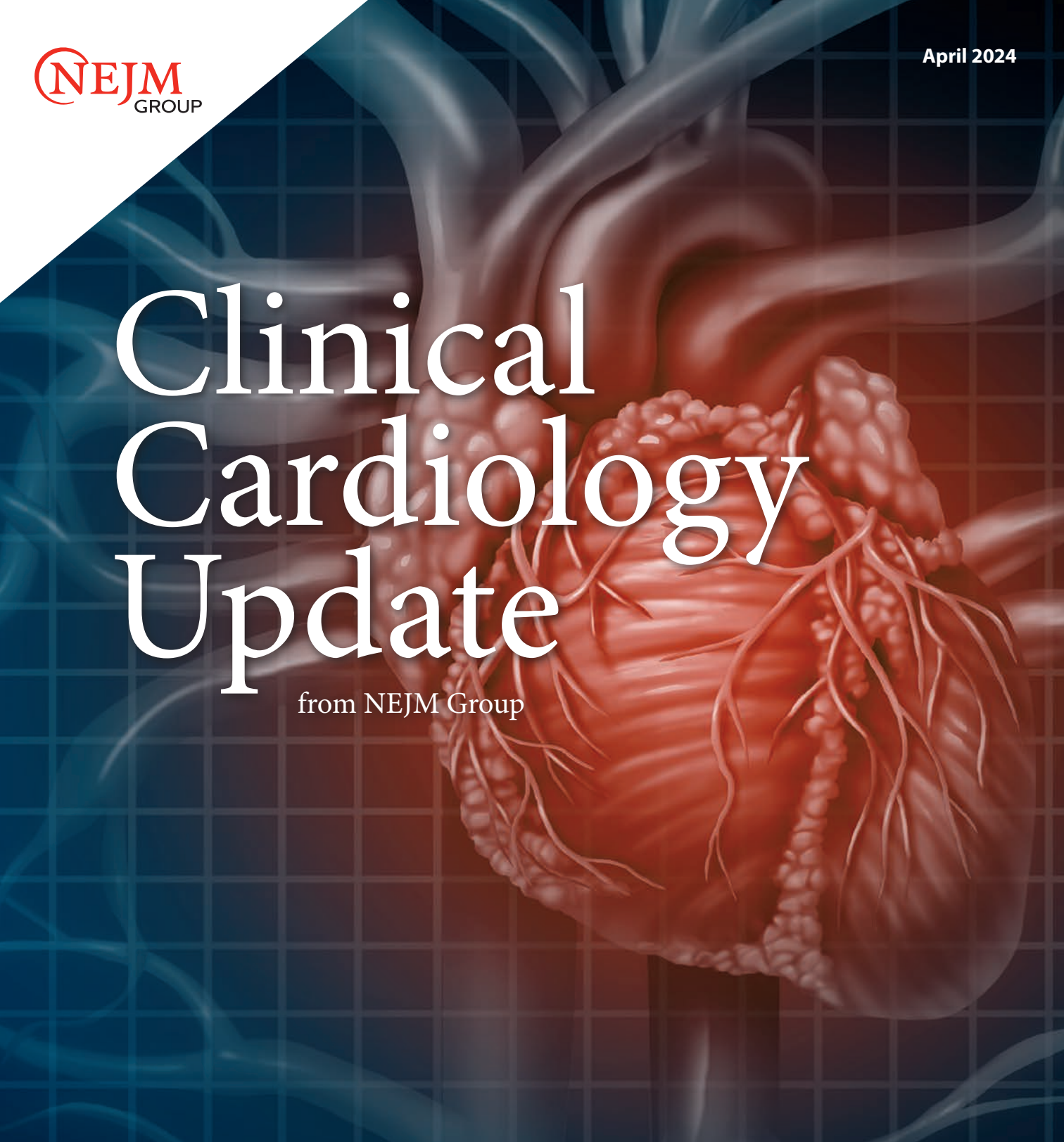
NEJM GROUP

April 2024

Clinical Cardiology Update

from NEJM Group



- Anti-Obesity Drugs & CV Risk
- Cardiovascular-Kidney-Metabolic Syndrome
- Pregnancy Outcomes & Future CV Events
- Guidelines: Managing Atrial Fibrillation

Editor
Karol E. Watson, MD, PhD, FACC

NEJM Group
David Sampson, Vice President
Robert D. Dall, Editorial Director, Clinical Programs
Kelly Young, Managing Editor
Christine Judge, Christine Murphy, Editors
Anne Russ, Business Manager

Shared Services & Operations
Robin Buttner, Director, Publishing Operations
Jeff Burgess, Cindy Dunn, Jonathan Kravetz, Mark LeBlanc, MJ Medas, Lisa Resnick, Renée Sekerak, Deb Visco, Sioux Waks, Design, Production, and Distribution

Global Sales Solutions
Jennifer Badua, Executive Director

Publisher
Clinical Cardiology Update is a publication of NEJM Group, a division of the Massachusetts Medical Society, 860 Winter Street, Waltham, MA 02451-1413.

Customer Service
(800) 843-6356, or email nejmcust@mms.org.

Clinical Cardiology Update, an editorially independent publication from NEJM Group, is curated, written, and edited by physician experts as a service of the publishing division of the Massachusetts Medical Society. The views expressed here do not necessarily represent the views of the *New England Journal of Medicine* or the Massachusetts Medical Society.

Any product mentioned in this update should be used in accordance with the prescribing information prepared by the manufacturer.

New from NEJM Group! Highlights of relevant conferences, including interviews with leading physician experts on the most exciting and practice-changing developments presented at the major medical meetings. Sign up now by emailing nejmcust@mms.org and asking to be added to our General Information email list.

Cover image by wildpixel via Getty Images. Image customization by NEJM Group staff.

TABLE of Contents

FROM the Editor

Cardiometabolic risk describes a group of risk factors that tend to cluster together and are likely linked by insulin resistance. Obesity is a central feature of cardiometabolic risk, and one of the hottest therapeutic areas in medicine is obesity medicine. In this issue of *Clinical Cardiology Update*, Dr. Josephine Harrington examines new medications to treat obesity that offer weight reductions rivaling what has previously been seen only with surgical therapies. And the remarkable thing about these therapies is that they have demonstrated cardiovascular benefit.

We also have a new paradigm, advocated by the American Heart Association, for thinking about cardiometabolic risk that includes incorporation of kidney disease risk. Dr. Chiadi E. Ndumele and Dr. Janani Rangaswami review the cardiovascular-kidney-metabolic health paradigm, which acknowledges that metabolic risk factors, chronic kidney disease, and cardiovascular health are all intricately intertwined. And therapies that benefit one arm tend to benefit the other arms.

In addition, Dr. Rachel M. Bond reviews how adverse pregnancy outcomes are associated with cardiovascular risk, as we now understand that a cluster of metabolic risk factors often underlie these adverse pregnancy outcomes. We know that understanding not only the intrapartum risk associated with these adverse pregnancy outcomes but also the long-term cardiovascular risk associated with adverse pregnancy outcomes is imperative for future cardiovascular protection.

Finally, we highlight some key summaries of studies and guidelines, including treatment with pitavastatin in persons with HIV infection; management of atrial fibrillation; guidance for care of heart failure with preserved left ventricular ejection fraction; torsemide versus furosemide after hospitalization for heart failure; treatment of chronic limb-threatening ischemia; and the global impact of modifiable cardiovascular risk factors.

We hope you enjoy this issue of *Clinical Cardiology Update* and find useful pearls for your clinical practice.

Karol E. Watson, MD, PhD, FACC

Dr. Watson is the John C. Mazziotta, MD, PhD, Term Endowed Chair and Professor of Medicine/Cardiology at the David Geffen School of Medicine at UCLA; Director of the UCLA Barbra Streisand Women's Heart Health Program and the UCLA Cardiology Fellowship Program; and Co-Director of the UCLA Program in Preventive Cardiology. She reports consultant or advisory board roles with Boehringer Ingelheim, Amgen, and Novartis and speakers' bureau activity with Boehringer Ingelheim.

Topic Update

Anti-Obesity Drugs and Cardiovascular Risk: Tipping the Scales in Patients' Favor

Josephine Harrington, MD

Obesity is a major driver of cardiovascular risk and death. High body-mass index (BMI) was responsible for an estimated 4 million deaths globally in 2015, even after adjustment for other metabolic comorbidities, with two thirds of those 4 million from cardiovascular conditions (*N Engl J Med* 2017; 377:13). In the United States, about 39% to 49% of people live with overweight or obesity (*Front Public Health* 2017; 4:279). Although high BMI is well known to drive poor clinical outcomes, modifying it via intentional weight loss is challenging. Even in highly supported settings, intentional weight loss is rarely achieved or maintained without surgical intervention (*N Engl J Med* 2013; 369:145). As a result, it is difficult for clinicians to manage obesity in clinical practice and for researchers to show that intentional weight loss improves clinical outcomes in randomized, controlled trials.

Clinicians and researchers now have an additional tool: incretin-based therapy, which makes it possible for patients with high BMI to achieve significant weight loss without surgery. Two clinically available glucagon-like peptide-1 (GLP-1) receptor agonists — semaglutide and tirzepatide — have shown efficacy in inducing intentional weight loss, and they either have been or are currently being evaluated for their impact on cardiovascular clinical outcomes in patients with overweight or obesity (Figure). The following is a review of the current data on and upcoming trials of these therapies, discussing implications for clinical practice and future directions for cardiovascular research.

Semaglutide

In SELECT — a randomized, placebo-controlled trial involving 17,604 patients without type 2 diabetes and with BMI ≥27 and a preexisting cardiovascular condition — high-dose (2.4 mg weekly) semaglutide showed a 20% reduction in a composite end point of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke (hazard ratio, 0.80; 95% confidence interval, 0.72–0.90) during a mean follow-up of 40 months (*N Engl J Med* 2023; 389:2221). Results were significant for each end point component and for heart failure hospitalization. Interestingly, although semaglutide recipients lost an average of 9.4% of their body weight (vs. 0.9% in placebo recipients), semaglutide's clinical benefit surfaced early in the trial, suggesting that the drug's advantage may be partially independent from the weight loss it achieves.

Semaglutide was tested specifically in 529 patients with both obesity (BMI ≥30) and heart failure with preserved ejection fraction (HFpEF) in the STEP-HFpEF randomized, placebo-controlled trial. Recipients of semaglutide (2.4 mg weekly) had statistically significant advantages in weight loss (13.3%, vs. 2.6% for placebo recipients), change from baseline in the Kansas City Cardiomyopathy Questionnaire — Clinical Summary Score (KCCQ-CSS; 16.6 vs. 8.7 points, respectively), and 6-minute walk test distance (*N Engl J Med* 2023; 389:1069).

Josephine Harrington, MD, is an advanced heart failure and transplant cardiology fellow at Duke University. Her clinical and research work is focused on the impact of cardiometabolic disease and obesity on cardiovascular conditions, including heart failure.

Disclosures: Dr. Harrington reports external grant support from the National Institutes of Health.

Tirzepatide

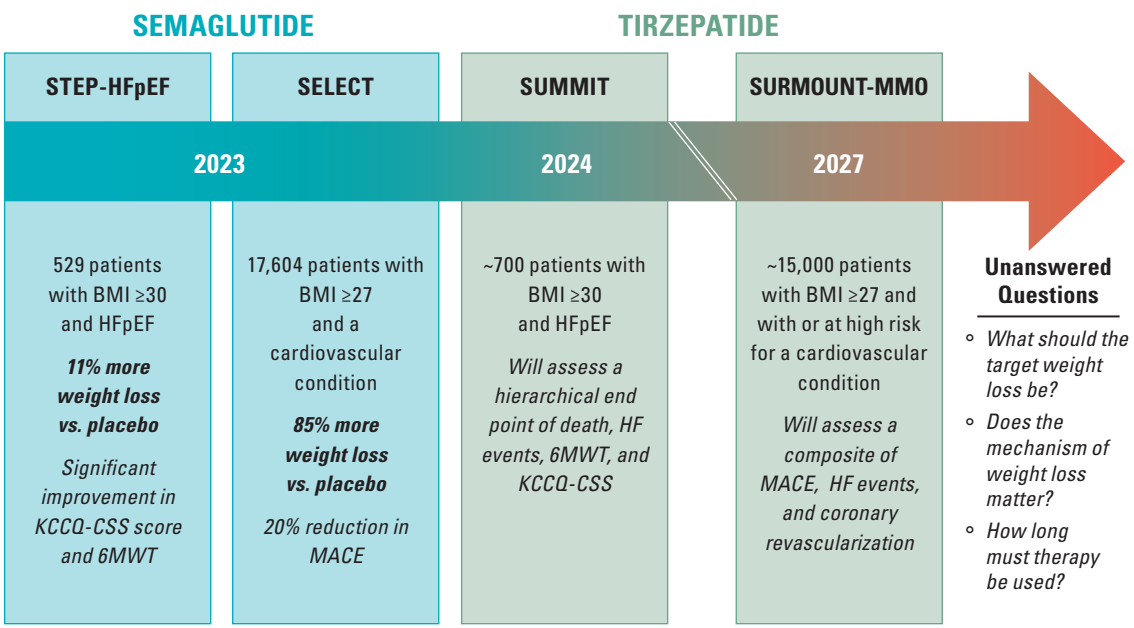
Tirzepatide, like semaglutide, is a GLP-1 receptor agonist but also has further actions as a glucose-dependent insulinotropic polypeptide (GIP) agonist. The drug has shown an up to 21% reduction in body mass, a percentage that rivals that from bariatric surgery (*N Engl J Med* 2022; 387:205). Tirzepatide is now being tested in multiple, ongoing cardiovascular outcomes trials. The SURMOUNT-MMO (NCT05556512) trial will test tirzepatide's effect on a composite of death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and HF in people with a BMI ≥27 without diabetes and with, or at high risk for, a cardiovascular condition. The SUMMIT trial (NCT04847557), involving patients with HFpEF and obesity, will assess the drug's effect on a hierarchical outcome of all-cause mortality, HF events, 6-minute walk test distance, and KCCQ-CSS.

Unanswered Questions

Although data from existing and ongoing trials of incretin-based therapies will help to elucidate their effects on both weight loss and cardiovascular clinical outcomes, important questions remain. It is not yet clear whether the cardiovascular benefit observed with semaglutide is driven by weight loss, other related effects of GLP-1 receptor agonists, or a combination of the two. If some or all of the cardiovascular benefit is related to weight loss, it will be crucial to learn how much weight loss is necessary to deliver benefit and whether additional weight loss beyond such a threshold offers further incremental benefit.

In addition, given the high price of these medications, the optimal duration of therapy remains a critically important matter. Prior studies have

FIGURE. Recent and Upcoming Trials of GLP-1 Receptor Agonists in Cardiovascular Disease



6MWT — 6-minute walk test; BMI — body-mass index; GLP-1: glucagon-like peptide-1; HFpEF — heart failure with preserved ejection fraction; KCCQ-CSS — Kansas City Cardiomyopathy Questionnaire — Clinical Summary Score; MACE — major adverse cardiovascular event

Clinical trials: STEP-HFpEF (**N Engl J Med** 2023; 389:1069); SELECT (**N Engl J Med** 2023; 389:2221); SUMMIT (NCT04847557); SURMOUNT-MMO (NCT05556512)

shown that after approximately 1 year off semaglutide, patients regained two-thirds of weight lost, with reversion of observed cardiometabolic risk factors to higher pre–weight-loss levels (*Diabetes Obes Metab* 2022; 24:1553). It is not known whether withdrawing these therapies after sustained treatment for longer time periods might lead to better long-term weight stability or what effect withdrawal might have on long-term cardiovascular risk.

Until recently, clinicians had few pharmacologic options for treating overweight or obesity. Newly FDA-approved therapies such as semaglutide and tirzepatide are now available to support intentional weight loss for patients with overweight or obesity. Notably, the use of these drugs appears not only to drive weight loss but also to directly reduce the risk for cardiovascular events in patients with established cardiac conditions. Although future work is needed to elucidate the best way to reduce the cardiovascular risk of overweight and obesity, we may finally have the chance to tip the scales in patients' favor.

Topic Update

Cardiovascular-Kidney-Metabolic Syndrome: A Clinically Focused Introduction

Chiadi E. Ndumele, MD, PhD, FAHA, and Janani Rangaswami, MD, FACP, FAHA

The American Heart Association (AHA) recently defined cardiovascular-kidney-metabolic (CKM) syndrome as a health disorder reflecting interrelationships among metabolic risk factors, such as obesity and diabetes, chronic kidney disease, and the cardiovascular system (*Circulation* 2023; 148:1606). CKM syndrome results in multiorgan dysfunction with a high burden of cardiovascular disease (CVD), which leads to premature mortality. The individual components of CKM syndrome are inherently interconnected, so a confluence of them (e.g., diabetes plus chronic kidney disease) is common and synergistically increases mortality risk (*J Am Soc Nephrol* 2013; 24:302).

People affected by CKM syndrome, as the AHA defines it, include those at risk for CVD because of metabolic risk factors, chronic kidney disease, or both, as well as people with existing CVD for whom the presence of metabolic risk factors or chronic kidney disease should influence management. Social determinants of health (SDOHs) — the social context in which people live, eat, work, and play — strongly influence the likelihood of CKM syndrome and its related complications (*National Health Statistics Reports*; June 14, 2021; Number 158). The consequently higher burden of CKM syndrome among people with adverse SDOHs is a key contributor to health disparities. Furthermore, the need for multiple subspecialists and primary care clinicians to comanage CKM syndrome often leads to fragmented care for patients, with resulting suboptimal clinical management and outcomes.

Guidance for Managing Patients with CKM Syndrome

Clinicians caring for patients with CKM syndrome have at their disposal some practical guidance.

STAGING

Most CKM syndrome originates from excess and/or dysfunctional adipose tissue, leading to the development of metabolic risk factors, chronic kidney disease, or both — and subsequent subclinical and clinical CVD (*Circulation* 2023; 148:1636). The AHA staging construct for CKM syndrome therefore reflects its progressive pathophysiology and corresponding graded increase in CVD risk (Figure). Stage 1 is defined by the presence of overweight/obesity, abdominal obesity, or impaired glucose tolerance. Excess and dysfunctional adiposity are markedly under addressed in clinical practice, and the AHA guidance highlights a toolkit from the STOP Obesity Alliance that facilitates nonjudgmental, effective approaches to weight-loss discussions (*Obesity* 2021; 29:821). The staging system also emphasizes interdisciplinary weight-management

Chiadi E. Ndumele, MD, PhD, FAHA, is Associate Professor of Medicine and Epidemiology and Director of Obesity and Cardiometabolic Research in the Division of Cardiology at Johns Hopkins University. He is a preventive cardiologist whose work focuses on defining risk pathways related to cardiometabolic disease and developing related preventive strategies. Dr. Ndumele is Chair of the American Heart Association's Presidential Advisory and Scientific Statement on Cardiovascular-Kidney-Metabolic Health. **Disclosures:** Dr. Ndumele reports external grant support from the National Institutes of Health and the AHA.

Janani Rangaswami, MD, FACP, FAHA, is Professor of Medicine at the George Washington University School of Medicine and Chief of Nephrology at the Veterans Affairs Medical Center in Washington, D.C. She is a nephrologist who studies cardiorenal syndrome, with emphasis on implementation strategies for evidence-based therapies in patients with cardiovascular disease and kidney disease. She is Chair of the American Heart Association's Council on the Kidney in Cardiovascular Disease and Vice Chair of the AHA's Presidential Advisory and Scientific Statement on Cardiovascular-Kidney-Metabolic Health. **Disclosures:** Dr. Rangaswami reports fees or compensation from Boehringer Ingelheim/Lilly, Bayer, and Edwards Lifesciences.

teams for helping patients navigate lifestyle, pharmacologic, and surgical weight-loss approaches, which can prevent progression and even promote regression along CKM stages.

UNRECOGNIZED AND UNTREATED RISK

In CKM syndrome, unrecognized risk factors are common and are especially prevalent in people with adverse SDOHs. Indeed, more than 90% of U.S. adults with chronic kidney disease are unaware of it (*Am J Prev Med* 2017; 53:300). The use of a CKM staging construct, with accompanying recommended screening strategies, is intended to promote systematic, more equitable identification of CKM components in the population to support timely implementation of preventive strategies.

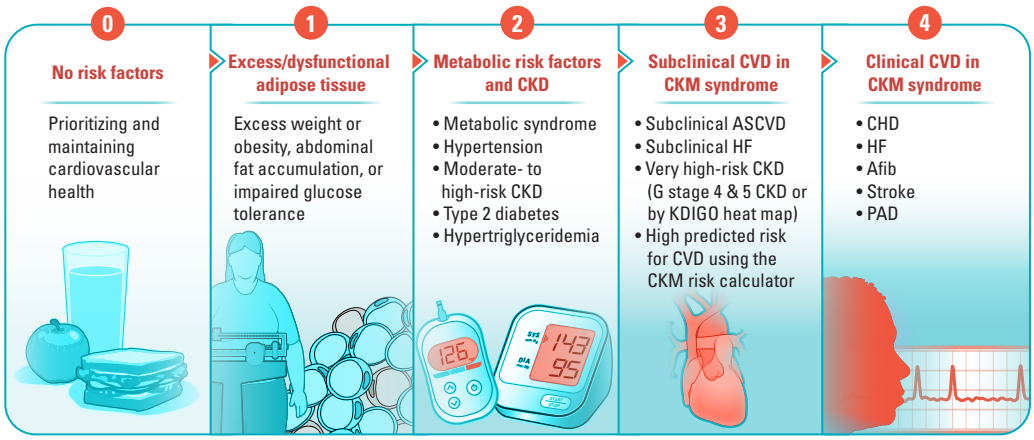
RISK-PREDICTION UPDATE

The recognition of CKM syndrome necessitated important updates to the CVD risk-prediction approach in the pooled cohort equation (PCE; *Circulation* 2014; 129:S49). A new risk-prediction tool, called PREVENT, now includes measures of chronic kidney disease, glycemic control, and a place-based measure of SDOH (*Circulation* 2023; 148:1982). Given that CVD often develops earlier among patients with CKM syndrome, the PREVENT model begins predicting risk at age 30 years, in contrast with age 40 years in the PCE model. In addition, while the PCE focused on risk for atherosclerotic CVD (ASCVD), PREVENT predicts incident heart failure (HF), incident ASCVD, and total CVD (HF plus ASCVD) — reflecting additional adverse outcomes relevant to the CKM syndrome population. PREVENT assesses both 10-year and 30-year risk for CVD events; the latter is particularly important for communicating risk to younger adults with risk factors who may have low short-term but elevated long-term CVD risk.

AVAILABILITY OF THERAPIES

An increasing array of therapies favorably affect metabolic risk factors, chronic kidney disease, or both and also improve cardiovascular outcomes. Recent large randomized, controlled trials have established the multisystem clinical benefits of sodium–glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and the nonsteroidal mineralocorticoid receptor agonist finerenone (*Circulation* 2019; 139:2022; and *Eur Heart J* 2022; 43:474). AHA guidance on CKM syndrome provides a framework for how to use these increasingly powerful therapies in clinical populations, with an emphasis on aligning the nature and intensity of the interventions, including

FIGURE. Staging of CKM Syndrome



Afib — atrial fibrillation; ASCVD — atherosclerotic cardiovascular disease; CHD — coronary heart disease; CKD — chronic kidney disease; CKM — cardiovascular-kidney-metabolic; CVD — cardiovascular disease; HF — heart failure; KDIGO — Kidney Disease: Improving Global Outcomes; PAD — peripheral arterial disease

combination therapies, with absolute predicted CVD risk, CKM stage, and individual risk profiles.

How the CKM Syndrome Paradigm Influences Clinical Care

The evolving approach to CKM syndrome will change clinical practice in several ways. The use of a CKM staging construct for both youth and adults will facilitate earlier detection of CKM factors and an enhanced focus on preventing CVD and kidney failure. Categorizing largely asymptomatic individuals by CKM stage requires a systematic approach, with the frequency and intensity of screening for CKM factors tied to CKM stage. Some screening tests are indicated for specific subpopulations. For example, testing for urine albumin-to-creatinine ratio to fully characterize chronic kidney disease–related risk is advised for people with CKM stage 2 or higher. As a complement to CKM staging, use of the new PREVENT model is emphasized for short- and long-term risk assessments for total CVD and for CVD subtypes. This prediction tool may inform future updates of clinical guidelines.

A focus on holistic, patient-centered care will also address multifactorial risk related to metabolic, kidney, and cardiovascular disease (Table). Guidance for how to use novel cardioprotective therapies includes a comorbidity-based approach to selecting SGLT2 inhibitors, GLP-1 receptor agonists, or both in patients with diabetes. Given the key influence of SDOHs on CKM syndrome, systematically identifying adverse SDOHs is a core part of the clinical care model. Furthermore, integrating community health workers, care navigators, and social workers into the care team to help mitigate and address adverse SDOHs is fundamental to providing optimal care for patients with CKM syndrome. Finally, the comprehensive clinical approach to CKM syndrome emphasizes interdisciplinary coordination among primary care providers, subspecialists (cardiologists, nephrologists, endocrinologists), nurses, pharmacists, and other members of the care team.

The CKM syndrome construct has the potential to enhance risk prediction, prevention, and management for the growing number of people with elevated risk for adverse outcomes from combinations of metabolic risk factors, chronic kidney disease, and CVD. This new paradigm is critical for addressing the premature morbidity and mortality that are strongly linked to the presence of CKM syndrome.

Table. Multifactorial Challenges for Patients with Cardiovascular-Kidney-Metabolic (CKM) Syndrome

CKM Component	Features
Cardiovascular disease	• *Subclinical*: myocardial dysfunction, coronary atherosclerosis • *Clinical*: coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral arterial disease
Chronic kidney disease	• Estimated glomerular filtration rate • Urine albumin-to-creatinine ratio
Metabolic risk factors	• Overweight/obesity • Diabetes • Hypertension • Dyslipidemia
Social determinants of health	• Sociodemographic factors • Food insecurity • Housing instability • Financial strain • Limited access to health care
Fragmented care	• Gaps in care • Conflicting guidance from different providers • Difficulties with care navigation

Topic Update

Weighing Adverse Pregnancy Outcomes and Future Cardiovascular Risk

Rachel M. Bond, MD, FACC

Cardiovascular disease (CVD) remains the leading cause of death in the United States, regardless of sex, gender, and race/ethnicity. It's responsible for one in five premature deaths in people ages 25 to 64 years, according to the CDC, and 12% of total U.S. health care expenditures are for CVD (*Circulation* 2022; 8:e153). Progress in improving CVD-related mortality has been notably slow in people younger than 55 years, particularly women aged 25 to 54 (*Circulation* 2015; 132:997). In the United States and globally, CVD in women is often understudied, underdiagnosed, and undertreated, exacerbated by women's underrepresentation in clinical trials (*Lancet* 2021; 397:P2385). With one in four women still dying from CVD, we clearly do not do enough. Still apt is the term "bikini medicine," reflecting how women are viewed as "little men" with respect to health conditions that don't pertain to breasts or reproductive organs, particularly for women of reproductive age (<55 years).

For example, the pooled cohort equation for risk stratification does not include female-specific cardiometabolic risk factors, such as adverse pregnancy outcomes (APOs; *Circulation* 2011; 123:1243) and may underestimate risk (*J Am Coll Cardiol* 2018; 71:e127). Although cholesterol treatment guidelines incorporate APOs as risk-enhancing factors to guide decisions about preventive interventions (*Circulation* 2019; 139:e1082), screening for them is still not routine. Screening of APOs when women present for care as they get older is inadequate because it overlaps with existing inclusion of conventional, often age-associated risk factors in standard risk models (*J Am Coll Cardiol* 2020; 75:2602), thereby limiting any potentially enhanced predictive value of those models.

CVD prevention in women needs an updated approach, one that includes standard screening for APOs as early as possible in the lives of reproductive-age women, preferably before conventional risk factors develop. The goal would be to facilitate the use of aggressive strategies for preventing or delaying early-onset cardiometabolic disease by lessening the impact of more conventional risk factors as women age, ultimately improving their clinical outcomes.

APOs: Cardiometabolic Risk That Persists Far Beyond Pregnancy

Adverse pregnancy outcomes occur at crucial times in a woman's life course, when primary- and secondary-prevention strategies can alter the potential cardiometabolic disease trajectory and long-term health outcomes. One or more APOs affect roughly 20% of pregnancies (*J Am Heart Assoc* 2020; 9:e015569), substantially contributing to the overall burden of both maternal and fetal health.

Indeed, APOs — hypertensive disorders of pregnancy, including chronic hypertension (cHTN), preeclampsia (with severe features), eclampsia, gestational hypertension, and hemolysis, elevated liver

Rachel M. Bond, MD, FACC, is a board-certified attending cardiologist in Arizona whose clinical interests include heart health prevention and maternal health. She is System Director of the Women's Heart Health Program at Dignity Health; Assistant Director of Diversity, Equity, and Inclusion at Dignity Health East Valley Internal Residency Program; and Assistant Professor of Internal Medicine at Creighton University School of Medicine. **Disclosures:** Dr. Bond has nothing to disclose.

enzymes, low platelet count (HELLP) syndrome; gestational diabetes; placental abruption; fetal growth restriction; pregnancy loss in the form of stillbirth or miscarriage; premature labor — have a strong association with future CVD risk. That's not surprising, as APOs are interrelated disorders secondary to placental dysfunction and vascular abnormalities such as endothelial dysfunction, inflammation, and vasospasm (*J Am Coll Cardiol* 2019; 73:2106).

Women who experience APOs such as preeclampsia, often the leading cause of severe maternal morbidity (SMM) and mortality, are twice as likely to develop cardiometabolic disease and die of CVD (*Clin Obstet Gynecol* 2022; 65:632). These same women may also face a fourfold increase in the likelihood of transitioning to cHTN. Therefore, APO-related disease states and their long-term consequences must be viewed in direct relation to what we already know about initially preclinical — but ultimately progressive — manifestations of plaque development, cardiometabolic risk, and ischemic heart disease. For a visual frame of reference about this known progression, see Figure 3 in *J Am Coll Cardiol* 2009; 54:1561 (freely available at ncbi.nlm.nih.gov/pmc/articles/PMC2789479/figure/F3).

"CVD prevention in women needs an updated approach — one that includes standard screening for [adverse pregnancy outcomes] as early as possible."
— Rachel M. Bond, MD, FACC

Most alarming is that although APO-related disease states largely appear to resolve postpartum, affected patients remain at risk for future cardiometabolic and cardiovascular disease, even beyond 20 years after the inciting incident (*J Womens Health* 2021; 30:285). This risk may extend to their offspring, who are at a greater risk for cHTN, diabetes, and CVD (*J Clin Med* 2021; 10:3154), a generational impact that underscores the urgency of screening for and managing APOs.

The highest prevalence of APOs is among people who identify as American Indian, Asian, Hispanic, Pacific Islander, and Black (*JAMA* 2022; 327:421), and Black women are two to three times more likely than white women to experience SMM and mortality even after adjusting for sociodemographic factors (*Circ Cardiovasc Qual Outcomes* 2021; 14:e007643). Such data highlight how the greatest determinants of health are structural and social (*J Am Coll Cardiol* 2021; 78:1919), including cumulative psychosocial stress (*Circulation* 2022; 145:507), emphasizing the need for a more holistic view of health and health care.

Toward an Approach to Screening for and Managing APOs

Pregnancy, sometimes called "nature's cardiac stress test," may constitute a risk exposure during a critical window in a woman's health. A life-course approach to APOs views them as risk exposures with an additive or modifying effect on pregnancy and long-term health outcomes (*Curr Cardiovasc Risk Rep* 2022; 16:171).

To effectively integrate APO screening into CVD risk assessment, it must occur within three months postpartum. A summary of updated recommendations for primary prevention of CVD in women (*J Am Coll Cardiol* 2020; 75:2602) specifically advises conducting a detailed medical history, a thorough physical examination, and laboratory testing (including lipid profile, diabetes screening, and urine protein-to-creatinine ratio assessment), thereby allowing for early identification of potential cardiovascular risks — before plaque develops and traditional CVD risk factors are evident. Early CVD risk assessment that includes APO screening would lay the groundwork for proactively initiating tailored interventions to mitigate risks effectively — by referring women of reproductive age with APOs to primary care clinicians, cardiologists, or both for long-term risk-reduction strategies. Maternal complications of APOs extend beyond the gestational period; therefore, obtaining a

detailed obstetric history in all age groups, including women of reproductive age before the onset of conventional risk factors, would aid in identifying maternal and fetal cardiometabolic risk.

Recognizing the intricate interplay between APOs and future CVD risk is imperative for advancing women's health. The global burden of CVD in women demands a paradigm shift from the aforementioned male-derivative "bikini" approach to a more inclusive, holistic model that considers the complex web of determinants of health. Proactively screening for and managing APOs, particularly in women of reproductive age before conventional risk factors develop, could significantly affect risk stratification and contribute to better outcomes for women for generations to come. It's time to embrace a more comprehensive, equitable approach to health care that encompasses the entire life course, addressing not only current challenges but also preventing future health disparities.

NEJM Research Summary

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Grinspoon SK et al. DOI: 10.1056/NEJMoa2304146

CLINICAL PROBLEM

In persons with HIV infection, the risk of atherosclerotic cardiovascular disease is twice that in the general population. Randomized studies of primary prevention strategies in this population are needed.

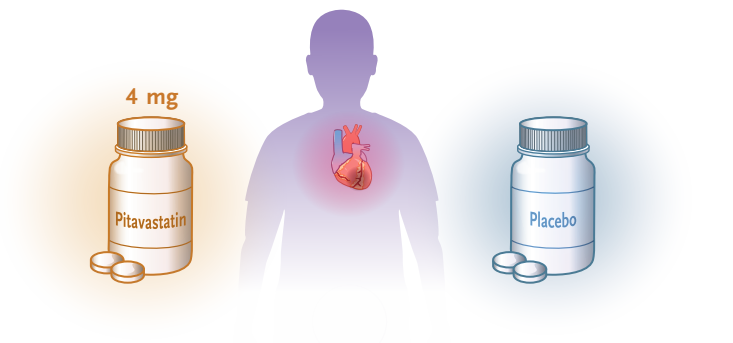
CLINICAL TRIAL

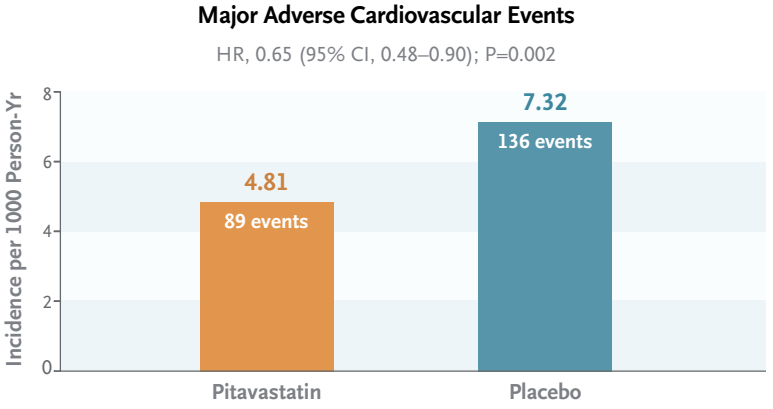
Design: A phase 3, multinational, randomized, placebo-controlled trial assessed the efficacy and safety of pitavastatin for the prevention of cardiovascular events in persons with HIV infection and low-to-moderate risk of atherosclerotic cardiovascular disease.

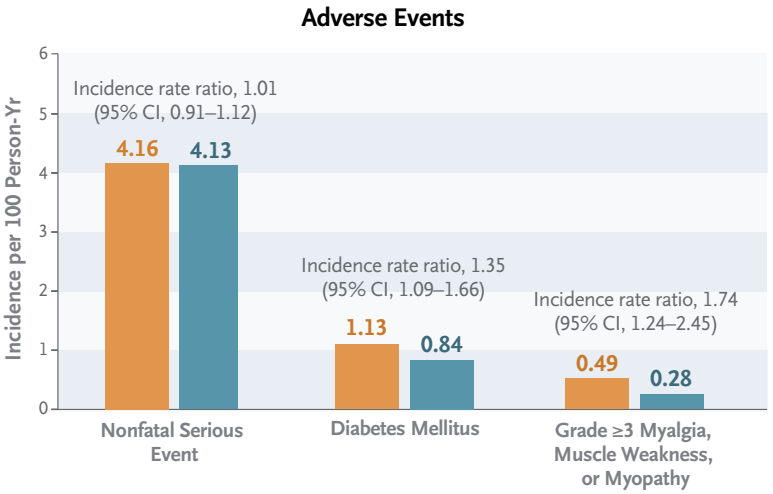
Intervention: 7769 participants between the ages of 40 and 75 years (median screening LDL cholesterol, 108 mg/dl) receiving stable antiretroviral therapy were assigned to receive oral pitavastatin calcium (4 mg) (3888 participants) or placebo (3881 participants) daily. The primary outcome was the occurrence of a major adverse cardiovascular event — cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined cause, as measured in a time-to-event analysis.

RESULTS

Efficacy: During a median follow-up of 5.1 years, the incidence of major adverse cardiovascular events was







significantly lower in the pitavastatin group than in the placebo group.

Safety: The incidence of nonfatal serious adverse events was similar in the two groups. Participants in the pitavastatin group were more likely than those in the placebo group to have newly diagnosed diabetes mellitus and grade ≥3 myalgia, muscle weakness, or myopathy.

LIMITATIONS AND REMAINING QUESTIONS

- Although other statins that do not interact with HIV medications may have similar protective effects, the results reported are specific to pitavastatin.
- Other strategies that lower LDL cholesterol may be useful in this population and need to be compared with statin therapy with respect to efficacy, safety, and cost.

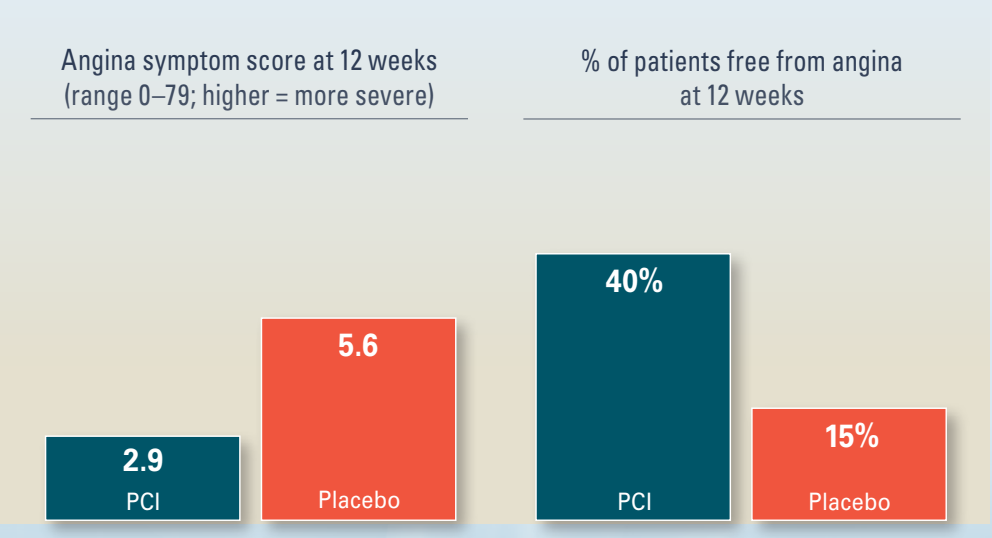
CONCLUSIONS

In persons with HIV infection receiving stable antiretroviral therapy and at low-to-moderate cardiovascular risk, daily treatment with pitavastatin resulted in a significantly lower risk of major adverse cardiovascular events than placebo over approximately 5 years of follow-up.

Visual Summary

Is Percutaneous Coronary Intervention (PCI) Just an Expensive Placebo?

301 patients (mean age, 64 years; 21% women; 80% single-vessel disease) with stable angina and documented coronary ischemia were randomized to undergo PCI or a sham PCI procedure (placebo).



Comment

This is the first trial to demonstrate definitively that for patients with stable angina and documented myocardial ischemia, PCI improves angina (and related symptoms) better than placebo. Nonetheless, only 40% of patients were rendered angina-free after PCI — emphasizing the challenge of identifying patients in whom epicardial coronary disease is the primary cause of angina. These findings reinforce current guidelines and practice, in which PCI for stable coronary artery disease is recommended primarily for symptom relief.

David J. Cohen, MD, MSc, reviewing Rajkumar CA et al. *N Engl J Med* 2023 Nov 11

Dr. Cohen is Director of Clinical and Outcomes Research at the Cardiovascular Research Foundation (New York, NY) and Director of Academic Affairs at St. Francis Hospital (Roslyn, NY). He reports consultant and advisory board roles with Medtronic, Edwards Lifesciences, Abbott Vascular, Boston Scientific, Svelte, Inc., Corvia Medical, Impulse Dynamics, AngioInsight, and HeartBeam; editorial board roles with *American Heart Journal*, *EuroIntervention*, and *JSCAI*; leadership positions with the Society of Thoracic Surgeons/American College of Cardiology TVT Registry (Co-Chair, Risk Model Development Committee) and Cardiovascular Research Foundation (Co-Director, TCT Annual Meeting); and grant or research support from Edwards Lifesciences, Abbott Vascular, Corvia Medical, National Heart, Lung, and Blood Institute, Phillips, Inc., Svelte, Inc., Brain-Q, St. Paul's Hospital, V-Wave, Inc., Saranas, Inc., I-Rhythm, Inc., Zoll Medical, CathWorks, and ANCORA.

Guideline Watch

Updated Guideline for Atrial Fibrillation Management

Major changes include greater support for early rhythm control and consideration of ablation as first-line therapy.

SPONSORING ORGANIZATIONS

The American Heart Association (AHA), American College of Cardiology (ACC), American College of Clinical Pharmacy (ACCP), and Heart Rhythm Society (HRS)

BACKGROUND AND OBJECTIVE

A joint AHA/ACC/ACCP/HRS committee has conducted a comprehensive update of the clinical guidelines for management of atrial fibrillation (AF) based on a systematic review of evidence published through November 2022. Apart from a limited update of the AF guidelines in 2019, the last comprehensive update was published in 2014, and management of AF has changed considerably since its release.

KEY RECOMMENDATIONS

- Early rhythm control is recommended rather than trying a rate-control strategy. Rhythm control could include antiarrhythmic drugs or ablation.
- Performing ablation without first trying antiarrhythmic drugs is now strongly recommended (Class I).
- Catheter ablation for patients with heart failure with reduced ejection fraction also received an upgrade to a Class I indication.
- Use of left atrial appendage occlusion devices is now more broadly recommended. It was upgraded to a Class 2A recommendation in those with a contraindication to anticoagulation and to a Class 2B recommendation in those who wish to avoid anticoagulation.
- In patients with device-detected AF, a holistic approach to anticoagulation should be taken. In particular, AF lasting ≥24 hours should be treated as clinical AF, and for AF lasting <24 hours, the decision on anticoagulation would depend on total density of AF and the CHA_2DS_2-VASc score.
- Similar to heart failure, AF is now acknowledged to be a progressive disease, classification of which is reflected by stages along the continuum of progression: Stage I denotes risk for AF because of risk factors; Stage II is considered pre-AF because of structural or electrical findings; Stage III is AF that begins as paroxysmal and transitions to Stage IV, which is permanent.
- Risk-factor modification and prevention are emphasized more than in the previous guidelines.

(continued on page 16)

(continued from page 15)

Comment

We were due for a comprehensive AF update given the increasing data we have about AF, not only regarding ablation but also early rhythm-control strategies and modification of risk factors. This guideline will change the way we care for this patient population.

Mark S. Link, MD

Dr. Link is Professor of Medicine and Director of Cardiac Electrophysiology at UT Southwestern Medical Center in Dallas. He serves on the editorial boards of *Circulation* and UpToDate.

Joglar JA et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. **Circulation** 2023 Nov 30; [e-pub]. (https://doi.org/10.1161/CIR.0000000000001193)

Guideline Watch

Consensus Statement on the Care of Heart Failure with Preserved LVEF

This document is the first to provide clinicians with guidance on caring for this population.

SPONSORING ORGANIZATION

American College of Cardiology

BACKGROUND AND OBJECTIVE

After decades of disappointing results from trials of treatments for heart failure (HF) with preserved ejection fraction (HFpEF), evidence has emerged recently to guide diagnostic testing and treatment. This consensus document provides guidance for the care of this clinically challenging population.

KEY POINTS

- The causes of dyspnea in individuals with preserved left ventricular ejection fraction (LVEF) are numerous; in addition to heart failure, noncardiac causes (e.g., lung disease) must be considered. The Universal Definition of HF requires both symptoms or signs of HF and either elevated natriuretic peptides or objective evidence of cardiogenic pulmonary or systemic congestion.
- Peripheral edema is nonspecific and can be related to decreased capillary oncotic pressure (e.g., cirrhosis, nephrosis) and noncardiac causes of increased capillary hydrostatic pressure (e.g., renal failure, portal hypertension).
- Clinical risk scores — including the H2FPEF and the HFA-PEFF scores — can refine the estimate of the likelihood of HFpEF. The former depends upon readily available clinical data; the latter incorporates infrequently used functional testing.
- The recommended diagnostic approach in patients with dyspnea and/or edema is: a) to assess for noncardiac sources; b) apply the Universal Definition of HF; c) assess for mimics of HF (both noncardiac and cardiac), and; d) assess the likelihood of HFpEF based upon the H2FPEF score. Notably, the document considers specific causes such as myopathic processes, valvular, or pericardial disease as HFpEF mimics.
- The cornerstone of pharmacologic management of HFpEF is sodium–glucose cotransporter 2 (SGLT2) inhibitors, based upon randomized trials demonstrating clear and meaningful benefits of this class (*N Engl J Med* 2021; 385:1451; *N Engl J Med* 2022; 387:1089). Loop diuretics are used to manage volume overload. Other therapies to consider include mineralocorticoid receptor antagonists (*N Engl J Med* 2014; 370:1383), angiotensin receptor–neprilysin inhibitors (ARNIs; *N Engl J Med* 2019; 381:1609), or angiotensin-receptor blockers in those who cannot tolerate ARNIs, although the evidence for these treatments is not as strong as for SGLT2 inhibitors.
- Nonpharmacological management approaches include weight loss, regular exercise, and — in higher-risk patients — the consideration of implantable pulmonary artery pressure monitoring.

(continued on page 18)

(continued from page 17)

- Comorbidities are common and can interact adversely with HFpEF. Those requiring particular attention include atrial fibrillation, hypertension, coronary artery disease, diabetes, chronic kidney disease, sleep apnea, and obesity.
- Because of the complexity of the population with HFpEF, collaborative care is critical. The document provides guidance for referral to cardiovascular or advanced heart failure specialists.
- The role of palliative care should be considered in many cases, although it is important to dispel any misunderstanding that palliative care is synonymous with hospice.

Comment

This document consolidates the evidence to diagnose and treat HFpEF into a digestible format. In addition to incorporating promising recent developments, it also highlights the substantial need for further research to optimize care for this population.

Frederick A. Masoudi, MD, MSPH, MACC, FAHA

Dr. Masoudi is Chief Science Officer and Vice President of Research and Analytics at Ascension Health and a Clinical Professor of Medicine at the University of Colorado Anschutz Medical Campus. He reports consultant or advisory board roles with Bristol Myers Squibb; grant or research support from the National Heart, Lung, and Blood Institute; editorial board roles with UpToDate and the American College of Cardiology Self-Assessment Program; and a leadership position with the American College of Cardiology (Chief Scientific Advisor, NCDR; Chair, Innovations Development Work Group).

Kittleson MM et al. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: A report of the American College of Cardiology Solution Set Oversight Committee. **J Am Coll Cardiol** 2023 May; 81:1835. (https://doi.org/10.1016/j.jacc.2023.03.393)

NEJM Journal Watch Summary

Torsemide vs. Furosemide After Hospitalization for Heart Failure

Results of a large clinical trial counter previous findings of benefit with torsemide.

Several small studies have suggested that the loop diuretic torsemide produces better outcomes than the more commonly used furosemide in patients with heart failure. However, the two agents have never been directly compared in a major clinical trial despite potentially important differences in their bioavailability and other properties. Now, investigators for the TRANSFORM-HF trial (NCT03296813) report similar 1-year outcomes with use of torsemide versus furosemide in this setting.

In this open-label, pragmatic, multicenter trial, 2859 participants hospitalized for heart failure were randomized to receive torsemide or furosemide. Recruited patients had treatment plans indicating anticipated long-term use of a loop diuretic. The primary outcome was all-cause mortality in a time-to-event analysis. A key secondary outcome was all-cause mortality or all-cause hospitalization assessed over 12 months. Results included the following:

- 12-month death rates of 26.1% in the torsemide group and 26.2% in the furosemide group
- Death or hospitalization in 47.3% and 49.3%, respectively
- A 7% crossover rate from torsemide to furosemide and a 3.8% crossover rate the other way

The authors noted that loss to follow-up and participant crossover and nonadherence were key limitations.

Comment

This study provides evidence that there is little to choose between furosemide and torsemide. As a pragmatic trial, it had broad entry criteria and included people with a range of ejection fractions, which may be good for generalizability, although an editorialist notes challenges in assessing whether there were important differences in subgroups. Also, the trial enrolled fewer patients than planned, reducing the power of subgroup analyses. Nevertheless, it is a solid counterweight to the small and observational studies that noted an immense benefit with torsemide.

Harlan M. Krumholz, MD, SM

Dr. Krumholz is the Harold H. Hines, Jr., Professor of Medicine in the Section of Cardiovascular Medicine at the Yale University School of Medicine, New Haven, Connecticut. He serves as Director of the Yale–New Haven Hospital Center for Outcomes Research and Evaluation (CORE). He reports consultant or advisory board roles for United Healthcare, Element Science, Aetna, Reality Labs, Tesseract, and Martin/Baughman Law Firm. He reports equity in Hugo Health and Refactor Health. He reports grant or research support from the Agency for Healthcare Research and Quality, Johnson & Johnson (Janssen), SI-BONE Inc., National Institute of Biomedical Imaging and Engineering, National Heart, Lung, and Blood Institute, Centers for Disease Control and Prevention, National Cancer Institute, State of Connecticut Department of Public Health, Foundation for a Smoke-Free World, and the American Heart Association.

Mentz RJ et al. Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: The TRANSFORM-HF randomized clinical trial. **JAMA** 2023 Jan 17; 329:214. (https://doi.org/10.1001/jama.2022.23924)

Kittleson MM. TRANSFORM-HF — Can we close the loop on diuretics in heart failure? **JAMA** 2023 Jan 17; 329:211. (https://doi.org/10.1001/jama.2022.21692)

NEJM Journal Watch Summary

A New Hope for Treatment of Chronic Limb-Threatening Ischemia

For patients with chronic limb-threatening ischemia due to infrapopliteal peripheral artery disease, a novel drug-eluting resorbable scaffold provided benefit over conventional angioplasty.

Patients with chronic limb-threatening ischemia (CLTI) have high rates of both limb loss and mortality, driven in part by low rates of sustained patency of both surgical and catheter-based revascularization for infrapopliteal peripheral artery disease (PAD). Although metallic drug-eluting coronary stents have shown benefit for these patients, there are concerns that the permanent scaffold may limit future treatment options. Resorbable vascular scaffolds have the potential to overcome the limitations of metallic drug-eluting stents by providing temporary scaffolding to treat elastic recoil and dissection after balloon angioplasty, allowing sustained local drug elution to limit neointimal proliferation and providing gradual resorption to facilitate future treatment.

In an industry-sponsored trial, investigators studied the efficacy and safety of a novel, investigational everolimus-eluting resorbable vascular scaffold device among 261 patients with CLTI and 1 or 2 stenotic or occlusive infrapopliteal lesions. Patients were randomized in a 2:1 ratio to undergo revascularization with the resorbable vascular scaffold or balloon angioplasty alone. At 1-year follow-up, the primary endpoint — freedom from above-ankle amputation of the target limb, target vessel occlusion, clinically driven repeat revascularization of the target lesion, and restenosis of the target lesion — was observed in a significantly greater proportion of the scaffold group compared with the angioplasty group (74% vs. 44%; absolute risk difference, 30%). Both treatments were safe; the rate of periprocedural death or major adverse limb events at 6 months was low.

Comment

Given the poor outcomes of current therapies for patients with CLTI and infrapopliteal PAD, any device that leads to improved outcomes would be a welcome addition to our armamentarium. Long-term follow-up of these patients will be necessary to understand whether these 1-year benefits are sustained as the vascular scaffold resorbs (expected by 3-year follow-up), and larger studies will be required to see if this approach reduces major adverse limb events — especially amputation.

David J. Cohen, MD, MSc

Dr. Cohen is Director of Clinical and Outcomes Research at the Cardiovascular Research Foundation (New York, NY) and Director of Academic Affairs at St. Francis Hospital (Roslyn, NY). He reports consultant or advisory board roles with Medtronic, Edwards Lifesciences, Abbott Vascular, Boston Scientific, Svelte Inc., Corvia Medical, United Healthcare, Impulse Dynamics, MyoKardia, AngioInsight, McKinsey and Co., Richner Consultants, Humacyte, Prolocor, Gerson Lehrman Group, and Arthroscopy Association of North America. He reports receiving grant or research support from Edwards Lifesciences, Abbott Vascular, Corvia Medical, CSI Inc., National Heart, Lung, and Blood Institute, Phillips Inc., Svelte Inc., BrainQ, St. Paul's Hospital, V-Wave Inc., Saranas Inc., iRhythm Technologies, and Zoll Medical. He reports serving on the editorial boards of *American Heart Journal*, *EuroIntervention*, and *JSCAI*. He reports leadership roles in the following professional societies: Society of Thoracic Surgeons/American College of Cardiology TVT Registry (Co-Chair, Risk Model Development Committee) and Cardiovascular Research Foundation (Co-Director, TCT Annual Meeting).

Varcoe RL et al. Drug-eluting resorbable scaffold versus angioplasty for infrapopliteal artery disease. **N Engl J Med** 2023 Oct 25; [e-pub]. (https://doi.org/10.1056/NEJMoa2305637)

NEJM Journal Watch Summary

The Worldwide Impact of Modifiable Cardiovascular Risk Factors

Quantifying the region- and sex-specific consequences of these risk factors can help to shape policy efforts and patient care.

We know the traditionally identified modifiable cardiovascular risk factors: body-mass index, systolic blood pressure, non–high-density lipoprotein cholesterol level, tobacco smoking, and diabetes. But what are their quantifiable global consequences? Investigators pooled individual-level data from 112 cohort studies in 34 countries and 8 geographic regions to assess the regional and sex-specific prevalence of these risk factors and their worldwide impact (NCT05466825).

The combined studies involved more than 1.5 million participants (mean age, 54 years; 54% women). The incidence of age- and sex-standardized 10-year cardiovascular disease events varied by region (10% in North America, 8% in North Africa and the Middle East, 8% in Eastern Europe and Russia, 5% in Western Europe, and 3% in Asia). The event rates were 4% in women and 8% in men. The five risk factors accounted for 57% of the cardiovascular disease in women and 53% in men. For all five factors combined, the population-attributable fraction was similar across regions (ranging from 50% to 64%), with the highest contribution from systolic blood pressure (29% for women, 22% for men).

Comment

Not surprisingly, this study confirms that these five risk factors cause much harm from cardiovascular disease. The data's novel value is in detailing the risk factors' global and region-specific prevalence and in highlighting the opportunities to focus on improving large numbers of clinical outcomes worldwide.

Harlan M. Krumholz, MD, SM

Dr. Krumholz is the Harold H. Hines, Jr., Professor of Medicine in the Section of Cardiovascular Medicine at the Yale University School of Medicine, New Haven, Connecticut. He serves as Director of the Yale–New Haven Hospital Center for Outcomes Research and Evaluation (CORE). He reports consultant or advisory board roles for United Healthcare, Element Science, Aetna, Reality Labs, Tesseract, and Martin/Baughman Law Firm. He reports equity in Hugo Health and Refactor Health. He reports grant or research support from the Agency for Healthcare Research and Quality, Johnson & Johnson (Janssen), SI-BONE Inc., National Institute of Biomedical Imaging and Engineering, National Heart, Lung, and Blood Institute, Centers for Disease Control and Prevention, National Cancer Institute, State of Connecticut Department of Public Health, Foundation for a Smoke-Free World, and the American Heart Association.

The Global Cardiovascular Risk Consortium. Global impact of modifiable risk factors on cardiovascular disease and mortality. **N Engl J Med** 2023 Aug 26; [e-pub]. (https://doi.org/10.1056/NEJMoa2206916)

NEJM Journal Watch Summary

Optimal Daily Step Count for Cardiovascular Risk Reduction

Based on a meta-analysis, it's lower than the often quoted 10,000 steps.

Walking is a common form of physical activity that many people use to improve cardiovascular health. However, the optimal daily "step count" for cardiovascular disease (CVD) risk reduction is debated. To examine the dose-response association between step count and clinical outcomes, investigators performed a systematic review and meta-analysis of studies that quantified daily step count using objective methods (accelerometers and pedometers).

Data came from 111,309 individuals in 12 studies. Compared with 2000 or fewer steps/day, the researchers found statistically significant risk reductions for all-cause mortality at 2517 steps/day (adjusted hazard ratio, 0.92) and for incident CVD at 2735 steps/day (aHR, 0.89). Additional steps were associated with further risk reductions in a nonlinear fashion, up to a threshold of 8763 steps for reduction in all-cause mortality (aHR, 0.40) and 7126 steps for reduced CVD risk (aHR, 0.49). Increasing from a low to an intermediate cadence was associated with a further 33% decrease in all-cause mortality risk, and a 38% risk reduction from a low to high cadence.

Comment

This study found that taking fewer than 3000 steps/day was associated with statistically significant risk reductions in mortality and incident CVD. Maximal benefits were observed at about 8700 and 7100 steps/day, respectively. These findings suggest that health benefits from walking accrue at much lower step counts than the regularly cited threshold of 10,000 steps/day, which reinforces the message I give to my patients: "just keep moving." Encouraging more daily steps is obviously desirable, but we should also counsel patients not to give up if they cannot reach a particular threshold.

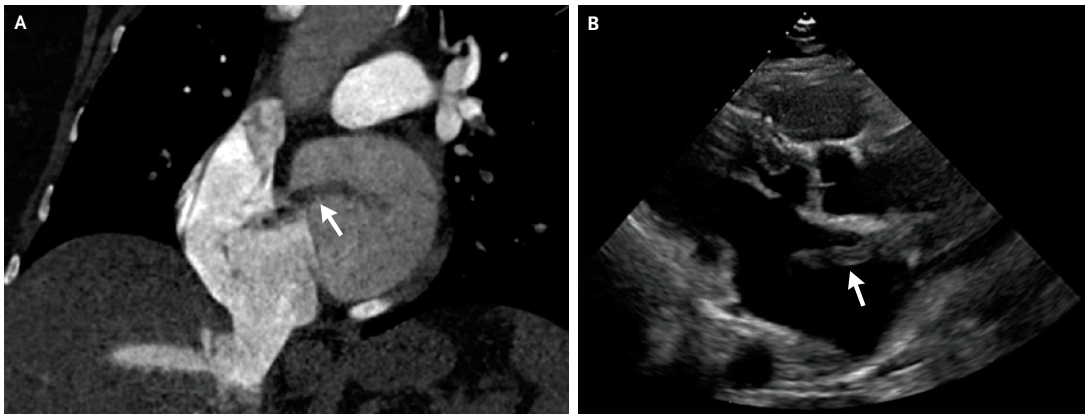
Harlan M. Krumholz, MD, SM

Dr. Krumholz is the Harold H. Hines, Jr., Professor of Medicine in the Section of Cardiovascular Medicine at the Yale University School of Medicine, New Haven, Connecticut. He serves as Director of the Yale–New Haven Hospital Center for Outcomes Research and Evaluation (CORE). He reports consultant or advisory board roles for United Healthcare, Element Science, Aetna, Reality Labs, Tesseract, and Martin/Baughman Law Firm. He reports equity in Hugo Health and Refactor Health. He reports grant or research support from the Agency for Healthcare Research and Quality, Johnson & Johnson (Janssen), SI-BONE Inc., National Institute of Biomedical Imaging and Engineering, National Heart, Lung, and Blood Institute, Centers for Disease Control and Prevention, National Cancer Institute, State of Connecticut Department of Public Health, Foundation for a Smoke-Free World, and the American Heart Association.

Stens NA et al. Relationship of daily step counts to all-cause mortality and cardiovascular events. **J Am Coll Cardiol** 2023 Sep 6; [e-pub]. (https://doi.org/10.1016/j.jacc.2023.07.029)

Images in Clinical Medicine

Thrombus in Transit across a Patent Foramen Ovale



Hypoxemia and shock developed suddenly in a 67-year-old woman with atrial fibrillation who had been admitted to the hospital for management of an acute ischemic stroke. She had stopped taking apixaban 2 days before a colon polypectomy that had been performed 3 days before the current admission. At the current presentation, her heart rate was 118 beats per minute, blood pressure 70/36 mm Hg, and oxygen saturation 72% while she was breathing ambient air. After her condition was stabilized, a computed tomographic pulmonary angiogram was obtained. It showed pulmonary emboli in the main pulmonary arteries, right ventricular dilatation, and a large thrombus in transit through a previously unknown patent foramen ovale (PFO; Panel A, arrow). A subsequent transthoracic echocardiogram showed a thrombus crossing through the PFO into the left atrium (Panel B). Advanced interventional therapies were deemed by a multidisciplinary team to be too high risk. Treatment with heparin was initiated. Four days later, new cerebellar infarcts (thought to be cardioembolic from the thrombus) developed, along with hemorrhagic transformation of the left middle cerebral artery infarct that had been present on admission. Therapeutic anticoagulation was stopped to allow for stabilization of the intracranial hemorrhage. On hospital day 20, therapeutic anticoagulation was restarted, and the patient was discharged to a stroke rehabilitation facility 15 weeks after admission.

Simon Daly, M.R.C.P.I., and Tim Cassidy, F.R.C.P.Edin.

St. Vincent's University Hospital Dublin, Ireland

November 23, 2023; **N Engl J Med** 2023; 389:e45; DOI: 10.1056/NEJMicm2208610