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Clinical Cardiology Update

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- The Role of Artificial Intelligence in Cardiology
- Treating Heart Failure with Preserved Ejection Fraction
- A New Era in Atrial Fibrillation Ablation
- RNA Interference Therapy for Mixed Hyperlipidemia

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FROM the Editor

The field of cardiovascular medicine has recently experienced transformative advances. This acceleration of innovation reflects the broader revolution in health care driven by technological breakthroughs and sophisticated data analytics. These developments have reshaped numerous aspects of practice, from novel therapeutics to enhanced diagnostic capabilities. This edition of *Clinical Cardiology Update* explores several rapidly evolving areas where these advances are already improving patient outcomes, demonstrating how the integration of technology and clinical expertise can generate new possibilities for cardiovascular care.

Atrial fibrillation ablation has evolved over recent decades, becoming more widely used as technological innovations, methodological refinements, and clinical trials have expanded its role in treating this common arrhythmia. In the ongoing search for more effective and safer treatment approaches, pulse field ablation (PFA), which underwent clinical trials comparing it to traditional radiofrequency methods, was first approved by the FDA in late 2023. The technology offers greater tissue selectivity and consistent lesion formation, though practitioners must consider both its higher implementation costs and the potential for coronary artery spasm. The rapid adoption of PFA in U.S. electrophysiology centers suggests that many clinicians view these advantages as outweighing the associated challenges. Dr. Mark S. Link provides his perspective on this emerging technology.

Historically, evidence-based therapy for heart failure with preserved ejection fraction (HFpEF) has been frustratingly and persistently lacking. Recent clinical trials have entirely transformed this once-static field into one of the most exciting areas in cardiology. Evidence has now emerged to support the use of several agents in this patient population, including sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists, both of which originated as therapies for diabetes mellitus. Other trials demonstrated the impact of renin–angiotensin–aldosterone system (RAAS) inhibitors for HFpEF. Drs. Abdelghani El Rafei and Larry A. Allen summarize these developments and their impact on treatment options for the growing population with HFpEF.

The emergence of artificial intelligence (AI) has generated both excitement and concern both inside and outside of the medical field. In cardiovascular medicine, machine learning has been employed for many purposes, including to generate more robust and nuanced risk models to inform care delivery. The more recent emergence of generative AI has the potential to transform care in many ways, bringing with it several challenges that must be addressed. Dr. Ami B. Bhatt reviews the promise and peril of AI for cardiovascular clinicians.

This edition also features additional content highlighting some of the transformational advances in cardiovascular disease, including a Plain Language Summary of an RNA interference therapy for mixed hyperlipidemia; a review of a study of an RNA silencer to treat transthyretin amyloid cardiomyopathy; a summary of a pivotal trial of drug-coated balloons for in-stent restenosis; and the results of two trials of GLP-1 inhibitors for HFpEF. The contents of this issue demonstrate how quickly the field of cardiovascular medicine has evolved and how once futuristic therapies are now becoming a reality.

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

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Topic Update

The Evolving Landscape of Catheter Ablation in Atrial Fibrillation

Mark S. Link, MD

For the past 15 years, radiofrequency and cryothermal energy have been the traditional sources of energy used for catheter ablation in atrial fibrillation (AF); however, we have recently entered a new era. Pulsed field ablation (PFA), in which microsecond-scale high-voltage electric shocks are used to selectively ablate myocardial tissue, has become increasingly popular in AF ablation, with many cardiac electrophysiology (EP) laboratories now using it almost exclusively.

The Evolution of PFA

PFA involves electroporation, in which an electric field is used to increase the permeability of a cell membrane, either to allow the introduction of a foreign substance into the cell temporarily or to permanently kill the cell. The potential of electroporation was first documented in the 18th century when electric shocks applied to the skin were noted to cause red spots and then in the late 19th century when electric fields were used to purify water by killing bacteria.

The first medical application of electroporation emerged in 1987, when researchers used fast electric pulses to create transient pores in cell membranes to permit the entry of cytotoxic agents. Twenty years later, researchers showed that applying such pulses directly to cardiac myocytes in an animal model created permanent pores in the cell membranes, causing those cells to die without damaging other cell types. This finding supported the hypothesis that myocardial cells might be more susceptible to pulsed field energy than other cells, such as those in the pulmonary veins, nervous system, and esophagus, and that PFA might therefore be safer than thermal AF ablation. One concern, however, is coronary spasm, which appears to be a unique adverse consequence of PFA that is particularly troublesome with both tricuspid and mitral flutter ablations (*Circulation* 2022; 146:1808). This risk can be mitigated by pretreatment with nitroglycerin.

Clinical Trials and Real-World Studies of PFA

During the past 2 years, several studies have evaluated the safety and efficacy of PFA in patients with AF. The most notable of these was the ADVENT trial, sponsored by the maker of the Farapulse catheter for PFA (Boston Scientific). Approximately 600 patients with drug-refractory AF were randomized to undergo either PFA or thermal ablation, with the choice of thermal energy determined by site investigators (*N Engl J Med* 2023; 389:1660). At 1 year, the primary efficacy end point (freedom from a composite of procedural failure, documented atrial arrhythmias lasting ≥30 seconds after a 3-month blanking period, antiarrhythmic drug use, cardioversion, or repeat ablation) was met in 73% of patients randomized to PFA and 71% of those randomized to thermal ablation (Figure). Primary safety end points (including acute and chronic device- and procedure-related serious adverse events) occurred in 2.1% and 1.5% of patients, respectively. The authors concluded that PFA was noninferior to thermal ablation. It is important to note that this trial did not show superior efficacy or safety of PFA as had been hoped. However, the numbers were small, and complication rates were low in all treatment groups.

Since the ADVENT trial, two real-world observational studies of PFA have been published. The first was conducted among 707 patients undergoing AF ablation — 208 with PFA, 325 with cryoballoon, and

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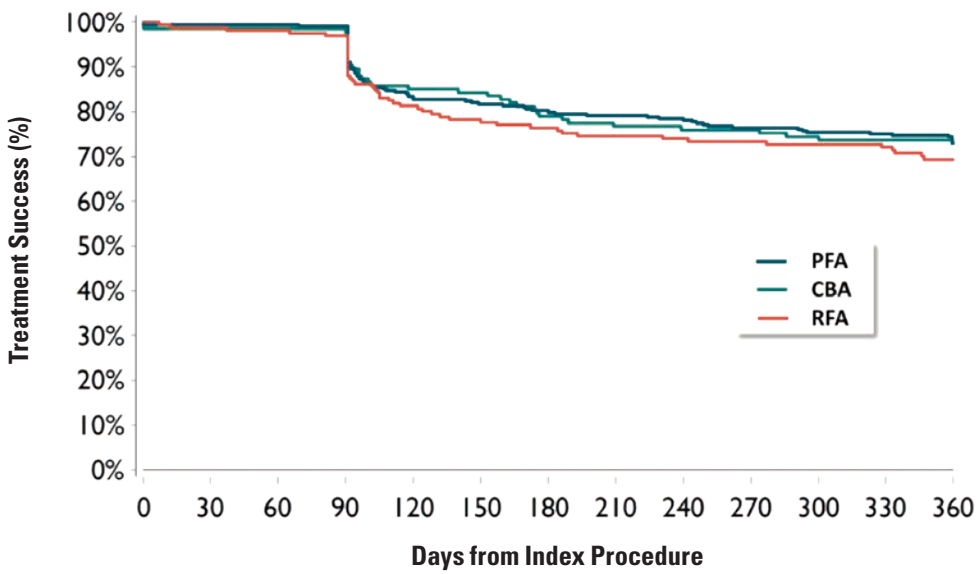
Disclosures: Dr. Link is Deputy Editor of *NEJM Journal Watch Cardiology*, Associate Editor at *Circulation*, and a member of the editorial board of UpToDate.

174 with radiofrequency (*Heart Rhythm* 2024; 21:1537). PFA required significantly less time than the other approaches but more often required general anesthesia and was associated with higher procedural costs. The rate of complications was similar (~1%) in all groups. In the second study, 533 patients with persistent AF underwent ablation — 214 with PFA, 190 with cryoballoon, and 129 with radiofrequency (*Heart Rhythm* 2024; 21:1227). Results were similar to those in the first study: PFA cases were shorter, and acute safety events were similar in all groups. The proportion of patients who experienced at least 1 year of freedom from atrial arrhythmias was 62% with cryoballoon, 55% with PFA, and 48% with radiofrequency.

As of this writing, two FDA-approved PFA systems are available: Farapulse, which uses a catheter that can be configured to a basket or flower shape, and PulseSelect (Medtronic), which uses a catheter shaped like a lasso. The two systems have not been compared head-to-head, nor has PulseSelect been compared with thermal ablation.

FIGURE. Primary Efficacy Outcome of Pulsed Field Ablation (PFA) vs. Radiofrequency Ablation (RFA) or Cryoablation (CBA) in the ADVENT Trial



N at Risk

Rate					
PFA	301	298	238	228	176
	99.3%	99.0%	79.7%	76.4%	73.1%
CBA	132	131	104	100	78
	98.5%	97.8%	79.0%	75.9%	73.6%
RFA	164	161	124	119	72
	98.8%	97.0%	76.4%	73.3%	69.2%

Kaplan–Meier survival curves are shown for freedom from primary efficacy events, a composite of atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia) lasting ≥30 seconds after a 3-month blanking period, procedural failure to isolate the pulmonary veins using only the randomized treatment modality, use of class I or III antiarrhythmic drugs or cardioversion after the blanking period, or amiodarone use or repeat ablation at any time.

My Perspective on PFA

PFA technology has become popular because it is quicker than thermal ablation and possibly safer. Many EP laboratories have exclusively switched to PFA, but I have concerns. The most notable is the potential for coronary vasospasm. In addition, long-term freedom from AF recurrence is not necessarily better with PFA. Ganglionic ablation is predictive of a good outcome but only occurs with cryoballoon and radiofrequency.

Personally, I am a fan of cryoablation and believe that it is as successful and safe as PFA. It is also relatively quick. For straightforward pulmonary vein isolations, the technologies are equivalent, but for posterior wall ablations, PFA is easier and more likely to be successful.

Overall, PFA is here to stay. Its higher cost may impede its potential to be the dominant energy source for all ablations, but its ease of use, safety, and efficacy make it a major game-changer.

Topic Update

Evidence-Based Therapy for Heart Failure with Preserved Ejection Fraction (HFpEF): From Rags to Riches

Abdelghani El Rafei, MD, MS, and Larry A. Allen, MD, MHS

Heart failure with preserved ejection fraction (HFpEF) is the prototypical chronic disease, causing significant morbidity and mortality. One out of every five adults in the United States is affected by HFpEF during their lifetime, and the prognosis is typically poor. The median life expectancy at age 65 is only 4.5 years for a person with HFpEF, compared with 19 years for the average person (*J Card Fail* 2023; 29:1412). These poor outcomes have been largely attributable to a lack of effective treatment options. As recently as 2021, the only guideline-recommended interventions for HFpEF were diuretics to manage fluid overload and control of coexisting conditions including hypertension, obesity, diabetes, coronary disease, and atrial fibrillation. However, during the past several years, treatment options have expanded markedly with the introduction of three new drug classes for HFpEF.

The Rapid Evolution of HFpEF Treatment

The first signal of a breakthrough in HFpEF therapeutics emerged with the TOPCAT trial, which evaluated the steroidal mineralocorticoid receptor antagonist (MRA) spironolactone, and the PARAGON-HF trial, which evaluated the angiotensin receptor–neprilysin inhibitor (ARNi) sacubitril–valsartan. Although both trials were negative with respect to their primary end points, subgroup analyses demonstrated potential benefits, ultimately leading to a class IIb recommendation for both drugs in the 2022 AHA/ACC/HFSA guidelines for HF management (*Circulation* 2022; 145:e895 and *JAMA* 2023; 329:827). In TOPCAT, spironolactone was associated with significantly reduced risks of heart failure hospitalization (HFH) and cardiovascular (CV) mortality in the subgroup that did not include participants from Russia and Georgia. This subgroup analysis was motivated by the discovery that many enrollees from this region did not likely have heart failure and may not have been taking the study therapy. In PARAGON-HF, sacubitril–valsartan was associated with improved outcomes in two specific subgroups: women and those on the lower spectrum of ejection fraction (EF: 45%–57%). Based on these findings, the U.S. Food and Drug Administration (FDA) expanded the ARNi label in February 2021 to include use in HFpEF.

The landscape began to shift definitively later in 2021 with the publication of the EMPEROR-Preserved trial, followed by the DELIVER trial in 2022. In both studies, the use of **sodium–glucose cotransporter 2 (SGLT2) inhibitors** in patients with HFpEF led to an approximate 20% relative risk reduction in the composite outcome of CV deaths and HFH (*N Engl J Med* 2021; 385:1451 and *N Engl J Med* 2022; 387:1089). The FDA subsequently approved empagliflozin for HFpEF in February 2022, marking a pivotal advance in HFpEF therapeutics.

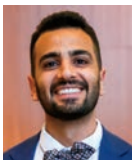


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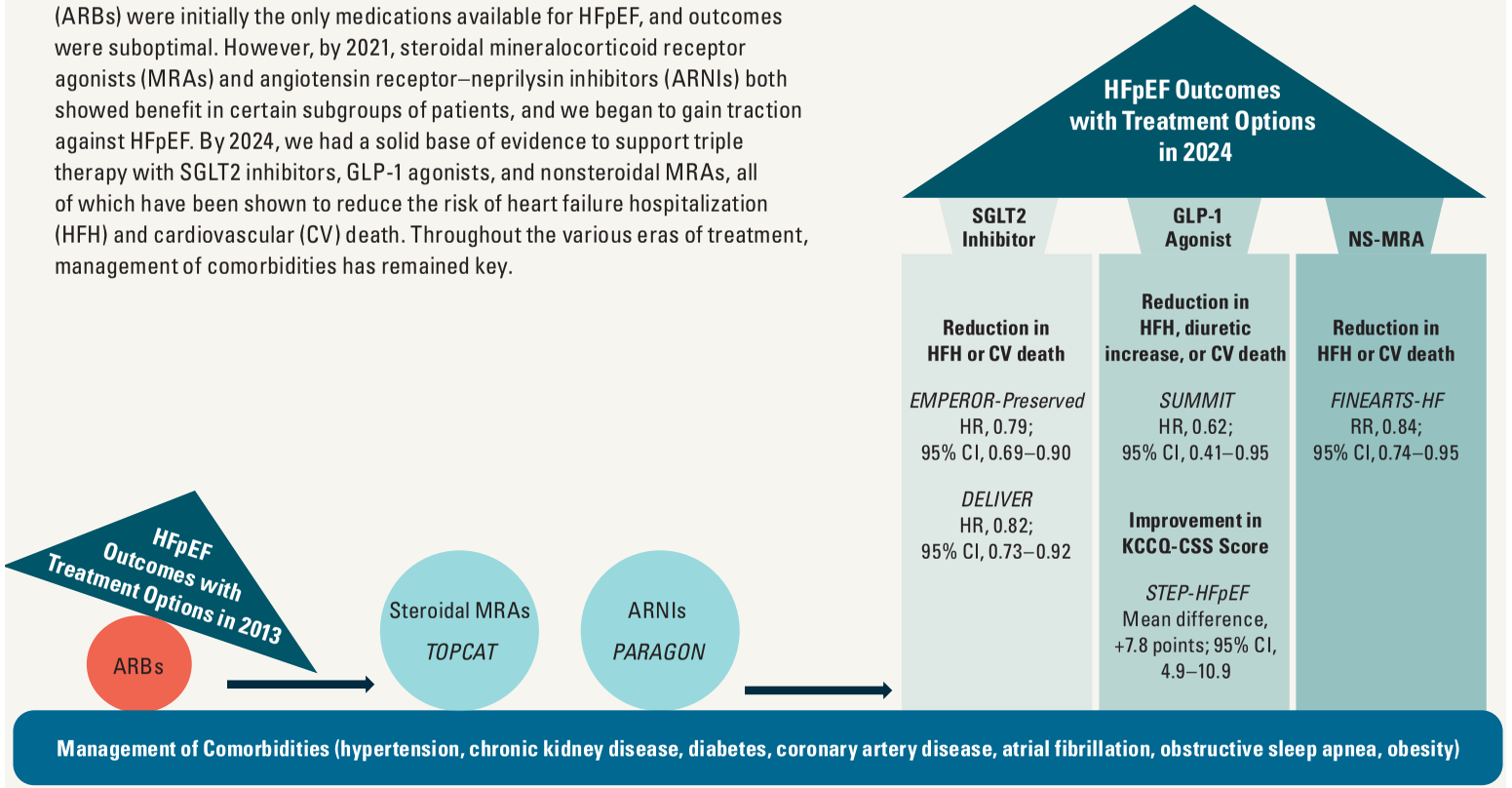
FIGURE. Evolution of HFpEF Management

Management of heart failure with preserved ejection fraction (HFpEF) has evolved remarkably during the past decade. Angiotensin-receptor blockers (ARBs) were initially the only medications available for HFpEF, and outcomes were suboptimal. However, by 2021, steroidal mineralocorticoid receptor agonists (MRAs) and angiotensin receptor–neprilysin inhibitors (ARNIs) both showed benefit in certain subgroups of patients, and we began to gain traction against HFpEF. By 2024, we had a solid base of evidence to support triple therapy with SGLT2 inhibitors, GLP-1 agonists, and nonsteroidal MRAs, all of which have been shown to reduce the risk of heart failure hospitalization (HFH) and cardiovascular (CV) death. Throughout the various eras of treatment, management of comorbidities has remained key.



CI — confidence interval; GLP-1 — glucagon-like peptide-1; HR — hazard ratio; KCCQ-CSS — Kansas City Cardiomyopathy Questionnaire clinical summary score; NS — nonsteroidal; RR — rate ratio; SGLT2 — sodium–glucose cotransporter 2

Shortly thereafter, a second drug class — the **glucagon-like peptide-1 (GLP-1) agonists** — was found to have substantial benefits in HFpEF. In the SELECT trial, conducted among patients with obesity in the absence of diabetes, the GLP-1 agonist semaglutide significantly reduced the composite HF end point (*N Engl J Med* 2023; 389:2221), and in the STEP-HFpEF trial, the use of semaglutide in patients with HFpEF improved symptom burden and physical activity, with a marked 16.6-point improvement in the Kansas City Cardiomyopathy Questionnaire clinical summary score (*N Engl J Med* 2023; 389:1069). More recently, the SUMMIT trial demonstrated the merits of tirzepatide, a long-acting dual agonist of both GLP-1 and glucose-dependent insulinotropic polypeptide receptors. Among patients with HFpEF and obesity with or without diabetes, tirzepatide reduced the risk of CV death or worsening HF by 38% compared with placebo and led to significantly improved HF symptoms and physical limitations in conjunction with a –13.9% change in body weight (*N Engl J Med* 2024 Nov 16; [e-pub]; DOI: 10.1056/NEJMoa2410027). Although both SGLT2 inhibitors and GLP-1 agonists were initially developed for diabetes, their effects on HF are independent of diabetes status, suggesting alternative mechanisms. (For more on this trial, see the Visual Summary on page 19.)

In late 2024, HFpEF therapeutics reached a new milestone when a third class of medications — **nonsteroidal MRAs** — proved beneficial. In the FINEARTS-HF trial, use of the nonsteroidal MRA finerenone resulted in a significant 16% reduction in the composite outcome of HFH and CV death (*N Engl J Med* 2024; 391:1475). Compared with steroidal MRAs, which are substantially less expensive, nonsteroidal MRAs have a more balanced distribution between cardiac and renal effects, with fewer off-target receptor effects. As a result, they may have a broader therapeutic index and provide more benefits, but a comparative outcomes study has not yet been performed.

The Challenges of Treating HFpEF

After more than two decades without new therapeutics that offer definitive benefit in HFpEF, clinicians now have three distinct classes of medication to support their patients (Figure). Despite the remarkable breakthroughs, significant challenges remain. HFpEF is underdiagnosed, in part because the diagnostic criteria are less specific than in HF with reduced ejection fraction (HFrEF). Because HFpEF is a particularly heterogeneous syndrome, a one-size-fits-all approach to treatment is unlikely to be appropriate. To stimulate research in this area and better tailor therapeutic approaches, the European Society of Cardiology recently introduced a new category of HF — heart failure with mildly reduced ejection fraction (HFmrEF), which includes patients with an EF of 41% to 49%. These patients share more in common with those who have HFrEF than HFpEF in terms of baseline characteristics and response to therapeutics (particularly ARNis and nonsteroidal MRAs). However, even within the new definitions, morphological and pathophysiological differences are present in the ≥50% EF category, and whether these differences can explain variation in response to therapeutics remains speculative (*Circulation* 2022; 146:506).

Historically, the uptake of guideline-directed medical therapy has been slow. For example, only 13% of patients with HFrEF were receiving ARNis 3 years after FDA approval, despite a class IA recommendation in American and European guidelines (*J Am Coll Cardiol* 2018; 72:351, *Circulation* 2022; 145:e895, and *Eur J Heart Fail* 2024; 26:5). Implementation research is needed to evaluate the safety and efficacy of early initiation of these drugs and the ability of patients to reliably adhere to complex multidrug regimens. The overall cost of these therapeutics presents a challenge for patients and society overall. The incremental cost-effectiveness ratio of SGLT2 inhibitor therapy in patients with HFpEF was recently estimated to be $141,200 per quality-adjusted life-year gained, indicating low-to-intermediate value (*JAMA Cardiol* 2023; 8:419). Triple therapy with an SGLT2 inhibitor, GLP-1 agonist, and nonsteroidal MRA — all of which have ongoing patent protections — is currently cost-prohibitive for many patients in the United States. Given that the average patient with HFpEF has 4 to 5 comorbidities and is already taking 10 different medications per day, efforts to address cost and polypharmacy are necessary, including additional research on which drugs to use preferentially in which patients.

Notwithstanding these challenges, the field of HFpEF therapeutics has rapidly transformed from an empty toolbox to a robust, three-pronged armamentarium — a "rags to riches" story in medicine — offering an array of effective treatments for this complex syndrome. Now we must turn to the work of disseminating these therapies to the millions of people with HFpEF who need them.

Topic Update

Artificial Intelligence in Cardiology

Ami B. Bhatt, MD, FACC

Implementation of artificial intelligence (AI) in cardiovascular medicine was inevitable, given the abundance of algorithms, remote monitoring, image interpretation, and predictive analytics in the field (*npj Cardiovascular Health* 2024; 1:26). Furthermore, the sheer volume of medical and scientific information — and the pace at which it becomes available — far exceeds the ability of the human brain to source, parse, and apply knowledge in a time-limited medical encounter, thus providing the impetus for the additional adoption of generative AI.

Next Steps in Scale for Machine Learning

AI holds immense promise to improve diagnostics, enhance decision making, and optimize clinical workflows (*Circulation* 2024; 149:e1028). Although machine learning is not new, its integration into health care delivery requires addressing critical challenges, including equitable implementation, data privacy, and appropriate human–AI collaboration.

EQUITABLE AI IMPLEMENTATION

The importance of diverse and equitable datasets to create AI models is well established. The opportunity now is at a public health level. First, we must integrate data from all modes of electronic health data and clinical registries, taking care to include social determinants of health (*JACC Adv* 2024; 3:101050). Once AI outputs are available, we must determine whether the information amplifies structural inequities or counters biases, a task as important as measuring outcomes. Lastly, if we are to improve cardiovascular care in all populations, we must address digital literacy, which is a new social determinant of equitable implementation of AI systems.

THE UNDERAPPRECIATION OF CYBERSECURITY RISK

AI represents a range of cybersecurity risks that may not be readily apparent to the average clinician. There are three key risks worth knowing about:

- Adversarial attacks, which consist of subtle changes to input data (such as images or speech signals) that can result in misclassification or misinterpretation, thereby affecting image analysis and voice assistants (NIST AI 100-2E2023)
- Data leakage, or unintentional sharing of sensitive information, which may expose patterns that can be exploited and allow reverse engineering or extraction of patient-identifiable data
- Presentation of AI-generated information as humanistic, giving the impression of real intelligence and posing a threat to patient or clinician safety (https://www.nature.com/articles/d41586-024-03905-1)

THE IMPORTANCE OF HUMAN–AI COLLABORATION

The initial administrative and diagnostic applications of AI in cardiology are well defined. However, implementation at scale remains a challenge. Human-led collaboration with AI must be central to the design of systems at scale. This includes understanding clinician and patient needs. The use of diagnostic AI in echocardiography is an excellent example.

Despite longstanding awareness that AI increases accuracy in echocardiogram interpretation, adoption remains slow. A major barrier is the concern that efficiency will translate to increased clinician workload in an already stressed system. Thoughtful design supported by human–AI collaboration could

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Dr. Bhatt codesigned the MGH Elevate Leadership Program and is inaugural Chair of the FDA Digital Health Advisory Committee. She has nothing to disclose.

increase uptake. For example, programs that rank order echocardiograms, such that the next study evaluated in an electronic list is the most urgent in the hospital, may lead to earlier, lifesaving treatment. Such a system could also allow the human interpreter more time to communicate directly with the clinical team so that a synchronous human-to-human report of an urgent finding and the response in the clinical context is achieved with greater fidelity and timeliness. AI can facilitate this interaction but cannot recreate it. At the other end of the severity spectrum, prompt identification of normal imaging with clinical confirmation could allow patients to return home more expeditiously from the health care setting. Finally, professional sonographers and other health care workers in the community could be trained to use AI to facilitate the acquisition of optimal images, which is a global need.

The driver of change in all these scenarios is the improvement of clinical care rather than efficiency alone, and the care is enhanced through human–AI collaboration rather than the application of AI alone.

The Exponential Rise of Generative AI

The advent of generative AI is an opportunity to increase access to care, a particularly important endeavor given the increasing prevalence of chronic cardiovascular disease and the shrinking clinical workforce in cardiology. To achieve the potential of generative AI at scale, four key elements must be addressed: trustworthy global cardiovascular datasets to fuel generative AI platforms, a proactive regulatory infrastructure, further research on clinician and patient interaction with AI, and funding to enable sustainable implementation of technologic advances in care delivery, and further research on clinician and patient interaction with AI.

FUELING GENERATIVE AI WITH GLOBAL CARDIOVASCULAR DATA

The evidence on the usability, successful implementation, and enhancement of clinical outcomes with generative AI in cardiovascular practice is developing. Generative AI is difficult to evaluate because of its qualitative nature; the challenge in detecting errors; the intensive resources needed (in terms of both computing power and human oversight) to ensure accuracy and safety; and the inability to control, predict, and test all potential inputs.

The development of trustworthy global datasets for generative AI via public–private partnerships can make identifying at-risk populations, evaluating the data at scale, and applying resources appropriately a reality. The focus on improving access to cardiovascular care can also ease tensions regarding regional data sovereignty because improving access to health care can in turn improve regional economic drivers, including workforce productivity, trust in systems, civic engagement, and improved maternal and child health.

"Cardiovascular AI programs will only have potential for global adoption if they are financially sustainable, seamlessly integrated into the clinical workflow, and improve CV outcomes."
— Ami B. Bhatt, MD, FACC

CREATING A SUPPORTIVE REGULATORY INFRASTRUCTURE FOR GENERATIVE AI

Cardiology is an excellent field in which to assess a proactive regulatory infrastructure for generative AI. The pathways to evaluate and scale remote monitoring with cardiovascular devices and the use of cardiovascular clinical risk-prediction tools have been in place for decades and can serve as a foundation for the development of an infrastructure for continuous safety monitoring.

Whether machine learning or generative AI offers concordant or discordant results compared to human reports with varying levels of automation is being studied. FDA systems such as the Predetermined Change Control Plans for Medical Devices (https://www.fda.gov/media/180978/download) can be a framework for continuous AI evaluation during implementation. Such a framework would include a prestated description of modifications, level of automation, and scope of implementation. It would allow for modification protocols to ensure data management and performance evaluation as well as an impact assessment not only for quality and safety but also for equitable use and outcomes. Finally, government regulatory programs and subspeciality

societies play a vital role providing clinical implementation and workflow guidance for algorithms.

FISCAL RESPONSIBILITY IN GENERATIVE AI

Cardiovascular AI programs will only have potential for global adoption if they are financially sustainable, seamlessly integrated into the clinical workflow, and improve CV outcomes. As a new infrastructure for care delivery is developed and fiscal incentives are attached to the "greater good," there is a risk of unsustainably escalating costs. Achieving scale will require local environments to develop the capacity to monitor and evaluate algorithms effectively.

To avoid rising costs that could inhibit the widespread application of AI, we must focus on embedding quality and safety paradigms into the algorithms, devices, and care delivery pathways themselves. For example, the following mechanisms can be used to embed checks and balances into the process of scale rather than creating a new layer of costly evaluation:

- Ensembling, or having embedded quality-assurance checks
- Audits using synthetic data or locked datasets (available through large health care systems, government entities, and cardiovascular industry partners)
- Stochastic sampling of deidentified images used in multimodal generative AI models by the manufacturer
- Comparison of local data to AI model training data before implementation to ensure similarity

HUMAN INTERACTION WITH GENERATIVE AI

End users (in this scenario, clinicians and patients) should be included in ongoing surveillance monitoring to understand whether generative AI captured the intent of the assignment and whether the output was helpful and resulted in a favorable clinical outcome.

Conclusion

The amount of biomedical data available in cardiovascular disease to make the best clinical decision for a patient outstrips a single human's clinical acumen. It is a different world than when I started practice, when the knowledge base of adult congenital heart disease lived in books, articles, and experience that only a few possessed. The vast data and multimodal inputs that might inform the "best decision" require complex algorithmic evaluation. AI offers an opportunity to find at-risk patients, diagnose them correctly, direct them to appropriate care, and support chronic disease management. AI must be created with the distinct objective of enhancing care access and equity, supported by a proactive regulatory infrastructure, and in a fiscally responsible manner. Most importantly, cardiovascular clinicians must engage with AI, as these models will only succeed if clinicians evaluate them, challenge them, and demand that they serve our patients' needs.

NEJM Plain Language Summary

Plozasiran for Mixed Hyperlipidemia

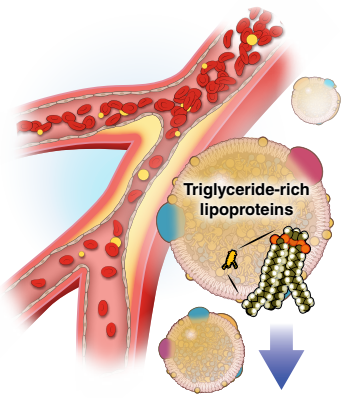
Based on the NEJM publication: Plozasiran, an RNA Interference Agent Targeting APOC3, for Mixed Hyperlipidemia by C.M. Ballantyne et al. (published May 28, 2024)

In this trial, researchers assessed the efficacy and safety of various doses of plozasiran for reducing triglyceride levels in participants with mixed hyperlipidemia.

Mixed hyperlipidemia is characterized by elevated levels of low-density lipoprotein (LDL) cholesterol and triglyceride-rich lipoproteins.

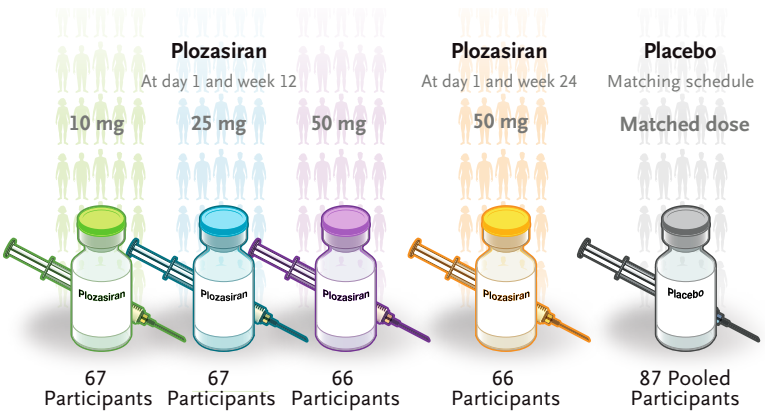
WHY WAS THE TRIAL DONE?

Persons with mixed hyperlipidemia are at risk for atherosclerotic cardiovascular disease due to elevated non–high-density lipoprotein (HDL) cholesterol, which is primarily remnant cholesterol in triglyceride- rich lipoproteins. Current treatments for lowering the LDL cholesterol level do not eliminate this excess risk. In a phase 1 trial, plozasiran, a small interfering RNA that targets apolipoprotein C3 (APOC3), showed promise for lowering triglyceride levels.



HOW WAS THE TRIAL CONDUCTED?

353 adults with mixed hyperlipidemia were assigned to receive either plozasiran or placebo within each of four cohorts. In three cohorts, participants received quarterly subcutaneous injections of plozasiran (10, 25, or 50 mg) or placebo on day 1 and at week 12. In the fourth cohort, participants received half-yearly doses of 50 mg of plozasiran or placebo on day 1 and at week 24. Data from all the placebo recipients were pooled. The primary end point was the percent change in the fasting plasma triglyceride level from baseline to week 24.



PARTICIPANTS

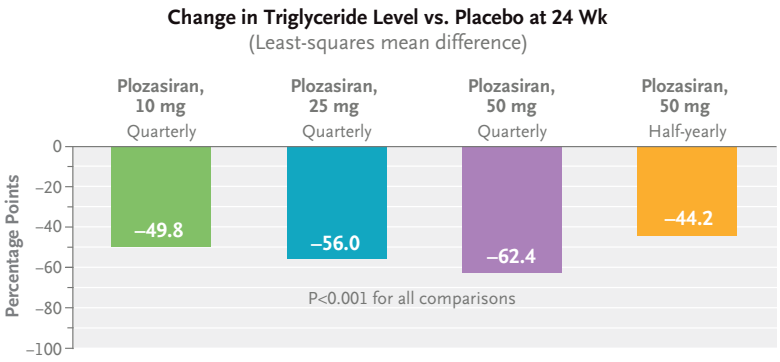
WHO	353 men and nonpregnant, nonlactating women Mean age, 61 years Mean BMI, 32
CLINICAL STATUS	Fasting triglyceride level, 150 to 499 mg/dl LDL cholesterol level of at least 70 mg/dl or non-HDL cholesterol level of at least 100 mg/dl Stable statin regimen for at least 4 weeks, unless the participant was unable to receive a statin because of adverse effects

TRIAL DESIGN

- Phase 2b
- Double-blind
- Randomized
- Placebo-controlled
- Location: 36 centers in the United States, Europe, New Zealand, Australia, and Canada

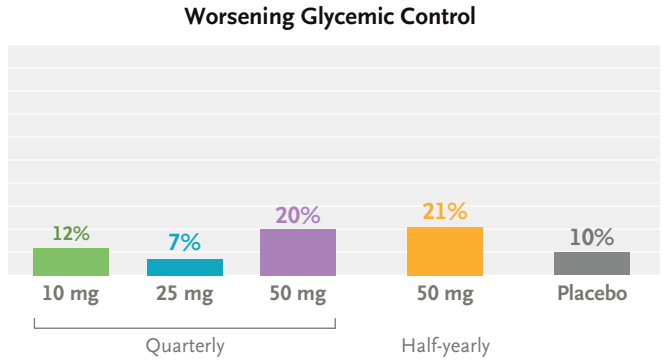
RESULTS

At week 24, plozasiran was associated with significant reductions in fasting plasma triglyceride levels at all the doses evaluated, as compared with placebo. The largest reduction was observed with the quarterly 50-mg dose.



NORMALIZED TRIGLYCERIDES

Among the participants who received plozasiran at a quarterly dose of 25 mg (the dose chosen for phase 3 trials), 92% had a normalized fasting triglyceride level by week 24.



Approximately 20% of the participants in the quarterly and half-yearly 50-mg groups and 10% of those in the placebo and lower-quarterly-dose groups had adverse events related to glycemic control.

LIMITATIONS AND REMAINING QUESTIONS

- 90% of participants were White, which limits the generalizability of the findings.
- The trial did not assess the effect of plozasiran on the risk of atherosclerotic cardiovascular disease, so the effect of the drug on clinical outcomes is unknown.

CONCLUSIONS

In adults with mixed hyperlipidemia, the small interfering RNA plozasiran significantly reduced triglyceride levels at 24 weeks.

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT04998201

Trial funding: Arrowhead Pharmaceuticals

Full citation: Ballantyne CM, Vasas S, Azizad M, et al. Plozasiran, an RNA interference agent targeting APOC3, for mixed hyperlipidemia. **N Engl J Med** 2024;391:899-912. DOI: 10.1056/NEJMoa2404143

NEJM Journal Watch Summary

Vutrisiran for Cardiomyopathy Associated with Transthyretin Amyloidosis

The RNA silencer reduced the risk for death and cardiovascular events in both hereditary and wild-type disease.

Transthyretin (TTR) amyloidosis causes amyloid fibrils to accumulate in tissue, including cardiac muscle, which can lead to cardiomyopathy. The condition, stemming from a genetic abnormality (variant) or aging (wild-type), is characterized by progressive physical decline and risk for early mortality. Tafamidis, a TTR stabilizer, is the only FDA-approved treatment for TTR amyloidosis with cardiomyopathy (ATTR-CM), but a recent trial showed the efficacy of another stabilizer, acoramidis (*N Engl J Med* 2024; 390:132). Researchers have now conducted a manufacturer-funded trial (NCT04153149) of vutrisiran, which inhibits hepatic synthesis of both wild-type and variant *TTR* messenger RNA.

The investigators randomized 655 patients (median age, 77 years; 92% men; 88% with wild-type disease) with ATTR-CM (defined as evidence of TTR on tissue biopsy or nuclear imaging) to vutrisiran (25 mg subcutaneously every 12 weeks) or placebo. Participants also had echocardiographic evidence of left-ventricular hypertrophy, a clinical history of heart failure, and N-terminal pro–B-type natriuretic peptide levels within a specified range.

Vutrisiran was associated with significantly lower risks (vs. placebo) for the primary endpoint of death from any cause or recurrent cardiovascular events at up to 36 months (hazard ratios, 0.72 in the overall population, 0.67 among patients not taking baseline tafamidis) and for all-cause mortality at 42 months (HR, 0.65). Findings were consistent across subgroups. Vutrisiran also resulted in less deterioration in 6-minute walk distance and health status. Serious adverse events occurred in 62% of the vutrisiran group and 67% of the placebo group.

Comment

This trial identifies a new class of therapy for ATTR-CM, demonstrating the exciting capability of RNA silencing in disease modification. Vutrisiran is currently FDA approved for use in ATTR-related polyneuropathy; this trial may cause the indication to be expanded. The drug's cost, however, is high (roughly $450,000 per year), which will certainly limit its availability, especially in economically disadvantaged populations.

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

Dr. Masoudi is Chief Science Officer and Vice President of Research and Analytics at Ascension Health and Clinical Professor of Medicine at the University of Colorado Anschutz Medical Campus. He serves as Chair of the Innovations Committee for the American College of Cardiology (ACC) and is on the editorial boards of *NEJM Journal Watch Cardiology*, UpToDate, and the ACC Self-Assessment Program. Dr. Masoudi reports consultant/advisory board roles with Bristol Myers Squibb and CPC Clinical Research and grant/research support from the National Heart, Lung, and Blood Institute.

Fontana M et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. **N Engl J Med** 2025; 392:33. (https://doi.org/10.1056/NEJMoa2409134)

NEJM Journal Watch Summary

Drug-Coated Balloons for In-Stent Restenosis

A paclitaxel-coated balloon reduced target-lesion failure better than an uncoated balloon.

In-stent restenosis occurs in up to 10% of patients undergoing percutaneous coronary intervention (PCI) with contemporary drug-eluting stents. In this multicenter, randomized trial, investigators assessed the efficacy and safety of a drug-coated balloon versus an uncoated balloon for treatment of in-stent restenosis.

Six hundred patients were randomized 2:1 to receive a paclitaxel-coated balloon or an uncoated balloon during PCI. Baseline characteristics were similar between groups; mean age was 68 years, 26% of participants were women, and 43% of patients had multiple-layer in-stent restenosis.

The incidence of the primary composite end point — ischemia-driven target-lesion revascularization, target-vessel myocardial infarction, or cardiac death at 12 months — was significantly lower with the drug-coated balloon than with the uncoated balloon (18% vs. 29%; hazard ratio, 0.59). Both target-lesion revascularization (13% vs. 25%) and target-vessel myocardial infarction (6% vs. 11%) were also significantly reduced with the drug-coated balloon. The results were similar in multiple subgroups, and there was no apparent increase in the risk for stent thrombosis with the drug-coated balloon.

Comment

Drug-coated balloons have been approved internationally, and the findings from this first U.S. trial resulted in FDA approval in 2024. This option for patients with in-stent restenosis, particularly those with failure of multiple drug-eluting stents, has been eagerly awaited by interventional cardiologists in the U.S. How drug-coated balloon treatment compares with insertion of an additional drug-eluting stent remains unclear, but having this therapy will improve options for our patients. It will also likely lead to trials of drug-coated balloons in many other clinical scenarios.

Howard C. Herrmann, MD

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Yeh RW et al. Paclitaxel-coated balloon vs uncoated balloon for coronary in-stent restenosis: The AGENT IDE randomized clinical trial. **JAMA** 2024; 331:1015. (https://doi.org/10.1001/jama.2024.1361)

Kundu A and Moliterno DJ. Drug-coated balloons for in-stent restenosis — Finally leaving nothing behind for US patients. **JAMA** 2024; 331:1011. (https://doi.org/10.1001/jama.2024.0813)

NEJM Journal Watch Summary

Semaglutide Improves Outcomes in Patients with Obesity, HFpEF, and Type 2 Diabetes

In a randomized, controlled trial, semaglutide resulted in greater weight loss, improved symptoms, and fewer serious adverse events compared with placebo.

Obesity and type 2 diabetes are common comorbidities in patients with heart failure with preserved ejection fraction (HFpEF). Currently, there are no FDA-approved therapies that specifically treat all three conditions at the same time; however, semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has the potential to do so.

In an industry-funded trial (NCT04916470), investigators randomized 616 adults with HFpEF (left ventricular ejection fraction ≥45%), body-mass index >30, and type 2 diabetes to receive semaglutide (2.4 mg) or matching placebo once weekly for 52 weeks. They assessed dual primary end points of change in heart failure symptoms via Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; range, 0–100, with higher score indicating fewer symptoms) and change in body weight.

The mean change in the KCCQ-CSS was +13.7 points with semaglutide and +6.4 points with placebo, indicating improved symptoms with semaglutide. The mean change in body weight was −9.8% with semaglutide and −3.4% with placebo. Confirmatory secondary end points also favored semaglutide, including 6-minute walk distance, a composite end point (including death, heart failure events, and differences in KCCQ-CSS and 6-minute walk distance), and C-reactive protein level. Serious adverse events occurred in 18% of patients in the semaglutide group and 29% in the placebo group.

Comment

Semaglutide once again shows clinical benefit. Prior research has shown improved outcomes in patients with diabetes and high cardiovascular risk, in patients with overweight or obesity and high cardiovascular risk, and in patients with HFpEF and obesity but no diabetes. Now, this research shows efficacy in patients with HFpEF, obesity, and type 2 diabetes. The many benefits of semaglutide make me very likely to recommend this therapy in appropriate patients for improving symptoms and reducing cardiovascular risk.

Karol E. Watson, MD, PhD, FACC

Dr. Watson is 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 Codirector of the UCLA Program in Preventive Cardiology. She reports consultant or advisory board roles with Boehringer Ingelheim, Amgen, and Novartis and Speaker's Bureau activity with Boehringer Ingelheim.

Kosiborod MN et al. Semaglutide in patients with obesity related heart failure with preserved ejection fraction and type 2 diabetes. **N Engl J Med** 2024; 390:1394. (https://doi.org/10.1056/NEJMoa2313917)

NEJM Journal Watch Summary

Should We Perform Up-Front PCI in Patients with Significant Coronary Disease Undergoing TAVR?

New randomized trial findings suggest limiting this strategy to patients with the most severe disease.

Up to 50% of patients referred for treatment of severe aortic stenosis (AS) have significant coronary artery disease (CAD). While guidelines generally recommend that these patients undergo concurrent coronary bypass grafting at the time of surgical aortic valve replacement, the optimal management for patients undergoing transcatheter aortic valve replacement (TAVR) is uncertain.

To address this gap in knowledge, researchers conducted the partially industry-funded NOTION-3 trial (NCT03058627), randomizing 455 patients with at least one significant coronary lesion (defined as an angiographic stenosis ≥90% by visual estimate or a fractional flow reserve [FFR] ≤0.8) to receive up-front percutaneous coronary intervention (PCI) or conservative treatment. Patients with significant left main CAD or a recent acute coronary syndrome were excluded. In the PCI group, 91% of PCIs were performed either prior to or concurrent with TAVR.

During a median 2-year follow-up, the primary end point — a composite of death, myocardial infarction (MI), or urgent coronary revascularization — was significantly less frequent in the PCI group (26% vs. 36%); the benefit was driven primarily by urgent revascularization (2% vs. 11%) and to a lesser extent by MI (7% vs. 14%). There was no difference in all-cause mortality. Subgroup analyses suggested that virtually all of the benefit of up-front PCI was in patients with an angiographic stenosis ≥90% (hazard ratio, 0.53) with little to no benefit in the subgroup with FFR ≤0.8 (HR, 1.04). Bleeding occurred in 28% of the up-front group and 20% of the conservative-treatment group.

Comment

These are the first high-quality data to demonstrate a benefit of PCI for patients with significant CAD undergoing TAVR for severe aortic stenosis. Among the most useful findings is that the benefit of up-front PCI in this population appears to be limited to patients with very severe disease (at least 90% stenosis by visual estimation). Given the increased risk for bleeding with up-front PCI, these data provide a compelling rationale to defer PCI for patients undergoing TAVR with only noncritical coronary lesions.

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, AngioInsight, and HeartBeam. He reports Speaker's Bureau activity with Boston Scientific. He reports receiving grant or research report from Edwards Lifesciences, Abbott Vascular, Boston Scientific, Medtronic, Corvia Medical, the National Heart, Lung, and Blood Institute, Phillips, Svelte, Brain-Q, St. Paul's Hospital, V-Wave, Saranas, I-Rhythm, Zoll Medical, CathWorks, and Ancora. 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 (Cochair, Risk Model Development Committee) and Cardiovascular Research Foundation (Codirector, TCT Annual Meeting; Codirector, New York Valves Annual Meeting).

Lønborg J et al. PCI in patients undergoing transcatheter aortic-valve implantation. **N Engl J Med** 2024; 391:2189. (https://doi.org/10.1056/NEJMoa2401513)

NEJM Journal Watch Summary

Does Colchicine Reduce Cardiac Events after Myocardial Infarction?

Study results have been mixed, but a new large trial shows no significant benefit.

Some recent studies suggest that colchicine may reduce cardiac events, presumably through its anti-inflammatory properties. In the CLEAR study (NCT03048825), more than 7000 individuals were randomized to receive colchicine or placebo (as well as spironolactone or placebo, in a 2×2 factorial design) after myocardial infarction. The investigators have reported colchicine trial results.

During a median follow-up of 3 years, a combined outcome of cardiovascular death, myocardial infarction, stroke, or unplanned revascularization was similar between the two groups (9.1% in the colchicine group and 9.3% in the placebo group). Moreover, C-reactive protein level, a measure of inflammation, was lower in the colchicine group at 3 months (2.98 mg/L vs. 4.27 mg/L), and colchicine significantly increased diarrhea (10.2% vs. 6.6%).

Comment

Despite a plausible biologic mechanism and encouraging prior data, this trial was convincingly negative, suggesting no benefit for colchicine after myocardial infarction. Prior trials have been mixed, and it's not immediately clear why this trial conflicts with slightly smaller positive trials like COLCOT (*N Engl J Med* 2019; 381:2497) and LODOCO-2 (*N Engl J Med* 2020; 383:1838), although the latter was conducted in those with stable coronary artery disease rather than acute myocardial infarction. We'll have to wait and see whether these trial results lead to a downgrading of the 2a recommendation for colchicine after myocardial infarction in the European guidelines or our own 2b recommendation in U.S. guidelines, but these results, along with the diarrhea issue, will make me think twice about prescribing colchicine after myocardial infarction.

Kirsten E. Fleischmann, MD, MPH, FACC

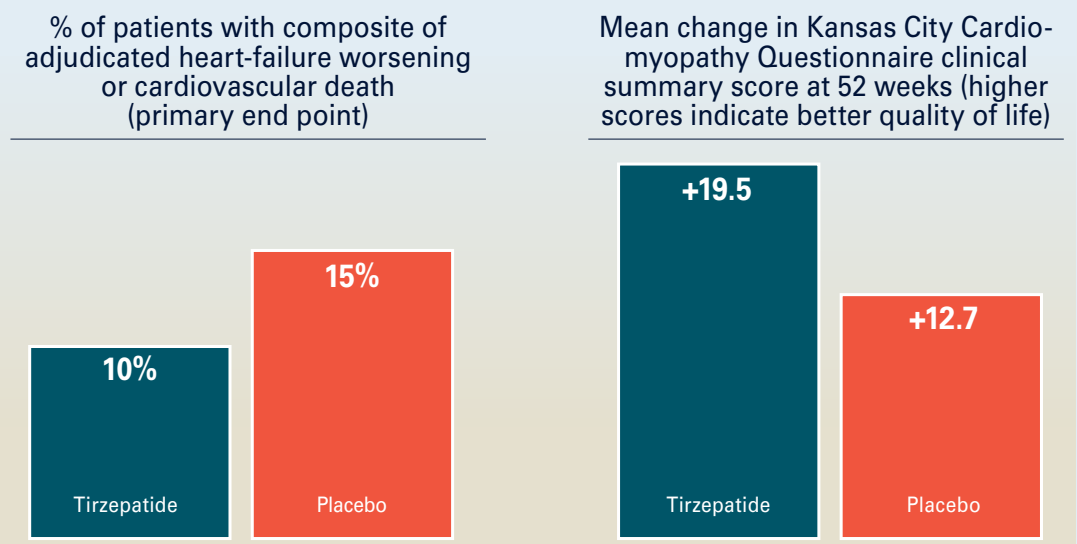
Dr. Fleischmann is a cardiologist and Professor of Clinical Medicine at the University of California San Francisco School of Medicine. She reports grant or research support from the National Institutes of Health and leadership position in the American College of Cardiology/American Heart Association.

Jolly SS et al. Colchicine in acute myocardial infarction. **N Engl J Med** 2024 Nov 17; [e-pub]. (https://doi.org/10.1056/NEJMoa2405922)

Visual Summary

Cardiovascular Outcomes of Tirzepatide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

In the industry-funded SUMMIT trial, 731 study participants with heart failure with preserved ejection fraction (HFpEF) and obesity were randomized to once-weekly subcutaneous tirzepatide (up to 15 mg) or placebo for a median follow-up of 104 weeks. Participants had elevated filling pressures or an elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, and a heart failure exacerbation event within the prior 12 months or a decreased estimated glomerular filtration rate <70 mL/min/1.73 m^2.



Comment

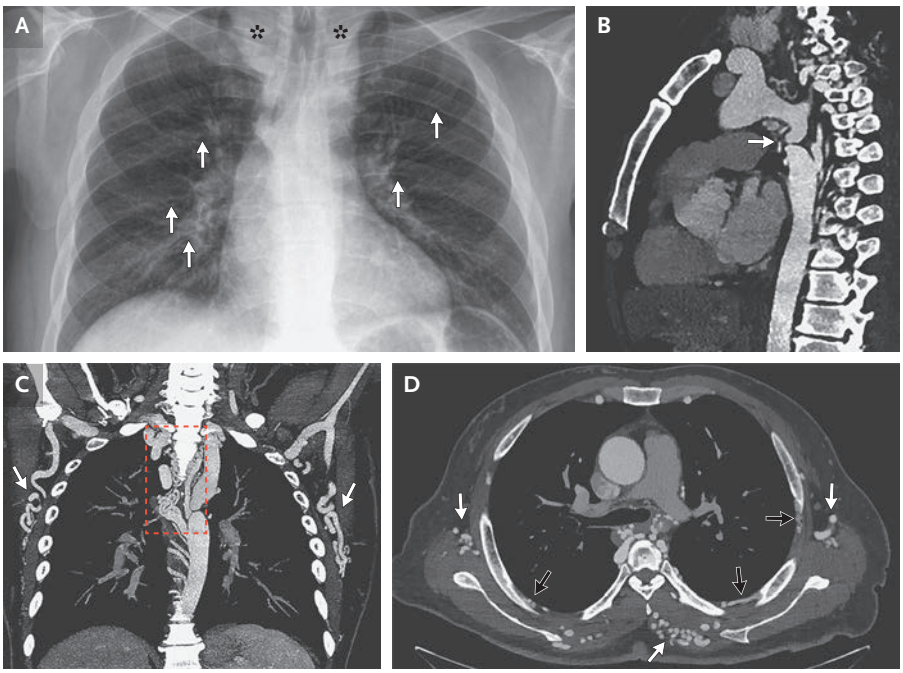
These findings support a class effect of glucagon-like peptide-1 receptor agonists in HFpEF, previously shown with semaglutide in the STEP-HFpEF and STEP-HFpEF DM trials. Moreover, this trial provides more-translatable data for clinical practice by not requiring participants to have an increase in NT-proBNP, which many patients with overweight or obesity do not have. This allows me to add tirzepatide to my clinical toolbox for patients with a body-mass index >27 and evidence of HFpEF by increased intracardiac pressures. Overall, these results support and expand the use of tirzepatide for medical weight management as a primary approach to improve weight-related cardiometabolic comorbid conditions.

Vlad G. Zaha, MD, PhD, FACC, FAHA, reviewing Packer M et al. *N Engl J Med* 2024 Nov 16

Dr. Zaha is an Associate Professor of Medicine/Cardiology, Biomedical Engineering and Cancer Biology, at the UT Southwestern Medical Center, Dallas, Texas, and the Section Chief of Cardio-Oncology. He reports grant or research support from the Cancer Prevention and Research Institute of Texas and the National Institutes of Health and serves on the editorial board of *Circulation* and as section chair of cardio-oncology of the Texas Chapter of the American College of Cardiology.

Images in Clinical Medicine

Aortic Coarctation



A 35-year-old man was referred to his primary care physician for evaluation of previously unknown hypertension that had been identified during a medical screening for his rugby team. The patient was asymptomatic. The blood pressure was 146/89 mm Hg in the left arm, 146/99 mm Hg in the right arm, 104/83 mm Hg in the left leg, and 109/90 mm Hg in the right leg. On physical examination, a radial–femoral delay was present. A chest radiograph showed notching of posterior ribs 3 through 8 (Panel A, arrows) and widened paratracheal stripes (Panel A, asterisks). Computed tomographic (CT) angiography of the chest revealed coarctation of the descending aorta, with the isthmus measuring 3 mm in diameter (reference range for the patient's age and size, 18 to 25) (Panel B, arrow). CT angiography also showed extensive collateral arterial circulation in the soft tissues (Panels C and D, white arrows), along the trachea (which accounted for the paratracheal stripes seen on chest radiography) (Panel C, dashed box), and in the intercostal spaces (which accounted for the notching of the ribs seen on chest radiography) (Panel D, black arrows). A transthoracic echocardiogram showed left ventricular hypertrophy and a pressure gradient of 25 mm Hg across the coarctation. No other cardiac abnormalities were identified. Percutaneous stenting of the aortic coarctation was performed without complications. At a follow-up visit 1 month after the procedure, the patient's blood pressure had improved. At a 3-month follow-up visit, repeat imaging showed a marked decrease in collateral arterial circulation.

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April 17, 2024; **N Engl J Med** 2024; 390:15; DOI: 10.1056/NEJMicm2313075