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A SPECIAL SUPPLEMENT ON
HOT TOPICS
in Primary Care
2026

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Introduction

Primary care clinicians must remain up to date across the broad range of conditions encountered in daily practice. New approvals, emerging evidence, and changing treatment strategies continue to reshape clinical decision-making. To highlight advances with immediate relevance to patient care, *Hot Topics in Primary Care 2026* brings together focused articles addressing timely challenges across a variety of diseases.

Cardiovascular, kidney, and metabolic disorders remain central to primary care. This supplement explores the use of continuous glucose monitoring to translate glucose data into treatment decisions and examines automated insulin delivery as an option for managing type 2 diabetes. Additional articles address nonsteroidal mineralocorticoid receptor antagonists for cardiovascular-kidney-metabolic syndrome, the cardiometabolic contributions of dairy foods, and hypercortisolism as an underrecognized cause of resistant hypertension. You'll also find practical guidance on personalizing low-density lipoprotein cholesterol management beyond statins, incorporating lipoprotein(a) into risk assessment, and revisiting low-dose aspirin through the lens of newer prediction tools. A primary care roadmap for severe hypertriglyceridemia highlights opportunities to recognize high-risk patients and reduce the risk of acute pancreatitis.

Respiratory care is also featured prominently. Articles examine the addition of inhaled corticosteroids to rescue

therapy for mild-to-moderate asthma, recognition of severe asthma requiring specialist referral and consideration of biologic therapy, and practical escalation with long-acting muscarinic antagonists in asthma and chronic obstructive pulmonary disease.

Other topics reflect expanding treatments across common conditions. These include managing vasomotor symptoms due to menopause, integrating oral therapies into obesity care, and providing effective acute pain treatment while reducing reliance on opioids.

Each article in this special issue is designed to provide practical, actionable insights that can be readily incorporated into clinical care. We hope that *Hot Topics in Primary Care 2026* serves as a valuable resource for continuing education and clinical practice.

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

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

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- 6) Closing Lipid Management Gaps in Primary Care (ends 7/5/27)



#1 (1 hr)



#2 (1 hr)



#3 (1 hr)



#4 (4 hr)



#5 (1 hr)



#6 (1 hr)

Revisiting the Low-Dose Aspirin Benefit-Risk Discussion in the Context of New Risk Assessment Tools

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Stephen Brunton, MD, FAAFP Professor, Department of Family and Preventive Medicine	DISCLOSURES Dr. Weisman discloses that he is the Global President, Clinical and Regulatory at Lumanity, a consultancy to the pharmaceutical industry, and he has received consultancy fees from Bayer related to the topic of this manuscript.	

INTRODUCTION

Low-dose aspirin has been extensively studied for the prevention of major cardiovascular (CV) events. Aspirin consistently demonstrates meaningful reductions in both relative and absolute risk, with the highest absolute benefit in patients with the highest underlying risk of a CV event. The central challenge is not aspirin's effectiveness, but in the separation between potential benefit and risk without CV risk stratification. Accurately identifying high-risk but asymptomatic patients who would benefit from aspirin therapy has been challenging for those clinicians most dependent on population-based risk calculators.

Careful patient selection and a personalized approach to treatment may substantially improve the benefit-risk balance.¹ Individuals with a meaningful baseline CV risk are more likely to derive net benefit from aspirin therapy, making them appropriate candidates for consideration. To make informed recommendations, primary care clinicians must assess both the underlying risk of CV events and the potential benefits and risks of aspirin use.

This review examines the current evidence about the benefits and risks of low-dose aspirin, with a focus on practical application in primary care. It highlights newer data suggesting that adverse events may occur less frequently than is often assumed and discusses how newer analytical methods might be used to optimize the benefit-risk balance. It also outlines strategies for pretreatment evaluation to help more individuals benefit from aspirin in preventing CV events and

Key takeaways

- Aspirin retains clear value for patients at risk of ischemic CV events, both in those with a prior event and in those without a prior event but with an equivalent level of risk.
- While the use of aspirin for secondary prevention is well established, use for primary prevention should be based on patient-specific risk profiles.
- Reliance solely on conventional risk factors can miss many high-risk patients, resulting in both overtreatment (low-risk individuals exposed to bleeding risk without benefit) and undertreatment (high-risk patients not offered aspirin despite potential benefit).
- Imaging and emerging biomarkers are promising tools to identify patients in whom the absolute CV benefit of aspirin outweighs bleeding risk.
- Discussions between clinicians and patients are necessary to ensure that aspirin is used appropriately, safely, and in alignment with individual risk profiles.

demonstrates the importance of clinician awareness of available tools to better guide therapy.

Bleeding risks from aspirin are well known yet often misunderstood or exaggerated and may be a barrier to patient interest and clinician recommendations. This article aims to support clinicians in making informed, individualized decisions about aspirin therapy, helping them counsel patients effectively and enhance adherence where preventive benefit is likely to outweigh risk.

BRIEF HISTORY OF ASPIRIN USE FOR CV EVENT PREVENTION

Building on observations from the 1960s that aspirin inhibits platelet aggregation and reduces thrombosis,^{2,3} several large clinical trials established aspirin's role in the prevention of myocardial infarction (MI), stroke, and CV death (**TABLE 1**).

In 1994, the Antiplatelet Trialists' Collaboration analyzed 174 clinical trials involving approximately 70,000 high-risk patients. Medium-dose aspirin (75-325 mg/day) consistently reduced major CV events, with similar efficacy across this dose range. There was no significant evidence that either a higher aspirin dose or alternative antiplatelet agents were more effective than a medium aspirin dose in preventing nonfatal MI, nonfatal strokes, or vascular deaths.⁴

Collectively, these findings informed the US Food and Drug Administration (FDA) approvals for aspirin use after stroke (1980), after MI (1985), and for suspected MI (1996) (**FIGURE 1**).⁵

Today, daily low-dose aspirin use is well established and widely recommended for the prevention of atherosclerotic CV disease (ASCVD) in patients who have had a previous CV event or who are at high risk of CV events (strength of recommendation IIb). Evidence suggests that the benefits of low-dose aspirin might outweigh the risks in individuals with a higher ASCVD risk but not an increased bleeding risk.⁶ In contrast, clinical trials of aspirin for patients who have not had a previous event have provided less clarity. Most of these trials randomized patients to aspirin treatment based on conventional risk factors and yielded inconsistent results, leading to the conclusion that aspirin's net value in these patients remains uncertain.⁷

Given the collective findings from studies of at-risk

patients, in 2016, the US Preventive Services Task Force (USPSTF) updated its guidance citing evidence that aspirin was beneficial to reduce risk of CV events in adults aged 50 to 69 years with increased CV disease (CVD) risk, but major bleeding risk also increased. The USPSTF also noted that absolute bleeding risk varied considerably depending on an individual's baseline risk profile. Based on this evidence, the Task Force recommended initiating low-dose aspirin for the primary prevention of CVD in adults aged 50 to 59 years with a 10% or greater 10-year CVD risk and not at an increased risk of bleeding.⁸

CURRENT CLINICAL PRACTICE GUIDELINES AND RECOMMENDATIONS

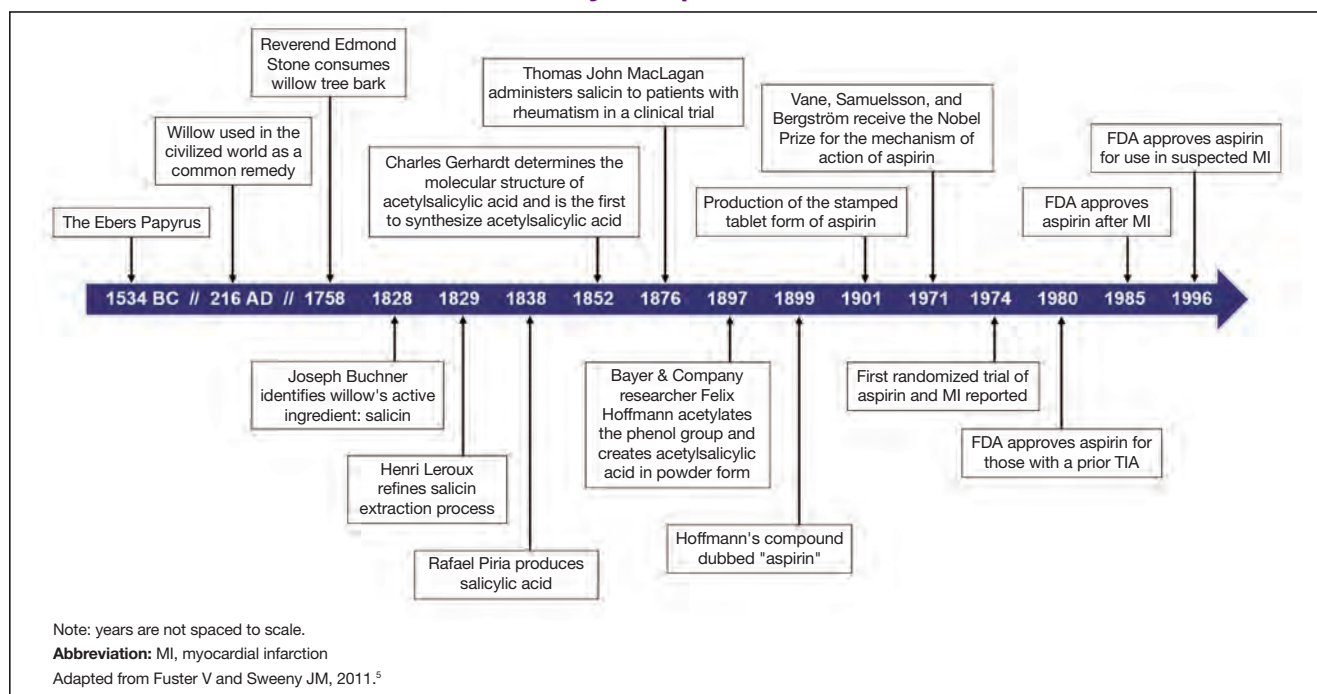
Three major trials published in 2018 had a substantial impact on the clinical approach to aspirin use for CV prevention in patients without a previous event. The Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial evaluated low-dose aspirin (100 mg daily) in individuals at moderate estimated risk for a first CV event (defined by conventional risk assessment). Over an average follow-up of 60 months, the composite endpoint (i.e., time to first occurrence of CV death, MI, unstable angina, stroke, or transient ischemic attack [TIA]) occurred in 269 participants (4.29%) in the aspirin group vs 281 participants (4.48%) in the placebo group. Although predominantly mild, GI bleeding events occurred in 61 aspirin participants (0.97%) compared with 29 placebo participants (0.46%).¹⁴

The A Study of Cardiovascular Events in Diabetes (ASCEND) trial assessed low-dose aspirin (100 mg daily) in individuals with diabetes but without established CVD. Over a mean follow-up of 7.4 years, aspirin significantly reduced the percentage of serious vascular events in the aspirin

TABLE 1. Evidence establishing aspirin's role in CV prevention.⁹⁻¹³

Elwood et al, 1974	Canadian cooperative study, 1978	ISIS-2, 1988	SALT, 1991	UK-TIA, 1991
300 mg daily	325 mg QID	160 mg daily	75 mg daily	300 mg or 1200 mg daily
Patients with MI	Patients with threatened stroke	Patients within 24 hours of suspected acute MI	Patients 1 to 4 months after TIA or minor stroke	Patients with TIA or minor ischemic stroke
12% reduction in total mortality at 6 months 25% reduction in total mortality at 1 year	19% reduction in composite outcome of continuing TIAs, stroke, or death 31% reduction in stroke or death No bleeds observed	23% reduction in 5 week vascular mortality; 42% reduction when combined with streptokinase Lowered rates of nonfatal stroke and nonfatal reinfarction No significant increase in cerebral hemorrhage or bleeds requiring transfusion	18% reduction in stroke or death 16% to 20% reductions in secondary outcome events More frequent bleeding episodes	15% reduction in major stroke, MI, or vascular death More GI toxicity at 1200 mg

Abbreviations: GI, gastrointestinal; ISIS-2, Second International Study of Infarct Survival Collaborative Group; QID, four times daily; SALT, Swedish Aspirin Low-Dose Trial; UK-TIA, United Kingdom Transient Ischaemic Attack trial.

FIGURE 1. Timeline of events in the history of aspirin use.⁵

group (658 participants or 8.5%) compared with placebo (743 or 9.6%). However, major bleeding events occurred in 314 aspirin participants (4.1%) vs 245 placebo participants (3.2%).¹⁵

The Aspirin in Reducing Events in the Elderly (ASPREE) trial investigated low-dose aspirin (100 mg daily) in healthy adults aged 70 years or older. Aspirin did not extend disability-free survival and was associated with a higher rate of major hemorrhage. These findings suggested that, in elderly individuals, aspirin use for primary prevention may be more harmful than beneficial.¹⁶

A subsequent meta-analysis of 13 primary prevention trials, including ARRIVE, ASCEND, and ASPREE, found that aspirin use was associated with a reduction in composite CV outcomes (hazard ratio, 0.89; 95% confidence interval [CI]: 0.84, 0.94; absolute risk reduction, 0.41%; 95% CI: 0.23, 0.59); however, in 11 trials, there were 2029 bleeding events in the aspirin groups vs 834 in the control groups. It should be noted that event rates in several of these trials were lower than anticipated, with an estimated 10-year risk of composite CV outcome <10% in 6 studies.¹⁷ These findings under-

score the importance of careful patient selection when considering aspirin as primary prevention in those with atherosclerosis and low bleeding risk.

Current guidelines discourage aspirin use for low-risk individuals. The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) CVD prevention guidelines recommend infrequent use for primary prevention because of lack of net benefit, but in individuals aged 40 to 70 years who have higher ASCVD risk without increased bleeding risk, aspirin might be considered (see recommendation IIb, TABLE 2).⁶

TABLE 2. 2019 ACC/AHA recommendations for aspirin use.⁶

Recommendations	Class of Recommendation	Level of Evidence
Low-dose aspirin ^a might be considered for primary prevention of ASCVD among select adults 40 to 70 years of age at higher ASCVD risk but not at increased risk of bleeding.	IIb (Weak) Benefit ≥ Risk	A (High-quality RCT evidence)
Low-dose aspirin ^a should not be routinely used for primary prevention of ASCVD in adults older than 70 years of age.	III: Harm (Strong) Risk > Benefit	B-R (Moderate-quality RCT evidence)
Low-dose aspirin ^a should not be used for primary prevention of ASCVD in adults with increased bleeding risk.	III: Harm (Strong) Risk > Benefit	C-LD (Limited Data; observational or physiological/mechanistic studies)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; RCT, randomized controlled trial

^aLow-dose aspirin refers to 75-100 mg of aspirin by mouth daily.

Adapted from Arnett DK et al, 2019.

TABLE 3. Current guidelines for aspirin use for primary prevention.^{6,18}

	Adults younger than 40 years of age	Adults aged 40-70 with $\geq 10\%$ CVD risk	Adults older than 70 years of age
2019 ACC/AHA guidelines	There is insufficient evidence to judge risk-benefit ratio of aspirin for primary prevention of ASCVD	Low-dose aspirin might be considered for primary prevention among adults at higher ASCVD risk but not increased bleeding risk	Low-dose aspirin should not be administered for primary prevention of ASCVD
	Adults aged 40 to 59 with $\geq 10\%$ CVD risk	Adults aged 60-69 with $\geq 10\%$ CVD risk	Adults older than 60 years of age
2022 USPSTF recommendation	The decision to initiate low-dose aspirin for primary prevention of CVD should be an individual one	The decision to initiate low-dose aspirin for primary prevention of CVD should be an individual one	Low-dose aspirin for primary prevention of CVD is not recommended

Similarly, in its 2021 CVD prevention guidelines, the European Society of Cardiology (ESC) concluded that aspirin should not be prescribed to individuals without ASCVD. However, in selected patients at high or very high CVD risk, the potential benefits of aspirin may outweigh the risks. For adults over 70 years of age with high CVD risk, the ESC advised that decisions be made on a case-by-case basis.¹⁹

In 2022, the USPSTF released an updated systematic review evaluating the effectiveness of aspirin in reducing CVD events. The Task Force concluded that for adults aged 40 to 59 years, with $\geq 10\%$ estimated 10-year CVD risk, aspirin use for primary prevention offers a small net benefit. However, individuals who are not at increased risk for bleeding and take low-dose aspirin daily are more likely to derive benefit. Consistent with the 2019 ACC/AHA guidelines, the USPSTF recommends low-dose aspirin for primary prevention in adults ≥ 60 years of age.¹⁸ Current guidelines emphasize the importance of determining individual net benefit of aspirin use for primary prevention (TABLE 3).

Nevertheless, physician and public perceptions have increasingly shifted toward caution in aspirin use, largely due to concerns over bleeding risk. This shift has resulted in underuse in patients who stand to benefit, and in some cases, overuse in low-risk individuals, exposing them to bleeding risk with few benefits.²⁰ These trends underscore the need for greater clarity in identifying the clinical characteristics of patients for whom aspirin's net benefit outweighs its risks. It also highlights the need to better educate clinicians on the importance of continued aspirin use in patients at risk of recurrent CV events.

Traditionally, aspirin recommendations were segmented based on either evidence of a previous event (secondary prevention) or usual or elevated risk (primary prevention). This approach presumed that aspirin's benefits outweighed its bleeding risks only once a patient had an event or was risk equivalent based on risk calculators largely built on data derived from epidemiologic studies. However, as demonstrated by primary prevention studies, the conven-

tional tools that were used to select patients were not effective in identifying those at sufficient risk to benefit from aspirin use.²¹

Yet it is clearly understood that someone can have elevated CV risk without having had an event, as evidenced by the large number of first events that occur every year. The goal, therefore, should be to better identify these patients, as they are most likely to benefit from aspirin treatment. These patients, particularly those with subclinical atherosclerosis, while technically classified as "primary prevention," may have event risks comparable to or greater than patients who have had a previous event.²²

A patient's CV risk is influenced by a combination of atherosclerotic disease and thrombotic risks; features that are not easily assessed by conventional risk factors, such as age, diabetes, hypertension, smoking, or family history. Evidence of subclinical atherosclerosis (e.g., coronary artery calcium [CAC] score, carotid plaque score [CPS]) or biomarkers (e.g., lipoprotein(a) [Lp(a)], platelet reactivity, genetic susceptibility) are individualized risk indicators that are becoming more clinically available.

This more analytical perspective reframes the benefit-risk calculation for aspirin use. The question is no longer whether a patient has had a clinical event, but rather how their absolute CVD risk compares to their bleeding risk. Applying new analytical tools may offer a more personalized approach to determine a patient's position on the CVD risk continuum and improve the ability to identify individuals whose absolute benefit outweighs bleeding harm in primary prevention. These approaches are reviewed below.

Imaging

Coronary imaging modalities, such as CAC or CPS, are increasingly used to identify asymptomatic, higher-risk individuals (i.e., those with advanced subclinical atherosclerosis) who may be appropriate candidates for aspirin use as primary prevention. Research has shown that ASCVD risk rises sharply with higher CAC scores, while bleeding risk

does not appear to increase proportionally.²²⁻²⁴ Studies suggest that aspirin may be beneficial in individuals with a CAC score >100 or moderate plaque burden on carotid ultrasound (CPS ≥ 2), provided they have no major bleeding risk factors.²⁵ Similarly, a recent systematic review found that, in the absence of significant bleeding risk, both elevated ASCVD risk and higher CAC scores correlated with greater net benefit from aspirin use.²⁶

Biomarkers

Lp(a)

In individuals with elevated Lp(a), aspirin use has been associated with a reduction in CV events. For example, recent evidence suggests that aspirin for primary prevention may benefit elderly individuals with elevated Lp(a)-associated genotypes. In an analysis of more than 12,000 participants enrolled in the ASPREE trial, low-dose aspirin (100 mg daily) reduced major adverse CV events (MACE) by 1.7 events per 1000 person-years, while increasing clinically significant bleeding by 1.7 events per 1000 person-years. However, in subgroups carrying Lp(a)-associated genotypes, specifically rs3798220-C and Lp(a) genomic risk score, aspirin reduced MACE by 11.4 and 3.3 events per 1000 person-years, respectively, without a statistically significant increase in bleeding risk.²⁷

Similarly, findings from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort showed a relationship between aspirin use and CV events in individuals with elevated Lp(a). A subgroup of participants with Lp(a) concentrations >50 mg/dL had a higher burden of traditional CVD risk factors, more frequent aspirin use, and a significantly higher rate of coronary heart disease incidents. Aspirin use was associated with a significant reduction in coronary heart disease events. Although overall bleeding risk was increased with aspirin use, no significant differences in bleeding rates were observed between those with elevated Lp(a) and those without.²⁸

Platelet activity

Aspirin's CV benefits stem from its antithrombotic effects, raising the possibility that assessing platelet activity could enable more targeted patient selection for therapy. Individuals with elevated platelet reactivity may be at higher risk for thrombotic events and, therefore, would be more likely to derive meaningful benefit from aspirin for primary prevention. Conversely, those with low platelet reactivity are generally more prone to bleeding and less likely to experience net benefit. Prospective clinical studies are needed to determine whether a platelet-guided approach can reliably identify candidates for aspirin as primary prevention. The development of protein biomarker signatures that predict both platelet

activity and CV event risk could make such an approach scalable in routine practice.^{29,30}

Genetic predisposition

Genetic markers may offer another approach to personalized aspirin therapy. Recent research suggests that low-dose aspirin (100 mg) for primary prevention may be beneficial in high-risk individuals with an elevated genetic predisposition to coronary artery disease (CAD). Using data from the ASPREE trial, it was shown that among participants with the highest CAD polygenic risk score (GPSMult), there was a 47% reduction in risk of CAD events with aspirin ($P = .02$) without a statistically significant increase in bleeding risk ($P = .80$).³¹

SUMMARY

While aspirin use is well established for the prevention of recurrent stroke and MI (secondary prevention) and acute or evolving MI, its role in individuals without an event (primary prevention) remains uncertain. In line with the 2019 ACC/AHA guidelines, recent trends show a decline in aspirin use for primary prevention, particularly among adults ≥ 70 years. Nevertheless, about one-third of adults in this age group continue to use aspirin for primary prevention.³² Conversely, a decline in use has been observed among adults <60 years with ASCVD risk factors.³³

Traditionally, patients were categorized as either high risk (secondary prevention) or moderate risk (primary prevention). However, this approach can potentially overlook a subset of individuals who have not had a CV event but who are risk equivalent due to the presence of subclinical atherosclerosis and may benefit from aspirin. Emerging evidence supports tailoring treatment decisions to a patient's atherosclerotic/thrombotic status using more precise analytical methods. Using such tools will allow improved decision-making regarding initiating aspirin therapy and provide a better ability to weigh potential benefits against possible harms, integrating clinical characteristics, CV and bleeding risks, and other relevant factors.¹

The challenge lies in identifying individuals with sufficiently high CV event risk in which aspirin's benefits outweigh potential harms. Reliance solely on conventional risk factors often underestimates aspirin's potential benefit and overstates its risks. While patient-facing CV risk-assessment tools can help initiate discussions between clinician and patient, they may be inadequate for guiding treatment decisions. Current risk stratification tools may be refined by the addition of more personalized emerging imaging and biomarkers.

Incorporating CAC and CPS scoring into clinical practice is an effective strategy for improving clinician-patient decision-making in primary prevention. CAC is a highly reli-

able method for identifying asymptomatic, higher-risk individuals who are likely to benefit from aspirin. A score ≥ 100 offers a practical threshold for considering aspirin, whereas a score of 0 generally supports avoiding use due to the low expected net benefit. Making CAC-guided aspirin therapy a standard of care will require integrating CAC data into electronic medical records, opportunistically using prior imaging to calculate scores, and enhancing clinician education on interpreting results in the context of both bleeding risk and overall CV risk.

Targeted education for health care professionals, covering appropriate imaging and interpretation for prevention decisions, is essential. Equally important are informed, shared discussions between clinicians and patients to ensure aspirin is used appropriately, safely, and in alignment with individual risk profiles. Communication must be simple and precise.

For clinicians: If a patient has documented atherosclerosis and low bleeding risk, aspirin should be considered. For the public, the message becomes: *aspirin can help prevent heart attacks and strokes in certain higher-risk individuals, but it is not appropriate for everyone.*

Ultimately, an integrated approach combining clinical risk factors, imaging, and biomarkers is needed to identify patients in whom aspirin's benefits outweigh its risks. Current guidelines do not yet incorporate imaging-based risk stratification, though this may represent the future of preventive care. Until such tools become routine, clinician education and individualized decision-making are key. ●

REFERENCES

- Santilli F, Albrecht G, Blaha M, et al. Needs-based considerations for the role of low-dose aspirin along the CV risk continuum. *Am J Prev Cardiol.* 2024;18:100675. doi:10.1016/j.ajpc.2024.100675
- Weiss H, Aledort L. Impaired platelet/connective-tissue reaction in man after aspirin ingestion. *The Lancet.* 1967;290(7514):495-497. doi:10.1016/s0140-6736(67)91658-3
- Weiss HJ, Aledort LM, Kochwa S. The effect of salicylates on the hemostatic properties of platelets in man. *J Clin Invest.* 1968;47(9):2169-2180. doi:10.1172/JCI105903
- Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ.* 1994; 308(6921):81-106.
- Fuster V, Sweeney JM. Aspirin: a historical and contemporary therapeutic overview. *Circulation.* 2011;123(7):768-778. doi:10.1161/circulationaha.110.963843
- Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;74(10):1376-1414. doi:10.1016/j.jacc.2019.03.009
- Antithrombotic Trialists' (ATT) Collaboration; Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *The Lancet.* 2009;373(9678):1849-1860. doi:10.1016/S0140-6736(09)60503-1
- Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2016;164(12):836-845. doi:10.7326/M16-0577
- Elwood PC, Cochrane AL, Burr ML, et al. A randomized controlled trial of acetylsalicylic acid in the secondary prevention of mortality from myocardial infarction. *Br Med J.* 1974;1(5905):436-440. doi:10.1136/bmj.1.5905.436
- Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med.* 1978;299(2):53-59. doi:10.1056/NEJM197807132990201
- Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. (Second International Study of Infarct Survival) Collaborative Group. *J Am Coll Cardiol.* 1988;12(6 suppl A):3A-13A. doi:10.1016/0735-1097(88)92635-6
- The SALT Collaborative Group. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. *The Lancet.* 1991;338(8779):1345-1349.
- Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry.* 1991;54(12):1044-1054. doi:10.1136/jnnp.54.12.1044
- Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *The Lancet.* 2018;392(10152):1036-1046. doi:10.1016/S0140-6736(18)31924-X
- ASCEND Study Collaborative Group; Bowman L, Mafham M, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med.* 2018;379(16):1529-1539. doi:10.1056/NEJMoa1804988
- McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. *N Engl J Med.* 2018;379(16):1499-1508. doi:10.1056/NEJMoa1800722
- Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA.* 2019;321(3):277-287. doi:10.1001/jama.2018.20578
- US Preventive Services Task Force; Davidson KW, Barry MJ, et al. Aspirin use to prevent cardiovascular disease: US Preventive Services Task Force recommendation statement. *JAMA.* 2022;327(16):1577-1584. doi:10.1001/jama.2022.4983
- Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: developed by the Task Force for Cardiovascular Disease Prevention in Clinical Practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). *Rev Esp Cardiol (Engl Ed).* 2022;75(5):429. doi:10.1016/j.rec.2022.04.003
- Luepker RV, Oldenburg NC, Misialek JR, et al. Aspirin use and misuse for the primary prevention of cardiovascular diseases. *Am J Prev Med.* 2021;60(4):513-519. doi:10.1016/j.amepre.2020.10.025
- Verma KP, Inouye M, Meikle PJ, Nicholls SJ, Carrington MJ, Marwick TH. New cardiovascular risk assessment techniques for primary prevention: JACC review topic of the week. *J Am Coll Cardiol.* 2022;80(4):373-387. doi:10.1016/j.jacc.2022.05.015
- Blaha MJ, Abdelhamid M, Santilli F, Shi Z, Sibbing D. Advanced subclinical atherosclerosis: a novel category within the cardiovascular risk continuum with distinct treatment implications. *Am J Prev Cardiol.* 2022;13:100456. doi:10.1016/j.ajpc.2022.100456
- Ajufo E, Ayers CR, Vigen R, et al. Value of coronary artery calcium scanning in association with the net benefit of aspirin in primary prevention of atherosclerotic cardiovascular disease. *JAMA Cardiol.* 2021;6(2):179-187. doi:10.1001/jamacardio.2020.4939
- Dzaye O, Razavi AC, Dardari ZA, et al. Carotid ultrasound-based plaque score for the allocation of aspirin for the primary prevention of cardiovascular disease events: the Multi-Ethnic Study of Atherosclerosis and the Atherosclerosis Risk in Communities study. *J Am Heart Assoc.* 2024;13(12):e034718. doi:10.1161/JAHA.123.034718
- Blaha MJ, Santilli F, Sibbing D, et al. Advanced subclinical atherosclerosis and low-dose aspirin: guideline-based extension into asymptomatic chronic coronary syndromes. *JACC Adv.* 2025;4(7):101855. doi:10.1016/j.jaccadv.2025.101855
- Doshi A, Gandhi H, Patel KN, Majmundar M, Doshi R. Aspirin for primary prevention in patients with elevated coronary artery calcium score: a systematic review of current evidences. *Am J Cardiol.* 2024;220:9-15. doi:10.1016/j.amjcard.2024.03.021
- Lacaze P, Bakshi A, Riaz M, et al. Aspirin for primary prevention of cardiovascular events in relation to lipoprotein(a) genotypes. *J Am Coll Cardiol.* 2022;80(14):1287-1298. doi:10.1016/j.jacc.2022.07.027
- Bhatia HS, Trainor P, Carlisle S, et al. Aspirin and cardiovascular risk in individuals with elevated lipoprotein(a): the multi-ethnic study of atherosclerosis. *J Am Heart Assoc.* 2024;13(3):e033562. doi:10.1161/JAHA.123.033562
- Berger JS. Aspirin for primary prevention—time to rethink our approach. *JAMA Netw Open.* 2022;5(4):e2210144. doi:10.1001/jamanetworkopen.2022.10144
- Cofler LB, Barrett TJ, Berger JS. Aspirin for the primary prevention of cardiovascular disease: time for a platelet-guided approach. *Arterioscler Thromb Vasc Biol.* 2022;42(10):1207-1216. doi:10.1161/ATVBAHA.122.318020
- Yu C, Natarajan P, Patel AP, et al. Polygenic risk, aspirin, and primary prevention of coronary artery disease. *Eur Heart J Cardiovasc Pharmacother.* 2025;11(1):84-91. doi:10.1093/ehjcvp/pvae085
- Boakye E, Uddin SMI, Obisesan OH, et al. Aspirin for cardiovascular disease prevention among adults in the United States: trends, prevalence, and participant characteristics associated with use. *Am J Prev Cardiol.* 2021;8:100256. doi:10.1016/j.ajpc.2021.100256
- Murugiah K, See C, Huang C. Recent trends in aspirin use for cardiovascular disease prevention in the United States, 2015 to 2023. *JACC Adv.* 2025;4(6 Pt 2):101699. doi:10.1016/j.jaccadv.2025.101699

Beyond Statins: Personalizing LDL-C Management to Reduce Residual CV Risk

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

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

- **Assess** patients with hyperlipidemia for residual cardiovascular (CV) risk.
- **Describe** innovative treatment options to reduce low-density lipoprotein cholesterol (LDL-C) including in patients who have had inadequate response to or cannot tolerate statins.
- **Compare and contrast** recent evidence and CV outcomes trials for nonstatin therapies.
- **Design** an individualized therapeutic plan for management of hyperlipidemia.

TARGET AUDIENCE

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

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INTRODUCTION

Cardiovascular disease (CVD), encompassing coronary heart disease, heart failure, stroke, and hypertension, is the leading cause of mortality in the United States.¹ CVD has an estimated prevalence of 48.6% in adults ages 20 and older and increases with age.¹

Atherosclerotic cardiovascular disease (ASCVD) is a form of CVD that is characterized by dyslipidemia, usually involv-

ing elevated low-density lipoprotein cholesterol (LDL-C).² Elevated LDL-C is a main cause of atherosclerosis in ASCVD and correlates with worse CV outcomes.³ Randomized controlled trials of low-density lipoprotein (LDL) reduction demonstrate that lower LDL levels are associated with reductions in ASCVD and major coronary events.^{3,4} Of note, in the landmark INTERHEART study, lipids accounted for approximately 50% of the risk for myocardial infarction.^{5,6} Other major risk factors for

Key takeaways

- While statins are foundational to LDL-C lowering and CV risk reduction, adverse effects and residual risk often necessitate additional lipid-lowering therapy.
- Nonstatin lipid-lowering therapies such as ezetimibe, bile acid sequestrants, PCSK9 inhibitors, bempedoic acid, and inclisiran lower LDL-C through different mechanisms and can further reduce CV risk.
- Few patients with high or very high CV risk achieve their LDL-C goals in current clinical practice, suggesting that most of these patients would benefit from optimizing lipid-lowering therapy.
- PCCs are often the first to detect and manage hyperlipidemia, presenting important opportunities for patient education and initiating/intensifying lipid-lowering therapy to achieve LDL-C goals.

atherosclerosis include smoking, poor diet, lack of exercise, psychosocial stressors, hypertension, elevations in blood glucose, metabolic syndrome, and other lipid abnormalities.⁴

In addition to managing modifiable risk factors for worsening ASCVD, therapy with statin drugs is a cornerstone of CVD risk reduction.² Extensive evidence from clinical trials has established the role of statins as first-line treatment for lowering LDL-C in ASCVD. The 2018 American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Cholesterol Guidelines, as well as the 2022 ACC Expert Consensus Decision Pathway (ECDP), suggest treatment with statins for primary and secondary prevention of CV events.^{3,7,8}

Although statins are effective and often prescribed to reduce the risk of primary or secondary major adverse CV events, up to 29% of patients report adverse musculoskeletal events while taking statins, limiting their therapy to inadequate duration and/or subtherapeutic doses. Withdrawing from statin therapy is associated with a higher risk of adverse CV events; thus, the consideration and use of alternative lipid-lowering therapies is essential to maintain protection in these patients.⁹

Even with statin treatment, many patients remain at elevated risk for CV events due to lower statin doses, persistently elevated LDL-C, or other causes.⁹ Several classes of medications, including several newer therapies, have shown additional CV event risk reduction when added to statins.¹⁰ Ezetimibe, bile acid sequestrants, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and bempedoic acid are all approved by the US Food and Drug Administration (FDA) as adjuncts to statins for treatment of primary hyperlipidemia and in ASCVD for additional LDL-C lowering. Of note, bempedoic acid is approved for primary and secondary prevention for myocardial infarction (MI) and CV procedures, regardless of statin use.¹¹

The role of primary care clinicians (PCCs) in hyperlipidemia management

PCCs have a unique opportunity to target primary prevention of CVD by treating dyslipidemia early and effectively.¹² This involves identifying hyperlipidemia through lipid profile measurements and history/physical examination and performing an initial risk assessment to determine statin intensity.¹²

Monitoring and follow-up of patients treated with statins are essential to determine whether LDL-C targets are being reached, to confirm adherence to therapy, and to identify needs for additional lowering of CV risk, including initiating nonstatin therapies, when appropriate.¹² Achieving LDL-C targets through patient education and shared decision-making is imperative in CV risk reduction. In an ideal clinical scenario patients receive appropriate lipid-lowering therapy to achieve optimal risk reduction.¹³

CASE STUDY

A 62-year-old woman presents to her PCC for an annual visit. She has a history of hypertension, hyperlipidemia, and hypothyroidism as well as a recent history of coronary artery disease. She currently takes telmisartan 80 mg daily, rosuvastatin 40 mg daily, aspirin 81 mg daily, and levothyroxine 75 mcg daily.

She was started on rosuvastatin 1 year ago following an MI. Her LDL-C was 157 mg/dL when she started therapy, and it has improved to 87 mg/dL a year later. The PCC and her cardiologist have collaboratively determined that she needs additional LDL-C lowering to reach a target of LDL-C <70 mg/dL.

In this case study, the patient has achieved reasonable LDL-C lowering on a high-intensity statin but remains at risk for recurrent CV events due to her present LDL-C level. Initiating a nonstatin lipid-lowering therapy would reduce her residual CV risk and may help her achieve the target LDL-C of <70 mg/dL.

CLINICAL EVIDENCE FOR NONSTATIN LIPID-LOWERING DRUGS

Due to widespread use of statins for lipid lowering, many clinicians are familiar with how statins work—primarily through blocking hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase.¹⁴ This enzyme is responsible for a rate-limiting step in the pathway to cholesterol synthesis; thus, statins decrease the amount of cholesterol made by the body, which in turn decreases serum cholesterol.

Ezetimibe, bile acid sequestrants, PCSK9 inhibitors, bempedoic acid, and inclisiran all have a different mechanism of action than statins.¹¹ The different mechanisms of action of alternative statin therapies may give rise to clinical variability in the overall efficacy seen with these drugs.

Ezetimibe

Ezetimibe reduces cholesterol through inhibition of cholesterol absorption, reducing the delivery of cholesterol to the liver and increasing LDL receptor synthesis, which results in reduced serum LDL-C.¹⁵ The molecular target of ezetimibe is Niemann-Pick C1-Like 1 (NPC1L1), which regulates absorption of cholesterol and phytosterols. Unlike other LDL-C-lowering therapies, ezetimibe does not inhibit synthesis of cholesterol in the liver.¹⁵

The SHARP trial randomized patients with chronic kidney disease to simvastatin 20 mg plus ezetimibe 10 mg or placebo. Those receiving simvastatin plus ezetimibe had fewer 4-point major atherosclerotic events vs those receiving placebo (rate ratio, 0.83; 95% confidence interval [CI]: 0.74, 0.94; $P = .0021$).¹⁶ The IMPROVE-IT trial randomized patients with acute coronary syndrome to either simvastatin 40 mg plus ezetimibe 10 mg or simvastatin 40 mg and placebo. Patients receiving simvastatin plus ezetimibe had a lower rate of 4-point CV events than those receiving simvastatin monotherapy (hazard ratio [HR], 0.936; 95% CI: 0.89, 0.99; $P = .016$).¹⁷ Ezetimibe is recommended as monotherapy for statin intolerance or as an add-on to statin therapy for hyperlipidemia.⁸

Bile acid sequestrants: cholestyramine, colestevam, and colestipol

Bile acid sequestrant drugs bind to bile in the intestinal tract, which reduces enterohepatic circulation of bile acid and increases fecal excretion.¹⁸ This binds more cholesterol to bile acid and results in lower serum cholesterol.

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was a study published in 1984 that randomized patients with primary hypercholesterolemia to cholestyramine or placebo. Those who received cholestyramine had a 19% lower risk of the composite outcome (CV death or nonfatal MI) vs placebo ($P < .05$).¹⁹ While bile acid sequestrants remain a potential nonstatin treatment for hyperlipidemia, they are not frequently used due to pill burden, drug interactions, and gastrointestinal adverse effects.⁸

PCSK9 inhibitors: evolocumab and alirocumab

These injectable agents inhibit the PCSK9 protein, which regulates circulating LDL-C by acting on LDL receptors. When circulating PCSK9 binds to LDL receptors, it prompts degradation of the receptors, reducing the number of receptors on the cell surface. By inhibiting PCSK9, there are more LDL-C receptors and increased cellular uptake of LDL-C, resulting in lower serum LDL-C levels.²⁰

In the FOURIER trial, patients with ASCVD and LDL-C ≥ 70 mg/dL who were receiving statin therapy were randomized to evolocumab or placebo. Patients who received evo-

locumab had a lower risk of 3-point composite CV events vs those who received placebo (HR, 0.85; 95% CI: 0.79, 0.92; $P < .001$).²¹ More recently, the VESALIUS trial showed reductions in 3-point (HR, 0.75; 95% CI: 0.65, 0.86; $P < .001$) and 4-point (HR, 0.81; 95% CI: 0.73, 0.89; $P < .001$) composite CV outcomes for patients without a previous MI or stroke and LDL-C ≥ 90 mg/dL who were receiving evolocumab compared with those receiving placebo.²² The ODYSSEY OUTCOMES trial randomized patients with acute coronary syndrome who were receiving statin therapy and had LDL-C ≥ 70 mg/dL to either alirocumab or placebo. Fewer patients receiving alirocumab than placebo experienced a 4-point composite CV event (HR, 0.85; 95% CI: 0.78, 0.93; $P < .001$).²³

Bempedoic acid

Bempedoic acid is an orally administered drug that decreases LDL-C primarily through enzymatic inhibition upstream from HMG-CoA reductase, the target for statins.¹¹ Bempedoic acid inhibits adenosine triphosphate-citrate lyase (ACL) in the liver when activated. ACL inhibition subsequently reduces the amount of substrate for synthesis of fatty acids and cholesterol, resulting in decreased cholesterol synthesis in the liver and lower serum LDL-C via upregulation of LDL receptors.^{2,11} Bempedoic acid also activates adenosine monophosphate-activated protein kinase, which has decreased cholesterol synthesis in mouse models.²⁴ This agent was approved by the FDA in 2020 and subsequently received an expanded indication for primary and secondary prevention of MIs and CV procedures in patients with hyperlipidemia, regardless of treatment with a statin.¹¹

Bempedoic acid was evaluated in a series of randomized clinical trials including the CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) trials. One of these, the CLEAR Outcomes trial, focused specifically on CV outcomes (TABLE 1).²⁵⁻³⁰ Based on these data, bempedoic acid may be considered in patients who need additional LDL-C lowering despite maximally tolerated statin therapy, including patients who are already receiving other nonstatin therapies.⁸ Patients with statin intolerance and those who prefer to avoid injectable medications are also strong candidates for treatment with bempedoic acid.⁸

Inclisiran

Inclisiran is an injectable synthetic small interfering ribonucleic acid (siRNA) that targets PCSK9. It blocks PCSK9 production in the liver, prolonging activity of LDL receptors.⁸ It was approved by the FDA in 2021. The 2022 ACC ECDP recommends the addition of inclisiran as second-line therapy after ezetimibe and/or PCSK9 inhibitors in patients with ASCVD requiring additional LDL-C reduction.⁸ Inclisiran may be a good option for nonadherent patients or those who

TABLE 1. Pivotal clinical evidence for bempedoic acid.²

Trial	Publication date	Patients	Intervention and comparator	Main findings
CLEAR Harmony ²⁶	2019	ASCVD and/or hyperlipidemia	Bempedoic acid vs placebo	No difference in adverse events, significant improvement in LDL-C (percent change –16.5% for bempedoic acid vs 1.6% for placebo; $P < .001$)
CLEAR Wisdom ²⁷	2019	ASCVD and/or hyperlipidemia	Bempedoic acid vs placebo	Significant improvement in LDL-C at weeks 12 and 24. At week 12, percent change –15.1% for bempedoic acid vs 2.4% for placebo; $P < .001$
CLEAR Serenity ²⁸	2019	Primary ASCVD prevention or hyperlipidemia and history of statin intolerance	Bempedoic acid vs placebo	Significant improvement in LDL-C at 12 weeks (percent change –23.6% for bempedoic acid vs –1.3% for placebo, $P < .001$)
CLEAR Tranquility ²⁹	2018	LDL-C ≥ 100 mg/dL with history of statin intolerance	Bempedoic acid + ezetimibe vs placebo + ezetimibe	Significant reduction in LDL-C for bempedoic acid + ezetimibe compared to placebo + ezetimibe (percent change –22.5% vs 5.0% respectively, $P < .001$)
Ballantyne et al. ³⁰	2020	ASCVD or hyperlipidemia or multiple CV risk factors	Bempedoic acid + ezetimibe, bempedoic acid, ezetimibe, or placebo	Significant reduction in LDL-C for bempedoic acid + ezetimibe compared to ezetimibe alone and bempedoic acid alone, $P < .001$
CLEAR Outcomes ²⁵	2023	ASCVD or high CV risk with history of statin intolerance	Bempedoic acid vs placebo	Significant reduction of 4-point major adverse CV events (11.7% for bempedoic acid vs 13.3% with placebo, HR, 0.87; 95% CI: 0.79, 0.96; $P = .004$)

Adapted from Marrs JC et al, 2020.²

have an aversion to self-injecting PCSK9 inhibitors, as it is a clinician-administered therapy injected subcutaneously in the office.³¹

CLINICAL USE OF NONSTATIN LIPID-LOWERING THERAPIES

The 2018 AHA/ACC Blood Cholesterol Guidelines and the ACC 2022 ECDP on the role of nonstatin therapies for LDL-C lowering in the management of ASCVD risk provide guidance for best practices in evidence-based management of hyperlipidemia.^{3,8} The 2018 guidelines list ezetimibe, bile acid sequestrants, and PCSK9 inhibitors as potential therapies to use in combination with statins for additional LDL-C-lowering. Bempedoic acid and inclisiran are not listed in the 2018 guidelines because they were approved after its publication, but these agents are included in the 2022 ACC ECDP.⁸

Several studies demonstrate that many patients do not achieve the recommended LDL-C goals, even with the historically recommended higher targets. In 1 study, fewer than one-third of patients with established ASCVD achieved an LDL-C goal of <70 mg/dL, and only 14.7% achieved <55 mg/dL. Of concern, only 17.1% of patients with ASCVD and LDL-C ≥ 70 mg/dL had their therapy intensified over a 2-year study period (the GOULD registry). Clinicians who identi-

fied an LDL-C <70 mg/dL as the ideal goal for patients with established ASCVD were more likely to have patients achieve LDL-C goals than those who did not identify it as an ideal goal.³² Only 19.5% of patients with established ASCVD not at LDL-C goal were receiving ≥ 2 lipid-lowering therapies, highlighting an overreliance on statin monotherapy.³³ Additionally, in the VESALIUS trial mentioned previously, most high-risk patients aged ≥ 50 years with ASCVD were neither adequately tested for LDL-C nor treated with lipid-lowering therapy.²²

The publication of the 2018 guidelines shifted treatment goals from a focus on statin intensity to a percentage reduction and an associated LDL-C target.³ As an update to the 2018 recommendations, the 2022 ACC ECDP recommends achievement of a $\geq 50\%$ reduction in LDL-C and a goal of <55 mg/dL for secondary prevention in adults with clinical ASCVD at very high risk.⁸ Additionally, evidence from the IMPROVE-IT, FOURIER, and ODYSSEY OUTCOMES trials supports targeting LDL-C levels below that of previous trials; targeting LDL-C levels as low as 30 mg/dL is safe and effective for preventing CV events in patients with established ASCVD.^{17,21,23} The LDL-C goals from the 2022 ACC ECDP are a significant change from the 2018 guidelines, and clinicians are encouraged to incorporate these revised targets when treating patients in practice.

Generally, adding ezetimibe to a statin could lead to a 15% to 25% LDL-C reduction, adding a bile acid sequestrant reduces LDL-C by 10% to 27%, and adding a PCSK9 inhibitor reduces LDL-C by 45% to 64%. Inclisiran provides a 48% to 52% reduction.^{3,8} Bempedoic acid has reduced LDL-C by 15% to 25% in clinical trials and by up to 38% in combination with ezetimibe.^{2,8,34} See **TABLE 2** for a summary of LDL-C lowering of the nonstatin therapies discussed in this article.

The 2022 ACC ECDP recommends treatment algorithms for various patient groups who should receive lipid-lowering therapy, including primary prevention in adults with and without diabetes and those with primary severe hypercholesterolemia (LDL-C ≥ 190 mg/dL), as well as secondary prevention in adults with clinical ASCVD. These algorithms detail recommendations for nonstatin therapies, as well as approaches for addressing statin-associated adverse effects. Readers are referred to the 2022 ACC ECDP publication for detailed guidance in managing these patient populations at <https://www.jacc.org/doi/10.1016/j.jacc.2022.07.006>.



CASE STUDY (CONTINUED)

In the case study mentioned previously, the patient was started on bempedoic acid 180 mg by mouth once daily, in addition to her high-intensity statin, as she preferred oral therapy vs using an injectable.¹¹ Upon reassessment of her lipid levels at a 6-month follow-up appointment, her LDL-C had improved from 87 mg/dL to 69 mg/dL, achieving her target of <70 mg/dL.

COLLABORATIVE CARE AND REFERRAL CRITERIA

As part of the holistic care of patients with hyperlipidemia, lifestyle modifications, such as adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight, should be addressed regularly.⁸ In addition to collaborative management of overall CV risk, engaging members of the multidisciplinary health care team can help optimize lifestyle and pharmacologic interventions for lipid lowering.

Multidisciplinary care can include placing appropriate referrals for patients who may need additional management outside of primary care settings. The 2022 ACC ECDP recommends specific criteria for referral of patients with hyperlipidemia to lipid specialists and registered dietitians (**TABLE 3**).⁸

SUMMARY

Statins are the foundation of LDL-C lowering and CVD risk reduction, but adverse effects and residual risk due to incomplete LDL-C goal attainment necessitate additional intervention. Evidence supports several nonstatin therapies—ezetimibe, bile acid sequestrants, PCSK9 inhibitors, bempedoic acid, and inclisiran—that lower LDL-C through different mechanisms and can further reduce CV events when used appropriately.

In most patients with high or very high CV risk, LDL-C goals are not being achieved. Clinicians should aim for better LDL-C goal achievement and associated risk reduction through collaborative education and decision-making with patients and the use of additional lipid-lowering therapies available to achieve these goals. PCCs are often the first to detect and man-

TABLE 2. Mean reduction in LDL-C of nonstatin therapies.⁸

	Ezetimibe	Bile acid sequestrants	PCSK9 inhibitors	Bempedoic acid	Inclisiran
Mean % reduction in LDL-C (per PI)	Monotherapy: 18% Combination with statin therapy (incremental reduction): 25%	Colesevelam: 15% (6 tablets daily); in combination with low- to moderate-intensity statin therapy, there is an additional 10% to 16% reduction in LDL-C Cholestyramine: monotherapy: 10.4% vs placebo Colestipol: not provided in PI; in dose-ranging RCT with monotherapy, doses of 5, 10, and 15 g resulted in 16.3%, 22.8%, and 27.2% reductions in LDL-C, respectively	Alirocumab: when added to maximally tolerated statin therapy, alicumab 75 mg and 150 mg SC every 2 weeks reduced LDL-C by an additional 45% and 58%, respectively, when added to maximally tolerated statin therapy Evolocumab: 140 mg every 2 weeks and 420 mg SC every 4 weeks lowers LDL-C by an additional 64% and 58%, respectively	Combination therapy with statin therapy (placebo-corrected incremental reduction): 17% to 18%	48% to 52%

Abbreviations: ACSVL1, acyl-CoA synthetase-1; PI, Prescribing Information; RCT, randomized controlled trial; SC, subcutaneous.

TABLE 3. 2022 ACC ECDP recommendations for referral of patients with hyperlipidemia.⁸

Referral to lipid specialist	<p>Referral may be considered for patients</p> <ul style="list-style-type: none"> • With ASCVD and/or baseline LDL-C ≥ 190 mg/dL • With baseline LDL-C ≥ 190 mg/dL • With intolerance of at least 2 (preferably 3) statin therapies with 1 attempt at the lowest FDA-approved dose and a trial of an alternative statin therapy regimen (e.g., every-other-day dosing) • With ASCVD and baseline LDL-C ≥ 190 mg/dL who did not achieve LDL-C lowering $\geq 50\%$ and LDL-C < 70 mg/dL (or non-HDL-C < 100 mg/dL) on maximally tolerated statin therapy in combination with nonstatin therapy • Who are unable to achieve adequate LDL-C reduction
Referral to registered dietitian	<p>Referral may be considered for patients</p> <ul style="list-style-type: none"> • With ASCVD and/or baseline LDL-C ≥ 190 mg/dL or baseline LDL-C ≥ 190 mg/dL • With ASCVD and baseline LDL-C ≥ 190 mg/dL who did not achieve LDL-C lowering $\geq 50\%$ and LDL-C < 70 mg/dL (or non-HDL-C < 100 mg/dL) on maximally tolerated statin therapy in combination with nonstatin therapy • Who are unable to achieve adequate LDL-C reduction

Abbreviation: HDL-C, high-density lipoprotein cholesterol.

age hyperlipidemia and have opportunities to intensify lipid-lowering treatment to achieve LDL-C targets. Additionally, they can coordinate multidisciplinary care and referrals to optimize long-term prevention of adverse CV outcomes. ●

REFERENCES

- Martin SS, Aday AW, Almarazooq ZI, et al. 2024 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association. *Circulation*. 2024;149(8). doi:10.1161/CIR.0000000000001209
- Marrs JC, Anderson SL. Bempedoic acid for the treatment of dyslipidemia. *Drugs Context*. 2020;9:2020-6-5. doi:10.7573/dic.2020-6-5
- Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082-e1143. doi:10.1161/CIR.0000000000000625
- Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA*. 2016;316(12):1289-1297. doi:10.1001/jama.2016.13985
- McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *The Lancet*. 2008;372(9634):224-233. doi:10.1016/S0140-6736(08)61076-4
- Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *The Lancet*. 2004;364(9438):937-952. doi:10.1016/S0140-6736(04)17018-9
- Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *The Lancet*. 2016;388(10059):2532-2561. doi:10.1016/S0140-6736(16)31357-5
- Writing Committee, Lloyd-Jones DM, Morris PB, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006
- Wong ND, Zhao Y, Quek RGW, et al. Residual atherosclerotic cardiovascular disease risk in statin-treated adults: The Multi-Ethnic Study of Atherosclerosis. *J Clin Lipidol*. 2017;11(5):1223-1233. doi:10.1016/j.jacl.2017.06.015
- Dobkowski D. Novel drugs, new targets expand options for lipid management. June 2020. Accessed February 20, 2024. <https://www.healio.com/news/cardiology/20200612/novel-drugs-new-targets-expand-options-for-lipid-management>
- Nexletol® (bempedoic acid). Prescribing Information. Esperion Therapeutics, Inc.; 2025. Accessed September 7, 2026. <https://pi.esperion.com/nexletol/nexletol-pi.pdf>
- Thongtang N, Sukmawan R, Llanes EJB, Lee ZV. Dyslipidemia management for primary prevention of cardiovascular events: best in-clinic practices. *Prev Med Rep*. 2022;27:101819. doi:10.1016/j.pmedr.2022.101819
- Levinow SN, Reading SR, Noshad S, et al. Lipid testing trends before and after hospitalization for myocardial infarction among adults in the United States, 2008-2019. *Clin Epidemiol*. 2022;14:737-748. doi:10.2147/CLEP.S361258
- Ward NC, Watts GF, Eckel RH. Statin toxicity: mechanistic insights and clinical implications. *Circ Res*. 2019;124(2):328-350. doi:10.1161/CIRCRESAHA.118.312782
- Bruckert E, Giral P, Tellier P. Perspectives in cholesterol-lowering therapy: the role of ezetimibe, a new selective inhibitor of intestinal cholesterol absorption. *Circulation*. 2003;107(25):3124-3128. doi:10.1161/01.CIR.0000072345.98581.24
- Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *The Lancet*. 2011;377(9784):2181-2192. doi:10.1016/S0140-6736(11)60739-3
- Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397. doi:10.1056/NEJMoa1410489
- Ross S, D'Mello M, Anand SS, et al. Effect of bile acid sequestrants on the risk of cardiovascular events: a mendelian randomization analysis. *Circ Cardiovasc Genet*. 2015;8(4):618-627. doi:10.1161/CIRCGENETICS.114.000952
- The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984;251(3):351-364. doi:10.1001/jama.1984.03340270029025
- Handelsman Y, Lepor NE. PCSK9 inhibitors in lipid management of patients with diabetes mellitus and high cardiovascular risk: a review. *J Am Heart Assoc*. 2018;7(13):e008953. doi:10.1161/JAHA.118.008953
- Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713-1722. doi:10.1056/NEJMoa1615664
- Bohula EA, Marston NA, Bhatia AK, et al. Evolocumab in patients without a previous myocardial infarction or stroke. *N Engl J Med*. 2026;394(2):117-127. doi:10.1056/NEJMoa2514428
- Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379(22):2097-2107. doi:10.1056/NEJMoa1801174
- Samssoondar JP, Burke AC, Sutherland BG, et al. Prevention of diet-induced metabolic dysregulation, inflammation, and atherosclerosis in *Ldlr*^{-/-} mice by treatment with the ATP-citrate lyase inhibitor bempedoic acid. *Arterioscler Thromb Vasc Biol*. 2017;37(4):647-656. doi:10.1161/ATVBAHA.116.308963
- Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med*. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024
- Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med*. 2019;380(11):1022-1032. doi:10.1056/NEJMoa1803917
- Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR Wisdom randomized clinical trial. *JAMA*. 2019;322(18):1780-1788. doi:10.1001/jama.2019.16585
- Laufs U, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. *J Am Heart Assoc*. 2019;8(7):e011662. doi:10.1161/JAHA.118.011662
- Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. *Atherosclerosis*. 2018;277:195-203. doi:10.1016/j.atherosclerosis.2018.06.002
- Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol*. 2020;27(6):593-603. doi:10.1177/2047487319864671
- Wilkinson MJ, Bajaj A, Brousseau ME, Taub PR. Harnessing RNA interference for cholesterol lowering: the bench-to-bedside story of inclisiran. *J Am Heart Assoc*. 2024;13(6):e032031. doi:10.1161/JAHA.123.032031
- Cannon CP, De Lemos JA, Rosenson RS, et al. Use of lipid-lowering therapies over 2 years in GOULD, a registry of patients with atherosclerotic cardiovascular disease in the US. *JAMA Cardiol*. 2021;6(9):1060. doi:10.1001/jamacardio.2021.1810
- Alam S, Agha A, Kosiborod M, et al. Underuse of combination pharmacotherapy for management of dyslipidaemia versus diabetes and hypertension among patients with atherosclerotic cardiovascular disease (ASCVD): insights from the Getting to an Improved Understanding of Low-Density Lipoprotein-Cholesterol and Dyslipidemia Management (GOULD) registry. *Heart Lung Circ*. 2021;30:S249-S250. doi:10.1016/j.hlc.2021.06.344
- Katzmann JL, Stürzebecher PE, Kruppert S, Laufs U. LDL cholesterol target attainment in cardiovascular high- and very-high-risk patients with statin intolerance: a simulation study. *Sci Rep*. 2024;14(1):474. doi:10.1038/s41598-023-50847-1

Lipoprotein(a) in Clinical Practice: From Risk Marker to Actionable Signal

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INTRODUCTION

Residual cardiovascular (CV) risk persists even when low-density lipoprotein cholesterol (LDL-C) is treated according to contemporary standards, and a meaningful portion of that burden reflects inherited biology that is not captured by routine lipid panels or by most commonly used risk calculators.^{1,2} Lipoprotein(a), or Lp(a), represents a key component adding to CV risk, though it has only recently been comprehensively studied. It remains underrecognized and under tested in clinical practice. Lp(a) is a low-density lipoprotein (LDL)-like, apolipoprotein B (apoB)-containing particle with an attached apolipoprotein(a) (apo[a]) moiety that confers atherogenic, pro-inflammatory, and possibly antifibrinolytic/thrombogenic properties.^{3,4}

Interest in Lp(a) has accelerated as the evidence base has moved beyond association toward causality, with genetic, epidemiologic, and mechanistic data linking elevated Lp(a) to both atherosclerotic CV disease (ASCVD) and calcific aortic valve stenosis.^{5,6} Additionally, an expanding therapeutic pipeline has made identification of elevated Lp(a) more clinically relevant, though no approved Lp(a)-specific agents currently are available.^{7,8}

Primary care clinicians (PCCs) are central to this shift because first-line preventive risk assessment often occurs in primary care. PCCs can determine whether a patient with borderline or intermediate risk needs treatment intensification, and Lp(a) can explain why a patient with a seemingly modest LDL-C level may carry substantial inherited risk.^{9,10} However, testing for Lp(a) is rare in routine practice.

Key takeaways

- Elevated Lp(a) is common, largely inherited, and causally linked to ASCVD and calcific aortic valve stenosis, yet often missed in many routine preventive evaluations.
- One-time Lp(a) measurement in adulthood is recommended based on current evidence and guidelines, making primary care a critical setting for detection and risk classification.
- An elevated Lp(a) result is actionable because it supports earlier and more intensive management of LDL-C, blood pressure, diabetes risk, smoking, and other modifiable contributors to risk.
- Although lifestyle change does not meaningfully lower Lp(a) in most patients, therapeutic lifestyle changes reduce CV risk and are important as part of comprehensive CV risk reduction.
- Multiple investigational agents, including small interfering RNA, antisense, and small-molecule therapies, have lowered Lp(a) by roughly 80% to more than 95% in clinical trials. CV outcomes trials from Lp(a)-targeted therapies are ongoing with no results yet; comprehensive risk reduction remains the present standard of care.

In one recent US outpatient analysis, only 3.7% of 450,412 patients who had at least 1 lipid panel also had Lp(a) measured, despite rising order volumes over time.¹¹ Another US study assessed the electronic medical record data of 266,612 patients and found that only 0.8% of patients received Lp(a) testing, of whom 86% had clinical CV disease.¹² Broadening Lp(a) testing improves risk identification, supports family cascade testing, reframes conversations about lifelong risk,

and justifies more aggressive control of modifiable risk factors, especially LDL-C, in patients whose risk would otherwise be underestimated.^{9,13} Accordingly, guidelines from the National Lipid Association (NLA) and the American College of Cardiology (ACC)/American Heart Association (AHA) multisociety collaboration now recommend at least 1 Lp(a) measurement in adulthood, moving Lp(a) testing from a niche specialty test toward a standard component of preventive lipid care.^{9,14}

CASE STUDY

MR is a 45-year-old woman seen for an annual preventive visit. She has a history of hypertension, does not have diabetes, and has never smoked. Today, her laboratory and clinical findings are as follows:

- Total cholesterol: 214 mg/dL (5.5 mmol/L)
- High-density lipoprotein cholesterol (HDL-C): 54 mg/dL (1.4 mmol/L)
- LDL-C: 110 mg/dL (2.85 mmol/L)
- Triglycerides: 250 mg/dL
- Blood pressure: 128/78 mmHg
- Estimated glomerular filtration rate: 95 mL/min/1.73 m²
- Glycated hemoglobin: 5.8%
- Body mass index: 28 kg/m²

Her father had a myocardial infarction at age 52 years. She currently takes amlodipine 10 mg daily and losartan 100 mg daily.

Her 10-year ASCVD risk estimate is 1.4% and her 30-year ASCVD risk estimate is 8.9% (using the AHA PREVENT Calculator [available at <https://professional.heart.org/en/guidelines-and-statements/prevent-calculator>]), but the mismatch between that estimate and her family history raises concern for inherited residual risk not captured by traditional assessment tools.

WHAT IS Lp(a)?

Lp(a) is an LDL-like particle that contains apoB and an additional apo(a) molecule linked by a disulfide bond to the apoB moiety; this apo(a) component is what makes Lp(a) biologically and clinically distinct from ordinary LDL (FIGURE 1).^{3,5} Apo(a) contains a variable number of kringle IV type 2 repeats, creating marked size polymorphism between individuals and contributing to the wide variability in circulating Lp(a) concentrations across patients.^{2,3}

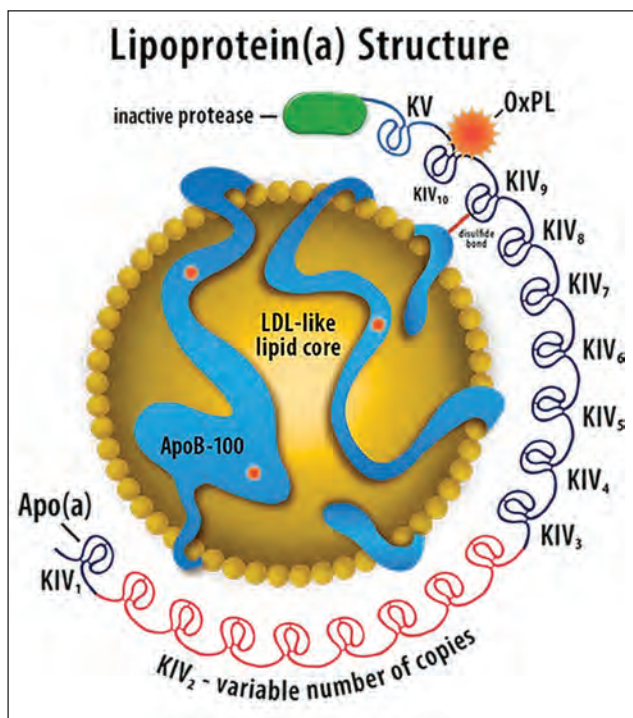
The pathophysiology of Lp(a) is multifactorial. The LDL-like core contributes to arterial cholesterol delivery and plaque formation, whereas the apo(a) moiety has high affinity for oxidized phospholipids. Thus, Lp(a) is the major carrier of oxidized phospholipids into the arterial wall, which amplifies vascular inflammation, endothelial dysfunction, and plaque instability.^{4,15} Because apo(a) is structurally homologous to plasminogen, Lp(a) also has biologic plausibility as

an antifibrinolytic and prothrombotic factor, although the relative contribution of this pathway likely varies across clinical contexts.^{5,16}

Elevated Lp(a) is common and affects roughly 1 in 5 people worldwide; however, the population distribution is highly skewed and varies by ancestry, with particularly high concentrations observed in individuals of African and South Asian ancestry.^{1,9} Unlike LDL-C, Lp(a) is largely genetically determined, with approximately 70% to 90% of interindividual variation attributable to inherited factors, and it is not meaningfully lowered by diet or exercise.^{1,3} Adult levels generally are reached by early childhood and remain relatively constant across adult life, so a single measurement is typically sufficient unless testing occurs during major inflammation, in settings such as menopause, or in the presence of significant liver or kidney disease that affects Lp(a) levels.^{1,14,17}

The clinical importance of Lp(a) lies in causality as well as prevalence. Mendelian randomization, population studies, and consensus guidance support elevated Lp(a) as a likely risk factor for ASCVD, and additional data implicate it in calcific aortic valve disease and stenosis progression.^{5,18} Risk rises in a continuous, approximately log-linear fashion rather than at

FIGURE 1. Structure of the Lp(a) molecule.



Abbreviations: Apo(a), apolipoprotein a; KIV, Kringle IV; KV, Kringle V; OxPL, oxidized phospholipid.

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Source: <https://familyheart.org/family-sharing-tools/high-lpa-family-tools>

TABLE 1. Practical interpretation of Lp(a) concentration and potential clinical actions.^{9,13}

Lp(a) concentration ^a	Risk category	Practical interpretation	Potential clinical response
<75 nmol/L (<30 mg/dL)	Low	Lower Lp(a)-associated risk	Continue standard prevention according to the overall absolute risk
75 to <125 nmol/L (30 to <50 mg/dL)	Intermediate	Gray zone that can still meaningfully raise risk when other risk enhancers are present	Review family history, refine statin discussion, and optimize LDL-C and other modifiable factors
≥125 nmol/L (≥50 mg/dL)	High	Clear risk-enhancing factor for ASCVD and often for family screening discussions	Intensify LDL-C lowering and global risk-factor control; discuss cascade testing and referral when residual risk remains high

^aRisk is continuous, and these thresholds are pragmatic clinical decision aids rather than biologic cliffs; the same Lp(a) value confers greater absolute risk when baseline CV risk is already high.

a single biologic cliff, which is why thresholds are best viewed as practical decision aids instead of absolute dividing lines.^{1,2}

The continuous risk spectrum is reflected in recent US guidance, which links Lp(a) thresholds with different risk levels (**TABLE 1**). For example, an Lp(a) concentration of ≥125 nmol/L (≥50 mg/dL) is associated with about a 1.4-fold higher long-term risk of myocardial infarction or stroke, whereas an Lp(a) concentration around 250 nmol/L is associated with at least a doubling of long-term risk.^{9,14} The same Lp(a) value, therefore, has a larger absolute-risk implication in a patient who already has hypertension, diabetes, smoking exposure, chronic kidney disease, or established ASCVD than in a patient with otherwise low baseline risk.^{1,13} This is a primary reason Lp(a) is clinically useful in patients whose standard risk assessment seems

discordant with their personal or family history. Most widely used risk calculators do not explicitly incorporate Lp(a), so risk may be underestimated when Lp(a) is high.^{1,2} For patient-facing discussion, the Lp(a) Clinical Guidance tool (accessible at <https://www.lpaclinicalguidance.com/>) can help visualize how much incremental risk may be attributable to Lp(a) and how more aggressive LDL-C or blood pressure control can partially offset that burden. The tool also provides guidance on lowering risk with elevated Lp(a).

Lp(a) TESTING RECOMMENDATIONS

With the incorporation of Lp(a) testing recommendations into recent guidelines, the clinical takeaways for implementation into practice have become clearer (**TABLE 2**). The 2024 NLA focused update recommends risk stratification of

TABLE 2. Current guideline and consensus recommendations for Lp(a) testing.

Source	Lp(a) testing recommendation	Cascade testing	Implications for primary care
NLA 2024 ⁹	Measure Lp(a) at least once in every adult for risk stratification	Cascade screen first-degree relatives when Lp(a) is elevated	Use Lp(a) to refine risk when history and calculated risk do not match
ESC/EAS 2025 ¹³	Measure Lp(a) at least once in adults and interpret within absolute global risk	Consider cascade testing in families with premature ASCVD, FH, or very high Lp(a)	Integrate Lp(a) into broader prevention rather than treating it as an isolated number
ACC/AHA Multisociety 2026 ¹⁴	Measure Lp(a) at least once in adulthood	Cascade testing in first-degree family members of patients with elevated Lp(a)	Treat elevated Lp(a) as a risk-enhancing biomarker that can justify more intensive preventive therapy

Abbreviation: FH, familial hypercholesterolemia.

all adults by measuring Lp(a) at least once.⁹ The 2025 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) update also recommends at least 1 lifetime measurement in adults; this also was recommended in the previous (2019) guideline and the 2022 EAS consensus document.^{5,13,19} Similarly, the Brussels International Declaration on Lp(a) testing and management recommends testing all adults once during their lifetime, ideally at an early age.²⁰ Most recently, the 2026 ACC/AHA multisociety dyslipidemia guideline now explicitly recommends that Lp(a) be measured at least once in adulthood, noting that ASCVD risk is particularly high for patients with elevated Lp(a) who also have other risk factors. Lp(a) measurement helps with risk stratification,¹⁴ and the best time to conduct Lp(a) testing is anytime in any clinical setting.

Lp(a) is inherited in an autosomal codominant fashion. Therefore, once a patient is found to have high Lp(a), cascade screening is recommended to identify family members with elevated Lp(a).²¹ The NLA endorses cascade screening of first-degree relatives when a patient has elevated Lp(a), and ESC/EAS guidance likewise supports cascade testing in families with premature ASCVD, familial hypercholesterolemia, or very high Lp(a) concentrations.^{9,13} The 2026 ACC/AHA multisociety guidelines suggest that cascade testing in first-degree family members of patients with elevated Lp(a) can identify other family members who may have increased ASCVD risk.¹⁴

Practical barriers, including cost and reimbursement, for Lp(a) are real but manageable. Insurance coverage of Lp(a) testing varies. Quest Diagnostics lists Lp(a) testing under CPT code 83695.²² Coverage may be subject to Medicare policies requiring a signed advance beneficiary notice, while payer coverage policies vary and may limit reimbursement frequency. Some insurance carriers consider Lp(a) testing once per lifetime.²³ For patients facing access barriers, the Family Heart Foundation currently offers a free at-home Cholesterol Connect screening program that includes Lp(a), accessible at <https://familyheart.org/cholesterol-connect>. This can be useful for both index patients and relatives identified through cascade screening.

GUIDELINE-DIRECTED LIPID AND Lp(a) MANAGEMENT

An elevated Lp(a) result is actionable now, even in the absence of an approved Lp(a)-specific drug, because it supports earlier and more intensive lowering of modifiable risk factors that reduce absolute CV risk.^{9,10} The most important actionable target is LDL-C, since observational studies and post hoc analyses of randomized trials suggest that lowering LDL-C in a patient with elevated Lp(a) will mitigate some of the CV risk.^{13,14}

In primary prevention, elevated Lp(a) can justify earlier initiation of statin therapy and support escalation to moderate- or high-intensity treatment when overall risk, family history, or subclinical atherosclerosis suggests that usual care may leave the patient undertreated.^{1,9} Statins do not meaningfully lower Lp(a), and some studies suggest a modest increase, but this should not discourage their use because they remain the cornerstone of apoB and LDL-C lowering.^{7,9} When LDL-C remains above goal, the addition of ezetimibe, bempedoic acid, or injectable LDL-lowering therapy should be considered according to overall risk and guideline thresholds, rather than waiting for recurrent events to justify intensification.^{13,14}

In secondary prevention, elevated Lp(a) identifies a higher residual risk phenotype and should prompt aggressive management of LDL-C and other modifiable risk factors, including blood pressure, glycemia, smoking, body weight, physical activity, sleep, and diet quality.^{9,24} It is also reasonable to consider therapies with modest Lp(a)-lowering effects when they otherwise align with guideline-based care. In the FOURIER trial, which was a randomized trial of evolocumab vs placebo in patients with established ASCVD, evolocumab reduced Lp(a) by a median of 26.9% at 48 weeks, while pooled phase 3 analyses showed that alirocumab lowered Lp(a) by approximately 25%.^{25,26} Whether these reductions contribute independently to clinical benefit beyond LDL-C lowering remains uncertain.

Inclisiran appears to have a similar but smaller effect on Lp(a) than the proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies. Across the phase 3 ORION-10 and ORION-11 programs, placebo-adjusted Lp(a) reductions were approximately 25.6% and 18.6%, respectively, which could be directionally helpful when combined with robust LDL-C lowering and improved adherence from infrequent dosing.^{27,28}

Lipoprotein apheresis remains a niche option for select, very high-risk patients, particularly when elevated Lp(a) coexists with progressive ASCVD despite maximal medical therapy. US Food and Drug Administration approval of lipoprotein apheresis applies to high-risk patients with familial hypercholesterolemia and ASCVD whose Lp(a) is ≥ 60 mg/dL (approximately ≥ 150 nmol/L) and whose LDL-C remains ≥ 100 mg/dL despite maximally tolerated therapy.⁹ A single apheresis session can acutely lower Lp(a) by approximately 60% to 75%, but the treatment burden and limited availability restrict use to a small subset of patients.^{29,30}

CASE STUDY (CONTINUED)

In MR's case, a one-time Lp(a) measurement is ordered because her family history and standard risk estimate appear discordant. The result returns at 250 nmol/L, placing her in a high-risk cat-

egory by current guideline thresholds. Moreover, her Lp(a) doubles her estimated 10-year and 30-year ASCVD risk. The result does not mandate a unique Lp(a)-specific therapy, but it meaningfully shifts shared decision-making toward initiating statin therapy earlier, maintaining blood pressure control, adopting lifestyle strategies, and recommending cascade screening for first-degree relatives.

POTENTIAL LP(a)-TARGETING THERAPIES ON THE HORIZON

The therapeutic landscape for Lp(a)-targeting therapies is changing rapidly. Several targeted agents have produced reductions that are far greater than those achievable with currently available lipid therapies, making present-day testing increasingly relevant for future treatment eligibility and trial referral.^{7,8}

In a phase 2b dose-finding study, pelacarsen, an anti-sense oligonucleotide, produced reductions in Lp(a) of up to 80% at the highest dose.³¹

Small interfering RNA therapies are injectable agents that degrade the mRNA responsible for apo(a) synthesis, showing evidence that hepatic apo(a) silencing can produce large and durable effects. Olpasiran has demonstrated reductions in Lp(a) concentrations. In the phase 2 OCEAN(a)-DOSE extension analysis, higher-dose olpasiran given every 12 weeks lowered circulating Lp(a) by more than 95%. Participants receiving doses of at least 75 mg every 12 weeks maintained an approximately 40% to 50% placebo-adjusted reduction nearly 1 year after the last dose.³² Lepodisiran has shown significant and prolonged reductions in Lp(a). In the phase 2 ALPACA trial, placebo-adjusted, time-averaged daily reductions from day 60 to day 180 were 40.8% with 16 mg, 75.2% with 96 mg, and 93.9% in the pooled 400-mg groups.³³ Similarly, zerlasiran has produced robust Lp(a) reductions in clinical trials. In its phase 2 randomized trial, zerlasiran was well tolerated and reduced time-averaged Lp(a) concentrations by more than 80% during 36 weeks of treatment in patients with ASCVD.³⁴

Muvalaplin is an oral small molecule therapy that inhibits Lp(a) particle assembly. In the phase 2 KRAKEN trial, it lowered Lp(a) by placebo-adjusted 47.6%, 81.7%, and 85.8% at week 12 with daily doses of 10 mg, 60 mg, and 240 mg, respectively, using an intact Lp(a) assay, without major safety or tolerability concerns.³⁵

Phase 3 trials for investigational Lp(a)-targeting therapies are ongoing, with variable expected timelines for results. Results from the HORIZON study of pelacarsen (NCT04023552) are expected in late 2026. While the therapeutic pipeline for Lp(a)-targeting therapies may provide future options for additional CV risk reduction, current management

remains centered on addressing modifiable risk factors and implementing available, evidence-based therapies.^{9,13,14}

SUMMARY

Lp(a) has moved from a neglected biomarker to being recognized as an important CV risk modifier. Lp(a) is common, inherited, stable across adult life, and causally related to ASCVD and calcific aortic valve disease. Still, it is often absent from most routine risk calculations and is not frequently measured in practice. Current guidelines recommend measuring Lp(a) at least once in adulthood, interpreting the result in the context of absolute risk, intensifying LDL-C lowering and other modifiable risk-factor management when Lp(a) is elevated, and extending cascade testing to first-degree relatives when appropriate. As targeted therapies continue to mature, clinicians who identify elevated Lp(a) will now be better positioned to reduce excess CV risk and be prepared for potential future therapies directly targeting Lp(a). ●

REFERENCES

- Irvine A, Watt J, Kurth MJ, et al. Lipoprotein(a): the neglected risk factor in cardiovascular health. *Front Cardiovasc Med*. 2025;12:1710557. doi:10.3389/fcvm.2025.1710557
- Kronenberg F, Mora S, Stroes ESG. Consensus and guidelines on lipoprotein(a) - seeing the forest through the trees. *Curr Opin Lipidol*. 2022;33(6):342-352. doi:10.1097/MOL.0000000000000855
- Reyes-Soffer G, Ginsberg HN, Berglund L, et al. Lipoprotein(a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2022;42(1):e48-e60. doi:10.1161/ATV.0000000000000147
- Koschinsky ML, Boffa MB. Oxidized phospholipid modification of lipoprotein(a): epidemiology, biochemistry and pathophysiology. *Atherosclerosis*. 2022;349:92-100. doi:10.1016/j.atherosclerosis.2022.04.001
- Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *Eur Heart J*. 2022;43(39):3925-3946. doi:10.1093/eurheartj/ehac361
- Wambua P, Wahinya M, Khan Z. The role of elevated lipoprotein(a) in aortic valve disease: a systematic review. *Front Cardiovasc Med*. 2025;12:1610395. doi:10.3389/fcvm.2025.1610395
- Manzato M, Wright RS, Jaffe AS, Vasile VC. Lipoprotein (a): underrecognized risk with a promising future. *Rev Cardiovasc Med*. 2024;25(11):393. doi:10.31083/j.rcm2511393
- Zhang J, Navar AM, Tokgozoglu L. Lipoprotein(a)-lowering therapies: a promising future. *Eur Heart J*. 2026;47(26):3375-3385. doi:10.1093/eurheartj/ehag092
- Koschinsky ML, Bajaj A, Boffa MB, et al. A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice. *J Clin Lipidol*. 2024;18(3):e308-e319. doi:10.1016/j.jacl.2024.03.001
- Parcha V, Bittner VA. Lipoprotein (a) in primary cardiovascular disease prevention is actionable today. *Am Heart J Plus*. 2025;57:100581. doi:10.1016/j.jahjo.2025.100581
- Mangla M, Bimal T, Akhabue E, et al. Trends in lipoprotein(a) testing and impact on clinical care: a contemporary systemwide analysis. *Am J Prev Cardiol*. 2026;25:101402. doi:10.1016/j.japc.2025.101402
- Razavi AC, Richardson LC, Coronado F, et al. Prevalence and correlates of lipoprotein(a) testing in a diverse cohort of U.S. adults. *JACC Adv*. 2025;4(6 Pt 1):101826. doi:10.1016/j.jaccadv.2025.101826
- Mach F, Koskinas KC, Roeters van Lennep JE, et al. 2025 focused update of the 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J*. 2025;46(42):4359-4378. doi:10.1093/eurheartj/ehaf190
- Writing Committee Members, Blumenthal RS, Morris PB, et al. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/AHA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2026;153(17):e1154-e1276. doi:10.1161/CIR.0000000000001423
- Gilliland TC, Liu Y, Mohebi R, et al. Lipoprotein(a), oxidized phospholipids, and coronary artery disease severity and outcomes. *J Am Coll Cardiol*. 2023;81(18):1780-1792. doi:10.1016/j.jacc.2023.02.050
- Simantiris S, Antonopoulos AS, Papastamos C, et al. Lipoprotein(a) and inflammation - pathophysiological links and clinical implications for cardiovascular disease. *J Clin Lipidol*. 2023;17(1):55-63. doi:10.1016/j.jacl.2022.10.004
- Corral P, Matta MG, Aguilar-Salinas C, et al. Lipoprotein(a) throughout life in women. *Am J Prev Cardiol*. 2024;20:100885. doi:10.1016/j.japc.2024.100885
- Arsenault BJ, Loganath K, Girard A, et al. Lipoprotein(a) and calcific aortic valve stenosis progression: a systematic review and meta-analysis. *JAMA Cardiol*. 2024;9(9):835-842. doi:10.1001/jamacardio.2024.1882
- Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the Management

- of Dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455
20. Kronenberg F, Bedlington N, Ademi Z, et al. The Brussels International Declaration on Lipoprotein(a) Testing and Management. *Atherosclerosis*. 2025;406:119218. doi:10.1016/j.atherosclerosis.2025.119218
 21. Reeskamp LF, Tromp TR, Patel AP, et al. Concordance of a high lipoprotein(a) concentration among relatives. *JAMA Cardiol*. 2023;8(12):1111-1118. doi:10.1001/jamacardio.2023.3548
 22. Lipoprotein (a). Quest Diagnostics. Accessed April 6, 2026. <https://testdirectory.questdiagnostics.com/test/test-detail/34604/lipoprotein-a?cc=MASTER>
 23. United Healthcare. Cardiovascular Disease Risk Assessment Policy, Professional and Facility. Published 2025. Accessed February 16, 2026. <https://www.uhcprovider.com/content/dam/provider/docs/public/policies/medadv-reimbursement/MEDADV-Cardiovascular-Disease-Risk-Assessment-Policy.pdf>
 24. Lloyd-Jones DM, Allen NB, Anderson CAM, et al. Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. *Circulation*. 2022;146(5):e18-e43. doi:10.1161/CIR.0000000000001078
 25. O'Donoghue ML, Fazio S, Giugliano RP, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk: insights from the FOURIER Trial. *Circulation*. 2019;139(12):1483-1492. doi:10.1161/CIRCULATIONAHA.118.037184
 26. Ray KK, Vallejo-Vaz AJ, Ginsberg HN, et al. Lipoprotein(a) reductions from PCSK9 inhibition and major adverse cardiovascular events: pooled analysis of alirocumab phase 3 trials. *Atherosclerosis*. 2019;288:194-202. doi:10.1016/j.atherosclerosis.2019.06.896
 27. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med*. 2020;382(16):1507-1519. doi:10.1056/NEJMoa1912387
 28. Pirillo A, Catapano AL. Inclisiran: how widely and when should we use it? *Curr Atheroscler Rep*. 2022;24(10):803-811. doi:10.1007/s11883-022-01056-0
 29. Gianos E, Duell PB, Toth PP, et al. Lipoprotein apheresis: utility, outcomes, and implementation in clinical practice: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2024;44(12):e304-e321. doi:10.1161/ATV.0000000000000177
 30. Waldmann E, Parhofer KG. Lipoprotein apheresis to treat elevated lipoprotein (a). *J Lipid Res*. 2016;57(10):1751-1757. doi:10.1194/jlr.R056549
 31. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. *N Engl J Med*. 2020;382(3):244-255. doi:10.1056/NEJMoa1905239
 32. O'Donoghue ML, Rosenson RS, López JAG, et al. The off-treatment effects of olpasiran on lipoprotein(a) lowering: OCEAN(a)-DOSE extension period results. *J Am Coll Cardiol*. 2024;84(9):790-797. doi:10.1016/j.jacc.2024.05.058
 33. Nissen SE, Ni W, Shen X, et al. Lepodisiran — a long-duration small interfering RNA targeting lipoprotein(a). *N Engl J Med*. 2025;392(17):1673-1683. doi:10.1056/NEJMoa2415818
 34. Nissen SE, Wang Q, Nicholls SJ, et al. Zerasiran-a small-interfering RNA targeting lipoprotein(a): a phase 2 randomized clinical trial. *JAMA*. 2024;332(23):1992-2002. doi:10.1001/jama.2024.21957
 35. Nicholls SJ, Ni W, Rhodes GM, et al. Oral muvalaplin for lowering of lipoprotein(a): a randomized clinical trial. *JAMA*. 2025;333(3):222-231. doi:10.1001/jama.2024.24017

Severe Hypertriglyceridemia to Familial Chylomicronemia Syndrome: Roadmap to Reduce Pancreatitis

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INTRODUCTION

Severe hypertriglyceridemia (sHTG), defined as fasting triglycerides (TGs) ≥ 500 mg/dL, increases the risk of acute pancreatitis due to the presence of TG-carrying lipoproteins called chylomicrons in the circulation.^{1,2} Often first detected in primary care settings on a routine lipid panel, sHTG commonly reflects interactions between inherited susceptibility, insulin resistance, diet, alcohol use, and the use of TG-raising medications.^{2,3} Primary care clinicians (PCCs) are positioned to detect sHTG early in patients with predisposing conditions including diabetes, obesity, hypothyroidism, and chronic kidney disease; timely recognition and intervention can reduce the risk of pancreatitis and cardiovascular (CV) complications.¹

Hypertriglyceridemia (HTG) occurs in ~28% of the general population (1 in 4).^{4,5} In comparison, the estimated prevalence of sHTG globally is 1.14% (1 in 88).^{4,5} In a US claims-based analysis of 1.8 million adults with TG values, 12,050 (0.7%) individuals had TGs 500 to 879 mg/dL and 3944 (0.2%) had TGs ≥ 880 mg/dL, indicating that sHTG may be uncommon enough to be overlooked but common enough to appear routinely in patient panels.⁶ The primary immediate risk of sHTG is acute pancreatitis, and the long-term risk is atherosclerotic cardiovascular disease (ASCVD).⁷ Acute pancreatitis and CV event rates are higher in patients with higher TG levels. Among adults with TGs <150 mg/dL, acute pancreatitis rates are 0.6 per 1000 person-years and CV events rates are 3.3 per 1000 person-years. Among adults with TGs

Key takeaways

- sHTG (fasting TGs ≥ 500 mg/dL) is associated with an increased risk of acute pancreatitis and CV events.
- Most sHTG in primary care is polygenic and multifactorial, so assessment should consider risk factors such as diabetes, obesity, alcohol use, medications, kidney disease, hypothyroidism, pregnancy, and acute illness.
- Chylomicronemia syndromes may occur with TGs ≥ 880 mg/dL and include familial chylomicronemia syndrome (FCS), which is characterized by persistent chylomicronemia and responds poorly to standard TG-lowering therapy.
- Treatment of sHTG begins with pancreatitis risk reduction through dietary changes, correction of hyperglycemia if present, and removal of TG-raising drugs, followed by pharmacologic TG lowering and reassessment of CV risk.
- Lifestyle interventions are critical to treating sHTG and include reducing total fat, avoiding alcohol, limiting refined carbohydrates and sugar-sweetened beverages, consuming lean protein and non-starchy vegetables, and pursuing weight reduction when appropriate.
- Apolipoprotein C-III (apoC-III)-targeted treatments, such as olezarsen and plozasiran, are changing the sHTG landscape, showing $>80\%$ reductions in the risk of acute pancreatitis.

≥ 880 mg/dL, acute pancreatitis rates are 9.9 per 1000 person-years (a nearly 20-fold increase from TGs <150 mg/dL) and CV event rates are 10.3 per 1000 person-years.^{1,6}

CASE STUDY

You are seeing a 47-year-old man for a visit regarding type 2 diabetes and hypertension. He reports mild epigastric discomfort after meals, and weekend alcohol use of up to 14 beers. His medications include metformin, valsartan, and hydrochlorothiazide. On a quick dietary review, he reports consumption of high-carbohydrate, high-fat foods (including doughnuts, bagels/cream cheese, pancakes/syrup, fruit juices) on a daily basis. His body mass index (BMI) is 29 kg/m², glycated hemoglobin (HbA1c) 7.1%, blood pressure 128/84 mmHg, fasting TGs 930 mg/dL, direct low-density lipoprotein cholesterol (LDL-C) 94 mg/dL, and high-density lipoprotein cholesterol (HDL-C) 27 mg/dL.

THE SPECTRUM OF HTG

Physiology of HTG

TGs are a source of fat derived from food and produced by the liver. TGs are primarily carried in chylomicrons, derived from food, and in very low-density lipoprotein (VLDL), derived from synthesis by the liver.² TG-carrying lipoproteins are cleared from the circulation by the enzyme lipoprotein lipase (LPL), which is found in adipose tissue, skeletal muscle, and the heart. LPL hydrolyzes TGs in chylomicrons and VLDL into free fatty acids for storage or energy use; the chylomicron remnants and VLDL remnants thus formed are then cleared by the liver.² ApoC-III is carried on TG-rich lipoproteins and inhibits LPL activity, resulting in elevated TG levels.⁸

TG levels reflect the production and clearance of TG-rich lipoproteins from the liver and chylomicrons from the intestine. When production of TGs is increased or clearance is impaired, TG-rich particles accumulate and severely elevated levels of TGs can result, increasing pancreatitis risk.^{2,9}

Pathophysiology of sHTG and its complications

sHTG commonly encountered in clinical practice is polygenic rather than caused by a single-gene disorder. When ≥ 1 secondary factors such as diabetes, obesity/weight gain, excessive alcohol use, suboptimal eating patterns, chronic kidney disease, hypothyroidism, pregnancy, and TG-increasing medications are present, TG levels rise and contribute to the onset and severity of HTG.^{2,3}

Pancreatitis is the most urgent and immediate consequence of sHTG, particularly if TGs are ≥ 880 mg/dL. Acute pancreatitis due to HTG is thought to involve hydrolysis of excess TGs by pancreatic lipase, local free fatty acid toxicity, microvascular injury, inflammatory signaling, and acinar cell damage.⁹ Clinically, HTG-induced acute pancreatitis may present with epigastric pain, nausea, vomiting, and systemic illness, and it can progress to pancreatic necrosis, organ failure, prolonged hospitalization, and recurrent episodes if TG levels remain uncontrolled.^{9,10} Although mild acute pancreatitis usually

resolves with supportive care, severe acute pancreatitis carries substantial morbidity, and mortality can reach approximately 15% to 30% in severe or infected necrotizing disease.^{10,11}

CV risk in sHTG is phenotype specific; sHTG often clusters with high-risk cardiometabolic features and elevated non-HDL-C or apolipoprotein B (apoB).^{12,13} Elevated non-HDL-C indicates increased cholesterol across atherogenic particles such as VLDL, intermediate-density lipoproteins, LDL-C, and remnants.¹ Elevated apoB indicates an increased number of atherogenic particles and may better capture residual ASCVD risk when TG-rich lipoproteins are abundant.^{1,2} To reduce CV risk in patients with sHTG, after urgent TG lowering, PCCs should reassess ASCVD prevention using LDL-C, non-HDL-C, apoB when available, diabetes control, blood pressure, smoking status, and statin eligibility or intensity.^{1,7}

SCREENING, IDENTIFICATION, AND DIAGNOSIS

A standard lipid panel will usually identify sHTG, but fasting confirmation is important when TGs are ≥ 500 mg/dL or when the result will change management. A fasting repeat lab will help classify HTG severity and determine whether pancreatitis risk reduction measures should begin immediately.^{1,2} Very high TGs can interfere with obtaining an LDL-C value, since it is calculated, so a direct LDL-C measurement, non-HDL-C, apoB, or repeat testing after TGs improve is often needed to evaluate ASCVD risk accurately.¹ When TGs are markedly elevated (i.e., ≥ 880 mg/dL), TG lowering is the primary focus prior to addressing LDL-C lowering.

Confirmation of sHTG should be accompanied by assessment of symptoms and potential urgency for intervention. This should include evaluation for secondary causes of sHTG as they are common and often modifiable. Metabolic contributors include new-onset or suboptimally managed diabetes, obesity, and hypothyroidism, while renal, endocrine, and physiologic contributors include chronic kidney disease or nephrotic syndrome, pregnancy, Cushing syndrome, and acute inflammatory illness.^{1,2} Exposure to TG-increasing medications should be reviewed; these include alcohol, estrogens, retinoids, glucocorticoids, atypical antipsychotics, human immunodeficiency virus (HIV) protease inhibitors, some beta blockers, thiazides, bile acid sequestrants, and immunosuppressants.^{1,2} Clinical evaluation for abdominal pain, nausea, vomiting, history of prior pancreatitis, alcohol intake, diabetes management if present, pregnancy, and recent medication changes should be performed.

Clinical features and differential diagnosis

Chylomicronemia syndrome is an umbrella term for clinically important chylomicron accumulation, generally with fasting TGs ≥ 880 mg/dL; causes include FCS (rare, 2% of cases) and the more common multifactorial chylomicronemia syndrome

(MCS, 98% of cases seen in clinical practice).^{13,14} Thus, if fasting TGs are ≥ 880 mg/dL, FCS and MCS should be considered as potential diagnoses. FCS is driven by biallelic loss-of-function variants affecting the LPL pathway. MCS is not associated with single gene mutations and is polygenic in etiology.

Differentiating between MCS and FCS

MCS usually presents in adulthood, fluctuates with secondary triggers, and often improves with glycemic control, alcohol cessation, weight loss, medication changes, and standard TG-lowering therapy including fibrates or omega-3 fatty acids.^{2,12} Individuals often have high BMI and high apoB and non-HDL-C levels; TG levels may improve when secondary factors are corrected.^{12,13} In contrast, FCS is rare, typically begins in childhood or adolescence, and results in persistent extreme TG elevations that do not respond to conventional TG-lowering therapies. Secondary factors such as diabetes or obesity are absent. These individuals have normal or sometimes low BMI. FCS is associated with recurrent pancreatitis risk.¹³ Abdominal pain, eruptive xanthomas (yellowish skin papules encircled by an erythematous halo), lipemia retina-

lis (creamy white discoloration of retinal blood vessels), and pancreatitis can occur in both MCS and FCS.^{1,12,13,15-18} The risk of acute pancreatitis in MCS is less than that observed in FCS. Characteristics of the various hypertriglyceridemic diseases across the TG spectrum are summarized in **TABLE 1**.

Although FCS is rare, the diagnosis should be entertained in an individual with normal or low BMI, childhood or adolescent onset of sHTG, persistent extremely elevated TGs despite the absence of secondary drivers, and history of recurrent pancreatitis. A clinical scoring tool (the North American FCS score) can help with diagnosing FCS and is available at <https://www.lipid.org/nla/north-american-familial-chylomicronemia-calculator-or-na-fcs-scoring-tool>.¹⁷ Based on the score obtained, referral to a lipid specialist for evaluation and genetic testing should be pursued as appropriate.

Patients with symptoms concerning for acute pancreatitis should be promptly referred for emergency evaluation rather than managed in the outpatient setting.^{1,9} TG levels fall rapidly after fasting, intravenous fluids, or acute illness management, so delayed sampling can underestimate the triggering TG burden in pancreatitis.⁹

TABLE 1. Spectrum of hypertriglyceridemic diseases by phenotype.^{1-3,6,13,17}

Feature	Moderate HTG	sHTG	Very severe/extreme HTG	MCS	FCS
TG levels	150 to 499 mg/dL	≥ 500 mg/dL	≥ 880 mg/dL	Usually ≥ 880 mg/dL, with levels that fluctuate over time	Usually persistently ≥ 880 mg/dL; often >1500 to 2000 mg/dL
Causes	Insulin resistance, obesity, type 2 diabetes, metabolic syndrome, alcohol use, high refined-carbohydrate intake, and other secondary causes	Polygenic susceptibility plus secondary triggers such as uncontrolled diabetes, obesity, alcohol use, medications, or hypothyroidism	Major secondary triggers superimposed on polygenic risk or on chylomicronemia syndromes	Polygenic or multifactorial disorder with obesity, insulin resistance or diabetes, alcohol use, and medication triggers	Rare monogenic disorder due to biallelic loss-of-function variants in the lipoprotein lipase pathway
Primary disease mechanism	Increased VLDL production with impaired TG-rich lipoprotein clearance	Marked accumulation of VLDL and TG-rich lipoproteins; pancreatitis risk begins to rise	Chylomicron accumulation with severe impairment of TG-rich lipoprotein clearance	Chylomicronemia driven by combined genetic susceptibility and secondary factors	Profound defect in chylomicron clearance
Clinical hallmark	Usually asymptomatic; cardiometabolic risk phenotype	Often asymptomatic, but postprandial abdominal discomfort may occur; pancreatitis prevention becomes a priority	Abdominal pain, nausea, eruptive xanthomas, lipemia retinalis, and high pancreatitis risk	Adult onset, fluctuating TG levels, recurrent abdominal pain or pancreatitis, and metabolic syndrome features are common	Childhood or adolescent onset, recurrent pancreatitis, eruptive xanthomas, lipemia retinalis, low apoB/LDL-C, and minimal metabolic syndrome
Dietary therapeutic response	Responds to weight loss, reduced refined carbohydrates or sugar-sweetened beverages, less alcohol, and improved overall diet quality	Usually improves with lower fat intake, alcohol elimination, reduced simple sugars, and correction of secondary causes	Requires urgent very low-fat nutrition (about 10% to 15% of calories from fat or ≤ 20 to 30 g/day), no alcohol, and rapid treatment of hyperglycemia	Often shows substantial improvement when secondary causes are corrected and a very low-fat diet is used short term	Requires lifelong strict very low-fat nutrition; response to conventional TG-lowering drugs is often limited

Abbreviations: apoB, apolipoprotein B; FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia; LDL-C, low-density lipoprotein cholesterol; MCS, multifactorial chylomicronemia syndrome; sHTG, severe hypertriglyceridemia; TG, triglyceride; VLDL, very low-density lipoprotein.

Besides dietary nonadherence, PCCs should assess for concomitant diseases and factors that increase the risk of HTG.^{3,13} **FIGURE 1** summarizes a diagnostic pathway that can be useful for the workup and clinical decision-making in patients with TGs ≥ 500 mg/dL and ends with treatment, monitoring, and referral triggers.^{1,17}

SHTG TREATMENT APPROACHES

The first treatment priority in sHTG is prevention of pancreatitis, especially when TGs are ≥ 880 mg/dL or symptoms suggest acute pancreatitis.

Immediate approach

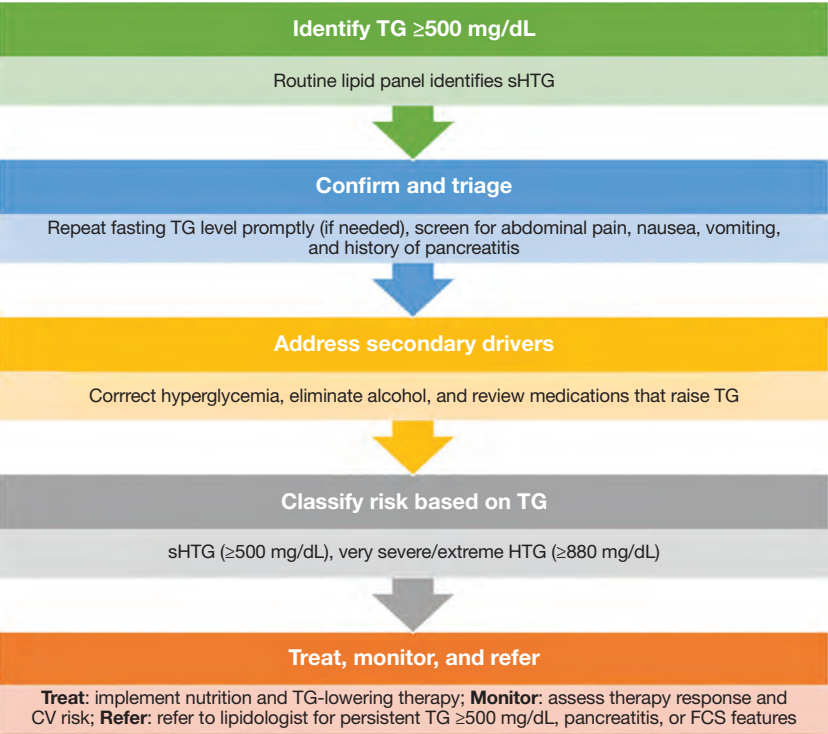
For TGs ≥ 880 mg/dL, clinicians should counsel patients to initiate a chylomicron-clearing very low-fat diet, eliminate alcohol consumption, rapidly correct hyperglycemia if present, and stop or substitute TG-raising medications when clinically feasible.^{1,2} Details for rapid TG-lowering nutrition and immediate interventions for reducing pancreatitis risk in patients with TGs ≥ 880 mg/dL are described in **TABLE 2**.^{1,2}

General principles

Lifestyle measures: Dietary counseling for sHTG should include recommendations to reduce total fat, avoid alcohol, limit refined carbohydrates and sugar-sweetened beverages, use lean protein and non-starchy vegetables, and pursue weight reduction when appropriate.^{1,2} When TGs are in the chylomicronemia range (≥ 880 mg/dL), fat restriction is more stringent than typical cardiometabolic diets and requires referral to a dietitian fam-

iliar with counseling for sHTG, particularly when food insecurity, cultural food patterns, or limited access to low-fat options complicate adherence.^{1,12} Recommended very low-fat diets typically consist of 10% to 15% of calories from fat or ≤ 20 to 30 g/day; limiting dietary fat to $<5\%$ for a few days until TG falls below 880 mg/dL in severe elevations may be appropriate.^{1,2} Of note, low-fat diets can be challenging in patients with concomitant diabetes. Lifestyle interventions are critical for management of

FIGURE 1. Pathway for sHTG in primary care.^{1,13}



Abbreviations: CV, cardiovascular; FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia; sHTG, severe hypertriglyceridemia; TG, triglyceride.

TABLE 2. Rapid TG-lowering interventions for TGs ≥ 880 mg/dL or impending pancreatitis.^{1,2}

Goal for TGs ≥ 880 mg/dL	Comments/practical actions
Clear chylomicrons quickly	Use a very low-fat diet: 10% to 15% of calories from fat or ≤ 20 to 30 g/day; consider $<5\%$ until TGs fall below 880 mg/dL
Eliminate major triggers	Avoid alcohol completely; avoid sugar-sweetened beverages, added sugars, high-fat foods, and refined carbohydrates
Correct metabolic drivers	Treat hyperglycemia promptly and address insulin deficiency or severe insulin resistance; recommend 150 minutes per week of moderate-intensity aerobic activity or 75 minutes per week of vigorous-intensity aerobic activity; weight loss of 5% to 10%
Review medications	Stop or substitute TG-raising agents when clinically feasible, including thiazides, some beta blockers, estrogens, glucocorticoids, retinoids, and atypical antipsychotics
Support dietary adherence	Use lean protein, non-starchy vegetables, and very low-fat or nonfat foods; involve a dietitian when sHTG is severe, recurrent, or complicated by FCS or access barriers. Dietary plans should account for culture, cost, food access, literacy, and comorbidities
TG-lowering therapies	Initiate TG-lowering therapy based on diagnosis/indication. Conventional TG-lowering therapies are less effective; use apoC-III-targeted therapies for significant reduction in TGs and pancreatitis risk

Abbreviations: apoC-III, apolipoprotein C-III; FCS, familial chylomicronemia syndrome; sHTG, severe hypertriglyceridemia; TG, triglyceride.

sHTG, as significant reductions in TG are associated with certain measures¹:

- Weight loss (~5% to 10%)—may result in up to a 70% reduction in TGs, although most patients experience about a 10% to 20% reduction
 - Dietary modification (includes alcohol restriction or abstinence)—70% reduction in TGs or higher depending on baseline TGs and adherence to diet
 - Physical activity and exercise—up to a 30% reduction in TGs depending on type, duration, and intensity of activity

Conventional TG-lowering therapies: Fibrates and prescription omega-3 fatty acids remain common TG-lowering options for pancreatitis risk reduction in sHTG, while statins are used to reduce ASCVD risk, especially in patients with MCS. Fibrates and prescription omega-3 fatty acids lower TGs by approximately 20% to 50%, and statins lower TGs by about 15% to 30%.¹⁹ Medication selection should account for renal function, drug-drug interactions, tolerability, pregnancy potential, cost, and whether the TG elevation appears driven by a remediable secondary cause.^{1,2} If a statin is used, concomitant fenofibrate is generally preferred over gemfibrozil as TG-lowering therapy; gemfibrozil should be avoided in combination with statins because of an elevated risk of muscle-related adverse events.^{1,7}

Aspects of management specific to FCS

FCS management centers on lifelong very low-fat nutrition, avoidance of alcohol, prevention of pancreatitis, and care coordination with a lipid specialist and dietitian. Conventional TG-lowering therapies have limited to no effect in FCS because the central defect is in the LPL pathway, causing impaired chylomicron clearance. It is important to note that omega-3 fatty acids may worsen TG levels in FCS as they are an added fat source; therefore, they should be avoided.² The new injectable apoC-III-directed therapies olezarsen and plozasiran are now approved as adjuncts to diet to reduce TGs in adults with FCS (see below).^{18,20,21}

Monitoring and referral

Monitoring depends on baseline disease severity and the timing of interventions. A fasting TG level should be rechecked 1 to 2 weeks after an immediate intervention, especially when baseline TGs are very high. The monitoring interval should be adjusted according to medication changes, glycemic control, adherence, symptoms, and TG stability. Follow-up should also monitor non-HDL-C, apoB when available, HbA1c/blood glucose, liver enzymes when clinically indicated, renal function for fibrate dosing and/or concomitant kidney disease, and barriers to dietary or medication adherence.^{1,2}

Collaboration with a lipidologist is beneficial for patients with sHTG. If specialist involvement is not available, clini-

cians should be encouraged to use appropriate diagnostic approaches and clinical management strategies to help ensure patients receive optimal care.²

CASE STUDY (CONTINUED) – NEXT STEPS

At the visit, due to the identification of sHTG (TGs 930 mg/dL), the patient is first evaluated for pancreatitis symptoms (which only consist of mild abdominal pain after heavy meals). Hydrochlorothiazide is discontinued as it can contribute to raising TGs. He is counseled to avoid alcohol and begin a low-fat diet. He is asked to return in a month to repeat a fasting lipid panel and to discuss dietary changes, alcohol cessation, and weight and glucose management. On his return visit, fasting TGs were 660 mg/dL.

This patient's TGs improved with management of secondary contributors. However, his TGs are still >500 mg/dL, and he can benefit from targeted TG-lowering therapy to further reduce his CV risk and his risk of pancreatitis. ApoC-III-targeted therapies should be considered in addition to ongoing multifactorial management.

NEW TARGETED THERAPIES FOR sHTG

While lifestyle changes and standard therapies remain foundational for sHTG management, many patients with severe, refractory, or genetically driven HTG do not achieve stable TG control and/or remain at risk for pancreatitis. New agents targeting apoC-III are olezarsen for treatment of FCS and sHTG and plozasiran for treatment of FCS.^{2,22,23}

Olezarsen is an antisense oligonucleotide targeting apoC-III that was approved in 2024 for treatment of FCS as an 80 mg once-monthly subcutaneous injection.²⁰ In the Balance trial of 66 adults with genetically identified FCS, olezarsen 80 mg monthly reduced fasting TGs by a placebo-adjusted mean of 43.5% at 6 months.²⁴ At 53 weeks, the incidence of acute pancreatitis was reduced in the pooled olezarsen groups (80 mg and 50 mg) vs placebo (rate ratio 0.12; 95% confidence interval [CI]: 0.02, 0.66).²⁴

In June 2026, olezarsen was approved for sHTG.²⁰ In the phase 3 CORE-TIMI 72a and CORE2-TIMI 72b trials, which collectively enrolled 1061 patients with sHTG, monthly olezarsen led to placebo-adjusted TG reductions across studied doses and reduced acute pancreatitis incidence compared with placebo.²⁵ Placebo-adjusted reductions from baseline in TGs were –62.9% (olezarsen 50 mg) and –72.2% (olezarsen 80 mg) in CORE-TIMI 72a, and –49.2% (olezarsen 50 mg) and –54.5% (olezarsen 80 mg) in CORE2-TIMI 72b ($P < .001$ for all comparisons with placebo).²⁵ The incidence of acute pancreatitis was 85% lower with olezarsen than placebo (mean rate ratio 0.15; 95% CI: 0.05, 0.40; $P < .001$).²⁵ Adverse events were similar across trial groups; injection site reactions and elevations in liver enzymes occurred in ≥2% of patients and more commonly than with placebo. Injection site reactions were seen in 12% of patients receiving ole-

zarsen 50 mg, 18% of those receiving olezarsen 80 mg, and 2% of those receiving placebo; liver enzyme elevations were observed in 3% of the olezarsen 50 mg group, 4% of the olezarsen 80 mg group, and 1% of the placebo group.²⁰ At baseline, patients in the trials were receiving stable lipid-lowering therapy according to standard of care, which could include statins and other lipid-lowering therapies.²⁵ Based on results of these phase 3 studies in sHTG, the US Food and Drug Administration (FDA) approved olezarsen for reducing TGs and the risk of acute pancreatitis in adults with sHTG at a dose of 50 mg subcutaneously once monthly, which may be increased to 80 mg once monthly if the 50 mg dose is tolerated and if clinically indicated.^{20,23}

Plozasiran is a small interfering RNA (siRNA) therapy targeting apoC-III that was approved in 2025 for FCS and is administered as a 25 mg subcutaneous injection every 3 months.²¹ In PALISADE, patients with persistent chylomicronemia (includes FCS) who received plozasiran had significantly lower median placebo-adjusted TG levels at 10 months (–59% in the 25 mg plozasiran group and –53% in the 50 mg plozasiran group; $P < .001$ for all comparisons with placebo).²⁶ Additionally, an 83% lower incidence of acute pancreatitis was observed in those receiving plozasiran (pooled 25 mg and 50 mg data) vs placebo (odds ratio 0.17; 95% CI: 0.03, 0.94; $P = .03$).²⁶ Plozasiran received an FDA Breakthrough Designation for sHTG, and phase 3 trials are currently ongoing in populations with sHTG.

Additional targets being studied for sHTG treatment include angiopoietin-like protein-3, fibroblast growth factor 21, and gene-editing technologies.²²

SUMMARY

sHTG carries a significant risk of acute pancreatitis and adverse cardiometabolic outcomes; thus, TGs ≥ 500 mg/dL are more than a simple laboratory abnormality. Markedly elevated TGs ≥ 880 mg/dL are more commonly due to polygenic etiology but rarely may indicate the presence of the rare monogenic lipid disorder FCS. PCCs can improve the care of patients with sHTG by identifying severe TG elevations early and initiating appropriate management or referral when necessary. This involves confirming severe TG elevations, screening for pancreatitis symptoms, correcting secondary drivers, initiating low-fat nutrition and standard TG-lowering therapy when indicated, and reassessing ASCVD risk once the immediate TG lowering has been accomplished. Distinguishing multifactorial sHTG from FCS should be a consideration due to the expected lack of response to standard therapy, available treatment options, and the differing needs for referral and treatment. The landscape of sHTG treatment is evolving, with apoC-III-directed therapies demonstrating reductions in TGs and acute pancreatitis risk; as of the time of this writing, olezarsen has been approved to lower TGs and reduce the risk of acute pancreatitis in adults with sHTG, offering a new option for targeted treatment. ●

REFERENCES

- Virani SS, Morris PB, Agarwala A, et al. 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;78(9):960-993. doi:10.1016/j.jacc.2021.06.011
- Subramanian S. Hypertriglyceridemia: pathophysiology, role of genetics, consequences, and treatment. Published online January 8, 2024. Accessed May 26, 2026. <https://www.ncbi.nlm.nih.gov/books/NBK326743/>
- Hegele RA, Ginsberg HN, Chapman MJ, et al. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol*. 2014;2(8):655-666. doi:10.1016/S2213-8587(13)70191-8
- Ballena-Cacedo J, Zuzunaga-Montoya FE, Loayza-Castro JA, et al. Global prevalence of dyslipidemias in the general adult population: a systematic review and meta-analysis. *J Health Popul Nutr*. 2025;44(1):308. doi:10.1186/s41043-025-01054-3
- Baass A, Paquette M, Lam O, Hofer K, Collet J, McClain MR. Prevalence, incidence, and definition of severe hypertriglyceridemia: a comprehensive review and weighted summary. *J Clin Lipidol*. 2025;19(6):1550-1563. doi:10.1016/j.jacl.2025.08.012
- Sikora Kessler A, Baum SJ, Kutrieb E, et al. Rates of acute pancreatitis and cardiovascular events among adults with severe or extreme hypertriglyceridemia in US clinical practice. *Lipids Health Dis*. 2025;24(1):252. doi:10.1186/s12944-025-02658-8
- Writing Committee Members, Blumenthal RS, Morris PB, et al. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2026;153(17):e1154-e1276. doi:10.1161/CIR.0000000000001423
- Bornfeldt KE. Apolipoprotein C3: form begets function. *J Lipid Res*. 2024;65(1):100475. doi:10.1016/j.jlr.2023.100475
- Qiu M, Zhou X, Zippi M, et al. Comprehensive review on the pathogenesis of hypertriglyceridaemia-associated acute pancreatitis. *Ann Med*. 2023;55(2):2265939. doi:10.1080/07853890.2023.2265939
- Beij A, Verdonk RC, van Santvoort HC, de-Madaria E, Voermans RP. Acute pancreatitis: an update of evidence-based management and recent trends in treatment strategies. *United European Gastroenterol J*. 2025;13(1):97-106. doi:10.1002/ueg2.12743
- Lu J, Wang Z, Mei W, et al. A systematic review of the epidemiology and risk factors for severity and recurrence of hypertriglyceridemia-induced acute pancreatitis. *BMC Gastroenterol*. 2025;25(1):374. doi:10.1186/s12876-025-03954-4
- Spagnuolo CM, Wang J, McIntyre AD, Kennedy BA, Hegele RA. Comparison of patients with familial chylomicronemia syndrome and multifactorial chylomicronemia syndrome. *J Clin Endocrinol Metab*. 2025;110(4):1158-1165. doi:10.1210/clinem/dgae613
- Javed F, Hegele RA, Garg A, et al. Familial chylomicronemia syndrome: an expert clinical review from the National Lipid Association. *J Clin Lipidol*. 2025;19(3):382-403. doi:10.1016/j.jacl.2025.03.013
- Saadatagah S, Larouche M, Naderian M, et al. Recognition and management of persistent chylomicronemia: a Joint Expert Clinical Consensus by the National Lipid Association and the American Society for Preventive Cardiology. *J Clin Lipidol*. 2025;19(4):723-736. doi:10.1016/j.jacl.2025.03.012
- Lee SY, Sheth CA. Eruptive xanthoma associated with severe hypertriglyceridemia and poorly controlled type 1 diabetes mellitus. *J Community Hosp Intern Med Perspect*. 2019;9(4):344-346. doi:10.1080/20009666.2019.1650591
- Lai CC, Chang CH. Lipemia retinalis with different therapeutic responses: a report of two cases. *Taiwan J Ophthalmol*. 2021;11(4):405-407. doi:10.4103/tjo.tjo_73_20
- Hegele RA, Ahmad Z, Ashraf A, et al. Development and validation of clinical criteria to identify familial chylomicronemia syndrome (FCS) in North America. *J Clin Lipidol*. 2025;19(1):83-94. doi:10.1016/j.jacl.2024.09.008
- Brinton EA, Eckel RH, Gaudet D, et al. Familial chylomicronemia syndrome and treatments to target hepatic APOC3 mRNA. *Atherosclerosis*. 2025;403:119114. doi:10.1016/j.atherosclerosis.2025.119114
- Zimodro JM, Rizzo M, Gouni-Berthold I. Current and emerging treatment options for hypertriglyceridemia: state-of-the-art review. *Pharmaceuticals (Basel)*. 2025;18(2):147. doi:10.3390/ph18020147
- Tryngolza (olezarsen). Prescribing Information. Ionis Pharmaceuticals Inc.; June 2026. Accessed June 25, 2026. <https://ionis.com/medicines/TRYNGOLZA/TRYNGOLZA-FPI.pdf>
- Redemphlo (plozasiran). Prescribing Information. Arrowhead Pharmaceuticals Inc.; November 2025. Accessed June 8, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219947s000lbl.pdf
- Alhomoud IS. Current and emerging pharmacological therapies for hypertriglyceridemia. *Int J Mol Sci*. 2026;27(8):3573. doi:10.3390/ijms27083573
- FDA approves first treatment shown to reduce the risk of acute pancreatitis in adults with severe hypertriglyceridemia. US Food & Drug Administration. June 24, 2026. Accessed June 25, 2026. <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-shown-reduce-risk-acute-pancreatitis-adults-severe-hypertriglyceridemia>
- Stroes ESG, Alexander VJ, Karwowska-Prokopczuk E, et al. Olezarsen, acute pancreatitis, and familial chylomicronemia syndrome. *N Engl J Med*. 2024;390(19):1781-1792. doi:10.1056/NEJMoa2400201
- Marston NA, Bergmark BA, Alexander VJ, et al. Olezarsen for managing severe hypertriglyceridemia and pancreatitis risk. *N Engl J Med*. 2026;394(5):429-441. doi:10.1056/NEJMoa2512761
- Watts GE, Rosenson RS, Hegele RA, et al. Plozasiran for managing persistent chylomicronemia and pancreatitis risk. *N Engl J Med*. 2025;392(2):127-137. doi:10.1056/NEJMoa2409368

A New Era in the Management of T2D: Automated Insulin Delivery

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INTRODUCTION

Diabetes affects an estimated 38.4 million people in the United States, with an increasing prevalence of both type 1 diabetes (T1D) and type 2 diabetes (T2D).¹ Approximately 90% of adults with T2D and 50% of adults with T1D receive diabetes care from a primary care clinician (PCC).² However, PCCs face many challenges in diabetes management, including inadequate clinic time and resources.³ Advanced diabetes technology, such as automated insulin delivery (AID) systems, may help alleviate the burden on PCCs and improve diabetes management in primary care. Additionally, the use of diabetes technology in primary care allows more people living with diabetes to be reached, given the geographic gaps in the availability of endocrinologists across the United States.⁴

WHAT IS AID?

AID is a technology that helps patients optimize their insulin use. Each AID system contains 3 components: 1) an insulin pump, 2) a continuous glucose monitoring (CGM) system, and 3) an algorithm that determines insulin delivery.⁵ These components allow AID systems to automatically deliver, monitor, and titrate insulin based on real-time data. Depending on the model and brand of the AID system, the algorithm can be hosted in the pump hardware itself, with tubed and tubeless options, or on a separate phone app.⁵

All currently available AID systems integrate with ≥ 1 CGM systems and adjust insulin delivery either by modulating the pre-programmed basal rates or by using an algorithm-derived rate with microboluses, or microdoses, of insulin delivered every 5 minutes.⁵ AID systems, which can adjust

Key takeaways

- Rates of type 2 diabetes continue to increase and, despite the advancement of noninsulin therapeutics, there remains a need for insulin and for access to improved insulin delivery methods.
- Diabetes technology, including automated insulin delivery (AID), has advanced substantially and provides better diabetes management support for the patient, family, and health care team.
- Providing AID in primary care practice improves efficiencies in diabetes care, glycemic control without increasing hypoglycemia risk, and time in range compared to multiple daily injections of insulin and continuous subcutaneous insulin infusion.
- Implementing diabetes technology like continuous glucose monitoring and AID systems is feasible, supports data interpretation in primary care practice, and provides benefits to patients and clinicians.

insulin delivery based on sensor glucose values, are preferred over nonautomated pumps and multiple diabetes injections (MDI) in people with T1D and T2D and have largely replaced the use of standard insulin pumps.⁵ At the time of this writing, 3 AID systems are currently approved for use by people with T2D in the United States.⁵

BENEFITS OF NEW AID SYSTEMS

While AID systems have been available for years, they are increasingly recognized for their benefits in both T1D and T2D, leading to improved care.⁵ New AID systems are simpler and easier to implement than older systems, and PCCs can bill for technology integration as part of care, making them

more practical to incorporate. Implementing AID can help save time and effort in clinic while also improving patient outcomes and quality of life.⁵ With the recognition of AID systems as the preferred insulin delivery method for not only T1D but recently T2D, now is the time for PCCs to reconsider how they use AID.⁵ PCCs can play an active role in implementing these systems in their own clinical practices, as well as in providing guidance to patients with diabetes who want to learn and collaborate more effectively with specialists.

Management of insulin therapy in primary care presents many challenges, including therapeutic inertia, insulin titration difficulties, and suboptimal adherence to insulin therapy, especially in those receiving MDI.^{6,7} Therapeutic inertia, when driven by a lack of treatment adjustment to reach glycemic targets, can be addressed in part with AID, which enables faster treatment intensification. Optimally, a basal insulin titration strategy involves twice-weekly self-titration adjustments supported by clinicians. This is not feasible in most primary care practices.⁸ Since some AID systems automate insulin titration, they enable more effective dose adjustment with fewer touchpoints between the patient and clinician. Median time to treatment intensification with insulin following an above-target glycated hemoglobin (HbA1c) ranged from 1.3 to 4.9 years for patients taking ≥ 2 oral antihyperglycemic drugs.⁹ The use of AID may help patients be more accepting of the change to insulin therapy by simplifying management compared with MDI.

CASE STUDY

A 45-year-old man with a 6-year history of T2D presents to his primary care clinic for a diabetes follow-up visit. The patient's HbA1c today is 9.1%, which is largely unchanged from his values during the past year, despite titration of basal insulin. His fasting blood glucose values average 80-90 mg/dL on most days.

The patient is currently taking metformin 2000 mg daily, glipizide extended-release 20 mg daily, empagliflozin 25 mg daily, and 65 units of insulin glargine daily. He previously had a severe adverse reaction to a glucagon-like peptide-1 (GLP-1) receptor agonist and is not a candidate for GLP-1 therapy. The patient understands that he needs mealtime insulin to achieve glycemic control, but he is concerned about his ability to remember and accurately deliver mealtime injections.

In this case study, the patient is somewhat willing to intensify therapy by adding mealtime insulin to his diabetes regimen but has legitimate concerns. The use of an AID system could reduce his apprehension about remembering and accurately delivering mealtime insulin doses. While he did not mention injection burden, AID would automate his basal insulin injection, helping him achieve glycemic targets more safely and effectively. This is important due to his history of elevated HbA1c values.

EFFECTIVENESS OF AID SYSTEMS

AID systems offer the ability to achieve glycemic outcomes more quickly and effectively than MDI, addressing therapeutic inertia and problems with persistence that often accompany MDI, while protecting against hypoglycemia (**TABLE 1**).^{7,8,10-12} Additionally, AID systems can ease the burden of insulin use and management for both clinicians and patients. Some systems automatically titrate insulin delivery based on changing insulin needs and allow for a simplified bolus approach that minimizes the need for carbohydrate counting. Beyond glycemic endpoints, use of AID systems is associated with meaningful improvements in patient-reported outcomes, such as higher treatment satisfaction, improved quality of life, and reduced diabetes distress.

There are certain limitations and precautions that should be considered.¹³ AID systems require the user to wear multiple components, with a pump site and a sensor attached to the skin. While infrequently resulting in adverse events, technical problems can occur with each of the components—the insulin pump, the insulin, and the CGM device—and the algorithm may not always compensate completely for malfunctions.^{14,15} Alert fatigue from alarms (e.g., high or low glucose, battery life, and insulin remaining) and cost concerns are other challenges that patients may face.¹⁴ Additionally, patients, providers, and caregivers require special training, ideally with a certified diabetes educator, at regular intervals.

CLINICAL EVIDENCE FOR AID SYSTEMS IN T2D

Studies of AID systems have shown that they are effective and safe for improving glycemic outcomes in insulin-requiring T2D, including both clinical trials and real-world studies. Based on the outcomes of these studies, there are currently 3 AID systems approved for patients with T2D, key details of which are described in **TABLE 2**.¹⁶

Omnipod® 5

In the SECURE-T2D nonrandomized clinical trial, 305 adults with T2D from 21 clinical centers in the United States were enrolled to evaluate the association of tubeless AID with HbA1c.¹⁷ Participants were aged 18 to 75 years, had T2D, and had been using insulin for at least 3 months before screening; none had used AID prior to trial enrollment. Investigators intentionally enrolled participants across diverse racial, ethnic, and socioeconomic backgrounds, who not only reflect the US population with T2D but are also often underrepresented in clinical trials.

After a 14-day standard therapy phase, participants used the Omnipod 5 AID System for 13 weeks. Following AID use, HbA1c levels decreased from a mean of 8.2% at baseline to 7.4% at 13 weeks ($P < .001$), and time in range (TIR) (70-180 mg/dL) increased from a mean of 45% to 66% ($P < .001$). These

TABLE 1. Comparison of approaches for insulin delivery in diabetes.

Dimension	Insulin injection therapy	CSII pumps	AID systems
Hypoglycemia prevention strategy	Reactive, limited, and relies on patient vigilance	Smaller increments of insulin dosing but still limited prevention	Proactive, with reduction or suspension of insulin based on CGM
Adaptable to changing insulin needs	Unable to adapt	Manual, temporary basal rates and corrections	Some systems adapt automatically without PCC or patient input
Daily cognitive load for patient	High (carbohydrate counting, dose calculations, estimating active insulin) ¹⁰	High (carbohydrate entry, basal tuning, frequent manual corrections)	Reduced, automation handles corrections based on predicted trends in CGM values
Flexibility to personalize therapy	Yes, but burden to remember different carbohydrate ratios or targets sits with patient for daily dose decisions	Yes, can program different settings by time of day into pump, requires manual adjustments	Yes, some systems offer personalized glucose target options to avoid compromising, algorithm softens math on daily basis
Need to wear devices	No, CGM optional	Yes, pump; CGM optional	Yes, pump and CGM
Lifestyle flexibility	Limited given long-acting insulin profiles	Moderately flexible, tubing and infusion sets can be limiting	Higher flexibility; exercise and sleep modes along with automation support variable lifestyles
Discreetness	No visible device, patients report hesitations around delivering injections in social settings	Pump may be visible, tubing may be inconspicuous, many patients prefer tubeless form factor	Pump may be visible, most patients prefer tubeless form factor, CGM may be inconspicuous
Ongoing titration needed	Yes, full reliance on manual titration continuously	Yes, full reliance on manual adjustment of pump settings	Reduced significantly; though settings should be reviewed periodically to optimize or troubleshoot
Data visibility and remote monitoring	Minimal (SMBG logs)	Some (pump downloads, SMBG logs, optional CGM reports)	Rich (CGM + insulin delivery reports), enables virtual care

Abbreviations: CSII, continuous subcutaneous insulin infusion; SMBG, self-monitoring of blood glucose.

glycemic improvements occurred alongside a reduction in total daily insulin requirements with a change from a mean of 0.80 u/kg/d at baseline to 0.57 u/kg/d with AID ($P < .001$).¹⁷

A subanalysis of SECURE-T2D evaluated outcomes in participants who previously used basal-only (without bolus) insulin.¹⁸ Of the 305 participants enrolled, 63 used basal-only insulin. HbA1c decreased from a mean of 8.6% at baseline to 7.5% ($P < .001$) and mean TIR (70-180 mg/dL) increased from 40% to 64%. Total daily insulin was reduced by 6.3 units per day ($P = .04$) with negligible weight gain of 0.9 kg ($P = .03$).¹⁸ Outcomes improved regardless of GLP-1 receptor agonist or sodium-glucose cotransporter-2 (SGLT-2) inhibitor use.¹⁷

Another study evaluated the Omnipod 5 in a 26-week extension phase, following an 8-week single-arm trial in patients with T2D and baseline HbA1c $\geq 8\%$.¹⁹ From baseline through the end of the extension phase, HbA1c decreased by 1.6% ($P < .0001$) and TIR increased by 22.4% ($P < .0001$) with Omnipod 5. There were no significant changes in body mass index (BMI) or increases in total daily insulin requirements, demonstrating positive longer-term outcomes with Omnipod 5 use in T2D.

A real-world study of the Omnipod 5 System in adults

with T2D was a retrospective analysis of 23,664 patients who had ≥ 90 days of sufficient CGM data ($\geq 75\%$ of days with ≥ 220 readings).²⁰ Those using the 110 mg/dL target glucose setting achieved the highest TIR (68%), followed by the 120 mg/dL setting (63%), and the 130-150 mg/dL setting (55%). There were improvements in the glucose management indicator (GMI)²¹ for those with higher self-reported baseline HbA1c levels, while those meeting the HbA1c clinical target at baseline maintained a low GMI with Omnipod 5.²⁰

Control-IQ+ (Mobi or t:slim X2)

In a 13-week multicenter randomized trial, 319 adults with insulin-treated T2D were assigned 2:1 to AID with Control-IQ+ or to continue their usual insulin-delivery method, with both groups using CGM.²² At 13 weeks, AID produced a larger HbA1c reduction than control (-0.9% vs -0.3% ; adjusted difference -0.6% ; $P < .001$). TIR (70-180 mg/dL) increased with AID (48% to 64%) but was essentially unchanged in the control group (51% to 52%). Other CGM hyperglycemia metrics favored AID. Hypoglycemia was uncommon in both groups, with 1 severe event in the AID group.²² Additionally, a reduction in mean total daily insulin dose was observed in the AID

group (95 to 87 units per day) compared to the control group (102 to 104 units per day), and mean body weight increased from baseline in the AID group (+2.4 kg) compared to the control group (+0.9 kg).²²

Another randomized study of the t:slim X2 pump with Control-IQ+ in adults with insulin-treated T2D stratified participants by C-peptide status into high (n=195) and low (n=59) groups.²³ AID reduced HbA1c by 0.8% from baseline and achieved significantly greater HbA1c improvement than control in both the high ($P < .001$) and low ($P = .02$) C-peptide subgroups, with similar findings in adults ≥ 65 years.²³

MiniMed 780G

A 13-site, single-arm, open-label study evaluated the safety and effectiveness of the MiniMed 780G AID in 95 adults with insulin-requiring T2D previously using basal-bolus insulin. After a ~21-day run-in and ~90-day study period, mean HbA1c decreased from 7.9% to 7.2% ($P < .001$), and TIR (70-180 mg/dL) during the last 6 weeks reached 80.9% (95% CI: 78.4%, 83.1%), meeting prespecified effectiveness criteria

($P < .001$). Total daily insulin dose increased by 14 units/day, with no significant changes in weight or BMI. No severe hypoglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic state, or serious/unanticipated device-related adverse effects were reported, supporting safe insulin intensification and improved glycemic outcomes.²⁴

A real-world analysis of de-identified US CareLink data evaluated glycemic outcomes in 8542 MiniMed 780G users with either T1D or T2D who were aged ≥ 65 years. It showed a mean TIR (70-180 mg/dL) of 78.4% with very low time below range (0.9%) and a GMI of 6.8%.²⁵ Users with recommended optimal settings (100 mg/dL target and 2-hour active insulin time; n=2753) achieved higher TIR and time in tight range (70-140 mg/dL; 81.9% and 55.9%) and lower hyperglycemia metrics vs users who did not use recommended optimal settings (all $P < .001$). Similar patterns were seen in those ≥ 75 years, with no meaningful differences between people with T1D vs T2D, supporting that AID can help older adults meet consensus glycemic targets and that optimal settings further improve control.²⁵

TABLE 2. Comparison of AID systems approved for T2D.¹⁶

Characteristic	Omnipod 5	Tandem Control-IQ+ (Mobi or t:slim X2)	MiniMed 780G
CGM type	Dexcom G6, Dexcom G7, FreeStyle Libre 2 Plus Sensor, FreeStyle Libre 3 Plus Sensor	Dexcom G6, Dexcom G7, FreeStyle Libre 3 Plus Sensor	Guardian 4, Simplerla Sync, Abbott Instinct
CGM wear	10-15 days (Dexcom) 14-15 days (Libre) Dexcom G6: reusable transmitter with battery life of 3 months Dexcom G7: disposable transmitter Libre: disposable transmitter	10-15 days (Dexcom) 14-15 days (Libre) Dexcom G6: reusable transmitter with battery life of 3 months Dexcom G7: disposable transmitter Libre: disposable transmitter	7 days (Guardian 4, Simplerla Sync) 15 days (Instinct) Reusable transmitter needs to be charged between changes Disposable transmitter (Simplera Sync Sensor) also available Instinct: disposable transmitter
Real-time CGM data sharing	Dexcom Share or LibreLinkUp	Dexcom Share and/or Sugarmate	Medtronic Carelink Connect App, which also shows pump data
Considerations	If using a Dexcom sensor, requires Dexcom CGM run on a compatible phone in order to access Closed Loop in addition to PDM device and Pod on body, except when using a 15-day Dexcom G7, which can be used with the receiver Libre sensor can be directly connected and managed by the Omnipod controller Can use pharmacy benefit vs DME Only true tubeless option Also has auto-cannula insertion	Pump is metal and alarms in metal detectors CGM signal loss can be common if pump is facing away from CGM or toward body Remote bolusing is an option on the Tconnect app	Option for 7-day extended wear infusion set and cartridge Guardian 4 utilizes a reusable transmitter that requires charging in between sensor changes

Abbreviations: DME, durable medical equipment; PDM, Personal Diabetes Manager.

Note: Support for writing the prescription for components of the AID systems mentioned in this article and navigating prior authorization can be found at pro.diabeteswise.org.

Adapted from Town M, 2026.

GUIDELINE RECOMMENDATIONS FOR AID USE IN T2D

Clinicians have often taken a “technology-forward” approach with T1D management, incorporating available advances into practice. In contrast, use of technology for insulin-requiring T2D patients has often been treated as a last resort. Recently, uptake of CGM in T2D has been increasing in primary care.²⁶ Similarly, AID systems are commonly used in patients with T1D but less often in insulin-requiring adults with T2D, despite mounting evidence supporting AID use.²⁷ One analysis of studies on the Omnipod 5 System in patients with T1D or T2D found that, across clinical studies, there was no difference in TIR or HbA1c outcomes by diabetes type, after accounting for baseline HbA1c.²⁸

In the 2026 American Diabetes Association (ADA) *Standards of Care*, AID is noted as the preferred insulin delivery system for both those with T1D and those with insulin-requiring T2D. Key ADA recommendations are as follows⁵:

- AID systems are suggested for individuals on MDI and those with other forms of insulin-deficient diabetes.
- Consider AID systems for those people with T2D treated with basal insulin not achieving individualized glycemic goals.
- People with T2D who continue to produce insulin have been shown to benefit from AID. There should be no requirement of C-peptide level, presence of islet autoantibodies, or duration of insulin treatment before initiation of AID.
- Choice of an AID system should be made based on the individual’s circumstances, preferences, and needs.

HOW TO USE AID IN PRIMARY CARE

While implementing AID in primary care may be unfamiliar to many, the overall process is straightforward and similar to other medical devices and diabetes technology, such as CGM. Patients who are prescribed AID should receive education and counseling on what to expect, how to use the technology, and how they will receive the equipment. In contrast to CGM, for which patients can often self-educate with provided training materials, AID instruction usually requires a trained diabetes educator.⁵ For those new to AID systems, manufacturers of the devices support patient training and use. Explaining the nuances of the systems used for AID can help patients select the one that best suits their needs, as well as prepare them to use it correctly.¹³ Essential discussion points include how to use its data, the expected duration of each wearable, and basic troubleshooting for technical issues.¹³

A rule-in approach for prescribing AID in T2D may be helpful; clinicians might consider clinical cues that indicate a

patient may benefit from AID, including those who:

- Require rapid-acting insulin in addition to basal insulin
- Want improved glycemic control without increased hypoglycemia
- Demonstrate recently unchanged HbA1c results, indicating a stall in progress
- Hope for a simpler and safer glycemic control regimen

PCCs can prescribe AID systems electronically, sometimes requiring a statement of medical necessity and prescription order.^{29–31} Other clinic staff can assist the patient in navigating insurance coverage and obtaining the AID, as well as providing training on proper use. While clinicians do not need to understand all the intricacies of how AID algorithms work, it is important to be familiar with the parameters that can be adjusted to optimize insulin delivery, as these differ by system.¹³ Details and instructional resources for clinicians and patients are available on the manufacturers’ websites.^{29–31}

AID systems offer PCCs a way to achieve glycemic targets safely and more effectively than with injection therapy, automate titration in between clinic visits, and reduce the burden for people living with T2D. After completing the process of prescribing and monitoring an AID system even once, each subsequent effort becomes easier and more familiar.

SUMMARY

AID offers a practical and meaningful way to improve diabetes management in the primary care setting, where most adults with T2D are treated. It combines an insulin pump, a CGM device, and a dosing algorithm to automate insulin delivery. For patients, AID offers simplification and reduced burden, with adaptive systems that adjust insulin delivery to a patient’s need outside of clinician touchpoints.

Clinical trials and real-world studies in insulin-requiring T2D show significant improvements in HbA1c and TIR, with low hypoglycemia risk in older adults, independent of C-peptide level.

Implementation of AID is similar to that of other diabetes technologies. It uses a “rule-in” approach for patients who need treatment intensification, struggle with injections, or seek simpler and safer glycemic control. Implementation requires education, training, and support for clinicians and patients and relies on a team that includes a diabetes educator. Goals encompass coordination of coverage support, optimization of the AID settings, and integration with typical workflows.

For additional information on AID systems, readers are directed to the 2022 Consensus Recommendations for the Use of Automated Insulin Delivery Tech-

nologies in Clinical Practice, freely accessible online: <https://academic.oup.com/edrv/article/44/2/254/6692818>.³² ●

REFERENCES

- National diabetes statistics report. Centers for Disease Control and Prevention. January 21, 2026. Accessed May 15, 2026. <https://www.cdc.gov/diabetes/php/data-research>
- Primary care diabetes lab. University of Colorado Anschutz. Accessed May 15, 2026. <https://medschool.cuanschutz.edu/practice-innovation-program/current-initiatives/primary-care-diabetes-lab/about>
- Rushforth B, McCrorie C, Glidewell L, Midgley E, Foy R. Barriers to effective management of type 2 diabetes in primary care: qualitative systematic review. *Br J Gen Pract*. 2016;66(643):e114-127. doi:10.3399/bjgp16X683509
- Oser SM, Oser TK. Diabetes technologies: we are all in this together. *Clin Diabetes*. 2020;38(2):188-189. doi:10.2337/cd19-0046
- American Diabetes Association Professional Practice Committee for Diabetes. 7. Diabetes technology: standards of care in diabetes—2026. *Diabetes Care*. 2026;49(Supplement_1):S150-S165. doi:10.2337/dc26-S007
- Gavin JR, Abaniel RM, Virdi NS. Therapeutic inertia and delays in insulin intensification in type 2 diabetes: a literature review. *Diabetes Spectr*. 2023;36(4):379-384. doi:10.2337/ds22-0084
- Robinson S, Newson RS, Liao B, Kennedy-Martin T, Battelino T. Missed and mistimed insulin doses in people with diabetes: a systematic literature review. *Diabetes Technol Ther*. 2021;23(12):844-856. doi:10.1089/dia.2021.0164
- Boonpattharathiti K, Wechkunanukul K, Mayang N, et al. Comparison of insulin titration strategies for glycemic control in type 2 diabetes: a systematic review and network meta-analysis. *Diabetes Care*. 2025;48(5):837-845. doi:10.2337/dc24-2661
- Khunti K, Gomes MB, Pocock S, et al. Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: a systematic review. *Diabetes Obes Metab*. 2018;20(2):427-437. doi:10.1111/dom.13088
- Brixner D, Edelman SV, Sieradzan R, Gavin JR. Addressing the burden of multiple daily insulin injections in type 2 diabetes with insulin pump technology: a narrative review. *Diabetes Ther*. 2024;15(7):1525-1534. doi:10.1007/s13300-024-01598-3
- Flatt AJ, Peleckis AJ, Dalton-Bakes C, et al. Automated insulin delivery for hypoglycemia avoidance and glucose counterregulation in long-standing type 1 diabetes with hypoglycemia unawareness. *Diabetes Technol Ther*. 2023;25(5):302-314. doi:10.1089/dia.2022.0506
- Bilal A, Osorio S, Casu A. Severe hypoglycemia in insulin-treated type 2 diabetes: a call to revisit diabetes education. *Diabetes Care*. 2026;49(2):236-238. doi:10.2337/dci25-0117
- Sherr JL, Heinemann L, Fleming GA, et al. Automated insulin delivery: benefits, challenges, and recommendations. A consensus report of the Joint Diabetes Technology Working Group of the European Association for the Study of Diabetes and the American Diabetes Association. *Diabetes Care*. 2022;45(12):3058-3074. doi:10.2337/dci22-0018
- Heile M, Hollstegge B, Broxterman L, Cai A, Close K. Automated insulin delivery: easy enough to use in primary care? *Clin Diabetes*. 2020;38(5):474-485. doi:10.2337/cd20-0050
- Zhang X, Reid JL, Walker TC, Welsh J, Balo A. 648-P: lag times in a seventh-generation continuous glucose monitoring system. *Diabetes*. 2022;71(Supplement_1):648-P. doi:10.2337/db22-648-P
- Town M. Looking at automated insulin delivery systems. Children with Diabetes. May 14, 2026. Accessed May 15, 2026. <https://childrenwithdiabetes.com/cwd-news/automated-insulin-delivery-systems-2024/>
- Pasquel FJ, Davis GM, Huffman DM, et al. Automated insulin delivery in adults with type 2 diabetes: a nonrandomized clinical trial. *JAMA Netw Open*. 2025;8(2):e2459348. doi:10.1001/jamanetworkopen.2024.59348
- Carlson AL, Pasquel FJ, Davis GM, et al. 945-P: Improved glycemic outcomes with the Omnipod 5 AID system in adults with type 2 diabetes (T2D) previously using basal without bolus insulin—subanalysis of the SECURE-T2D Study. *Diabetes*. 2025;74(Supplement_1):945-P. doi:10.2337/db25-945-P
- Davis GM, Peters AL, Bode BW, et al. Glycaemic outcomes in adults with type 2 diabetes over 34 weeks with the Omnipod® 5 automated insulin delivery system. *Diabetes Obes Metab*. 2025;27(1):143-154. doi:10.1111/dom.15993
- Oser SM, Peters AL, Pasquel FJ, et al. Real-world glycemic outcomes in adults with type 2 diabetes (T2D) using the Omnipod 5 automated insulin delivery (AID) system. *Diabetes*. 2025;74(Supplement_1):130-OR. <https://doi.org/10.2337/db25-130-OR>
- Bergental RM, Beck RW, Close KL, et al. Glucose management indicator (GMI): a new term for estimating A1C from continuous glucose monitoring. *Diabetes Care*. 2018;41(11):2275-2280. doi:10.2337/dc18-1581
- Kudva YC, Raghinaru D, Lum JW, et al. A randomized trial of automated insulin delivery in type 2 diabetes. *N Engl J Med*. 2025;392(18):1801-1812. doi:10.1056/NEJMoa2415948
- Hirsch IB, Kudva YC, Ahn DT, et al. Adults with type 2 diabetes benefit from automated insulin delivery irrespective of C-peptide level. *Diabetes Care*. 2025;48(12):2061-2066. doi:10.2337/dc25-1125
- Bhargava A, Bergenstal RM, Warren ML, et al. Safety and effectiveness of MiniMed™ 780G advanced hybrid closed-loop insulin intensification in adults with insulin-requiring type 2 diabetes. *Diabetes Technol Ther*. 2025;27(5):366-375. doi:10.1089/dia.2024.0586
- Chien A, Shin JJ, Liu M, et al. Real-world effectiveness of the MiniMed™ 780G advanced hybrid closed-loop system for people ≥65 years with type 1 or type 2 diabetes in the United States. *Diabetes Technol Ther*. 2025;27(12):989-996. doi:10.1177/15209156251376654
- Mayberry LS, Guy C, Hendrickson CD, McCoy AB, Elasy T. Rates and correlates of uptake of continuous glucose monitors among adults with type 2 diabetes in primary care and endocrinology settings. *J Gen Intern Med*. 2023;38(11):2546-2552. doi:10.1007/s11606-023-08222-3
- Lumb AN. Now is the time to remove barriers to AID treatment for those with detectable C-peptide. *Diabetes Care*. 2025;48(12):2007-2009. doi:10.2337/dci25-0108
- Shah VN, Laffel LM, Carlson AL, et al. How do outcomes with the Omnipod® 5 automated insulin delivery (AID) system compare for persons with type 1 versus type 2 diabetes? Learnings across studies. *Diabetes Technol Ther*. 2025;27(S2):e108-e109.
- Control-IQ+ technology. Tandem Diabetes Care. Accessed May 15, 2026. <https://www.tandemdianabetes.com/products/automated-insulin-delivery/control-iq-plus>
- Simplify life with Omnipod. Insulet. Accessed May 15, 2026. <https://www.omnipod.com/what-is-omnipod/omnipod-5>
- Life with type 2 diabetes just got easier: people who use insulin can experience automation with the MiniMed™ 780G system. Medtronic. Accessed May 15, 2026. <https://www.medtronicdiabetes.com/products/minimed-780g-system-type-2-diabetes>
- Phillip M, Nimri R, Bergenstal RM, et al. Consensus recommendations for the use of automated insulin delivery technologies in clinical practice. *Endocr Rev*. 2023;44(2):254-280. doi:10.1210/edrv/bnac022

CGM in Primary Care: From Data to Decisions

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

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

- **Apply** accurate strategies for interpreting continuous glucose monitoring (CGM) data to inform diabetes treatment decisions and support integration of CGM into clinical practice.
- **Integrate** CGM into routine care of patients with diabetes in primary care settings and understand who would benefit from CGM use.
- **Describe** new and emerging CGM technologies, including longer wear, over-the-counter CGM devices, and continuous ketone monitoring, including how they can be integrated into clinical practice.
- **Collaborate** with the multidisciplinary health care team for diabetes care and incorporation of CGM into diabetes management.

TARGET AUDIENCE

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

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Davida F. Kruger serves as a consultant for Abbott Diabetes, Ascencia, Insulet, Lilly, MannKind, and Medtronic. She is on the speakers bureaus of Abbott, CeQur, Corcept, Dexcom, Insulet, Lilly, Luna, Novo, Sanofi, Sequel, and Tandem. She participates in institutional research for Abbott, Insulet, Sequel, and Tandem.

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Visit <https://www.pcmg-us.org/toolkit/cgm> for a resource toolkit.

References from this article, including the described video, are available from the toolkit.



INTRODUCTION

Diabetes affects an estimated 38.4 million people in the United States, with 22.8% of adults undiagnosed.¹ Approxi-

mately 90% of diabetes care in the United States occurs in the primary care setting, indicating that the majority of patients with diabetes are managed by primary care clini-

Key takeaways

- CGM offers numerous benefits to patients and clinicians, including increased engagement in diabetes care, improved health behaviors, better indicators of glucose management, and improved clinical outcomes.
- Every patient with diabetes will benefit from using CGM; CGM insurance coverage is possible for many, and the cash price is often affordable.
- Over-the-counter CGM devices are newer technologies that may help patients access CGM, although limitations in glucose measurement ranges and data sharing should be considered.
- Continuous glucose-ketone monitoring is a newer tool that may help prevent and manage diabetic ketoacidosis, pending US Food and Drug Administration approval.
- Clinicians should seek to empower patients and members of the health care team to utilize CGM data for improved clinical care of diabetes.

cians (PCCs).² The need for PCCs in diabetes care is emphasized by the shortage of endocrinologists available to treat diabetes.³

Progress in the understanding of diabetes pathophysiology and new treatments have advanced the care of patients with type 1 diabetes (T1D) and type 2 diabetes (T2D), yet many patients still do not achieve glycemic targets.⁴ Diabetes technology, including continuous glucose monitoring (CGM), has also improved overall care of patients with diabetes in recent years and has the potential to make a larger impact with optimal implementation in primary care settings.⁵ The American Diabetes Association (ADA) and the American Association of Clinical Endocrinology (AACE) recommend the use of CGM for many patients with diabetes and recognize the benefits of CGM use.^{6,7}

CASE STUDY 1

A 42-year-old woman with a 5-year history of T2D and a glycated hemoglobin (A1c) of 8.2% presents to her primary care clinic for a routine diabetes follow-up. She is currently taking metformin 2000 mg daily, empagliflozin 25 mg daily, and insulin glargine 30 units daily.

Her A1c has improved over the past few years from treatment intensification, but she feels that her diet and exercise could be further enhanced and she heard that CGM may help with regulating her blood glucose. She asks her PCC about CGM and what her options might be.

In this case study, the patient is an excellent candidate for CGM. As her primary care team describes CGM and helps her access the technology, she is likely to benefit from using CGM. The detailed information on blood glucose patterns helps to inform treatment decisions, as well as lifestyle behaviors, in patients with diabetes.⁸

The usefulness and benefits of CGM are increasingly recognized in monitoring and treating patients with T2D. The ADA 2026 *Standards of Care in Diabetes* recommends that CGM should be used in patients with diabetes who are 1) on insulin therapy, 2) on noninsulin therapies that can cause hypoglycemia, and 3) on any diabetes treatment in which CGM helps in management.⁶ These recommendations are based on data from randomized controlled trials, real-world studies, and observational analyses.^{6,9}

CGM is associated with many benefits for patients with diabetes, including improved health behaviors, reductions in A1c, less hypoglycemia, decreases in body weight, reduced caloric intake, increased physical activity, improved treatment satisfaction, and adherence to a personal eating plan.⁵ For clinicians, CGM benefits include increased patient engagement, better hypoglycemic awareness and improved prevention, greater insight into therapeutic impacts on glucose management, and use of the ambulatory glucose profile (AGP), a compiled analysis of the data for enhanced understanding of glucose patterns that can aid in data visualization.¹⁰ Additionally, in patients for whom A1c measurements are less reliable, such as those with hemoglobinopathies, CGM is a valuable option for assessing glycemic control.¹¹

Despite these benefits, rates of CGM use remain low, with a 2021 retrospective study finding that only about 13% of patients with T2D had used CGM.¹² Patients who used CGM were more likely to receive care in endocrinology compared to primary care in the study (35.7% vs 23.2%, respectively). Among patients who were not taking insulin, new CGM prescriptions were more common in primary care (28%) than in endocrinology (5%). Notably, the number of patients being prescribed CGM in primary care settings grew at a more rapid rate from 2020 to 2021 (125%) than in endocrinology (5%), highlighting the potential impact of widespread implementation of CGM in primary care.¹²

USING CGM IN PRACTICE: THE AGP AND ADJUSTING TREATMENT

While A1c and fingerstick blood glucose levels continue to be utilized, they are point-of-care metrics and are limited because they do not provide real-time glucose data, variability, and AGP analysis that CGM offers. CGM metrics measured and reported in the AGP are important and more comprehensive indicators for diabetes management.⁵

CASE STUDY 2

A 68-year-old man with a 10-year history of T2D and chronic kidney disease who is using CGM presents to his PCC with the most recent AGP report available. He takes metformin 2000 mg daily, empagliflozin 10 mg daily, and insulin glargine 34 units daily. He is unable to tolerate glucagon-like peptide-1 receptor agonists.

The AGP shows trends of 81% time in range (TIR) (70–180 mg/dL), 18% high (181–250 mg/dL), and 1% low (54–69 mg/dL) with CGM active 89% of the time (FIGURE 1). Upon closer examination, the PCC notices several days of low glucose readings occurring in the morning, as early as 5:00 am and as late as 11:30 am (FIGURE 2). The patient's A1c today is 6.8%, achieving the goal of <7.0%.

In this case study, the patient is achieving his A1c goal and has an overall well-managed glycemic profile, based on the AGP report. However, he is having occasional low blood glucose readings some mornings a few hours after breakfast. While the patient was able to manage these hypoglycemic episodes at home, a reduction in his insulin glargine (e.g., to 28 units daily) will help improve the safety of his treatment regimen, while retaining adequate glucose control for his goals. A collaborative discussion about his lifestyle behaviors that may have prompted hypoglycemic events (such as delayed meals and increased activity) may also be helpful. Of note, based only on A1c measurements, the insulin regimen may not have been adjusted, but with the additional information provided by CGM, a need for adjustment was identified.

Understanding the AGP is an essential component of incorporating and applying CGM use in diabetes management. The AGP provides CGM summary statistics such as the average glucose, glucose management indicator, and percentage of time the CGM is active over a given time period (usually about 14–15 days).¹³ The aggregated glucose profile shows variability in the mean glucose and patterned areas of highs and lows, displaying all values as if collected over a single 24-hour period.⁶

Metrics reported in the AGP that may assist with an assessment of blood glucose control and inform treatment adjustments include^{8,14}:

- **Number of days the sensor is active:** recommended minimum duration is 14 consecutive days.
- **Percentage of sensor data captured:** for reliable analysis of glycemic indices, recommended minimum is 70%.
- **Mean glucose concentration:** mean value of glucose measurements during the period analyzed.

- **Glucose management indicator:** assesses glycemic control based on mean glucose levels.
- **Glucose variability:** variance in glucose measurements during the time period analyzed.
- **Time above target glucose range:** percentage of time during the analyzed period when glucose is above a certain threshold (e.g., 180 mg/dL [high], <25%; or 250 mg/dL [very high], <5%).¹⁵
- **TIR:** percentage of time during the analyzed period when glucose is within a certain range (e.g., 70–180 mg/dL [target range], >70%).¹⁵
- **Time in tight range:** percentage of time during the ana-

FIGURE 1. AGP report for case study 2.

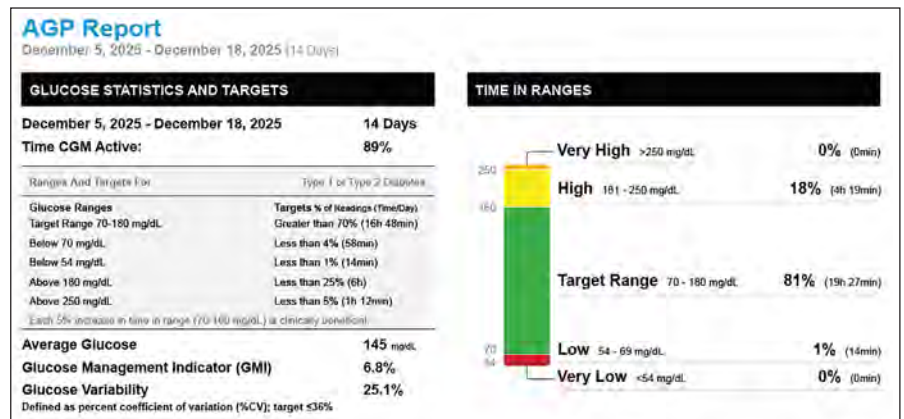
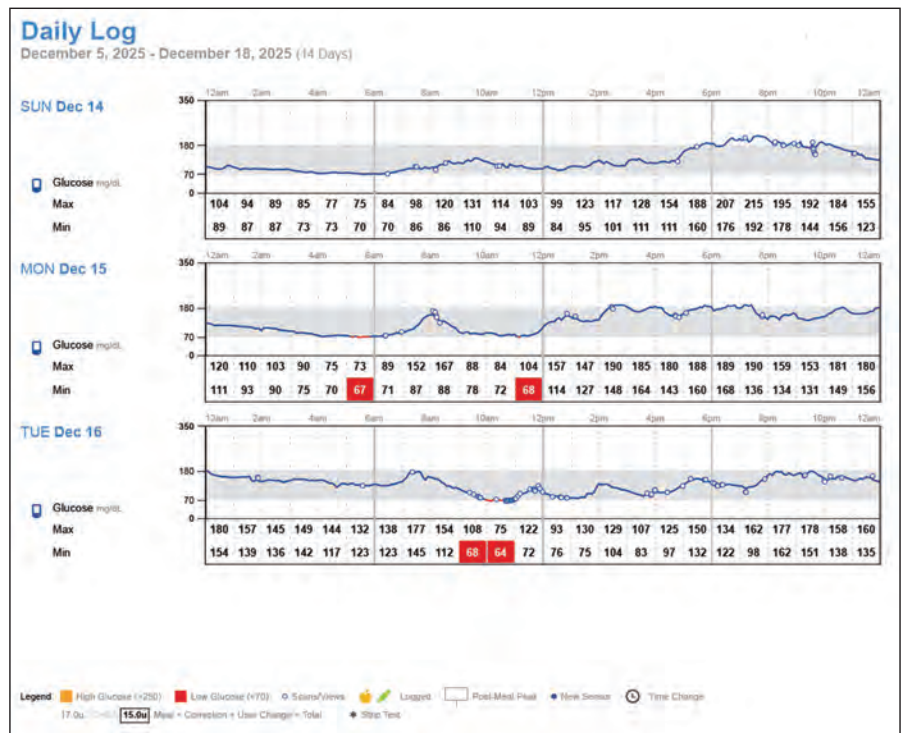


FIGURE 2. AGP report for case study 2.



lyzed period when glucose is within a narrower range than TIR; may be more appropriate when glucose levels are closer to normal or tighter glycemic control is required.¹⁶

- **Time below target glucose range:** percentage of time during the analyzed period when glucose is below a certain threshold (e.g., 70 mg/dL [low], <4%; or 54 mg/dL [very low], <1%).¹⁵

Over-the-counter (OTC) CGM devices provide similar data to an AGP report, though the objective of these devices is typically to deliver patient-focused information about how diet and lifestyle impacts blood glucose, rather than information to evaluate treatment modification.¹⁷ In this sense, OTC CGM devices may be more appropriate for patients who are less dependent on glucose trends for treatment adjustments, such as those who are not receiving multiple daily insulin injections. Notably, OTC CGM devices are intended for people with prediabetes and those who are not using insulin; they are discussed in more detail below.

PRACTICAL TIPS FOR INTEGRATING CGM INTO PRIMARY CARE PRACTICE

Identifying the right patient for CGM is critical. Patients who are good candidates for a CGM might include those who¹⁸:

- Need or want more engagement with their diabetes.
- Are at risk for hypoglycemia (e.g., patients of younger or older age, patients taking insulin).
- Need modification of current treatment or are experiencing clinical inertia.
- Have poorly managed diabetes and would benefit from greater understanding of diet, activity, and medication on glycemic management.
- Want to actively participate in their diabetes care, including making lifestyle changes.

Every person with diabetes could benefit from the information offered by a real-time CGM, but not all patients may be able to obtain a CGM or be willing to wear one. A key benefit of using CGM in any patient with diabetes is addressing clinical inertia; CGM can help facilitate interventions in patients who may otherwise see little change in their blood glucose control.¹⁹

Cost and lack of insurance coverage prevents many patients from using CGM. Clinicians can help Medicare patients navigate these challenges. In 2023, the Centers for Medicare & Medicaid Services expanded coverage for CGM to allow any Medicare patient using insulin to have access to a CGM device and related services.²⁰

Appropriate coding and reimbursement processes can also help support clinic time spent on CGM implementation and monitoring. Coding for CGM includes the following²¹: 95249: personal CGM start-up and training; 95250: profes-

sional CGM; 95251: CGM interpretation; 99212-99215: evaluation and management of CGM.

Furthermore, involving the health care team can improve diabetes outcomes and access to CGM. This includes incorporating clinic staff such as nurse practitioners, physician associates, nurses, pharmacists, and diabetes educators to assist with patient education and access to CGM and referring to specialists when necessary.²²

To understand patient perspectives on CGM use and its application in practice, visit <https://www.pcmg-us.org/toolkit/cgm>, where a patient with diabetes explains their CGM journey, including the health benefits since starting CGM, the process of accessing and obtaining CGM, and perspectives about interactions with clinicians about their CGM.

NEW AND EMERGING CGM TECHNOLOGIES

CGM technologies began with the first CGM device approval in the US in 1999 and have continued to evolve over the past few decades.^{17,23,24} Notable recent advances include OTC CGM devices and continuous glucose-ketone monitoring. Additionally, insulin pump integration is another benefit of certain CGM devices for patients who use insulin pumps. There are currently several CGM and insulin pump devices that automatically adjust insulin dosing based on CGM data to predict future glucose levels and reduce the risk of hyperglycemia and hypoglycemia.^{25,26}

OTC CGM devices

One reason OTC CGM devices have been developed is to expand use of CGM to those who do not qualify for insurance coverage of CGM because they have prediabetes or are not using insulin. Some have suggested that these OTC technologies may bridge the gap in access to wearable glucose-monitoring technologies in select populations.¹⁷ Differentiating between the available OTC CGM products can help clinicians determine which may be most appropriate for certain patients.¹⁷

Three OTC CGM devices are currently approved: the Stelo Glucose Biosensor System, the Lingo Continuous Glucose Monitor, and the Libre Rio Continuous Glucose Monitoring System (**TABLE 1**).¹⁷ Lingo is intended for healthy individuals who want to track blood glucose for overall health and wellness. Libre Rio was created for those with prediabetes or patients with diabetes who do not use insulin. Stelo is intended for patients who are aged 18 years or older with diabetes and who do not use insulin.¹⁷

Continuous ketone monitoring

Both patients with T1D and T2D are at risk for acute complications such as diabetic ketoacidosis (DKA).²⁷ DKA is a

TABLE 1. Characteristics of currently approved OTC CGM devices.¹⁷

Characteristic	Lingo Continuous Glucose Monitor	Libre Rio Continuous Glucose Monitoring System	Stelo Glucose Biosensor System
Duration of wear	14 days	15 days	15 days (+12-hour grace period)
Frequency of measured glucose	Every 15 minutes	—	Every 15 minutes
Glucose measurement range	55-200 mg/dL	40-400 mg/dL	70-250 mg/dL
Smart device compatibility ^a	Yes	No	Yes
Alarm for low/high glucose levels	No	No	No
Data sharing	Download and export	—	Connects to Clarity software
Patient population	Aged ≥ 18 y and healthy	Aged ≥ 18 y with prediabetes or diabetes who are not on insulin	Aged ≥ 18 y with diabetes who are not on insulin
Mean monthly retail price, \$	89 ^b	—	89 ^b
Mean absolute relative difference, %	8.4%	—	8.3%

Abbreviation: USD, United States dollar.

^aUsers must have a compatible smartphone; no separate data readers are available.

^bSubscription required for pricing shown; can be purchased in a 3-month subscription for an additional discount.

Adapted from Arriazola J et al, 2025.

life-threatening metabolic emergency resulting from insulin deficiency and increased ketogenesis, characterized by hyperglycemia, metabolic acidosis, and dehydration.²⁷⁻²⁹

While traditional blood and urine ketone testing has enabled detection of DKA, these methods are rarely used, and emerging continuous ketone monitoring (CKM) technologies, including combined glucose-ketone monitoring sensors, promise enhanced real-time assessment, trend analysis, and early intervention to predict and prevent DKA.^{27,30,31} While knowledge of CKM remains limited among clinicians, this has been an active area of research and development for years, including the publication of a CKM consensus report in 2021 and international expert recommendations published in January 2026.^{32,33}

Ketone monitoring is critical to early detection of DKA, but it is rarely done in practice, as the traditional methods for testing are cumbersome and have several limitations. Historically, detection of ketosis has relied on either urine or blood ketone testing (breath-based ketone testing has been studied but lacks evidence for medical use)²⁷:

- **Urine ketone testing:** This testing uses nitroprusside-based dipsticks to detect acetoacetate. While inexpensive and noninvasive, urine testing has several limitations: it reflects ketone accumulation over hours rather than real-time status, measures only a fraction (~20%) of circulating ketones, may produce false-positive or false-negative results due to interfering substances, and requires proactive patient initiation. These factors reduce sensitivity and may delay recognition of impending DKA.

- **Blood ketone testing:** Capillary blood measurement of β-hydroxybutyrate provides a more accurate assessment and better correlation with DKA risk. However, finger-prick testing is painful, inconvenient, requires strips with limited shelf life, and depends on patient adherence and awareness. Surveys of patients with T1D reveal that up to 64% do not routinely perform ketone testing at home, highlighting significant real-world barriers.^{34,35}

The reliance on episodic testing and its shortcomings in the real world indicate that clinicians may not fully understand the limitations of these approaches or their implications for early DKA detection and patient safety. CKM is poised to address the limitations of current approaches to ketone monitoring, as these devices are designed with many expert-recommended “desirable characteristics” of ketone testing methods (TABLE 2).^{27,32} Of note, a dual glucose-ketone sensing device was authorized by the FDA in August 2026 for people aged 2 years and older living with diabetes.³⁶

SUMMARY

PCCs play an increasingly important role in diabetes management in the United States. The use of CGM and data posted on the AGP report provide clinicians, patients, and caregivers more detailed information than historically available with A1c and traditional blood glucose testing alone. CGM and AGP reporting also provide blood glucose data when patients are not in a clinical setting (e.g., at home). Every person with diabetes will benefit from CGM, yet, unfortunately, not all have CGM covered by insurance.

TABLE 2. Desirable characteristics of ketone testing technologies.^{27,32}

Accurate at lower end of range
Relevant dynamic range (0-10 mmol/L)
Does not require user to initiate check
Provides trend information and alarms
Reliable (low failure rate)
Durable (similar life to other analyte sensors [7-14 d])
Minimally intrusive
Single insertion multianalyte platform
Signal integrated with other technologies (e.g., CGM, automated insulin delivery)
Factory calibrated
Cost effective

Increased adoption of CGM by PCCs will result in improved glycemic control for patients. New and emerging technologies in CGM include OTC CGM devices, CKM, and the prospect of continuous glucose-ketone monitoring. Expansion of the use of OTC CGM devices in those with prediabetes or diabetes without insulin use will further help patients collaborate with their clinicians to manage blood glucose levels. ●

REFERENCES

- National diabetes statistics report. Centers for Disease Control and Prevention. May 15, 2024. Accessed September 29, 2026. <https://www.cdc.gov/diabetes/php/data-research/index.html>
- Unger J, Kushner P, Anderson JE. Practical guidance for using the FreeStyle Libre flash continuous glucose monitoring in primary care. *Postgraduate Med*. 2020;132(4):305-313. doi:10.1080/00325481.2020.1744393
- Schaffer R. "We have to make it easy": barriers hinder CGM access for some people with diabetes. May 24, 2023. Accessed September 29, 2026. <https://www.healio.com/news/endocrinology/20230524/we-have-to-make-it-easy-barriers-hinder-cgm-access-for-some-people-with-diabetes>
- Carls G, Huynh J, Tuttle E, Yee J, Edelman SV. Achievement of glycated hemoglobin goals in the US remains unchanged through 2014. *Diabetes Ther*. 2017;8(4):863-873. doi:10.1007/s13300-017-0280-5
- Oser TK, Hall TL, Dickinson LM, et al. Continuous glucose monitoring in primary care: understanding and supporting clinicians' use to enhance diabetes care. *Ann Fam Med*. 2022;20(6):541-547. doi:10.1370/afm.2876
- American Diabetes Association Professional Practice Committee for Diabetes, Bajaj M, McCoy RG, et al. 7. Diabetes technology: standards of care in diabetes—2026. *Diabetes Care*. 2026;49(suppl 1):S150-S165. doi:10.2337/dc26-S007
- Grunberger G, Sherr J, Allende M, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: the use of advanced technology in the management of persons with diabetes mellitus. *Endocr Pract*. 2021;27(6):505-537. doi:10.1016/j.eprac.2021.04.008
- Simonson GD, Holt EH, Grady M, Hurrell G, Gaudiani LM, Bergenstal RM. Unleashing the potential of blood glucose monitoring data with the ambulatory glucose profile report. *Clin Diabetes*. 2024;42(4):550-560. doi:10.2337/cd23-0092
- Ferreira ROM, Trevisan T, Pasqualotto E, et al. Continuous glucose monitoring systems in noninsulin-treated people with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Technol Ther*. 2024;26(4):252-262. doi:10.1089/dia.2023.0390
- 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
- Mayberry LS, Guy C, Hendrickson CD, McCoy AB, Elasy T. Rates and correlates of uptake of continuous glucose monitors among adults with type 2 diabetes in primary care and endocrinology settings. *J Gen Intern Med*. 2023;38(11):2546-2552. doi:10.1007/s11606-023-08222-3
- Ajjan R, Slattery D, Wright E. Continuous glucose monitoring: a brief review for primary care practitioners. *Adv Ther*. 2019;36(3):579-596. doi:10.1007/s12325-019-0870-x
- Czupryniak L, Dzida G, Fichna P, et al. Ambulatory glucose profile (AGP) report in daily care of patients with diabetes: practical tips and recommendations. *Diabetes Ther*. 2022;13(4):811-821. doi:10.1007/s13300-022-01229-9
- 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
- Zhang Z, Wang Y, Lu J, Zhou J. Time in tight range: a key metric for optimal glucose control in the era of advanced diabetes technologies and therapeutics. *Diabetes Obes Metab*. 2025;27(2):450-456. doi:10.1111/dom.16033
- Arriazola J, Wollen J, Davis S, Wang EM, Tran G, Rosario N. Review of over the counter and prescription continuous glucose monitoring. *J Pharm Pract*. 2025;38(6):493-498. doi:10.1177/08971900251328832
- Chamberlain JJ. Patient selection for continuous glucose monitoring. In: *Role of Continuous Glucose Monitoring in Diabetes Treatment*. American Diabetes Association; 2018. <http://www.ncbi.nlm.nih.gov/books/NBK538972>
- Martens TW, Parkin CG. How use of continuous glucose monitoring can address therapeutic inertia in primary care. *Postgrad Med*. 2022;134(6):576-588. doi:10.1080/00325481.2022.2080419
- Glucose monitors (L33822). Centers for Medicare & Medicaid Services. October 9, 2024. Accessed December 18, 2024. <https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lclid=33822>
- Adkison JD, Chung PE. Implementing continuous glucose monitoring in clinical practice. *Fam Pract Manag*. 2021;28(2):7-14. <https://www.aafp.org/fpm/2021/0300/p7>
- Zadel AH, Chiampas K, Maktaz K, et al. Continuous glucose monitoring in primary care: multidisciplinary pilot implementation study. *JMIR Diabetes*. 2025;10:e69061. doi:10.2196/69061
- Bergenstal RM. Roadmap to the effective use of continuous glucose monitoring: innovation, investigation, and implementation. *Diabetes Spectr*. 2023;36(4):327-336. doi:10.2337/ds123-0005
- Jin X, Cai A, Xu T, Zhang X. Artificial intelligence biosensors for continuous glucose monitoring. *Interdiscip Mater*. 2023;2(2):290-307. doi:10.1002/idm2.12069
- Vetoretto 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
- CGM & pump integration. Association of Diabetes Care & Education Specialists (ADCES). January 25, 2025. Accessed September 29, 2026. <https://www.adces.org/danatech/insulin-pumps/training-clients-patients/cgm-pump-integration>
- Kong YW, Morrison D, Lu JC, Lee MH, Jenkins AJ, O'Neal DN. Continuous ketone monitoring: exciting implications for clinical practice. *Diabetes Obes Metab*. 2024;26(S7):47-58. doi:10.1111/dom.15921
- Dhatriya K. Blood ketones: measurement, interpretation, limitations, and utility in the management of diabetic ketoacidosis. *Rev Diabet Stud*. 2016;13(4):217-225. doi:10.1900/RDS.2016.13.217
- Jaromy M, Miller JD. Potential clinical applications for continuous ketone monitoring in the hospitalized patient with diabetes. *Curr Diab Rep*. 2022;22(10):501-510. doi:10.1007/s11892-022-01489-6
- Kerr D. Integrating ketone and glucose monitoring for optimized diabetes management: key ketone monitoring updates and highlights from the ADA 2025 Conference [Podcast]. *Diabetes Metab Syndr Obes*. 2025;18:2623-2628. doi:10.2147/DMSO.S555697
- American Diabetes Association. Panel to spotlight potential of continuous ketone monitoring. ADA Meeting News. June 11, 2025. Accessed September 29, 2026. <https://www.adameetingnews.org/panel-to-spotlight-potential-of-continuous-ketone-monitoring>
- Nguyen KT, Xu NY, Zhang JY, et al. Continuous ketone monitoring consensus report 2021. *J Diabetes Sci Technol*. 2022;16(3):689-715. doi:10.1177/19322968211042656
- Dhatriya K, Bergenstal RM, Al-Sofiani M, et al. Continuous ketone monitoring for people with diabetes: international expert recommendations on the application of a new technology. *The Lancet Diabetes Endocrinol*. 2026;14(1):82-92. doi:10.1016/S2213-8587(25)00331-6
- Hepprich M, Roser P, Stiebitz S, et al. Awareness and knowledge of diabetic ketoacidosis in people with type 1 diabetes: a cross-sectional, multicenter survey. *BMJ Open Diabetes Res Care*. 2023;11(6):e003662. doi:10.1136/bmjdr-2023-003662
- Albanese-O'Neill A, Wu M, Miller KM, et al. Poor adherence to ketone testing in patients with type 1 diabetes. *Diabetes Care*. 2017;40(4):e38-e39. doi:10.2337/dc16-2620
- US Food and Drug Administration. FDA authorizes first wearable device that continuously monitors both ketone levels and blood sugar. August 25, 2026. Accessed August 26, 2026. <https://www.fda.gov/news-events/press-announcements/fda-authorizes-first-wearable-device-continuously-monitors-both-ketone-levels-and-blood-sugar>

From Needles to Tablets: Integrating Oral Treatments Into Obesity Care

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INTRODUCTION

Obesity is a chronic disease characterized by excess adiposity that impairs health, and current estimates suggest the clinical burden will continue to expand over the coming decades in the United States.^{1,2} A recent cross-sectional analysis suggests that approximately 46.9% of US adults will be living with obesity by 2035, compared to 42.5% in 2022 and 19.3% in 1990.³ The consequences of obesity extend far beyond body weight alone to include cardiometabolic disease, obstructive sleep apnea, steatotic liver disease, osteoarthritis, physical limitations, and impaired quality of life.^{2,4}

Framing obesity as a chronic disease is essential when approaching treatment. Diagnostic and treatment algorithms emphasize that body mass index (BMI) remains a screening tool, though used in association with other measures such as waist-to-height ratio. Treatment should be individualized according to complications, health goals, and patient characteristics.^{2,5,6} As described in the “Comprehensive Obesity Management” series published in *Hot Topics in Primary Care 2025* (<https://www.medscape.com/infosites/432972.3>), obesity care is strengthened when clinicians use person-first language, ask permission to discuss weight, and structure management around the 5 As: Ask, Assess, Advise, Agree, and Assist.^{7,8}

Historically, oral obesity pharmacotherapy offered convenience but often only modest efficacy. Short-course phentermine, long-term orlistat, naltrexone/bupropion, and phentermine/topiramate remain clinically useful in selected patients, yet most oral options before the incretin era were limited by single-digit mean weight loss, contraindications, or adverse-effect profiles that narrowed long-term use.^{9,10}

Key takeaways

- Oral obesity pharmacotherapy now spans legacy agents that deliver modest weight loss and newer incretin-based therapies that can produce double-digit reductions in body weight.
- Choice of an oral obesity agent should be individualized based on efficacy, complications, route preference, dosing burden, gastrointestinal (GI) tolerability, cost, and expected long-term persistence.
- Successful implementation of oral obesity therapies involves approaching obesity as a chronic disease.
- Primary care clinicians (PCCs) should emphasize shared decision-making, appropriate dose titration, proactive mitigation of GI adverse events, nutrition and exercise, behavioral therapy if indicated, and regular follow-up when managing obesity with oral treatments.

Other oral obesity therapies were withdrawn from the market: sibutramine was removed after cardiovascular safety concerns, and lorcaserin left the market after a postmarketing safety review identified cancer signals.^{11,12} The historical landscape of oral obesity therapies can remind PCCs that convenience alone does not outweigh potential risks in some cases.

Today, oral incretin therapy represents a meaningful shift toward increased efficacy and acceptable tolerability for obesity therapy. Oral semaglutide 25 mg is approved as a once-daily treatment for weight management, and orforglipron—also taken once daily—was approved in April 2026 for the same indication.^{13,14} These advances present important alternatives to injectable obesity therapies, which were pre-

viously the only incretin-based treatments for obesity.¹⁰ Oral obesity therapy offers another route of administration based on preferences, helping patients access the medication and remain adherent to treatment to maximize potential benefit.^{10,15} Considerations for initiating oral obesity therapy are similar to considerations for injectable incretin-based therapies, such as titration dosing, minimizing and managing GI adverse effects, and helping patients access and adhere to the treatment to maximize potential benefit.^{10,15} Current and emerging options for oral obesity pharmacotherapy are summarized in **TABLE 1**.^{13,16-22}

CASE STUDY

SB is a 57-year-old woman with obesity (from Part 1 and Part 2 of this series) who has done well on tirzepatide 10 mg once weekly for the past 2 years and reports better sleep, improved function, and more confidence in long-term treatment.

Her 32-year-old daughter, KB, accompanies her and has an appointment to discuss weight management immediately following her mother's appointment. KB's BMI is 33 kg/m² and she asks about obesity treatment. She is interested in obesity medication but says that injections her mom is taking are not her preference. Using the 5 As, the PCC frames the discussion around whether the daughter meets criteria for pharmacotherapy, what outcomes

matter most to her, and whether an oral regimen would improve the likelihood that she can start and persist with treatment.

OVERVIEW OF CURRENT ORAL OBESITY THERAPIES

Current guidelines continue to position pharmacotherapy as an adjunct to nutrition, physical activity, sleep, stress management, and behavioral support for adults with obesity or overweight plus at least 1 weight-related complication.^{5,10,23} Within that framework, oral therapies encompass 2 broad roles in practice: established nonincretin agents that are indicated in certain clinical scenarios and newer incretin-based tablets that may offer much greater compliance by patients who prefer not to use injectable therapies.^{5,9}

Cost, coverage, and financial durability remain central to treatment selection. Oral therapy may be less expensive or easier to access than injectable therapy, though the practical success of any medication depends on whether the patient can obtain it consistently after the initial prescription and through titration to maintenance dosing.^{10,15} For many patients, the best obesity medication is selected based on a combination of factors such as efficacy, tolerability, accessibility, dosing, persistence, and patient preference.^{5,6}

TABLE 1. Current and emerging oral obesity agents.

Agent	FDA approval	Mechanism	Efficacy	Key practical considerations
Phentermine ¹⁷	1959 (short-term use)	Sympathomimetic appetite suppression	Modest, generally single-digit mean weight loss	Low cost in some settings; avoid where stimulatory effects or misuse risk are problematic
Orlistat ¹⁸	1999	Gastrointestinal lipase inhibition	Modest mean weight loss	Noncentral mechanism; counsel on oily stools, meal fat content, and fat-soluble vitamin use
Phentermine/topiramate ER ¹⁹	2012	Sympathomimetic plus central appetite effects	Upper single-digit to near-double-digit mean weight loss	More effective than older oral monotherapies; consider teratogenicity, paresthesia, and contraindications
Naltrexone/bupropion ER ²⁰	2014	Opioid antagonism plus norepinephrine/dopamine reuptake inhibition	Modest-to-moderate mean weight loss	Can help patients with hedonic eating concerns; avoid when seizure risk or uncontrolled hypertension is present
Oral semaglutide 25 mg ¹³	2025	Peptide GLP-1 receptor agonist	Double-digit mean weight loss demonstrated in phase 3 obesity trial	Once daily but must be taken fasting with up to 4 oz water and 30-minute wait before food, drink, or other oral medications
Orforglipron ¹⁶	2026	Small-molecule, nonpeptide GLP-1 receptor agonist	Double-digit mean weight loss demonstrated in phase 3 obesity trial	Once daily without fasting or water restrictions
Zenagamtide (amycretin) ²¹	Investigational; early phase	GLP-1 and amylin receptor agonist	Positive data from early trials	Additional clinical trials ongoing

Abbreviations: ER, extended release; FDA, US Food and Drug Administration; GLP-1, glucagon-like peptide 1.

Legacy oral agents may remain an option for certain patients even though newer incretin therapies are more effective on average. Phentermine/topiramate can provide greater efficacy than older single agents when the risk-benefit profile is acceptable. Naltrexone/bupropion can be useful when food cravings or depression history shape treatment goals. Orlistat may fit patients who prefer a noncentral mechanism and are willing to accept GI tradeoffs.^{5,9} These agents rarely produce the magnitude of weight loss seen with newer incretins, but they remain relevant if cost is lower, coverage is better, large amounts of weight reduction are not needed, and/or the patient values a noninjectable option with a long clinical track record.

Oral semaglutide and orforglipron have shown double-digit weight loss in clinical trials, as described below. Selecting between the 2 therapies involves matching the right drug to the right patient by aligning attributes of medications with preferences. For example, a key difference between oral semaglutide and orforglipron is administration. Oral semaglutide is a peptide GLP-1 receptor agonist formulated for once-daily use, but it must be taken on an empty stomach with no more than 4 oz of plain water, followed by a wait of at least 30 minutes before food, beverages, or other oral medications.¹³ Orforglipron is a nonpeptide small-molecule GLP-1 receptor agonist with once-daily dosing that does not require fasting or water-volume restrictions. This may reduce dosing complexity and align with patient preferences, especially for those who take multiple medications in the morning or have strict dietary requirements.²⁴ Characteristics of oral semaglutide and orforglipron are discussed in **TABLE 2**.

These distinctions between older and newer oral obesity therapies underscore an important principle of obesity care: matching drug attributes to patient preferences can improve persistence. Route of administration, timing restrictions, GI tolerability, work and travel patterns, privacy concerns, and coexisting diabetes or other comorbidities all shape whether an oral therapy is a practical long-term option for a particular patient.^{25,26}

CLINICAL EVIDENCE FOR NEWER ORAL OBESITY THERAPIES

Orforglipron

Orforglipron is a small-molecule GLP-1 receptor agonist taken orally once daily. Of note, this article presents efficacy and safety data from the investigational orforglipron capsule formulation (1 mg, 3 mg, 6 mg, 12 mg, 24 mg, and 36 mg) shown as equivalent doses of once daily orforglipron tablets (0.8 mg, 2.5 mg, 5.5 mg, 9 mg, 14.5 mg, and 17.2 mg) approved in the United States.¹⁴ In the phase 3 ATTAIN-1 trial in adults with obesity or overweight with at least 1 obesity-related complication except diabetes, the mean change in body

weight at 72 weeks was −7.5%, −8.4%, and −11.2% with 5.5, 9, and 17.2 mg, respectively, vs −2.1% with placebo.¹⁶ At the 17.2 mg dose, 54.6% of participants achieved at least 10% weight loss, 36.0% achieved at least 15% loss, and 18.4% achieved at least 20% loss. Discontinuation due to adverse events ranged from 5.3% to 10.3% vs 2.7% with placebo. The most common adverse events with orforglipron were GI related: nausea, constipation, diarrhea, vomiting, and dyspepsia.¹⁶

In ATTAIN-2, which enrolled adults with obesity or overweight plus type 2 diabetes, efficacy was smaller than in the nondiabetes population but still clinically relevant. Mean body-weight change at week 72 was −5.1%, −7.0%, and −9.6% with 5.5, 9, and 17.2 mg, respectively, vs −2.5% with placebo, with parallel improvements in glycemia and cardiometabolic risk markers.²⁷ GI symptoms were the most common adverse event observed, and discontinuation because of adverse events ranged from 6.1% to 10.6% with orforglipron vs 4.6% with placebo.²⁷

Oral semaglutide

For oral semaglutide, FDA approval was based on pivotal obesity data from the OASIS 4 trial. In adults with overweight or obesity, once-daily oral semaglutide 25 mg produced a mean body weight change of −13.6% at 64 weeks compared with −2.2% for placebo, for an estimated treatment difference of −11.4 percentage points. GI adverse events (nausea, vomiting, constipation, dyspepsia, and diarrhea) were the most common adverse events reported in those taking oral semaglutide, and discontinuation due to adverse events was 6.9% with oral semaglutide and 5.9% with placebo.²⁸

Emerging agents

Several earlier-stage investigational oral obesity therapies are currently being studied. Oral zenaglutide (amycetin), a GLP-1 and amylin receptor agonist, has shown significant weight loss and acceptable safety and tolerability in a phase 1b/2a trial, supporting continued development.^{21,29}

PRACTICAL STRATEGIES TO IMPLEMENT ORAL OBESITY THERAPIES

Patients most likely to benefit from oral obesity therapy are those who meet standard criteria for pharmacotherapy but decline injections; those who may have stopped an injectable primarily because of route burden rather than lack of effect; and those whose work, travel, privacy, or caregiving constraints make oral dosing more acceptable.^{10,15} Oral therapy also may be attractive in patients with obesity and type 2 diabetes when the clinician recommends a drug with an incretin-based mechanism of action but the patient strongly prefers a tablet.¹⁰

How oral therapy is introduced matters; PCCs should

TABLE 2. Characteristics of oral semaglutide and oral orforglipron for obesity treatment.

Feature	Oral semaglutide 25 mg ¹³	Orforglipron ¹⁴
Molecule/class	Peptide GLP-1 receptor agonist	Small-molecule nonpeptide GLP-1 receptor agonist
FDA approval	December 2025	April 2026
Indication	In combination with a reduced-calorie diet and increased physical activity: <ul style="list-style-type: none"> • Reduce the risk of major adverse events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in adults with established cardiovascular disease and either obesity or overweight • Reduce excess body weight and maintain weight reduction long term in adults with obesity, or in adults with overweight in the presence of at least one weight-related comorbid condition 	In combination with a reduced-calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition
Administration	Morning dose on empty stomach with up to 4 oz plain water only; wait at least 30 minutes before food, beverages, or other oral medications	Once-daily oral dosing without fasting, water-volume, or timing restrictions
Dosing and titration	<ul style="list-style-type: none"> • Starting dosage: 1.5 mg orally once daily • After 30 days on the 1.5 mg dosage, increase the dosage to 4 mg once daily • After 30 days on the 4 mg dosage, increase the dosage to 9 mg once daily • After 30 days on the 9 mg dosage, increase to the maintenance dosage of 25 mg once daily 	<ul style="list-style-type: none"> • Starting dosage: 0.8 mg orally once daily • After at least 30 days on the 0.8 mg dosage, increase the dosage to 2.5 mg once daily • After at least 30 days on the 2.5 mg dosage, increase the dosage to 5.5 mg once daily • The dosage may be increased to the next dosage level (9 mg, 14.5 mg, or 17.2 mg once daily) after at least 30 days on the current dosage, based on treatment response and tolerability
Evidence base in obesity	Positive phase 3 obesity trial with double-digit mean weight loss (OASIS 4) ²⁸	Positive phase 3 obesity trial data with dose-related weight loss (ATTAIN-1) ¹⁶ Positive phase 3 obesity plus type 2 diabetes data (ATTAIN-2) ²⁷
Common adverse effects	Mainly gastrointestinal: nausea, diarrhea, vomiting, constipation	Mainly gastrointestinal: nausea, diarrhea, vomiting, constipation
Likely best-fit patient	Patient who prefers an oral tablet and can reliably follow fasting/timing rules	Patient who prefers an oral tablet without requirements for meal timing administration

present oral options not as a shortcut, but as part of chronic disease care that still requires a long-term plan, realistic expectations, and ongoing follow-up.^{5,6} It may be useful to frame the conversation by discussing average weight response in percentage terms, emphasize that early GI symptoms are common but often improve, and explain that the goal is not to “try a pill” briefly but to identify a safe and effective therapy that can be sustained long-term.¹⁵

Counseling about dose titration should also be presented to patients clearly. They should know in advance that nausea, early satiety, constipation, diarrhea, and occasional vomiting are usually most prominent during initiation and

dose escalation, that slower eating and smaller meals can help, and that temporary dose holds or slower escalation may be appropriate when symptoms interfere with adherence.^{30,31} Monitoring should include body weight, appetite, adverse effects, blood pressure, glycemia when relevant, and adequacy of nutrition and hydration.^{30,32}

Because appetite suppression can substantially reduce overall caloric intake, nutrition counseling remains essential even with oral therapy. Patients should be encouraged to preserve diet quality, emphasize protein and fiber, maintain hydration, and incorporate resistance exercise to reduce loss of lean mass during weight reduction.^{30,33} Referral to a

registered dietitian can be especially helpful when reduced intake, persistent constipation, or uncertainty about protein intake threatens long-term success.³²

Additionally, clinicians should revisit oral therapy in the same way as with any chronic therapy. When response is suboptimal, consider steps that could facilitate the patient's health goals. Options include medication administration technique, continued titration, more intensive nutrition support, reassessment of access (if relevant), or transition to an injectable agent or another medication class.^{5,10}

Maintenance therapy expectations should also be discussed before treatment begins. As with injectable obesity medications, stopping an effective oral therapy is likely to be followed by partial or substantial weight regain, so continuation should be communicated as long-term treatment for a chronic disease rather than a finite course intended only to reach a target weight.^{5,6} That conversation can improve adherence by aligning the patient's expectations with the biology of relapse and by normalizing dose adjustment or therapy changes over time rather than treating them as failure.^{2,32}

CASE STUDY (CONTINUED)

KB's daughter elects to start oral therapy for obesity. After reviewing her access options, the administration requirements for various treatments, and average weight loss efficacy, she notes that oral orforglipron would be most convenient considering her busy schedule and other medications she takes in the morning. She titrates to the maintenance dose and reports that early nausea was manageable after she slowed meal pace, reduced portion size, and paid more attention to hydration.

At follow-up, the PCC again uses the 5 As: (Ask, Assess, Advise, Agree, and Assist) to confirm that treatment goals remain centered on health improvement, reinforce that maintenance therapy will likely be ongoing, and discuss what would prompt a change in strategy if weight loss plateaus or regimen complexity becomes a barrier.

SUMMARY

Advancements in oral pharmacotherapy in recent years now offer patients the option of highly effective weight management therapy without injections. While older, established oral agents still have a role, newer oral incretin therapies have changed what is realistically achievable with a tablet by moving expected weight loss from the modest range toward double-digit reductions in selected patients. Clinicians can facilitate improved obesity outcomes by matching the right oral therapy to the right patient through accurate diagnosis, stigma-sensitive communication, setting realistic expectations, and careful attention to dosing burden, tolerability, access, nutrition, and follow-up. When oral therapy

is integrated into comprehensive chronic obesity care, it can expand options for patients who might otherwise never start or stay on treatment. ●

REFERENCES

- Ng M, Dai X, Cogen RM, et al. National-level and state-level prevalence of overweight and obesity among children, adolescents, and adults in the USA, 1990–2021, and forecasts up to 2050. *The Lancet*. 2024;404(10469):2278–2298. doi:10.1016/S0140-6736(24)01548-4
- Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. *The Lancet Diabetes Endocrinol*. 2025;13(3):221–262. doi:10.1016/S2213-8587(24)00316-4
- DeCleele NK, Kahn E, Yuan CW, et al. US state-level prevalence of adult obesity by race and ethnicity from 1990 to 2022 and forecasted to 2035. *JAMA*. 2026;335(11):975. doi:10.1001/jama.2025.26817
- Yuen MMA. Health complications of obesity. *Gastroenterol Clin North Am*. 2023;52(2):363–380. doi:10.1016/j.gtc.2023.03.006
- Nadolsky K, Garvey WT, Agarwal M, et al. American Association of Clinical Endocrinology consensus statement: algorithm for the evaluation and treatment of adults with obesity/adiposity-based chronic disease – 2025 update. *Endocr Pract*. 2025;31(11):1351–1394. doi:10.1016/j.eprac.2025.07.017
- Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. *CMAJ*. 2020;192(31):E875–E891. doi:10.1503/cmaj.191707
- Kushner RF, Lazarus E, Miller EM. Comprehensive obesity management part 1: assessment and initiation of treatment. *Fed Pract*. 2025;42(Suppl 7):S13–S18.
- Kushner RF, Lazarus E, Miller EM. Comprehensive obesity management part 2: ongoing assessment and individualization of the treatment plan. *Fed Pract*. 2025;42(Suppl 7):S19–S24.
- Gudzune KA, Kushner RF. Medications for obesity: a review. *JAMA*. 2024;332(7):571. doi:10.1001/jama.2024.10816
- American Diabetes Association Professional Practice Committee for Obesity. Pharmacologic treatment of obesity in adults: standards of care in overweight and obesity. *BMJ Open Diabetes Res Care*. 2026;13(Suppl 1):e005729. doi:10.1136/bmjdr-2025-005729
- James WPT, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med*. 2010;363(10):905–917. doi:10.1056/NEJMoa1003114
- Sharretts J, Galescu O, Gomatam S, Andraca-Carrera E, Hampf C, Yanoff L. Cancer risk associated with lorcaserin — the FDA's review of the CAMELLIA-TIMI 61 trial. *N Engl J Med*. 2020;383(11):1000–1002. doi:10.1056/NEJMp2003873
- Wegovy (semaglutide). Prescribing Information. Novo Nordisk Inc.; 2026. Accessed March 30, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/215256s029lbl.pdf
- Founday (orforglipron). Prescribing Information. Eli Lilly and Company; 2026. Accessed April 10, 2026. <https://nctr-crs.fda.gov/fda/label/services/spl/set-ids/8ac446c5-feba-474f-a103-23facb9b5c62/spl-doc>
- McVay MA, Moore WS, Wilkins FL, Jackson JR, Robinson MD. Patient perspectives on incretin-based weight loss medications and relationship with demographic factors. *Obesity Sci Pract*. 2024;10(4):e783. doi:10.1002/osp4.783
- Wharton S, Aronne LJ, Stefanski A, et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist for obesity treatment. *N Engl J Med*. 2025;393(18):1796–1806. doi:10.1056/NEJMoa2511774
- Phentermine hydrochloride. Prescribing Information. PD-Rx Pharmaceuticals, Inc; 2023. Accessed March 31, 2026. <https://nctr-crs.fda.gov/fda/label/services/spl/set-ids/b425840f-380e-42bd-852a-6ee3641977ce/spl-doc>
- Xenical (orlistat). Prescribing Information. H2-Pharma LLC; 2024. Accessed March 31, 2026. <https://nctr-crs.fda.gov/fda/label/services/spl/set-ids/6240792b-9224-2d10-e053-2a91aa0a2c3e/spl-doc>
- Qsymia (phentermine/topiramate ER). Prescribing Information. Vivus LLC; 2026. Accessed March 31, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/022580s031lbl.pdf
- Contrave (naltrexone HCl/bupropion HCl). Prescribing Information. Currax Pharmaceuticals LLC; 2025. Accessed March 31, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/200063s024s026lbl.pdf
- Dahl K, Toubro S, Dey S, et al. Amycretin, a novel, unimolecular GLP-1 and amylin receptor agonist administered subcutaneously: results from a phase 1b/2a randomised controlled study. *The Lancet*. 2025;406(10499):149–162. doi:10.1016/S0140-6736(25)01185-7
- Buckelridge C, Cobain S, Bays HE, et al. Efficacy and safety of danuglipron (PF-06882961) in adults with obesity: a randomized, placebo-controlled, dose-ranging phase 2b study. *Diabetes Obes Metab*. 2025;27(9):4915–4926. doi:10.1111/dom.16534
- Pedersen SD, Manjoo P, Dash S, Jain A, Pearce N, Poddar M. Pharmacotherapy for obesity management in adults: 2025 clinical practice guideline update. *CMAJ*. 2025;197(27):E797–E809. doi:10.1503/cmaj.250502
- Ma X, Liu R, Pratt EJ, Benson CT, Bhattachar SN, Sloop KW. Effect of food consumption on the pharmacokinetics, safety, and tolerability of once-daily orally administered orforglipron (LY3502970), a non-peptide GLP-1 receptor agonist. *Diabetes Ther*. 2024;15(4):819–832. doi:10.1007/s13300-024-01554-1
- Lu L, Brady BL, Xie L, Guevarra M, Turchin A. Adherence and persistence among people with type 2 diabetes newly initiating oral semaglutide versus DPP-4is in a US real-world setting. *Prim Care Diabetes*. 2024;18(5):511–517. doi:10.1016/j.pcd.2024.06.013
- Boye K, Ross M, Mody R, König M, Gelhorn H. Patients' preferences for once-daily oral versus once-weekly injectable diabetes medications: the REVISE study. *Diabetes Obes Metab*. 2021;23(2):508–519. doi:10.1111/dom.14244

27. Horn DB, Ryan DH, Kis SG, et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist, for the treatment of obesity in people with type 2 diabetes (ATTAIN-2): a phase 3, double-blind, randomised, multicentre, placebo-controlled trial. *The Lancet*. 2025;406(10522):2927-2944. doi:10.1016/S0140-6736(25)02165-8
28. Wharton S, Lingvay I, Bogdanski P, et al. Oral semaglutide at a dose of 25 mg in adults with overweight or obesity. *N Engl J Med*. 2025;393(11):1077-1087. doi:10.1056/NEJMoa2500969
29. Gasiorek A, Heydorn A, Gabery S, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of the first-in-class GLP-1 and amylin receptor agonist, amycetin: a first-in-human, phase 1, double-blind, randomised, placebo-controlled trial. *The Lancet*. 2025;406(10499):135-148. doi:10.1016/S0140-6736(25)01176-6
30. Almandoz JP, Wadden TA, Tewksbury C, et al. Nutritional considerations with antiobesity medications. *Obesity*. 2024;32(9):1613-1631. doi:10.1002/oby.24067
31. Wharton S, Davies M, Dicker D, et al. Managing the gastrointestinal side effects of GLP-1 receptor agonists in obesity: recommendations for clinical practice. *Postgrad Med*. 2022;134(1):14-19. doi:10.1080/00325481.2021.2002616
32. Gigliotti L, Warshaw H, Evert A, et al. Incretin-based therapies and lifestyle interventions: the evolving role of registered dietitian nutritionists in obesity care. *J Acad Nutr Diet*. 2025;125(3):408-421. doi:10.1016/j.jand.2024.10.023
33. Locatelli JC, Costa JG, Haynes A, et al. Incretin-based weight loss pharmacotherapy: can resistance exercise optimize changes in body composition? *Diabetes Care*. 2024;47(10):1718-1730. doi:10.2337/dci23-0100

Nonsteroidal MRAs for Patients With Cardiovascular-Kidney-Metabolic Syndrome

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INTRODUCTION

Cardio-kidney-metabolic (CKM) risk factors including obesity, type 2 diabetes (T2D), and chronic kidney disease (CKD) contribute to heightened risk for development of cardiovascular disease (CVD), including heart failure (HF), atrial fibrillation, stroke, coronary artery disease, and peripheral arterial disease.¹ Recognition of the interplay between cardiometabolic risk and the progression of cardiorenal disease (included within CKM syndrome) has focused attention on strategies to optimize management of patients with CKM syndrome.

Epidemiologic data suggest that nearly three-fourths of the US population have CKM risk factors (CKM stage 1-2) including excess or dysfunctional adiposity, hypertension, metabolic syndrome, diabetes, or CKD, and approximately 1 in 8 have advanced disease (CKM stage 3-4) including sub-clinical or established CVD (atherosclerotic CVD or HF).² Advanced CKM disease is more common in the presence of adverse social determinants of health, underscoring that risk is not evenly distributed and may be impacted by sociodemographic factors.^{1,2} Given the high burden of health care utilization in this population, the economic consequences are substantial.³

Key takeaways

- CKM syndrome refers to the interplay between cardiometabolic risk factors including obesity, T2D, CKD, and CVD.
- Data from outcomes trials suggest that treatment with finerenone, a nonsteroidal mineralocorticoid receptor antagonist (nsMRA), may improve cardiorenal outcomes across a broad range of CKM conditions both alone and in combination with a sodium-glucose cotransporter 2 inhibitor (SGLT2i).
- Finerenone is indicated to reduce the risk of adverse kidney and cardiovascular (CV) outcomes in patients with CKD and T2D, and to reduce the risk of adverse CV outcomes in patients with HF and left ventricular ejection fraction (LVEF) $\geq 40\%$ (see Table 5 for complete information).
- Primary care clinicians (PCCs) play an essential role in early recognition of CKM syndrome and can facilitate early initiation of disease-modifying therapy when indicated.
- Multidisciplinary coordination with cardiology/nephrology/endocrinology specialists for CKM care can reduce care fragmentation and further enhance patient outcomes.

Recognition of a shared pathophysiology of CKM disease centered on the systemic consequences of excess or dysfunctional adipose tissue contributing to maladaptive adipokine signaling highlights an opportunity to prevent disease progression through early intervention.⁴ Use of SGLT2is is established as an effective strategy for prevention of incident CKD and CVD in patients with T2D at high CV risk as well as prevention of disease progression in established CKD and HF with and without diabetes.⁵⁻⁷ Accordingly, these drugs are now prioritized by consensus guidelines for treatment of eligible patients across the CKM spectrum. More recently, data have emerged to highlight the potential for additional modification of cardiometabolic risk with the use of nsMRAs.^{8,9}

MINERALOCORTICOID RECEPTOR ACTIVATION AND CKM SYNDROME

A key shared mechanism in the progression of CKM syndrome is activation of the renin-angiotensin-aldosterone system (RAAS), which plays a central role in the regulation of blood pressure and fluid homeostasis.¹⁰ Aldosterone, a key downstream effector of this system, acts primarily through binding of the mineralocorticoid receptor (MR), a nuclear receptor that is expressed in multiple tissues including the kidney, heart, and fibroblasts. Enhanced MR expression and activation leading to increased pro-inflammatory and profibrotic signaling are common in the setting of cardiometabolic risk states.¹⁰ MR overactivation is now understood to be a key factor in driving systemic inflammation, plasma volume expansion, and cardiac hypertrophy and fibrosis as well as the development and progression of CKD and HF.^{10,11} Accordingly, blockade of the MR with mineralocorticoid receptor antagonists (MRAs) has been an increasingly attractive therapeutic target for the management of CKM-related disease.¹²

Steroidal MRAs (sMRAs) including spironolactone and eplerenone have long been utilized in clinical practice for the management of hypertension (particularly resistant hypertension) and heart failure with reduced ejection fraction (HFrEF), where ample data support efficacy in prevention of morbidity and mortality across the spectrum of disease severity.^{13,14} Utilization of these agents in clinical practice, however, remains suboptimal, in part due to concerns for hyperkalemia as well as the potential for off-target, anti-androgen side effects (particularly with spironolac-

tone).¹⁵ Data for use of sMRAs in patients with HF and mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) have been mixed.^{7,16,17}

Since sMRAs resemble naturally occurring steroid hormones, they may bind and block other steroid hormone receptors, including those for testosterone and progesterone; this anti-androgen effect may contribute to the risk for side effects including gynecomastia, diminished libido, and erectile dysfunction.¹⁸ By contrast, nsMRAs lack a steroidal ring, contributing to a distinct molecular structure that limits cross-reactivity with other steroid hormone receptors, allowing for potent and highly selective blockade of the MR.¹⁸ Although hyperkalemia remains a concern with all MRAs, a more balanced tissue distribution between heart and kidney for nonsteroidal in comparison with steroidal MRAs may provide a more favorable safety profile, particularly in patients with CKD.¹⁰ Key differences between sMRAs and nsMRAs are summarized in **TABLE 1**.^{10,19-21}

Two large, randomized trials of patients with diabetes and CKD (FIDELIO-DKD and FIGARO-DKD) have shown that treatment with finerenone lowers the incidence of HF and CKD progression despite heightened risk for hyperkalemia.^{22,23} In FIDELIO-DKD, finerenone resulted in an 18% lower risk of CKD progression or death from renal causes vs placebo, and in FIGARO-DKD, the incidence of hospitalization for HF was 29% lower with finerenone vs placebo.^{22,23} More recently, among 6001 patients with symptomatic HFmrEF/HFpEF enrolled in the FINEARTS-HF trial, treatment with finerenone was associated with lower rates of the composite of total worsening HF events and CV death vs placebo.⁸ Notably, these effects were observed as early as 1

TABLE 1. Pharmacologic characteristics of steroidal and nonsteroidal MRAs.^{10,19-21}

Characteristic	sMRAs		nsMRA
	Spironolactone	Eplerenone	Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
Potency to MR	Highly potent	Somewhat potent	Highly potent
Selectivity to MR	Somewhat selective	Selective	Highly selective
Central nervous system penetration	Some penetration	Some penetration	None
Sexual side effects	Gynecomastia, decreased libido, breast and nipple pain	Few reports of gynecomastia and abnormal vaginal bleeding	None
Half-life	>20 hours ^a	4-6 hours ^a	2-3 hours ^b
Active metabolites	Present	None	None
Effect on blood pressure lowering	Significant	Moderate	Mild

^aIn patients with HF.

^bIn healthy volunteers.

month following initiation of finerenone treatment and were robust in patients treated and not treated with an SGLT2i at baseline, suggesting additive treatment benefits.²⁴ Subanalyses of FINEARTS-HF also noted potential improvement in CV and HF event-free survival up to 3.1 years, reduction in the risk of new-onset diabetes, and preserved efficacy and safety across LVEF categories.²⁵⁻²⁷ Additionally, benefits observed in FINEARTS-HF were not affected by baseline atrial fibrillation status.²⁸ In a pooled analysis of these trials representing a broad spectrum of patients with CKM disease, treatment with finerenone did not influence CV mortality but was associated with lower rates of all-cause mortality, HF hospitalization, and composite kidney outcomes.²⁹ Another pooled analysis of these trials suggested that finerenone reduces the risk of new-onset atrial fibrillation or atrial flutter.³⁰ Collectively, these data suggest potential for use of nsMRAs with or without SGLT2is for treatment of patients with CKM syndrome.

In the CONFIDENCE trial, participants with CKD, albuminuria, and T2D already receiving a RAAS inhibitor were randomized to finerenone alone, empagliflozin alone, or the combination.⁹ At 180 days, combination therapy produced a ~30% greater reduction in urine albumin-to-creatinine ratio (UACR) than either monotherapy, without a concerning signal of safety. Results were consistent in patients treated and not treated with glucagon-like peptide-1 (GLP-1) receptor agonists.⁹ Additionally, the CONFIDENCE trial established UACR as a mediating biomarker that can be used as a marker of CKD progression, as it is associated with kidney failure.^{9,31} These data suggested that combination therapy was associated with greater albuminuria reductions. Furthermore, a subanalysis of CONFIDENCE suggested that the benefits of combination therapy with finerenone and empagliflozin are preserved across a spectrum of predicted kidney disease risk.³²

Extrapolating from the results of the DELIVER trial of dapagliflozin and the FINEARTS-HF trial, one analysis projected that the treatment of HFmrEF/HFpEF with the combination of an SGLT2i and finerenone would lead to significant improvements in event-free survival over the lifetime, adding a projected 3.6 years of life free from CV death or worsening HF events for an average 65-year-old with HFmrEF/HFpEF.³³ A trial-level analysis of multiple CKM trials suggested that CKM multimorbidity is substantial, increases over time, and is associated with adverse events, confirming the need for timely identification and intervention.³⁴ Key data from recent clinical trials of finerenone and notable subanalyses from phase 3 studies of CKD in T2D and from HF with LVEF $\geq 40\%$, which are important conditions within CKM syndrome, are summarized in **TABLE 2** and **TABLE 3**.

In addition to CKD associated with T2D and HF with LVEF $\geq 40\%$, finerenone may extend options for patients with CKD associated with type 1 diabetes (T1D) according to a recently published study.^{35,36} CKD in T1D represents a major unmet need, as up to 40% of patients with T1D develop CKD.³⁵ Furthermore, up to 40% of adults >30 years who were eventually diagnosed with T1D were originally diagnosed and treated as T2D, highlighting that PCCs do not have to definitively rule out T1D.³⁶ Historically, disease-modifying options have been more limited in T1D than in T2D. Results from the FINE-ONE randomized trial in patients with T1D and CKD indicate that finerenone significantly reduced UACR over 6 months by 25% compared to placebo.³⁷

Trials of other MRAs in CKM syndrome are also informative (**TABLE 2**).^{16,38,39} In the TOPCAT randomized, double-blind trial, which enrolled patients with symptomatic HF and LVEF $\geq 45\%$, there was no difference between spironolactone and placebo in the primary composite outcome of death from CV causes, aborted cardiac arrest, or HF hospitalization, but hyperkalemia was increased with spironolactone.¹⁶ However, spironolactone significantly reduced the incidence of hospitalization for HF by 17% compared to placebo.¹⁶ In the BARACKD randomized, open, blinded endpoint trial, older adults with stage 3b CKD who received spironolactone did not have improved CV outcomes compared to placebo, and spironolactone was frequently discontinued due to safety concerns.³⁸ An investigational nsMRA, balcinrenone, was combined with dapagliflozin in adults with estimated glomerular filtration rate (eGFR) 25 to <60 mL/min/1.73 m², UACR >100 to ≤ 5000 mg/g, and serum potassium 3.5 to 5.0 mmol/L in the MIROCKD phase 2b randomized controlled trial.³⁹ The combination of balcinrenone and dapagliflozin reduced UACR up to 32.8% compared with dapagliflozin alone after 12 weeks.³⁹

GUIDELINE-DIRECTED MANAGEMENT OF CKM SYNDROME

Patients with early manifestations of CKM syndrome are commonly encountered in primary care, making this the optimal setting for early intervention to prevent disease progression. PCCs can adopt a practical screening mindset that includes evaluating for silent organ injury before symptoms drive care, which means routine kidney surveillance (eGFR and UACR) in high-risk patients, proactive assessment for HF risk and early HF (symptoms, volume status, and consideration of natriuretic peptide-based risk assessment), and periodic review of CVD risk factors, including blood pressure, lipids, smoking, and weight trajectory.^{5-7,40} When abnormal findings emerge, PCCs can address CKM conditions early by implementing interventions and coordinating multidisciplinary care. Of note, the recently published 2026 American Heart Association/American College of Cardiology

TABLE 2. Notable clinical trials of MRAs in CKM syndrome.

Study	Condition	Evidence focus	Design	Population	Key findings
FIDELIO-DKD Trial ²²	T2D + CKD	Composite kidney outcome in patients with T2D + CKD	RCT; finerenone + placebo	Stage 1 or stage 2 CKD with albuminuria and T2D	Reduced kidney failure, sustained decrease $\geq 40\%$ in eGFR, or reduced death from renal causes (HR, 0.82; 95% CI: 0.73, 0.93; $P = .001$)
FIGARO-DKD Trial ²³	T2D + CKD	Composite CV outcome in patients with T2D + CKD	RCT; finerenone vs placebo	Stage 1 or stage 2 CKD with albuminuria and T2D	Reduced CV death, nonfatal MI, nonfatal stroke, or hospitalization for HF (HR, 0.87; 95% CI: 0.76, 0.98; $P = .03$)
FINEARTS-HF Trial ⁸	HF	HFmrEF/HFpEF clinical outcomes	RCT; finerenone vs placebo	Symptomatic HF, LVEF $\geq 40\%$	Reduced total worsening HF events and death from CV causes with finerenone (RR, 0.84; 95% CI: 0.74, 0.95; $P = .007$)
CONFIDENCE Trial ⁹	T2D + CKD	Combination therapy in T2D + CKD	RCT; finerenone, empagliflozin, or finerenone + empagliflozin	CKD with albuminuria and T2D	Combination therapy reduced UACR by 29% compared to finerenone alone (mean ratio 0.71; 95% CI: 0.61, 0.81; $P < .001$) and empagliflozin alone (mean ratio 0.68; 95% CI: 0.59, 0.79; $P < .001$)
FINE-ONE Trial ³⁶	T1D + CKD	Reduction in UACR	RCT; finerenone vs placebo	T1D and CKD	Finerenone significantly reduced UACR over 6 months by 25% (HR, 0.75; 95% CI: 0.65, 0.87; $P = .0001$)
TOPCAT Trial ¹⁶	HF	Composite CV outcome in patients with HFpEF	RCT; spironolactone vs placebo	Symptomatic HF and LVEF $\geq 45\%$	No significant difference in primary composite outcome; increased risk of hyperkalemia with spironolactone; reduction in hospitalization for HF with spironolactone (HR, 0.83; 95% CI: 0.69, 0.99; $P = .04$)
BARACK-D Trial ³⁸	CKD	Composite CV outcome in older adults with CKD	Prospective, randomized, open, blinded endpoint trial; spironolactone vs usual care	Older adults (mean age 74.8 years) with stage 3b CKD	No significant difference in CV outcomes; increased risk of hyperkalemia with spironolactone and frequent discontinuation of spironolactone due to safety concerns
MIRO-CKD Trial ³⁹	CKD	Reduction in UACR	RCT dose-finding phase 2b trial; balcinrenone + dapagliflozin vs dapagliflozin	Adults with CKD (eGFR 25 to < 60 mL/min/1.73 m ² , UACR > 100 to ≤ 5000 mg/g, and serum potassium 3.5 to 5.0 mmol/L)	Reduction in UACR of 22.8% with balcinrenone 15 mg ($P = .0038$) and reduction of 32.8% with balcinrenone 40 mg ($P = .0001$) after 12 weeks

Abbreviations: CI, confidence interval; HR, hazard ratio; RCT, randomized controlled trial; RR, rate ratio.

Multisociety Guideline for CKM Syndrome endorses the use of nsMRA (finerenone) for treatment of patients with HFpEF, T2D, CKD, and albuminuria.⁴¹ Readers are referred to the full guideline publication for specific recommendations (<https://www.ahajournals.org/doi/10.1161/CIR.0000000000001453>).

CASE STUDY

An overweight 62-year-old man with T2D, CKD, hypertension, and HFpEF presents to the primary care clinic for a follow-up visit following a recent hospitalization for management of worsening HF.

Measurements and laboratory values from recent hospitalization:

- Body mass index 26 kg/m²

- Waist-to-height ratio 0.55 (normal < 0.5)
- Blood pressure 135/86 mmHg
- Heart rate 75 bpm
- Exam: No jugular venous distension, clear lungs to auscultation, normal cardiac exam without murmur or gallop, no peripheral edema
- LVEF 55% (by echocardiography)
- Glycated hemoglobin (HbA1c) 8.5%
- Potassium 4.8 mEq/L
- eGFR 35 mL/min/1.73 m² (Kidney Disease: Improving Global Outcomes Stage 3b CKD)
- NT-proBNP 1000 pg/mL
- Urine albumin:creatinine ratio: 100 mg/g

Medications:

- Empagliflozin 25 mg once daily
- Metformin 1000 mg twice daily
- Losartan 100 mg daily
- Hydrochlorothiazide 25 mg daily

What additional therapies should be considered for this patient?

Hospitalization for management of worsening HF is a sentinel event and identifies patients at high risk for recurrent HF exacerbation and death. This early post-discharge

Table 3. Notable subanalyses of clinical trials of finerenone in CKM conditions.

Study	Condition	Evidence focus	Design	Population	Key findings
FINEARTS-HF Time to Benefit Analysis ²⁴	HF	Time to significant benefit of finerenone in HF	Prespecified analysis	Symptomatic HF, LVEF $\geq 40\%$	First statistical significance observed within 1 month of therapy initiation and sustained until final follow-up
FINEARTS-HF Long-Term Benefits ²⁵	HF	Estimated long-term benefit of finerenone in HF	Prespecified analysis	Symptomatic HF, LVEF $\geq 40\%$	Projected mean event-free survival gains: 2.0 years (age 65), 3.1 years (age 55) free from CV death or worsening HF events
FINEARTS-HF Across the EF Spectrum ²⁶	HF	Finerenone efficacy in HF across LVEF	Prespecified analysis	Symptomatic HF, LVEF $\geq 40\%$	Finerenone reduced CV death and total HF events consistently across LVEF categories (LVEF $<50\%$: RR, 0.84 [95% CI: 0.68, 1.03]; LVEF $\geq 50\%$ to $<60\%$: RR, 0.80 [9% CI: 0.66, 0.97]; and LVEF $\geq 60\%$: RR, 0.94 [95% CI: 0.70, 1.25]; $P_{\text{interaction}} = .70$)
FINEARTS-HF New-Onset Diabetes Analysis ²⁷	HF	New onset of diabetes	Prespecified analysis	Symptomatic HF, LVEF $\geq 40\%$	Risk of new-onset diabetes reduced by 24% with finerenone (HR, 0.76; 95% CI: 0.59, 0.97)
FINEARTS-HF New-Onset AF Analysis ²⁸	HF	New onset of AF or AFL	Prespecified analysis	Symptomatic HF, LVEF $\geq 40\%$	Benefit of finerenone on CV and HF not modified by baseline AF status; new onset AF was nonsignificantly reduced with finerenone (subdistribution HR, 0.77; 95% CI: 0.57, 1.04; $P = .05$)
FINE-HEART Pooled Analysis ³⁰	HF	New onset of AF or AFL	Pooled analysis of FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF	Cross trial T2D + CKD; symptomatic HF, LVEF $\geq 40\%$	During 2.9 years of median follow-up, finerenone reduced the risk of new-onset AF/AFL by 17% (HR, 0.83; 95% CI: 0.71, 0.97, $P = .019$)
Lifetime Benefits of Comprehensive Medical Therapy ³³	HF	Combination SGLT2i + finerenone therapy in HF	Cross-trial analysis of DELIVER, FINEARTS-HF, and PARAGON-HF	Cross trial HFmrEF/HFpEF	Combined use of SGLT2i and finerenone estimated to reduce risk of CV death or first HF worsening event by 31% (HR, 0.69; 95% CI: 0.59, 0.81)
CONFIDENCE Kidney Risk Subanalysis ³²	T2D + CKD	Combination therapy in T2D + CKD across spectrum of kidney risk	Prespecified analysis	CKD with albuminuria and T2D	Relative efficacy and safety of simultaneous finerenone and empagliflozin combination therapy were consistent across a wide spectrum of predicted kidney disease risk
FINE-HEART Pooled Analysis ²⁹	CKM	CV, kidney, and mortality outcomes	Cross-trial analysis of FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF	Cross trial T2D + CKD; symptomatic HF, LVEF $\geq 40\%$	Over 2.9 years of follow-up, finerenone reduced the risk of CV death (HR, 0.89; 95% CI: 0.78, 1.01; $P = .076$), death from any cause (HR, 0.91; 95% CI: 0.84, 0.99; $P = .027$), hospitalization from HF (HR, 0.83; 95% CI: 0.75, 0.92; $P < .001$), and the composite kidney outcome (HR, 0.80; 95% CI: 0.72, 0.90; $P < .001$)
CKM Trial-Level Analysis ³⁴	CKM	Progression and overlap of CKM conditions	Trial-level analysis of I-PRESERVE, TOPCAT, PARAGON-HF, DELIVER, and FINEARTS-HF trials	Cross trial HFmrEF or HFpEF	CKM multimorbidity was substantial, increased over time, and was associated with adverse outcomes

Abbreviation: AFL, atrial flutter.

TABLE 4. The stages of CKM syndrome.¹

Stage and description	Characteristics
Stage 0 No risk factors	<ul style="list-style-type: none"> Focus on primordial prevention and preserving cardiovascular health
Stage 1 Excess/dysfunctional adipose tissue	<ul style="list-style-type: none"> Overweight/obesity Abdominal obesity Impaired glucose tolerance
Stage 2 Metabolic risk factors and CKD	<ul style="list-style-type: none"> Hypertension <ul style="list-style-type: none"> Nonmetabolic etiologies of hypertension Metabolic syndrome Moderate- to high-risk CKD <ul style="list-style-type: none"> Nonmetabolic etiologies of CKD Type 2 diabetes Hypertriglyceridemia
Stage 3 Subclinical CVD in CKM syndrome ^a	<ul style="list-style-type: none"> Subclinical atherosclerotic CVD Subclinical HF
Stage 4 Clinical CVD in CKM syndrome	<ul style="list-style-type: none"> HF Peripheral arterial diseases Stroke Atrial fibrillation Coronary heart disease

^aRisk equivalents of subclinical CVD in CKM Stage 3: very high-risk CKD, high predicted risk for CVD using risk calculator.

visit is an opportunity to reduce the risk of recurrent HF. This patient has T2D, CKD (based on a reduced eGFR and high albuminuria), elevated BMI, high waist-to-height ratio, uncontrolled blood pressure, and HFpEF consistent with a broad range of cardiometabolic risks typical of Stage 4 CKM syndrome (CKM stages are summarized in **TABLE 4**). Targets for optimization include agents that will reduce risk of CKD progression, lower blood pressure, and lower overall cardiometabolic risk. Improvement in glycemic control is certainly important given evidence of diabetic kidney disease and the tight linkage between intensive control of blood glucose and microvascular outcomes; however, tight glycemic control alone has not been associated with improvement in CV outcomes, so additional interventions are needed for CV risk reduction.

The patient is already managed with an SGLT2i, which has been shown to reduce risk of recurrent HF in patients with HF, including those recently hospitalized for HF management.^{42,43} Data from the FINEARTS-HF trial suggest that the addition of an nsMRA, finerenone, in this setting may further reduce risk of recurrent HF, and the benefits appear to be amplified in the early post-discharge interval.²⁶ The patient also has a secondary indication for finerenone based

on the underlying diagnosis of diabetes and CKD, where data from FIGARO-CKD and FIDELIO-CKD suggest CV benefits. While use of an sMRA in this context may be considered as an alternative if finerenone is not accessible, it remains unclear whether the balance of safety and efficacy is consistent across the class; while data supporting use of sMRAs is robust in HFrEF, data supporting sMRA efficacy for HFpEF have been mixed, including a recently presented study that was terminated prematurely and was accordingly underpowered for the primary efficacy assessment.⁴⁴ Additionally, the safety profile of sMRAs in patients with advanced CKD is a concern.^{16,43} Other attractive targets for intervention include blood pressure, which remains elevated above guideline-recommended targets (<130/80 mmHg), and central adiposity. Screening for sleep apnea, an important and treatable cause of secondary hypertension, should be considered, particularly if the patient has suggestive symptoms of snoring or daytime somnolence. Use of an angiotensin receptor-neprilysin inhibitor (ARNI) in place of losartan is a consideration given the possibility for greater reduction in blood pressure, though data supporting greater efficacy of ARNI compared with angiotensin II receptor blockers in patients with HFpEF is less compelling when LVEF is in the normal or supranormal range.⁴⁵ An alternative in this case is to use a GLP-1 or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist such as semaglutide or tirzepatide, since it might allow for simultaneous reduction in blood glucose, weight, and blood pressure with benefits for functional capacity and quality of life; however, data regarding the impact of this strategy on long-term CV outcomes in HFpEF are limited.⁴⁶⁻⁴⁸ Practical guidance for use of finerenone, including strategies for dosing and laboratory surveillance, is outlined in **TABLE 5**.⁴⁹⁻⁵¹

SUMMARY

CKM syndrome provides a clinically useful framework for understanding how metabolic risk, CKD, and CVD amplify each other, and why therapies with multidomain benefit can be especially valuable. Evolving therapies targeting the spectrum of cardiometabolic risk including SGLT2 inhibitors, nsMRAs, and GLP-1/GIP receptor agonists are emerging that may favorably modulate risk in patients with CKM across the risk spectrum, including patients with HF and mildly reduced or preserved ejection fraction. In particular, data regarding the use of finerenone from large, prospective clinical trials enrolling patients across the CKM spectrum (including those with HFpEF) suggest significant benefits with regard to CV risk reduction. While the use of sMRAs (spironolactone, eplerenone) may be preferred in patients with HFrEF, where the evidence base is strong, the weight of evidence may favor use of finerenone in patients with

TABLE 5. FDA-approved indications, dosing, and potassium monitoring for nonsteroidal and steroidal MRAs.

MRA	FDA-approved indications	Dosing	Potassium monitoring
Finerenone ⁴⁸	To reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, nonfatal myocardial infarction, and hospitalization for HF in adult patients with CKD associated with T2D To reduce the risk of CV death, hospitalization for HF, and urgent HF visits in adult patients with HF with LVEF ≥ 40	Starting dose: <ul style="list-style-type: none"> 20 mg once daily if eGFR ≥ 60 mL/min/1.73 m² 10 mg once daily if eGFR ≥ 25 to < 60 mL/min/1.73 m² Initiation not recommended if eGFR < 25 mL/min/1.73 m² Target dose: <ul style="list-style-type: none"> CKD associated with T2D: 20 mg daily For patients with HF with LVEF $\geq 40\%$, the target dose is 20 mg if baseline eGFR is ≥ 25 to < 60 mL/min/1.73 m² and 40 mg if baseline eGFR is ≥ 60 mL/min/1.73 m² Doses are increased, maintained, or decreased based on serum potassium monitoring	Measure serum potassium at baseline and 4 weeks after initiating treatment If serum potassium levels are > 4.8 to 5.0 mEq/L, initiation may be considered with additional serum potassium monitoring within the first 4 weeks Measure serum potassium 4 weeks after a dose adjustment and periodically throughout treatment, and adjust dose if needed, according to drug labeling
Spironolactone ⁴⁹	Treatment of HF with reduced ejection fraction ^a	If serum potassium is ≤ 5.0 mEq/L and eGFR > 50 mL/min/1.73 m ² , initiate 25 mg daily. Can increase to 50 mg daily or reduce to 25 mg every other day depending on response If eGFR is between 30 and 50 mL/min/1.73 m ² , consider initiating treatment at 25 mg every other day	Monitor potassium at baseline and approximately 1 month after initiation or dose changes and routinely throughout treatment
	Treatment of hypertension	Recommended initial dose is 25 to 100 mg daily, can be titrated at 2-week intervals	
	Treatment of edema associated with hepatic cirrhosis or nephrotic syndrome	In patients with cirrhosis, initiate in a hospital setting and titrate slowly Initial dose is 100 mg daily, but can range from 25 to 200 mg daily	
	Treatment of primary hyperaldosteronism	100 to 400 mg doses in preparation for surgery	
Eplerenone ⁵⁰	Improving survival of patients with symptomatic HFrEF after an acute myocardial infarction	Initiate at 25 mg once daily and titrate to the recommended dose of 50 mg once daily, preferably within 4 weeks Adjust dose based on serum potassium level	Monitor potassium at baseline and approximately 1 month after initiation or dose changes and routinely throughout treatment; adjust dose if needed, based on drug labeling
	Treatment of hypertension	50 mg once daily; if blood pressure response is inadequate, can increase to 50 mg twice daily after 1 month	

^aGuidelines indicate that the use of spironolactone may be appropriate for HFpEF, provided that potassium is < 5.0 mEq/L and eGFR is > 30 mL/min/1.73 m².

HF and higher ejection fractions, particularly where there is an overlap with other cardiometabolic risk factors such as diabetes and CKD. The practical challenge now is implementation: reducing inertia through routine screening and identification, promptly initiating and maintaining effective therapies, and monitoring for adverse effects or disease worsening. PCCs play a key role in collaborating with cardiology, nephrology, and endocrinology specialists to implement comprehensive CKM care. ●

REFERENCES

1. 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
2. Zhu R, Wang R, He J, et al. Prevalence of cardiovascular-kidney-metabolic syndrome stages by social determinants of health. *JAMA Netw Open*. 2024;7(11):e2445309. doi:10.1001/jamanetworkopen.2024.45309
3. Yejin Lee L, Epstein AJ, Chatterjee S, Marcum ZA, Bengtson LGS. Clinical and economic burden of chronic kidney disease in Medicare Fee-for-Service beneficiaries with and without comorbid type 2 diabetes and heart failure: a retrospective cohort study. *J Manag Care Spec Pharm*. 2026;32(2):152-165. doi:10.18553/jmcp.2025.25167
4. Packer M. The adipokine hypothesis of heart failure with a preserved ejection fraction. *JACC*. 2025;86(16):1269-1373. doi:10.1016/j.jacc.2025.06.055
5. American Diabetes Association Professional Practice Committee for Diabetes, Bajaj

- M, McCoy RG, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026. *Diabetes Care*. 2026;49(Supplement_1):S183-S215. doi:10.2337/dc26-S009
6. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2024;105(4S):S117-S314. doi:10.1016/j.kint.2023.10.018
7. Heidenreich PA, Bozkurt B, Aguilar D, 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
8. Solomon SD, McMurray JJV, Vaduganathan M, et al. Finerenone in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2024;391(16):1475-1485. doi:10.1056/NEJMoa2407107
9. Agarwal R, Green JB, Heerspink HJL, et al. Finerenone with empagliflozin in chronic kidney disease and type 2 diabetes. *N Engl J Med*. 2025;393(6):533-543. doi:10.1056/NEJMoa2410659
10. Bozkurt B, Januzzi JL, Bansal S. Cardiovascular-kidney-metabolic effects: steroid and nonsteroidal mineralocorticoid receptor antagonists. *Rev Cardiovasc Med*. 2025;26(7):38690. doi:10.31083/RCM38690
11. Bauersachs J, Jaissner F, Toto R. Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases. *Hypertension*. 2015;65(2):257-263. doi:10.1161/HYPERTENSIONAHA.114.04488
12. Jaissner F, Barrera-Chimal J. Mineralocorticoid receptor antagonism for non-diabetic kidney disease. *Nephrol Dial Transplant*. 2025;40(Supplement_1):i29-i36. doi:10.1093/ndt/gfae241
13. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364(1):11-21. doi:10.1056/NEJMoa1009492
14. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341(10):709-717. doi:10.1056/NEJM199909023411001
15. Matsumoto S, Kondo T, Jhund PS, et al. Underutilization of mineralocorticoid antagonists in patients with heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2023;82(11):1080-1091. doi:10.1016/j.jacc.2023.06.021
16. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370(15):1383-1392. doi:10.1056/NEJMoa1313731
17. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. *Circulation*. 2015;131(1):34-42. doi:10.1161/CIRCULATIONAHA.114.013255
18. Maron BA, Leopold JA. The role of the renin-angiotensin-aldosterone system in the pathobiology of pulmonary arterial hypertension (2013 Grover Conference series). *Pulm Circ*. 2014;4(2):200-210. doi:10.1086/675984
19. Jhund PS, Talebi A, Henderson AD, et al. Mineralocorticoid receptor antagonists in heart failure: an individual patient level meta-analysis. *The Lancet*. 2024;404(10458):1119-1131. doi:10.1016/S0140-6736(24)01733-1
20. Ferreira JP, Pitt B, Zannad F. Mineralocorticoid receptor antagonists in heart failure: an update. *Circ Heart Fail*. 2024;17(12):e011629. doi:10.1161/CIRCHEARTFAILURE.124.011629
21. Kintscher U, Edelmann F. The non-steroidal mineralocorticoid receptor antagonist finerenone and heart failure with preserved ejection fraction. *Cardiovasc Diabetol*. 2023;22(1):162. doi:10.1186/s12933-023-01899-0
22. 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
23. 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
24. Vaduganathan M, Claggett BL, Desai AS, et al. Time to significant benefit of finerenone in patients with heart failure. *J Am Coll Cardiol*. 2025;85(2):199-202. doi:10.1016/j.jacc.2024.09.018
25. Vaduganathan M, Claggett BL, Desai AS, et al. Estimated long-term benefits of finerenone in heart failure: a prespecified secondary analysis of the FINEARTS-HF randomized clinical trial. *JAMA Cardiol*. 2025;10(2):176. doi:10.1001/jamacardio.2024.3782
26. Docherty KF, Henderson AD, Jhund PS, et al. Efficacy and safety of finerenone across the ejection fraction spectrum in heart failure with mildly reduced or preserved ejection fraction: a prespecified analysis of the FINEARTS-HF trial. *Circulation*. 2025;151(1):45-58. doi:10.1161/CIRCULATIONAHA.124.072011
27. Butt JH, Jhund PS, Henderson AD, et al. Finerenone and new-onset diabetes in heart failure: a prespecified analysis of the FINEARTS-HF trial. *The Lancet Diabetes Endocrinol*. 2025;13(2):107-118. doi:10.1016/S2213-8587(24)00309-7
28. Matsumoto S, Henderson AD, Jhund PS, et al. Finerenone and atrial fibrillation in heart failure: a secondary analysis of the FINEARTS-HF randomized clinical trial. *JAMA Cardiol*. 2025;10(7):696. doi:10.1001/jamacardio.2025.0848
29. Vaduganathan M, Filippatos G, Claggett BL, et al. Finerenone in heart failure and chronic kidney disease with type 2 diabetes: FINE-HEART pooled analysis of cardiovascular, kidney and mortality outcomes. *Nat Med*. 2024;30(12):3758-3764. doi:10.1038/s41591-024-03264-4
30. Pabon MA, Filippatos G, Claggett BL, et al. Finerenone reduces new-onset atrial fibrillation across the spectrum of cardio-kidney-metabolic syndrome: the FINE-HEART pooled analysis. *J Am Coll Cardiol*. 2025;85(17):1649-1660. doi:10.1016/j.jacc.2025.03.429
31. Heerspink HJL, Grams ME, Sang Y, et al. Proteinuria or albuminuria as markers of kidney and cardiovascular disease risk: an individual patient-level meta-analysis. *Ann Intern Med*. 2026;179(1):32-41. doi:10.7326/ANNALS-25-02117
32. Vaduganathan M, Green JB, Heerspink HJL, et al. Simultaneous initiation of finerenone and empagliflozin across the spectrum of kidney risk in the CONFIDENCE trial. *Nephrol Dial Transplant*. 2025;41(1):161-170. doi:10.1093/ndt/gfaf160
33. Vaduganathan M, Claggett BL, Chatur S, et al. Lifetime benefits of comprehensive medical therapy in heart failure with mildly reduced or preserved ejection fraction. *Nat Med*. 2026;32(1):325-331. doi:10.1038/s41591-025-04037-3
34. Ostrominski JW, Claggett BL, Miao ZM, et al. Cardiovascular-kidney-metabolic overlap in heart failure with mildly reduced or preserved ejection fraction: a trial-level analysis. *J Am Coll Cardiol*. 2024;84(2):223-228. doi:10.1016/j.jacc.2024.05.005
35. Heerspink HJL, Birkenfeld AL, Cherney DZI, et al. Rationale and design of a randomised phase III registration trial investigating finerenone in participants with type 1 diabetes and chronic kidney disease: the FINE-ONE trial. *Diabetes Res Clin Pract*. 2023;204:110908. doi:10.1016/j.diabres.2023.110908
36. Wright EE, Low Wang CC, Novak LM, Shubrook JH. Misclassification of type 1 diabetes as type 2 diabetes in adults: practical guidance for screening and diagnosis for primary care providers. *Postgrad Med*. 2026;1-12. doi:10.1080/00325481.2026.2672192
37. Heerspink HJL, Birkenfeld AL, Cherney DZI, et al. Finerenone in type 1 diabetes and chronic kidney disease. *N Engl J Med*. 2026;394(10):947-957. doi:10.1056/NEJMoa2512854
38. Hobbs FDR, McManus RJ, Taylor CJ, et al. Low-dose spironolactone and cardiovascular outcomes in moderate stage chronic kidney disease: a randomized controlled trial. *Nat Med*. 2024;30(12):3634-3645. doi:10.1038/s41591-024-03263-5
39. Heerspink HJL, Cardona JF, Jolly S, et al. Balcinrenone in combination with dapagliflozin compared with dapagliflozin alone in patients with chronic kidney disease and albuminuria: a randomised, active-controlled double-blind, phase 2b clinical trial. *The Lancet*. 2025;406(10518):2449-2460. doi:10.1016/S0140-6736(25)02014-8
40. American Diabetes Association Professional Practice Committee for Diabetes, Bajaj M, McCoy RG, et al. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2026. *Diabetes Care*. 2026;49(Supplement_1):S216-S245. doi:10.2337/dc26-S010
41. Writing Committee Members, Ndumele CE, Rodriguez F, et al. 2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2026;154(4):e50-e158. doi:10.1161/CIR.0000000000001453
42. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. 2022;28(3):568-574. doi:10.1038/s41591-021-01659-1
43. Berg DD, Patel SM, Haller PM, et al. Dapagliflozin in patients hospitalized for heart failure: primary results of the DAPA ACT HF-TIMI 68 randomized clinical trial and meta-analysis of sodium-glucose cotransporter-2 inhibitors in patients hospitalized for heart failure. *Circulation*. 2025;152(20):1411-1422. doi:10.1161/CIRCULATIONAHA.125.076575
44. American College of Cardiology. SPIRIT-HF: Does spironolactone benefit patients with HFpEF? HFmrEF? March 29, 2026. Accessed May 21, 2026. <https://www.acc.org/latest-in-cardiology/articles/2026/03/25/21/27/sun-1045am-spirit-hf-acc-2026>
45. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381(17):1609-1620. doi:10.1056/NEJMoa1908655
46. Kosiborod MN, Petrie MC, Borlaug BA, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. *N Engl J Med*. 2024;390(15):1394-1407. doi:10.1056/NEJMoa2313917
47. Packer M, Zile MR, Kramer CM, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. *N Engl J Med*. 2025;392(5):427-437. doi:10.1056/NEJMoa2410027
48. Leavens ELS, Arnold MJ, Nollen NL, Sanderson Cox L, Brown KA, Ellerbeck EF. GLP-1 receptor agonist indications and prescriptions among adults who do and do not smoke. *medRxiv*. 2025;48(11):e150-e151. doi:10.2337/dca25-0090
49. Kerendia (finerenone). Prescribing Information. Bayer HealthCare Pharmaceuticals Inc.; August 2025. Accessed February 18, 2026. https://labeling.bayerhealthcare.com/html/products/pi/Kerendia_PI.pdf
50. Spironolactone. Prescribing Information. NorthStar Rx LLC; January 2026. Accessed February 18, 2026. <https://nctr-crs.fda.gov/ldlabel/services/spl/set-ids/ae0dc4b6-63df-459c-8e60-0caa817b8135/spl-doc>
51. Eplerenone. Prescribing Information. AvKARE; March 2022. Accessed February 18, 2026. <https://nctr-crs.fda.gov/ldlabel/services/spl/set-ids/d953457e-0aff-6c38-e053-2995a90a7d32/spl-doc>

Beyond the Usual Suspects: Hypercortisolism as a Key Cause of Resistant Hypertension

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INTRODUCTION

Hypertension (HTN) is one of the most common disorders in the United States, affecting approximately 50% of adults.¹ Despite multiple medications for managing blood pressure, resistant HTN occurs in 10% to 20% of patients treated for HTN.² According to the American Heart Association (AHA), resistant HTN is defined as above-goal elevated blood pressure despite concurrent use of 3 antihypertensive drug classes, commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system, and a diuretic, at maximally tolerated doses.² Resistant HTN also includes patients who achieve blood pressure targets on ≥4 antihypertensive medications.²

Hypercortisolism can result in HTN and other cardiometabolic comorbidities. Primary care clinicians (PCCs) usually manage patients with HTN and are often the first clinicians to evaluate the clinical picture that might trigger suspicion of hypercortisolism. Identifying patients with HTN who may have hypercortisolism is critical for improving outcomes.

BURDEN OF ENDOGENOUS HYPERCORTISOLISM IN HTN

Hypercortisolism is a disease spectrum characterized by excess cortisol and is associated with increased cardiometabolic comorbidities and mortality.³ Endogenous hypercortisolism can be classified into 2 main categories^{4,5}:

- **ACTH-dependent hypercortisolism:** Includes excess adrenocorticotropic hormone (ACTH) secretion by

Key takeaways

- Hypercortisolism has detrimental systemic effects that can result in HTN and other cardiometabolic comorbidities, increasing the risk of mortality.
- Hypercortisolism may act as a potential driver for HTN due to a variety of pathophysiologic mechanisms affecting the blood pressure regulatory system.
- Data from multiple studies, including the recent MOMENTUM study, show the prevalence of hypercortisolism in patients with resistant HTN to be as high as 27.3%.
- Screening for hypercortisolism is currently underutilized and should be considered in at-risk populations with resistant HTN who have physical characteristics or comorbidities that may indicate an increased likelihood of hypercortisolism.

pituitary tumors (Cushing disease) and nonpituitary tumors (ectopic ACTH secretion).

- **ACTH-independent hypercortisolism:** Includes autonomous cortisol secretion by one or both adrenal glands.

Exogenous hypercortisolism refers to the intake of excess cortisol from external sources. This is most commonly from prescribed steroid medication, though sometimes cortisol is taken surreptitiously for other reasons. While Cushing syndrome (increased cortisol due to any cause) may be endogenous or exogenous, this review primarily aims to describe the role of endogenous hypercortisolism in patients with HTN, and we refer to endogenous hypercortisolism as hypercortisolism.

No matter how severe the clinical presentation or the degree of excess cortisol, hypercortisolism results in detrimental systemic effects, leading to various cardiometabolic comorbidities and increased mortality (TABLE 1).^{3,6} Certain cardiometabolic risks of hypercortisolism, such as type 2 diabetes (T2D), have been established by prior studies such as CATALYST, which found a hypercortisolism prevalence of 24% in patients with T2D.⁷⁻⁹ HTN is a prominent cardiometabolic risk of hypercortisolism; 89.3% of patients with hypercortisolism had HTN in the CATALYST population.⁹ The risk of HTN in hypercortisolism is substantial, ranging from 40% to 90%.³ Additionally, surgical resolution of hypercortisolism improves blood pressure control in about 30% to 70% of patients, indicating that hypercortisolism is often an underlying cause of HTN.^{10,11}

THE UNDERLYING PATHOPHYSIOLOGY OF HTN SECONDARY TO HYPERCORTISOLISM

The relationship between hypercortisolism and HTN is complex and thought to be multifactorial.^{12,13} There are several proposed mechanisms by which excess cortisol disrupts blood pressure regulatory systems, including effects on the renin-angiotensin-aldosterone system (RAAS), mineralocorticoid receptor activity, vasoregulatory factors, and the sympathetic nervous system (FIGURE 1).¹⁴⁻²¹

- Excess endogenous cortisol causes increased hepatic synthesis of angiotensinogen and angiotensin II receptors type 1a, leading to increased vasoconstriction.¹³
- An estimated 5% to 21% of adrenal tumors cosecrete cortisol and aldosterone; increases in aldosterone lead to higher fluid volume and HTN.^{13,22}
- Aldosterone and glucocorticoids bind to mineralocorticoid receptors; in hypercortisolism, excess cortisol leads to receptor activation, which increases sodium reabsorption, potassium secretion, and plasma volume, causing HTN.¹³
- Hypercortisolism affects vasoregulatory factors by glucocorticoid-mediated impairment of the nitric oxide pathway and disruption of the synthesis of vasodilators (kallikrein-kinin system), causing increased vasoconstriction and higher levels of endothelin-1 and erythropoietin.¹³
- Hypercortisolism adversely affects the sympathetic nervous system as excess cortisol is associated with enhanced pressor sensitivity to noradrenaline and beta-adrenergic agonists, resulting in increased blood pressure.¹³

Thus, hypercortisolism may act as a potential driver for HTN due to a variety of pathophysiologic mechanisms.

TABLE 1. Increased cardiometabolic risk and mortality across the hypercortisolism spectrum.³

	Cardiometabolic risk, %*		
	Lower	Higher	
	NFAI	ACS	Overt CS
Cardiovascular disease	3	10-20	20-30
Osteoporosis	20-40	40-60	40-50
HTN	40-75	60-80	50-90
T2D	10-25	20-40	20-50
Metabolic syndrome	70-80	70-90	80-90
Mortality	—	HR 12 (compared to NFAI)	HR 2-4 (compared to general population)
Serum cortisol post 1-mg DST	<1.8 µg/dL	≥1.8 µg/dL	

Abbreviations: ACS, autonomous cortisol secretion; CS, Cushing syndrome; DST, dexamethasone-suppression test; HR, hazard ratio; NFAI, nonfunctioning adrenal incidentalomas; T2D, type 2 diabetes.

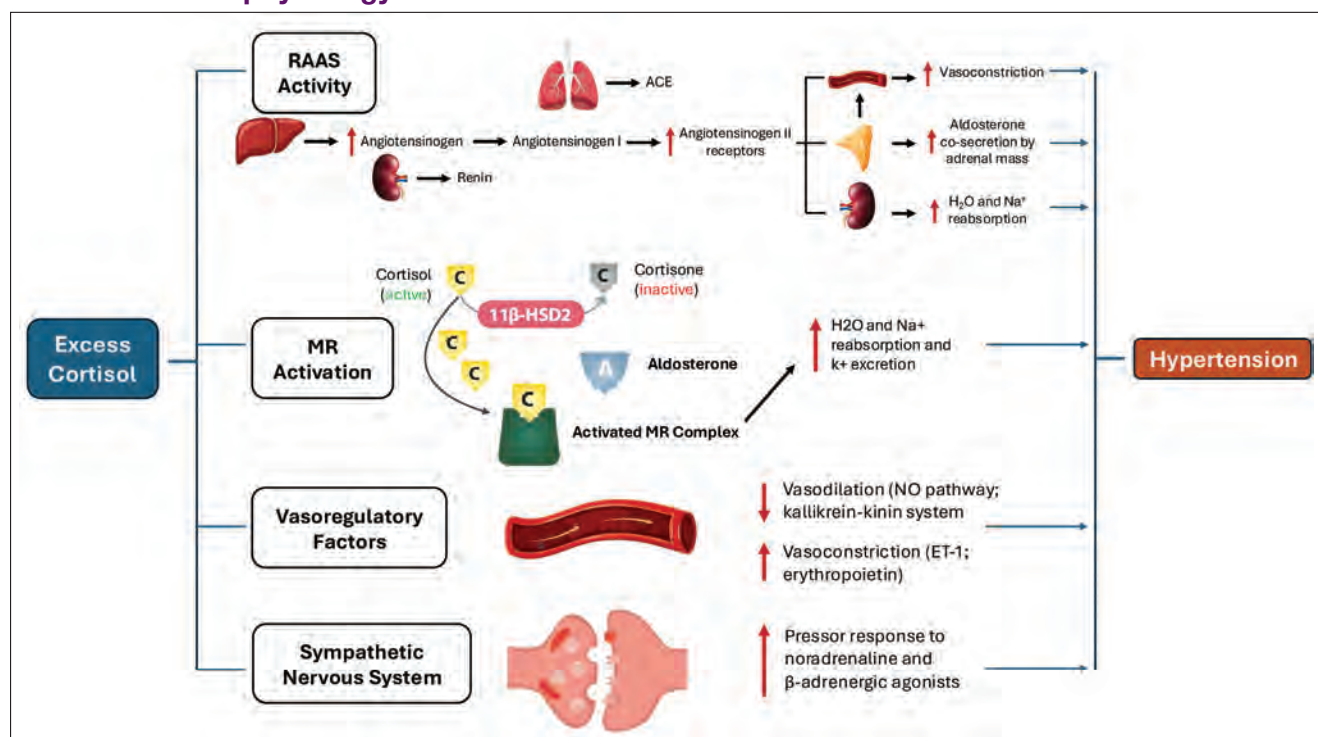
*Percentages indicate the proportion of the populations with hypercortisolism who have the cardiometabolic conditions listed.

PREVALENCE OF HYPERCORTISOLISM IN PATIENTS WITH HTN

The prevalence of hypercortisolism in patients with HTN ranges widely depending on the population studied, with higher rates reported in select at-risk populations (TABLE 2).^{4,23-31} A hypercortisolism prevalence of 0.1% to 7.5% has been reported in unselected patient populations with HTN, compared with a 7.5% to 18.3% prevalence of hypercortisolism in selected populations with HTN.²³⁻³¹ Selected population characteristics include resistant HTN, onset at <40 years, and individuals with adrenal lesions.²⁶⁻²⁸

MOMENTUM was a prospective study designed to provide an estimate of hypercortisolism prevalence and its associated clinical characteristics in a US population of adults with resistant HTN.³² The study included 1000 adults with resistant HTN, defined by the AHA criteria noted previously, using a systolic blood pressure target of <130 mmHg. Patients with investigator-determined white-coat HTN, nonadherence to BP medications, and individuals whose DST results could be difficult to interpret were excluded.³²

BP was measured by an automated device, which takes 3 measurements separated by 1 minute and provides the mean result. Patients with confirmed resistant HTN were tested for hypercortisolism at a second visit, using the 1-mg DST, and those with a post-DST cortisol level >1.8 µg/dL and dexamethasone ≥140 ng/dL were classified as having hypercortisolism.³² Results indicate findings from the MOMENTUM study showed 27.3% prevalence of hypercortisolism in patients

FIGURE 1. Pathophysiology of cortisol-mediated HTN.¹⁴⁻²¹

Abbreviations: ACE, angiotensin-converting enzyme; ET-1, endothelin-1; H₂O, water; K, potassium; MR, mineralocorticoid receptor; Na, sodium; NO, nitric oxide. Red arrows indicate changes with elevated cortisol. Images designed by Freepik.

with resistant HTN. Results also showed adrenal nodules in 24.3% of patients with hypercortisolism. In addition, the prevalence of hypercortisolism was >30% in patients with diabetes and cardiac disorders (e.g., atrial fibrillation, coronary artery disease, heart failure), and >40% in patients with kidney disease. According to the MOMENTUM findings, screening for hypercortisolism may be warranted in individuals with resistant HTN.³³

SCREENING FOR HYPERCORTISOLISM IN PATIENTS WITH HTN

Although the links between hypercortisolism and HTN are known, clinicians are challenged to identify patient phenotypes and to determine those recommended by guidelines for hypercortisolism screening.⁴ Additionally, hypercortisolism screening in at-risk patients with HTN is low, leading to missed diagnoses and suboptimal patient outcomes.³⁴

Identifying patients with HTN who should be screened for hypercortisolism involves assessing characteristics that indicate a higher risk of hypercortisolism, such as age of onset of HTN, severity of HTN, HTN phenotype (dipping, nondipping, etc.), radiologic features (adrenal lesions), and clinical features of hypercortisolism.¹² Combining these characteris-

tics with the use of a sensitive test for hypercortisolism—the 1-mg DST (described in more detail below) is recommended as first-line—can help clinicians more effectively identify patients with hypercortisolism.

HTN phenotypes in patients with HTN

The prevalence of HTN is approximately equal among men and women and across etiologies of hypercortisolism.^{35,36} However, a nondipping circadian rhythm blood pressure profile is associated with hypercortisolism and may represent another clinical characteristic indicating a higher risk of hypercortisolism among patients with HTN.^{37,38} Dipping refers to a decline in nighttime blood pressure of 10% to 20% compared to daytime levels, and various dipping patterns are associated with differing degrees of cardiovascular risk.³⁷ Nighttime blood pressure dipping patterns include the following³⁷:

1. Reverse dipping (increase in nighttime blood pressure)
2. Nondipping (≤10% decline in nighttime blood pressure)
3. Dipping (>10% and ≤20% decline in nighttime blood pressure)
4. Extreme dipping (>20% decline in nighttime blood pressure)

TABLE 2. Prevalence of hypercortisolism in patients with HTN.

Study	Study design	Sample size	HTN population	Screening test(s)	Cutoff	Prevalence
Non-select patient populations						
Rudnick et al (1977) ²³	Retrospective, single-center	665	16-29 years: BP $\geq$ 140/90 mmHg 30-69 years: BP $\geq$ 160/100 mmHg $\geq$ 70 years: BP $\geq$ 170/100 mmHg	Not defined	Not defined	0.2%
Danielson et al (1981) ²⁴	Retrospective, single-center	1000	<40 years: BP $\geq$ 160/95 mmHg 40-60 years: BP $\geq$ 170/105 mmHg >60 years: BP $\geq$ 180/110 mmHg	Serum cortisol	Not defined	0.1%
Sinclair et al (1987) ²⁵	Prospective, cross-sectional, single-center	3783	Nonmalignant HTN not further defined Mean BP for men was 181/111 mmHg Mean BP for women was 185/109 mmHg	Not defined	Not defined	0.1%
Anderson et al (1994) ³⁰	Cross-sectional (1-day blood pressure study)	4429	Patients with HTN referred to a HTN referral center	Serum cortisol	Not defined	0.5%
Omura et al (2004) ²⁹	Prospective, cross-sectional, single-center	1020	Adults with HTN (BP >140/90 mmHg) with suspected endocrinologic diseases	1-mg DST	3.0 μ g/dL	1.0%
Musolino et al (2025) ³¹	Prospective, cross-sectional, single-center	106	Patients aged 30-70 years with HTN (BP >140/90 mmHg or the use of any antihypertensive treatment), without diabetes, and without obesity who were referred to a hypertension clinic	1-mg DST	1.8 μ g/dL	7.5%
Select patient populations						
Martins et al (2012) ²⁶	Prospective, cross-sectional, single-center	430	Resistant HTN (BP $\geq$ 140/90 mmHg despite at least 3 antihypertensive drugs at full dosages, including a diuretic)	1-mg DST + LNSC	DST: 50 nmol/L LNSC: 3.6 nmol/L	8.0%
Trifanescu et al (2013) ²⁷	Retrospective, single-center	80	$\leq$ 40 years of age at HTN onset (BP range 145-300/80-170 mmHg)	1-mg DST	1.8 μ g/dL	7.5%
Aoe et al (2020) ²⁸	Retrospective, single-center	104	HTN (BP $\geq$ 140/90 mmHg) + adrenal masses	Possible subclinical CS 1-mg DST	DST: 1.8 μ g/dL	18.3%

Abbreviations: BP, blood pressure; LNSC, late-night salivary cortisol.

These profiles have various levels of cardiovascular risk, with nondipping profiles associated with elevated risk.^{37,38} About 40% to 56% of patients with hypercortisolism have a nondipping blood pressure.^{39,40} Furthermore, the nondipping profile may be more prevalent in patients with adrenal hypercortisolism, among hypercortisolism etiologies.^{39,40} Of note, identifying dipping blood pressure patterns typically requires 24-hour ambulatory blood pressure monitoring, which may not be feasible for all patients with HTN.

Screening for and diagnosing hypercortisolism in patients with HTN

In addition to a nondipping HTN phenotype, other patient characteristics indicate an increased likelihood for hypercortisolism, and such patients should be screened.¹²

- **Age:** <40 years of age with Grade 2 HTN or HTN in childhood
- **Onset:** acute worsening in patients with previously stable HTN or diabetes
- **Severity:** resistant HTN
- **Radiologic findings:** adrenal incidentalomas and adrenal lesions (these patients should also be screened for pheochromocytomas and aldosteronomas)^{41,42}
- **Clinical features of hypercortisolism:** easy bruising, facial plethora, striae; proximal myopathy or muscle weakness; osteoporosis at young age; unusual features for age or multiple, progressive features

There are several tests available for identifying hypercortisolism, including the 1-mg DST, the 24-hour urinary

free cortisol (UFC), and the LNSC tests. The 1-mg DST is the most sensitive test and is the recommended first-line screening method.⁴³ The post-DST serum cortisol threshold for hypercortisolism is 1.8 µg/dL, and along with adequate dexamethasone plasma levels (>140 ng/dL) to prove adherence to the 1 mg dose, this is associated with a 100% sensitivity.⁴⁴ While the 24-hour UFC and LNSC tests are available, they are less sensitive for hypercortisolism screening, and the 24-hour UFC is not as practical for patients.⁴⁴

A diagnosis of hypercortisolism is typically established by biochemical testing in patients with a clinical picture suggesting hypercortisolism.^{12,43} Diagnostic flowcharts for hypercortisolism may be helpful for clinicians to implement a standardized process for detecting and diagnosing the disease in patients with HTN.^{12,43} If PCCs suspect hypercortisolism based on clinical presentation and testing results (**FIGURE 2**), they should engage the multidisciplinary health care team for further workup and treatment, potentially including a referral to endocrinology and cardiology.⁴⁵ While PCCs may refer for further workup and diagnosis, this is a diagnosis that can be made by a PCC, and PCCs can properly diagnose and manage hypercortisolism to achieve timely treatment and optimal patient outcomes.

CASE STUDY

A 52-year-old man with a 15-year history of HTN is being managed by his primary care team in collaboration with a cardiologist. He currently takes losartan, hydrochlorothiazide, and amlodipine at maximum doses. His blood pressure today is 158/96 mmHg. It has been increasing over the past 2 years, and his cardiologist has noted a nondipping nocturnal blood pressure pattern. His PCC decides to screen him for hypercortisolism using the 1-mg DST.

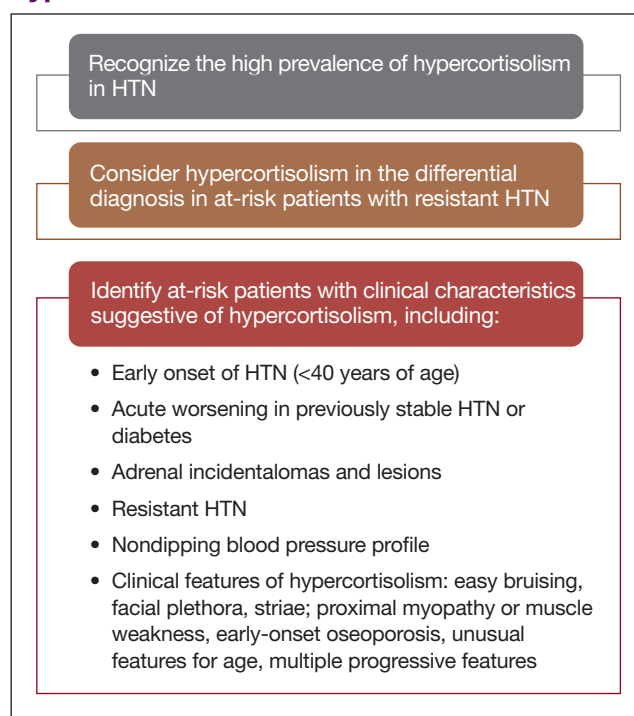
Laboratory evaluations

- Morning cortisol: 17 µg/dL (normal 10-25 µg/dL)⁴⁶
- Serum cortisol after 1-mg DST: 3.8 µg/dL (normal is <1.8 µg/dL)⁴⁷
- Serum dexamethasone after 1-mg DST: 417.2 ng/dL (expected is >140 ng/dL for adequate serum cortisol suppression)⁴⁸
- 24-hour UFC: 47 µg/24 hr (normal range varies depending on specific test; example normal range is <11-53 µg/24 hr)⁴⁹

Clinical assessment

This patient with resistant HTN has a strong likelihood of hypercortisolism, as evidenced by the results of the 1-mg DST and characteristics such as a nondipping blood pressure pattern and early onset of HTN (<40 years of age).

FIGURE 2. Key takeaways and action items for PCCs regarding resistant HTN and hypercortisolism.



Clinical learning

This case highlights the need to screen for hypercortisolism in patients with HTN and clinical characteristics that raise suspicion for cortisol-mediated elevations in blood pressure. While the patient may not receive a full diagnosis of hypercortisolism in primary care, the PCC can initiate a referral process, sending the 1-mg DST results to an endocrinologist to speed the process of a definitive diagnosis.

The PCC can also implement measures to mitigate cardiovascular risk, such as optimizing antihypertensive therapy and addressing other cardiometabolic factors. The PCC might also consider hypercortisolism-directed therapy, as addressing the underlying hypercortisolism is likely to improve the patient's blood pressure and cardiovascular risk.

SUMMARY

Hypercortisolism has detrimental systemic effects that can result in HTN and other cardiometabolic comorbidities, increasing the risk of mortality. Hypercortisolism may act as a potential driver for HTN due to a variety of pathophysiologic mechanisms. Data from multiple studies, including MOMENTUM, suggest a prevalence of hypercortisolism in up to 27.3% patients with resistant HTN. Screening should be considered in patients with resistant HTN and features suggesting an increased likelihood of hypercortisolism. ●

REFERENCES

- Estimated hypertension prevalence, treatment, and control among U.S. adults. Million Hearts. May 12, 2023. Accessed September 7, 2026. <https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html>
- Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension*. 2018;72(5):e53-e90. doi:10.1161/HYP.0000000000000084
- Araujo-Castro M, Pascual-Corralles E, Lamas C. Possible, probable, and certain hypercortisolism: a continuum in the risk of comorbidity. *Ann Endocrinol (Paris)*. 2023;84(2):272-284. doi:10.1016/j.ando.2023.01.005
- Martino MCD, Canu L, Bonaventura I, Vitiello C, Sparano C, Cozzolino A. Hypertension and Cushing's syndrome: hunt for the red flag. *J Endocrinol Invest*. 2025;48(8):1909-1918. doi:10.1007/s40618-024-02453-9
- Reincke M, Fleseriu M. Cushing syndrome: a review. *JAMA*. 2023;330(2):170. doi:10.1001/jama.2023.11305
- Pelsma ICM, Fassnacht M, Tsagarakis S, et al. Comorbidities in mild autonomous cortisol secretion and the effect of treatment: systematic review and meta-analysis. *Eur J Endocrinol*. 2023;189(4):S88-S101. doi:10.1093/ajendo/lvad134
- Kushner P, Brown DR, Busch RS. Hypercortisolism is more common than you think—here's how to find it. *Fed Pract*. 2024;41(Suppl 6):S23-S28. doi:10.12788/fp.0532
- Kushner P, Anderson JE. Breaking through difficult-to-control T2D: targeting hypercortisolism. *Fed Pract*. 2025;42(Suppl 7):S1-S6. doi:10.12788/fp.0634
- Buse JB, Kahn SE, Aroda VR, et al. Prevalence of hypercortisolism in difficult-to-control type 2 diabetes. *Diabetes Care*. 2025;48(12):2012-2020. doi:10.2337/dc24-2841
- Koh JM, Song K, Kwak MK, et al. Adrenalectomy improves body weight, glucose, and blood pressure control in patients with mild autonomous cortisol secretion: results of a randomized controlled trial by the Co-work of Adrenal Research (COAR) Study. *Ann Surg*. 2024;279(6):945-952. doi:10.1097/SLA.00000000000006183
- Morelli V, Frigerio S, Aresta C, et al. Adrenalectomy improves blood pressure and metabolic control in patients with possible autonomous cortisol secretion: results of a RCT. *Front Endocrinol (Lausanne)*. 2022;13:898084. doi:10.3389/fendo.2022.898084
- 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.00000000000003252
- Barbot M, Ceccato F, Scaroni C. The pathophysiology and treatment of hypertension in patients with Cushing's syndrome. *Front Endocrinol (Lausanne)*. 2019;10:321. doi:10.3389/fendo.2019.00321
- Isidori AM, Graziadio C, Paragliola RM, et al. The hypertension of Cushing's syndrome: controversies in the pathophysiology and focus on cardiovascular complications. *J Hypertens*. 2015;33(1):44-60. doi:10.1097/HJH.00000000000000415
- Sato A, Suzuki H, Murakami M, Nakazato Y, Iwata Y, Saruta T. Glucocorticoid increases angiotensin II type 1 receptor and its gene expression. *Hypertension*. 1994;23(1):25-30. doi:10.1161/01.hyp.23.1.25
- van der Pas R, van Esch JHM, de Bruin C, et al. Cushing's disease and hypertension: in vivo and in vitro study of the role of the renin-angiotensin-aldosterone system and effects of medical therapy. *Eur J Endocrinol*. 2014;170(2):181-191. doi:10.1530/EJE-13-0477
- Quinkler M, Stewart PM. Hypertension and the cortisol-cortisone shuttle. *J Clin Endocrinol Metab*. 2003;88(6):2384-2392. doi:10.1210/jc.2003-030138
- Saruta T. Mechanism of glucocorticoid-induced hypertension. *Hypertens Res*. 1996;19(1):1-8. doi:10.1291/hyres.19.1
- Kelly JJ, Martin A, Whitworth JA. Role of erythropoietin in cortisol-induced hypertension. *J Hum Hypertens*. 2000;14(3):195-198. doi:10.1038/sj.jhh.1000959
- Kirilov G, Tomova A, Dakovska L, Kumanov P, Shinkov A, Alexandrov AS. Elevated plasma endothelin as an additional cardiovascular risk factor in patients with Cushing's syndrome. *Eur J Endocrinol*. 2003;149(6):549-553. doi:10.1530/eje.0.1490549
- Heaney AP, Hunter SJ, Sheridan B, Brew Atkinson A. Increased pressor response to noradrenaline in pituitary dependent Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1999;51(3):293-299. doi:10.1046/j.1365-2265.1999.00766.x
- Jinna S, Taftaf R, Petros FG, Jun JY. Aldosterone- and cortisol co-secreting adrenal cortical neoplasm with lipomatous and myelolipomatous metaplasia. *JCEM Case Rep*. 2023;1(2):luad012. doi:10.1210/jcemcr/luad012
- Rudnick KV, Sackett DL, Hirst S, Holmes C. Hypertension in a family practice. *Can Med Assoc J*. 1977;117(5):492-497.
- Danielson M, Dammström B. The prevalence of secondary and curable hypertension. *Acta Med Scand*. 1981;209(6):451-455. doi:10.1111/j.0954-6820.1981.tb11628.x
- Sinclair AM, Isles CG, Brown I, Cameron H, Murray GD, Robertson JW. Secondary hypertension in a blood pressure clinic. *Arch Intern Med*. 1987;147(7):1289-1293.
- 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
- Trifanescu R, Carsote M, Carageorghopol A, et al. Screening for secondary endocrine hypertension in young patients. *Maedica (Bucur)*. 2013;8(2):108-115.
- Aoe M, Okada A, Usui T, Nangaku M, Makita N. Comparison between the clinical characteristics of patients with adrenal incidentalomas and those with hypertension-associated adrenal tumors in a single center in Japan. *Endocr J*. 2020;67(6):645-654. doi:10.1507/endocrj.EJ19-0262
- Omura M, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. *Hypertens Res*. 2004;27(3):193-202. doi:10.1291/hyres.27.193
- Anderson GH, Blakeman N, Streeten DH. The effect of age on prevalence of secondary forms of hypertension in 4429 consecutively referred patients. *J Hypertens*. 1994;12(5):609-615. doi:10.1097/00004872-199405000-00015
- Musolino A, Parazzoli C, Delle Donne E, et al. Prevalence of hypercortisolism in hypertension and its link to carotid atherosclerosis markers. *Endocr Pract*. 2026;32(3):329-336. doi:10.1016/j.eprac.2025.10.013
- Plutzky J, Auchus RJ, Basile JN, et al. The design of MOMENTUM: a prospective study of the prevalence of endogenous hypercortisolism in individuals with resistant hypertension. Presented at: Annual Meeting of the Endocrine Society (ENDO); July 12-15, 2025; San Francisco, CA. Poster MON-302. <https://corcep.com/wp-content/uploads/ENDO2025-4.pdf>
- Bhatt D. Prevalence and clinical impact of hypercortisolism in individuals with resistant hypertension: primary results from the MOMENTUM study. Presented at: American College of Cardiology's Annual Scientific Session; March 27-30, 2026; New Orleans, LA. <https://corcep.com/wp-content/uploads/ACC2026-1.pdf>
- Di Dalmazi G, Goi J, Burrello J, et al. Screening of hypercortisolism among patients with hypertension: an Italian nationwide survey. *J Endocrinol Invest*. 2024;47(12):3029-3038. doi:10.1007/s40618-024-02387-2
- Mancini T, Kola B, Mantero F, Boscaro M, Arnaldi G. High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines. *Clin Endocrinol (Oxf)*. 2004;61(6):768-777. doi:10.1111/j.1365-2265.2004.02168.x
- Valassi E, Santos A, Yaneva M, et al. The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. *Eur J Endocrinol*. 2011;165(3):383-392. doi:10.1530/EJE-11-0272
- Tang A, Yang E, Ebinger JE. Non-dipping blood pressure or nocturnal hypertension: does one matter more? *Curr Hypertens Rep*. 2024;26(1):21-30. doi:10.1007/s11906-023-01273-1
- Huati J, Persu A, Lengel JP, Krzesinski JM, Jouret F, Stergiou GS. Pathophysiology of the non-dipping blood pressure pattern. *Hypertension*. 2023;80(4):719-729. doi:10.1161/HYPERTENSIONAHA.122.19996
- Zacharieva S, Orbetzova M, Stoynev A, et al. Circadian blood pressure profile in patients with Cushing's syndrome before and after treatment. *J Endocrinol Invest*. 2004;27(10):924-930. doi:10.1007/BF03347534
- Pecori Giraldo F, Toja PM, De Martin M, et al. Circadian blood pressure profile in patients with active Cushing's disease and after long-term cure. *Horm Metab Res*. 2007;39(12):908-914. doi:10.1055/s-2007-992813
- Mao JJ, Baker JE, Rainey WE, Young WF, Bancos I. Concomitant pheochromocytoma and primary aldosteronism: a case series and literature review. *J Endocr Soc*. 2021;5(8):bvab107. doi:10.1210/endo/bvab107
- Ugi S, Yonishi M, Sato D, et al. Coexistence of pheochromocytoma and primary aldosteronism due to multiple aldosterone-producing micronodules in the ipsilateral adrenal gland. *Intern Med*. 2023;62(18):2685-2691. doi:10.2169/INTERNALMED.1012-22
- 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
- Sherlock M, Scarsbrook A, Abbas A, et al. Adrenal incidentaloma. *Endocr Rev*. 2020;41(6):775-820. doi:10.1210/endo/bnaa008
- Busch R. Importance of multidisciplinary care in hypercortisolism management. The Educated Patient. November 5, 2025. Accessed September 7, 2026. <https://www.theeducatedpatient.com/view/importance-of-multidisciplinary-care-in-hypercortisolism-management>
- 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
- Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008; 93(5):1526-1540. doi:10.1210/jc.2008-0125
- 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 (Oxf)*. 2014;80(2):261-269. doi:10.1111/cen.12259

The Contributions of Dairy Foods to Cardiometabolic Health

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INTRODUCTION

Nutrient-dense dairy foods (e.g., milk, yogurt, cheese, and kefir), which are the focus of this article, are foundational components of many healthy eating patterns.¹ Evidence supporting the health benefits of dairy foods extends over several decades, with clinical and observational evidence linking consumption of milk, cheese, and yogurt with favorable effects on body weight, as well as reduced risk of type 2 diabetes (T2D), cardiovascular disease (CVD), osteoporosis, sarcopenia, and colorectal cancer.^{2,3} Notably, the benefits of dairy foods on cardiometabolic (CM) health, which refers to both cardiovascular and metabolic health outcomes, have been well documented through the landmark Dietary Approaches to Stop Hypertension (DASH) trial and the Prospective Urban Rural Epidemiology (PURE) study. Subsequent studies also support that dairy foods at a range of fat levels, both alone and as part of dietary patterns, can have neutral to beneficial effects on blood pressure, blood lipids, and CM outcomes.⁴⁻⁸ These outcomes have advanced our understanding of the nutritional and health attributes of dairy foods and increasingly are attributed to the unique package of nutrients and bioactive compounds within the dairy food matrix.

Consistent with this growing body of evidence, nutrition guidance has continued to shift focus from isolated nutrients to a more food- and eating pattern-based approach.⁹⁻¹²

Key takeaways

- Nutrient-dense dairy foods are foundational components of many healthy eating patterns. Ninety percent of the US population does not meet daily dairy recommendations, contributing to shortfalls in key nutrient intakes. Closing this consumption gap offers an opportunity to achieve nutrient adequacy, improve overall diet quality, and support CM health.
- Saturated fats from dairy foods do not appear to confer CM risk in the same way as saturated fats from other dietary sources, challenging traditional diet-heart paradigm assumptions.
- Dairy foods provide high-quality protein that may help promote muscle preservation, particularly among older adults or patients using obesity medications. Maintaining muscle during weight loss may act as a protective mechanism for CM health.
- Decades of research show that dairy foods have neutral to beneficial effects on CM health, supporting their role in a balanced diet.
- The dairy food matrix helps explain why dairy foods—regardless of fat content—can support CM health. It reflects how the micronutrients, macronutrients, and bioactive compounds in dairy foods interact within a food's physical structure to shape health outcomes.
- 3 servings of nutrient-dense dairy foods at a variety of fat levels can be part of a cardioprotective eating pattern that also meets patients' personal preferences and health goals.

Dietary guidance from a variety of leading health and medical organizations, including the American Heart Association, the American Diabetes Association, and the 2025-2030 US Dietary Guidelines for Americans, recognizes regular consumption of nutrient-dense dairy foods in balanced, calorie-appropriate dietary patterns.¹³⁻¹⁵ Mounting attention among scientific and medical communities also has highlighted that whole- and reduced-fat dairy foods affect health differently than isolated saturated fats or other saturated fat-containing foods, contributing to a growing consensus on the role of the dairy food matrix to inform a holistic, food-based lens for public health guidance.¹⁶⁻¹⁹ Nevertheless, dairy consumption remains low. Approximately 90% of people in the United States do not meet dairy intake recommendations and fall short of key nutrients, including calcium, vitamin D, and potassium, that may benefit CM health.²⁰ Yet, messaging related to CM health more frequently highlights the importance of consuming whole grains, fruits, and vegetables without equal emphasis on consuming nutrient-dense dairy foods.

Evidence-based strategies to help close the dairy food gap, aligned with the state of the science linking dairy foods to CM health, offer a practical opportunity to improve overall diet quality and CM health. This article explores how dairy foods at a variety of fat levels can contribute to CM health outcomes and offers practical strategies for primary care clinicians (PCCs) to guide patients on how to incorporate 3 daily servings of dairy foods while acknowledging their preferences and health goals.

DAIRY FOODS AND CM HEALTH: THE BODY OF OBSERVATIONAL AND CLINICAL EVIDENCE

The latest state of the evidence on CM health includes more than a dozen reviews published since 2020. They assessed decades of clinical and observational research on dairy food consumption and its relationship with overweight and obesity, T2D risk, and CVD outcomes (TABLES 1 and 2).

Dairy foods and overweight and obesity

Obesity is a major risk factor for and cause of T2D and CVD.²¹ Dairy foods consumed as part of healthy, calorie-balanced dietary patterns can contribute to healthy weight management, which can reduce long-term health risks.^{22,23} Studies link dairy food consumption with neutral to beneficial impacts on weight management.^{22,24-31} In fact, when dairy food consumption is increased without energy restriction in clinical research, results suggest no significant effects on weight, fat mass, lean mass, or waist circumference, while increased dairy food consumption as part of an energy-restricted diet may result in lower fat mass and body weight.²⁹ Because of the high-quality protein dairy foods provide, sev-

eral health organizations, including the Obesity Medicine Association, the American Society for Nutrition, the American College of Lifestyle Medicine, and the Academy of Nutrition and Dietetics, recommend dairy foods for individuals taking glucagon-like peptide 1 (GLP-1) receptor agonist medications to help them meet protein consumption targets and preserve lean mass during rapid weight loss.^{32,33} In addition to being high in protein, dairy foods also provide multiple important micronutrients (e.g., calcium, vitamin D, magnesium, phosphorus, and potassium) that have been linked with bone mass retention during weight loss.³⁴⁻⁴² The retention of both muscle and bone mass during weight loss is associated with better CM health outcomes.^{43,44}

Clinical Relevance: Preservation of lean mass during weight loss is clinically meaningful, especially in older adults and patients using obesity medications such as GLP-1 receptor agonists. Dairy foods provide complete protein that may help promote satiety,⁴⁵ muscle preservation,⁴⁶ and healthy weight management²² among adult patients across the weight spectrum.

Dairy foods and T2D

Obesity is a leading driver of T2D development, and obesity-related T2D increases the risks of CVD since the combination creates a high-risk state of metabolic dysfunction, chronic inflammation, hypertension (HTN), and dyslipidemia.⁴⁷⁻⁴⁹ Thus, strategies that support glycemic control are central to CM health. Several major studies have summarized the research on dairy foods and glycemic control, prediabetes, and/or T2D risk.^{2,22,50-56} The findings from these reviews and recent randomized controlled trials (RCTs) indicate that dairy foods support normal glucose regulation across a range of populations, including those who are healthy as well as those who have prediabetes, metabolic syndrome, or T2D.⁵⁷⁻⁶² Total dairy consumption of ~3 servings/day was linked to a 25% lower risk of developing prediabetes compared with 0 servings/day.⁵⁰ Higher consumption of total dairy, low-fat dairy, and yogurt was associated with lower risk for T2D, whereas whole-fat dairy foods and cheese generally were linked with neutral associations and not an increased risk.^{22,51,54} Based on the evidence, regular daily consumption of dairy foods at a variety of fat levels is associated with neutral to beneficial effects on glucose homeostasis.⁵⁷⁻⁶²

Higher consumption of yogurt may have unique glucoregulatory benefits.^{51,63-67} In 2024, the US Food and Drug Administration (FDA) announced a qualified health claim that identifies a potential link between regular yogurt consumption and a reduced risk of T2D, stating, “Eating yogurt regularly, at least 2 cups (3 servings per week), may reduce the risk of T2D according to limited scientific evidence.”⁶³

TABLE 1. Dairy foods and cardiometabolic health biomarkers: clinical evidence reviews published since 2020.

Study type	Population	Key findings
Systematic review of 15 meta-analyses of RCTs ⁵⁵	Healthy adults	Neutral effects of total dairy, full-fat, and low-fat dairy on blood lipids or BP Modest benefits of probiotic yogurt for BP, blood lipids, and HbA1c
Systematic review and meta-analysis of 19 RCTs ⁴⁸	Healthy adults	Both low-fat and full-fat dairy improved SBP but, concomitantly, may impair glycemic control Yogurt improved waist circumference, TG, and HDL compared with milk
Systematic review and meta-analysis of 10 RCTs ⁵⁶	Healthy adults	Dairy fat from cheese improved blood lipid profiles relative to dairy fat from butter Reductions in fasting TC, LDL, and HDL with cheese consumption but not with butter
Systematic review and meta-analysis of 18 RCTs ⁵⁷	Adults with or without metabolic abnormalities	Higher consumption of dairy foods had neutral effects on blood lipids
Systematic review and meta-analysis of 39 RCTs ⁵⁸	Adults with high cholesterol	Reductions in TC and LDL with probiotic fermented milk consumption Neutral effects on HDL and TG levels with probiotic fermented milk consumption
Systematic review and meta-analysis of 7 RCTs ⁶	Adults with high cholesterol	Reductions in TC and LDL with probiotic yogurt consumption No differences in HDL and TG with probiotic yogurt consumption
Systematic review and meta-analysis of 6 RCTs ⁵⁹	Mixed populations	Reductions in fasting blood glucose and insulin levels with kefir consumption
Systematic review and meta-analysis of 6 RCTs ⁶⁰	Mixed populations	Reductions in fasting insulin and HOMA-IR with kefir consumption Neutral effects on blood lipids with kefir consumption
Systematic review of 14 RCTs and 37 noncontrolled interventions ⁶¹	Healthy adults	Beneficial to neutral effects on blood lipids with yogurt and kefir consumption

Abbreviations: BP, blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin; LDL, low-density lipoprotein; RCT, randomized controlled trial; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

This qualified health statement acknowledges the health benefits of yogurt as a food. Similarly, other dairy foods can provide important nutrients such as calcium, vitamin D, and protein; however, some products may also contain added sugars. Both the FDA and the Centers for Disease Control and Prevention emphasize limiting added sugar intake as

part of a healthy diet. Additionally, the 2025-2030 US Dietary Guidelines for Americans recommends limiting added sugar within healthy eating patterns to consuming no more than 10 g of added sugar per meal and, for snacks, following limits set by the FDA (i.e., no more than 2.5 g of added sugar per $\frac{2}{3}$ cup equivalent of dairy snacks like yogurt).¹³ Taken

TABLE 2. Dairy foods and cardiovascular disease risk and clinical endpoints: observational evidence reviews published since 2020.

Study type	Total dairy	Dairy by fat level	Milk	Yogurt	Cheese
Systematic review of 17 meta-analyses ⁵⁵	≤200 g/day: no association with CVD or CHD incidence or mortality	Whole and low-fat: no association with CVD or mortality	≤200 mL/day: no association with CVD	≥200 g/day: ▼ CVD	50 g/day: ▼ CHD
Systematic review and meta-analysis of 42 studies ¹⁸		Low-fat: ▼ 6% HTN	▼ 6% HTN per 200 g/day increase		
Systematic review of 33 studies and meta-analysis of 20 studies ⁶²	No association with CHD or stroke	Whole and low-fat: no association with CHD or stroke	▼ 12% ischemic stroke ▲ 8% CHD with whole milk		▼ 4% CHD per 20 g/day
Scoping review of 25 systematic reviews ⁴²	Neutral/favorable for CVD				
Scoping review of 24 systematic reviews and/or meta-analyses ⁴³	Neutral/beneficial for CM outcomes	Neutral to beneficial CVD effects		Neutral to beneficial CVD effects	Neutral to beneficial CVD effects
Umbrella review of 26 meta-analyses ⁶³	▼ 11% HTN ▼ 4% CVD ▼ 13% stroke	Whole-fat: ▼ 8% stroke Low-fat: ▼ 11% stroke ▼ 13% HTN	▼ 3% CVD ▼ 10% stroke	▼ 8% CVD	
Systematic review and meta-analysis of 55 studies ⁶⁴	▼ 9% HTN ▼ 4% CHD ▼ 10% stroke	Whole and low-fat ▼ stroke			

Abbreviations: CHD, coronary heart disease; HTN, hypertension.

together, a variety of yogurt and other nutrient-rich dairy foods, including options across a range of fat levels and those that are lightly sweetened, may fit into a calorie-appropriate, balanced eating pattern that emphasizes nutrient-dense foods to reduce the risk of T2D and promote CM health.

Clinical Relevance: Nutrient-dense dairy foods at a range of fat levels can help support blood glucose regulation in healthy patients as well as those with prediabetes or T2D. Yogurt may have distinct benefits for glucose homeostasis.

Dairy foods and CVD

CVD is the leading global cause of mortality and is responsible for nearly 1 in 3 deaths.⁶⁸ Dietary modifications generally are recommended as a primary preventive treatment against developing CVD and as a secondary preventive treatment against CVD recurrence and mortality.^{69,70} Multiple studies have shown neutral to beneficial effects of dairy food consumption on anthropometrics, blood lipids, and blood pressure (**TABLE 1**).^{6,7,61,71-77} Clinical studies found that consuming ~3 servings/day of dairy foods regardless of

fat content had a neutral impact on anthropometrics and CVD biomarkers.^{7,58,61,62,78} Additionally, short-term (3 to 12 weeks) yogurt consumption, including whole-fat options, had moderate yet consistent benefits on body composition and blood lipids.^{61,62}

Several evidence reviews also have concluded that higher total consumption of dairy foods is linked to beneficial to neutral effects on CVD risk and mortality (**TABLE 2**).^{22,76,79-81} Lower rates of HTN and stroke were linked to total- and low-fat dairy and milk consumption.^{2,79-81} Fermented dairy foods like yogurt and cheese were also linked to lower risk for CHD, CVD, and CVD mortality.^{52,76,79,81-84} Conversely, 1 study found that whole milk consumption had a negative effect on CVD risk.

Clinical Relevance: Adequate consumption of dairy foods at a variety of fat levels can help support healthy blood lipid profiles and may reduce patient risk for CVD and CVD mortality. Fermented dairy foods may have distinct benefits for CM health.

Re-examining the diet-heart paradigm: saturated fat compared to whole foods

Reducing dietary saturated fat is a hallmark of the diet-heart paradigm that originated in the 1950s, which proposed that saturated fat consumption elevates low-density lipoprotein cholesterol (LDL-C) and increases CVD risk. Research indicates that whole- and reduced-fat dairy foods are not linked with the same CVD risks as other foods containing saturated fats.^{10,62} In fact, the intake of naturally occurring saturated fats in nutrient-dense dairy foods is linked with neutral to beneficial effects on blood lipid profiles, including total LDL-C, particle size distribution, and high-density lipoprotein cholesterol (HDL-C).^{61,62,72,85}

LDL-C remains the mainstream biomarker to assess CVD risk; however, emerging research indicates predicting risk may be more complex, and a suite of biomarkers and risk factors may assess risk better than LDL-C alone. Dietary-induced change in LDL cholesterol does not always lead to a corresponding change in CVD endpoints, as many other mediators of risk may be contributing to the atherosclerotic process. Other emerging risk factors include LDL particle sizes, blood triglycerides, apolipoproteins A1 and B, HDL function, ratios of total cholesterol to HDL-C or total triglycerides to HDL-C, coronary and carotid artery atherosclerotic plaques, markers of inflammation, and measures of insulin resistance.^{86,87}

Clinical Relevance: Dairy foods across a range of fat levels may be a part of a balanced, calorie-appropriate, and healthy eating pattern.

DAIRY FOOD MATRIX EFFECTS AND CM HEALTH

Different types of dairy foods—including milk, yogurt, cheese, and kefir—each have a unique food matrix. The dairy food matrix refers to the array of nutrients and bioactive compounds found within the unique physical structures of dairy foods.^{19,88} The food matrix effect is an emerging concept in research that may provide support for dairy foods' benefits on CM health (**TABLE 3**). Emerging research indicates nutrients and bioactive compounds may work together to affect digestion and absorption, potentially creating a greater impact of dairy on CM health.^{9,53,89,90} Therefore, a food matrix and food-based approach may provide a deeper understanding of why whole- and reduced-fat dairy foods affect CM outcomes differently than isolated saturated fats or other saturated fat-containing foods.¹⁶⁻¹⁸

The unique combination of nutrients and bioactive ingredients in the dairy food matrix includes high-quality protein, vitamins and minerals, bioactive peptides and lipids, prebiotics, and live and active cultures in some fermented dairy foods. Emerging research has linked dairy components with potential benefits on CM health.^{18,91-100} For example, whey and casein are the main proteins in milk; they are high-quality proteins based on their amino acid profiles.⁴² The combination of whey and casein offers both fast- and slow-digesting proteins, which may favorably affect food intake, blood pressure, and metabolism.^{101,102} Milk fat is also complex, containing more than 400 fatty acid types as well as unique polar lipids that are part of the milk fat globule membrane.¹⁰³ These lipids have been linked to potential benefits on inflammation and gut health and may favorably influence lipid metabolism.^{19,104,105} While more research is needed to understand better the role of the food matrix in CM health, the current evidence supports a greater emphasis on whole-food approaches, including dairy foods, in nutrition and clinical guidance.

IMPLICATIONS FOR EVIDENCE-BASED PRACTICE

For more than 4 decades, authoritative nutrition and medical dietary guidance to improve CM health has emphasized consuming multiple daily servings of dairy foods to achieve nutrient adequacy.¹⁰⁶⁻¹⁰⁸ While public health recommendations historically have been directed toward low-fat and fat-free dairy options, decades of research link dairy foods at various fat levels with CM health. This distinguishes the health effects of saturated fat in dairy foods from other dietary sources of saturated fat.^{4-8,16-19} However, the majority of people in the United States do not meet dairy intake recommendations and fall short of key nutrients that dairy foods can provide.²⁰ Given persistent gaps between recommended and actual dairy food consumption, routine clinical visits can be an opportunity for PCCs to help patients

TABLE 3. Dairy food components and potential mechanisms to promote cardiometabolic health.

Dairy component	Potential protective mechanisms
High-quality protein	Can support weight management and lean muscle mass retention during weight loss ³²
Bioactive peptides	Linked with potential benefits for oxidative stress and inflammation, blood pressure regulation, immune health, and glucose control ⁴²
Bioactive lipids ^a : milkfat globule membrane, polar lipids, fatty acids	Linked with potential benefits on inflammation, gut health, metabolism, and body weight regulation ¹⁰⁴
Calcium	Plays a critical role in heart muscle contraction and blood vessel constriction/dilation; adequate calcium levels are linked with better weight management, insulin sensitivity, and lipid metabolism ⁹¹⁻⁹²
Magnesium	Supports blood pressure regulation, vascular tone, lipid metabolism, and insulin sensitivity ^{93,94}
Potassium	Helps offset and balance sodium levels to help reduce blood pressure; enhances endothelial function and stabilizes cardiac electrophysiology ⁹⁵⁻⁹⁷
Vitamin D ^b	Supports calcium absorption; helps reduce inflammation; regulates the renin-angiotensin-aldosterone system, which influences blood pressure and heart function ⁹⁸
Live and active cultures and fermentation metabolites ^b	Linked with potential benefits in supporting healthy gut microbiota, reducing inflammation, improving blood lipid profiles, reducing blood pressure, and enhancing insulin sensitivity ^{99,100}

^aPresent in dairy foods except for fat-free varieties.
^bFound in some, but not all dairy foods.

meet recommendations for 3 daily servings as part of healthy dietary patterns (**TABLE 4** and **FIGURE**).

Collective evidence indicates that recommending fat flexibility, such as consuming a balanced mix of whole- and low-fat dairy foods, and engaging in discussions with lactose-intolerant patients about available dairy options that include lactose-free and lower-lactose dairy foods are part of an approach toward reaching dairy food recommendations within overall nutritionally adequate, healthy diets. PCCs play a critical role in translating food-based dietary guidance into practical, patient-centered recommendations.

SUMMARY

Dietary guidance for CM health typically has focused on improving consumption of whole grains, fruits, and vegetables without similar acknowledgment of dairy foods. However, the body of evidence consistently shows that dairy

foods and the nutrients they provide can be beneficial for CM health, with emerging insights into the dairy food matrix helping to explain benefits associated with whole- and reduced-fat dairy foods. Despite this evidence and authoritative nutrition guidance recognizing the contributions of dairy foods to healthy diets, most people in the United States do not meet recommendations for nutrient-dense dairy foods like milk, yogurt, cheese, and kefir. There are multiple dairy foods with different amounts of fat and lactose that can help meet a range of patient preferences and health needs. PCCs can play a key role in providing food-based guidance to help their patients achieve nutrient adequacy, meet dairy recommendations, and improve CM health. Closing this gap through routine assessment of dairy consumption, individualized guidance for lactose intolerance, and referral to registered dietitians to support fat-flexible, calorie-appropriate dietary patterns represents an opportunity to improve diet quality and CM health. ●

TABLE 4. Practical applications: strategies for food-based guidance to support adequate dairy food consumption and CM health for patients.

- **Screen** patients for adequate consumption of all food groups; refer them to a registered dietitian for counseling as needed to achieve healthy, calorie-balanced eating patterns.
- **Order testing** beyond LDL to examine a comprehensive set of risk factors and biomarkers. When appropriate, follow up with direct assessments of carotid artery atherosclerotic plaque by ultrasound.¹⁰⁹
- **Advise** patients to meet dairy food recommendations to help achieve intake of nutrients that support CM health and that most Americans under consume, including calcium, vitamin D, and potassium. Dairy foods contain essential nutrients that are hard to replace with nondairy foods that are similar in price and calories.¹¹⁰
- **Manage** lactose intolerance to maintain adequate dairy intake:
 - o Many dairy food options are lactose free (e.g., lactose-free milk) or are naturally lower in lactose, such as yogurt, kefir, and certain cheeses.
 - o Consume lactose-containing foods in small doses at mealtimes.
 - o Consider taking lactase or probiotic supplements.¹¹¹
- **Incorporate** fat flexibility:
 - o Dairy foods across a range of fat levels may be a part of a balanced, calorie-appropriate, and healthy eating pattern.
 - o Consider taste, personal preferences, and health and wellness needs when providing guidance about how to achieve dairy adequacy.
 - o Well-balanced, low-carbohydrate diets, which often are higher in fat, may be beneficial for those with impaired glucose metabolism.¹¹²

FIGURE. Guiding patients to support cardiometabolic health with dairy foods.



REFERENCES

- Comerford KB, Miller GD, Boileau AC, Masiello Schuette SN, Giddens JC, Brown KA. Global review of dairy recommendations in food-based dietary guidelines. *Front Nutr*. 2021;8:671999. doi:10.3389/fnut.2021.671999
- Godos J, Tieri M, Ghelfi F, et al. Dairy foods and health: an umbrella review of observational studies. *Int J Food Sci Nutr*. 2020;71(2):138-151. doi:10.1080/09637486.2019.1625035
- Gil A, Ortega RM. Introduction and executive summary of the supplement, role of milk and dairy products in health and prevention of noncommunicable chronic diseases: a series of systematic reviews. *Adv Nutr*. 2019;10(suppl 2):S67-S73. doi:10.1093/advances/nmz020
- Dehghan M, Mente A, Rangarajan S, et al. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. *The Lancet*. 2018;392(10161):2288-2297. doi:10.1016/S0140-6736(18)31812-9
- Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med*. 1997;336(16):1117-1124. doi:10.1056/NEJM199704173361601
- Pourrajab B, Fatahi S, Dehnad A, Kord Varkaneh H, Shidfar F. The impact of probiotic yogurt consumption on lipid profiles in subjects with mild to moderate hypercholesterolemia: a systematic review and meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis*. 2020;30(1):11-22. doi:10.1016/j.numecd.2019.10.001
- Anderson GH, Chen Zhou CZ, Vien S, et al. The effect of three daily servings of full-fat dairy for 12 weeks on body weight, body composition, energy metabolism, blood lipids, and dietary intake of adults with overweight and obesity. *J Nutr*. 2026;154(4):101373. doi:10.1016/j.jnut.2026.101373
- Juliano S, Hare DL, Vogrin S, et al. Consumption of dairy foods to achieve recommended levels for older adults has no deleterious effects on serum lipids. *Nutr Metab Cardiovasc Dis*. 2024;34(10):2353-2359. doi:10.1016/j.numecd.2024.06.004
- O'Sullivan TA, Schmidt KA, Kratz M. Whole-fat or reduced-fat dairy product intake, adiposity, and cardiometabolic health in children: a systematic review. *Adv Nutr*. 2020;11(4):928-950. doi:10.1093/advances/nmaa011
- Duarte C, Boccardi V, Amaro Andrade P, Souza Lopes AC, Jacques PF. Dairy versus other saturated fats source and cardiometabolic risk markers: systematic review of randomized controlled trials. *Crit Rev Food Sci Nutr*. 2021;61(3):450-461. doi:10.1080/10408398.2020.1736509
- Taormina VM, Unger AL, Kraft J. Full-fat dairy products and cardiometabolic health outcomes: does the dairy-fat matrix matter? *Front Nutr*. 2024;11:1386257. doi:10.3389/fnut.2024.1386257
- Hirahatake KM, Astrup A, Hill JO, Slavin JL, Allison DB, Maki KC. Potential cardiometabolic health benefits of full-fat dairy: the evidence base. *Adv Nutr*. 2020;11(3):533-547. doi:10.1093/advances/nmz132
- U.S. Department of Agriculture, U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2025-2030. 10th ed. Published January 2026. <https://cdn.erafood.gov/DGA.pdf>
- Eating for diabetes management. American Diabetes Association. Published 2026. Accessed May 27, 2026. <https://diabetes.org/food-nutrition/eating-for-diabetes-management>
- Lichtenstein AH, Khera A, Anderson CAM, et al. 2026 dietary guidance to improve cardiovascular health: a scientific statement from the American Heart Association. *Circulation*. Published online March 31, 2026. doi:10.1161/CIR.0000000000001435
- Astrup A, Magkos F, Bier DM, et al. Saturated fats and health: a reassessment and proposal for food-based recommendations: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;76(7):844-857. doi:10.1016/j.jacc.2020.05.077
- Astrup A, Bertram HC, Bonjour JP, et al. WHO draft guidelines on dietary saturated and trans fatty acids: time for a new approach? *BMJ*. 2019;366:14137. doi:10.1136/bmj.14137
- Lamarche B, Astrup A, Eckel RH, et al. Regular-fat and low-fat dairy foods and cardiovascular diseases: perspectives for future dietary recommendations. *Am J Clin Nutr*. 2025;121(5):956-964. doi:10.1016/j.ajcnut.2025.03.009
- Comerford KB, Unger AL, Cifelli CJ, et al. Decrypting the messages in the matrix: the proceedings of a symposium on dairy food matrix science and public health opportunities. *Crit Rev Food Sci Nutr*. 2025;65(30):7105-7118. doi:10.1080/10408398.2025.2460606
- USDA. Federal Data Analysis Report for the 2025 Dietary Guidelines Advisory Committee: Current Intakes of Food Groups. Published 2024. Accessed May 27, 2026. https://www.dietaryguidelines.gov/sites/default/files/2024-12/DA_Report_Current_Intakes_of_Food_Groups.pdf
- Papadakis RD, Bantouna D, Livadas S, Angelopoulos N. The association of obesity with cardiovascular disease risk and risk-enhancing factors. *J Clin Lipidol*. 2026;20(1S):26-37. doi:10.1016/j.jacl.2025.08.018
- Feng Y, Zhao Y, Liu J, et al. Consumption of dairy products and the risk of overweight or obesity, hypertension, and type 2 diabetes mellitus: a dose-response meta-analysis and systematic review of cohort studies. *Adv Nutr*. 2022;13(6):2165-2179. doi:10.1093/advances/nmac096
- Mozaffarian D. Dairy foods, obesity, and metabolic health: the role of the food matrix compared with single nutrients. *Adv Nutr*. 2019;10(5):917S-923S. doi:10.1093/advances/nmz053
- Hashemi Javaheri FS, Nasiri Jounaghani M, Sahebkar A, et al. The effect of fermented dairy intake and abdominal obesity in adults: a systematic review and dose-response meta-analysis of cohort studies. *Eat Weight Disord*. 2025;30(1):23. doi:10.1007/s40519-025-01733-4
- Hidayat K, Yu LG, Yang JR, et al. The association between milk consumption and the metabolic syndrome: a cross-sectional study of the residents of Suzhou, China and a meta-analysis. *Br J Nutr*. 2020;123(9):1013-1023. doi:10.1017/S0007114520000227
- Habumugisha T, Engebretsen IMS, Maren IE, Kaiser CWM, Dierkes J. Reducing meat and/or dairy consumption in adults: a systematic review and meta-analysis of effects on protein intake, anthropometric values, and body composition. *Nutr Rev*. 2024;82(3):277-301. doi:10.1093/nutrit/nuad055
- Hong JY, Lee JS, Woo HW, Om AS, Kwok CK, Kim MK. Meta-analysis of randomized controlled trials on calcium supplements and dairy products for changes in body weight and obesity indices. *Int J Food Sci Nutr*. 2021;72(5):615-631. doi:10.1080/09637486.2020.1856794
- Kristoffersen E, Hjort SL, Thomassen LM, et al. Umbrella review of systematic reviews and meta-analyses on the consumption of different food groups and the risk of overweight and obesity. *Nutrients*. 2025;17(4):662. doi:10.3390/nu17040662
- Lopez-Sobaler AM, Aparicio A, Lopez Diaz-Ufano ML, Ortega RM, Alvarez-Bueno C. Effect of dairy intake with or without energy restriction on body composition of adults: overview of systematic reviews and meta-analyses of randomized controlled trials. *Nutr Rev*. 2020;78(11):901-913. doi:10.1093/nutrit/nuaa003
- Mayer-Davis E, Leidy H, Mattes R, et al. *Beverage Consumption and Growth, Size, Body Composition, and Risk of Overweight and Obesity: A Systematic Review*. Published July 2020. Accessed May 27, 2026. doi:10.52570/NESR.DGAC2020.SR0401
- Shahinfar H, Payandeh N, Zeraattalab-Motlagh S, et al. Comparative effects of different beverages on weight loss in adults: a systematic review and network meta-analysis of randomized trials. *Int J Obes (Lond)*. 2025;49(4):578-585. doi:10.1038/s41366-024-01673-6
- Mozaffarian D, Agarwal M, Aggarwal M, et al. Nutritional priorities to support GLP-1 therapy for obesity: a joint advisory from the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association, and the Obesity Society. *Obesity (Silver Spring)*. 2025;33(8):1475-1503. doi:10.1002/oby.24336
- Gigliotti L, Warshaw H, Evert A, et al. Incretin-based therapies and lifestyle interventions: the evolving role of registered dietitian nutritionists in obesity care. *J Acad Nutr Diet*. 2025;125(3):408-421. doi:10.1016/j.jand.2024.10.023
- Ilich JZ, Kelly OJ, Liu PY, et al. Role of calcium and low-fat dairy foods in weight-loss outcomes revisited: results from the randomized trial of effects on bone and body composition in overweight/obese postmenopausal women. *Nutrients*. 2019;11(5):1157. doi:10.3390/nu11051157
- Wallace TC, Bailey RL, Lappe J, et al. Dairy intake and bone health across the lifespan: a systematic review and expert narrative. *Crit Rev Food Sci Nutr*. 2021;61(21):3661-3707. doi:10.1080/10408398.2020.1810624
- Mean nutrient values for vitamin D-fortified fluid milk across fat levels. US Department of Agriculture FoodData Central. Published 2020. Accessed May 27, 2026. <https://fdc.nal.usda.gov/>
- Cheese, colby. US Department of Agriculture FoodData Central. Published 2018. Accessed May 27, 2026. <https://fdc.nal.usda.gov/food-details/173416/nutrients>
- Cheese, cheddar, sharp, sliced. US Department of Agriculture FoodData Central. Published 2018. Accessed May 27, 2026. <https://fdc.nal.usda.gov/food-details/170899/nutrients>
- Yogurt, vanilla, low fat. US Department of Agriculture FoodData Central. Published 2018. Accessed May 27, 2026. <https://fdc.nal.usda.gov/food-details/170888/nutrients>
- National Institutes of Health Office of Dietary Supplements. Iodine Fact Sheet for Health Professionals. Updated November 5, 2024. Accessed May 27, 2026. <https://ods.od.nih.gov/factsheets/Iodine-HealthProfessional/>
- Potassium fact sheet for health professionals. National Institutes of Health Office of Dietary Supplements. Accessed September 3, 2026. <https://ods.od.nih.gov/factsheets/Potassium-HealthProfessional/>
- Auestad N, Layman DK. Dairy bioactive proteins and peptides: a narrative review. *Nutr Rev*. 2021;79(Suppl 2):36-47. doi:10.1093/nutrit/nuab097
- Harper ME, Dent RRM, McPherson R. High-quality weight loss in obesity: importance of skeletal muscle. *Diabetes*. 2025;74(12):2191-2198. doi:10.2337/dbi25-0003
- Stefanakis K, Kokkorakis M, Mantzoros CS. The impact of weight loss on fat-free mass, muscle, bone and hematopoiesis health: implications for emerging pharmacotherapies aiming at fat reduction and lean mass preservation. *Metabolism*. 2024;161:156057. doi:10.1016/j.metabol.2024.156057
- Onvani S, Haghighatdoost F, Surkan PJ, Azadbakht L. Dairy products, satiety and food intake: a meta-analysis of clinical trials. *Clin Nutr*. 2017;36(2):389-398. doi:10.1016/j.clnu.2016.01.017
- Du Y, Oh C, No J. Advantage of dairy for improving aging muscle. *J Obes Metab Syndr*. 2019;28(3):167-174. doi:10.7570/jomes.2019.28.3.167
- Lean MEJ, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DIRECT): an open-label, cluster-randomised trial. *The Lancet*. 2018;391(10120):541-551. doi:10.1016/S0140-6736(17)33102-1
- Boren J, Oorni K, Catapano AL. The link between diabetes and cardiovascular disease. *Atherosclerosis*. 2024;394:117607. doi:10.1016/j.atherosclerosis.2024.117607
- Yur WQ, He YH, Li PH, et al. Exploring the link between visceral fat and cardiovascular disease in type 2 diabetes: evidence from CT measurements. *Front Endocrinol (Lausanne)*. 2025;16:1635282. doi:10.3389/fendo.2025.1635282
- Slurink IA, Vogtschmidt YD, Brummel B, Smeets T, Kupper N, Soedamah-Muthu SS. Dairy intake in relation to prediabetes and continuous glycemic outcomes: a systematic review and dose-response meta-analysis of prospective cohort studies. *Curr Dev Nutr*. 2024;8(11):104470. doi:10.1016/j.cdnut.2024.104470
- Zhang K, Bai P, Deng Z. Dose-dependent effect of intake of fermented dairy foods on the risk of diabetes: results from a meta-analysis. *Can J Diabetes*. 2022;46(3):307-312. doi:10.1016/j.jcjd.2021.09.003
- Zhang M, Dong X, Huang Z, et al. Cheese consumption and multiple health outcomes: an umbrella review and updated meta-analysis of prospective studies. *Adv Nutr*. 2023;14(5):1170-1186. doi:10.1016/j.adnut.2023.06.007
- Compans J, Pla-Pagà L, Calderón-Pérez L, et al. Fermented dairy products, probiotic

- supplementation, and cardiometabolic diseases: a systematic review and meta-analysis. *Adv Nutr*. 2020;11(4):834–863. doi:10.1093/advances/nmaa030
54. Björklund Holven K, Sonestedt E. Milk and dairy products—a scoping review for Nordic Nutrition Recommendations 2023. *Food Nutr Res*. 2024;68:10486. doi:10.29219/fnr.v68.10486
 55. Akyil S, Winkler S, Meyer D, et al. Association between dairy intake and multiple health outcomes: a scoping review of systematic reviews and meta-analyses. *Eur J Clin Nutr*. 2026;80(1):16–27. doi:10.1038/s41430-025-01639-5
 56. Salari A, Ghodrati S, Gheflati A, Jarahi L, Hashemi M, Afshari A. Effect of kefir beverage consumption on glycemic control: a systematic review and meta-analysis of randomized controlled clinical trials. *Complement Ther Clin Pract*. 2021;44:101443. doi:10.1016/j.ctcp.2021.101443
 57. Skelly LE, Barbour-Tuck EN, Kurgan N, et al. Neutral effect of increased dairy product intake, as part of a lifestyle modification program, on cardiometabolic health in adolescent girls with overweight/obesity: a secondary analysis from a randomized controlled trial. *Front Nutr*. 2021;8:673589. doi:10.3389/fnut.2021.673589
 58. Mitri J, Tomah S, Mottalib A, et al. Effect of dairy consumption and its fat content on glycemic control and cardiovascular disease risk factors in patients with type 2 diabetes: a randomized controlled study. *Am J Clin Nutr*. 2020;112(2):293–302. doi:10.1093/ajcn/nqaa138
 59. Rancourt-Bouchard M, Giguère J, Guay V, et al. Effects of regular-fat and low-fat dairy consumption on daytime ambulatory blood pressure and other cardiometabolic risk factors: a randomized controlled feeding trial. *Am J Clin Nutr*. 2020;111(1):42–51. doi:10.1093/ajcn/nqz251
 60. Schmidt KA, Cromer G, Burhans MS, et al. The impact of diets rich in low-fat or full-fat dairy on glucose tolerance and its determinants: a randomized controlled trial. *Am J Clin Nutr*. 2021;113(3):534–547. doi:10.1093/ajcn/nqaa301
 61. Kiesswetter E, Stadelmaier J, Petropoulou M, et al. Effects of dairy intake on markers of cardiometabolic health in adults: a systematic review with network meta-analysis. *Adv Nutr*. 2023;14(3):438–450. doi:10.1016/j.advnut.2023.03.004
 62. Taormina VM, Eisenhardt S, Gilbert MP, Poynter ME, Kien CL, Kraft J. Full-fat yogurt compared with non-fat yogurt reduces blood triacylglycerol concentrations and lowers the triacylglycerol content in specific lipoprotein subclasses in adults with prediabetes: an exploratory analysis of a randomized controlled trial. *Lipids Health Dis*. 2025;24(1):201. doi:10.1186/s12944-025-02616-4
 63. U.S. Food and Drug Administration. Petition for a qualified health claim for yogurt and reduced risk of type 2 diabetes mellitus (Docket No. FDA-2019-P-1594). March 1, 2024. Accessed May 27, 2026. <https://www.fda.gov/media/176608/download?attachment>
 64. Tabatabaeizadeh SA, Tafazoli N. Effect of probiotic yogurt on gestational diabetes mellitus: a systematic review and meta-analysis. *Diabetes Metab Syndr*. 2023;17(4):102758. doi:10.1016/j.dsx.2023.102758
 65. Wakayama R, Araki M, Nakamura M, Ikeda N. The cost-effectiveness of increased yogurt intake in type 2 diabetes in Japan. *Nutrients*. 2025;17(14):2278. doi:10.3390/nu17142278
 66. Barengolts E, Smith ED, Reutrakul S, Tonucci L, Anothaisintawee T. The effect of probiotic yogurt on glycemic control in type 2 diabetes or obesity: a meta-analysis of nine randomized controlled trials. *Nutrients*. 2019;11(3):671. doi:10.3390/nu11030671
 67. Mirjalili M, Salari Sharif A, Sangouni AA, Emami H, Mozaffari-Khosravi H. Effect of probiotic yogurt consumption on glycemic control and lipid profile in patients with type 2 diabetes mellitus: a randomized controlled trial. *Clin Nutr ESPEN*. 2023;54:144–149. doi:10.1016/j.clnesp.2023.01.014
 68. Heart disease facts. Centers for Disease Control and Prevention. October 24, 2024. Accessed May 27, 2026. <https://www.cdc.gov/heart-disease/data-research/facts-stats/index.html>
 69. Chareonrungrueangchai K, Wongkawnwot K, Anothaisintawee T, Reutrakul S. Dietary factors and risks of cardiovascular diseases: an umbrella review. *Nutrients*. 2020;12(4):1088. doi:10.3390/nu12041088
 70. Yu E, Malik VS, Hu FB. Cardiovascular disease prevention by diet modification. *J Am Coll Cardiol*. 2018;72(8):914–926. doi:10.1016/j.jacc.2018.02.085
 71. Pradeilles R, Norris T, Sellem L, Markey O. Effect of isoenergetic substitution of cheese with other dairy products on blood lipid markers in the fasted and postprandial state: an updated and extended systematic review and meta-analysis of randomized controlled trials in adults. *Adv Nutr*. 2023;14(6):1579–1595. doi:10.1016/j.advnut.2023.09.003
 72. Ziaei R, Ghavami A, Khalesi S, Ghiasvand R, Mokari Yamchi A. The effect of probiotic fermented milk products on blood lipid concentrations: a systematic review and meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis*. 2021;31(4):997–1015. doi:10.1016/j.numecd.2020.12.023
 73. Derakhshandeh-Rishehri SM, Ghobadi S, Akhlaghi M, Faghih S. No adverse effects of dairy products on lipid profile: a systematic review and meta-analysis of randomized controlled clinical trials. *Diabetes Metab Syndr*. 2021;15(6):102279. doi:10.1016/j.dsx.2021.102279
 74. Yahyapoor F, Haghighat N, Sohrabi Z, et al. Effects of kefir consumption on cardiometabolic risk factors: a systematic review and meta-analysis of randomized controlled trials. *Curr Drug Targets*. 2023;24(7):599–612. doi:10.2174/138945012466230427095742
 75. Yilmaz B, Alvanoudi P, Kalogeropoulou A, et al. Fermented dairy product consumption and blood lipid levels in healthy adults: a systematic review. *Front Nutr*. 2025;12:1651134. doi:10.3389/fnut.2025.1651134
 76. Giosuè A, Calabrese I, Vitale M, Riccardi G, Vaccaro O. Consumption of dairy foods and cardiovascular disease: a systematic review. *Nutrients*. 2022;14(4):831. doi:10.3390/nu14040831
 77. Ranjbar YR, Nasrollahzadeh J. Comparison of the impact of saturated fat from full-fat yogurt or low-fat yogurt and butter on cardiometabolic factors: a randomized cross-over trial. *Eur J Nutr*. 2024;63(4):1213–1224. doi:10.1007/s00394-024-03352-8
 78. Schmidt KA, Cromer G, Burhans MS, et al. Impact of low-fat and full-fat dairy foods on fasting lipid profile and blood pressure: exploratory endpoints of a randomized controlled trial. *Am J Clin Nutr*. 2021;114(3):882–892. doi:10.1093/ajcn/nqab131
 79. Jakobsen MU, Trolle E, Outzen M, et al. Intake of dairy products and associations with major atherosclerotic cardiovascular diseases: a systematic review and meta-analysis of cohort studies. *Sci Rep*. 2021;11(1):1303. doi:10.1038/s41598-020-79708-x
 80. Chen Z, Ahmed M, Ha V, et al. Dairy product consumption and cardiovascular health: a systematic review and meta-analysis of prospective cohort studies. *Adv Nutr*. 2022;13(2):439–454. doi:10.1093/advances/nmab118
 81. Sharifan P, Roustae R, Shafiee M, et al. Dairy consumption and risk of cardiovascular and bone health outcomes in adults: an umbrella review and updated meta-analyses. *Nutrients*. 2025;17(17):2723. doi:10.3390/nu17172723
 82. Zhang K, Chen X, Zhang L, Deng Z. Fermented dairy foods intake and risk of cardiovascular diseases: a meta-analysis of cohort studies. *Crit Rev Food Sci Nutr*. 2020;60(7):1189–1194. doi:10.1080/10408398.2018.1564019
 83. Gao X, Jia HY, Chen GC, Li CY, Hao M. Yogurt intake reduces all-cause and cardiovascular disease mortality: a meta-analysis of eight prospective cohort studies. *Chin J Integr Med*. 2020;26(6):462–468. doi:10.1007/s11655-020-3085-8
 84. Tutunchi H, Naghshi S, Naeimi M, Naeini F, Esmailzadeh A. Yogurt consumption and risk of mortality from all causes, CVD and cancer: a comprehensive systematic review and dose-response meta-analysis of cohort studies. *Public Health Nutr*. 2023;26(6):1196–1209. doi:10.1017/S1368980022002385
 85. Ulven SM, Holven KB, Gil A, Rangel-Huerta OD. Milk and dairy product consumption and inflammatory biomarkers: an updated systematic review of randomized clinical trials. *Adv Nutr*. 2019;10(suppl 2):S239–S250. doi:10.1093/advances/nmy072
 86. Upadhyay RK. Emerging risk biomarkers in cardiovascular diseases and disorders. *J Lipids*. 2015;2015:971453. doi:10.1155/2015/971453
 87. Andersen CJ, Fernandez ML. Emerging biomarkers and determinants of lipoprotein profiles to predict CVD risk: implications for precision nutrition. *Nutrients*. 2024;17(1):42. doi:10.3390/nu17010042
 88. Timon CM, O'Connor A, Bhargava N, Gibney ER, Feeney EL. Dairy consumption and metabolic health. *Nutrients*. 2020;12(10):3040. doi:10.3390/nu12103040
 89. Savaiano DA, Hutkins RW. Yogurt, cultured fermented milk, and health: a systematic review. *Nutr Rev*. 2021;79(5):599–614. doi:10.1093/nutrit/naaa013
 90. Connolly G, Wang Y, Bergia RE, et al. Hg protein supplementation and type 2 diabetes mellitus risk factors: an umbrella systematic review of randomized controlled trials. *Curr Dev Nutr*. 2023;7(12):102017. doi:10.1016/j.cdnut.2023.102017
 91. Reid IR, Birstow SM, Bolland MJ. Calcium and cardiovascular disease. *Endocrinol Metab (Seoul)*. 2017;32(3):339–349. doi:10.3803/EnM.2017.32.3.339
 92. Das S, Choudhuri D. Role of dietary calcium and its possible mechanism against metabolic disorders: a concise review. *J Food Biochem*. 2021;45(4):e13697. doi:10.1111/jfbc.13697
 93. Fritzen R, Davies A, Veenhuizen M, et al. Magnesium deficiency and cardiometabolic disease. *Nutrients*. 2023;15(10):2355. doi:10.3390/nu15102355
 94. Nielsen FH. The role of dietary magnesium in cardiovascular disease. *Nutrients*. 2024;16(23):4223. doi:10.3390/nu16234223
 95. Castro H, Raj L. Potassium in hypertension and cardiovascular disease. *Semin Nephrol*. 2013;33(3):277–289. doi:10.1016/j.semephrol.2013.04.008
 96. Tremblay JO, Swift SL, Rundek T, et al. High sodium and low potassium are associated with incident cardiovascular disease among United States Hispanic/Latino adults: prospective results from the HCHS/SOL study. *Am J Clin Nutr*. 2026;123(2):101143. doi:10.1016/j.ajcnut.2025.101143
 97. Sica DA, Struthers AD, Cushman WC, Wood M, Banas JS Jr, Epstein M. Importance of potassium in cardiovascular disease. *J Clin Hypertens (Greenwich)*. 2002;4(3):198–206. doi:10.1111/j.1524-6175.2002.01728.x
 98. Varzideh F, Mone P, Kansakar U, Santulli G. Vitamin D in cardiovascular medicine: from molecular mechanisms to clinical translation. *Nutrients*. 2026;18(3):499. doi:10.3390/nu18030499
 99. Li KJ, Burton-Pimentel KJ, Vergères G, Feskens EJM, Brouwer-Brolsma EM. Fermented foods and cardiometabolic health: definitions, current evidence, and future perspectives. *Front Nutr*. 2022;9:976020. doi:10.3389/fnut.2022.976020
 100. Shi X, Li Y, Cheng Y, et al. Emerging roles of lactic acid bacteria in health management: insights from fermented foods to microbiota. *Food Biosci*. 2026;75:108088. <https://doi.org/10.1016/j.fbio.2025.108088>
 101. Zhou S, Xu T, Zhang X, Luo J, An P, Luo Y. Effect of casein hydrolysate on cardiovascular risk factors: a systematic review and meta-analysis of randomized controlled trials. *Nutrients*. 2022;14(19):4207. doi:10.3390/nu14194207
 102. Kim J. Pre-sleep casein protein ingestion: new paradigm in post-exercise recovery nutrition. *Phys Act Nutr*. 2020;24(2):6–10. doi:10.20463/pan.2020.0009
 103. Torres-Gonzalez M, Rice Bradley BH. Whole-milk dairy foods: biological mechanisms underlying beneficial effects on risk markers for cardiometabolic health. *Adv Nutr*. 2023;14(6):1523–1537. doi:10.1016/j.advnut.2023.09.001
 104. Astrup A, Geiker NRW, Magkos F. Effects of full-fat and fermented dairy products on cardiometabolic disease: food is more than the sum of its parts. *Adv Nutr*. 2019;10(5):924S–930S. doi:10.1093/advances/nmz069
 105. Poppitt SD. Cow's milk and dairy consumption: is there now consensus for cardiometabolic health? *Front Nutr*. 2020;7:574725. doi:10.3389/fnut.2020.574725
 106. U.S. Department of Agriculture, U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 1980. Published 1980. <https://www.dietaryguidelines.gov/sites/default/files/2019-05/1980%20DGA.pdf>
 107. U.S. Department of Agriculture, U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2020–2025. 9th ed. Published December 2020. https://www.dietaryguidelines.gov/sites/default/files/2021-03/Dietary_Guidelines_for_Americans-2020-2025.pdf

108. American Heart Association. Life's Essential 8: How to Eat Better. Published February 2026. Accessed May 27, 2026. https://www.heart.org/-/media/Healthy-Living-Files/LE8-Fact-Sheets/LE8_Eat_Better_Fact_Sheet.pdf?sc_lang=en
109. Johri AM, Nambi V, Naqvi TZ, et al. Recommendations for the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and evaluation of cardiovascular risk: from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2020;33(8):917-933. doi:10.1016/j.echo.2020.04.021
110. Cifelli CJ, Auestad N, Fulgoni VL. Replacing the nutrients in dairy foods with non-dairy foods will increase cost, energy intake and require large amounts of food: NHANES 2011–2014. *Public Health Nutr*. 2022;25(2):332-343. doi:10.1017/S1368980020001937
111. Comerford K, Lawson Y, Young M, et al. The role of dairy food intake for improving health among black Americans across the life continuum: a summary of the evidence. *J Natl Med Assoc*. 2024;116(2 Pt 2):292-315. doi: 10.1016/j.jnma.2024.01.020
112. Tian W, Cao S, Guan Y, et al. The effects of low-carbohydrate diet on glucose and lipid metabolism in overweight or obese patients with T2DM: a meta-analysis of randomized controlled trials. *Front Nutr*. 2024;11:1516086. doi:10.3389/fnut.2024.1516086

Rethinking Rescue in Mild-Moderate Asthma: Adding ICS to Reduce Exacerbations

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INTRODUCTION

Asthma is a chronic inflammatory airway disease with a high population burden, affecting approximately 27.8 million people (~8.4%) in the United States.¹ Mild or moderate disease typically is classified based on the level of treatment needed to maintain symptom control, and patients with these types of “less severe” disease still can experience serious attacks.²⁻⁴ Most patients with asthma are managed in primary care settings, where periodic refills of reliever therapy may serve as the main touchpoint for asthma reassessment.^{3,5}

Uncontrolled asthma is not confined to patients with more severe disease; mild-moderate asthma also may be classified as uncontrolled. Expert guidelines and studies are available for the treatment of all asthma severities; this article focuses solely on uncontrolled mild-moderate asthma. In a large analysis using short-acting β_2 -agonist (SABA) and systemic corticosteroid (SCS) prescription fills as impairment and risk markers, 80.9% of US patients who had uncontrolled asthma were treated for mild-moderate disease. This analysis defined uncontrolled asthma as ≥ 2 annual exacerbations and the use of rescue therapy > 2 times weekly (3 annual SABA canister refills).⁶

Severe attacks frequently lead to treatment with SCS, which remains an effective acute intervention but carries cumulative risk.^{7,8} Repeated courses of SCS and chronic exposure are associated with a broad range of short- and long-term adverse effects. The study data highlight that exacerbation

Key takeaways

- As defined by the Global Initiative for Asthma (GINA), mild to moderate asthma is not inherently low risk; many patients have poorly controlled symptoms and are at risk for exacerbations.
- Inhaled corticosteroid (ICS) rescue strategies align treatment with asthma pathophysiology and can reduce severe exacerbations and systemic corticosteroid exposure compared with SABA-only rescue therapy.
- Since 2019, GINA has recommended ICS-based rescue therapy. However, despite this recommendation and the 2023 US Food and Drug Administration approval of albuterol-budesonide combination inhaler for rescue in adults with asthma, implementation in primary care remains low.
- Primary care implementation can include systematized workflows to identify patients who use SABA-only rescue therapy, provide education to those patients, and adjust therapy to ICS-based rescue therapy through shared decision-making.

risk and SCS exposure can accumulate from months to years in patients who have infrequent symptoms, especially for patients who remain on albuterol-only rescue treatment.^{7,9}

Despite clear recommendations from Global Initiative for Asthma (GINA), as well as other guidelines suggesting that rescue therapy should include ICS, SABA-only rescue therapy remains a prevalent prescribing pattern for patients with mild-moderate asthma.^{2,10} More frequent SABA exposure is consistently associated with an increased risk of severe

exacerbations and asthma-related mortality.^{9,11} Recent US data among adults with SABA-only prescriptions demonstrated higher exacerbation rates as the number of SABA prescriptions increased, even when patients had greater inhaler use.² This pattern suggests that reliance on SABA alone may reflect and perpetuate inadequate control of the underlying inflammatory disease process.^{11,12}

Additionally, strategies to reduce adverse effects should prioritize minimizing avoidable SCS exposure.⁷ Integrating ICS into rescue therapy can be a key tactic for implementation in the primary care setting. The benefit is twofold: ICS can reduce the risk of exacerbation and asthma-related mortality, as well as future SCS burden, rather than being used only as a symptom-control intervention.

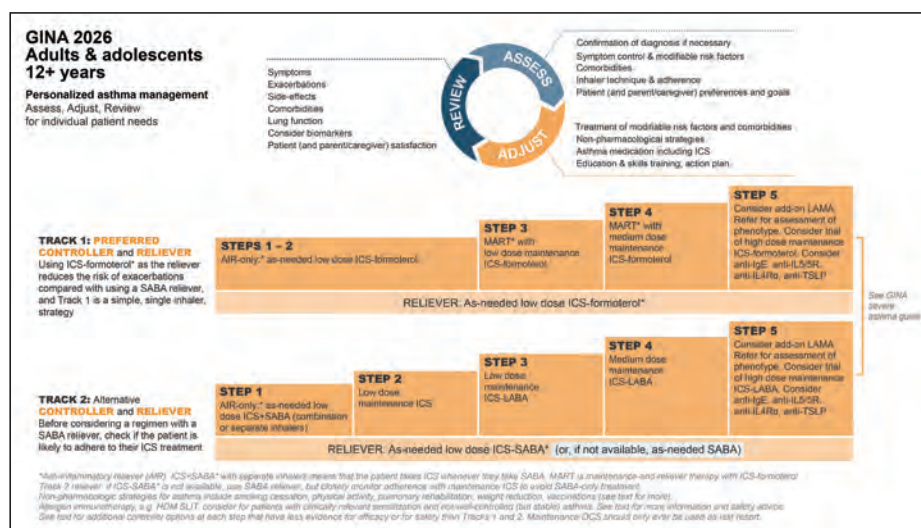
INFLAMMATION IN MILD-MODERATE ASTHMA

Airway inflammation is central to asthma pathophysiology, and inflammatory activity can persist even when symptoms are intermittent or perceived as mild.^{3,4,9} This helps explain why severe attacks can occur unexpectedly in patients who otherwise report low day-to-day symptom burden. Traditional rescue strategies built around SABA-only rescue therapy provide rapid bronchodilation but do not address airway inflammation, leaving the key driver of exacerbations untreated.^{12,13} In 2019, GINA made a fundamental shift by recommending against SABA-only treatment for adults and adolescents and by positioning ICS-based rescue as foundational therapy for all patients, regardless of asthma severity.¹³

Because SABA relieves symptoms rapidly, patients may develop strong preferences for albuterol and may interpret symptom relief as evidence that daily anti-inflammatory therapy is unnecessary.^{3,5} However, worsening symptoms can signal an impending exacerbation, especially when patients are not using any ICS.^{9,14}

Current GINA guidance continues to recommend ICS-containing regimens, including symptom-driven approaches that deliver ICS whenever a reliever is used. Despite these changes in global recommendations, continued SABA-only use in clinical practice means many patients remain exposed to preventable exacerbation risk and cumulative SCS exposure.^{7,11}

FIGURE 1. GINA Tracks 1 and 2: personalized asthma management for adults and adolescents to control symptoms and minimize future risk.⁹



GINA ©2026 Global Initiative for Asthma, reprinted with permission. Available from www.ginasthma.org.

IMPLEMENTING ICS + FAST-ACTING BRONCHODILATOR THERAPY IN MILD ASTHMA

For adults and adolescents with mild asthma, GINA now prioritizes reliever strategies that include an ICS.^{9,12} GINA preferred Track 1 recommends as-needed low-dose ICS-formoterol. Track 2 recommends SABA as the reliever together with low-dose ICS taken whenever SABA is used, or a combination of SABA-ICS in a single inhaler (**FIGURE 1**). Overall, GINA recommends that every patient with asthma should receive anti-inflammatory treatment of some type, whether rescue, maintenance, or both.⁹

Although the 2020 National Asthma Education and Prevention Program (NAEPP) guideline predated some of the newer evidence on the critical need to include ICS in all inhaler regimens, it still recommends concomitant ICS use with quick-relief therapy, which can help clinicians move away from SABA monotherapy in US practice.¹⁵

CHALLENGES AND SOLUTIONS TO ICS + FAST-ACTING BRONCHODILATOR IMPLEMENTATION

In the United States, implementation of ICS + fast-acting bronchodilator historically has been complicated by the lack of an approved ICS-containing rescue inhaler. In 2023, that changed with the approval of albuterol-budesonide for as-needed treatment or prevention of bronchoconstriction for reducing the risk of exacerbations in adults.¹⁶ The recent BATURA trial provided evidence for the use of ICS + fast-acting bronchodilator (albuterol-budesonide) in patients with mild asthma, including intermittent or persistent dis-

ease. In BATURA, as-needed albuterol-budesonide reduced the risk of severe exacerbation compared to the control group (albuterol alone) by 47%, lowered SCS exposure, and improved disease control.¹⁴

The paradigm shift from SABA-only rescue therapy is a significant change from past practice and requires educating clinicians so they can implement the latest guidelines in their practices. Furthermore, the shift also requires clinicians to educate patients to address the traditional teaching that ICS is a maintenance (not rescue) therapy and to explain the popularity and overuse of albuterol.¹² Common barriers to educating patients and implementing ICS in asthma care include lack of time and cost. Using a patient-friendly, evidence-based handout, such as the one shown in **FIGURE 2**, may facilitate patient education and reduce resistance to modifying the usual treatment regimen. A full-size, printable version of the handout can be found by scanning the QR code.



Adherence to daily ICS often is poor in people with infrequent symptoms, so a rescue-based, self-administered inhaled therapy better aligns with patient behavior for symptom relief.^{5,12} Shared decision-making remains essential, however, because availability through insurance, cost, device familiarity, and patient preferences all can influence whether a theoretically optimal regimen actually is used.^{17,18} In a discrete-choice study, patients placed greater value on fewer exacerbations and simpler, more convenient inhaler approaches.¹⁷

In practice, primary care clinicians (PCCs) can implement ICS + fast-acting bronchodilator rescue therapy in multiple ways.^{9,12,15} Standardization of clinic workflows to identify patients on SABA-only rescue therapy at all touchpoints of a health care encounter is needed. Electronic health record (EHR) notifications regarding SABA use and refill intervals also help alert clinicians of utilization patterns that could lead to asthma morbidity and may help increase rates of uptake in clinical practice. For example, system adjustments to remove

FIGURE 2. Patient education tool that might be used as part of shared decision-making to reduce barriers to ICS implementation in asthma care.

Use of an Inhaled Corticosteroid (ICS) as Part of Rescue/Reliever Therapy

Traditionally, there have been two types of therapy used to treat asthma:

Maintenance Therapy for Inflammation

Most people with asthma have chronic (long-lasting) inflammation in their airways. The amount of airway inflammation can change over time.

Rescue/Reliever Therapy for Symptoms

Sudden increases in airway inflammation can lead to symptoms such as shortness of breath, wheezing, coughing, and chest tightness.

Airway in a patient with asthma

A daily maintenance inhaler containing **ICS** aids in controlling inflammation and helps prevent symptoms and flare-ups.

Airway during an asthma flare-up

A rescue inhaler containing a short-acting beta₂-agonist (SABA) is used to temporarily relieve asthma symptoms. Yet, a **SABA** alone does not address the underlying problem of inflammation.

TODAY, treating **both symptoms AND inflammation** with your rescue/reliever therapy is supported by asthma experts

See how ICS can be included as part of your rescue/reliever strategy!

Options for Including ICS as Part of Your Asthma Rescue/Reliever Strategy

Anti-inflammatory Reliever (AIR)

A rescue/reliever inhaler that contains both an ICS and a rapid-acting bronchodilator

- Use combination ICS-formoterol (a long-acting beta₂-agonist or LABA) as needed

OR

- Use combination SABA-ICS as needed, with or without maintenance ICS-containing therapy

ICS-formoterol inhalers are not FDA-approved for use as rescue/reliever therapy in the United States.

Patient Activated Reliever-Triggered Inhaled Corticosteroid (PARTICS)

Follow your current asthma treatment plan and take ICS when using as-needed SABA as rescue/reliever therapy

Continue your current asthma treatment plan. In addition:

- Take one puff of ICS for each puff of as-needed SABA inhaler

OR

- Take five puffs of ICS after using a SABA nebulizer treatment

ICS-only inhalers are not FDA-approved for use as rescue/reliever therapy in the United States.

Maintenance And Reliever Therapy (MART)

One inhaler for both maintenance and rescue/reliever therapy

- Use combination ICS-formoterol as both maintenance and as-needed for rescue/reliever

This approach does not include use of a SABA-only inhaler or a SABA-ICS inhaler as rescue/reliever and cannot be used with combinations of ICS with non-formoterol LABAs

ICS-formoterol inhalers are not FDA-approved for use as MART in the United States.

This document was prepared using asthma expert recommendations for educational purposes only. Together, you and your healthcare clinician will determine the best treatment for your asthma. Never ignore worsening asthma symptoms. If your rescue/reliever treatment isn't helping, seek medical attention immediately.

automatic SABA-only inhaler refills and limiting SABA-only inhaler prescription refills can help reduce SABA use. By working with other clinicians and staff, such as pharmacists, nurses, and medical assistants, PCCs can identify patients on SABA-only rescue therapy and educate them on switching to ICS-based rescue therapy.

CASE STUDY

A 29-year-old woman with a history of mild asthma presents for another albuterol refill after using her inhaler several times most weeks during exercise and spring allergy season. Over the past 12 months, she has had 2 urgent care visits for wheezing and received 2 short courses of oral prednisone, but she has never used an ICS because she feels well between episodes.

A review of pharmacy records shows 5 albuterol inhaler fills in the past year. The patient says that albuterol “always works” even though her flares seem to be happening more often. She wants a simple plan that she can use when symptoms occur, but she also wants to lower her chance of another severe attack.

In this case study, the patient’s limited day-to-day symptom burden does not translate into low future risk, because repeated SABA fills, urgent care use, and repeated SCS bursts are markers of uncontrolled asthma and denote a higher risk of exacerbations. A reasonable next step is to transition away from albuterol-only rescue and initiate an ICS-containing rescue strategy that fits her preferences (e.g., an as-needed albuterol-budesonide inhaler or low-dose ICS taken with each SABA use) while reassessing whether maintenance ICS therapy also is indicated. Because adherence to daily ICS is often poor in patients with infrequent symptoms, linking anti-inflammatory therapy to symptom-driven inhaler use can improve the likelihood that the patient takes ICS-containing treatment. The patient also should receive inhaler technique review, a written action plan, and close follow-up to evaluate symptom control, exacerbations, and refill patterns after the change in therapy.

REAL-WORLD IMPLEMENTATION OF ICS IN PRIMARY CARE PRACTICES

Implementation in primary care means translating guidelines into repeatable clinic behaviors, including identifying appropriate patients, changing default prescribing patterns, teaching device use, addressing coverage barriers, and monitoring follow-up.¹⁹ However, shifting away from SABA-only rescue therapy prescribing is challenging. Implementation science suggests that applying research findings and evidence-based practices into routine care facilitates narrowing the gap between what improves outcomes and what actually is delivered in practice.^{20,21} There are few better places to apply these principles than asthma in primary care, where barriers across clinician, workflow, patient, and system domains may

persist.²²⁻²⁴ The Knowledge to Action framework is particularly relevant in this setting because it links knowledge creation to a practical action cycle that includes identifying the problem, adapting evidence to the local context, assessing barriers, selecting and tailoring interventions, monitoring uptake, evaluating outcomes, and sustaining change over time.^{25,26} This structured approach is important because the time from evidence generation to routine implementation in clinical practice is approximately 17 years, highlighting the need for deliberate, practice-based strategies to accelerate adoption of effective asthma care in the primary care setting.²¹

A practical starting point is proactive case finding.¹⁸ Patients with recent exacerbations, repeated SABA fills, frequent SCS bursts, emergency care use, or no evidence of ICS exposure are most likely to benefit from discontinuing albuterol-only rescue therapy.^{6,11,18} Clinical tools such as EHR reports, refill history, and pre-visit planning processes can identify these patients proactively and in advance, making the treatment change feel systematic rather than opportunistic, which can increase implementation success rates.¹⁹ Focused, practice-level audits and soliciting clinician feedback may also be useful because this creates visibility around SABA overreliance and allows clinics to track whether prescribing patterns are changing.¹⁹

Implementation is facilitated by simplifying the visit.¹⁸ A short explanation about how asthma symptoms involve inflammation and airway constriction and how an ICS-containing rescue regimen treats both tight airways and inflammation can reframe the conversation without requiring a lengthy and detailed discussion.^{5,9} Pairing that message with inhaler technique assessment is important, because technique errors are common and can erode treatment effectiveness over time, even after initial instruction.²⁷ Therefore, education should be iterative rather than one time, with technique checks and regimen reinforcement embedded into follow-up visits, refill encounters, or outreach calls.

Multidisciplinary, interprofessional involvement in asthma care can improve the feasibility and sustainability of implementation approaches. For example, in a pediatric primary care quality-improvement (QI) initiative, a respiratory therapist-driven protocol substantially increased completion of spirometry and asthma education, illustrating how health care team members can improve adherence to best practices when responsibilities are formalized.²⁸ The same implementation logic applies in adult primary care: nurses and pharmacists can support access and device teaching, nurses and medical assistants can provide education and follow-up care, and respiratory therapists can reinforce technique and objective assessment, where available.^{18,19}

Implementation is more likely to succeed when practices treat the switch to ICS-containing rescue as a QI priority

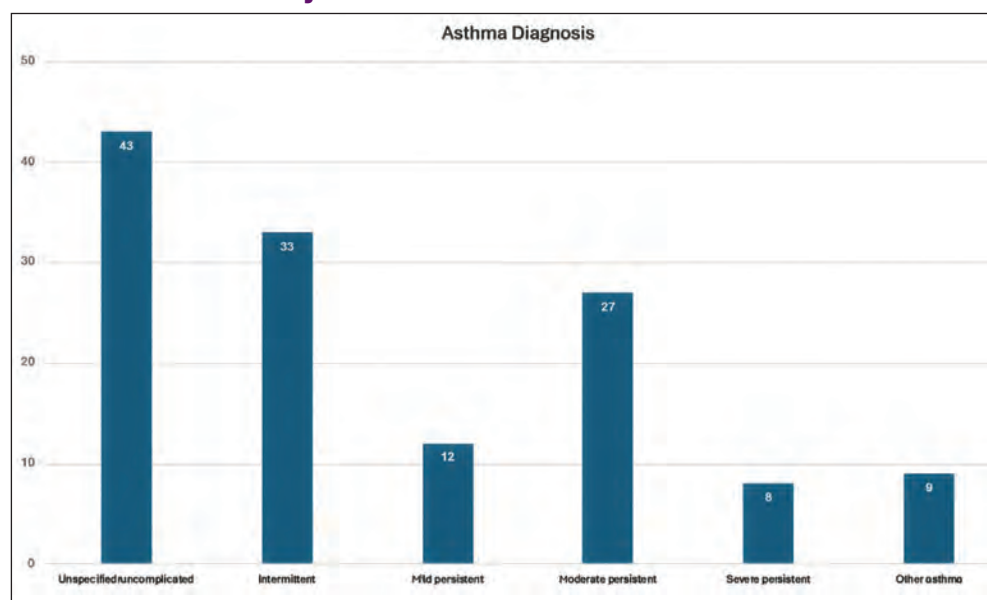
rather than as an optional medication substitution. Codesigned asthma interventions emphasize clinician education, gold-standard prescribing, targeted reviews, patient support, and real-time monitoring as core pillars for sustainable change.¹⁹ That framework fits asthma especially well in primary care, where small workflow changes can influence large patient volumes and meaningfully reduce future exacerbations through successful implementation of ICS-containing rescue therapy.

In the authors' current asthma practices, GINA recommendations are foundational in treating patients with asthma. Accordingly, spirometry is embedded into clinic workflows, with medical assistants or other staff obtaining these objective data before the clinician sees the patient. These data provide a base from which to begin a conversation about asthma, similarly to how glycated hemoglobin objectively provides information about a patient's glycemic status. The operational goal of asthma care is transitioning all patients with asthma who currently use SABA-only rescue therapy to an ICS-containing rescue or rescue and maintenance therapy regimen. We do this by incorporating a conversation about transitioning to ICS into every well visit or asthma-related follow-up visit.

QI study

In a rural family medicine clinic in South Carolina, a 2025-2026 QI project implemented ICS-based rescue therapy in all patients with asthma.²⁹ The project was based on switching from SABA-only rescue to anti-inflammatory reliever (AIR) for patients not requiring maintenance therapy (either SABA-ICS or ICS-formoterol), and either SABA-ICS as-needed with maintenance or ICS + formoterol rescue and maintenance for patients requiring maintenance therapy. Clinicians (including physicians, nurse practitioners, family medicine residents, and a clinical pharmacist) used a systematized workflow process in the EHR to identify patients for intervention and to support prescribing decisions.²⁹ Standard order sets in the EHR for ICS-based rescue included an option for prescribing as-needed albuterol-

FIGURE 3. Baseline classification of asthma severity in patients participating in a US-based asthma QI study assessing implementation of AIR in a rural family medicine clinic.^{29a}



^aClassification of asthma was obtained via chart review, based on clinician impression, and not guided by objective criteria.

budesonide with or without maintenance treatment, or budesonide-formoterol or mometasone-formoterol as maintenance and as-needed therapy.

Researchers identified 132 patients with asthma. At baseline, most patients had mild-moderate or unspecified/uncomplicated asthma (**FIGURE 3**), and only 5 patients (3.85%) were receiving AIR therapy.²⁹ Clinicians contacted patients on SABA-only rescue to recommend discussing therapeutic options with the pharmacist or their clinician at the next visit, where they would be offered AIR alternative therapy. Interim results from monthly audits of asthma patients 3 months after project initiation revealed an increase in the percentage of patients receiving AIR therapy from 3.85% to 25%, an increase in the percentage of visits during which asthma was addressed (30% to 55%), and a decrease in the percentage of "unspecified asthma" diagnoses (25% to 10%).²⁹

The QI project will be evaluated after completion and potentially rolled out to remaining practices within the health care system.

SUMMARY

Mild-moderate asthma should not be equated with a low risk for exacerbations or adverse outcomes. Many patients with mild-moderate disease have uncontrolled symptoms, elevated exacerbation risk due to persistent SABA-only use, and experience severe attacks that lead to avoidable SCS use. Because airway inflammation persists even when symp-

toms are intermittent, rescue strategies that address bronchospasm alone leave the underlying driver of future risk untreated.

Improving mild-moderate asthma care in primary care settings involves moving away from SABA-only rescue and toward ICS-based rescue strategies that treat both symptoms and inflammation. However, implementing a paradigm shift from a long history of SABA-only rescue prescribing requires significant effort and intervention. Success depends not only on choosing an evidence-aligned regimen, but also on proactive case finding, effective patient education, and workflow changes that make ICS-based rescue easier to prescribe and use in daily practice. As ICS-containing rescue becomes more accessible in the United States, primary care teams have an important opportunity to reduce exacerbations, lower SCS exposure, and improve long-term outcomes for patients with mild-moderate asthma. ●

REFERENCES

- Centers for Disease Control and Prevention. Most recent asthma data. July 31, 2026. Accessed August 25, 2026. <https://www.cdc.gov/asthma-data/about/most-recent-asthma-data.html>
- Lugogo N, Moon R, Chung Y, et al. Disease burden of asthma patients utilizing short-acting beta-2 agonist-only inhalers as rescue in the United States. *J Asthma Allergy*. 2026;19:564966. doi:10.2147/JAA.S564966
- Jenkins CR. Mild asthma: conundrums, complexities and the need to customize care. *Respirology*. 2024;29(2):94-104. doi:10.1111/resp.14646
- Mohan A, Lugogo NL, Hanania NA, et al. Questions in mild asthma: an official American Thoracic Society research statement. *Am J Respir Crit Care Med*. 2023;207(11):e77-e96. doi:10.1164/rccm.202304-0642ST
- Skolnik N. Use of ICS and fast-acting bronchodilators in asthma: past, present, and future. *J Fam Pract*. 2023;72(suppl 6). doi:10.12788/jfp.0625
- 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):302-3094. doi:10.1016/j.anai.2024.05.003
- Bleecker ER, Al-Ahmad M, Bjermer L, et al. Systemic corticosteroids in asthma: a call to action from World Allergy Organization and Respiratory Effectiveness Group. *World Allergy Organ J*. 2022;15(12):100726. doi:10.1016/j.waojou.2022.100726
- 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
- Global Initiative for Asthma. Global strategy for asthma management and prevention, 2026. Accessed May 27, 2026. <https://ginasthma.org/wp-content/uploads/2026/05/GINA-2026-Strategy-Report-WMS.pdf>
- Lugogo NL, Gilbert IA, Gandhi HN, Tkacz JP, Lanz MJ. Exacerbation burden in patients treated as intermittent or mild-persistent asthma using short-acting beta2-agonist rescue. *Ann Allergy Asthma Immunol*. 2025;134(5):539-547. doi:10.1016/j.anai.2025.02.009
- Quint JK, Arnetorp S, Kocks JWH, et al. Short-acting beta-2-agonist exposure and severe asthma exacerbations: SABINA findings from Europe and North America. *J Allergy Clin Immunol Pract*. 2022;10(9):2297-2309.e10. doi:10.1016/j.jaip.2022.02.047
- Krings JG, Beasley R. The role of ICS-containing rescue therapy versus SABA alone in asthma management today. *J Allergy Clin Immunol Pract*. 2024;12(4):870-879. doi:10.1016/j.jaip.2024.01.011
- Reddel HK, FitzGerald JM, Bateman ED, et al. GINA 2019: a fundamental change in asthma management: treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J*. 2019;53(6):1901046. doi:10.1183/13993003.01046-2019
- LaForce C, Albers F, Danilewicz A, et al. As-needed albuterol-budesonide in mild asthma. *N Engl J Med*. 2025;393(2):113-124. doi:10.1056/NEJMoa2504544
- Cloutier MM, Baptist AP, Blake KV, 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
- Airsupra (albuterol and budesonide) inhalation aerosol. Prescribing Information. AstraZeneca Pharmaceuticals LP; September 2025. https://drdsvrdh9yh09.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/fe598cda-d255-4446-998e-617607f61552/fe598cda-d255-4446-998e-617607f61552_viewable rendition_v.pdf
- Israel E, Farooqui N, Gandhi H, et al. A discrete choice experiment to assess patient preferences for asthma rescue therapy and disease management. *J Allergy Clin Immunol Pract*. 2023;11(9):2781-2791.e4.
- Skolnik N, Yawn BP, Correia de Sousa J, et al. Best practice advice for asthma exacerbation prevention and management in primary care: an international expert consensus. *NPJ Prim Care Respir Med*. 2024;34(1):39. doi:10.1038/s41533-024-00399-2
- Crowther L, Pearson M, Cummings H, Crooks MG. Towards redesign in respiratory care: development of an implementation-ready intervention to improve guideline-adherent adult asthma care across primary and secondary care settings (The SENTINEL Project). *BMJ Open Respir Res*. 2022;9(1):e001155. doi:10.1136/bmjresp-2021-001155
- Wensing M. Implementation science in healthcare: introduction and perspective. *Z Evid Forbild Qual Gesundheitswes*. 2015;109(2):97-102. doi:10.1016/j.zefq.2015.02.014
- Rubin R. It takes an average of 17 years for evidence to change practice—the burgeoning field of implementation science seeks to speed things up. *JAMA*. 2023;329(16):1333-1336. doi:10.1001/jama.2023.4387
- McFarlane M, Morra A, Loughheed MD. Integrating asthma care guidelines into primary care electronic medical records: a review focused on Canadian knowledge translation tools. *Eur Respir Rev*. 2024;33(174):230247. doi:10.1183/16000617.0247-2023
- Gilchrist FJ, Carroll WD, Clayton S, et al. Implementation of a primary care asthma management quality improvement programme across 68 general practice sites. *NPJ Prim Care Respir Med*. 2023;33(1):21. doi:10.1038/s41533-023-00341-y
- Yamada J, Lam Shin Cheung J, Gagne M, et al. Barriers and enablers to objective testing for asthma and COPD in primary care: a systematic review using the theoretical domains framework. *Chest*. 2022;161(4):888-905. doi:10.1016/j.chest.2021.10.030
- Graham ID, Logan J, Harrison MB, et al. Lost in knowledge translation: time for a map? *J Contin Educ Health Prof*. 2006;26(1):13-24. doi:10.1002/chp.47
- Field B, Booth A, Iltott I, Gerrish K. Using the Knowledge to Action framework in practice: a citation analysis and systematic review. *Implement Sci*. 2014;9:172. doi:10.1186/s13012-014-0172-2
- Bosnic-Anticevich S, Bender BG, Shuler MT, Hess M, Kocks JWH. Recognizing and tackling inhaler technique decay in asthma and chronic obstructive pulmonary disease (COPD) clinical practice. *J Allergy Clin Immunol Pract*. 2023;11(8):2355-2364. e5. doi:10.1016/j.jaip.2023.04.031
- Long HM, Cobb KA, Leisenring PA, et al. Implementation of a respiratory therapist-driven protocol for spirometry and asthma education in a pediatric outpatient primary care setting. *Respir Care*. 2023;68(9):1195-1201. doi:10.4187/respcare.10930
- Primary Care Education Consortium. Asthma AIR Project. 2026. Data on file.

LAMAs Across COPD and Asthma: Practical Escalation Strategies With a Sustainability Lens

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and asthma remain major public health issues in the United States and present a substantial clinical burden for patients.^{1,2} In 2023, the age-adjusted prevalence of diagnosed COPD in adults was approximately 3.8%, and in 2024 about 4.2% of adults were diagnosed with COPD, emphysema, or chronic bronchitis.^{2,3} The prevalence of asthma in 2024 was estimated at 8.6% of adults and 6.5% of children.^{1,4} In both COPD and asthma, certain populations experience disproportionate disease burden. National surveillance data show persistent disparities in the prevalence of COPD among people who smoke, older adults, and those living in rural communities.^{2,3} In an analysis of asthma trends, prevalence increased among adults from 2013 through 2021 and remained disproportionately high among non-Hispanic Black children and adults (12.5% and 10.6%, respectively) compared with non-Hispanic White children and adults (5.7% and 8.2%).⁴

Uncontrolled disease remains common after diagnosis for both COPD and asthma. In a US study of patients newly diagnosed with COPD, only about 36% received maintenance therapy, underscoring undertreatment early in the disease course.⁵ In severe asthma, observational studies indicate that approximately 35% to 51% of US patients with evidence of uncontrolled disease had no specialist visit or medication escalation afterward, despite the risk of future exacerbations and health care use.^{6,7} Exacerbations remain a dominant driver of morbidity in both COPD and asthma. For COPD, poor adherence to inhaled therapy was associated with a 40% higher exacerbation risk in a 2024 meta-analysis.⁸ For asthma, recent claims analyses show increased costs

Key takeaways

- Long-acting muscarinic antagonists (LAMAs) occupy a central role in care for COPD and asthma. In COPD, they are foundational bronchodilators from initial treatment onward; LAMAs are add-on therapy for patients with asthma whose disease remains uncontrolled despite optimized ICS-based treatment.
- In COPD, LAMAs improve bronchodilation, mucus biology, small-airway physiology, and airway remodeling pathways and reduce exacerbations. Dual LABA/LAMA combinations are preferred for many symptomatic patients; triple therapy is used when exacerbation risk and eosinophilic disease indicate the addition of ICS would be helpful.
- In asthma, escalation to LAMA-containing regimens improves lung function and can reduce exacerbations in selected patients, although biologics should still be considered in those with severe type 2–driven disease.
- Sustainability in chronic airway disease is an increasingly important consideration, but it should reinforce rather than override clinical judgment. The most environmentally responsible inhaler is the one that the patient can use correctly and consistently while maintaining disease control.

among patients who remain uncontrolled while on long-acting beta₂-agonist (LABA) and inhaled corticosteroid (ICS) maintenance therapy.^{6,9}

The economic burden for these airway diseases is substantial. A 2023 US analysis estimated annual COPD-specific direct costs at \$24.0 billion, with prescription drugs contributing \$10.5 billion; national projections estimate that COPD-attributable medical costs will rise to \$60.5 billion by 2029.^{10,11} For asthma, the economic burden is estimated at approximately \$50 billion in direct medical costs and \$32 billion in

indirect and mortality-related costs in the United States.¹² Furthermore, uncontrolled symptoms and health care utilization are linked to undertreatment, nonadherence, and shortcomings in care delivery in asthma and COPD.^{13,14}

LAMAs play a key role in improving disease control and reducing burden for certain patients with COPD and/or asthma.^{13,14} In COPD, the Global Initiative for Obstructive Lung Disease (GOLD) 2026 recommendations place LAMAs in initial and follow-up pharmacotherapy algorithms, either alone or as part of dual and triple therapy (GOLD Groups B and E).¹⁴ Additionally, LAMA monotherapy has shown a lower incidence of exacerbation and nonserious adverse events than LABA monotherapy.¹⁵ In asthma, a meaningful proportion of patients remain uncontrolled even when adherent to ICS/LABA, supporting step-up strategies. The Global Initiative for Asthma (GINA) recommends LAMAs for patients who remain uncontrolled on at least medium-dose ICS/LABA, positioning them as an inhaled therapy escalation before or alongside specialist-directed severe asthma evaluation.¹³ LAMAs also improve lung function in patients with asthma and asthma-COPD overlap.^{16,17}

MECHANISTIC RATIONALE FOR LAMAs

The mechanistic rationale for LAMAs in both COPD and asthma is understood in the context of acetylcholine signaling and muscarinic acetylcholine receptors, especially the M3 subtype.^{18,19} Parasympathetic cholinergic signaling contributes directly to airway smooth-muscle contraction, mucus secretion, and increased bronchomotor tone in obstructive airway disease, with the muscarinic M3 receptor playing an important role in bronchoconstriction.¹⁹ LAMAs provide prolonged bronchoprotection by antagonizing muscarinic signaling, particularly at the M3 receptor, addressing one of the most consistent reversible components of airflow obstruction.^{18,19}

Muscarinic biology also extends beyond airway smooth muscle. Preclinical data show that tiotropium inhibits and can reverse interleukin-13-induced goblet cell metaplasia in human airway epithelial cells, supporting the clinical observation that antimuscarinic therapy may help temper mucus-related morbidity as well as bronchospasm.²⁰ Additional translational evidence further suggests anti-inflammatory and antifibrotic effects that may complement bronchodilation.^{19,21} A 2025 position paper by the European Academy of Allergy and Clinical Immunology notes that LAMAs influence muscarinic pathways in airway smooth muscle, epithelial cells, and inflammatory cells, supporting their value in phenotypes marked by persistent bronchoconstriction and mucus hypersecretion.²¹ In practical terms, LAMAs connect pharmacology with physiology because activation of the cholinergic pathway narrows airways, amplifies reflex bronchomotor tone, and contributes to mucus-related obstruction. Blocking this pathway has multiple complementary effects: relaxation of airway

smooth muscle, improved airway caliber, less mucus-driven plugging, and potential moderation of remodeling signals that sustain chronic airflow limitation.¹⁸⁻²¹ This helps explain why LAMA benefits can appear clinically as improved forced expiratory volume in 1 second (FEV₁), reduced rescue therapy use, improved symptoms, and fewer exacerbations rather than simply as a short-term bronchodilator response.^{13,14}

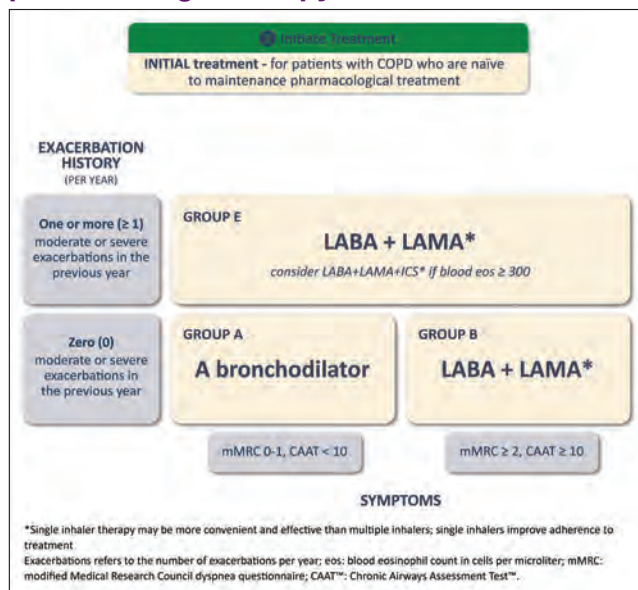
In COPD, LAMA use results in reduced sputum production, goblet cell differentiation, and hyperplasia. Muscarinic blockade can be the backbone of maintenance therapy because bronchodilation is a core treatment target in COPD, whereas in asthma these same benefits are most useful as an adjunct to ICS.^{13,14,22}

CLINICAL USE OF LAMAs IN COPD

GOLD 2026 recommendations place LAMAs at the center of COPD pharmacotherapy. For initial treatment, patients in GOLD Group A may start with any bronchodilator (LAMA or LABA), but patients in GOLD Group B are recommended to receive LABA/LAMA dual therapy, and patients in GOLD Group E should also receive LABA/LAMA, with consideration of LABA/LAMA/ICS when blood eosinophils are at least 300 cells/ μ L (**FIGURE 1**).¹⁴ LAMA monotherapy remains clinically relevant in COPD, particularly for symptomatic patients with a lower exacerbation burden or for those beginning maintenance therapy.¹⁴ In a 2020 systematic review and meta-analysis, LAMA therapy produced a lower incidence of exacerbation and nonserious adverse events than LABA monotherapy and delivered higher FEV₁.¹⁵ The long-term UPLIFT trial similarly showed that tiotropium improved lung function, health-related quality of life, and exacerbation outcomes over 4 years.²³ Of note, both LAMA and LABA monotherapy improve lung function, symptoms, health status, exercise tolerance, and exacerbations in COPD, and GOLD does not prefer one over the other for patients in GOLD Group A.¹⁴ Data suggest that LAMAs may be preferred for exacerbation prevention and some experts propose that LABAs may be preferred for symptom reduction.²⁴ In a recent US analysis, LAMA monotherapy was prescribed more often in patients with COPD (23.5%) than LABA monotherapy (1.7%).⁵

When symptoms persist and/or in the event of a moderate or severe exacerbation, the escalation after inhaled monotherapy is usually dual bronchodilation rather than switching to a different monotherapy.¹⁴ Meta-analysis data note that LABA/LAMA dual therapy is superior to either LABA or LAMA monotherapy for symptomatic COPD, with lower risks of exacerbations and hospitalizations and no signal for more treatment-emergent adverse effects.²⁵ Among fixed-dose combinations, head-to-head and comparative analyses also show that dual bronchodilation can improve lung function and rescue-medication use beyond what is achieved with single bronchodilators alone.²⁶

FIGURE 1. GOLD recommendations for initial pharmacologic therapy for COPD.¹⁴



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The LAMA component remains important even when treatment advances to triple therapy. For patients with continued exacerbations on bronchodilator monotherapy or dual therapy, GOLD recommendations consider exacerbation history and blood eosinophils to determine whether escalation to an ICS-containing regimen is warranted and if LAMAs remain part of that intensified strategy (FIGURE 2).¹⁴ Of note, many patients still receive legacy LABA/ICS regimens, which are no longer recommended for COPD.^{5,14}

Patient selection for LAMA-based therapy includes factors such as symptom burden, prior exacerbations, comorbid cardiovascular disease, inhaler technique, cognitive or physical limitations, and likelihood of adherence, some of which determine GOLD Group and therapy progression based on GOLD algorithms.^{8,14} Of note, a 2025 meta-analysis showed significant trough FEV₁ improvement with LAMAs vs placebo and suggested that older adults with COPD may derive at least comparable, and possibly greater, benefit from once-daily LAMA treatment as younger patients.¹⁸ In COPD, clinicians can pair symptom scores, such as the COPD Assessment Test (CAT) or modified Medical Research Council scale, with exacerbations, rescue medication use, adherence and technique checks, spirometry, and blood eosinophils when ICS escalation is being considered.¹⁴ Electronic medical record questionnaires or visit templates can make these data easier to visualize

across encounters. For patients with frequent exacerbations, rapidly declining lung function, diagnostic uncertainty, or persistent symptoms despite optimized bronchodilation, clinicians should promptly collaborate with pulmonology or other relevant specialists.¹⁴

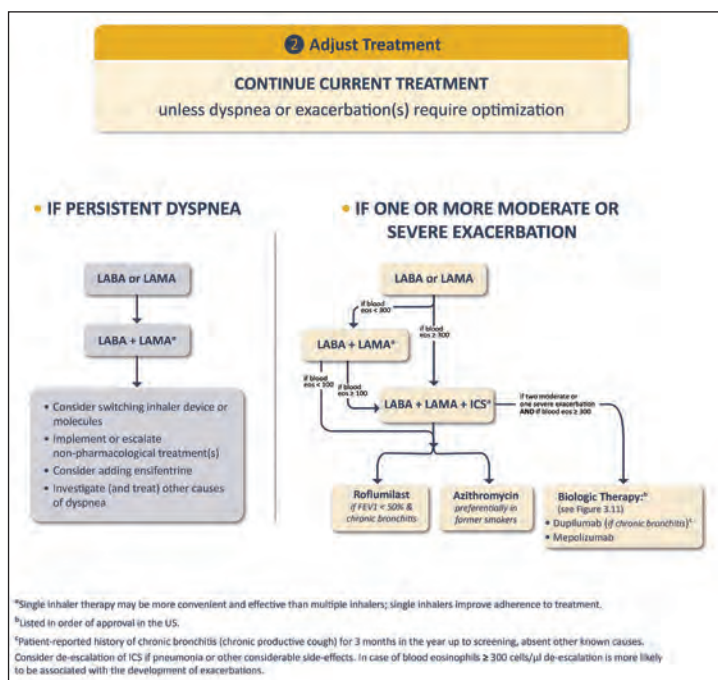
Device selection plays an important role in effective therapy for COPD. Single-inhaler therapy may be more convenient and effective than multiple inhalers because it can improve adherence, and guideline-directed follow-up includes switching device or molecules when dyspnea persists despite appropriate treatment.¹⁴ The best COPD regimen is the one that matches the patient's inspiratory ability, dexterity, routine, and willingness to use it consistently.^{8,14} In COPD, LAMAs are a core therapeutic component across monotherapy, dual-therapy, and triple-therapy regimens.

CLINICAL USE OF LAMAs IN ASTHMA

The role of LAMAs in asthma is somewhat more selective than in COPD, but their role in therapy has been increasingly established. GINA recommends considering a LAMA as add-on therapy for adults and adolescents whose asthma remains uncontrolled despite maintenance ICS/LABA at Step 5, after adherence, inhaler technique, comorbidities, and modifiable risk factors have been reassessed (FIGURE 3).¹³

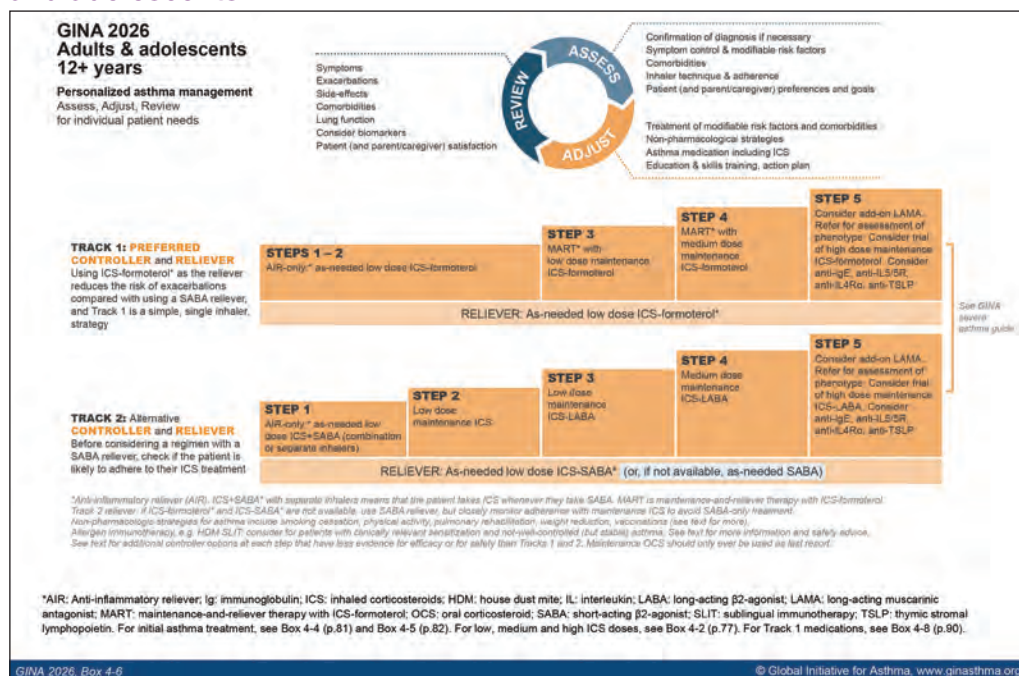
Classic trial evidence for LAMAs in asthma comes from

FIGURE 2. GOLD recommendations for follow-up pharmacologic therapy for COPD.¹⁴



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FIGURE 3. GINA recommendations for asthma treatment steps in adults and adolescents.¹³



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tiotropium studies.^{27,28} In adults with asthma poorly controlled on ICS/LABA, add-on tiotropium increased the time to first severe exacerbation from 226 days to 282 days and reduced the overall risk of severe exacerbation by 21% (hazard ratio, 0.79, $P=.03$).²⁸ A Cochrane review likewise found that adding a LAMA to ICS lowered the odds of exacerbations requiring oral corticosteroids vs the same ICS dose alone, with an odds ratio of 0.65 (95% confidence interval [CI]: 0.46, 0.93).²⁷

More recent evidence has expanded the LAMA role in asthma from tiotropium add-on therapy to single-inhaler triple therapy. In IRIDIUM, both high- and medium-dose mometasone/indacaterol/glycopyrronium significantly improved trough FEV₁ vs the corresponding ICS/LABA comparator, with between-group gains of 65 mL and 76 mL at week 26.¹⁶ In TRIMARAN and TRIGGER, extrafine beclomethasone/formoterol/glycopyrronium reduced severe exacerbations over 52 weeks in adults with uncontrolled asthma receiving ICS/LABA.²⁹ Other phase 3 trials show similar benefits of LAMAs as part of triple inhaled therapy for asthma. The ARGON study showed that once-daily indacaterol/glycopyrronium/mometasone provided noninferior quality-of-life improvement vs high-dose salmeterol/fluticasone plus tiotropium.³⁰ CAPTAIN showed that adding umeclidinium to fluticasone furoate/vilanterol improved lung function in inadequately controlled disease.³¹

KALOS and LOGOS were large phase 3 trials that provide data for single-inhaler triple therapy in asthma. These repli-

cate, randomized, double-blind trials enrolled adolescents and adults with asthma that remained inadequately controlled despite medium- or high-dose ICS/LABA and compared budesonide/glycopyrronium/formoterol (BGF) with dual budesonide/formoterol comparators over 24 to 52 weeks.³² There were 2 BGF groups: BGF 28.8 (BGF 320 µg, 28.8 µg, 10 µg) and BGF 14.4 (BGF 320 µg, 14.4 µg, 10 µg). In pooled analyses, BGF 28.8 improved morning pre-dose trough FEV₁ by 76 mL and FEV₁ area under the curve from 0 hours to 3 hours by 90 mL over 24 weeks vs combined ICS/LABA comparators, and it reduced severe exacerbations by 14% (incidence rate ratio, 0.86; 95% CI: 0.76, 0.97).³² Safety was broadly similar across treatment groups, and no deaths were considered treatment-related.

A meta-analysis of triple vs dual inhaled therapy showed better lung function and fewer severe exacerbations, but gains were generally smaller than those seen with biologics in carefully phenotyped severe type 2 asthma.³³ Accordingly, GINA places LAMA add-on therapy and biologics in the same step (Step 5), although these therapies are not interchangeable and treatment selection depends on patient characteristics.^{13,34}

In practice, the patients most likely to benefit from a LAMA are those with persistent symptoms or exacerbations despite optimized ICS/LABA, especially when airflow limitation remains evident and bronchoconstriction appears to be a major contributor to impairment.^{13,21} Single-inhaler triple therapy may also be attractive for patients whose disease is uncontrolled in part due to regimen complexity; US real-world data show better adherence and persistence with single-inhaler vs multiple-inhaler triple therapy.^{13,35} For many patients, adding a LAMA represents an option for inhaled therapy escalation before biologic initiation; single-inhaler triple therapy can be a useful adjunct even after specialist referral, particularly when the goal is to improve lung function, simplify inhaled therapy, and reduce exacerbation risk without moving immediately to injectable treatment.^{13,35}

TABLE 1. Key considerations for LAMA use in COPD and asthma.^{13,14}

Domain	COPD	Asthma
Guideline placement	Foundational bronchodilator across initial and follow-up treatment	Add-on therapy for uncontrolled disease despite ICS/LABA (Step 5)
Typical escalation trigger	Persistent dyspnea or exacerbations prompt movement from LAMA to LABA/LAMA or LABA/LAMA/ICS depending on eosinophils	Persistent symptoms or exacerbations after optimization of adherence, technique, and comorbidity management
Potential benefits	Improved FEV ₁ , dyspnea, and health status plus exacerbation reduction ^{15,23}	Improved lung function and selected exacerbation outcomes, especially with add-on or single-inhaler triple therapy ^{16,28}
Illustrative data	LAMA lowered exacerbation incidence vs LABA in meta-analysis; tiotropium outperformed salmeterol for exacerbation prevention ^{15,36}	Tiotropium extended time to first severe exacerbation to 282 vs 226 days; improved trough FEV ₁ by 65 to 76 mL ^{16,28}
Device strategy	Choose regimen and device according to symptoms, exacerbation history, dexterity, and adherence likelihood; single inhaler often preferred when possible ^{8,14}	Align device with technique and treatment complexity; single-inhaler triple therapy improves adherence vs multiple inhalers ^{13,35}
Sustainability lens	Preventing COPD exacerbations is environmentally meaningful because health care utilization carries a carbon burden ^{37,38}	Device switches should not compromise control; clinical fit and correct use remain the first priorities ^{39,40}

Structured reassessment can improve escalation decisions in asthma. For example, clinicians can confirm adherence and inhaler technique, use validated questionnaires such as the Asthma Control Test (ACT) or Asthma Impairment and Risk Questionnaire (AIRQ), review exacerbation and oral corticosteroid history, repeat spirometry when control is uncertain, and evaluate type 2 biomarkers, such as blood eosinophils or fractional exhaled nitric oxide, when severe asthma or biologic eligibility is being considered.¹³ This approach may help clinicians clarify whether the next move should be escalation to LAMA-containing inhaled therapy, biologic evaluation, specialist referral, or additional workup for comorbidities and alternative diagnoses.¹³

Clinical considerations for the use of LAMAs in COPD and asthma as discussed in this article are described in **TABLE 1**.

SUSTAINABILITY IN RESPIRATORY CARE

Sustainability is increasingly recognized as a component of respiratory care due to the environmental footprint of inhalers and health care utilization (e.g., emergency visits, hospitalizations).^{37,41} The clinically relevant application of sustainability is that poor disease control can be environmentally costly and medically harmful, because increased health care utilization carries a carbon burden; therefore, preventing exacerbations is a high-impact strategy to potentially reduce the system-level carbon footprint of care.^{37,38}

Studies have estimated the environmental impact of airway disease–related care. In a 2025 serial cross-sectional US analysis, 1.6 billion inhalers dispensed from 2014 to 2024 generated an estimated 24.9 million metric tons of carbon dioxide emissions, with metered-dose inhalers responsible for 98% of emissions.⁴¹ After the 2021 US Department of Veterans

Affairs formulary transition from budesonide-formoterol metered-dose inhaler to fluticasone-salmeterol dry-powder inhaler to reduce propellant use, most facilities switched more than 80% of patients, with 14.2% later switching back.⁴² The subsequent outcomes study associated the original transition from metered-dose inhalers to dry-powder inhalers with increased hospital-based utilization; these findings may reflect health-system-specific implementation factors and may not be generalizable to all switching approaches.³⁹

For clinicians, a practical sustainability principle may be summarized as “best for the patient first, then the planet.”^{13,40} Shared decision-making should include consideration of access, likelihood of correct use, treatment goals, inhaler continuity, and environmental impact rather than carbon metrics alone. This is particularly relevant for LAMA-containing regimens because they are available across multiple device platforms and as both single- and multiple-inhaler combinations.

Encouragingly, newer propellants may reduce the trade-off between clinical familiarity and environmental performance. HFO-1234ze(E) has been proposed as a near-zero-global-warming-potential propellant for pressurized metered-dose inhalers, and current modeling and nonclinical assessment suggest negligible trifluoroacetic-acid deposition and an acceptable safety profile for continued development.^{43,44}

SUMMARY

COPD and asthma continue to impose a major burden in the United States, with substantial prevalence, persistent disparities, frequent uncontrolled disease, ongoing exacerbations, and high health care costs. Many patients remain undertreated after diagnosis or continue to have poor control despite maintenance therapy, which contributes to future exacerbations,

greater health care utilization, and rising economic and environmental impact. LAMAs help address these gaps by targeting cholinergic bronchoconstriction and related mucus and inflammatory pathways, making them a central part of COPD management and a useful step-up option in asthma. Their clinical value depends not only on efficacy, but also on selecting the right regimen and device for the individual patient to support adherence. Sustainability considerations increasingly favor approaches that improve control and prevent exacerbations while minimizing avoidable environmental impact. ●

REFERENCES

- Asthma. Centers for Disease Control and Prevention. February 20, 2026. Accessed April 10, 2026. <https://www.cdc.gov/nchs/fastats/asthma.htm>
- Weeks JD, Elgaddal N. Chronic obstructive pulmonary disease in adults age 18 and older: United States, 2023. *NCHS Data Brief*. 2025;(529):1. doi:10.15620/cdc/174596
- Workman B, Nabors L. Health and demographic factors for chronic obstructive pulmonary disease among Hispanic adults in the United States: analysis of behavioral risk factor surveillance system survey data. *Hisp Health Care Int*. 2024;22(2):67-73. doi:10.1177/15404153231210863
- Pate CA, Zahran HS. The status of asthma in the United States. *Prev Chronic Dis*. 2024;21:E53. doi:10.5888/pcd21.240005
- Anzueto A, Rogers S, Donato B, et al. Treatment patterns in patients with newly diagnosed COPD in the USA. *BMC Pulm Med*. 2024;24(1):395. doi:10.1186/s12890-024-03194-4
- 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*. 2024;12(7):1775-1782.e2. doi:10.1016/j.jaip.2024.03.018
- Most JF, Ambrose CS, Chung Y, et al. Real-world assessment of asthma specialist visits among U.S. patients with severe asthma. *J Allergy Clin Immunol Pract*. 2021;9(10):3662-3671.e1. doi:10.1016/j.jaip.2021.05.003
- Vauterin D, Van Vaerenbergh F, Grymonprez M, Vanoverschelde A, Lahousse L. Medication adherence to inhalation therapy and the risk of COPD exacerbations: a systematic review with meta-analysis. *BMJ Open Respir Res*. 2024;11(1):e001964. doi:10.1136/bmjresp-2023-001964
- Duh MS, Roberts MH, Rothnie KJ, et al. Frequency and economic burden of exacerbations in inhaled corticosteroid/long-acting beta-agonist-treated patients with asthma: a retrospective US claims study. *Respir Med*. 2024;226:107629. doi:10.1016/j.rmed.2024.107629
- Shah CH, Reed RM, Wastila L, Onukwugha E, Gopalakrishnan M, Zafari Z. Direct medical costs of COPD in the USA: an analysis of the medical expenditure panel survey 2017-2018. *Appl Health Econ Health Policy*. 2023;21(6):915-924. doi:10.1007/s40258-023-00814-8
- Mannino DM, Roberts MH, Mapel DW, et al. National and local direct medical cost burden of COPD in the United States from 2016 to 2019 and projections through 2029. *Chest*. 2024;165(5):1093-1106. doi:10.1016/j.chest.2023.11.040
- Patel KB, Mims JW, Clinger JD. The burden of asthma and allergic rhinitis: epidemiology and health care costs. *Otolaryngol Clin North Am*. 2024;57(2):179-189. doi:10.1016/j.otc.2023.09.007
- Global Initiative for Asthma. 2026 GINA Strategy Report. Global Strategy for Asthma Management and Prevention, 2025. <https://ginasthma.org/2026-gina-strategy-report/>
- Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2026 Report. https://goldcopd.org/wp-content/uploads/2026/01/GOLD-REPORT-2026-v1.3-8Dec2025_WMV2.pdf
- Koara I, Sugiura H, Yamada M, et al. Treatment with LABA versus LAMA for stable COPD: a systematic review and meta-analysis. *BMC Pulm Med*. 2020;20(1):111. doi:10.1186/s12890-020-1152-8
- Kerstjens HAM, Maspero J, Chapman KR, et al. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. *The Lancet Respir Med*. 2020;8(10):1000-1012. doi:10.1016/S2213-2600(20)30190-9
- Qin J, Wang G, Han D. Benefits of LAMA in patients with asthma-COPD overlap: A systematic review and meta-analysis. *Clin Immunol*. 2022;237:108986. doi:10.1016/j.clim.2022.108986
- Calzetta L, Pistocchini E, Laitano R, Gholamalishahi S, Cazzola M, Rogliani P. Efficacy and safety of long-acting muscarinic antagonists in COPD: a meta-analysis and meta-regression with a focus on aging. *Respir Med*. 2025;238:107956. doi:10.1016/j.rmed.2025.107956
- Gosens R, Gross N. The mode of action of anticholinergics in asthma. *Eur Respir J*. 2018;52(4):1701247. doi:10.1183/13993003.01247-2017
- Kistemaker LEM, Hiemstra PS, Bos IST, et al. Tiotropium attenuates IL-13-induced goblet cell metaplasia of human airway epithelial cells. *Thorax*. 2015;70(7):668-676. doi:10.1136/thoraxjnl-2014-205731
- Agache I, Adcock IM, Akdis CA, et al. The bronchodilator and anti-inflammatory effect of long-acting muscarinic antagonists in asthma: an EAACI position paper. *Allergy*. 2025;80(2):380-394. doi:10.1111/all.16436
- D'Urzo A, Kerwin E, Overend T, D'Andrea P, Chen H, Goyal P. Once daily glycopyrronium for the treatment of COPD: pooled analysis of the GLOW1 and GLOW2 studies. *Curr Med Res Opin*. 2014;30(3):493-508. doi:10.1185/03007995.2013.858618
- Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543-1554. doi:10.1056/NEJMoa0805800
- D'Urzo AD, Kardos P, Wiseman R. Practical considerations when prescribing a long-acting muscarinic antagonist for patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1089-1104. doi:10.2147/COPD.S160577
- Mammen MJ, Pai V, Aaron SD, Nici L, Alhazzani W, Alexander PE. Dual LABA/LAMA therapy versus LABA or LAMA monotherapy for chronic obstructive pulmonary disease. A systematic review and meta-analysis in support of the American Thoracic Society clinical practice guideline. *Ann Am Thorac Soc*. 2020;17(9):1133-1143. doi:10.1513/AnnalsATS.201912-915OC
- Alcázar Navarrete B, Boucot I, Naya I, et al. Umeclidinium/vilanterol versus tiotropium/olodaterol in maintenance-naïve patients with uncontrolled symptomatic chronic obstructive pulmonary disease: a post hoc analysis. *Pulm Ther*. 2018;4(2):171-183. doi:10.1007/s41030-018-0057-7
- Anderson DE, Kew KM, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma. *Cochrane Database Syst Rev*. 2015;2015(8):CD011397. doi:10.1002/14651858.CD011397.pub2
- Kerstjens HAM, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med*. 2012;367(13):1198-1207. doi:10.1056/NEJMoa1208606
- Virchow JC, Kuna P, Paggiaro P, et al. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. *The Lancet*. 2019;394(10210):1737-1749. doi:10.1016/S0140-6736(19)32215-9
- Gessner C, Kormmann O, Maspero J, et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: a randomised, Phase IIb, non-inferiority study (ARGON). *Respir Med*. 2020;170:106021. doi:10.1016/j.rmed.2020.106021
- Nakamura Y, Hozawa S, Sagara H, et al. Efficacy and safety of once-daily, single-inhaler fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol in Japanese patients with inadequately controlled asthma: the CAPTAIN study. *Curr Med Res Opin*. 2021;37(9):1657-1665. doi:10.1080/03007995.2021.1944849
- Papi A, Wise RA, Jackson DJ, et al. Budesonide-glycopyrronium-formoterol fumarate dihydrate in uncontrolled asthma (KALOS and LOGOS): twin multicentre, double-blind, double-dummy, parallel-group, randomised, phase 3 trials. *The Lancet Respir Med*. 2026;14(4):350-362. doi:10.1016/S2213-2600(25)00457-6
- Kim LHY, Saleh C, Whalen-Browne A, O'Byrne PM, Chu DK. Triple vs dual inhaler therapy and asthma outcomes in moderate to severe asthma: a systematic review and meta-analysis. *JAMA*. 2021;325(24):2466-2479. doi:10.1001/jama.2021.7872
- Oba Y, Anwer S, Maduke T, Patel T, Dias S. Effectiveness and tolerability of dual and triple combination inhaler therapies compared with each other and varying doses of inhaled corticosteroids in adolescents and adults with asthma: a systematic review and network meta-analysis. *Cochrane Database Syst Rev*. 2022;12(12):CD013799. doi:10.1002/14651858.CD013799.pub2
- Busse WW, Abbott CB, Germain G, et al. Adherence and persistence to single-inhaler versus multiple-inhaler triple therapy for asthma management. *J Allergy Clin Immunol Pract*. 2022;10(11):2904-2913.e6. doi:10.1016/j.jaip.2022.06.010
- Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med*. 2011;364(12):1093-1103. doi:10.1056/NEJMoa1008378
- Wilkinson A, Maslova E, Janson C, et al. Environmental sustainability in respiratory care: an overview of the healthCARE-Based environmental CO2 of treatment (CARBON) programme. *Adv Ther*. 2022;39(5):2270-2280. doi:10.1007/s12325-022-02076-7
- Bell J, Graul E, Nordon C, et al. EXACOS CARBON: describing the greenhouse gas emissions of healthcare resource utilization by frequency and severity of COPD exacerbation in England. *Am J Respir Crit Care Med*. 2024;209(Suppl 1):A2113. doi:10.1164/ajrccm-conference.2024.209.1.MeetingAbstracts.A2113
- Rabin AS, Seelye SM, Weinstein JB, et al. Budesonide-formoterol metered-dose inhaler vs fluticasone-salmeterol dry-powder inhaler. *JAMA Intern Med*. 2025;185(8):1005-1013. doi:10.1001/jamainternmed.2025.2299
- Gupta S, Couillard S, Digby G, Tse SM, Green S, Penz E. Climate change and inhaler selection in patients with respiratory disease. *Chest*. 2024;165(3):503-506. doi:10.1016/j.chest.2023.09.025
- Feldman WB, Han J, Raymakers AJN, Furie GL, Chesebro BB. Inhaler-related greenhouse gas emissions in the US: a serial cross-sectional analysis. *JAMA*. 2025;334(18):1638-1649. doi:10.1001/jama.2025.16524
- Rabin AS, Weinstein JB, Whittington TN, et al. Implementation of a metered-dose inhaler to dry-powder inhaler national formulary transition. *JAMA Netw Open*. 2024;7(12):e2449234. doi:10.1001/jamanetworkopen.2024.49234
- Tewari SG, Bell JP, Budgen N, et al. Pressurized metered-dose inhalers using next-generation propellant HFO-1234ze(E) deposit negligible amounts of trifluoroacetic acid in the environment. *Front Environ Sci*. 2023;11:129720. doi:10.3389/fenvs.2023.129720
- Giffen PS, Kilgour JD, Jacobsen M, Thacker K, Holmberg AA. The nonclinical assessment of trans-1,3,3,3-tetrafluoropropene (HFO-1234ze (E)), a near zero global warming potential propellant for use in metered dose inhalation products. *Int J Toxicol*. 2024;43(1):4-18. doi:10.1177/10915818231206025

Severe Asthma in Primary Care: Specialist Referral for Biologic Therapy

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DISCLOSURES

Dr. Gupta is on the advisory boards of AstraZeneca, Sanofi, and Regeneron and is on the advisory board and speakers bureau of GSK.

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INTRODUCTION

Severe asthma (SA) is asthma that is inadequately controlled despite adherence to optimized high-dose inhaled corticosteroid/long-acting beta₂-agonist (ICS/LABA) therapy and appropriate management of contributory factors, including inhaler technique, medication adherence, environmental exposures, and comorbidities. SA differs from uncontrolled or difficult-to-treat asthma in that symptoms are persistent and exacerbations continue despite the correction of these modifiable factors and the use of maximal guideline-directed therapy.¹ SA affects a relatively small proportion of patients with asthma, with estimates ranging from approximately 3.7% to 10% depending on the population studied and the criteria used to define severe disease, yet SA disproportionately contributes to asthma-related morbidity and mortality, health care utilization, and costs.^{1,2} Asthma-related mortality remains a persistent concern, with 9 to 11 deaths occurring each day in the United States and little meaningful improvement observed over the past decade.³ Although SA is often first recognized and treated in the primary care setting, referral to a specialist for further management is often warranted. Referral by the primary care clinician (PCC) enables collaboration with specialists to manage side effects, prevent exacerbations, preserve lung function, reduce systemic corticosteroid (SCS) use, and prevent medication-related side effects.¹

Key takeaways

- PCCs play a crucial role in distinguishing uncontrolled asthma from SA by first addressing modifiable factors, such as adherence, inhaler technique, comorbidities, and environmental triggers, before escalating therapy or referring to a specialist.
- Structured assessment tools and proactive follow-up after exacerbations, including timely reassessment, reinforcement of action plans, education on inhaler technique, and medication optimization, can help PCCs better track disease control, predict future risk, and support more informed treatment decisions.
- Ongoing symptoms, frequent exacerbations, high short-acting beta₂-agonist (SABA) use, or repeated SCS bursts despite optimized therapy can prompt specialist referral by the PCC. Biomarker assessment identifies type 2 (T2) inflammation and guides biologic eligibility. Further need for SCS-sparing strategies is necessary to reduce the risk of associated adverse effects.
- Early and coordinated collaboration between PCCs and specialists improves outcomes by reducing exacerbations, hospitalizations, and SCS exposure while ensuring timely access to advanced therapies and appropriate follow-up after acute events.

SCS exposure in asthma management can be limited through the use of targeted biologic therapies that reduce exacerbations, improve symptom control, and decrease ste-

roid dependence.^{1,2,4-6} Evidence has demonstrated that even relatively low cumulative lifetime SCS exposure, estimated at approximately 0.5 to 1.0 g prednisolone equivalent, or roughly 2 to 4 short bursts of daily steroid therapy may significantly increase the risk of adverse effects including osteoporosis, cardiovascular disease, hypertension, diabetes, infections, weight gain, sleep disturbance, and neuropsychiatric complications.⁷⁻⁹ Importantly, these risks go beyond patients receiving chronic daily therapy. Repeated intermittent bursts also are associated with cumulative toxicity and increased health care utilization.⁷ Current SA management strategies increasingly emphasize SCS stewardship, the early identification of uncontrolled disease, optimization of maintenance therapy, and timely referral for phenotype assessment and biologic consideration in appropriate patients.^{1,4,6,8} Repeated SCS exposure signals a need for reassessment and treatment escalation to reduce preventable morbidity and preserve long-term positive patient outcomes.^{1,6,7,8}

National Heart, Lung, and Blood Institute and Global Initiative for Asthma (GINA) recommendations suggest referral to a specialist for an evaluation in all patients with potential severe disease to optimize disease treatment and control, identify, and treat relevant comorbidities.^{1,4} In patients who manifest uncontrolled SA, targeted biologic therapies that reverse specific aspects of the dysregulated immune responses in asthma can effectively reduce exacerbations, including exacerbation-related hospitalizations and emergency department (ED) visits, while improving lung function and symptom control and minimizing SCS use.^{2,5} Biologics for SA are typically initiated in specialist settings and have demonstrated reductions in the frequency of asthma exacerbations along with asthma symptom reduction, reduced dosage of controller medication, and improved quality of life. Additionally, several biologics have been found to improve lung function in patients with SA.¹⁰ Injectable biologic initiation is recommended in those with ≥ 2 asthma exacerbations in a year, 1 asthma hospitalization in the past year, poor symptom control despite high-dose ICS/LABA treatment, or the need for daily maintenance SCS for disease control.⁶ Biologic therapies for asthma have been available since 2003, with 7 biologics currently approved for SA. Biologics can be administered with schedules ranging from every 2 weeks to every 6 months depending on the selected agent and indication.^{1,10}

Despite the benefit of specialist involvement and these targeted therapy options, many patients with SA are not referred to a specialist in the year after an asthma exacerbation. In an analysis conducted from January 2015 to

December 2017, 62% of patients did not have a specialist visit in the year before or after the identification of SA.¹¹ A separate analysis conducted from 2015 to 2020 found that up to 51% of SA patients assessed had no specialist visit or medication escalation following an event indicating uncontrolled disease (hospitalization, ED visit, or outpatient visit for asthma with SCS use).¹² Further, evidence demonstrated that up to 64% of these patients had subsequent exacerbations following the initial occurrence. Specialist visits positively impact patient outcomes, with associated decreases in exacerbations, hospitalizations, ED visits, and SCS use (**TABLE 1**).^{11,12}

PCCs are central to the early identification of patients with SA who would be appropriate candidates for specialist referral and biologic evaluation to better mitigate SA symptoms, reduce health care resource utilization, and improve quality of life.

CASE STUDY

MR is a 46-year-old woman seen in primary care for worsening asthma symptoms over the past 6 months. She reports daily wheezing, nighttime awakenings 3 to 4 times per week, and albuterol inhaler use multiple times per day. Over the past year, she has required 3 courses of SCS for exacerbations, and she went to the ED once as well. Her current medications include high-dose inhaled ICS/LABA therapy, montelukast 10 mg daily, and albuterol as needed. On exam, spirometry shows a forced expiratory volume in 1 second (FEV₁) of 68% predicted, and laboratory evaluation reveals a blood eosinophil count of 320 cells/ μ L.

Despite adherence to optimized inhaled therapy and appropriate inhaler technique, her persistent symptoms, frequent exacerbations, and repeated SCS use suggest uncontrolled SA with underlying eosinophilic inflammation.

SCS STEWARDSHIP: WHEN REPEATED BURSTS SHOULD TRIGGER ESCALATION

SCS are typically prescribed to help manage acute asthma exacerbations.^{1,7} However, SCS can be utilized as daily maintenance therapy in patients with SA. Step 5 in the GINA recommendations suggests that chronic SCS may be used as a last resort.¹ Frequent corticosteroid bursts and chronic utilization are associated with significant side effects, includ-

TABLE 1. Outcome improvement with specialist intervention.¹¹

	Any exacerbation	Hospitalization	ED visit	SABA use	SCS use
Before intervention	49%	3%	16%	83%	69%
After intervention	38%	1%	11%	67%	54%

Outcomes were evaluated among commercially insured US patients aged ≥ 6 years with SA who had their first observed asthma specialist visit during the study period (N=5988).

Adapted from Most JF et al, 2021.

ing an increased risk for pneumonia, cardiovascular events, hypertension, diabetes, osteoporosis, weight gain, and neuropsychiatric effects such as insomnia, depression, and behavioral disturbance (FIGURE 1).⁷ Chronic and frequent SCS use contributes to higher morbidity and mortality, reduced quality of life, and higher health care costs and is associated with higher ED use and inpatient visits.² For these reasons, chronic exposure poses a significant safety issue, and clinicians should adjust symptom management to prevent complications associated with SCS use in patients with SA.

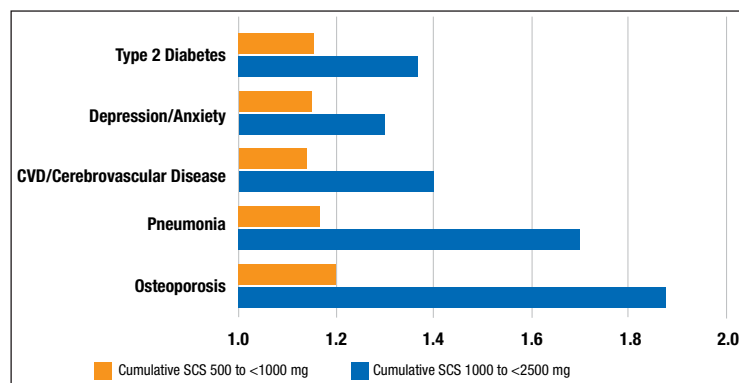
In a 2018 Asthma and Allergy Foundation of America survey, investigators found that 85% of 519 patients with asthma used at least 1 course of SCS in the previous 12 months and 64% had done so ≥ 2 times.⁹ Alarming, 78% of these patients who were seeing an asthma specialist reported having received a different SCS prescription from another provider. PCCs should inform patients and their caregivers about the risks associated with SCS use and asthma maintenance therapy nonadherence. PCCs should also facilitate referral to qualified asthma specialists when available and collaborate closely with those individuals to reinforce SCS-sparing strategies. However, access to specialty care can be limited in some communities; therefore, patients in rural and underserved areas who are experiencing acute worsening of symptoms are often more likely to seek care from their PCC. In these situations, PCCs play a critical role in recognizing patterns of recurrent exacerbations and repeated SCS use, reinforcing adherence to maintenance therapy, reassessing inhaler technique, and identifying when treatment escalation or re-referral may be necessary. By monitoring cumulative SCS exposure and educating patients about the risks associated with repeated SCS use, PCCs can help support earlier intervention and reduce the likelihood of preventable complications associated with redundant prescriptions and long-term SCS exposure.^{4,9}

SCS-sparing techniques create a unique opportunity for the PCC to discuss alternative treatment options such as biologics. Data have shown up to a 61% reduction in SCS-related adverse events in patients with SA on biologic therapy, which is estimated to lead to a 2- to 3-fold higher probability of achieving complete SCS cessation.⁴ Although these agents are usually prescribed by specialists, PCCs can provide patients with education regarding their benefits and limitations.

CLINICAL REMISSION AND ASTHMA

Clinical remission is defined as a period of >12 months in which the patient has not experienced any asthma exacerbations or significant symptoms and has not received SCS (ICS allowed) in the absence of declining lung function (prebron-

FIGURE 1. Cumulative SCS dose (mg) and likelihood of an adverse effect.⁷



Abbreviation: CVD, cardiovascular disease

Adapted from Price DB et al, 2018. Adults with active asthma from UK primary care databases (N=48,234 [24,117 matched pairs]).

chodilator FEV₁ $>95\%$ of baseline). PCCs can help patients work toward achieving this treatment goal.^{1,8} Importantly, clinical remission is a relatively new and evolving concept that has gained increasing attention with the emergence of biologic therapies capable of reducing exacerbation burden and SCS exposure.⁸ Historically, SA management primarily focused on symptom reduction and prevention of acute exacerbations. More recent expert consensus statements now recognize clinical remission as an achievable treatment target in patients receiving optimized therapy. As frontline clinicians managing patients longitudinally, PCCs play an important role in recognizing when patients may be approaching remission goals, reinforcing adherence to maintenance therapy, monitoring symptom control over time, and coordinating follow-up care with specialists. A key aspect of clinical remission focuses on avoiding SCS use during this 12-month period. PCCs should actively participate in a collaborative effort to curb SCS use to reduce the side effects associated with frequent and chronic use. Clinicians should recognize signs such as repeated rescue prescriptions, SABA overuse, and exacerbations; these signal that a patient may need an updated treatment plan, support with adherence concerns, and reassessment of maintenance therapy.

IDENTIFYING PATIENTS WITH UNCONTROLLED ASTHMA WHO MAY NEED BIOLOGIC THERAPY

SA differs from uncontrolled asthma; some patients may have SA but have controlled disease if persistent symptoms and exacerbations related to SA are improved with treatment. As part of differential diagnosis, PCCs should assess for nonsevere, uncontrolled asthma by evaluating such factors as poor inhaler technique, suboptimal medication adherence, comorbidities, and ongoing exposure to triggers in the patients' homes or social environments. Once these variables have been assessed

and determined not to be the primary driver for symptoms, the clinician can use questionnaires aimed at assessing recent symptom control. A particularly useful assessment is the Asthma Impairment and Risk Questionnaire (AIRQ), available at <https://www.airqscore.com/>.¹³ This 10-item asthma control tool assesses both symptom impairment and exacerbation risk, evaluates patients' asthma control, and supports shared decision-making conversations to optimize management. By assessing patients' asthma medications, respiratory symptoms (including exacerbation history) and lung function, as well as utilization of health care resources (inpatient or ED use), PCCs can develop a treatment plan better tailored to address the issues identified in the assessment, predict potential future exacerbations, and escalate concerns to a specialist for further management. This assessment can help clinicians recognize when therapy modifications with biologics are warranted and guideline-driven recommendations are necessary.^{1,4,13}

Biomarkers

PCCs also play a role in the early assessment of phenotypic and clinical biomarkers. Phenotyping refers to the identification of underlying asthma characteristics that may influence treatment selection, particularly the presence of T2 inflammation and eligibility for biologic therapy. In the primary care setting, initial biomarker assessment can include readily available tests such as a complete blood count (with differential) to obtain a blood eosinophil count (BEC), serum immunoglobulin E (IgE) measurement, and spirometry. These assessments can help identify patients who may benefit from further evaluation. More comprehensive phenotypic characterization, including fractional exhaled nitric oxide (FeNO) testing, advanced pulmonary function testing, assessment of comorbid conditions, and biologic eligibility determination, is often performed in specialist settings where additional diagnostic resources are available.^{1,4,6} SA is often driven by T2 inflammation, which is characterized by highly activated immune cells (eosinophils, mast cells, and T-cells) that release inflammatory mediators such as cytokines (e.g., interleukins 4, 5, and 13) and IgE antibodies, resulting in inflammation in the airways, greater risk for asthma exacerbations, and decreased lung function.^{1,2,4} BEC is a biomarker used to determine if a patient has eosinophilic asthma. Levels >150 cells/ μ L suggest the presence of T2 inflammation and may identify the patients who are more likely to benefit from T2-targeted therapies.¹ In patients with persistently elevated eosinophil counts, particularly those >150 cells/ μ L, alternative or coexisting causes of eosinophilia should be evaluated as part of the diagnostic evaluation, which may include parasitic infection and other eosinophilic disorders. Despite this, one retrospective analysis found that eosinophils were only drawn in around 70% of patients with asthma who had frequent exacerbations.¹⁴ Fur-

ther, it is important for the clinician to recognize that eosinophil levels may vary significantly depending on age, sex, race, time of day (lower in the afternoon than early morning), obesity, and allergen and corticosteroid exposure.¹⁵

In addition to BEC, FeNO provides complementary information regarding airway inflammation that can further support the identification of T2 disease.¹ Elevated FeNO levels (>50 parts per billion [ppb] in adults) are considered to be consistent with significant T2 airway inflammation, while values between 25 ppb and 50 ppb should be interpreted in the context of the patient's clinical presentation and other biomarkers. It is important for the clinician to understand that these levels are not absolute; FeNO levels can vary based on patient-specific factors such as age, sex, and smoking history. Given the variability in FeNO laboratory tests, they should be repeated a minimum of 3 times before assuming the patient is not eligible for T2-targeted therapy. Another biomarker that can be used for T2 identification is IgE, which can be evaluated using a blood test or a skin prick test. Clinicians should recognize that, regardless of method, there is not a universally accepted IgE cutoff that defines T2 asthma. An elevated IgE level, detectable allergen-specific IgE, or positive allergen skin test could increase the possibility of the presence of T2 asthma when taken into consideration with other clinical findings and biomarkers.

PCCs can establish an SA diagnosis, optimize inhaled treatment, document exacerbation burden, help patients create an action plan, use assessment tools (like the AIRQ), and refer the right patient at the right time to a specialist when further phenotype/biomarker assessment is warranted. Collaboration is essential to investigate comorbidities, examine differential diagnoses, and consider injectable biologic therapy initiation.^{1,6,11}

Biologic therapies

Once the assessment is completed and biologic therapy is deemed necessary, a specialist can choose from among 7 biologics currently approved for SA.^{1,6,11} The choice of agent is based on a variety of factors, including biomarker history, patient comorbidities, exacerbation frequency, SCS dependency, cost, and patient preferences regarding administration frequency and delivery route.^{1,10} Biologic therapies are administered most commonly as subcutaneous injections.¹⁰ Maintenance dosing depends on the choice of agent, with administration schedules ranging from once or twice monthly to every 2 to 6 months. Side effects are typically mild, with injection site soreness, headache, sore throat, and fatigue as the most commonly reported symptoms. Anaphylaxis risk and other adverse events noted in the Prescribing Information for each biologic should be monitored. Monitoring biologic therapy response requires a collaborative partnership between the specialist and

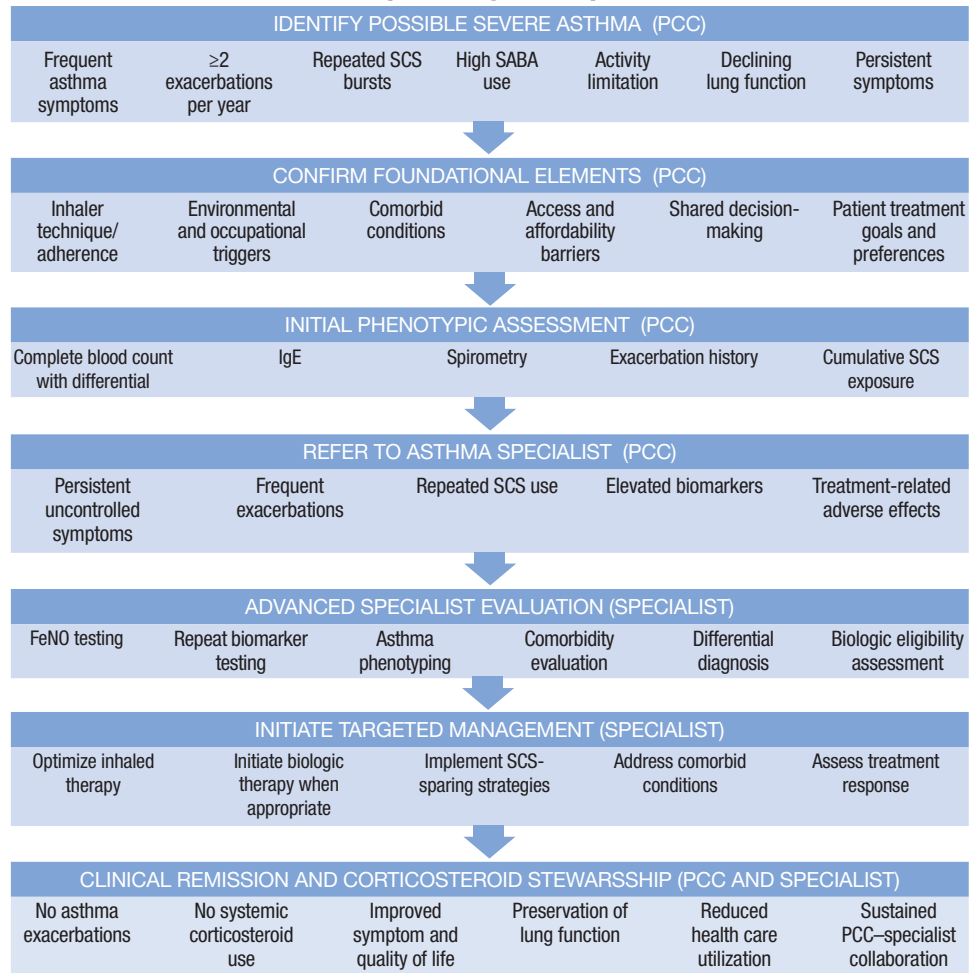
the PCC and includes assessing exacerbation frequency, symptom control, lung function, clinical biomarkers, adverse events, and patient satisfaction (**FIGURE 2**).¹ Based on response, therapy can be modified if needed to further optimize management.

MAKING THE REFERRAL

Once a diagnosis of SA is made, a PCC should consider referral to an asthma specialist (e.g., allergist/immunologist and/or pulmonologist), as a collaborative approach will be the best for managing symptoms and developing the future treatment plan. Referral is also necessary in scenarios when there is diagnostic uncertainty, when patients have high-risk disease (e.g., recurrent exacerbations, hospitalization, or lung function decline) or comorbid conditions, in the presence of treatment-related side effects, and in those with persistent uncontrolled symptoms despite proper inhaler technique and adherence.¹ When considering biologic use, specialists should be included, as their practices typically have access to the testing necessary to assess pulmonary function and phenotypic disease types, which will guide future treatment decisions.

PCCs also play an influential role following the discharge of patients who have experienced an asthma exacerbation. Clinicians should encourage follow-up appointments within 2 to 7 days (1 to 2 days for children) and reinforce education aimed at improving asthma management, such as medication adherence, inhaler skills, and a written asthma action plan (**FIGURE 3**).¹ After an exacerbation, patients should be prescribed an ICS-containing treatment and additional guideline-directed treatment as necessary to reduce the risk of further exacerbations. Collaboration between the PCC and specialist is critical as it provides an opportunity for the clinicians to work together to help the patient understand the cause of their exacerbation, while modifying risk factors for future exacerbations through the optimization of guideline-directed therapy options, obtaining lung function tests, and

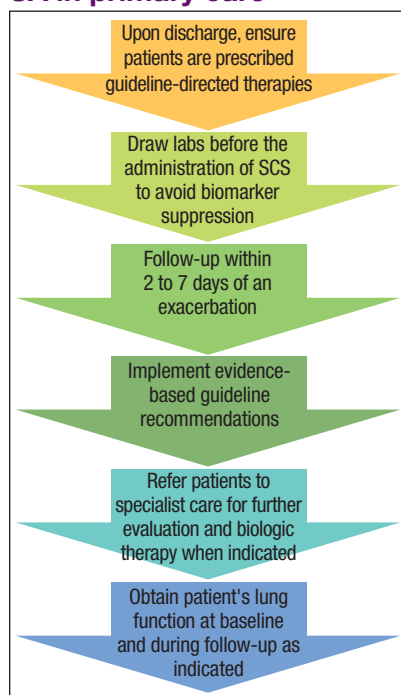
FIGURE 2. Asthma referral pathway and specialist collaboration.¹



Adapted conceptually from the Global Initiative for Asthma (GINA) Severe Asthma Guide.¹

ordering follow-up biomarker laboratory testing and monitoring. Additionally, as of 2026, a new Healthcare Effectiveness Data and Information Set metric has been added to measure follow-up after acute care and urgent care visits for asthma, with the intent of incentivizing coordination of timely follow-up care for patients who have experienced an asthma exacerbation.^{1,4,16}

Collaboration among PCCs and specialists can improve SA patient outcomes, reduce medication errors, optimize therapy, and lower health care utilization and costs. As the first practitioner to see an asthma patient, PCCs are in a critical position to collect key information (e.g., symptom frequency, exacerbation history, lung function, biomarker results, prior therapies, comorbidities, and evidence of SCS burden) that is necessary to diagnose SA and rule out confounding conditions.¹⁷ Specialist settings typically have the infrastructure and resources required to further evaluate patients and address phenotypic data and biomarker values, investigate comorbid-

FIGURE 3. Call to action for SA in primary care^{1,2,4,16}

vention results in a significant decrease in ED visits and all-cause hospitalization.^{19,20} Consequently, when specialist referral is delayed, there is a greater likelihood of persistent symptoms, improper management, frequent ED visits, and irreversible lung damage.^{1,4}

CASE STUDY (CONTINUED)

In MR's case, her PCC refers her to a pulmonologist due to persistent symptoms, frequent exacerbations, and repeated SCS use despite optimized therapy. At the specialist visit, severe eosinophilic asthma is confirmed after testing shows repeated eosinophil counts >150 cells/ μ L, an elevated FeNO of 45 ppb, and an IgE of 210 IU/mL. Inhaler technique and comorbidities are also reassessed. Based on her clinical profile and biomarker findings, she is identified as an appropriate candidate for biologic therapy and is initiated on guideline-indicated biologic treatment. An SCS-sparing strategy is implemented with close follow-up, while her PCC continues to reinforce adherence and coordinate care. Over the next few years, she experiences improved symptom control, reduced rescue inhaler use, and no further exacerbations.

SUMMARY

SA is defined as uncontrolled asthma despite maximally optimized therapy and treatment of contributory factors, or asthma that worsens when high-dose ICS is reduced. SA

ities, perform differential diagnoses, and adjust medication regimens, which often will involve the prescribing and administration of biologic therapies.¹¹ Despite these added benefits of specialist involvement, it has been reported that fewer than half of US patients with SA are evaluated by a specialist, with the smallest frequency observed in older adult patients with greater non-respiratory comorbidities.^{11,18} Multiple studies have found that specialist inter-

affects up to 10% of patients living with asthma and accounts for a disproportionate share of asthma-related health care utilization. Because these patients are often first seen in the primary care setting, PCCs play a central role in early identification, initial evaluation, and ongoing management. Specialist referral is essential for patients with persistent symptoms and those who may benefit from advanced therapies. Biologic treatments, typically initiated in specialist settings, have demonstrated reductions in exacerbations, hospitalizations, and SCS use while improving symptom control and quality of life. ●

REFERENCES

1. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2026. Available from: www.ginasthma.org
2. Chen W, Tran TN, Townend J, et al. Impact of biologics initiation on oral corticosteroid use in the international severe asthma registry and the optimum patient care research database: A pooled analysis of real-world data. *J Allergy Clin Immunol Pract*. 2025;13(8):2033-2048. doi:10.1016/j.jaip.2025.04.032
3. Asthma capitals: health outcomes that impact ranking. Asthma and Allergy Foundation of America. Accessed June 29, 2026. <https://aafa.org/asthma-allergy-research/our-research/asthma-capitals/asthma-health-outcomes/>
4. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI), 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
5. Trevor J, Lugogo N, Carr W, et al. Severe asthma exacerbations in the United States: Incidence, characteristics, predictors, and effects of biologic treatments. *Ann Allergy Asthma Immunol*. 2021;127(5):579-587.e1. doi:10.1016/j.anai.2021.07.010
6. Holguin E, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2020;55(1):1900588. doi:10.1183/13993003.00588-2019.
7. 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
8. Blaiss M, Oppenheimer J, Corbett M, et al. Consensus of an American College of Allergy, Asthma, and Immunology, American Academy of Allergy, Asthma, and Immunology, and American Thoracic Society workgroup on definition of clinical remission in asthma on treatment. *Ann Allergy Asthma Immunol*. 2023;131(6):782-785. doi:10.1016/j.anai.2023.08.609
9. Oral corticosteroids. Allergy and Asthma Foundation of America. Accessed June 29, 2026. <https://aafa.org/asthma/asthma-treatment/asthma-treatment-oral-corticosteroids-prednisone/>
10. Biologics for the management of severe asthma. Academy of Allergy, Asthma, and Immunology. Accessed June 29, 2026. <https://www.aaaai.org/tools-for-the-public/conditions-library/asthma/biologics-for-the-management-of-severe-asthma>
11. Most JE, Ambrose CS, Chung Y, et al. Real-world assessment of asthma specialist visits among U.S. patients with severe asthma. *J Allergy Clin Immunol Pract*. 2021;9(10):3662-3671.e1. doi:10.1016/j.jaip.2021.05.003
12. 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*. 2024;12:1775-1782.e2. doi:10.1016/j.jaip.2024.03.018
13. 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
14. Mathur S, Corbridge T, Packnett E, et al. Eosinophil count testing in patients with asthma varies by healthcare provider type in the US: a retrospective study. *Allergy Asthma Clin Immunol*. 2024;20(1):56. doi:10.1186/s13223-024-00917-4
15. Caspard H, Ambrose C, Tran T, et al. Associations between individual characteristics and blood eosinophil counts in adults with asthma or COPD. *J Allergy Clin Immunol Pract*. 2020;8(5):1606-1613. doi:10.1016/j.jaip.2019.12.019
16. HEDIS MY 2026: what's new, what's changed, what's retired. NCQA. Accessed June 29, 2026. <https://www.ncqa.org/blog/hedis-my-2026-whats-new-whats-changed-whats-retired/>
17. Trevor J, Chipps B. Severe asthma in primary care: identification and management. *Am J Med*. 2018;131:484-491. doi:10.1016/j.amjmed.2017.12.034
18. Cardet JC, Patel B, Bradford P, et al. Primary care provider referral patterns and awareness of biologic therapy for uncontrolled asthma. *J Allergy Clin Immunol Glob*. 2025;5(2):100607. doi:10.1016/j.jacig.2025.100607
19. Ambrose CS, Chipps BE, Moore WC, et al. The CHRONICLE study of US adults with subspecialist-treated severe asthma: objectives, design, and initial results. *Pragmat Obs Res*. 2020;11:77-90. doi:10.2147/POR.S251120
20. Rosman Y, Hornik-Lurie T, Meir-Shafir K, et al. The effect of asthma specialist intervention on asthma control among adults. *World Allergy Organ J*. 2022;15(11):100712. doi:10.1016/j.waojou.2022.100712

New Tools, Same Goal: Fast Acute Pain Control With Fewer Opioids

Bill McCarberg, MD

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

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

- **Integrate** emerging nonopioid therapies, including selective Na_v1.8 inhibitors, into individualized, opioid-sparing treatment regimens for common acute pain presentations in primary care.
- **Understand** the role of voltage-gated sodium channels in C-fiber nociceptors for transmitting pain signals from the peripheral nervous system to the central nervous system.
- **Apply** newer acute pain treatments for eligible patients to maximize effectiveness and minimize adverse events.

TARGET AUDIENCE

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

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INTRODUCTION

Pain remains one of the most common and challenging reasons patients seek care, accounting for an estimated 30% to 40% of all primary care visits.^{1,2} Despite a shared goal of balancing pain relief, functional improvement, and minimal adverse medication effects, pain management often is frustrating for patients and clinicians alike.² Many clinicians have learned a bitter lesson from the opioid era: well-intentioned efforts to relieve suffering, when not grounded in careful risk assessment and clear treatment

goals, can lead to unintended harm at both the individual and population levels.

Analgesics, key in acute pain treatment, are mainly divided into opioids and nonopioids.³ Opioids, used for moderate to severe pain, bind to receptors in the brain and spinal cord to inhibit pain transmission and boost descending inhibition.^{3,4} Nonopioid options for milder acute pain include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and topical agents such as lidocaine, topical diclofenac, and capsaicin or counterirritants such

Key takeaways

- Customize the analgesic choice to each patient, considering comorbidities and individual risk factors.
- Start with optimized nonopioid multimodal care and prescribe opioids (immediate-release, low-dose, and time-limited) only if the benefits will outweigh risks to the patient.
- Na_v1.8 inhibitors expand opioid-sparing options by targeting peripheral nociceptive signaling.
- Base pharmacologic and nonpharmacologic treatment on function, not a pain score.
- With an understanding of how Na_v1.8 channels in peripheral C-fibers transmit pain signals, clinicians can better explain the rationale for targeted therapy to patients and support adherence.

as menthol, methyl salicylate, and camphor when pain is localized. NSAIDs inhibit cyclooxygenase enzymes, reducing prostaglandin-mediated inflammation and peripheral sensitization. Acetaminophen has a less fully defined mechanism but appears to act primarily within the central nervous system, possibly through inhibition of central prostaglandin synthesis and modulation of descending serotonergic pain pathways, with minimal peripheral anti-inflammatory activity.^{3,5}

Primary care clinicians (PCC) face a dilemma: opioids are effective but carry risks, including misuse, sedation, respiratory depression, and dependence, along with regulatory scrutiny. Nonopioid options are limited by ceiling effects, incomplete pain relief, or patient contraindications like renal, gastrointestinal, or cardiovascular issues. This creates a narrow window where clinicians must balance undertreating pain against the harms of potent therapies, often lacking clear intermediate options.²⁻⁵

WHAT IS NEXT?

The acute pain toolkit is evolving. In January 2025, the US Food and Drug Administration (FDA) approved suzetrigine, the first nonopioid analgesic for moderate-to-severe acute pain in adults.⁶ This, along with the 2022 Centers for Disease Control and Prevention (CDC) guidelines' focus on nonopioid strategies and reassessment, offers clinicians a new option and an updated framework.⁷

Suzetrigine provides pain relief by selectively inhibiting the Na_v1.8 sodium channel in peripheral neurons that transmits pain signals to the central nervous system (CNS). This mechanism avoids CNS side effects like respiratory depression and the addiction risks associated with opioids.^{6,8}

BOX 1. From poppy to periphery: a historical perspective

Historically, pain management has relied heavily on 2 approaches: opioids and anti-inflammatory agents, supplemented by acetaminophen.⁹ Suzetrigine represents a new mechanism—a selective Na_v1.8 inhibitor that blocks pain signals in peripheral C-fiber nociceptors without impacting the brain. It delivers efficacy comparable to opioid combinations while avoiding many of the limitations that have long constrained pain management.¹

ACUTE PAIN

Acute pain, sudden in onset and lasting less than 1 month, may be viewed as an expected physiologic response to a noxious stimulus (such as injury, trauma, or surgery). However, inadequately or ineffectively treated pain has serious consequences, including delayed recovery, increased health care utilization, and prolonged postsurgical recovery. Unresolved acute pain can progress to subacute pain (lasting 1 to 3 months) and then to chronic pain, which typically lasts more than 3 months.^{10,11}

Acute pain management today incorporates the 2022 CDC guidelines, outlining treatment decisions based on function rather than pain scores alone and individualized multimodal nonopioid or opioid-sparing treatment plans.² Nonpharmacologic strategies, including early mobilization and guided activity, remain essential complements to pharmacologic care.^{7,12} Selective Na_v1.8 inhibitors have the potential to be integral to these plans.

BOX 2. Local anesthetics vs Na_v1.8 inhibitors: a mechanistic distinction.

Lidocaine and other traditional local anesthetics are nonselective sodium channel blockers affecting multiple channel subtypes throughout the body, limiting their systemic use due to dose-dependent cardiovascular and CNS toxicity.¹³ In contrast, suzetrigine is a highly selective Na_v1.8 inhibitor targeting sodium channels predominantly expressed on peripheral nociceptive neurons, C-fibers. This peripheral selectivity enables oral, mechanism-based analgesia for moderate-to-severe acute pain without engaging opioid receptors or resulting in the systemic toxicity associated with nonselective sodium channel blockade.⁸ Genetic studies of SCN10A, the gene encoding Na_v1.8, further support this target: gain-of-function variants are associated with increased pain sensitivity, whereas loss-of-function variants are linked to reduced pain perception.¹⁴

Initial evaluation: brief framework

Step 1: Structured evaluation of medical and psychosocial factors influencing the patient's pain. The primary goal is to identify and address the underlying cause of pain.⁷ When the cause cannot be eliminated immediately or if pain persists despite treatment, classify the pain mechanism as nociceptive, inflammatory, neuropathic, or mixed to guide analgesic selection.^{7,8}

Step 2: Using a shared decision-making process, create a plan focused on functional improvement, minimizing unnecessary opioid use, and outline follow-up steps for clinical deterioration or unexpected responses (see **FIGURE 1**).^{7,15}

CASE STUDY 1

Maria R., a 44-year-old teacher, presents 4 days after arthroscopic rotator cuff repair with persistent postoperative pain. She was discharged on oxycodone 5 mg every 6 hours as needed and acetaminophen 650 mg every 6 hours, also as needed. Her medical history includes hypertension, obesity, and remote postpartum depression.

She reports pain severity of 8/10 at its worst and about 5/10 at rest, taking approximately 3 oxycodone tablets daily. She describes opioid-related adverse effects, including sedation and nausea, and expresses significant anxiety about opioid use. She notes her brother struggled with opioid addiction after being prescribed oxycodone, and she worries about heading down “that same path.”

She messaged her surgeon and was told to maximize the oxycodone use for the next 3 days, and keep her scheduled postoperative appointment the following week. Uncomfortable with this plan, she turns to her PCC for help with nonopioid pain management.

On examination, vital signs are stable, aside from mildly elevated blood pressure. The surgical site appears appropriate for postoperative day 4.

Gaps in current care

Her analgesics are being used reactively rather than on a scheduled basis—a common but suboptimal pattern that allows pain to escalate before treatment. The American Society of Anesthesiologists recommends that, unless contraindicated, patients receive a scheduled regimen of an NSAID (nonselective or COX-2 selective), with or without acetaminophen. This proactive approach is well supported and helps maintain more consistent analgesia, reduce peak pain intensity, and limit the need for rescue medications.¹⁶

Maria has no renal, gastrointestinal, or hepatic issues, so she can use first-line therapies.

The plan

- Acetaminophen 1000 mg every 6 hours, an NSAID if blood pressure remains controlled, ice and guided mobilization, and oxycodone for breakthrough pain only.

Why her concerns matter clinically

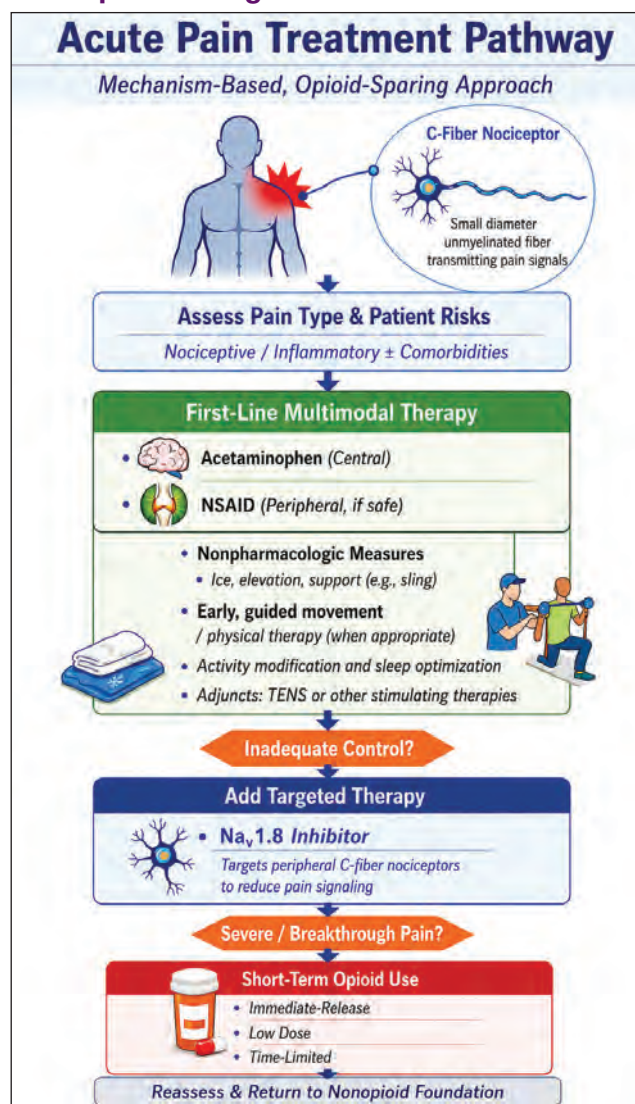
The 2022 CDC guideline highlights that patient preferences, values, and goals should guide prescribing, and effective communication about pain expectations and treatment length boosts adherence to nonopioid strategies. Treatment should focus on functional improvement—sleep, dressing, returning to work—rather than complete pain elimination.⁷

A NEW OPTION

For a patient wanting to reduce opioid exposure and suffering adverse effects, the usual approach was to optimize acetaminophen and NSAIDs. Suzetrigine offers a different, peripherally targeted mechanism, selectively inhibiting $\text{Na}_v1.8$ sodium channels on C-fiber nociceptive neurons, potentially replacing opioids rather than supplementing them (see **FIGURE 2**).⁸

The FDA approval was based on two phase 3, randomized, double-blind trials evaluating suzetrigine for acute postoperative pain after abdominoplasty and bunionectomy, with 2191 adults enrolled across the studies. Suzetrigine was administered as a 100 mg loading dose on an empty stomach to avoid delayed onset, followed by 50 mg every 12 hours.

FIGURE 1. Mechanism-based approach to acute pain management.



Abbreviation: TENS, transcutaneous electrical nerve stimulation.

In both surgical models, suzetrigine produced statistically significant pain reduction compared with placebo ($P < .001$ for abdominoplasty; $P = .0002$ for bunionectomy), supporting its role as an effective nonopioid analgesic option. Available comparative data suggest its analgesic effect is broadly in the range of NSAIDs, while slightly lower than higher-dose opioid regimens. Direct claims of equivalence or superiority to hydrocodone/acetaminophen should be avoided because the pivotal trials were not designed or powered to establish opioid non-inferiority or superiority, and comparator findings were not fully consistent across models.¹⁷

Discontinuation rates due to lack of efficacy were substantially higher in the placebo group (22% after abdominoplasty and 16% after bunionectomy) than in the suzetrigine group (9% and 12%, respectively), and overall completion rates were lower in placebo patients (75% and 82%) than in suzetrigine patients (89% and 87%).^{8,17} These differences, while not formally tested for statistical significance, are directionally consistent across all models and suggest a clinically relevant advantage in treatment persistence with suzetrigine, particularly in the abdominoplasty model, where the difference was most pronounced.^{8,17}

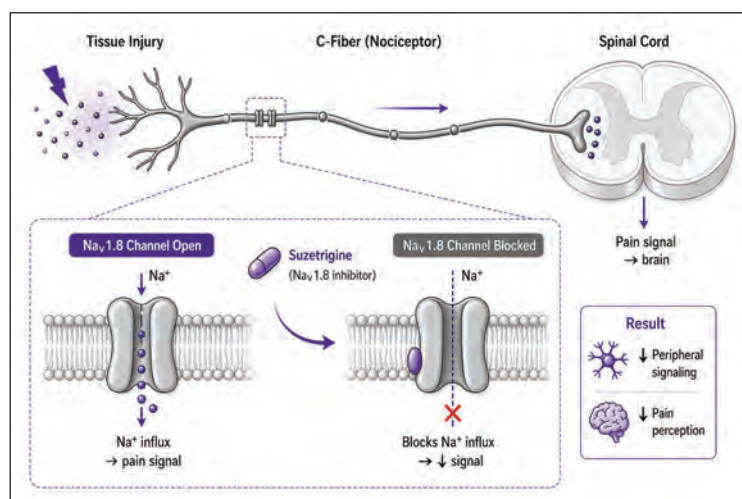
The average age of participants in the trials was mid-40s. The trials were short-term and looked only at acute pain relief over 48 hours. Approval is based on safety data up to 14 days.^{8,17}

A 2026 meta-analysis of 4 randomized datasets ($N=1584$) found statistically significant pain reduction with suzetrigine vs placebo at 24 hours (mean difference -0.93 on a scale; 95% confidence interval [CI]: $-1.38, -0.48$) and 48 hours (mean difference -1.02 ; 95% CI: $-1.32, -0.72$). A separate 2026 meta-analysis of 5 randomized controlled trials (RCTs) ($N=2855$) similarly found improved 48-hour summed pain intensity difference vs placebo, with fewer adverse events than placebo or hydrocodone/acetaminophen and no superiority in pain relief vs hydrocodone/acetaminophen. Overall, suzetrigine shows consistent short-term analgesic benefit vs placebo, but opioid-sparing conclusions remain limited because opioid consumption was not consistently reported.^{18,19}

A separate, phase 3, single-arm open-label study ($N=256$) evaluated suzetrigine across surgical and nonsurgical moderate-to-severe acute pain conditions. Using a 5-point patient global assessment scale (poor, fair, good, very good, or excellent), 83.2% of all participants rated suzetrigine's effectiveness as good, very good, or excellent at the end of treatment; this included 82.0% of surgical participants and 91.2% of nonsurgical participants.²⁰

In Case Study 1, Maria strongly prefers to stop opioids; therefore, suzetrigine is a reasonable option to consider. It

FIGURE 2. Mechanism of action of selective $\text{Na}_v1.8$ inhibition in acute pain.



Tissue injury activates peripheral nociceptors through inflammatory mediators. $\text{Na}_v1.8$ contributes to action potential upstroke and sustained firing. Suzetrigine blocks $\text{Na}_v1.8$ channels, reducing pain signal transmission. The result is attenuated pain transmission from the peripheral nerve to the spinal cord.^{22,23}

is important to discuss the 14-day maximum use (which should fit Maria's postoperative course). Shared decision-making frames treatment around functional recovery and patient goals, with timely follow-up to reassess benefit, tolerability, and progress. A clear plan to taper and discontinue all acute analgesics as recovery advances reinforces that the goal is short-term support rather than ongoing medication use. Communication with her surgeon about her concerns regarding opioids and the revised analgesic plan support continuity of care.³

PREScribing CONSIDERATIONS AND SIDE EFFECTS

Most reported side effects of suzetrigine were mild and included pruritus, muscle spasms, and rash. Although nausea and vomiting were reported, these occurred at a significantly lower rate than with the opioid comparator and were even lower than placebo in both surgical models.¹⁷⁻²⁰

Suzetrigine is primarily metabolized by cytochrome P450, family 3, subfamily A (CYP3A) (mainly CYP3A4) and also induces CYP3A. Clinically, this means it should not be used with strong CYP3A inhibitors, while moderate CYP3A inhibitors require dose reduction. On the other hand, strong or moderate CYP3A inducers may markedly reduce suzetrigine concentrations, potentially resulting in a loss of efficacy. Remind patients to avoid grapefruit because of potential CYP-mediated interactions, and in relevant cases, discuss that suzetrigine could limit the effectiveness of certain oral contraceptives.^{7,8}

No dose adjustment is required for mild hepatic impairment. For moderate hepatic impairment, the recommended regimen is 100 mg initially on an empty stomach, followed by 50 mg every 12 hours for doses 2 through 4, then 50 mg every 24 hours thereafter. Suzetrigine should be avoided in severe hepatic impairment, as it has not been studied in this population. Routine hepatic laboratory monitoring is not recommended in the Prescribing Information, although clinical reassessment is appropriate if symptoms or laboratory abnormalities suggest liver injury.^{6,8,21}

Clinical Takeaway: Scheduled multimodal nonopioid therapy remains the core of acute pain management. If acetaminophen and NSAIDs are inadequate, clinicians may consider suzetrigine to reduce opioid exposure.

CASE STUDY 2

James L., a 59-year-old construction worker, presents 2 days after an acute low back injury.

His medical history includes stage 3 chronic kidney disease (estimated glomerular filtration rate [eGFR] 48 mL/min/1.73 m²), type 2 diabetes, hypertension, chronic low back pain previously treated with tramadol, and alcohol use disorder in remission. He prefers to avoid medications with dependence risk.

Chronic medications: metformin, sodium-glucose cotransporter 2 inhibitor, ACE inhibitor, and a statin.

On examination, he demonstrates guarded movement, focal paraspinal tenderness, and muscle spasm without neurologic deficit. James exemplifies a typical primary care case: a patient with comorbidities that eliminate first-line options. Chronic kidney disease makes NSAIDs risky.^{3,4} James wants to avoid medications with dependence potential, making opioid therapy less appealing.³ Acetaminophen is renal safe but less effective for low back pain.^{24,25}

Where suzetrigine fits

Suzetrigine avoids NSAID renal and gastrointestinal toxicity and opioid CNS effects, respiratory depression, and addiction due to its peripheral action.^{5,6} The FDA label requires no renal dose adjustment for patients with eGFR ≥ 15 mL/min/1.73 m². However, in the pivotal trials, eGFR decreases of $\geq 25\%$ (but $< 50\%$) occurred in 2.5% of suzetrigine patients vs 0.9% on placebo; these appeared to resolve after discontinuation in the open-label, phase 3 study. Safety in patients with eGFR < 15 mL/min or on dialysis has not been studied, and baseline monitoring of renal function is prudent in patients with CKD.^{17,20,21}

The pivotal RCTs were in postoperative models, not acute low back pain.⁶ The phase 3, open-label study (see Maria's case) included surgical and nonsurgical acute pain.²⁰ Highlighting potential benefits and suzetrigine data on related conditions supports shared decision-making and a comprehensive approach.

The plan

- Superficial heat and early guided mobilization
- Suzetrigine 100 mg loading dose on an empty stomach, then 50 mg every 12 hours (short term)
 - o Consider a consult with a clinical pharmacist (review medication list for CYP3A interactions and consider changing the statin: simvastatin and lovastatin are most susceptible)²⁶
- Short-course cyclobenzaprine 5 to 10 mg at bedtime if spasm is prominent
- Acetaminophen 650 to 1000 mg every 6 hours as adjunctive, recognizing limited efficacy for low back pain
- Opioids avoided given substance use disorder history and patient preference; if severe breakthrough pain is present, a brief course could be used with close follow-up per CDC guideline

Treatment goals: ability to sit comfortably, return to modified work duties, and progressive increase in activity tolerance.

Suzetrigine's 14-day maximum studied duration provides a built-in endpoint. Reassess at 3 to 5 days to evaluate functional improvement (not simply whether pain persists) and include diagnostic reassessment rather than dose escalation if goals are unmet.⁶⁻⁸

Clinical Takeaway: When comorbidities eliminate first-line options, mechanism-based thinking reveals new pathways.

CASE STUDY 3

Danielle M., a 52-year-old business owner in a rural area, presents 6 days after bunion surgery with persistent pain. At her postoperative appointment she was told healing was on track and advised to discontinue oxycodone. She reports pain persisting from 3/10 at rest to 6/10 with movement, despite scheduled acetaminophen and ibuprofen and nonpharmacologic care. The pain is draining and affecting sleep. She wonders, "Isn't there something else to try?"

Practical opioid stewardship in acute pain

Opioid stewardship means using opioids deliberately, briefly, and with defined goals, not eliminating them.

Key principles: reserve opioids for severe pain after nonopioid optimization; prescribe immediate-release formulations in limited quantities; establish functional goals and an exit strategy at initiation; review Prescription Drug Monitoring Program data; and avoid concurrent benzodiazepines.⁷

Danielle's clinical scenario, moderate-to-severe postoperative pain after bunionectomy with opioid intolerance, aligns closely with the pivotal trial population.¹⁷

The plan

- Continue scheduled acetaminophen and ibuprofen
- Add suzetrigine 100 mg loading dose on an empty stomach, then 50 mg every 12 hours (short term)
- Restrict oxycodone to severe breakthrough pain only, with an explicit exit strategy
- Continue nonpharmacologic measures: icing, elevation, and gradual mobilization
- Follow up in 1 to 2 weeks to assess functional improvement and de-escalate therapies

Treatment goals: ability to bear weight comfortably, return to normal footwear, and progressively increase walking tolerance.

Clinical Takeaway: Suzetrigine offers a nonopioid alternative for patients with moderate-to-severe acute pain who are intolerant of opioids, with pain reduction comparable to hydrocodone/acetaminophen and lower rates of nausea and dizziness.

SUMMARY

Acute pain care is evolving, yet the primary care goal remains consistent: relieve pain, restore function, and reduce downstream harm. Suzetrigine adds a targeted nonopioid option within multimodal care, especially when opioid risks, intolerance, or patient preference make opioid-sparing strategies important.

Optimal treatment still depends on structured assessment, mechanism-informed medication choice, nonpharmacologic recovery strategies, functional goals, follow-up, and careful opioid stewardship when opioids are used. ●

REFERENCES

1. St Sauver JL, Warner DO, Yawn BP, et al. Why patients visit their doctors: assessing the most prevalent conditions in a defined American population. *Mayo Clin Proc.* 2013;88(1):56-67. <https://doi.org/10.1016/j.mayocp.2012.08.020>
2. Finley CR, Chan DS, Garrison S, et al. What are the most common conditions in primary care? Systematic review. *Can Fam Physician.* 2018;64(11):832-840. <https://www.cfp.ca/content/64/11/832.long>
3. Alorfi NM. Pharmacological methods of pain management: narrative review of medication used. *Int J Gen Med.* 2023;16:3247-3256. <https://doi.org/10.2147/ijgm.s419239>
4. Paul AK, Smith CM, Rahmatullah M, et al. Opioid analgesia and opioid-induced adverse effects: a review. *Pharmaceuticals (Basel).* 2021;14(11):1091. <https://doi.org/10.3390/ph14111091>
5. Hochberg MC. NSAIDs: mechanisms and pathways of action. *Hosp Pract.* 1989;24(3):185-198. <https://doi.org/10.1080/21548331.1989.11703684>
6. Keam SJ. Suzetrigine: first approval. *Drugs.* 2025;85(6):845-851. <https://doi.org/10.1007/s40265-025-02178-w>
7. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain—United States, 2022. *MMWR Recomm Rep.* 2022;71(RR-3):1-95. <https://doi.org/10.15585/mmwr.rr7103a1>
8. Mach M, Giba A, Miedziaszczuk M, et al. Suzetrigine as a novel nonopioid analgesic drug in pain management: a review of clinical evidence and therapeutic perspectives. *Cureus.* 2025;17(8):e90755. <https://doi.org/10.7759/cureus.90755>
9. Brune K. Next generation of everyday analgesics. *Am J Ther.* 2002;9(3):215-223. [doi:10.1097/00045391-200205000-00007](https://doi.org/10.1097/00045391-200205000-00007)
10. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *The Lancet.* 2019;393(10180):1537-1546. [https://doi.org/10.1016/s0140-6736\(19\)30352-6](https://doi.org/10.1016/s0140-6736(19)30352-6)
11. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *The Lancet.* 2006;367(9522):1618-1625. [https://doi.org/10.1016/s0140-6736\(06\)68700-x](https://doi.org/10.1016/s0140-6736(06)68700-x)
12. Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low backpain: a clinical practice guideline. *Ann Intern Med.* 2017;166(7):514-530. <https://doi.org/10.7326/m16-2367>
13. Körner J, Albani S, Sudha Bhagavath Eswaran V, et al. Sodium channels and local anesthetics — old friends with new perspectives. *Front Pharmacol.* 2022;13:837088. [doi:10.3389/fphar.2022.837088](https://doi.org/10.3389/fphar.2022.837088)
14. Waxman SG, Merkies ISJ, Gerrits MM, et al. Sodium channel genes in pain-related disorders: phenotype-genotype associations and recommendations for clinical use. *The Lancet Neurol.* 2014;13(11):1152-1160. [doi:10.1016/S1474-4422\(14\)70150-4](https://doi.org/10.1016/S1474-4422(14)70150-4)
15. Bello CM, Mackert S, Harnik MA, Filipovic MG, Urman RD, Luedi MM. Shared decision-making in acute pain services. *Curr Pain Headache Rep.* 2023;27(7):193-202. [doi:10.1007/s11916-023-01111-8](https://doi.org/10.1007/s11916-023-01111-8)
16. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology.* 2012;116(2):248-273. <https://doi.org/10.1097/aln.0b013e31823c1030>
17. Bertoch T, D'Aunno D, McCoun J, et al. Suzetrigine, a nonopioid Nav1.8 inhibitor for treatment of moderate-to-severe acute pain: two phase 3 randomized clinical trials. *Anesthesiology.* 2025;142(6):1085-1099. <https://doi.org/10.1097/md.00000000000005460>
18. Alvarez-Aguilar P, Picado-Loaiza S. Suzetrigine (a Nav1.8 inhibitor) versus placebo for acute postoperative pain: a systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2026;105(10):e47877. <https://doi.org/10.1097/md.000000000000047877>
19. Irfan Q, Zaidi SMM, Zohair M, et al. Safety and efficacy of suzetrigine (VX-548) for acute moderate to severe pain in adults: a systematic review and meta-analysis. *J Clin Anesth.* 2026;111:112156. <https://doi.org/10.1016/j.jclinane.2026.112156>
20. McCoun J, Winkle P, Solanki D, et al. Suzetrigine, a nonopioid Nav1.8 inhibitor with broad applicability for moderate-to-severe acute pain: a phase 3 single-arm study. *J Pain Res.* 2025;18:1569-1576. <https://doi.org/10.2147/jpr.s509144>
21. Journavx (suzetrigine). Prescribing Information. Vertex Pharmaceuticals Inc.; January 2026. Accessed September 7, 2026. https://pi.vrtx.com/files/uspi_suzetrigine.pdf
22. Chen R, Liu Y, Qian L, et al. Sodium channels as a new target for pain treatment. *Front Pharmacol.* 2025;16:1573254. <https://doi.org/10.3389/fphar.2025.1573254>
23. Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. Sodium channels in normal and pathological pain. *Annu Rev Neurosci.* 2010;33:325-347. [doi:10.1146/annurev-neuro-060909-153234](https://doi.org/10.1146/annurev-neuro-060909-153234)
24. Saragiotto BT, Machado GC, Ferreira ML, Pinheiro MB, Sheehed CA, Maher CG. Paracetamol for low back pain. *Cochrane Database Syst Rev.* 2016;(6):CD012230.
25. US Department of Veterans Affairs, Department of Defense. VA/DoD Clinical Practice Guideline for the Diagnosis and Treatment of Low Back Pain. Version 3.0. US Dept of Veterans Affairs; 2022. Accessed June 7, 2026. <https://www.healthquality.va.gov/HEALTHQUALITY/guidelines/Pain/lbp/VADODLBPCPGFinal508.pdf>
26. Wiggins BS, Saseen JJ, Page RL II, et al. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation.* 2016;134(21):e468-e495. [doi:10.1161/CIR.0000000000000456](https://doi.org/10.1161/CIR.0000000000000456)

Managing Vasomotor Symptoms Due to Menopause With Elinzanetant—Hypothetical Clinical Case Scenarios

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INTRODUCTION

Vasomotor symptoms (VMS; also known as hot flashes) are among the most common and disruptive features of menopause, affecting 60% to 80% of women during menopause.¹ Hot flashes (or night sweats, if occurring at night) are sudden bursts of warmth, characterized by flushing and vasodilation, that are usually most intense over the face, neck, and chest and last for approximately 1 to 5 minutes. The experience of menopause and symptom severity can vary significantly among women of different races and nationalities.²⁻⁷ On average, women experience hot flashes for more than 7 years, but up to one-third of women endure VMS for 10 years or longer.²⁻⁴ Moderate hot flashes are defined as a sensation of heat with sweating and the ability to continue activity, whereas severe hot flashes are defined as the sensation of heat with sweating that causes cessation of activity.^{8,9} The sensation of heat frequently is accompanied by a cascade of other disruptive symptoms such as anxiety, palpitations, dizziness, and nausea.¹⁰

When severe, these symptoms can significantly disrupt daily activities and diminish quality of life, leading to sleep disturbances in 40% to 60% of menopausal women (e.g., trouble falling asleep, nighttime awakenings), reduced energy, and mood changes.^{11,12} The presence of VMS has been consistently associated with adverse health outcomes, including higher cardiovascular risk,¹³⁻¹⁹ neurocognitive risk, and bone loss.²⁰⁻²²

Key takeaways

- For many women, VMS significantly disrupt daily activities, causing adverse workplace outcomes, negatively impacting interpersonal relationships, and diminishing quality of life.
- A limited number of therapies are approved for the management of VMS, and not all are suitable for every patient due to medical conditions, drug-drug interactions, side effects, or patient preferences. In addition, the strength of evidence supporting efficacy and safety varies across available options, and some treatments used in practice are not approved by the US Food and Drug Administration (FDA) for VMS, resulting in off-label use.
- Elinzanetant, the only approved dual neurokinin-targeted (NKT) therapy, is a neurokinin 1 (NK1) and neurokinin 3 (NK3) receptor antagonist that is FDA approved for moderate-to-severe VMS due to menopause.
- NKT therapies (elinzanetant and fezolinetant) offer a unique hormone-free option for women who seek effective VMS control.
- Patient education and shared decision-making are important aspects of VMS care to select the most appropriate treatment.

Despite the availability of therapeutic options for VMS, many women experiencing moderate-to-severe VMS remain untreated. A recent study showed that, of more than 100,000

women diagnosed with VMS, 79.5% had no treatment.³ Prior to FDA approval of NKT therapies for moderate-to-severe VMS, the most commonly prescribed medications were menopausal hormone therapy (MHT) or selective serotonin/norepinephrine reuptake inhibitors (SSRIs/SNRIs).^{23,24} With the exception of paroxetine 7.5 mg, SSRIs and SNRIs are not FDA approved for VMS.

Discontinuation rates of MHT and SSRI/SNRI exceed 50% within about 7 months, reflecting wide variation in individual preferences, tolerability, and response to therapy.²⁵ Recent research has advanced our understanding of the underlying pathways involved in the etiology of hot flashes, leading to the development of NKT therapies. Considering the evolving therapeutic landscape with novel emerging options, treatment of VMS should be tailored to meet individual patient needs, medical history, tolerability, response, and preferences. This article aims to support clinicians in making informed decisions on treatment and in counseling women on the available options for menopausal VMS management.

MECHANISM OF ACTION, CLINICAL EVIDENCE, AND INDICATIONS FOR NKT THERAPIES

NKT therapies target the brain's thermoregulatory center within the hypothalamus, where kisspeptin/neurokinin B/dynorphin (KNDy) neurons are located. During menopause, KNDy neurons become hyperactive due to the decline of estrogen. Overexpression of substance P (SP) and neurokinin B (NKB) causes overstimulation of the thermoregulatory center, which disrupts normal temperature regulation, triggering hot flashes and night sweats. On KNDy neurons, SP binds and activates NK1 receptors, while NKB binds and activates NK3 receptors. Elinzanetant blocks NK1 and NK3 receptors, preventing SP and NKB from binding to KNDy neurons. Such antagonism reduces KNDy neuron hyperactivity, restoring thermoregulatory balance (**FIGURE 1**). Additionally, SP and NK1 receptors may further contribute to peripheral vasodilation, as well as primary insomnia.²⁰

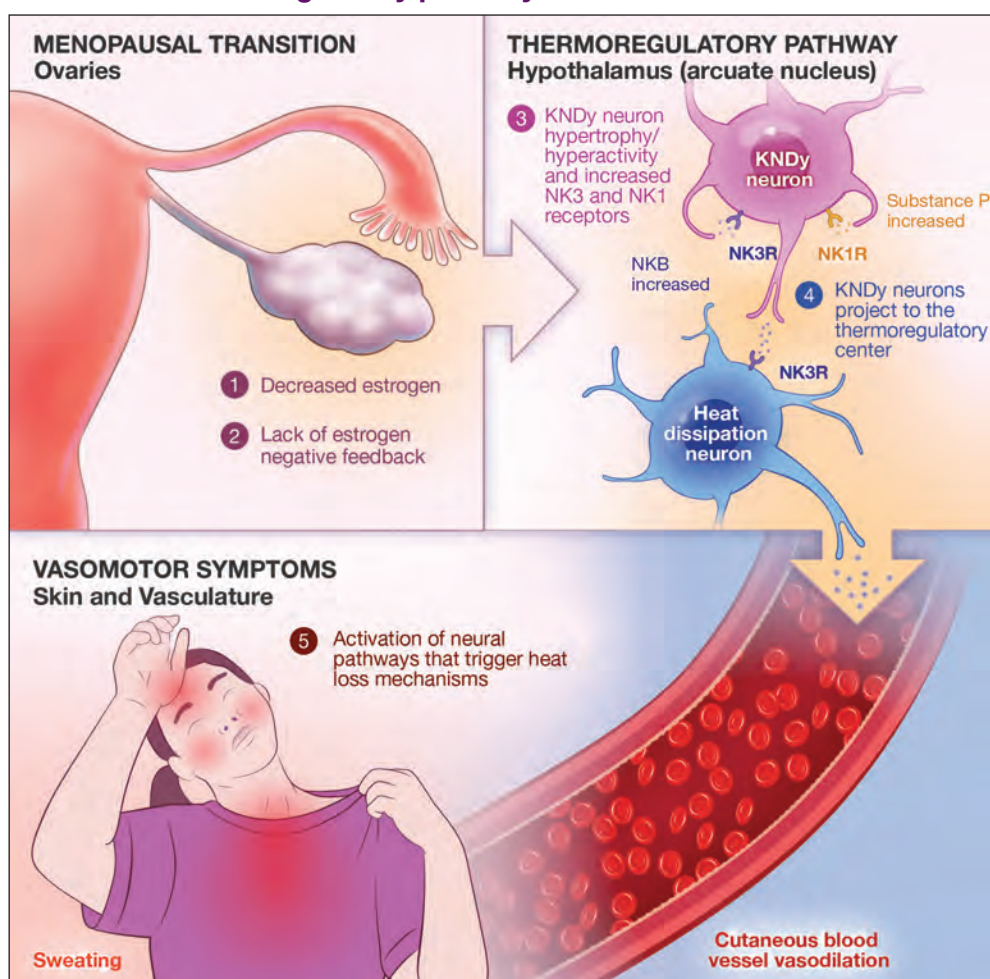
In 2025, the FDA approved elinzanetant, the first and only dual NK1 and NK3 receptor antagonist, for the treatment of moderate-to-severe VMS due to menopause. Elinzanetant is a

hormone-free, dual NKT therapy that has also demonstrated benefit in improving sleep disturbances and menopause-related quality of life in clinical trials. The recommended dosage is 120 mg (two 60 mg capsules) administered orally once daily at bedtime.²⁶⁻³¹ In 2023, fezolinetant, a selective NK3 receptor antagonist,³² was approved for moderate-to-severe VMS at a dose of 45 mg daily. In clinical trials of fezolinetant, a small percentage of patients experienced elevations in liver function tests, necessitating frequent hepatic laboratory testing during the first year of treatment,³³ which may be burdensome for patients. Aggregated phase 1 to 3 clinical trial data suggest there is a low risk of liver toxicity for elinzanetant.³⁴

Elinzanetant clinical evidence

Elinzanetant's efficacy and safety at a 120 mg daily dose

FIGURE 1. Thermoregulatory pathway.²⁰



have been evaluated in the phase 3 clinical trial program OASIS,²⁸⁻³¹ demonstrating VMS reduction as early as week 1, as well as improvements in sleep disturbances and menopause-related quality of life, with low risk of liver-related adverse events.

OASIS-1 and OASIS-2

OASIS-1 and OASIS-2 were multicenter, placebo-controlled, phase 3 trials. Participants included natural or surgical (bilateral oophorectomy with or without hysterectomy) postmenopausal women aged 40 to 65 years, experiencing ≥ 50 moderate-to-severe VMS per week. A total of 796 menopausal women were randomized 1:1 to receive elinzanetant 120 mg or placebo for 12 weeks, followed by 14 weeks of elinzanetant 120 mg.²⁹ Both trials demonstrated statistically significant reductions in VMS frequency and severity compared to placebo at weeks 4 and 12. Additionally, reduction in VMS frequency was statistically significant as early as week 1 in both trials. Clinically meaningful reductions in VMS frequency were observed as early as week 1 in OASIS-1 and at weeks 4 and 12 in both trials, with the effect maintained for 26 weeks. Elinzanetant also significantly improved sleep disturbances and menopause-related quality of life at week 12 (TABLE 1).²⁹

Common adverse events included headache and fatigue; these were mild or moderate in severity. Participants taking elinzanetant reported a lower incidence of headache and fatigue between weeks 13 and 26 vs weeks 1 and 12. Reductions in VMS frequency and improvements in severity were maintained in the elinzanetant group, and benefits were consistently observed in participants switching from placebo to elinzanetant.²⁹

OASIS-3

The OASIS-3 trial was a double-blind, placebo-controlled, randomized phase 3 study evaluating the long-term safety and efficacy of elinzanetant for moderate-to-severe VMS in postmenopausal women. More than 600 postmenopausal women aged 40 to 65 years with no minimum requirement of VMS events were randomized to receive 120 mg elinzanetant or placebo daily. The change in moderate-to-severe VMS frequency from baseline to week 12 showed a statistically significant reduction in VMS frequency ($P < .001$). Descriptive analyses demonstrated improvements for participants taking elinzanetant vs placebo in VMS frequency and severity over 50 weeks, as well as sleep disturbances and menopause-related quality of life over 52 weeks.³⁰

Over 52 weeks, the safety profile remained consistent with prior studies. Treatment-emergent adverse events (TEAEs) were more frequent with elinzanetant vs placebo (70% vs 61.1%) but were mostly mild to moderate and included somnolence, fatigue, and headache. There were no serious TEAEs that were considered treatment related. Although a few liver enzyme level elevations were observed, there were no severe liver enzyme elevations or signs of hepatotoxicity.³⁵ Elinzanetant was not associated with an increased risk of endometrial hyperplasia or cancer.³⁰

OASIS-4

The phase 3, placebo-controlled OASIS-4 trial included women experiencing at least 35 moderate-to-severe VMS per week associated with endocrine therapy for treatment or prevention of hormone receptor-positive (HR+) breast cancer. Participants were randomized 2:1 to receive either once-daily elinzanetant 120 mg for 52 weeks or once daily placebo

TABLE 1. Efficacy of elinzanetant across primary and secondary endpoints vs placebo in women with moderate-to-severe VMS due to menopause.^{29a}

Endpoints	OASIS-1			OASIS-2		
	Week 1	Week 4	Week 12	Week 1	Week 4	Week 12
VMS frequency	LS: -2.5 [95% CI: -3.4, -1.6] $P < .001$	LS: -3.3 [95% CI: -4.5, -2.1] $P < .001$	LS: -3.2 [95% CI: -4.8, -1.6] $P < .001$	LS: -1.7 [95% CI: -2.7, -0.6] $P < .001$	LS: -3.0 [95% CI: -4.4, -1.7] $P < .001$	LS: -3.2 [95% CI: -4.6, -1.9] $P < .001$
VMS severity		LS: -0.3 [95% CI: -0.4, -0.2] $P < .001$	LS: -0.4 [95% CI: -0.5, -0.3] $P < .001$		LS: -0.2 [95% CI: -0.3, -0.1] $P < .001$	LS: -0.3 [95% CI: -0.4, -0.1] $P < .001$
Sleep disturbance (PROMIS-SD-SF 8b)			LS: -5.6 [95% CI: -7.2, -4.0] $P < .001$			LS: -4.3 [95% CI: -5.8, -2.9] $P < .001$
Menopause-related quality of life			LS: -0.4 [95% CI: -0.6, -0.2] $P < .001$			LS: -0.3 [95% CI: -0.5, -0.1] $P = .0059$

Abbreviations: CI, confidence interval; LS, least squares; PROMIS-SD-SF 8b, Patient-Reported Outcomes Measurement Information System Sleep Disturbance-Short Form 8b.

^aMean daily change from baseline.

for 12 weeks followed by once daily elinzanetant 120 mg for 40 weeks. Participants who completed 52 weeks of the trial regimen were offered the opportunity to continue treatment with elinzanetant for an additional 2 years. Elinzanetant significantly reduced VMS frequency at weeks 4 and 12 vs placebo ($P < .001$); improvements were noted as early as week 1. Improvements were observed in sleep disturbances, menopause-related quality of life, and VMS severity (weeks 4 and 12).³¹

Improvements in VMS frequency were sustained for up to 50 weeks, and participants switching from placebo to elinzanetant showed improvements across all endpoints. Somnolence, fatigue, and headache were the most reported adverse events during weeks 1 through 12; adverse events were mostly mild or moderate. Based on the available 52-week data for participants who received elinzanetant, the liver safety monitoring board concluded there was no substantive hepatotoxicity signal.³¹

Fezolinetant clinical evidence

SKYLIGHT 1 and SKYLIGHT 2

In 2 pivotal randomized, double-blind, placebo-controlled trials, women with an average of ≥ 7 moderate-to-severe hot flashes per day were randomized to daily fezolinetant 45 mg, fezolinetant 30 mg, or placebo for 12 weeks, with a 40-week extension.^{36,37} Fezolinetant 45 mg reduced daily VMS frequency and severity vs placebo at weeks 4 and 12 (TABLE 2); improvements were observed by week 1 and were maintained through week 52 of the extension.^{36,37}

SKYLIGHT 4

The phase 3 SKYLIGHT 4 trial was a double-blind, 52-week safety study that randomized postmenopausal women experiencing VMS to fezolinetant or placebo.³⁴ TEAEs occurred in 67.9% and 63.9% of the fezolinetant 30 mg and 45 mg groups, respectively, compared to 64.1% of the placebo group. Liver enzyme elevations more than 3 times the upper limit of normal occurred in 1% of the placebo group, 1.4% of the fezolinetant 30 mg group, and 2% of the fezolinetant 45 mg group.³⁴ Of note, there are limitations in comparing elinzanetant and fezolinetant clinical evidence, as no head-to-head tri-

als have been conducted, and cross-trial comparisons have inherent limitations.

Indications, contraindications, interactions, and testing

Elinzanetant is indicated for the treatment of moderate-to-severe VMS due to menopause. Although no human data are available, based on animal data, it is contraindicated in pregnancy; exposure to elinzanetant may cause pregnancy loss or stillbirth (but not fetal malformations). Pregnancy should be excluded in females of reproductive potential before initiating treatment. Elinzanetant is a substrate and a weak inhibitor of cytochrome P450 (CYP) 3A4. It is primarily metabolized by the CYP3A4 enzyme via the liver. Concomitant use of strong CYP3A4 inhibitors should be avoided as this may increase elinzanetant exposure, which may increase risk of adverse events. When moderate CYP3A4 inhibitors must be used concomitantly, the daily dose of elinzanetant should be reduced to 60 mg. Its use with strong or moderate CYP3A4 inducers is discouraged, as these may lower elinzanetant exposure and reduce its effectiveness.⁸ The FDA recommends evaluations of liver enzymes at baseline and 3 months post treatment initiation to assess hepatic function and injury.²⁶

Fezolinetant is indicated for the treatment of moderate-to-severe VMS due to menopause.³² It is contraindicated in patients with known cirrhosis and severe, end-stage kidney disease, and it should not be used concomitantly with CYP1A2 inhibitors. Cases of serious drug-induced hepatotoxicity have led to a boxed warning and recommendations for baseline hepatic testing, monthly testing for the first 3 months, and repeated testing at 6 and 9 months.^{32,35-44}

CHALLENGES IN VMS MANAGEMENT

Managing VMS in primary care presents numerous challenges. Treatment options are expanding, but many are unsuitable for some women due to medical history, age, time elapsed since menopausal onset, tolerability, contraindications, or personal preference.³⁸

Furthermore, women of racial and ethnic minorities (such as Black and Hispanic populations) may experience menopause earlier, experience more severe symptoms for longer durations, and have worse health outcomes, highlighting the need for clinicians to consider race and ethnicity when evaluating women with VMS.^{23,39} Accordingly, addressing VMS in varying patient presentations requires an individualized, shared decision-making approach.^{21,40}

The following hypothetical clinical case studies high-

TABLE 2. Efficacy of fezolinetant 45 mg vs placebo in SKYLIGHT 1 and SKYLIGHT 2 phase 3 trials.^{36,37}

Endpoints	SKYLIGHT 1		SKYLIGHT 2	
	Week 4	Week 12	Week 4	Week 12
VMS frequency ^a	-2.07 [SE, 0.42] $P < .001$	-2.55 [SE, 0.43] $P < .001$	-2.55 [SE, 0.46] $P < .001$	-2.53 [SE, 0.55] $P < .001$
VMS severity ^a	-0.19 [SE, 0.06] $P = .002$	-0.20 [SE, 0.08] $P = .007$	-0.29 [SE, 0.06] $P < .001$	-0.29 [SE, 0.08] $P < .001$

Abbreviation: SE, standard error.

^aDifference in change in least squares mean.

light distinct challenges and opportunities for managing VMS due to menopause, illustrating scenarios in which elinzanetant could be considered.

CASE STUDY 1

A 46-year-old Black woman, who is a high school teacher, with natural menopause presents with severe, persistent VMS, including up to 20 hot flashes daily and sleep disturbances that markedly impair her quality of life. As a result, she experiences reduced self-confidence, frequent clothing changes, and day and night tiredness, which interfere with her job. Lifestyle modifications, including caffeine reduction, produce minimal benefits. She has an elevated body mass index (BMI) and takes medication for hyperlipidemia. She has tried MHT and despite trying several dosages, she is frustrated by adverse effects, including edema and severe breast tenderness.

In this case scenario, the challenges of life-disruptive VMS, comorbidities, and concomitant medications are further compounded by the earlier onset and more severe VMS experienced by Black women. An alternative to MHT should be considered for this patient, given the adverse effects noted. While paroxetine 7.5 mg is an approved option, it may inadequately address her severe symptoms and cause problematic adverse effects such as weight gain and fatigue. An NKT therapy such as elinzanetant or fezolinetant may be more appropriate. While both fezolinetant and elinzanetant are effective in reducing the frequency and severity of VMS, elinzanetant has additionally demonstrated consistent sleep benefits and requires less frequent liver safety monitoring.²⁸⁻³² Importantly, clinical studies have demonstrated efficacy of elinzanetant in Black women and in women with higher BMIs, achieving clinically meaningful reductions in daily VMS frequency observed as early as week 1.⁴¹

CASE STUDY 2

A 50-year-old professional Asian woman presents with severe hot flashes and night sweats up to 4 times an hour, leading to significant trouble sleeping and impaired quality of life. The patient describes her hot flashes as lasting more than 10 minutes, accompanied by sweating and a rapid heartbeat. Her medical history includes HR+ breast cancer, now in remission, for which she takes endocrine therapy. The patient discontinued an SSRI after 4 months due to several intolerable side effects.

MHT is typically considered contraindicated in patients with a history of breast cancer, and the patient noted prior intolerance of an SSRI; thus, an NKT therapy such as elinzanetant or fezolinetant should be considered. Notably, in OASIS-4, women with VMS associated with adjuvant endocrine therapy for treatment or prevention of HR+ breast cancer experienced a reduction in symptom frequency, as well as improvements in sleep disturbances and menopause-related quality of life, while taking

elinzanetant.³¹ Based on OASIS-4 results, the National Comprehensive Cancer Network® Survivorship Guidelines now list elinzanetant as a preferred NKT option for the management of VMS in female breast cancer survivors, offering a safe and effective, hormone-free option to help improve VMS and quality of life.⁴² To date, there are no data on fezolinetant in the breast cancer population.

POINTS TO CONSIDER AND SHARED DECISION-MAKING

Before prescribing therapy for VMS, clinicians should assess a patient's potential risks and consider individual characteristics and preferences, which may include choosing to avoid hormones and the burden of monitoring. Patients may also base decisions on potential for sleep improvement, route of administration, cost, and prior treatment experiences. Because menopause affects each person differently, it is important that women receive care from a clinician committed to understanding symptoms and improving quality of life, while also limiting potential health risks. Treatment decisions should be made collaboratively between the patient and clinician and should be revisited over time based on outcomes and changes in health status.

Shared decision-making should begin with proactive symptom inquiry, as many women normalize VMS as an unavoidable part of aging, may feel embarrassed discussing menopause, are unaware that newer hormone-free treatments are available, or may assume that treatment options are limited to MHT or over-the-counter products. Clinicians may also fail to address VMS because of limited menopause-specific training, competing priorities during brief visits, uncertainty about treatment guidance, or concerns about treatment safety.^{40,43-45}

A practical approach might involve an ask-assess-align-adjust framework: ask routinely about hot flashes, night sweats, sleep disruption, mood changes, concentration, work impairment, and relationship burden; assess symptom severity, medical history, contraindications, concurrent medications, and prior treatment experiences; align treatment selection with the patient's goals and tolerance for monitoring or adverse events; and adjust the plan through scheduled follow-up based on symptom response, tolerability, adherence, and changes in health status.^{38,43,45}

SUMMARY

VMS remain among the most common and disruptive features of menopause and can significantly impact daily activities and diminish quality of life. Increased understanding of the underlying pathways in the etiology of VMS has led to the development of NKT therapies that have been shown to treat menopausal VMS effectively.

Elinzanetant exerts an early, sustained effect on VMS due

to menopause and provides additional benefits in sleep quality and quality of life. By antagonizing 2 key receptors within the KNDy neuronal pathway (the central driver of thermoregulatory dysfunction), it offers a mechanism of action distinct from MHT and other hormone-free treatment options. In contrast, fezolinetant is an NK3 receptor-targeted therapy that, while effective for reducing frequency and severity of VMS, requires frequent monitoring of hepatic enzymes.

NKT therapies offer a unique option for women who are not candidates for, or who wish to avoid, MHT and seek effective and safe symptom control beyond over-the-counter treatments or lifestyle changes. Incorporating patient education on all available treatment options and aligning treatment with patients' preferences and characteristics through shared decision-making can help optimize VMS care. ●

REFERENCES

- Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *Am J Public Health*. 2006;96(7):1226-1235. doi:10.2105/AJPH.2005.066936
- Im EO, Chang SJ, Chee E, Chee W. The relationships of multiple factors to menopausal symptoms in different racial/ethnic groups of midlife women: the structural equation modeling. *Women Health*. 2019;59(2):196-212. doi:10.1080/03630242.2018.1450321
- Shiozawa A, Mancuso S, Young C, Friderici J, Tran S, Trenz HM. Comparison of healthcare costs for women with treated versus untreated vasomotor symptoms due to menopause. *Adv Ther*. 2024;41(5):1885-1895. doi:10.1007/s12325-024-02821-0
- Thurston RC, Chang Y, Buysse DJ, Hall MH, Matthews KA. Hot flashes and awakenings among midlife women. *Sleep*. 2019;42(9):zsz131. doi:10.1093/sleep/zsz131
- Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med*. 2015;175(4):531-539. doi:10.1001/jamainternmed.2014.8063
- Thurston RC. Vasomotor symptoms: natural history, physiology, and links with cardiovascular health. *Climacteric*. 2018;21(2):96-100. doi:10.1080/13697137.2018.1430131
- Nappi RE, Kroll R, Siddiqui E, et al. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. *Menopause*. 2021;28(8):875-882. doi:10.1097/GME.0000000000001793
- Menopause topics: hot flashes. The Menopause Society. Accessed March 9, 2026. <https://menopause.org/patient-education/menopause-topics/hot-flashes>
- US Food and Drug Administration. Guidance for Industry: estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal symptoms — recommendations for clinical evaluation. August 24, 2018. Accessed March 9, 2026. <https://www.fda.gov/media/71359/download>
- ACOG Practice Bulletin No. 141: management of menopausal symptoms. *Obstet Gynecol*. 2014;123(1):202-216. doi:10.1097/01.AOG.0000441353.20693.78
- Santoro N, Rocca C, Peters BA, Neal-Perry G. The menopause transition: signs, symptoms, and management options. *J Clin Endocrinol Metab*. 2021;106(1):1-15. doi:10.1210/clinem/dgaa764
- Nelson HD. Menopause. *The Lancet*. 2008;371(9614):760-770. doi:10.1016/S0140-6736(08)60346-3
- Armeni A, Anagnostis P, Armeni E, Nili N, Goulis D, Lambrinoudaki I. Vasomotor symptoms and risk of cardiovascular disease in peri- and postmenopausal women: a systematic review and meta-analysis. *Maturitas*. 2023;171:13-20. doi:10.1016/j.maturitas.2023.02.004
- El Khoudary SR, Aggarwal B, Beckie TM, et al. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. *Circulation*. 2020;142(25):e506-e532. doi:10.1161/CIR.0000000000000912
- Lee E, Anselmo M, Tahsin CT, et al. Vasomotor symptoms of menopause, autonomic dysfunction, and cardiovascular disease. *Am J Physiol Heart Circ Physiol*. 2022;323(6):H1270-H1280. doi:10.1152/ajpheart.00477.2022
- Muka T, Oliver-Williams C, Colpani V, et al. Association of vasomotor and other menopausal symptoms with risk of cardiovascular disease: a systematic review and meta-analysis. *PLoS One*. 2016;11(6):e0157417. doi:10.1371/journal.pone.0157417
- Nappi RE, Chedraui P, Lambrinoudaki I, Simoncini T. Menopause: a cardiometabolic transition. *The Lancet Diabetes Endocrinol*. 2022;10(6):442-456. doi:10.1016/S2213-8587(22)00076-6
- Thurston RC. Vasomotor symptoms and cardiovascular health: findings from the SWAN and the MsHeart/MsBrain studies. *Climacteric*. 2024;27(1):75-80. doi:10.1080/13697137.2023.2196001
- Zhu D, Chung HF, Dobson AJ, et al. Vasomotor menopausal symptoms and risk of cardiovascular disease: a pooled analysis of six prospective studies. *Am J Obstet Gynecol*. 2020;223(6):898.e1-898.e16. doi:10.1016/j.ajog.2020.06.039
- Young Moss S, Lee A, Simon JA. Advances in pharmacotherapy for menopausal vasomotor symptoms. *Drugs*. 2025;85(11):1363-1379. doi:10.1007/s40265-025-02231-8
- Thurston RC, Maki P, Chang Y, et al. Menopausal vasomotor symptoms and plasma Alzheimer disease biomarkers. *Am J Obstet Gynecol*. 2024;230(3):342.e1-342.e8. doi:10.1016/j.ajog.2023.11.002
- Thurston RC, Wu M, Chang YF, et al. Menopausal vasomotor symptoms and white matter hyperintensities in midlife women. *Neurology*. 2023;100(2):e133-e141. doi:10.1212/WNL.00000000000021401
- Kingsberg S, Banks V, Caetano C, et al. Real-world evaluation of treatment utilization by women experiencing vasomotor symptoms associated with menopause in the United States and Europe: findings from the REALISE study. *Maturitas*. 2024;189:108096. doi:10.1016/j.maturitas.2024.108096
- The 2022 Hormone Therapy Position Statement of The North American Menopause Society Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767-794. doi:10.1097/GME.0000000000002028
- Charafi L, Bolling K, Schroader BK, Halvorson L. Characterization and treatment patterns of peri/menopausal and postmenopausal women with and without vasomotor symptoms in a retrospective database study. *Women's Health Rep (New Rochelle)*. 2025;6(1):742-751. doi:10.1017/26884844251366113
- Lynkiet (elinzanetant). Prescribing Information. Bayer HealthCare Pharmaceuticals Inc.; October 2025. Accessed March 9, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219469s000lbl.pdf
- Bayer's Lynkiet™ (elinzanetant) approved in the U.S. for treatment of moderate to severe vasomotor symptoms due to menopause. Bayer Global. October 24, 2025. Accessed March 9, 2026. <https://www.bayer.com/media/en-us/bayers-lynkiet-elinzanetant-approved-in-the-us-for-treatment-of-moderate-to-severe-vasomotor-symptoms-due-to-menopause/>
- Hager M, Goldstein T, Fitz V, Ott J. Elinzanetant, a new combined neurokinin-1/-3 receptor antagonist for the treatment of postmenopausal vasomotor symptoms. *Expert Opin Pharmacother*. 2024;25(7):783-789. doi:10.1080/14656566.2024.2358131
- Pinkerton JV, Simon JA, Joffe H, et al. Elinzanetant for the treatment of vasomotor symptoms associated with menopause: OASIS 1 and 2 randomized clinical trials. *JAMA*. 2024;332(16):1343-1354. doi:10.1001/jama.2024.14618
- Panay N, Joffe H, Maki PM, et al. Elinzanetant for the treatment of vasomotor symptoms associated with menopause: a phase 3 randomized clinical trial. *JAMA Intern Med*. 2025;185(11):1319-1327. doi:10.1001/jamainternmed.2025.4421
- Cardoso F, Parke S, Brennan DJ, et al. Elinzanetant for vasomotor symptoms from endocrine therapy for breast cancer. *N Engl J Med*. 2025;393(8):753-763. doi:10.1056/NEJMoa2415566
- Veozah (fezolinetant). Prescribing Information. Astellas Pharma US, Inc.; December 2024. Accessed May 29, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216578s004lbl.pdf
- Mughal ZUN, Mussarat A, Oduoye MO. Revolutionary treatment for menopausal symptoms: Veozah (Fezolinetant) receives FDA approval. *Ann Med Surg (Lond)*. 2024;86(12):6905-6907. doi:10.1097/MS9.0000000000001659
- Neal-Perry G, Cano A, Lederman S, et al. Safety of fezolinetant for vasomotor symptoms associated with menopause: a randomized controlled trial. *Obstet Gynecol*. 2023;141(4):737-747. doi:10.1097/AOG.0000000000005114
- US Food and Drug Administration. Guidance for industry. Drug-induced liver injury: premarketing clinical evaluation. July 2009. Accessed March 9, 2026. <https://www.fda.gov/media/116737/download>
- Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *The Lancet*. 2023;401(10382):1091-1102. doi:10.1016/S0140-6736(23)00085-5
- Johnson KA, Martin N, Nappi RE, et al. Efficacy and safety of fezolinetant in moderate to severe vasomotor symptoms associated with menopause: a phase 3 RCT. *J Clin Endocrinol Metab*. 2023;108(8):1981-1997. doi:10.1210/clinem/dgad058
- Crandall CJ, Mehta JM, Manson JE. Management of menopausal symptoms: a review. *JAMA*. 2023;329(5):405-420. doi:10.1001/jama.2022.24140
- Kochersberger A, Coakley A, Millheiser L, et al. The association of race, ethnicity, and socioeconomic status on the severity of menopause symptoms: a study of 68,864 women. *Menopause*. 2024;31(6):476-483. doi:10.1097/GME.0000000000002349
- Kingsberg S, Banks V, Caetano C, et al. Real-world clinical evaluation of natural and induced vasomotor symptoms in the USA and Europe. *Climacteric*. 2024;27(4):364-372. doi:10.1080/13697137.2024.2340472
- Neal-Perry G, Dunsmoor-Su R, Trigg A, et al. Efficacy of elinzanetant for the treatment of vasomotor symptoms associated with menopause in US African American women: pooled data from two phase 3 studies. Abstract S-20. Presented at: The Menopause Society 2025 Annual Meeting; October 21-25, 2025; Orlando, FL. https://menopause.org/wp-content/uploads/annual-meeting/MENOPAUSE25_Oral-and-Poster-Abstracts.pdf
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- Barber K, Charles A. Barriers to accessing effective treatment and support for menopausal symptoms: a qualitative study capturing the behaviours, beliefs and experiences of key stakeholders. *Patient Prefer Adherence*. 2023;17:2971-2980. doi:10.2147/PPA.S430203
- Kingsberg S, Nappi RE, Scott M, et al. Physician-patient alignment on menopause-associated symptom burden: real-world evidence from the USA and Europe. *Climacteric*. 2024;27(6):534-541. doi:10.1080/13697137.2024.2401366
- New Collective Author. The 2023 nonhormone therapy position statement of The North American Menopause Society. *Menopause*. 2023;30(6):573-590. doi:10.1097/GME.0000000000002200

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