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## Residents and Fellows Edition



February 20, 2025

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On behalf of the entire staff of the *New England Journal of Medicine*, please accept my wishes for a rewarding career.

Sincerely,

Eric J. Rubin, MD, PhD



## Physician Employment Contracts Update: Problematic Clauses Persist in the Marketplace

By Bonnie Darves, a freelance health care writer

Even if there haven't been any seismic shifts in the realm of physician employment contracts in recent years, the trends that contract lawyers are seeing as they review the documents are worth noting — and being mindful of as physicians consider job offers. For starters, even though the hoped-for national legislation that will eradicate or ameliorate the non-compete clauses that are onerous for physicians who decide to leave a job before the contract period ends is moving forward, it's too early to count on it sticking as is.

The Federal Trade Commission in late April demonstrated that it is committed to addressing those non-compete clauses, which essentially dictate exactly where and how a departing physician may practice, by issuing a final rule outlawing them. Within hours, however, the new rule spawned a spattering of legal challenges — and a tsunami of backlash will likely ensue. As such, physicians shouldn't count on the rule to end their worries about non-competes, according to employment lawyers.

Lauren Kaufman, an attorney with the MorganTheeler LLP health law practice in Mitchell, South Dakota, offers her view of the proceedings to date. “Let's say that I'm optimistic but skeptical,” she said, saying that the

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final rule will settle the issue. Even with the rule's initial passage, Ms. Kaufman noted, "There will likely be litigation." In addition, it's not yet clear how the rule will address contracts offered by not-for-profit health care organizations, which account for a large number of physician employers.

"The bottom line is that you should assume that your covenant not to compete is valid and enforceable, and not take any action that would violate its provisions," said Dennis Hursh, managing partner of Physician Agreements Health Law in Middletown, Pennsylvania.

*"Basically, the higher the sign-on bonus, the longer the employer will want the physician to stay. The majority of contracts will have clawbacks within one, two, or three years."*

— Lauren Kaufman, MorganTheeler LLP

Physicians who signed existing non-compete clauses, in the meantime, should also be very clear about the clauses' potential reach. "I've seen non-competes completely uproot physicians' lives," Ms. Kaufman said. That's because the geographical restrictions of non-competes may force physicians to relocate altogether, against their will. It's not unheard of, after all, to see employers prohibit departing physicians from practicing within a 60- or even 80-mile radius of the current location for a period of two years, and even a 15-mile radius could prove problematic in a dense urban area. "Even though most of these clauses max out at two years, that's a long time," she said.

### Avoiding onerous non-competes

Employment lawyers who specialize in physician contracts concur that the best time to contest an unreasonable non-compete clause is before the contract reaches the final draft stage. This might entail requesting the prospective employer's proposed non-compete verbiage at the letter-of-intent stage, if possible. That way, an attorney can review that clause and other key terms before the final contract is presented. The following are recommendations for pursuing needed alterations to non-competes:

**Be specific about circumstances for enforcing non-competes.** Richard H. Levenstein, who heads the health law practice at **Nason, Yeager, Gerson, Harris & Fumero, P.A.** in Palm Beach Gardens, Florida, and who consults

to the American Medical Association on physician employment contracts, urges limiting the conditions that permit the non-compete. "I try to negotiate with employers to have the non-competes effective only if the physician is terminated for cause," Mr. Levenstein said.

*"When a physician employee ends up owing money to an employer, he or she effectively becomes an indentured servant."*

— Richard H. Levenstein, Nason, Yeager, Gerson, Harris & Fumero, P.A.

**Be mindful of the practice locations included in the geographical radius.** In recent years, the consolidation among hospitals and the tendency within health systems to purchase or affiliate with hospitals or clinics far flung from the mother ship can make non-competes even more problematic. If the clause states that the geographical radius applies to "any location" where the employer conducts business, for example, physicians could find themselves having to leave the state.

"I recommend that physicians actually pull up their Google Maps application to see what that restriction would look like in real life," said Scott Weavil, a health law attorney at Weavil Law PC in Sacramento, California. "I counsel my clients to make sure that, at the end of the day, they can live with the restrictive covenant." If not, physicians should have their lawyers request a more reasonable radius or enforceable time period, he added. Ideally, any geographical radius should apply only to the primary place of practice.

**Don't assume that the non-compete won't be enforceable.** Outside of a handful of states where physician-employment restrictive covenants have been either outlawed or limited substantially in scope by regulation — these include California, New York, Washington, Delaware, and, recently, North Dakota and the District of Columbia — the provisions should be considered enforceable, and physicians should expect the employers to litigate, according to Dennis Hursh, managing partner of Physician Agreements Health Law in Middletown, Pennsylvania. "Even if it seems unimaginable that a judge would enforce an unreasonable non-compete, you don't want to have the burden of fighting it," Mr. Hursh said. That might prove a very expensive proposition with an uncertain outcome, all sources agreed.

"Physicians should understand that non-competes should be addressed at the contract stage because the courts are not knocking them out. You

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don't want to sign a contract and ask questions later," said Neil Talegaonker, a partner in the law firm Kaufman & Canoles, P.C., in Richmond, Virginia.

### **Contract pitfalls: They're in the fine print**

Another potentially problematic contract clause is the so-called "clawback," in which physicians receive enticements to employment, such as generous signing bonuses, education-loan repayments, or five-figure relocation packages. If the physician decides that the job wasn't as advertised or wants (or needs) to leave for any reason, employers may require that some portion of those employer-incurred expenses be repaid, especially if the physician leaves, for example, after one year of a two- or three-year contract (the most common durations).

"Most employers will require physicians to pay back all or a portion of those offer-associated benefits, and physicians need to understand what those requirements are before they sign a contract," Ms. Kaufman said. "Basically, the higher the sign-on bonus, the longer the employer will want the physician to stay. The majority of contracts will have clawbacks within one, two, or three years."

Although most lawyers agree that employers should be entitled to a return of some funds if the physician decides to leave early for personal reasons, it's important to understand how that repayment would be apportioned. Generally, as Mr. Weavil explained, employers will seek the return of sign-on bonuses and relocation expenses, so those terms should be understood and acceptable. For example, it might be reasonable to expect full payback if a physician leaves at the end of the first year, but not if she or he leaves 20 months or two years into a three-year contract.

In those cases, physicians should ensure that any required repayment is prorated on a monthly basis from the time of departure to the contract's end date. "You really want to avoid a clause that states that if the physician leaves before two years, those expenses must be repaid in full," said Mr. Weavil, who said that he has seen such unreasonable terms.

The other important issue with clawbacks is when they would apply. Mr. Weavil and other sources agreed that if an employer lays off a physician without cause, for reasons such as the entity's sale to another organization or its decision to narrow the physician workforce, physicians should be relieved of any obligation to repay those funds.

### **Performance expectations: beware of pitfalls**

One aspect of contracts that may prove especially problematic involves any clause related to employers' requirements for meeting performance thresholds. Simply put, this boils down to the level of required productivity, usually in terms of either work relative value units (W-RVUs) or patient census numbers. W-RVUs, which define the value of a service or procedure relative to all services and are based on the extent of physician work required, are assigned by the Centers for Medicare & Medicaid. These W-RVUs enter into contracts in two ways.

For starters, employers may set an expectation that physicians reach a certain number of W-RVUs either per month or annually, in year one and subsequent contract years. That's reasonable provided the expectation is in line with what other physicians in the same specialty achieve. For example, if the median number of W-RVUs, as reported in national compensation surveys, for an internist is 4,800 annually and the prospective employer expects 5,200, that level might not be doable for an internist starting out in practice. Mr. Talegaonker advises physicians to conduct due diligence to establish reasonable W-RVU expectations, with the following questions in mind:

- Will the employer's market support this level of productivity performance?
- What are the historical W-RVU patterns in the practice/organization for same-specialty physicians, and what percentage of those physicians actually meet or exceed those expectations?
- What is the patient population like, and how much organizational assistance will the new physician receive to ensure an adequate patient census?

The other factor to consider is the dollar value assigned to each W-RVU. For example, according to the Medical Group Management Association's survey data, the median W-RVU dollar value for family medicine physicians was \$59.69 in 2021. If the hiring organization proposes a much lower value, the physician's compensation will be lower accordingly. This is complicated stuff, Mr. Talegaonker acknowledges, so it's best to do some homework and to have an experienced health care lawyer review the data early on. This helps ensure that the physician's proposed compensation will be competitive regionally and nationally. Physicians should expect their legal counsel to obtain and be familiar with such survey data.

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*“Even if the employer states that the contract is ‘standard’ and can’t be changed, physicians should not assume that there’s no room for movement, or compromise.*

— Dennis Hursh, Physician Agreements Health Law

Health law attorney Richard H. Levenstein, with **Nason, Yeager, Gerson, Harris & Fumero, P.A.** in Palm Beach Gardens, Florida, further recommends that physicians request that an example of the formula used for determining physician productivity or performance and how it’s applied for the purposes of compensation be included in the contract. In addition, the contract should clearly state what happens if the physician doesn’t achieve the stipulated productivity level. For instance, if physicians are “docked” for not achieving the required number of expected W-RVUs, they could end up in an untenable financial position.

“When a physician employee ends up owing money to an employer, he or she effectively becomes an indentured servant,” said Mr. Levenstein, who also teaches at Tulane University Law School in New Orleans, Louisiana, and lectures at Tulane’s medical school. If the physician encounters push-back when asking for details on productivity formulas and associated compensation levels — specifically how the organization makes calculations regarding what’s owed to, or potentially by, the physician — that’s a serious red flag, in Mr. Levenstein’s view.

### Understanding post-employment issues, like tail coverage

Surely no physician accepts a new job expecting to leave in short order, but that can and does happen for reasons ranging from personal or family issues to serious professional dissatisfaction. As such, physicians should be sure that they review any proposed contract from a what-if perspective, ideally with their lawyers and not necessarily in the context of face-to-face discussions with a potential employer. This means ensuring that any clause that’s unacceptable be either removed or modified, even if slightly.

One example of where this future perspective is important is the tail malpractice coverage provision, which can range considerably from one contract to another. Of course, it’s ideal if the employer agrees to pay the full cost of tail coverage when a physician leaves after the contract’s end date, but that responsibility might have to be negotiated if the physician leaves early, according to Ms. Kaufman.

If an employer won’t provide tail coverage outright, Ms. Kaufman recommends requesting a vesting or cost-sharing period of three years. If the

physician leaves after one year of a two- or three-year contract, she suggests that the employer be required to pay one-third and the physician two-thirds of the coverage cost. After two years, those portions would switch, with the employer paying two-thirds and the physician one-third. If the physician stays for three years, she recommends that the policy then convert to fully employer paid.


In addition, Ms. Kaufman notes that the type of malpractice liability policy is important to understand; if it’s “claims-made” coverage, meaning that claims could arise after the physician leaves, the repayment schedule might be an issue. If it’s an “occurrence” policy, tail coverage wouldn’t be needed. Finally, as with clawbacks, the reason for termination is a key consideration in tail coverage responsibility. If the contract is terminated “without cause” by the employer (versus “for cause,” in the case of an employee breaching the contract), the employer should assume responsibility for the cost of coverage.

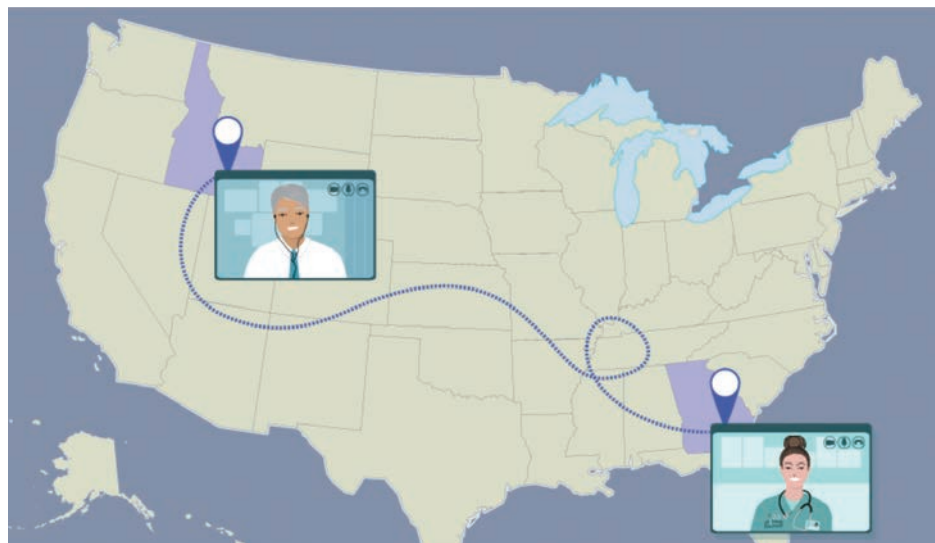
In the big picture, and given all the potential risks outlined above, how should the physician prepare to avoid patently unreasonable or downright unfair employment-contract clauses? First of all, physicians should choose a labor and employment attorney who specializes in physician contracts and engage that individual as early in the negotiation process as possible.

Second, physicians should not expect that, even in this age of “boilerplate” contracts, prospective employers won’t accommodate reasonable requests. “Even if the employer states that the contract is ‘standard’ and can’t be changed, physicians should not assume that there’s no room for movement or compromise,” Mr. Hursh said. “There usually is.”

Mr. Weavil points out that contract adjustments, either through a language change or a new addendum, do occur. “The key is to ask nicely for accommodation on a reasonable number of issues,” he said.

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## Exploring Remote Physician Mentoring Opportunities

**Professional organizations and technology resources make it easier for early-career physicians to connect with distant mentors**

By Bonnie Darves, a freelance health care writer

Traditional one-on-one, in-person mentor-mentee arrangements are perhaps still the gold standard for young physicians seeking guidance from their older, more experienced colleagues, but physicians today often benefit from seeking a mentor, or an additional mentor, who is outside their training program or practice organization.

Such remote-mentoring arrangements can be especially valuable for young physicians who want to emulate the career trajectory of an esteemed physician who is across the country — or on the other side of the world — or who need help navigating a tricky professional or political environment in their city or region. And physician scientists working in a relatively small, niche research area may be compelled by geographical logistics to seek counsel from a colleague in a distant location. Further, many young physicians sometimes find themselves somewhat adrift in early career, when they're no longer in proximity to the mentors from their training years.

The good news is that there are lots of ways to establish remote-mentoring relationships today for physicians who are prepared to do some research

and some legwork. For starters, most physician professional organizations operate established regional and national programs connecting mentors with prospective mentees, and a simple email or phone call can get the process started. Another option is to identify national special-interest groups and participate in them with the intention of finding a future mentor. And increasingly, physicians are connecting remotely because the available technology makes that easy to accomplish.

“If there’s one thing COVID has taught us, among many other lessons, it’s that we can make satisfying virtual connections to broaden the possibilities if we’re looking for guidance,” said Anna Pereira, MD, MPH, a staff physician in palliative medicine and leadership development coach at Hennepin Healthcare and p of medicine at University of Minnesota Medical School. “A lot has changed in the past five years.”

### Professional organizations provide starting point for mentor connections

It was actually during the early pandemic that the American Society of Regional Anesthesia and Pain Medicine (ASRA) launched its formal Physician Mentorship and Leadership Special Interest Group, when it recognized the growing need for early-career physicians to connect with their older counterparts, regardless of their location, said Brett J. Elmore, MD, who is vice chair of the group. “We wanted to create a space where ASRA members could easily connect for networking and mentoring, based on their needs or interests,” said Dr. Elmore, an associate professor of anesthesiology and orthopedic surgery who directs the regional anesthesia and acute pain medicine fellowship program at the University of Virginia.

ASRA’s mentor match pairing, which links early-career members with either mid- or late-career members in structured nine-month mentoring sessions, has proved immensely successful, Dr. Elmore reports, and to date has created more than 400 pairings. “It has really become entrenched in our society, and some of the pairs have continued their relationships,” he said. He added that video technology such as Zoom has been a boon to the program and that pairs are intentionally matched in advance of the society’s national meeting to give pairs an opportunity to meet face to face.

Jen Brull, MD, president-elect of the American Academy of Family Physicians, recommends that early-career physicians seeking mentors start with their professional organization and broaden their search from there, as needed

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or desired. “Many physicians are willing and available to mentor, and structured programs are a great way to start looking for one,” said Dr. Brull. She has mentored scores of medical students and trainees, including young physicians who eventually came to work in her former rural Kansas practice. “I have always enjoyed meeting the needs of physicians who need me,” said Dr. Brull, “and AAFP has lots of resources to help early-career physicians connect with senior colleagues willing to mentor them.”

One benefit of tapping into a professional organization’s resources as a starting point is that such mentoring programs serve as a platform for making remote connections, according to Jennifer E. Rosen, MD, regional chief of endocrine surgery at MedStar Washington Hospital Center and Georgetown University Medical Center.

*“Remote mentoring requires having some way to introduce prospective mentors and mentees, and organizations’ programs also provide a way to break the ice.”*  
— Jennifer E. Rosen, MD, MedStar Washington Hospital Center, and Georgetown University Medical Center

Dr. Rosen, who has been involved with several American College of Surgeons (ACS) programs that connect young surgeons with senior colleagues throughout the country. “Such programs also can help young physicians figure out what they’re seeking in a mentor,” Dr. Rosen said, thus avoiding an awkward introductory conversation.

The ACS’ Young Fellows Association (YFA), for example, operates two mentoring programs that provide career and skill-building opportunities as well as engagement experiences. Interestingly, YFA has offered successful mentor-mentee pairing programs that specifically and intentionally match mentees with mentors who aren’t in the same geographical location. “During the pandemic, we took full advantage of all that can be done with Zoom and other technology, and we found that it was very powerful for the pairs to see each other in person,” she said.

“One of the benefits of having mentors ‘from away’ is that it’s potentially a non-competitive [environment], and ‘remote’ exchanges can be less threatening,” said Dr. Pereira. “It’s sometimes easier to be open and honest about what you’re unsure about,” she said, if mentors and mentees aren’t in the same town.

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## Creating a mentor ‘ecosystem’ is essential

Young physicians, and even those entering their mid-career years who want to make new connections, might benefit from seeking out several types of mentors: clinical mentors, career mentors, life mentors, and, if applicable, research mentors. The mentor who can help you plan a future career move, cultivate a specialty niche, or obtain your next grant might not be the same person who can help you surmount organizational or political roadblocks. And the mentor who can help you navigate the perennial challenge of balancing your family life and your work life without compromising one or the other, by sharing wisdom and experience, might not even be in your field.

*“The point is, we can’t all be everything for each other, and most of us need multiple mentors over the course of our careers.”*  
— Ana Núñez, MD University of Minnesota

Ana Núñez, vice dean for diversity, equity, and inclusion and a professor of medicine at the University of Minnesota. And some of the best prospective mentors for young physicians, she said, might be colleagues they’ve never encountered.

Dr. Núñez added that it’s vital for underrepresented physicians to seek mentors to help them navigate environments and situations that may be unfamiliar to them. In such cases, she said, it can be helpful for physicians to seek out both senior colleagues and their peers. “There’s a real need for this kind of navigation mentoring. And don’t ignore peer mentors, former fellow medical students or residents who might be excellent mentors,” Dr. Núñez said, based on their professional experiences in the intervening years.

Dr. Pereira has long urged physicians to create a quilt of mentors to accommodate the various aspects of their professional and personal lives. She thinks it’s especially important for community practicing physicians to cultivate a range of mentors — both local individuals and some based elsewhere — and to ensure that the mix includes a life-planning mentor. “With the high rates of burnout and moral distress we’re seeing, it can be very helpful for young physicians to have a senior mentor,” she said, who has weathered such crises.

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Dr. Rosen believes that mentoring relationships have become more important than ever for community practicing surgeons because of the increasingly complex compensation structures and time constraints surgeons face today. “There’s just less intellectual free time now,” she said, to discuss clinical and professional matters with colleagues, and having mentors, even remote ones, can help fill that gap. “People are stressed, and they’re looking for connections now — ways to get external input outside their institutions.”

For example, a surgeon working in a small hospital who wants to make the case to leadership for expanding procedure offerings over time will benefit from working with a distant mentor who has done that successfully, Dr. Rosen noted.

### **How to approach a prospective mentor**

For physicians who want to explore remote mentoring possibilities and have a specific individual in mind, their chances of establishing a fruitful relationship increase substantially if they’re strategic, assertive, and thoughtful in their approach. The strategy part entails finding out as much as possible about the prospective mentor. In other words, read their work, review their presentations, and become generally knowledgeable about their career path to date. It’s also advisable to set down in writing precisely what the mentee is seeking initially and how that might connect to career goals over the longer term. In other words, be prepared to spend time and energy before approaching the individual via email.

Then craft the email. That missive should make it clear that the prospective mentee knows the possible mentor’s work. In Dr. Rosen’s view, an effective way to begin is to reference a recently published work or presentation. “You might start by saying that you saw the physician’s talk or read a recent article on a subject of mutual interest,” she said, “and that you’d like to connect with them.” The writer should also briefly describe who they are and why they want to make the connection. “Be very clear about exactly what you’re asking,” she said.

“It’s very important to personalize that initial communication by ensuring [the recipient] that you’ve read as much as possible about them and that you have a specific objective in reaching out,” Dr. Pereira said. For example, if the young physician wants to combine clinical practice and teaching and the prospective mentor is exemplary in that regard, state that.

“Good communication is key, and young physicians can expect that a personalized and well-written email will be well received by a prospective mentor,” Dr. Elmore said.

One of the huge benefits of the internet and this technology-aided world we live in is that it’s easy to find a prospective mentor’s contact information. But just because it’s easy to connect, that doesn’t mean that the starting missive should be informal. It shouldn’t. It should be crafted in a concise, professional, thoughtful, and ideally mildly persuasive tone that might interest the prospective mentor in making contact.

It’s also important to recognize that even the best-crafted request might not work out, said Dr. Brull, and to prepare for that possibility. “It’s easy to track down someone’s email. The trick is in crafting your ‘ask’ so that people [possible mentors] can respond graciously if their lives just won’t support establishing a new mentor relationship,” she said.

Several sources interviewed for this article acknowledged that it can be difficult to make that initial mentor connection. Physicians, especially those in leadership roles, are extremely busy, and email inboxes are quickly cluttered. Physicians who don’t receive a reasonably timely response (a few weeks) should reach out again, gently, to remind the prospective mentor of their interest. It can also be helpful to identify a potential conduit to the individual and reach out that way. “Email with no response usually just means that people are very busy. When you don’t hear back, consult the institution’s organization chart and try to find the physician’s administrative assistant, and ask for help,” said Dr. Núñez. “Sometimes, that works.”

### **What to expect in a successful mentor-mentee relationship**

Young physicians seeking remote mentors will likely find them, provided they are strategic in their search and specific — and explicit — in making their request. Once they succeed in identifying a willing mentor, mentees should be ready and able to meet their responsibilities to ensure they hold up their side of the arrangement. Following are several key considerations for mentees as they proceed to establish and sustain mutually beneficial relationships with mentors.

### **When asking for a mentor’s time and assistance, be very specific in your request.**

It’s best to state exactly what you’re seeking, whether that’s guidance on a particular project or counsel about making a career pivot, and to start



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with a small, time-limited email request. Rather than simply saying, “Will you be my mentor?” tell the prospective mentor specifically why you’ve reached out — as in, “I saw your talk on X, or I’ve been following your career/research.” Then ask if they’re amenable to a 20-minute phone or video conversation on a specific topic. “Keep it short and sweet,” Dr. Núñez advised, and make it clear and concise. “Don’t subject the person to a wall of words. Keep it to a half-screen on your computer.”

### **Be prepared to do the heavy lifting.**

One mistake some mentees make, all sources agreed, is expecting that mentors will simply dole out advice while the mentee passively “receives” it. That’s not a relationship; it’s an information exchange, and one that’s not likely to be gratifying for the mentor. Instead, come to the mentoring session with specific questions (sent in advance) or an observation or reported clinical development, for example, that might interest the mentor or spark a discussion both will be interested in.

*“When it’s a two-way street, it’s more rewarding for both the mentor and mentee. Mentees need to help with their side of the street.”*

— Jen Brull, MD, AAFP President-elect

The heavy lifting also means completing any homework the mentor assigned or following up on the mentor’s recommendations. If the mentor suggests reading some studies, show up prepared to discuss them. If the mentor recommends taking a course, sign up and report that you’re on track to complete the course. And unless a clinical or personal emergency has occurred, mentees should always show up on time and ready to work, sources agreed.

### **Understand what a mentor relationship is — and isn’t — and establish a reasonable meeting cadence.**


Mentor relationships are essentially business and professional relationships, at least initially, and should be treated as such. The meetings should be fairly formal, not just conversational, and should be structured to produce measurable or qualifiable results. That means mentees should respect the time that mentors have set aside for the engagement by contributing as

actively as possible. “Mentees really have to prepare, and they must understand their responsibilities. One nice conversation does not a mentorship make. You must plan ahead to best honor the time together,” said Dr. Núñez.

Dr. Elmore urges young physicians to keep in mind that the relationship should be structured to “move” the mentee forward so that it produces measurable results. “It needs to have a prescription about what the relationship will do,” he said, even if the relationship also develops into a friendship over time. “If you’re too relaxed about it, the mentorship won’t be as fulfilling.”

Establishing an ideal cadence for the sessions in a remote-mentoring relationship can be difficult at first, especially if distant time zones are involved. Several sources recommended first asking what has worked in the past for the prospective mentor and proceeding from there. It’s unlikely, all agreed, that a mentor will have time to devote to weekly sessions, and even monthly ones might be too frequent for some busy mentors. Dr. Núñez recommended that mentees also avoid overloading themselves by committing to a too-frequent cadence. “You have to make sure that you can also commit to the schedule and your responsibilities for the sessions,” she said.

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CLINICAL PRACTICE

Patrick G. O'Malley, M.D., M.P.H., *Editor*

## Heart Failure with Preserved Ejection Fraction

Antonio Cannata, M.D., and Theresa A. McDonagh, M.D.

*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

**A 75-year-old woman with a history of type 2 diabetes mellitus, resistant hypertension, obesity, and chronic obstructive pulmonary disease (COPD) is admitted with severe peripheral edema and exertional dyspnea on minimal effort. After an evaluation that rules out an acute coronary syndrome, she receives a diagnosis of heart failure. The N-terminal pro-B-type natriuretic peptide (NT-proBNP) level is 1529 pg per milliliter. Echocardiography reveals left ventricular dimensions within the normal range, left ventricular hypertrophy, left ventricular ejection fraction of 52%, dilated atria, right ventricular size and function within the normal range, and a pulmonary arterial systolic pressure of 65 mm Hg (normal, <35). How would you further evaluate and treat this patient?**

From King's College Hospital, London (A.C., T.A.M.) and the British Heart Foundation Centre of Research Excellence, School of Cardiovascular Medicine, Faculty of Life Science, King's College London, London (A.C., T.A.M.). Dr. McDonagh can be contacted at [theresa.mcdonagh@kcl.ac.uk](mailto:theresa.mcdonagh@kcl.ac.uk) or at King's College Hospital, Denmark Hill, London SE5 9RS, United Kingdom.

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CME



### THE CLINICAL PROBLEM

**H**EART FAILURE HAS BEEN DEFINED PHYSIOLOGICALLY AS THE INABILITY of the heart to supply sufficient oxygen to the metabolizing tissues despite an adequate filling pressure.<sup>1</sup> It is not a single pathological diagnosis but rather a clinical syndrome of symptoms and signs of cardiac origin. Most definitions require the presence of cardinal symptoms (e.g., breathlessness, ankle swelling, and fatigue), which may be accompanied by signs (jugular venous distension, pulmonary rales, and peripheral edema) and the presence of cardiac dysfunction. These definitions are independent of the presence or absence of systolic dysfunction traditionally based on the percentage of the left ventricular ejection fraction (LVEF).<sup>2-4</sup>

Our contemporary phenotypic classification of chronic heart failure according to left ventricular function is based on a cutoff point of an LVEF above or below 50%. Although the ejection-fraction cutoff for heart failure with preserved ejection fraction has changed, the current nomenclature defines heart failure with reduced ejection fraction as heart failure with an LVEF of 40% or less, heart failure with preserved ejection fraction as heart failure with an LVEF of 50% or greater, and heart failure with mildly reduced ejection fraction as heart failure with an LVEF of 41 to 49%.

When the contemporary definition is applied, heart failure with preserved ejection fraction is present in up to 50% of all adult patients who are hospitalized for heart failure. That prevalence increased from 38% in the late 1980s to 54% in the early 2000s.<sup>5-9</sup> The incidence of the condition among adults is between 7 per 1000 and 18 per 1000 persons per year.<sup>10-12</sup> Owing to the aging of the global population and the increased prevalence of coexisting conditions such as obesity, the incidence

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KEY POINTS

HEART FAILURE WITH PRESERVED EJECTION FRACTION

- Heart failure with preserved ejection fraction is a heterogeneous syndrome.
- The diagnosis of the condition requires ruling out potential confounders such as respiratory disease, ischemic heart disease, hypertensive or valvular heart disease, cardiomyopathies, and amyloidosis.
- Symptoms and signs of heart failure, a left ventricular ejection fraction of 50% or greater, and evidence of cardiac structural abnormalities at rest or with exercise are required for the diagnosis.
- Contemporary guidelines recommend diuretic therapy and treatment with sodium–glucose cotransporter 2 (SGLT2) inhibitors for acute heart failure to reduce congestion and the continuation of SGLT2 inhibitors to reduce the risk of hospitalization for heart failure.
- New cardiometabolic drugs such as glucagon-like peptide-1 agonists have been shown to reduce symptoms and improve quality of life and exercise tolerance in patients with both heart failure with preserved ejection fraction and obesity.
- No available medical therapy has resulted in a reduction in mortality among patients with heart failure with preserved ejection fraction. Therefore, the current aims of medical treatment are to reduce the risk of hospitalization and improve quality of life.

of heart failure with preserved ejection fraction is expected to increase.<sup>13</sup>

Heart failure with preserved ejection fraction is heterogeneous and caused by multiple pathophysiological mechanisms, including cardiac aging and cardiometabolic disorders (Fig. 1).<sup>14,15</sup> Patients with the condition are often older and female. In addition, there is a higher prevalence of obesity, type 2 diabetes mellitus, hypertension, atrial fibrillation, chronic kidney disease, and other noncardiovascular conditions among patients with heart failure with preserved ejection fraction than among those with heart failure with reduced ejection fraction.<sup>16</sup> These multiple coexisting conditions have a substantial effect on outcomes.<sup>17</sup> Mortality associated with heart failure with preserved ejection fraction ranges between 15% at 1 year to 75% at 5 to 10 years after hospitalization.<sup>5,15,18</sup>

When both clinical trials and community-based studies are considered, the risk of death from any cause among patients with heart failure with preserved ejection fraction is lower than that among patients with heart failure with reduced ejection fraction after adjustment for age, sex, and causes of heart failure (hazard ratio, 0.68; 95% confidence interval [CI], 0.64 to 0.71).<sup>19</sup> Each year, approximately 6 to 10% of patients with heart failure with preserved ejection fraction are hospitalized for decompensated heart failure.

Until recently, specific etiologic factors that are associated with a poorer prognosis, such as cardiac amyloidosis (average prevalence of 6.3% among patients with heart failure with preserved ejection fraction and up to 21% among patients

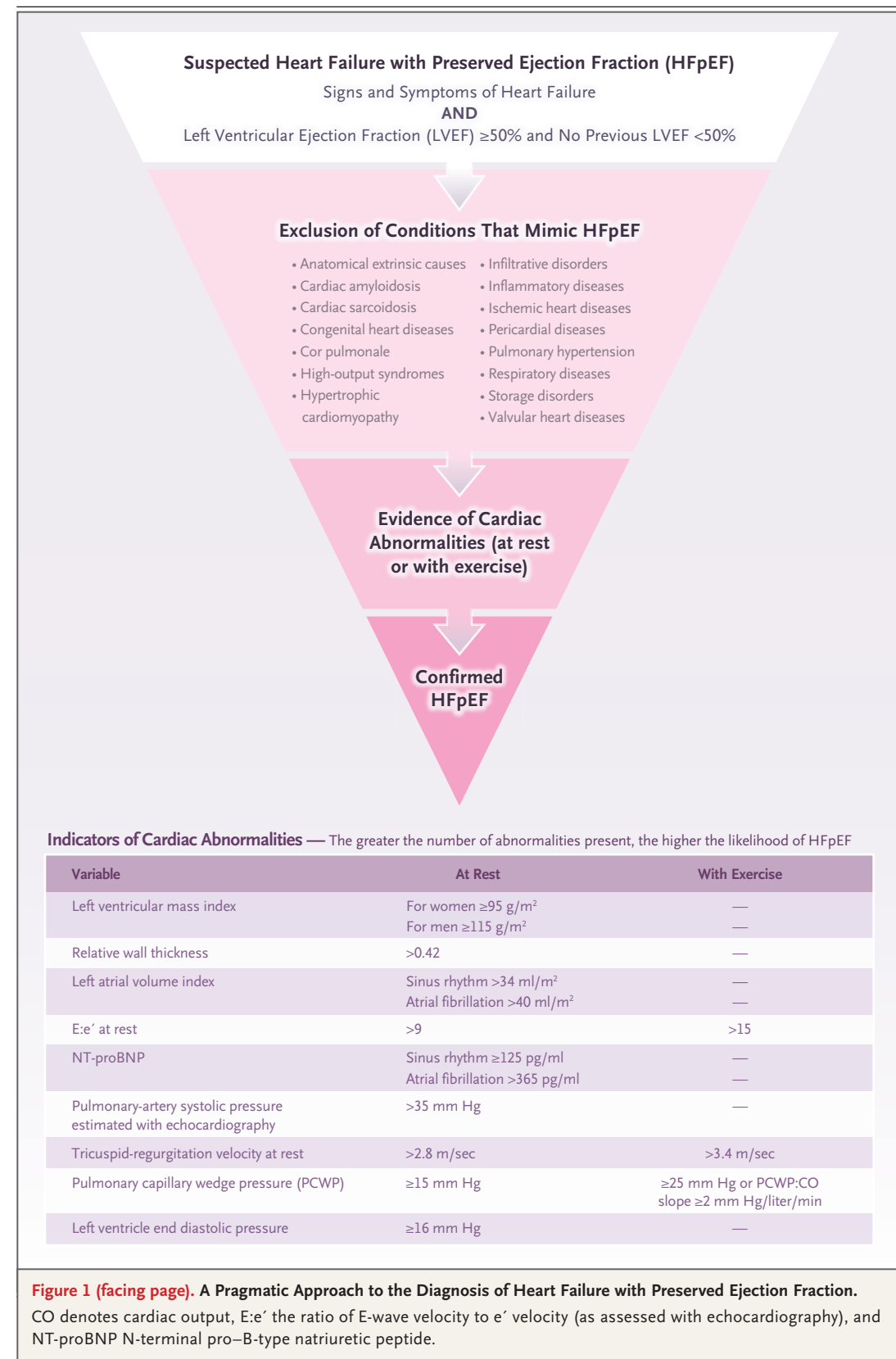
>90 years of age<sup>20</sup>) and hypertrophic cardiomyopathy, were considered part of the spectrum of conditions defined as heart failure with preserved ejection fraction. Diagnosis of these conditions is important because there are now targeted treatments available.

STRATEGIES AND EVIDENCE

DIAGNOSIS

Making the diagnosis of heart failure with preserved ejection fraction is challenging owing to the presence of multiple overlapping conditions that mimic it and several phenotypic subtypes that contribute to the pathophysiologic features of the condition (Fig. 1). Patients often present with dyspnea and signs of congestion. In these patients, a pragmatic approach to the diagnosis requires an echocardiographic estimate of an LVEF of 50% or greater (excluding patients with recovered LVEF) and objective evidence of left ventricular diastolic dysfunction or raised left ventricular filling pressures. In these patients, the ruling out of potential mimickers such as respiratory disease, hypertrophic cardiomyopathy, and storage and infiltrative disorders, such as Fabry's disease or cardiac amyloidosis, is pivotal.<sup>4,21</sup>

The presence of cardiac structural or functional abnormalities is fundamental for making the diagnosis and for ruling out noncardiovascular causes of the clinical presentation (Fig. 1). Measuring natriuretic peptide levels is useful when heart failure is suspected. In patients with suspected heart failure, levels of NT-proBNP of 125 pg per milliliter or greater are diagnostic of



**Figure 1 (facing page). A Pragmatic Approach to the Diagnosis of Heart Failure with Preserved Ejection Fraction.** CO denotes cardiac output, E:e' the ratio of E-wave velocity to e' velocity (as assessed with echocardiography), and NT-proBNP N-terminal pro-B-type natriuretic peptide.

heart failure, with a sensitivity of 0.98 and a specificity of 0.35; the negative predictive value is high (0.97) for the ruling out of the diagnosis.<sup>22</sup> However, it is important to note that natriuretic peptide levels may be either falsely elevated in specific conditions, such as renal impairment or atrial fibrillation, or inappropriately low, particularly in the presence of obesity.

The presence of noncardiovascular coexisting conditions, such as obesity, insulin resistance, cardiometabolic disorders, physical inactivity, and respiratory disease, also confounds the diagnosis of heart failure with preserved ejection fraction because these conditions cause exertional dyspnea.<sup>23,24</sup> Diagnostic scoring systems exist but lack robust diagnostic validation.<sup>21,25</sup> When these scores are used, the diagnosis of the condition remains in doubt in approximately 30% of patients. For these patients, either invasive left ventricular hemodynamic assessments at rest or during exercise or diastolic stress testing (or both) may confirm the diagnosis. In addition, cardiac magnetic resonance imaging may help to rule out other mimickers of heart failure with preserved ejection fraction, such as hypertrophic cardiomyopathy or cardiac amyloidosis.

**TREATMENT**

*Goals of Treatment*

The main goals of therapy for patients with heart failure with preserved ejection fraction are to address the signs and symptoms of heart failure, improve quality of life, and reduce the risk of hospitalization. To date, no treatment has shown a significant reduction in mortality. Until recently, treatment has been largely supportive, and several clinical trials of potential disease-modifying agents have not shown evidence of benefit (Fig. 2). Most clinical trials of the condition have recruited patients with LVEFs of greater than 40% or 45%, making it difficult to infer conclusions specific to heart failure with preserved ejection fraction when a threshold ejection fraction of 50% is used.

*Treatment of the Underlying Cause and Coexisting Conditions*

Treatment of the underlying cause and concomitant cardiovascular and noncardiovascular coexisting conditions (e.g., hypertension, atrial fibrillation, diabetes, respiratory disease, ischemic heart disease, valvular heart disease, and obesity)

is the basis for the treatment strategies in patients with heart failure with preserved ejection fraction.

**PHARMACOTHERAPY**

*Renin–Angiotensin–System Inhibitors*

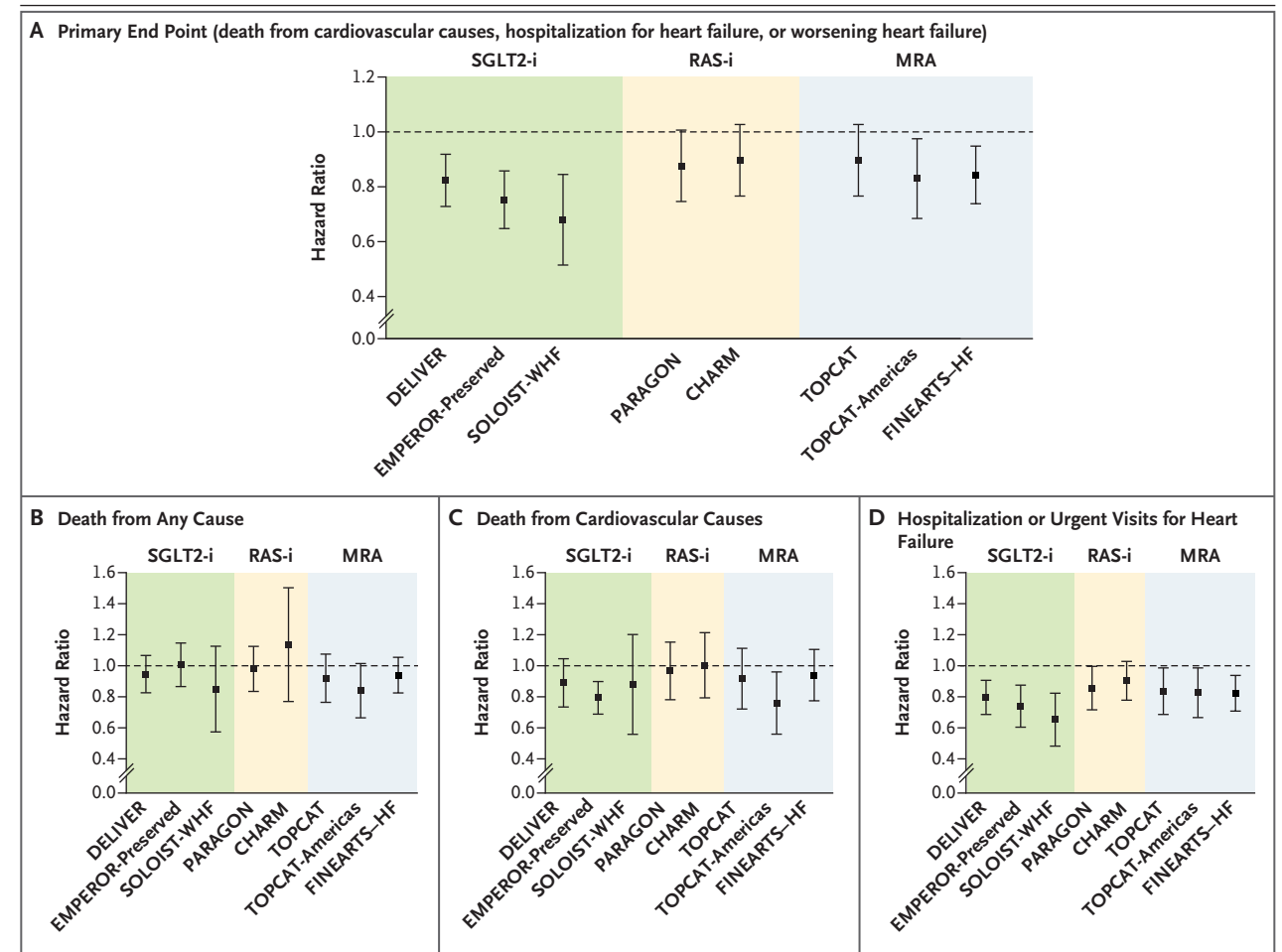
Inhibition of the renin–angiotensin system (RAS) in heart failure with preserved ejection fraction has been the focus of many treatment trials (Fig. 2). The CHARM (Candesartan in Heart Failure — Assessment of Reduction in Mortality and Morbidity)–Preserved trial did not show a significant benefit for the use of the angiotensin-receptor blocker (ARB) candesartan on the primary composite end point of death from cardiovascular causes or hospitalization for heart failure over a median follow-up of 36 months (hazard ratio, 0.89; 95% CI, 0.77 to 1.03); however, ARB therapy was associated with a lower incidence of hospitalizations for heart failure than placebo (15% vs. 18%; P=0.02).<sup>26</sup> The I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial, using irbesartan, showed similar results to those in the CHARM–Preserved trial, which suggests no beneficial role for ARBs in patients with heart failure with preserved ejection fraction (hazard ratio for the composite end point, 0.95; 95% CI, 0.86 to 1.05) aside from their known benefit in the treatment of hypertension.<sup>27</sup> Likewise, in the PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) trial of the angiotensin-converting enzyme (ACE) inhibitor perindopril, the incidence of death or hospitalization for heart failure (the primary composite end point), at a median follow-up of 2.1 years, was similar in patients who received perindopril and those who received placebo (hazard ratio, 0.92; 95% CI, 0.70 to 1.21). However, perindopril was associated with a lower risk of hospitalization for heart failure at 1 year (hazard ratio, 0.63; 95% CI, 0.41 to 0.97).<sup>28,29</sup> Despite the lack of significant benefit shown in trials of RAS inhibitors in heart failure with preserved ejection fraction specifically, these drugs are indicated for use in treating the underlying causes of heart failure and coexisting conditions, such as hypertension.

*Angiotensin Receptor–Neprilysin Inhibitors*

The PARAGON-HF (Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB Global Outcomes in HF with

Preserved Ejection Fraction) trial evaluated the use of sacubitril–valsartan in 4822 patients with heart failure who had an LVEF of greater than 45%.<sup>30,31</sup> The trial did not show a significant reduction in the incidence of the primary end point of death from cardiovascular causes or hospitalization for heart failure (rate ratio, 0.87; 95% CI, 0.75 to 1.01; P=0.06). However, there was a signal of possible benefit in women (rate ratio, 0.73; 95% CI, 0.59 to 0.90) and patients with an LVEF below the median value of 57%

(rate ratio, 0.78; 95% CI, 0.64 to 0.95). The PARAGLIDE-HF (Prospective Comparison of ARNI with ARB Given Following Stabilization in Decompensated HFpEF) trial, which involved 466 patients whose condition was stabilized after worsening heart failure with an LVEF of greater than 40%, showed that sacubitril–valsartan, as compared with valsartan alone, reduced the incidence of the primary outcome of neurohormonal activation (15% greater reduction in NT-proBNP level between baseline and week 8;



**Figure 2. Treatment Effect Shown in Trials of Recommended Drug Therapies in Heart Failure with Preserved Ejection Fraction.**

Shown are hazard ratios or risk ratios, from the results of eight clinical trials, for the primary composite end point of death from cardiovascular causes, hospitalization for heart failure, or worsening heart failure (Panel A), and for death from any cause, death from cardiovascular causes, and hospitalization or urgent visits for heart failure (Panels B through D), in patients with heart failure with preserved ejection fraction who were treated with a sodium–glucose cotransporter 2 inhibitor (SGLT2-i), renin–angiotensin–system inhibitor (RAS-i), or mineralocorticoid receptor antagonist (MRA). The trials, and the treatments they investigated, were DELIVER (dapagliflozin), EMPEROR-Preserved (empagliflozin), SOLOIST-WHF (sotagliflozin, in patients with heart failure with reduced ejection fraction and patients with heart failure with preserved ejection fraction), PARAGON (sacubitril and valsartan), CHARM (candesartan), TOPCAT and TOPCAT-Americas (spironolactone), and FINEARTS-HF (finerenone). Hazard ratios are shown for all trials except for hospitalizations or urgent visits for heart failure in the PARAGON trial, for which risk ratios are shown (Panel D). I bars indicate 95% confidence intervals.

geometric mean ratio, 0.85; 95% CI, 0.73 to 0.10), with a greater effect in patients with an LVEF of less than 60%. However, this reduction was at the expense of a greater incidence of symptomatic hypotension (odds ratio, 1.73; 95% CI, 1.09 to 2.76).<sup>32</sup> Similarly, the PARALLAX (Prospective Comparison of ARNI versus Comorbidity-Associated Conventional Therapy on Quality of Life and Exercise Capacity) trial, which involved 2572 patients with heart failure and an LVEF of greater than 40%, showed a greater reduction in the first primary end point of change in the NT-proBNP level at 12 weeks with sacubitril-valsartan than with standard medical therapy (i.e., either enalapril or valsartan) or placebo (geometric mean ratio, 0.84; 95% CI, 0.80 to 0.88). However, there was no change in the other primary end point of improvement in 6-minute walk distance from baseline to week 24.<sup>33</sup> The data from these trials support the indication from the Food and Drug Administration for the potential use of sacubitril-valsartan on the basis of the results of the subgroup of patients with LVEFs below the normal range.

#### Mineralocorticoid Receptor Antagonists

The evidence for the use of mineralocorticoid receptor antagonists (MRAs) in the treatment of heart failure with preserved ejection fraction comes mainly from three trials. Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) was a phase 2 trial that involved 422 patients and investigated the effect of spironolactone at a daily dose of 25 mg on diastolic and functional characteristics. It showed a reduction in left ventricular mass and natriuretic peptide levels and improvements in measures of diastolic function but no changes in the symptoms and signs of heart failure or in quality of life.<sup>34</sup> In the larger phase 3 TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, patients with heart failure with preserved ejection fraction and an LVEF of greater than 45% were randomly assigned to receive either spironolactone or placebo.<sup>35</sup> This trial did not show a reduction in the primary outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure.<sup>36</sup> However, FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure)

recently showed that in patients with an LVEF of 40% or greater, finerenone increased to a maximum dose of 40 mg daily reduced the incidence of the primary composite end point of death from cardiovascular causes and total heart-failure events, thus supporting its use in patients with heart failure with preserved ejection fraction.<sup>37</sup>

#### Beta-Blockers

According to observational data, up to 80% of patients with heart failure with preserved ejection fraction receive beta-blockers for other clinical indications. However, trials involving patients with the condition who have received either nebivolol or carvedilol have not shown a reduction in death or hospitalizations for heart failure or an improvement in quality of life.<sup>38-45</sup>

#### Diuretics

Until recently, diuretics were the only pharmacologic therapy indicated for heart failure with preserved ejection fraction despite a lack of randomized clinical trials. For patients with the condition, diuretics are recommended to reduce congestion, symptoms, and the risk of hospitalization for heart failure.<sup>3,4</sup> Loop diuretics are used in approximately 90% of patients with acute heart failure.<sup>46</sup> Guidelines recommend the use of the lowest possible dose of diuretics and possible discontinuation when euolemia is achieved.<sup>3,4</sup> In patients with concomitant hypertension, thiazide diuretics are also an option.<sup>3</sup>

#### SGLT2 Inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a group of drugs first studied for type 2 diabetes mellitus, and they have subsequently been shown to be effective in reducing adverse events in patients with heart failure. The evidence for their use in patients with heart failure with preserved ejection fraction comes from two large trials, EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure).<sup>47,48</sup> In these trials, SGLT2 inhibitors showed a reduction in the primary outcome of death from cardiovascular causes or hospitalization for heart failure as compared with placebo — empagliflozin at a dose of 10 mg

daily in the EMPEROR-Preserved trial (hazard ratio, 0.79; 95% CI, 0.69 to 0.90;  $P < 0.001$ ) and dapagliflozin at a dose of 10 mg daily in the DELIVER trial (hazard ratio, 0.82; 95% CI, 0.73 to 0.92;  $P < 0.001$ ). There was no heterogeneity in the treatment effect on the basis of sex or ejection fraction. A subsequent meta-analysis of both trials corroborated the results and showed a consistent reduction in death from cardiovascular causes or hospitalization for heart failure (hazard ratio, 0.80; 95% CI, 0.73 to 0.87;  $P < 0.001$ ). However, the reduction in the incidence of the primary end point was driven by fewer hospitalizations for heart failure (hazard ratio, 0.74; 95% CI, 0.67 to 0.83;  $P < 0.001$ ), and the reduction in death from cardiovascular causes was not significant (hazard ratio, 0.88; 95% CI, 0.77 to 1.00;  $P = 0.052$ ). Current guidelines recommend the use of SGLT2 inhibitors in patients with heart failure with preserved ejection fraction on the basis of the composite primary end points used in the trials but stress that the observed effect is mainly owing to the reduction in hospitalizations for heart failure.

#### Glucagon-like Peptide-1 Receptor Agonists

Heart failure with preserved ejection fraction is often associated with cardiometabolic derangement and a high prevalence of diabetes and obesity, both of which may reduce exercise capacity. Therefore, improvement in the cardiometabolic profile, weight loss, and reduction in inflammation may also be therapeutic targets. A recent trial, STEP-HFpEF (Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-related Heart Failure with Preserved Ejection Fraction), showed that, as compared with placebo, a weekly injection of 2.4 mg of semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, improved quality of life (mean change in score on the Kansas City Cardiomyopathy Questionnaire [KCCQ; scores range from 0 to 100, with higher scores indicating better health status], 16.6 points with semaglutide vs. 8.7 points with placebo;  $P < 0.001$ ), led to significant weight loss (mean percentage change in body weight,  $-13.3\%$  vs.  $-2.6\%$ ;  $P < 0.001$ ), improved exercise tolerance (mean change in 6-minute walk distance, 21.5 m vs. 1.2 m;  $P < 0.001$ ), and reduced inflammation (mean percentage change in C-reactive protein level,  $-43.5\%$  vs.  $-7.3\%$ ;  $P < 0.001$ ).<sup>49</sup> In a similar trial involving patients

with heart failure with preserved ejection fraction and type 2 diabetes, semaglutide therapy led to a greater reduction in heart failure-related symptoms and more weight loss than placebo at 1 year.<sup>50</sup> In a pooled analysis of both these trials, semaglutide was associated with a significant reduction in major adverse cardiac events.<sup>51</sup> The recent SUMMIT trial showed the efficacy of tirzepatide, a long-acting agonist of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. In this trial, in which 364 patients with heart failure with preserved ejection fraction (LVEF  $> 50\%$ ) and obesity received tirzepatide, treatment with tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo (hazard ratio, 0.62; 95% CI, 0.41 to 0.95;  $P = 0.026$ ) and improved health status (between-group difference in change in KCCQ score, 6.9 points; 95% CI, 3.3 to 10.6;  $P < 0.001$ ).<sup>52</sup>

These trials have shown efficacy for GLP-1 receptor agonism in patients with heart failure with preserved ejection fraction and obesity. However, we await further trials to expand the evidence.

#### TREATMENT DEVICES

Monitoring pulmonary pressures to control fluid status is a potential strategy for reducing hospitalization in patients with heart failure. The CardioMEMS system is a small, invasive, remote monitoring system that constantly measures pulmonary arterial pressure and transmits the readings to clinicians who then adjust medical therapy in response. In the single-blind CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial involving 550 patients, CardioMEMS-guided optimization of medical therapy was associated with a significant reduction in hospitalizations for heart failure as compared with standard care, irrespective of the LVEF.<sup>53</sup> Similarly, the MONITOR-HF trial, an open-label trial involving 348 patients with chronic heart failure (28% with an LVEF  $> 40\%$ ), showed that hemodynamic monitoring with CardioMEMS improved the primary end point of change in quality of life (mean change in KCCQ score, 7.05) as compared with usual care (mean change in KCCQ score,  $-0.08$ ).<sup>54</sup>

Treatment with another device, an iatrogenic interatrial shunt, did not show a difference in

**Table 1. Guideline Recommended Treatment for Heart Failure with Preserved Ejection Fraction.\***

Treatment	Initial Daily Dose	Maximum Daily Dose	Use	Class of Recommendation				Common Side Effects and Contraindications	
				ACC-AHA 2022	ESC 2021, 2023	CCS-CHFS 2017, 2020	JCS-JHFS 2017, 2021		NHFA-CSANZ 2018
<b>Diuretics</b>				Class I	Class I	Recommend	Class I	Recommend	
Loop diuretics			To relieve congestion; minimum dose possible						Hypokalemia, hyponatremia, hypovolemia, worsening renal function
Furosemide	20–40 mg	600 mg							
Bumetanide	0.5–1 mg	10 mg							
Torsemide	10–20 mg	200 mg							
<b>Thiazides</b>			To relieve congestion and reduce blood pressure						Hypokalemia, hypochloremia, hyperglycemia, hyperuricemia, nausea, postural hypotension
Chlorthalidone	25 mg	200 mg							
Hydrochlorothiazide	25 mg	200 mg							
Bendroflumethiazide	2.5 mg	10 mg							
Indapamide	2.5 mg	5 mg							
Metolazone	2.5 mg	20 mg							
<b>SGLT2 inhibitors</b>			To reduce the risk of hospitalization	Class IIIa†	Class I	NS‡	NS‡	NS‡	Diabetes ketoacidosis, UTI
Empagliflozin	10 mg	10 mg							
Dapagliflozin	10 mg	10 mg							
Sotagliflozin	200 mg	400 mg	SGLT1/2 inhibitor; for use in patients with diabetes and heart failure						
<b>MRAS</b>									
Spirolonactone	12.5–25 mg	100 mg	For coexisting conditions; can decrease hospitalization among patients with low LVEF	Class IIb	For coexisting conditions§	Suggest¶	Class IIb	Consider	Hyperkalemia, worsening renal function, gynecomastia
Finerenone	10 mg	40 mg		NA	NA	NA	NA	NA	Hyperkalemia, worsening renal function

<b>RAS inhibitors</b>			For coexisting conditions; can decrease hospitalization, particularly among patients with LVEF lower than the normal range	Class IIb	For coexisting conditions§	Suggest	Class IIb	For coexisting conditions	Worsening renal function, hypotension, renal-artery stenosis
Candesartan	4 mg	32 mg							
Irbesartan	75 mg	300 mg							
Losartan	25 mg	150 mg							
Valsartan	20 mg	160 mg							
Sacubitril–valsartan	24–26 mg BID	97–103 mg BID							
<b>Beta-blockers</b>			For coexisting conditions; careful dose adjustment necessary; may exacerbate respiratory disease	For coexisting conditions	For coexisting conditions	For coexisting conditions	Class IIb	For coexisting conditions	Severe asthma, bradycardia, hypotension
Bisoprolol	1.25 mg	10 mg							
Nebivolol	1.25 mg	10 mg							
Carvedilol	3.125 mg BID	25 mg BID							
Metoprolol	12.5–25 mg	200 mg							
<b>GLP-1 receptor agonist</b>				NA	NA	NA	NA	NA	Diabetic ketoacidosis, nausea, vomiting
Semaglutide	2.4 mg weekly								
<b>GLP-1 and GIP receptor agonist</b>				NA	NA	NA	NA	NA	Alopecia, nausea, vomiting, asthenia, constipation, diarrhea, dizziness, lethargy, malaise
Tirzepatide	2.5 mg weekly	15 mg weekly							

\* Recommendation classifications are as follows: I, recommended; IIa, should be considered; IIb, may be considered; and III, not recommended or harmful. ACC denotes American College of Cardiology, AHA American Heart Association, BID twice daily, CCS Canadian Cardiovascular Society, CHFS Canadian Heart Failure Society, CSANZ Cardiac Society of Australia and New Zealand, ESC European Society of Cardiology, GIP glucose-dependent insulinotropic polypeptide, GLP-1 glucagon-like peptide 1, JCS Japanese Circulation Society, JHFS Japanese Heart Failure Society, LVEF left ventricular ejection fraction, MRA mineralocorticoid-receptor antagonist, NA not available, NHFA National Heart Foundation of Australia, RAS renin–angiotensin system, SGLT2 sodium–glucose cotransporter 2, and UTI urinary tract infection.

† At the time the guideline was published, only results from the EMPEROR-Preserved trial were available.

the incidence of the composite primary end point of death from cardiovascular causes, stroke, hospitalization for heart failure, and quality of life in patients with heart failure with preserved ejection fraction in the phase 3 REDUCE LAP-HF II (Study to Evaluate the Corvia Medical IASD System II to Reduce Elevated Left Atrial Pressure in Patients with Heart Failure).<sup>55</sup> Moreover, the preliminary results of the RELIEVE-HF (Reducing Lung Congestion Symptoms in Advanced Heart Failure) trial, which did not show a significant difference in the primary outcome (win ratio, 0.86; 95% CI, 0.61 to 1.22;  $P=0.20$ ), suggested that in patients with an LVEF of greater than 40%, implantation of interatrial shunt systems may be harmful on the basis of the incidence of adverse events among patients with preserved ejection fraction who received shunts (60.2%) as compared with patients who did not (35.9%) ( $P=0.001$ ).<sup>56</sup>

#### AREAS OF UNCERTAINTY

There is uncertainty regarding heart failure with preserved ejection fraction classification and the precise diagnostic criteria that should be used. More disease-modifying therapies are needed. The term “heart failure with preserved ejection fraction” is nonspecific and based on an arbitrary LVEF cutoff value and therefore may not provide adequate nomenclature for this heterogeneous disease.<sup>57,58</sup> Although patients with the condition share many common characteristics, distinct subgroups are emerging. Patients with specific phenotypic features of the condition, such as obesity, may benefit from specific medical treatment. We do not know whether GLP-1 receptor agonists and GIP agonists are useful in treating patients with heart failure with preserved ejection fraction who are not obese.<sup>20</sup> Beneficial treatments are now available for patients with cardiac amyloidosis, but more are needed. More specific noninvasive diagnostic tools would improve diagnostic accuracy and rule out confounding diagnoses. New biomarkers and techniques to measure increases in intracardiac pressures and volumes could improve diagnostic pathways. Treatment of coexisting conditions and use of preventive strategies may also reduce the incidence of the condition and resultant medical treatment.

Despite recent reductions in composite morbidity and mortality end points in clinical trials, no single trial of therapy has yet shown a sig-

nificant reduction in mortality or in death from cardiovascular causes in patients with heart failure with preserved ejection fraction. Several clinical trials are ongoing in this area (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

#### GUIDELINES

Therapies for heart failure with preserved ejection fraction that are recommended in international guidelines are summarized in Table 1.<sup>3,4,59-61</sup> All international guidelines recommend diuretic treatment for patients with the condition. The main difference among the guidelines is the strength of recommendations for the use of SGLT2 inhibitors in patients with heart failure with preserved ejection fraction, which reflects the timing of trial publications relative to the guideline publications. The more recent 2023 focused update of the European guidelines indicates the use of SGLT2 inhibitors as a class I recommendation (“recommend”).

The U.S. and the Japanese guidelines give a class IIb recommendation (“may be considered”) for the use of ARNIs and MRAs in patients with heart failure with preserved ejection fraction. The Canadian guidelines suggest the use of RAS inhibitors and MRAs, but the European Society of Cardiology guideline does not give any recommendations on these agents because the task force avoided issuing recommendations that were based on subgroup analyses of trials in which the primary outcomes showed no benefit.

#### CONCLUSIONS

Regarding the patient in the vignette, we would introduce guideline-directed therapies for heart failure with preserved ejection fraction. First, we would address the patient’s pulmonary and vascular congestion with intravenous diuretics. Once euolemia had been reached, we would switch to an oral loop diuretic. We would also add an SGLT2 inhibitor to reduce symptoms and the risk of subsequent hospitalization for heart failure. Effective decongestion should result in the reduction of her pulmonary arterial pressure and respiratory symptoms. We would target treatments to control both her hypertension and her obesity. Because the patient has resistant hypertension, with a blood pressure of greater than

130/80 mm Hg despite treatment with ramipril and amlodipine, we would add spironolactone. For her obesity, we could consider introducing a GLP-1 receptor agonist. We would assess her for sleep-disordered breathing and treat any obstructive sleep apnea found. In the longer term,

promotion of a healthy lifestyle, monitoring of disease progression, and treatment of coexisting conditions may avoid hospitalizations in the future and improve her quality of life.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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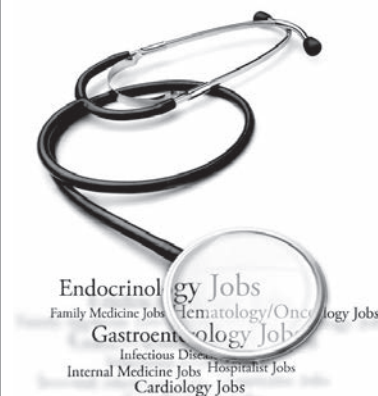


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