

# Development of Therapeutics for Heart Failure

## Developing New Treatments for Heart Failure Focus on the Heart

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**Abstract**—Compared with heart failure (HF) care 20 to 30 years ago, there has been tremendous advancement in therapy for ambulatory HF with reduced ejection fraction with the use of agents that block maladaptive neurohormonal pathways. However, during the past decade, with few notable exceptions, the frequency of successful drug development programs has fallen as most novel therapies have failed to offer incremental benefit or raised safety concerns (ie, hypotension). Moreover, no therapy has been approved specifically for HF with preserved ejection fraction or for worsening chronic HF (including acutely decompensated HF). Across the spectrum of HF, preliminary results from many phase II trials have been promising but are frequently followed by unsuccessful phase III studies, highlighting a disconnect in the translational process between basic science discovery, early drug development, and definitive clinical testing in pivotal trials. A major unmet need in HF drug development is the ability to identify homogeneous subsets of patients whose underlying disease is driven by a specific mechanism that can be targeted using a new therapeutic agent. Drug development strategies should increasingly consider therapies that facilitate reverse remodeling by directly targeting the heart itself rather than strictly focusing on agents that unload the heart or target systemic neurohormones. Advancements in cardiac imaging may allow for more focused and direct assessment of drug effects on the heart early in the drug development process. To better understand and address the array of challenges facing current HF drug development, so that future efforts may have a better chance for success, the Food and Drug Administration facilitated a meeting on February 17, 2015, which was attended by clinicians, researchers, regulators, and industry representatives. The following discussion summarizes the key takeaway dialogue from this meeting. (*Circ Heart Fail*.2016;9:e002727.DOI:10.1161/CIRCHEARTFAILURE.115.002727.)

**Key Words:** clinical trial ■ heart failure ■ growth and development ■ pharmaceutical preparations  
■ United States Food and Drug Administration

### Persistent Unmet Need for Better Treatments for Heart Failure

Morbidity and mortality for ambulatory patients with heart failure (HF) and reduced ejection fraction (HFrEF) have improved in recent decades through neurohormonal modulation using renin–angiotensin–aldosterone system blockade,  $\beta$ -adrenergic blockade, and most recently, neprilysin

inhibition.<sup>1,2</sup> However, despite provision of all available therapies, ambulatory patients with HFrEF continue to have poor long-term outcomes, and with few notable exceptions, successful phase III clinical trials with this population during the past decade have been rare.<sup>1,3,4</sup> Moreover, and perhaps most alarming, there have been no successful phase III trials in worsening chronic HF (WCHF) or HF with preserved EF

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(HFpEF), populations that together account for the majority of the HF burden.

Overall, HF remains the most common cause of hospital admission for people over the age of 65 years in the United States.<sup>5</sup> More than 80% of hospitalized patients with HF have decompensated chronic HF, now termed WCHF,<sup>6</sup> with <20% having a first-event (ie, de novo HF) or end-stage HF at admission.<sup>5,6</sup> Although rapid and substantial improvements in signs and symptoms are generally achieved during hospitalization with simple therapies (ie, diuretics), postdischarge outcomes for patients with WCHF remain poor, with ≈25% readmission risk within 30 days<sup>7,8</sup> and ≈30% mortality risk within 1 year of discharge.<sup>9</sup> During the past 2 decades, despite advances in evidence-based therapies in ambulatory HFpEF, national policy measures to augment guideline adherence, and the investment of billions of dollars into trials of promising interventions for WCHF, there has been no significant reduction in the postdischarge adverse event rate.<sup>9</sup>

Thus, the patients at the greatest need for effective therapies remain without options. A disconnect exists between the promise of basic science, clinical research, and drug development and the desired improvement in human health. Many causes have been cited for the recent negative trials in HF, including the drugs themselves, over optimistic interpretation of phase II data, heterogeneity of the HF syndrome (with poor matching of patients/pathophysiologies to appropriate therapies), patient selection protocols, chosen clinical end points, or trial execution.<sup>10–15</sup> Any one of these possibilities or their combination may underlie the reason that clinical findings observed in phase II trials have not been substantiated in phase III trials for HF.<sup>16</sup> To better understand and address the array of challenges facing current HF drug development, so that future efforts may have a better chance for success, the Food and Drug Administration facilitated a meeting on February 17, 2015, which was attended by clinicians, researchers, regulators, and industry representatives. The following discussion summarizes the key messages from this meeting.

### Reaching the Limit of Benefit From Modulating the Periphery

Neurohormonal agents, such as renin–angiotensin–aldosterone system blockers and  $\beta$ -blockers, undoubtedly have myocardial effects, but their effects on the peripheral circulation are substantial. The majority of the current therapeutic armamentarium for HFpEF, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers,  $\beta$ -blockers, hydralazine, nitrates, mineralocorticoid receptor blockers, and neprilysin inhibitors, all have blood pressure–lowering effects that are often additive in an individual patient.<sup>17</sup> Although neprilysin inhibition with LCZ696 (valsartan/sacubitril) was recently shown to improve outcome in stable outpatients with HFpEF,<sup>1</sup> all trials to date of treatments for patients with WCHF have been negative, which may suggest that neurohormonally focused strategies have reached a point of diminishing return (Table 1). In addition, further reducing blood pressure in HFpEF with therapies that cause vasodilation may increase the risk of myocardial injury and hypoperfusion of critical organ systems, such as kidney, gut, and brain, with

the potential for a J-shaped benefit curve.<sup>17</sup> In HFpEF, modulation of the peripheral circulation is still an important possible therapeutic target; however, neurohormonal modulation with renin–angiotensin–aldosterone system blockade or  $\beta$ -blockade has failed to show major benefits in HFpEF. An ongoing phase III trial will determine if clinical benefits of neprilysin inhibition in chronic ambulatory HFpEF are generalizable to HFpEF patients (<http://www.clinicaltrials.gov> NCT01920711). Thus, the heart itself remains a target in HFpEF that has been understudied from a clinical trial standpoint.

**Table 1. Summary Points**

Point 1: Lack of therapies for WCHF and HFpEF continues to be a huge unmet need
Mortality and morbidity among patients with stable systolic dysfunction has improved by modulating neurohormonal abnormalities, but the long-term clinical outcomes are still poor. We have thus far failed to improve outcomes in WCHF and HFpEF.
Point 2: The macroscopic and microscopic structural abnormalities of the heart should be the focus of HF research and drug development
Structural cardiac abnormalities represent the proximal causes of HF, but interventions often target issues secondary to the failing heart. Most patients die with considerable dysfunctional viable myocardium, unlike end-stage renal disease or liver failure/cirrhosis where residual tissue viability (ie, tissue capital) is minimal at the point of clinical organ failure.
Point 3: A potential path for greater probability of translational success involves an early T1 mechanistic phase
This is a 2-step approach: 1) Demonstrate benefit in animal studies; 2) Test the hypothesis and agent in small mechanistic clinical models (termed T1 trials) that investigate mechanism–function relationships using biomarkers and imaging. Reverse remodeling could be redefined as long-lasting improvement in myocardial function, with concomitant recovery of structural, electric, signaling pathway activity, or metabolic function. Confirmation of efficacy could include improvement in the target that lasts substantially longer than drug exposure. Irrespective of the models and analytical methods used, demonstration that target/pathway engagement corresponds with reverse remodeling in early T1 trials would build scientific, clinical, and regulatory confidence in the intervention and promote advanced investigation in broader populations of HF patients.
Point 4: Advanced imaging may be useful in proof-of-mechanism studies for novel interventions
Novel imaging can detect relevant anatomic and functional features on which many diverse pathophysiological pathways converge. Whether a drug targets calcium signaling, microcirculation, mitochondrial function, substrate shifts, or myocardial regeneration, clinically relevant markers include ventricular function, cardiac structure, perfusion, viability, and energetics, all of which can be inferred through advanced imaging.
Point 5: Testing novel therapeutic hypotheses to extend healthy life among HF patients must continue
Identifying homogenous patient subsets whose condition is clearly or likely to be driven by the mechanism targeted by the therapeutic intervention is challenging, but not limiting. We should match the therapeutic mechanism of an agent with the patient subgroup most likely to benefit. Given the unmet need for therapy in WCHF and HFpEF, testing novel hypotheses for extending healthy life among HF patients must continue aggressively.

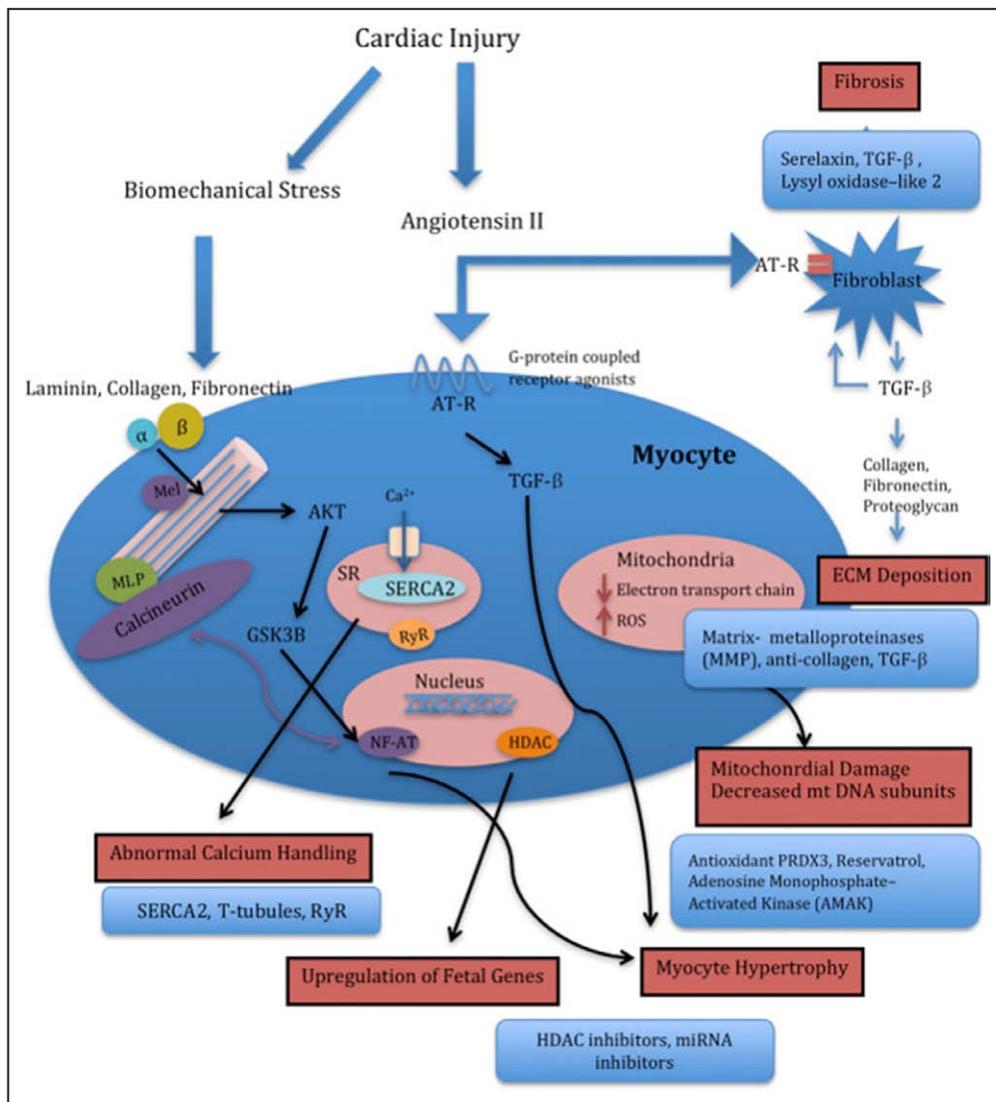
HFpEF indicates heart failure with preserved ejection fraction; and WCHF, worsening chronic heart failure.

### Cardiac Reserve in HF Versus Other End-Organ Failure

Similar to patients with kidney or liver failure, patients with HF may have severe impairment in organ function and significant macroscopic distortion of organ structure. However, unlike patients with end-stage renal disease or cirrhosis where fibrosis may predominate and residual viable tissue (ie, tissue capital) is minimal at the point of clinical organ failure, most patients with HF, even at the time of death, have an abundance of cardiac reserve.<sup>18</sup> Typically, more than two thirds of the myocardial segments in patients with HFrEF have either no scar or scar limited to the subendocardium with <50% transmural involvement, suggesting that these patients have ample viable myocardium and hence the potential to improve. Although failure of any end-organ will undoubtedly always be correlated with some unescapable risk of morbidity and

mortality regardless of therapeutic advancements, it is this unique presence of significant viable tissue that may differentiate HF and suggests that significant further therapeutic gains are possible but yet to be defined. This is supported by the finding that patients with dysfunctional viable myocardium experience more robust response to proven HF therapies, including greater reductions in clinical events and improvements in left ventricular function.<sup>19,20</sup> Even patients with dilated hearts can show significant improvement with therapies, such as  $\beta$ -blockers.<sup>2</sup> Clinically, the majority of these treatment responders do not have end-stage HF based on their blood pressure, renal function, biomarker profile, and rapid response to diuretics. Thus, in HFrEF, the potential for myocardial recovery is possible for many patients.<sup>18</sup>

These observations when coupled with the poor recent success rate for phase III trials of interventions targeting



**Figure 1.** Molecular mechanisms of myocardial dysfunction with potential therapeutic targets. AKT indicates protein kinase B; AT-R, angiotensin receptor; Ca<sup>2+</sup>, calcium; ECM, extracellular matrix; GSK3B, glycogen synthase kinase 3- $\beta$ ; HDAC, histone deacetylase; Mel, Melusin (integrin-bound protein); miRNA, micro-RNA; MLP, muscle LIM protein; mtDNA, mitochondrial DNA; NF-AT, nuclear factor of activated T cells; PRDX3, peroxiredoxin; ROS, reactive oxygen species; RyR, ryanodine receptors; SERCA2a, sarco(endo)plasmic reticulum Ca<sup>2+</sup>-ATPase; SR, sarcoplasmic reticulum; and TGF, transforming growth factor. Reprinted from Wilcox et al<sup>18</sup> with permission of the publisher. Copyright © 2015, Elsevier.

systemic neurohormones generate the hypothesis that structural and molecular components of the heart should be the main therapeutic targets for future HF drug developmental efforts.<sup>21,22</sup> Thus, the potential to re-engage residual capital in the heart to improve left ventricular structure and function seems to represent a significant opportunity for eventual success in HF.

### The Heart Is the Main Therapeutic Target

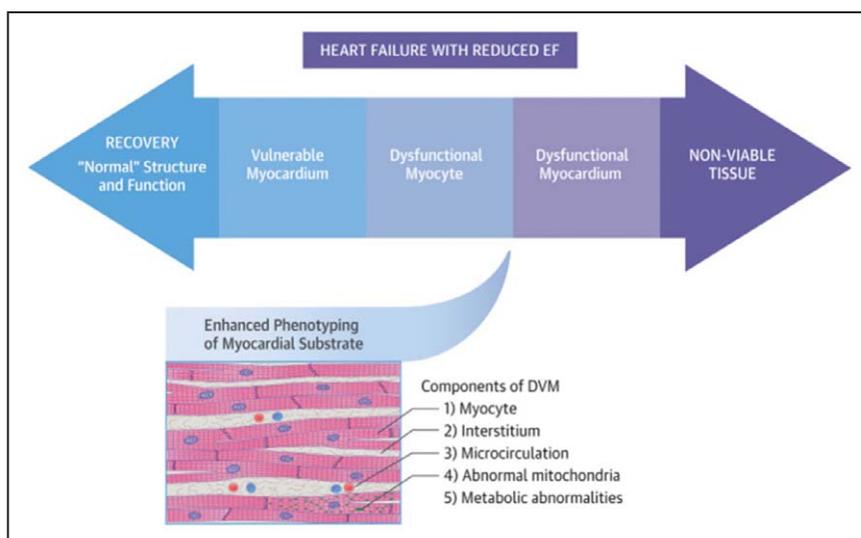
Although it seems logical to focus on the heart as the main target of drug development for HF, this has not been the case of late. This diversion away from the heart is likely, in part, due to previous early experiences with inotropes and the finding that brisk short-term improvements in cardiac function and hemodynamics may come at the price of increased adverse events and mortality. Subsequently, the treatment paradigm shifted toward agents that, if anything, may actually worsen short-term hemodynamics (ie, reduce contractility and cause hypotension) but improve longer-term clinical outcomes. Industry representatives noted that internal HF research and development has now shifted back to the heart itself rather than following the approach of unloading the heart. Such an approach may be increasingly possible as novel biomarkers and imaging modalities allow more focused and direct assessment of drug effect on pathophysiology early in drug development, a feature that was less available in the past. It was noted that as a field, we may be reaching the limit of benefit we can extract from manipulation of systemic neurohormones, particularly after the discovery of neprilysin inhibition. Likewise, neprilysin inhibitors and agents that block the sympathetic and renin–angiotensin–aldosterone system may lower blood pressure as an intended or unintended consequence, and continued stepwise addition of novel hemodynamically active agents to target doses of existing therapies raises safety and tolerability concerns.<sup>17</sup>

Accordingly, the potential for development of hemodynamically neutral pharmacotherapeutics targeting myocardial hibernation, energetics, cardiomyofiber isoform switching, and excessive apoptosis, among others, were cited as targets for which therapeutic strategies are being pursued by industry.

However, to fix the heart through appropriate intervention at  $\geq 1$  of these putative targets, we need to understand the specific defects that are present and not merely identify that some uncharacterized defect must exist given that there is reduced function. Unfortunately, as a field, we lag in understanding the development, evolution, and course of major cardiac abnormalities yielding pump dysfunction. These include abnormalities in the cardiomyocyte (eg, signaling pathways, myofibrillar function, mitochondrial energetics, and calcium handling), interstitium, microcirculation, and varied interaction of these components (eg, the effect of fibrosis on the microcirculation and vice versa; Figure 1).<sup>18</sup> Abnormalities in the heart represent the proximal causes of HF, but much research to date has focused on the secondary effects of HF (eg, neurohormonal activation, arrhythmias, congestion, hemodynamics, and renal function). Although efforts to identify treatments for these secondary effects and other end organs (ie, cardio-renal syndrome) should not be abandoned, we think that there should be new added focus on therapies that directly target the heart with the goal of improving cardiac structure and function.

The goal of direct cardiac modulation should be to slow and halt degradation of cardiac function and then to reverse its clinical course back toward normal with the use of restoration therapies. Here, it is important to distinguish between transient and long-term restoration. For example, inotropes improve cardiac output acutely but cause myocyte damage and predispose to arrhythmias that precludes chronic use.<sup>23</sup> New strategies should aim beyond a transient improvement in pump function and attempt to improve microscopic and macroscopic abnormalities, including those in interstitium, cardiomyocytes, cardiac microcirculation, and in metabolic pathways (Figure 2). In other words, they should aim to reverse the deleterious organ remodeling that has occurred at multiple levels.

There is no universally agreed upon definition of reverse remodeling. In the context of contemporary clinical trials, reverse remodeling in HFrEF is generally equated to an improvement in EF or ventricular volumes; however, neither parameter offers a direct assessment of myocardial function, and both are affected by preload and afterload.<sup>24</sup> Furthermore, neither is applicable to



**Figure 2.** Enhanced phenotyping of myocardial substrate leading to targeted therapies with the goal of achieving myocardial recovery. DVM indicates dysfunctional but viable myocardium; and EF, ejection fraction. Reprinted from Wilcox et al<sup>18</sup> with permission of the publisher. Copyright © 2015, Elsevier.

**Table 2. Broad Categories of Targets for Cardiac-Focused Heart Failure Therapies**

Tissues
Cardiomyocytes
Extracellular matrix
Coupling of cardiomyocyte to extracellular matrix
Circulation
Coronary macrocirculation
Coronary microcirculation
Cardiac lymphatics
Whole organ coordination
Myocardial scar
Focal
Diffuse
Valvular heart disease
Synchrony
Electric
Mechanical
Atrioventricular, interventricular, and intraventricular
Right ventricular function
Metabolism
Glucose utilization
Mitochondrial function
Calcium handling
Vascular coupling
Venous/arterial interactions
Pulmonary/systemic interactions
Ventricular–vascular coupling

HFpEF. To better create and evaluate effective, restorative HF therapies targeting the heart itself, reverse remodeling could be redefined as a long-lasting improvement in myocardial function, with a concomitant recovery in structural (ventricular and atrial, fibrosis, and vascular), electric (conduction and arrhythmias), signaling pathways, or metabolic components. An empirically testable early confirmation of efficacy would be evidence that improvements in function (systolic or diastolic) last substantially longer than drug exposure. These changes may include not only classic HF end points of mechanical function but also electric and even metabolic function. Thus, reverse remodeling encompasses both gross remodeling and remodeling on the cellular level. Table 2 lists categories of cardiac-focused targets for HF therapies that greatly expand the traditional clinical trial notions of reverse remodeling. Successful improvement in these markers will be most easily observed by their application to etiologically homogeneous HF populations.

### Need for Detailed Early Evaluation of Effects on Cardiac Function

When considering the potential efficacy of a tested therapeutic, it is important not only to select homogeneous HF populations but

also to use technologies that provide metrics of early response to treatment. In this way, one can theoretically obtain mechanistic insight if a positive signal is seen in a distinct pathway. Whether an intervention targets calcium signaling, microcirculation, mitochondria, or regeneration, the relevant evaluation could include cardiac structure, function, perfusion, viability, fibrosis, and energetics. Although infrequently performed in HF trials,<sup>19</sup> the importance of understanding the cardiac substrate for better targeting of therapies cannot be overstated.<sup>10,25</sup> This is not to say that systemic pathways that contribute to disease progression (eg, inflammation and endogenous catecholamines) should not be assessed. It may be prudent, however, to focus on whether modulation of such mechanisms can improve the metrics of specific cardiac pathways.

Proper use of animal models and appropriate decision making based on their results are important considerations as animal testing and other preclinical studies will continue to play an important role in the development of new HF therapies. Some improvements to past practices may be advisable. Traditional animal HF models may be too simplistic. For example, a tachycardia-pacing model of systolic HF is unlikely to have the same level of microvascular or energetics dysfunction as a genetic metabolic disorder model, leading to ventricular dysfunction. Hence, a generic model may not allow assessment of specific mechanistic aspects of the target pathway, and future models should be tailored to the specific disease process underlying the cardiac dysfunction. Although several animal models of HF exist, more are needed, and in particular, there remains a pressing need for better animal models of HFpEF.<sup>26</sup>

With the caveat that there may be differences between animal species and humans, it may be useful to conduct animal testing with standard-of-care therapies as background. This may require weeks of background treatment before initiation of the test drug to ensure that observed changes are driven by the intervention rather than initiation of background therapy. Thus, such an approach will have cost and time consequences. In addition, it is unclear which and how many background therapies should be included in animal studies. Moreover, it seems reasonable to consider age and select comorbidities in development of animal models, but practical means for incorporating these factors remain to be determined.

Several clinical trial considerations, such as independent study replication, double-blind randomization, prespecification of analysis plans and outcome measures, independent core-laboratory analysis of imaging and other biomarkers, and multicenter enrollment, among others, have indisputable value in clinical research but are rarely implemented in animal research. Although these elements may result in higher initial upfront trial costs, they may curtail costs overall by preventing unwarranted graduation of molecules with low likelihood of success to the expensive phase III testing stage. Nonetheless, key questions with respect to preclinical animal studies remain. For example, (1) what are the best parameters in animal studies that might predict clinical benefit in humans? (2) what is the magnitude of benefit in animals that is considered exciting and supportive of clinical experimentation? and (3) what biomarkers included in clinical trial studies should be given more weight in animal studies?

A current handicap in HF drug discovery is our inability to measure improvements in human heart function before overt clinical events. Novel imaging options using advanced echocardiographic or cardiac magnetic resonance imaging or other modalities may improve such evaluation<sup>24</sup> but will require dedicated protocols and expertise and centers to perform them. In addition, molecular imaging with positron emission tomography can provide insights into pathophysiology, target receptor dynamics, quantitative assessment of the target of interest, drug dose and receptor engagement, and perfusion and metabolic state of the heart. For example, positron emission tomography can validate a molecular target of interest by showing abnormalities in patients with HF compared with controls and occupancy of the target by a novel pharmaceutical, thereby helping in early go/no-go decisions. An advantage of cardiac magnetic resonance and 3-dimension (3D) compared with conventional 2D echocardiography is an improvement in reproducibility of measurements, leading to potential reduction in the sample size needed to demonstrate a signal.

Given its multifaceted nature, cardiac magnetic resonance may be particularly useful in proof-of-mechanism studies for novel HF interventions because this tool can assess multiple relevant anatomic and functional metrics on which pathophysiological pathways converge. As noted earlier, whether an intervention targets calcium signaling, the microcirculation, mitochondrial biogenesis, substrate shifts, or myocardial regeneration, important imaging biomarkers may include ventricular function, cardiac structure, and myocardial perfusion, viability and fibrosis, all of which can be measured by cardiac magnetic resonance.

### Clinical Models

One benefit of animal research is the homogeneity of the underlying cardiac substrate. However, the translation from findings in animals to humans is often problematic. One approach that weds the homogeneity of animal studies with the clinical applicability of human studies is the development of clinical model. Clinical models of HF in this context would be defined as groups of prototypical patients who have a defined, uniform phenotype and therefore may reflect a more homogeneous mechanistic basis for the development of HF. Although undoubtedly some heterogeneity will remain, the goal is to minimize heterogeneity, so future trials can be targeted toward specific types of patients. Patients can be grouped into clinical models using a variety of metrics. For example, nonischemic cardiomyopathy patients with no fibrosis is an example of a clinical model that could be targeted with specific therapies.<sup>27</sup>

Clinical models may improve specificity and provide focus on the primary cause and its pathophysiological consequences. This could facilitate mapping of cellular and physiological pathways with the potential for finding unique biomarkers that track when a target and a pathway are engaged. The concept of testing a specific hypothesis in a small, well-defined cohort with a distinct pathophysiology has been termed the T1 phase of clinical development.<sup>15,28</sup> During subsequent stages in larger cohorts, it will be important to demonstrate correlation between laboratory and imaging markers, which reflect

mechanism of action and biological target engagement, with clinically relevant outcomes.

An important limitation to the rational generation and testing of therapeutic hypotheses in HF is the difficulty in prospectively identifying patients whose disease is clearly driven by the mechanism of action to be tested. For example, it is not obvious how to segment patients into subsets where worsening HF is primarily driven by a myocardial energy deficit, or poor relaxation caused by stiffening by excess fibrosis, or poor relaxation caused by a calcium-handling deficit. Although undoubtedly multiple overlapping impaired processes may be present in any particular patient, the inability to determine the primary mechanism underlying HF in a specific patient impairs our ability to test novel hypotheses. It is for these reasons that the development of defined clinical HF models is so important.

### Practical Considerations From Industry Sponsors

There is decreasing interest to fund large HF trials when insurers are unwilling to pay for expensive drugs. The current reimbursement landscape, combined with the difficulty of selecting patients based on the identification of a specific mechanism of action responsible for the phenotype, represents a growing threat to the resourcing of new drug development. Industry HF programs will continue to face internal pressure if they cannot credibly offer precision medicine strategies for management as investment opportunities are becoming more prevalent in other therapeutic arenas. HF drug discovery requires ample time and money to transition from preclinical to large, outcome-based studies. These features make HF drug development less appealing compared with other areas where it is easier to target a new medication to a distinct subset of patients who will likely benefit. For example, simple serum biomarkers or tissue biopsy results can be used to identify subsets of patients with cancer most likely to benefit from a candidate therapy. HF should consider analogous strategies to present better investment cases.

An additional challenge facing HF drug development is the decreasing appetite to fund the large outcomes trials traditionally needed for registration. In contrast, other fields, such as oncology, make drug discovery more palatable by using trial designs with softer outcome measures, such as progression-free survival, that are still recognized as sufficient by regulatory bodies. Approaches to reduce sample sizes for morbidity and mortality trials by selecting high-risk patients must be balanced with the consideration that a positive response may be less likely in patients with end-stage disease.

Accelerated approval allows a therapy to be approved in the United States on the basis of a surrogate end point thought reasonably likely to predict the ultimate clinical outcome of interest. Such approval comes with the obligation to verify that actual clinical benefit in the postmarketing setting. Perhaps some new therapy's effects on a novel mechanism will sustain the case for being reasonably likely, but it will be necessary that the confirmatory study be considered feasible to use this regulatory pathway. For chronic therapy, this may be difficult.

## Conclusions

Despite the growing public health and economic burden, phase III clinical trials have failed to produce positive results in WCHF and HFpEF. A variety of small and large animal models have been used to mimic the complex human HF phenotype; yet, the transition from bench to bedside has borne little fruit and perhaps relates more to serendipity than to science. We firmly believe that future research, discovery, and development efforts in HF should have the macroscopic and microscopic abnormalities of the heart as the principal target for therapy. Although laboratory science will continue to play an important role in the development of new therapies, its interpretation and use for decision making must improve. The conduct of early phase translational research with identification of well-phenotyped human patients for highly focused clinical trials investigating therapeutic mechanisms in human patients is critical for success. The advent of sophisticated cardiac imaging offers a novel approach to characterize and define the myocyte and interstitium, creating phenotypic models of HF for enrollment. This roadmap should help resolve some of the challenges of conducting clinical trials in HF, especially WCHF and HFpEF, with the ultimate goal of improving HF outcomes worldwide. We believe that therapeutic approaches directly targeting specific macroscopic and microscopic defects in cardiac structure and function have the best chance of meeting this challenge.

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