Over the past 4 decades, patients with heart failure (HF) have derived substantial benefit from the major advances in our understanding of pathophysiology of the HF syndrome, which have led to evolving treatment paradigms. Morbidity and mortality for patients as documented in clinical trials for HF with reduced ejection fraction (HFrEF) have steadily decreased, and many patients with this syndrome have also enjoyed improved functional capacity and quality of life. However, there are major unmet needs. Hospital discharges with a primary HF diagnosis, an index of population disease burden and economic impact, remain ≥1 million annually with little change between 2000 and 2010. According to the American Heart Association’s Heart and Stroke Facts,2 the prevalence of HF will increase ≈50% between 2012 and 2030, resulting in >8 million people ≥18 years of age with HF.3 This daunting future reflects the increased prevalence of HF as the population ages, acute myocardial infarction survival improves, and HF survival itself increases at rates that exceed our impact to prevent the development of HF.

The national and, indeed, international burden of HF reflects a growing component of HF with preserved ejection fraction (HFpEF), for which trials have been neutral, in contrast to the progress for HFrEF. These frustrating trial results reflect our incomplete understanding of the more heterogeneous complex of the HFpEF syndrome, which was only defined as an entity more recently. Knowledge in this area has evolved over the past few years, however, suggesting that positive results may be enabled by more targeted treatments rather than broad-brush interventions and a shift in focus to symptoms and daily quality of life as primary outcomes.

In this review, we will use the lessons of the recent past to illuminate pathways forward in how the HF syndrome is conceptualized, how we might better use the proliferating information at our fingertips to parse subsets of patients into how we might better target any of these therapies to individual patients to a degree that has entered practice.

The only therapy that has become more narrowly targeted after an initial broader indication is cardiac resynchronization therapy, by refining the indication using an electrical biomarker, the ECG. In 2009, HF guidelines recommended cardiac resynchronization therapy as a class I indication for all symptomatic HF patients with EF≤35% with QRS duration ≥120 ms.12 In the 2013 Guidelines, the class I cardiac resynchronization therapy

Heart Failure With Reduced EF

During the past 30 years, HFrEF has evolved from a rapidly fatal disease to a chronic condition requiring long-term team management (Figure 1). Improved survival has been documented in symptomatic HF from outpatient populations,5-6 in patients discharged from hospitalization,7,8 and for patients after referral for advanced therapies.9,10 The threat of sudden death in symptomatic HF has diminished markedly, associated with increasing penetration of early β-blocker therapy and mineralocorticoid receptor antagonism, as shown by a 75% decrease from before 2000 to after 2005 in the prospective outpatient registries in the United Kingdom, even in patients without implantable cardioverter defibrillators.6,8 As patients travel a longer journey with HF, each of the stages now provides more scope for intervention, as shown in Figure 2.11

The major advances in treatment of HFrEF have been based on large randomized controlled trials (RCTs), with subsequent incorporation of the data into Guidelines,12,13 resulting in what is commonly referred to as guideline-directed medical therapy. These recommendations were then incorporated into systematic quality improvement efforts with landmark success14 For all patients with reduced EF, HF symptoms, adequate renal function and blood pressure, angiotensin-converting enzyme inhibition (ACEi, or alternatively angiotensin receptor blockers [ARBs]), β-adrenergic receptor blockers, and mineralocorticoid antagonists are strongly recommended. It is actually remarkable that review of trial data and subgroup analyses for these therapies support benefit for essentially every subgroup evaluated. Thus, we treat virtually all HFrEF patients (within the bounds of trial enrollment populations) with the same therapies titrated, as tolerated, to the same target doses as in the trials. Despite innumerable published articles using clinical risk models or serum biomarkers, none have provided any insight into how we might better target any of these therapies to individual patients to a degree that has entered practice.

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indication narrowed to include only those with left bundle-branch block configuration as the driver of the wide QRS, based both on clinical registry experience of >15,000 patients and subset reanalysis of large trials. Thus, it is possible to better target therapy to those most likely to benefit, but we as a community have not often done so given the tools at our hands.

Targeting therapy is likely to become more important in our approach to HF patients in the near future. Nonetheless, we may not yet have reached an asymptote with nonselective application of neurohormone-based therapy, because further benefit was seen with the large RCT comparing valsartan/sacubitril with enalapril in patients tolerating previous ACEI/ARB therapy, with consistent and important favorable effects on HF outcomes and progression. Common targets may still exist for broad therapeutic strategies, in this case, angiotensin-blockade and neutral endopeptidase inhibition, to alter the balance of opposing neurohormonal systems.

### Potential Approaches to Individualization of Therapy for HFrEF

#### Mosaic Models of Disease

Our models of HF pathophysiology have been drawn both from direct measurements in humans and animal models and from inferences resulting from empirically effective therapies. The most visible and earliest recorded feature of the clinical syndrome is congestion, with the earliest medical writings describing relief from drainage of fluid through multiple routes. Impairment of contractility was quantitated in catheterization studies and later associated with abnormal calcium handling and excitation-contraction coupling from isolated muscle studies. Echocardiography and nuclear imaging revealed structural changes of left ventricular dilation and atrioventricular valve regurgitation that increase wall stress, further challenge myocardial oxygen demands, detract from forward perfusion, and increase pulmonary pressures and lung water content. Distortion of the delicate architecture of cardiac collagen and the lymphatic system may also accelerate cardiac remodeling. Electric dysynchrony from left bundle-branch block has been implicated retrospectively as an occasional cause of cardiomyopathy in the superresponder, but more often complicates cardiomyopathy of other etiology.

Although multiple inflammatory components are elevated in severe HF, inhibition of the inflammatory cascade has not improved outcomes, perhaps because immune activation occurs relatively late in disease progression as right heart failure leads to compromise of the intestinal barrier, hepatic congestion, and cachexia.

The major model credited with the improvement in prognosis thus far is the neurohormonal model, in which inhibition of the renin-angiotensin-aldosterone system and β-adrenergic blockade have led to the delay and, in some cases, reversal of ventricular remodeling and disease progression. Antagonism of neurohormonal activation has also led to the major decrease seen in premature sudden death, observed even before and in countries without routine use of implantable cardioverter defibrillators for primary prevention in patients with reduced left ventricular (LV) EF.

Looking forward however, HF progression will be increasingly appreciated as a mosaic of different system models. Because different models may dominate for different patients and at different times, there is little future in advocating the overall supremacy of 1 model over the others, particularly in the case of the neurohormonal model versus the hemodynamic model, when both are so inextricably linked from the
asymptomatic stage of elevated wall stress through to refractory end-stage disease. Similarly, once HF symptoms begin to limit daily life, there is a strong link between relief of symptoms and treatment to delay or reverse the progression of HF as a disease. For advanced HF, worsening symptoms decrease quality of life and lead to hospitalizations, and all 3 predict disease progression and death. This is a setting where focused study of home inotropic therapy may show different results from those studied in a stable population without resting symptoms of congestion.23–25

Two examples of systems with well-demonstrated perturbation in the setting of HF are abnormalities of myocardial metabolism and of the peripheral skeletal musculature. To the extent that we are approaching an asymptote with addressing neurohormonal activation, these systems are fertile targets, especially if imaging tools such as MRI or positron emission tomography can be used to identify those patient subsets with the most marked changes for early study of targeted therapeutics.26,27

Disrupting the Successful Stack of Therapies

Once the benefit of ACEi was demonstrated in the Studies of Left Ventricular Dysfunction (SOLVD) trial, additional agents have each been stacked on top of previous standard evidence-based therapy. Orthogonal to the stack has been the principle that assessment and correction of fluid retention is a crucial adjunct to all therapies for HF.13

The newly available valsartan/sacubitril, combining an ARB and a neprolysin inhibitor, promises to disrupt this stack of therapies.18,19 First, this agent is anticipated to displace the cornerstone of ACEi/ARB, on top of which the other therapies have been tested. Will the other therapies have the same benefit when combined with the multisite hormonal alterations from neprolysin inhibition? Perhaps not, but will the community be able to mount a trial to prove or disprove the benefit of combining therapies? In fact, it has never been proven that the current stack has been required for each patient. It has been long queried whether the apparent benefit from an additional neurohormonal agent reflects the need for multisite neurohormonal intervention in every patient, or, alternatively, a heterogeneous population of patients each responding preferentially to one of several agents in the stack (Jay Cohn, MD, personal communication, 2015). It is highly challenging to assess the ongoing need for a specific therapy in the setting of evolution of other therapies in a syndrome requiring polypharmacy as with the HF syndrome. It is possible to conceptualize withdrawal trials as has been done with digoxin in the past,28 or diuretics after the addition of ACEi.29 However, investigating β-adrenergic receptor blocker withdrawal after titration of a new therapy, such as valsartan/sacubitril, would certainly test our ethical fortitude when the price of an incorrect hypothesis could be unnecessarily worse outcomes.

The advent of valsartan/sacubitril also blurs the previous distinction between treating hemodynamics and treating neurohormones. This compound simultaneously blocks the angiotensin receptor of the renin-angiotensin system and increases circulating natriuretic peptides, which can produce immediate effects from increased sodium excretion and vasodilation.
before neurohormonal effects that counter sympathetic activation, apoptosis, and fibrosis. It remains to be seen whether the current approach to relieving congestion before uptitrating neurohormonal therapy will be redirected by an agent that can affect both.

Redesign of Therapy

**Better Initial Selection: From Phenotypes to Polyn-ome-ials**

In the future, how will we profile our patients to select therapies most likely to provide benefit, once the stack concept has been disrupted or exhausted? Pivotal clinical trials, designed to maximize the target market after approval, often describe the broadest possible population. Both for approved therapies and for new therapies under development, patients will need more rational and innovative profiling, recognizing that everyone can no longer get everything by virtue of EF or an HF hospitalization. Phenotyping can encompass more common clinical information, but would hopefully move toward a profile of reflex system activation to guide what might be inhibited or activated to restore favorable integration. Relevance of the genome alone to drug selection is currently limited to a few specific disease etiologies or prediction of drug responses, until better understanding of genetic-environment interaction ensues. The polyn-ome-ials composed of the genome, transcriptome, proteomics, and metabolomics may evolve to guide phenotyping and prescription, initially from a statistical machine-learning basis until hopefully more mechanistic logic is applicable as the hot spots are decoded.

One approach that has been used recently has been to assess the wealth of available clinical and demographic data in trial or registries and use statistical techniques such as cluster analysis in an attempt to create subsets of HF patients with some common, clustered clinical characteristics that can have differing trajectories of outcomes. In theory, this may open the door to subsets of common pathophysiologies, which may in turn be better targeted for treatment strategies. As an example, Ahmad and colleagues leveraged the highly annotated demographic and clinical baseline data, and adjudicated outcomes in the National Heart, Lung, and Blood Institute (NHLBI)—sponsored Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial to identify 4 clusters of patients with HFrEF with distinct clinical characteristics and differing outcomes. In concept, such data could be used to select better patients for trials of new therapies, not only by enriching the outcome event rate, but also to target better therapies, if the clinical cluster can be linked with a distinct pathophysiologic driver that might be amenable to focused intervention.

The assumption implicit in any discussion of using either simple clinical phenotyping or more complex -omic typing is that the identification of a subpopulation or individuals with a common profile to target will lead directly to a therapeutic arrow that specifically addresses the pathophysiology or trait, with the expectation of favorably treating the human condition. To date, such a treatment strategy based on a highly specific omic target (except for rare causal gene deficiencies such as Fabry disease) has not been undertaken. Usually this strategy is limited, at least in part, by lack of the therapeutic arrow. However, even when a therapy is designed to target a specific defect, trials have encompassed a broad population of patients who may or may not be compromised by that defect. Presumably this approach is chosen to win the widest potential indication after regulatory approval. However, with complex cause-effect and bystander perturbations in a disease syndrome, abnormalities detected in some patients may not be universal. For instance, the expression and activity of SERCA2a is not invariably or uniformly depressed in HFrEF patient populations, even in tissue samples from late-stage patients undergoing transplant. Ideally, HFrEF patients could be interrogated as to their SERCA2a expression and activity, and only those with depressed values would be entered into a trial of a SERCA2a therapy. We may not yet have the knowledge to make such selection practical, but the price for not doing so may be to irretrievably overlook the benefit of a new therapy by inclusion of patients unlikely to benefit.

**Titrating Up, Down, or Off?**

The current approach is to treat to the doses tolerated in the trials, although trial patients usually differ with younger age, fewer comorbidities, and more rigorous surveillance than our usual patients in practice. For instance, the combined ACEi and β-blocker doses achieved are usually substantially lower in clinical practice than in trials, sometimes from physician reluctance, but also because of hypotension, renal dysfunction, or patient insistence. In the shadow of the therapy stack, our previous approach has been to continue all recommended therapies for as long as they were tolerated, and sometimes longer. This tradition derives from trials in which a tested therapy was held constant to determine its impact on hard end points such as death. However, in a disease made dynamic both by underlying physiology and therapeutic response, perhaps therapy should also be more dynamic.

We need better targets for titration. As we move away from one size fits all, we need to explore which measurements should guide a custom fit. The surrogate of left ventricular remodeling has received considerable consensus. But the data on remodeling emanate from clinical trials, where substantial population samples can allow the emergence of useful signals from the well-known noise of test-to-test variability of our existing imaging tests, particularly echocardiography. These responses to therapies may be hard to discern for targets such as remodeling within an individual patient. Targets available from serial blood testing or imaging may include markers of cardiac fibrosis, valvular regurgitation, pulmonary hypertension, and right ventricular function. Profiling of autonomic function may supplement current standard biomarkers, but none have yet been shown useful to guide adjustment of therapies. As we move into Big Data with its big numbers (and big noise), the hope is that the integrated polyn-ome-ials may eventually help discern the targets necessary to adjust the regimen for each patient with HF. The future will test the circular paradox that the harnessing of Big Data from populations may provide the ultimate precision to personalize care.

We also believe it is highly likely that patient-reported outcomes will be awarded more legitimacy as targets for therapy, as trade-offs between side effects and target effects can be aligned with patient preferences and goals of care.
Patient-reported outcomes or functional measurements may allow more relevant separation of a responder from a nonresponder before the irreversible end point of mortality. This opens the door to an approach whereby therapies directed at shorter-term end points such as symptoms or functional capacity can be stopped in the absence of an obvious change in the response variable, the threshold for which can be set working in partnership with the individual patient.

We will need to refine not only when to start and how to uptitrate therapy, but when therapy that is part of guideline-directed medical therapy can be decreased or stopped. Although guideline-directed medical therapy is generally continued into stage D HFrEF as standard of care, there are virtually no data that continuation of neurohormonal antagonism is beneficial in the irreversibly remodeled heart, which remains an open question. Some patients without anticipation of long-term survival might feel better with higher blood pressure, better diuresis, and (possibly) better end-organ perfusion after withdrawal of ACEi or β-blockers. A fruitful area for research in the near future may be reduction in polypharmacy in stage D in favor of therapies focused specifically on symptom burden and other patient-reported outcomes.

**Mixed Modality Therapy in the Future**

Once targets are better defined, more creative pathways to reach them may combine multiple interventions. Within the pharmacological options, vasodilators may complement diuretics in the relief of congestion more than currently used. Mixing modes, cardiac contractility may be enhanced both pharmacologically and with electric devices. Low doses of inotropic stimulation for palliation of advanced disease have already been rendered safer by the implantable defibrillators. New MRAs that became prevalent after this class of agents was abandoned in the previous decades. The therapeutic window of potent mineralocorticoid antagonist.

**Devices to Address Remodeling**

Although continuing the pharmacological regimen that has been proven so beneficial to reduce remodeling after myocardial infarction, the recent past and near future include innovative mechanical approaches to remodel, repair, augment, modulate, assist, or ultimately replace dysfunctional myocardium (Figure 3). Because most therapies which slow or reverse remodeling also favorably affect the natural history of the HFrEF syndrome, substantial ongoing investigative efforts are examining whether various mechanical approaches to reshaping the ventricle may be a useful therapeutic strategy. Approaches include a percutaneously placed device that internally excludes akinetic or dyskinetic territories leading to less mechanical contractile inefficiency, a hybrid interventional and minimally invasive surgical approach that involves placing anchors across scarred myocardium that are then cinched to exclude the scar and recreate a more normal LV shape, and multiple injections of a biopolymer gel meant to reduce wall stress and prevent further remodeling. These and other approaches have shown signs of efficacy in models or very early human trials, which are often unblinded however, by the nature of the intervention.

Although attractive in concept, it is worth noting that previous efforts to restore ventricular shape by surgical methods, such as surgical ventricular restoration, the Batista operation, or the CoCap support device, while indeed resulting in more normal shape of the LV or reduced end-diastolic volume, have not resulted in favorable clinical or natural history effects, and in theory may worsened diastolic properties. It is possible that isolated attention to ventricular shape or structure without addressing some or many of the other pathophysiological components of the HF syndrome may not eventuate in clinically relevant effects.

**Mechanical Circulatory Support**

The Artificial Heart Program established at the National Institutes of Health in 1964 was focused on implantable...
mechanical circulatory support devices originally conceived as heart replacement therapy for life. Setbacks in development shifted the emphasis to shorter-term use as bridge to transplant, viewed as a laboratory for the development of more successful long-term support. Left ventricular assist device (LVAD) for lifetime therapy has finally upstaged its bridge-to-plant role, which will become a progressively lesser indication. The target populations for initial durable devices have evolved away from Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Profile 1 (crash and burn), for which most patients now receive temporary external support, to INTERMACS Profile 1 (crash and burn), for which most patients now receive temporary external support for initial stabilization. For this group, the liberal use of extracorporeal membrane oxygenation will come under increasing scrutiny as a resource-intensive initial strategy that ultimately leads to discharge for only ≤50%. Extracorporeal membrane oxygenation and more focused circulatory support from short-term devices will yield the best outcomes as multidisciplinary teams decide systematically when to initiate and terminate support.

Currently, the durable devices offer a survival and quality-of-life advantage to many recipients who otherwise are compromised by inadequate organ perfusion and unremitting class IV symptoms. Major adverse outcomes are stroke, bleeding, infection, and pump thrombosis, for which the event rates are similar regardless of the acuity of HF at the time of implant. Unless these adverse effects can be dramatically reduced, the risk-benefit calculation will not favor LVADs in the less-sick ambulatory population (INTERMACS profiles 5–6) who currently account for <5% of implants. Although device development continues toward full implantation without the need for a transcutaneous driveline power supply, more physiological control systems, less dependence on low afterload, and lower component failure rate, it is not clear whether incremental progress will be sufficient, or whether wider application of mechanical circulatory support will await a quantum leap in technology.

Right heart failure currently heralds not only the failure of medical therapy but also ineligibility for successful LVAD support. Clinical right heart failure and a right ventricular assist device presence predict poor outcomes with LVAD support. The sicker the patient, the more likely that the right heart is failing. It was estimated by the NHLBI task force in 1998 that 10% to 20% of candidates for mechanical circulatory support would need biventricular devices and, thus, possibly be served by a total artificial heart. However, as patients survive longer with HF, secondary right heart failure increases, so the proportion needing biventricular support will increase as well. The smallest LVADs are sometimes placed side by side to support both ventricles. The current total artificial heart replaces both ventricles, with >300 implanted clinically since approval in the United States. Enthusiasm for expanding total artificial heart use is limited by challenges in management and particularly with achieving stability for discharge. There is yet no approved mechanical option for biventricular failure for lifetime therapy.

**Limited Late Recovery**

Although multiple histological and biochemical derangements improve in the myocardium between the time of device implant and explant for transplantation, recovery of left ventricular function sufficient to allow device removal remains rare, documented in <5% of ventricular assist device implantations. Most examples of recovery occur in young patients with short duration of illness without coronary artery disease. Ventricular assist device support does provide a sturdy platform on which to try multiple approaches to reengineer functional myocardium, including use of stem cells, growth factor combinations, and gene transfection. It is not clear whether support and recovery strategies are best aimed at the terminal stage of disease when full circulatory support is required, or earlier when limited support from smaller devices may more effectively prevent disease progression.

**Cardiac Transplantation**

Heart transplant recipients will continue to enjoy good outcomes, but the numbers of cardiac transplants remains ≈2200 annually in the United States, in comparison with an estimated 150,000 who might reasonably be expected to benefit. The modest improvement in recent survival results from better early survival, which has been seen even though recipients have been waiting longer and are receiving older donor hearts than in previous eras. The current median life expectancy for 1-year survivors has remained unchanged at ≈11 years, still limited most often by infection, graft vasculopathy, and malignancy. Progress will include better tailoring of immunosuppression to the competing individual risks of immunemediated injury and consequences of immunosuppression. Serial assessment will be refined by better tracking of host-donor responses and noninvasive detection of preclinical rejection through proteomics (or other -omic analyses), exemplified by the Allomap blood test already in limited use, hopefully with fewer biopsies and coronary angiograms.

Transplant candidates will face decreasing likelihood of actually undergoing transplantation. During 2016, ≈7000 patients have been awaiting cardiac transplantation, with a total of only ≈2200 hearts available. This crisis on the waiting list has developed as each year ≈50% more patients are listed than undergo transplantation in the United States. The crisis is also developing in other countries in which listing has increased without an increase in donor supply, such as Germany. In the near future, patients throughout the country will undergo transplantation only if they are at the highest priority (status I), which is already the only route to transplantation in some regions of the country. Paradoxically, the median waiting time in these regions exceeds 6 months and is often longer than a year for status I patients, although status I is defined as an expected survival of <7 days without transplantation. The availability of VADs to bridge patients to transplant has redistributed the waiting list and waiting list mortality. By the end of the first year with a bridging device, 12% of patients have died, and 25% of the survivors have been rendered no longer eligible for transplantation.

The crisis on the waiting list will encourage continued development of technology to improve donor heart recovery after brain death and after harvesting, which may eventually allow organ preservation for sharing across the country. Seeing the hearts as a shared national resource should encourage consensual constraint of listing practices to more closely
Evidence of chronotropic incompetence can be documented, and have an important role in symptomatology in these patients. Numerous other aspects of pathophysiology that appear to be present, which could include LV hypertrophy or left atrial enlargement, or evidence of diastolic dysfunction. Moreover, a similar type of cluster analysis has been applied to HFP EF patients to identify commonalities in phenotype that tend to travel together. Shah et al used data from a highly annotated sample of HFP EF patients and phenomapped the population, using techniques adapted from genomapping. These authors identified 3 clusters of HFP EF patients whose clinical characteristics differed in such features as age, comorbidity burden, ventricular and atrial structure, and distinct outcome trajectories. It is likely that in the coming years these threads will eventually be woven together, with a more nuanced multitiered approach to making a diagnosis of HFP EF, and that the clustering concept can be used to inform trial design and enrollment.

Greater Appreciation of Pathophysiologic Subsets
For many years, in general, it was thought that the syndrome now generally referred to as HFP EF was predominantly if not completely driven by abnormalities in diastolic function, thus the commonly used terminology of diastolic HF. The seminal study of Zile and colleagues clearly documented abnormalities of invasively measured indexes of left ventricular relaxation and stiffness. The HF patients included in that study, however, were relatively young in comparison with contemporary HFP EF cohorts (mean age, 59 years) and two-thirds were men, a much higher proportion than usual clinical populations. Thus, this study was very important in that diastolic dysfunction could clearly be documented, but the selected nature of this population left open the possibility that there was much more to the story.

In the past few years, publications have documented numerous other aspects of pathophysiology that appear to have an important role in symptomatology in these patients. Evidence of chronotropic incompetence can be documented, and abnormal oxygen extraction by the peripheral skeletal musculature, as well, both of which would limit oxygen delivery to the periphery and result in symptoms of exertional intolerance. An interesting group of patients was highlighted who have almost completely normal invasive hemodynamic measures at rest (including normal brain natriuretic peptide levels) but who develop very abnormal hemodynamics only during exercise. Finally, it has been proposed that the HFP EF syndrome may be the final common pathway of inflammatory and cytokine effects on the myocytes, cardiac interstitium, and the myocardial microvasculature, driven by the commonly occurring comorbidities such as diabetes mellitus, obesity, and the metabolic syndrome. There are multiple lines of evidence to support this concept, including autopsy studies of patients with HFP EF reporting microvascular abnormalities, and a significant increase in interstitial fibrosis, as well. Indeed, this concept may not be limited to HFP EF per se, and may well apply to patients with the phenotype of HFr EF, and could be considered under a rubric of metabolic/inflammatory HF.

Heart Failure With Preserved EF
Since early descriptions of abnormalities of the diastolic phase of the cardiac cycle in myocardial tissue, our knowledge of this complex syndrome has grown substantially. It is well accepted that at least half if not more of the HF population burden is accompanied by a preserved EF. Although commonly thought to involve abnormalities of relaxation, compliance, and filling of the left ventricle, recent data speak to the pathophysiologic complexity of the syndrome, and provide some explanation for the therapeutic frustration that has resulted from numerous RCTs that have failed to find an approach that affects the natural history of the syndrome.

Making the Diagnosis
The 2013 American Heart Association/American College of Cardiology HF Guidelines are not very specific regarding making a definitive diagnosis of HFP EF, in part, because of the absence of consensus in the community or data in the literature. The recommendations essentially involve establishing that the HF clinical syndrome is present in the absence of other etiologies for dyspnea and volume overload. There are no specific recommendations regarding structural changes or diastolic indexes that should accompany, inform, or support the diagnosis. The 2013 European Society of Cardiology HF Guidelines have in common the requirement to identify signs and symptoms of the HF syndrome in the absence of other causes, and a preserved EF in a nondilated LV, as well, but add that evidence of relevant structural heart disease should be present, which could include LV hypertrophy or left atrial enlargement, or evidence of diastolic dysfunction.

Although they are appropriate in concept, in practice, the literature suggests the important limitations of these recommendations. In the published echocardiographic substudies of some of the major HFP EF trials, approximately one-third of patients do not have evidence of LV hypertrophy, left atrial enlargement, or abnormalities of echocardiographic diastolic performance. Moreover, some of the echocardiographic measures thought to reflect diastolic filling pressures have not held up in carefully performed studies with simultaneous invasive measures of pressures with maneuvers.

We believe that, in the near future, it is imperative for the stakeholder professional groups to align diagnostic recommendations, incorporating the latest literature on underlying pathophysiologies to arrive at a consensus diagnostic approach to this syndrome. This could evolve as a multitiered approach, with the goal of identifying that there is a significant cardiovascular limitation driving the symptoms of dyspnea and functional intolerance. As an example, for patients who had been hospitalized with a clear diagnosis of HF based on signs, symptoms, radiographic congestion, and response to therapy, supported by natriuretic peptide levels, who also have preserved EF, this phenotypic constellation could be sufficient to establish the diagnosis. For out-patients who have not been hospitalized, who have dyspnea and functional impairment suspected of having HFP EF as the etiology, cardiopulmonary exercise testing and biomarkers such as natriuretic peptide levels might be the next step in the tiered approach.
to establishing a diagnosis. If establishing a cardiac limitation remains murky, the next step could be invasive evaluation, including invasive cardiopulmonary exercise testing in an experienced laboratory, to interrogate for the possibility of exercise-induced (only) hemodynamic perturbations and the possible contribution of chronotropic incompetence.28 It would be anticipated that each successive tier would involve a smaller proportion of patients in whom the diagnosis remains unclear.

Creating a more uniform approach to diagnosis would be of great benefit not only to clinicians, but also to trialists and those developing new therapies. Subsetting by the nature of the hemodynamic or pathophysiologic abnormality, or the cluster phenotype, could then come into play based on the therapeutic target.

**What Can We Learn From the HFrEF and HFpEF RCTs to Inform Trial Design in the Future?**

As noted, over the almost 3 decades since the publication of the initial Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial results,69 there has been incrementally favorable impact on natural history outcomes from neurohormonal antagonists including ACEi/ARBs, β-adrenergic receptor antagonists, mineralocorticoid antagonists, and finally with the addition of neprolysin inhibition in the HFrEF syndrome across the symptomatic spectrum. It is also noteworthy that when subgroup analyses are presented in the primary trial results articles, virtually all subgroups (including parsing the populations by age, sex, etiology, comorbidities, etc) appear to benefit from the therapies. To some degree, that all of these neurohormonal antagonists slow progression of disease in all subgroups suggests that once left ventricular dilatation and dysfunction are present, HFrEF patients follow a trajectory largely driven by neurohormonal activation and remodeling, no matter the etiology or course of how they may have arrived at that stage of remodeling (Figure 4A). Put another way, at this point in the course of the illness, regardless of inciting etiology, all patients have a predominantly convergent phenotype.

In contrast, among the major HFpEF trials, results have been uniformly neutral with regard to impact on natural history, with almost no subgroups showing any favorable signals either, save for the possibility of mineralocorticoid antagonist effects in HFpEF patients enrolled in the Americas in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial.70 When viewed in the light of the homogeneously favorable effects of neurohormonal antagonists in HFrEF, the totality of the data suggest that the natural history of HFpEF patients is unlikely to follow a path predominantly driven by a single model/system such as neurohormonal activation. Rather, it seems likely that the widely varying pathophysiologies may each have distinct natural history pathways, and when grouped together in a broad-brush trial with 1 intervention (such as an ARB), any possible favorable effect in 1 small subgroup may be diluted by no effect in many others (Figure 4B). More information on influencing natural history with a single intervention will be forthcoming with the results of long-term therapy modifying the natriuretic peptide system with its many effects using the neprolysin inhibitor sacubitril.71

If this speculation is correct, it suggests that, in the future, it may not be fruitful to continue the pursuit of agents to affect the natural history outcomes in broad populations of HFpEF patients. An approach most likely to eventuate in
natural history benefit would involve 1 more targeted to carefully selected patients having a pathophysiology likely to be affected. For example, an agent that affects the interstitial collagen network might best be used in a trial where HFpEF patients were selected by way of extracellular volume measurements on cardiac MRI.\textsuperscript{32}

This conceptual approach directly engages the tension between the need for large market share for sponsors of expensive drug development programs and the likelihood of trial success by a narrower focus on a patient subset, but is an approach in which progress is most likely to be made.

**Therapeutic Approaches to HFpEF in the Near Future**

Given the evidence to date of no benefit with multiple drug interventions on natural history outcomes, we believe that attention should shift to therapeutic effects on symptoms, functional capacity and other patient-reported outcomes that reflect the significant day-to-day burden of this syndrome on patients. These outcomes could be assessed in trials using several indexes available from cardiopulmonary exercise testing, 6-minute walk tests, accelerometer testing of activity levels, quality-of-life instruments, and other tools.

Although much attention has focused on the neutral results of major natural history RCTs for HFpEF, it should be noted that there have also been numerous published trials focusing on symptoms and functional capacity, most of which have also shown no benefit on functional or symptomatic measures, including interventions such as ACEI,\textsuperscript{73} sildenafil,\textsuperscript{74} mineralocorticoid antagonists,\textsuperscript{75} and isosorbide mononitrate.\textsuperscript{76} In fact, one of the only interventions to demonstrate benefit has been an exercise training program in a population of predominantly elderly women with HFpEF over a 4-month period, with improvements in peak \( V_{O_2} \), 6-minute walk distance, and some quality-of-life indexes.\textsuperscript{77} Ongoing trials focused on symptomatic or functional benefit are testing the impact of agents such as soluble guanylate cyclase stimulators, inhaled sodium nitrite, and interleukin-1 blockade\textsuperscript{78} among others.

A myriad of devices are being studied, each in theory addressing a specific pathophysiologic abnormality associated with the HFpEF syndrome. A percutaneous transapical approach is used to implant an elastic device within the ventricle meant to enhance recoil and improve diastolic filling.\textsuperscript{70} Pacing therapy is being studied in HFpEF patients with evidence of chronotropic incompetence.\textsuperscript{80} A percutaneously placed device to create an intra-atrial shunt is meant to decompress elevated left atrial pressure.\textsuperscript{81} The success of these approaches will, to an important degree, depend on the appropriate selection of patients with the specific pathophysiology amenable to improvement with the intervention.

From a trial design and analytic perspective, a shift in focus to effects on symptomatic or functional end points will also require collaboration with regulatory authorities to sculpt trial designs to ensure sufficient patients and follow-up time to understand safety signals and absence of an unfavorable effect on longer-term outcomes. It is likely that hierarchical approaches to composite end points, especially those that allow assessment of both natural history outcomes and longitudinal measures of symptoms or functional capacity, as well, will become increasingly important. These include analytic techniques as proposed by Finkelstein and Schoenfeld,\textsuperscript{82} an adaptation of the Win-ratio approach,\textsuperscript{83} or other global rank score analytic methodologies.\textsuperscript{84}

**The Conundrum of the Acute HF Syndrome**

In much the same way that there has been therapeutic frustration around trials in HFpEF patients, the past 15 years have also seen similarly bleak results in many attempts to improve the speed or extent of symptomatic responses and outcomes in patients presenting and being hospitalized for acute HF. Also analogous to the HFpEF syndrome is the very heterogeneous pathophysiology driving the presentation of acute HF, which we have learned from registries and other studies over the years. Hypertensive versus normotensive, volume overloaded versus volume redistributed,\textsuperscript{85} preserved versus impaired systolic function, and the presence or absence of renal dysfunction are only some of the features that may alone or in combination be contributing to the clinical acute HF state, making a broadly applied single therapeutic intervention across this heterogeneous substrate unlikely to achieve favorable results.

Investigation of new therapies for acute HF is also challenged by the dynamic nature of standard care and its short-term results during an episode, in contrast to the situation in studying new drugs in chronic HF, where the background is usually stable. Apart from the small proportion of patients with in-hospital mortality, virtually all hospitalized HF patients improve with standard-of-care therapies, and are discharged. Trials in which patients could be enrolled up to 36 to 48 hours after admission are testing therapies that are thus trying to catch up and surpass a therapeutic course that has had quite a head start. Contemporary trials such as Trial of Ularitide’s Efficacy and Safety In Patients With Acute Heart Failure (TRUE-AHF) are now designed to enroll patients more quickly after presentation,\textsuperscript{86} which may increase the likelihood of success.

Even if an agent improves the speed of recovery and symptom relief, more important is that the subsequent relatively high risk postdischarge period be a major focus for improving longer-term outcomes. Ongoing studies have incorporated events during this vulnerable period into composite end points.\textsuperscript{86,87} An alternative approach will be to focus completely on the postdischarge period, as the event rate is enriched, and start therapy versus placebo at the time of discharge or soon thereafter.\textsuperscript{88}

Although substantial attention has focused on finding therapeutic advances in the acute HF syndrome, this entity and its aftermath have also been the arena for demonstrating the value of disease management programs, and also for cost reduction efforts, the latter often involving the metric of reducing 30-day postdischarge readmissions.\textsuperscript{89} In the future, we would hope that this oversimplified metric, which is more focused on reducing cost than on optimizing quality and cost-effectiveness, will give way to a broader view of the post-HF discharge aftermath, including the longer time course of vulnerability beyond 30 days and the complexity of HF and comorbid conditions that drive the vulnerability.\textsuperscript{90}
Specific Cardiomyopathies

Hypertrophic Cardiomyopathy

Over the coming years, it is likely that a more refined methodology will emerge to stratify risk for patients with hypertrophic cardiomyopathy for outcomes such as sudden cardiac death or advanced heart failure. An ongoing multicenter, multinational study is examining imaging markers from cardiac MRI and genetic markers and serum markers of collagen metabolism, as well, to create a risk model for predicting outcomes in a 2750 patient cohort.91 Building on previous data showing the importance of cardiac MRI of fibrosis in hypertrophic cardiomyopathy,92 the data should enable more rigorous studies of interventions such as implantable cardioverter defibrillators. In addition, a very large multicenter, multinational registry will illuminate genotype-phenotype correlations and prognostic implications of specific genetic findings in ways not previously possible in smaller predominantly singe-center data sets.93

Moreover, RCTs of pharmaceuticals specifically targeting some of the cellular abnormalities in hypertrophic cardiomyopathy are ongoing,94,95 potentially providing for the first time larger-scale evidence-based treatment strategies in this disorder to the level of rigor that the HF community has seen for the HFrEF syndrome.

Cardiac Amyloidosis

Several factors have driven increasing interest in the syndrome of cardiac amyloidosis. First, advances in cardiac imaging are making the diagnosis more accessible,96 in concert with a rising level of suspicion given the knowledge of the increasing prevalence of transthyretin cardiac amyloidosis with ageing.97 Moreover, there are now several ongoing RCTs of treatments directed at transthyretin cardiac amyloid,98–100 which has prompted interest identifying such patients from among those initially labeled as HFrEF. We may in the upcoming few years witness for the first time an evidence-based drug treatment strategy for this currently very challenging condition.

Cardiac Sarcoidosis

Analogous to cardiac amyloidosis, the cardiology and HF communities have been identifying more patients with cardiac involvement in sarcoidosis given advances in cardiac imaging, especially the use of cardiac MRI. This modality identifies cardiac involvement in a significantly higher proportion of patients than the Japanese Ministry of Health criteria for cardiac involvement that have been used for many years.101 Unfortunately, there are few rigorous studies to guide drug therapy or even implantable cardioverter defibrillator decisions, because the literature is predominantly observational and retrospective. An important advance would be to mount trials of even basic therapeutic strategies such as dose and duration of steroid therapy.

Target Populations of Survivors for Future Therapies

Advances in treatment of many cancers or HIV/AIDS have created new populations of survivors with long-term chronic health issues. Similarly, remarkable improvement in outcomes for patients with cardiac disease are creating new HF populations that we anticipate will continue to expand. For instance, the declining mortality from acute infarction has led to increased chronic HF post–myocardial infarction, treatment of which is the major cause for improved post–myocardial infarction survival during the past decade.102 These populations present novel targets and opportunities for focused therapeutic efforts.

Adults With Congenital Heart Disease

More than 1 million survivors of childhood surgery for complex congenital heart disease in the United States are now adults, many of whom are at risk to develop symptoms and underlying ventricular dysfunction compatible with HF, particularly right heart failure. Most general cardiologists and even HF specialists find this group daunting to assess and manage. Clearly, this calls for multidisciplinary approaches, with specialists treating adults with congenital heart disease working closely with HF providers and often electrophysiologists to sculpt a management plan, while looking for opportunities to develop earlier management strategies.

Survivors of Cancer and Cancer Therapy

Programs for comprehensive evaluation of these patients are rapidly growing, both for the prevention of cardiotoxicity and for earlier diagnosis and therapy when it occurs. Recent data indicate that almost all adriamycin cardiotoxicity can be detected in the first year by screening asymptomatic patients for EF decline, which will likely expand the stage B population.103 The accelerating clinical introduction of new agents, such as the many tyrosine kinase and proteasome inhibitors, requires constant vigilance for evidence of off-target cardiovascular effects. It is in this area that early signals of ventricular dysfunction from biomarkers or newer modalities of cardiac imaging will play a role for ongoing surveillance and ultimately for best targeting of preventive therapeutics.104 However, there is emerging evidence that HF from cancer therapy, which often includes both medications and radiation, may present a unique hormonal and autonomic profile.105 For many patients whose cancer has already been treated, survivorship programs are catalyzing new collaborations to manage both cancer and HF when they coexist as chronic diseases.

Heart Failure With Comorbid Chronic Diagnoses

The expansion of the HF population will support increased focus on specific disease intersections that are important regardless of ejection fraction. Diabetes mellitus is now present in ≤50% of hospitalized patients enrolled in the NHLBI HF Network studies.105 Specific interactions of importance include the strong relationship between diabetes mellitus and worse outcome in HF with coronary artery disease, which was reported in the SOLVD trials106 and needs new examination on contemporary therapies for both HF and diabetes mellitus. The increasing body mass index, now an average of >30 in the NHLBI hospitalized HF trials,105 warrants focused attention on pharmacological and surgical interventions and should lead to better understanding of the role of nutrients and carbohydrate/lipid proportions in HF. Pulmonary disease is present in up to one-third of patients admitted with HF, regardless of
EF. The strategy to monitor and reduce ambulatory pulmonary artery filling pressures has been shown to decrease pulmonary and HF admissions, as well, which may reflect either the sensitivity of airway function to fluid or the overlap of pulmonary and cardiac dyspnea. The combination of HF and intrinsic kidney disease presents very different challenges with and without dialysis, but both operate within a narrow window for optimal volume and blood pressure, and are associated with high prevalence of other vascular disease.

**HF With Improved EF**

This entity provides us with one of the most gratifying targets for future research, and one which challenges our unidirectional staging system. These are patients with symptomatic HF in whom a severely reduced left ventricular ejection fraction has improved substantially to >40% to 50% (depending on the study), most often attributed to β-blocker therapy or cardiac resynchronization in a superresponder. Several academic centers have reported that HF better EF accounts for as many as one-third of their clinic patients. They have not been systematically studied, except to demonstrate that nonischemic HF etiology is more common and that most HF biomarkers are still abnormal. The subsequent clinical picture often includes persistent limitation of exercise capacity out of proportion to the improved EF, with evidence of diastolic dysfunction. Exercise limitation and diastolic dysfunction provide targets of therapy in this new group. However, function and quality of life are substantially better than in most stage C HF patients. A fruitful area of investigation will be to understand why these patients improve, how long they will remain at stage B, and what can be done to sustain their stability there.

**Right Heart Failure**

Patients with evidence of right-sided HF are increasing in prevalence with the prolonged duration of left heart failure, which often leads to chronic World Health Organization group 2 pulmonary hypertension. It is increasingly recognized as a secondary development in HFrEF and a major trigger of decline in adults with congenital heart disease. The onset of right heart failure sets in play numerous processes that amplify the abnormalities simmering in the HF syndrome, and thus can be considered as a tipping point into a downward trajectory. Venous congestion exacerbates hepatic and renal dysfunction, and reduces barriers to intestinal microbes that can gain access to the circulation, thus enhancing the inflammatory cascade. Malnutrition and eventually cachexia result from liver dysfunction, anorexia, and poor absorption of nutrients. Ventricular interdependence and the congestion of coronary venous pressure further impair diastolic and systolic function of the left ventricle. New attention has been focused on the contribution and possibly therapeutic importance of lymphatic system alterations in patients with chronic peripheral fluid retention.

With advanced imaging methods such as cardiac MRI to better assess the geometrically unusual right ventricle and earlier identification of inflammatory cascades, the first appearance of right ventricular compromise may represent an ideal target in the journey of an HF patient for targeted future therapies, aimed either at reducing pulmonary pressures or providing focused support of the right heart itself.

**The Cardiorenal Syndrome**

As with right heart failure, patients with cardiorenal syndrome are seen with similar prevalence during hospitalization in HFrEF and HFrEF, although there may be a greater component of intrinsic kidney dysfunction in HFrEF. For both syndromes, the cardiorenal syndrome heralds a declining trajectory. Progressive renal dysfunction was rare in early HF cohorts who had high early mortality, but longer survival brings longer exposure to diuretics and elevated right-sided filling pressures, which are the major hemodynamic correlate of the cardiorenal syndrome. The prevalence of comorbid conditions such as diabetes mellitus and hypertensive vascular disease suggests that that the prevalence of this challenging syndrome will increase over time. No therapy has been proven beneficial for acute cardiorenal syndrome during HF hospitalization, although it is becoming clear that transient increases in creatinine may not always be adverse if indicative of successful decongestion. Careful definition of the clinical criteria for progressive cardiorenal dysfunction may include serial increases in diuretic needs, and in creatinine and blood urea nitrogen, as well, and will be crucial to define the setting for new investigation.

Given the likely increasing prevalence of this syndrome, another fertile target for investigation are those patients with HFrEF and levels of renal dysfunction that would disqualify them for most of the major HFrEF trials. There is virtually no evidence-based therapy for this group of patients. Although guidelines suggest that hydralazine/nitrates can be useful in patients with renal insufficiency when ACEi or ARBs cannot be given, there is no evidence that is a correct or useful strategy. Moreover, there is also currently no evidence for either continuation or removal of neurohormonal antagonists in this population.

**Stage D HF**

Patients with advanced, end-stage or stage D HF will continue to undergo redefinition as therapies are shown to delay or reverse its trajectory while supporting a quality of life that remains acceptable to patients. Heralded often by the cardiorenal syndrome or right heart failure, stage D heart failure may look remarkably similar to the final common pathway for both HFrEF and HFrEF, although the earlier routes differ.

Clinicians involved in the early definition of this field came to dread the frequent calls from the newly bereaved after coming on premature sudden death. At that time, the misery of refractory class IV was mercifully short before patients died peacefully in their sleep, and there was rarely time for consideration of hospice. Now, stage D heart failure is a major cause of repeated hospital admissions; because we have prolonged life with HF, we have also prolonged death. Beyond cardiac transplantation and mechanical circulatory support devices for highly selected patients with HFrEF, we have no proven therapies for stage D heart failure. This is a major target population for testing of interventions that do not necessarily need to address longevity. Continuous isotropic therapy has not been trialed in the stage D population or in any population with implanted defibrillators. Because survival with the encumbrance of home intravenous infusions has now approached a year, it may be time to restudy these old wines without lines.
For HFrEF, the congestion of the cardiorenal syndrome and right heart failure are not often accompanied by hypotension, but more often complicated by comorbidities. Sometimes the decline is precipitated by a new event such as a hip fracture or stroke, or can be accelerated by chronic conditions such as dementia, frailty, or pulmonary disease.

Fortunately, the management of stage D is facilitated by the growing experience and expertise of hospice for HF patients, which does decrease rehospitalization\textsuperscript{115} and has been suggested to improve the journey for both the patient and the spouse. A common missed opportunity, however, is for patients to be able to put their affairs in order and communicate their desires for the last phase of the journey. Stage C symptomatic HF is time to introduce an annual review, and certainly repeated hospitalizations or other milestones of disease progression should trigger a more urgent review of prognosis, any remaining options for therapy, and patient discussion of the what ifs, preferences, and goals for the rest of the journey.\textsuperscript{116}

**Prevention of Ventricular Dysfunction and HF**

Although studies such as the SOLVD Prevention\textsuperscript{117} and the Reversal of Ventricular Remodeling with Toprol-XL (REVERT) trials\textsuperscript{118} aimed to slow the progression of HF with reduced LVEF from stage B to stage C HF, the ability to interrupt progression from stage A to B would have the highest impact on a population level. This should result in decreased progression to both HFrEF and HFrEF, which arise from populations with similar risk factors. Epidemiological studies have shown that biomarkers such as brain natriuretic peptide can identify subjects in the general population who are at risk for incident HF. However, as with most markers identifying risk of incident disease in a population, the positive predictive value and incident rate are quite low, making a preventive layer of genomic/proteomic markers, to enrich the population for pretreatment likelihood of progression.

In an analogous way, it may be possible to move to a more refined definition of stage B HF beyond a simple structural phenotype of asymptomatic LV dysfunction to better identify those at risk of progression to symptoms who may benefit from even more aggressive preventive therapies beyond current guideline-directed therapies.

**Empowering Patients and Curating Information**

**Empowering Patients to Monitor and Manage**

The growing cadre of implantable and wearable devices to interrogate an ever-expanding number of pathophysiologic markers and processes offers our patients the unprecedented opportunity for empowerment to become full members of their HF management team. This would enable and facilitate dynamic changes in medical regimens such as diuretic dosing, and could encourage adherence to medication, diet, and exercise prescriptions. Although extant disease management programs track weights and symptoms, new experience is being gained regarding both physiology and work flow for daily monitoring devices reflecting pulmonary pressures or lung fluid. One can envision a near future in which peptide biomarkers or electrolytes can be monitored routinely via microsensors and treated through implantable drug pumps.

**Clinical Teams as Curators of Information**

Challenges to effective patient participation begin with the need for patients to demonstrate a higher level of health literacy to optimize partnership and outcomes.\textsuperscript{120} Moreover, it will be key to ensure that neither patients nor care providers fall victim to the too-much-information syndrome, because the density of available information may very well exceed our capacity or knowledge to act on it.\textsuperscript{121} For example, despite multiple trials, it remains uncertain how and whether guiding therapy by natriuretic peptide levels improves quality of life or outcomes. The greater incorporation of patients into the circle of care will undoubtedly occur, but it should be firmly constrained by our ability to curate information in a way that enhances optimal management and outcomes.

**The Social Network for Support and Research**

Expert translation and delivery of information is becoming particularly important as more patients seek advice from websites, both authorized and unauthorized. Many patients have already found virtual communities of patients self-identified as having HF. Far from replacing clinical teams, these networks need responsible input from qualified clinicians. They can also be shaped to form a dynamic new platform for partnership in research with approved diagnostics and therapeutics, using principles of pragmatic effectiveness research. This design approach will potentially offer focus, velocity, and magnitude far greater than traditional clinical trials, and will incorporate multiple dimensions of outcomes important to patients. In the vision of this research collaborative, patients will find their voice and help to create what they seek as the future of therapy for HF.

**Disclosures**

None.

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