tachypnea develops during increased acidosis. In severe cases, altered mental status, hypotension, and tachycardia can also occur.<sup>15</sup> High serum levels of metformin can also cause hypoglycemia, especially when taken concomitantly with other glucose-lowering medications. Hyperglycemia has also been reported.<sup>15</sup> Metformin-associated lactic acidosis, although rare, was associated with a mortality rate of 18% (2 of 11) in an analysis of 330 patients with diabetes.<sup>16</sup> While this patient's symptoms may resemble those of metformin toxicity, the pill counts indicate that the patient did not take more than his prescribed dosage. Metformin was a maintenance medication prescribed at a low initial dose of 500 mg twice daily. Since there were no new medications that may have contributed to metformin accumulation, metformin toxicity is not the most likely cause of the patient's symptoms.

## CASE CONTINUED

After 3 days in the ICU, the patient was weaned off vasopressors and mechanical ventilation due to improved hemodynamic status and respiratory function. He was then transferred to the medical floor and appeared to be at his baseline emotional and cognitive state. There was no readily identified reason for his medical presentation; therefore, psychiatry was consulted to evaluate the patient for possible overdose. The patient denied any intentional overdose. Of note, he was recently discharged from a 10-day hospital stay at a psychiatric unit following a manic episode. There, medications were changed including initiation of aripiprazole and fluoxetine. A pharma-

cogenomics consult was ordered to ascertain the role that drug-drug and drug-gene interactions may have played in his presentation.

### Pharmacogenomics overview

Pharmacogenomics is the study of how an individual's genes affect the response to drugs and possible clinically significant changes to drug metabolism. Given the complexity of translating genetic variants to clinical recommendations, pharmacogenomic test results are typically classified by metabolizer status (ie, phenotype) for each genetic variant (ie, genotype)—for example, CYP2D6 normal metabolizer or CYP2C19 poor metabolizer.<sup>17</sup> Zanger and Schwab<sup>18</sup> reported CYP2D6 is involved in the metabolism of an estimated 25% of prescribed medications as cited in Meloche et al,<sup>17</sup> and dosing recommendations or impacts of pharmacogenomic variants can be found in select US Food and Drug Administration-approved package inserts or in the guidelines from the Clinical Pharmacogenetics Implementation Consortium.<sup>19–21</sup>

**Of the more than 50 cytochrome P450 enzymes, 6 are involved in the metabolism of more than 90% of medications**

### Drug metabolism

The pharmacokinetics of medications involves 4 stages: absorption, distribution, metabolism, and elimination. Variations in genes that code for enzymes can potentially impact the pharmacokinetics of many drugs. Of the more than 50 cytochrome P450 (CYP) enzymes, 6 are involved in the metabolism of more than 90% of medications.<sup>22</sup> Drugs that are activated or inactivated by CYP enzymes are known as substrates, while drugs that impact the functioning or production of CYP enzymes are known as inhibitors or inducers.

Baseline enzyme activity can also vary based on inherited genetic variants for different enzymes. For any given CYP enzyme, the majority of the population are normal metabolizers. However, for certain CYP enzymes, an individual could be a rapid metabolizer, which indicates an increase in that specific enzyme activity. Intermediate metabolizers have reduced enzyme activity, and poor metabolizers have even further reduction in enzyme activity. Other factors such as age, organ function, and other medications can affect CYP-mediated metabolism of medications, or exert their own, independent effect. All of these

factors taken together ultimately inform the patient's therapeutic response and possible occurrence of adverse effects.

### POTENTIAL DRUG-DRUG AND DRUG-GENE INTERACTIONS

**2** Which of the patient's home medications have potential drug-drug and drug-gene interactions with metoprolol?

- ☐ Clonazepam
- ☐ Aripiprazole
- ☐ Fluoxetine

Before admission, the patient was taking standard doses of 2 CYP2D6 substrates: metoprolol 100 mg daily (usual range 100–200 mg daily)<sup>20</sup> and aripiprazole intramuscular (400 mg every 4 weeks).<sup>19</sup> The prescribing information for aripiprazole recommends a 50% dose reduction for known CYP2D6 poor metabolizers.<sup>18</sup> The metoprolol prescribing information reports higher plasma concentrations of metoprolol in CYP2D6 poor metabolizers.<sup>20</sup> A heart rate reduction of 3 beats per minute while taking metoprolol was reported in a 15-study meta-analysis (N = 1,146) in CYP2D6 poor metabolizers, though the clinical significance of these findings is unclear.<sup>17</sup>

When these medications had been previously prescribed, the CYP2D6 phenotype for the patient was unknown. CYP2D6 genotyping was performed during this admission to help guide selection and dosing of future medications. The patient's pharmacogenomic testing results are shown in **Table 2**.

Pharmacogenomic testing showed the patient to be a CYP2D6 (\*4/\*33)2N genotype, which correlates to an intermediate metabolizer phenotype. In CYP2D6 intermediate metabolizers, drug-gene interactions associated with metoprolol and aripiprazole have not been demonstrated to have a clinically significant impact on drug response.

However, 29 days before presentation, the patient started fluoxetine 20 mg daily (usual range 20–60 mg daily), a CYP2D6 inhibitor shown to cause clinically significant inhibition of CYP2D6 enzyme activity.<sup>23</sup> The inhibition of CYP2D6 in a patient with baseline decreased CYP2D6 enzyme activity, such as an intermediate metabolizer, can lead to “phenoconversion” in which the CYP2D6 enzyme activity is similar to that in a CYP2D6 poor metabolizer.<sup>24</sup> It is hypothesized that this combination of drug-drug and drug-gene interactions resulted in an effective beta-blocker overdose, supported by the finding of hypo-

**TABLE 2**  
**Pharmacogenomic testing results**

Gene	Genotype	Phenotype
CYP2C19	*1/*17	Rapid metabolizer
CYP2D6	(*4/*33)2N	Intermediate metabolizer

glycemia, hypotension, and altered mental status at presentation.

Clonazepam does not have known drug-drug interactions with metoprolol. It is primarily metabolized by CYP3A enzymes.

## MEDICATIONS THAT REQUIRE PHARMACOGENOMIC TESTING

**3** Which of the following medications requires pharmacogenomic testing in at-risk populations?

- ☐ Aripiprazole
- ☐ Fluoxetine
- ☐ Metoprolol
- ☐ Carbamazepine

All these medications have known potential drug-gene interactions. Populations at risk include patients concurrently taking medications with potential drug-drug interactions or patients with comorbidities making them more vulnerable to adverse reactions. No requirement on dose adjustment for metoprolol or fluoxetine based on CYP2D6 phenotype currently exists. The aripiprazole package insert recommends dose adjustment in known CYP2D6 poor metabolizers, but testing is not required prior to therapy initiation.<sup>19</sup> Only a few medications have mandated pharmacogenomic testing prior to use in the FDA-approved prescribing information. These are typically drug-gene associations with high safety risk that provide straightforward and clinically actionable results, such as the avoidance of carbamazepine in patients who are *HLA-B\*15:02*-positive.<sup>25</sup> Other commonly used medications that impact the CYP pathway have been previously described.<sup>26</sup>

## Routine pharmacogenomic testing

There are several challenges to implementing routine, universal pharmacogenomic testing, as well as logistical concerns regarding cost and availability. Currently, only a limited number of third-party payers reimburse for testing. Those that cover pharmacogenomic testing may have limited coverage based on

indication or previous medication history. Most laboratories do not offer point-of-care testing, which is needed in urgent care situations.

The lack of strong clinical data limits decision-making based on pharmacogenomic test results for many drug-gene pairs. A few pairings, such as carbamazepine and *HLA-B\*15:02*, have clearly defined appropriate action based on results of pharmacogenomic testing. However, for other pairs, such as the heart rate reduction with metoprolol seen in CYP2D6 poor metabolizers demonstrated by Meloche et al,<sup>17</sup> it is not clear what, if any, clinical action should be taken.<sup>17,25</sup>

The utility of routine pharmacogenomic testing must also consider other patient-specific clinical factors, such as comorbid disease states and drug-drug interactions. There are reports of patients tolerating metoprolol even while taking an antidepressant that acts as a strong CYP2D6 inhibitor, making it unclear if routine, empiric dose adjustments should be made.<sup>27</sup> Evaluation of these common yet complex interactions necessitates the continued involvement of a pharmacotherapy specialist and disease-state expert to interpret and apply the results of pharmacogenomics testing.

## FURTHER MANAGEMENT

The patient's symptoms were suspected to be a result of possible drug-drug and drug-gene interactions. Pharmacogenomic testing revealed that the patient is a CYP2D6 intermediate metabolizer, which puts him at potential risk for adverse reactions to medications metabolized by CYP2D6. The use of a strong CYP2D6 inhibitor likely further decreased his CYP2D6 enzyme activity. From the clinical team's standpoint, the use of several medications metabolized by this enzyme likely precipitated a "perfect storm" of decreased metabolism and increased serum concentrations of those agents. This combination may have ultimately led to the patient's symptoms, which were indicative of beta-blocker overdose and respiratory failure. This understanding of a potential drug-drug and drug-gene interaction identified by inpatient pharmacogenomic testing resulted in discontinuation of the strong CYP2D6 inhibitor fluoxetine.

On day 7, the patient was discharged to an acute care facility to receive intensive physical therapy due to deconditioning. He was in stable condition with good hemodynamic status and respiratory function. He was instructed to follow up with his psychiatrist regarding changes to his medications. Lab values such

as electrolytes, creatinine, glucose, and lithium levels continued to be monitored.

Medical records indicate the patient has been mentally and physically stable since his medications were adjusted according to his pharmacogenomics testing results. He has been saving money by working alongside his father and losing weight through regular exercise. Although he endorses some generalized anxiety, no acute psychiatric or medical episodes have been reported since his hospitalization.

### ■ UTILITY OF PHARMACOGENOMIC TESTING

Our patient's experience could lend credence to an argument favoring increased use of preemptive pharmacogenomic testing. Knowledge of CYP2D6 intermediate metabolizer status in the setting of fluoxetine initiation could have allowed for anticipation of the patient's "phenoconversion" to a poor metabolizer. This may have in turn led to dose reduction of aripiprazole to account for a new effective phenotype of CYP2D6 poor metabolizer. This knowledge could also have led to use of an alternative beta-blocker not metabolized by CYP2D6 or use of an alternative medication class. Similarly, these results may have led to avoidance of fluoxetine in favor of another selective serotonin reuptake inhibitor without CYP2D6 inhibition.

While pharmacogenomics may have illuminated these drug-gene interactions, the theorized inciting interaction of fluoxetine inhibition of CYP2D6 is a well-known drug-drug interaction. Fluoxetine-mediated inhibition of CYP2D6 would be expected to reduce aripiprazole metabolism, irrespective of baseline phenotype. Similarly, symptomatic bradycardia with metoprolol in the presence of the CYP2D6 inhibitor bupropion has also been described in a non-poor metabolizer.<sup>28</sup> Therefore, some degree of drug-drug interaction could have been anticipated, and selection of alternatives to fluoxetine and metoprolol would have been reasonable and clinically appropriate even without pharmacogenomics testing results.

Clinicians can routinely use available drug-drug interaction checkers, many of which are integrated into electronic medical record and prescribing systems. Sources also exist for evaluating drug-gene interactions, but they are rarely embedded in the

prescribing process and therefore can easily be missed.

The true challenge often lies in understanding possible drug interactions and their clinical significance if they occur. Medications are routinely used in combination without clinically significant interactions or adverse reactions when managed with appropriate monitoring. A good steward of healthcare resources would conclude that preemptive pharmacogenomic testing was likely not necessary in this case. The selection of an alternative to fluoxetine such as citalopram, sertraline, or escitalopram would have been an appropriate first-line selective serotonin reuptake inhibitor. The use of any of these medications would have avoided the known drug-drug interactions between fluoxetine and both aripiprazole and metoprolol. However, a role remains for pharmacogenomics testing in specific circumstances such as if these interactions were unavoidable due to previous therapy failure with alternative agents.

### ■ TAKE-HOME POINTS

- Pharmacogenomic testing can identify patients at higher risk for adverse events related to drug-drug and drug-gene interactions.
- Potential drug-drug interactions should be checked and patients appropriately monitored for adverse reactions.
- Universal pharmacogenomic testing is currently not feasible due to cost, availability, insurance, and other limitations.
- Careful assessment of the severity of potential reactions, cost, and the opportunity to use an alternative regimen that avoids the interaction of concern entirely should be considered before performing pharmacogenomic testing.
- As more is known about pharmacogenomics and possible personalization of therapeutic regimens, continual evaluation of clinical considerations that warrant testing should occur to facilitate both resource stewardship and optimal patient care. ■

### ■ DISCLOSURES

Dr. Hockings has disclosed consulting for MCG Health. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.



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## Q: Do all patients with primary pulmonary coccidioidomycosis need antifungal therapy?

**A:** No. Patients diagnosed with primary pulmonary coccidioidomycosis (PPC) who are asymptomatic or mildly symptomatic do not require treatment and can be monitored closely. Treatment should be initiated in patients with severe disease, extrathoracic dissemination, or risk factors such as immunosuppression.

### ■ WHEN SHOULD WE SUSPECT PRIMARY PULMONARY COCCIDIOIDOMYCOSIS?

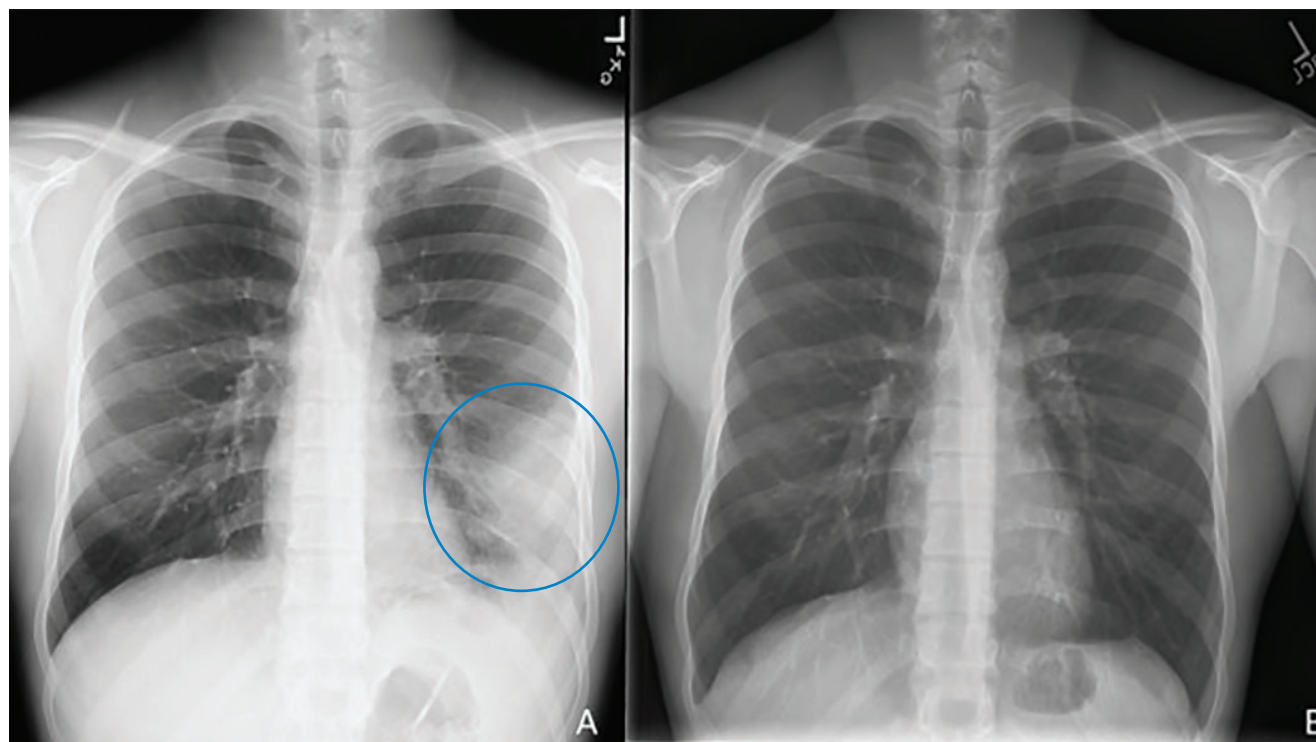
Coccidioidomycosis, known colloquially as “valley fever,” is a fungal infection caused by the dimorphic fungus *Coccidioides*.<sup>1</sup> It is endemic to the southwestern United States (Arizona and California) and northwestern Mexico. In fact, up to 29% of community-acquired pneumonia cases in Arizona are secondary to PPC.<sup>2</sup> More recently, eastern Washington state has also been recognized as an endemic region.<sup>3</sup>

Inhalation of coccidioidal spores from dust can result in this illness, and the symptoms are clinically indistinguishable from those of community-acquired pneumonia.<sup>4</sup> The most common presenting symptoms include fatigue, cough, headache, and night sweats.<sup>5</sup> Patients may also have various systemic or rheumatologic complaints. It is important to note, however, that approximately 60% of patients with PPC are asymptomatic, and symptomatic patients often have self-limited disease.<sup>6</sup> PPC should be suspected in individuals with an appropriate travel history who present with symptoms of pneumonia, and further laboratory testing should be undertaken to confirm the diagnosis.

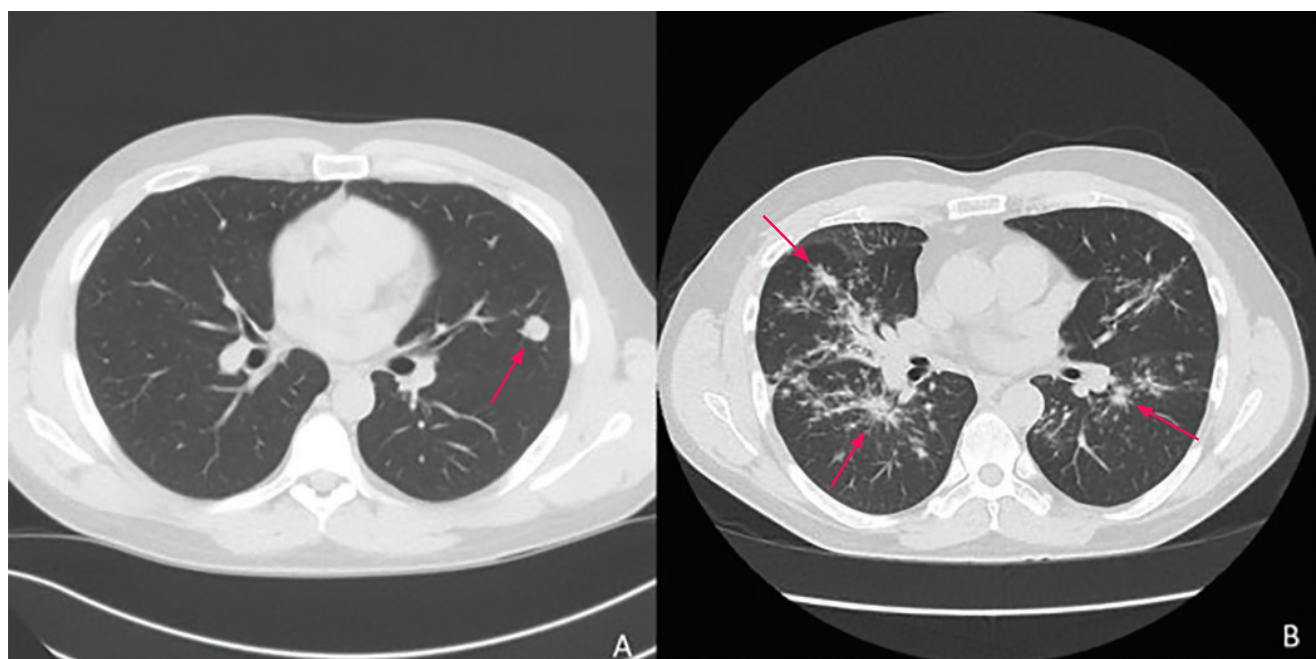
### ■ HOW IS PRIMARY PULMONARY COCCIDIOIDOMYCOSIS DIAGNOSED?

Diagnosis begins with clinical suspicion and an appropriate exposure history, along with clinical, radiographic, and laboratory features suggestive of PPC. Typical symptoms resemble pneumonia or bronchitis and are hard to distinguish from other bacterial and viral infections. Radiologic features (**Figure 1, Figure 2**) vary from pulmonary infiltrates (in most patients) to less common findings of pulmonary nodules or cavities, pleural effusions, and “tree-in-bud” changes.<sup>7</sup>

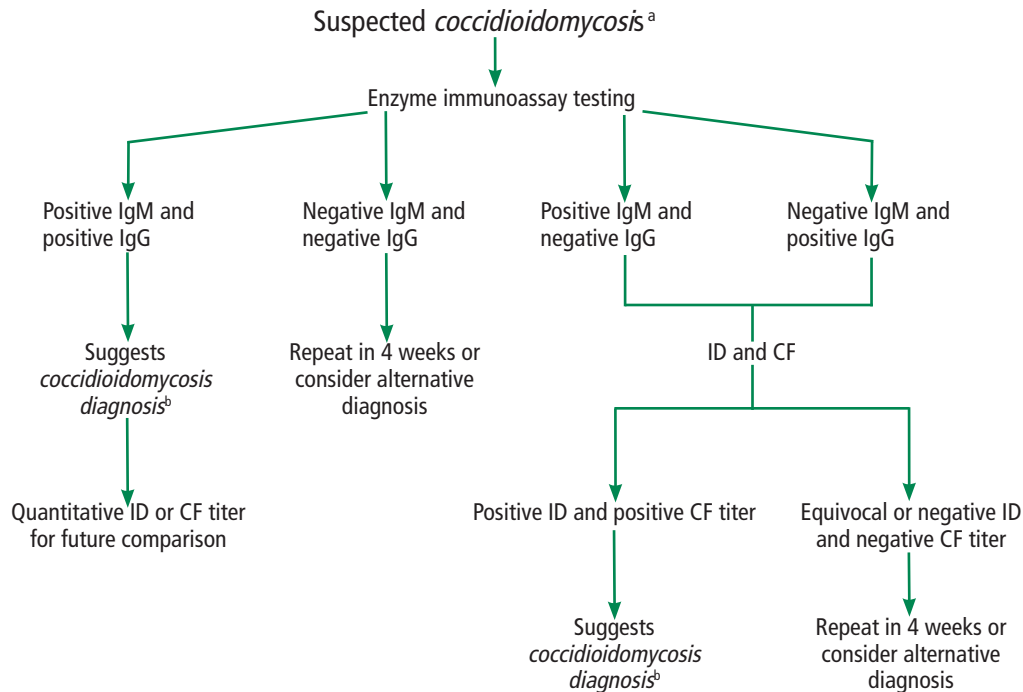
If sputum is available, culture provides a proven diagnosis since there is no state of colonization. However, most patients manifest a dry cough, and serologic tests are most commonly used for diagnosis.<sup>8</sup> These include enzyme immunoassay (EIA), immunodiffusion, and complement fixation testing to detect immunoglobulin (Ig) M and IgG antibodies. Maximal sensitivity for diagnosis of coccidioidomycosis occurs with positive test results for both IgM and IgG by EIA (**Figure 3**).<sup>7</sup> An isolated positive IgM by EIA is often a false-positive and thus requires either repeat testing to demonstrate seroconversion or subsequent microbiologic, cytologic, or histopathological testing from tissue biopsy or body fluid (eg, bronchoalveolar lavage). An isolated positive IgG by EIA antibody titer is typically confirmed by further testing with immunodiffusion and complement fixation IgG and IgM. Complement fixation IgG provides a baseline quantitative titer that can be followed over time. However, the turnaround time for immunodiffusion and complement fixation testing is long because these tests often have to be sent to a reference laboratory.<sup>1,7</sup> Sensitivity of immu-



**Figure 1.** (A) A 22-year-old male with a left lower lung infiltrate (circle). (B) Repeat imaging 8 months after initiation of treatment showed interval clearance of previously visualized opacity.



**Figure 2.** (A) A 1.5-cm lingular nodule with adjacent satellite nodularity (arrow) likely a noncalcified granuloma related to coccidioidomycosis. (B) Bilateral bronchovascular and perilymphatic nodules (arrows) seen in all lung fields, with subsequent bronchoalveolar lavage studies growing *Coccidioides* spp.



**Figure 3.** Algorithm for serologic testing in suspected coccidioides infection.

<sup>a</sup> Suspected in the presence of typical symptoms and radiographic findings.

<sup>b</sup> Definitive diagnosis requires positive biopsy, tissue culture, or body fluid culture.

CF = complement fixation testing; ID = immunodiffusion testing; IgG = immunoglobulin G; IgM = immunoglobulin M

nodiffusion is approximately 73%, and for complement fixation approximately 75%.<sup>7</sup> In the case of extrathoracic coccidioidomycosis (ie, involvement of skin and soft tissue, bone and joint, or meninges), especially in immunosuppressed patients, testing for serum or urine antigen may also be useful.<sup>7</sup>

## TREATMENT OPTIONS

The decision to treat PPC should be individualized, since most patients will not require antifungal treatment (Table 1). The current Infectious Diseases Society of America (IDSA) guidelines recommend patient education, close observation, and supportive measures such as a reconditioning physical therapy program for patients with mild symptoms, or for those who have significantly improved by the time of diagnosis.<sup>4</sup> Treatment is recommended for patients with prolonged symptoms (for example, symptoms that persist for > 2 months or severe night sweats for > 3 weeks), extensive pulmonary involvement (eg, > 50% involvement of one or both lungs), or severe disease

requiring hospitalization. Additionally, guidelines recommend treating patients with concurrent diabetes and those with underlying cellular immune deficiencies, such as transplant patients on antirejection therapy, persons with human immunodeficiency virus infection with CD4 counts below 250, and patients on high-dose corticosteroids. Treatment can be considered for patients of African or Filipino descent.<sup>4</sup>

No randomized trials have been conducted to assess whether treatment of uncomplicated coccidioid infection improves time to symptom-free period or prevents progression of disease. However, experts have observed benefit in treatment of patients with severe disease. Expert opinion varies, but IDSA guidelines suggest that severe disease can be considered when one or more of the following are present: weight loss greater than 10%, intense night sweats for more than 3 weeks, involvement of more than half of one lung or of both lungs, significant adenopathy, antibody titers greater than 1:16, symptoms for longer than 2 months, or inability to work.<sup>4</sup>

**TABLE 1**  
**Situations in which to consider antifungal therapy**

- Risk factors for severe disease: diabetes mellitus, African or Filipino descent, age over 65, immune compromise
- Worsening symptoms for 4 to 6 weeks
- Persistent symptoms for 8 weeks
- Extrapulmonary dissemination

If initiated, treatment of mild to moderate PPC should begin with an orally absorbed azole such as fluconazole at a daily dose of at least 400 mg, for approximately 3 to 6 months or as driven by illness course. It is important to counsel patients on possible fluconazole-related adverse effects such as gastrointestinal upset, frequent cheilitis, reversible alopecia, and skin and nail changes, as these effects could result in medication nonadherence. Itraconazole is another first-line option, but fluconazole is usually preferred due to its lower cost, fewer drug interactions, and better patient tolerance.

In patients whose PPC is rapidly progressing—as evidenced clinically by signs such as need for hospitalization, worsening mental status, or increasing oxygen requirements—IDSA guidelines recommend consideration of liposomal amphotericin B.<sup>4</sup> With biopsy-proven extrapulmonary disseminated disease, higher doses of fluconazole (such as 800 mg daily) should be considered. Patients failing to improve on fluconazole or itraconazole should be considered for higher-generation azole therapy such as posaconazole. Infectious disease consultation for these patients should be considered.

## ■ EXPERT OPINION ON MONITORING OF PATIENTS WITH PPC

Patients should be followed regularly for improvement in clinical symptoms, serology, and radiographic findings in order to monitor for disease complications. These include symptomatic cavitary lung lesions accompanied by secondary bacterial infection, pain, or hemoptysis (hemoptysis would require consideration of surgical excision), or dissemination to the meninges, skin, or bone and joint.

Patients can initially be seen in the office at least every 4 to 12 weeks, depending on how ill they are, and this monitoring can be extended to every 6

months as symptoms improve. Complement fixation testing for anticoccidioid antibodies should also be repeated every 12 weeks, even with clinical improvement, to ensure titers decrease, as an increase in titers could be a sign of treatment failure or progression to extrapulmonary dissemination. Titers greater than 1:32 may suggest continued fungal growth or refractory disease, and changes in treatment could be considered.<sup>9</sup> Similarly, if there is evidence of abnormal imaging on initial evaluation, this should be checked again at approximately 12 weeks and again several months later to monitor for residual disease or resolution. Serum transaminase levels should be monitored initially and then periodically, as antifungal therapy has been associated with hepatocellular injury.<sup>10</sup>

## ■ SPECIAL CONSIDERATIONS IN PREGNANCY

Pregnant patients with nonsevere disease can be monitored as other immunocompetent patients. Azole therapy has been associated with increased rates of spontaneous abortion and birth defects in infants, thus warranting a US Food and Drug Administration warning.<sup>6</sup> Thus, azoles should be avoided when possible during the first trimester. Amphotericin is effective for pregnant patients and safe for the fetus but has multiple known adverse effects, including effects on the kidneys and electrolytes of the patient. Because of the potential for both severe coccidioidomycosis and harms from treatment, an infectious disease consultation is reasonable.

## ■ THE BOTTOM LINE

PPC is a fungal infection found most commonly in the southwestern United States and northern Mexico, but outbreaks of travel-associated coccidioidomycosis have been identified around the world. PPC should be considered in the differential diagnosis of patients with recent travel to endemic areas who present with symptoms of pneumonia and bronchitis.

Most patients do not require treatment, but the decision to treat should be individualized and based on a variety of factors. First-line antifungal treatment consists of fluconazole at least 400 mg daily, with certain exceptions such as avoiding its use in the first trimester of pregnancy. Whether treatment is or is not provided, close follow-up of all patients is recommended. ■

## ■ DISCLOSURES

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



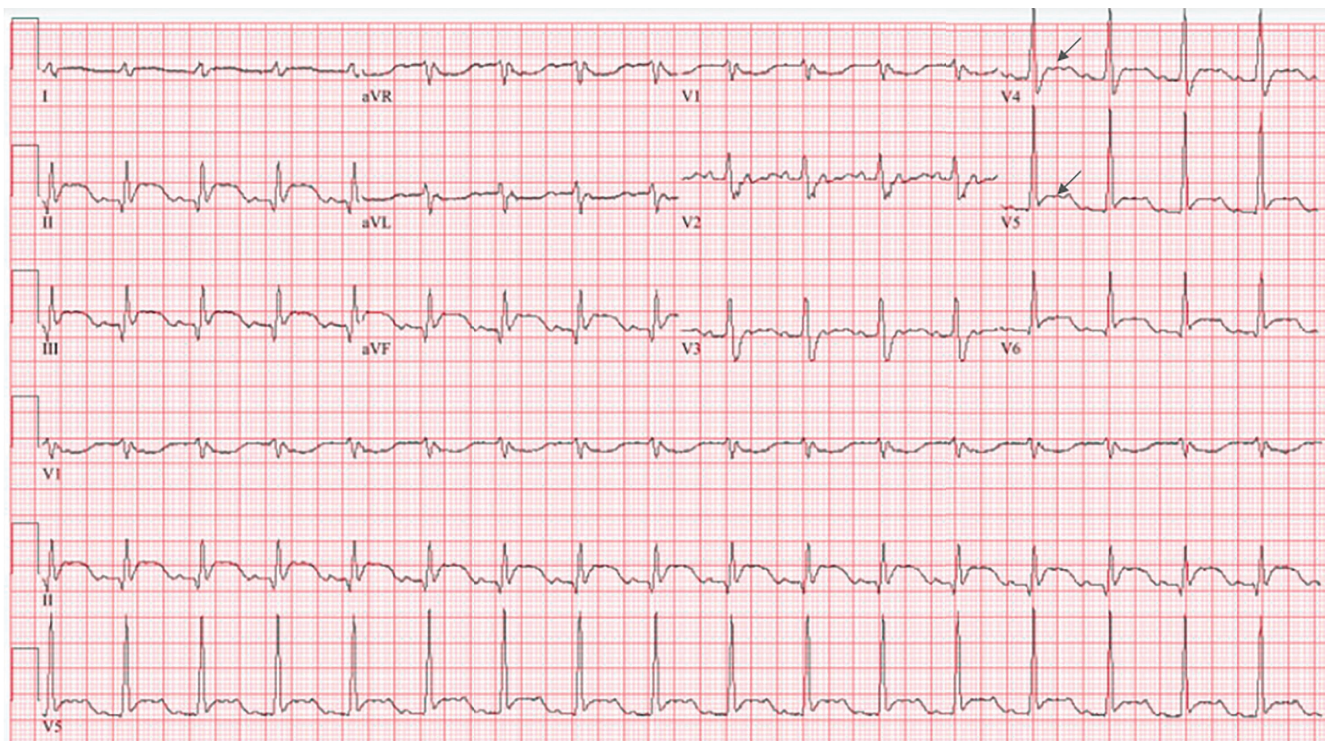
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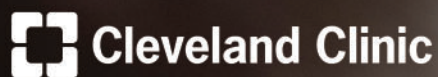
## CORRECTION

In the July 2022 issue, an error appeared in Ganesan S, Kelemen B, Dhaliwal G, Zier L. *An unexpected turn: A 71-year-old man with myocardial infarction*. *Cleve Clin J Med* 2022;89(7):401–407. doi:10.3949/ccjm.89a.21030. The arrows in **Figure 3** were incorrectly placed. The correct figure appears below:

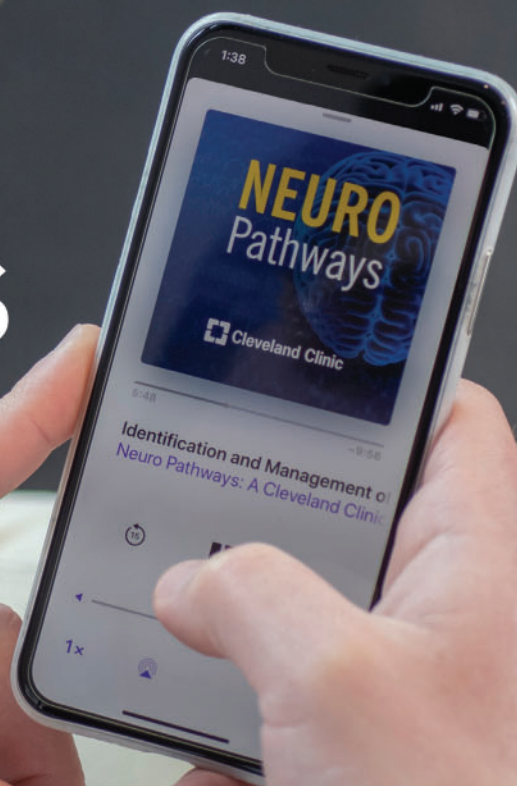


**Figure 3.** On repeat electrocardiography 48 hours after presentation, the ST-segment elevations in leads II, III, and aVF were still present. The ST-segment depressions in aVL and V<sub>1</sub>–V<sub>3</sub> had resolved, and new ST-segment elevations were present in V<sub>4</sub> and V<sub>5</sub> (arrows).

This is now correct on ccjm.org.



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# The role of GLP-1 receptor agonists in managing type 2 diabetes

## ABSTRACT

Glucagon-like peptide-1 (GLP-1) receptor agonists improve glycemic control in patients with type 2 diabetes mellitus, have cardioprotective and renoprotective effects, and do not cause weight gain or significant hypoglycemia. In fact, they have been found to be effective for weight loss in patients with obesity with and without diabetes. They are now the preferred drugs to add to the regimen when oral metformin by itself is not enough to meet the patient's hemoglobin A1c goal.

## KEY POINTS

Long-acting GLP-1 receptor agonists control glycemia a little better than short-acting agents and better than insulin, lowering hemoglobin A1c by about 1%.

Large, randomized clinical trials of GLP-1 receptor agonists have had positive or at worst neutral results in terms of preventing major adverse cardiovascular events in patients with type 2 diabetes who either had cardiovascular disease at baseline or were at high risk of it.

GLP-1 receptor agonists have a protective effect on the kidneys, reducing the risk of macroalbuminuria, but perhaps do not help preserve the glomerular filtration rate as much as sodium-glucose transporter-2 inhibitors.

GLP-1 receptor agonists are recommended as either first-line or second-line therapy regardless of baseline hemoglobin A1c in patients who have established atherosclerotic cardiovascular disease, high risk of atherosclerotic cardiovascular disease, chronic kidney disease, or heart failure.

**T**WO NEW CLASSES OF DRUGS have brought on a major shift in how we manage type 2 diabetes mellitus: glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. We discussed SGLT-2 inhibitors in an earlier article in this *Journal*.<sup>1</sup> Here, we review the evidence regarding the benefits and adverse effects of GLP-1 receptor agonists, aiming to help guide primary care clinicians in using these agents while taking care of their patients who have type 2 diabetes mellitus or obesity.

## ■ HOW THE GUT TALKS TO THE PANCREAS

In healthy people without diabetes, glycemic homeostasis is regulated by pancreatic hormones such as insulin, amylin, and glucagon, as well as by incretin hormones released from the gastrointestinal cells, eg, GLP-1 and glucose-dependent insulinotropic polypeptide.

In response to ingestion of glucose, the L and K intestinal cells release incretin hormones that stimulate pancreatic beta cells, leading to insulin secretion. This mechanism is mainly activated after oral ingestion of glucose rather than intravenous administration, and may be impaired in patients with impaired glucose tolerance or non-insulin-dependent diabetes, leading to hyperglycemia.<sup>2</sup> Incretin's role in reducing hyperglycemia is also mediated by glucagon suppression and delayed gastric emptying.<sup>3,4</sup>

## ■ LONG-ACTING AGENTS LOWER HEMOGLOBIN A1c ABOUT 1%

Several GLP-1 receptor agonists are approved by the US Food and Drug Administration

**TABLE 1**  
**Glucagon-like peptide-1 receptor agonists approved for use in the United States**

Drug	Available doses	Frequency and route	Dose approved for weight management
Exenatide	5 µg, 10 µg	Twice daily subcutaneously	Not approved
Liraglutide	0.6 mg, 1.2 mg, 1.8 mg	Once daily subcutaneously	0.6 mg once daily for 1 week, increase by 0.6 mg daily at weekly intervals to a target dose of 3 mg once daily
Exenatide extended-release	2 mg	Once weekly subcutaneously	Not approved
Dulaglutide	0.75 mg, 1.5 mg, 3 mg, 4.5 mg	Once weekly subcutaneously	Not approved
Semaglutide	0.25 mg, 0.5 mg, 1 mg, 2 mg	Once weekly	Titrate every 4 weeks: 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2.4 mg once weekly
Semaglutide, oral	3 mg, 7 mg, 14 mg	Once daily by mouth	Not approved
Liraglutide-insulin degludec	0.36 mg-10 U 0.5 mg-16 U	Once daily subcutaneously	Not approved
Lixisenatide-insulin glargine	5 µg-15 U 10 µg-30 U	Once daily subcutaneously	Not approved
Tirzepatide	2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg	Once weekly subcutaneously	Not approved

(FDA) for use in patients with type 2 diabetes mellitus, with various formulations intended for use as short-acting monotherapy, long-acting monotherapy, and in combination with basal insulin (Table 1).

Huthmacher et al<sup>5</sup> performed a meta-analysis of 14 clinical trials and calculated that overall, the change in hemoglobin A1c with GLP-1 receptor agonists was  $-0.7\%$  (95% confidence interval [CI]  $-1.2$  to  $-0.2$ ,  $P = .006$ ), and that the reduction was somewhat smaller with short-acting agents ( $-0.5\%$ , 95% CI  $-0.7$  to  $-0.3$ ,  $P < .0001$ ) and greater with long-acting agents ( $-1.0\%$ , 95% CI  $-1.2$  to  $-0.8$ ,  $P < .0001$ ). Notably, more patients achieved their hemoglobin A1c targets ( $< 7\%$  or  $\leq 6.5\%$ , depending on the trial) if they received long-acting agents.<sup>5</sup>

Abd El Aziz et al<sup>6</sup> performed a meta-analysis of 19 clinical trials comparing the addition of GLP-1 receptor agonists vs insulin treatment in patients already receiving oral glucose-lowering agents. GLP-1 receptor agonists lowered hemoglobin A1c by 0.12% more than insulin did ( $P < .0001$ ), with the difference being entirely due to the longer-acting agents. On the other hand, insulin lowered fasting plasma glucose by 32.4 mg/dL more than GLP-1 receptor agonists did ( $P < .0001$ ).<sup>6</sup>

For these reasons, guidelines from the American Diabetes Association (ADA) have shifted.<sup>7</sup> For patients with type 2 diabetes who have atheroscle-

rotic cardiovascular disease or are at high risk for it or who have kidney disease or heart failure, either a GLP-1 receptor agonist or an SGLT-2 inhibitor with demonstrated cardiovascular benefit with or without metformin is recommended, independent of the hemoglobin A1c level (level of evidence A).<sup>7</sup>

## ■ PROTECTING THE HEART AND BRAIN

GLP-1 receptor agonists interfere with several molecular and cellular steps of the atherogenesis process. GLP-1 plays key roles in reducing the production of reactive oxygen species, reducing platelet activation, reducing activation of macrophages and monocytes and their consecutive accumulation in the vascular wall, and inhibiting endothelin production, which in turn, leads to vasodilation. GLP-receptor agonists boost the effects of GLP-1, enhancing these desirable actions.<sup>8-11</sup> Furthermore, these drugs stabilize endothelial cells and reduce plaque hemorrhage and rupture.<sup>12-14</sup> The result of these actions is a slower progression of atherosclerosis.

## Results of randomized trials

Six large randomized trials and a post hoc analysis<sup>15-21</sup> have investigated the safety and efficacy of GLP-1 receptor agonists in patients with type 2 diabetes who also either had known cardiovascular disease or were at high risk of it, using a composite of major adverse



TABLE 2

**Effects of glucagon-like peptide-1 receptor agonists on major adverse cardiovascular events in clinical trials**

Trial	Number of patients	Median follow-up	Cardiovascular disease at baseline <sup>a</sup>	Treatment	Number needed to treat <sup>b</sup>
REWIND <sup>15</sup>	9,901	5.4 years	31.5%	Dulaglutide 1.5 mg subcutaneously weekly	323
SUSTAIN-6 <sup>16</sup>	3,297	2.1 years	2.1 years 60.5%	Semaglutide 0.5 or 1 mg subcutaneously weekly	83
LEADER <sup>17</sup>	9,340	3.8 years	81.3%	Liraglutide 1.6 mg subcutaneously daily	200
ELIXA <sup>18</sup>	6,068	2.1 years	100%	Lixisenatide 10 or 20 µg subcutaneously daily	No benefit
EXSCEL <sup>19</sup>	14,752	3.2 years	70%	Exenatide extended-release 2 mg subcutaneously weekly	No benefit
PIONEER-6 <sup>21</sup>	3,183	1.3 years	85%	Semaglutide 14 mg by mouth daily	No benefit

<sup>a</sup> All patients had longstanding type 2 diabetes and also either had a history of cardiovascular disease or were at risk of it.

<sup>b</sup> Number of patients needed to be treated for 1 year to prevent 1 major adverse cardiovascular event (myocardial infarction, stroke, or death from cardiovascular causes, plus, in the ELIXA trial, hospitalization for heart failure), calculated as the inverse of the absolute risk reduction.

ELIXA = Lixisenatide in Patients With Type 2 Diabetes and Acute Coronary Syndrome; EXSCEL = Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; PIONEER-6 = Oral Semaglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes; REWIND = Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SUSTAIN-6 = Semaglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes

cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes) as the primary end point (Table 2).<sup>15–19,21</sup>

The **REWIND trial** (Researching Cardiovascular Events With a Weekly Incretin in Diabetes)<sup>15</sup> reported statistically significant reductions in major adverse cardiovascular events (relative risk reduction 12%, with a number needed to treat [NNT] of 323, ie, the number of patients who would need to be treated for 1 year to prevent 1 event) and nonfatal stroke (relative risk reduction 24%, NNT 588) in patients who received dulaglutide 1.5 mg once a week compared with placebo. Differences in the rates of nonfatal myocardial infarction and death from cardiovascular causes were not statistically significant. Notably, the REWIND trial had the lowest proportion of randomized patients who had established cardiovascular disease at baseline (only 31%) of the 6 major trials of GLP-1 receptor agonists.<sup>15–21</sup>

The **SUSTAIN-6 trial** (Semaglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes)<sup>16</sup> showed a significant relative risk reduction of 26% (NNT 83) in major adverse cardiovascular events in those who received semaglutide 0.5 or 1 mg compared

with placebo. This difference was primarily driven by a significant relative risk reduction of 39% (NNT 196) in nonfatal stroke in the semaglutide group.<sup>16</sup>

The **LEADER trial** (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results)<sup>17</sup> showed a relative risk reduction in major adverse cardiac events of 13% (NNT 200) and in cardiovascular death of 22% (NNT 250) in patients with type 2 diabetes who received liraglutide compared with placebo. Rates of nonfatal myocardial infarction and nonfatal stroke were lower in the liraglutide group than in the placebo group, but these differences were not statistically significant.<sup>17</sup>

The trial was criticized for differences in the use of cardioprotective medication between the treatment groups. More patients with established cardiovascular disease in the liraglutide group were using beta-blockers, statins, angiotensin-converting enzyme inhibitors, and platelet aggregation inhibitors than in the placebo group, which might have skewed the results in favor of liraglutide.

The **ELIXA trial** (Lixisenatide in Patients With Type 2 Diabetes and Acute Coronary Syndrome)<sup>18</sup> failed to show the same benefit. The ELIXA trial did not have

the between-group differences for baseline cardioprotective medications as in the LEADER trial, and the trial population included patients with type 2 diabetes with a history of either myocardial infarction or hospitalization for unstable angina within the previous 180 days.

**The EXSCEL trial** (Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes)<sup>19</sup> compared 2-mg weekly doses of exenatide with placebo. The incidence of major adverse cardiovascular outcomes was 9% lower in the exenatide group than in the placebo group, but the difference was not statistically significant ( $P = .06$ ).<sup>19</sup> A post hoc analysis of the EXSCEL trial showed that use of SGLT-2 drugs in the placebo group led to a lower incidence of all-cause mortality, which consequently confounded the effect of exenatide in the treatment group.<sup>20</sup>

**The PIONEER 6 trial** (Oral Semaglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes)<sup>21</sup> found that the incidence of major adverse cardiovascular events was 21% lower with oral semaglutide than with placebo, but the difference was not statistically significant ( $P = .17$ ).

## A meta-analysis found that SGLT-2 inhibitors protected the kidney better than GLP-1 receptor agonists

### ■ PROTECTING THE KIDNEYS

The mechanisms underlying the renal protective effects of GLP-1 receptor agonists are not completely understood. What is known is that these drugs lower hemoglobin A1c, weight, and blood pressure, thereby modifying traditional risk factors for progression of chronic kidney disease and diabetic nephropathy.<sup>22,23</sup> Moreover, GLP-1 receptors can be found in the renal proximal convoluted tubular cells and preglomerular vascular smooth muscle cells in the kidneys, and direct stimulation of these receptors inhibits the sodium-hydrogen exchanger 3 at the brush border of the proximal convoluted tubular cells. This leads to increased natriuresis and consequently reduced blood pressure.

**The AWARD-7 trial**<sup>24</sup> was an open-label multicenter trial that randomized 577 patients with stage 3 and 4 chronic kidney disease and type 2 diabetes to receive dulaglutide 0.75 mg once a week, dulaglutide 1.5 mg once a week, or daily insulin glargine, in combination with insulin lispro for 1 year. The estimated glomerular filtration rate declined more slowly in the 2 dulaglutide groups than in the insulin group, but the

urine albumin-creatinine ratio did not differ between the 3 groups.

Post hoc analysis of some of the large cardiovascular outcome trials of GLP-1 receptor agonists confirmed the renal protective effects:

**The LEADER trial**,<sup>25</sup> in further analysis, showed a relative risk reduction in nephropathic events of 22% (NNT 25) in the liraglutide group compared with placebo. This difference was mainly due to a statistically significant relative risk reduction in new-onset persistent macroalbuminuria of 26% (NNT 32).

**The REWIND trial**,<sup>26</sup> in an exploratory analysis, similarly showed that patients receiving dulaglutide had a relative risk reduction of 15% (NNT 167) in the composite renal outcome and 23% in new macroalbuminuria compared with placebo.

**Zelniker et al**<sup>27</sup> performed a meta-analysis and found that SGLT-2 inhibitors protected the kidney better than GLP-1 receptor agonists did. The relative risk reduction in the composite kidney outcome (new-onset macroalbuminuria, sustained doubling of serum creatinine or a 40% decline in estimated glomerular filtration rate, end-stage kidney disease, or death of renal causes) was 18% with GLP-1 receptor agonists compared with 38% with SGLT-2 inhibitors ( $P < .001$ ). This benefit was mainly driven by a reduction in macroalbuminuria. GLP-1 receptor agonists did not demonstrate the same renal benefits of SGLT-2 inhibitors with regard to reducing the risks of worsening estimated glomerular filtration rate, end-stage renal disease, and renal death.<sup>27</sup>

### ■ EFFECT ON WEIGHT

In studies in rats, stimulation of GLP-1 receptors in the hypothalamus by GLP-1 receptor agonists prevented meal initiation and induced meal termination.<sup>28,29</sup> Evidence of reduced energy intake, suppressed appetite, and reduced food-craving was also noted in human studies, and patients receiving GLP-1 receptor agonists have had modulated taste preference, with lower preference for fatty and energy-dense food, and less pleasure in eating.<sup>30-32</sup> These hypothalamic effects are thought to vary among patients treated with GLP-1 receptor agonists.

#### Clinical trials of GLP-1 agonist for weight loss

Numerous observational and interventional studies of the glycemic effects of GLP-1 receptor agonists in patients with type 2 diabetes have noted that patients receiving these drugs lose weight. Subsequently, several studies evaluated their weight-loss effect in patients without diabetes:

The SCALE (Satiety and Clinical Adiposity—Liraglutide Evidence in Nondiabetic and Diabetic Individuals) Obesity and Prediabetes trial<sup>33</sup> confirmed the efficacy of high-dose liraglutide (3 mg) in combination with lifestyle modifications for weight reduction over 56 weeks.

Frias et al<sup>34</sup> found that patients lost more weight with higher doses of dulaglutide, ie, 3 mg and 4.5 mg, than with 1.5 mg.

The STEP 1 trial (Semaglutide Treatment Effect in People With Obesity)<sup>35</sup> showed that semaglutide in a high weekly dose (2.4 mg) in addition to lifestyle intervention yielded a statistically significant weight reduction of 14.9% from baseline, compared with 2.4% with placebo.

O'Neil et al<sup>36</sup> compared the effects of semaglutide in various doses, liraglutide 3 mg daily, and placebo on weight loss in a head-to-head trial. Patients lost more weight with the active agents than with placebo and lost significantly more weight with semaglutide 0.2 mg or more than with liraglutide 3 mg.

### **Semaglutide is approved for weight loss in patients without diabetes**

High-dose semaglutide is the most effective of the available weight-loss drugs thus far. Of all these drugs, only semaglutide 2.4 mg has been shown to cause a mean weight reduction of at least 10% compared with placebo. Moreover, the weight-reduction plateau noted with other antiobesity medications between 30 and 40 weeks was not seen in the STEP 1 trial.<sup>37–39</sup>

In light of the results of the STEP 1 trial, a weekly subcutaneous dose of semaglutide of 2.4 mg, which is higher than the 1 mg weekly currently approved for diabetes, was recently approved by the FDA for chronic obesity management in patients without diabetes.

## **ADVERSE EFFECTS OF GLP-1 RECEPTOR AGONISTS**

### **Gastrointestinal effects**

Nausea, vomiting, and diarrhea are the most commonly reported adverse effects of GLP-1 receptor agonists. These effects are dose-dependent, often spontaneously resolve with continued treatment, and are more frequent with the short-acting agents than with the long-acting ones. Slow titration of these agents is helpful in increasing their gastrointestinal tolerability.<sup>40</sup>

### **Pancreatitis**

Acute pancreatitis has been linked to the use of exenatide in postmarketing reports submitted to the FDA Adverse Event Reporting System and in observational studies.<sup>41</sup> But large randomized controlled trials did not

confirm this linkage. The LEADER and SUSTAIN-6 trials showed significantly higher levels of amylase and lipase in patients receiving liraglutide and semaglutide compared with placebo, but without a concomitant higher incidence of acute pancreatitis. Similarly, other cardiovascular outcome trials did not show any difference in the rates of acute pancreatitis between patients receiving GLP-1 receptor agonists vs placebo. Furthermore, 2 large meta-analyses revealed that the incidence of acute pancreatitis and pancreatic cancer with GLP-1 receptor agonists was not statistically different from that observed in the comparator groups.<sup>42,43</sup>

The current guidelines of the American Association of Clinical Endocrinologists<sup>44</sup> recommend using GLP-1 receptor agonists with caution if they are needed in patients with type 2 diabetes who have a history of pancreatitis. GLP-1 receptor agonists should be discontinued if patients develop acute pancreatitis while using them.

### **Retinopathy**

Retinopathy has been reported to occur at higher rates in patients treated with semaglutide, liraglutide, dulaglutide, and albiglutide, but this difference was statistically significant only for patients who received semaglutide.<sup>15,17,18</sup> Most of these patients had retinopathy at baseline, and worsening of retinopathy was similarly reported when insulin was started. This suggests that retinopathy could be attributable to rapid glucose lowering rather than to a drug class effect.<sup>18</sup>

### **Hypoglycemia**

Hypoglycemia has occurred at similar rates in patients receiving GLP-1 receptor agonists compared with placebo in the major cardiovascular outcome trials.<sup>45</sup>

### **Medullary thyroid cancer, pancreatic cancer**

Medullary thyroid cancer and pancreatic cancer have occurred in higher rates in studies of rats receiving GLP-1 receptor agonists, but not in human trials.<sup>46,47</sup> Nevertheless, the FDA requires GLP-1 receptor agonists to carry a black-box warning regarding the risk of thyroid C-cell tumors, and it recommends against using them in patients with a personal or family history of medullary thyroid cell cancer or multiple endocrine neoplasia syndrome type 2a or 2b.<sup>48</sup>

## **FUTURE DIRECTIONS**

### **Reversing fatty liver disease**

GLP-1 receptor agonists could, in theory, play a role in slowing and reversing the progression of nonalcoholic fatty liver disease (NAFLD).<sup>49</sup>

In the Lira-NAFLD trial,<sup>50</sup> patients who received liraglutide 1.2 mg daily for 6 months experienced a reduction in liver fat content of 31% ( $P < .0001$ ). Multivariate analysis showed that the reduction in liver fat was associated with baseline liver fat content, age, and reductions in body weight, triglycerides, and hemoglobin A1c. Patients who lost no weight had no reduction in liver fat content.

Newsome et al<sup>51</sup> performed a phase 2 clinical trial that revealed significant resolution of nonalcoholic steatohepatitis (NASH) in 59% of patients treated with semaglutide 0.4 mg for 72 weeks compared with only 17% in patients who received placebo ( $P < .001$ ). The trial found no difference in fibrosis between patients treated with semaglutide compared with placebo.

The current recommended management of NASH and NAFLD remains limited to lifestyle modification, vitamin E supplementation, and pioglitazone in selected patients.<sup>52</sup> GLP-1 receptor agonists are expected to be recommended in the future for treating NAFLD and NASH, if more trials confirm their benefits in treating this condition.

### **Use in polycystic ovary syndrome**

Studies in patients with polycystic ovary syndrome showed a significant drop in testosterone levels and body mass index in those receiving liraglutide or exenatide compared with placebo or metformin.<sup>53,54</sup> Neither of the GLP-1 receptor agonists had effects on menstrual frequency or the levels of sex hormone-binding globulin, fasting glucose, or fasting insulin. Further studies are still needed to evaluate the benefits of GLP-1 receptor agonists in patients with polycystic ovary syndrome.

### **Use in type 1 diabetes**

The ADJUNCT ONE trial (Efficacy and Safety of Liraglutide as Adjunct Therapy to Insulin in the Treatment of Type 1 Diabetes),<sup>55</sup> the ADJUNCT TWO trial,<sup>56</sup> and a large meta-analysis<sup>57</sup> found reductions in hemoglobin A1c, body weight, and total daily dose of insulin, but also highlighted an increase in hyperglycemia with ketosis in patients with type 1 diabetes mellitus receiving liraglutide or exenatide in combination with insulin. This might have been due to insulin dose reductions when liraglutide was initiated. No significant changes in C-peptide were reported in these studies.<sup>55–57</sup>

Currently, GLP-1 receptor agonists are neither recommended nor FDA-approved for use in type 1 diabetes.<sup>7,44</sup> However, in our opinion, adding them off-label to insulin in patients with type 1 diabetes can help the patients lose weight and stabilize their blood sugar levels.

### **Use in combination with glucose-dependent insulinotropic polypeptide**

Evidence is emerging on the benefit of adding glucose-dependent insulinotropic polypeptide (GIP) to boost and complement the efficacy of GLP-1 receptor agonists in multiple ways. GIP has a glucose-dependent effect, stimulating insulin secretion when blood glucose levels are high and increasing glucagon secretion when they are low, hence improving glycemic control without increasing hypoglycemia.

Tirzepatide is an injectable combination GIP and GLP-1 receptor agonist that is currently being investigated as a treatment for type 2 diabetes mellitus. Studies have shown greater reductions in hemoglobin A1c and weight in patients receiving tirzepatide compared with placebo or weekly subcutaneous semaglutide 1 mg.<sup>58</sup> The FDA approved tirzepatide for use in treating type 2 diabetes mellitus on May 13, 2022.<sup>59</sup>

## **REVIEW OF THE GUIDELINES**

According to the ADA 2022,<sup>7</sup> for patients with type 2 diabetes who also have established or a high risk of atherosclerotic cardiovascular disease, established kidney disease, or heart failure, an SGLT-2 inhibitor or GLP-1 receptor agonist with demonstrated cardiovascular benefit with or without metformin is recommended. For patients with heart failure or chronic kidney disease, initiating an SGLT-2 inhibitor first is preferred. Of note, this recommendation is independent of baseline hemoglobin A1c level or individualized A1c target and needs to take into account efficacy, hypoglycemia risk, impact on weight, high cost, risk of side effects, and patient preferences.

The ADA guidelines also suggest prioritizing adding a GLP-1 receptor agonist over initiating basal insulin in patients who need potent injectable therapy for glucose control. However, basal insulin remains the first injectable treatment option in patients with evidence of ongoing catabolism or symptomatic hyperglycemia when hemoglobin A1c is higher than 10%, blood glucose levels are 300 mg/dL or higher, or type 1 diabetes is suspected.

Similarly, the 2020 guidelines of the American Association of Clinical Endocrinologists<sup>44</sup> recommend long-acting GLP-1 receptor agonists or SGLT-2 inhibitors in patients with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease with or without chronic kidney disease, regardless of glycemic control.



## THE BOTTOM LINE

GLP-1 receptor agonists are recommended as either first-line or second-line therapy regardless of baseline hemoglobin A1c in patients who have established atherosclerotic cardiovascular disease, high risk of atherosclerotic cardiovascular disease, chronic kidney disease, or heart failure. Some agents are also approved

for weight management in patients with a body mass index of 27 kg/m<sup>2</sup> or higher with weight-related comorbidities or a body mass index of 30 kg/m<sup>2</sup> or higher. ■

## DISCLOSURES

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

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## SYMPTOMS TO DIAGNOSIS

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# Unilateral atrophic kidney in a 45-year-old woman

A 45-YEAR-OLD WOMAN with a history of hypertension and ischemic stroke at age 26 presented to the emergency department with right-sided flank pain, which had started 2 days earlier. The pain was constant, sharp, nonradiating, worse with movement and coughing, and severe enough to limit ambulation and induce nausea and vomiting. She said she had not recently been injured.

She also reported that for 5 years she has had intermittent left-sided low back pain that radiates to her left foot. Earlier imaging of the lumbar spine showed spinal stenosis and L1-L2 vertebral disc extrusion.

Her hypertension was diagnosed 20 years ago, and she said she adhered to her antihypertensive regimen of amlodipine 10 mg and hydrochlorothiazide 25 mg daily. She previously took lisinopril, but it was discontinued because it made her cough.

The etiology of her prior stroke was undetermined. The patient had never been diagnosed with diabetes mellitus, atrial fibrillation, coronary artery disease, or peripheral vascular disease, but had been actively smoking cigarettes since age 30 (10 pack-years). She reported no residual deficits from her stroke.

## INITIAL EVALUATION AND MANAGEMENT

Her blood pressure was 196/106 mm Hg, pulse regular at 75 beats per minute, temperature 37.5°C (99.5°F), and oxygen saturation between 95% and 100% while breathing room air. She did not appear to be in distress. Pulses were slightly diminished throughout her body, rated 2+ on a scale of 0 to 4+, and there was no carotid bruit. Heart sounds S<sub>1</sub> and S<sub>2</sub> were normal, there were no murmurs, and the point of maximal impulse was not displaced.

Findings on respiratory and abdominal examinations were normal. Her right lumbar region was tender to palpation, but not the costovertebral angle. Her extremities were without edema, joints were without synovitis, and ranges of motion were within normal limits. The cranial nerves were intact, and sensory and motor examinations had no focal findings.

## Laboratory test results

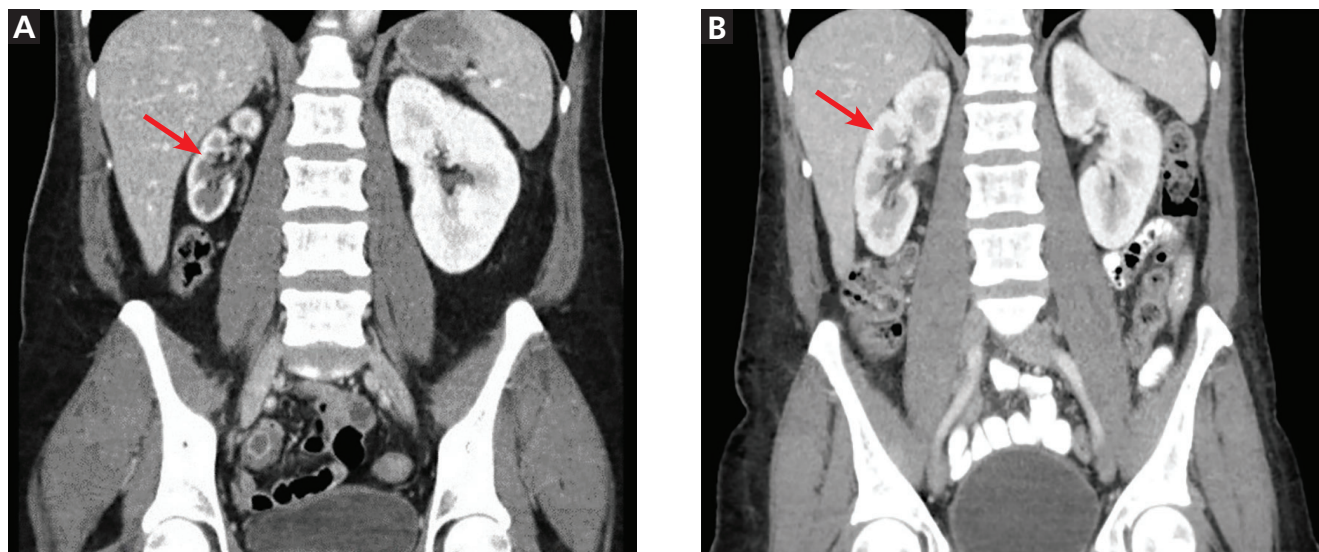
### Results of blood testing were as follows:

- White blood cell count  $6.16 \times 10^9/L$  (reference range 3.70–11.0)
- Hemoglobin 14.5 g/dL (12.3–15.3)
- Hematocrit 40.5% (36.0%–46.0%)
- Platelet count  $290 \times 10^9/L$  (150–400)
- Sodium 135 mmol/L (136–144)
- Potassium 2.4 mmol/L (3.7–5.1)
- Chloride 96 mmol/L (97–105)
- Bicarbonate 27 mmol/L (22–30)
- Creatinine 0.90 mg/dL (0.58–0.96; previous values ranged from 0.75–0.96 mg/dL over a period of 10 years)
- Estimated glomerular filtration rate (eGFR) 89 mL/min/1.73 m<sup>2</sup>
- Calcium 9.5 mg/dL (8.5–10.2)
- Albumin 4.4 g/dL (3.9–4.9)
- Alkaline phosphatase 101 U/L (34–123)
- Total bilirubin 0.4 mg/dL (0.2–1.3)
- Alanine aminotransferase 9 U/L (7–38)
- Aspartate aminotransferase 22 U/L (13–35).

### Urinalysis with microscopic examination showed the following:

- Clear
- Hemoglobin negative
- Red blood cells 0–3 per high-power field (0–4)
- White blood cells 0–5 per high-power field (0–5)





**Figure 1.** (A) At presentation, computed tomography showed the right kidney (arrow) measuring only 6.2 cm. (B) One year earlier, the right kidney (arrow) had measured 10.1 cm.

- Protein 1+ on a scale of trace to 4+
  - Urine sediment negative for casts
  - Random urine protein-to-creatinine ratio 0.52.
- Results of additional testing were as follows:**
- Urine toxicology screen positive for cannabinoids, negative for amphetamines and cocaine
  - Plasma aldosterone concentration 16.2 ng/dL (3.1–35.4)
  - Plasma renin concentration 103.1 pg/mL (2.5–81.6)
  - Serum AM cortisol 5.4 µg/dL (5.3–22.5).

**Comment.** These laboratory results reveal hypokalemia, normal renal function, and elevated renin. The urine toxicology screen and aldosterone, renin, and cortisol levels were obtained as part of a secondary hypertension workup. The hypokalemia was attributed to elevated renin.

### A new finding on imaging

The patient's pain was initially believed to be musculoskeletal, so she was given acetaminophen, cyclobenzaprine, and a lidocaine patch. However, this gave only minimal relief, prompting computed tomography (CT) of the abdomen and pelvis with intravenous contrast to look for other causes.

CT showed that the right kidney measured only 6.2 cm in length, while the left kidney was 10.2 cm. This was new: 1 year earlier, the right kidney had measured 10.1 cm (**Figure 1**). There were no acute radiographic abnormalities in the lumbar spine or visceral organs. Even though the study was not tailored to evaluate

the renal arteries, it showed the right renal artery to be very narrow in caliber.

The patient's history of hypertension along with this new radiographic finding of right kidney atrophy with small caliber of the right renal artery raised suspicion for renal artery stenosis, and the patient was admitted for further evaluation.

### FIBROMUSCULAR DYSPLASIA: A CAUSE OF RENAL ARTERY STENOSIS

**1** All of the following features of our patient's case raise suspicion of fibromuscular dysplasia, except which one?

- ☐ Ischemic stroke at age 26
- ☐ Onset of hypertension before age 35
- ☐ Unilateral atrophic kidney
- ☐ Preserved eGFR, inactive urine sediment, and non-nephrotic-range proteinuria

All of the above clinical characteristics, except for the patient's preserved eGFR, inactive urine sediment, and non-nephrotic-range proteinuria, raised our suspicion for renal artery stenosis due to fibromuscular dysplasia. This is because several other causes of secondary hypertension, including primary aldosteronism, atherosclerotic renal artery stenosis, pheochromocytoma, hypercortisolism, hypothyroidism, and primary hyperparathyroidism, are also characterized by preserved kidney function and a relatively bland urinalysis.



The narrowing of the patient's right renal artery could have been due to several pathologic processes, including stenosis or dissection. Renal artery stenosis and dissection may have similar clinical manifestations including progressive renovascular hypertension, changes in kidney function, and symptoms of kidney infarction such as flank pain.<sup>1</sup> Therefore, a definitive diagnosis cannot be discerned until additional imaging studies are performed.<sup>2</sup>

Atherosclerotic disease is the most common cause of renal artery stenosis, accounting for up to 90% of all cases.<sup>3</sup>

Fibromuscular dysplasia, the second most common cause, is a noninflammatory vascular disorder affecting multiple arterial beds.<sup>4</sup> In addition to stenosis, it can cause aneurysm and dissection.<sup>5</sup> It mainly affects the renal arteries and extracranial cerebrovascular arteries, and nearly half of patients may have disease in more than 1 site.<sup>6</sup>

Fibromuscular dysplasia commonly manifests as hypertension, flank pain, headache, tinnitus, neck pain, and stroke, reflecting involvement of the aforementioned arteries.<sup>7,8</sup> Transient ischemic attack and stroke are due to complications such as aneurysm rupture, dissection, or cerebral thromboembolism.<sup>9</sup> Our patient's history of ischemic stroke at age 26 without traditional risk factors for atherosclerosis aside from hypertension, and in the absence of atrial fibrillation, points to fibromuscular dysplasia.

The patient's early onset of hypertension made us suspect renovascular hypertension rather than primary hypertension. Renal fibromuscular dysplasia causes renovascular hypertension through decreased renal perfusion leading to activation of the renin-angiotensin-aldosterone system with subsequent sodium and water retention. These effects are prominent in patients with a solitary functioning kidney or with bilateral involvement. There are also downstream effects: increased intrarenal prostaglandin concentrations, increased sympathetic nervous system activity, and decreased nitric oxide production. Flank pain, renal infarction, and eventually, atrophic kidneys can manifest later in the disease with development of active renal ischemia, aneurysm rupture, or renal artery dissection.

In adults, kidney size is clinically less relevant than kidney function. Atrophy is usually defined as a reduction in kidney length of more than 1 cm,<sup>10,11</sup> and this patient's right kidney had decreased in size by almost 4 cm, to less than 7 cm. Although our patient does have some atherosclerotic risk factors (hypertension and tobacco use), her history of ischemic

stroke at age 26 expanded the differential diagnosis to include nonatherosclerotic causes of kidney atrophy, especially fibromuscular dysplasia. In addition, smoking increases the risk of developing atherosclerosis as well as fibromuscular dysplasia.<sup>12</sup>

## ■ DIAGNOSIS OF RENAL ARTERY STENOSIS

**2** What would be the best initial diagnostic test for renal artery stenosis in this patient?

- ☐ CT angiography
- ☐ Duplex ultrasonography
- ☐ Magnetic resonance angiography
- ☐ Digital subtraction angiography

Noninvasive diagnostic testing for renal artery stenosis with CT angiography, magnetic resonance angiography, or duplex ultrasonography should be pursued if clinical findings suggest the patient's hypertension may be due to renovascular disease.

**Atherosclerotic disease is the most common cause of renal artery stenosis, accounting for up to 90% of all cases**

CT angiography and magnetic resonance angiography are highly sensitive and specific for diagnosing atherosclerotic renal artery stenosis and are preferred over duplex ultrasonography, especially in patients with normal renal function, as they involve the use of contrast media.<sup>13,14</sup> Duplex ultrasonography has lower spatial resolution and is highly operator-dependent.<sup>13,14</sup>

However, we suspected our patient had fibromuscular dysplasia, which frequently involves distal renal arterial segments. Although CT angiography has respectable diagnostic accuracy for fibromuscular dysplasia involving the main renal arteries,<sup>15</sup> both CT angiography and magnetic resonance angiography have low sensitivity, ranging from 22% to 28%, for detecting distal disease in the intrarenal portion of the renal artery.<sup>16,17</sup> Duplex ultrasonography can detect increased blood flow velocities and hemodynamically significant stenotic lesions in the middle and distal portions of the renal artery, which are frequently involved in fibromuscular dysplasia.<sup>18</sup>

Invasive diagnostic procedures such as digital subtraction angiography are warranted if a patient's clinical characteristics are such that the benefits of a

potential revascularization of a stenotic lesion would outweigh the risks of undertaking the procedure (see “Indications for renal revascularization” section, below).<sup>19</sup> Digital subtraction angiography is the standard and has the highest spatial resolution. It is less frequently performed as the initial test, but when clinical suspicion is high and the results of noninvasive tests are inconclusive, it is recommended to establish the diagnosis of renal artery stenosis.<sup>20</sup> In practice, it may also be performed once the diagnosis of renal artery stenosis is established by a noninvasive imaging test and revascularization is planned, after weighing the potential risks and benefits.<sup>21</sup>

For patients with diminished renal function that prohibits the use of radiocontrast agents, carbon dioxide angiography can be performed for diagnosis, treatment, or both,<sup>22</sup> although its image quality is sometimes suboptimal.

## Renal artery duplex ultrasonography suggested a hemodynamically significant diffuse stenosis of the right renal artery with normal flow on the left

In our patient’s case, we strongly suspected renal artery stenosis, the potential benefit of revascularization was initially unclear, and the patient was at a high-volume medical center with expertise in duplex ultrasonography. For these reasons, duplex ultrasonography was done. However, since duplex ultrasonography is operator-dependent, had the patient not been at a facility with expertise in duplex ultrasonography, CT angiography would have been a reasonable alternative.

## FURTHER EVALUATION

Renal artery duplex ultrasonography suggested a hemodynamically significant diffuse stenosis of the right renal artery with normal flow on the left.

Since imaging did not reveal a characteristic focal or multifocal stenotic lesion, the patient’s renal artery stenosis could not be definitively attributed to fibromuscular dysplasia. Nephrologists were consulted to guide antihypertensive therapy, and vascular surgeons were consulted regarding whether the patient could benefit from a revascularization procedure for renal artery stenosis.

We decided to perform split-function testing to elucidate the contribution of the patient’s right kidney to her total GFR. This involves injection of radioactive technetium 99m diethylenetriamine pen-

taacetate and subsequent imaging as the substance is excreted. Therefore, we did not yet start treatment with an inhibitor of the renin-angiotensin-aldosterone system, which could have affected renal perfusion and confounded the results of the study. Instead, the patient’s blood pressure was controlled with amlodipine 10 mg daily and hydralazine 25 mg twice a day. Split-function testing demonstrated that her left kidney was doing almost all the work, with the right kidney contributing only 10% of the total.

## INDICATIONS FOR RENAL REVASCULARIZATION

3 Which of the following is an appropriate indication for renal revascularization for renal artery stenosis due to fibromuscular dysplasia?

- ☐ Multifocal fibromuscular dysplasia with beaded appearance of the renal artery on angiography
- ☐ Systemic fibromuscular dysplasia with involvement of multiple vascular beds
- ☐ Progressive renal insufficiency with preserved kidney size and difficult-to-control hypertension
- ☐ Concomitant atherosclerotic vascular disease

Patients with renal fibromuscular dysplasia can undergo renal artery revascularization if the procedure is necessary to prevent progressive renal loss or if it is likely to cure their hypertension or at least improve control of blood pressure. Patients are most likely to benefit if they are young, have focal fibromuscular dysplasia, do not have underlying atherosclerotic vascular disease, have resistant recent-onset hypertension despite taking multiple antihypertensive agents, or have unexplained progressive renal insufficiency.

## Managing hypertension in fibromuscular dysplasia

In patients with renal fibromuscular dysplasia, the primary goal of revascularization is to cure difficult-to-control hypertension. This is a more reasonable goal for this patient group than for those who have renal artery stenosis that is due to atherosclerosis.

A meta-analysis<sup>23</sup> of 8 randomized trials in patients with atherosclerotic unilateral renal artery stenosis found no benefit in adding percutaneous transluminal renal angioplasty to antihypertensive therapy in terms of relevant clinical outcomes, including end-stage kidney disease, major adverse cardiovascular events, or death.

Further, very few patients who have unilateral atherosclerotic renal artery stenosis are cured of their hypertension by undergoing percutaneous renal angioplasty (with cure defined as normalization of

blood pressure and stopping antihypertensive therapy).<sup>24,25</sup> Rates are higher in those with unilateral fibromuscular dysplasia,<sup>26,27</sup> 45% in one study.<sup>26</sup>

To date, however, no randomized trials have been done to study percutaneous transluminal renal angioplasty in patients with renal fibromuscular dysplasia. The differences in pathophysiology between atherosclerosis and fibromuscular dysplasia make it difficult to draw conclusions about this treatment for renal fibromuscular dysplasia from data in patients with atherosclerotic renal artery stenosis.

### Focal vs multifocal fibromuscular dysplasia

Fibromuscular dysplasia differs according to whether it is focal or multifocal.

Carbon dioxide digital subtraction angiography, though not necessary for the initial diagnosis of renal fibromuscular dysplasia, may help to classify it as focal or multifocal. Using this imaging, multifocal fibromuscular dysplasia has a beaded appearance, whereas focal fibromuscular dysplasia appears as concentric, smooth, band-like focal or tubular stenosis. It is suggested that young hypertensive patients with focal fibromuscular dysplasia should undergo revascularization, since many of them have resistant hypertension and are at distinct risk of kidney atrophy.<sup>28</sup>

On the other hand, multifocal fibromuscular dysplasia usually presents as hypertension that can typically be controlled on an average of 2 antihypertensive medications.<sup>28</sup> Studies have shown that there is a lower likelihood of hypertension cure after revascularization in patients with multifocal fibromuscular dysplasia, as well as those with longer duration of hypertension and underlying chronic kidney disease.<sup>26,29</sup> The same can be said for extrarenal fibromuscular dysplasia: renal revascularization to cure hypertension in fibromuscular dysplasia is less successful in patients with systemic involvement of multiple vascular beds than in patients with isolated renal fibromuscular dysplasia.<sup>30</sup>

Since the primary goal of revascularization in patients with fibromuscular dysplasia is to cure difficult-to-control hypertension, revascularization may have a minimal role for patients with multifocal fibromuscular dysplasia.

In adults with focal fibromuscular dysplasia, progressive renal insufficiency may occur secondary to either stenosis from intimal fibroplasia or renal artery dissection. Revascularization is indicated in focal fibromuscular dysplasia to prevent kidney atrophy and chronic kidney disease.<sup>6</sup>

Duration of hypertension is also something to

consider. One study suggested that the blood pressure is unlikely to fall after renal revascularization if the duration of renovascular hypertension has been more than 5 years.<sup>31</sup>

### Balloon angioplasty vs stenting

For revascularization, balloon angioplasty is preferred over stenting. There is some evidence that drug-coated balloon therapy may provide a longer-lasting benefit. Revascularization of fibromuscular dysplasia with ex vivo reconstruction and autotransplantation is an appropriate consideration for patients with distal renal artery stenosis or stenosis involving the segmental level vessel. Nephrectomy may be considered for patients with an atrophic kidney and hypertension that is refractory to pharmacologic management.

### ACE inhibitors or ARBs preferred

Hypertension in patients with renal fibromuscular dysplasia is caused by a reduction in kidney perfusion and the subsequent activation of the renin-angiotensin-aldosterone system. This dictates that the initial antihypertensive therapy for these patients be either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB).<sup>32</sup> When kidney perfusion is low, angiotensin II mediates a preferential increase in the resistance of the efferent arteriole. Starting an ACE inhibitor or an ARB blunts this normal autoregulatory response and causes a hemodynamically mediated decline in the GFR.<sup>33</sup> However, despite the initial reduction in filtration in the stenotic kidney, the total GFR is usually maintained due to an approximately equivalent increase in filtration in the contralateral kidney. This is because blocking the vasoconstrictive effect of angiotensin II eventually decreases renal vascular resistance and ultimately preserves renal blood flow.<sup>34</sup>

### CASE CONCLUDED

Our patient had an atrophic right kidney associated with a right renal artery stenotic lesion with lateralization of renal function on split-function testing. She may have been a candidate for percutaneous transluminal renal angioplasty to preserve kidney function if her condition had been discovered earlier, before the kidney had atrophied.

Additional components in this patient's case that we considered included the following: she had long-standing hypertension, she had not yet received optimal antihypertensive therapy, she did not have

intolerance to these medications, and she did not have refractory heart failure.

We explained the risks and benefits of revascularization, with assistance from a vascular surgeon. The patient's atrophic right kidney and diffuse stenosis of the right renal artery precluded her from undergoing revascularization. Instead, we initiated renin-angiotensin-aldosterone system blockade with an ARB. Amlodipine and hydrochlorothiazide were maintained for additional blood pressure control while hydralazine was discontinued.

The patient's right-sided flank pain eventually improved during her hospitalization with conservative management with acetaminophen in combination with muscle relaxants. As mentioned previously, flank pain may be a manifestation of active renal ischemia in patients with renal artery stenosis or dissection prior to the development of kidney atrophy. However, this was less likely to be the cause of flank pain in our patient since there was no evidence of renal infarction on imaging, the right kidney was already atrophied indicating chronic rather than active renal ischemia, and her flank pain improved with conservative measures alone.

The patient was subsequently discharged home on an antihypertensive regimen consisting of losartan, amlodipine, and hydrochlorothiazide. The patient was provided with a list of warning signs for uncontrolled hypertension that would require immediate medical attention. Multidisciplinary follow-up appointments with specialists in vascular medicine and nephrology were arranged. Treatment goals included continued risk-factor reduction to maintain the function of her left kidney.

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## TAKE-HOME POINTS

- Renal artery stenosis refers to impaired blood flow to the kidney secondary to a renovascular lesion, which is most commonly caused by atherosclerotic disease. The most common nonatherosclerotic cause of renal artery stenosis is fibromuscular dysplasia.
- Noninvasive diagnostic testing for renal artery stenosis (CT angiography, magnetic resonance angiography, duplex ultrasonography) should be pursued if there are clinical clues that suggest the patient's hypertension may be due to renovascular disease.
- If the healthcare facility has expertise in duplex ultrasonography, this imaging study should be done for initial diagnosis of renal artery stenosis in patients with suspected renal fibromuscular dysplasia. CT angiography is the imaging test of choice if ultrasonography experience is limited. For patients in whom duplex ultrasonography is not diagnostic, carbon dioxide digital subtraction angiography should be considered to diagnose and treat renal fibromuscular dysplasia.
- Patients with renal fibromuscular dysplasia can undergo renal artery revascularization if the procedure is necessary to prevent progressive renal loss or to treat hypertension.

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## DISCLOSURES

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### AMA/PRA Category 1 Credit™

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Release date: August 1, 2022

Expiration date: July 31, 2023

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