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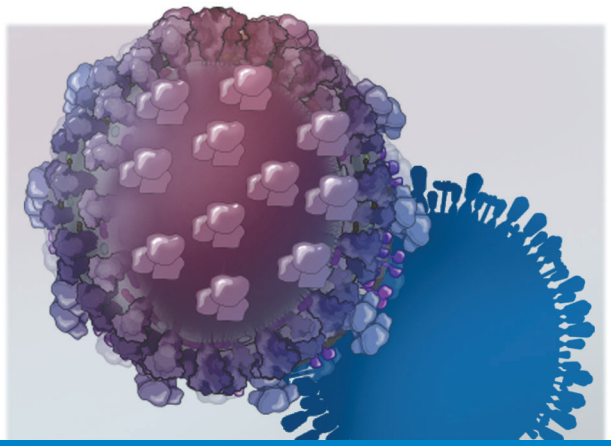

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Table of Contents

CONTINUED ON PAGE 587

Upcoming Features

- Current trends in contraception
- Venous outflow obstruction
- Cardiac considerations in liver transplantation

CONTINUED FROM PAGE 586

SGLT-2 inhibitors are potential game-changers (for more than diabetes)

For years there has been discussion about the appropriateness of a glucocentric focus in the management of patients with diabetes. Studies demonstrated the benefit of glucose control on slowing some microvascular complications of diabetes, but the ability to ameliorate renal and particularly cardiovascular events, major causes of morbidity and mortality, has remained elusive. The concern that drugs designed to treat hyperglycemia might be detrimental to cardiovascular health prompted the US Food and Drug Administration to mandate that pharmaceutical sponsors monitor and document cardiovascular safety within their diabetes drug development programs.

A very positive and to me surprising result of this approach has been the robust demonstration of a cardioprotective effect of the sodium-glucose cotransporter 2 (SGLT-2) inhibitors, drugs that lower the blood glucose through decreased renal reabsorption of filtered glucose and sodium, independent of any effect on insulin levels or function.

In January of this year, we published 2 papers that included discussion of the role of SGLT-2 inhibitors in the treatment of diabetes and their renal benefits,[1,2] and we recently posted on our website a video podcast, "Conversation With Leaders," that focuses on the impact of SGLT-2 inhibitors in patients with chronic kidney disease (https://www.ccjm.org/page/conversations/ckd).

In this issue of the *Journal*, Drs. Ferro, Pitt, and Bhatt[3] offer their perspective on the incorporation of SGLT-2 inhibitors into the routine medication cocktail for patients with heart failure. Large studies in patients with heart failure with reduced ejection fraction demonstrated efficacy of these drugs (seemingly as a class effect) in reducing mortality and hospitalizations due to heart failure. Recent studies, commented on by Drazner,[4] note that SGLT-2 inhibitors are also efficacious in reducing heart failure-related hospital admissions in patients with heart failure with mildly reduced and even preserved ejection fraction—a seminal finding in patients with this syndrome.

Several intriguing preliminary generalizations arise from a review of these studies. The renal, heart failure, and cardiovascular mortality advantages attributed to SGLT-2 inhibitors appear to be independent of the presence of diabetes or changes in the hemoglobin A1c level. The heart failure benefit seems to be independent of the effect on renal disease, and in patients with preserved ejection fraction the benefit seems to be in reduced heart failure admissions, but not reduced mortality. The differences between the various SGLT-2 inhibitors will best be sorted out by head-to-head comparison studies. But as the history of new drug development has shown us, this is not likely to happen soon.

SGLT-2 inhibitor therapy is not without risks. The risk of genital mycotic infections, which may be severe, is increased but can be ameliorated to a degree by careful hygiene. Dehydration can occur due to urinary sodium and water loss, and the ordinarily uncommon syndrome of euglycemic ketoacidosis can occur due to decreased insulin

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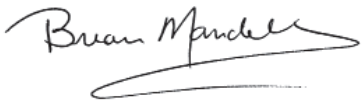
levels of the diabetic state in the setting of systemic stress, with increased glucagon levels and fatty acid oxidation, while the glucose levels remain low due to glucosuria induced by SGLT-2 inhibition. However, these all seem to be manageable issues.

As Ferro and colleagues note in this issue, incorporation of SGLT-2 inhibitors into routine practice has been slow. The reasons are not fully defined, but a number of factors are likely at play, such as reduced patient visits for routine care in the time of COVID-19. Another factor could be an increased distrust of new medications and new medical information as fallout of the vaccine dialogues, and I have heard this in my clinic. There are also the usual concerns of unknown and known side effects, polypharmacy, and cost.

But despite these concerns, the rapidly growing amount of large-scale clinical outcome data and an improved understanding of the biologic effects of these drugs[5] will hopefully provide sufficient comfort in the safe use of SGLT-2 inhibitors and thus change the expectations for the clinical course of our patients with diabetes, as well as those with chronic kidney disease and heart failure resulting from other etiologies.



Brian F. Mandell, MD, PhD
Editor in Chief

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2021

NOVEMBER

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November 4
Live stream

GASTROENTEROLOGY UPDATE: CONTROVERSIES, INNOVATIONS, RESEARCH
November 6
Live stream/Virtual

IMPROVING END-OF-LIFE CARE IN THE ICU: CHALLENGES AND OPPORTUNITIES
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November 17
Live stream

WASOG/AASOG 2021: MULTIDISCIPLINARY MEETING FOR SARCOIDOSIS AND ILD
November 29–December 2
Hollywood, FL

DECEMBER

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December 3
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December 3–4
New York, NY, and live stream

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December 4
Live stream

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December 4–5
Live stream

RESUSCITATING A DYING MARROW: EMERGING CONCEPTS AND TREATMENT ADVANCES IN MYELOID MALIGNANCIES
December 10
Atlanta, GA

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February 25
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MARCH

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MANAGEMENT OF CHECKPOINT INHIBITOR-RELATED TOXICITY
March 3–4
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PAIN MANAGEMENT SYMPOSIUM
March 5–9
Orlando, FL

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March 16
Live stream

MULTIDISCIPLINARY HEAD AND NECK CANCER UPDATE
March 18–19
Fort Lauderdale, FL

APRIL

COMPREHENSIVE CARE FOR THE LIFETIME TREATMENT OF ADULT CONGENITAL HEART DISEASE
April 22–23
Chicago, IL

MAY

HEART, VASCULAR, AND THORACIC INSTITUTE ADVANCED PRACTICE PROVIDER SYMPOSIUM
May 20–21
Live stream

JUNE

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June 1–3
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Gastrointestinal varicella-zoster virus infection

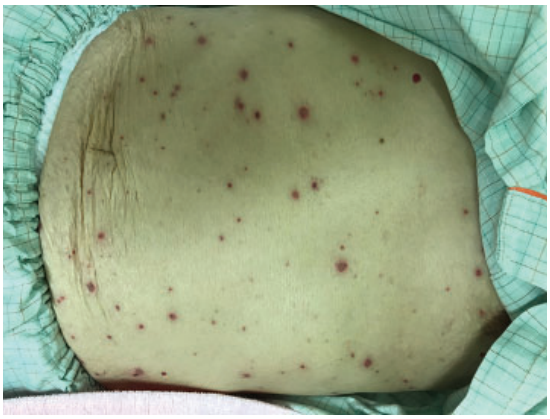

Figure 1. Hemorrhagic vesicles with red haloes of various sizes distributed over the whole body.

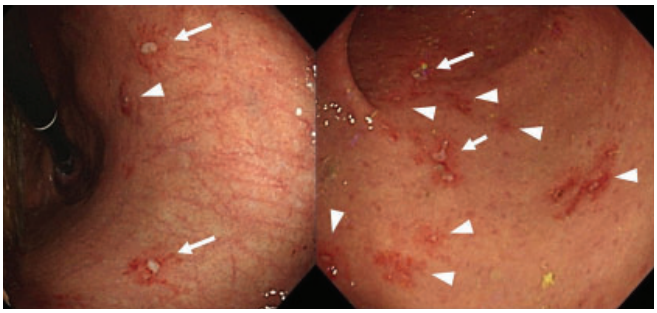

Figure 2. Esophagogastroduodenoscopy of the stomach showed small, shallow ulcers (arrows) and erosions (arrowheads) surrounded by red haloes spread diffusely in the stomach and duodenum.

A 70-year-old woman was admitted for epigastric pain and generalized skin eruptions. Three months before admission, she was on chemotherapy for acute lymphocytic leukemia.

She had a history of herpes zoster and was vaccinated against varicella. She was taking 2 nonsteroidal anti-inflammatory drugs (NSAIDs), loxoprofen and celecoxib, for chronic back pain caused by degenerative lumbar spondylosis.

On hospital day 1, she described the epigastric pain as of gradual onset, intermittent, and crampy. She reported no odynophagia. Eruptions appeared on her head on day 6. The NSAIDs were discontinued on suspicion of NSAID-related gastritis, and a proton pump inhibitor was administered. However, the epigastric pain worsened, and the eruptions spread to the trunk.

On day 11, partly hemorrhagic vesicles of various sizes with red haloes were observed on her entire body (**Figure 1**). With a tentative diagnosis of varicella, intravenous acyclovir 250 mg every 8 hour was initiated. Varicella-zoster virus (VZV) antigen was detected from the vesicular lesions via fluorescent antibody assay. On day 17, esophagogastroduodenoscopy showed small, shallow ulcers and erosions surrounded by red haloes, spread diffusely throughout the stomach and duodenum (**Figure 2**). No esophageal lesions were observed, and the mucosal biopsy was negative for gastric infiltration of acute lymphocytic leukemia. Immunostaining was negative for cytomegalovirus, and VZV-DNA was detected by polymerase chain reaction. She was diagnosed with gastrointestinal VZV infection. After 8 days of antiviral therapy, her symptoms improved, and she was discharged.

RECOGNIZING RISK FOR GASTROINTESTINAL VZV

Gastrointestinal VZV infection should be considered in immunocompromised patients

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with a history of VZV infection presenting with abdominal pain. Visceral VZV infection is related to reactivation of the latent virus in the enteric nervous system.[1] It occurs in 3% to 15% of immunocompromised patients with herpes zoster, with some developing gastrointestinal manifestations.[2] In patients who have undergone bone marrow transplant, the risk factors include a highly immunosuppressed state, active graft-vs-host disease, and possibly a history of nondisseminated herpes zoster.

The mortality rate in patients with gastrointestinal VZV infection has been reported to range from 28.6% to 50% despite antiviral therapy.[3,4] Although this patient had not undergone bone marrow transplant, the chemotherapy she had received was a potential predisposing factor.[2] Esophagogastroduodenoscopy should be considered in patients with these risk factors.

Suspicion of gastrointestinal VZV infection and prompt initiation of antiviral therapy are important when gastric ulcers similar to the skin lesions are present. With NSAID-related ulcers, multiple, irregularly shaped lesions are frequently observed in the gastric antrum.[5] In contrast, VZV infection-related lesions present as multiple erosions disseminated in the stomach.[6] Furthermore, the esophagus, duodenum (as observed in this patient), and the small and large intestines can be involved.[7]

It is also important to differentiate gastrointestinal VZV infection from gastrointestinal cytomegalovirus infection observed in immunocompromised patients. There has been no direct comparison of gastrointestinal VZV and cytomegalovirus. In one report, the endoscopic appearance of upper-gastrointestinal cytomegalovirus infection was variable and nonspecific, ranging from normal or minimally inflamed mucosa to deep ulceration.[8] Therefore, it may be difficult to distinguish gastrointestinal VZV from cytomegalovirus infection based on endoscopic findings alone. However, in the case of gastrointestinal VZV infection, abdominal symptoms can precede the skin lesions by 1 to 10 days, and this more strongly supports VZV.[2,3]

In this patient, the epigastric pain that preceded the varicella-like skin eruptions, and the diffuse gastroduodenal erosions that resembled the skin lesions revealed on esophagogastroduodenoscopy led to the diagnosis. Treatment with acyclovir before obtaining the definitive diagnosis (by polymerase chain reaction testing) ameliorated the patient's symptoms. Thus, clinicians should be vigilant for gastrointestinal VZV infection in patients with gastric ulcers and skin lesions.

DISCLOSURE:

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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COMMENTARY

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Another influenza season in the shadow of the COVID-19 pandemic

The 2020 to 2021 influenza season took a backstage to the COVID-19 pandemic, when the COVID-19 vaccines were in their initial stages of distribution in the northern hemisphere. Although only 50% to 55% of US adults received the 2020 to 2021 influenza vaccination,[1,2] influenza activity was very low compared with prior seasons,[1,2] certainly the result of behavioral measures instituted to mitigate the COVID-19 pandemic.

With the current 2021 to 2022 influenza season coinciding with another increase of COVID-19 cases, lower COVID-19 vaccine uptake and relaxed mitigation measures in some areas of the United States have resulted in vaccine breakthroughs, increased hospitalizations, and an ominous milestone of more than 722,000 deaths.[3]

Routine age-appropriate vaccination of all persons ≥ 6 months of age without contraindications continues to be recommended

Vaccinations, in general, are helping ease the strain of the upcoming influenza season, with an estimated 62% of Americans experiencing immunity against COVID-19 as a result of prior infection or immunization.[4] Further, a recent, retrospective cohort study involving 74,754 patients showed that COVID-19–positive patients were less likely to develop sepsis, stroke, deep venous thrombosis, require admission to the intensive care unit, or subsequent emergency department visits if they received influenza vaccination 2 weeks to 6 months prior to their COVID-19-positive diagnosis.[5]

US CENTERS FOR DISEASE CONTROL AND PREVENTION GUIDANCE

Currently, no data suggest that the COVID-19 pandemic impacted seasonal influenza virus mutations, and the 2021 to 2022 influenza vaccine available in the United States includes updated influenza A(H1N1)pdm09 and influenza A(H3N2) components.[6] All US influenza vaccines for the 2021 to 2022 season are quadrivalent, and routine age-appropriate vaccination of all persons ≥ 6 months of age without contraindications continues to be recommended.[6] Primary updates by the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) to this season's influenza vaccination[6] include the following:

- US-licensed influenza vaccines available for the 2021 to 2022 influenza season are egg-based inactivated influenza vaccines (IIV4s), cell culture-based inactivated influenza vaccines [*Flucelvax Quadrivalent (ccIIV4)*], recombinant influenza vaccines (RIV4), and live attenuated influenza vaccines (LAIV4).[6]
- The approved age indication for ccIIV4 has been expanded from ages ≥ 4 years to ≥ 2 years.[6]
- Current guidance states that influenza and COVID-19 vaccines can be coadministered on the same day as well as within 14 days of each other[7] and should be administered in separate anatomic sites.[6] Providers should consult current ACIP COVID-19 vaccine recommendations and CDC guidance if concerned about coadministration.[6]
- Pregnant women should consider vaccination with IIV4, ccIIV4, or RIV4 in the third trimester, but not LAIV4 at any time during pregnancy or postpartum.[6]
- Regarding the timing of influenza vaccination, the new recommendation this

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year was that vaccine administration to nonpregnant adults should be after August and ideally before the end of October to optimize vaccine protection during the expected seasonal epidemics.[6] This new recommendation is expected to continue into the future.

- A history of severe allergic reaction to IIV4s, RIV4, or LAIV4 other than urticaria (such as angioedema, respiratory distress, lightheadedness, or recurrent emesis) or requiring epinephrine or emergency medical intervention is now considered a precaution, not a contraindication for ccIIV4. Similarly, a history of severe allergic reaction to IIV4s, ccIIV4, or LAIV4 other than the aforementioned reactions is now considered a precaution, not a contraindication for RIV4. These patients should be vaccinated in an inpatient or outpatient medical setting, supervised by a healthcare provider who is able to recognize and manage such reactions.[6]

OTHER INFLUENZA VACCINATION RECOMMENDATIONS

Other relevant issues pertaining to influenza vaccination during the ongoing COVID-19 pandemic have been outlined.[6–8] Influenza vaccine recipients and those who administer these vaccines should recognize that vaccine side effects can mimic COVID-19.[7] Nevertheless, those who develop fever after vaccination should stay home until they defervesce for 24 hours without the use of antipyretics.[7] Importantly, if fever persists or new respiratory symptoms develop, patients should contact their healthcare provider.[7]

In a nonprobability-based, convenience sample of 698 US adults infected with SARS-CoV-2 and 2,437 uninfected adults, 65.9% of those infected experienced long-term symptoms lasting > 4 weeks while 42.9% of those uninfected reported such symptoms, representing an emerging public health concern.[8] This may impact influenza vaccine uptake, as well as recognition of influenza-like illness; deferring influenza vaccination until resolution of another acute viral illnesses, such as COVID-19 is generally recommended.[9] Safe vaccination practice calls for postponing influenza vaccination for those in quarantine after COVID-19 exposure or in isolation after mild COVID-19 illness for 10 days, and after severe COVID-19 illness for 20 days.[6]

COVID-19 AND INFLUENZA COINFECTION

With several common clinical features of influenza and COVID-19, the overlap of the two epidemics occurring at the same time can complicate diagnosis, treatment, and prognosis.[10] Although a small proportion of COVID-19 patients are coinfected with influenza, the risk for high-risk individuals is of concern.[10] While both have some distinct features (**Table 1**),[11,12] they can be hard to distinguish.

VACCINE EFFICACY

Safety and efficacy of the influenza vaccination for pregnant women has been documented, and a recent study noted 91.5% efficacy of transfer of antibodies in preventing hospitalization of newborns and infants, in whom the vaccine is not approved before 6 months of age.[13] Another recent study has shown safety and humoral immunogenicity of messenger ribonucleic acid COVID-19 vaccines in maternal sera, as well as cord blood and breast milk, indicating transfer of immunity to neonates.[14]

A recent study showed that COVID-19 vaccination of healthcare workers reduces the risk of COVID-19 in members of their households.[15] Indirect effects of influenza vaccination have been shown to be greater than direct effects, with 4 to 7 times the influenza cases prevented in non-vaccinated compared with vaccinated individuals, and complications including influenza-associated deaths among the unvaccinated elderly reduced by a factor of 20 to 30.[16]

Researchers have been evaluating both influenza and COVID-19 vaccination efficacy in how they decrease risk of infection and reduce disease severity in breakthrough infections.[17] Currently approved or emergently authorized-for-use COVID-19 vaccines trigger innate, durable immunity, although the emergence of protein variants could potentially limit efficacy.[18] Preliminary data suggest that enhancing the interferon response could offer an immu-

Current guidance states that influenza and COVID-19 vaccines can be coadministered on the same day as well as within 14 days of each other

TABLE 1

Distinct features of influenza and COVID-19

	Influenza	COVID-19
Seasonality	Fall–winter	Year-round
Annual incidence		
Overall	8% (3%–11%)	6%–8%
Children	20% (unvaccinated)	Not applicable (no vaccine)
Adults	10% (unvaccinated)	6%–8% (unvaccinated)
Age distribution	Children > adults	Adults > children
Incubation period (days)	1–4 days	2–14 days
Duration of infectivity	1 day before to 7 days after onset of illness	2 days before to 10 (20 for severe cases) days after onset of illness
Onset of symptoms	More acute	More subacute
Super-spreaders (1 person infects 8 persons)	Not reported	1%
Typical or characteristic features at onset of illness	Fever, headache, dry cough	Loss of sense of taste or smell
Severity of illness		
Asymptomatic	5%–50%	30%–40%
Symptomatic		
Mild	98%	80%
Moderate	1%–2%	15%
Severe	0.2%	5%
Fatal	0.04%–0.1%	3%–4%
Duration of acute illness	5–7 days	2–6 weeks
Incidence of long-term symptoms lasting longer than 4 weeks	Clinically silent viral shedding for weeks to months in immunocompromised individuals	60%–70% regardless of viral shedding
Complications	Pneumonia Exacerbation of underlying chronic heart and lung diseases	Deep venous thrombosis and pulmonary embolism Multisystem inflammatory disorders

Data from references 11 and 12.

nological advantage to control viral infections.[19]

FUTURE DIRECTION

Hopefully, COVID-19 will eventually become an endemic viral infection with predictable annual (or other interval) epidemics. It would make perfect sense for developing combined universal influenza and COVID-19 vaccinations, as several pharmaceutical companies are in the process of developing.[20,21]

DISCLOSURES

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

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Generalized acute cutaneous lupus erythematosus in a young female

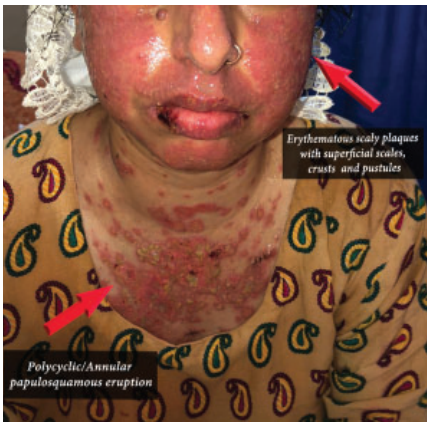

Figure 1. Erythematous scaly plaques with superficial scales, crusts, and pustules on the face, and polycyclic/annular papulosquamous eruption on the chest.

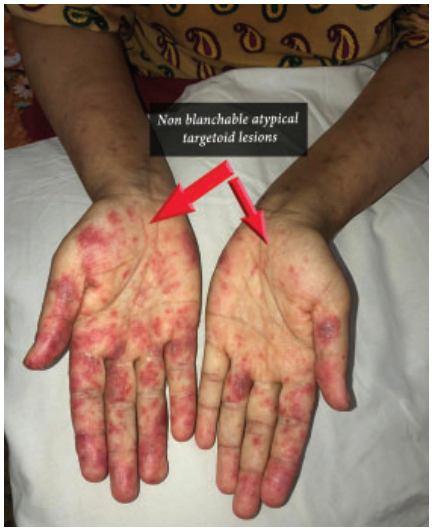

Figure 2. Symmetrical nonblanching atypical targetoid lesions on the palms.

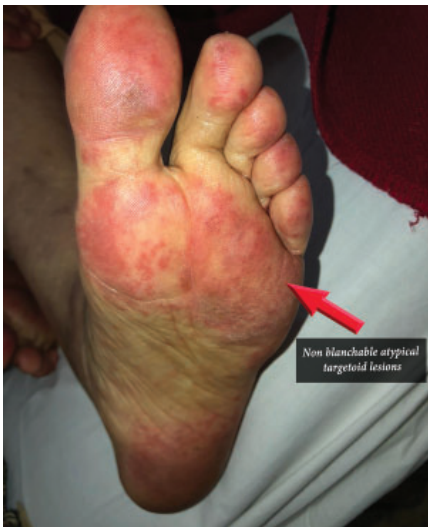

Figure 3. Symmetrical nonblanching atypical targetoid lesions on the soles.

A 28-year-old woman with systemic lupus erythematosus (SLE) presented to the emergency department with erythematous plaques on sun-exposed areas of the body that had developed in the previous 24 to 36 hours after sun exposure, as well as oral ulcers and joint pain. She had been prescribed oral steroids, hydroxychloroquine, and methotrexate 1 year previously when she was diagnosed with SLE but had stopped taking these medications 3 months ago because of herpes zoster infection.

Her temperature was 101°F (38.3°C) and her heart rate was 110 beats per minute. On examination, erythematous scaly plaques with superficial scales, crusts, and pustules were seen on her face with sparing of the nasolabial fold, along with an annular papulosquamous eruption on the chest (**Figure 1**). Symmetrical nonblanching targetoid lesions were seen on the palms and soles (**Figures 2 and 3**). Examination of the dorsum of the hands revealed periungual erythema and erythematous macules on the fingers, hands, and forearms, with sparing of the knuckles (**Figure 4**). Significant laboratory testing results included the following:

- Positive antinuclear antibody titer of 1:1280 (less than 1:160 is considered negative)
- Anti-dsDNA 80 IU/mL (reference range < 35 IU/mL)
- Hemoglobin concentration of 9 g/dL (ref-

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erence range 12–16 g/dL)
- Erythrocyte sedimentation rate 45 mm/hour (reference range 0–29 mm/hour)
- Complement component 3 = 40 mg/dL (reference range 75–175 mg/dL); complement component 4 = 10 mg/dL (reference range 14–40 mg/dL)
- Blood urea nitrogen 16 mmol/L (reference range 3–8 mmol/L)
- Creatinine 160 µmol/L (reference range 60–120 µmol/L)
- Urinalysis: 10–12 red blood cells per high-power field (reference range < 4 cells); 8–10 erythrocyte casts per high-power field (reference range 0–4 casts)
- 24-hour urinary protein 1.2 g/24 hours (reference range <0.45 g/24 hours).

Histopathologic study of the skin lesions was consistent with generalized acute cutaneous lupus erythematosus (ACLE). The patient's abnormal renal function test results and proteinuria raised suspicion for lupus nephritis. Renal biopsy revealed subendothelial deposits in glomerular capillaries and hematoxylin bodies. Endocapillary proliferation, glomerular tuft necrosis, and thickening of capillary walls were also observed. Hence, a diagnosis of diffuse (class IV) lupus nephritis was made.

The patient was started on topical and intravenous corticosteroids along with hydroxychloroquine 200 mg for generalized ACLE. Optimal wound care and strict sun avoidance were advised. Renal biopsy-proven lupus nephritis was treated with oral prednisolone 60 mg/day along with mycophenolate mofetil 2 g/day. On follow-up at 2, 4, and 8 weeks, the patient's skin lesions had resolved without scarring.

CUTANEOUS LUPUS ERYTHEMATOSUS

Cutaneous lupus erythematosus is common in patients with SLE, but the lesions can often be seen in the absence of SLE.[1]

Our patient was diagnosed with generalized ACLE which, compared with the localized form, is an extremely rare cutaneous manifestation of SLE, occurring in 5% to 10% of SLE patients and having a wide variety of presentations in a photosensitive distribution.[2] In our patient, a history of SLE and discontinuation of medications for 3 months led to increased disease activity, which has previously been associated with generalized ACLE.[1] Scarring is seldom seen once skin lesions resolve. However, dyspigmentation is common.[2]

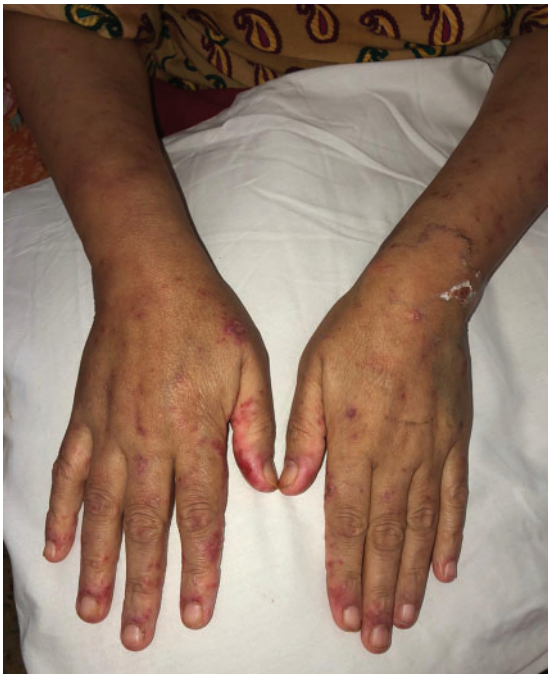

Figure 4. Periungual erythema and erythematous macules on the fingers, hands, and forearms, with sparing of the knuckles.

Diagnosis is made with skin biopsy. The classic histologic findings of localized and generalized ACLE are consistent with interface dermatitis (ie, at the interface between the dermis and epidermis) and include apoptotic keratinocytes, vacuolization of the basal cell layer of the epidermis, lymph histiocytic infiltrate in the superficial dermis, and dermal mucin deposition.[3] Management includes topical and intravenous corticosteroids along with antimalarials such as hydroxychloroquine.[4]

Management includes topical and intravenous corticosteroids along with antimalarials such as hydroxychloroquine

Considering its rarity, generalized ACLE may be missed or mistakenly diagnosed as one of a number of other conditions:
- Drug-induced photosensitivity, for which a history of initiation of a photosensitizing drug must be present
- Dermatomyositis, which is diagnosed based on the presence of skin findings such as heliotrope rash, Gottron sign and papules, and shawl sign[5]
- Pemphigus erythematosus, which is excluded if there is involvement of any other organ besides the skin

- Atopic dermatitis, which is diagnosed after taking a careful history and performing a physical examination that reveals the presence of chronic lesions and a history of other atopic conditions.[6]

This makes it imperative for clinicians to be aware of such rare disease presentations and familiarize themselves with the essential diagnostic criteria for optimal management.

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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SGLT-2 inhibitors in heart failure: Time for broader eligibility and earlier initiation

In recent years, the treatment of heart failure with reduced ejection fraction (HFrEF) has been revolutionized by collaborative efforts among healthcare practitioners, pharmaceutical industry leaders, and regulators regarding the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors.[1] A series of cardiovascular outcome trials led to the discovery of powerful and broad cardiorenal benefits associated with this class of drugs, originally developed as noninsulin therapy for type 2 diabetes mellitus. Studies have shown that SGLT-2 inhibitors result in statistically significant reductions in the rates of major adverse cardiovascular events, major adverse kidney events, and hospitalizations for heart failure in patients with diabetes.[2–6]

Notably, these benefits seemed to apply to all patients with HFrEF, whether or not they had diabetes. This initial observation led to a second wave of cardiovascular outcome trials focused on patients with chronic HFrEF (ejection fraction ≤ 40%) managed in ambulatory settings. In these trials,[7,8] SGLT-2 inhibitors dapagliflozin and empagliflozin conferred impressive reductions in risks of cardiovascular mortality and hospitalizations for heart failure, translating to a number-needed-to-treat of about 20 patients per year, regardless of the presence or absence of diabetes.

HOW DO SGLT-2 INHIBITORS WORK?

The broad cardiorenal benefits of SGLT-2 inhibitors are mediated by several beneficial mechanisms in addition to the well-characterized reduction in glucose reabsorption in the proximal tubule of the kidney, the pathway originally targeted for noninsulin treatment of hyperglycemia.[9,10] SGLT-2 is a cotransporter of both glucose and sodium; thus, its inhibition promotes diuresis and reduces preload, afterload, and blood pressure.[11] It may also directly increase renal erythropoietin and the oxygen-carrying capacity of the blood, perhaps mimicking benefits seen with intravenous iron in patients with HFrEF.[12] In addition to the kidneys, constant glycosuria by itself has a direct cardiac benefit by shifting metabolism in favor of oxidation of free fatty acids, which in turn optimizes mitochondrial function in cardiac myocytes (improving contractile function) and reduces epicardial fat (decreasing noxious inflammation and fibrosis associated with heart failure). These mechanisms may explain the reduction in left ventricular mass index, a known predictor of major adverse cardiovascular events, seen on cardiac magnetic resonance imaging and associated with empagliflozin and dapagliflozin use.[11,13] Furthermore, SGLT-2 inhibitors may cross-react with cardiac sodium-hydrogen exchangers, which has been linked to decreased arrhythmia burden.[14]

CLINICAL ROLES ARE EXPANDING

While the synergistic mechanisms of action of SGLT-2 inhibitors require further characterization, their safety and net clinical benefits have been so rigorously demonstrated that all major international guidelines now recommend them as treatment for diabetes and associated kidney disease, administered

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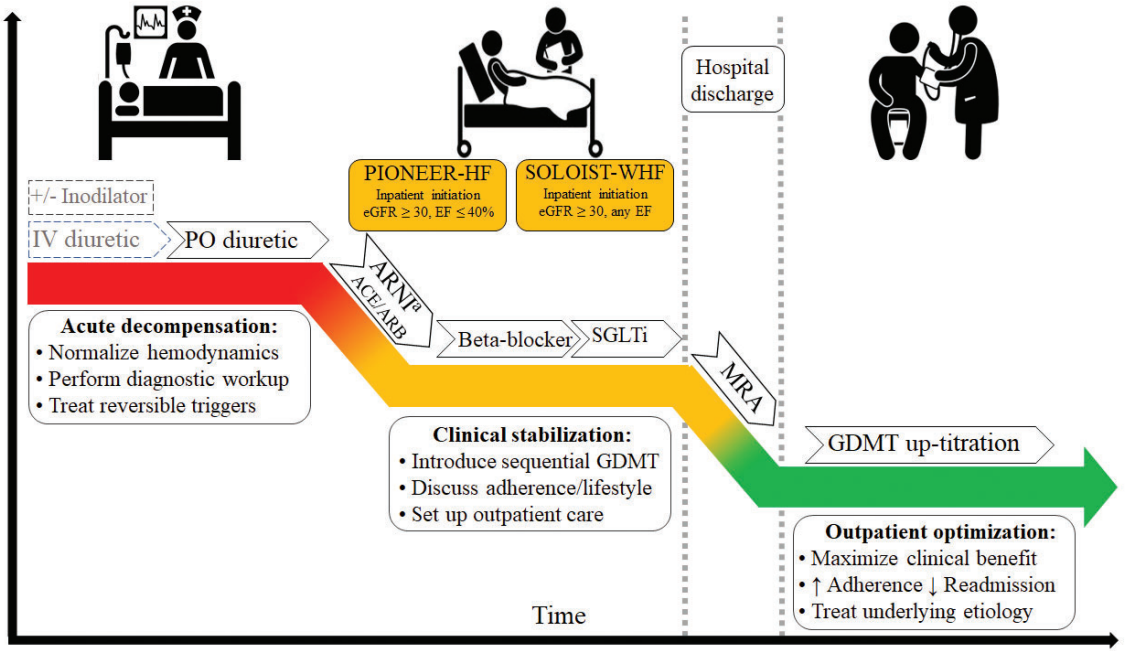

Figure 1. Guideline-directed medical therapy for a hospitalized patient with heart failure, showing early initiation of SGLT-2 inhibitor therapy. If an ARNI cannot be used as first-line therapy because it is contraindicated or not tolerated, consider an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; EF = ejection fraction; eGFR = estimated glomerular filtration rate (mL/min/1.73m^2); GDMT = guideline-directed medical therapy; IV = intravenous; MRA = mineralocorticoid receptor antagonist; PO = per os (by mouth); PIONEER-HF = Comparison of Sacubitril–Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode; SGLTi = sodium-glucose cotransporter inhibitor; SOLOIST-WHF = Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure

concurrently with metformin or even as first-line therapy.[15,16] Given the overwhelming evidence of benefit in all patients with HFrEF, whether or not they have diabetes,[7,8] consensus statements from the cardiology community uniformly encourage physicians to prioritize SGLT-2 inhibitor initiation in this patient population, potentially even as the initial therapy alongside beta-blockers.[17,18] In addition, the accumulating evidence of benefit in patients with chronic proteinuric kidney disease regardless of diabetes[6,19,20] led the US Food and Drug Administration to approve dapagliflozin to treat patients with chronic kidney disease regardless of diabetes, making it the first SGLT-2 inhibitor to achieve a triple indication: type 2 diabetes, HFrEF, or chronic kidney disease. This will likely lead to guideline updates and significant increases in patient eligibility.

While other SGLT-2 inhibitors have not yet received such broad regulatory approval, the evidence generated by clinical trials to date suggests an overall class effect that applies to all available agents.[21]

INCREASINGLY PROVEN, YET UNDERUSED

Despite the impressive cardiorenal benefits of SGLT-2 inhibitors and endorsement by many medical societies, real-world use of these drugs is low. A retrospective analysis of 5,006 US patients with high cardiovascular risk examined SGLT-2 inhibitor use from 2016 to 2018,[22] about 1 to 2 years after publication of the landmark SGLT-2 inhibitor trials,[2,3] and found use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers to be high (72% of patients), whereas concurrent use of SGLT-2 inhibitors was alarmingly low at 9%.[22] SGLT-2 inhibitors are particularly under-

used outside of endocrine practices. A retrospective analysis of approximately 1,800 patients who were started on SGLT-2 inhibitors in 2017 in Massachusetts found that 45.4% of patients were started on this treatment by endocrinologists, 22.7% by primary care physicians, and only 4.5% by cardiologists.[23]

Targeted interventions are needed to increase SGLT-2 inhibitor use in patients with diabetes and nondiabetes proteinuric kidney disease, as trials have demonstrated substantial benefit in patients with increasingly lower estimated glomerular filtration rate and milder proteinuria, thus expanding eligibility.[19,20,24,25]

THE FUTURE FOR SGLT-2 INHIBITORS IN HEART FAILURE THERAPY

Patients hospitalized for HFrEF represent a population in whom an updated guideline-directed medical therapy protocol can be safely started or advanced. This protocol calls for early addition of SGLT-2 inhibitor therapy (**Figure 1**), a strategy shown to reduce morbidity and mortality as early as 30 days after initiation.[18,26] In-hospital initiation of therapy with an SGLT-2 inhibitor is also an independent predictor of higher adherence to therapy in patients with worsening heart failure,[27] thus maximizing the clinical benefit of these agents.

The conventional therapeutic approach was to start with an ACE inhibitor or angiotensin receptor blocker followed by a beta-blocker, mineralocorticoid receptor antagonist, and a neprilysin inhibitor, and then an SGLT-2 inhibitor, primarily in the outpatient setting. The feasibility and benefits of the conventional approach were based on established evidence from clinical trials. However, the evidence for SGLT-2 inhibitors from those trials was limited to patients with chronic ambulatory heart failure and excluded patients hospitalized with heart failure fewer than 4 weeks before enrollment.[27]

SOLOIST-WHF trial: More evidence

The clinical trial Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF)[28] enrolled 1,222 patients with diabetes and heart failure (reduced ejection fraction [< 50%] or preserved ejection fraction [≥ 50%]) with elevated N-terminal B-type natriuretic peptide who were hospitalized for worsening heart failure and had been clinically stabilized, ie, no hypotension or need for supplemental oxygen, intravenous inotropic therapy, or intravenous diuretics. Patients were randomized to either sotagliflozin (an inhibitor of SGLT-1 and SGLT-2) or placebo.

The trial was terminated early due to loss of funding at the onset of the COVID-19 pandemic, resulting in a smaller sample size and shorter follow-up than anticipated. Nonetheless, after a median follow-up of 0.75 years, sotagliflozin recipients had a 33% relative risk reduction (P = .0009) and a 25% absolute risk reduction (translating to a number needed to treat of 4 patients for a year) in the primary end point of total cardiovascular deaths, hospitalizations for heart failure, and urgent visits for heart failure.[28]

Of note, the first dose of the trial medication was administered before discharge in about half of the patients and at a median of 2 days after discharge in the other half (with no major difference in safety issues compared with placebo). Overall, this trial demonstrated the feasibility, safety, and early clinical benefit of the in-hospital initiation of an SGLT-1 and SGLT-2 inhibitor, given that the cumulative incidence curves for the primary outcome were already significant by day 28 postrandomization.[27,28]

WHAT'S THE CLINICAL IMPACT?

We and others believe it is time for a shift in the timing and sequence of SGLT-2 inhibitor therapy.[17,18,27] Impressive reductions in major adverse cardiovascular events, major adverse kidney events, and hospitalizations for heart failure consistently shown in SGLT-2 inhibitor trials,[7,8,12] together with the safety and early benefit of in-hospital initiation shown by SOLOIST-WHF,[28] provide rigorous evidence to support initiating SGLT-2 inhibitors as first-line treatment for HFrEF as soon as the patient is clinically stable.[26]

It is time for a shift in the timing and sequence of SGLT-2 inhibitor therapy in patients with heart failure

For example, as part of guideline-directed medical therapy, SGLT-2 inhibitor therapy can be prioritized as the first agent coupled with beta-blockers, which continue to be the single most effective drug class for HFrEF.[18] As the other 2 cornerstones of HFrEF therapy (an

angiotensin receptor-neprilysin inhibitor and a mineralocorticoid receptor agonist) are then added to this background of SGLT-2 inhibition, the diuretic effect of SGLT-2 inhibition can further reduce the risk of hyperkalemia, increasing safety and tolerability.[18] Others, including the American College of Cardiology,[17] propose initiating renin-angiotensin-aldosterone system inhibitors as the first step, prioritizing an angiotensin receptor-neprilysin inhibitor over an ACE inhibitor or angiotensin receptor blocker, as this may be better tolerated when the patient is still mildly congested and approaching clinical stabilization, followed by a beta-blocker and SGLT-2 inhibitor.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

The SOLOIST-WHF trial[28] also uncovered an additional benefit of SGLT inhibition that may further solidify the role of this drug class as the pillar of modern heart failure treatment—ie, therapeutic applications to patients with preserved ejection fraction.

The SOLOIST-WHF trial[28] was the first heart failure-focused trial of SGLT inhibition to enroll patients with preserved ejection fraction, in order to investigate whether the beneficial effect of this drug class might apply irrespective of the patient's ejection fraction. Although the study planned to enroll 50% of patients with a preserved ejection fraction of 50% or greater, its early termination resulted in only 20% of the final sample size meeting this criterion.[28] Despite the modest sample size, there was no evidence of heterogeneity of treatment effect according to ejection fraction.[27,28] This promising finding suggested that SGLT-2 inhibitors may also become the first therapeutic option for heart failure with preserved ejection fraction, a very common yet elusive disease for which no treatment had yet convincingly reduced rates of morbidity or mortality.

Over the past 5 years, SGLT-2 inhibitors have changed the treatment paradigm for diabetes, chronic kidney disease, and heart failure

Recently, the EMPEROR-Preserved trial[29] showed a significant reduction in the rate of cardiovascular death or hospitalization for heart failure in patients with preserved ejection fraction, extending the findings of SOLOIST-WHF to include not only patients with diabetes but also those without diabetes. A trial of dapagliflozin in a similar population should report relatively soon. Therefore, it appears likely that SGLT-2 inhibitors as a class will now be a therapy for heart failure with either preserved or reduced ejection fraction in those with or without diabetes.[29]

ADDITIONAL CARDIOVASCULAR BENEFITS

Sotagliflozin inhibits the SGLT-1 receptor as well as the SGLT-2 receptor. The SGLT-1 transporter mediates only 10% of kidney glucose reabsorption. Its primary role is in the small intestines, where its inhibition delays glucose absorption and reduces postprandial glycemia.[9] SGLT-1 inhibition, whether alone or together with SGLT-2 inhibition, may confer additional cardiovascular benefit. This observation is supported by the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial,[24] in which sotagliflozin demonstrated an early and significant reduction in myocardial infarction and stroke, with a relative risk reduction (compared with placebo) that seemed larger compared with more selective SGLT-2 inhibitors, such as empagliflozin or canagliflozin, in similar patient populations.[2,3,21,24] While promising, these findings warrant additional study to determine if SGLT-1 inhibition really does add to SGLT-2 inhibition in terms of cardiovascular risk reduction.

STILL AN UNDERUSED RESOURCE

Over the past 5 years, SGLT-2 inhibitors have changed the treatment paradigm for patients with diabetes, chronic kidney disease, and heart failure. These drugs have become a powerful resource that is shared by primary care, endocrinology, cardiology, and nephrology specialists, yet they remain vastly underused in clinical practice despite their broad cardiorenal benefits. By providing the evidence and rationale for use of SGLT-2 inhibitors in this patient population, we hope that practitioners from all specialties will readily integrate these agents into their routine clinical practice.

DISCLOSURES

Dr. Pitt served as co-chair of SOLOIST (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) and was on the executive committee of SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk), and received consulting fees from Sanofi/Lexicon. In addition, Dr. Pitt discloses the following: consulting fees from Bayer, Astra Zeneca, Boehringer Ingelheim/Lilly, and Phasebio; and consulting fees and stock options from SCPharmaceuticals, SQinnovations, G3pharmaceuticals, Relypsa/Vifor, Cereno scientific, KBP Pharmaceuticals, Sarfez, Tricida, Proton Intel, and Brainstorm Medical. Dr. Pitt is chairman of the steering committee for the National Heart, Lung, and Blood Institute's TRANSFORM (Torsemide Comparison With Furosemide For Management of Heart Failure) trial and co-chair of SPIRRIT (Spironolactone Initiation Registry Randomized Interventional Trial) from the National Heart, Lung, and Blood Institute–Swedish Heart Foundation. He holds US Patent No. 9931412 on site-specific delivery of eplerenone to the myocardium and has a pending US Patent (63/045,784) on histone acetylation-modulating agents for the treatment and protection of organ damage.

Dr. Deepak L. Bhatt discloses the following relationships: Advisory Board: Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, MyoKardia, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Lexicon, Lilly, Medtronic, MyoKardia, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Takeda.

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Options for preserving fertility in women undergoing gonadotoxic treatment

ABSTRACT

Cancer chemotherapy and radiotherapy can be toxic to the ovaries, but women can improve their chances of preserving their fertility. Three options are available: gonadotropin-releasing hormone (GnRH) analogues, oocyte cryopreservation, and ovarian tissue cryopreservation. A fourth option, ovarian transposition, is valid for patients undergoing pelvic radiation but is not useful in patients undergoing chemotherapy.

KEY POINTS

GnRH analogues provide only uncertain or temporary benefit, and should be offered only together with other options, or if other methods are not feasible.

Oocyte cryopreservation is now the standard of care and should be offered to all postpubertal patients who can wait at least 2 weeks before they start chemotherapy or radiotherapy.

Ovarian tissue cryopreservation is no longer experimental, although it poses a risk of reseeding in bloodborne cancers such as leukemia. It should be offered to prepubertal girls, who cannot undergo oocyte cryopreservation, and to postpubertal patients who do not have 2 weeks before starting therapy.

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MANY GIRLS AND YOUNG WOMEN with cancer receive gonadotoxic chemotherapy or radiotherapy, which can threaten their ability to have children later on, or even put them into premature menopause (primary ovarian insufficiency). The probability of having a live birth is 30% to 50% lower in cancer survivors than in females without cancer. Even females who receive a moderate or low dose of chemotherapy and who do not experience primary ovarian insufficiency have significantly lower rates of conception.[1,2]

The risk of infertility is a source of considerable distress for women undergoing cancer treatment, as they typically have a very strong desire to have their own biological offspring after completing their treatment.[3,4] For these patients, proactive treatment can help preserve the possibility of having children.

OVARIAN FOLLICLES MATURE IN STEPS

The functional units of the ovary are the follicles in the ovarian cortex, each consisting of an egg (oocyte) surrounded by granulosa cells. These follicles mature in steps:

Primordial follicles are very small with only 1 layer of granulosa cells, which are flat or fusiform, surrounding the oocyte. Primordial follicles can progress to:

Primary follicles, in which the granulosa cells become more cube-shaped, and the egg is slightly bigger with a bigger cytoplasm. These in turn progress to:

Secondary follicles, in which the layers of granulosa cells increase. The cytoplasm around the nucleus of the egg increases in size, and so the egg increases in size as well.

Tertiary follicles, the last developmental stage, are characterized by the presence

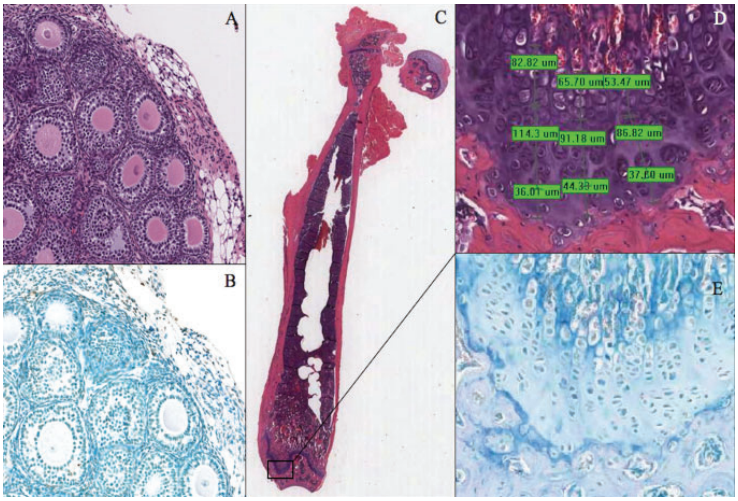

Figure 1. Ovarian follicles stained with hematoxylin and eosin (A) and with TUNEL (terminal nucleotidyl transferase-mediated nick-end labeling) (B) in a prepubertal mouse that received cyclophosphamide 200 mg/kg 2 days earlier. Apoptosis in the granulosa cells surrounding the central oocytes is more evident on TUNEL than on hematoxylin and eosin staining. (C) Mature mouse femur stained with hematoxylin and eosin. (D) Detail of the growth plate section (with computerized measurements). (E) Detail of the growth plate section stained with TUNEL, showing apoptosis.

With permission, from Detti L, Uhlmann RA, Zhang J, et al. Goserelin fosters bone elongation but does not prevent ovarian damage in cyclophosphamide-treated prepubertal mice. Fertil Steril 2014; 101(4): 1157–1164. doi:10.1016/j.fertnstert.2013.12.028

of an antrum, which is an accumulation of fluid. Tertiary follicles are also called *antral follicles*.

Progression from primordial to tertiary follicles takes approximately 120 days, which is incidentally the same time it takes for the germinal cells that will eventually become sperm to mature.

The stimulus for primordial follicles to enter the first developmental stage and become primary follicles is not well understood. However, an inhibitory hormone, anti-Müllerian hormone (AMH), keeps primordial follicles from entering the first developmental step to become primary follicles. After this first step, primary, secondary, and tertiary follicles are regulated in their development by follicle-stimulating hormone (FSH), produced by the pituitary gland. These follicles in turn secrete AMH, which can be considered the gatekeeper of ovarian follicle reserve throughout a female's reproductive life.

OOCYTES ARE LOST OVER TIME, AND WITH CHEMOTHERAPY

Females are born with all the eggs they will ever have, and the number declines with age. The peak number is actually reached before birth at about 20 weeks of gestation. At that time, the eggs lack the surrounding granulosa cells, and they start organizing into follicles. As this organization progresses, many of the eggs are lost by apoptosis. At birth, there are approximately 2 million follicles, but the number decreases throughout childhood, so that at puberty there are only about 400,000 to 500,000, and at menopause, basically none.

Any damage to the ovaries—eg, from chemotherapy with alkylating agents such as cyclophosphamide or from radiotherapy—can cause loss of follicles.[5] Under the microscope, the damage may not be apparent on hematoxylin and eosin staining, but TUNEL staining (terminal nucleotidyl transferase-mediated nick-end labeling) may reveal apoptosis in the nuclei of the granulosa cells (**Figure 1**),[6] but not necessarily of the eggs, because it is the granulosa cells that are actively replicating and are therefore more vulnerable to apoptosis than the eggs themselves.[7]

Therefore, systemic chemotherapy tends to directly damage the primary, secondary, and tertiary follicles, which contain more granulosa cells, and these granulosa cells are more metabolically active than those in the primordial follicles, which also contain fewer. However, it also damages primordial follicles through an indirect process. The secondary and tertiary follicles secrete AMH, which inhibits further maturation of primordial follicles. By damaging secondary and tertiary follicles, chemotherapy causes a major decrease in AMH, so that more primordial follicles, lacking this inhibitory signal, enter the next developmental stage, leading to burnout of primordial follicles and depletion of ovarian reserve.

Earlier onset of menopause

The immediate outcome is fewer follicles, followed by faster loss of follicles as the patient ages than in healthy women. The average age at menopause in the general population is 51. With high-dose chemotherapy, such as what patients receive in preparation for bone marrow transplant, an 18-year-old patient could lose all

her follicles at once and go into menopause immediately. A moderate dose could cause an immediate loss of follicles followed by a gradual but still accelerated loss, resulting in menopause before age 51. With low-dose chemotherapy, the loss is more gradual, but the patient will still go into menopause earlier than normal.

We cannot actually count the follicles in the ovaries of a female patient who undergoes chemotherapy, but we can measure her AMH level to assess ovarian reserve. AMH levels can drop very low soon after the gonadotoxic insult, but over 2 to 3 years they gradually come back up as the primary, secondary, and tertiary follicles start producing it again. After low-dose or moderately low-dose gonadotoxic treatment, AMH levels can return to a plateau and stay there for about 10 to 15 years, but after highly gonadotoxic treatment the plateau is much lower and does not last as long, and eventually these women go into menopause very early. Unfortunately, younger age does not protect against ovarian damage.[8] Some girls who receive chemotherapy go into menopause before ever reaching puberty.

Of the chemotherapeutic agents, the alkylating agents are considered the most harmful to the gonads, and the damage is dose-dependent.[9–11] Cancer treatment causes primary ovarian insufficiency, or premature menopause, in about 10% to 25% of prepubertal patients and in 36% of postpubertal patients.[12–14]

With radiotherapy, exposure of the ovaries to about 5 to 20 Grays is enough to cause primary ovarian insufficiency regardless of the age of the patient, and even a dose less than 2 Grays can destroy 50% of the oocyte reserve, enough to cause infertility if not immediate primary ovarian insufficiency. In addition, uterine irradiation can limit the final adult uterine volume.[15] This issue should always be addressed when patients undergo radiotherapy to the pelvic area because they could have major complications in pregnancy if they do become pregnant.

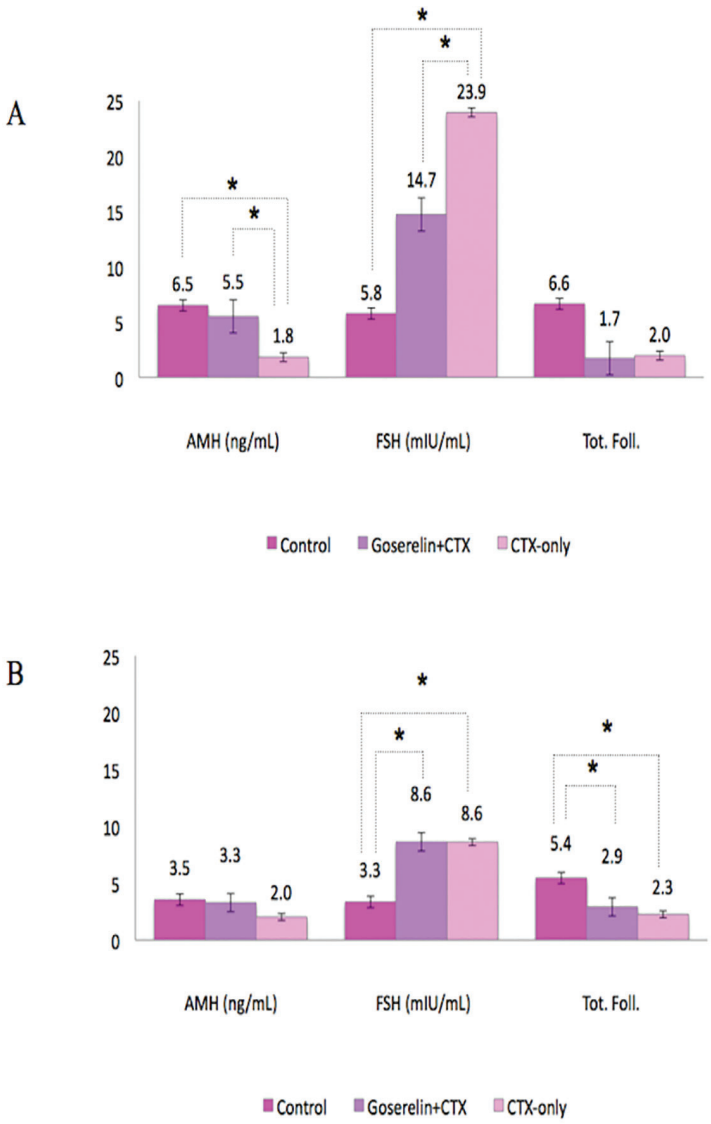

Figure 2. Antimüllerian hormone (AMH) and follicle-stimulating hormone (FSH) levels and total follicle counts at age 56 days (A) and 92 days (B) in mice that had received cyclophosphamide (CTX) alone, CTX plus goserelin, or neither drug (controls) at age 18 days. Goserelin temporarily protected the ovaries, but the protection waned over time (*$P < .05$).

With permission, from Detti L, Uhlmann RA, Zhang J, et al. Goserelin fosters bone elongation but does not prevent ovarian damage in cyclophosphamide-treated prepubertal mice. Fertil Steril 2014; 101(4): 1157–1164. doi:10.1016/j.fertnstert.2013.12.028

PRESERVING FERTILITY

Young women receiving gonadotoxic therapy have 3 main options for preserving fertility: gonadotropin-releasing hormone (GnRH) analogues, oocyte or embryo cryopreservation, and ovarian tissue cryopreservation.

GnRH analogues

GnRH analogues have been used for fertility preservation since the 1980s, although their mechanism of action and effectiveness are still debated.

How do they work? Because GnRH ana-

logues inhibit ovarian function, in theory, they could protect the ovary through several mechanisms:

- Down-regulating ovarian function[16]
- Decreasing utero-ovarian perfusion[17,18]
- Up-regulating intragonadal antiapoptotic factors such as sphingosine 1 phosphate
- Directly protecting developing follicles and germinal cells[17–19]
- Maintaining AMH production, thus keeping primordial follicles in their quiescent state, preventing "burnout," and preserving ovarian reserve.[6,20]

In a study of these effects, prepubescent mice (age 20 days) were given either cyclophosphamide alone or cyclophosphamide plus goserelin (a GnRH analogue), while a third group (controls) received neither.[6] At age 56 days, when the mice were in puberty, AMH levels were higher in those that received goserelin plus cyclophosphamide than in those who received cyclophosphamide alone, but at 92 days, when the mice were fully mature, AMH levels were similar across the 3 groups (**Figure 2**).[6] FSH levels at 56 days were lower with goserelin than with cyclophosphamide alone, though still higher than in the control group, reflecting damage to the ovaries even with goserelin treatment. At 92 days, FSH levels were the same in the 2 groups that got cyclophosphamide and lower than at 56 days, though still higher than in the control group. The total number of follicles was lower in the cyclophosphamide groups with or without goserelin, and lower than in the control group at 92 days. The conclusion was that goserelin did not fully prevent ovarian damage in this mouse model, and that the effect was only temporary, although it did foster bone elongation.[6]

The number of follicles at birth is 2 million; at puberty, 500,000; at menopause, 0

However, in an in vitro experiment,[20] recombinant AMH was found to decrease the replication of granulosa cells, leading to the conclusion that if a GnRH analogue decreased damage to the developing follicles, then it could also maintain an AMH level that would prevent that initial burnout of primordial follicles, which would remain a reservoir in the ovaries.

How effective are GnRH analogues? They increase the chances of resuming menses after chemotherapy. However, resumption of menses does not mean fertility, and many times it does not mean that the ovarian reserve is still intact.

A comprehensive review of studies up to 2013[21] found that these agents have a positive impact on resumption of menses. In addition, Lambertini et al[22] reviewed randomized clinical trials published up to April 2015 and concluded that luteinizing hormone-releasing factor (the equivalent to a GnRH analogue) is associated with a significantly reduced risk of primary ovarian failure and "seems to" increase the pregnancy rate.[22]

Limitations of the studies were that they did not all report how long the GnRH analogues were given, the age stratification of the patients, how long after receiving the GnRH analogue the patients became pregnant (there is possibly an immediate effect of GnRH treatment, but perhaps less protection in the long run), or the length of follow-up.

A 2018 American Society of Clinical Oncology guideline[23] stated that although evidence is conflicting, GnRH agonists may be offered when oocyte or ovarian tissue cryopreservation is not feasible, and in young women with breast cancer. I would go beyond this guideline and offer these agents to girls and women undergoing gonadotoxic therapy for any reason. I agree that GnRH analogues provide only uncertain or temporary benefits and should be offered only together with other options or if other methods are not feasible. Ideally, they should be given 2 weeks before the start of chemotherapy and should then be held between the chemotherapy cycles to let the ovary recoup follicle development and AMH production to protect the primordial follicle pool.

Oocyte cryopreservation

Oocyte cryopreservation (freezing the eggs) is a relatively new technique to preserve fertility in females who have already achieved puberty. It first requires stimulation with gonadotropins for about 10 to 12 days, during which follicular development is followed with transvaginal ultrasonography. Before stimulation, the follicles measure 5 to 10 mm, and when they reach approximately 18 mm, ovulation is induced to allow the eggs to mature.

Only mature eggs at the stage of metaphase 2 can be frozen. Oocytes are retrieved under ultrasonographic guidance, with a long needle

attached to a transvaginal ultrasound probe. The eggs are frozen (vitrified) and kept in liquid nitrogen, where they can be stored indefinitely. (An ordinary freezer is not cold enough.) When feasible, another option is to fertilize the eggs in vitro immediately after harvesting them and freeze the resulting embryos after they have developed for 5 days, at the blastocyst stage.

When the woman is considered cured of her primary cancer, the eggs or embryos can be thawed and the eggs fertilized in vitro, and then they can be transferred into the uterus under ultrasonographic guidance.

Oocyte cryopreservation was considered experimental until 2012, when the American Society for Reproductive Medicine lifted the experimental label.[24] Since then, oocyte cryopreservation in female patients undergoing gonadotoxic therapy has become the standard of care.

How many eggs should we obtain and freeze? We don't know the magic number, and the calculation is complicated because the genetic quality of the eggs declines with the age of the patient: ie, the older the woman, the more eggs are needed to allow her to have a pregnancy. Fertility decreases with age even in healthy women, and early pregnancy loss is due in most cases to genetic abnormalities in the oocytes and embryos. At age 22, only about 5% of eggs have a chromosomal abnormality, but this increases to 22% at age 32 and 65% at age 40 to 41.

Goldman et al[25] calculated that at least 10 eggs are needed to provide a 75% chance of pregnancy at age 34, 20 eggs are needed at age 37, and 61 are needed at age 42. Therefore, if we can retrieve about 20 oocytes, at age 34, there would be about a 90% chance of pregnancy, decreasing to 75% at age 37 and to only 37% at age 42 with oocyte cryopreservation and in vitro fertilization. In comparison, in healthy, sexually active females not using contraception, the probability of becoming pregnant during any given menstrual cycle is only about 20% to 25%. This technique is thus very effective.

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation, or freezing the ovary, is a newer method. Usually, the whole ovary is extracted and the ovarian cortex is separated from the medullary portion, which is more vascular. Next, the cortex is sectioned in small fragments and frozen in liquid nitrogen. The ovarian cortex is thawed and transplanted back into the woman after she is cancer-free.[26,27]

An advantage of tissue cryopreservation is that once the ovarian tissue is transplanted back, not only can the patient possibly conceive (just as with egg preservation), but she can also produce her own estrogen and progesterone and will not need hormone replacement therapy to prevent hot flashes, bone loss, and the other consequences of menopause.

Women in primary ovarian insufficiency have very high FSH concentrations, in the menopausal range of 80 mU/mL. After ovarian tissue is transplanted back into the pelvis, the FSH level gradually comes back down to normal levels of 7 to 8 mU/mL after approximately 6 months, an interval reflecting the 120 days it takes for primordial follicles to develop into tertiary follicles, which are the ones that produce the most estradiol, which feeds back with the FSH produced by the pituitary.[28]

In May 2021, in a report by Dolmans et al[29] on the effectiveness of tissue cryopreservation, almost all women who underwent the procedure recovered their ovarian function, and about 25% gave birth to a healthy child. However, most of them had to undergo in vitro fertilization to become pregnant, and a 25% pregnancy rate with in vitro fertilization is considered low. Nonetheless, this is a great outcome for patients who underwent cancer therapy. With radiation therapy, the rates of success are much lower than with chemotherapy.

Alkylating agents are considered the most harmful for the gonads

Starting chemotherapy before ovarian tissue cryopreservation does not impair the chances for fertility, and it may reduce the risk of reintroducing cancer with the autotransplant. Especially for blood-borne cancers like leukemia, cancerous cells may lurk in the transplant, but 2 or 3 cycles of chemotherapy before harvesting can lower the risk.

In 2019, the American Society for Reproductive Medicine lifted the experimental label from tissue cryopreservation and now recommends it for clinical practice, particularly for prepubescent patients, for whom oocyte cryopreservation is not possible.[30]

OVARIAN TRANSPOSITION

Ovarian transposition is an established method to protect the ovary from pelvic radiation and to preserve future ovarian function and fertility. The technique, introduced in the 1970s, entails elevation of the ovaries from their pelvic position to an abdominal position.[31] Today, it can be performed laparoscopically or robotically. However, this procedure should be offered only if the patient is undergoing pelvic radiation as it is not useful if the patient is treated with chemotherapy.

DISCLOSURES

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

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REVIEW

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DXA and clinical challenges of fracture risk assessment in primary care

ABSTRACT

Dual-energy x-ray absorptiometry (DXA) can detect bone mineral density loss before it can be identified on usual skeletal radiography, making it possible to diagnose osteoporosis in postmenopausal women and older men before clinical fractures arise. However, when DXA is used outside these populations or if the clinical picture does not match the reported T-scores, mistakes can arise in interpreting results and determining the need for pharmaceutical therapy.

KEY POINTS

While DXA is the gold standard test for measuring bone density, clinical judgment should take precedence if results contradict clinical information.

T-scores are not reliable indicators of fracture risk in premenopausal women, younger men, and children; Z-scores should be used for these populations.

Bone strength is now understood to depend on factors besides bone mineral density, sometimes causing discordance between DXA results and true fracture risk.

The Fracture Risk Assessment Tool incorporates clinical factors and can help guide treatment decisions.

New technologies directed at bone microarchitecture may one day improve risk analysis.

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Our understanding of dual-energy x-ray absorptiometry (DXA) is evolving as new information emerges about skeletal qualities that contribute to bone strength apart from bone mineral density (BMD). Some of these characteristics are not detectable by DXA analysis. Hence, overdependence on DXA results, particularly for patient populations that the test was not designed for, may lead to poor clinical decisions.

This article reviews the use of DXA and its limitations. Using case studies, clinical challenges of DXA scan interpretation are discussed, and guidance is provided in the diagnostic process and treatment decisions when clinical and DXA data are discordant.

WHAT DXA DOES WELL

DXA, originally developed for assessing fracture risk in postmenopausal women,[1] is the gold standard test for diagnosing osteoporosis and monitoring its treatment. It can detect small but clinically relevant deficiencies in bone mass years before they are apparent on standard clinical radiographs, thereby allowing clinicians to intercede early to prevent fractures.

T-scores

DXA measures areal BMD (ie, bone mineral content divided by the bone scanned area) in the spine, hip, or forearm. Risk of fragility fracture is based on a calculated value called the T-score, which is the standard deviation of a patient's measurement from the mean of a young, healthy reference population. Values

and their significance are as follows:

- -2.5 or below: highest fracture risk, diagnostic of osteoporosis and the need for pharmaceutic therapy
- -2.5 to -1.0: intermediate fracture risk, diagnostic of osteopenia (therapeutic approach may be uncertain)
- Above -1.0: lowest fracture risk, diagnosed as normal (usually no immediate concern for drug therapy).

As an assessment of fracture risk, T-scores are applicable only to untreated postmenopausal women and older men. Once drug therapy has started, T-scores do not accurately reflect risk.

With the widespread availability of DXA, physicians often use it to investigate skeletal concerns in populations other than postmenopausal women, including men, premenopausal women, children, teenagers, and young adults of both sexes. Such usage leads to challenges when interpreting DXA results.

Scientific advances have brought about a more complex understanding of the relationships between fracture risk, bone strength, and bone density. T-scores do not always correlate with fracture risk or even with a patient's history of fracture and hence can be misinterpreted, leading to inappropriate treatment recommendations. A T-score should not solely determine diagnosis and treatment, and clinical data should appropriately modify the interpretation of results.

A T-score alone should not determine diagnosis and treatment

THE DXA REPORT VS THE CLINICAL PRESENTATION: CASE SCENARIOS

The following cases illustrate commonly encountered challenges if the DXA data and clinical presentation are incongruous.

Case 1: A young runner with 'shin splints'

A 35-year-old woman was referred for further guidance regarding a recent abnormal DXA test that had been ordered because of suspected "shin splints," ie, shin pain due to running. She was in good health, had been a recreational runner for decades with normal menstrual function, and had a healthy diet with no tobacco or alcohol use. She had no history of fractures but reported that a maternal relative may have had osteoporosis. She said that all women in her family were petite, had small stature, and had low bone density. Her examination showed small skeletal structure but was otherwise normal. Blood tests were normal. Review of the recent DXA report revealed T-scores of -0.6 for spine and -2.5 for hip. The report also included "borderline osteoporosis" in the hip and recommended drug therapy. The patient was psychologically traumatized by this information and sought further guidance.

Case 2: A postmenopausal woman with intermediate T-scores

A 60-year-old woman underwent her first DXA test, resulting in a T-score of -1.5 for spine and a score of -2.0 for the femoral neck. Her physician was pleased that the scores were not in the osteoporotic range, since she had undergone surgical menopause 30 years earlier. The physician's advice was to continue her healthy lifestyle, which included regular exercise, a vegan diet, and daily calcium and vitamin D supplements. However, she had a radiologic and clinical diagnosis of spinal osteoarthritis, as well as bilateral wrist fractures from falls when she was in her 50s. Her family history included fractures in her mother and maternal grandmother. She used hormonal therapy after surgical menopause but stopped at age 45 due to concerns about risks and side effects. She has required no other prescription medication. Her blood test results were normal.

The challenge of interpreting T-scores

T-scores can be misinterpreted and lead to inappropriate treatment recommendations. Paradoxically, the patient in case 1 with a low hip T-score score may not be at immediate high risk of fracture, and a conservative approach maybe reasonable if there are no significant risk factors, while the patient in case 2 with the osteopenic T-score is at very high fracture risk and requires aggressive therapy.

What are the reasons for this paradox? Advances in clinical science have revealed more complexities in the concepts of fracture risk, bone strength, and bone density. A T-score alone should not be the final arbiter of diagnosis and treatment. Clinical data can modify the interpretation. The following discussion addresses the development of this concept, how it modified the notion of bone strength, DXA, and T-scores, and its clinical implications.

TABLE 1

Observations contributing to new understanding of bone density and bone strength

Treatment with different antiresorptive drug classes led to similar vertebral fracture reduction despite different magnitudes of change in bone density.[4,5]
Early fracture rate improved with risedronate therapy despite no observable bone density changes.[6]
High and low doses of teriparatide led to similar rates of vertebral fracture reduction but different increases in bone density.[7]
Large-dose sodium fluoride to treat osteoporosis led to more fractures despite increased bone density.[8]
A high prevalence of low-impact fractures occurred despite abnormally elevated bone mineral density in 2 patients with autosomal-dominant osteopetrosis.[9]
Patients with diabetes have increased fracture risk despite normal bone density.[10,11]
Patients with hyperparathyroidism exhibit discordance between fracture rates and central and peripheral bone density.[12]
Fracture risk with glucocorticoids is independent of bone mineral density and correlates better with bone microarchitecture measures.[13,14]
More than half of older women with incident hip fracture did not have a diagnosis of osteoporosis up to 5 years previously.[15]

BONE STRENGTH DEPENDS ON MORE THAN BONE MINERAL DENSITY

DXA measures the amount of x-ray energy passing through bone and correlates it with the amount of mineral present. In theory, more mineral in bone (ie, greater density) indicates increased bone strength and fracture resistance, while less mineral indicates weaker bone that is more prone to fracture. Large population studies conducted in the development of DXA supported these correlations in postmenopausal women.[1] This led to the T-score system becoming the norm for diagnosing osteoporosis and high fracture risk and for determining the need for treatment.

But our understanding of the relationship between skeletal strength and bone density has evolved. Bone quality is now recognized to depend not only on density but also on skeletal characteristics that are not measured by DXA, including bone size and geometry, microarchitecture of trabecular and cortical compartments, cell turnover (reflecting metabolic activity), and composition of the mineralized protein matrix.[2]

Drug trials reveal complexity

Osteoporosis drugs produce a spectrum of changes in vertebral bone density. A 2019 meta-analysis[3] that included 38 randomized drug trials and 19 antiresorptive and anabolic drugs found a strong correlation between improvements in BMD and greater reductions in rates of vertebral and hip fracture, reassuring practitioners of the usefulness of DXA to monitor treatment. However, drug effects on bone density explained only 48% to 63% of fracture reduction at the hip and spine.

Oddities have emerged in post hoc analyses of clinical trials that have led to new notions of bone strength (**Table 1**).[4–15] In early pivotal trials, different drugs increased spinal BMD annually by different amounts while leading to similar incidences of clinical or radiologic vertebral fracture after 3 years of therapy: calcitonin (BMD increased 1.1%; 33% fracture reduction), risedronate (BMD increased 3.0-3.9%; fracture reduction 41-49%), raloxifene (BMD increased 2.6%; fracture reduction 30-50%), and alendronate (BMD increased 3.2-5.7%; fracture reduction 30-48%).[4,5] In addition, some risedronate studies found that fracture reduction arose within 6 to 12 months of treatment without measurable changes in bone density, suggesting that other factors play a role.[6]

Microarchitecture has become a central tenet of the changing view of bone strength

TABLE 2

Clinical risk factors for fractures

Older age
Low body weight and skeletal size
Family history of osteoporosis or fractures
Patient history of fractures
History of falls and imbalance
History of adult diseases compromising bone: endocrine disorders, bowel disease, nutritional disorders, renal disease
History of use of bone-toxic drugs: glucocorticoids, antiestrogens, antiandrogens, oncology agents
History of childhood disease impacting skeletal development
History of pubertal problems: delayed or absent puberty, amenorrhea, anorexia nervosa
History of harmful lifestyle: alcohol, tobacco, inactivity
Increased bone turnover markers

Age is a major risk factor for fracture, independent of bone density

Microarchitecture emerges as a critical strength determinant

Microarchitecture has become a central tenet of the changing view of bone strength. The 3-dimensional structure of interlocking bone plates, analogous to girders in buildings, confers intrinsic resistance to fracture. Increased osteoclastic and diminished osteoblastic activities in osteoporosis produce a degraded architectural network that is weakened and susceptible to fracture.[16]

New measures of bone quality and strength

Recent imaging technology has helped elucidate factors related to bone strength. Microarchitecture of bone can be visualized, and engineering protocols can be employed to measure its strength. High-resolution peripheral quantitative computed tomographic scanning is an important tool that produces 3-dimensional images of cortical and trabecular compartments in appendicular bone, with strength analyzed by finite element analysis.[17–21] This technology, however, is generally limited to research centers.

The trabecular bone score uses a proprietary program to analyze information (ie, the gray-scale texture) in DXA images to generate data about the integrity of the trabecular framework of vertebrae and, secondarily, fracture risk. High scores correlate with intact, nondegraded structure with low risk, and low scores correlate with degraded structure and high risk. Although available clinically, this program is not yet in widespread use.[22,23]

INCORPORATING CLINICAL RISK INTO DXA INTERPRETATION

DXA is unquestionably a useful tool to detect early bone loss, but results must be tempered with clinical judgment. Fractures can occur in a patient with any T-score,[24] analogous to occurrence of stroke with normal blood pressure and coronary events with normal lipid levels. The opportunity to prevent bone degradation may be missed if a practitioner waits for a high-risk patient's bone density to reach the T-score osteoporosis threshold.[25]

Because standard DXA analysis cannot detect microstructural change, clinicians must turn to other approaches to generate information about skeletal quality. In daily practice, the clinical history provides important data about risk factors, which in the broadest sense reveal information on microarchitecture (**Table 2**).

Clinical risk calculators

Most of the clinical risk factors are binary variables, and weighing their importance is subject to interpretation, often making a physician's experience the determining factor in estimating risk. Fracture risk calculators provide an objective numerical score to help guide decisions.[26]

Of the 13 risk calculators in use, the Fracture Risk Assessment Tool (FRAX), Garvan, and QFracture have been studied extensively. They are especially useful when access to DXA is limited. They vary in the number of variables used in their analyses. Their use may be restricted to specific geographic populations, and they do not quantify factors in the calculations such as duration and amount of glucocorticoid use and the severity of secondary diseases. They are intended for older people and have limited applicability to young patients. They may underestimate actual risk.

Age is a critical risk factor

More than 3 decades ago, a seminal study found that age is a major risk factor for fracture, independent of bone density.[27] With aging, fracture rates rise exponentially as bone density decreases. Fractures are less likely to occur in younger people than in older people, even with similar bone density measurements.[28] Clinical data show that this paradox reflects age-dependent microarchitecture degradation. As a result, a young patient with low bone density may not be at high risk for fracture unless other clinical factors are present, and an older patient with nonosteoporotic T-scores could be at high risk for fracture because of other clinical risk factors.

Age is a variable in all clinical risk calculators. FRAX uses age to generate intervention thresholds for fracture with or without measured bone density.

FRAX: The most important risk calculator

FRAX has worldwide applicability and validation in different countries.[29] Its calculations may be part of a DXA report, or clinicians may use web-based tools to run the calculations. It provides an intervention threshold for decision analysis.

Although FRAX is used worldwide, studies suggest that its thresholds may not be universal but ideally should be generated based on the specific geographic population of the patient.[29] Many countries use the US National Osteoporosis Foundation guidelines, specifying that drug therapy be initiated if hip fracture risk is at least 3% or major osteoporotic fracture risk at least 20%.

FRAX can provide fracture risk assessment from age alone but is more precise if hip BMD is added, with or without associated risk factors such as previous fracture, parental hip fracture, current smoking status, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and alcohol use ($\geq$ 3 units per day). These are dichotomous variables in the calculator, but practitioners often consider quantitative aspects (eg, amount and duration of glucocorticoid use, severity and type of secondary osteoporosis) in their assessment and decision.

FRAX now allows the use of trabecular bone score data to help calculate intervention thresholds for major and hip osteoporotic fractures. It significantly improves risk prediction in patients with otherwise borderline FRAX results.[30]

BONE TURNOVER MARKERS ADD INFORMATION

For clinical use, the International Osteoporosis Foundation proposed the C-telopeptide of type 1 collagen (CTX) as a biochemical marker of bone resorption and N-propeptide of type 1 procollagen (P1NP) as a marker of bone formation.[31,32] These are not diagnostic tools for osteoporosis and are not a substitute for DXA analysis.

These markers reflect bone metabolism or turnover. During menopause and in untreated osteoporosis, bone markers can be increased and indicate high skeletal turnover. Based on test results, menopausal women can be grouped as fast or slow "bone-losers." Cohort studies show bone loss is greater and fracture risk is higher as these biomarkers increase. However, for an individual patient, it is difficult to quantify this relationship, and the markers do not accurately predict bone loss or its magnitude.

But in clinical practice, these markers can help monitor patient adherence and drug efficacy[33]: antiresorptive drugs reduce levels of CTX and P1NP. The least significant change (ie, the smallest difference between successive measurements likely to be real change rather than chance) varies with the type of assay used. Depending on the assay, the least significant change in CTX is 50% to 54%, and the least significant change in P1NP is 23% to 29%. The expected clinical response is a 74% to 75% reduction in CTX and a 51% to 54% reduction in P1NP.[31] Individual measurement variability occurs from circadian rhythms, meal patterns, and laboratory techniques. Consistency in sample acquisition (eg, early morning, fasting specimens) and use of the same testing laboratory help minimize variability.[34]

Fracture risk calculators provide an objective numerical score to help guide decisions

Z-SCORES FOR YOUNGER PATIENTS

The Z-score, calculated as standard deviations from the mean of a reference group matched by age, ethnicity, and sex, should be used instead of the T-score when assessing fracture

risk in children, premenopausal women, and men younger than age 50.[35] Some advocate its use in older patients in addition to the T-score.

The Z-score is infrequently seen in dictated patient reports but can be found in the scan images of the DXA test. A low value, ie, less than -2.0, signals a lower bone mass than predicted and should prompt further investigation if the clinical history warrants.

CASE 1 REVISITED

The 35-year-old runner with a diagnosis of osteoporosis based on a low DXA hip T-score exemplifies a cascade of errors in fracture risk assessment. She may actually not be at immediate high risk of fracture, and a conservative approach may be reasonable.

The initial mistake was to order DXA for shin splints, which is not an indication for the test. This led to inappropriate use of T-scores, an incorrect diagnosis, prescription of a bisphosphonate in a healthy premenopausal woman with low fracture risk (and a chance of pregnancy), and unnecessary psychological turmoil for the patient.

The Z-score is used for children, premenopausal women, and men younger than 50

Clinical factors are paramount in this case. The patient's normal menstrual function implies sufficient estrogen production that should protect her skeleton without requiring additional medication. However, a low bone density may be suspicious for secondary problems and warrants a thorough family and clinical history to reveal possible causes. Laboratory testing would corroborate treatable options. A conundrum arises when no firm diagnosis can be found and the patient is healthy.

A diagnosis of borderline osteoporosis is contrary to guidelines of the International Society for Clinical Densitometry,[36] and "low bone mass for age" is the preferred diagnostic term. Assessment with Z-scores rather than T-scores is appropriate for this healthy premenopausal woman. It is unclear whether her low bone density represents a loss of bone from a higher baseline, which may represent an underlying disease state, or whether she may have a genetic phenotype of low density despite having strong bone.[37] Her family history and clinical examination are notable for small skeletal structure, suggestive of genetic inheritance of low bone mass. Studies of healthy premenopausal women with low bone mass show a spectrum of microarchitectural changes that mimic, to a minor degree, changes similar to osteoporosis. However, these women have a low risk of fracture. It is speculated that such architectural changes represent a pre-osteoporosis state.[38]

Management involves monitoring

A T-score indicating low bone density should not be ignored. Striving to maintain bone mass should be the guiding management principle, as she will enter menopause with a low bone mass and may experience fractures from estrogen deficiency earlier than expected for her age. A healthy lifestyle with adequate exercise and diet is the minimal therapeutic strategy. Attention should also be directed to any problems in menstrual function, eating, and hormonal disorders that may arise that would accelerate bone loss. However, skeletal pharmaceutical agents should not be considered unless evidence of bone fragility develops.

Surveillance of bone density with DXA is warranted, but a recommended interval has not been established in a premenopausal patient this young. In our practice, we consider every 5 to 10 years to be reasonable if no skeletal problems or illnesses arise.

CASE 2 REVISITED

In the case of the 60-year-old woman, the bone density report was misleading and discordant with the history of wrist fractures. Although vertebral and hip fractures attract the most attention from clinicians, wrist fractures also occur frequently and, unfortunately, are less likely to raise concern for osteoporosis evaluation and treatment. Data from a Medicare cohort showed only 7% of patients with wrist fractures have DXA testing within 6 months of such injuries, yet 20% later develop fractures of the hip or spine.[39]

The American Association of Clinical Endocrinologists and the American College of Endocrinology point out that errors in DXA scan acquisition and analysis can affect interpretation, and they encourage clinicians to review actual scan images and data rather than rely solely on a report, especially when

it is discordant with the clinical picture.[40] Assuming this patient's DXA report was of good quality, there are other reasons to question whether it reflects actual bone risk. Spinal arthritis can cause spinal DXA to be falsely normal and obscure bone deficiency.[41,42] In women with a history of fracture, trabecular bone score technology usually reveals abnormal bone even when T scores are normal.[43]

Pharmaceutical management recommended

This patient's multiple risk factors (ie, age, history of fractures, and estrogen deficiency since stopping hormone replacement after hysterectomy) attest to a weakened skeleton from osteoporosis, and a T-score that meets the osteoporosis threshold is not required to begin pharmaceutical treatment.

Further, advising only the use of calcium and vitamin D is inadequate management. Her provider should recommend that she use an antiresorption agent as first-line therapy and consider anabolic drugs if there are problems with the initial drug choice. She should not reinstate hormone therapy at her age for bone health alone as there may be increased risk for cardiovascular disease.[44] However, this caveat is not absolute and requires a balance of risk and reward if hormone therapy is also needed for vasomotor, genitourinary, or other problems.

RECOMMENDATIONS FOR ASSESSING FRACTURE RISK

Clinicians can expect to see patients similar to those in these 2 cases. Population data indicate that 2.5% of premenopausal women have T-scores below the reference range, and 6% of patients with any fracture have normal BMD tests.[45] We recommend the following approach.

Assess patients using DXA and FRAX

These are still the major tools for assessing fracture risk. However, their results should not be regarded as absolute. The practitioner, not the technology, is the final arbiter for diagnosing disease.

Use T-scores as a guide for postmenopausal women and older men

A T-score of less than -2.5 is the intervention threshold for diagnosing and treating osteoporosis. However, keep in mind that patients with spine or hip T-scores in the normal or osteopenic range may require treatment for osteoporosis if the clinical history shows fractures. In such cases, one should not wait for T-scores to reach the critical -2.5 before intervening.

Use Z-scores for premenopausal women and young patients of both sexes. A low bone Z-score in healthy men or women indicates a generally low risk for fracture and is adequately treated with good nutrition, exercise, healthy lifestyle, and skeletal surveillance. In the presence of fractures, illness that might affect the skeleton, or other risk factors, a more aggressive therapeutic approach may be indicated. ■

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REVIEW

CME MOC

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Spontaneous coronary artery dissection: Principles of management

ABSTRACT

Spontaneous coronary artery dissection (SCAD) is an acute noniatrogenic tear in the coronary arterial wall, leading to disruption of coronary blood flow and myocardial infarction. Previously considered rare, it is now recognized as a common cause of acute coronary syndrome, particularly in young women. Despite growing awareness of this disease, there is a paucity of data on acute and long-term therapy. This review summarizes the existing literature on treatment of SCAD and describes a comprehensive management strategy.

KEY POINTS

Diagnosing SCAD requires a high index of suspicion for young patients presenting with acute coronary syndrome.

SCAD is primarily managed medically in clinically stable patients.

Revascularization is recommended only for patients at high risk due to left main coronary artery dissection, ongoing ischemia, severely limited flow, hemodynamic instability, or refractory arrhythmia.

Long-term management includes screening for fibromuscular dysplasia and other arteriopathies, monitoring for recurrence, and cardiac rehabilitation.

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Spontaneous coronary artery dissection (SCAD)—an acute noniatrogenic tear in the coronary artery wall compressing the coronary lumen and possibly causing myocardial infarction—was once thought to be a rare condition but is increasingly recognized as a common cause of acute coronary syndrome (ACS), particularly in young women.[1]

Despite growing awareness of the phenomenon, there is a paucity of data on acute and long-term management. Treatment has traditionally paralleled medical management of atherosclerotic ACS, but the distinct pathophysiology of SCAD behooves us to consider other strategies. A growing body of observational data and retrospective studies is helping to better define SCAD care, but no randomized controlled trials and only a few large-scale prospective studies have focused on management, and few studies have reported outcomes beyond the first few years after dissection. The absence of robust literature has resulted in heterogeneous practice patterns, and guidelines on management remain largely based on expert consensus.

This review summarizes the literature on treatment of SCAD and, based on that, describes a comprehensive management strategy, including the role of revascularization, medical therapy, and long-term follow up.

RISK FACTORS

The true prevalence of SCAD is unknown, largely due to underdiagnosis. It is overwhelmingly seen in women, particularly young women lacking classic cardiovascular risk factors. Just 10% of cases occur in men, often following a physical stressor such as exercise or heavy

lifting.[2] Studies suggest that SCAD accounts for 1% to 4% of cases of ACS overall,[3] 15% to 20% of peripartum ACS cases,[2] and up to 35% of ACS in women under age 60.[4,5]

A number of conditions have been associated with SCAD, most notably fibromuscular dysplasia, and less commonly chronic systemic inflammatory disease, connective-tissue disorders, pregnancy, and hypothyroidism.[6–8] More recently, a few genetic loci have been identified and associated with an increased risk of SCAD.[2] In addition, various precipitants have been reported including illicit drug use, emotional turmoil, intense exercise, retching, Valsalva maneuver, straining, and other physical stressors.[6]

DIAGNOSIS BY IMAGING

Diagnosis of SCAD requires a high index of suspicion in all young patients presenting with ACS, particularly women without traditional risk factors for atherosclerosis. A variety of imaging studies are helpful in the diagnosis. However, instrumentation of the vessel wall is associated with risk of propagating the dissection, and intracoronary imaging is thus reserved for clarifying the diagnosis or for guidance during percutaneous coronary intervention (PCI).[9]

Revascularization is associated with high failure rates and poor outcomes

Coronary angiography

As with ACS caused by disruption of atherosclerotic plaque, SCAD is most commonly diagnosed during coronary angiography. However, unlike in plaque rupture, the angiographic appearance of a dissected coronary artery includes multiple radiolucent lines, contrast staining with delayed clearance, and diffuse long narrowing without evidence of significant atherosclerosis apparent in other coronary arteries.[10] Coronary angiography is regarded as the gold standard to confirm the presence of SCAD, but if not definitive, an adjunctive technique such as intravascular ultrasonography[11] or optical coherence tomography may be used, with the choice usually based on availability and local expertise.

Optical coherence tomography is particularly useful as it has high spatial resolution (< 10 µm), facilitating detection of true and false lumens, intramural hematoma, and entry tears.[12] However, it requires additional strong contrast injections and faster pullback speeds that could theoretically extend the dissection plane.

Intravascular ultrasonography is more familiar and more widely available than optical coherence tomography.

Coronary computed tomography angiography is an attractive option due to its ability to demonstrate dissection flaps and intramural hematomas. However, false-negative results are common.[13] Coronary arterial defects may be subtle, and the distal vessels (often affected by SCAD) are poorly visualized. Current technology has a potential role in evaluating recurrent symptoms or in follow-up, but it has not yet demonstrated adequate sensitivity to rule out SCAD in the acute setting.[14]

MANAGEMENT OF SCAD VS ATHEROSCLEROTIC ACS

All patients presenting with ACS should be managed in accordance with evidence-based guidelines. Once the diagnosis of SCAD is established, the treatment strategy diverges from that for atherosclerotic ACS. Although culprit-lesion revascularization is the cornerstone of atherosclerotic ACS management, SCAD is primarily managed medically in most clinically stable patients. There are two reasons for this strategy:

- Dissected vessels tend to heal over time: The natural history of SCAD appears to be spontaneous gradual healing of the vessel wall, with complete angiographic resolution of the lesion reported in most cases (73% to 97%) within 4 to 6 weeks[4,15]
- Revascularization is associated with high failure rates and poor outcomes in the setting of disrupted arterial wall integrity. Instrumentation of the damaged and friable vessel may worsen the disease and impair the healing process. Passage of the guidewire into a dissected artery risks entry into the false lumen, leading to propagation of dissection[15] and requiring more stents than expected.[16] Furthermore, balloon dilation can lead to proximal or distal extension or migration of intramural hematoma, worsening the luminal diameter. Lastly, the eventual healing of the vessel and changing architecture can result in stent malposition and future complications of stent thrombosis over the long term.

Data supports a conservative approach

Observational studies have consistently demonstrated that PCI in the setting of SCAD is associated with worse outcomes and high complication rates.[17]

In a retrospective study of 189 patients with SCAD, the procedural failure rate was 53% in those managed with PCI.[18] Reasons for technical failure included wire entry into a false lumen, final loss of flow after stent placement, and significant residual stenosis. In addition to procedural failure, PCI was associated with a high risk for emergency coronary artery bypass grafting (CABG), ie, 13% vs 2% in the medically managed group. These data are consistent with other observational studies citing high PCI failure rates. In a large Vancouver cohort of 327 patients with SCAD, 54 were treated with PCI; only 43.1% of procedures were deemed successful.[4] In a smaller study of 134 patients with SCAD in Italy, the procedure success rate was reported at 72.5%, with a trend toward higher incidence of major adverse cardiovascular events in the invasive group, driven by a higher rate of repeat revascularization.[19]

Revascularization appropriate in some cases

Despite these often poor outcomes, revascularization procedures may be appropriate in patients with the following high-risk features:

- Left main coronary artery dissection
- Ongoing ischemia
- Thrombolysis in Myocardial Infarction (TIMI) grade 0–1 flow in a proximal vessel
- Hemodynamic instability
- Refractory arrhythmia.[10,20,21]

The goals of PCI are somewhat different for SCAD than for traditional ACS. The goal of PCI in atherosclerotic ACS is to restore flow to TIMI grade 3, with residual stenosis of 20% or less. The goal in SCAD is to improve baseline TIMI flow by at least 1 grade or to maintain or achieve TIMI grade 2 or 3, and to reduce residual stenosis to less than 50%.[22]

However, neither PCI with intracoronary stenting nor CABG appears to be protective against recurrent dissection.[18,19] A study that included 20 patients who underwent CABG for SCAD found that at 5 years, 1 patient had recurrent SCAD, 3 had heart failure, and 6 had target-vessel revascularization, presumably secondary to healing of native coronary arteries resulting in competitive flow.[18]

TABLE 1

Medications for spontaneous coronary artery dissection

Indicated

Aspirin 81 mg daily

P2Y12 inhibitor if patient has undergone percutaneous coronary intervention (PCI)

Beta-blocker

Debated

P2Y12 inhibitor if no PCI: consider a 1- to 3-month course as tolerated

Statin (appropriate if otherwise indicated)

Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in patients with left ventricular dysfunction

Contraindicated

Thrombolysis

Mechanical support for shock

For SCAD complicated by cardiogenic shock, mechanical circulatory support may be considered in accordance with consensus guidelines for non-SCAD ACS treatment.[23] While case reports suggest that an intraaortic balloon pump and extracorporeal membrane oxygenation can be used safely in patients with SCAD,[24,25] they should be used with caution because, given the high incidence of concomitant arteriopathies in patients with SCAD, insertion of large-bore arterial catheters can theoretically result in iatrogenic dissection of the iliac arteries or aorta.

For patients who do not undergo PCI, the addition of a second antiplatelet agent is controversial

MEDICAL THERAPY

Medical therapy recommendations are summarized in **Table 1**.

Antiplatelet therapy

In the absence of randomized controlled trials to guide antiplatelet therapy for SCAD, data from traditional atherosclerotic ACS literature are extrapolated for this patient population. Aspirin is widely used based on its favorable side-effect profile and extensive literature supporting its benefits in traditional athero-

sclerotic ACS.[26] Patients who undergo stent placement should be treated in accordance with current ACS guidelines and receive dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 inhibitor for 12 months.

For patients who do not undergo PCI, the addition of a second antiplatelet agent is controversial. Expert consensus states that a course of DAPT may be considered[2] with the goal of minimizing thrombus burden and maintaining patency of the true lumen. While clopidogrel is most commonly prescribed, evidence is limited comparing clopidogrel, ticagrelor, and prasugrel in SCAD. Furthermore, the optimal duration of DAPT is unknown. Some authors recommend treatment for up to 12 months, while others advocate discontinuing the P2Y12 inhibitor after 1 to 3 months or when healing of the dissection is confirmed.[27]

Although DAPT in SCAD has been shown to be safe in several observational studies, there is a theoretical concern about the use of antiplatelet agents in a disease state that may be triggered by intramural bleeding.[28] In a cohort of 64 patients with SCAD,[29] 59 (92%) received DAPT with aspirin plus either clopidogrel (69%), prasugrel (14%), or ticagrelor (9%). Of the 40 patients who underwent repeat angiography, healing of dissection was demonstrated in all but 1. DAPT was well tolerated, with no specific medication-related complications noted.[29]

As of this writing, no data have been published on the use of glycoprotein IIb/IIIa inhibitors in SCAD.

Thrombolysis is contraindicated in any patient with SCAD as it may propagate dissection and lead to coronary rupture and cardiac tamponade

Limited role for anticoagulation

In line with contemporary ACS guidelines, anticoagulation is often appropriately initiated before SCAD is diagnosed. Once SCAD is identified as the cause of ACS, there is no clear benefit to continuing this therapy.[2] Anticoagulation involves a theoretical risk of increased intramural bleeding and extension of dissection, although there is a paucity of evidence on this. According to expert consensus, anticoagulants should be stopped upon confirmation of SCAD in the absence of another compelling indication for anticoagulation such as left ventricular thrombus or other thromboembolic disease.[28] The few published case reports on SCAD complicated by left ventricular thrombus report safe treatment with anticoagulation.[30]

No role for thrombolysis

Thrombolysis is contraindicated in SCAD, as it may propagate dissection and lead to coronary rupture and cardiac tamponade.[28] Several case reports have been published documenting the adverse effects of thrombolysis in SCAD.[31,32]

Beta-blockers as tolerated

Beta-blockers are central to the management of acute aortic dissection, reducing shear stress on the vessel wall and minimizing risk of propagation.[33] It follows that they would be similarly beneficial for SCAD. Beta-blockers serve not only to lower blood pressure but also to modulate heart rate, the cornerstone of impulse control. In a recent study of 327 patients with SCAD, beta-blocker use was associated with reduced risk of recurrent SCAD (hazard ratio 0.36, $P = .004$).[4] If validated in future studies, these findings would provide the first evidence for recurrence risk-reduction through medical therapy.

In practice, the use of beta-blockers is often limited by hypotension and fatigue, especially as patients are often young women without coexisting hypertension.[10] No studies to date have evaluated the efficacy of different types of beta-blockers, goal heart rate, or blood pressure after SCAD. Nonetheless, it is reasonable to escalate beta-blocker therapy to the maximally tolerated dose. In patients unable to tolerate beta-blockers, a nondihydropyridine calcium channel blocker should be considered.

Lipid-lowering therapy if otherwise indicated

As no proven connection has been identified between cholesterol and risk of SCAD, statins and other lipid-lowering agents are generally reserved for patients with traditional indications for those medications. In a retrospective single-center cohort study of 87 patients, statin use was associated with subsequent risk of SCAD recurrence.[17] However, as this analysis was limited by small sample size and incomplete information on statin use, it should be interpreted with caution. The signal for increased recurrence of SCAD with statin use has not been demonstrated in larger stud-

ies.[4] In the absence of any other indication for lipid-lowering therapy, we do not routinely prescribe statins in patients with SCAD.

LONG-TERM MANAGEMENT

Chronic management of SCAD is based on several key principles, ie, screening for fibromuscular dysplasia, monitoring for chest pain and recurrence, and cardiac rehabilitation.

Screen for fibromuscular dysplasia and other arteriopathies

Fibromuscular dysplasia is an idiopathic arteriopathy not caused by underlying atherosclerosis or inflammation, with a predilection for medium-sized vessels. It is the condition most commonly associated with SCAD, with an estimated prevalence of 25% to 86%.[3,4] This wide range reflects differences between screening methods and the number of vascular territories screened. The hallmark feature on imaging is the "string of beads," which occurs where areas of fibrosis (causing narrowing) alternate with regions of dilation.[35] The renal, carotid, and vertebral arteries are most often affected, but nearly any site may be involved.

Other arteriopathies associated with SCAD include Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, alpha-1 antitrypsin deficiency, and polycystic kidney disease.[7,8]

Given these associations, a vascular medicine evaluation is recommended for all patients diagnosed with SCAD. The evaluation should include a comprehensive vascular history, examination, and brain-to-pelvis imaging.[10] Patients with a family history or physical examination findings suggestive of known arteriopathies may benefit from a genetics evaluation. Coronary computed tomography angiography is preferred for imaging when possible, as it has higher spatial resolution than magnetic resonance angiography or ultrasonography. Screening provides valuable data to guide management, develop a longitudinal follow-up plan, and inform prognosis.

Monitor for chest pain and recurrence

Although the prognosis for long-term survival is favorable, patients are at risk of chronic angina, recurrent SCAD, and noncardiac chest pain. Optimal management requires regular follow-up with a cardiologist experienced in the care of SCAD.

Chronic angina. Of the approximately 20% of patients with SCAD who are readmitted within 30 days of the index event, many develop chronic nitrate-responsive chest pain.[3] This is suspected to be related to coronary microvascular dysfunction, which is common in this population. In a small study of 17 patients undergoing coronary flow reserve testing on coronary angiography at least 3 months post-SCAD, more than 70% had coronary microvascular dysfunction defined by a coronary flow reserve < 2.5 or an index of microcirculatory resistance > 25 units.[36] A long-acting nitrate or calcium channel blocker, or both, may be considered as needed.

Recurrent SCAD. In a prospective series of 327 patients, the recurrent SCAD rate was 10.4% over a median follow-up of 3.1 years.[4] Higher recurrence rates have been reported, with one retrospective study of 189 patients finding 27%.[18] Patients should therefore be monitored closely for new or worsening cardiac symptoms, which should prompt further testing.

While no consensus-based recommendations for a particular noninvasive imaging method have been developed, we find positron emission tomography stress imaging with coronary flow reserve most helpful, as it allows evaluation of ischemia in the previously affected territory.

Coronary computed tomography angiography can be beneficial for follow-up, particularly in patients with known large-vessel proximal SCAD and concern for recurrence soon after the index event. The main limitation with this imaging method is the possibility of missing middle or distal small-vessel disease.[13]

Lastly, cardiac magnetic resonance imaging is useful in stable patients with recent SCAD and suspicion for pericarditis. There is growing interest in its use as a surveillance tool, with evidence that it can be used to quantify infarct size.[37] Further research is needed to define its role in SCAD.

A vascular medicine evaluation is recommended for all patients diagnosed with SCAD

Recommend cardiac rehabilitation

Cardiac rehabilitation is an important component of management following SCAD, but it remains significantly underused. Young and otherwise healthy women, comprising the ma-

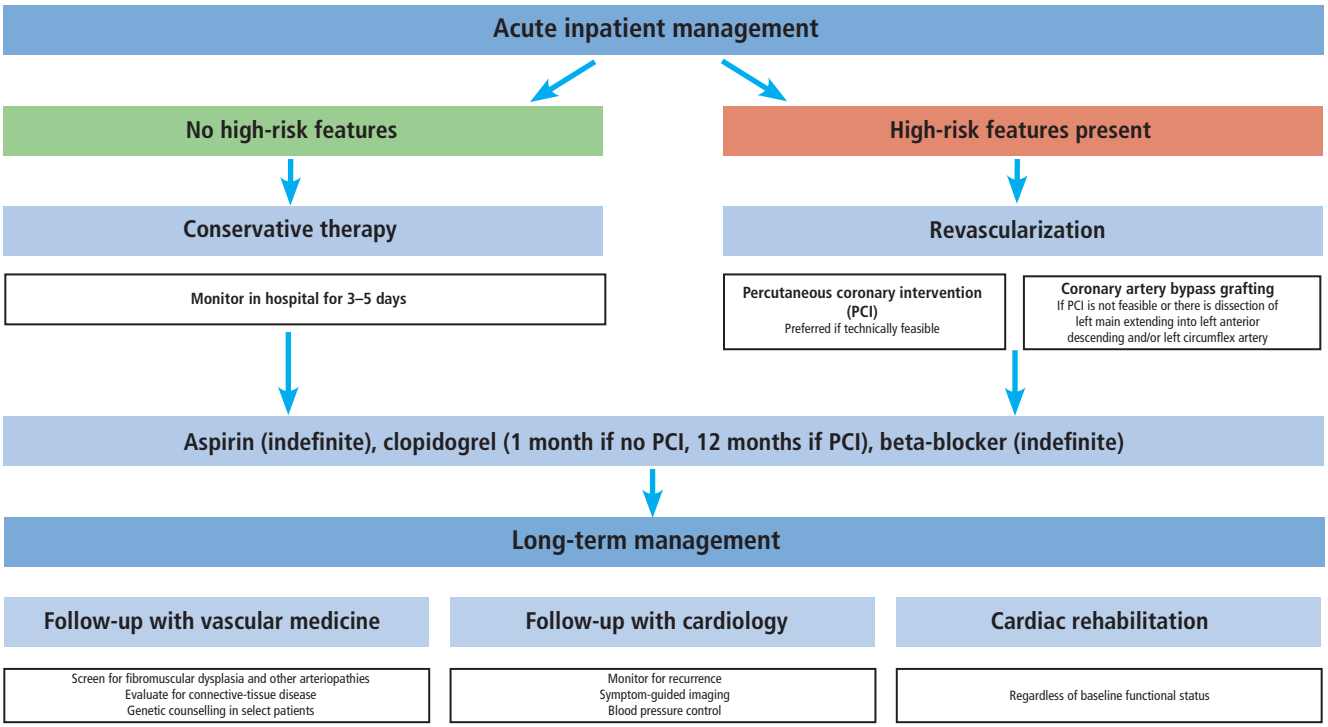

Figure 1. Our approach to the management of spontaneous coronary artery dissection.

Isometric resistance training should be avoided; strength training should be light-intensity

jority of patients with SCAD, are infrequently referred for cardiac rehabilitation. There is also concern about the safety of cardiac rehabilitation in light of the association of SCAD with physical activity.[17] Collectively, these barriers result in low enrollment, adherence, and completion rates.

However, cardiac rehabilitation has clear short-term and long-term benefits for perceived physical and mental health, and it has consistently been shown to be safe in patients with SCAD.[38,39] In a cohort of 70 women with SCAD participating in cardiac rehabilitation, improvements were found in exercise capacity, symptoms (specifically chest pain), and psychosocial well-being at the conclusion of the program.[39] Similarly, of the 269 patients who participated in cardiac rehabilitation from the Mayo Clinic SCAD registry, 82% reported physical health benefits and 75% reported emotional health benefits.[40]

We recommend referring all patients with SCAD for cardiac rehabilitation, including young women without other comorbidities. Our aerobic exercise plan involves training set at a target heart rate zone equivalent to 50% to 70% heart rate reserve based on initial exercise stress testing. The frequency of cardiac rehabilitation and aerobic exercise participation should be at least 3 times weekly for 20 to 30 minutes per session as a starting point. As patient fitness and comfort with exercise gradually improve, program progression should be encouraged but implemented conservatively and without including high-intensity interval-training methods. The long-term goal is for patients to comfortably exercise 45 to 60 minutes per session on most days of the week.

Resistance training involving isometric (constant muscle length) contraction, particularly using large muscle groups, should be avoided in patients with a history of SCAD, as these activities are often associated with temporary loading of muscles, closely followed by acute periods of high power and pressure generation.

Similarly, strength training should be limited to light intensity. Greater intensity is typically associated with Valsalva-type maneuvers, which rapidly generate transient bursts of high-to-extreme levels of intrathoracic,

cardiac, and aortic pressures. This yields high levels of localized vascular wall mechanical shear stress and compensatory spikes in heart rate, all of which should be avoided in patients with a history of SCAD.

OUR APPROACH

At our institution, we use a stepwise approach to the treatment of SCAD (**Figure 1**) that starts with assessing the patient for high-risk features that may prompt an invasive strategy for management rather than medical management. Then medical therapy is started as outlined in **Table 1**. All patients with SCAD should undergo a vascular medicine evaluation and should be followed regularly by a cardiologist with expertise in SCAD. In addition, referral for cardiac rehabilitation is essential, offering physical and mental health benefits.

NEEDED: MORE EVIDENCE FOR BEST MANAGEMENT

Prospective and randomized-controlled studies are needed to facilitate development of an evidence-based treatment algorithm for SCAD. In particular, studies to investigate the role and duration of DAPT, use of statin therapy, and indications for and timing of revascularization would greatly enhance management. With increasing clinician awareness of SCAD, coupled with advancement in angiographic diagnostic techniques, the prevalence of this disease will likely continue to grow. Hence, the need for a clear treatment approach becomes all the more pressing.

DISCLOSURES

Dr. Cho has disclosed consulting and research/independent contracting for Amgen, AstraZeneca Pharmaceuticals, and Esperion, and research/independent contracting for Novartis Pharmaceuticals. The other authors report no financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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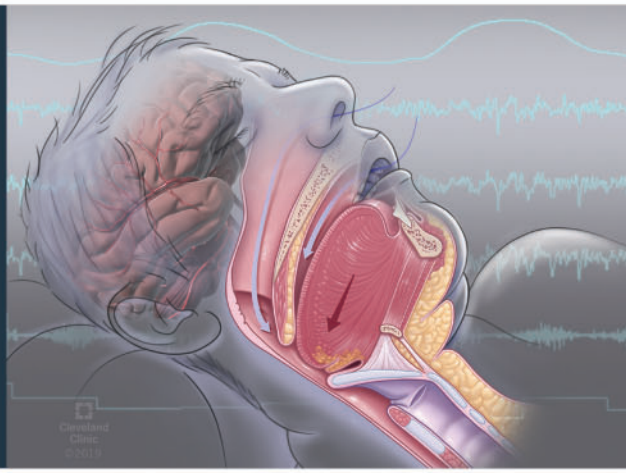

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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should my older adult patients take aspirin for primary prevention of cardiovascular disease?

Proposed USPSTF guidelines recommend against initiating aspirin for primary prevention for adults age 60 and older, citing evidence of potential harm

A: No. Recent evidence shows that the harms of aspirin use for the primary prevention of cardiovascular disease usually outweigh the benefits for patients age 70 and older.

An updated draft of the United States Preventive Services Task Force (USPSTF) recommendations for aspirin use was released for public comment on October 12, 2021.[1,2] These guidelines have a grade C recommendation for initiating low-dose aspirin for primary prevention of cardiovascular disease in patients ages 40 to 59 with a 10% or greater 10-year risk of cardiovascular disease. (Grade C: Recommends use based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.) These guidelines offer a grade D recommendation for initiating low-dose aspirin for primary prevention of cardiovascular disease in adults age 60 and older. (Grade D: Recommends against. There is at least moderate certainty of no net benefit or that harms outweigh benefit). This guidance is a change from their 2016 recommendation, which was equivocal on adults ages 60 to 69 and avoided a recommendation for adults age 70 and older, citing insufficient evidence.[3,4] Trials reviewed in this article were included in these updated draft recommendations, which are still open for comment at the time of this writing.

In 2018, results from 3 large double-blind, randomized, placebo-controlled trials offered insight into how to approach aspirin use for primary prevention in older adults. These trials—Aspirin in Reducing Events in the Elderly (ASPREE),[5,6] Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE),[7] and Aspirin for Primary Prevention in Persons With Diabetes Mellitus (ASCEND)[8]—provide substantial data to fill knowledge gaps on how to consider prescribing or de-prescribing aspirin for older patients.

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WHAT DID THE TRIALS FIND?

The ASPREE trial

This trial enrolled 19,114 community-dwelling older adult patients at least 70 years old, or at least 65 years old for Black and Hispanic patients, without evidence of cardiovascular disease (overall median age was 74).[5,6] During a median follow-up of 4.7 years, researchers found that 100 mg/day of aspirin provided no benefit in preventing nonfatal cardiovascular events or death, or in increasing disability-free survival. Aspirin use increased the risk of clinically significant, nonfatal major hemorrhage, defined as a composite measure of intracranial and upper or lower gastrointestinal bleeding that required transfusion, hospitalization, or surgical intervention, or that prolonged hospitalization. Unexpectedly, the aspirin cohort had higher all-cause mortality, attributed to increased cancer-related mortality (including a significant increase in colorectal cancer-related death in aspirin users). Mortality from major bleeding events, including hemorrhage or hemorrhagic stroke, was no different between groups.[5,6]

The ARRIVE trial

This trial enrolled 12,546 patients age 55 and older for men and age 60 and older for women with moderate cardiovascular disease risk assessed by the presence of risk factors including current tobacco use, low levels of high-density lipoprotein cholesterol, elevated systolic blood

pressure (> 140 mm Hg), prescriptions for antihypertensive medications, or positive family history of cardiovascular disease.[7] The trial was focused on primary prevention, so investigators excluded participants with prior cardiovascular events or interventions (eg, stenting, angioplasty, bypass surgery). Patients with diabetes were also excluded. The intent-to-treat analysis showed no significant benefit for aspirin use of 100 mg/day during the median 5-year follow-up. A subgroup analysis showed no benefit for patients age 65 and older. As in earlier studies,[9] the aspirin-receiving cohort had an increased risk of gastrointestinal bleeding.

The ASCEND trial

This trial enrolled 15,480 participants with diabetes but without known cardiovascular disease; nearly one-quarter of participants enrolled were at least 70 years of age.[8] Although 100 mg/day of aspirin provided an overall benefit in reducing first vascular events, a subgroup analysis revealed no benefit for patients age 70 and older. Aspirin use was associated with a higher risk of major bleeding events, defined as bleeding requiring transfusion, hospitalization, surgical intervention, or that prolonged hospitalization, required intensive care unit admittance, or caused death. This risk was significant for patients age 60 and older but was not significant for patients under age 60.[8]

HOW DID MEDICAL SOCIETIES REACT?

In light of these findings, the American College of Cardiology (ACC) updated its practice guidelines, published in September 2019, to state that low-dose aspirin should not be administered on a routine basis for the primary prevention of atherosclerotic cardiovascular disease in adults over age 70.[10] The American Diabetes Association (ADA), in its practice guidelines published in January 2021, similarly recommended that for patients over age 70 (with or without diabetes), aspirin use appears to have greater risk than benefit and thus is not recommended in these patients.[11]

Complementary interventions aimed at reducing the risk of cardiovascular events—statins for hyperlipidemia, improved antihypertensive medications, and aggressive anti-smoking campaigns—may further reduce the utility of aspirin for primary prevention. Nevertheless, data from the National Health and Nutrition Examination Survey (2011-2018) showed that aspirin use for primary prevention significantly increased as patients age, from 24% in those ages 50 to 54 to 45.3% in those age 75 and older.[12]

WHAT ABOUT ASPIRIN USE FOR COLORECTAL CANCER?

In addition, there is increasingly clear evidence supporting discontinuation of aspirin use in older adults for colorectal cancer prevention. The USPSTF had previously made a grade B recommendation for low-dose aspirin in adults ages 50 to 59 in part because of evidence supporting reduced colorectal cancer incidence after 5 to 10 years of use.[3,4] A more recent pooled analysis of data on 94,540 participants age 70 and older from both the longitudinal Nurses' Health Study and the Health Professionals Follow-up Study found that aspirin use was associated with a lower incidence of colorectal cancer after age 70 for patients who initiated aspirin before age 70 with at least 5 years of use.[13] Initiating aspirin after age 70 was not associated with reduced colorectal cancer incidence. The ASPREE investigators reported increased cancer-associated mortality risk in the aspirin-use cohort (including higher colorectal cancer mortality); however, they noted that this result was unexpected in the context of other well-designed aspirin trials and should be interpreted cautiously.[14]

There is increasingly clear evidence supporting discontinuation of aspirin use in older adults for colorectal cancer prevention

THE BOTTOM LINE

The proposed updates to its 2016 guidance for aspirin use for primary prevention in adults age 60 and older[1,2] put the USPSTF recommendations in line with those of the ACC and ADA,[9,11] which both previously incorporated evidence from the trials discussed above into their recommendations against aspirin use for primary prevention in older adults.

Our clinical recommendation is in line with the USPSTF's proposed update: the risks outweigh the benefits for aspirin in older adults. Providers, in conjunction with patients, should de-prescribe aspirin as able. ■

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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REVIEW

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Elevated hCG can be a benign finding in perimenopausal and postmenopausal women

ABSTRACT

In a perimenopausal or postmenopausal woman, an elevation in human chorionic gonadotropin (hCG) can raise the concern of malignancy or even pregnancy, but it can also be a benign physiologic finding due to production in the pituitary gland in this patient population. Diagnosing the underlying cause of hCG elevation can be challenging, especially if a pituitary source is not considered. Pituitary hCG production remains largely underrecognized and can lead to unnecessary testing, harmful therapy such as chemotherapy, or delay in receiving appropriate care for other unrelated diseases. It is therefore important to establish guidelines to aid medical evaluation.

KEY POINTS

We do not recommend further evaluation in perimenopausal or postmenopausal women when hCG levels are less than 14 IU/L and follicle-stimulating hormone (FSH) levels are 40 IU/L or higher.

In patients with hCG levels of 14 IU/L or higher and FSH levels lower than 40 IU/L, we recommend following the USA hCG Reference Service protocol, which starts with confirming the high hCG level using multiple other assays.

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The human chorionic gonadotropin (hCG) level is routinely measured to diagnose and monitor pregnancy. In addition, because hCG can be elevated in females with trophoblastic disease, germ cell tumors, and other malignancies, it is often used as a prognostic marker and for disease monitoring.[1] These days, more women, even those in perimenopause and menopause, are having their hCG levels measured to rule out pregnancy before they undergo imaging studies or treatments that could harm a fetus.

However, elevated hCG levels have been detected in as many as 0.2% to 10.6% of perimenopausal and postmenopausal women who are not pregnant and have no disease or tumor.[2–4] This phenomenon remains underrecognized, and appropriate patient care may be delayed while the source of the elevation is being sought.

In this paper, we review the evidence regarding how to assess perimenopausal and postmenopausal hCG elevation.

STRUCTURE AND BIOLOGY OF hCG

The heterodimeric glycoprotein hCG is composed of an alpha subunit and a beta subunit. Its alpha subunit is identical to the alpha subunits of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone. The beta subunit, on the other hand, differs among these hormones and determines the hormone's specificity and function.[1]

Fifteen variants of hCG have been detected,[5] some of which are biologically active, while others are breakdown products and are inactive. The

TABLE 1

Common detectable variants of human chorionic gonadotropin (hCG)

Variant	Biological activity	Structure
Intact hCG	Active	Attached alpha and beta subunit
Nicked hCG	Inactive	Beta-subunit bond broken Quickly splits into separate alpha and nicked beta subunits
Nicked free beta subunit	Inactive	Degraded product of nicked hCG
Free alpha subunit	Inactive	
Free beta subunit	Inactive	
B-core fragment	Inactive	Final breakdown product of hCG
Hyperglycosylated hCG	Active	Similar to intact hCG, with more carbohydrate side chains attached

Based on information in reference 6.

most common variants are listed in **Table 1**.[6]

The variant can suggest the source of the hCG elevation. In normal pregnancy, intact hCG is the predominant form, whereas in trophoblastic disease or testicular tumors, the free beta subunit or hyperglycosylated hCG predominates.[7,8] More than 100 immunoassay test kits are available to measure hCG.[9] All kits measure intact hCG along with one additional variant, and it is important to be aware of which hCG variant is being measured in the immunoassay used, especially when evaluating for trophoblastic disease.

A finding of elevated hCG can lead to confusion and delay in therapy

Measurement of hCG is usually done using a 2-site noncompetitive immunoassay in which the analyte (hCG) is sandwiched between two antibodies. Certain factors can interfere with the assay and lead to erroneous results. False-positive results can occur from cross-reactivity with other serum glycoproteins or from heterophilic antibodies that can bind to the antibodies used in the hCG assay.[10,11] False-negative results can occur in cases in which the true hCG level is so high that the assay antibodies become supersaturated. This is known as the "hook effect" and can be avoided through serial dilutions.

ELEVATED hCG IN PERIMENOPAUSAL AND POSTMENOPAUSAL WOMEN

The exact role of hCG outside of pregnancy remains unclear. In premenopausal women, hCG and LH levels rise during ovulation.[2] As women get older, hCG levels, like those of FSH and LH, rise due to loss of negative feedback inhibition from estrogen and progesterone.[2–4,12–16] Levels of hCG and FSH reach a peak between the ages of 45 and 55 and remain at a plateau thereafter.[14] In pregnant women, hCG levels have a diurnal variation, rising in the day and decreasing at night.[17]

Confusion can arise when hCG values are higher than the normal laboratory cutoff of 5 IU/L in nonpregnant perimenopausal and postmenopausal women. The prevalence of hCG levels of 5 IU/L or higher in women between the ages of 41 and 55 is 0.2% to 0.3%, while in older women it is 8% to 10.6%.[14,15] When hCG is "elevated," physicians often pursue an evaluation for gynecologic disease, malignancy, or paraneoplastic syndrome. Often overlooked, however, is the possibility that the hCG is coming from the pituitary gland.

THE ROLE OF PITUITARY PRODUCTION OF hCG

Pituitary hCG production was first described in the 1970s after hCG staining was seen in pituitary gland extracts.[16,18,19] The pituitary gland was also confirmed as a source of hCG production by Stenman et al,[16] whose work in 1987 showed that hCG levels rose 2- to 3-fold in healthy nonpregnant women and men who were given gonadotropin-releasing hormone

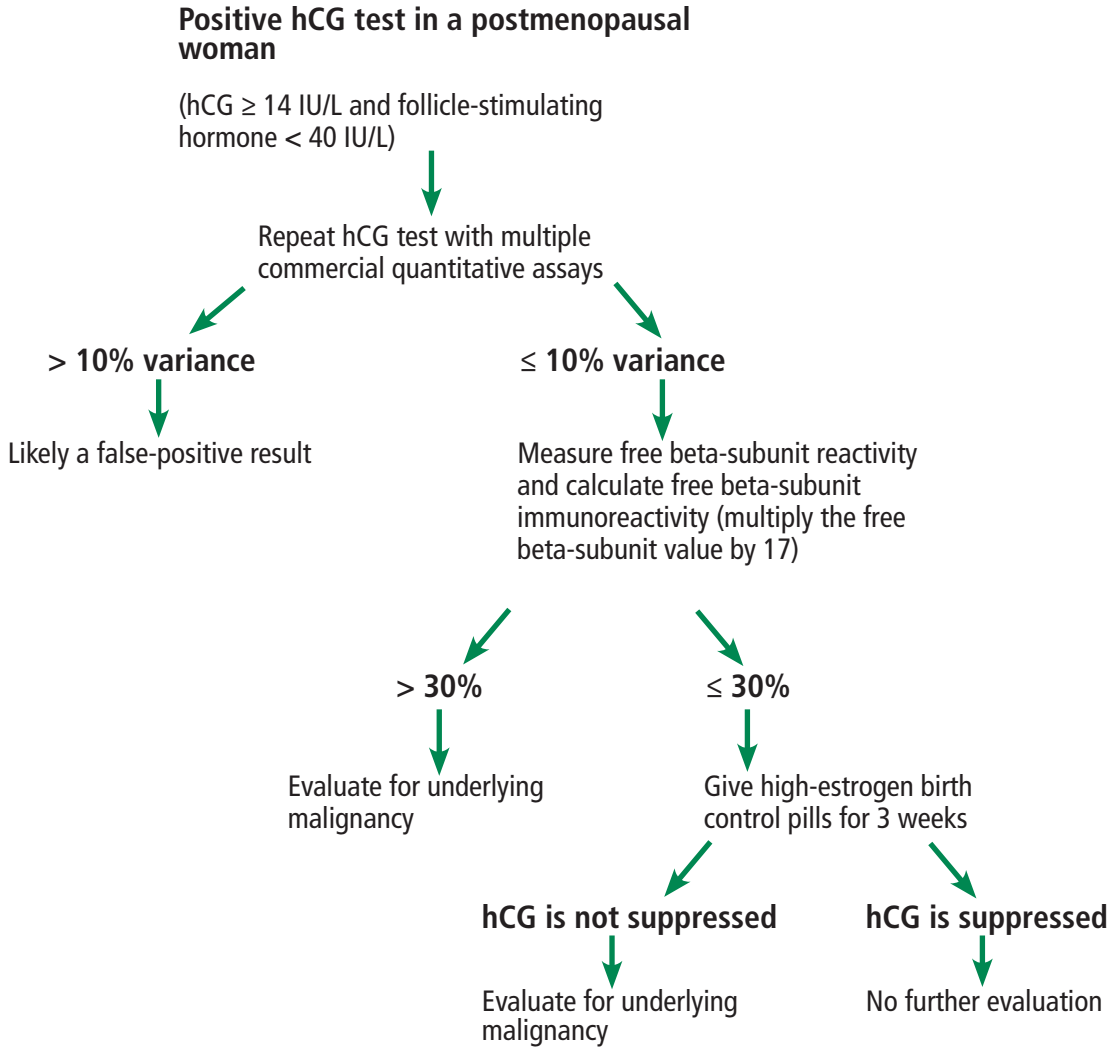

Figure 1. Recommended protocol for evaluating elevated human chorionic gonadotropin (hCG) in postmenopausal women.

Based on information in reference 2 and the authors' recommendations.

(GnRH), and fell in postmenopausal women who were given combined estrogen and progesterone. (In this study, estradiol valerate 2 mg with medroxyprogesterone acetate 10 mg daily).[16]

Several studies have since investigated this physiologic phenomenon in an attempt to establish hCG cutoff values to help differentiate between a normal physiologic rise in hCG and a rise related to an underlying pathologic disease.[2–4,17,19–21] In postmenopausal women, an hCG value of 14 IU/L has been established as the normal upper limit, while in perimenopausal women no clear cutoff value has yet been defined. This is important, as most laboratories give only the reference range for premenopausal nonpregnant women and not the reference range for postmenopausal women.

The FSH level can help distinguish the source of the excess hCG in perimenopausal women, ie, the pituitary vs the placenta (in pregnancy). FSH levels higher than 45 IU/L were found to have a 100% negative predictive value for a pituitary origin of elevated hCG.[14] FSH levels were not found to correlate with hCG levels in postmenopausal women.[15]

Physiologic hCG elevations in perimenopausal and postmenopausal women are still largely unrecognized, and the confusion can delay medical therapy and even lead to unnecessary treatment. Cole et al[3] described 28 cases of elevated hCG levels in which unnecessary chemotherapy was given, inappropriate surgery was done, or therapy for other medical conditions was delayed pending workup. The mean hCG level was 9.5 IU/L (range 2.1–32 IU/L), and the median was 7.7 IU/L. In 18 of these cases, a pituitary source was confirmed by hCG suppression after 2 weeks of hormone therapy.

In another study,[2] 18 of 36 perimenopausal and postmenopausal women with elevated hCG either received inappropriate medical therapy or experienced delay in surgery. The average hCG level in the perimenopausal women was 6.4 IU/L, and in the postmenopausal women it was 11.6 IU/L. In this series, 24 patients were given high-estrogen birth control pills, which suppressed hCG production in 23, confirming a pituitary origin. In contrast, hCG levels originating from germ cell tumors are generally significantly higher, as shown in a study by Arrieta et al in which the mean hCG level was 14,772 IU/L.[22]

After menopause, the normal upper limit of hCG is 14 IU/L

A PROTOCOL FOR EVALUATING ELEVATED hCG IN POSTMENOPAUSAL WOMEN

The USA hCG Reference Service provides a consulting service, maintains a database of cases of elevated hCG, and has presented a protocol for evaluating hCG elevations measured using commercial assays in postmenopausal women (**Figure 1**).[2,23]

The first step is to confirm hCG elevations and to exclude false-positive readings due to interfering heterophilic antibodies by repeating the measurement using different commercial assays. If the results differ by less than 10%, then interference can be excluded.

The next step is to exclude nontrophoblastic malignancy by measuring the free beta subunit and calculating the free beta subunit immunoreactivity (by multiplying the free beta subunit value by 17). If the calculated free beta subunit immunoreactivity is 30% or less, then malignancy is unlikely.

The last step is to confirm the pituitary gland as the source of hCG by demonstrating hCG suppression after 3 weeks of hormone therapy. High-estrogen birth control pills containing 50 µg of ethinyl estradiol plus progesterone are recommend. Hormone therapy can be discontinued after 3 weeks unless medically indicated for other reasons.

Women who cannot undergo hormone suppression can instead be tested using a GnRH analogue such as leuprolide 3.75 intramuscularly. Despite an initial surge of hCG after GnRH stimulation, the level becomes suppressed within 1 week through desensitization of the pituitary to a continuous GnRH output, as opposed to the pulsatile GnRH secretion seen in the physiologic state. Levels of hCG of pituitary origin will be suppressed several days after GnRH analogues are given, whereas hCG secreted from a tumor will not. A pituitary source is confirmed if hCG is suppressed to normal levels 10 days after injection.[20,21]

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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