

This supplement was sponsored by Primary Care Respiratory Group, Primary Care Education Consortium and Primary Care Metabolic Group.

The articles were previously published in *Federal Practitioner*®.

Copyright © 2024
Frontline Medical Communications Inc.

A SPECIAL SUPPLEMENT ON
HOT TOPICS
in Primary Care
2024

**S1 Case Studies in Continuous
Glucose Monitoring**

Eden M. Miller, DO

FREE
1.0 CME CREDIT

**S7 Detection and Diagnosis of Early
Symptomatic Alzheimer's Disease
in Primary Care**

Dani Cabral, MD; Thomas O. Obisesan, MD, MPH

**S13 Elevating the Importance of Asthma Care
in the United States**

Gary C. Steven, MD, PhD, CPI, FAAAAI, FAAAAI, FAPCR;
Neil Skolnik, MD; Mike Devano, MD;
Wendy L. Wright, DNP, ANP-BC, FNP-BC, FAANP, FAAN, FNAP;
Maureen George PhD, RN, AE-C, FAAN

**S23 Hypercortisolism Is More Common
Than You Think—Here's How to Find It**

Pamela Kushner, MD, FAAFP; David R. Brown, MD, PhD;
Robert S. Busch, MD, FACE

**S29 Improving COPD Management at
Transitions of Care**

Alan Kaplan, MD, CCFP(EM) FCFP CPC(HC)

**S35 Improving Patient-Centric
COPD Management**

Barbara P. Yawn, MD, MSc, FAAFP

**S41 The Role of Finerenone in Optimizing
Cardiovascular-Kidney-Metabolic Health:
Everything PCPs Should Know**

Eugene E. Wright Jr, MD;
Richard B. Frady, DNP, APRN, ACNP-BC, CCRN-CMC;
Chigozie Uko, DNP, APRN, FNP-C

**S47 What Primary Care Clinicians Need
to Know About Once-Weekly Insulins**

Jay H. Shubrook, DO

FREE
1.0 CME CREDIT

FREE
1.0 CME CREDIT

Introduction

Primary care clinicians are often challenged to stay abreast of the vast scope of diseases we are expected to manage. To help you stay updated on the latest advances in key areas of primary care, *Hot Topics in Primary Care 2024* compiles targeted articles on key disease states relevant to your practice.

Most patients with diabetes are managed in primary care settings, and several articles discuss important aspects of diabetes care, such as advances in continuous glucose monitoring (CGM) and a review the potential role of once-weekly insulins. You'll also find a discussion on optimizing cardiovascular-kidney-metabolic health for patients with or at risk for these complications.

Updates in chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and asthma, are discussed in detail, reflecting their frequent occurrence in primary care settings. You'll find updated treatment approaches and evidence-based decision-making strategies to enhance patient-centered care, transitions of care, and management across the disease continuum.

You'll also explore the nuances of detecting, diagnosing, and referring patients with hypercortisolism, a condition that can often be challenging to diagnose and manage in primary care. You'll find details about recognizing signs and symptoms, as well as guidance on how to best screen

and refer patients for specialty care. Furthermore, you'll have the opportunity to review detailed information about best practices for identifying and diagnosing Alzheimer's disease, which is frequently missed or misdiagnosed.

Each piece in this special issue is crafted to offer practical, actionable insights that can be readily applied to improve patient outcomes in your health care setting. Whether you are seeking to expand your knowledge of cardiometabolic diseases, review the latest in CGM technology, better detect hypercortisolism, improve your ability to diagnose Alzheimer's disease, or refine your approach to managing respiratory diseases like COPD and asthma, this supplement offers the tools and information to support your ongoing commitment to delivering high-quality primary care.

We hope that this collection of articles in *Hot Topics in Primary Care 2024* will serve as a valuable resource for your practice.

May you and your patients enjoy continued well-being and health.

Stephen Brunton, MD, FAAFP, CDCES
Executive Vice President
Primary Care Education Consortium

Case Studies in Continuous Glucose Monitoring

Eden M. Miller, DO

Fed Pract. 2024;41(suppl 6):S1-S6. doi:10.12788/fp.0529

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Comfortably prescribe continuous glucose monitoring (CGM) for all appropriate patients.
- Recognize patterns shown in the ambulatory glucose profile (AGP) that may create challenges for the treatment plan.
- Modify the treatment plan based on CGM data to improve patient outcomes and increase time in range (TIR).
- Recognize and address treatment disparities in an effort to make CGM more accessible to patients.

KEY TAKEAWAYS

- Use of CGM is an important consideration for treating all patients with diabetes, including those with type 2 diabetes who are not taking insulin.
- Clinicians should select patients who are candidates for CGM based on their clinical characteristics, ability to access the equipment and supplies, and willingness to use CGM.
- Accurately interpreting the AGP, including metrics such as TIR, is necessary for making treatment decisions based on CGM data.
- Clinicians should seek to be aware of Medicare requirements for CGM coverage and reimbursement, including billing codes for CGM.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge of and greater competency regarding primary care management of diabetes.

DISCLOSURES

As a continuing medical education provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), Primary Care Education Consortium (PCEC) requires any individual in a position to influence educational content to disclose any financial interest or other personal relationship with any commercial interest. This includes any entity producing, marketing, reselling, or distributing health care goods or services consumed by, or used on, patients. Mechanisms are in place to identify and mitigate any potential conflict of interest prior to the start of the activity. All relevant financial relationships have been mitigated. In addition, any discussion of off-label, experimental, or investigational use of drugs or devices will be disclosed by the faculty.

Eden M. Miller, DO, discloses that she serves on the advisory board and/or speakers bureau for Abbott, Bayer, Boehringer Ingelheim-Lilly, Insulet, and Novo Nordisk.

SPONSORSHIP

This article is sponsored by Primary Care Education Consortium and Primary Care Metabolic Group.

ACCREDITATION

The Primary Care Education Consortium (PCEC) is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION

Primary Care Education Consortium designates this enduring material for a maximum of 1.0 AMA PRA Category 1 credit(s)[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

PA's AND NURSE PRACTITIONERS

AANP, ANCC, and AAPA accept certificates of participation from educational activities certified for AMA PRA Category 1 Credit[™] from organizations accredited by ACCME.

CME is available from November 1 2024 to Oct 31, 2025.

To receive credit: Visit <https://www.pcmg-us.org/survey/fu/cgmht2024>



ADDITIONAL RESOURCES

Visit <https://www.pcmg-us.org/toolkit/cgm> for a resource toolkit. All the links noted in the article are available from the toolkit webpage.



FACULTY

Eden M. Miller, DO, Founder, Diabetes and Obesity Care, Bend, Oregon.

ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, at Primary Care Education Consortium.

SUPPORTER

This article is supported by an educational grant from Abbott Diabetes Care.

INTRODUCTION

The usefulness and benefits of continuous glucose monitoring (CGM) are increasingly recognized in evaluating and treating patients with diabetes. The American Diabetes Association (ADA) recommends that patients diagnosed with

diabetes that requires insulin management should be offered CGM at the outset of treatment.¹ Data from a recent systematic review and meta-analysis also indicate that patients with type 2 diabetes (T2D) without insulin treatment may benefit from CGM use.² CGM allows clinicians and patients to move

beyond traditional self-monitoring of blood glucose, with access to more data obtained outside of the clinic, and more insights into patients' blood glucose patterns. Once the data are obtained, however, the clinician must act on the information for it to be of benefit to the patient.

Recognized benefits of CGM to patients include opportunities for increased engagement with their own disease; ability to predict future glucose trends using the rate of change arrows on CGM devices, which show the direction and rate of glucose changes; recognition of the glycemic effects of food, time of day, activity level, and illness; and peace of mind for loved ones or caregivers.³ For clinicians, CGM benefits include increased patient engagement, better hypoglycemic awareness that can improve prevention, greater insight into therapeutic impacts on glucose management, and use of automated documentation to aid in data visualization.⁴ Additionally, in patients for whom glycated hemoglobin (HbA1c) measurements are less reliable, such as those with hemoglobinopathies, CGM is a valuable option for assessing glycemic control.⁵

Candidates for CGM. Identifying the right patient for CGM is critical. Patients who are candidates for CGM might include those ≥ 2 years of age who need or want more engagement with their diabetes, those who are at risk for hypoglycemia (eg, patients of younger or older age, patients taking insulin), those who need modification of current treatment or are experiencing clinical inertia, and those with poorly managed diabetes who would benefit from greater understanding of diet, activity, and medication on glycemic management.⁶

Assessing whether a patient is a good candidate for CGM might involve asking 3 questions to determine accessibility and utility:

- Will my patient have insurance coverage for a CGM device or be able to afford it?
- Is my patient willing to wear a CGM device?
- Is my office ready to take full advantage of the wealth of information CGM can offer?

Currently approved CGM devices. Two general categories of CGM devices are currently approved by the US Food and Drug Administration (FDA): personal and professional (TABLE 1).⁷ Personal devices are patient owned and can be used daily. They can be stand-alone devices or link to other compatible devices (such as insulin pumps). Professional CGM devices are owned by the clinician and loaned to the patient, and some are approved for multiple uses when cleaned and used according to labeling. Professional devices tend to be used for a shorter duration (3–14 days) than personal CGM devices, which can be used

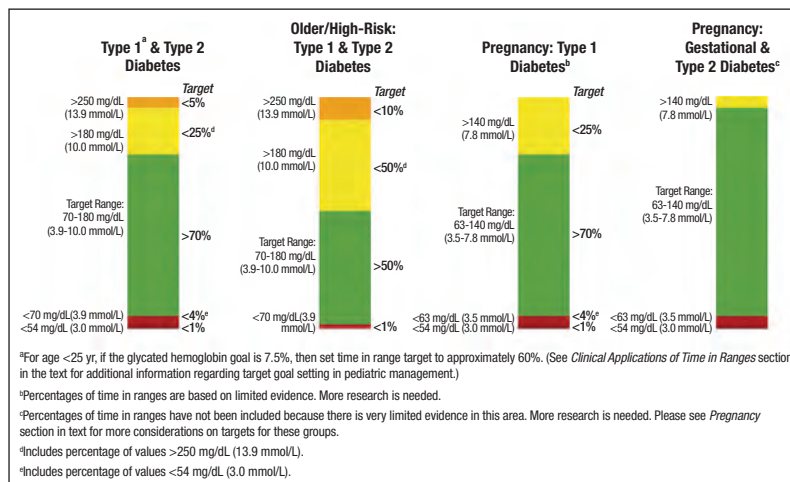
indefinitely as long as the patient obtains supplies. Professional CGM devices can be set to have the data “blinded” or “unblinded” to the patient, depending on the scenario.¹

Interpreting the AGP. The ambulatory glucose profile (AGP) is a report detailing the patient's blood glucose trends. Further explanation of this report will be illustrated later in the article in the context of the case studies. Glucose profile metrics included in the AGP include ideal time in range (TIR) depending on patient characteristics (FIGURE 1).⁸ Generally, there are 9 steps that can be applied to successful AGP interpretation⁹:

1. Download and print AGP report
2. Check for adequate data (70% active sensor time over 14 days)
3. Look for patterns of low glucose levels/hypoglycemic risk
4. Look for patterns of high glucose levels
5. Look for areas of wide glucose variability/range of glucose values (glycemic variability target $\leq 36\%$)
6. Determine appropriate TIR
7. Ask the patient what they see when they look at the AGP
8. Discuss potential solutions and agree on an action plan based on the AGP
9. Mark the AGP report and copy at the end of the visit for the patient

Selected CGM studies. A retrospective, observational study presented at the 80th ADA scientific sessions in 2020 evaluated the change in HbA1c at 6 and 12 months in patients with T2D after starting CGM.¹⁰ The 2 patient groups were those taking long-acting insulin and those on non-insulin treatment. Adults who had a baseline HbA1c $\geq 6.5\%$ within 6 months prior

FIGURE 1. CGM-based blood glucose targets for different populations with diabetes, according to the International Consensus on Time in Range⁸



Source: Battelino T, Danne T, Bergenstal RM, et al. *Diabetes Care*. 2019;42(8):1593–1603. Reprinted with permission of the American Diabetes Association, Inc. Copyright 2019.

TABLE 1. FDA-approved personal and professional CGM devices⁷

Personal CGM devices				
	Abbott FreeStyle Libre 14-day/2 and 2 Plus/3	Dexcom G6/G7/ Stelo	Medtronic Guardian Sensor 3 and 4 (pump integrated) and Guardian Connect (stand-alone)	Senseonics Eversense
Approved labeling	Replaces fingersticks for treatment decisions; no fingerstick calibration required	Replaces fingersticks for treatment decisions; no fingerstick calibration required	Requires ≥2 fingerstick calibrations/d	Replaces fingersticks for treatment decisions; requires 1 fingerstick calibration/d after 21 d
Age	≥18 y/≥2 y	≥2 y	≥14 y/≥7 y	≥18 y
Medicare coverage	Yes/Yes	Yes	Sensor 3/4: Yes Connect: No	Yes
Wear length	14 d/2 and 3 – up to 15 d new 2 plus	10 d	7 d	90–180 d
Warmup	1 h	2 h/27 min	2 h	24 h after implantation
Alarms	No/Yes	Yes	Yes	Yes
Data display/integration	Reader; Android, iPhone apps; Libre 2 plus integrated with Tandem (Pending integration with Omnipod 5 in 2024)	Reader; Android, iPhone apps; smartwatches; Tandem pump, iLet (Pending Omnipod 5 in 2024)	630G, 670G, 770G, 780G pump (Sensor 4 only); Guardian Connect; Android, iPhone apps	Android, iPhone apps
Form	Disposable transmitter integrated with sensor patch	G6: Transmitter (3-month use) separate from sensor/G7 integrated transmitter	Transmitter (rechargeable) separate from sensor	Transmitter (rechargeable) separate from sensor
Accuracy^a	3=7.9% (others less accurate)	9%/8.2%	9.6%/9%–11%	8.5%–9.5%
Professional CGM devices				
	Abbott FreeStyle LibrePRO	Dexcom G6 Pro	Medtronic IPro 2	—
Blinded or unblinded	Blinded	Either	Blinded	—
Wear time	14 d	10 d	6 d	—
Calibration	0	0	3–4 times daily	—
Care between use	Disposable sensor/transmitter	Disposable sensor/transmitter	Sensor must be cleaned and disinfected	—
Insertion	Single-step process with auto-inserter	Two-step process that includes inserting sensor and attaching transmitter	Multistep process that includes inserting and taping both the sensor and transmitter	—
Site	Upper arm	Abdomen	Abdomen	—
Downloading/data reports	LibreView (download in office)	Blinded: Clarity (download in office) Unblinded: apps only	Carelink (download in office)	—

^aAccuracy measured by mean absolute relative difference relative to venous glucose; lower values mean the CGM is more accurate. Accuracy figures provided by manufacturers.

Abbreviations: CGM, Continuous glucose monitoring; FDA, US Food and Drug Administration.

to the index date were included. Significant reductions in HbA1c were observed for both groups at 6 and 12 months.¹⁰ After 6 and 12 months of CGM use, HbA1c was reduced by 0.8% (n=774) and 0.6% (n=207), respectively. Patients in the non-insulin group experienced a greater reduction in HbA1c at 6 months (0.9%, n=497) and 12 months (0.7%, n=120) com-

pared to the overall population ($P < .0001$).

In a randomized trial, Martens et al evaluated the effectiveness of CGM in adults with T2D treated with basal insulin (without prandial insulin) in primary care practice.¹¹ The trial took place from July 2018 to July 2020, and patients were randomly assigned 2:1 to CGM (n=116) or traditional blood glu-

cosse meter (BGM) monitoring (n=59). Among participants who completed the trial (n=165), mean baseline HbA1c was 9.1%. The mean HbA1c at 8 months decreased to 8.0% in the CGM group and 8.4% in the BGM group (adjusted difference, -0.4%; 95% CI, -0.8% to -0.1%; $P=.02$). Compared with BGM, adults with T2D using a CGM device had significantly lower HbA1c levels at 8 months.¹¹

Coverage and billing codes. To effectively implement CGM within practice settings, clinicians must be aware of CGM coverage (primarily Medicare criteria) and billing codes for CGM. Relevant CGM billing codes are reviewed in **TABLE 2**.^{12,13}

Medicare criteria when ordering CGM include the following¹⁴:

- Patient has diagnosis of diabetes
- Patient is insulin treated with at least 1 injection daily, has had an acute related diabetes event, or has a chronic condition that puts them at risk for hypoglycemia (no documentation of fingerstick required)
- Insulin regimen requires frequent adjustments on basis of CGM data
- Clinic visit within 6 months prior to ordering CGM to evaluate glucose control and determine that the above criteria are met
- Following initial prescription of CGM, in-person visit with clinician every 3–6 months to assess adherence to CGM regimen and diabetes treatment plan (document in chart as notes may be requested)

Note that for some patients, CGM may be covered under the Part B (durable medical equipment) Medicare benefit. The 2 case studies below illustrate examples of how CGM might be used in clinical practice.

CASE STUDY 1

67-year-old White man who has Medicare and lives in a rural area

Past medical history (PMHX): T2D (diagnosed at age 51), coronary artery disease (CAD), hypertension, obesity, hyperlipidemia, and kidney disease with macroalbuminuria

Labs: Stage 3a A3 kidney disease with proteinuria, HbA1c was 9.4% 2 months ago

Estimated glomerular filtration rate (eGFR), 57 mL/min/1.73 m²; urine albumin-creatinine ratio (UACR), 460; weight, 312 pounds; height, 73 inches; body mass index (BMI), 41.5 kg/m²; blood pressure, 141/89 mm Hg

Medications:

- Metformin 1000 mg twice daily
- Glipizide 4 mg twice daily
- Dulaglutide 3 mg once weekly
- Empagliflozin 10 mg daily started approximately 3 months ago (no HbA1c testing since start of empagliflozin)
- Lisinopril 10 mg daily, fenofibrate 48 mg daily, aspirin 81 mg daily, simvastatin 40 mg daily
- Currently takes 2 injections of basal insulin per day (not FDA approved); insulin glargine 50 units in the morning and 65 units in the evening

Chief complaint: The patient would like “better results” with his T2D and comorbidities. He’d like better glycemic control and is interested in medication therapies that are specifically designed for his unique health care needs and comorbidities since he felt this wasn’t the case in the past. He notes that he has not typically had previous problems with hypoglycemia.

In this case scenario, the patient is a candidate for CGM. A professional CGM device was applied in office, with instructions for the patient to begin keeping a record of how his life-

TABLE 2. Codes for billing CGM^{12,13}

ICD Codes	Description
95249	Personal CGM—Startup/Training: Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; patient-provided equipment, sensor placement, hookup, calibration of monitor, patient training, printout, or copy of report (Do not report more than once while patient owns device)
95250	Professional CGM—Ambulatory continuous glucose monitoring of interstitial fluid via a subcutaneous sensor for a minimum of 72 hours; clinician-provided equipment, sensor placement, hookup, calibration of monitor, patient training, removal of sensor, and printout of recording (Do not report more than once per month)
95251	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; interpretation and report (Do not report more than once per month) May be billed separately or with an E & M visit in person or remote
99212–99215	Evaluation and Management (E/M) codes; established patient visit or G0463 (Medical Outpatient Clinic Visits)
0446T–0448T	Eversense-only codes 0446T: creation of subcutaneous pocket with insertion of implantable sensor, including system activation and patient education 0447T: removal of implantable sensor from subcutaneous pocket via incision 0448T: removal of sensor with creation of new pocket for new sensor at a different location, including system activation

Abbreviations: CGM, continuous glucose monitoring; E/M, evaluation and management.

FIGURE 2. Case study 1: AGP report at 3-week follow-up (A) and 6-month follow-up (B)

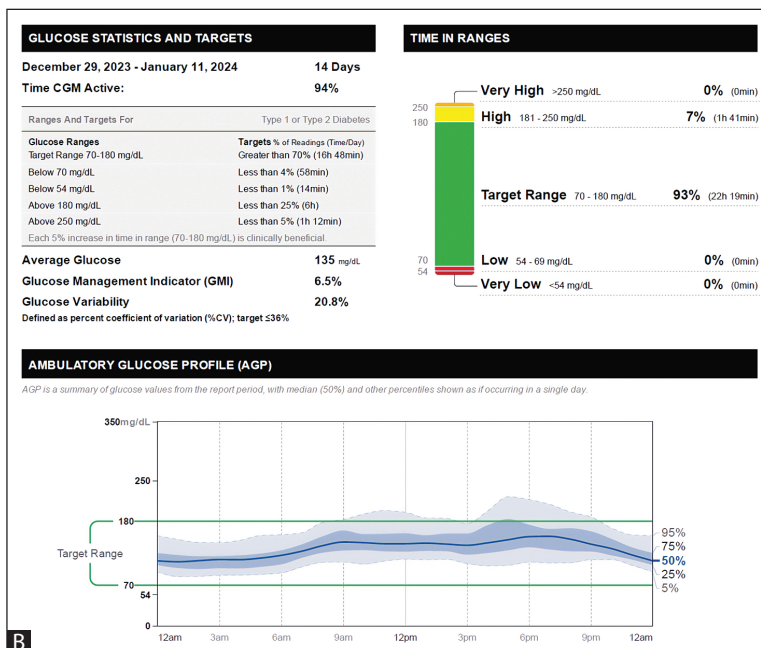


remained 57 mL/min/1.73 m². The patient had reached a dose of tirzepatide 15 mg once weekly and insulin glargine 108 units once daily. Note that on the 6-month follow-up AGP, his TIR is 93% compared to 54% at the 3-week follow-up (FIGURE 2).

CASE STUDY 2

42-year-old Asian woman with T2D
PMHx: T2D, microalbuminuria without hypertension, hyperlipidemia
At her last appointment with her primary care physician, initiation of insulin was discussed.

Labs: HbA1c, 8.2%; eGFR, 62 mL/min/1.73 m²; UACR, 34; Body mass index, 27.98 m/kg²; height, 62 inches; weight, 153 pounds; blood pressure, 121/89 mm Hg



Medications:

- Glipizide 4 mg twice daily
- Metformin 1000 mg twice daily
- Lisinopril 10 mg daily
- Stopped statin due to muscle aches
- Previous medications tried and discontinued include a sodium-glucose cotransporter-2 (SGLT-2) inhibitor (side effect: yeast infections) and dulaglutide (side effect: severe gastrointestinal heartburn)

Chief complaint: The patient is frustrated with her overall glucose control but does not want to take insulin. She doesn't have a lot of time and works all day with her hands (as a hairdresser), which makes it difficult to use a traditional self-monitoring blood glucose system.

The patient is willing to try a CGM device to help manage her T2D in addition to other medication changes. A CGM device was applied in the office, glipizide was discontinued, tirzepatide was

titrated to 7.5 mg once weekly over 3 months, dapagliflozin was started with perineal care instructions to avoid vulvar irritation, and the patient was engaged to be attentive to the effects of food, stress, and exercise on glycemia.

A review of 3-week follow-up AGP data (FIGURE 3) revealed to the patient that she had high blood sugar most of the time (time above range 89%). The patient could see that there were opportunities to improve her meal choices. At a 5-month follow-up, the patient's blood glucose demonstrated a significant clinical response to lifestyle intervention and medication change (FIGURE 3).

The AGP was reviewed 3 weeks after application, and the patient reported seeing the effects that food choices and exercise have on his glucose numbers (FIGURE 2). At the 6-month follow-up, his weight had decreased to 284 pounds, BMI to 37.47 kg/m², HbA1c to 6.7%, UACR to 123, and his eGFR

FUTURE DIRECTIONS

In addition to expanded CGM coverage expected in the future, clinicians can look forward to newer concepts in CGM use such as insulin pump integration and continuous glucose-ketone monitoring. There are currently several CGM and insulin pump devices that automatically adjust insulin dosing based on CGM measurements via integration to mitigate the risks of critical glucose episodes.^{15,16} Of note, several new over-the-counter CGM systems were recently approved in the US: Lingo (Abbott), Libre Rio (Abbott), and Stelo (Dexcom).

The need for continuous ketone monitoring has been recognized as potentially useful for certain conditions such as recurrent diabetic ketoacidosis, pregnancy, and anorexia, as well as during exercise, on sick days, and with medications that can increase the risk of diabetic ketoacidosis.¹⁷ Integration of continuous ketone monitoring and CGM in the same sensor platform is an important consideration for potential implementation of these concepts.¹⁷ Integrated CGM-ketone sensors are actively being studied in clinical trials, with 1 device receiving FDA breakthrough designation status. This technology may reach clinical practice in the next few years.

SUMMARY

Use of CGM is an important consideration for all patients with diabetes, including those with T2D who are not taking insulin. Before prescribing CGM, clinicians should consider both the patient's ability to successfully access the CGM device and supplies and their willingness to use CGM. Future advances in CGM might include expanded coverage, smaller and more accurate devices with better connectivity, and devices tailored to patients with T2D.

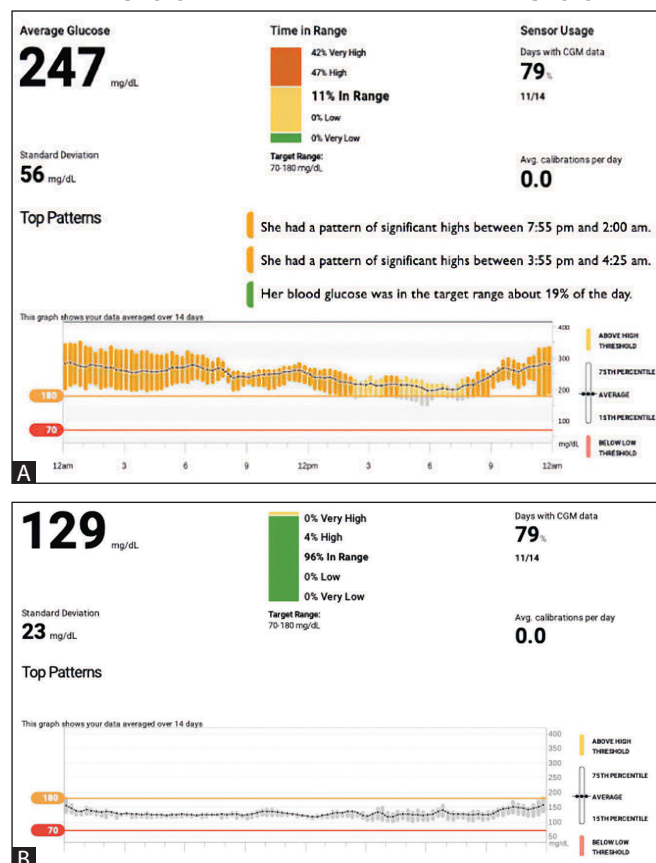
More information on CGM is available; a resource toolkit page can be found at <https://www.pcmg-us.org/toolkit/cgm>. This toolkit offers an array of links to help clinicians establish an effective CGM practice workflow. The toolkit also includes a webinar (offering additional CME credit), links to every source cited in this article, additional case studies, and explanations of AGPs, as well as specific information about device insertion, data access, and details on each device currently approved by the FDA. ●

REFERENCES

URLs must be entered manually, rather than copied and pasted.

- American Diabetes Association Professional Practice Committee; ElSayed NA, Aleppo G, Bannuru RR, et al. 7. Diabetes Technology: Standards of Care in Diabetes—2024. *Diabetes Care*. 2024;47(Suppl 1):S126–S144. doi:10.2337/dc24-S007
- Ferreira ROM, Trevisan T, Pasqualotto E, Chavez MP, Marques BE, Lamounier RN, van de Sande-Lee S. Continuous glucose monitoring systems in non-insulin-treated people with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Technol Ther*. Published online December 13, 2023. doi:10.1089/dia.2023.0390
- American Diabetes Association. Continuous glucose monitors. Accessed February 8, 2024. <https://diabetes.org/advocacy/cgm-continuous-glucose-monitors>
- Miller EM. Using continuous glucose monitoring in clinical practice. *Clin Diabetes*. 2020;38(5):429–438. doi:10.2337/cd20-0043
- Klonoff DC. Hemoglobinopathies and hemoglobin A1c in diabetes mellitus. *J Diabetes Sci Technol*. 2020;14(1):3–7. doi:10.1177/1932296819841698

FIGURE 3. Case study 2: AGP report at 3-week follow-up (A) and at 5-month follow-up (B)



Abbreviations: CGM, continuous glucose monitoring; GMI, glucose management indicator.

- Chamberlain JJ. Patient selection for continuous glucose monitoring. In: *Role of Continuous Glucose Monitoring in Diabetes Treatment*. American Diabetes Association; 2018. Accessed February 8, 2024. <http://www.ncbi.nlm.nih.gov/books/NBK538972>
- Professional Practice Committee, Association of Diabetes Care & Education Specialists. The Diabetes Care and Education Specialist's Role in Continuous Glucose Monitoring. Published online March 2021. Accessed February 8, 2024. <https://www.adces.org/docs/default-source/practice/practice-documents/practice-papers/diabetes-care-education-role-in-continuous-glucose-monitoring.pdf>
- Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. *Diabetes Care*. 2019;42(8):1593–1603. doi:10.2337/dci19-0028
- Used with permission of Richard Bergenstal, MD, International Diabetes Center.
- Miller E, Wright E. HbA1c Reduction after initiation of the FreeStyle Libre System in type 2 diabetes patients on long-acting insulin or noninsulin therapy. Poster presented at: American Diabetes Association 80th Scientific Sessions; June 12-16, 2020; Poster 84-LB. Accessed February 8, 2024. <https://ada.scientificposters.com/epsAbstractADA.cfm?id=1>
- Martens T, Beck RW, Bailey R, et al. Effect of continuous glucose monitoring on glycemic control in patients with type 2 diabetes treated with basal insulin: a randomized clinical trial. *JAMA*. 2021;325(22):2262. doi:10.1001/jama.2021.7444
- Reimbursement. Ascensia Diabetes. Accessed February 8, 2024. <https://www.ascensiadabetes.com/eversense/health-care-professionals/reimbursement/>
- Adkison JD, Chung PE. Implementing continuous glucose monitoring in clinical practice. *Fam Pract Manag*. 2021;28(2):7–14
- Centers for Medicare & Medicaid Services. Glucose monitor—policy article A52464. Published online January 1, 2024. Accessed February 8, 2024. <https://www.cms.gov/medicare-coverage-database/view/article.aspx>
- Vettoretti M, Facchinetti A. Combining continuous glucose monitoring and insulin pumps to automatically tune the basal insulin infusion in diabetes therapy: a review. *Biomed Eng Online*. 2019;18(1):37. doi:10.1186/s12938-019-0658-x
- Association of Diabetes Care & Education Specialists (ADCES). Insulin pumps: understanding CGM & pump integration. ADCES. Published March 2021. Accessed March 22, 2024. <https://www.adces.org/danatech/insulin-pumps/training-clients-patients/cgm-pump-integration>
- Briskin A. Avoiding DKA with continuous ketone monitoring. *diaTribe*. Published April 3, 2023. Accessed March 22, 2024. <https://diatribe.org/avoiding-dka-with-continuous-ketone-monitoring-devices>

Detection and Diagnosis of Early Symptomatic Alzheimer's Disease in Primary Care

Dani Cabral, MD; Thomas O. Obisesan, MD, MPH

Fed Pract. 2024;41(suppl 6):S7-S12. doi:10.12788/fp.0530

KEY TAKEAWAYS

- Alzheimer's disease (AD) is commonly seen in primary care settings, and primary care clinicians (PCCs) are often the first to encounter patients presenting with cognitive impairment.¹
- Despite the high prevalence of AD in individuals aged 65 years and older, diagnosis is often delayed or missed, resulting in delayed treatment and negative impacts on patients, care partners, and health care systems.³
- Current diagnosis of AD is clinical-neuropathologic based both on clinical presentation as well as underlying neuropathology.²
- PCCs are critical in the detection and initial evaluation of patients with early symptomatic AD.²

FACULTY

Dani Cabral, MD, Assistant Professor, Departments of Neurology and Psychiatry, University of Arizona, Tucson.

Thomas O. Obisesan, MD, MPH, Professor of Medicine and Geriatrics, Department of Medicine, Howard University, Washington, DC.

DISCLOSURES

Dr. Cabral serves on the speakers' bureau and advisory board of Eisai Pharmaceuticals and on the advisory boards of Eli Lilly and Company, Otsuka, and Roche/Genentech. Dr. Obisesan serves as a member of the advisory boards of Eisai Pharmaceuticals, Eli Lilly and Company, and Roche/Genentech. Austin Ulrich,

PharmD, BCACP, has no disclosures to report.

ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, at Primary Care Education Consortium.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium.

SUPPORTER

This activity is supported by funding from Eli Lilly and Company.

INTRODUCTION

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disease that affects cognition, behavior, and function.^{1,2} AD is a highly prevalent disease in the United States and presents a continually increasing health care challenge as the size of the aging population grows.³ The population of Americans aged 65 years and older is projected to increase from 58 million in 2022 to 82 million in 2050, resulting in a higher number of individuals with AD and other dementias, as the risk for dementia increases with advancing age.³ Mortality rates are higher in people with dementia due to AD, and AD is the fifth-leading cause of death for people in the United States aged 65 years and older (2021 data).³ Inaccurate, delayed, or generalized diagnoses (eg, dementia unspecified) can result in less time for care planning, inappropriate or insufficient disease management, higher health care costs and utilization, and a negative impact on the individual's and care partner's mental and physical health. Estimates suggest that diagnosing AD in the early stages could save approximately \$7 trillion in medical and long-term care costs, based on patients who were alive in 2018 and would develop AD.³

Despite the substantial and increasing burden of AD,

patients remain underdiagnosed by clinicians in multiple settings, including primary care.³ Outside research, a high proportion of patients who meet the diagnostic criteria for AD are not diagnosed; eg, as many as 8 million people in the US may have undiagnosed mild cognitive impairment (MCI) (though not all individuals with MCI develop dementia).¹ Based on claims data, of those patients covered by Medicare with a diagnosis of AD or other dementia, only half were made aware of their diagnosis by their clinician.² Delayed diagnosis and underdiagnosis can result in potential harms, necessitating a change in approach to early evaluation and diagnosis of AD.³

Primary care clinicians (PCCs) are often the first to encounter patients with symptoms of cognitive impairment that could be detected during a routine medical visit.¹ The current diagnostic process to evaluate patients presenting with cognitive decline is complex and varies across health-care settings.^{4,5} It is vital for PCCs to recognize early signs and symptoms of AD, use appropriate assessment tools, and refer patients with suspected AD for further workup, including imaging and biomarker testing; this could potentially result in earlier disease management.^{1,2,6} The focus of this article

will be on early symptomatic AD, which is inclusive of MCI due to AD and mild dementia due to AD.

CASE STUDY

A 67-year-old Black woman presents to her PCC for an annual wellness visit. She reports cognitive concerns she has been having for the past year. She works part-time as an insurance agent and has noticed some difficulty managing multiple tasks associated with her job. She is feeling more stress than in the past about completing tasks accurately. Her supervisor has not mentioned anything related to her work performance, but her husband has noted she seems more stressed at home. The patient denies any recent changes in mood or sleep and has no other identifiable new psychosocial stressors.

Current medications: lisinopril 20 mg once daily, atorvastatin 10 mg once daily.

Past medical history: hypertension, hyperlipidemia, osteoarthritis.

Social history: She lives with her husband and has 3 grown children. She occasionally drinks alcohol (1 to 2 drinks per week) and does not use tobacco products or recreational drugs. She exercises 3 days per week for 60 minutes at a gym.

Family history: The patient's mother was diagnosed with dementia in her 70s and died at age 78 of stroke. Her father died at age 70 of a myocardial infarction. She has 2 siblings aged 69 and 74 years with no known cognitive or neurologic issues.

Physical exam: Blood pressure 128/86 mm Hg, heart rate 68 beats per minute, other vital signs stable, body mass index 28 kg/m², no focal neurologic findings.

Cognitive testing in the office¹: The Montreal Cognitive Assessment (MoCA) score is 25 (out of 30); the patient missed all 5 points on delayed recall. The MoCA Memory Index Score (MIS) is 8 (out of 15). The patient does not have depression as assessed by the Patient Health Questionnaire-9 (PHQ-9).

Laboratory evaluation: Complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone, vitamin B12, and glycated hemoglobin (HbA1c) are all unremarkable.

Imaging: Brain magnetic resonance imaging (MRI) without gadolinium contrast shows mild diffuse atrophy with mild bihippocampal atrophy and mild subcortical white matter hyperintensities. Ventricular size is consistent with diffuse brain atrophy.

The patient in the case scenario is referred by her PCC for evaluation by a neurologist based on history, cognitive testing, and brain imaging suggestive of MCI due to AD. The patient denied symptoms (other than those previously stated) and did not present with signs of other types of dementia. The neurologist ordered an amyloid positron emission tomography (PET)

scan that was consistent with a diagnosis of MCI due to AD, thus confirming the initial diagnostic impression of the PCC.

PREVALENCE OF AD AND UNMET NEED

Prevalence of AD

Recent estimates suggest that 6.9 million adults aged 65 years and older in the US have AD, which is about 1 in 9 individuals in that age group.³ Additionally, low proportions of patients with dementia (11%) or AD (24%) have cognitive testing documented in electronic medical records within the 5 years before diagnosis, contributing to potential underreporting of cognitive symptoms and further raising concerns for underdiagnosis.^{7,8}

Early-onset AD is defined as AD occurring in individuals younger than 65 years of age and is relatively rare; it is not the focus of this discussion.³ The lifetime risk for AD is higher for women than men (1 in 5 vs 1 in 10, respectively).³ Additionally, Black older adults are twice as likely and Hispanic older adults are 1 to 1.5 times as likely to have AD and other dementias compared with White older adults.³ Black and Hispanic populations are often diagnosed later at more advanced stages.^{3,9} These facts underscore the need for a timely and accurate diagnosis across population groups.

Unmet need in AD

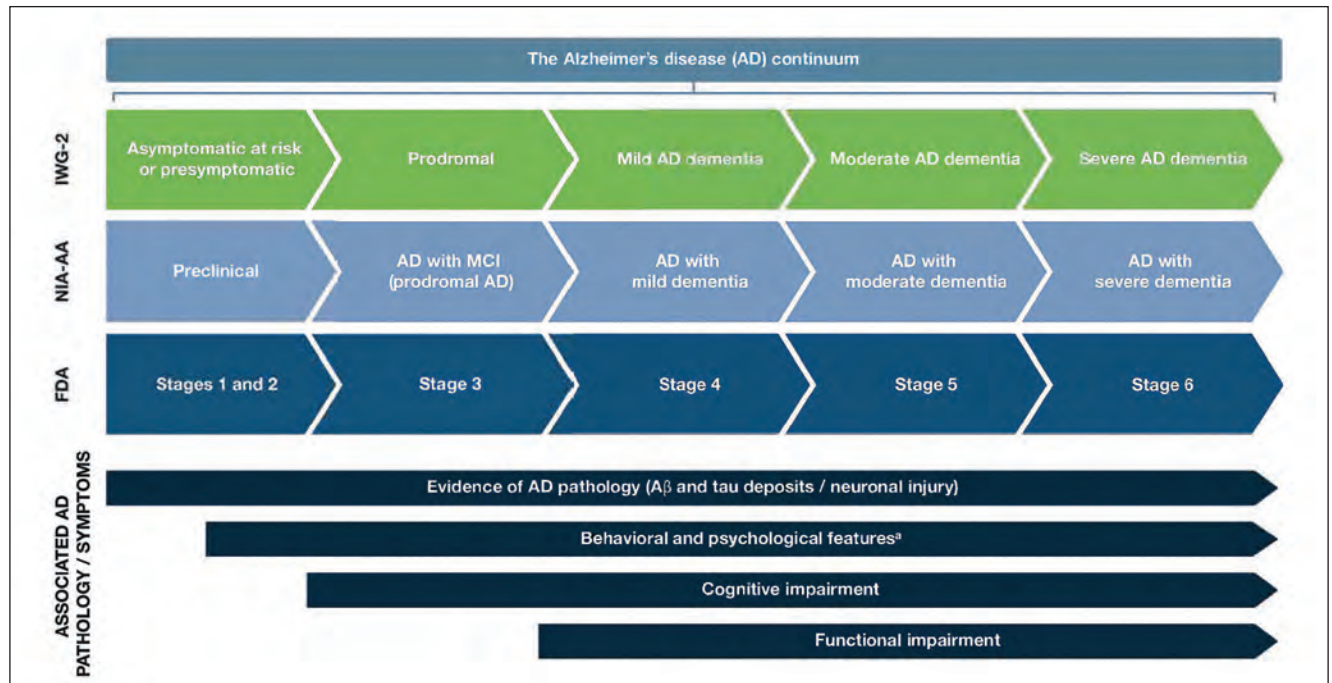
Underdiagnosis of AD is most common in the early stages of the disease when symptoms are mild, leading to low rates of MCI diagnosis.³ Estimates suggest that as few as 8% of older Americans who have MCI receive a formal diagnosis.³ Furthermore, rates of dementia misdiagnosis are estimated to be as high as 35% in specialty clinics, especially when biomarkers are not used.¹⁰ Historically, AD diagnosis has been one of exclusion, made usually in the later stages of the disease, and therefore, years after the initial development of symptoms.¹ Many conditions may have more overt symptoms than early symptomatic AD, competing for clinicians' attention during clinic visits.

The benefits of early AD diagnosis for patients, care partners, and clinicians include an explanation of signs and symptoms the patient is experiencing, time for care partners to adjust to their role, opportunities for early intervention, better management of symptoms, and postponement of advanced care needs.^{5,11,12}

AD DEFINITIONS AND STAGES

AD follows a progressive continuum, and staging terminology varies based on the professional organization, government authority, or group that develops models of AD progression. However, they all agree on the presence and detection of pathology and the timing and severity of clinical features across the disease continuum (**FIGURE 1**).¹ According to the National Institute on Aging—Alzheimer's Association (NIA-AA), there is a long asymptomatic phase in which clinical manifestations of cognitive or functional decline are

FIGURE 1. The Alzheimer's disease continuum and stages according to clinical and research classifications¹



Abbreviations: A β , amyloid beta; AD, Alzheimer's disease; FDA, Food and Drug Administration; IWG, International Working Group; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging—Alzheimer's Association.

The AD continuum can be classified into different stages from preclinical AD to severe AD dementia; the nomenclature associated with each stage varies between the different clinical and research classifications. This figure provides a summary of the different naming conventions that are used within the AD community and the symptoms associated with each stage of the continuum.

^aMild behavioral impairment is a construct that describes the emergence of sustained and impactful neuropsychiatric symptoms that may occur in patients \geq 50 years old prior to cognitive decline and dementia.

Source: Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of early Alzheimer's disease: clinical practice in 2021. *J Prev Alzheimers Dis.* 2021;8(3):371-386. Figure licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction. The license can be viewed at this link: <https://creativecommons.org/licenses/by/4.0/legalcode>

not evident; however, AD pathology may be present for 10 to 20 years before symptom onset.^{1,13} Patients may then progress to MCI due to AD, where cognition is impacted but their ability to complete instrumental activities of daily living (iADLs) and basic activities of daily living (ADLs) are essentially preserved.^{1,13} ADLs include core daily tasks such as eating, dressing, and bathing, while iADLs are more complex tasks, such as preparing meals, managing finances, and doing housework.¹⁴ Once patients progress to mild dementia due to AD, functional impairment in iADLs becomes more evident and then progressively worsens over time. During the next phases of AD, the disease impacts ADLs, and patients become increasingly dependent and require more advanced care.^{1,13}

RISK FACTORS FOR AD

Knowledge of risk factors associated with AD may support more timely detection. Lifestyle risk factors for AD include a sedentary lifestyle, poor diet, stress, poor sleep, social isolation, loneliness, and smoking. Environmental factors, such as air pollution and adverse social determinants of health, may

also have an impact.^{3,12} Chronic diseases, such as diabetes, hypertension, and overweight or obesity, are correlated with an increased risk for dementia.^{3,12}

Genetic risk factors for AD have also been identified. The most well-known and common genetic risk factor associated with AD is the apolipoprotein E (*APOE*) gene. *APOE*-e4 is correlated with an increased risk for developing AD.³ Notably, individuals with 1 copy of *APOE*-e4 (heterozygous) are at higher risk for AD, and those with 2 copies of *APOE*-e4 (homozygous) are at even higher risk.³ Among patients aged 65 to 69 years, the risk for dementia by the early to mid-80s is estimated to be up to 7% with no copies of *APOE*-e4, up to 16% with 1 copy, and up to 40% in those with 2 copies.³ The number of copies of *APOE*-e4 also plays a role in inheritance patterns.³ Other genes have also been shown to increase the risk for AD, particularly in very rare and early-onset forms of AD.³

NEUROPATHOLOGY OF AD

AD is characterized by 2 underlying neuropathologic hallmarks: amyloid plaques and tau neurofibrillary tangles

(NFTs). Extracellular beta-amyloid plaques and intracellular NFTs accumulate over time, leading to inflammation, synaptic dysfunction, and progressive neurodegeneration. Amyloid plaques form 10 to 20 years prior to symptom onset, whereas NFTs develop 5 to 10 years prior to cognitive symptoms.^{1,3,13}

Historically, prior to progress with in vivo biomarkers, the diagnosis of AD was considered either clinical (using primarily clinical data) or neuropathologic (formulated post-mortem by demonstrating corresponding neuropathologic changes). However, recent guidance supports the concept of a clinical-neuropathologic diagnosis.^{2,15} Thus, an accurate diagnosis of AD requires clinical evaluation of history, risk factors, signs and symptoms, physical examination, and cognitive assessment, as well as biomarker testing to identify underlying neuropathologic changes.² Due to variable accessibility and specificity of testing, biomarker testing is often conducted after the patient has been referred to a dementia care specialist and can include amyloid PET scans, cerebrospinal fluid (CSF) testing, and/or plasma analysis.²

CLINICAL AND NEUROPATHOLOGIC DIAGNOSIS OF AD

PCCs are often the first health care providers in a multidisciplinary care team to see patients presenting with cognitive impairment. This enables them to identify early symptomatic AD at the first signs and symptoms of cognitive decline.² Distinguishing between deficits in ADLs and iADLs can help identify early symptomatic AD.¹⁴ The level of functional impairment related to iADLs is a core clinical distinction between MCI and dementia.¹⁴

However, due to insidious and variable presentations, distinguishing changes associated with normal cognitive aging vs MCI or mild dementia due to AD can be difficult (TABLE).^{2,16}

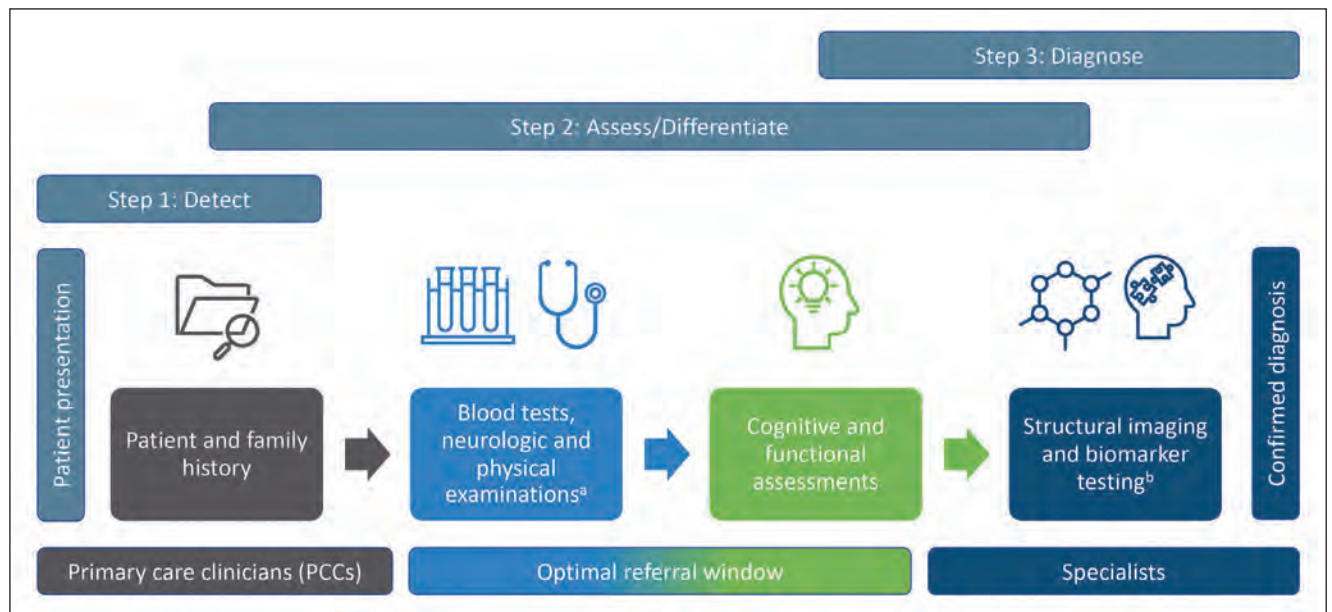
Newness and worsening of symptoms over time are suggestive of dementia. Additional challenges and barriers to AD diagnosis in primary care include time constraints among PCCs and clinic staff; difficulty in accurately identifying AD pathology; the tendency among patients, care partners, and clinicians to dismiss or deny symptoms as part of the normal aging process; and the stigma associated with an AD diagnosis.^{1,2,5,17,18}

The differential diagnosis in evaluating patients with suspected AD is challenging. There are mimickers of AD including other neurodegenerative diseases, insomnia, untreated depression, excessive alcohol use, and certain medications. AD is the most common type of dementia, accounting for an estimated 60% to 80% of cases.³ Vascular dementia accounts for 5% to 10% of cases, an estimated 5% of patients with dementia have Lewy body disease, and Parkinson disease accounts for about 3.6% of cases of dementia.³ Mixed dementias are frequently observed in research studies and clinical practice, and more than 50% of patients with AD have mixed dementia.³ By age 85, 85% of patients with any type of dementia will have a second type.³

The varied presentations of dementia pose challenges in accurately diagnosing AD because the dementia etiology is often multifactorial.³ In fact, most individuals with neuropathology of AD also have a coexisting non-AD neuropathology, such as Lewy body disease.³ Thus, it is not always clear which etiology or pathology is predominantly contributing to clinical symptoms.³ As such, detection of AD neuropathology and associated neurodegenerative disease through structural imaging and biomarkers has emerged as a key component of the diagnostic workup.^{1,2} The need for a multifaceted and holistic assessment warrants involvement of a multidisciplinary team and may include a thorough evaluation by a specialist for certain patients.¹

TABLE. Examples of cognitive signs and symptoms due to normal aging vs dementia^{2,16}

Signs of normal aging	Signs of dementia
May not recall information as quickly they used to	Having difficulty, or an inability, to learn new information (or having trouble with familiar tasks and following directions)
Sometimes forgetting names or appointments but remembering them later	Forgetting recently learned information and increasingly needing to rely on memory aids (eg, reminder notes); asking the same questions repeatedly
Occasionally needing help to use microwave settings or record a television show	Have difficulty driving to a familiar location, organizing a grocery list, or remembering the rules of a favorite game
Sometimes having trouble finding the right word	May have trouble naming a familiar object or use the wrong name (eg, calling a watch a "hand clock"); may stop in the middle of a conversation not knowing how to continue
Making a bad decision once in a while	Making poor judgments frequently
Missing a monthly payment once	Persistent problems managing bills
Forgetting which day it is and remembering it later	Losing track of the date or time of year
Losing things from time to time	Misplacing things frequently and being unable to find them

FIGURE 2. Example algorithm of a diagnostic pathway for AD¹

^aBasic blood work and examination to help rule out alternative or reversible causes of cognitive impairment; may also include genetic testing.

^bMight include MRI or amyloid PET imaging, CSF testing, and/or plasma biomarker testing.

Source: Porsteinsson AP, et al. *J Prev Alzheimers Dis.* 2021;8(3):371-386.

Guidelines for AD detection and diagnosis have been proposed that can be applied in primary care.^{1,2} One recent example of a diagnostic algorithm is shown in **FIGURE 2**. Most often—in up to 70% of cases—evaluation of cognition is prompted by cognitive complaints, so PCCs are in the best position to take action and further investigate when patients report these symptoms or when they are evident through objective measures and observations.⁴ PCCs can also play a critical role in proactively asking cognition and memory-related questions to assess changes over time.

Other strategies for establishing an early, accurate AD diagnosis include initial screening using standardized assessment tools and questionnaires such as the Montreal Cognitive Assessment (MoCA), the Mini-Mental State Examination (MMSE), and the Mini-Cog.¹ These tools can be used during a routine clinic visit, such as a Medicare annual wellness visit, which includes an assessment of cognition.^{2,6}

Clinicians should also consider cultural aspects of AD diagnosis and care, as the increased risk for dementia among socially disadvantaged racial and ethnic groups is directly influenced by social and physical environments.³ These factors can also influence diagnosis of AD, resulting in a higher rate of missed diagnoses among Black and Hispanic older adults compared with White older adults.³

When discussing cognitive concerns with a patient, asking certain questions of patients and family members or informants may be helpful in initially distinguishing between a suspected diagnosis of early symptomatic AD and other,

potentially treatable causes of cognitive decline. Such questions might include the following¹:

- What does a typical day look like? Are there changes to mood or forgetting/misplacing things? Is there frequent repetition of questions?
- Is there more trouble or less confidence with organizing, multitasking, or completing tasks that were previously done without difficulty?
- Have you noticed any changes in personality or behavior?
- Have you (the family member) had to take over for certain tasks that are no longer possible or require additional effort (eg, managing finances, organizing medications and appointments)?
- Have there been any recent acute illnesses, surgeries, or medication changes that could impact memory (eg, use of general anesthesia, urinary tract infection, antihistamines and other anticholinergics, sedative hypnotics, or narcotics)?
- Have there been any:
 - Recent falls?
 - Changes in sleep (quality, duration, any nighttime events)?
 - Vision or hearing problems?

Variability in coverage of diagnostics, including amyloid PET, CSF, and plasma tests, is a limitation of these approaches in detection and diagnosis. The adoption of biomarker tests

has historically been relatively low and slow due to challenges with availability, cost, reimbursement, and PCC confidence in interpretation. However, tests for specific biomarkers, such as β -amyloid, total tau, and phosphorylated tau, are becoming increasingly available clinically and can be used to help distinguish between different disorders and neurodegenerative diseases.^{4,19}

CONCLUSION

AD is a common and profoundly burdensome disease that is frequently underdiagnosed and misdiagnosed, resulting in delays in diagnosis and disease management. PCCs are often the first to encounter patients with signs and symptoms of cognitive impairment and play a crucial role in establishing a diagnosis of early symptomatic AD through collaboration with specialists and other multidisciplinary care team members. The current diagnosis of AD is clinical-neuropathologic—based both on clinical presentation as well as biomarker findings—and both aspects are needed to support timely and accurate diagnosis to help enable appropriate disease management.

For more information and additional resources on detection and diagnosis of AD, as well as patient communication, readers are encouraged to visit the Alzheimer's Association clinical resources page (<https://www.alz.org/professionals/health-systems-medical-professionals/clinical-resources>) or Alzheimers.gov (<https://www.alzheimers.gov/professionals/health-care-providers>). ●

REFERENCES

URLs must be entered manually, rather than copied and pasted.

1. Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of early Alzheimer's disease: clinical practice in 2021. *J Prev Alz Dis*. 2021;8(3):371-386. doi:10.14283/jpad.2021.23
2. Hampel H, Au R, Mattke S, et al. Designing the next-generation clinical care pathway for Alzheimer's disease. *Nat Aging*. 2022;2(8):692-703. doi:10.1038/s43587-022-00269-x
3. Alzheimer's Association. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2024;20(5):3708-3821. doi:10.1002/alz.13809
4. Judge D, Roberts J, Khandker RK, Ambegaonkar B, Black CM. Physician practice patterns associated with diagnostic evaluation of patients with suspected mild cognitive impairment and Alzheimer's disease. *Int J Alzheimers Dis*. 2019;2019:1-8. doi:10.1155/2019/4942562
5. Dubois B, Padovani A, Scheltens P, Rossi A, Dell'Agnello G. Timely diagnosis for Alzheimer's disease: a literature review on benefits and challenges. *J Alzheimers Dis*. 2016;49(3):617-631. doi:10.3233/JAD-150692
6. Galvin JE, Aisen P, Langbaum JB, et al. Early stages of Alzheimer's disease: evolving the care team for optimal patient management. *Front Neurol*. 2021;11:592302. doi:10.3389/fneur.2020.592302
7. Maserejian N, Krzywy H, Eaton S, Galvin JE. Cognitive measures lacking in EHR prior to dementia or Alzheimer's disease diagnosis. *Alzheimers Dement*. 2021;17(7):1231-1243. doi:10.1002/alz.12280
8. Shao Y, Zeng QT, Chen KK, Shutes-David A, Thielke SM, Tsuang DW. Detection of probable dementia cases in undiagnosed patients using structured and unstructured electronic health records. *BMC Med Inform Decis Mak*. 2019;19(1):128. doi:10.1186/s12911-019-0846-4
9. Lennon JC, Aita SL, Bene VAD, et al. Black and white individuals differ in dementia prevalence, risk factors, and symptomatic presentation. *Alzheimers Dement*. 2022;18(8):1461-1471. doi:10.1002/alz.12509
10. Barthélemy NR, Salvadó G, Schindler SE, et al. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. *Nat Med*. 2024;30(4):1085-1095. doi:10.1038/s41591-024-02869-z
11. Barnett JH, Lewis L, Blackwell AD, Taylor M. Early intervention in Alzheimer's disease: a health economic study of the effects of diagnostic timing. *BMC Neurol*. 2014;14:101. doi:10.1186/1471-2377-14-101
12. Rasmussen J, Langerman H. Alzheimer's disease—why we need early diagnosis. *Degener Neurol Neuromuscul Dis*. 2019;9:123-130. doi:10.2147/DNND.S228939
13. Jack CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562. doi:10.1016/j.jalz.2018.02.018
14. Hall JR, Vo HT, Johnson LA, Barber RC, O'Bryant SE. The link between cognitive measures and ADLs and IADL functioning in mild Alzheimer's: what has gender got to do with it? *Int J Alzheimers Dis*. 2011;2011:276734. doi:10.4061/2011/276734
15. Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *Lancet Neurol*. 2021;20(6):484-496. doi:10.1016/S1474-4422(21)00066-1
16. Memory problems, forgetfulness, and aging. National Institute on Aging. Published November 22, 2023. Accessed May 22, 2024. <https://www.nia.nih.gov/health/memory-loss-and-forgetfulness/memory-problems-forgetfulness-and-aging>
17. Judge D, Roberts J, Khandker R, Ambegaonkar B, Black CM. Physician perceptions about the barriers to prompt diagnosis of mild cognitive impairment and Alzheimer's disease. *Int J Alzheimers Dis*. 2019;2019:1-6. doi:10.1155/2019/3637954
18. Bernstein Sideman A, Al-Rousan T, Tsou E, et al. Facilitators and barriers to dementia assessment and diagnosis: perspectives from dementia experts within a global health context. *Front Neurol*. 2022;13:769360. doi:10.3389/fneur.2022.769360
19. Dubois B, von Arnim CAF, Burnie N, Bozeat S, Cummings J. Biomarkers in Alzheimer's disease: role in early and differential diagnosis and recognition of atypical variants. *Alzheimers Res Ther*. 2023;15(1):175. doi:10.1186/s13195-023-01314-6

Elevating the Importance of Asthma Care in the United States

Gary C. Steven, MD, PhD, CPI, FAAAAI, FAAAAI, FAPCR; Neil Skolnik, MD; Mike Devano, MD; Wendy L. Wright, DNP, ANP-BC, FNP-BC, FAANP, FAAN, FNAP; Maureen George, PhD, RN, AE-C, FAAN

Fed Pract. 2024;41(suppl 6):S13-S22. doi:10.12788/fp.0531

KEY TAKEAWAYS

- Primary care clinicians (PCCs) play a key role in managing care of patients with asthma across the disease continuum, which includes mild to severe asthma.
- Rescue/reliever regimens containing inhaled corticosteroids (ICS) are preferred to short-acting beta₂-agonist-only treatment because of the reduced risk for exacerbations.
- PCCs should refer patients with severe asthma to a specialist when indicated for further evaluation and management, which may include biologic therapy.
- Effective use of asthma action plans can help patients initiate anti-inflammatory therapy in a “window of opportunity” leading up to an exacerbation.
- Asthma quality metrics and incentives in the US currently lack alignment with best practices, and policymakers are urged to update these measures as new evidence and guidance emerge.

FACULTY

Gary C. Steven, MD, PhD, CPI, FAAAAI, FAAAAI, FAPCR, Medical Director, American Academy of Allergy, Asthma & Immunology Registry; Assistant Clinical

Professor of Medicine, Medical College of Wisconsin; Adjunct Clinical Instructor, College of Nursing, University of Wisconsin-Milwaukee, Allergy, Asthma & Sinus Center.

Neil Skolnik, MD, Professor of Family and Community Medicine, Sidney Kimmel Medical College, Associate Director, Family Medicine Residency Program, Thomas Jefferson University, Philadelphia, PA

Mike Devano, MD, Resident, Family Practice Residency Program, Thomas Jefferson University, Philadelphia, PA

Wendy L. Wright, DNP, ANP-BC, FNP-BC, FAANP, FAAN, FNAP, Adult/Family Nurse Practitioner, Wright and Associates Family Healthcare, Amherst, NH

Maureen George, PhD, RN, AE-C, FAAN, Professor of Nursing, Assistant Dean, Scholarship & Research, Director, PhD Program, Columbia University Irving Medical Center, New York, NY

DISCLOSURES

Neil Skolnik serves as an advisory board member and/or consultant to Abbott,

Astellas, AstraZeneca Pharmaceuticals LP, Bayer, Boehringer Ingelheim, GSK, Genentech, Idorsia, Lilly, Novartis, Novo Nordisk, Sanofi, Sanofi Pasteur, and Teva Pharmaceuticals. Wendy L. Wright is a consultant and advisory board/speakers bureau member of AstraZeneca Pharmaceuticals LP. Maureen George serves as a consultant, speaker, and advisory board member for AstraZeneca. She is a member of the advisory board/speakers bureau of Insmad, Regeneron, and Teva Pharmaceuticals. Gary C. Steven, Mike Devano, and Austin Ulrich, PharmD, BCACP, have no disclosures to report.

ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, Primary Care Education Consortium.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and Primary Care Respiratory Group.

SUPPORTER

This article is supported by funding from AstraZeneca Pharmaceuticals LP.

INTRODUCTION

According to the most recent Global Initiative for Asthma (GINA) report (2024), the definition of asthma is “a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness, and cough, that vary over time and in intensity, together with variable expiratory airflow limitation.”¹ In the US, an estimated 8.7% of adults and 6.2% of children have asthma, and asthma is the reason for approximately 6.3% of office-based physician visits (2022 data).² Asthma is most common in American Indian/Alaskan Native populations (12.3%), followed by Black non-Hispanic (10.9%) and White non-Hispanic (7.6%) populations.³

Asthma severity is currently assessed retrospectively based on how difficult the patient’s asthma is to treat. Mild

asthma is defined as asthma that is well controlled with low-intensity treatment (eg, as-needed low-dose inhaled corticosteroid [ICS] and fast-acting bronchodilator or low-dose ICS plus as-needed short-acting beta₂-agonist [SABA]) and moderate asthma defined as asthma that is well controlled with GINA Step 3 or Step 4 treatment (eg, low- or medium-dose ICS plus long-acting beta₂-agonist [LABA]). Severe asthma is defined as “asthma that is uncontrolled despite adherence with maximal optimized high-dose ICS/LABA treatment and management of contributory factors, or that worsens when high-dose treatment is decreased.”¹ Asthma should not be classified as severe if it improves when modifiable contributory factors such as adherence and inhaler technique are addressed.¹ Severe asthma is considered a subset of difficult-to-treat asthma, which is asthma that remains uncontrolled

despite use of medium- or high-dose ICS with a second controller, or frequent steroid bursts; asthma that requires chronic use of systemic corticosteroids (SCS); or asthma that requires high-dose ICS treatment to maintain symptom control and reduce exacerbation risk.¹ Up to 14% of people with asthma in the US have severe asthma.⁴

Severe asthma incurs a heavy health burden, including symptoms, exacerbations, and medication side effects.¹ Examples include frequent shortness of breath, chest tightness, coughing, and wheezing that interfere with daily living, sleeping, and physical activity; exacerbations in patients with severe asthma can be unpredictable or frightening. Severe asthma frequently results in limitations in family, social, and working lives and affects mental and emotional well-being.¹ Significant medication side effects in severe asthma are most often associated with SCS, which cause both long-term and short-term adverse effects. Contrary to traditional thinking, analyses over the past decade have shown that even short-term (<30 days) and intermittent SCS use can increase risk for bone fracture, venous thromboembolism, and sepsis.⁵ Higher cumulative doses of SCS over a patient's lifetime may contribute to increases in cardiovascular disease, osteoporosis, pneumonia, kidney impairment, cataracts, cerebrovascular disease, depression, anxiety, weight gain, sleep apnea, and type 2 diabetes.^{6,7}

Uncontrolled asthma is different from severe asthma—it can occur across all severities of asthma. Patients with uncontrolled asthma have one or both of the following characteristics¹:

- Poor symptom control, indicated by frequent reliever use or symptoms, night waking due to asthma, or activity limited by asthma
- Frequent exacerbations that require SCS, emergency department visits, and/or hospitalization

Recently in the United States, approximately 60% of adults and 44% of children were reported to have uncontrolled asthma^{8,9}; of those, more than 80% had mild or moderate asthma.¹⁰ In an international cohort of 1115 patients classified as GINA Step 1 or Step 2, 25% had uncontrolled asthma and about 33% reported rescue inhaler use in the previous 4 weeks.¹¹

Similarly, asthma exacerbations can occur in all severities of asthma despite guideline-directed treatment.¹² A history of emergency department visits and hospitalization for an asthma exacerbation increases the risk for future exacerbations, irrespective of disease severity, patient demographics, or clinical characteristics.^{12,13}

As previously discussed^{14,15} and as reflected in the GINA report, inclusion of ICS with rescue/reliever therapy is preferred for patients with asthma, including those

with uncontrolled asthma, regardless of disease severity.¹ Furthermore, extensive data show that use of ICS and fast-acting bronchodilator combinations as maintenance and rescue/reliever therapy or as rescue/reliever therapy alone leads to decreased asthma exacerbations compared to either the same or a higher dose of maintenance ICS plus SABA.^{16–27}

PRIMARY CARE CLINICIANS' ROLE IN ASTHMA AND SEVERE ASTHMA MANAGEMENT

More than 60% of patients with asthma receive care from a primary care clinician (PCC), and incorporating best practices for asthma management in primary care is essential to improving care across the disease continuum.^{28–30} Although many patients can be successfully managed in primary care, those with an unclear asthma diagnosis, a less-than-expected response to appropriate therapy, or who have severe, persistently uncontrolled asthma should be considered for referral for specialist care.^{1,31}

There are several benefits to appropriately referring patients with severe asthma to specialists, including testing for and identifying disease phenotypes to ensure appropriate treatment, evaluating for asthma masqueraders (comorbidities that may produce asthma-like symptoms but do not respond well to asthma therapies), maintaining symptom control, and reducing health care utilization and associated costs.³² US guidelines recommend appropriate medication escalation and referral of patients with severe asthma to a specialist for consultation or co-management, especially following an exacerbation.³³ However, findings from a recent study suggest that many patients with severe, uncontrolled asthma (35% to 51%) do not receive medication escalation or specialist referral. More Black patients (41%) and Hispanic/Latinx patients (38%) did not receive specialist referral or medication escalation than non-Hispanic White patients (33%). Furthermore, Black and Hispanic/Latinx patients have worse asthma outcomes compared to White patients and are the patient groups in most need of appropriate referral and treatment escalation. These findings indicate a need to improve guideline-based care delivery for patients with severe asthma, particularly those who experience the greatest burden and the greatest disparities.³³

Furthermore, patients experience delays in diagnosis and treatment initiation, resulting in suboptimal symptom control and quality of life. An international survey of clinicians in 2021 suggests that the average time from first symptoms to diagnosis was 2 years.³⁴ The average time between severe asthma diagnosis and biologic treatment ranges from 2 to 12 months, with an average length of 6.5 months. Additionally, the average time for referral to a specialist from primary care is approximately 5.5 months.³⁴

Current recommendations for treating asthma in the United States are based on the 2020 Focused Update of the National Asthma Education and Prevention Program (NAEPP) and the 2007 Expert Panel Report-3 (EPR-3) guidelines.^{31,35} Global asthma recommendations are based on the 2024 GINA report.¹ Suggested approaches for applying these recommendations in primary care, highlighting the importance of concurrent ICS use with bronchodilators, have been reviewed previously.^{14,15}

Treatment goals suggested by EPR-3 and GINA are closely aligned. Both recommend that achieving good symptom control, maintaining normal activity levels, and reducing negative asthma outcomes such as exacerbations, adverse effects, persistent airflow limitation, and asthma-related death, are important clinical goals for asthma management.^{1,35}

Assessing asthma control is fundamental to asthma management and to optimize medication therapy, prevent exacerbations, improve quality of life, and achieve patient and clinical treatment goals.^{1,35} Many common asthma assessment tools are focused only on evaluation of symptoms, but an ideal tool for assessing asthma should include questions that reveal both symptoms and exacerbation risk. This topic is discussed in further detail later in this article.

CHALLENGES IN PRIMARY CARE ASTHMA MANAGEMENT

There are many asthma management challenges in primary care clinical settings, several of which are discussed in this article. These challenges include the following^{28,32,33,36,37}:

- Misaligned quality metrics and national incentives
- Lack of adequate assessment and infrequent use of validated tools
 - Results in missing patients whose asthma is uncontrolled and those at risk for exacerbations
- Lack of time, staffing, reimbursement, and staff competency
- Lack of access to asthma care and treatments
- Barrier to multidisciplinary team care management approach
 - Include collaboration with specialists such as pulmonologists; allergists; and ear, nose, and throat specialists; emergency department clinicians for management of acute exacerbations and transitions of care; and other members of the outpatient care team, including pharmacists, respiratory therapists, and certified asthma educators
- Challenges related to patient factors such as access to care and treatments, insurance coverage, adherence, and knowledge gaps

- Result in many patients experiencing long wait times and traveling long distances to specialists, further diminishing access to care

The remainder of this article discusses additional details regarding barriers to optimal asthma management encountered in primary care along with potential solutions. Key areas of focus include asthma quality metrics and incentives, unmet needs in asthma populations, considerations for clinicians and clinic staff in practice, use of biologic therapies, referral to specialists, and the use of asthma action plans.

CASE STUDY

A 42-year-old woman presents to her primary care clinic for an asthma follow-up visit. She is currently treated with moderate-dose ICS-LABA for maintenance therapy, with SABA-only rescue therapy. She has had 1 exacerbation within the past year and currently does not have an asthma action plan in place. When asked how she is doing with her asthma, she responds, “It’s been okay, I’m glad I have my rescue inhaler because I really need it when I get out of breath.”

No changes to treatment are recommended, as the clinician decides that the patient’s current regimen seems to be working fine, reasoning that 1 burst of SCS per year is “not that bad and likely unavoidable anyway.” The patient is scheduled for another follow-up visit in 6 months.

The patient in this case scenario is at risk for exacerbations, especially because she is regularly using SABA-only rescue therapy. However, more information is needed to accurately assess the patient’s status. Either a more detailed history, or the use of a validated tool such as the Asthma Impairment and Risk Questionnaire (AIRQ[®]) could highlight exacerbation risk and focus attention on improving symptom control. Additionally, the clinician in the scenario appears to be unaware of updated guidance for ICS-containing rescue therapy, which would optimize the patient’s treatment regimen. Notably, current asthma quality metrics and incentives in the US would not promote different management of this patient.

ASTHMA QUALITY METRICS AND INCENTIVES

In the US health care system, quality metrics and incentives play a prominent role, monitoring and reporting performance of clinical interventions across health systems, health plans, and clinicians.³⁶ However, the number and complexity of quality measures continue to increase, placing a growing burden on clinicians and health systems. Additionally, measures that are not aligned to evidence-based practice can hinder optimal asthma care.

TABLE 1. Current CMS measures that apply to asthma care in the United States

Measure	Description
MIPS #398: Optimal Asthma Control ⁴¹ Data submitted by individual MIPS-eligible clinicians, groups, or third-party intermediaries for reimbursement	Composite measure of the percentage of pediatric and adult patients whose asthma is well controlled as demonstrated by 1 of 3 age-appropriate patient-reported outcome tools and not at risk for exacerbation
MIPS #444: Medication Management for People with Asthma ⁴² Data submitted by individual MIPS-eligible clinicians, groups, or third-party intermediaries for reimbursement	The percentage of patients aged 5-64 years during the measurement year who were identified as having persistent asthma and were dispensed appropriate medications that they remained on for at least 75% of their treatment period
HEDIS: Asthma Medication Ratio ⁴³ Data submitted by individual clinicians, groups, or third-party intermediaries for health plan performance reporting	Assessment of adults and children aged 5-64 years who were identified as having persistent asthma and had a ratio of controller medications to total asthma medications of 0.50 or greater during the measurement year
ACO #9: Prevention Quality Indicator: Ambulatory sensitive conditions admissions for COPD or asthma in older adults ⁴⁴ Data submitted by individual clinicians, groups, or third-party intermediaries for reimbursement	All discharges <i>ICD-9-CM</i> principal diagnosis code for COPD or asthma in adults aged 40 years and older, for ACO-assigned or aligned Medicare beneficiaries with COPD or asthma, with risk-adjusted comparison of observed discharges to expected discharges for each ACO

Abbreviations: ACO, Accountable Care Organization; CMS, Centers for Medicare and Medicaid Services; COPD, chronic obstructive pulmonary disease; HEDIS, Healthcare Effectiveness Data and Information Set; MIPS, Merit-based Incentive Payment System.

Current state of asthma quality metrics and national incentive schemes in the United States

The current asthma quality metrics and national incentive schemes include the Merit-based Incentive Payment System (MIPS), Health care Effectiveness Data and Information Set (HEDIS) measures, and Accountable Care Organization (ACO) measures established by the Centers for Medicare and Medicaid Services (CMS).³⁸⁻⁴⁰ Several of the current MIPS, HEDIS, and ACO measures apply to asthma care (TABLE 1).⁴¹⁻⁴⁴

Notably, guidance in the US lacks updated recommendations for asthma screening and control assessment. Furthermore, accountability measures of readmission are currently not applied to asthma (despite being applied to chronic obstructive pulmonary disease), which can lead to suboptimal exacerbation management with increased visits to the emergency department or unplanned hospitalizations.

Challenges with metrics and incentives for asthma

Despite the intention of current metrics and incentives to improve asthma care, they lack alignment with evidence-based practice recommendations and leave gaps in care. For example, national priority and composite measures currently do not align with best practices for escalation of asthma therapies, and they miss an opportunity for regulating ongoing harms of the overuse of SCS. Additionally, current care patterns often result in allowing patients to worsen and remain unnecessarily uncontrolled for a period before an intervention is made (treating to failure), as compared to proactive treatment implementation to prevent clinical worsening.

Many clinicians, even those in specialty practice, may not know about quality metrics for asthma, or the requirements are so burdensome that they may avoid using them. Current measures typically do not reward optimal asthma care. For example, optimal care suggests that validated asthma assessment tools should be used. The MIPS asthma control measure mandates use of 1 of 3 symptom-based validated control tools, the Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), or Asthma Therapy Assessment Questionnaire. However, these tools do not assess exacerbation risk. Newer data on the composite AIRQ, which assess the risk for future exacerbations in addition to current symptom control, are not included in the MIPS measure because of the measure’s development before collection of the AIRQ longitudinal data.⁴⁵⁻⁴⁹ Moreover, although the MIPS measure’s current assessment of future exacerbation risk is linked to the number of emergency department visits or hospitalizations within the last year, this is not a validated measure, and it can be difficult for clinicians to accurately access exacerbation history without use of a validated tool designed for this purpose.⁴⁵

Importantly, current metrics are cumbersome and therefore not used. As a pre-COVID-19 pandemic benchmark, of 130,225 PCCs reporting MIPS measures in 2019, only 109—0.08%—reported on MIPS 398 (the asthma control measure). With the reduction of quality reporting due to pandemic waivers, only 7 of 89,718—0.01%—clinicians reporting MIPS measures in 2022 reported on MIPS 398.

Other measures may be outdated as well; the asthma

medication ratio (AMR) HEDIS measure, which “assesses adults and children aged 5 to 64 years who were identified as having persistent asthma and had a ratio of controller medications to total asthma medications of 0.50 or greater during the measurement year,” is outdated considering evidence that supports use of maintenance and reliever therapy (ICS plus fast-acting bronchodilator treatment regimens). Additionally, clinicians may be incentivized to spend excessive time meeting the metrics or incentive measures to boost payment, rather than focusing on quality care.⁵⁰

Potential solutions to these challenges with asthma metrics and incentives stem from an updated understanding of best practices in asthma and corresponding updates in quality measures. Some changes have already been recognized, such as the retirement of HEDIS Medication Management for People with Asthma in 2020 with the release of the NAEPP 2020 Focused Update.⁵¹ Stakeholders should design quality metrics to better align with guidelines while also limiting the burden of data collection and submissions on clinicians. This may include a more proactive, earlier intervention approach to treat and lower the risk for irreversible lung damage and rescue medication side effects, rather than waiting for disease worsening, as well as early identification of patients appropriate for specialist referral.

SELECT UNMET NEEDS IN ASTHMA POPULATIONS

Disparities in asthma care

The burden of asthma can uniquely affect patients and their families across various age, socioeconomic, and racial and ethnic groups. For example, disparate patient groups may face additional barriers accessing asthma care due to language and cultural barriers, lack of familiarity with or distrust of health care systems and resources, poverty, and low numbers of primary care facilities and health systems.⁵²

Inadequate assessment of asthma

Asthma assessment may be inadequate in many instances; specifically, current practices may miss patients at risk for exacerbations, across all severities. Use of validated tools in practice requires planning to implement effectively but has been reported to save clinician time in continuity of care.⁵³

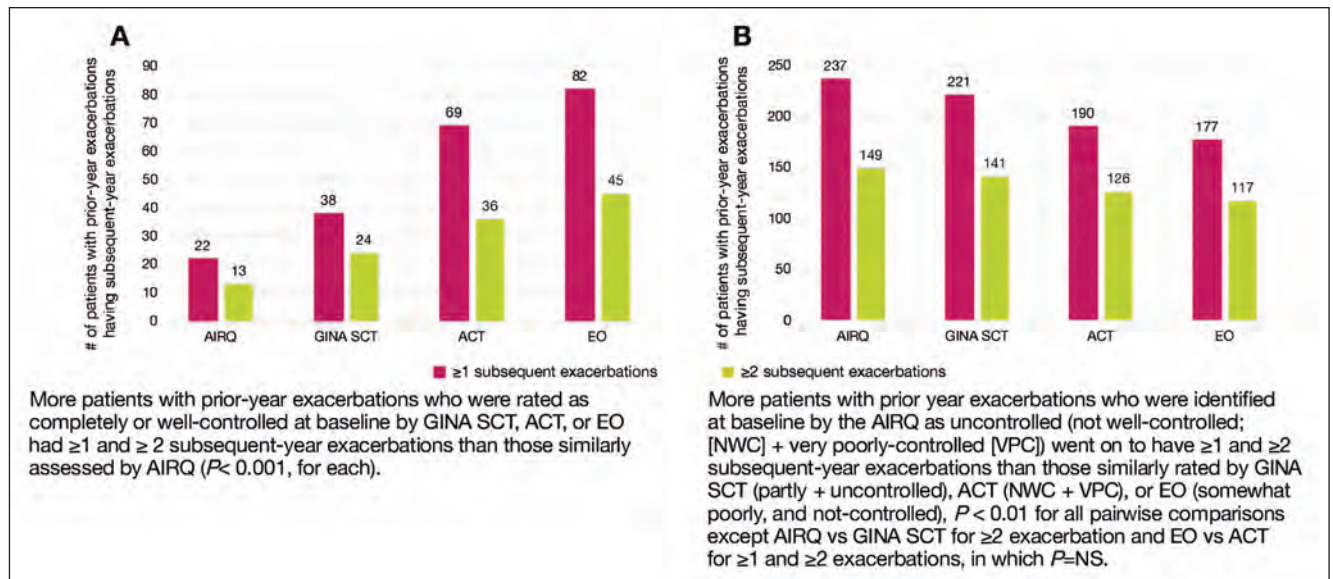
Implementation of validated assessments of asthma control may include asking patients to complete questions before seeing the clinician, with assistance from the receptionist, rooming staff, or an online portal. The reading levels of these questions should not pose a high literacy demand on patients. The clinician could then quickly review the results and incorporate them into treatment decisions, without using time during the appointment to conduct the assessment. The validated tools listed here, as well as the GINA

questions, can help ensure the necessary information is obtained rather than asking less useful questions such as, “How is your asthma?”

Validated asthma assessment tools include:

- **AIRQ.** The AIRQ is a recently developed and validated tool comprising of 10 “yes/no” questions that incorporates both symptom and exacerbation risk assessment.⁴⁶ Scores range from 0 to 10, with a score of 0 to 1 indicating well-controlled asthma and higher scores representing worsening asthma control.⁴⁶ The AIRQ control level has been found to predict risk for future exacerbations across the following 12 months.⁴⁵ Additionally, the assessment tool is linked to suggestions for further evaluation of each question domain. Between annual visits, a 3-month follow-up version of the AIRQ can be used to assess ongoing disease status and the impact of interventions.⁴⁷ The AIRQ has been shown to have low literacy demand, increasing its usability among patient groups.
- Data suggest that the AIRQ may serve to improve determination of asthma control compared to other validated tools by assessing previous exacerbations (**FIGURE 1**).^{48,49}
 - Link to the AIRQ: <https://www.asthmaresourcecenter.com/home/for-your-practice.html>
- **ACT.** The ACT includes 5 multi-answer questions with 4-week recall. Scores range from 5 to 25, and higher scores indicate better control.⁵⁴ A score of 20 to 25 indicates well-controlled asthma, and the minimum clinically important difference is 3 points.⁵⁵
 - Link to ACT questions: <https://www.asthmacontroltest.com/welcome>
- **Asthma APGAR.** The Asthma APGAR (Activities, Persistent, triGers, Asthma medications, Response to therapy) includes 6 questions with 2-week recall; the 3 multi-answer questions are scored with the other 3 to identify potential reasons for lack of control. Scores of >2 are considered inadequate control. It is linked to a care algorithm based on NAEPP guidelines.^{53,56}
 - Link to the Asthma APGAR questions and care algorithm: https://www.aafp.org/dam/AAFP/documents/patient_care/nrn/nrn19-asthma-apgar.pdf
- **ACQ.** The ACQ includes 5 symptom-based questions with 4-week recall.^{1,57} Scores range from 0 to 6, with higher scores indicating worse asthma control; the total score is an average of individual items.¹ Because the ACQ is a proprietary tool, permission must be obtained before using it.
 - Link to the ACQ: <https://www.qoltech.co.uk/acq.html>

FIGURE 1. Accuracy of asthma control assessments in predicting future exacerbations within 12 months, based on prior 12-month exacerbation history⁴⁹



Abbreviations: ACT; AIRQ; EO; GINA SCT; NS; NWC and VPC

Patients represented in panel A were assessed as well controlled at baseline and those in panel B were assessed as uncontrolled at baseline.

Source: Chipps BE, Zeiger RS, Beuther DA, et al. Advancing assessment of asthma control with a composite tool: The Asthma Impairment and Risk Questionnaire. *Ann Allergy Asthma Immunol.* 2024;133(1):49-56. doi:10.1016/j.anaai.2024.03.011

The GINA report suggests 4 areas be covered when assessing control. The GINA questions are not validated but can serve as a guide to what to ask if a validated questionnaire is not used. The 4 questions are¹:

- In the past 4 weeks, has the patient had
 - Daytime asthma symptoms more than twice a week?
 - Any night waking due to asthma?
 - SABA reliever use for symptoms more than twice a week?
 - Any activity limitation due to asthma?

Reducing exacerbation frequency and severity

Incorporating ICS as part of rescue therapy is supported by extensive data, as previously mentioned. Specifically, budesonide-formoterol has been studied as maintenance and rescue therapy in those with moderate to severe asthma¹⁶⁻²³ and as rescue therapy in patients with mild or mild to moderate asthma.^{24-26,58} These trials highlight the effectiveness of an ICS plus fast-acting bronchodilator combination inhaler in managing asthma and preventing exacerbations (formoterol is a long-acting bronchodilator with rapid onset). Meta-analysis of budesonide-formoterol studies evaluating use as maintenance and rescue therapy in patients with uncontrolled moderate-to-severe asthma indicated a statistically significant decreased risk for exacerbations with budesonide-formoterol compared

to previous GINA Step 3 or Step 4 (13.2% vs 17.7%; hazard ratio 0.70; 95% CI, 0.58-0.85; $P < .001$).²³

More recently, an albuterol-budesonide combination inhaler was approved by the US Food and Drug Administration (FDA) for patients 18 years and older with asthma. This approval was based largely on the MANDALA trial, which showed a 24% decrease in the annualized rate of severe asthma exacerbations (0.45 vs 0.59; rate ratio, 0.76; 95% CI, 0.62-0.93) and a 33% lower mean annualized total dose of SCS (86.2 ± 262.9 mg prednisone equivalents vs 129.3 ± 657.2 mg) in patients receiving the fixed-dose combination of albuterol-budesonide 180/160 µg compared to albuterol alone (preplanned efficacy analysis).²⁷ Data suggest that exposure to ICS with rescue/reliever therapy in addition to ICS used for maintenance therapy would remain within the range of FDA-approved doses of ICS, even for most patients using high-dose ICS in their maintenance regimen.⁵⁹

Approximately 10 to 14 days before an asthma exacerbation, progressive rising inflammation accompanies the decrease in lung function (peak expiratory flow, or PEF) and increase in symptoms,^{60,61} which may result in patients increasing SABA-only rescue use.⁶¹⁻⁶³ SABA-only rescue use can provide symptomatic relief, but it does not address airway inflammation.^{60,61} The approximately 10- to 14-day period leading up to an exacerbation has been suggested to represent a “window of opportunity” across asthma

TABLE 2. Basic characteristics of biologic therapies for severe asthma available in the United States⁶⁵

Biologic (target)	Age	Administration	GINA recommendation
Omalizumab (IgE)	≥6 y	SC injection	Severe exacerbations within last year, sensitization to inhaled allergens, total serum IgE and weight within local dosing range
Mepolizumab (IL-5)	≥6 y	SC injection	Severe exacerbations within last year, blood eosinophil ≥150 cells/μL or ≥300 cells/μL
Reslizumab (IL-5)	≥18 y	IV infusion	Severe exacerbations within last year, blood eosinophil ≥150 cells/μL or ≥300 cells/μL
Benralizumab (IL-5Ra)	≥6 y	SC injection	Severe exacerbations within last year, blood eosinophil ≥150 cells/μL or ≥300 cells/μL
Dupilumab (IL-4Ra)	≥6 y	SC injection	Severe exacerbations within last year, blood eosinophil ≥150 cells/μL and ≤1500 cells/μL, or FeNO ≥25 ppb, or maintenance SCS
Tezepelumab (TSLP)	≥12 y	SC injection	Severe exacerbations within last year

Abbreviations: FeNO, fractional exhaled nitric oxide; IV, intravenous; IgE, immunoglobulin e; SC, subcutaneous.

Adapted from Shah and Brightling, 2023.

severities to minimize airway inflammation and either reduce the severity of or prevent an exacerbation by ensuring anti-inflammatory therapy is part of rescue treatment.⁶⁴

BARRIERS TO AND POTENTIAL SOLUTIONS FOR DELIVERING OPTIMAL ASTHMA CARE

To address unmet needs in asthma populations, clinicians should consider reducing barriers to delivering optimal asthma care. Barriers to optimal asthma care may include²⁸:

- Lack of familiarity with recommendations from national and international guidelines and reports
- Failure to recognize uncontrolled and/or severe asthma
- Failure to implement updated treatment recommendations, such as ICS-containing rescue therapy
- Clinic workflow challenges, which may include
 - Lack of time within appointments
 - Inadequate staffing to assist with administrative functions of asthma care
- Patients' lack of access to asthma care and treatments
- Lack of access to specialists for patients with severe uncontrolled asthma, who need more intensive evaluation for complicating diagnoses, or who are indicated for initiation of biologic therapy

Addressing these barriers involves increased familiarity among clinicians with the NAEPP 2020 guideline and the GINA report, as well as educating patients to improve their knowledge of and adherence to the best asthma treatment for the patient's severity level. Addressing access to asthma care and treatments includes a heightened awareness of disparities in access between patient groups, assisting patients with factors including prior authorization, free or low-cost health care facilities, and financial assistance programs.

PATIENT CASE REVISITED 6 MONTHS LATER

The patient in the case scenario returns to her primary care clinic for a 6-month follow-up visit. At this visit, the PCC asks the patient to complete the AIRQ, recognizing its utility in identifying exacerbation risk. The patient is determined to have uncontrolled asthma, remaining at risk for exacerbations. Her PCC implements ICS-containing rescue therapy to reduce exacerbation risk and improve overall asthma control.

NAVIGATING BIOLOGICS FOR ASTHMA IN PRIMARY CARE

Biologics represent an important option for additional disease control in patients with severe asthma. Those who have frequent exacerbations and/or poor symptom control despite use of medium- to high-dose ICS/LABA therapy ± long-acting muscarinic antagonists, ± leukotriene receptor antagonists, or who are dependent on SCS should be considered for biologic therapy.^{1,65} An overview of biologic therapies approved in the US for asthma is provided in **TABLE 2**,⁶⁵ including patient age, mode of administration, and GINA recommendation.^{1,65} Approved biologic therapies for severe asthma in the US (in approval order) include omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab, which have all demonstrated benefit in eosinophilic type 2 severe asthma.⁶⁵

Although biologic therapies are not typically prescribed in primary care settings, increased awareness of their benefits for severe asthma treatment may prompt referral for appropriate patients. A variety of factors influence eligibility for and ability to access biologic therapies, such as labeled indications and local payor criteria and affordability, as well as clinical characteristics such as age, use of SCS, degree of asthma control, lung function, biomarkers, and comorbidi-

ties.⁶⁵ Patient preferences should also be considered and may be informed by dosing frequency and route of administration.^{65,66} Additionally, widespread adoption at the national and local level of guidance that prioritizes biologic therapies over SCS may help reduce avoidable health care resource utilization by promoting adequate disease management.

PATIENT CASE REVISITED ANOTHER YEAR LATER

Another year later, the patient’s asthma has worsened to become severe, evidenced by multiple severe exacerbations secondary to worsening outdoor environmental triggers in her area of residence. Her PCC is meeting with her at a post-hospitalization visit. Her inhaled maintenance and rescue therapies have been maximized, and she is now indicated for biologic therapy. Therefore, a referral for specialist care is made to further evaluate and manage her severe asthma.

EFFECTIVE AND EFFICIENT USE OF ASTHMA ACTION PLANS

Effective use of asthma action plans can help clinicians give patients and families specific guidance to take action in identifying and using early treatment for an exacerbation.⁶⁷ As part of an asthma action plan, triggers should be identified and addressed for preventing future exacerbations. Asthma self-management education may include helping patients understand self-monitoring of symptoms and/or lung function (via PEF measurement) and their written asthma action plan.¹ At a follow-up visit after an exacerbation, the clinician should review and update the asthma action plan with the patient.¹ Clinicians should also recognize that SABA-only treatment is no longer the optimal rescue option.

Policy changes surrounding asthma action plans may also help influence their effective and efficient use. This may include alignment in payor reimbursement, national enforcement in policy, and regulations and health system performance measures that drive the optimal asthma care for patients across disease severities.

Principles of self-management of exacerbations using a written asthma action plan may include¹:

- Consulting with the patient and any caregivers to

FIGURE 2. Example of an asthma action plan

Source: American Lung Association. My Asthma Action Plan. 2022. Used with permission. <https://www.lung.org/getmedia/dc79f142-a963-47bc-8337-afe3c3e87734/FY22-ALA-Asthma-Action-Plan-with-QR-codes.pdf>

- develop the action plan using shared decision-making
 - Assessing symptoms early and detecting worsening symptoms early that may precede an exacerbation
 - Determining when and how to escalate rescue/reliever (ICS plus rapid-acting bronchodilator) treatment (ie, during a “window of opportunity” just preceding an exacerbation)
 - Deciding when and how to escalate controller therapy
 - Reviewing response to treatment and assessing next steps
 - Contacting the clinician or emergency services
- An example of an asthma action plan is shown in

FIGURE 2.

SUMMARY

PCCs play a critical role in managing care of patients with asthma across the disease continuum, which includes mild to severe asthma. For patients with uncontrolled asthma, regardless of severity, there is an increased risk for exacerbations. This should be addressed by escalating maintenance therapy and/or by the addition of ICS-containing rescue/reliever therapy. ICS rescue/reliever therapy can now be in the form of budesonide-albuterol used as rescue with any maintenance regimen, or by the use of a single maintenance and reliever therapy regimen. Strong randomized trial evidence shows the inclusion of ICS in rescue therapy reduces the risk for exacerbations. PCCs should refer patients with severe, uncontrolled asthma to a specialist when indicated for further evaluation and management, which may include biologic therapy. ●

REFERENCES

URLs must be entered manually, rather than copied and pasted.

- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024. Accessed August 23, 2024. https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf
- Centers for Disease Control and Prevention. FastStats. April 30, 2024. Accessed June 29, 2024. <https://www.cdc.gov/nchs/fastats/asthma.htm>
- Centers for Disease Control and Prevention. Most recent national asthma data. June 17, 2024. Accessed June 29, 2024. https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm
- Chupp G, Murphy KR, Gandhi HN, Gilbert I, Bleecker ER. Asthma control in the United States: relationships between short-acting β_2 -agonist and systemic corticosteroid use. *Ann Allergy Asthma Immunol*. 2024;133(3):302-309. doi:10.1016/j.anaai.2024.05.003
- Waljee AK, Rogers MAM, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ*. 2017;357:j1415. doi:10.1136/bmj.j1415
- Price DB, Trudo F, Voorham J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy*. 2018;11:193-204. doi:10.2147/JAA.S176026
- Heatley H, Tran TN, Bourdin A, et al. Observational UK cohort study to describe intermittent oral corticosteroid prescribing patterns and their association with adverse outcomes in asthma. *Thorax*. 2023;78(9):860-867. doi:10.1136/thorax-2022-219642
- AsthmaStats: uncontrolled asthma among adults, 2019. Centers for Disease Control and Prevention. August 12, 2022. Accessed March 31, 2023. https://www.cdc.gov/asthma/asthma_stats/uncontrolled-asthma-adults-2019.htm
- AsthmaStats: uncontrolled asthma among children with current asthma, 2018-2020. Centers for Disease Control and Prevention. August 22, 2022. Accessed March 31, 2023. https://www.cdc.gov/asthma/asthma_stats/uncontrolled-asthma-children-2018-2020.htm
- Bleecker ER, Gandhi H, Gilbert I, Murphy KR, Chupp GL. Mapping geographic variability of severe uncontrolled asthma in the United States: management implications. *Ann Allergy Asthma Immunol*. 2022;128(1):78-88. doi:10.1016/j.anaai.2021.09.025
- Ding B, Small M. Disease burden of mild asthma: findings from a cross-sectional real-world survey. *Adv Ther*. 2017;34(5):1109-1127. doi:10.1007/s12325-017-0520-0
- Castillo JR, Peters SP, Busse WW. Asthma exacerbations: pathogenesis, prevention, and treatment. *J Allergy Clin Immunol Pract*. 2017;5(4):918-927. doi:10.1016/j.jaip.2017.05.001
- Miller MK, Lee JH, Miller DP, Wenzel SE, TENOR Study Group. Recent asthma exacerbations: a key predictor of future exacerbations. *Respir Med*. 2007;101(3):481-489. doi:10.1016/j.rmed.2006.07.005
- Lugogo N, Skolnik N, Jiang Y. A paradigm shift for asthma care. *J Fam Pract*. 2022;71(6 suppl). doi:10.12788/jfp.0437
- Skolnik N. Use of ICS and fast-acting bronchodilators in asthma: past, present, and future. *J Fam Pract*. 2023;72(6 suppl). doi:10.12788/jfp.0625
- Rabe KF, Pizzichini E, Ställberg B, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. *Chest*. 2006;129(2):246-256. doi:10.1378/chest.129.2.246
- Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin*. 2004;20(9):1403-1418. doi:10.1185/030079904X2051
- O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med*. 2005;171(2):129-136. doi:10.1164/rccm.200407-884OC
- Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet*. 2006;368(9537):744-753. doi:10.1016/S0140-6736(06)69284-2
- Vogelmeier C, D'Urzo A, Pauwels R, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J*. 2005;26(5):819-828. doi:10.1183/09031936.05.00028305
- Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract*. 2007;61(5):725-736. doi:10.1111/j.1742-1241.2007.01338.x
- Bousquet J, Boulet LP, Peters MJ, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med*. 2007;101(12):2437-2446. doi:10.1016/j.rmed.2007.07.014
- Beasley R, Harrison T, Peterson S, et al. Evaluation of budesonide-formoterol for maintenance and reliever therapy among patients with poorly controlled asthma: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(3):e220615. doi:10.1001/jamanetworkopen.2022.0615
- O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med*. 2018;378(20):1865-1876. doi:10.1056/NEJMoal1715274
- Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med*. 2018;378(20):1877-1887. doi:10.1056/NEJMoal1715275
- Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med*. 2019;380(21):2020-2030. doi:10.1056/NEJMoal1901963
- Papi A, Chipps BE, Beasley R, et al. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma. *N Engl J Med*. 2022;386(22):2071-2083. doi:10.1056/NEJMoal2203163
- Fletcher MJ, Tsiligianni I, Kocks JWH, et al. Improving primary care management of asthma: do we know what really works? *NPJ Prim Care Respir Med*. 2020;30(1):29. doi:10.1038/s41533-020-0184-0
- Wu TD, Brigham EP, McCormack MC. Asthma in the primary care setting. *Med Clin North Am*. 2019;103(3):435-452. doi:10.1016/j.mcna.2018.12.004
- Akinbami LJ, Salo PM, Cloutier MM, et al. Primary care clinician adherence with asthma guidelines: the National Asthma Survey of Physicians. *J Asthma*. 2020;57(5):543-555. doi:10.1080/02770903.2019.1579831
- Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier MM, Baptist AP, et al. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. 2020;146(6):1217-1270. doi:10.1016/j.jaci.2020.10.003
- Price D, Bjermer L, Bergin D, Martinez R. Asthma referrals: a key component of asthma management that needs to be addressed. *J Asthma Allergy*. 2017;10:209-223. doi:10.2147/JAA.S134300
- Carr T, Tkacz J, Chung Y, et al. Gaps in care among uncontrolled severe asthma patients in the United States. *J Allergy Clin Immunol Pract*. Published online March 2024. doi:10.1016/j.jaip.2024.03.018
- Efthymiadou O, Kamphuis B, Tzouma V, Kanavos P. *Treatment gaps in severe asthma across nine OECD countries and recommendations for addressing them: An international survey of clinicians*. The London School of Economics and Political Science. Published online May 2021. Accessed July 30, 2024. https://eprints.lse.ac.uk/110360/1/Severe_asthma_care_and_treatment_WP2_Final_May_2021.pdf
- National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR-2 1997)*. NIH Publication No. 97-4051. US Department of Health and Human Services; National Institutes of Health. 2007. Accessed May 12, 2023. https://www.nhlbi.nih.gov/sites/default/files/media/docs/EPR-3_Asthma_Full_Report_2007.pdf
- Herman E, Beavers S, Hamlin B, Thaker K. Is it time for a patient-centered quality measure of asthma control? *J Allergy Clin Immunol Pract*. 2019;7(6):1771-1777. doi:10.1016/j.jaip.2019.02.016
- Price C, Agarwal G, Chan D, et al. Large care gaps in primary care management of asthma: a longitudinal practice audit. *BMJ Open*. 2019;9(1):e022506. doi:10.1136/bmjopen-2018-022506
- Centers for Medicare & Medicaid Services. Traditional MIPS overview. Quality Payment Program. Accessed June 29, 2024. <https://qpp.cms.gov/mips/traditional-mips>
- Centers for Medicare & Medicaid Services. Healthcare Effectiveness Data and Information Set (HEDIS). Accessed June 29, 2024. <https://www.cms.gov/medicare/enrollment-renewal/special-needs-plans/data-information-set>
- Centers for Medicare & Medicaid Services. Accountable care organizations (ACOs): general information. Accessed June 29, 2024. <https://www.cms.gov/priorities/innovation/innovation-models/aco>
- Centers for Medicare & Medicaid Services. *Quality ID #398: Optimal Asthma Control*. Published online November 2022. Accessed June 29, 2024. https://qpp.cms.gov/docs/QPP_quality_measure_specifications/CQM-Measures/2023_Measure_398_MIPSCQM.pdf
- Centers for Medicare & Medicaid Services. *Quality ID #444: Medication Management for People with Asthma*. Published online 2018. Accessed June 29, 2024. https://qpp.cms.gov/docs/QPP_quality_measure_specifications/CQM-Measures/2019_Measure_444_MIPSCQM.pdf
- National Committee for Quality Assurance (NCQA). Asthma medication ratio (AMR). NCQA. Accessed June 29, 2024. <https://www.ncqa.org/hedis/medasures/medication-management-for-people-with-asthma-and-asthma-medication-ratio/>
- Centers for Medicare & Medicaid Services. *ACO #9—Prevention Quality Indicator (PQI): Ambulatory Sensitive Conditions Admissions for Chronic Obstructive Pulmonary Disease (COPD) or Asthma in Older Adults*. Published online October 31, 2012.

- Accessed June 29, 2024. <https://www.cms.gov/medicare/medicare-fee-for-service-payment/sharedsavingsprogram/downloads/measure-aco-9-asthma.pdf>
45. Beuther DA, Murphy KR, Zeiger RS, et al. The Asthma Impairment and Risk Questionnaire (AIRQ) control level predicts future risk of asthma exacerbations. *J Allergy Clin Immunol Pract*. 2022;10(12):3204-3212.e2. doi:10.1016/j.jaip.2022.08.017
 46. Murphy KR, Chipps B, Beuther DA, et al. Development of the Asthma Impairment and Risk Questionnaire (AIRQ): a composite control measure. *J Allergy Clin Immunol Pract*. 2020;8(7):2263-2274.e5. doi:10.1016/j.jaip.2020.02.042
 47. Chipps BE, Murphy KR, Wise RA, et al. Assessing construct validity of the Asthma Impairment and Risk Questionnaire using a 3-month exacerbation recall. *Ann Allergy Asthma Immunol*. 2022;128(5):544-552.e3. doi:10.1016/j.anai.2022.01.035
 48. Chipps B, Zeiger RS, Beuther DA, et al. The Asthma Impairment and Risk Questionnaire enhances the assessment of asthma control. *Ann Allergy Asthma Immunol*. 2023;131(4):436-443.e1. doi:10.1016/j.anai.2023.04.024
 49. Chipps BE, Zeiger RS, Beuther DA, et al. Advancing assessment of asthma control with a composite tool: The Asthma Impairment and Risk Questionnaire. *Ann Allergy Asthma Immunol*. 2024;133(1):49-56. doi:10.1016/j.anai.2024.03.011
 50. Cohn JR, Ford MK, Fung SM. Asthma outcomes and quality metrics: improving health or teaching to the test? *J Allergy Clin Immunol Pract*. 2019;7(4):1330-1331. doi:10.1016/j.jaip.2018.12.015
 51. National Committee for Quality Assurance (NCQA). *Proposed Retirement for HEDIS Medication Management for People with Asthma (MMA)*. Published online March 13, 2020. Accessed June 29, 2024. https://www.ncqa.org/wp-content/uploads/2020/02/20200212_03_MMA.pdf
 52. Nanda A, Siles R, Park H, et al. Ensuring equitable access to guideline-based asthma care across the lifespan: tips and future directions to the successful implementation of the new NAEPP 2020 guidelines, a Work Group Report of the AAAAI Asthma, Cough, Diagnosis, and Treatment Committee. *J Allergy Clin Immunol*. 2023;151(4):869-880. doi:10.1016/j.jaci.2023.01.017
 53. Yawn BP, Wollan PC, Rank MA, Bertram SL, Juhn Y, Pace W. Use of Asthma APGAR tools in primary care practices: a cluster-randomized controlled trial. *Ann Fam Med*. 2018;16(2):100-110. doi:10.1370/afm.2179
 54. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the Asthma Control Test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59-65. doi:10.1016/j.jaci.2003.09.008
 55. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol*. 2009;124(4):719-723.e1. doi:10.1016/j.jaci.2009.06.053
 56. Yawn B. Introduction of Asthma APGAR tools improve asthma management in primary care practices. *J Asthma Allergy*. 2008;31(1):1-10. doi:10.2147/JAA.S3595
 57. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902-907. doi:10.1034/j.1399-3003.1999.14d29.x
 58. Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet*. 2019;394(10202):919-928. doi:10.1016/S0140-6736(19)31948-8
 59. Lugogo N, Gilbert I, Pollack M, Gandhi H, Tkacz J, Lanz MJ. Estimating inhaled corticosteroid exposure from short-acting β_2 -agonist-inhaled corticosteroid rescue. *J Asthma Allergy*. 2023;16:579-584. doi:10.2147/JAA.S408504
 60. Aldridge RE, Hancox RJ, Robin Taylor D, et al. Effects of terbutaline and budesonide on sputum cells and bronchial hyperresponsiveness in asthma. *Am J Respir Crit Care Med*. 2000;161(5):1459-1464. doi:10.1164/ajrccm.161.5.9906052
 61. Tattersfield AE, Postma DS, Barnes PJ, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. *Am J Respir Crit Care Med*. 1999;160(2):594-599. doi:10.1164/ajrccm.160.2.9811100
 62. Ghebre MA, Pang PH, Desai D, et al. Severe exacerbations in moderate-to-severe asthmatics are associated with increased pro-inflammatory and type 1 mediators in sputum and serum. *BMC Pulm Med*. 2019;19(1):144. doi:10.1186/s12890-019-0906-7
 63. Shrestha Palikhe N, Wu Y, Konrad E, et al. Th2 cell markers in peripheral blood increase during an acute asthma exacerbation. *Allergy*. 2021;76(1):281-290. doi:10.1111/all.14543
 64. Lanz MJ, Gilbert IA, Gandhi HN, Pollack M, Tkacz JP, Lugogo NL. Patterns of rescue and maintenance therapy claims surrounding a clinical encounter for an asthma exacerbation. *Ann Allergy Asthma Immunol*. 2023;131(4):458-465.e1. doi:10.1016/j.anai.2023.06.018
 65. Shah PA, Brightling C. Biologics for severe asthma—which, when and why? *Respirology*. 2023;28(8):709-721. doi:10.1111/resp.14520
 66. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. *N Engl J Med*. 2022;386(2):157-171. doi:10.1056/NEJMr2032506
 67. Dabbs W, Bradley MH, Chamberlin SM. Acute asthma exacerbations: management strategies. *Am Fam Physician*. 2024;109(1):43-50.

Hypercortisolism Is More Common Than You Think—Here’s How to Find It

Pamela Kushner, MD, FAAFP; David R. Brown, MD, PhD; Robert S. Busch, MD, FACE

Fed Pract. 2024;41(suppl 6):S23-S28. doi:10.12788/fp.0532

KEY TAKEAWAYS

- Hypercortisolism as a diagnosis is often delayed or missed, leading to detrimental consequences for patients, including unnecessary morbidity and mortality.
- Current data suggest the prevalence of hypercortisolism is higher than previously estimated.
- Hypercortisolism is a heterogeneous, multisystemic disease with variable presentation along a spectrum of signs and symptoms from clinically inapparent to classically overt.
- Hypercortisolism occurs along a continuum associated with cardiometabolic risks that increase with disease severity and duration.
- Screening for hypercortisolism in primary care requires appropriate patient selection with a high pretest probability, use of a sensitive screening test, and interpretation of results within the clinical context of the patient’s medical history and presentation.

- A successful referral to endocrinology requires communicating the patient’s relevant medical history and clinical findings, reasons for suspecting hypercortisolism, and results of screening tests.

FACULTY

Pamela Kushner, MD, FAAFP, University of California Irvine Medical Center, Clinical Professor of Family Medicine, Irvine, CA

David R. Brown, MD, PhD, Private Practice, Endocrinology, Diabetes, and Metabolism, Rockville, MD

Robert S. Busch, MD, FACE, Director of Clinical Research, Albany Medical Faculty Practice: Community Endocrine Group, Albany, NY

DISCLOSURES

Dr. Kushner is a paid consultant and a member of the advisory board and speakers

bureau to Corcept Therapeutics. Dr. Brown serves as a consultant to Corcept Therapeutics and as a member of its advisory board and speakers bureau. Dr. Busch is a research consultant to Corcept Therapeutics and on the speakers bureau for Amgen, Astra Zeneca, Lilly, Novo Nordisk, and Sanofi.

ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, at Primary Care Education Consortium.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium.

SUPPORTER

This article is supported by funding from Corcept Therapeutics.

UNDERSTANDING HYPERCORTISOLISM: SUMMARY FOR PRIMARY CARE

Endogenous hypercortisolism, also known as Cushing syndrome, is a multisystemic endocrine disorder characterized by prolonged excessive cortisol activity.¹ This condition often goes undiagnosed or is misdiagnosed, resulting in unnecessary progression of morbidity and increased cardiovascular-related mortality.²⁻⁵ Here we discuss the prevalence, variable presentation, and detrimental clinical consequences of hypercortisolism, emphasizing the importance of early detection and appropriate referral.

CLASSIFICATION OF HYPERCORTISOLISM

Hypercortisolism can be classified into 2 main categories¹:

- **ACTH-dependent hypercortisolism:** Includes excess adrenocorticotropic hormone (ACTH) secretion by pituitary tumors (Cushing disease) and nonpituitary tumors (ectopic ACTH secretion)
- **ACTH-independent hypercortisolism:** Includes autonomous cortisol secretion by one or both adrenal glands

Cushing disease with a pituitary source is traditionally viewed as the most common etiology of hypercortisolism. However, as routine abdominal imaging becomes increasingly common in medical practice, the recognition and understanding of adrenal hypercortisolism have grown substantially. Advances in imaging technologies, such as computed tomography and magnetic resonance imaging, have led to the detection of more incidental adrenal tumors, up to 50% of which are associated with autonomous cortisol secretion.⁶ These findings enhance the understanding of the disease and its prevalence, which is higher than previously thought.⁷

A MULTISYSTEMIC, HETEROGENEOUS DISEASE

The understanding of the disease’s presentation has also evolved, recognizing hypercortisolism as a multisystemic and heterogeneous condition. The “index case” of Cushing disease, described by Harvey Cushing in 1912, exhibited a full range of overt features, such as a round face, central obesity, purple striae, and proximal muscle wasting.^{1,8} However, contemporary understanding recognizes that

hypercortisolism presents with a broad spectrum of symptoms and comorbidities.⁹ These include nonspecific features that overlap with disorders common in the general population, such as weight gain, diabetes, hypertension, obesity, hypokalemia, dyslipidemia, osteoporosis, kidney stones, and reproductive and psychiatric disorders.^{2,3,5} Thus, it is crucial to adopt a personalized approach to diagnosis that considers the patient's comprehensive clinical picture.

A CONTINUUM WITH DETRIMENTAL CONSEQUENCES AND DELAYED DIAGNOSIS

The wide spectrum of clinical signs and symptoms that may vary among patients can complicate diagnosis, leading to significant diagnostic delays of up to 10 years.^{10,11} The consequences of delayed diagnosis can be detrimental, as prolonged exposure to elevated cortisol leads to an increased risk of cardiometabolic abnormalities (diabetes, hypertension, and cardiovascular disease), osteoporosis, and psychiatric disorders.²⁻⁵ Mortality rates 2 to 5 times higher than the general population are reported in untreated hypercortisolism.¹²⁻¹⁴ The detrimental impact of delayed diagnosis underscores the need for a heightened awareness and timely intervention in primary care settings.

Importantly, hypercortisolism should be viewed as a continuum, with increased cardiometabolic comorbidities and mortality across the spectrum.¹⁵ Even cases less clinically apparent and lacking the classically described overt features are linked to increased cardiometabolic comorbidities and mortality.¹⁵ Early detection and management are crucial to mitigate these risks.

WHO TO SCREEN FOR HYPERCORTISOLISM

Although the incidence of hypercortisolism in the general population is low, recent data suggest that the prevalence is higher in the at-risk population with certain risk factors. The 2008 Endocrine Society Clinical Practice Guideline recommends screening patients who have multiple risk factors for hypercortisolism to increase the pretest probability of hypercortisolism and the positive predictive value of the screening.¹⁶ If the pretest probability for hypercortisolism is high, further evaluation is recommended even in patients with normal test results.

The guideline recommends screening for hypercortisolism in the at-risk population, including patients with the following features¹⁶:

1. Patients with unusual features for their age, such as osteoporosis/fragility fracture, type 2 diabetes (T2D), or hypertension in young individuals
2. Patients with multiple and unexplained/progressive features, like worsening T2D outside

of the normal progression or unexplained recent weight gain

3. All patients with adrenal mass

Applying these screening criteria in a prospective hypercortisolism registry, up to a 50% prevalence of hypercortisolism was identified in the at-risk patient populations.² Additionally, the ongoing CATALYST study (NCT05772169) has shown that patients with difficult-to-control diabetes represent an at-risk population with a high pretest probability of hypercortisolism. CATALYST is the first prospective, multicenter, US-based, large study including >1000 patients with difficult-to-control T2D (glycated hemoglobin [HbA1c] 7.5%–11.5% despite receiving multiple therapies); the prevalence of hypercortisolism is 24% in this study.^{17,18}

These findings confirm a higher-than-expected prevalence of hypercortisolism, especially in patients with specific risk factors (TABLE).^{6, 17, 19-26} These patients constitute an at-risk population, in which screening for hypercortisolism is warranted.

HOW TO SCREEN FOR HYPERCORTISOLISM

Three tests are commonly used to screen for evidence of hypercortisolism: the 1-mg overnight dexamethasone suppression test (DST), late-night salivary cortisol (LNSC), and 24-hour urine-free cortisol (UFC).^{16,27} Each test has strengths and limitations.¹⁶ However, the 1-mg overnight DST, using a post-DST serum cortisol cutoff of >1.8 µg/dL, is recommended as the most sensitive first-line screening method due to its high sensitivity (up to 95%).¹⁶ Well-known causes of false-positive DST results should be excluded before diagnosing hypercortisolism. Specific medications and conditions to watch for are shown in FIGURE 1.⁸ It is also important to ensure adequate suppression of normal pituitary corticotroph function, indicated by serum dexamethasone levels ≥140 ng/dL, measured alongside serum cortisol post-DST.¹⁶ The 24-hour UFC and LNSC tests are less sensitive in patients with milder presentations, but an abnormally high result strongly supports a hypercortisolism diagnosis.⁸

When interpreting biochemical test results, clinicians must account for the clinical index of suspicion, especially in the context of patients' medical history and comorbidities. FIGURE 1 illustrates how to perform the tests and interpret the results, with testing considerations for primary care.

SUMMARY OF SCREENING IN PRIMARY CARE

Effective screening for hypercortisolism in primary care involves the following:

- **Appropriate patient selection:** Identifying patients with signs and symptoms suggestive of

TABLE. At-risk patient population to screen for hypercortisolism

Population	Prevalence of hypercortisolism	Examples of clinical presentation
Patients with adrenal incidentaloma	Up to 50% ⁶	Patients with unsuspected tumors discovered in one or both of their adrenal glands
Patients with poorly controlled T2D	Up to 24% ^{17, 19, 23-26}	Difficult-to-control T2D with HbA1c >7.5% despite multiple antihyperglycemic medications
		T2D with poor glucose control despite insulin treatment and other comorbidities, including obesity, hypertension, hyperlipidemia, and CVD
		T2D with high insulin dose requirements, especially prandial insulin
		Patients with T2D onset before 40 years of age
		Patients with both diabetes and hypertension, requiring 2 or more drugs to control blood pressure
		Patients with both diabetes and hypertension, requiring insulin to control blood sugar
		Patients with T2D and microvascular or macrovascular complications
Patients with osteoporosis/fragility fractures	Up to 10.8% ²⁰	Premenopausal women with fragility fracture
		Eugonadal men with fragility fracture
		Patients with very low or rapidly declining bone density, not responding to osteoporosis treatment
		Patients with a history of vertebral fracture, especially obese patients with vertebral fracture
Patients with hypertension	Up to 8% ^{21,22}	Treatment-resistant hypertension (on 3 or more antihypertensive drugs, including a diuretic)
		Patients with hypertension onset before 30 years of age

Abbreviations: CVD, cardiovascular disease; HbA1c, glycated hemoglobin A1c; T2D, type 2 diabetes.

hypercortisolism and selecting patients with a high pretest probability of hypercortisolism¹⁶

- **Sensitive screening tests:** Using a sensitive screening test such as the 1-mg overnight DST can help identify patients who need further investigation^{8,16}
- **Clinical context:** Interpreting test results within the context of the patient's medical history and presentation is necessary⁸

SUCCESSFUL REFERRAL TO ENDOCRINOLOGY

A successful referral to endocrinology hinges on clear communication with the endocrinologist. Primary care clinicians (PCCs) should include the following in the referral letter (**FIGURE 2**):

- The patient's relevant medical history and clinical findings
- Reasons for suspecting hypercortisolism, emphasizing the key factors contributing to high clinical suspicion

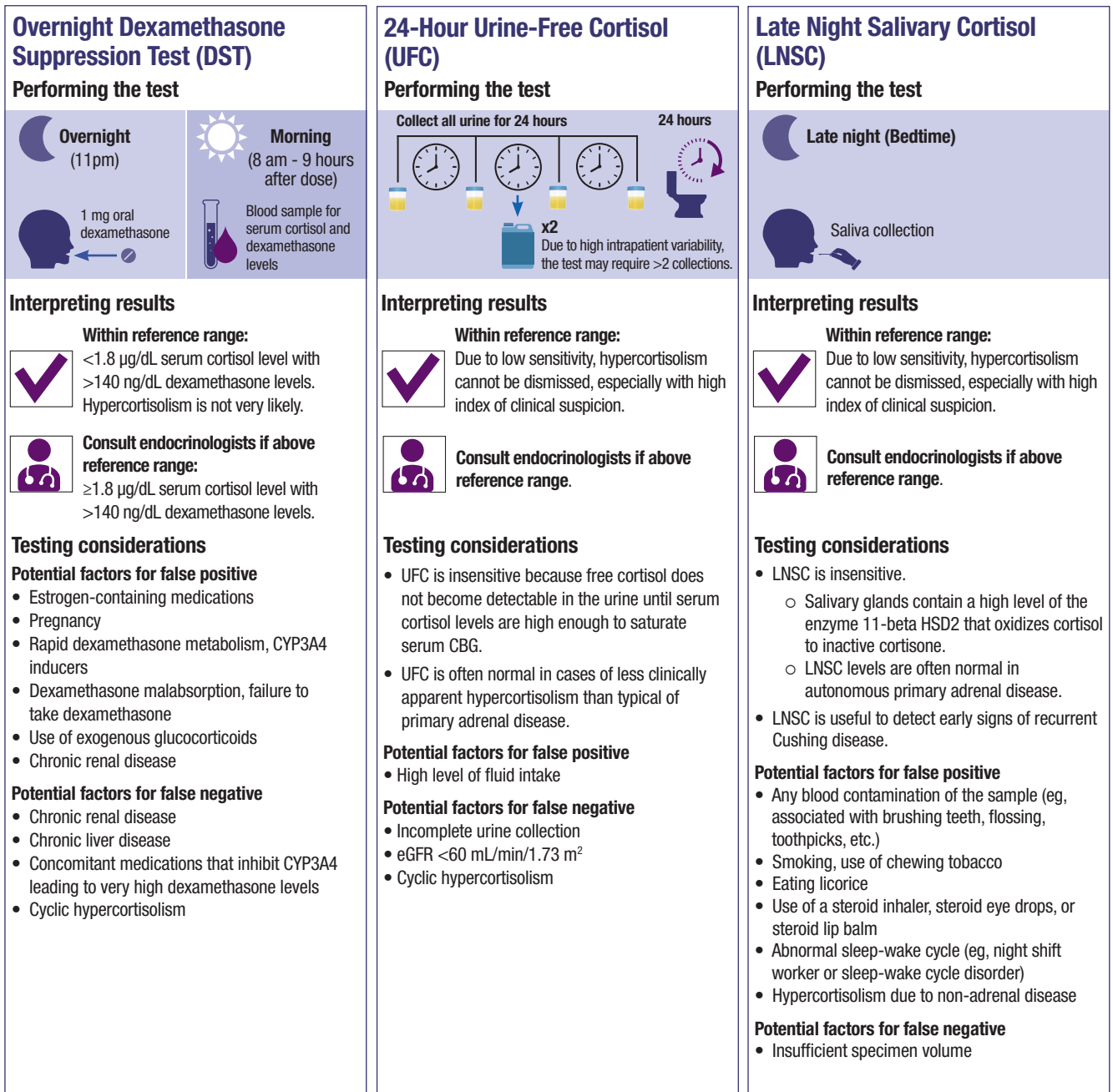
- Descriptions of the testing procedures and results of initial screening tests (including dexamethasone serum level for patients with 1-mg overnight DST)

By providing comprehensive and detailed referrals, PCCs can facilitate timely and effective specialist care, ultimately improving patient outcomes. **FIGURE 2** summarizes the process and considerations for screening, workup, and referral in primary care.

CONCLUSION

Awareness and understanding of hypercortisolism are essential for PCCs. Recognizing the signs and symptoms, selecting patients with a high pretest probability, utilizing appropriate screening methods, and making informed referrals can significantly impact patient health by reducing the delay in diagnosis and preventing the severe complications associated with this condition.

FIGURE 1. Screening tests for hypercortisolism: Process and considerations⁸



Abbreviations: CBG, cortisol-binding globulin; CYP3A4, cytochrome P450 isoform 3A4; eGFR, estimated glomerular filtration rate; HSD2, hydroxysteroid dehydrogenase type 2.

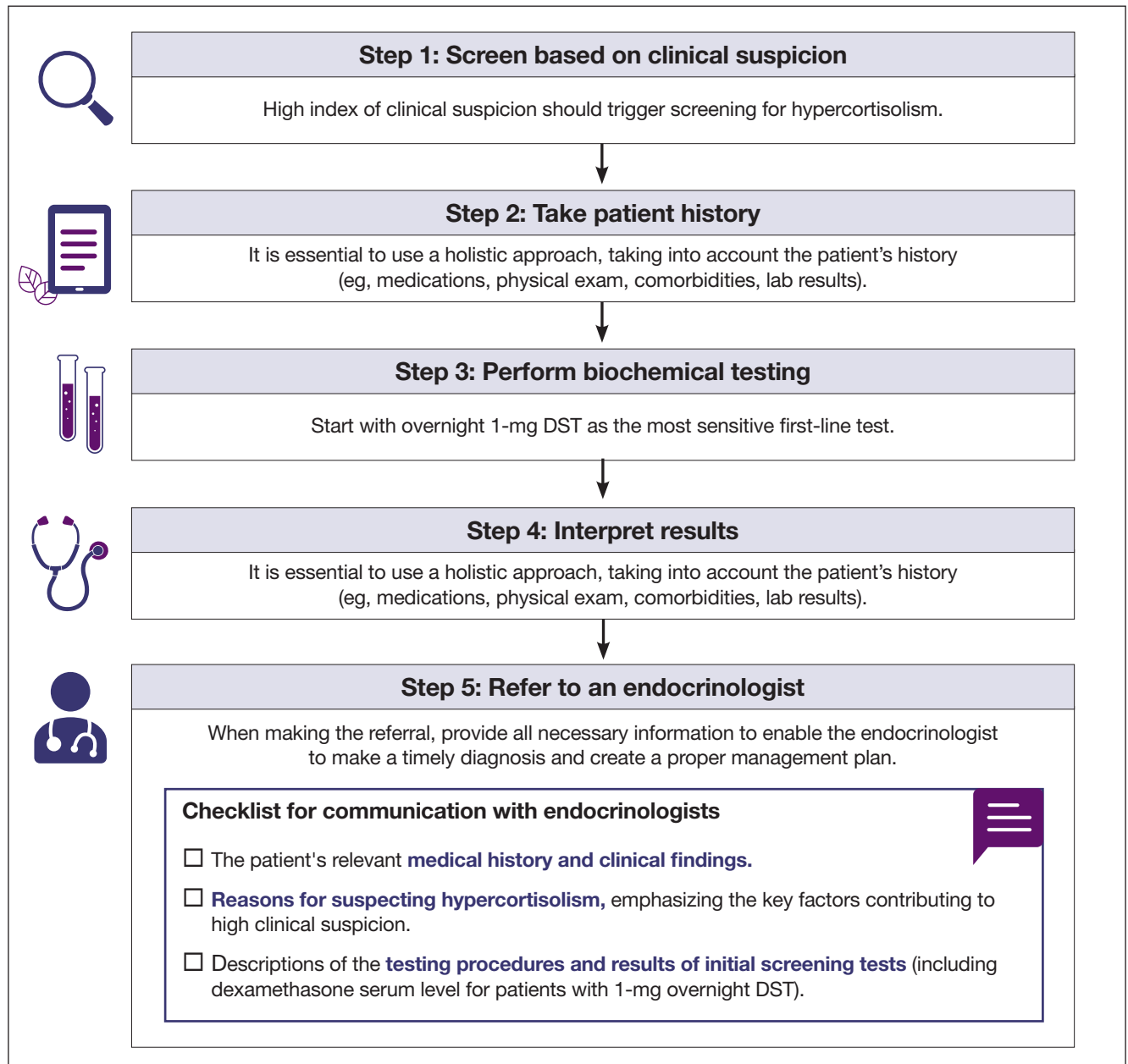
Source: Scoffings K et al. Recognising and diagnosing Cushing's syndrome in primary care: challenging but not impossible. *Br J Gen Pract.* 2022;72(721):399-401. Figure licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction. The license can be viewed at this link: <https://creativecommons.org/licenses/by/4.0/legalcode>.

CASE STUDY

A 68-year-old man presents with gradual abdominal weight gain over the past 4 years and finds it increasingly difficult to control his hypertension and T2D, especially postprandial blood glucose, despite adherence to multiple antihyperglycemic agents

and efforts to control his diet. He has a history of obesity (with recent, unexplained central weight gain), kidney stones, mixed hyperlipidemia, osteopenia (with a previous nontraumatic stress fracture), coronary artery disease, diabetic neuropathy, and peripheral polyneuropathy. He takes multiple blood pressure and

FIGURE 2. Process and considerations for screening, workup, and referral for hypercortisolism in primary care



Abbreviation: DST, dexamethasone suppression test.

antihyperglycemic medications. The patient presents to his PCC, noting, "I am taking too many drugs—you are missing something. There has got to be a better way!"

Laboratory Evaluations

- Glycated hemoglobin (HbA1c): 7.8%
- Fasting glucose: 124 mg/dL
- 4-hour postprandial glucose: 240–295 mg/dL, despite dietary carbohydrate control
- Morning cortisol: 19 µg/dL (normal 10–25 µg/dL)²⁸
- Post-1-mg DST serum cortisol: 3.5 µg/dL (normal range <1.8 µg/dL)¹⁶
- Post-1-mg DST serum dexamethasone: 412.7 ng/dL (expected range >140 ng/dL for adequate serum cortisol suppression)²⁹
- 24-hour UFC: 38 µg/24 hr (normal range varies depending on specific test; example normal range <11–53 µg/24 hr)³⁰

Clinical assessment

The patient has several risk factors that increase the pretest probability of hypercortisolism and should trigger screening. These include difficult-to-control T2D with microvascular and macrovascular complications, postprandial hyperglycemia elevated out of proportion to fasting glucose and HbA1c levels, resistant hypertension, unexplained central weight gain, kidney stones, osteopenia, and fragility fracture. In the presence of these risk factors, the diagnosis of hypercortisolism, with careful exclusion of known causes leading to false-positive results, is confirmed with a 1-mg DST serum cortisol level >1.8 µg/dL and serum dexamethasone >140 ng/dL.

Outcome

The patient was referred to an endocrinologist for further evaluation and confirmation of ACTH-independent autonomous adrenal hypercortisolism. Adrenal imaging confirmed a structural source of excess cortisol, and cortisol-directed therapy was provided. The patient experienced improvements in glucose control with an HbA1c reduction to 5.7%. In addition, this patient was able to discontinue 4 of his antihyperglycemic medications. Blood pressure control improved, even though 3 of 5 blood pressure medications were discontinued, and he lost 25 lbs.

Clinical learning

This patient could have been considered a “typical” patient seen in the primary care setting. This case underscores the importance of a holistic approach, taking into account the patient’s medical history and comorbidities. This comprehensive assessment enabled effective screening and appropriate treatment, ultimately improving the patient’s outcomes. ●

REFERENCES

URLs must be entered manually, rather than copied and pasted.

- Reincke M, Fleseriu M. Cushing syndrome: a review. *JAMA*. 2023;330(2):170. doi:10.1001/jama.2023.11305
- Braun LT, Vogel F, Zopp S, et al. Whom should we screen for Cushing syndrome? The Endocrine Society Practice Guideline Recommendations 2008 revisited. *J Clin Endocrinol Metabol*. 2022;107(9):e3723-e3730. doi:10.1210/clinem/dgac379
- Yorke E, Atiase Y, Akpalu J, Sarfo-Kantanka O. Screening for Cushing syndrome at the primary care level: what every general practitioner must know. *Int J Endocrinol*. 2017;2017:1-6. doi:10.1155/2017/1547358
- Limumpornpetch P, Morgan AW, Tiganeşcu A, et al. The effect of endogenous Cushing syndrome on all-cause and cause-specific mortality. *J Clin Endocrinol Metabol*. 2022;107(8):2377-2388. doi:10.1210/clinem/dgac265
- Fallo F, Di Dalmazi G, Beuschlein F, et al. Diagnosis and management of hypertension in patients with Cushing’s syndrome: a position statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension. *J Hypertens*. 2022;40(11):2085-2101. doi:10.1097/HJH.0000000000003252
- Fassnacht M, Tsagarakis S, Terzolo M, et al. European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol*. 2023;189(1):G1-G42. doi:10.1093/ajendo/lvad066
- Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, Bornstein SR. The clinically inapparent adrenal mass: update in diagnosis and management. *Endocr Rev*. 2004;25(2):309-340. doi:10.1210/er.2002-0031
- Scoffings K, Morris D, Pullen A, Temple S, Trigell A, Gurnell M. Recognising and diagnosing Cushing’s syndrome in primary care: challenging but not impossible. *Br J Gen Pract*. 2022;72(721):399-401. doi:10.3399/bjgp22X720449
- Kelsall A, Newell-Price J. Cushing’s disease—from Minnie G to key issues in the early 21st century. *Lancet Diabetes Endocrinol*. 2019;7(12):959-964. doi:10.1016/S2213-8587(19)30343-2
- Valassi E, Chiodini I, Felders RA, et al. Unmet needs in Cushing’s syndrome: the patients’ perspective. *Endocr Connect*. 2022;11(7):e220027. doi:10.1530/EC-22-0027
- Page-Wilson G, Oak B, Silber A, et al. Evaluating the burden of endogenous Cushing’s syndrome using a web-based questionnaire and validated patient-reported outcome measures. *Pituitary*. 2023;26(4):364-374. doi:10.1007/s11102-023-01314-7
- Lindholm J, Juul S, Jørgensen JOL, et al. Incidence and late prognosis of Cushing’s syndrome: a population-based study. *J Clin Endocrinol Metabol*. 2001;86(1):117-123. doi:10.1210/jcem.86.1.7093
- Dekkers OM, Horváth-Puhó E, Jørgensen JOL, et al. Multisystem morbidity and mortality in Cushing’s syndrome: a cohort study. *J Clin Endocrinol Metabol*. 2013;98(6):2277-2284. doi:10.1210/jc.2012-3582
- Clayton RN, Raskauskienė D, Reulen RC, Jones PW. Mortality and morbidity in Cushing’s disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. *J Clin Endocrinol Metabol*. 2011;96(3):632-642. doi:10.1210/jc.2010-1942
- Araujo-Castro M, Pascual-Corrales E, Lamas C. Possible, probable, and certain hypercortisolism: a continuum in the risk of comorbidity. *Ann Endocrinol*. 2023;84(2):272-284. doi:10.1016/j.ando.2023.01.005
- Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing’s syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metabol*. 2008;93(5):1526-1540. doi:10.1210/jc.2008-0125
- Auchus R, DeFronzo R, Phillis-Tsimikas A, Fonseca V, Buse J. Prevalence of hypercortisolism in difficult-to-control Type 2 Diabetes P at the 84th American Diabetes Association (ADA) Scientific Sessions, June 21-24, 2024, Orlando, FL
- DeFronzo RA, Auchus RJ, Bancos I, et al. Study protocol for a prospective, multicentre study of hypercortisolism in patients with difficult-to-control type 2 diabetes (CATALYST): prevalence and treatment with mifepristone. *BMJ Open*. 2024;14(7):e081121. doi:10.1136/bmjopen-2023-081121
- Costa DS, Conceição FL, Leite NC, Ferreira MT, Salles GF, Cardoso CRL. Prevalence of subclinical hypercortisolism in type 2 diabetic patients from the Rio de Janeiro Type 2 Diabetes Cohort Study. *J Diabetes Complications*. 2016;30(6):1032-1038. doi:10.1016/j.jdiacomp.2016.05.006
- Chiodini I, Mascia ML, Muscarella S, et al. Subclinical hypercortisolism among outpatients referred for osteoporosis. *Ann Intern Med*. 2007;147(8):541. doi:10.7326/0003-4819-147-8-200710160-00006
- Trifanescu R, Carsote M, Carageorghieopol A, et al. Screening for secondary endocrine hypertension in young patients. *Maedica (Bucur)*. 2013;8(2):108-115.
- Martins LC, Conceição FL, Muxfeldt ES, Salles GF. Prevalence and associated factors of subclinical hypercortisolism in patients with resistant hypertension. *J Hypertens*. 2012;30(5):967-973. doi:10.1097/HJH.0b013e3283521484
- Chiodini I, Torlontano M, Scillitani A, et al. Association of subclinical hypercortisolism with type 2 diabetes mellitus: a case-control study in hospitalized patients. *Eur J Endocrinol*. 2005;153(6):837-844. doi:10.1530/eje.1.02045
- León-Justel A, Madrazo-Atutxa A, Alvarez-Rios AI, et al. A probabilistic model for Cushing’s syndrome screening in at-risk populations: a prospective multicenter study. *J Clin Endocrinol Metabol*. 2016;101(10):3747-3754. doi:10.1210/jc.2016-1673
- Catargi B, Rigalleau V, Poussin A, et al. Occult Cushing’s syndrome in type-2 diabetes. *J Clin Endocrinol Metabol*. 2003;88(12):5808-5813. doi:10.1210/jc.2003-030254
- Van Hulsteyn LJ, Pasquali R, Casanueva F, et al. Prevalence of endocrine disorders in obese patients: systematic review and meta-analysis. *Eur J Endocrinol*. 2020;182(1):11-21. doi:10.1530/EJE-19-0666
- Galm BP, Qiao N, Klibanski A, Biller BMK, Tritos NA. Accuracy of laboratory tests for the diagnosis of Cushing syndrome. *J Clin Endocrinol Metabol*. 2020;105(6):2081-2094. doi:10.1210/clinem/dgaa105
- Goder N, Gerstenhaber F, Gal Oz A, et al. Cortisol levels during first admission day are associated with clinical outcomes in surgical critically ill patients. *Crit Care Explor*. 2024;6(5):e1086. doi:10.1097/CCE.0000000000001086
- Farinelli DG, Oliveira KC, Hayashi LF, Kater CE. Overnight 1-mg dexamethasone suppression test for screening Cushing syndrome and mild autonomous cortisol secretion (MACS): what happens when serum dexamethasone is below cutoff? How frequent is it? *Endocr Pract*. 2023;29(12):986-993. doi:10.1016/j.eprac.2023.09.007
- Petersenn S, Newell-Price J, Findling JW, et al. High variability in baseline urinary free cortisol values in patients with Cushing’s disease. *Clin Endocrinol*. 2014;80(2):261-269. doi:10.1111/cen.12259

Improving COPD Management at Transitions of Care

Alan Kaplan, MD, CCFP(EM) FCFP CPC(HC)

Fed Pract. 2024;41(suppl 6):S29-S34. doi:10.12788/fp.0533

KEY TAKEAWAYS

- Chronic obstructive pulmonary disease (COPD) remains a substantial cause of morbidity and mortality in the United States.
- Patients with COPD are more likely to have cardiovascular disease (CVD) than those without COPD, and cardiopulmonary events are the most common reason for death.
- Notable updates in the 2024 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report include additional information on hyperinflation, leveraging lung cancer screening to assess for COPD, the role of blood eosinophil count, choice of inhaler device, and pharmacotherapy for smoking cessation.
- Optimizing transitional care management post-hospitalization or post-emergency department discharge for patients with COPD is essential and should include

cardiopulmonary risk evaluation including both future respiratory exacerbation and CVD risk, recognizing that future exacerbations and hospitalizations are more likely after an episode.

- Primary care clinicians (PCCs) can work with a multidisciplinary team and support staff to develop approaches to transitional care that enhance overall patient care and treatment outcomes.

FACULTY

Alan Kaplan, MD, CCFP(EM) FCFP CPC(HC), Chair, Family Physician Airways Group of Canada; Vice President, Respiratory Effectiveness Group; Primary Care Cancer Lead, Central Region, Cancer Care Ontario.

DISCLOSURES

Dr. Kaplan serves as a consultant and member of the advisory board and speak-

ers bureau for Astra Zeneca, Chiesi Pharmaceuticals, GSK, and Trudel Healthcare Solutions. Austin Ulrich, PharmD, BCACP, has no disclosures to report.

ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, Primary Care Education Consortium.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and the Primary Care Respiratory Group.

SUPPORTER

This article is supported by funding from AstraZeneca.

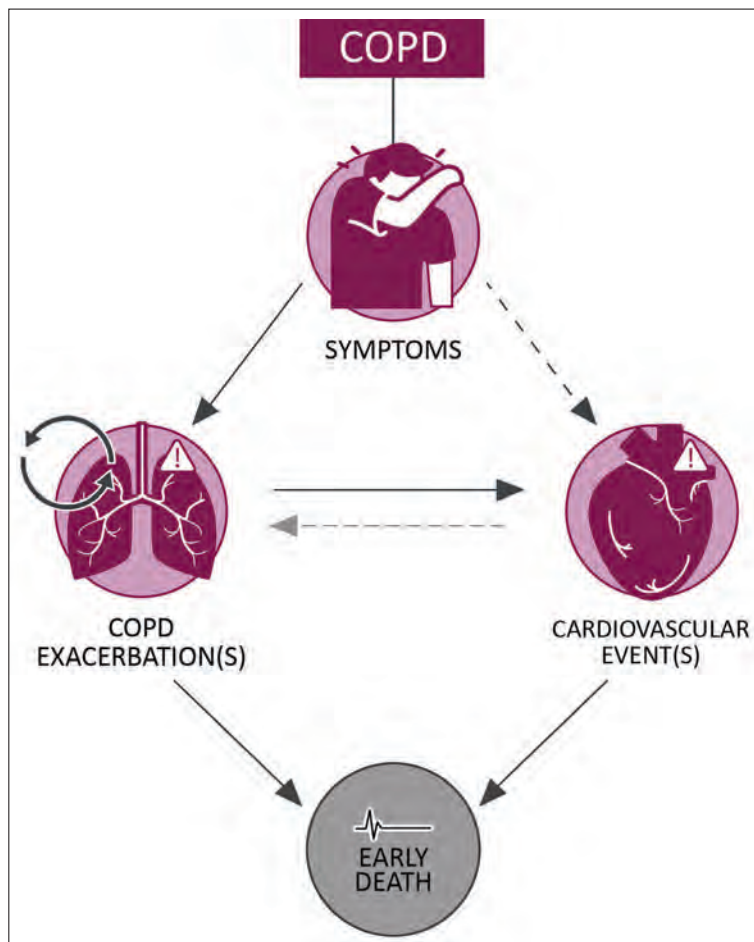
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease worldwide and in the United States that causes significant morbidity and mortality.^{1,2} As of 2021, COPD was the sixth leading cause of death in the US and accounted for most of the deaths from chronic lower respiratory diseases.³ Mechanisms of COPD and exacerbations increase the risk for both pulmonary and cardiovascular (CV) events (cardiopulmonary risk).⁴⁻⁶ A proposed definition of cardiopulmonary risk is “the risk for serious respiratory and/or CV events in patients with COPD. These include, but are not limited to, COPD exacerbations, myocardial infarction, stroke, heart failure decompensation, arrhythmia, and death due to any of these events” (FIGURE).⁷ Cardiopulmonary causes are the most common reasons for death in patients with COPD and can lead to early death.^{8,9} In addition to patient morbidity, costs and health care utilization are significant impacts of COPD.

Costs of COPD in the US increased 72% from 2000 to 2018 and are estimated at approximately \$24 billion each year among adults 45 years of age and older, including \$11.9 billion in prescription drug costs, \$6.3 billion in inpatient costs, \$2.4 billion in office-based costs, \$1.6 billion in home health

costs, \$900 million in emergency department (ED) costs, and \$800 million in outpatient costs.¹⁰ The average annual cost per patient per year is estimated at \$4,322.¹⁰ Hospitalizations and ED visit rates for COPD remain high, although rates decreased from 2016 to 2020, driven significantly by the COVID-19 pandemic, which led to avoidance of health care facilities and limited capacity in these institutions.¹⁰ In 2020, there were 335,000 hospitalizations for COPD in the US (101.3 per 100,000 population) and 925,000 ED visits (279.1 per 100,000 population).¹⁰

Results of a recent US cross-sectional study indicate that adults living with COPD were more likely to be unemployed than those without COPD (56.2% vs 45.3%), were unable to work due to illness or disability (30.1% vs 12.1%), and had difficulty paying bills (16.1% vs 8.8%).¹¹ Additionally, those with COPD reported worse perceived health (36.2% vs 14.4%), missed more work days because of illness or injury per year (median, 2.5 days vs 0.0 days), and had limitations in physical function (40.1% vs 19.4%). Adults who self-reported as Black were more likely to have CV-risk conditions, worse socioeconomic and health-related quality of life outcomes, and higher health care expenses than those who self-reported as White or of other races.¹¹

FIGURE. COPD-associated cardiopulmonary risk

Abbreviation: COPD, chronic obstructive pulmonary disease.

Arrow type and shade indicate strength of association: strong association, with substantial supporting data (dark grey solid); emerging association, with some supporting data (dark grey dotted); suspected association, with data yet to be generated (light grey dotted).

Source: Singh D, et al. Implications of cardiopulmonary risk for the management of COPD: a narrative review. *Adv Ther.* 2024;41(6):2151-2167. No changes were made to the figure prior to reprinting. Figure licensed under a Creative Commons Attribution-Noncommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution, and reproduction. The license can be viewed at this link: <https://creativecommons.org/licenses/by-nc/4.0/legalcode>

Risk for morbidity and mortality from COPD is particularly pronounced surrounding transitions of care, which are defined by the Centers for Medicare & Medicaid Services (CMS) as “the movement of a patient from one setting of care (hospital, ambulatory primary care practice, ambulatory specialty care practice, long-term care, home health, rehabilitation facility) to another.”^{12,13} Data suggest that implementing transitions of care best practices can optimize COPD care and lead to lower readmission rates.^{12,14}

Because approximately 80% of patients with COPD are managed in the primary care setting, primary care clinicians (PCCs) play a major role in managing COPD, including maximizing quality of life, addressing CV risk, preventing

and treating exacerbations, and ensuring adequate intervention at care transitions.^{15,16} Specific tasks performed at transitions of care (after hospital or ED discharge) by PCCs or other office staff include a follow-up, post-discharge visit, medication reconciliation, and multidisciplinary team coordination, including referrals to a specialist when needed.^{15,17}

CASE STUDY

A 62-year-old man with COPD is admitted to the hospital with difficulty breathing due to an infectious exacerbation of his COPD, and with treatment, his status improves during the course of his stay. He starts with prednisone and antibiotics, and his long-acting muscarinic antagonist (LAMA) inhaler is intensified to a long-acting beta agonist (LABA) + LAMA + inhaled corticosteroid (ICS) inhaler, based on his high risk for recurrent exacerbation. He is discharged with a prescription for a LABA + LAMA + ICS inhaler that is not covered by insurance. At a post-discharge follow-up visit, the patient tells his PCC that he cannot afford the inhaler and has not picked it up yet. His overall management is complicated by a history of transient ischemic attack after a previous COPD exacerbation, though he did not experience any CV events during this most recent hospitalization.

The patient in the case scenario above is at increased cardiopulmonary risk due to his recent exacerbation and subsequent nonadherence to prescribed exacerbation prevention triple-inhaled therapy. During this transitional care visit, the PCC and other members of the care team should seek to reduce the patient’s risk for mortality and other adverse outcomes, improve access to COPD and CV treatments, and reduce the risk for future exacerbations.

2024 GOLD REPORT UPDATES

The 2024 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report includes a variety of updates, many of which are described below, that clinicians need to be aware of to remain updated on the best practices for COPD management. Additional key updates that are not reviewed in this article include information on preserved ratio impaired spirometry, clarification of the role of prebronchodilator spirometry, and interstitial lung abnormalities.¹⁷

Hyperinflation. A section on hyperinflation has been added. Hyperinflation is defined as increased gas volume in the lungs compared to normal values at the end of spontaneous expiration. It places additional strain on the heart by reducing preload and afterload and is common in patients

with COPD. Hyperinflation contributes to impaired exercise tolerance, dyspnea, increased risk for hospitalization, development of respiratory failure, and increased mortality.¹⁷ Interventions that can improve hyperinflation include bronchodilators, supplemental oxygen, pulmonary rehabilitation, pursed lip breathing, inspiratory muscle training, sputum management, and lung reduction surgery (in certain cases of severe hyperinflation).

COPD identification and screening. Certain patients, such as those undergoing screening for lung cancer or investigation for lung abnormalities, can be screened using low-dose chest computed tomography (LDCT), leveraging this imaging to identify unrecognized symptoms of COPD and assess airflow limitation.¹⁷ Additionally, the role of spirometry has been re-emphasized for diagnosis, assessment of severity of airflow obstruction for prognosis, and follow-up assessment including therapeutic decision-making and identification of rapid decline.¹⁷ Of note, the GOLD report recommends case finding, or screening for symptoms, but not proactive, routine screening for COPD.¹⁷

Blood eosinophil count. The 2024 report further emphasizes the role of measuring blood eosinophils in patients with COPD. Blood eosinophil counts predict the magnitude of effect of ICS in preventing exacerbations and are recommended to guide use of ICS as a component of pharmacologic management of COPD.¹⁷

Choice of inhaler device. GOLD recognizes the differences in device size, portability, steps to prepare and inhale a dose, technique, and cleaning procedures between inhaler devices.¹⁷ Patients who are correctly using their current inhaled therapy who undergo treatment adjustment have a better chance of correct use if the new therapy uses the same device. The ability to use inhaled devices correctly depends on cognitive ability, dexterity, coordination, inspiratory flow ability, experience with other inhaler devices, and previous education on inhaler technique.¹⁷

Pharmacotherapy for smoking cessation. Consistent with evidence of the benefit of pharmacologic interventions to increase the likelihood of successful smoking cessation, GOLD recognizes the effectiveness of interventions such as nicotine replacement therapy, bupropion, nortriptyline, and varenicline.¹⁷

Vaccine recommendations. Recommendations for vaccines in patients with COPD were updated to align with current guidance from the Centers for Disease Control and Prevention, and vaccine recommendations are reviewed briefly below.

CARDIOPULMONARY DISEASE AND COPD

The pathophysiology and treatment of cardiopulmonary disease are interrelated and affect overall health outcomes.^{2,4,18-21} COPD increases the odds of having CV disease by a factor

of 2.7, compared with patients without COPD.²² A recent National Health and Nutrition Examination Survey population-based, cross-sectional study examined the prevalence of CV disease in patients with COPD using data from 2013-2018 in US adults aged 40 years and older.²³ The CV diseases considered were coronary heart disease, heart failure, angina pectoris, heart attack, diabetes, and stroke. Of 11,425 patients included, 661 had COPD and 10,764 did not. Patients with COPD had a significantly higher prevalence of CV disease (59.6%) than those without COPD (28.4%). After adjustment for covariates, COPD was significantly associated with the prevalence of 1 (odds ratio [OR], 2.2; $P < .001$), ≥ 2 (OR, 3.3; $P < .001$), and ≥ 3 (OR, 4.3; $P < .001$) CV diseases.²³

Patients with cardiopulmonary disease experience worse cardiac outcomes than those without COPD, as major adverse CV events are more likely after an acute COPD exacerbation, and CV events are one of the most common causes of death in patients with COPD.^{8,9,17} CV risk can remain elevated for up to 1 year following a COPD exacerbation, and as few as 1 severe COPD exacerbation can double the risk for heart attack and increase the risk for hospitalization and cardiopulmonary-related death.²⁴⁻²⁹

Suggested pathophysiologic mechanisms for cardiopulmonary disease include physiologic links between COPD and CV disease, such as dyspnea, hypoxemia, hyperinflation, and systemic inflammation.⁴ Risk factors that contribute to cardiopulmonary disease include age, smoking, physical inactivity, unhealthy diet, air pollution, genetic background, and health conditions such as diabetes, hypertension, hyperlipidemia, and infections.^{18,30}

Potential strategies to address cardiopulmonary disease associated with COPD include approaching COPD treatment as proactive (rather than reactive), appropriately initiating or escalating therapy to reach treatment goals, implementing triple-inhaled therapy (LAMA + LABA + ICS) for appropriate candidates, detecting and treating COPD earlier, and placing an increased focus on multidisciplinary management to treat COPD as a CV risk factor and manage CV risk appropriately.⁷ This includes implementing interventions that reduce CV and all-cause mortality in COPD, such as smoking cessation, early initiation of pulmonary rehabilitation, and fixed-dose combination triple therapy.⁷

COPD EXACERBATION FOLLOW-UP AT TRANSITIONS OF CARE

Optimizing management of COPD at transitions of care to mitigate exacerbations is essential, as an initial hospitalization for a COPD exacerbation is associated with recurrent exacerbations and other factors leading to short-term readmission and increased all-cause mortality.¹⁷ Hospital discharge bundles are often used to include key actions

intended to facilitate successful transition to outpatient care. Discharge criteria include the following¹⁷:

- Review of clinical and laboratory data
- Check maintenance therapy and patient understanding
- Reassess inhaler technique
- Ensure understanding of acute medication regimen (steroids/antibiotics)
- Assess need for continuing oxygen therapy, if applicable
- Provide management and follow-up plan for comorbidities
- Confirm follow-up arrangements for outpatient visits
- Step up therapies for COPD to help reduce the risk for further exacerbations
- Consider vaccination status for influenza, COVID, pneumonia, tetanus-pertussis, and respiratory syncytial virus (RSV)

Discharge instructions should also aim to prevent further exacerbations and should include recommendations that the patient participate in pulmonary rehabilitation, keep their scheduled follow-up visit, and receive recommended vaccines.¹⁷ Pharmacotherapy considerations at discharge should include optimizing CV medications (if applicable) and considering COPD treatments that can reduce exacerbations such as triple therapy in a single inhaler.¹⁷ Other preventive therapies such as roflumilast, azithromycin, mucolytic therapy, and an oscillating positive expiratory pressure device to help with mucus clearance may be considered based on patient characteristics.

Effective and early post-discharge follow-up is recommended to optimize transitions of care, regardless of any pre-discharge interventions. Early follow-up within 1 month following discharge is associated with fewer exacerbation-related readmissions and is recommended where possible.³¹ Multiple patient-related factors may preclude early follow-up after hospitalization for COPD, including poor adherence to medical recommendations, limited social support, the presence of more severe disease, and limited access to medical care. Regardless of the reason, patients who do not receive early post-discharge follow-up have increased 90-day mortality.¹⁷

Components of a post-discharge follow-up might include a variety of actions, including evaluation of patients' understanding of treatment regimens, assessment of symptoms, and determining the status of relevant comorbidities, such as CV risk assessment.¹⁷ Recommended actions during a short-term (1 to 4 weeks) and long-term (12 to 16 weeks) follow-up visit are similar, though at the short-term follow-up, patients' eligibility for pulmonary rehabilitation should be assessed, and at the long-term follow-up, spirometry should be conducted.¹⁷ If not already in place, transitional care visits provide opportunities to place referrals to specialists, where needed. A more comprehensive "checklist" set of post-discharge follow-up actions has also been suggested (TABLE).³²

Prevention of future exacerbations should also be addressed at post-discharge follow-up visits. Patients may be more motivated immediately following an episode to engage

TABLE. Example transitions of care COPD checklist for post-hospital discharge and chronic management³²

Post-hospital discharge follow-up
<i>Pharmacologic considerations</i>
<input type="checkbox"/> Provide medication reconciliation
<input type="checkbox"/> Apply GOLD treatment strategies/evidence-based treatment strategies
<input type="checkbox"/> Symptom assessment/strategy review
○ Action plan: importance of early symptom recognition
○ Review action plan
○ COPD assessment test (CAT)
Link: https://www.catestonline.org/patient-site-test-page-english.html
○ Modified British Medical Research Council (mMRC) questionnaire
Link: https://www.uptodate.com/contents/image?imageKey=PULM/86426
○ Symptom diary
<input type="checkbox"/> Provide continued patient education and counseling on role of long-term preventive and acute rescue medications
<input type="checkbox"/> Assess inhaler technique and concerns with inhaled medications
<input type="checkbox"/> Measure spirometry: forced expiratory volume in 1 second (FEV ₁)
<input type="checkbox"/> Consider measuring peak inspiratory flow in those prescribed a dry powder inhaler
<input type="checkbox"/> Perform cognitive and functional assessment and relation to appropriate device use
<input type="checkbox"/> Assess for changes in delivery device/medication
<input type="checkbox"/> Manage comorbidities, including cardiopulmonary risk
<input type="checkbox"/> Ensure vaccinations are up to date
<input type="checkbox"/> Assess need for starting or continuing supplemental oxygen administration
<i>Nonpharmacologic considerations</i>
<input type="checkbox"/> Evaluate durable medical equipment care/concerns/issues
<input type="checkbox"/> Assess home health care needs and plan to start if necessary
<input type="checkbox"/> Address nutritional concerns
<input type="checkbox"/> Evaluate for smoking cessation/second-hand exposure avoidance
<input type="checkbox"/> Assess goals of care/advanced directives
<input type="checkbox"/> Apply Transitional Care Management Codes for Medicare patients (99495 and 99496)

CONTINUED ON NEXT PAGE

in interventions that can help prevent exacerbations. When determining the patient's treatment regimen at transitional care visits to reduce the risk for exacerbations, clinicians should consider the use of nonpharmacologic and pharmacologic therapies that reduce the frequency of COPD exacerbations.¹⁷

Real-world evidence for transitional care programs. Although transitional care is recommended for all patients with COPD who are hospitalized, data are mixed as to the impact of formalized transitional care programs on outcomes. A recent systematic review and meta-analysis examined 9 randomized trials across multiple countries (including the US) assessing the effects of transitional care programs

on health care utilization and quality of life in patients with COPD.¹⁴ There was no statistically significant difference observed in the number of hospital readmissions and ED visits due to COPD between patients who were enrolled in a transitional care program and those who were not. However, patients in transitional care programs had a lower risk for readmission (risk ratio, 0.68; 95% CI, 0.56-0.84; $P = .0004$) and a numerically higher respiratory-related quality of life (mean difference on St. George's Respiratory Questionnaire, -10.58, 95% CI, -26.48 to 5.33; $P = .19$).¹⁴

Another study describing pharmacist-led transitions of care service for underserved patients with COPD noted that a significant decrease in the composite outcome (180-day COPD-related hospitalizations and ED visits) was observed in the pharmacist intervention group compared with usual care (mean difference, 0.82; 95% CI, 0.05-1.60; $P = .04$).¹² This was mostly driven by lower 30-day hospitalizations in the intervention group (mean difference, 0.15; 95% CI, 0.04-0.27; $P = .01$).¹² An additional pharmacist-led transition of care service for patients admitted with a principal diagnosis of COPD resulted in a decrease in the 30-day readmission rate from 25% at baseline to a mean of 16.2% after implementation.³³

If an institution were to develop or implement a transitional care program for patients with COPD, it would seem prudent to include the elements mentioned previously as recommended in the GOLD report, focusing on interventions supported by evidence.

Patient case scenario, revisited. In the patient case scenario presented previously, the primary care team should engage in the recommended post-discharge actions to prevent exacerbations and readmission to the hospital. The team might consider checking the patient's insurance coverage to determine if there is an alternative LABA + LAMA + ICS inhaler that would be covered and more affordable for the patient. If possible, the treatment should be prescribed in the same (or a similar) device so the patient is familiar with how to use it. The care team might also help the patient pursue other cost-savings options such as copay cards or patient assistance programs where

TABLE. (continued)

Chronic care management
<i>Pharmacologic considerations</i>
<input type="checkbox"/> Continue to monitor for any COPD exacerbations
<input type="checkbox"/> Apply GOLD treatment strategies/evidence-based treatment strategies
<input type="checkbox"/> Monitor for change in symptoms
<input type="checkbox"/> Provide continued patient education and counseling on role of long-acting and short-acting medications
<input type="checkbox"/> Review inhaler technique and assess for changes in delivery device/medication
<input type="checkbox"/> Consider measuring peak inspiratory flow in those prescribed a dry powder inhaler
<input type="checkbox"/> Perform cognitive and functional assessment and relation to appropriate device use
<input type="checkbox"/> Review all medications and provide medication reconciliation at each visit
<input type="checkbox"/> Review action plan
<input type="checkbox"/> Symptom and strategy review
○ CAT
Link: https://www.catestonline.org/patient-site-test-page-english.html
○ mMRC questionnaire
Link: https://www.uptodate.com/contents/image?imageKey=PULM/86426
<input type="checkbox"/> Assess inhaler technique at every visit
<input type="checkbox"/> Assess need for resting and exertional oxygen assessment
<input type="checkbox"/> Ensure vaccinations are up to date
<input type="checkbox"/> Screen for alpha-1 antitrypsin deficiency if not already done
<input type="checkbox"/> Screen as appropriate for lung cancer
<input type="checkbox"/> Bone density tests per guidelines
<input type="checkbox"/> Consider sleep study (screening tool for obstructive sleep apnea: https://www.fpagc.com/tools-resources)
<i>Nonpharmacologic considerations</i>
<input type="checkbox"/> Discuss and address medication access concerns/affordability issues
<input type="checkbox"/> Continue to evaluate durable medical equipment care/concerns
<input type="checkbox"/> Address caregiver concerns and provide education resources
<input type="checkbox"/> Address potential barriers to pulmonary rehabilitation
<input type="checkbox"/> Manage comorbidities that impact COPD, including cardiopulmonary risk
<input type="checkbox"/> Smoking cessation/second-hand exposure avoidance
<input type="checkbox"/> Promote physical activity
<input type="checkbox"/> Assess for advanced care planning

Source: American Society of Health-Systems Pharmacists, 2023.³²

applicable. Ensuring the patient receives and is adherent to the prescribed treatment will help reduce his risk for mortality and future exacerbations, in addition to other benefits from a thorough transitional care visit.

Additional considerations include ensuring the patient's understanding of the role of acute relievers vs maintenance medications; verifying adequate inhaler technique and medication delivery; considering the measurement of peak inspiratory flow when using dry powder inhalers; arranging pulmonary rehabilitation; reinforcing and supporting smoking cessation efforts; considering mucus clearance techniques (if there is a persistent cough and mucus); arranging vaccination for influenza, COVID, pneumococcal pneumonia, and RSV at the appropriate time of year; reviewing and treating comorbidities including CV risk; optimizing nutrition; assessing oxygenation at rest and with activity; and creating a COPD action plan for further exacerbations that includes prompt therapy initiation.

CONCLUSION

PCCs are urged to incorporate best practices for managing COPD into clinical practice, due to the essential role of primary care in improving outcomes in COPD. This includes recognizing the health burden of COPD and associated cardiopulmonary risk, employing optimal approaches for transitional care visits, and optimizing treatment through practice change initiatives. ●

REFERENCES

URLs must be entered manually, rather than copied and pasted.

- Liu Y, Carlson SA, Watson KB, Xu F, Greenlund KJ. Trends in the prevalence of chronic obstructive pulmonary disease among adults aged ≥ 18 years—United States, 2011–2021. *MMWR Morb Mortal Wkly Rep*. 2023;72(46):1250–1256. doi:10.15585/mmwr.mm7246a1
- Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095–2128. doi:10.1016/S0140-6736(12)61728-0
- Xu J, Murphy SL, Kochanek KD, Arias E. Mortality in the United States, 2021. NCHS data brief, no. 456. Atlanta, GA: National Center for Health Statistics; 2022. <https://www.cdc.gov/nchs/data/databriefs/db456.pdf>
- Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? *Eur Respir Rev*. 2018;27(149):180057. doi:10.1183/16000617.0057-2018
- Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax*. 2012;67(11):957–963. doi:10.1136/thoraxjnl-2011-201518
- Swart KMA, Baak BN, Lemmens L, et al. Risk of cardiovascular events after an exacerbation of chronic obstructive pulmonary disease: results from the EXACOS-CV cohort study using the PHARMO Data Network in the Netherlands. *Respir Res*. 2023;24(1):293. doi:10.1186/s12931-023-02601-4
- Singh D, Han MK, Hawkins NM, et al. Implications of cardiopulmonary risk for the management of COPD: a narrative review. *Adv Ther*. 2024;41(6):2151–2167. doi:10.1007/s12325-024-02855-4
- García-Sanz MT, Cánive-Gómez JC, Senín-Rial L, et al. One-year and long-term mortality in patients hospitalized for chronic obstructive pulmonary disease. *J Thorac Dis*. 2017;9(3):636–645. doi:10.21037/jtd.2017.03.34
- Mannino DM, Doherty DE, Sonia Buist A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. *Respir Med*. 2006;100(1):115–122. doi:10.1016/j.rmed.2005.03.035
- American Lung Association. COPD trends brief: burden. Accessed April 18, 2024. <https://www.lung.org/research/trends-in-lung-disease/copd-trends-brief/copd-burden>
- Roberts MH, Mannino D, Mapel DW, et al. Disease burden and health-related quality of life (HRQoL) of chronic obstructive pulmonary disease (COPD) in the US—evidence from the Medical Expenditure Panel Survey (MEPS) from 2016–2019. *COPD*. 2024;19:1033–1046. doi:10.2147/COPD.S446696
- Kim J, Lin A, Absher R, Makhlof T, Wells C. Comprehensive and collaborative pharmacist transitions of care service for underserved patients with chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis*. 2021;8(1):152–161. doi:10.15326/jcopdf.2019.0175
- Centers for Medicare & Medicaid Services. Eligible Professional Meaningful Use Menu Set Measures Measure 7 of 9: Transitions of Care Summary. Published May 2014. Accessed February 27, 2024. https://www.cms.gov/regulations-and-guidance/legislation/ehrincentiveprograms/downloads/8_transition_of_care_summary.pdf
- Park Y, Kim J, Kim S, Moon D, Jo H. Effects of transitional care after hospital discharge in patients with chronic obstructive pulmonary disease: an updated systematic review and meta-analysis. *Int J Environ Res Public Health*. 2023;20(11):6053. doi:10.3390/ijerph20116053
- American Society of Health-System Pharmacists. Ensuring safe transitions of care in patients with chronic obstructive pulmonary disease. Published December 5, 2023. Accessed April 18, 2024. <https://web.archive.org/web/20231205180935/https://copdcare.org/>
- Criner RN, Han MK. COPD care in the 21st century: a public health priority. *Respir Care*. 2018;63(5):591–600. doi:10.4187/respcare.06276
- Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2024 report. <https://www.goldcopd.org>
- Decramer M, Janssens W. Chronic obstructive pulmonary disease and comorbidities. *Lancet Respir Med*. 2013;1(1):73–83. doi:10.1016/S2213-2600(12)70060-7
- Müllerova H, Agustí A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: systematic literature review. *Chest*. 2013;144(4):1163–1178. doi:10.1378/chest.12-2847
- Feary JR, Rodrigues LC, Smith CJ, Hubbard RB, Gibson JE. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax*. 2010;65(11):956–962. doi:10.1136/thx.2009.128082
- Curkendall SM, DeLuise C, Jones JK, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol*. 2006;16(1):63–70. doi:10.1016/j.annepidem.2005.04.008
- Finkelstein J, Cha E, Scharf SM. Chronic obstructive pulmonary disease as an independent risk factor for cardiovascular morbidity. *Int J Chron Obstruct Pulmon Dis*. 2009;4:337–349. doi:10.2147/copd.s6400
- Chen H, Luo X, Du Y, et al. Association between chronic obstructive pulmonary disease and cardiovascular disease in adults aged 40 years and above: data from NHANES 2013–2018. *BMC Pulm Med*. 2023;23(1):318. doi:10.1186/s12890-023-02606-1
- Kunisaki KM, Dransfield MT, Anderson JA, et al. Exacerbations of chronic obstructive pulmonary disease and cardiac events. A post hoc cohort analysis from the SUMMIT randomized clinical trial. *Am J Respir Crit Care Med*. 2018;198(1):51–57. doi:10.1164/rccm.201711-2239OC
- Halpin DMG, Decramer M, Celli BR, Mueller A, Metzendorf N, Tashkin DP. Effect of a single exacerbation on decline in lung function in COPD. *Respir Med*. 2017;128:85–91. doi:10.1016/j.rmed.2017.04.013
- Whittaker H, Rubino A, Müllerová H, et al. Frequency and severity of exacerbations of COPD associated with future risk of exacerbations and mortality: a UK routine health care data study. *Int J Chron Obstruct Pulmon Dis*. 2022;17:427–437. doi:10.2147/COPD.S346591
- Rothnie KJ, Müllerová H, Smeeth L, Quint JK. Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2018;198(4):464–471. doi:10.1164/rccm.201710-2029OC
- Ho TW, Tsai YJ, Ruan SY, et al. In-hospital and one-year mortality and their predictors in patients hospitalized for first-ever chronic obstructive pulmonary disease exacerbations: a nationwide population-based study. *PLoS One*. 2014;9(12):e114866. doi:10.1371/journal.pone.0114866
- Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest*. 2010;137(5):1091–1097. doi:10.1378/chest.09-2029
- Crisan L, Wong N, Sin DD, Lee HM. Karma of cardiovascular disease risk factors for prevention and management of major cardiovascular events in the context of acute exacerbations of chronic obstructive pulmonary disease. *Front Cardiovasc Med*. 2019;6:79. doi:10.3389/fcvm.2019.00079
- Gavish R, Levy A, Dekel OK, Karp E, Maimon N. The association between hospital readmission and pulmonologist follow-up visits in patients with COPD. *Chest*. 2015;148(2):375–381. doi:10.1378/chest.14-1453
- American Society of Health-System Pharmacists. Transition of care checklist | COPD Resource Center. Published September 22, 2023. Accessed April 18, 2024. <https://web.archive.org/web/20230922085705/https://www.copdcare.org/transition-of-care-checklist.php#step3>
- Brunson A, Waddell D. Implementation of a pharmacist-led COPD transitions of care service. *Pharmacy Practice in Focus: Health Systems*. 2024;13(3). Accessed June 27, 2024. <https://www.pharmacytimes.com/view/implementation-of-a-pharmacist-led-copd-transitions-of-care-service>

Improving Patient-Centric COPD Management

Barbara P. Yawn, MD, MSc, FAAFP

Fed Pract. 2024;41(suppl 6):S35-S40. doi:10.12788/fp.0534

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- **Employ** recommended diagnostic strategies to enhance prompt and accurate diagnosis of chronic obstructive pulmonary disease (COPD) in primary care settings.
- **Describe** evidence-based diagnostic and treatment approaches for COPD based on the most recent GOLD report.
- **Design** patient-specific treatment plans for adjusting therapy for COPD, based on individual preferences and characteristics.
- **Implement** proven processes for educating patients with COPD regarding correct inhaler technique and adherence.

KEY TAKEAWAYS

- Primary care clinicians (PCCs) play a critical role in COPD diagnosis and management since most patients with COPD are treated in the primary care setting.
- Gaps persist between real-world care and recommendations from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report.
- GOLD recommendations for diagnosis and treatment of COPD emphasize a patient-centered approach to care that incorporates patient characteristics and preferences.
- Along with pharmacologic therapy, key interventions for patients with COPD include smoking cessation, appropriate vaccinations, and pulmonary rehabilitation.
- Patient-centered COPD treatment focuses on individualizing inhaled therapy to promote efficacy and adherence and regular follow-up.

TARGET AUDIENCE

Family physicians and clinicians who wish

to gain increased knowledge and greater competency regarding primary care management of COPD.

DISCLOSURES

As a continuing medical education provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), Primary Care Education Consortium (PCEC) requires any individual in a position to influence educational content to disclose any financial interest or other personal relationship with any commercial interest. This includes any entity producing, marketing, reselling, or distributing health care goods or services consumed by, or used on, patients. Mechanisms are in place to identify and mitigate any potential conflict of interest prior to the start of the activity. All relevant financial relationships have been mitigated. In addition, any discussion of off-label, experimental, or investigational use of drugs or devices will be disclosed by the faculty.

Dr. Yawn serves on the advisory board and/or as a consultant/research support for AstraZeneca, GSK, Boehringer Ingelheim, and Mylan and has served in the past as a consultant for TEVA. Austin Ulrich, PharmD, BCACP, has no disclosures to report.

SPONSORSHIP

This article is sponsored by Primary Care Education Consortium and Primary Care Respiratory Group.

ACCREDITATION

The Primary Care Education Consortium is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION

Primary Care Education Consortium designates this enduring material 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.

PAs AND NURSE PRACTITIONERS

AANP, ANCC, and AAPA accept certificates of participation from educational activities certified for AMA PRA Category 1 Credit™ from organizations accredited by ACCME.

CME is available from November 1, 2024–October 31, 2025.

To receive credit: Visit <https://www.pcrp-us.org/survey/post/copd1ht24>



FACULTY

Barbara P. Yawn, MD, MSc, FAAFP, Department of Family and Community Health, Adjunct Professor, University of Minnesota, Minneapolis, MN

ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, at Primary Care Education Consortium.

SUPPORTER

This article is supported by an educational grant from GSK.

INTRODUCTION

Primary care's role in patient-centered COPD care

Primary care clinicians (PCCs) play a critical role in the care of patients with chronic obstructive pulmonary disease (COPD). Between 10% and 20% of their adult patients have

COPD, many of whose cases are unrecognized.¹⁻³ Especially in the United States, PCCs are involved with caring for most patients with COPD (approximately 80%) across the disease continuum, sometimes in collaboration with specialists.^{1,4} However, despite the availability of evidence-based guide-

lines and implementation of various location-specific COPD protocols, gaps persist between guideline-recommended COPD care and real-world clinical practice.⁵⁻⁷

COPD is a common, preventable, and treatable disease with persistent respiratory symptoms and airflow limitation.⁸ It is a significant public health and clinical challenge, ranking in the top 3 causes of mortality worldwide.^{4,8} The 11.7% global prevalence of COPD is expected to rise over the next 40 years.⁸ In the US, COPD is the leading lower respiratory cause of death and is the fourth leading overall cause of death.⁹ An estimated \$49 billion per year in medical costs are attributed to COPD.^{5,8} Exacerbations account for the largest proportion of COPD costs, resulting in 725,000 hospitalizations and 1.5 million emergency department visits each year.^{5,8,10,11}

COPD is characterized by several pathophysiologic respiratory changes, including obstruction (defined spirometrically as forced expiratory volume in 1 second [FEV₁]/forced vital capacity [FVC] <0.7) and an accelerated decline in FEV₁.^{8,12} Gas exchange abnormalities result in hypoxemia and hypercapnia. Mucus hypersecretion can cause a chronic productive cough, dyspnea, increased sputum production, lower oxygen saturation, worsened quality of life, and increased risk of all-cause mortality.^{8,13-15} Common complications of COPD include exacerbations, cardiac disease, muscle wasting, depression, and osteoporosis.⁸ Secondary late effects may also include pulmonary hypertension due to hypoxic vasoconstriction of pulmonary arteries.¹⁶

CASE STUDY

A 54-year-old woman with a diagnosis of COPD presents to her PCC with complaints of occasional increased dyspnea the past few weeks. She reports that her COPD has been “under control” for a few years, but now she’s having more symptoms. She is currently prescribed tiotropium (a long-acting muscarinic antagonist [LAMA]) and salmeterol (a long-acting beta₂-agonist [LABA]) in separate inhalers. She notes that she uses tiotropium pretty regularly but admits that she has had trouble paying for her medications and has not filled the salmeterol prescription in the past several months.

Upon further assessment, the patient does say she has been to urgent care and then on to the emergency department twice in the past year, where she was diagnosed with exacerbations and treated with oral “prednisone.” Her COPD Assessment Test (CAT) score today is elevated (12), and her eosinophil count is 400 cells/mL. The patient smokes “a few cigarettes a day” and says her activities are limited to attending church, going to the grocery store, and participating in a card club each week.

The patient in the case scenario could benefit from individualized COPD care that better addresses her needs and preferences. She continues to smoke, which increases her risk for

exacerbations, disease progression, and adverse outcomes, and her adherence to therapy is suboptimal due to financial constraints. She would also benefit from more physical activity.

DIAGNOSIS OF COPD IN PRIMARY CARE

Since most patients with COPD are managed by PCCs in the US, PCCs are often tasked with establishing the initial COPD diagnosis.^{4,17} A COPD diagnosis requires suspicion of the diagnosis, confirmation of symptom burden, and spirometry, the latter of which tends to be underused in primary care settings.¹⁸ Lack of obtaining diagnostic spirometry, time pressures in primary care offices, and barriers to referral for spirometry (patient acceptance, distance, and costs) are reasons for low rates of spirometry use.⁴ When spirometry results are obtained, inexperience and lack of knowledge of spirometry interpretation may result in misdiagnoses in 10%-40% of individuals.¹⁹⁻²¹ Other factors that make COPD diagnoses challenging include underestimation of symptoms by patients and the progressive nature of the disease.²²

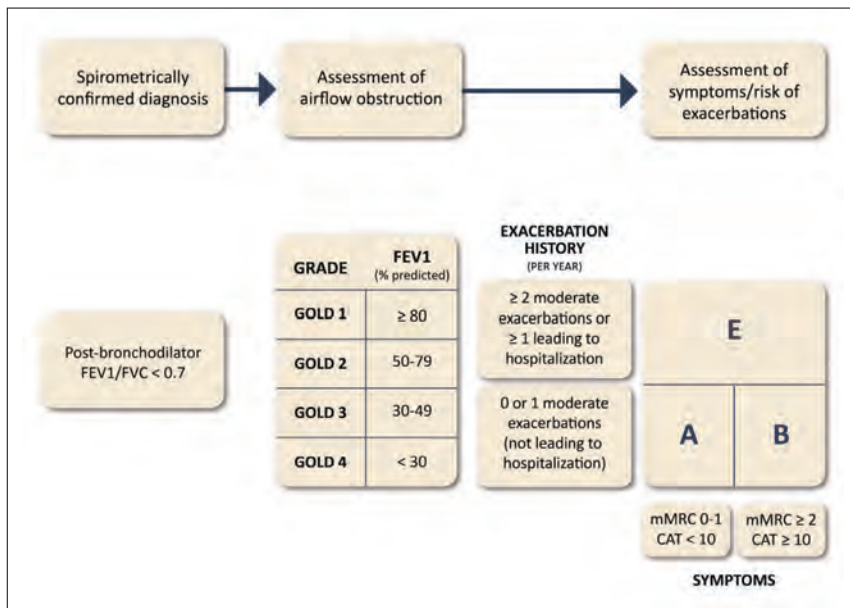
The Global Initiative for Chronic Obstructive Lung Disease (GOLD) was established in 1998 to try to summarize current evidence and guide improvements in prevention and management of COPD through a worldwide coordinated effort. The first GOLD report was released in 2001, is updated annually, and has become a respected resource—the most often consulted resource when one is used by clinicians (79.4% of PCCs and 91.3% of pulmonologists).^{8,17} However, several studies indicate that substantial discrepancies continue to exist between GOLD recommendations and actual clinical practice.⁵⁻⁷

While PCCs may implement some components of recommended COPD care, such as assessing oxygen saturation and levels of dyspnea, many essential components are missed.⁵ Less than half of patients diagnosed with COPD receive spirometry, and many use inhaled treatments that are not consistent with GOLD recommendations.^{23,24} Additionally, fewer than 5% of patients with COPD undergo pulmonary rehabilitation (PR), although significant evidence supports its benefits.^{25,26} The next sections of this article discuss the most recent GOLD 2024 recommendations for diagnosis and treatment of COPD, with an emphasis on practical application and patient-centered approaches in primary care settings.

2024 GOLD report recommendations for diagnosing COPD

Diagnosis of COPD is based on a recognition of symptoms, presence of risk factors, and confirmation of the diagnosis via spirometry (**FIGURE 1**).⁸ Of note, screening for COPD is not recommended for asymptomatic adults, even if other risk factors are present.²⁷ The identification of postbroncho-

FIGURE 1. GOLD recommendations for assessment of COPD⁸



Abbreviations: CAT, COPD Assessment Test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council dyspnea questionnaire.

© 2023, Global Initiative for Chronic Obstructive Lung Disease, available from www.goldcopd.org, published in Deer Park, IL, USA.

dilator FEV₁/FVC ratio <0.70 is considered to be required for a diagnosis of COPD.⁸ Inaccurate and delayed PCC diagnoses of COPD can lead to inappropriate treatment and disease progression.⁴ Correct interpretation of spirometry is a key factor in limiting misdiagnosis of COPD. Resources are available to improve PCC interpretation of spirometry.²⁸

Once a COPD diagnosis is established, patients are classified by degree of symptom burden using 1 of 2 standardized assessments, the modified Medical Research Council (mMRC) dyspnea scale or the CAT and the frequency of exacerbation-like events in the prior 12 months.⁸ The mMRC is a dyspnea questionnaire with scores (or grades) ranging from 0 to 4 based on severity of dyspnea, with 4 being the most severe. The CAT is an 8-item questionnaire intended to assess health status in patients with COPD. CAT scores range from 0 to 40, with higher scores indicating more severe COPD symptoms.⁸

Patients are then classified into GOLD groups A, B, or E, which correspond to initial treatment recommendations. Additionally, disease severity based on airflow limitation (actual FEV₁ compared to predicted) can be divided into GOLD grades 1 to 4, ranging from mild to very severe, which may be useful for assessment of disease progression and need for supplemental oxygen evaluation.⁸ Smoking status, α₁-antitrypsin, vaccination status, and comorbidities should also be assessed to help guide treatment and next steps.⁸ Additionally, blood eosinophil count may be measured for

certain patients already receiving COPD treatment, as blood eosinophils predict the magnitude of the effect of inhaled corticosteroids (ICS) added to maintenance bronchodilator therapy in preventing exacerbations.⁸

PRACTICAL MANAGEMENT OF COPD IN PRIMARY CARE

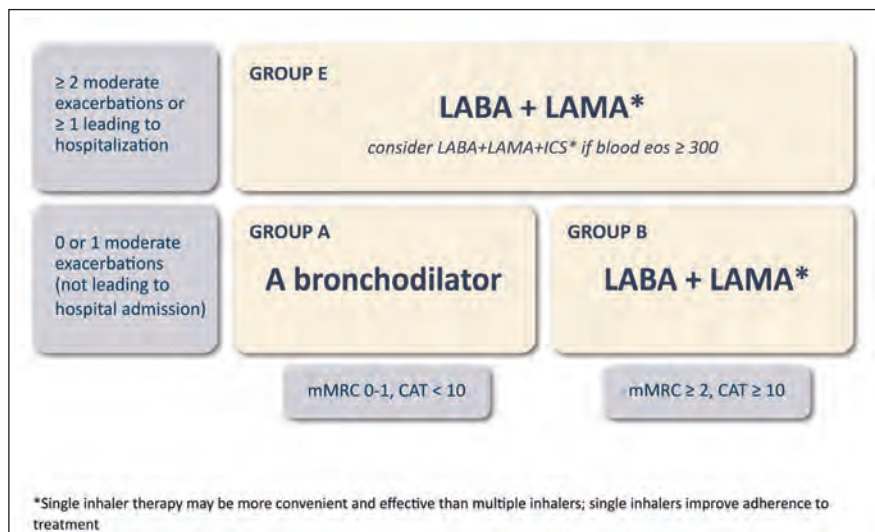
Therapeutic regimens for GOLD A, B, and E treatment groups consist of various combinations of pharmacotherapy and nonpharmacotherapy. The primary medications used include short-acting beta₂-agonists (SABAs) or muscarinic antagonists (SAMAs)—used only for those with few symptoms and rare exacerbations and as supplemental “rescue therapy” for all others; LABAs and LAMAs; and ICS only for prevention in those at high risk of exacerbations (FIGURE 2).⁸ Important nonpharmacotherapy management includes general COPD education, inhaler technique education, smoking cessation support,

vaccinations, and pulmonary rehabilitation or, at least, activity enhancement.⁸ Once initial treatment is selected, patients should be evaluated regularly to assess disease/symptom control, and therapy should be modified accordingly. While routine follow-up patients with COPD is essential, the frequency and intervals are individualized based on the disease severity.

There are many components of COPD care (FIGURE 3),⁸ and PCCs should not feel obligated to address every part of treatment during any single visit, this being the importance of continuity care.⁸ Based on the patient’s individual needs and preferences, PCCs can select which components of COPD care would be the most impactful and choose to focus on those interventions. In the example of the patient case scenario, inhaled therapy including inhaler technique education, general information on the synergistic effects of LABA+LAMA, and smoking cessation support may have the most significant current impact for this patient. Over time, other interventions can be added to further optimize management. Vaccination status review is a usual part of all primary care visits and can be supported by the team approach.

Pharmacologic treatment

For patients classified in GOLD group A, a short- or long-acting bronchodilator can be used, but long-acting bronchodilators are preferred, unless patients have only very occasional breathlessness. For patients classified in GOLD group B, LAMA+LABA or “dual” inhaled therapy is pre-

FIGURE 2. GOLD recommendations for initial pharmacologic treatment of COPD⁸

Abbreviations: CAT, COPD Assessment Test™; eos, blood eosinophil count in cells per microliter; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council dyspnea scale.

Exacerbations refers to the number of exacerbations per year.

© 2023, Global Initiative for Chronic Obstructive Lung Disease, available from www.goldcopd.org, published in Deer Park, IL, USA.

ferred, as it is superior to LAMA-only therapy.^{8,29} For patients in GOLD group E—those with frequent or severe exacerbations—LABA+LAMA is preferred, but if there is an indication for ICS (ie, the patient has blood eosinophils ≥ 300 cells/microliter or concomitant asthma), then LABA+LAMA+ICS (triple therapy) is preferred and has been shown to be superior to LABA+ICS.^{8,30,31} After prescribing initial inhaled pharmacotherapy for COPD, clinicians should regularly review patients' symptoms, exacerbation risk, inhaler technique, and adherence, and adjust pharmacologic treatment based on clinical findings.⁸

Smoking cessation

For the approximately 40% of individuals with COPD who smoke, smoking cessation is a key intervention that should be addressed at every clinic visit.⁸ This can be challenging because many individuals continue to smoke despite knowing its negative impact on COPD.³² Smoking is an addiction that may be more difficult for people with COPD to break because of the lower self-efficacy, lower self-esteem, and greater nicotine dependence often seen in these individuals.³³⁻³⁵ Despite the challenges, smoking cessation and abstinence have the greatest potential for reducing disease progression and exacerbations and improving symptoms.^{36,37}

Individualizing smoking cessation treatment using a combination of counseling and pharmacotherapy can help increase the effectiveness of interventions. PCCs can implement strate-

gies such as the “5 As” (Ask, Advise, Assess, Assist, Arrange), effective pharmacotherapy (nicotine replacement therapy, bupropion, nortriptyline, and varenicline), and promotion of smoking cessation by clinic support staff.⁸ Tools and resources for helping patients with smoking cessation include those produced and maintained by the Centers for Disease Control and Prevention (CDC): <https://www.cdc.gov/tobacco/patient-care/clinical-tools/index.html>.

Vaccination

Appropriate vaccinations for individuals with COPD can reduce serious illness and death and should be administered based on relevant local guidelines.⁸ In the US, the CDC maintains regularly updated vaccine recommendations.³⁸ Vaccines recommended for patients with COPD include influenza; COVID-19; pneumococcal; respiratory syncytial virus (age >60 years);

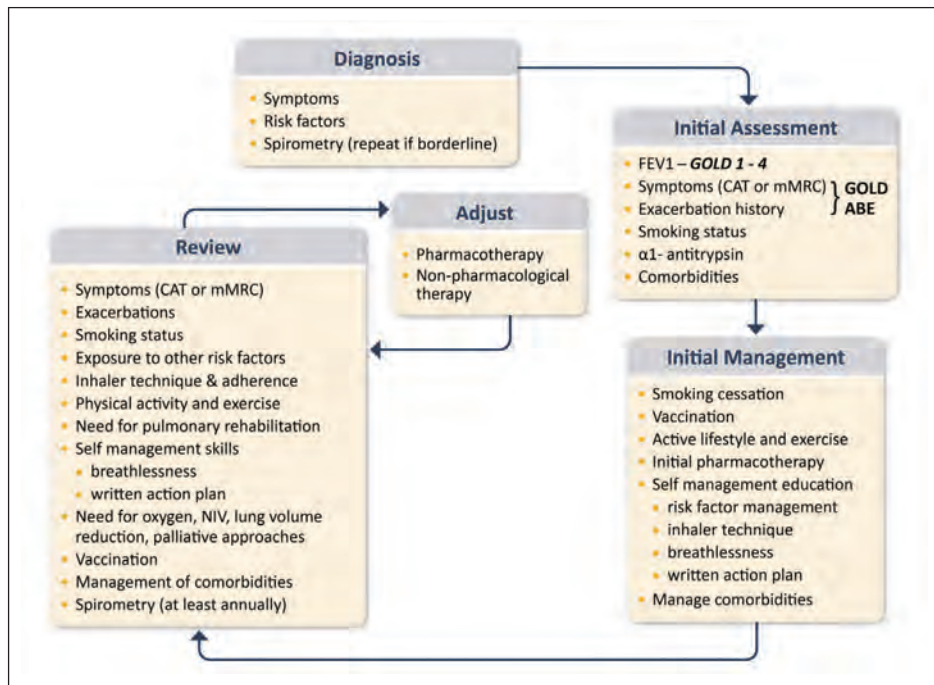
tetanus, diphtheria, and pertussis (every 10 years); and zoster (age >50 years).^{8,38}

Pulmonary rehabilitation

PR is a comprehensive intervention that includes exercise training, self-management intervention, and education designed to improve physical and psychological well-being and enhance adherence to healthy behaviors.^{8,26} PR is an essential component of managing chronic respiratory diseases such as COPD, but despite its known benefits, PR is underused in clinical settings.²⁶ The American Thoracic Society (ATS) recently produced a clinical practice guideline that PCCs may find useful in reviewing the evidence and recommendations for implementing PR.²⁶ In brief, PR is strongly recommended for adults with stable COPD and after hospitalization for COPD exacerbation. Patients may be offered a choice between center-based PR or telerehabilitation, depending on preference and availability.²⁶

IMPLEMENTING PATIENT-CENTRIC COPD TREATMENT REGIMENS

Patient-based selection of inhaler devices, teaching and evaluating inhaler technique, and assessing and supporting adherence to prescribed therapies are essential to developing effective patient-centered treatment regimens.^{17,39} Patient-centered management of COPD also includes an emphasis on patient counseling and self-management when appropriate.⁴⁰ Therapies should consider patient prefer-

FIGURE 3. GOLD recommendations for overall management of COPD⁸

Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council dyspnea questionnaire; NIV, noninvasive ventilation.

© 2023, Global Initiative for Chronic Obstructive Lung Disease, available from www.goldcopd.org, published in Deer Park, IL, USA.

ences and needs, in addition to being clinically appropriate. This includes consideration of insurance status, number of inhaled medication doses to be taken per day, type of inhaler (dry powder or metered-dose inhaler, soft mist inhaler, or nebulizer), and use of combination inhalers. Using combination inhalers can simplify regimens, may reduce costs associated with obtaining multiple inhalers, and may improve adherence and clinical outcomes.³⁹

Treatment adherence and proper inhaler technique are key components in overall COPD care and self-management.^{8,40,41} In addition to worsened health status, poor adherence and inaccurate inhaler technique can lead to increased symptoms and exacerbations and, when not assessed, prescribing of additional medications.^{41,42} Correcting the high frequency of poor inhaler technique and addressing adherence issues can improve quality of life, reduce symptoms and exacerbations, and enhance overall COPD management.⁴³

Educating patients on inhaler technique can seem time consuming and difficult in busy clinical practice.⁴¹ There are many online inhaler technique education videos that can be used by office staff and patients and families at home to learn, review, and update inhaler technique (<https://www.copdfoundation.org/Learn-More/Educational-Materials-Resources/Educational-Video-Series.aspx>).

For some practices, brief, 5-minute, one-on-one training sessions can be implemented in those with the greatest problems to significantly improve inhaler technique. Multicomponent interventions that include education and motivational or behavioral counseling delivered by health care professionals can improve adherence but may be difficult in many primary care practices.⁴⁴ Assessing technique using the patient's own devices should be done as often as feasible since technique can decline in 3 months or less.⁴⁵ Selection of inhalers based on the patient's physical and mental capabilities and preferences, such as combination inhalers and drugs that are dosed fewer times per day to simplify regimens, can result in improved adherence rates.³⁹

In the case scenario, the patient's PCC should review inhaler technique and adher-

ence and consider adjusting her 2-device inhaled therapy, addressing smoking cessation, and offering PR. To improve adherence and potentially reduce costs, the patient could be prescribed combination LAMA+LABA therapy in a single inhaler. The PCC may also want to consider the risks and benefits of LAMA+LABA+ICS due to her exacerbations and eosinophil count >300 cells/microliter. The PCC could direct the patient to available manufacturer patient assistance programs and copay cards to help her afford the new combination inhaler and improve access to treatment. Where available, engaging clinic staff such as medical assistants, nurses, and pharmacists can also help facilitate access to treatment.

SUMMARY

COPD remains a significant health challenge, and PCCs play a key role in managing COPD since most patients are treated in primary care settings. Current diagnostic and treatment guidance provided by the GOLD report emphasize individualized patient-centered approaches to care. Pharmacologic treatment regimens should incorporate patient and disease characteristics as well as patient preferences, with a focus on promoting adherence and facilitating appropriate inhaler technique. Smoking cessation, appropriate vaccinations, and PR are important nondrug

interventions with significant potential to improve patients' disease status and quality of life. ●

REFERENCES

URLs must be entered manually, rather than copied and pasted.

- Pace WD, Brandt E, Carter VA, et al. COPD population in US primary care: data from the Optimum Patient Care DARTNet Research Database and the Advancing the Patient Experience in COPD registry. *Ann Fam Med*. 2022;20(4):319-327. doi:10.1370/afm.2829
- Bednarek M, Maciejewski J, Wozniak M, Kuca P, Zielinski J. Prevalence, severity and underdiagnosis of COPD in the primary care setting. *Thorax*. 2008;63(5):402-407. doi:10.1136/thx.2007.085456
- Hill K, Goldstein RS, Guyatt GH, et al. Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. *CMAJ*. 2010;182(7):673-678. doi:10.1503/cmaj.091784
- Ragaišienė G, Kibarskytė R, Gauronskaitė R, et al. Diagnosing COPD in primary care: what has real life practice got to do with guidelines? *Multidiscip Respir Med*. 2019;14:28. doi:10.1186/s40248-019-0191-6
- Keller TL, Wright J, Donovan LM, et al. Association of patient and primary care provider factors with outpatient COPD care quality. *Chronic Obstr Pulm Dis*. 2022;9(1):55-67. doi:10.15326/jcopdf.2021.0232
- Mularski RA, Asch SM, Shrank WH, et al. The quality of obstructive lung disease care for adults in the United States as measured by adherence to recommended processes. *Chest*. 2006;130(6):1844-1850. doi:10.1378/chest.130.6.1844
- López-Campos JL, Abad Arranz M, Calero-Acuña C, et al. Guideline adherence in outpatient clinics for chronic obstructive pulmonary disease: results from a clinical audit. *PLoS ONE*. 2016;11(3):e0151896. doi:10.1371/journal.pone.0151896
- Global Initiative for Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2024 Report*. Global Initiative for Obstructive Lung Disease; 2023. https://goldcopd.org/wp-content/uploads/2023/12/GOLD-2024_v1.1-1Dec2023_WMv.pdf
- Carlson SA, Wheaton AG, Watson KB, Liu Y, Croft JB, Greenlund KJ. Geographic differences in sex-specific chronic obstructive pulmonary disease mortality rate trends among adults aged ≥25 years - United States, 1999-2019. *MMWR Morb Mortal Wkly Rep*. 2022;71(18):613-618. doi:10.15585/mmwr.mm7118a1
- Ford ES. Hospital discharges, readmissions, and ED visits for COPD or bronchiectasis among US adults. *Chest*. 2015;147(4):989-998. doi:10.1378/chest.14.2146
- Jiang X, Xiao H, Segal R, Mobley WC, Park H. Trends in readmission rates, hospital charges, and mortality for patients with chronic obstructive pulmonary disease (COPD) in Florida from 2009 to 2014. *Clin Ther*. 2018;40(4):613-626.e1. doi:10.1016/j.clinthera.2018.03.006
- Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(26):2645-2653. doi:10.1056/NEJMoa032158
- Burgel PR, Nadel JA. Epidermal growth factor receptor-mediated innate immune responses and their roles in airway diseases. *Eur Respir J*. 2008;32(4):1068-1081. doi:10.1183/09031936.00172007
- Diaz AA, Orejas JL, Grumley S, et al. Airway-occluding mucus plugs and mortality in patients with chronic obstructive pulmonary disease. *JAMA*. 2023;329(21):1832-1839. doi:10.1001/jama.2023.2065
- Okajima Y, Come CE, Nardelli P, et al. Luminal plugging on chest CT scan: association with lung function, quality of life, and COPD clinical phenotypes. *Chest*. 2020;158(1):121-130. doi:10.1016/j.chest.2019.12.046
- Sakao S, Voelkel NF, Tatsumi K. The vascular bed in COPD: pulmonary hypertension and pulmonary vascular alterations. *Eur Respir Rev*. 2014;23(133):350-355. doi:10.1183/09059180.00007913
- Mannino D, Siddall J, Small M, Haq A, Stiegler M, Bogart M. Treatment patterns for chronic obstructive pulmonary disease (COPD) in the United States: results from an observational cross-sectional physician and patient survey. *Int J Chron Obstruct Pulmon Dis*. 2022;17:749-761. doi:10.2147/COPD.S340794
- Joo MJ, Sharp LK, Au DH, Lee TA, Fitzgibbon ML. Use of spirometry in the diagnosis of COPD: a qualitative study in primary care. *COPD*. 2013;10(4):444-449. doi:10.3109/15412555.2013.766683
- Strong M, Green A, Goyder E, et al. Accuracy of diagnosis and classification of COPD in primary and specialist nurse-led respiratory care in Rotherham, UK: a cross-sectional study. *Prim Care Respir J*. 2014;23(1):67-73. doi:10.4104/pcrj.2014.00005
- Calle Rubio M, Alcázar Navarrete B, Soriano JB, et al. Clinical audit of COPD in outpatient respiratory clinics in Spain: the EPOCONSUL study. *COPD*. 2017;12:417-426. doi:10.2147/COPD.S124482
- Liang J, Abramson MJ, Zwar NA, et al. Diagnosing COPD and supporting smoking cessation in general practice: evidence-practice gaps. *Med J Aust*. 2018;208(1):29-34. doi:10.5694/mja17.00664
- Spyratos D, Chloros D, Sichelidīs L. Diagnosis of chronic obstructive pulmonary disease in the primary care setting. *Hippokratia*. 2012;16(1):17-22
- Nishi SPE, Wang Y, Kuo YE, Goodwin JS, Sharma G. Spirometry use among older adults with chronic obstructive pulmonary disease: 1999-2008. *Ann Am Thorac Soc*. 2013;10(6):565-573. doi:10.1513/AnnalsATS.201302-0370C
- Keller T, Spece LJ, Donovan LM, et al. Association of guideline-recommended COPD inhaler regimens with mortality, respiratory exacerbations, and quality of life. *Chest*. 2020;158(2):529-538. doi:10.1016/j.chest.2020.02.073
- Lindenauer PK, Stefan MS, Pekow PS, et al. Association between initiation of pulmonary rehabilitation after hospitalization for COPD and 1-year survival among Medicare beneficiaries. *JAMA*. 2020;323(18):1813. doi:10.1001/jama.2020.4437
- Rochester CL, Alison JA, Carlin B, et al. Pulmonary rehabilitation for adults with chronic respiratory disease: American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2023;208(4):e7-e26. doi:10.1164/rccm.202306-10665T
- US Preventive Services Task Force, Mangione CM, Barry MJ, et al. Screening for chronic obstructive pulmonary disease: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2022;327(18):1806. doi:10.1001/jama.2022.5692
- International Primary Care Respiratory Group (IPCRG). Quick guide to spirometry. Revised June 2023. Accessed December 18, 2023. https://www.ipcr.org/sites/ipcr/files/content/attachments/2023-06-05/IPCRG_DTH_14_Quick_guide_to_Spirometry_0.pdf
- Maltais F, Bjermer L, Kerwin EM, et al. Efficacy of umecclidinium/vilanterol versus umecclidinium and salmeterol monotherapies in symptomatic patients with COPD not receiving inhaled corticosteroids: the EMAX randomised trial. *Respir Res*. 2019;20(1):238. doi:10.1186/s12931-019-1193-9
- Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383(1):35-48. doi:10.1056/NEJMoa1916046
- Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med*. 2018;378(18):1671-1680. doi:10.1056/NEJMoa1713901
- Montes de Oca M. Smoking cessation/vaccinations. *Clin Chest Med*. 2020;41(3):495-512. doi:10.1016/j.ccm.2020.06.013
- Shahab L, Jarvis MJ, Britton J, West R. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. *Thorax*. 2006;61(12):1043-1047. doi:10.1136/thx.2006.064410
- Wagena EJ, Arrindell WA, Wouters EFM, van Schayck CP. Are patients with COPD psychologically distressed? *Eur Respir J*. 2005;26(2):242-248. doi:10.1183/09031936.05.00010604
- van Eerd EAM, van der Meer RM, van Schayck OCP, Kotz D. Smoking cessation for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2016;2016(8):CD010744. doi:10.1002/14651858.CD010744.pub2
- Willemsse BWM, Postma DS, Timens W, ten Hacken NHT. The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. *Eur Respir J*. 2004;23(3):464-476. doi:10.1183/09031936.04.00.012704
- Bauer CMT, Morissette MC, Stämpfli MR. The influence of cigarette smoking on viral infections: translating bench science to impact COPD pathogenesis and acute exacerbations of COPD clinically. *Chest*. 2013;143(1):196-206. doi:10.1378/chest.12-0930
- Centers for Disease Control and Prevention. Immunization Schedules. Centers for Disease Control and Prevention. Published February 10, 2023. Accessed December 14, 2023. <https://www.cdc.gov/vaccines/schedules/index.html>
- Alcázar-Navarrete B, Jamart L, Sánchez-Covisa J, Juárez M, Graefenhain R, Sicras-Mainar A. Clinical characteristics, treatment persistence and outcomes among patients with COPD treated with single- or multiple-inhaler triple therapy: a retrospective analysis in Spain. *Chest*. 2022;162(5):1017-1029. doi:10.1016/j.chest.2022.06.033
- Steuere-Stey C, Dalla Lana K, Braun J, Riet GT, Puhan MA. Effects of the "Living well with COPD" intervention in primary care: a comparative study. *Eur Respir J*. 2018;51(1):1701375. doi:10.1183/13993003.01375-2017
- Kim JS, Hashweh N, Li H, Choudhary S, Santosh S, Charbek E. Effectiveness of one-on-one coaching in improving pressurized metered dose inhaler (pMDI) technique among COPD patients: a prospective clinical study. *BMC Pulm Med*. 2021;21(1):266. doi:10.1186/s12890-021-01627-y
- Cooke CE, Sidel M, Belletti DA, Fuhlbrigge AL. Review: clinical inertia in the management of chronic obstructive pulmonary disease. *COPD*. 2012;9(1):73-80. doi:10.3109/15412555.2011.631957
- Khurana A, Dubey K, Goyal A, Pawar K, Phulwaria C, Pakhare A. Correcting inhaler technique decreases severity of obstruction and improves quality of life among patients with obstructive airway disease. *J Family Med Prim Care*. 2019;8(1):246. doi:10.4103/jfmpc.jfmpc_259_18
- Janjua S, Pike KC, Carr R, Coles A, Fortescue R, Batavia M. Interventions to improve adherence to pharmacological therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev*. 2021;9(9):CD013381. doi:10.1002/14651858.CD013381.pub2
- Barnestein-Fonseca P, Cotta-Luque VM, Aguiar-Leiva VP, Leiva-Fernández J, Martos-Crespo F, Leiva-Fernández F. The importance of reminders and patient preferences to improve inhaler technique in older adults with COPD. *Front Pharmacol*. 2022;13:989362. doi:10.3389/fphar.2022.989362

The Role of Finerenone in Optimizing Cardiovascular-Kidney-Metabolic Health: Everything PCPs Should Know

Eugene E. Wright Jr, MD; Richard B. Frady, DNP, APRN, ACNP-BC, CCRN-CMC; Chigozie Uko, DNP, APRN, FNP-C

Fed Pract. 2024;41(suppl 6):S41-S46. doi:10.12788/fp.0535

KEY TAKEAWAYS

- Cardiovascular, kidney, and metabolic (CKM) syndrome is a complex health disorder attributable to the substantial overlap and connections among obesity, diabetes, chronic kidney disease, and cardiovascular disease resulting from shared risk factors, and interconnected, interdependent pathophysiology.
- Primary care professionals (PCPs) should detect CKM syndrome early and aggressively treat all patients who are at risk.
- Nonsteroidal mineralocorticoid receptor antagonists like finerenone can favorably affect the progression of CKM syndrome at each stage.
- PCPs should become familiar with the benefits of a 4-pillar approach across different management phases of CKM syndrome.

FACULTY

Eugene E. Wright Jr, MD, Consulting Associate, Department of Medicine, Duke University Medical Center, Durham, NC

Richard B. Frady, DNP, APRN, ACNP-BC, CCRN-CMC, Critical Care Nurse Practitioner, Adjunct Clinical Faculty, College of Nursing, Mercer University, Atlanta, GA

Chigozie Uko, DNP, APRN, FNP-C, Nurse Practitioner/Subinvestigator, Cowry Medical Group/American Clinical Trials, Nephrology and Internal Medicine, Acworth, GA

DISCLOSURES

Eugene E. Wright reports royalties or licenses from UpToDate; consulting fees from Abbott Diabetes Care, Ascencia, Bayer, Boehringer Ingelheim, Embecta, GSK, Lilly, Medtronic, Renalytix, and Sanofi; also, fees from lectures, writing, speakers bureau or expert testimony for Abbott Diabetes Care, Ascencia, Bayer, Boehringer Ingelheim, Embecta, GSK, Lilly, Medtronic, Renalytix, and Sanofi.

Richard B. Frady does not have any disclosures.

Chigozie Uko reports prior membership with the Bayer Speaker Bureau and has

served on the Bayer Nursing Advisory Board for finerenone.

Khaled Shelbaya and Aqsa Dar do not have any disclosures.

ACKNOWLEDGMENT

The authors would like to acknowledge the medical writing provided by Khaled Shelbaya, MBBCH, MD, MMSCI, of ILM Consulting Services, LLC. The authors would also like to acknowledge the editorial support, visualizations, and graphic abstract development provided by Aqsa Dar, ScM, of ILM Consulting Services, LLC.

SPONSORSHIP

This article is sponsored by Primary Care Education Consortium and Primary Care Metabolic Group.

SUPPORTER

This article is supported by funding from Bayer US.

BACKGROUND

Substantial overlap exists among cardiovascular, kidney, and metabolic (CKM) diseases because of shared risk factors and an interconnected, interdependent pathophysiology. As one condition worsens, it increases the risk and severity of others, leading to a cycle of worsening outcomes and a higher risk for mortality.^{1,2} Conceptual frameworks and expanded tools can enhance the appreciation and comprehension of physiological changes, diagnosis, and treatment of patients with underlying diabetes, chronic kidney disease (CKD), and/or cardiovascular disease (CVD) among health care providers. In this effort, the American Heart Association Presidential Advisory introduced a new concept of CKM syndrome, defined as a health disorder attributable to connections among obesity, diabetes, CKD, and CVD, including atherosclerotic cardio-

vascular disease and heart failure.³ CKM syndrome stages were defined to reflect the pathophysiology, spectrum of risk, and opportunities for prevention and care optimization by health care providers, including primary care professionals (PCPs) who have a significant role in integrating the available therapeutic options and different guidelines into their clinical practice (TABLE).¹¹⁻¹⁸ The age-adjusted prevalence of advanced CKM syndrome stages (ie, stages 3 and 4) among US adults 20 years or older is 14.6%, which did not improve between 2011 and 2020.⁴⁻⁷

Finerenone, a nonsteroidal mineralocorticoid receptor antagonist (nsMRA), is one of the therapeutic pillars available for CKD associated with type 2 diabetes or diabetic kidney disease (DKD) that can favorably affect CKM syndrome progression at stages 1-4 (TABLE).^{5,9,10} Evidence suggests that

TABLE. Definitions of CKM syndrome stages

CKM stages	Definition	Potential role of finerenone
Stage 0: No CKM risk factors	Normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or subclinical or clinical CVD	
Stage 1: Dysfunctional adiposity	BMI ≥ 25 , waist circumference $\geq 88/102$ cm in women/men, ^a fasting blood glucose ≥ 100 to 124 mg/dL, or HbA1c between 5.7% and 6.4% (prediabetes)	Preventing the metabolic alterations in obesity observed from animal studies using MRA ^{11,12}
Stage 2: Metabolic risk factors and CKD	Hypertriglyceridemia ≥ 135 mg/dL, hypertension, diabetes, MetS, ^b or CKD (moderate to high risk per KDIGO classification)	Decreasing CKD risk category at early stages among patients with diabetes by decreasing UACR and preserving eGFR ^{13,14}
Stage 3: Subclinical CVD in CKM or risk equivalent	Individuals with metabolic risk factors who have subclinical ASCVD by imaging, subclinical HF: diagnosed by elevated biomarkers (NT-proBNP ≥ 125 pg/mL, or hs-troponin ^c), or combination of the 2, indicating highest HF risk in echocardiography	Same as stage 2 + decreasing the risk for incident HF hospitalization ¹⁵
	High predicted 10-year CVD risk ($\geq 20\%$), ^d or very high risk CKD per KDIGO classification	
Stage 4: Clinical CVD in CKM	4a: ASCVD or heart failure without kidney failure	Beneficial role irrespective of prevalent ASCVD ¹⁶
	4b: ASCVD or heart failure with kidney failure	Potential role in treating HFrEF ¹⁷ and HFmr/pEF ¹⁸

^aOr BMI ≥ 23 kg/m² or waist circumference $\geq 80/90$ cm in women/men of Asian ancestry.

^bMetS is defined by the presence of 3 or more of the following: (1) waist circumference ≥ 88 cm for women and ≥ 102 cm for men; (2) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women; (3) triglycerides ≥ 150 mg/dL; (4) elevated blood pressure (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mm Hg and/or use of antihypertensive medications); and (5) fasting blood glucose ≥ 100 mg/dL.

^chs-troponin (high sensitivity troponin) T ≥ 14 ng/L for women and ≥ 22 ng/L for men or hs-troponin I ≥ 10 ng/L for women and ≥ 12 ng/L for men.

^dCalculated using the American Heart Association PREVENT risk calculator (<https://professional.heart.org/en/guidelines-and-statements/prevent-calculator>).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CKM, cardiovascular, kidney, and metabolic; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmr/pEF, heart failure with preserved or midrange ejection fraction; KDIGO, Kidney Disease Improving Global Outcomes; MetS, metabolic syndrome; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; UACR, urinary albumin-to-creatinine ratio.

finerenone may be beneficial in the patient journey across CKM syndrome stages in tandem with other therapeutic pillars, such as maximally dosed renin-angiotensin-aldosterone-system inhibitors (RAAsi), sodium-glucose cotransporter 2 inhibitors (SGLT2is), and/or glucagon-like peptide-1 receptor agonists (GLP-1 RAs). In this article, a hypothetical case is used to demonstrate how to optimize the role of finerenone in different management phases that include risk stratification, finerenone initiation, patient monitoring, and involvement of an interdisciplinary care team.

CASE STUDY

K.A. is a 60-year-old male diagnosed with type 2 diabetes (T2D) 10 years ago and hypertension 5 years ago. He recently moved from another state and has no history of atherosclerotic cardiovascular disease. He is not experiencing any particular symptoms.

Examination:

No jugular vein distention, other signs of heart failure, or signs of peripheral arterial disease.

Blood Pressure: 120/80 *Heart Rate:* 70 *BMI:* 32.7

Weight: 89 kg (196 lb) *Height:* 1.65 m (65 in)

Lab results:

Serum creatinine: 1.7 mg/dL *eGFR:* 52 mL/min/1.73 m²

BUN: 40 mg/dL

Total cholesterol: 140 mg/dL *Triglyceride:* 100 mg/dL

LDL: 65 mg/dL

HDL: 40 mg/dL *UACR:* 340 mg/g (38.42 mg/mmol)

Na: 140 mmol/L

K: 4.2 mmol/L *HbA1c:* 7%

NT-proBNP: 70 pg/mL

Current medication:

Optimum dose of RAAsi (perindopril 8 mg once daily)

Rosuvastatin: 20 mg; *Metformin:* 500 mg twice daily;

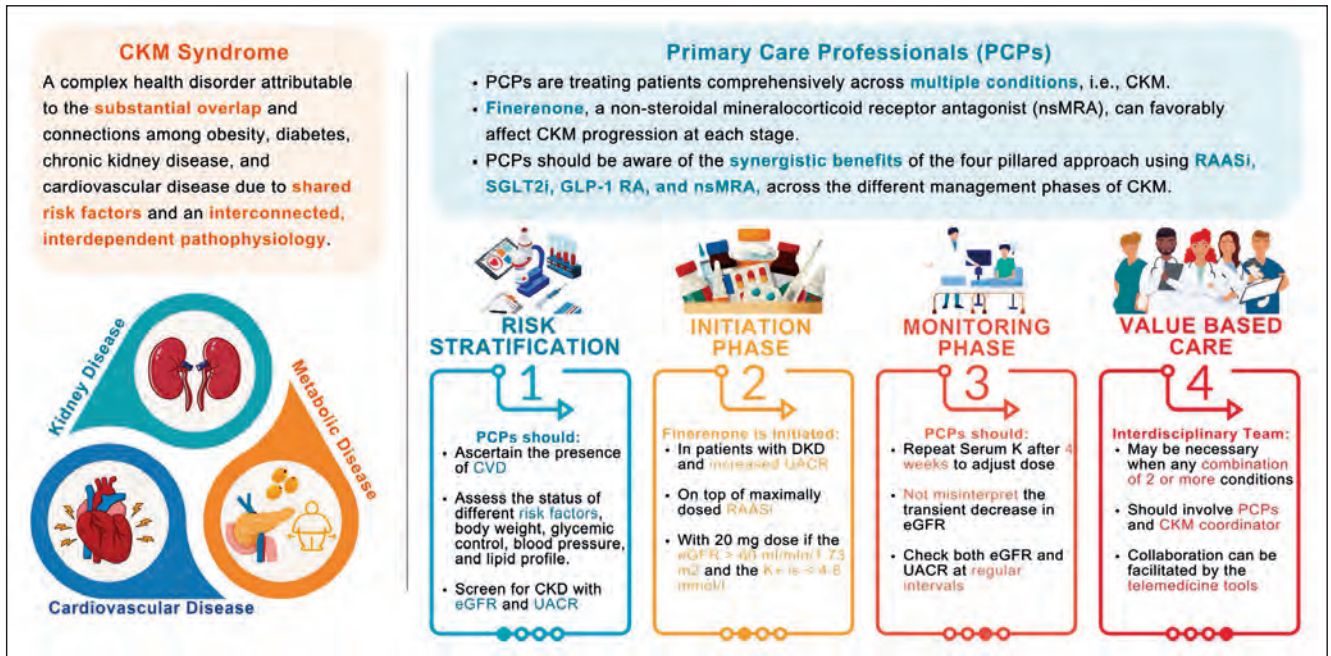
Empagliflozin: 25 mg once daily

Primary care professional decision:

Started finerenone 10 mg and advised to repeat K after 1 month

Abbreviations: BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; K, potassium; LDL, low-density lipoprotein; UACR, urine albumin-creatinine ratio.

GRAPHIC ABSTRACT



Abbreviations: CKM, cardiovascular, kidney, and metabolic; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; RAASi, renin-angiotensin aldosterone system inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

RISK STRATIFICATION PHASE: ROLE OF PCPS

CASE COMMENT:

K.A. had stage 2 CKM syndrome; he had metabolic risk factors and high-risk CKD attributed mainly to the elevated UACR (FIGURE 1).⁵ However, he should be screened for the presence of subclinical CVD if there is a suggestive clinical presentation or elevated cardiac biomarkers, and the 10-year CVD predicted score should be calculated using the American Heart Association PREVENT online risk calculator (<https://professional.heart.org/en/guidelines-and-statements/prevent-calculator>) to confirm that K.A. is not in stage 3 CKM syndrome.

To define the stage of CKM syndrome, PCPs have to ascertain the prevalence of CVD and assess the status of different risk factors, including body weight, glycemic control, blood pressure, and lipid profile. In addition to the metabolic CVD risk factors, screening for CKD with eGFR, estimated glomerular filtration rate (eGFR) and UACR is mandatory because CKD can modify the CKM syndrome stage (TABLE).¹¹⁻¹⁸ CKD should be evaluated by using the Kidney Disease Improving Global Outcomes (KDIGO) Heatmap that classifies patients with CKD according to the level of UACR and eGFR (FIGURE 1). In clinical practice, glomerular filtration rate is typically estimated from serum creatinine concentration and/or cystatin-C using a race-free eGFR equation developed by the CKD Epidemiology Collaboration in 2021.¹⁹ The National Kidney Foundation

recommended replacing race-based equations with a new equation and provided a web-based tool for determining the eGFR from serum creatinine²⁰ (https://www.kidney.org/professionals/kdoqi/gfr_calculator). UACR is the preferred and most predictive measure for CKD staging and CVD risk assessment,²¹ and the effect of a medication like finerenone against CKD progression is largely mediated by UACR reduction.²²

The role of PCPs at this stage is not just to identify risk factors and classify the patient's risk category but also to educate patients and personalize lifestyle modifications that are the foundation for managing diabetes and CKD.²³ Building and maintaining positive health behaviors, such as regular physical exercise, weight management, and smoking cessation, are crucial to achieving personalized treatment goals, including slowing CKM syndrome progression.²⁴

INITIATION PHASE: THERAPEUTIC OPTIONS INITIATED BY PCPS

CASE COMMENT:

The patient's PCP recommended 10 mg of finerenone because K.A. had a UACR >300 mg/g, despite receiving an SGLT2i and the maximum tolerable dose of RAASi, perindopril 8 mg once daily (ie, angiotensin-converting enzyme [ACE] inhibitors or angiotensin II receptor blockers [ARBs]) and had good blood pressure and an HbA1c of 7%. (If the eGFR was >60 mL/min/1.73 m² and the K⁺ was <4.8 mmol/L, finerenone could be initiated at a higher dose

FIGURE 1. KDIGO heatmap showing the case scenario baseline and status after 4 months⁵

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–299 mg/g 3–29 mg/mmol	A3 Severely increased ≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73 m ²) Description and range	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

■ Low risk (if no other markers of kidney disease, no CKD) ■ High risk
■ Moderately increased risk ■ Very high risk

lished more than 20 years ago. These trials demonstrated a 16% to 43% reduction in doubling of serum creatinine, death, or kidney failure over 2 to 3 years.^{27–29} In addition to glycemic control by medication with cardiorenal protection like SGLT2is, the maximum dose of RAASi should be the first-line therapy for treating hypertension in patients with diabetes when albuminuria is present.^{5,6,23} RAASi is also recommended for patients with DKD and moderately to severely increased UACR (KDIGO classification G1–G4, A2, and A3), even in the absence of high blood pressure.^{5,6,23} However, the hazardous effects of aldosterone on CKM syndrome persist despite using RAASi, justifying the addition of a MRA to minimize the residual risk for CKM syndrome progression that exists even while using an SGLT2i.^{30,31}

Two large phase 3 trials, FIDELIO-DKD and FIGARO-DKD, and their pooled analysis, FIDELITY, demonstrated the compelling evidence of a nsMRA, finerenone, in reducing the risk for CKD and CVD progression in a broad range of patients with DKD who were on maximum tolerable dose of RAASi.^{32–34} Although a small number of patients (6.7% to 7.2%) were receiving SGLT2i or GLP-1 RA therapy, they also saw

Cause refers to the cause of CKD as ascertained by the clinician. Most patients who fit into the CKM staging framework will have CKD attributable to diabetes, hypertension, and other metabolic risk factors. *PCPs may wish to discuss with their nephrology service, depending on local practice patterns on monitoring or referring. **Numbers: Represent a recommendation for the number of times per year the patient should be monitored.⁵**

Abbreviations: CKD; chronic kidney disease; CKM; cardiovascular, kidney, metabolic; eGFR; estimated glomerular filtration rate; PCP, primary care provider

Adapted from KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.

[ie, 20 mg]). Serum potassium and eGFR should be repeated after 4 weeks to adjust the dose accordingly. Note that up to a 30% reduction in eGFR initially is acceptable. Blood pressure and lipid profile levels did not mandate intensifying the relevant medications; however, adding other glucose-lowering medications to achieve better glycemic control is reasonable.

Several updated guidelines are available to guide therapy for patients with CKM syndrome. Alongside the annual publication of the Standards of Care in Diabetes guideline by the American Diabetes Association (ADA), KDIGO published its 2024 guideline, and both organizations endorsed their consensus report about diabetes management in CKD, which was published in 2022.^{5,6,23} However, a significant barrier to implementing the recommendations in primary care is the lack of guidance on how PCPs can effectively implement the guidelines in their real-world practices.²⁵ The prescription pattern analysis at a single institution revealed that finerenone was prescribed more frequently by specialists than PCPs.²⁶

RAASi are considered the first-line therapy for patients with diabetes and CKD based on clinical trials that were pub-

lished more than 20 years ago. These trials demonstrated a 16% to 43% reduction in doubling of serum creatinine, death, or kidney failure over 2 to 3 years.^{27–29} In addition to glycemic control by medication with cardiorenal protection like SGLT2is, the maximum dose of RAASi should be the first-line therapy for treating hypertension in patients with diabetes when albuminuria is present.^{5,6,23} RAASi is also recommended for patients with DKD and moderately to severely increased UACR (KDIGO classification G1–G4, A2, and A3), even in the absence of high blood pressure.^{5,6,23} However, the hazardous effects of aldosterone on CKM syndrome persist despite using RAASi, justifying the addition of a MRA to minimize the residual risk for CKM syndrome progression that exists even while using an SGLT2i.^{30,31}

Two large phase 3 trials, FIDELIO-DKD and FIGARO-DKD, and their pooled analysis, FIDELITY, demonstrated the compelling evidence of a nsMRA, finerenone, in reducing the risk for CKD and CVD progression in a broad range of patients with DKD who were on maximum tolerable dose of RAASi.^{32–34} Although a small number of patients (6.7% to 7.2%) were receiving SGLT2i or GLP-1 RA therapy, they also saw benefit.^{35,36} During a median follow-up of 2.6 years, the finerenone group showed 18% lower risk for a composite of kidney failure, 40% or more decline in eGFR, or death from renal cause compared to placebo in FIDELIO-DKD.³² In the FIGARO-DKD trial, finerenone reduced the risk for death from CVD, nonfatal myocardial infarction, nonfatal stroke, or hospitalizations from heart failure by 13%.³³ Such robust evidence is not available for steroidal MRAs, spironolactone, and eplerenone, and according to a recent meta-analysis, steroidal MRAs are associated with a higher incidence of adverse events such as hyperkalemia than finerenone when added to RAASi.³⁷ Furthermore, spironolactone can produce off-target endocrinal side effects such as gynecomastia.³⁸

According to ADA Standards of Care in Diabetes, finerenone is indicated for the case patient K.A. to slow CKD progression. He had normal potassium and highly elevated UACR despite being on the maximum tolerated dose of RAASi. A ≥30% reduction in UACR is the goal since his UACR was ≥300 mg/g (≥30 mg/mmol).³⁹ Furthermore, for CVD risk management, finerenone, in addition to an SGLT2i, is indicated in patients with DKD to reduce the risk for progression to symp-

FIGURE 2. Serum potassium monitoring during treatment with finerenone according to KDIGO guidelines⁵

K ⁺ ≤ 4.8 mmol/L	K ⁺ 4.9-5.5 mmol/L	K ⁺ > 5.5 mmol/L
<ul style="list-style-type: none"> • Initiate finerenone <ul style="list-style-type: none"> - 10 mg daily if eGFR 25-59 mL/min/1.73 m² - 20 mg daily if eGFR ≥60 mL/min/1.73 m² • Monitor K⁺ at 1 month after initiation and then every 4 months • Increase dose to 20 mg daily, if on 10 mg daily • Restart 10 mg daily if previously held for hyperkalemia and K⁺ now ≤5.0 mmol/L 	<ul style="list-style-type: none"> • Continue finerenone 10 mg or 20 mg • Monitor K⁺ every 4 months 	<ul style="list-style-type: none"> • Hold finerenone • Consider adjustments to diet or concomitant medications to mitigate hyperkalemia • Recheck K⁺ • Consider reinitiation if/when K⁺ ≤5.0 mmol/L

Abbreviations: K⁺, potassium; mmol/L, millimoles per liter.

tomatic heart failure (stage C).⁴⁰ As with blood pressure management practice, it would not be reasonable to wait until someone has advanced CKD or heart failure to be treated.

MONITORING PHASE: RECOMMENDED FOLLOW-UP PLAN

CASE:

Follow-up lab after 4 weeks:

K: 4.4 mmol/L

Serum creatinine: 1.8 mg/dL

eGFR^a: 48 mL/min/1.73 m²

Primary care professional decision: Increase finerenone dose to 20 mg and follow up every 4 months^b

Follow-up after 4 months: No symptoms or signs of heart failure or peripheral arterial disease

Blood pressure: 119/79 mm Hg HR: 69 Weight: 93 kg (205 lb)
BMI: 34

Serum creatinine: 1.7 mg/dL

eGFR: 53 mL/min/1.73 m²

UACR: 200 mg/g (22.6 mg/mmol)^c LDL: 65 mg/dL

Na: 140 mmol/L HbA1c: 7.5% K: 4.6 mmol/L

Primary care professional decision: Consider adding subcutaneous semaglutide (GLP-1 RA) 1.0 mg weekly

^a30% initial reduction in eGFR is expected and acceptable.⁵

^bSerum potassium should be monitored 4 weeks after a dose adjustment and throughout treatment.⁴¹

^c30% reduction in UACR is considered “renoprotective” by the ADA, the Food and Drug Administration, and the European Medicines Agency.^{39,42}

Regular reassessment for risk factors (every 3 to 6 months) is a critical part of the holistic approach to improving outcomes in people with diabetes and CKD.³⁹ Furthermore, the KDIGO Heatmap shows the recommended frequency of kidney function monitoring by PCPs.^{5,6,23} UACR and eGFR should be reassessed at regular intervals according to the KDIGO Heatmap to evaluate treatment response and anticipate the progression of CKD or any adverse events.^{5,6,23} Several therapeutic interventions, including RAASi^{28,29} and SGLT2is,^{43,44} reduce glomerular hyperfiltration by affecting glomerular blood flow, inducing a transient

lowering of eGFR that usually does not exceed 30% in the absence of volume depletion. Similar conditions can occur after starting an nsMRA and should not be interpreted as acute kidney injury that requires medication cessation.

The dose-adjustment guideline for finerenone based on hyperkalemia risk was provided in the latest KDIGO guidelines (FIGURE 2).⁵ In this case example, the potassium level is below 4.8 mmol/L after 1 month from finerenone initiation; dose intensification to 20 mg is needed to achieve the ADA target of decreasing albuminuria by 30% in patients with baseline UACR >300 mg/g.³⁹ Finerenone can reduce UACR within 3 months in a dose-dependent manner, with a significant reduction in UACR reaching 38%.¹³ Diuretic or SGLT2i use is associated with lower hyperkalemia risk, and the currently available potassium binder and dietary modification might mitigate the hyperkalemia risk, facilitating the use of a 20-mg concentration of finerenone.⁴⁵ As with ACE inhibitors or ARBs, the target treatment dose of finerenone is the maximum tolerated label dose.

CASE COMMENT:

Although patient K.A.'s KDIGO risk category improved after 4 months, it is justifiable to add a GLP-1 RA as K.A.'s glycemic and body weight control worsened during the last 4 months (FIGURE 1). The use of GLP-1 RAs in populations with T2D enhances glycemic control, reduces body weight, mitigates CVD risk, and, most recently, has been shown to slow CKD progression.^{46,47} Adding a GLP-1 RA will fulfill the 4 pillars of DKD management and is expected to offer relevant additional benefits in CKM survival.^{10,48}

MULTIDISCIPLINARY CARE PHASE

It is important for PCPs to be familiar with guideline-directed medical therapies for conditions like CKM syndrome and to know when and how to use them.²⁵ However, involving an interdisciplinary care team may be necessary when any combination of 2 or more conditions of CKD, diabetes, and subclinical/clinical CVD are present. The team should include PCPs, certified diabetes care and education specialists, and subspecialists such as nephrologists, endocrinologists, and cardiolo-

gists. CKM syndrome coordinators are proposed to implement value-based care in comparison to volume-based care, which targets referrals of high-risk patients to subspecialists.³ CKM syndrome coordinators can improve collaboration between the team and help with patient navigation across primary care and multiple specialists.³

CONCLUSION

PCPs play a crucial role as frontline clinicians, treating the patient comprehensively across multiple conditions such as CKM syndrome. PCPs should be aware of the potential role of finerenone across the different management phases of CKM syndrome. The synergistic benefits of the 4-pillar approach using RAASis, SGLT2is, GLP-1 RAs, and nsMRA, in addition to a collaborative care model, are recommended to provide the best care for patients with CKM syndrome. ●

REFERENCES

URLs must be entered manually, rather than copied and pasted.

- Marassi M, Fadini GP. The cardio-renal-metabolic connection: a review of the evidence. *Cardiovasc Diabetol*. 2023;22(1):195. doi:10.1186/s12933-023-01937-x
- Vallianou NG, Mitesh S, Gkogkou A, et al. Chronic kidney disease and cardiovascular disease: is there any relationship? *Curr Cardiol Rev*. 2018;15(1):55-63. doi:10.2174/1573403x14666180711124825
- Ndumele CE, Rangaswami J, Chow SL, et al. Cardiovascular-kidney-metabolic health: a Presidential Advisory from the American Heart Association. *Circulation*. 2023;148(20):1606-1635. doi:10.1161/cir.0000000000001184
- Handelsman Y, Anderson JE, Bakris GL, et al. DCRM Multispecialty practice recommendations for the management of diabetes, cardiorenal, and metabolic diseases. *J Diabetes Complications*. 2022;36(2):108101. doi:10.1016/j.jdiacomp.2021.108101
- Stevens PE, Ahmed SB, Carrero JJ, et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2024;105(4):S117-S314. doi:10.1016/j.kint.2023.10.018
- American Diabetes Association Professional Practice C. 10. Cardiovascular disease and risk management: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(suppl 1):S179-S218. doi:10.2337/dc24-S010
- Writing Committee M, Heidenreich PA, Bozkurt B, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):e263-e421. doi:10.1016/j.jacc.2021.12.012
- Aggarwal R, Ostrominski JW, Vaduganathan M. Prevalence of cardiovascular-kidney-metabolic syndrome stages in US adults, 2011-2020. *J Am Med Assoc*. 2024;331(21):1858-1860. doi:10.1001/jama.2024.6892
- American Diabetes Association Professional Practice C. 11. Chronic kidney disease and risk management: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(suppl 1):S219-S230. doi:10.2337/dc24-S011
- Naaman SC, Bakris GL. Diabetic nephropathy: update on pillars of therapy slowing progression. *Diabetes Care*. 2023;46(9):1574-1586. doi:10.2337/dc23-0030
- Marzolla V, Feraco A, Limana F, et al. Class-specific responses of brown adipose tissue to steroidal and nonsteroidal mineralocorticoid receptor antagonists. *J Endocrinol Invest*. 2022;45(1):215-220. doi:10.1007/s40618-021-01635-z
- Marzolla V, Feraco A, Gorini S, et al. The novel non-steroidal MR antagonist finerenone improves metabolic parameters in high-fat diet-fed mice and activates brown adipose tissue via AMPK-ATGL pathway. *FASEB J*. 2020;34(9):12450-12465. doi:10.1096/fj.202000164r
- Bakris GL, Agarwal R, Chan JC, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *J Am Med Assoc*. 2015;314(9):884-894. doi:10.1001/jama.2015.10081
- Bakris GL, Ruilope LM, Anker SD, et al. A prespecified exploratory analysis from FIDELITY examined finerenone use and kidney outcomes in patients with chronic kidney disease and type 2 diabetes. *Kidney Int*. 2023;103(1):196-206. doi:10.1016/j.kint.2022.08.040
- Filippatos G, Anker SD, Agarwal R, et al. Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes: analyses from the FIGARO-DKD trial. *Circulation*. 2022;145(6):437-447. doi:10.1161/CIRCULATIONAHA.121.057983
- Filippatos G, Anker SD, Pitt B, et al. Finerenone efficacy in patients with chronic kidney disease, type 2 diabetes and atherosclerotic cardiovascular disease. *Eur Heart J Cardiovasc Pharmacother*. 2022;9(1):85-93. doi:10.1093/ehjcvp/pvac054
- Pitt B, Kober L, Ponikowski P, et al. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. *Eur Heart J*. 2013;34(31):2453-2463. doi:10.1093/ehj/ehj31/ehf187
- Vaduganathan M, Claggett BL, Lam CSP, et al. Finerenone in patients with heart failure with mildly reduced or preserved ejection fraction: rationale and design of the FINEARTS-HF trial. *Eur J Heart Fail*. 2024;26(6):1324-1333. doi:10.1002/ejhf.3253
- Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med*. 2021;385(19):1737-1749. doi:10.1056/nejmoa2102953
- Delgado C, Baweja M, Burrows NR, et al. Reassessing the inclusion of race in diagnosing kidney diseases: an interim report from the NKF-ASN Task Force. *Am J Kidney Dis*. 2021;78(1):103-115. doi:10.1053/j.ajkd.2021.03.008
- Koeda Y, Tanaka F, Segawa T, et al. Comparison between urine albumin-to-creatinine ratio and urine protein dipstick testing for prevalence and ability to predict the risk for chronic kidney disease in the general population (Iwate-KENCO study): a prospective community-based cohort study. *BMC Nephrol*. 2016;17(1). doi:10.1186/s12882-016-0261-3
- Agarwal R, Tu W, Farjat AE, et al. Impact of finerenone-induced albuminuria reduction on chronic kidney disease outcomes in type 2 diabetes. *Ann Int Med*. 2023;176(12):1606-1616. doi:10.7326/m23-1023
- de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care*. 2022;45(12):3075-3090. doi:10.2337/dci22-0027
- American Diabetes Association Professional Practice C. 5. Facilitating positive health behaviors and well-being to improve health outcomes: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(suppl 1):S77-S110. doi:10.2337/dc24-S005
- Wright EE, Nicholas SB. Making treatment guideline recommendations in chronic kidney disease and type 2 diabetes more accessible to primary care providers in the United States. *Postgrad Med*. 2024;1-11. doi:10.1080/00325481.2024.2350924
- Zhang RM. Single institution prescribing pattern of finerenone in patients with type 2 diabetes and/or chronic kidney disease in the USA. *Clin Kidney J*. 2023;16(9):1538-1539. doi:10.1093/ckj/sfad073
- Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med*. 1993;329(20):1456-1462. doi:10.1056/nejm19931113292004
- Brenner BM, Cooper ME, De Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12):861-869. doi:10.1056/nejmoa011161
- Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345(12):861-869. doi:10.1056/nejmoa011161
- Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. doi:10.1056/nejmoa1811744
- Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816
- Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med*. 2020;383(23):2219-2229. doi:10.1056/NEJMoa2025845
- Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med*. 2021;385(24):2252-2263. doi:10.1056/NEJMoa2110956
- Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J*. 2022;43(6):474-484. doi:10.1093/eurheartj/ehab777
- Rossing P, Anker SD, Filippatos G, et al. Finerenone in patients with chronic kidney disease and type 2 diabetes by sodium-glucose cotransporter 2 inhibitor treatment: the FIDELITY analysis. *Diabetes Care*. 2022;45(12):2991-2998. doi:10.2337/dc22-0294
- Rossing P, Agarwal R, Anker SD, et al. Finerenone in patients across the spectrum of chronic kidney disease and type 2 diabetes by glucagon-like peptide-1 receptor agonist use. *Diabetes Obes Metab*. 2023;25(2):407-416. doi:10.1111/dom.14883
- Whitlock R, Leon SJ, Manacsa H, et al. The association between dual RAAS inhibition and risk of acute kidney injury and hyperkalemia in patients with diabetic kidney disease: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2023;38(11):2503-2516. doi:10.1093/ndt/gfad101
- Trinchieri A, Perletti G, Magri V, et al. Drug-induced gynecomastia: a systematic review and meta-analysis of randomized clinical trials. *Arch Ital Urol Androl*. 2021;93(4):489-496. doi:10.4081/aiua.2021.4.489
- Section 11: Chronic kidney disease and risk management. *Clin Diabetes*. 2024;42(2):212-213. doi:10.2337/cd24-a011
- Section 10: Cardiovascular disease and risk management. *Clin Diabetes*. 2024;42(2):209-211. doi:10.2337/cd24-a010
- Kerendia. Package insert. Bayer; 2022. <https://www.bayer.com/en/pharma/package-inserts>. Accessed August 30, 2024
- Levey AS, Gansevoort RT, Coresh J, et al. Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in Collaboration With the US Food and Drug Administration and European Medicines Agency. *Am J Kidney Dis*. 2020;75(1):84-104. doi:10.1053/j.ajkd.2019.06.009
- Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388(2):117-127. doi:10.1056/NEJMoa2204233
- Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446. doi:10.1056/nejmoa2024816
- Agarwal R, Joseph A, Anker SD, et al. Hyperkalemia risk with finerenone: results from the FIDELIO-DKD trial. *J Am Soc Nephrol*. 2022;33(1):225-237. doi:10.1681/asn.2021070942
- Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021;9(10):653-662. doi:10.1016/s2213-8587(21)00203-5
- Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med*. 2024;391(2):109-121. doi:10.1056/NEJMoa2403347
- Neuen BL, Heerspink HJL, Vart P, et al. Estimated lifetime cardiovascular, kidney, and mortality benefits of combination treatment with SGLT2 inhibitors, GLP-1 receptor agonists, and nonsteroidal MRA compared with conventional care in patients with type 2 diabetes and albuminuria. *Circulation*. 2024;149(6):450-462. doi:10.1161/CIRCULATIONAHA.123.067584

What Primary Care Clinicians Need to Know About Once-Weekly Insulins

Jay H. Shubrook, DO

Fed Pract. 2024;41(suppl 6):S47-S52. doi:10.12788/fp.0536

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Initiate basal insulin therapy without unnecessary delays for patients with type 2 diabetes (T2D) for whom insulin treatment is appropriate.
- Review the clinical efficacy and safety data for new and emerging ultra-long-acting, once-weekly insulins.
- Compare and contrast the potential benefits and risks of once-weekly insulins compared with traditional basal insulins.

KEY TAKEAWAYS

- Basal insulin remains an essential and effective glucose-lowering treatment for many patients with T2D.
- Ultra-long-acting, once-weekly insulins may soon be approved and provide an additional option for basal insulin therapy.
- Once-weekly insulins may improve adherence and persistence, increase flexibility in administration time, and reduce glycemic variability compared with once-daily basal insulins.
- Potential concerns with once-weekly insulins may include challenges with dose calculations and concerns about hypoglycemia, which may be resolved as clinicians become more familiar with these insulin formulations.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of diabetes.

DISCLOSURES

As a continuing medical education provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), Primary Care Education Consortium requires any individual in a position to influence educational content to disclose any financial interest or other personal relationship with any commercial interest. This includes any entity producing, marketing, reselling, or distributing health care goods or services consumed by, or used on, patients. Mechanisms are in place to identify and mitigate any potential conflict of interest prior to the start of the activity. All relevant financial relationships have been mitigated. In addition, any discussion of off-label, experimental, or investigational use of drugs or devices will be disclosed by the faculty.

Dr. Shubrook serves as a consultant to Abbott Laboratories, Bayer, and Novo Nordisk, and is on the advisory boards of Eli Lilly, Madrigal Pharmaceuticals, and Nevro. Austin Ulrich has no disclosures to report.

SPONSORSHIP

This article is sponsored by Primary Care Education Consortium and the Primary Care Metabolic Group.

ACCREDITATION

The Primary Care Education Consortium is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION

Primary Care Education Consortium designates this enduring material for a maximum of 1.0 AMA PRA Category 1 credit(s)TM. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

PAs AND NURSE PRACTITIONERS

AANP, ANCC, and AAPA accept certificates of participation from educational activities certified for AMA PRA Category 1 CreditTM from organizations accredited by ACCME.

CME is available from November 1, 2024 – October 31, 2025.

To receive credit: <https://www.pcmg-us.org/survey/post/owih2024>



FACULTY

Jay H. Shubrook, DO, Professor and Diabetologist, Tuoro University California, College of Osteopathic Medicine, Vallejo, CA

ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, Primary Care Education Consortium.

SUPPORTER

This article is supported by an educational grant from Novo Nordisk.

INTRODUCTION

Type 2 diabetes (T2D) is a chronic and progressive disease characterized by impaired blood glucose control. It is increasingly recognized as a serious public health concern globally.¹ In the US, an estimated 14.7% of adults have diabetes; of these, up to 95% have T2D.¹⁻³ Patients with T2D often experience significant morbidity due to microvascular and macrovascular complications resulting from elevated blood glucose, and they can

also have diminished functional capacity, lower quality of life, and premature death.^{4,6}

Primary care clinicians (PCCs) treat at least 90% of patients in the US with T2D and are often the first clinicians to diagnose the disease.^{7,8} While some patients with T2D may see an endocrinologist, projections indicate current and future shortages for this medical specialty. Thus, PCCs play a critical role in the management of patients with T2D, which often involves the use of basal insulin.^{8,9}

THE ROLE OF BASAL INSULIN IN T2D

Despite the emergence of newer agents to treat T2D, insulin is still an essential and effective glucose-lowering treatment for many patients.¹⁰ Over the years, insulin therapy has evolved with corresponding advances in molecular biology, chemistry, and technologies for drug delivery. According to current American Diabetes Association guidelines, basal insulin should be considered as the first injectable therapy when a patient with T2D has significant (blood glucose ≥ 300 mg/dL or glycated hemoglobin [HbA1c] $>10\%$) or symptomatic hyperglycemia or signs of catabolism due to glucotoxicity.¹¹

Many patients with T2D do not achieve glycemic control, and few achieve simultaneous control of associated cardiovascular risk factors (glucose, blood pressure, and lipids). Data extrapolated from the National Health and Nutrition Examination Survey (NHANES) 2013-2016 showed that 55.8% of people with T2D were at their target HbA1c level, while only 17.3% reached control of the composite of HbA1c, blood pressure, and blood lipids.¹² Inclusion of body mass index (BMI) targets lowered the finding to $<10\%$.¹² Analysis of NHANES data from 2005 to 2016 showed that the cascade of diabetes care, defined as the composite of diabetes diagnosis, linkage to care, and achievement of individual and combined treatment targets, did not significantly improve over time.¹³ Of US adults diagnosed with diabetes, 23% met therapeutic targets from 2005-2008, 25% met targets from 2009-2012, and 23% met targets from 2013-2016.¹³

Recent advances in insulin development have been largely focused on improving ease and convenience for the patient and greater stability in glucose readings. This has led to newer formulations of basal insulins, such as ultra-long-acting, once-weekly insulins, which are nearing US Food and Drug Administration (FDA) approval. Once-weekly basal insulins are predicted to increase treatment adherence, decrease clinical inertia, and improve patient quality of life, provided that potential risks are properly addressed.¹⁰

An estimated 7.4 million Americans with diabetes use one or more form of insulin to manage their condition.¹⁴ The goals of insulin therapy are to replicate as closely as possible a normal glycemic profile without unacceptable weight gain or hypoglycemia. For patients with T2D, initiating insulin therapy should start with basal insulin with a preference for basal insulin analogs.¹¹ However, acceptability of insulin is still low among patients with T2D, leading to reluctance to initiate and continue insulin therapy.¹⁵ Moreover, a large proportion of people interrupt or discontinue treatment shortly after initiation.^{16,17} According to 1 analysis, only 20% of people initiating basal insulin continued with insulin treatment within the year after initiation.¹⁶

Clinical inertia in reaching T2D treatment goals

A retrospective cohort study of more than 80,000 patients showed that median time to treatment intensification with insulin was longer than 7 years for those who were not meeting glycemic goals on oral antihyperglycemic medications alone.¹⁸ In another study, clinicians waited for an average of 9 years before insulin initiation, at which point the average HbA1c was 9.5% and diabetic complications had emerged. Even after insulin initiation, the clinicians did not intensify therapy adequately, and average HbA1c remained at 7.9% after 4 years.¹⁹

Clinical inertia is characterized by lack of treatment initiation or intensification resulting in failure to achieve glycemic goals and is a common reason for poor glycemic control.²⁰ Unfortunately, clinical inertia is very prevalent in clinical settings in the US. One study showed that fewer than 50% of patients with T2D and a high HbA1c had their treatment appropriately intensified.²¹ Another study showed that clinical inertia was seen in more than 26% of patients who had an HbA1c of $\geq 7\%$, and more than 18% of patients with an HbA1c of $\geq 8\%$ —with failure to intensify the medication regimen over a median 4.2 years of follow-up.²² Additionally, clinical inertia has resulted in inadequate glycemic control in 40% to 60% of patients with T2D.^{23,24} These findings are remarkable considering the focus of guidelines on the importance of glycemic control, indicating that increased attention is needed to achieve glycemic targets in patients with T2D.

CASE STUDY

A 59-year-old woman with a 20-year history of T2D presents to her primary care clinic for a follow-up visit 3 months after starting basal insulin once daily, despite her hesitation to use an injectable medication. After about 1 month of titrating her basal insulin dose via twice-weekly phone appointments, she had reached a dose of 45 units of insulin glargine once daily (0.5 units/kg), with a fasting glucose level ranging from 130 mg/dL to 140 mg/dL over a week of measurements and no hypoglycemic episodes. Since then, she says that she has had a difficult time remembering to do her daily injections on her own. She also doesn't like having to give herself an injection every day.

Her fasting blood glucose in clinic today is 195 mg/dL and her HbA1c is 9.6%, which is improved from her HbA1c of 10.3% measured 3 months ago. Her other antihyperglycemic medications include metformin 2000 mg daily and oral semaglutide 14 mg once daily. She states that she would like to try to work on her diet and exercise to get her HbA1c lower, toward her goal of $<7\%$.

The patient in this case scenario originally responded well to basal insulin therapy, with fasting blood glucose values that indicated improvement in overall glucose control. However,

after she was no longer under close follow-up, she began to miss doses and is at risk for clinical inertia, raising her chances of complications that can result from hyperglycemia. This patient may be a good candidate for receiving a once-weekly basal insulin and more support to improve her adherence and overall glucose control.

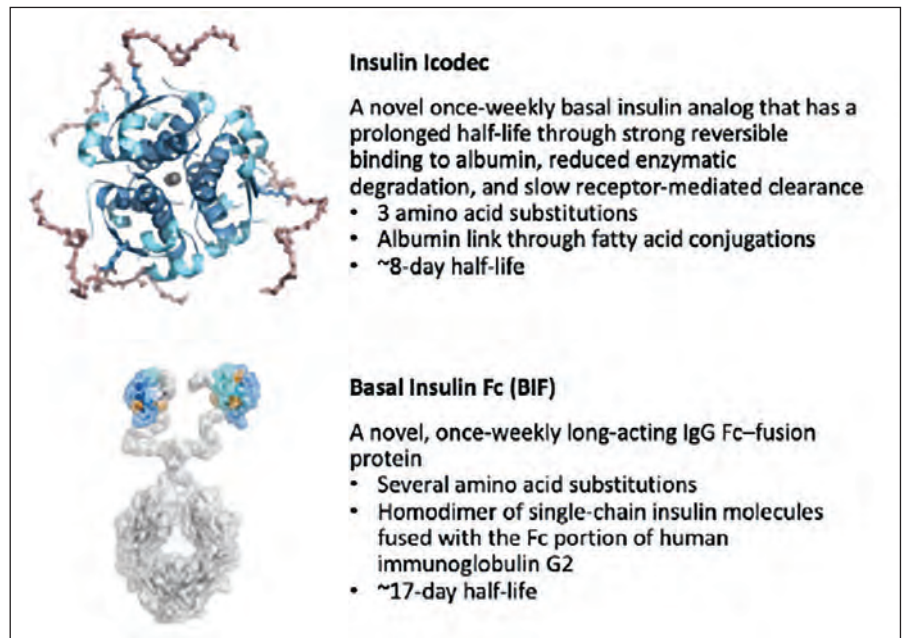
NEW AND EMERGING ONCE-WEEKLY BASAL INSULINS

Innovative insulin formulations and delivery systems have resulted in an expansion of choices that include basal insulins, rapid-acting insulins, and intermediate-acting formulations.²⁵ Now, once-weekly basal insulin formulations are in late-stage development, with insulin icodec receiving a recommendation for marketing approval in Europe and an FDA decision expected soon.^{26,27} Insulin icodec is a novel once-weekly basal insulin analog that has a prolonged half-life through strong reversible binding to albumin, reduced enzymatic degradation, and slow receptor-mediated clearance.²⁸ Basal insulin Fc (BIF) is a novel, once-weekly, long-acting IgG Fc-fusion protein that is currently being assessed for diabetes treatment.²⁹ While these once-weekly insulins are not yet clinically available, evidence supports their comparable efficacy and safety in patients with T2D¹⁰ (FIGURE 1).³⁵

Both insulin icodec and BIF have been investigated in late-stage trials (TABLE 1), with overall positive results.³⁰⁻³⁵ Results of the phase 3 ONWARDS trials evaluating insulin icodec are summarized in TABLE 2.³⁰⁻³⁶ As a whole, the ONWARDS trials showed noninferiority of insulin icodec compared to basal insulin analogs (insulin glargine and insulin degludec) for HbA1c reduction.³⁰⁻³⁴ In ONWARDS 2 and ONWARDS 5, insulin icodec also demonstrated superiority compared to other basal insulins in reducing HbA1c from baseline.^{31,34} In ONWARDS 1 and ONWARDS 3, more patients receiving insulin icodec (10% more and 15% more, respectively) achieved target HbA1c without significant hypoglycemia.^{30,32} In all ONWARDS trials, the rates of hypoglycemia were similar between insulin icodec and other basal insulins.

As of the time of this publication, all phase 3 QWINT trials evaluating BIF are still ongoing, with no results reported. As clinical data continue to emerge for once-weekly insulins, their potential role in clinical practice will be further clarified.

FIGURE 1. Key considerations for new and emerging once-weekly insulins with late-stage trial data³⁵



Source: Trevisan R, Conti M, Ciardullo S. Once-weekly insulins: a promising approach to reduce the treatment burden in people with diabetes. *Diabetologia*. Published online April 29, 2024. doi:10.1007/s00125-024-06158-9. Figure licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction. The license can be viewed at this link: <https://creativecommons.org/licenses/by/4.0/legalcode>

LOOKING TO THE FUTURE: ONCE-WEEKLY INSULINS IN CLINICAL PRACTICE

As once-weekly insulin formulations become available, PCCs will be at the forefront of providing practical strategies for the integration of these formulations into clinical practice. Indications for once-weekly insulin are likely to be similar to those for once-daily insulin, but treatment adherence and quality of life may be important considerations, especially for patients who frequently miss doses of antihyperglycemic medications. New insulin titration strategies will be needed because glucose-lowering will not achieve a steady state for several weeks after initial dosing. Clinicians will need to learn these approaches and educate patients on how to manage dosing and concomitant prandial insulin.¹⁰ Though these strategies are not yet well defined, they will become clearer in the coming years with the potential approval of once-weekly insulin products in the US.

Potential candidates for receiving once-weekly insulins, if approved, include patients with T2D who are inadequately controlled on multiple glucose-lowering agents and require basal insulin therapy.³⁷ Patients who prefer flexibility in dose timing and those who have difficulty with adherence to daily injections may also be good candidates, as they may benefit from a reduced injection burden and attenuated consequences of missing a dose.³⁷

TABLE 1. Phase 3 trials evaluating the once-weekly insulins icodec and BIF in patients with T2D³⁵

Trial	Design	Patients with T2D	Comparator	Baseline treatment	Duration, wks
Insulin icodec					
ONWARDS 1 ³⁰	Open label	Insulin-naïve N=984	Glargine U100	Any noninsulin drugs	78
ONWARDS 2 ³¹	Open label	Insulin-treated N=526	Degludec	Basal insulins ± noninsulin glucose-lowering agents	26
ONWARDS 3 ³²	Double blind	Insulin-naïve N=588	Degludec	Any noninsulin drugs	26
ONWARDS 4 ³³	Open label	Insulin-treated N=582	Glargine U100	Multiple daily insulin injections ± noninsulin drugs	26
ONWARDS 5 ³⁴	Open label	Insulin-naïve N=1085	Glargine U100/300 and degludec	Any noninsulin drugs	52
BIF					
QWINT-1 NCT05662332	Open label	Insulin-naïve N=670	Glargine U100	At least 1 glucose-lowering medication	52
QWINT-2 NCT05362058	Open label	Insulin-naïve N=912	Degludec	At least 1 glucose-lowering medication	52
QWINT-3 NCT05275400	Open label	Insulin-treated N=986	Degludec	Basal insulins ± up to 3 noninsulin drugs (except SUs)	78
QWINT-4 NCT05462756	Open label	Insulin-treated N=670	Glargine U100	Multiple daily insulin injections	26

Abbreviation: BIF, basal insulin Fc, T2D, type 2 diabetes.

Adapted from Trevisan R, Conti M, Ciardullo S. Once-weekly insulins: a promising approach to reduce the treatment burden in people with diabetes. *Diabetologia*. Published online April 29, 2024. doi:10.1007/s00125-024-06158-9

CC License: Figure licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction. The license can be viewed at this link: <https://creativecommons.org/licenses/by/4.0/legalcode>

Compared to once-daily basal insulins, once-weekly basal insulins have a variety of potential benefits, including improved adherence and persistence, flexibility in time of administration, and reduced glycemic variability (**FIGURE 2**).³⁷ Potential concerns include lack of familiarity, challenges with dose calculations, and hypoglycemia.³⁷

Potential benefits of once-weekly insulins

T2D regimens are complex for a large proportion of affected individuals and include dietary management, physical exercise, receiving multiple antihyperglycemic medications, and blood glucose monitoring. Injection burden is a major barrier to insulin adherence as prescribed and results in one-third of those prescribed insulin not being adherent or persistent in treatment.³⁸ Fewer injections may reduce this burden and improve the likelihood of treatment adherence. Once-weekly insulins may provide an option to improve convenience, adherence, and quality of life as compared to once-daily basal insulins.²⁸

Once-weekly insulins may provide more flexibility in dose timing and provide better glucose coverage in the case of

missed doses.³⁷ When once-weekly insulins reach steady state, a missed dose does not result in immediate loss of efficacy due to the agent's long half-life. Additionally, due to the flatter pharmacokinetic profile of once-weekly insulins, a decrease in day-to-day glycemic variability is expected.

Potential concerns about once-weekly insulins

Because clinicians are less familiar with once-weekly insulins, they may have concerns such as worry over a "large dose" of insulin injected at once and hypoglycemia management.³⁷ As such, there is a need for education about the pharmacokinetics of weekly insulins. As with any insulin, a potential safety concern with once-weekly insulins is the risk for hypoglycemia. A meta-analysis of 7 randomized trials found an increased risk for hypoglycemic events with insulin icodec compared to once-daily basal insulins (risk ratio 1.24; 95% CI, 1.02-1.50; $P = .03$) and a numerically decreased risk for severe hypoglycemia (risk ratio 0.81; 95% CI, 0.31-2.08).³⁹

To manage hypoglycemia that occurs while a patient is receiving once-weekly insulin, the fundamental principles are similar to treating typical hypoglycemia episodes, as

TABLE 2. Key results and hypoglycemic events of the phase 3 ONWARDS trials evaluating insulin icodec in patients with T2D³⁰⁻³⁶

Trial	Main results	Hypoglycemic events
ONWARDS 1 ³⁰	Icodec compared to glargine: <ul style="list-style-type: none"> HbA1c reduction: -0.2% Increase in patients at target HbA1c without significant hypoglycemia: 10% TIR: increased 4.3% 	Icodec: 226 episodes in 61 patients (12.4%); 1 severe episode Glargine: 114 episodes in 66 patients (13.4%); 7 severe episodes
ONWARDS 2 ³¹	Icodec demonstrated noninferiority and superiority to degludec in reducing HbA1c from baseline	No significant differences in hypoglycemia rates
ONWARDS 3 ³²	Icodec compared to degludec: <ul style="list-style-type: none"> HbA1c reduction: -0.2% Increase in patients at target HbA1c without significant hypoglycemia: 15% 	Icodec: 53 episodes in 26 patients (9%); 0 severe episode Degludec: 23 episodes in 17 patients (6%); 2 severe episodes
ONWARDS 4 ³³	Icodec compared to glargine: <ul style="list-style-type: none"> Mean change in HbA1c: -1.16% in the icodec group (baseline 8.29%); -1.18% in the glargine group (baseline 8.31%) 	Icodec: 35 episodes in 22 patients (8%) Glargine: 33 episodes in 25 patients (9%)
ONWARDS 5 ³⁴	Icodec in conjunction with the dosing guide app demonstrated noninferiority and superiority compared with basal insulin analogs in reducing mean HbA1c from baseline	No significant differences in hypoglycemia rates

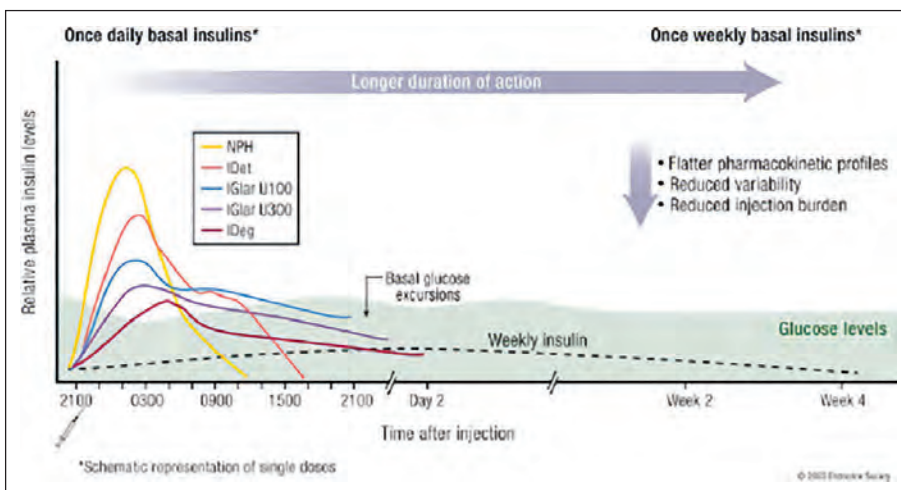
Abbreviations: HbA1c, glycated hemoglobin; TIR, time in range.

insulin icodec has a similar counterregulatory hormone response and recovery compared with insulin glargine.³⁷ Principles for treating hypoglycemia in patients with T2D typically include advising the patient to consume 15 g of glucose (or other fast-acting carbohydrate) for a blood glucose value of ≤ 70 mg/dL and recheck the blood glucose 15 minutes afterward.⁴⁰ If blood glucose remains at or near 70 mg/dL (or less), or if glucose is not rising, an additional 15 g of fast-acting carbohydrates should be consumed, repeating the process until glucose rises. In the case of continual ongoing hypoglycemia, the patient should seek additional care.

Patient case revisited

Revisiting the case scenario, use of a once-weekly insulin would likely help the patient be more adherent to her regimen, because she prefers to avoid daily injections. With improved adherence to her basal insulin regimen, her blood glucose would likely improve, lowering her risk for cardiometabolic complications associated with hyperglycemia.

Advice when talking to patients:

FIGURE 2. Comparison of once-daily and once-weekly basal insulins³⁷

Abbreviations: IDeg, insulin degludec; IDet, insulin detemir; IGlar, insulin glargine; NPH, neutral protamine Hagedorn.

Figure licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction. The license can be viewed at this link: <https://creativecommons.org/licenses/by/4.0/legalcode>

- Assess interest in once-weekly insulin injections
- Discuss the timing action curves for ultra-long-acting insulin
- Remind patients that the dose given will have a long 7-day time of action
- Base titrations on prescribing instructions and the patient's blood glucose values

CONCLUSION

PCCs manage most patients with T2D in the US, including many who receive or are appropriate candidates for basal insulin therapy. Despite insulin's long history in treating diabetes, clinical inertia routinely occurs due to a variety of factors, resulting in treatment delays and suboptimal glucose management. New and emerging once-weekly insulins offer additional approaches for basal insulin therapy in T2D that may reduce clinical inertia and improve treatment adherence and patient outcomes. ●

REFERENCES

URLs must be entered manually, rather than copied and pasted.

- Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes - global burden of disease and forecasted trends. *J Epidemiol Glob Health*. 2020;10(1):107-111. doi:10.2991/jegeh.k.191028.001
- About type 2 diabetes. Centers for Disease Control and Prevention. Published May 14, 2024. Accessed August 3, 2024. <https://www.cdc.gov/diabetes/about/about-type-2-diabetes.html>
- National Diabetes Statistics Report. Centers for Disease Control and Prevention. Published May 15, 2024. Accessed August 3, 2024. <https://www.cdc.gov/diabetes/php/data-research/index.html>
- American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2024. *Diabetes Care*. 2024;47(Suppl 1):S179-S218. doi:10.2337/dc24-S010
- Ramtahal R, Khan C, Maharaj-Khan K, et al. Prevalence of self-reported sleep duration and sleep habits in type 2 diabetes patients in South Trinidad. *J Epidemiol Glob Health*. 2015;5(4 Suppl 1):S35-43. doi:10.1016/j.jegh.2015.05.003
- American Diabetes Association Professional Practice Committee. 11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2024. *Diabetes Care*. 2024;47(Suppl 1):S219-S230. doi:10.2337/dc24-S011
- Davidson JA. The increasing role of primary care physicians in caring for patients with type 2 diabetes mellitus. *Mayo Clin Proc*. 2010;85(12 Suppl):S3-4. doi:10.4065/mcp.2010.0466
- Shrivastav M, Gibson W, Shrivastav R, et al. Type 2 diabetes management in primary care: the role of retrospective, professional continuous glucose monitoring. *Diabetes Spectr*. 2018;31(3):279-287. doi:10.2337/ds17-0024
- Vigersky RA, Fish L, Hogan P, et al. The clinical endocrinology workforce: current status and future projections of supply and demand. *J Clin Endocrinol Metab*. 2014;99(9):3112-3121. doi:10.1210/jc.2014-2257
- Rosenstock J, Del Prato S. Basal weekly insulins: the way of the future! *Metabolism*. 2022;126:154924. doi:10.1016/j.metabol.2021.154924
- American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2024. *Diabetes Care*. 2024;47(Suppl 1):S158-S178. doi:10.2337/dc24-S009
- Andary R, Fan W, Wong ND. Control of cardiovascular risk factors among US adults with type 2 diabetes with and without cardiovascular disease. *Am J Cardiol*. 2019;124(4):522-527. doi:10.1016/j.amjcard.2019.05.035
- Kazemian P, Shebl FM, McCann N, Walensky RP, Wexler DJ. Evaluation of the cascade of diabetes care in the United States, 2005-2016. *JAMA Intern Med*. 2019;179(10):1376-1385. doi:10.1001/jamainternmed.2019.2396
- Cefalu WT, Dawes DE, Gavlak G, et al. Insulin access and affordability working group: conclusions and recommendations. *Diabetes Care*. 2018;41(6):1299-1311. doi:10.2337/dci18-0019
- Brod M, Kongso JH, Lessard S, Christensen TL. Psychological insulin resistance: patient beliefs and implications for diabetes management. *Qual Life Res*. 2009;18(1):23-32. doi:10.1007/s1136-008-9419-1
- Perez-Nieves M, Kabul S, Desai U, et al. Basal insulin persistence, associated factors, and outcomes after treatment initiation among people with type 2 diabetes mellitus in the US. *Curr Med Res Opin*. 2016;32(4):669-680. doi:10.1185/03007995.2015.1135789
- Idris I, Gulati K, Perez-Nieves M, et al. Associated factors that influenced persistence with basal analog insulin therapy among people with type 2 diabetes: an exploratory analysis from a UK real-world sample. *Prim Care Diabetes*. 2019;13(2):106-112. doi:10.1016/j.pcd.2018.09.002
- Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care*. 2013;36(11):3411-3417. doi:10.2337/dc13-0331
- Harris SB, Kapur J, Lank CN, Willan AR, Houston T. Clinical inertia in patients with T2DM requiring insulin in family practice. *Can Fam Physician*. 2010;56(12):e418-424.
- Khunti S, Khunti K, Seidu S. Therapeutic inertia in type 2 diabetes: prevalence, causes, consequences and methods to overcome inertia. *Ther Adv Endocrinol Metab*. 2019;10:2042018819844694. doi:10.1177/2042018819844694
- Shah BR, Hux JE, Laupacis A, Zinman B, van Walraven C. Clinical inertia in response to inadequate glycemic control: do specialists differ from primary care physicians? *Diabetes Care*. 2005;28(3):600-606. doi:10.2337/diacare.28.3.600
- Mata-Cases M, Franch-Nadal J, Real J, et al. Therapeutic inertia in patients treated with two or more antidiabetics in primary care: factors predicting intensification of treatment. *Diabetes Obes Metab*. 2018;20(1):103-112. doi:10.1111/dom.13045
- Blonde L, Aschner P, Bailey C, et al. Gaps and barriers in the control of blood glucose in people with type 2 diabetes. *Diab Vasc Dis Res*. 2017;14(3):172-183. doi:10.1177/1479164116679775
- Pantalone KM, Misra-Hebert AD, Hobbs TM, et al. Clinical inertia in type 2 diabetes management: evidence from a large, real-world data set. *Diabetes Care*. 2018;41(7):e113-e114. doi:10.2337/dc18-0116
- Hirsch IB, Juneja R, Beals JM, Antalis CJ, Wright EE. The evolution of insulin and how it informs therapy and treatment choices. *Endocr Rev*. 2020;41(5):733-755. doi:10.1210/endo/bnaa015
- Novo Nordisk's once-weekly basal insulin icodex recommended for marketing approval in Europe. Reuters. Published March 21, 2024. Accessed March 27, 2024. <https://www.reuters.com/business/healthcare-pharmaceuticals/novo-nordisks-once-weekly-basal-insulin-icodex-recommended-marketing-approval-2024-03-21/>
- Bundgaard C. FDA extends review time for weekly Novo Nordisk insulin. Published February 5, 2024. Accessed March 27, 2024. https://medwatch.com/News/Pharma__Biotech/article16817544.ece
- Bajaj HS, Bergenstal RM, Christoffersen A, et al. Switching to once-weekly insulin icodex versus once-daily insulin glargine U100 in type 2 diabetes inadequately controlled on daily basal insulin: a phase 2 randomized controlled trial. *Diabetes Care*. 2021;44(7):1586-1594. doi:10.2337/dc20-2877
- Frias J, Chien J, Zhang Q, et al. Safety and efficacy of once-weekly basal insulin Fc in people with type 2 diabetes previously treated with basal insulin: a multicentre, open-label, randomised, phase 2 study. *Lancet Diabetes Endocrinol*. 2023;11(3):158-168. doi:10.1016/S2213-8587(22)00388-6
- Rosenstock J, Bain SC, Gowda A, et al. Weekly icodex versus daily glargine U100 in type 2 diabetes without previous insulin. *N Engl J Med*. 2023;389(4):297-308. doi:10.1056/NEJMoa2303208
- Phillis-Tsimikas A, Asong M, Franek E, et al. Switching to once-weekly insulin icodex versus once-daily insulin degludec in individuals with basal insulin-treated type 2 diabetes (ONWARDS 2): a phase 3a, randomised, open label, multicentre, treat-to-target trial. *Lancet Diabetes Endocrinol*. 2023;11(6):414-425. doi:10.1016/S2213-8587(23)00093-1
- Lingvay I, Asong M, Desouza C, et al. Once-weekly insulin icodex vs once-daily insulin degludec in adults with insulin-naive type 2 diabetes: the ONWARDS 3 randomized clinical trial. *JAMA*. 2023;330(3):228. doi:10.1001/jama.2023.11313
- Mathieu C, Ásbjörnsdóttir B, Bajaj HS, et al. Switching to once-weekly insulin icodex versus once-daily insulin glargine U100 in individuals with basal-bolus insulin-treated type 2 diabetes (ONWARDS 4): a phase 3a, randomised, open-label, multicentre, treat-to-target, non-inferiority trial. *Lancet*. 2023;401(10392):1929-1940. doi:10.1016/S0140-6736(23)00520-2
- Bajaj HS, Aberle J, Davies M, et al. Once-weekly insulin icodex with dosing guide app versus once-daily basal insulin analogues in insulin-naive type 2 diabetes (ONWARDS 5): a randomized trial. *Ann Intern Med*. 2023;176(11):1476-1485. doi:10.7326/M23-1288
- Trevisan R, Conti M, Ciardullo S. Once-weekly insulins: a promising approach to reduce the treatment burden in people with diabetes. *Diabetologia*. Published online April 29, 2024. doi:10.1007/s00125-024-06158-9
- Argano C, Priola L, Manno F, Corrao S. What is the role of basal weekly insulin in clinical practice? The state of the art. *Biomedicines*. 2024;12(4):900. doi:10.3390/biomedicines12040900
- Rosenstock J, Juneja R, Beals JM, Moyers JS, Ilag L, McCrimmon RJ. The basis for weekly insulin therapy: evolving evidence with insulin icodex and insulin efsitora alfa. *Endocr Rev*. 2024;45(3):379-413. doi:10.1210/endo/bnad037
- Vijan S, Hayward RA, Ronis DL, Hofer TP. Brief report: the burden of diabetes therapy: implications for the design of effective patient-centered treatment regimens. *J Gen Intern Med*. 2005;20(5):479-482. doi:10.1111/j.1525-1497.2005.0117.x
- Mukhopadhyay P, Chatterjee P, Pandit K, Sanyal D, Ghosh S. Once-weekly insulin icodex as compared to once-daily basal insulins: a meta-analysis. *Endocr Pract*. 2024;30(2):128-134. doi:10.1016/j.eprac.2023.11.004
- American Diabetes Association Professional Practice Committee. 6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes—2024. *Diabetes Care*. 2024;47(Suppl 1):S111-S125. doi:10.2337/dc24-S006

