VOLUME 92 • NUMBER 1 • JANUARY 2025 • www.ccjm.org

CME MOC

Cleveland Clinic Journal of Medicine

Sleep is like Rodney Dangerfield

Common electrolyte imbalance, uncommon cause

How can I better recognize and manage delirium in my hospitalized patients?

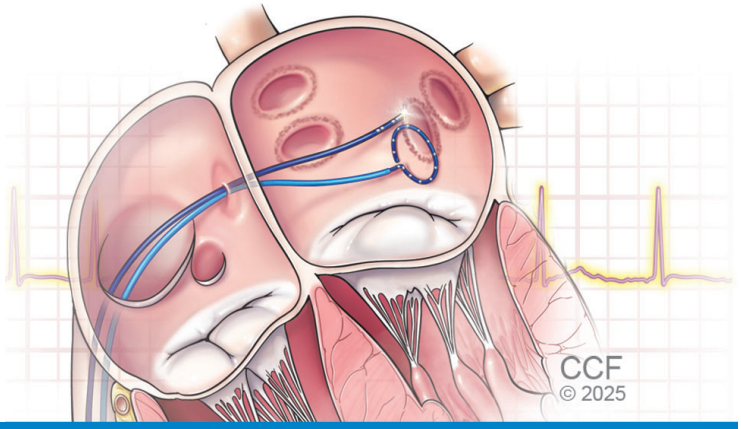
COMPLETE TABLE OF CONTENTS ON PAGE 7

Shortness of breath in a 52-year-old man with HIV and severe mitral regurgitation

Classic diabetic ketoacidosis and the euglycemic variant: Something old, something new

Insomnia in older adults: A review of treatment options

Risk-factor modification to prevent recurrent atrial fibrillation after catheter ablation



The Cleveland Clinic Foundation
9500 Euclid Ave., J44
Cleveland, Ohio 44195-0001

Nonprofit Organization
U.S. POSTAGE PAID
The Cleveland Clinic Foundation

CLEVELAND CLINIC JOURNAL OF MEDICINE

ADVERTISING
Sima Sherman, Director of Sales and Marketing
SHERMAN MEDICAL MARKETING GROUP
1628 John F. Kennedy Blvd., #2200, Philadelphia, PA 19103
(610) 529-0322 • sima@shermanmmg.com

SUBSCRIPTIONS
U.S. and possessions: Personal $160; institutional $188; single copy/back issue $20

Foreign: $205; single copy/back issue $20

Institutional (multiple-reader rate) applies to libraries, schools, hospitals, and federal, commercial, and private institutions and organizations. Individual subscriptions must be in the names of, billed to, and paid by individuals.

Please make check payable to *Cleveland Clinic Journal of Medicine* and mail to: Cleveland Clinic Education Foundation, P.O. Box 373291, Cleveland, OH 44193-3291. To purchase a subscription with a credit card, please visit www.ccjm.org.

REPRINTS
(610) 529-0322 • sima@shermanmmg.com

CHANGE OF ADDRESS
To report a change of address, send a recent mailing label along with new information to:

AMA, Data Verification Unit, 330 N. Wabash Ave., Suite 39300, Chicago, IL 60611-5885 • Phone (800) 621-8335 • Fax (312) 464-4880 • amasubs@ama-assn.org

Cleveland Clinic Journal of Medicine uses the AMA database of physician names and addresses. The database includes all US physicians and not just AMA members. Only the AMA can update changes of address and other data.

SUBSCRIPTIONS, EDITORIAL, BILLING, AND PRODUCTION
9500 Euclid Avenue, JJ44, Cleveland, OH 44195
• Phone (216) 444-2661 • ccjm@ccf.org • www.ccjm.org

Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published monthly by Cleveland Clinic at 9500 Euclid Avenue, JJ44, Cleveland, OH 44195.

Cleveland Clinic

Wellness and Preventive Medicine

Annual Conference

April 11, 2025

Cleveland Clinic Administrative Campus
3175 Science Park Drive, Building #4, 4th Floor
Beachwood, OH and Live Stream

Why Attend?

Identify specific evidence-based tools and review lifestyle assessments and interventions in the following four areas:

- Nourishing eating patterns
- Stress management
- Restorative sleep
- Healthy movement

Participate in evidence-based discussions of complementary medicine

Partake in engaging hands-on activities (non-CME) including yoga, acupuncture, cooking, and chiropractic demonstrations, and a Jeopardy game with Michael Roizen, MD!

Earn ABIM MOC Points

Live Stream option available!

Who Should Attend?

This activity is designed for practicing physicians and advanced practice providers in primary care and specialties who treat patients with chronic conditions.

Register Today! **ccfcme.org/Wellness**

This activity has been approved for *AMA PRA Category 1 Credit*™ ANCC Contact Hours, AAPA Category 1 CME Credits, and ABIM MOC Points.

Table of Contents

CONTINUED ON PAGE 8

Upcoming Features

- **Don't judge a book by its cover: Unusual presentations of pericardial disease**
- **Hypoglycemia after bariatric surgery: Management updates**

CONTINUED FROM PAGE 7

Sleep is like Rodney Dangerfield

The actor and comedian Rodney Dangerfield (1921–2004) was best known for his signature line, "I don't get no respect." If sleep were ever to deliver a monologue on late-night television, the same line would be apropos.

From my conversations with patients in the office or with friends over dinner, it seems almost no one is happy with their quality of sleep. Based on data from the National Health and Nutrition Examination Survey, the prevalence of participants with trouble sleeping was estimated by Nie et al[1] to be about 30% in 2018. The percentage of patients I see in rheumatology clinic for evaluation of generalized pain, "brain fog," and unexplained fatigue is strikingly high. Some have had a detected, but unrelated, circulating antinuclear antibody; almost all characterize their sleep as suboptimal.

And yet, there seems to be resistance in many patients and clinicians to accept a significant link between their malaise and pain and their sleep disorder. From the clinician's perspective (once malignancy and inflammatory, infectious, and metabolic disorders are reasonably believed to be unlikely), this management challenge is compounded by the fact that we don't have uniformly effective therapies to correct dysfunctional sleep. This challenge, as discussed in this issue of the *Journal*,[2] can be particularly vexing in the elderly. But there are successful approaches.

Sleep is a fascinating biologic phenomenon. There is a complex interplay between different anatomic areas of the brain that modulate wakefulness and the need for sleep. Identification of neuromediators in these different areas has resulted in the development of targeted pharmacologic therapies. Sleep in some form seems to be necessary in all species, although it may manifest differently between animals, based in part on their physiology and environmental survival pressures. Some sharks, birds, dolphins, seals, and manatees exhibit unihemispheric sleep, functionally sleeping with 1 eye open. This permits those sharks to keep moving and oxygenating and allows birds and other animals to gain the many benefits of sleep while remaining vigilant for predators.[3] Worms require a version of sleep to enable neuroplasticity sufficient to cement beneficial new olfactory learning behaviors,[4] and cellular biologic clock–controlled rest and activity cycles, akin to animal sleep and activity, have even been demonstrated in cell tissue cultures[5] and amoebae.

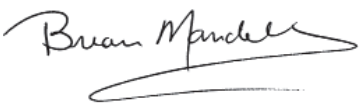
In humans and other mammals, sleep quantity (and, in some cases, quality) has been shown to impact memory and learning, mood, appetite, and pain. Many of these biologic effects ring true to those of us who are undergoing or recall the experience of medical or surgical residency. The desire for a large breakfast after a sleep-depriving night on call can be explained as an imbalance between the satiety and appetite-stimulant hormones leptin and ghrelin.[6] Acute and reversible attention loss and memory diminution have been demonstrated with acute sleep deprivation,[6] while a longer duration of sleep disruption has been linked to neurodegenerative effects, perhaps even including beta amyloid deposition.[7] Functional magnetic resonance imaging can demonstrate anatomic areas of reversible metabolic dysfunction associated with sleep deprivation, but a full neurochemical understanding is elusive. An interesting set of observations suggests that a sleep inactivity cycle is necessary for normal and efficient cerebrospinal fluid flow to clear waste molecules from interstitial spaces in the brain.[8]

Intuitive observation, and review of the above and some additional sleep research, leaves little surprise in recognizing cognitive and neuromuscular impairment in those who are not getting

doi:10.3949/ccjm.92b.01025

adequate sleep. The airline and other industries (and the Accreditation Council for Graduate Medical Education) have recognized this for years. What is less straightforward, but increasingly recognized in practice and in research settings, is the strong link between sleep quality disturbances and the presence of pain threshold diminution. The concept of central sensitization pain syndromes, or nociplastic pain, is now reasonably well entrenched in the medical literature and clinical practice (*CCJM* will have a paper devoted to this in the near future). While it is obvious that severe organ or anatomic (nociceptive) pain can lead to poor sleep, it is actually a bidirectional process. Chronic[9–11] and even transient, short-term[12] sleep disturbances can elicit or worsen pain by reducing the pain threshold and increasing sensitivity to sensory inputs. In studies, this seems to be a reversible effect.[13] In practice, reversibility is harder to accomplish, although some of the insights provided by León-Barriera et al[2] will hopefully be helpful. I have also found helpful suggestions provided by my patients who, through trial and error and word of mouth, have come upon successful creative strategies of their own, some of which have contradicted our standard teachings. It is certainly worth giving sleep the respect that it deserves—discussing sleep habits and perceived level of sleep satisfaction[14] with our patients, particularly those with difficult-to-manage pain, hypertension, and fatigue.

As we have closed out the year 2024, we at *CCJM* offer our readers, authors, and reviewers our sincere wishes that we can share a healthy, kind, and peace-filled 2025. And in the seasonal spirit of this commentary, I wish to all a good night.



Brian F. Mandell, MD, PhD
Editor in Chief

1. **Nie Q, Shen Y, Luo M, et al.** Analysis of sleep for the American population: result from NHANES database. J Affect Disord 2024; 347:134–143. doi:10.1016/j.jad.2023.11.082
2. **León-Barriera R, Chaplin M, Kaur J, Modesto-Lowe V.** Insomnia in older adults: a review of treatment options. Cleve Clin J Med 2025; 92(1):43–50. doi:10.3949/ccjm.92a.24073
3. **Mascetti GG.** Unihemispheric sleep and asymmetrical sleep: behavioral, neurophysiological, and functional perspectives [published correction appears in Nat Sci Sleep 2016; 9:1]. Nat Sci Sleep 2016; 8:221–238. doi:10.2147/NSS.S71970
4. **Chandra R, Farah F, Muñoz-Lobato F, et al.** Sleep is required to consolidate odor memory and remodel olfactory synapses. Cell 2023; 186(13): 2911–2928.e20. doi:10.1016/j.cell.2023.05.006
5. **Hinard V, Mikhail C, Pradervand S, et al.** Key electrophysiological, molecular, and metabolic signatures of sleep and wakefulness revealed in primary cortical cultures. J Neurosci 2012; 32(36):12506–12517. doi:10.1523/JNEUROSCI.2306-12.2012
6. **Krause AJ, Simon EB, Mander BA, et al.** The sleep-deprived human brain. Nat Rev Neurosci 2017; 18(7):404–418. doi:10.1038/nrn.2017.55
7. **Shokri-Kojori E, Wang GJ, Wiers CE, et al.** Beta-Amyloid accumulation in the human brain after one night of sleep deprivation. Proc Natl Acad Sci U S A 2018; 115(17):4483–4488. doi:10.1073/pnas.1721694115
8. **Fultz NE, Bonmassar G, Setsompop K, et al.** Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. Science 2019; 366(6465):628–631. doi:10.1126/science.aax5440
9. **Haack M, Simpson N, Sethna N, Kaur S, Mullington J.** Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications. Neuropsychopharmacology 2020; 45(1):205–216. doi:10.1038/s41386-019-0439-z
10. **Krause AJ, Prather AA, Wager TD, Lindquist MA, Walker MP.** The pain of sleep loss: a brain characterization in humans. J Neurosci 2019; 39(12):2291–2300. doi:10.1523/JNEUROSCI.2408-18.2018
11. **Simpson NS, Scott-Sutherland J, Gautam S, Sethna N, Haack M.** Chronic exposure to insufficient sleep alters processes of pain habituation and sensitization. Pain 2018; 159(1):33–40. doi:10.1097/j.pain.0000000000001053
12. **Chen S, Xie Y, Li Y, et al.** Sleep deprivation and recovery sleep affect healthy male resident's pain sensitivity and oxidative stress markers: the medial prefrontal cortex may play a role in sleep deprivation model. Front Mol Neurosci 2022; 15:937468. doi:10.3389/fnmol.2022.937468
13. **Aili K, Nyman T, Svartengren M, Hillert L.** Sleep as a predictive factor for the onset and resolution of multi-site pain: a 5-year prospective study. Eur J Pain 2015; 19(3):341–349. doi:10.1002/ejp.552
14. **Morin CM, Buysse DJ.** Management of insomnia. N Engl J Med 2024; 391(3):247–258. doi:10.1056/NEJMcp2305655

2025

JANUARY

PULMONARY HYPERTENSION SUMMIT
January 16–17
Hollywood, FL

ASH REVIEW
January 17
Cleveland, OH

BEST OF SAN ANTONIO BREAST CANCER SYMPOSIUM
January 18
Hollywood, FL

MULTISPECIALTY PATHOLOGY SYMPOSIUM
January 24–26
Las Vegas, NV

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: COACHING AND MENTORING ESSENTIALS FOR HEALTHCARE PROFESSIONALS
January 28
Live stream

FEBRUARY

BREAST CANCER UPDATE: REVIEW OF BREAST CANCER SYMPOSIA
February 12
Cleveland, OH

INTERNATIONAL COLORECTAL DISEASE SYMPOSIUM
February 13–15
Fort Lauderdale, FL

WOMEN AND HEART DISEASE: UNIQUE RISKS, RECOGNITION AND MANAGEMENT
February 14
Live stream

PAIN MANAGEMENT SYMPOSIUM
February 15–19
Orlando, FL

BASIC AND CLINICAL IMMUNOLOGY FOR THE BUSY CLINICIAN: SPECIAL SERIES ON CAR-T CELL AND OTHER CELLULAR THERAPIES FOR AUTOIMMUNE DISEASES
February 27
Live stream

RARE DISEASE DAY
February 27
Beachwood, OH

MARCH

STRUCTURAL VALVE IMAGING SUMMIT
March 6–9
Hollywood, FL

CLEVELAND CLINIC GUT INSIGHTS: EXPLORING THE LATEST IN GASTROENTEROLOGY
March 17–18
Hollywood, FL

APRIL

UPDATES IN PRIMARY IMMUNODEFICIENCY
April 4–5
Cleveland, OH, and Live stream

WELLNESS AND PREVENTIVE MEDICINE CONFERENCE
April 11
Beachwood, OH, and Live stream

NEPHROLOGY UPDATE
April 23–25
Cleveland, OH

PULSED FIELD ABLATION: CURRENT STATE AND FUTURE DIRECTIONS
April 24
San Diego, CA

INNOVATIONS IN NEUROSCIENCE
April 25
Avon, OH

ULTRASOUND COURSE: INTEGRATING POCUS INTO YOUR PRACTICE
April 30–May 3
Cleveland, OH

MAY

VASCULITIS 2025: ADVANCES AND CONTROVERSIES IN VASCULITIS
May 8
Cleveland, OH, and Live stream

BIOLOGIC THERAPIES SUMMIT
May 9–10
Cleveland, OH

DIABETES DAY
May 22
Cleveland, OH, and Live stream

PRIDE IN PRACTICE: STRATEGIES FOR LGBTQ+ INCLUSIVITY
May 30
Beachwood, OH

HEART OF THE CITY: CLEVELAND CLINIC HVTI CARDIOVASCULAR SYMPOSIUM
May 31
Hollywood, FL

JUNE

CLEVELAND CLINIC HEART FAILURE SUMMIT: EXPANDING THE FRONTIERS OF CONTEMPORARY TEAM MANAGEMENT
June 6–7
Cleveland, OH

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 9–13
Live stream

INNOVATIONS IN CEREBROVASCULAR CARE
June 10–11
Cleveland, OH

JULY

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: COACHING AND MENTORING ESSENTIALS FOR HEALTHCARE PROFESSIONALS
July 16–17
Live stream

AUGUST

NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN
August 1–3
Washington, DC

SEPTEMBER

GLOBAL EP
September 12–13
Cleveland, OH

NOVEMBER

PRIMARY CARE + UPDATES IN PRIMARY CARE, WOMEN'S HEALTH AND BEHAVIORAL MEDICINE
November 12–15
Beachwood, OH

FOR SCHEDULE UPDATES AND TO REGISTER, VISIT: WWW.CCFCME.ORG/LIVE

Cleveland Clinic

Addressing the Impact of **RSV and Vaccine Hesitancy**

An Educational Resource for Providers

- Master the Latest in Adult & Pediatric RSV Prevention: Vaccines & Monoclonal Antibodies
- Discover RSV Prevention Solutions for Pregnant Women & Immunocompromised Patients
- Optimize RSV Immunization & Vaccination: From Storage to Administration
- Build Trust & Confidence: Addressing Vaccine Concerns in RSV Prevention

Free CME! Participate Today!
www.ccfcme.org/RSV

This activity has been approved for *AMA PRA Category 1 Credits*™, ANCC Contact Hours, AAPA Category 1 CME Credits, Continuing Pharmacy Education (CPE) Credits

Saurav Shishir Agrawal, MD, DM
Senior Consultant and Head, Department of Endocrinology and Metabolism, Yatharth Super Speciality Hospitals, Greater Noida, Uttar Pradesh, India

Sunil Kumar, MD
Senior Consultant, Department of Internal Medicine, Yatharth Super Speciality Hospitals, Greater Noida, Uttar Pradesh, India

N. K. Soni, MD
Senior Consultant and Head, Department of Internal Medicine, Yatharth Super Speciality Hospitals, Greater Noida, Uttar Pradesh, India

Swati Paliwal, MD
Senior Consultant and Head, Department of Radiology, Yatharth Super Speciality Hospitals, Greater Noida, Uttar Pradesh, India

Common electrolyte imbalance, uncommon cause

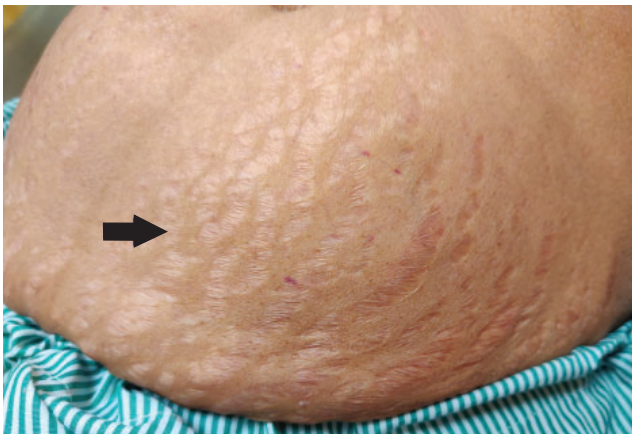


Figure 1. Striae on the patient's abdomen (arrow).

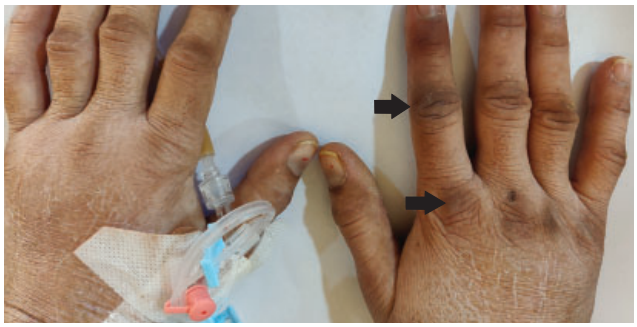


Figure 2. Hyperpigmentation of the patient's knuckles (arrows).

A 47-year-old woman was admitted to the emergency department because she had been struggling to stand up for the previous 10 days. She did not have difficulty breathing or history of similar episodes of weakness.

Physical examination showed high blood pressure (160/90 mm Hg) and the presence of wide purple striae on the abdomen (**Figure 1**). Marked hyperpigmentation was also noted on the knuckles (**Figure 2**).

Review of medical records revealed persistent severe hypokalemia, with a potassium of 2.3 mmol/L (reference range 3.5–5.1 mmol/L); however, the patient had no history of recent diarrhea, vomiting, or diuretic use.

A workup was performed, and the laboratory test results are listed in **Table 1**. The patient's transtubular potassium gradient and 24-hour urine potassium were 9 and 117 mmol, respectively, suggesting inappropriate renal loss of potassium. The patient's serum cortisol value after an overnight 1-mg dexamethasone suppression test was 48.0 µg/dL, suggesting endogenous cortisol excess, while the cortisol value after a high-dose (8 mg) dexamethasone suppression test was 42.7 µg/dL, indicating the presence of a nonpituitary adrenocorticotropic hormone (ACTH)–secreting tumor.

A provisional diagnosis of ACTH-dependent Cushing syndrome was made. Dynamic magnetic resonance imaging of the pituitary gland was performed and showed normal results. Contrast-enhanced computed tomography of the chest and abdomen revealed bilateral adrenal enlargement. Gallium-68 dotatate positron emission tomography-computed tomography to localize the source of ectopic ACTH secretion was negative. Therefore, a diagnosis of occult ectopic ACTH-secreting Cushing syndrome was made.

The patient was started on potassium supplementation, spironolactone 100 mg daily, and ketoconazole 400 mg daily, which was titrated to maintain potassium in the near-normal range.[1] Subcutaneous insulin was also administered for high plasma glucose, and oral trimethoprim-sulfamethoxazole was started as

doi:10.3949/ccjm.92a.24013

TABLE 1
Patient's laboratory test results

Laboratory test	Results (reference range)[a]
Arterial blood gas	
pH	**7.665** (7.35–7.45)
Partial pressure of carbon dioxide	43.4 mm Hg (35–48)
Partial pressure of oxygen	95.9 mm Hg (83–108)
Bicarbonate	**48.4 mmol/L** (21–28)
Sodium	138 mEq/L (135–145)
Fasting plasma glucose	**210 mg/dL** (70–100)
Magnesium	2.2 mg/dL (1.8–2.5)
Thyroid-stimulating hormone	2.2 mIU/L (0.4–4.8)
Urine electrolytes, 24-hour	
Potassium	**117 mmol/24 hours** (< 15)
Sodium	86 mmol/24 hours (40–220)
Calcium	172 mg/24 hours (< 228)
Magnesium	84 mg/24 hours (73–122)
Urine creatinine, 24-hour	16 mg/kg/24 hours (15–20)
Transtubular potassium gradient	**9** (< 2 in hypokalemia)
Plasma aldosterone concentration	5.24 ng/dL (2.2–35.3)
Direct renin concentration	6.09 mIU/L (4.4–46.1)
Serum cortisol	
Measured at 8 AM	**50.3 µg/dL** (6.2–18.0)
Overnight 1-mg dexamethasone suppression test	**48.0 µg/dL** (< 2.0)
High-dose (8 mg) dexamethasone suppression test	**42.7 µg/dL** (> 50% reduction from baseline)
Urine cortisol, 24-hour	**2,800 µg/24 hours** (28.5–213.7)
Plasma adrenocorticotropic hormone	**326 pg/mL** (15–65)

[a]Results outside reference range are shown in bold.

prophylaxis against *Pneumocystis jirovecii* infection because of the patient's markedly high cortisol level.[2] She showed symptomatic improvement.

The patient refused to undergo bilateral adrenalectomy, was discharged on ketoconazole, and is currently under regular follow-up care.

DIFFERENTIAL DIAGNOSIS OF HYPOKALEMIA

Hypokalemia, a common electrolyte abnormality in hospitalized patients, can occur because of decreased oral intake, transcellular shift, or renal or extrarenal loss of potassium.[3] Decreased oral intake is seen in states of starvation, whereas transcellular shift can occur because of alterations in acid-base homeostasis such as metabolic alkalosis; release of insulin, thyroid hormone, or catecholamines; or hypokalemic periodic paralysis. Extrarenal loss is predominantly caused by severe diarrhea or excessive sweating. The loss of gastrointestinal contents by vomiting causes secondary hyperaldosteronism and, subsequently, renal loss of potassium.

Other causes of renal loss include states of primary mineralocorticoid or cortisol excess and augmented distal urine flow that commonly occurs with diuretic therapy and salt-wasting nephropathies. Aldosterone activates the epithelial sodium channels in principal cells, increasing potassium excretion, which causes hypokalemic alkalosis. At the same time, the presence of excess cortisol in Cushing syndrome, as seen in our patient, overwhelms the 11-beta hydroxysteroid dehydrogenase enzyme in distal tubules and activates mineralocorticoid receptors, resulting in hypertension and hypokalemic alkalosis.[3]

Laboratory testing pointed to renal loss of potassium due to hypercortisolism resulting from a nonpituitary ACTH-secreting tumor as the cause of hypokalemia in this patient. A transtubular potassium gradient (calculated by dividing the urine potassium:plasma potassium ratio by the urine osmolality:plasma osmolality ratio) less than 2 and 24-hour urine potassium less than 15 mmol in the setting of hypokalemia suggests appropriate renal conservation of potassium[3]; both values were elevated for this patient.

Further, the patient's cortisol level was not suppressed in either the overnight or high-dose suppression test. In healthy individuals, serum cortisol after an overnight 1-mg dexamethasone suppres-

sion test is suppressed to less than 2.0 µg/dL, but patients with endogenous Cushing syndrome are resistant to this suppression.[1] After a high-dose (8 mg) dexamethasone suppression test, greater than 50% suppression of cortisol from baseline reflects a reduction in ACTH secretion in response to high-dose glucocorticoid, indicating Cushing disease (ie, Cushing syndrome caused by pituitary hypersecretion of ACTH). Less than 50% or no suppression occurs in ectopic ACTH-secreting Cushing syndrome, as nonpituitary ACTH-secreting tumors typically do not respond to glucocorticoid negative feedback.[1]

DIAGNOSIS AND TREATMENT

The diagnostic approach in a patient with hypokalemia includes a careful history to rule out common offending medications, such as diuretics and laxatives, and the presence of vomiting or diarrhea. A physical examination should be done to identify specific signs of a particular disease such as Cushing syndrome and thyrotoxicosis. Urine electrolyte measurements further help with diagnosis. A metabolic panel, including serum bicarbonate, along with an assessment of volume status identifies patients with renal potassium loss. The presence of a non–anion-gap metabolic acidosis suggests renal tubular acidosis.[3] Metabolic alkalosis indicates either Bartter syndrome, Gitelman syndrome, vomiting, or diuretic use, whereas the presence of hypertension points to hyperaldosteronism or Cushing syndrome.[4]

Treatment of hypokalemia includes either oral or intravenous potassium replacement and minimizing potassium loss by discontinuing any offending medications. Management of Cushing syndrome involves appropriate surgical resection after localizing the source of excess cortisol production.[2] Medical management includes ketoconazole and etomidate, which act by inhibiting multiple steroidogenic enzymes needed for cortisol synthesis. Despite recent advances, the source of ACTH remains occult in up to 20% of ectopic ACTH-secreting Cushing syndrome cases, and serial imaging with high-resolution computed tomography and somatostatin receptor-targeted positron emission tomography-computed tomography is needed to identify the tumor over time.[5] Bilateral adrenalectomy may be considered in severe, life-threatening cases.

DISCLOSURES

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

REFERENCES

1. **Alba EL, Japp EA, Fernandez-Ranvier G, et al.** The Mount Sinai clinical pathway for the diagnosis and management of hypercortisolism due to ectopic ACTH syndrome. J Endocr Soc 2022; 6(7):bvac073. doi:10.1210/jendso/bvac073
2. **Young J, Haissaguerre M, Viera-Pinto O, Chabre O, Baudin E, Tabarin A.** Management of endocrine disease: Cushing's syndrome due to ectopic ACTH secretion: an expert operational opinion. Eur J Endocrinol 2020; 182(4):R29–R58. doi:10.1530/EJE-19-0877
3. **Unwin RJ, Luft FC, Shirley DG.** Pathophysiology and management of hypokalemia: a clinical perspective. Nat Rev Nephrol 2011; 7(2):75–84. doi:10.1038/nrneph.2010.175
4. **Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A.** Hypokalemia: a clinical update. Endocr Connect 2018; 7(4):R135–R146. doi:10.1530/EC-18-0109
5. **Smushkin G, Phillips R, Chausse G.** The elusive neuroendocrine tumor: finding the ectopic ACTH source 16 years after the diagnosis of Cushing syndrome. JCEM Case Rep 2023; 1(1):luac035. doi:10.1210/jcemcr/luac035

Address: *Saurav Shishir Agrawal, MD, DM, Department of Endocrinology and Metabolism, Room No. 30, Yatharth Super Speciality Hospitals, Sector 110, Greater Noida, Uttar Pradesh 201304 India; docssagrawal@gmail.com*

Amanda Pomerantz, DO
Assistant Professor, Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham Hospital, Birmingham, AL

Anna P. Shapiro-Krew, MD
Director, Epilepsy Psychiatry, Center for Adult Behavioral Health, Cleveland Clinic, Cleveland, OH; Program Director, Consultation-Liaison Psychiatry Fellowship, Cleveland Clinic, Cleveland, OH; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Andrew Coulter, MD, MA
Attending Physician, UPMC Mercy Consultation-Liaison Psychiatry Service, Pittsburgh, PA; Assistant Professor, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA

ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: How can I better recognize and manage delirium in my hospitalized patients?

A: The following 4 steps can help clinicians to better recognize delirium: (1) familiarize yourself with the 3 phenotypes of delirium (hyperactive, hypoactive, and mixed) that describe the associated motor activity in patients with delirium; (2) take into account the patient's baseline mental status, medical history, and timeline of symptom onset; (3) use a delirium assessment tool; and (4) consider ordering an electroencephalogram.

Managing delirium in the hospital begins with prevention. There are numerous nonpharmacologic, multicomponent interventions to consider that include having the family at the bedside (as much as possible) and minimizing unnecessary overnight care that interrupts sleep. While there is no medication currently approved by the US Food and Drug Administration for the management of delirium, antipsychotics have historically been used to treat delirium-related agitation in hyperactive and mixed subtypes. Dexmedetomidine is often used for agitation in the intensive care unit (ICU) setting. There also has been growing interest in the use of clonidine and guanfacine. However, adverse cardiovascular effects, including hypotension and bradycardia, can limit the use of alpha-2 agonists.

KNOW THE 3 PHENOTYPES (BECAUSE DELIRIUM IS OFTEN MISSED)

Delirium, also known as encephalopathy, has an acute onset and is characterized by a fluctuating disturbance in attention and cognition that is accompanied by reduced environmental awareness. As delirium is a direct consequence of an underlying insult, such as another medical condition, toxin or medication exposure, or substance intoxication and withdrawal (or from multiple etiologies), it is commonly encountered in the acute hospital setting.[1] Estimated incidence during hospitalization ranges from 11% to 14% on general medical services, 20% to 29% on geriatric services, and up to 82% in the ICU.[2] This carries important implications, as delirium has been associated with increased risk of functional impairment, cognitive impairment, and mortality.[3,4]

Although delirium is a clinical diagnosis, the identification of delirium can be difficult because the way it manifests can vary by phenotype. Diagnosis is further confounded by delirium's waxing and waning course. Given these challenges, it is estimated that up to 70% of patients with delirium go undiagnosed.[5] Therefore, familiarity with the nuances of how delirium can manifest is crucial in early identification and treatment. The 3 phenotypes of delirium are hyperactive, hypoactive, and mixed, which describe the associated observed motor activity (**Table 1**).[6]

- **Hyperactive** delirium is typically associated with agitated behaviors, such as hypervigilance, restlessness, hallucinations, thought disorganization, elevated or irritable mood, and increased or loud speech. Clinically, this can manifest with the patient removing lines or medical devices, attempting to get out of bed, and experiencing disrupted sleep-wake cycles.
- Patients with **hypoactive** delirium, in contrast, often present with apathy, lethargy, psychomotor slowing, staring, decreased alertness, and reduced engagement in care.
- The **mixed** phenotype shares features of both hyperactive and hypoactive delirium.[6]

doi:10.3949/ccjm.92a.24048

TABLE 1
Delirium subtypes and features

Delirium subtype	Features
Hyperactive	Agitation Hypervigilance Restlessness Hallucinations Thought disorganization Elevated or irritable mood Increased or loud speech
Hypoactive	Apathy Staring Lethargy Decreased alertness Psychomotor slowing Reduced engagement in care
Mixed	Features of hyperactive and hypoactive subtypes

Based on information from reference 6.

TOOLS FOR RECOGNIZING DELIRIUM

Delirium is a common cause for psychiatric and neurologic consultations because it can mimic not only primary psychiatric disorders, such as mood, anxiety, and psychotic disorders, but also neurocognitive disorders, strokes, and seizures.[7] Therefore, knowledge of a patient's baseline mental status, medical history (such as underlying health conditions, recent medication changes, or hospitalizations), and timeline of symptom onset is essential in accurately assessing for delirium.

There are multiple clinical instruments to assist with both screening for delirium and determining its severity, with the Confusion Assessment Method being among the most widely used.[3,8] The 4 A's Test has also gained in popularity in identifying delirium because it is accurate (sensitivity = 0.88, 95% confidence interval 0.80–0.93; specificity = 0.88, 95% confidence interval 0.82–0.92) and quick to administer and does not require special training to use.[8] In a 2019 systematic review by Jones et al,[9] the Confusion Assessment Method, Delirium Rating Scale, and Memorial Delirium Assessment Scale were the most commonly used instruments to assess delirium severity.

The electroencephalogram is an additional tool that can be used when assessing for delirium. However, it does not currently have utility in predicting additional details such as risk, phenotype, or underlying causes of delirium.[10] Generalized slowing is a common finding of delirium on electroencephalogram.

HOW TO OPTIMIZE MANAGEMENT OF DELIRIUM

Nonpharmacologic approaches

Delirium management starts with prevention. In the ICU setting, this is best achieved through the ABCDEF bundle (assess, prevent, and manage pain; both spontaneous awakening and breathing trials; choice of analgesia and sedation; delirium assessment, prevention, and management; early mobility and exercise; family engagement and empowerment), which has been associated with a lower likelihood of delirium in a large, prospective, multicenter cohort study.[11]

There is also moderate-quality evidence supporting the use of nonpharmacologic, multicomponent interventions (colloquially known as "delirium precautions") in non-ICU hospital settings, as found in a 2021 Cochrane Review.[12] This review found that the interventions are likely effective in lowering the incidence of delirium in these settings by about 43%, and there is potential for their role in decreasing hospital length of stay.[12] There was less evidence to support these interventions in reducing delirium severity. In terms of interventions, the evidence appears strongest for reorientation, cognitive stimulation, and sleep hygiene in reducing delirium. There is less evidence for attending to nutrition, hydration, oxygenation, and bowel and bladder care; however, these interventions carry low risk. Additional techniques to reduce delirium include having family members at the bedside as much as possible, providing sensory aides (glasses, hearing aids), maintaining mobility, and minimizing unnecessary overnight care to promote uninterrupted sleep.

It is also important to minimize the use of restraints. While restraints can prevent a patient from harming themselves or others, early mobility (rather than restraint) prevents deconditioning and decreases days spent in delirium.[13] When restraints are needed, the healthcare team should use the least restrictive restraint for the shortest amount of time in an effort to prevent adverse outcomes.

Overall, these "precautions" represent low-risk, potentially high-benefit strategies to decrease the risk of delirium during hospitalization.

Pharmacologic approaches

The mainstay of delirium treatment has been to recognize and manage the underlying cause of the delirium. While the symptoms of delirium, such as agitation, hallucinations, or sleep-wake cycle disturbances, may require pharmacologic intervention, the current literature supports the use of pharmacotherapy as a means of symptom management rather than as a disease-

modifying treatment.[14] The challenges have been the limited evidence for pharmacotherapy-based treatment across delirium subtypes and the fact that no medication is approved by the US Food and Drug Administration for management of delirium.

Antipsychotics have been used for years in the treatment of delirium-related agitation in both hyperactive and mixed subtypes. Unfortunately, antipsychotics have limited evidence to support reductions in either severity or length of delirium.[14] Haloperidol, one of the more frequently studied antipsychotics in this population, has been shown to reduce agitation and improve outcomes in some, but not all, studies. Atypical (second-generation) antipsychotics, particularly risperidone, olanzapine, and quetiapine, also have been shown to improve agitation, but their antihistaminergic, antiadrenergic, and anticholinergic properties raise concerns over increased sedation, hypotension, and potential worsening of confusion.[14] When used, antipsychotics should be prescribed at the lowest effective dose and discontinued once delirium has resolved.

Dexmedetomidine, a commonly used intravenous alpha-2 agonist for agitation in the ICU setting, has been shown to decrease time on mechanical ventilation, length of ICU stay, and potentially length of delirium when compared with antipsychotics.[14] There has also been growing interest in both clonidine and guanfacine for delirium management, given that they have a similar mechanism of action to dexmedetomidine.[14,15] Guanfacine has been found to be beneficial, but clonidine remains controversial. Use of alpha-2 agonists can be limited because of adverse cardiovascular effects, including hypotension and bradycardia. A small retrospective study (N = 46) found that valproic acid may also reduce agitation and possibly length of delirium in critical care patients.[16] Although primarily studied in ICU populations, guanfacine, clonidine, and valproic acid may also be considered for use in patients on general medical floors given the various routes of administration.

For hypoactive delirium, there is currently limited evidence to support the use of medications, including antipsychotics and stimulants.[7]

Outside of agitation, the regulation of the circadian rhythm is an important component of delirium management. While melatonin is often prescribed to help restore disrupted sleep-wake cycles in patients with delirium, the evidence for its role in reducing (and even preventing) delirium incidence remains mixed.[14,17,18]

THE BOTTOM LINE

Delirium evaluation and management remain challenging, given delirium's multiple etiologies and varying manifestations across motor phenotypes, as well as the limited evidence for pharmacologic interventions. This highlights the importance of nonpharmacologic interventions in reducing the risk of delirium. By familiarizing themselves with common precipitants, mimickers, and considerations for workup, clinicians can implement nonpharmacologic strategies for prevention, better identify patients who are experiencing delirium, and optimize symptom 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.

REFERENCES

1. **American Psychiatric Association.** Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Neurocognitive disorders. https://psychiatryonline.org/doi/10.1176/appi.books.9780890425787.x17_Neurocognitive_Disorders
2. **Inouye SK, Westendorp RGJ, Saczynski JS.** Delirium in elderly people. Lancet 2013; 383(9920):911–922. doi:10.1016/S0140-6736(13)60688-1
3. **Hshieh TT, Inouye SK, Oh ES.** Delirium in the elderly. Psychiatr Clin North Am 2018; 41(1):1–17. doi:10.1016/j.psc.2017.10.001
4. **Pandharipande PP, Girard TD, Jackson JC, et al.** Long-term cognitive impairment after critical illness. N Engl J Med 2013; 369(14):1306–1316. doi:10.1056/NEJMoa1301372
5. **Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM.** Nurses' recognition of delirium and its symptoms: comparison of nurses and researcher ratings. Arch Intern Med 2001; 161(20):2467–2473. doi:10.1001/archinte.161.20.2467
6. **Liptzin B, Levkoff SE.** An empirical study of delirium subtypes. Br J Psychiatry 1992; 161:843–845. doi:10.1192/bjp.161.6.843
7. **Rosen JH, Bieber E, Matta SE, et al.** Hypoactive delirium: differential diagnosis, evaluation, and treatment. Prim Care Companion CNS Disord 2024; 26(1):23f03602. doi:10.4088/PCC.23f03602
8. **Tieges Z, Maclullich AMJ, Anand A, et al.** Diagnostic accuracy of the 4AT for delirium detection in older adults: systematic review and meta-analysis. Age Ageing 2021; 50(3):733–743. doi:10.1093/ageing/afaa224
9. **Jones RN, Cizginer S, Pavlech L, et al.** Assessment of instruments for measurement of delirium severity: a systematic review. JAMA Intern Med 2019; 179(2):231–239. doi:10.1001/jamainternmed.2018.6975
10. **Wiegand TLT, Rémi J, Dimitriadis K.** Electroencephalography in delirium assessment: a scoping review. BMC Neurol 2022; 22(1):86. doi:10.1186/s12883-022-02557-w
11. **Pun BT, Balas MC, Barnes-Daly MA, et al.** Caring for critically ill patients with the ABCDEF bundle: results of the ICU liberation collaborative in over 15,000 adults. Crit Care Med 2019; 47(1):3–14. doi:10.1097/CCM.0000000000003482
12. **Burton JK, Craig LE, Yong SQ, et al.** Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev 2021; 7(7):CD013307. doi:10.1002/14651858.CD013307.pub2

13. **Kress JP, Hall JB.** ICU-acquired weakness and recovery from critical illness. N Engl J Med 2014; 370(17):1626–1635. doi:10.1056/NEJMra1209390
14. **Sadlonova M, Duque L, Smith D, et al.** Pharmacologic treatment of delirium symptoms: a systematic review. Gen Hosp Psychiatry 2022; 79:60–75. doi:10.1016/j.genhosppsych.2022.10.010
15. **Jiang S, Hernandez M, Burke H, et al.** A Retrospective analysis of guanfacine for the pharmacological management of delirium. Cureus 2023; 15(1):e33393. doi:10.7759/cureus.33393
16. **Crowley KE, Urben L, Hacobian G, Geiger KL.** Valproic acid for the management of agitation and delirium in the intensive care setting: a retrospective analysis. Clin Ther 2020; 42(4):e65–e73. doi:10.1016/j.clinthera.2020.02.007
17. **Khaing K, Nair BR.** Melatonin for delirium prevention in hospitalized patients: a systematic review and meta-analysis. J Psychiatr Res 2021; 133:181–190. doi:10.1016/j.jpsychires.2020.12.020
18. **Wibrow B, Martinez FE, Myers E, et al.** Prophylactic melatonin for delirium in intensive care (Pro-MEDIC): a randomized controlled trial. Intensive Care Med 2022; 48(4):414–425. doi:10.1007/s00134-022-06638-9

Address: *Andrew Coulter, MD, MA, Department of Psychiatry, University of Pittsburgh School of Medicine, 1400 Locust Street, Pittsburgh, PA 15219; coulteram2@upmc.edu*

Cleveland Clinic

BEYOND THE PAGES:

Cleve Clin J Med Podcast

"Beyond the Pages: Cleve Clin J Med Podcasts" explore C*leveland Clinic Journal of Medicine* articles in depth through interviews with authors and experts in the field. Clinicians will learn more about clinical breakthroughs in medicine and how to practically apply them in patient care.

Listen today!

www.ccfcme.org/CCJMpodcast

Podcasts include

- Management of benign prostatic hyperplasia
- Treatments for obstructive sleep apnea: CPAP and beyond
- Metformin therapy for weight loss in patients without diabetes
- Antibiotics to prevent infective endocarditis before dental procedures

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

Join Our Team

Growth. Advancement. Opportunity.

These are just a few reasons to join our team of physicians and advance practice providers at Cleveland Clinic in Ohio, Florida, Nevada, Abu Dhabi and London. As a physician-led organization, we base our culture on collaboration and Patients First. Because we push the boundaries of performance, we offer competitive compensation and benefits that equal or surpass our peer organizations.

To learn more and view our physician staff and advanced practice listings, please visit jobs.clevelandclinic.org.

Cleveland Clinic is pleased to be an equal employment/ affirmative action employer: Women/Minorities/Veterans/ Individuals with Disabilities. Smoke/drug free environment.

Cleveland Clinic

Every life deserves world class care.

GREGORY W. RUTECKI, MD, Section Editor

Felix Wangmang, MD, PharmD
Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA

Achilles Aiken, MD
Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA

Kuang-Yuh Chyu, MD, PhD
Professor, Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA

Shortness of breath in a 52-year-old man with HIV and severe mitral regurgitation

A 52-year-old man presented to the emergency department with 3 weeks of acute on chronic dyspnea on exertion with progression to dyspnea at rest and associated orthopnea. He reported having experienced dyspnea with exertion for years, which he had attributed to work-related fatigue and which had not caused significant exercise limitations. However, starting 2 years earlier, his dyspnea progressively worsened without any acute triggers. At that time, he began using more pillows for orthopnea.

He denied recent travels, fevers, chills, diarrhea, chest pain, weight gain or loss, and sick contacts. His medical history included a history of well-controlled human immunodeficiency virus (HIV) infection, heart failure with preserved ejection fraction, and mitral valve prolapse with severe mitral regurgitation. He denied using tobacco or alcohol, currently using illicit drugs, or making any dietary changes. He reported briefly using methamphetamine 2 years ago, and he has since stopped. He endorsed taking his prescribed medications, which included emtricitabine-tenofovir alafenamide, dolutegravir, and furosemide 40 mg twice daily.

Three weeks before his current presentation, the patient was admitted to an outside hospital for an acute heart failure exacerbation. At that time, he had dyspnea on exertion after walking 1 flight of stairs and after walking to his car from his door. While hospitalized, he underwent aggressive diuresis, which resulted in only mild improvement in his symptoms. Therefore, he was referred for consideration for percutaneous mitral valve repair.

doi:10.3949/ccjm.92a.24060

EVALUATION ON ADMISSION

On admission, the patient was afebrile, and his blood pressure was 109/73 mm Hg, heart rate 103 beats per minute, and respiratory rate 22 breaths per minute with an oxygen saturation of 99% on room air. He was alert and oriented to person, place, and time. His lungs were clear to auscultation bilaterally. Heart rate and rhythm were regular, with a III/VI holosystolic murmur at the apex. No jugular venous distention or peripheral edema was noted.

Laboratory testing

Notable results of blood testing were as follows:

- B-type natriuretic peptide 2,122 pg/mL (reference range < 100)
- Troponin I 0.02 ng/mL (< 0.04)
- HIV RNA copies undetectable (undetectable)
- HIV antigen-antibody test reactive (negative)
- Sodium 140 mmol/L (136–145)
- Bicarbonate 23 mmol/L (22–31)
- Creatinine 0.9 mg/dL (0.72–1.25)
- Hemoglobin 15.8 g/dL (13.0–17.0)
- Hematocrit 46.7% (37.5–49.9)
- Platelet count 225 × 10^9/L (150–450)
- Aspartate aminotransferase 85 U/L (5–34)
- Alanine aminotransferase 84 U/L (0–55)
- Direct bilirubin 0.3 mg/dL (0–0.5)
- Total bilirubin 1.2 mg/dL (0.2–1.2)
- Albumin 4.3 g/dL (3.5–5.2).

Chest radiography and electrocardiography

A chest radiograph showed an enlarged cardiac silhouette without signs of pulmonary edema (**Figure 1**). An electrocardiogram (ECG) showed sinus tachycardia

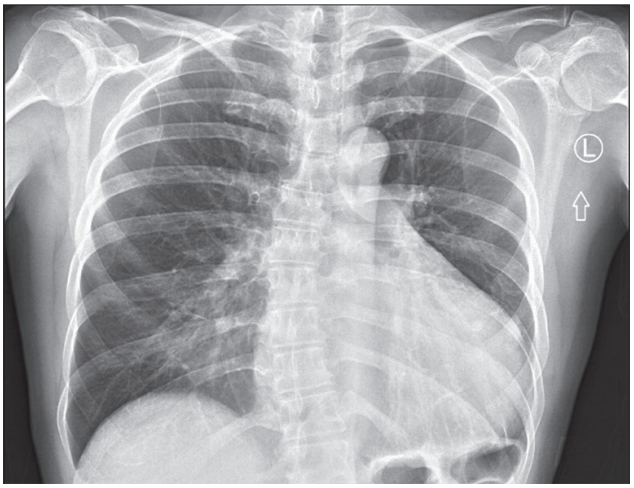


Figure 1. Chest radiograph on admission showing an enlarged cardiac silhouette without signs of pulmonary edema.

with right axis deviation, an S1Q3T3 pattern, and incomplete right bundle branch block (**Figure 2**).

DIFFERENTIAL DIAGNOSIS

1 What is the etiology of the patient's ECG findings?

- ☐ Chronic severe mitral regurgitation
- ☐ Pulmonary embolism
- ☐ Acute coronary syndrome
- ☐ Pulmonary hypertension

Given his presenting symptoms and history of chronic severe mitral regurgitation from mitral valve prolapse, the patient's presentation was consistent with acute heart failure exacerbation due to chronic severe mitral regurgitation. However, his ECG showed right axis deviation, incomplete right bundle branch block, the S1Q3T3 pattern (large S wave in lead 1, Q wave and inverted T wave in lead 3), and right ventricle strain in precordial leads, indicating right ventricular hypertrophy. These ECG features can be seen in acute pulmonary embolism or pulmonary hypertension, less so in acute coronary syndrome. The patient's younger age, minimal atherosclerotic risk factors, negative troponin, and lack of ECG signs of prior ischemic heart disease made acute coronary syndrome less likely.

Computed tomography pulmonary angiography showed no evidence of pulmonary embolism. It was thus possible that the patient's ECG pattern of right ventricular hypertrophy was due to pulmonary hypertension. Patients with severe mitral regurgitation can develop pulmonary hypertension.[1] However, the classic ECG pattern of mitral regurgitation includes left atrial enlargement, atrial fibrillation, left ventricular hypertrophy, or prior myocardial infarction. A recent study reported that in patients undergoing percutaneous mitral valve repair, the mean QRS axis before percutaneous mitral valve repair was −15.2 ± 6.1 degrees (mean ± standard error of the mean, n = 104),[2] whereas the QRS axis for this patient was 94 degrees. Additionally, the patient's ECG did not show a pattern of left ventricular hypertrophy, with small, narrow q waves, tall R waves with upright, tall T waves in leads V_5 and V_6, and deep S waves in leads V_1 and V_2, which, if present, would have been suggestive of left ventricular volume overload from mitral regurgitation.

CASE CONTINUED: TRANSTHORACIC ECHOCARDIOGRAPHY

Transthoracic echocardiography showed a left ventricular ejection fraction of more than 75%, severe right ventricular dilation, severe right ventricular systolic dysfunction, and severe eccentric, anteriorly directed mitral regurgitation due to severe posterior mitral valve leaflet prolapse (**Figure 3**). His left atrium was mildly dilated at 18.50 cm^2. His estimated pulmonary artery systolic pressure was 68 mm Hg.

A transthoracic echocardiogram obtained 5 years before this presentation was notable for severe mitral regurgitation due to prolapse of the posterior mitral valve leaflet with normal left atrium size, flow reversal in the pulmonary veins, and normal right ventricular size and function.

CAUSES OF PULMONARY HYPERTENSION

2 What is the etiology of the patient's pulmonary hypertension?

- ☐ Left heart failure from severe mitral regurgitation
- ☐ A complication of HIV therapy
- ☐ Other cause

The 2022 European Society of Cardiology and European Respiratory Society guidelines[3] define pulmonary hypertension as a mean pulmonary artery pressure of greater than 20 mm Hg and uses the following clinical classification structure:

- Group 1: Pulmonary arterial hypertension
- Group 2: Pulmonary hypertension due to left heart disease
- Group 3: Pulmonary hypertension associated with lung disease or hypoxemia, or both

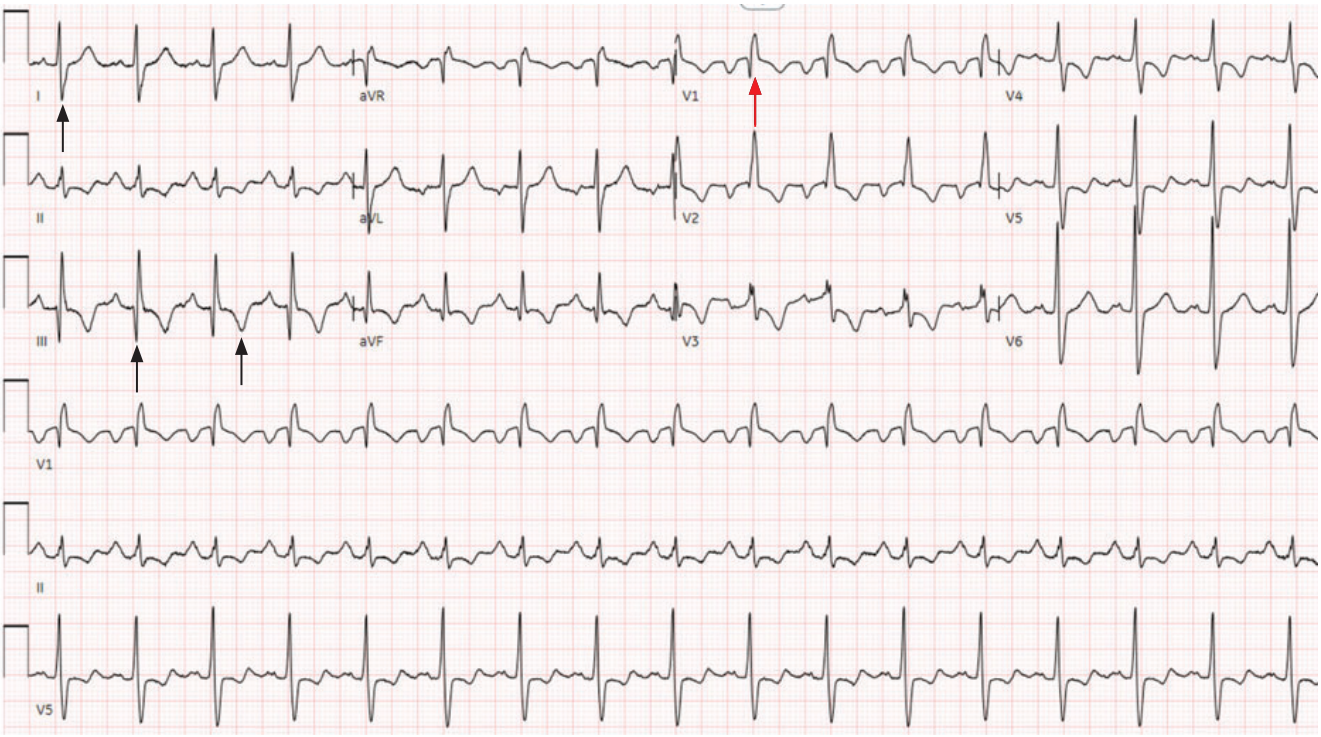


Figure 2. Twelve-lead electrocardiogram notable for sinus tachycardia with right axis deviation, S1Q3T3 pattern (large S wave in lead 1, Q wave and inverted T wave in lead 3 [black arrows]), and incomplete right bundle branch block (red arrow), indicating right ventricular hypertrophy.

- Group 4: Chronic thromboembolic pulmonary hypertension
- Group 5: Pulmonary hypertension due to unclear or multiple mechanisms.

Group 1 and group 2 pulmonary hypertension are relevant to this patient.

Mitral regurgitation and left heart disease

In this case, the patient has a known long-standing history of primary mitral regurgitation due to mitral valve prolapse. In the early compensated stage of mitral regurgitation, the volume overload associated with mitral regurgitation leads to left ventricle dilation and eccentric hypertrophy.[4] The left atrium also dilates to accommodate the increase in left atrium volume while maintaining left atrium compliance and thus normal filling pressures. Provided that forward stroke volume is maintained, patients can remain asymptomatic for years.

Over time, progressive left ventricle enlargement occurs because of the volume overload, causing left ventricle cavity dilation as well as mitral annular dilation, with progressively worsening mitral regurgitation. As mitral regurgitation worsens, the reversal of blood flow leads to volume overload and remodeling of the left atrium to accommodate the larger stroke volume, initially without a change in left atrial pressure. These anatomic changes explain the ECG findings of left atrial enlargement and left ventricular hypertrophy. Consequently, in the decompensated phase, left ventricle failure leads to increased left-sided filling pressures transmitted through the left ventricle, left atrium, and the pulmonary vasculature, leading to pulmonary hypertension.[4]

In a large multicenter international study of 437 patients with degenerative mitral regurgitation, pulmonary hypertension (defined as pulmonary artery systolic pressure > 50 mm Hg on transthoracic echocardiography) was noted in 23% of patients.[5]

HIV infection

In addition to mitral regurgitation, the patient also had a long-standing history of HIV, which increases the prevalence of pulmonary arterial hypertension by 100-fold, regardless of CD4 count.[6] While the exact mechanism is unknown, histopathologic characteristics of HIV-associated pulmonary arterial hypertension show the same findings associated with other forms of group 1 pulmonary hypertension—medial hypertrophy,

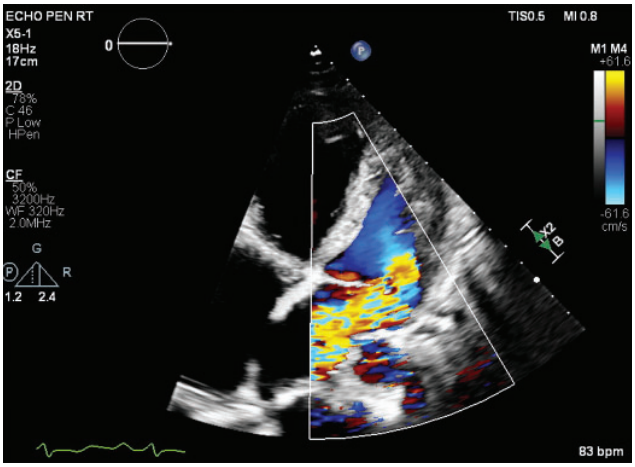


Figure 3. Transthoracic echocardiography apical 4-chamber color Doppler view showing severe eccentric, anteriorly directed mitral regurgitation (proximal isovelocity surface area radius 1.0 cm, aliasing velocity 61.6 cm/second, mitral regurgitation maximum velocity 411 cm/second, mitral valve velocity time integral 81.6 cm, effective regurgitant orifice area 0.94 cm^2, regurgitation volume 77 mL).

proliferation of endothelial and smooth muscle cells, and plexiform lesions, likely because of chronic inflammation and immune activation caused by HIV.[6]

At this juncture, it is unclear whether the patient's antiretroviral therapy contributed to his pulmonary hypertension. However, data from a retrospective study of more than 20,000 veterans suggest that improved HIV control with antiretroviral therapy is associated with a reduced risk of pulmonary hypertension detected on echocardiogram.[7]

DIAGNOSING PULMONARY HYPERTENSION

3 What is the next step in the workup for his pulmonary hypertension?

- ☐ Right heart catheterization
- ☐ Transesophageal echocardiography
- ☐ Computed tomography coronary angiography
- ☐ Left heart catheterization

The gold standard for diagnosis of pulmonary hypertension is right heart catheterization, which should be performed to confirm the diagnosis and support treatment decisions.[3] Transesophageal echocardiography, left heart catheterization, and computed tomography coronary angiography would not be able to measure precapillary and postcapillary pressures, which is necessary for the confirmation or diagnosis of pulmonary hypertension.

Pulmonary hypertension, defined by a mean pulmonary arterial pressure greater than 20 mm Hg, can be characterized as precapillary, postcapillary, and mixed pre- and postcapillary based on hemodynamic assessment by right heart catheterization.[3]

- Isolated postcapillary pulmonary hypertension: pulmonary capillary wedge pressure (PCWP) is higher than 15 mm Hg (normal ≤ 15) with a pulmonary vascular resistance of less than 2 Wood units (0.3–2.0)
- Precapillary pulmonary hypertension: PCWP is 15 mm Hg or less with a pulmonary vascular resistance of more than 2 Wood units
- Combined pre- and postcapillary pulmonary hypertension: PCWP is 15 mm Hg or more with a pulmonary vascular resistance of 2 Wood units or more.

A transpulmonary gradient (calculated as the difference between mean pulmonary artery pressure and PCWP) of 12 mm Hg or greater can be helpful for detecting intrinsic lung disease in the setting of cardiac disease and would result in the diagnosis of "out of proportion" pulmonary hypertension for the degree of left-sided cardiac disease.[8]

Elements of hemodynamic assessment

Obtaining accurate hemodynamic measurements during right heart catheterization starts with adequate preparation of patients. Further, the clinical context and imaging findings should always be considered when interpreting hemodynamic data.

The external pressure transducer should be zeroed at the phlebostatic axis, defined as the bisection of the fourth intercostal space at the midpoint between the anterior and posterior chest wall. Pressure should be measured at the end of expiration. Computer-generated digital mean pressure should not be used because the computer may not recognize and differentiate between an "a" wave and "v" wave, leading to erroneous readings.[9]

PCWP is commonly used in clinical practice to differentiate between pre- and postcapillary pulmonary hypertension; however, reliance on PCWP rather than left ventricle end-diastolic pressure can lead to misclassification of pulmonary venous hypertension as pulmonary arterial hypertension.[10] Thus, it is important to obtain measurements of PCWP and left ventricle end-diastolic pressure when hemodynamic measurements do not match the clinical context, such as in patients with chronic obstructive pulmonary disease or obesity.[11]

Preexisting medical conditions, particularly blood pressure and volume status, must be optimally controlled at the time of examination. Avoiding sedatives such as opioids or benzodiazepines is important as these drugs can cause hypotension and hypoventilation.[12]

CASE CONTINUED: RIGHT HEART CATHETERIZATION

After achieving clinical euvolemia by diuresis, the patient underwent right heart catheterization, during which the following measurements were obtained:

- Mean right atrial pressure 0 mm Hg (2–6)
- Mean pulmonary artery pressure 30 mm Hg (8–20)
- Pulmonary artery systolic 51 mm Hg (15–30)
- Pulmonary artery diastolic 18 mm Hg (4–12)
- PCWP 6 mm Hg
- Pulmonary vascular resistance 6.5 Wood units.

These findings indicate the presence of isolated precapillary pulmonary hypertension. His transpulmonary gradient was 24, suggestive of "out of proportion" pulmonary hypertension for his cardiac disease.

Workup for alternate etiologies of pulmonary hypertension, including connective tissue disease, chronic thromboembolic pulmonary hypertension, primary lung disease, sarcoidosis, and myeloproliferative disorder, was unremarkable. Medication history was unrevealing for any medications known to cause pulmonary hypertension, aside from a remote history of methamphetamine use. The only risk factor identified was the patient's history of HIV infection.

The patient was thus diagnosed with World Health Organization group 1 pulmonary hypertension, in addition to severe mitral regurgitation from mitral valve prolapse. After discussion about risks and benefits of intravenous prostanoid therapy, the patient opted to start oral sildenafil and selexipag for pulmonary arterial hypertension. Anticoagulation was discussed and ultimately deferred by the patient due to concerns about potential harm and pill burden.

MITRAL REGURGITATION TREATMENT OPTIONS

4 What is the next best step in the treatment of his severe mitral regurgitation from mitral valve prolapse?

- ☐ Clinical follow-up and serial echocardiography
- ☐ Referral to cardiac surgery for mitral valve repair
- ☐ Referral to interventional cardiology for percutaneous mitral valve clipping
- ☐ Guideline-directed medical therapy

TABLE 1
Variables used to calculate REVEAL 2.0 risk score

World Health Organization group 1 subgroup
Presence of renal insufficiency
Male age greater than 60
New York Heart Association/World Health Organization functional class
Systolic blood pressure
Heart rate
Six-minute walk test distance
Level of B-type natriuretic peptide
Presence of pericardial effusion
Diffusing capacity of the lung for carbon monoxide on pulmonary function test
Elevated atrial pressures
Any hospitalization within 6 months
Pulmonary vascular resistance

REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management

Information from reference 13.

There is no straight answer for this patient as he has 2 concomitant diseases, with pulmonary hypertension posing higher procedure risk for mitral valve intervention. The REVEAL 2.0 score (Registry to Evaluate Early and Long-Term PAH Disease Management) is used to predict survival in patients with pulmonary arterial hypertension based on 13 variables (**Table 1**).[13] The patient's REVEAL 2.0 score was 14, putting him in a high-risk subgroup (≥ 9) with 1-year survival predictions lower than 70%. (A REVEAL 2.0 calculator is available online: www.mdcalc.com/calc/10071/reveal-registry-risk-score-pulmonary-arterial-hypertension-pah)

The 2022 European Society of Cardiology and European Respiratory Society guidelines[3] recommend attempting to optimize peripheral arterial hypertension therapy before surgery, and also note that the mortality risk of surgical procedures is associated with the severity of pulmonary hypertension. Factors such as N-terminal pro–B-type natriuretic peptide higher than 300 pg/mL, New York Heart Association functional class 3 or 4, renal insufficiency, hospitalization within 6 months, and urgency of surgery have been independently associated with increased postoperative mortality in noncardiac surgery.[14,15] It stands to reason these risk factors are also associated with worse outcomes in patients undergoing cardiac surgery.

All patients with severe mitral regurgitation should undergo an assessment to determine the cause of

their mitral regurgitation.[16] Patients with symptomatic severe primary mitral regurgitation should be referred for mitral valve repair with cardiac surgery, which is preferred over mitral valve replacement but may not always be technically feasible. All patients with severe primary mitral regurgitation with features of cardiac remodeling (ejection fraction ≤ 60%, left ventricle end-systolic diameter ≥ 4 cm, pulmonary artery systolic pressure > 50 mm Hg, new atrial fibrillation, or progressive decrease in left ventricle ejection fraction over time) should be referred for surgical management as well.

Given the patient's initial presenting symptoms suggesting left-sided heart failure, referring him for mitral valve intervention after starting him on adequate pulmonary hypertension therapy would have been reasonable. Stress echocardiography to assess change of systolic pulmonary arterial pressure during exercise could have been helpful in attributing his symptoms to mitral regurgitation. Referral to pulmonary hypertension specialists to optimize his perioperative care also would have been appropriate.

The mode of mitral intervention, surgically vs percutaneously, in the setting of group 1 pulmonary hypertension is another concern. Given the patient's high REVEAL score, we believe percutaneous mitral valve repair was a reasonable option to avoid intubation, cardiopulmonary bypass, fluid shift, and postoperative pulmonary complications. Other surgical risk assessments for surgical vs percutaneous mitral valve repair should include the patient's Society of Thoracic Surgeons predicted risk of mortality, frailty assessment, cardiac or other major organ system compromise not to be improved postoperatively, and procedure-specific impediment.[17] The decision should be made by a multidisciplinary team involving a pulmonary hypertension specialist and based on individual risk vs benefit factors such as indication, urgency, severity of pulmonary hypertension, and patient preference.[3]

CASE DISCUSSION

This was an unusual case of a patient with heart failure symptoms that were initially attributed to severe mitral regurgitation and resultant group 2 pulmonary hypertension, with an initial plan for mitral valve intervention. However, the right ventricular hypertrophy patterns on ECG were less consistent with isolated severe mitral regurgitation and raised the suspicion that the patient's pulmonary hypertension was not due to severe mitral regurgitation alone. ECG findings in mitral regurgitation are often nonspecific and consist of left atrial enlargement, atrial fibrillation, left ventricular hypertrophy, or changes suggesting concomitant myocardial infarction.[2]

ECG signs suggesting pulmonary hypertension or right ventricular hypertrophy are not common in isolated mitral regurgitation. In a group of 65 patients with rheumatic mitral regurgitation, only 9.2% and 1.5% of patients had right ventricular hypertrophy and right ventricular hypertrophy with incomplete right bundle branch block, respectively.[18] In a group of 23 patients with mitral regurgitation of mixed etiology, only 4.3% and 8.6% of patients had right ventricular hypertrophy or combined ventricular hypertrophy, respectively.[19]

However, the presence of right ventricular hypertrophy on ECG in patients with mitral regurgitation does indicate advanced disease, with pulmonary hypertension and high PCWP indicating left heart failure as well.[20] These published data are from the pre-echocardiography era and included mostly patients with rheumatic mitral regurgitation. The true incidence of ECG patterns of right ventricular hypertrophy or right ventricular strain is not known in nonrheumatic mitral regurgitation as contemporary data from the the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study),[21] COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation),[22] and MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation)[23] trials did not provide ECG descriptions.

In addition, this case illustrates a potential anchoring bias, a common cognitive bias that influences physician decision-making. Anchoring bias refers to the practice of prioritizing information and data that support one's initial impressions, even if those impressions are incorrect. A 2016 systematic review of the available evidence on cognitive biases showed that cognitive bias may affect 50% to 100% of physicians and was associated with diagnostic inaccuracies in 36.5% to 77% of case scenarios.[24] In this case, the patient was being admitted for dyspnea and had a history of mitral regurgitation and heart failure exacerbations. The patient's dyspnea was attributed to heart failure exacerbation caused by mitral regurgitation, and the patient was evaluated for mitral valve intervention. Further review led to investigation with a right heart catheterization and a diagnosis of pulmonary arterial hypertension, which changed the patient's treatment trajectory.

Modern cardiology has evolved to rely heavily on echocardiography and advanced imaging modalities for diagnostic and therapeutic decision-making. Reliance on advanced imaging modalities is growing in daily practice due to the complexity of patient presentations and advances in therapeutics for patients with increasingly complex structural heart disease. Although ECG reading skills are still being taught at bedside daily, less time and effort has been spent analyzing and correlating ECG findings with clinical data and imaging findings. This case illustrated a potentially biased diagnosis and therapy plan based on history and imaging, with ECG interpretation playing a key role in correcting the bias.

CASE CONCLUSION

The patient was started on dual oral therapy for pulmonary arterial hypertension with sildenafil and selexipag, with plans to address his mitral valve prolapse after his pulmonary arterial hypertension was better controlled.

TAKE-HOME POINTS

- Patients who have discordant clinical presentations and diagnostic studies require a wide differential diagnosis to avoid premature closure or anchoring bias.
- Electrocardiography remains an integral part of diagnostic workup and should be interpreted together with the clinical picture to establish a diagnosis.

DISCLOSURES

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

REFERENCES

1. **Alexopoulos D, Lazzam C, Borrico S, Fiedler L, Ambrose JA.** Isolated chronic mitral regurgitation with preserved systolic left ventricular function and severe pulmonary hypertension. J Am Coll Cardiol 1989; 14(2):319–322. doi:10.1016/0735-1097(89)90180-0
2. **Bo H, Heinzmann D, Grasshoff C, et al.** ECG changes after percutaneous edge-to-edge mitral valve repair. Clin Cardiol 2019; 42(11):1094–1099. doi:10.1002/clc.23258
3. **Humbert M, Kovacs G, Hoeper MM, et al.** 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023; 61(1):2200879. doi:10.1183/13993003.00879-2022
4. **Patel H, Desai M, Tuzcu EM, Griffin B, Kapadia S.** Pulmonary hypertension in mitral regurgitation. J Am Heart Assoc 2014; 3(4):e000748. doi:10.1161/JAHA.113.000748
5. **Barbieri A, Bursi F, Grigioni F, et al.** Prognostic and therapeutic implications of pulmonary hypertension complicating degenerative mitral regurgitation due to flail leaflet: a multicenter long-term international study. Eur Heart J 2011; 32(6):751–759. doi:10.1093/eurheartj/ehq294
6. **Almodovar S, Cicalini S, Petrosillo N, Flores SC.** Pulmonary hypertension associated with HIV infection: pulmonary vascular disease: the global perspective. Chest 2010; 137(6 suppl):6S–12S. doi:10.1378/chest.09-3065
7. **Duncan MS, Alcorn CW, Freiberg MS, et al.** Association between HIV and incident pulmonary hypertension in US Veterans: a retrospective cohort study. Lancet Healthy Longev 2021; 2(7):e417–e425. doi:10.1016/s2666-7568(21)00116-1
8. **Naeije R, Vachiery JL, Yerly P, Vanderpool R.** The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J 2013; 41(1):217–223. doi:10.1183/09031936.00074312
9. **Krishnan A, Markham R, Savage M, Wong YW, Walters D.** Right heart catheterisation: how to do it. Heart Lung Circ 2019; 28(4): e71–e78. doi:10.1016/j.hlc.2018.08.005
10. **Halpern SD, Taichman DB.** Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. Chest 2009; 136(1): 37–43. doi:10.1378/chest.08-2784
11. **Bitar A, Selej M, Bolad I, Lahm T.** Poor agreement between pulmonary capillary wedge pressure and left ventricular end-diastolic pressure in a veteran population. PLoS One 2014; 9(1):e87304. doi:10.1371/journal.pone.0087304
12. **Gonzalez-Hermosillo LM, Cueto-Robledo G, Roldan-Valadez E, et al.** Right heart catheterization (RHC): a comprehensive review of provocation tests and hepatic hemodynamics in patients with pulmonary hypertension (PH). Curr Probl Cardiol 2022; 47(12):101351. doi:10.1016/j.cpcardiol.2022.101351
13. **Benza RL, Gomberg-Maitland M, Elliott CG, et al.** Predicting survival in patients with pulmonary arterial hypertension: The REVEAL Risk Score Calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. Chest 2019; 156(2):323–337. doi:10.1016/j.chest.2019.02.004
14. **Deljou A, Sabov M, Kane GC, et al.** Outcomes after noncardiac surgery for patients with pulmonary hypertension: a historical cohort study. J Cardiothorac Vasc Anesth 2020; 34(6):1506–1513. doi:10.1053/j.jvca.2019.10.059
15. **Rajagopal S, Ruetzler K, Ghadimi K, et al.** Evaluation and management of pulmonary hypertension in noncardiac surgery: a scientific statement from the American Heart Association. Circulation 2023; 147(17):1317–1343. doi:10.1161/CIR.0000000000001136
16. **Bonow RO, O'Gara PT, Adams DH, et al.** 2020 focused update of the 2017 ACC expert consensus decision pathway on the management of mitral regurgitation: a report of the American College of Cardiology Solution Set Oversight Committee [published correction appears in J Am Coll Cardiol 2020; 75(23):3000]. J Am Coll Cardiol 2020; 75(17):2236–2270. doi:10.1016/j.jacc.2020.02.005
17. **Otto CM, Nishimura RA, Bonow RO, et al.** 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation 2021; 143(5):e229] [published correction appears in Circulation 2023; 148(8):e8] [published correction appears in Circulation 2023; 148(20):e185] [published correction appears in Circulation 2024; 150(12):e267]. Circulation 2021; 143(5):e72–e227. doi:10.1161/CIR.0000000000000923
18. **Bentivoglio LG, Uricchio JF, Waldow A, Likoff W, Goldberg H.** An electrocardiographic analysis of sixty-five cases of mitral regurgitation. Circulation 1958; 18(4 Part 1):572–580. doi:10.1161/01.cir.18.4.572
19. **Ross J Jr, Braunwald E, Morrow AG.** Clinical and hemodynamic observations in pure mitral insufficiency. Am J Cardiol 1958; 2(1):11–23. doi:10.1016/0002-9149(58)90244-3
20. **Bentivoglio L, Uricchio JF, Likoff W.** The paradox of right ventricular enlargement in mitral insufficiency. Am J Med 1958; 24(2):193–202. doi:10.1016/0002-9343(58)90307-3

21. **Feldman T, Foster E, Glower DD, et al.** Percutaneous repair or surgery for mitral regurgitation [published correction appears in N Engl J Med 2011; 365(2):189. Glower, Donald G [corrected to Glower, Donald D]]. N Engl J Med 2011; 364(15):1395–1406. doi:10.1056/NEJMoa1009355
22. **Stone GW, Lindenfeld J, Abraham WT, et al.** Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018; 379(24):2307–2318. doi:10.1056/NEJMoa1806640
23. **Obadia JF, Messika-Zeitoun D, Leurent G, et al.** Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018; 379(24):2297–2306. doi:10.1056/NEJMoa1805374
24. **Saposnik G, Redelmeier D, Ruff CC, Tobler PN.** Cognitive biases associated with medical decisions: a systematic review. BMC Med Inform Decis Mak 2016; 16(1):138. doi:10.1186/s12911-016-0377-1

Address: *Kuang-Yuh Chyu, MD, PhD, Department of Cardiology, Smidt Heart Institute, Cedars Sinai Medical Center, 127 South San Vicente Boulevard, Suite A-3318, Los Angeles, CA 90048; chyuk@cshs.org*

Cleveland Clinic

Improve Your Virtual Patient Visit Skills

Many patients are eager to visit their physicians virtually, but not all physicians are comfortable conducting virtual visits.

You can take advantage of a free series of self-directed online modules to help you build your virtual patient visit skills.

The free course offers:

- brief introduction to virtual visits
- guidance for demonstrating communication and empathy
- best practices for taking a patient history
- instructions for conducting a physical examination, based on organ system

To help you master the content, the free course includes many video demonstrations and knowledge checks throughout.

Visit clevelandclinic.org/virtual-training

With the exception of the physical examination module, these activities have been approved for *AMA PRA Category 1 Credit™*.

REVIEW

Adi E. Mehta, MD
Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic, Cleveland, OH; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Robert Zimmerman, MD
Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic, Cleveland, OH; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Classic diabetic ketoacidosis and the euglycemic variant: Something old, something new

ABSTRACT

Diabetic ketoacidosis (DKA) was historically considered a condition typical of type 1 diabetes. However, patients with type 2 diabetes may present with DKA, usually with higher blood glucose levels and milder ketoacidosis. With the increased use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, the variant euglycemic DKA has been described. SGLT-2 inhibitors cause a low level of ambient ketones; any additional ketone formation predisposes to ketoacidosis, while the agent's glycosuric effect limits hyperglycemia. The principles of DKA management are fluid administration, electrolyte control, and glucose control with insulin. In euglycemic DKA, the immediate use of a glucose-containing intravenous fluid induces endogenous insulin secretion and stops ketogenesis. Due to the half-life of SGLT-2 inhibitors, the duration of euglycemic DKA may be more prolonged.

KEY POINTS

- Management of DKA requires strict discipline and a hierarchal approach—fluid administration; electrolyte and, especially, potassium control; and hyperglycemia therapy.
- When ambient glucose levels are less than 200 to 250 mg/dL at presentation or during treatment, or if there is a history of SGLT-2 inhibitor therapy, the initial intravenous fluid must contain dextrose.
- Before starting or resuming an SGLT-2 inhibitor, an in-depth evaluation of euglycemic DKA risks and an explanation of how to mitigate them are essential.

doi:10.3949/ccjm.92a.24075

Ketoacidosis is a ubiquitous condition usually specified by its etiology. Thus, the forms of ketoacidosis—starvation, alcoholic, hyperemesis gravidarum, and diabetic—all have a common metabolic pathway to ketoacidosis: the inability to metabolize glucose as a primary fuel, setting into motion the production of secondary fuels that generate strongly acidic ketone bodies: acetoacetate, beta hydroxybutyrate, and acetone. That inability may stem from a lack of available glucose, like in starvation, or a decrease in hepatic gluconeogenesis induced by alcohol, leading to decreased insulin secretion, increased lipolysis, impaired shunting of fatty acids to mitochondria, fatty acid oxidation, and subsequent ketogenesis, causing an elevated anion-gap metabolic acidosis. In hyperemesis gravidarum, the lack of ingested glucose and the resultant decrease in insulin are amplified by the presence of insulin resistance during pregnancy. In these circumstances, the ambient glucose level is most frequently in the low-normal range, and mild hyperglycemia is rare.

Diabetic ketoacidosis (DKA), on the other hand, is defined by a triad of hyperglycemia with an ambient blood glucose level well greater than 250 mg/dL, high anion-gap acidosis, and increased plasma ketones, which are the unmeasured anions causing the gap.[1] Euglycemic DKA (EDKA) is a variant of DKA in which the blood glucose is less than 250 mg/dL but the other features of DKA are present. Although EDKA is not common, it can

GLUCAGON RELEASE IN EDKA: PLAUSIBLE PATHOPHYSIOLOGIC MECHANISMS

SGLT receptors are expressed by islet alpha cells. However, although SGLT-1 receptors have been described, evidence supporting the presence of SGLT-2 receptors in alpha cells is inconsistent, and cross-reactivity of SGLT-2 inhibitors on the SGLT-1 receptor is unlikely.[2]

Paracrine effects on the secretion of glucagonotropic and static substances from other islet cells have been proposed as an alternative mechanism, but this hypothesis has not been conclusively proven.

Of interest is the presence of a renal–pancreatic loop, which suggests that glycosuria caused by the SGLT-2 inhibitor and the associated lowering of circulating glucose triggers the increase in glucagon. This hypothesis is supported by data from glucose clamping experiments in which the rise in glucagon was prevented if the blood glucose level did not change during SGLT-2 inhibitor therapy.[2]

occur in type 1 diabetes and has become more frequent in type 2 diabetes, especially with the growing use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors.

This article reviews the disease process of diabetic ketoacidosis, what to consider before starting patients on SGLT-2 inhibitors, and the differences in the approach to managing DKA and EDKA.

PATHOPHYSIOLOGY

Ketoacidosis in diabetes

When there is an absolute deficiency of insulin (as in type 1 diabetes) or severely augmented insulin resistance (by elevation of stress hormones and inflammatory cytokines in individuals predisposed to insulin resistance), the normal suppressive effect of insulin on glucagon is no longer operative. The unrestrained rise in glucagon disrupts the insulin-to-glucagon ratio in favor of glucagon, resulting in enhanced gluconeogenesis and release of free fatty acids. Fatty acid oxidation results in the formation of ketone bodies, which are secondary fuels used by organs and tissues such as the heart and muscles. In these tissues, beta hydroxybutyrate is converted back to acetoacetate, which is a substrate for the tricarboxylic acid (or Krebs) cycle that synthesizes and metabolizes acetyl-coenzyme A to yield adenosine triphosphate and carbon dioxide.

The rate-limiting steps in the ongoing metabolism of ketone bodies are nicotinamide adenine dinucleotide and its metabolites and succinyl coenzyme A. When these steps are overwhelmed, ketones accumulate and, because they are strong acids, induce acidosis. At the same time, the lack of insulin does not allow for the removal of glucose from the bloodstream, causing hyperglycemia and leading to osmotic diuresis, which promotes dehydration.

The EDKA variant

EDKA due to SGLT-2 inhibitors has a somewhat different etiologic basis: SGLT-2 inhibitors intrinsically stimulate the release of glucagon.[2] The mechanism is unclear; the sidebar "Glucagon release in EDKA: Plausible pathophysiologic mechanisms" outlines the proposed mechanisms.

The rise in glucagon changes the glucagon-to-insulin ratio and ensures that treatment with SGLT-2 inhibitors fosters a higher level of circulating ketones in the steady non-EDKA state.[3] Any additional reasons for developing ketones, such as keto diets or "nothing by mouth after midnight" (who isn't?) and prolonged fasting, can tip the balance into ketoacidosis. The effect of SGLT-2 inhibitors on glycosuria continues, limiting hyperglycemia while promoting dehydration.

Notably, the half-life of SGLT-2 inhibitors ranges between 13 and 17 hours, so their effect can persist for up to 3 days (4.5 half-lives), prolonging the duration of EDKA and the treatment regimen. In addition, SGLT-2 inhibitor–induced glycosuria is accompanied by natriuresis, which disrupts the electrochemical gradient in the tubular fluid and drives the reabsorption of negatively charged ketone bodies,[4] further contributing to ketoacidosis.

CONSIDER RISK FACTORS

Table 1 shows the risk factors that need to be mitigated before starting a patient on an SGLT-2 inhibitor. In instances of significant defects in insulin secretion, basal insulin administered exogenously at an adequate dose negates the risk of EDKA. Creatinine is a byproduct of muscle metabolism; thus, a low value is highly suggestive of sarcopenia. Muscles use ketones as a fuel, and a person with low muscle mass will not use as much, allowing for a greater accumulation of ketones. It is crucial to establish and treat the cause of preexisting acidosis.

SGLT-2 inhibitors protect renal function, but their use in chronic kidney disease needs extra care because they can predispose individuals to dehydration, thereby precipitating an acute renal injury (in which case the agent must be discontinued at least temporarily). The need to maintain adequate hydration must always be stressed to patients starting an SGLT-2 inhibitor.

TABLE 1
Potential higher risk factors of euglycemic diabetic ketoacidosis and their mechanisms

Risk factor	Mechanism
History of prior diabetic ketoacidosis	Indicates significant insulin deficiency
Hemoglobin A1c > 10%	Suggests insulin deficiency
Bicarbonate < 18–20 mmol/L	Preexisting acidosis
Creatinine < 0.5 mg/dL	Low muscle mass with reduced ability to metabolize ketones
Chronic creatinine > 1.5 mg/dL	Acidosis risk higher
Acute renal injury	Preexisting acidosis

Factors predisposing to EDKA

As outlined previously, SGLT-2 inhibitor therapy is always accompanied by an increase in ketonemia. Thus, any circumstances that would normally cause ketogenesis will further enhance ketonemia and may lead to ketoacidosis. These factors, which need to be reviewed with the patient, are as follows:

- Prolonged fasting (pre- and postoperatively)
- Ketogenic diets
- Anorexia and bulimia
- Alcohol intoxication
- Insulin pump malfunction
- Gastroenteritis and pancreatitis
- Gastroparesis.

In the event of an emergency that necessitates fasting and the patient has not been able to discontinue the SGLT-2 inhibitor, an intravenous drip with dextrose (glucose 4–5 g per hour) to offset starvation and either a basal insulin dose or an intravenous insulin infusion, depending on the clinical status of the patient, must be started to induce a favorable insulin-to-glucagon ratio and to stop ketogenesis. There are no studies on the appropriate dose; however, in our experience, basal insulin 0.15 to 0.25 units/kg, without exceeding 20 to 25 units, is adequate to minimize risk of both EDKA and hypoglycemia.

PATIENT EDUCATION BEFORE STARTING SGLT-2 INHIBITORS

It is important to discuss the benefits and risks of SGLT-2 inhibitors with patients and to also outline some crucial dos and don'ts.

Dos

- Maintain hydration with water and a small amount of electrolyte solution
- Ensure 30% to 35% carbohydrate content in all meals and snacks
- Limit alcohol intake
- Know the identifying symptoms: fruity breath, thirst, polyuria and nocturia, nausea and vomiting, abdominal pain, confusion, and fever.

Don'ts

- If on basal insulin and self-managing, do not decrease the dose more than 20% without discussion with the supervising healthcare team
- No keto diets
- Do not take the SGLT-2 inhibitor starting 3 days before fasting longer than overnight.

Sick-day rules

In acute intercurrent illness with nausea, vomiting, or diarrhea, sip on calorie-dense electrolyte solutions (200 mL every 30 minutes), suck on hard candy, or consume a tablespoon of sugar every 15 to 20 minutes. If there is no improvement and symptoms persist, stop the SGLT-2 inhibitor and go to an emergency department or call the primary care clinician. Once in the emergency department, inform medical staff about the need to start a glucose-containing intravenous infusion.

MANAGEMENT PRINCIPLES

Regardless of cause, management of ketoacidosis requires strict discipline and, at least at the start, a hierarchal approach.

Fluids

The primary goal of fluid administration is to restore tissue perfusion. The standard requirement is 15 to 20 mL/kg in the first hour, which is about 1 to 1.5 L.[1] Two priorities are addressed: dehydration and resolution of the component of hypernatremia caused by

hemoconcentration before any significant electrolyte shifts happen between the intracellular and extracellular compartments. Normal saline remains the fluid of choice in the first hour, especially because the potassium level is initially not known and balanced electrolyte solutions contain potassium (albeit in low concentrations).

Fluid choice after the first bolus also depends on the corrected sodium level:

$$\textit{Corrected sodium} = \textit{measured sodium} + [(\textit{glucose level} - 100) \times 0.016]$$

If the result reveals hyponatremia (serum sodium < 134 mmol/L), changing to a balanced electrolyte solution is helpful; however, in the face of normo- or hypernatremia, delaying the change to isotonic crystalloid solutions and using half normal saline may be more advisable.

The choice of which fluid is optimal after the bolus of normal saline and achieving an appropriate sodium level is open for discussion. The option of continuing normal saline vs changing to a balanced crystalloid solution such as Ringer's lactate solution or a balanced electrolyte solution like Plasma-Lyte has been studied.[5,6] The higher chloride and osmolarity of normal saline are associated with the development of hyperchloremic metabolic acidosis.[5] Balanced crystalloids can be used for volume expansion and are not associated with hyperchloremic acidosis. In a subgroup analysis of 172 adults with DKA from 2 large cluster-randomized clinical trials, the median time to DKA resolution was significantly shorter with balanced crystalloids (13.0 hours) compared with saline (16.9 hours),[5] and balanced crystalloids resulted in less hyperchloremia and a faster recovery of bicarbonate levels.[6]

When the circulating glucose level is less than 250 mg/dL, giving a 5% dextrose solution containing balanced electrolytes is necessary to prevent hypoglycemia and to reduce the risk of cerebral edema caused by rapid correction of the extracellular compartment.[7]

In EDKA, hydration must be started with a dextrose-containing fluid to accomplish 4 crucial goals:

- Provide glucose to stop the ketogenic process
- Reinstitute secretion of endogenous insulin, if present, thereby starting to alter the insulin-to-glucagon ratio in favor of insulin, stopping the ketogenic process
- Rehydrate and replete solutes
- Counterbalance the effects of the infused insulin that was started to enhance recovery from ketoacidosis.

There are no specific studies related to fluid replacement in EDKA. However, in EDKA due to SGLT-2 inhibitors, hypernatremia is less of an issue because SGLT-2 inhibitors cause glycosuria, which also induces natriuresis. Theoretically, the persistence of acidosis caused by the continuing effect of SGLT-2 inhibitors in EDKA may make the use of a balanced electrolyte fluid even more beneficial.

Potassium

The serum potassium value is not an indicator of potassium status in either DKA or EDKA because in each form there is a total potassium deficit due to osmotic diuresis. Volume expansion, correction of acidosis, and insulin therapy all lower potassium levels. Therefore, once serum potassium levels are less than 5.3 mmol/L, potassium replacement is essential.[1] If hypokalemia is present at the time of diagnosis, potassium must be added to the initial fluid administered. Insulin should be started only after the serum potassium level is greater than 3.3 to 3.5 mmol/L to protect against arrhythmias, respiratory muscle weakness, and even death.

In SGLT-2 inhibitor–related EDKA, the SGLT-2 inhibitor generally lowers the risk of severe hyperkalemia in people with type 2 diabetes.[8]

Insulin therapy

Insulin therapy is optimally instituted after the first bolus of intravenous fluid. This delay allows for a more accurate estimation of hyperglycemia by correcting hemoconcentration and a more meaningful evaluation of the serum potassium level.

Intravenous insulin to treat DKA is preferable. Whereas hourly subcutaneous short-acting insulin analogs have been used successfully to treat mild to moderate DKA,[9,10] the consensus remains with intravenous therapy. Studies on the utility of an initial bolus followed by an infusion have shown no beneficial effect of a bolus dose on the rate of glucose decrease, the rate of anion-gap correction, or the hospital length of stay.[11] However, a bolus shows a trend toward more frequent development of hypoglycemia (6% vs 1%).

In EDKA, a simultaneous infusion of insulin and a dextrose-containing fluid is essential; insulin augments the effect of the infused glucose, as described above.

Bicarbonate

A systematic review of bicarbonate therapy in DKA showed adding bicarbonate produced a transient improvement in metabolic acidosis, but had no effect on glycemic improvement and also carried a risk of cerebral edema in children.[12] Even when used in severe acidotic DKA, bicarbonate therapy did not show any difference in time to resolution of acidosis, length of time intravenous insulin was required, potassium supplementation requirements, or hospital length of stay.[13]

TABLE 2
Differences between diabetic ketoacidosis and euglycemic diabetic ketoacidosis

Factor	Diabetic ketoacidosis	Euglycemic diabetic ketoacidosis
Endogenous insulin	Not stimulable	Stimulable
Administered glucose	No benefit at onset	Benefit at onset
Renal glucose threshold (reference 180 mg/dL)	Elevated above normal	Lower than normal
Duration of ketosis under treatment	Up to 15–20 hours	Up to 60 hours from the last dose of sodium-glucose cotransporter 2 inhibitor

There are no studies on bicarbonate administration in severe acidosis (pH < 6.9).[12] If pH is between 6.9 and 7.0 and bicarbonate therapy is being considered, 50 mmol of bicarbonate in 200 mL of sterile water with 10 mmol of potassium chloride can be given over 2 hours to achieve a pH greater than 7.0.[1] Adding potassium chloride simultaneously is dependent on ambient potassium levels because administering bicarbonate may increase risk for hypokalemia.

The discussion regarding bicarbonate therapy in EDKA is even more germane because bicarbonate levels may remain low until the SGLT-2 inhibitor is completely cleared (up to 4.5 half-lives, which is approximately 60–72 hours). Accordingly, it may be tempting to increase the bicarbonate level with exogenous bicarbonate therapy, but there is no proven benefit.[12,14]

Phosphate

Hypophosphatemia during DKA is common and increases with severe acidosis. The increased loss of phosphate is a result of transcellular shift, osmotic diuresis, and reduced phosphate reabsorption in the renal proximal tubule due to acidosis and hyperglycemia. With administration of insulin and fluids, phosphate shifts into the intracellular compartment and a nadir of phosphate is reached at a median 16 hours into therapy.[15] However, there appears to be no adverse effects from hypophosphatemia when left untreated, and no benefits from treatment have been observed.

There is a concern that very low phosphate levels (< 1 mg/dL) may contribute to cardiac and muscle weakness and respiratory depression. In such circumstances, potassium phosphate 20 to 30 mmol/L can be added to the replacement fluid to achieve a phosphate level just greater than 1 mg/dL.[14] Overenthusiastic replacement not only shows no benefit, but also can result in significant hypocalcemia.

In EDKA from SGLT-2 inhibitors, low phosphate is uncommon because these agents usually raise phosphate levels by increasing renal tubular reabsorption of phosphate.[16]

Transitioning from intravenous insulin to subcutaneous insulin

The current recommendations are to start subcutaneous insulin when the serum glucose level is less than 200 to 250 mg/dL, the anion gap is less than 12, and the bicarbonate level is greater than 15 mmol/L.[17] Under those circumstances, basal insulin needs to be administered at the preadmission dose (if known) or at 0.25 units/kg (if unknown) and should overlap with intravenous insulin for about 2 hours. Planning a transition without the use of basal insulin is harmful.

In addition, studies have shown benefits of early institution of basal insulin while using intravenous insulin to treat DKA, including less rebound hyperglycemia when intravenous insulin is discontinued, quicker resolution of DKA, reduced intravenous insulin requirements, and reduced hospital length of stay, with no increase in hypoglycemia or hypokalemia.[17]

In SGLT-2 inhibitor–related EDKA , the transition cutoffs need to be tempered because ketosis—and, therefore, a low bicarbonate level—may rebound after intravenous therapy is discontinued due to the persistent effect of the medication. Thus, it is important to ensure that the anion gap has normalized and the bicarbonate level is in the low-normal range before transitioning.

DO SGLT-2 INHIBITORS HAVE TO BE DISCONTINUED AFTER AN EPISODE OF EDKA?

A blanket *no* may be a medically and legally appropriate answer, but it should be noted that insulin is not discontinued even after serial episodes of DKA. The answer should be based on an in-depth review of the risk-benefit ratio and a discussion with the patient, as described above, because therapy must be individualized.

Before restarting the SGLT-2 inhibitor, a detailed review to discern the exact cause of the EDKA episode is essential. If the SGLT-2 inhibitor is restarted, the patient must be informed about the contributing factors that caused the DKA (fasting, surgery, and so on), so that, if faced with a similar situation in the future, the medication can be discontinued or early precautions started, as outlined above.

In relatively lean individuals with high hemoglobin A1c levels, there is a higher chance of insulin insufficiency. Thus, when restarting an SGLT-2 inhibitor, initiating basal insulin or, in rare circumstances, an insulin secretagogue like a sulfonylurea may be prudent.

Using an incretin, whether glucagon-like peptide-1 or dipeptidyl peptidase 4 inhibitor, in addition to an SGLT-2 inhibitor is not appropriate because these agents do not independently stimulate insulin release. Instead, they are dependent on ambient glucose to facilitate insulin release, so fasting and a falling glucose level will still deactivate insulin secretion while on these agents. There are reports of patients presenting with EDKA on combinations of incretins and SGLT-2 inhibitors. Development of EDKA is also possible while on glucagon-like peptide-1 receptor agonists[18,19] and dipeptidyl peptidase 4 inhibitors.[20] There are also reports of EDKA in patients without diabetes on SGLT-2 inhibitors for heart failure[21] due to the underlying insulin resistance common to heart failure.

CONCLUSION

Although ketoacidosis has a common pathophysiologic pathway to development, varied etiopathologies initiate the process, chief among them being diabetes. With the extensive use of SGLT-2 inhibitors, it has become clear that the pathophysiology of DKA is different from that of EDKA (**Table 2**). Therefore, most importantly, the management strategies for DKA and EDKA are different, as are the surveillance requirements for terminating acute interventions. Given these differences, significant modifications in the clinical approach are needed.

Acknowledgments: *The authors thank Dr. Charles Faiman for his invaluable help with formatting and editing this manuscript.*

DISCLOSURES

Dr. Mehta has disclosed teaching and speaking for Novo Nordisk, Inc. Dr. Zimmerman has disclosed ownership interest (stock, stock options in a publicly owned company) in Baxter, research funding from Bayer, and teaching and speaking for Xeris.

REFERENCES

1. **Gosmanov AR, Gosmanova EO, Kitabchi AE.** Hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. In: Feingold KR, Anawalt B, Blackman MR, et al, eds. Endotext. South Dartmouth, MA: MDText.com, Inc.; 2021.
2. **Kuhre RE, Deacon CF, Wewer Albrechtsen NJ, Holst JJ.** Do sodium-glucose co-transporter-2 inhibitors increase plasma glucagon by direct actions on the alpha cell? And does the increase matter for the associated increase in endogenous glucose production? Diabetes Obes Metab 2021; 23(9):2009–2019. doi:10.1111/dom.14422
3. **Ferrannini E, Baldi S, Frascerra S, et al.** Shift to fatty substrate utilization in response to sodium-glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. Diabetes 2016; 65(5):1190–1195. doi:10.2337/db15-1356
4. **Taylor SI, Blau JE, Rother KI.** SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab 2015; 100(8):2849–2852. doi:10.1210/jc.2015-1884
5. **Self WH, Evans CS, Jenkins CA, et al.** Clinical effects of balanced crystalloids vs saline in adults with diabetic ketoacidosis: a subgroup analysis of cluster randomized clinical trials. JAMA Netw Open 2020; 3(11):e2024596. doi:10.1001/jamanetworkopen.2020.24596
6. **Othman MI, Nashwan AJ, Alfayoumi M, Khatib M, Abujaber AA.** Plasma-Lyte-148 versus normal saline 0.9% in diabetic ketoacidosis management: a review. Cureus 2023; 15(6):e41079. doi:10.7759/cureus.41079
7. **Varela D, Held N, Linas S.** Overview of cerebral edema during correction of hyperglycemic crises. Am J Case Rep 2018; 19:562–566. doi:10.12659/AJCR.908465
8. **Neuen BL, Oshima M, Agarwal R, et al.** Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized, controlled trials. Circulation 2022; 145(19):1460–1470. doi:10.1161/CIRCULATIONAHA.121.057736
9. **Umpierrez GE, Latif K, Stoever J, et al.** Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. Am J Med 2004; 117(5):291–296. doi:10.1016/j.amjmed.2004.05.010
10. **Ersöz HO, Ukinc K, Köse M, et al.** Subcutaneous lispro and intravenous regular insulin treatments are equally effective and safe for the treatment of mild and moderate diabetic ketoacidosis in adult patients. Int J Clin Pract 2006; 60(4):429–433. doi:10.1111/j.1368-5031.2006.00786.x
11. **Goyal N, Miller JB, Sankey SS, Mossallam U.** Utility of initial bolus insulin in the treatment of diabetic ketoacidosis. J Emerg Med 2010; 38(4):422–427. doi:10.1016/j.jemermed.2007.11.033
12. **Chua HR, Schneider A, Bellomo R.** Bicarbonate in diabetic ketoacidosis—a systematic review. Ann Intensive Care 2011; 1(1):23. doi:10.1186/2110-5820-1-23
13. **Duhon B, Attridge RL, Franco-Martinez AC, Maxwell PR, Hughes DW.** Intravenous sodium bicarbonate therapy in severely acidotic diabetic ketoacidosis. Ann Pharmacother 2013; 47(7–8):970–975. doi:10.1345/aph.1S014
14. **Umpierrez GE, Davis GM, ElSayed NA, et al.** Hyperglycemic crises in adults with diabetes: a consensus report. Diabetes Care 2024; 47(8):1257–1275. doi:10.2337/dci24-0032
15. **van der Vaart A, Waanders F, van Beek AP, Vriesendorp TM, Wolffenbutel BHR, van Dijk PR.** Incidence and determinants of hypophosphatemia in diabetic ketoacidosis: an observational study. BMJ Open Diabetes Res Care 2021; 9(1):e002018. doi:10.1136/bmjdrc-2020-002018
16. **Blau JE, Taylor SI.** Adverse effects of SGLT2 inhibitors on bone health. Nat Rev Nephrol 2018; 14(8):473–474. doi:10.1038/s41581-018-0028-0
17. **Gilbert BW, Murray DS, Cox TR, He J, Wenski AM, Qualls KE.** What are we waiting for? A review of early basal insulin therapy in diabetic ketoacidosis management. Am J Emerg Med 2023; 72: 147–150. doi:10.1016/j.ajem.2023.07.049

18. **Yang Z, Yu M, Mei M, et al.** The association between GLP-1 receptor agonist and diabetic ketoacidosis in the FDA adverse event reporting system. Nutr Metab Cardiovasc Dis 2022; 32(2):504–510. doi:10.1016/j.numecd.2021.10.003
19. **Alduraibi RK, Alrebdi YM, Altowayan YF.** Euglycemic diabetic ketoacidosis after the initiation of dulaglutide in patient with type 2 diabetes. Medicine (Baltimore) 2023; 102(23):e34027. doi:10.1097/MD.0000000000034027
20. **Jeong SH, Vorachitti M, Fuentes F.** A case of euglycemic diabetic ketoacidosis (DKA), influenza, and a dipeptidyl peptidase-4 (DPP-4) inhibitor. Cureus 2023; 15(5):e39012. doi:10.7759/cureus.39012
21. **Umapathysivam MM, Gunton J, Stranks SN, Jesudason D.** Euglycemic ketoacidosis in two patients without diabetes after introduction of sodium-glucose cotransporter 2 inhibitor for heart failure with reduced ejection fraction. Diabetes Care 2024; 47(1):140–143. doi:10.2337/dc23-1163

Address: *Adi E. Mehta, MD, Department of Endocrinology, Diabetes, and Metabolism, F20, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; mehtaae@ccf.org*

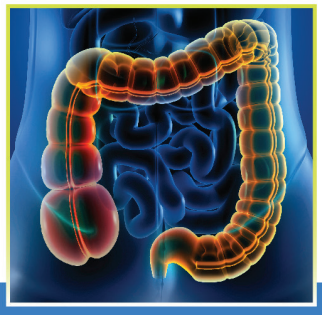
Cleveland Clinic
Florida

Save the Date

International Society for Fluorescence Guided Surgery
ISFGS

South Florida Chapter
ACS Chapters

International Colorectal Disease Symposium



An International Exchange of Medical and Surgical Concepts

February 13-15, 2025

Marriott Harbor Beach Resort & Spa, Fort Lauderdale, Florida

This activity is approved for *AMA PRA Category 1 Credits™*, ANCC Contact Hours, and AAPA Category 1 Credits.

www.ccfcme.org/ICDS2025

Cleveland Clinic

CME & MOC Credits Available

Cleveland Clinic Gut Insights: Exploring the Latest in Gastroenterology

March 17-18, 2025

Margaritaville Hollywood Beach Resort
Hollywood, Florida

www.ccfcme.org/GUT2025

Cleveland Clinic

Addressing the Impact of **RSV and Vaccine Hesitancy**

An Educational Resource for Providers

- Master the Latest in Adult & Pediatric RSV Prevention: Vaccines & Monoclonal Antibodies
- Discover RSV Prevention Solutions for Pregnant Women & Immunocompromised Patients
- Optimize RSV Immunization & Vaccination: From Storage to Administration
- Build Trust & Confidence: Addressing Vaccine Concerns in RSV Prevention

Free CME! Participate Today!
www.ccfcme.org/RSV

This activity has been approved for *AMA PRA Category 1 Credits*™, ANCC Contact Hours, AAPA Category 1 CME Credits, Continuing Pharmacy Education (CPE) Credits

Cleveland Clinic
Center for Continuing Education

JOIN THE CME COMMUNITY

Want to make sure you are updated on medical education that is available to you?

Need to earn continuing education credits?

Join our CME Community!

By becoming a part of the Cleveland Clinic Center for Continuing Education CME Community, you will always be on the cutting edge of educational opportunities available.

SIGN UP TODAY! **CCFCME.ORG/CMECOMMUNITY**

CME MOC

Roberto León-Barriera, MD
Assistant Professor, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA

Margaret M. Chaplin, MD
Consulting Psychiatrist, Farrell Treatment Center, New Britain, CT; Community Faculty, University of Connecticut, Farmington, CT

Jasleen Kaur, MD
Principal Psychiatrist, Department of Mental Health and Addiction Services, Connecticut Valley Hospital, Middletown, CT

Vania Modesto-Lowe, MD, MPH
Medical Director, Hartford Behavioral Health, Hartford, CT; Community Faculty, University of Connecticut, Farmington, CT

Insomnia in older adults: A review of treatment options

ABSTRACT

Insomnia is a common and challenging complaint in older adults (> 65 years) because of age-related alterations in sleep physiology. Cognitive behavioral therapy for insomnia is the gold standard for treatment of insomnia in young as well as older patients. Both clinicians and patients often prefer the simplicity of medication, but risks associated with some hypnotics increase with age. Pharmacologic options for older adults include low-dose doxepin, melatonin, ramelteon, and the dual orexin receptor antagonists. A well-informed clinician can help patients navigate the risks and benefits of both pharmacologic and behavioral options.

KEY POINTS

The need for sleep does not decrease with age, but changes in sleep physiology and architecture may make it more difficult to get adequate sleep.

Cognitive behavioral therapy for insomnia is the gold standard for treating insomnia in all populations, but it is time-intensive and does not offer immediate results.

Many medications used to treat insomnia do not have regulatory approval and have little evidence to support their use.

Doxepin, melatonin enhancers, and dual orexin receptor antagonists may be relatively safe alternatives to benzodiazepines and Z-drugs (zaleplon, eszopiclone, zolpidem, and others) and have evidence to support their use in older adults.

doi:10.3949/ccjm.92a.24073

Sleep, a physiologic process, is vital to overall health.[1] The National Sleep Foundation advises that adults 65 and older get 7 to 8 hours of sleep daily—a recommendation based on data that suggest older adults who sleep from 6 to 9 hours daily have better health, quality of life, and cognition compared with older adults who have other sleep durations.[2]

This article reviews the physiology of sleep and considers the benefits and hazards of pharmacologic and nonpharmacologic treatment options in older patients.

INSOMNIA DEFINED

Insomnia is a disturbance in sleep continuity associated with sleepiness, fatigue, headaches, and other somatic symptoms, as well as concerns about compromised cognitive or occupational functioning and mood disturbance. Insomnia occurs in up to one-third of the adult population worldwide[3] and is associated with increased risk of cardiovascular disease, depression, and neurocognitive impairment.[4,5] As many as 50% of older adults may have difficulty initiating or maintaining sleep, and 12% to 20% meet criteria for insomnia disorder.[6] A clinical diagnosis of insomnia is justified if difficulty sleeping occurs at least 3 times a week for at least 3 months and causes daytime impairments such as fatigue, irritability, and cognitive dysfunction.[5,7]

NORMAL ADULT CIRCADIAN RHYTHM AND SLEEP PHYSIOLOGY

Circadian rhythms oscillate over about 24 hours and impact physiologic processes, including the sleep-wake cycle. Circadian rhythm is

modulated by the light-dark cycle and the 24-hour clock time of the environment via external stimuli, termed *zeitgebers* (German for "time-givers"). Examples of zeitgebers include light exposure, social endeavors, and exercise. The suprachiasmatic nucleus in the anterior hypothalamus is a key regulator of circadian rhythm homeostasis.[8] Light striking the retinal ganglion cells is relayed to the suprachiasmatic nucleus, which then inhibits secretion of melatonin from the pineal gland.[8,9] As light fades at the end of the day, a progressive increase in melatonin levels leads to the onset of evening sleepiness.[9]

Neural circuits also regulate wakefulness and sleep. These wake- and sleep-promoting neurons compete for network dominance, creating a "switch" between wakefulness and sleep.

Wake-promoting neurons include noradrenergic neurons in the locus coeruleus, serotonergic neurons in the raphe nuclei, histaminergic neurons in the tuberomammillary nucleus, and hypocretin (also known as orexin) -producing neurons of the perifornical nuclei in the lateral hypothalamic area.[10] The hypocretin system also initiates arousal and, more important, inhibits rapid eye movement (REM) sleep.[11]

Sleep-promoting neurons work to keep us asleep. These include the melanin-concentrating hormone-producing neurons in the diencephalon and the gamma aminobutyric acid–producing neurons in the ventrolateral preoptic nuclei (also known as the intermediate nuclei of the preoptic area), median preoptic nuclei, and brainstem parafacial zone.[10]

Initiation of sleep is mediated in part by adenosine neurotransmission. Extracellular adenosine increases throughout the day, with rising levels activating the sleep-promoting neurons and serving as a "switch" to signal sleep.[12]

REM and non-REM sleep

Sleep is a rhythmic and cyclic process that alternates between 3 stages of non-REM (NREM) and REM sleep.[12] This alternation and cycling is known as sleep architecture; a good night's sleep includes 4 to 5 cycles. Each cycle lasts about 90 minutes and ends with an episode of REM sleep. NREM sleep is divided into stages NREM1, NREM2, and NREM3[6,12]:

- **Stage NREM1** is light sleep when arousal is very easy
- **Stage NREM2** is characterized by slower brain waves, deeper sleep, lower body temperature, and lower heart rate (sleep spindles and K-complexes appear in electroencephalogram tracings during stage NREM2)[6]
- **Stage NREM3** is deep sleep, also known as slow-wave or delta sleep,[6,12] during which tissue repair and immune strengthening are thought to occur[6]
- **REM sleep**, which follows stage NREM3, predominates during the second half of the night and is characterized by dreaming and muscle atonia; it is thought that much of memory consolidation occurs during REM sleep.[6,12]

Normal age-related changes

In healthy people, melatonin is secreted only in the evening, with higher serum levels in young people than in older adults.[9] Aging is associated with circadian rhythm changes, with the main change being phase advance, in which older adults have an earlier onset of sleepiness in the evening and earlier morning awakening. Psychosocial factors also may impact sleep, with effects on sleep hygiene and zeitgebers. Older adults, who may no longer have regular schedules and may be socially isolated, may be more prone to irregular bedtimes, increased napping, and poor sleep habits. Similarly, the lack of schedule and isolation may limit exposure to natural zeitgebers, such as light and social activities.[2]

Total sleep time declines in older adults, as does the amount of time spent in slow-wave NREM3 and REM sleep—phases that are associated with cognitive recovery and enhanced memory and learning.[2] Older adults wake up more often after sleep onset, resulting in increased time awake, but usually do not have greater difficulty falling back asleep. It also takes older adults more time than younger people to fall asleep initially, referred to as sleep latency. Finally, there is decreased sleep efficiency, or the percentage of time spent asleep while in bed.

Most of these changes plateau at age 60. Sleep efficiency, however, continues to decline after age 90. This is clinically significant because declining sleep efficiency is associated with greater morbidity.[2] The need for sleep does not decrease with age, but the changes in sleep physiology and architecture—especially the decline in sleep efficiency—may make it more difficult to get adequate sleep.[2]

SCREENING AND EVALUATION OF INSOMNIA

Patients who are symptomatic should maintain a sleep diary for 1 to 2 weeks[8] with a daily record of the time they go to bed, approximate time they fall asleep, wake-up time, time they get out of bed, and any naps. Patients also should record any use of caffeine, alcohol, prescription medications, or illicit drugs, and report on whether they use electronic devices or engage in

stimulating activities before bed.[6] A medication review is important, as many antidepressants, antihypertensives, sedatives, antihistamines, and steroids can interfere with sleep.[6] Patients should be asked about daytime fatigue and level of alertness.[3]

Before starting treatment of presumed insomnia, a thorough review of systems is indicated to rule out other conditions that may contribute to insomnia, such as sleep apnea, untreated psychiatric illness, endocrine disorders, neurologic disorders, chronic obstructive pulmonary disease, asthma, heart failure, and gastroesophageal reflux disease.[6] Any positive findings should be addressed or a referral for further evaluation should be made. If no underlying factors are uncovered or if insomnia persists after treatment of causative conditions, then treatment of presumed primary insomnia can be initiated.[6]

PHARMACOLOGIC TREATMENT

Ideally, medication should be reserved for patients for whom cognitive behavioral therapy for insomnia (CBTI) fails.[13] Despite the established efficacy and safety of CBTI, both clinicians and patients may prefer the "quick fix" of medication.[14] Many commonly used medications have significant risks and little established efficacy.[15] Hypnotics must be used sparingly in older adults, and when used, prescribing them for a short duration and at the lowest effective dose is recommended.[16]

Benzodiazepines, Z-drugs, and antihistamines

Benzodiazepines have been used for several decades to treat insomnia.[6,16] They are effective for short-term treatment of insomnia,[6] but the American Geriatrics Society warns that older adults have increased sensitivity to adverse effects of benzodiazepines.[13,15] Benzodiazepines, Z-drugs (zaleplon, eszopiclone, zolpidem, and others), and antihistamines such as diphenhydramine and chlorpheniramine are all included in the Beers Criteria list of medications that should be avoided or pose a higher risk in older adults.[17] Benzodiazepines and Z-drugs are on the list because they increase the risk of cognitive problems, delirium, falls, accidents, and fractures. Longer-acting agents such as diazepam and chlordiazepoxide are concerning because of their slow metabolism and the consequent risk of accumulating toxic levels. Sedating antihistamine medications such as diphenhydramine have significant anticholinergic effects and are also contraindicated in older adults because of risk of falls and confusion.[15]

Nonetheless, many patients have been taking these medications for years and are reluctant to discontinue them.[16] Given that patients also may resist CBTI because of the effort required,[14] it is worthwhile to consider safer medication alternatives. These include sedating psychotropics (both antidepressants and antipsychotics), melatonin enhancers, and the dual orexin receptor agonists.

Antidepressants and antipsychotics

Clinicians have long taken advantage of the sedating effect of many psychotropics to treat insomnia. Unlike benzodiazepines and Z-drugs, psychotropics have few or no reinforcing properties or discontinuation effects. However, much use of psychotropics for insomnia has been off-label and has limited supportive evidence. Many psychotropic drugs have anticholinergic effects at higher doses, which raises cognitive concerns in older adults.[18] A few are worth considering, however.

Doxepin is a tricyclic antidepressant that has high affinity for histaminergic (H1) receptors at low doses (< 10 mg), effectively acting as a selective H1 receptor antagonist.[18] It is the only antidepressant with US Food and Drug Administration approval for insomnia. It is indicated (3- or 6-mg doses) for patients who have difficulty staying asleep or experience early-morning awakenings.[6]

A 12-week randomized, double-blind, placebo-controlled trial examined the effects of doxepin, 1 mg and 3 mg, in older persons with chronic insomnia.[19] Participants were randomized to receive nightly treatment with doxepin, 1 mg or 3 mg, or placebo. The study found that doxepin at 1 mg and 3 mg resulted in significant and persistent improvements in most sleep variables. In addition, patients who took doxepin did not report any memory problems or complex sleep behaviors, and there was no significant difference in next-day residual sedation between either dose of doxepin and placebo. Anticholinergic effects were not present at the studied doses.

Subsequently, a systematic review of 9 randomized placebo-controlled trials investigated the hypnotic effects of doxepin.[18] Three studies of low-dose (< 10 mg daily) doxepin in older populations (≥ 65 years) showed that it had a modest advantage over placebo for sleep maintenance and duration but not for sleep initiation. Headache and somnolence were common side effects. Higher doses should be avoided in older adults because of anticholinergic effects that may cause cognitive difficulties. The low-dose doxepin studies were industry sponsored, and the patented medication remains expensive.

Amitriptyline, another tricyclic antidepressant, that has been used off-label at low doses (10 to 25 mg) to treat insomnia. It is often used in patients with pain syndromes, where it may indirectly improve sleep by

relieving pain. At these doses, it is mainly acting on histamine H1 receptors, although it likely has some serotonergic and cholinergic antagonism.[20] At higher doses, anticholinergic effects are common and may include urinary retention, constipation, dry mouth, blurred vision, orthostatic hypotension, and confusion.[15] There is little evidence of efficacy to support treatment with amitriptyline despite its common use.[20]

Trazodone is a serotonergic antidepressant that acts as an antagonist at serotonergic (5-HT2) and alpha-1 adrenergic receptors. Despite little evidence of efficacy,[13] it is widely prescribed off label in the United States for sleep disorders.[20] Studies have shown some efficacy for sleep latency and sleep efficiency that dissipate after a week.[20] Common side effects include dizziness, cardiac arrhythmias, orthostatic hypotension, and, potentially, priapism.[6]

Mirtazapine, an antidepressant with strong 5-HT2 antagonism, few drug interactions, and appetite-stimulating properties, is often used to treat insomnia, particularly in patients with depression.[6,21] Studies in adults (mean age 41 years) have shown improvement in sleep latency, sleep efficiency, and decreased awakenings after 2 weeks of treatment.[6] Overall limited evidence of efficacy remains, however, and patients may become habituated to its sedative effects. It may be preferable to histaminergic drugs but is not recommended for treatment of insomnia in patients who do not have depression.[6]

Atypical antipsychotics, particularly quetiapine and olanzapine, have been widely used to treat insomnia despite little controlled trial evidence. Antipsychotics may cause metabolic side effects, extrapyramidal symptoms, and tardive dyskinesia.[20] In older adults, they carry an increased risk of stroke and sudden cardiac death.[15] Given these potential effects, antipsychotics should not be used to treat insomnia in the absence of a primary indication such as psychosis.[20]

Melatonin and melatonin agonists

Melatonin and ramelteon enhance the melatonin system.[3] Intrinsic production of melatonin decreases with age—hence the rationale for using melatonin-enhancing medications to treat insomnia.[6] In the United States, melatonin is available over the counter and unregulated.[9] In Europe, a 2-mg prolonged-release formulation of melatonin is approved for insomnia in older adults.[6]

Ramelteon (8 mg), a melatonin receptor agonist of MT1 and MT2 (G protein–coupled receptors that mediate the effects of melatonin), is approved for treatment of insomnia with sleep-onset difficulty. A European meta-analysis found that both melatonin prolonged release and ramelteon are more efficacious than placebo for insomnia symptoms in adults.[22] Their overall clinical impact is modest, but a subgroup analysis suggested that these medications have large effect sizes in older adults.

Additional efforts to examine the effect of these agents in older populations found that patients receiving melatonin prolonged release or ramelteon fell asleep about 14 minutes earlier than those receiving placebo.[23] Patients who received melatonin or ramelteon also had an increase in total sleep time (21 minutes) relative to placebo. The authors concluded that melatonin or ramelteon given to older persons with insomnia improved objective total sleep time, sleep latency, and subjective sleep quality. Frequent side effects included somnolence, dizziness, fatigue, and headache. There was no significant rebound insomnia after discontinuation.

Melatonin or ramelteon (8 mg) may be an alternative treatment option for older adults, given their good tolerability and at least some demonstrated efficacy.

Dual orexin receptor antagonists

Dual orexin receptor antagonists, a newer class of medications for insomnia, target the orexin system. Orexin is thought to be part of the neuronal system that promotes wakefulness, and thus blocking orexin 1 and 2 is believed to inhibit the wake drive.[3] Three dual orexin receptor antagonists are approved by the US Food and Drug Administration: suvorexant, lemborexant, and daridorexant.

Suvorexant 30 mg for patients 65 and older (40 mg for those < 65) was compared with placebo in a randomized, placebo-controlled trial, which showed significant improvement in subjective total sleep time and subjective time to sleep onset during the first month in the suvorexant group over placebo.[24] These improvements persisted during the 1-year phase of the trial completed by approximately 62% of participants who received suvorexant.

The most common adverse events were daytime somnolence, fatigue, and dry mouth. Serious adverse effects, occurring in 5% of the sample, included sleep paralysis, hypnagogic hallucinations, cataplexy, and suicidal ideation. Overall, suvorexant was safe and effective for most patients during the 1-year trial.

Lemborexant was compared with placebo or zolpidem in older adults.[25] In a 1-month randomized, double-blind, placebo-controlled trial, lemborexant 5 mg and 10 mg significantly improved sleep latency and efficiency relative to placebo in adults 55 and older. Lemborexant 5 mg did not differ from placebo on cognitive performance and caused less postural instability than zolpidem in both doses. Lemborexant also effec-

tively reduced wakefulness after sleep onset and had significantly less risk of postural instability compared with zolpidem. It was not associated with residual morning sleepiness or reduced functioning, but given its long half-life, this remains a theoretical concern.

Daridorexant is approved in 25- and 50-mg doses. It has been shown to produce significant improvement in sleep parameters compared with placebo at 1 and 3 months, with improved daytime functioning.[26] It has also shown good tolerability in older adults. Daridorexant has the shortest half-life of the available dual orexin receptor antagonists (8 hours compared with 12 hours for suvorexant and 17 to 19 hours for lemborexant), which in theory may reduce risk for impaired next-day functioning.

Numbers needed to treat (NNT) and numbers needed to harm (NNH) for dual orexin receptor antagonists have been calculated as follows:

Suvorexant: NNT = 8, NNH = 13[27]

Lemborexant: NNT = 3, NNH ≥ 10[28]

Daridorexant 50 mg: NNT < 10, NNH = 78.[29]

These studies suggest good efficacy with low risk of harm.[27–29] Dual orexin receptor antagonists may be a safer and more effective long-term option than other pharmacologic products,[26] but as these medications remain patented, cost and insurance coverage may be limitations.[30]

Figure 1 summarizes the effects of medications on sleep and sleep architecture.[31]

CANNABINOID COMPOUNDS

Evolving research suggests that cannabidiol may have therapeutic potential for insomnia treatment. Cannabidiol is one of the psychoactive components of cannabis (marijuana). The other, tetrahydrocannabinol, or THC, is thought to account for most of the euphoric effect of marijuana. Despite mixed results of research on cannabis and insomnia, it is generally accepted that tetrahydrocannabinol may lead to tolerance and disruption of the sleep cycle, while cannabidiol seems to have a positive effect on total sleep time and awakening after sleep onset.[32]

Cannabidiol appears to be well tolerated by older patients, with infrequent (< 15%) reports of mild adverse effects such as dizziness, tinnitus, and dry mouth.[33] A recent small placebo-controlled study using 150 mg of cannabidiol showed improvement in sleep efficiency and subjective well-being, but not in other sleep parameters.[34] Further research is needed to determine whether cannabidiol has a true benefit for insomnia treatment.

NONPHARMACOLOGIC TREATMENT

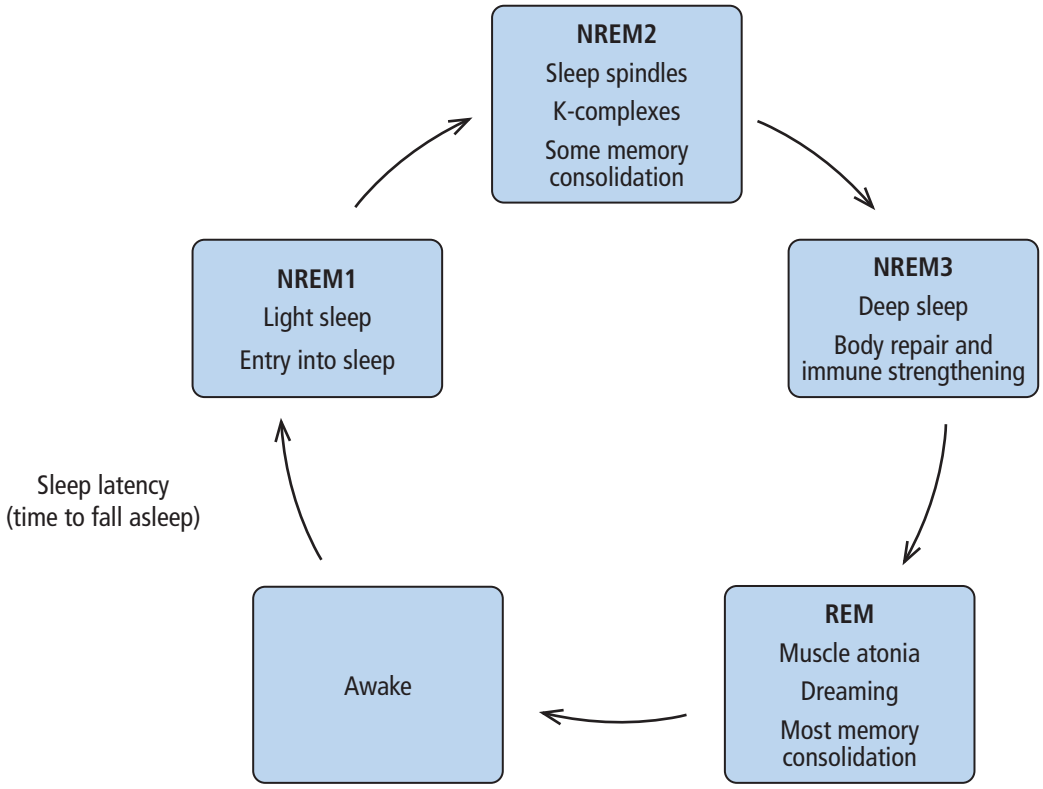
CBTI is recognized as the gold standard and first-line treatment for insomnia in young as well as aging patients.[14,35] It has established efficacy, safety, and durability compared with pharmacologic treatments.[14] Studies have shown a mean effect size with CBTI of 0.96 compared with 0.87 for pharmacotherapy.[36] These results suggest a similar efficacy between treatments in the short term, but CBTI seems to have longer-lasting effects. The 2 therapies combined can improve some parameters, such as subjective sleep efficiency, but pharmacotherapy overall is not superior to CBTI alone.[37] In the clinical setting, this suggests a ceiling effect past which adding more interventions to CBTI, such as pharmacotherapy, may not yield further benefit.

CBTI addresses maladaptive behaviors and cognitions that perpetuate insomnia. It incorporates psychoeducation, sleep hygiene, stimulus control, sleep restriction, relaxation training, and cognitive therapy techniques, such as cognitive restructuring. A course of CBTI generally takes 6 to 10 sessions delivered weekly or biweekly.[13] Sleep diaries are used to establish a baseline, make behavioral interventions, and monitor treatment response.[6]

Sleep hygiene can promote healthy sleep. Interventions include no alcohol or caffeine before bed, no clock watching while in bed, no daytime naps, going to bed and getting up at the same time each day, and ensuring a room environment that promotes sleep.[3,38]

Stimulus control interventions strengthen the association between the bed and sleep. Typical instructions include going to bed only when sleepy, getting out of bed if not asleep in 15 to 20 minutes, and using the bed only for sleep and sex.[3,38] This strategy is based on a model of insomnia suggesting that the development and maintenance of insomnia is a learned behavior. With more time spent in bed not sleeping, anxiety increases and promotes tension and frustration. Over time, the relationship between the bed and anxiety strengthens, leading to conditioned insomnia, and the bedroom becomes associated with wakefulness and frustration. The goal of stimulus control is to disrupt this coupling.[3]

Sleep restriction is a means of increasing sleep efficiency. Initially, patients limit time in bed to the approximate hours they have been sleeping and then gradually increase the time in bed as sleep efficiency improves.[3,38] For example, if a patient's average total sleep time is 5 hours and the average time in bed is 7 hours, the prescribed time in bed will be 7 hours. This "sleep window" must be followed each day irrespective of sleep quality. Sleep restriction may initially decrease



Medication	Effects on sleep architecture
Benzodiazepines and Z-drugs	↓ Sleep latency ↑ NREM2 sleep
Antihistamines (diphenhydramine)	↓ Sleep latency
Tricyclic antidepressants (amitriptyline)	↓ Sleep latency ↑ REM sleep latency ↓ REM sleep
Trazodone	↓ Sleep latency ↑ NREM3 sleep ↓ REM sleep
Mirtazapine	↓ Sleep latency ↑ REM sleep latency ↓ REM sleep ↑ NREM3 sleep
Melatonin and melatonin agonists	↓ Sleep latency ↑ NREM sleep duration
Dual orexin receptor agonists	↑REM sleep

Figure 1. Sleep stage functions and medication effects on sleep architecture.

NREM = nonrapid eye movement; REM = rapid eye movement; Z drugs = zaleplon, eszopiclone, zolpidem, and others

Based on information from reference 31.

total sleep time and increase daytime fatigue, but after several days it will lead to reduced sleep latency (time to fall asleep) and fewer nocturnal awakenings. As sleep efficiency increases, the sleep window increases—typically by 15 minutes each week—until the patient is getting an adequate amount of sleep each night.[3]

Sleep restriction has been studied as a single-component intervention in primary care settings. In a UK study, 642 patients were randomized to nurse-delivered sleep restriction therapy (combination of in-person and phone sessions) plus a sleep hygiene booklet or to a sleep hygiene booklet alone.[39] At 6 months, the sleep restriction therapy group had medium to large sustained treatment effects for reduced insomnia severity compared with the sleep hygiene-only group. All participants were college-educated adults and there were no restrictions on usual care for either group, so results may not generalize to older populations. Relative contraindications to sleep restriction include pregnancy, bipolar disorder, seizure disorders, additional sleep disorders, shift work, and cognitive impairment.[39]

CBTI may challenge physicians and patients

People with insomnia often have thinking errors (such as, "I am never going to sleep again") and nighttime worries that lead to autonomic hyperarousal and muscle or cognitive tension, all of which impair sleep.[6,40] They may have pessimistic and unhelpful thoughts and beliefs about sleep, and also tend to have erratic sleep schedules and "take their worries to bed." CBTI challenges dysfunctional beliefs about sleep, such as worrying about falling asleep or not getting enough sleep, and addresses maladaptive behaviors related to poor sleep.[3,38] CBTI targets the person's cognitive style as well as behavioral and hyperarousal factors associated with insomnia.[3] Cognitive restructuring seeks to modify maladaptive beliefs about sleep (such as catastrophizing effects of a poor night's sleep) and replace them with more helpful thinking.[40]

It is also helpful to teach patients relaxation strategies such as progressive muscle relaxation to decrease hyperarousal.[6]

Implementation of CBTI has challenges, as patients may resist participating or insist on medication. Another challenge may be lack of physician knowledge about CBTI. Research has shown that educating primary care physicians about CBTI results in clinically significant and sustained improvement in insomnia.[14] Multiple effective apps and websites for patient-guided CBTI are available.[16]

BETTER STUDIES, BETTER OPTIONS

Natural sleep is regulated by a complex and delicate balance of multiple systems that is easily disturbed, especially in older adults. CBTI is a well-studied, safe, and efficacious treatment for insomnia in this age group. The drawbacks are that it is time-consuming to implement and not immediately effective. As sleep physiology is better understood, newly developed medications are providing safer alternatives, but they may be prohibitively expensive. Armed with a basic knowledge of sleep pathology, clinicians can consider the risks and benefits of both pharmacologic and behavioral options to safely restore sleep in the older adult population.

DISCLOSURES

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

REFERENCES

1. **Edwards BA, O'Driscoll DM, Ali A, Jordan AS, Trinder J, Malhotra A.** Aging and sleep: physiology and pathophysiology. Semin Respir Crit Care Med 2010; 31(5):618–633. doi:10.1055/s-0030-1265902
2. **Miner B, Kryger MH.** Sleep in the aging population. Sleep Med Clin 2017; 12(1):31–38. doi:10.1016/j.jsmc.2016.10.008
3. **Perlis ML, Posner D, Riemann D, Bastien CH, Teel J, Thase M.** Insomnia. Lancet 2022; 400(10357):1047–1060. doi:10.1016/S0140-6736(22)00879-0
4. **Waterman L, Selsick H.** Insomnia and its treatment should be given more importance. Br J Gen Pract 2023; 73(733):344–345. doi:10.3399/bjgp23X734421
5. **Sexton CE, Sykara K, Karageorgiou E, et al.** Connections between insomnia and cognitive aging. Neurosci Bull 2020; 36(1):77–84. doi:10.1007/s12264-019-00401-9
6. **Patel D, Steinberg J, Patel P.** Insomnia in the elderly: a review. J Clin Sleep Med 2018; 14(6):1017–1024. doi:10.5664/jcsm.7172
7. **Aakre JA, Schulz J, Ballard C, et al.** Self-reported sleep fragmentation and sleep duration and their association with cognitive function in PROTECT, a large digital community-based cohort of people over 50. Int J Geriatr Psychiatry 2023; 38(11):e6022. doi:10.1002/gps.6022
8. **Steele TA, St Louis EK, Videnovic A, Auger RR.** Circadian rhythm sleep-wake disorders: a contemporary review of neurobiology, treatment, and dysregulation in neurodegenerative disease. Neurotherapeutics 2021; 18(1):53–74. doi:10.1007/s13311-021-01031-8
9. **Vasey C, McBride J, Penta K.** Circadian rhythm dysregulation and restoration: the role of melatonin. Nutrients 2021; 13(10):3480. doi:10.3390/nu13103480
10. **Oh J, Petersen C, Walsh CM, Bittencourt JC, Neylan TC, Grinberg LT.** The role of co-neurotransmitters in sleep and wake regulation. Mol Psychiatry 2019; 24(9):1284–1295. doi:10.1038/s41380-018-0291-2
11. **Scammell TE, Arrigoni E, Lipton JO.** Neural circuitry of wakefulness and sleep. Neuron 2017; 93(4):747–765. doi:10.1016/j.neuron.2017.01.014
12. **Baranwal N, Yu PK, Siegel NS.** Sleep physiology, pathophysiology, and sleep hygiene. Prog Cardiovasc Dis 2023; 77:59–69. doi:10.1016/j.pcad.2023.02.005
13. **Tighe CA, Bramoweth AD.** Recent developments in the management of insomnia in later life. Curr Treat Options Psychiatry 2018; 5: 195–210. doi:10.1007/s40501-018-0145-1
14. **Hinrichsen GA, Leipzig RM.** Implementation and effectiveness of cognitive behavioral therapy for insomnia in geriatric primary care. Clin Gerontol 2024; 47(3):507–514. doi:10.1080/07317115.2022.2104675

15. **The 2023 American Geriatrics Society Beers Criteria® Update Expert Panel.** American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2023; 71(7):2052–2081. doi:10.1111/jgs.18372
16. **Pottie K, Thompson W, Davies S, et al.** Deprescribing benzodiazepine receptor agonists: evidence-based clinical practice guideline. Can Fam Physician 2018; 64(5):339–351. pmid:29760253
17. **American Geriatrics Society 2015 Beers Criteria Update Expert Panel.** American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015; 63(11):2227–2246. doi:10.1111/jgs.1370
18. **Yeung WF, Chung KF, Yung KP, Ng TH.** Doxepin for insomnia: a systematic review of randomized placebo-controlled trials. Sleep Med Rev 2015; 19:75–83. doi:10.1016/j.smrv.2014.06.001
19. **Krystal AD, Durrence HH, Scharf M, et al.** Efficacy and safety of doxepin 1 mg and 3 mg in a 12-week sleep laboratory and outpatient trial of elderly subjects with chronic primary insomnia. Sleep 2010; 33(11):1553–1561. doi:10.1093/sleep/33.11.1553
20. **Wilson S, Anderson K, Baldwin D, et al.** British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: an update. J Psychopharmacol 2019; 33(8):923–947. doi:10.1177/0269881119855343
21. **Alam A, Voronovich Z, Carley JA.** A review of therapeutic uses of mirtazapine in psychiatric and medical conditions. Prim Care Companion CNS Disord 2013; 15(5):PCC.13r01525. doi:10.4088/PCC.13r01525
22. **Maruani J, Reynaud E, Chambe J, Palagini L, Bourgin P, Geoffroy PA.** Efficacy of melatonin and ramelteon for the acute and long-term management of insomnia disorder in adults: a systematic review and meta-analysis. J Sleep Res 2023; 32(6):e13939. doi:10.1111/jsr.13939
23. **Marupuru S, Arku D, Campbell AM, Slack MK, Lee JK.** Use of melatonin and/on ramelteon for the treatment of insomnia in older adults: a systematic review and meta-analysis. J Clin Med 2022; 11(17):5138. doi:10.3390/jcm11175138
24. **Michelson D, Snyder E, Paradis E, et al.** Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol 2014; 13(5): 461–471. doi:10.1016/S1474-4422(14)70053-5
25. **Rosenberg R, Murphy P, Zammit G, et al.** Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: a phase 3 randomized clinical trial [published correction appears in JAMA Netw Open 2020; 3(4):e206497] [published correction appears in JAMA Netw Open 2021; 4(8):e2127643]. JAMA Netw Open 2019; 2(12):e1918254. doi:10.1001/jamanetworkopen.2019.18254
26. **Rosenberg RP, Benca R, Doghramji P, Roth T.** A 2023 update on managing insomnia in primary care: insights from an expert consensus group. Prim Care Companion CNS Disord 2023; 25(1):22nr03385. doi:10.4088/PCC.22nr03385
27. **Citrome L.** Suvorexant for insomnia: a systematic review of the efficacy and safety profile for this newly approved hypnotic—what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract 2014; 68(12): 1429–1441. doi:10.1111/ijcp.12568
28. **Citrome L, Juday T, Frech F, Atkins N Jr.** Lemborexant for the treatment of insomnia: direct and indirect comparisons with other hypnotics using number needed to treat, number needed to harm, and likelihood to be helped or harmed. J Clin Psychiatry 2021; 82:20m13795. doi:10.4088/JCP.20m13795
29. **Chalet FX, Luyet PP, Rabasa C, et al.** Daridorexant for patients with chronic insomnia disorder: number needed to treat, number needed to harm, and likelihood to be helped or harmed. Postgrad Med 2024; 136(4):396–405. doi:10.1080/00325481.2024.2359891
30. **Monkemeyer N, Thomas SV, Hilleman DE, Malesker MA.** Insomnia treatment update with a focus on orexin receptor. US Pharm 2022; 47(5):43–48.
31. **Pagel JF, Parnes BL.** Medications for the treatment of sleep disorders: an overview. Prim Care Companion J Clin Psychiatry 2001; 3(3):118–125. doi:10.4088/pcc.v03n0303
32. **Babson KA, Sottile J, Morabito D.** Cannabis, cannabinoids, and sleep: a review of the literature. Curr Psychiatry Rep 2017; 19(4):23. doi:10.1007/s11920-017-0775-9
33. **MacNair L, Kalaba M, Peters EN, et al.** Medical cannabis authorization patterns, safety, and associated effects in older adults. J Cannabis Res 2022; 4(1):50. doi:10.1186/s42238-022-00158-5
34. **Narayan AJ, Downey LA, Rose S, Di Natale L, Hayley AC.** Cannabidiol for moderate-severe insomnia: a randomized controlled pilot trial of 150 mg of nightly dosing. J Clin Sleep Med 2024; 20(5): 753–763. doi:10.5664/jcsm.10998
35. **Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL.** Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2017; 13(2):307–349. doi:10.5664/jcsm.6470
36. **Smith MT, Perlis ML, Park A, et al.** Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry 2002; 159(1):5–11. doi:10.1176/appi.ajp.159.1.5
37. **Zhang Y, Ren R, Yang L, et al.** Comparative efficacy and acceptability of psychotherapies, pharmacotherapies, and their combination for the treatment of adult insomnia: a systematic review and network meta-analysis. Sleep Med Rev 2022; 65:101687. doi:10.1016/j.smrv.2022.101687
38. **Ree M, Junge M, Cunnington D.** Australasian Sleep Association position statement regarding the use of psychological/behavioral treatments in the management of insomnia in adults. Sleep Med 2017; 36(suppl 1):S43–S47. doi:10.1016/j.sleep.2017.03.017
39. **Kyle SD, Siriwardena AN, Espie CA, et al.** Clinical and cost-effectiveness of nurse-delivered sleep restriction therapy for insomnia in primary care (HABIT): a pragmatic, superiority, open-label, randomised controlled trial. Lancet 2023; 402(10406):975–987. doi:10.1016/S0140-6736(23)00683-9
40. **Song Y, Kelly MR, Fung CH, et al.** Change in dysfunctional sleep-related beliefs is associated with changes in sleep and other health outcomes among older veterans with insomnia: findings from a randomized controlled trial. Ann Behav Med 2022; 56(1):35–49. doi:10.1093/abm/kaab030

Address: *Roberto León-Barriera, MD, Department of Psychiatry, University of Pittsburgh Medical Center, 3811 O'Hara Street, Pittsburgh, PA 15213; leonbarrierara@upmc.edu*

Cleveland Clinic

Wellness and Preventive Medicine

Annual Conference

April 11, 2025

Cleveland Clinic Administrative Campus
3175 Science Park Drive, Building #4, 4th Floor
Beachwood, OH and Live Stream

Why Attend?

Identify specific evidence-based tools and review lifestyle assessments and interventions in the following four areas:

- Nourishing eating patterns
- Stress management
- Restorative sleep
- Healthy movement

Participate in evidence-based discussions of complementary medicine

Partake in engaging hands-on activities (non-CME) including yoga, acupuncture, cooking, and chiropractic demonstrations, and a Jeopardy game with Michael Roizen, MD!

Earn ABIM MOC Points

Live Stream option available!

Who Should Attend?

This activity is designed for practicing physicians and advanced practice providers in primary care and specialties who treat patients with chronic conditions.

Register Today! **ccfcme.org/Wellness**

This activity has been approved for *AMA PRA Category 1 Credit*™ ANCC Contact Hours, AAPA Category 1 CME Credits, and ABIM MOC Points.

Cleveland Clinic

BEYOND THE PAGES:

Cleve Clin J Med Podcast

"Beyond the Pages: Cleve Clin J Med Podcasts" explore C*leveland Clinic Journal of Medicine* articles in depth through interviews with authors and experts in the field. Clinicians will learn more about clinical breakthroughs in medicine and how to practically apply them in patient care.

Listen today!

www.ccfcme.org/CCJMpodcast

Podcasts include

- Management of benign prostatic hyperplasia
- Treatments for obstructive sleep apnea: CPAP and beyond
- Metformin therapy for weight loss in patients without diabetes
- Antibiotics to prevent infective endocarditis before dental procedures

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

Jack Hartnett, MB, BCh, BAO, MSc
Department of Cardiology, Mater Misericordiae University Hospital, Dublin, Ireland

Nour Chouman, MD
Tulane Research Innovation for Arrhythmia Discovery, Tulane University School of Medicine, New Orleans, LA

Eoin Donnellan, MD
Tulane Research Innovation for Arrhythmia Discovery, Tulane University School of Medicine, New Orleans, LA

Risk-factor modification to prevent recurrent atrial fibrillation after catheter ablation

ABSTRACT

More and more patients with atrial fibrillation are undergoing catheter ablation as a rhythm-control strategy, but the recurrence rate after the procedure is high. A wide array of risk factors contribute to the pathogenesis of atrial fibrillation, including hypertension, diabetes mellitus, dyslipidemia, obesity, obstructive sleep apnea, metabolic dysfunction–associated steatotic liver disease (MASLD), smoking, alcohol consumption, and physical inactivity. This review summarizes the emerging evidence for periablation risk-factor modification to optimize postablation outcomes.

KEY POINTS

- Because we lack sufficient evidence of benefit specifically in patients with atrial fibrillation undergoing catheter ablation, hypertension and diabetes mellitus should be treated according to guidelines in the general population.
- Current guidelines recommend an initial weight-loss goal of 10% in patients with obesity and atrial fibrillation, followed by a target body mass index of less than 25 kg/m^2.
- There is enough evidence to encourage continuous positive airway pressure (CPAP) use in those with atrial fibrillation and obstructive sleep apnea after catheter ablation, and early data suggest that ablation offers little to patients with atrial fibrillation and obstructive sleep apnea not on CPAP.
- Intensive periprocedural MASLD management may be beneficial in reducing recurrence risk after catheter ablation.

doi:10.3949/ccjm.92a.24011

Catheter ablation effectively controls atrial fibrillation, but in up to half of cases the atrial fibrillation comes back. Can this high recurrence rate be lowered by making sure that the risk factors for atrial fibrillation are under optimal control before patients undergo the procedure, and going forward from there?

We think so, although the evidence is scarce. And we think the best approach is to systematically hit all the risk factors simultaneously, in specialized periablation clinics. Here, we review the evidence supporting periprocedural risk-factor modification to reduce atrial fibrillation recurrence after catheter ablation.

SCOPE OF THE PROBLEM

Atrial fibrillation is the most common cardiac arrhythmia worldwide, affecting approximately 33.5 million people.[1] It is associated with significant morbidity and mortality, increasing the risk of systemic thromboembolic disease, heart failure, and sudden cardiac death.

The etiology of atrial fibrillation is multifactorial, with a wide array of risk factors that contribute to its pathogenesis. In recent years, various modifiable comorbidities such as obesity, diabetes mellitus, smoking, and alcohol intake have emerged as key risk factors. They are not only implicated in the onset of atrial fibrillation, but are also associated with worse response to various management approaches to the disease.

Catheter ablation is growing in popularity as a rhythm-control treatment, and is increasingly being offered to patients who have more complex

TABLE 1
Risk factors for atrial fibrillation

Hypertension
Diabetes mellitus
Dyslipidemia
Obesity
Obstructive sleep apnea
Metabolic dysfunction–associated steatotic liver disease
Smoking
Alcohol consumption
Physical inactivity

conditions and comorbidities. The 2023 American College of Cardiology and American Heart Association guidelines[2] give it a class 1 (strong) recommendation, level of evidence A (high-quality):

- To improve symptoms in patients with symptomatic atrial fibrillation in whom antiarrhythmic drugs have been ineffective, contraindicated, not tolerated, or not preferred, and continued rhythm control is desired.
- To improve symptoms and reduce progression to persistent atrial fibrillation in select patients (generally younger with few comorbidities) with symptomatic paroxysmal atrial fibrillation in whom rhythm control is desired.

But here's the problem: although catheter ablation initially works, the atrial fibrillation eventually recurs in 40% to 50% of cases.[3] About 11% of patients need a repeat ablation procedure within 1 year, and many undergo multiple ablations over a number of years.[4]

Fortunately, we should be able to lower this recurrence rate by optimally treating the risk factors for atrial fibrillation (**Table 1**).

HYPERTENSION: MIXED EVIDENCE, BUT USUAL GUIDELINES APPLY

Hypertension accounts for more cases of atrial fibrillation than any other risk factor—up to 20% of all new cases in population-based longitudinal studies.[5] Hypertensive heart disease involves concentric left ventricular hypertrophy and increased stiffness, resulting in chronically elevated left atrial pressures, which drive subsequent left atrial dilation and arrhythmogenesis.[6]

Studies of hypertension and atrial fibrillation

Although many studies have found a near-linear relationship between blood pressure and risk of new-onset atrial fibrillation, the evidence that intensive blood pressure control reduces the risk is equivocal.

SPRINT (the Systolic Blood Pressure Intervention Trial),[7] for example, found no difference in rates of new atrial fibrillation between patients whose blood pressure was treated intensively vs less restrictively.

The relationship between blood pressure control at the time of ablation and the risk of arrhythmia recurrence is equally complex.

Pallisgaard et al,[8] in a Danish nationwide registry, found hypertension to be an independent risk factor for recurrence after ablation.

Santoro et al,[9] in another study in 531 consecutive patients, found the risk of recurrence to be 40.6% in patients with uncontrolled hypertension, 28.1% in those with controlled hypertension, and 25.7% in those with no hypertension. The similar recurrence rates in patients with controlled hypertension vs no hypertension suggest that intensive blood pressure control in the periprocedural period should be beneficial.

The German Ablation Registry,[10] on the other hand, did not find hypertensive patients to be at higher risk of atrial fibrillation recurrence after catheter ablation compared with normotensive patients.

SMAC-AF (Substrate Modification with Aggressive Blood Pressure Control)[11] is the only randomized controlled trial to date investigating the influence of preprocedural blood pressure control on arrhythmia recurrence risk. One hundred eighty-four patients were randomized to either aggressive blood pressure control (target < 120/80 mm Hg) or standard blood pressure control (target < 140/90 mm Hg). At 6 months, the aggressive-treatment group had lower blood pressure than the standard-treatment group. However, the rates of recurrence were nearly identical (61.4% vs 61.2% at a median of 14 months follow-up). Notably, both groups lowered their blood pressure from their baseline levels, so the study may have underestimated the true effect of blood pressure control. Also, most participants had long-standing atrial fibrillation (and thus likely more advanced atrial myopathy), which would predispose them to recurrent rhythm disturbance.

ERADICATE-AF (Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation)[12] demonstrated that performing renal denervation at the time of the ablation procedure reduces blood pressure and arrhythmia recurrence risk. Although this randomized controlled trial may seem to show that intensive blood pressure control at the time of catheter ablation is beneficial, the reduction in arrhythmia recurrence was actually independent of the degree of blood pressure improvement. A unifying mechanism may be a reduction in central sympathetic output after renal denervation.

Blood pressure recommendations and questions

Although the evidence of benefit is mixed, most experts agree on the need to optimize periprocedural blood pressure. In a scientific statement, the American Heart Association recommends following the same guidelines in patients with atrial fibrillation as in the general population, as there are not enough data for atrial fibrillation–specific recommendations.[13] They cite the Joint National Committee targets for blood pressure, ie, less than 140/90 mm Hg for people younger than 60 or with diabetes or chronic kidney disease, and less than 150/90 mm Hg for those age 60 and older.

Which drugs to use? There is some evidence that mineralocorticoid receptor antagonists may reduce the risks of new-onset and recurrent atrial fibrillation. A single-center retrospective study found a higher rate of freedom from recurrent atrial fibrillation after ablation in patients receiving eplerenone than in those not receiving it.[14] However, the potential benefit of intensive periablation blood pressure control (particularly with mineralocorticoid receptor antagonists or angiotensin-converting enzyme inhibitors known to induce cardioprotective remodelling) in patients with paroxysmal atrial fibrillation—and thus a lesser degree of atrial myopathy—is yet to be explored.

DIABETES MELLITUS: USUAL GUIDELINES ALSO APPLY

There is a well-described association between diabetes mellitus and new-onset atrial fibrillation. A meta-analysis involving almost 1.7 million patients reported that those with diabetes mellitus had an approximately 40% higher risk of atrial fibrillation than those without it.[15]

Diabetes mellitus induces arrhythmogenesis through a cascade of microvascular ischemia leading to left ventricular diastolic dysfunction, hypertrophy, and eventual left atrial dilation.[16]

Studies of diabetes and atrial fibrillation

Although the association is not linear, there is strong evidence that the worse the diabetes, the greater the risk of atrial fibrillation. Higher hemoglobin A1c levels and longer duration of diabetes are both associated with higher risk of atrial fibrillation, and diabetes may promote progression of atrial fibrillation from paroxysmal to persistent and permanent.[17]

Emerging data suggest that preprocedural glycemic control affects the outcomes of catheter ablation in patients with diabetes.

Donnellan et al,[18] in an analysis of 298 patients with diabetes mellitus undergoing catheter ablation at a single institution, reported that arrhythmia recurred in only 2% of patients who lowered their hemoglobin A1c level by more than 10% before ablation, compared with 91.1% of patients whose hemoglobin A1c level went up before ablation. Moreover, the greater the hemoglobin A1c reduction, the lower the risk of atrial fibrillation recurrence. Limitations of this study include its retrospective design and confounding factors such as differences in patient motivation and compliance with medical therapy.

Wang et al[19] noted a higher rate of recurrent arrhythmias among patients with diabetes mellitus, but found only a nonsignificant trend toward higher risk with worse glycemic control.

Anselmino et al[20] included almost 1,500 patients in a meta-analysis of 15 studies, which revealed that higher baseline hemoglobin A1c was associated with a higher incidence of recurrent atrial fibrillation.

Diabetes recommendations and questions

As with hypertension, the American Heart Association scientific statement[13] recommends managing diabetes according to current general diabetes guidelines, as not enough data exist for atrial fibrillation–specific recommendations. For most adults with diabetes, this would mean a target hemoglobin A1c of less than 7%.

Which drugs to use? Further analysis is required to ascertain whether certain drugs are more efficacious in reducing recurrent arrhythmogenesis.

Pioglitazone and metformin have been associated with lower incidence of atrial fibrillation recurrence in observational studies.[21,22] The researchers hypothesized that the anti-inflammatory and antioxidant properties of these agents dampen arrhythmogenesis; however, these suggested pleiotropic effects (ie, independent of glycemic control) are not proven.

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors hold particular hope as potential adjunct therapy in the periablation period. Post hoc analysis has shown SGLT-2 inhibitors induce protective left atrial structural remodelling and reduce the incidence of atrial fibrillation onset in patients both with and without diabetes, independent of glycemic control.[23] In DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction),[24] the SGLT-2 inhibitor dapagliflozin decreased the incidence of reported episodes of atrial fibrillation in patients with diabetes at high risk. Data from randomized controlled trials of SGLT-2 inhibitors in the periablation setting are awaited.

DYSLIPIDEMIA: NO EVIDENT BENEFIT FROM TREATMENT

The association between dyslipidemia and atrial fibrillation risk remains inconclusive. Indeed, some studies

support a paradoxical relationship whereby lower lipid levels are associated with higher risk of new-onset atrial fibrillation.[25] Regarding recurrence rates after ablation, the data are equally mixed, with some studies finding a similar paradoxical association.[26]

Statins have known pleiotropic anti-inflammatory and antioxidant effects, so in theory they might be expected to reduce the risk of recurrence after catheter ablation. However, a meta-analysis of 9 studies found a protective effect in randomized controlled trials but not in retrospective studies or in the analysis as a whole.[27] The largest randomized controlled trial to date found that high-dose atorvastatin therapy did not decrease recurrence risk at 3 months after ablation (when ablation-induced inflammatory responses are known to trigger recurrent arrhythmogenesis) in patients who had no indication for a statin.[28]

OBESITY: WEIGHT LOSS RECOMMENDED

Numerous large epidemiologic studies have solidly shown that the risk of atrial fibrillation increases with weight. The Framingham Heart Study[29] reported a 4% increase in atrial fibrillation risk with each unit (1 kg/m^2) increase in body mass index, which was independent of confounding factors including hypertension and diabetes mellitus. In a continued observational study of women from the Women's Health Study, increasing body mass index was associated with enhanced risk of developing persistent or permanent atrial fibrillation in women who were free of atrial fibrillation at baseline.[30]

Why would this be? Obesity-induced systemic inflammation is thought to disrupt atrial conduction through fibrotic scar tissue deposition.[31] Diastolic dysfunction is common in patients with obesity and contributes to left atrial remodelling. Interestingly, pericardial and epicardial fat may influence atrial fibrillation development through local paracrine mechanisms.[32] These mechanisms ultimately converge on left atrial enlargement with resultant disruption in electrical conductivity. In The Framingham Heart Study,[29] after adjustment for left atrial diameter, obesity was no longer associated with increased risk of atrial fibrillation, suggesting at least part of the proarrhythmogenic burden of obesity is mediated through left atrial dilation.

Studies of obesity and atrial fibrillation

The relationship between weight and outcomes after catheter ablation for atrial fibrillation has been more extensively explored than that of other risk factors. Numerous large observational studies have proven an inverse relationship between weight and freedom from recurrent atrial fibrillation after ablation.[33,34] In a European study involving almost 2,500 patients, the risk of recurrent arrhythmia at 12 months increased with increasing body mass index.[33] Consequently, there has been significant interest in periprocedural weight loss to improve catheter ablation outcomes.

LEGACY (Long-Term Effect of Goal-Directed Weight Management on Atrial Fibrillation Cohort: A 5-Year Follow-Up Study)[35] enrolled 355 patients with body mass index greater than 27 kg/m^2 awaiting catheter ablation who participated in a multidisciplinary weight-reduction program. Weight loss was found to be inversely correlated with atrial fibrillation recurrence; patients who lost 10% or more of their body weight had 6 times greater likelihood of arrhythmia-free survival compared with those who lost less.

SORT-AF (Supervised Obesity Reduction Trial for AF Ablation Patients).[36] Only 1 randomized controlled trial to date has investigated whether weight reduction before catheter ablation alone improves outcomes. The SORT-AF was a multicenter randomized controlled trial in which 133 patients with paroxysmal or persistent atrial fibrillation and body mass index greater than 30 kg/m^2 were randomized to undergo weight reduction or usual care. A statistically significant reduction in body mass index was achieved in the weight-reduction group; however, no significant difference in recurrence rates was evident. Among those with persistent atrial fibrillation after ablation, a reduction in atrial fibrillation burden was noted in the weight-reduction group.

Although this was a well-executed trial with specialized weight-reduction input from endocrinologists, the mean weight reduction achieved in the treatment arm was only 3.9% of initial body weight, and the noncompliance-with-intervention rate at 12 months was 33%.[36] Previous publications report significantly reduced recurrent arrhythmogenesis when more than 10% loss of initial body weight is obtained; it is likely greater weight reduction was necessary to obtain a significant primary outcome.

Obesity recommendations and questions

The American Heart Association scientific statement[13] recommends an initial weight-loss goal of 10% in patients with atrial fibrillation, followed by an eventual target body mass index of less than 25 kg/m^2.

How to lose weight? There are little data regarding which weight-reduction strategy is most effective in the periablation setting, but the American Heart Association recommends a progressive-intensity exercise program in conjunction with a multidisciplinary diet, as used in most studies to date.[36,37]

A single-center observational study reported that preprocedural bariatric surgery reduced atrial fibrillation recurrence risk to that in nonobese patients.[38] The underlying therapeutic mechanism is likely multifactorial, as bariatric surgery was shown to not only decrease weight in this obese cohort, but also significantly reduce blood pressure and hemoglobin A1c. No randomized controlled trial with a sham-controlled arm has been performed.

Glucagon-like peptide-1 agonists such as semaglutide have emerged as highly effective pharmacotherapies for weight loss in both diabetic and nondiabetic cohorts. The SOCRATES-AF (Semaglutide for the Reduction of Arrhythmia Burden in Overweight AF Patients) trial is currently investigating whether semaglutide reduces atrial fibrillation burden in patients with symptomatic paroxysmal and early persistent atrial fibrillation. However, no studies to date have investigated the potential efficacy of glucagon-like peptide-1 agonists as adjunctive therapy in the periprocedural setting for obese patients with atrial fibrillation undergoing catheter ablation. Similar to that of bariatric surgery, any underlying therapeutic benefits are likely to be pleiotropic—extending beyond weight loss alone.

OBSTRUCTIVE SLEEP APNEA: CPAP ENCOURAGED

An association between obstructive sleep apnea and atrial fibrillation is well documented. Although both disorders share multiple risk factors including obesity and hypertension, the relationship is likely causal. Obstructive sleep apnea promotes atrial fibrillation through oxidative stress–induced left atrial remodelling and enhanced sympathetic tone during hypoxemic episodes—both of which combine to drive left atrial enlargement.[39]

Studies of obstructive sleep apnea and atrial fibrillation

Obstructive sleep apnea is strikingly prevalent in patients with atrial fibrillation.

Gami et al,[40] in a seminal study, found that the proportion of patients with obstructive sleep apnea was significantly higher in those with atrial fibrillation than in cardiology patients without atrial fibrillation with similar rates of key comorbidities (49% vs 32%, $P < .0004$).

Conversely, atrial fibrillation is more common in patients with obstructive sleep apnea.

MrOs Sleep (Outcomes of Sleep Disorders in Older Men Study)[41] found that increasing severity of sleep-disordered breathing was associated with a progressive increase in odds of atrial fibrillation and complex ventricular ectopy. However, sleep-disordered breathing includes both obstructive and central sleep apnea. Complex ventricular ectopy was associated most strongly with obstructive sleep apnea, while atrial fibrillation was more strongly associated with central sleep apnea.

Effective management of obstructive sleep apnea with nocturnal continuous positive airway pressure (CPAP) reduces the risk of progression of atrial fibrillation.

ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation)[42] found that patients with atrial fibrillation and obstructive sleep apnea on CPAP were less likely to progress to more persistent forms of atrial fibrillation compared with those not on CPAP.

Two studies to date have demonstrated that recurrence rates of atrial fibrillation after catheter ablation are approximately equal in patients with obstructive sleep apnea on CPAP and those without obstructive sleep apnea, and that atrial fibrillation was significantly more likely to recur in patients with obstructive sleep apnea not on CPAP.[43,44]

Naruse et al,[43] in the first study, prospectively recruited 153 Japanese patients. Atrial fibrillation recurred in 22% of those without obstructive sleep apnea, 30% with obstructive sleep apnea on CPAP, and 53% with obstructive sleep apnea but refusing CPAP. On multivariate analysis, CPAP reduced recurrence by roughly 60%.

Fein et al,[44] in the second study, retrospectively examined 62 patients with obstructive sleep apnea after catheter ablation, of whom 32 used CPAP and 30 did not. Compared with a control group without obstructive sleep apnea who underwent catheter ablation, obstructive sleep apnea was associated with increased atrial arrhythmia recurrence. However, as in the Naruse et al[43] study, arrhythmia-free survival at 1 year in the obstructive sleep apnea group using CPAP was similar to that of patients without obstructive sleep apnea (71.9% vs 66.7%). Summarizing the data, the authors suggest that obstructive sleep apnea therapy should be optimized prior to catheter ablation; otherwise, the efficacy of invasive ablation may be lost.

Although the findings were consistent across both studies, limitations preclude making definitive conclusions. Neither are randomized controlled trials, but rather are case-control studies subject to selection bias. Although some major confounders are accounted for, others are not. Patients with obstructive sleep apnea who are not on CPAP may be inherently less compliant with medical therapy or may have less severe disease compared with those using CPAP. No experimental studies investigating the effect of CPAP on obstructive sleep apnea–related atrial fibrillation pathogenesis have been published to date.

Obstructive sleep apnea recommendations

Clinically, there is enough emerging evidence to encourage CPAP use among patients with atrial fibrillation and obstructive sleep apnea after catheter ablation, and early data suggest that catheter ablation offers very little to patients with atrial fibrillation and obstructive sleep apnea not on CPAP. Current guidelines recommend CPAP for these patients.[2] However, randomized data demonstrating benefit on recurrence rates in the periablation setting are currently lacking.

METABOLIC DYSFUNCTION–ASSOCIATED STEATOTIC LIVER DISEASE

Atrial fibrillation shares many risk factors with metabolic dysfunction–associated steatotic liver disease (MASLD, formerly known as nonalcoholic fatty liver disease or NAFLD), including obesity, diabetes mellitus, and metabolic syndrome. Causality has yet to be proven, but multiple mechanisms of arrhythmogenesis have been proposed, including MASLD-induced proinflammatory stress, autonomic dysregulation, and diastolic dysfunction.[45]

Recent evidence suggests that MASLD is associated with increased recurrence risk after catheter ablation.

Donnellan et al,[46] in a case-control study of 89 patients with MASLD and 178 controls, all of whom underwent catheter ablation at Cleveland Clinic, reported that atrial fibrillation recurred more often in those with MASLD. While obstructive sleep apnea was significantly more common in the MASLD group, which could separately affect recurrence risk, the relationship persisted in multivariate models adjusted for obstructive sleep apnea and other potential confounders. Also, recurrence was more likely with worsening MASLD severity as defined by the NAFLD Fibrosis Score. No other publications to date have investigated this relationship; further data are required to support this association.

Few disease-specific therapies exist for MASLD. Existing data mostly support risk-factor modification such as weight loss and tight glycemic control, strategies that are often used in patients with atrial fibrillation regardless of their liver status.

Interestingly, the Donnellan et al[46] study found that postprocedural risk-factor modification reduced atrial fibrillation recurrence. Atrial fibrillation did not recur among any MASLD patient who lost at least 10% of their body weight after ablation, while 91% of patients who gained weight after catheter ablation had recurrent arrhythmia. Similarly, poor glycemic control before the procedure was associated with worse outcomes. All patients whose hemoglobin A1c rose in the 12 months leading up to ablation developed recurrent atrial fibrillation after catheter ablation, compared with only 36% of patients whose hemoglobin A1c fell before ablation.

Although this was only a single-center retrospective study, it suggests intensive periprocedural MASLD management may be beneficial in reducing recurrence risk after catheter ablation. No publications to date have investigated whether an association exists between MASLD-specific pharmacotherapies, such as vitamin E and pioglitazone, and recurrent arrhythmia risk. As proinflammatory oxidative stress is hypothesized to promote atrial fibrillation in MASLD, these antioxidant agents may be beneficial in patients with MASLD undergoing catheter ablation.

SMOKING AND ALCOHOL CONSUMPTION: QUITTING IS RECOMMENDED

Numerous studies demonstrate an increased risk of atrial fibrillation with both smoking and alcohol consumption. The relationship between smoking and new atrial fibrillation is dose-dependent,[47] while epidemiologic studies indicate that alcohol increases the risk only at moderate to high intake levels (defined as > 7 drinks per week).[48] After catheter ablation, multiple retrospective studies have found higher rates of atrial fibrillation recurrence in smokers (34%–43%) than in nonsmokers (14%).[49,50] Similarly, moderate to high levels of alcohol intake have been associated with recurrence after catheter ablation in multiple studies.[51]

Current guidelines therefore recommend smoking cessation treatment and encouragement to abstain from alcohol for all patients with atrial fibrillation.[2]

PHYSICAL INACTIVITY

Cardiorespiratory fitness is inversely correlated with new atrial fibrillation.

CARDIO-FIT (Impact of Cardiorespiratory Fitness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation),[52] in which patients with atrial fibrillation and obesity were offered a tailored exercise program, showed that improvements in cardiorespiratory fitness increased arrhythmia-free survival regardless of the rhythm-control strategy used. In the periablation setting, evidence suggests higher baseline cardiorespiratory fitness is associated with reduced atrial fibrillation recurrence after ablation.[53]

Although the underlying therapeutic mechanism is likely pleomorphic, echocardiography studies have

TABLE 2
Summary of evidence surrounding preablation and postablation risk-factor modification

Risk factor	Before the procedure	After the procedure
Hypertension	Hypertension increases incidence of atrial fibrillation[5] Periprocedural renal denervation reduces blood pressure and atrial fibrillation recurrence[12] Whether aggressive hypertension management before ablation provides additional benefit in preventing atrial fibrillation recurrences is unclear[11]	Hypertension increases postprocedural atrial fibrillation recurrence risk[8] Rates of recurrence in patients with controlled hypertension are similar to those of patients with no hypertension[9]
Diabetes mellitus	Diabetes mellitus increases incidence of atrial fibrillation[15] Periprocedural role of sodium-glucose cotransporter 2 inhibitors is unclear	Hemoglobin A1c control reduces atrial fibrillation recurrence[18]
Obesity	Obesity increases both incidence and severity of atrial fibrillation[29,30] Preprocedural weight management, including bariatric surgery, improves success[33–35,38]	
Obstructive sleep apnea		Continuous positive airway pressure reduces atrial fibrillation recurrence in patients with obstructive sleep apnea[43,44]
Metabolic dysfunction–associated steatotic liver disease	Preprocedural management is beneficial[46] Role of pharmacotherapy is unclear	

shown a correlation between higher cardiorespiratory fitness and reduced left atrial stiffness and improved left atrial systolic function, which may contribute to lower risk of atrial fibrillation recurrence.[54]

ACTIVE-AF (A Lifestyle-Based, Physical Activity Intervention for Patients With Symptomatic Atrial Fibrillation)[55] randomized 120 patients with atrial fibrillation with or without a history of catheter ablation to either a 6-month tailored exercise program or usual care. On Kaplan-Meier survival analysis, there was a clear arrhythmia-free advantage in the exercise group, with 40% in the exercise group vs only 20% in the usual-care group free from atrial fibrillation at 12 months. Additionally, atrial fibrillation symptom severity, measured by questionnaire, was significantly reduced in the exercise group at both 6- and 12-month follow-up.

Although this trial did not involve patients undergoing ablation, it hints at the likely benefit of periprocedural improvements in cardiorespiratory fitness. Randomized controlled trials directly addressing this question are needed.

The evidence on risk-factor modification before ablation and after ablation is summarized in **Table 2**.[5,8,9,11,12,15,18,29,30,33–35,38,43,44,46]

COMPLETE RISK-FACTOR MODIFICATION

Given the interwoven and synergistic nature of risk factors for atrial fibrillation, simultaneous modification of multiple risk factors in the periablation setting is required.

ARREST-AF (Aggressive Risk Factor Reduction Study for Atrial Fibrillation)[56] is the only published study to date to investigate this question. It was a cohort study in which 281 consecutive patients awaiting catheter ablation with body mass index 27 kg/m^2 or higher and at least 1 cardiovascular risk factor were offered risk-factor modification according to American Heart Association and American College of Cardiology guidelines. Addressed risk factors included weight loss, hypertension, glycemic control, dyslipidemia, alcohol intake, and smoking.

The intervention group significantly lowered their weight, blood pressure, hemoglobin A1c, and lipid levels.

Compared with a cohort that did not undergo any risk factor modification, they had a significantly lower rate of arrhythmia recurrence and lower arrhythmia burden and severity (among those in which atrial fibrillation did recur). The rate of single-ablation, arrhythmia-free survival was 32.9% in the risk-factor modification group vs 9.7% in the control group, and arrhythmia-free survival rates after final ablation was 87% in the intervention group vs 17.8% in the control group. Interestingly, the left atrial volume index decreased significantly more in the intervention group than in the control group.

Although limited by selection and observer bias as a nonrandomized study, ARREST-AF[56] offers very promising insight into the potential efficacy of complete risk-factor modification.

AGGRESSIVE OPTIMIZATION IS THE FUTURE

Despite the expanding use of catheter ablation in managing atrial fibrillation, recurrence outcomes remain suboptimal, particularly among patients with comorbidities. The pathogenesis of atrial fibrillation is complex, involving multiple intertwined risk factors that have a synergistic effect on atrial structural remodelling and atrial arrhythmogenesis. Although modification of each individual risk factor is certainly desirable, simultaneous aggressive optimization of multiple risk factors in specialized periablation clinics is the emerging future.

DISCLOSURES

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

REFERENCES

1. **Chugh SS, Havmoeller R, Narayanan K, et al.** Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 study. Circulation 2014; 129(8):837–847. doi:10.1161/CIRCULATIONAHA.113.005119
2. **Joglar JA, Chung MK, Armbruster AL, et al.** 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation 2024; 149(1):e167] [published correction appears in Circulation 2024; 149(9):e936] [published correction appears in Circulation 2024; 149(24):e1413]. Circulation 2024; 149(1):e1–e156. doi:10.1161/CIR.0000000000001193
3. **Ganesan AN, Shipp NJ, Brooks AG, et al.** Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc 2013; 2(2):e004549. doi:10.1161/JAHA.112.004549
4. **Piccini JP, Sinner MF, Greiner MA, et al.** Outcomes of Medicare beneficiaries undergoing catheter ablation for atrial fibrillation. Circulation 2012; 126(18):2200–2207. doi:10.1161/CIRCULATIONAHA.112.109330
5. **Huxley RR, Lopez FL, Folsom AR, et al.** Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2011; 123(14):1501–1508. doi:10.1161/CIRCULATIONAHA.110.009035
6. **Verdecchia P, Reboldi G, Gattobigio R, et al.** Atrial fibrillation in hypertension: predictors and outcome. Hypertension 2003; 41(2): 218–223. doi:10.1161/01.hyp.0000052830.02773.e4
7. **Parcha V, Patel N, Kalra R, et al.** Incidence and implications of atrial fibrillation/flutter in hypertension: insights from the SPRINT trial. Hypertension 2020; 75(6):1483–1490. doi:10.1161/HYPERTENSIONAHA.120.14690
8. **Pallisgaard JL, Gislason GH, Hansen J, et al.** Temporal trends in atrial fibrillation recurrence rates after ablation between 2005 and 2014: a nationwide Danish cohort study. Eur Heart J 2018; 39(6):442–449. doi:10.1093/eurheartj/ehx466
9. **Santoro F, Di Biase L, Trivedi C, et al.** Impact of uncontrolled hypertension on atrial fibrillation ablation outcome. JACC Clin Electrophysiol 2015; 1(3):164–173. doi:10.1016/j.jacep.2015.04.002
10. **Zylla MM, Hochadel M, Andresen D, et al.** Ablation of atrial fibrillation in patients with hypertension-an analysis from the German Ablation Registry. J Clin Med 2020; 9(8):2402. doi:10.3390/jcm9082402
11. **Parkash R, Wells GA, Sapp JL, et al.** Effect of aggressive blood pressure control on the recurrence of atrial fibrillation after catheter ablation: a randomized, open-label clinical trial (SMAC-AF [Substrate Modification with Aggressive Blood Pressure Control]). Circulation 2017; 135(19):1788–1798. doi:10.1161/CIRCULATIONAHA.116.026230
12. **Steinberg JS, Shabanov V, Ponomarev D, et al.** Effect of Renal Denervation and Catheter Ablation vs Catheter Ablation Alone on Atrial Fibrillation Recurrence Among Patients with Paroxysmal Atrial Fibrillation and Hypertension: The ERADICATE-AF randomized clinical trial [published correction appears in JAMA 2020; 323(9):896]. JAMA 2020; 323(3):248–255. doi:10.1001/jama.2019.21187
13. **Chung MK, Eckhardt LL, Chen LY, et al.** Lifestyle and risk factor modification for reduction of atrial fibrillation: a scientific statement from the American Heart Association. Circulation 2020; 141(16):e750–e772. doi:10.1161/CIR.0000000000000748
14. **Ito Y, Yamasaki H, Naruse Y, et al.** Effect of eplerenone on maintenance of sinus rhythm after catheter ablation in patients with long-standing persistent atrial fibrillation. Am J Cardiol 2013; 111(7):1012–1018. doi:10.1016/j.amjcard.2012.12.020
15. **Huxley RR, Filion KB, Konety S, Alonso A.** Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. Am J Cardiol 2011; 108(1):56–62. doi:10.1016/j.amjcard.2011.03.004
16. **Devereux RB, Roman MJ, Paranicas M, et al.** Impact of diabetes on cardiac structure and function: the Strong Heart Study. Circulation 2000; 101(19):2271–2276. doi:10.1161/01.cir.101.19.2271
17. **Seyed Ahmadi S, Svensson AM, Pivodic A, Rosengren A, Lind M.** Risk of atrial fibrillation in persons with type 2 diabetes and the excess risk in relation to glycaemic control and renal function: a Swedish cohort study. Cardiovasc Diabetol 2020; 19(1):9. doi:10.1186/s12933-019-0983-1
18. **Donnellan E, Aagaard P, Kanj M, et al.** Association between pre-ablation glycemic control and outcomes among patients with diabetes undergoing atrial fibrillation ablation. JACC Clin Electrophysiol 2019; 5(8):897–903. doi:10.1016/j.jacep.2019.05.018
19. **Wang A, Truong T, Black-Maier E, et al.** Catheter ablation of atrial fibrillation in patients with diabetes mellitus. Heart Rhythm O2 2020; 1(3):180–188. doi:10.1016/j.hroo.2020.04.006
20. **Anselmino M, Matta M, D'ascenzo F, et al.** Catheter ablation of atrial fibrillation in patients with diabetes mellitus: a systematic review and meta-analysis. Europace 2015; 17(10):1518–1525. doi:10.1093/europace/euv214
21. **Gu J, Liu X, Wang X, et al.** Beneficial effect of pioglitazone on the outcome of catheter ablation in patients with paroxysmal atrial fibrillation and type 2 diabetes mellitus. Europace 2011; 13(9): 1256–1261. doi:10.1093/europace/eur131

22. **Deshmukh A, Ghannam M, Liang J, et al.** Effect of metformin on outcomes of catheter ablation for atrial fibrillation. J Cardiovasc Electrophysiol 2021; 32(5):1232–1239. doi:10.1111/jce.14954
23. **Okunrintemi V, Mishriky BM, Powell JR, Cummings DM.** Sodium-glucose co-transporter-2 inhibitors and atrial fibrillation in the cardiovascular and renal outcome trials. Diabetes Obes Metab 2021; 23(1):276–280. doi:10.1111/dom.14211
24. **Zelniker TA, Bonaca MP, Furtado RHM, et al.** Effect of Dapagliflozin on Atrial Fibrillation in Patients with Type 2 Diabetes Mellitus: insights from the DECLARE-TIMI 58 trial. Circulation 2020; 141(15):1227–1234. doi:10.1161/CIRCULATIONAHA.119.044183
25. **Lee HJ, Lee SR, Choi EK, Han KD, Oh S.** Low lipid levels and high variability are associated with the risk of new-onset atrial fibrillation. J Am Heart Assoc 2019; 8(23):e012771. doi:10.1161/JAHA.119.012771
26. **Shang Y, Chen N, Wang Q, et al.** Blood lipid levels and recurrence of atrial fibrillation after radiofrequency catheter ablation: a prospective study. J Interv Card Electrophysiol 2020; 57(2):221–231. doi:10.1007/s10840-019-00543-w
27. **Peng H, Yang Y, Zhao Y, Xiao H.** The effect of statins on the recurrence rate of atrial fibrillation after catheter ablation: a meta-analysis. Pacing Clin Electrophysiol 2018; 41(11):1420–1427.doi:10.1111/pace.13485
28. **Suleiman M, Koestler C, Lerman A, et al.** Atorvastatin for prevention of atrial fibrillation recurrence following pulmonary vein isolation: a double-blind, placebo-controlled, randomized trial. Heart Rhythm 2012; 9(2):172–178. doi:10.1016/j.hrthm.2011.09.016
29. **Wang TJ, Parise H, Levy D, et al.** Obesity and the risk of new-onset atrial fibrillation. JAMA 2004; 292(20):2471–2477. doi:10.1001/jama.292.20.2471
30. **Sandhu RK, Conen D, Tedrow UB, et al.** Predisposing factors associated with development of persistent compared with paroxysmal atrial fibrillation. J Am Heart Assoc 2014; 3(3):e000916. doi:10.1161/JAHA.114.000916
31. **Mahajan R, Lau DH, Brooks AG, et al.** Electrophysiological, electroanatomical, and structural remodeling of the atria as consequences of sustained obesity. J Am Coll Cardiol 2015; 66(1):1–11. doi:10.1016/j.jacc.2015.04.058
32. **Wong CX, Abed HS, Molaee P, et al.** Pericardial fat is associated with atrial fibrillation severity and ablation outcome. J Am Coll Cardiol 2011; 57(17):1745–1751. doi:10.1016/j.jacc.2010.11.045
33. **Providência R, Adragão P, de Asmundis C, et al.** Impact of body mass index on the outcomes of catheter ablation of atrial fibrillation: a European observational multicenter study. J Am Heart Assoc 2019; 8(20):e012253. doi:10.1161/JAHA.119.012253
34. **Bunch TJ, May HT, Bair TL, et al.** Long-term influence of body mass index on cardiovascular events after atrial fibrillation ablation. J Interv Card Electrophysiol 2016; 46(3):259–265. doi:10.1007/s10840-016-0142-5
35. **Pathak RK, Middeldorp ME, Meredith M, et al.** Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). J Am Coll Cardiol 2015; 65(20):2159–2169. doi:10.1016/j.jacc.2015.03.002
36. **Gessler N, Willems S, Steven D, et al.** Supervised Obesity Reduction Trial for AF ablation patients: results from the SORT-AF trial. Europace 2021; 23(10):1548–1558. doi:10.1093/europace/euab122
37. **Mohanty S, Mohanty P, Natale V, et al.** Impact of weight loss on ablation outcome in obese patients with longstanding persistent atrial fibrillation. J Cardiovasc Electrophysiol 2018; 29(2):246–253. doi:10.1111/jce.13394
38. **Donnellan E, Wazni O, Kanj M, et al.** Outcomes of atrial fibrillation ablation in morbidly obese patients following bariatric surgery compared with a nonobese cohort [published correction appears in Circ Arrhythm Electrophysiol 2020; 13(2):e000047]. Circ Arrhythm Electrophysiol 2019; 12(10):e007598. doi:10.1161/CIRCEP.119.007598
39. **Romero-Corral A, Somers VK, Pellikka PA, et al.** Decreased right and left ventricular myocardial performance in obstructive sleep apnea. Chest 2007; 132(6):1863–1870. doi:10.1378/chest.07-0966
40. **Gami AS, Pressman G, Caples SM, et al.** Association of atrial fibrillation and obstructive sleep apnea. Circulation 2004; 110(4):364–367. doi:10.1161/01.CIR.0000136587.68725.8E
41. **Mehra R, Stone KL, Varosy PD, et al.** Nocturnal arrhythmias across a spectrum of obstructive and central sleep-disordered breathing in older men: outcomes of sleep disorders in older men (MrOS sleep) study. Arch Intern Med 2009; 169(12):1147–1155. doi:10.1001/archinternmed.2009.138
42. **Holmqvist F, Guan N, Zhu Z, et al.** Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation—results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J 2015; 169(5):647–654.e2. doi:10.1016/j.ahj.2014.12.024
43. **Naruse Y, Tada H, Satoh M, et al.** Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. Heart Rhythm 2013; 10(3):331–337. doi:10.1016/j.hrthm.2012.11.015
44. **Fein AS, Shvilkin A, Shah D, et al.** Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol 2013; 62(4):300–305. doi:10.1016/j.jacc.2013.03.052
45. **Mantovani A.** Nonalcoholic fatty liver disease (NAFLD) and risk of cardiac arrhythmias: a new aspect of the liver-heart axis. J Clin Transl Hepatol 2017; 5(2):134–141. doi:10.14218/JCTH.2017.00005
46. **Donnellan E, Cotter TG, Wazni OM, et al.** Impact of nonalcoholic fatty liver disease on arrhythmia recurrence following atrial fibrillation ablation. JACC Clin Electrophysiol 2020; 6(10):1278–1287. doi:10.1016/j.jacep.2020.05.023
47. **Aune D, Schlesinger S, Norat T, Riboli E.** Tobacco smoking and the risk of atrial fibrillation: a systematic review and meta-analysis of prospective studies. Eur J Prev Cardiol 2018; 25(13):1437–1451. doi:10.1177/2047487318780435
48. **Gémes K, Malmo V, Laugsand LE, et al.** Does moderate drinking increase the risk of atrial fibrillation? The Norwegian HUNT (Nord-Trøndelag Health) study. J Am Heart Assoc 2017; 6(10):e007094. doi:10.1161/JAHA.117.007094
49. **Giomi A, Bernardini A, Perini AP, et al.** Clinical impact of smoking on atrial fibrillation recurrence after pulmonary vein isolation. Int J Cardiol 2024; 413:132342. doi:10.1016/j.ijcard.2024.132342
50. **Fukamizu S, Sakurada H, Takano M, et al.** Effect of cigarette smoking on the risk of atrial fibrillation recurrence after pulmonary vein isolation. J Arrhythm 2010; 26(1):21–29. doi:10.1016/S1880-4276(10)80032-8
51. **Sagawa Y, Nagata Y, Miwa N, et al.** Alcohol consumption is associated with postablation recurrence but not changes in atrial substrate in patients with atrial fibrillation: insight from a high-density mapping study. J Am Heart Assoc 2022; 11(13):e025697. doi:10.1161/JAHA.121.025697
52. **Pathak RK, Elliott A, Middeldorp ME, et al.** Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals with Atrial Fibrillation: The CARDIO-FIT Study. J Am Coll Cardiol 2015; 66(9):985–996. doi:10.1016/j.jacc.2015.06.488
53. **Donnellan E, Wazni OM, Harb S, Kanj M, Saliba WI, Jaber WA.** Higher baseline cardiorespiratory fitness is associated with lower arrhythmia recurrence and death after atrial fibrillation ablation. Heart Rhythm 2020; 17(10):1687–1693. doi:10.1016/j.hrthm.2020.05.013
54. **Mishima RS, Ariyaratnam JP, Pitman BM, et al.** Cardiorespiratory fitness, obesity and left atrial function in patients with atrial fibrillation. Int J Cardiol Heart Vasc 2022; 42:101083. doi:10.1016/j.ijcha.2022.101083
55. **Elliott AD, Verdicchio CV, Mahajan R, et al.** An exercise and physical activity program in patients with atrial fibrillation: the ACTIVE-AF randomized controlled trial. JACC Clin Electrophysiol 2023; 9(4):455–465. doi:10.1016/j.jacep.2022.12.002
56. **Pathak RK, Middeldorp ME, Lau DH, et al.** Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol 2014; 64(21):2222–2231. doi:10.1016/j.jacc.2014.09.028

Address: *Jack Hartnett, MB, BCh, BAO, MSc, Department of Cardiology, Mater Misericordiae University Hospital, Eccles Street, Dublin, Leinster D07 AX57 Ireland; jhartne@tcd.ie*

Cleveland Clinic

Improve Your Virtual Patient Visit Skills

Many patients are eager to visit their physicians virtually, but not all physicians are comfortable conducting virtual visits.

You can take advantage of a free series of self-directed online modules to help you build your virtual patient visit skills.

The free course offers:

- brief introduction to virtual visits
- guidance for demonstrating communication and empathy
- best practices for taking a patient history
- instructions for conducting a physical examination, based on organ system

To help you master the content, the free course includes many video demonstrations and knowledge checks throughout.

Visit clevelandclinic.org/virtual-training

With the exception of the physical examination module, these activities have been approved for *AMA PRA Category 1 Credit™*.

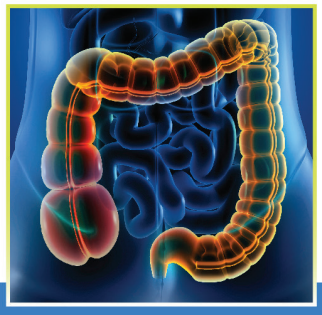
Cleveland Clinic
Florida

Save the Date

International Society for Fluorescence Guided Surgery
ISFGS

South Florida Chapter
ACS Chapters

International Colorectal Disease Symposium



An International Exchange of Medical and Surgical Concepts

February 13-15, 2025

Marriott Harbor Beach Resort & Spa, Fort Lauderdale, Florida

This activity is approved for *AMA PRA Category 1 Credits™*, ANCC Contact Hours, and AAPA Category 1 Credits.

www.ccfcme.org/ICDS2025

Cleveland Clinic

CME & MOC Credits Available

Cleveland Clinic Gut Insights: Exploring the Latest in Gastroenterology

March 17-18, 2025

Margaritaville Hollywood Beach Resort
Hollywood, Florida

www.ccfcme.org/GUT2025

How to earn *AMA PRA Category 1 Credit*™ and ABIM MOC points

AMA/PRA Category 1 Credit™

To read articles as CME activities and claim credit, go to www.ccjm.org, click on the "CME/MOC" menu, and then "Articles." Find the articles that you want to read as CME activities and click on the appropriate links. After reading an article, click on the link to complete the activity. You will be asked to log in to your MyCME account (or to create an account). Upon logging in, select "CME," complete the activity evaluation, and print your certificate.

Call 216-444-2661 or e-mail ccjm@ccf.org with questions.

Maintenance of Certification (MOC) Points

All *Cleveland Clinic Journal of Medicine* CME activities are eligible for ABIM MOC points. Physicians may claim MOC points in addition to CME credit.

Follow the instructions for completing and claiming credit for CME activities.

When you log into your MyCME account, select "CME & MOC" and enter your ABIM identification number and your date of birth. The system will store this information after you enter it the first time.

Complete the quiz and evaluation and print your CME certificate.

January 2025 CME/MOC activity:

Estimated time to complete the activity: up to 1 hour

Insomnia in older adults: A review of treatment options

Release date: January 1, 2025
Expiration date: December 31, 2025

FINANCIAL DISCLOSURES: In accordance with the Standards for Integrity and Independence issued by the Accreditation Council for Continuing Medical Education (ACCME), The Cleveland Clinic Center for Continuing Education mitigates all relevant conflicts of interest to ensure CE activities are free of commercial bias.

AUTHOR AND STAFF DISCLOSURES: Authors' potential conflicts of interest are disclosed within their articles. *Cleveland Clinic Journal of Medicine's* staff disclose the following financial relationships that may be relevant to their editorial roles: Dr. Brian F. Mandell (Editor in Chief) reports teaching and speaking for Genentech; and consulting for Horizon Pharma. Dr. Kristin Highland (Associate Editor) has disclosed financial interests (consulting, research, teaching, and speaking) with Actelion Pharmaceuticals, Bayer Healthcare, Boehringer Ingelheim, Eiger Biopharmaceuticals, Gententech, Gossamer Bio, Lilly, Reata Pharmaceuticals, United Therapeutics, and Viela Bio. Dr. Christian Nasr (Associate Editor) reports service on advisory committees or review panels for Exelixis, Horizon Pharma, Neurogastrx, and Nevro Corp.; and consulting for Siemens.

DISCLAIMER: The information in these educational activities is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options of a specific patient's medical condition. The viewpoints expressed in these CME activities are those of the authors. They do not represent an endorsement by The Cleveland Clinic Foundation. In no event will The Cleveland Clinic Foundation be liable for any decision made or action taken in reliance upon the information provided through these CME activities.

CME ACCREDITATION:
In support of improving patient care, Cleveland Clinic Center for Continuing Education is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Cleveland Clinic Center for Continuing Education designates this journal-based CME activity for a maximum of *1.0 AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Participants claiming CME credit from this activity may submit the credit hours to the American Osteopathic Association for Category 2 credit.

AMERICAN BOARD OF INTERNAL MEDICINE (ABIM):
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Please Note: To receive MOC you must select the MOC option during the online credit claiming process and complete the required steps. ABIM MOC points will be reported within 30 days of claiming credit.