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

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**ABSTRACT**

Developing effective therapies for heart failure (HF) is challenging. Despite several clear successes in the development and delivery of pharmacotherapies for ambulatory patients with HF and reduced ejection fraction (HFrEF), efforts to modulate adverse neurohormonal activation beyond the renin-angiotensin-aldosterone system and the sympathetic nervous system generally have failed to improve outcomes further and have met with safety concerns including low blood pressure or changes in end-organ function. Recently, neprilysin inhibition in conjunction with angiotensin receptor blockade has been shown to improve outcomes. There is however no therapy approved specifically for HF with preserved EF (HFpEF) or for worsening chronic HF resulting in hospitalizations (WCHF; including acutely decompensated HF). Many patients with chronic HFrEF have poor outcomes despite receiving guideline-recommended therapies. Although preliminary results from some phase 2 trials have been promising, many subsequent phase 3 trials have been neutral or negative, 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 the field of 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. To understand better and address the array of challenges facing current HF drug development so that future efforts have a better chance for success, the Food and Drug Administration facilitated a meeting on February 17th, 2015, which was attended by clinicians, researchers, regulators, and industry representatives. The following discussion represents the key messages from this meeting.

## **A PERSISTENT UNMET NEED FOR BETTER TREATMENTS FOR HEART FAILURE**

Morbidity and mortality in ambulatory patients with heart failure and reduced ejection fraction (HFrEF) has improved through neurohormonal modulation using renin-angiotensin-aldosterone system (RAAS) blockade, beta-adrenergic blockade, and recently neprilysin inhibition.<sup>1,2</sup> However, substantial unmet needs persist, including worsening chronic HF (WCHF) and HF with preserved EF (HFpEF). Furthermore, ambulatory patients with HFrEF continue to have poor long-term outcomes.<sup>3</sup> HF remains the most common cause of hospital admission for people aged >65 years in the United States.<sup>4</sup> Over 80% of hospitalized HF patients have decompensated chronic HF, now termed WCHF,<sup>5</sup> with less than 20% having a first-event (de-novo HF), or end-stage HF at admission.<sup>4,5</sup>

While rapid and substantial improvements in signs and symptoms are achieved during hospitalization, post-discharge outcomes for patients with WCHF remain poor, with ≈25% readmission risk within 30-days<sup>6,7</sup>, and ≈30% mortality risk within 1 year of discharge.<sup>8</sup> Over the past two decades, despite advances in evidence-based therapies in ambulatory HFrEF; national policy measures to augment implementation of guideline recommendations; and the investment of billions of dollars and effort in trials of promising interventions for WCHF, there has not been a significant reduction in the post-discharge adverse event rate.<sup>8</sup> Also, no specific therapies have shown benefit in patients with either stable or WCHF with HFpEF. Potential reasons include the heterogeneity of the HFpEF syndrome (with poor matching of patients/pathophysiologies to appropriate therapies),<sup>9,10</sup> the lack of predictability of phase 2 studies, and uncertainties about the proper definition of HFpEF for enrollment into trials.<sup>11</sup>

Thus the patients in most need for effective therapies remain without options. A disconnect thus exists between the promise of basic science, clinical research, and drug discovery and development; and the desired improvement in human health. Many causes have been cited for the recent negative trials in HF, including the drugs themselves, lack of phase 2 data, patient selection protocols, chosen clinical endpoints, and/or trial execution.<sup>12,13</sup> Any one of these possibilities or their combination may underlie the reason that clinical findings observed in phase 2 trials have not been substantiated in phase 3 trials for HF.<sup>14</sup>

## **REACHING THE LIMIT OF BENEFIT FROM MODULATING THE NEUROHORMONAL ABNORMALITIES**

Neurohormonal agents such as RAAS 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 HFrEF, 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. While neprilysin inhibition with LCZ696 (valsartan/sacubitril) was recently shown to improve outcome in stable outpatients with HF symptoms beyond that achieved by the standard of care,<sup>1</sup> all trials to date of treatments for patients with WCHF have been negative, which suggests that neurohormonally-focused strategies may have reached a point of diminishing return (**Table 1**). In addition, further reducing blood pressure in HFrEF 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. In HFpEF, modulation of the peripheral circulation is still an important possible therapeutic target; however, neurohormonal modulation with RAAS blockade or beta-blockade has failed to show major benefits in HFpEF. Thus, the heart remains a central target in HFpEF that has been understudied from a clinical trial standpoint.

## **CARDIAC RESERVE IN HEART FAILURE VERSUS OTHER END-ORGAN FAILURE**

Unlike patients with kidney or liver failure where residual "tissue capital" is minimal at the point of organ failure and death, most patients with HF even at the point of death have abundance of cardiac reserve.<sup>15</sup> Over two-thirds of the myocardial segments in patients with HFrEF have either no scar or scar limited to the subendocardium with <50% transmural involvement, revealing that these patients have amply viable myocardium and hence the potential to improve. Even patients with dilated hearts can show significant improvement with therapies such as beta-blockers.<sup>2</sup> 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.

These observations, when coupled with the recent failures of interventions targeting extra-cardiac manifestations of HF<sup>16, 17</sup> generate the hypothesis that the heart should be the main therapeutic target for future HF drug developmental efforts. Thus, the potential to re-engage residual capital in the heart to improve left ventricular function appears to represent a significant opportunity for eventual success in HF.

### **THE HEART IS THE MAIN THERAPEUTIC TARGET**

Although it appears logical to focus on the heart as the main target of drug development for HF, this has not been the case historically. Industry representatives noted that internal HF research and development has now shifted to the heart itself, rather than following the approach of unloading the heart. Accordingly, the potential for development of 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 drug discovery and development. However, in order to fix the heart through appropriate intervention at one or more 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 (e.g., signaling pathways, myofibrillar function, mitochondrial energetics, and calcium handling), in the interstitium, in the microcirculation, and in the varied interaction of these components (e.g. the effect of fibrosis on the microcirculation and vice versa). Abnormalities in the heart represent the proximal causes of HF, but much research to date has focused on the secondary effects of HF (e.g. neurohormonal activation, arrhythmias, congestion, hemodynamics, and renal 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 towards normal. It is important to realize that, barring beta-blockers and cardiac resynchronization, which alter secondary and primary HF abnormalities, other therapies such as RAAS modulation do not reverse cardiac function back to normal, though their population-level benefit in slowing or halting degradation of function cannot be minimized. Nevertheless, patients with persistently abnormal cardiac function need restoration therapies. Here, it is important to distinguish between transient and long-term restoration. Inotropes historically improve cardiac output acutely but cause myocyte damage and predispose to arrhythmias that precludes chronic use.<sup>18</sup> New strategies should aim beyond a transient improvement in pump function and attempt to improve micro and macroscopic abnormalities, including those in interstitium, cardiomyocytes, cardiac microcirculation, and in metabolic pathways. In other words, they should aim to reverse the deleterious organ remodeling that has occurred at multiple levels.

Currently, reverse remodeling in HFrEF is defined as improved EF or ventricular volumes; however, neither offers a direct assessment of myocardial function, and both are affected by preload and afterload.<sup>19</sup> Furthermore, neither is applicable to HFpEF. To better create and evaluate effective, restorative HF therapies targeting the heart itself, reverse remodeling needs to be redefined as “a long-lasting improvement in myocardial function, with a concomitant recovery in structural (ventricular and atrial, fibrosis, vascular), electrical (conduction, arrhythmias), signaling pathways, and/or metabolic components.” An empirically testable early confirmation of efficacy would be evidence that improvements in function (systolic and/or diastolic) that lasts substantially longer than drug exposure. Thus, *reverse remodeling encompasses both gross remodeling and remodeling on the cellular level.* A simple, empirically testable consequence of this approach and early confirmation of its efficacy would be demonstrable improvements in function that last beyond drug exposure. These changes may include not only classic HF endpoints of mechanical function but also electrical and even metabolic function. **Table 2** lists categories of cardiac-focused targets for HF therapies that greatly expand the traditional notions of reverse remodeling. Successful improvement in these markers will be most easily observed by their application to



etiologically homogeneous HF populations, for which an early assessment of response is key.

### **THE 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 obtain mechanistic insight if a positive signal is seen in a distinct pathway. An example would be the history of coronary disease drug development, in which assessment of drug impact on atherosclerotic plaque by intravascular ultrasound allowed early indications of disease-modifying effects of therapies. For HF, whether an intervention targets calcium signaling, microcirculation, mitochondria, or regeneration, analogous and relevant evaluation should include cardiac structure, function, perfusion, viability, fibrosis, and energetics. Although infrequently performed in HF trials,<sup>20</sup> the importance of understanding the cardiac substrate for better targeting of therapies cannot be overstated.<sup>9, 21</sup> This is not to say that systemic pathways that contribute to disease progression, e.g. inflammation, should not be assessed. The focus, however, should be on whether such a systemic mechanism can modify pathways of disease and 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. Given the modest record of HF drug development over the last two decades, no aspect of the discovery process should remain unexamined. Some improvements to past practices may be advisable. Often animal HF models are too simplistic, e.g. 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 question at hand. Although several animal models of HF exist,<sup>22</sup> more are needed, and in particular there remains a pressing need for better animal models of HFpEF.

With the caveat that there may be differences between the 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. This will have cost and time consequences. Additionally, it is unclear which and how many background therapies should be included in animal studies.

The importance of independent study replication, double-blind randomization, pre-specification of analysis plans and outcome measures, independent core-lab analysis of imaging and other biomarkers, multicenter trials, among others are indisputable in clinical research, but these are rarely implemented in animal research. Though initial cost may be higher but may result in future cost savings of phase III trials which are negative because the tested therapeutic was incompletely validated in animal models. Other questions that include: (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 prior to overt clinical events. Novel imaging options using advanced echocardiographic or cardiac magnetic resonance (CMR) imaging or other modalities may improve such evaluation,<sup>19</sup> but will require dedicated protocols, and expertise and centers to perform them. In addition, molecular imaging with positron emission tomography (PET) 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 PET can validate a molecular target of interest by showing abnormalities in HF patients compared to others and occupancy of the target by a novel pharmaceutical, thereby helping in early go/no-go decisions. This approach can be used to save unnecessary trial enrollment and millions of dollars in drug development. An advantage of CMR and 3D over conventional 2D echocardiography is an improvement in reproducibility of measurements, leading to a reduction in the sample size needed to demonstrate a signal.

CMR has significant promise to improve our understanding of pathophysiology and to allow drug development to “return” to the heart as the organ of interest.<sup>23</sup> Given its multi-faceted nature, CMR may be particularly useful in proof-of-mechanism studies for novel HF interventions, since this tool can assess multiple relevant anatomical and functional metrics upon which pathophysiological pathways converge. As noted earlier, whether an intervention targets calcium signaling, the microcirculation, mitochondrial biogenesis, substrate shifts, or myocardial regeneration, imaging biomarkers should include ventricular function, cardiac structure, and myocardial perfusion, viability and fibrosis, all of which can be measured by CMR.

### **CLINICAL MODELS**

One of the benefits of research in animals 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 are groups of prototypical patients who have a defined, uniform phenotype, and therefore *may* reflect a more homogeneous mechanistic basis for the development of HF. While it is acknowledged that some heterogeneity will remain, the goal is to minimize heterogeneity so future trials can be targeted towards specific types of patients. Patients can be grouped into clinical models using a variety of metrics, e.g. non-ischemic cardiomyopathy patients with no fibrosis is an example of a clinical model that could be targeted with specific therapies.

Clinical models improve specificity and provide focus on the primary etiology and its pathophysiological consequences. This allows mapping of cellular and physiologic pathways and the potential for finding unique biomarkers that track when a target and 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>24</sup> During subsequent stages in larger cohorts, it will be important to demonstrate correlation between proof-of-mechanism target engagement biomarkers and proof-of-principle pathway engagement end-points, to understand if this pathway is altered only in the narrow

initial cohort, or if it applies to larger more lengthy patient studies involving a more real-world sampling of patients. Of course, the ultimate validation of this approach is to determine whether the altered pathway-specific surrogates predict adverse clinical events.

An important limitation to the rational generation and testing of therapeutic hypotheses in the HF space 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 preferentially driven by a myocardial energy deficit, or poor relaxation due to stiffening by excess fibrosis, or poor relaxation due to a calcium-handling deficit. The inability to determine in a particular patient the primary mechanism underlying HF impairs our ability to test novel hypotheses. It is for these reasons that the development of defined clinical HF models is so important. The lack of clinical models is a hurdle that should not however inhibit future drug discovery. For the time being, if the selection of patients for proof-of-principle trial cannot yet be based on prospectively identifying patients in whom a single mechanism of action is responsible for driving the HF phenotype, it can still be based on if the target of the drug is embedded in the HF phenotype and, if so, whether the drug engages the target in that particular phenotype.

### **PRACTICAL CONSIDERATIONS FROM INDUSTRY SPONSORS**

There is decreasing interest to fund large trials in HF 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. HF programs in the industry 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

cancer patients most likely to benefit from a candidate therapy. HF needs to develop analogous strategies in order 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 utilizing trial designs with softer outcomes 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 post-marketing 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 in order to use this regulatory pathway. For chronic therapy, this may be difficult.

## **CONCLUSION**

Despite the growing problem, 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, owing more to serendipity than to science. Future research, discovery, and development efforts in HF should have 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. Conduct of early phase translational research beginning 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 myocardium 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 the outcomes of patients with HF worldwide. We believe that therapy targeting specific defects in cardiac structure and function in patients with WCHF and HFpEF have the best chance of improving the outcomes.

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**Table 1. Summary Points****Point 1. Lack of therapies for WCHF and HFpEF continues to be a huge unmet need**

Mortality and morbidity in stable systolic dysfunction has improved by modulating neurohormonal abnormalities, but the long-term morbidity and mortality are still high, and we have failed in improving outcomes in WCHF and HFpEF.

**Point 2. Heart should be the focus of heart failure research and drug development**

Etiologies of cardiac origin represent the proximal causes of HF, but often interventions target issues secondary to the failing heart. Most patients die with considerable dysfunctional viable myocardium, unlike kidney, liver, or brain failure where residual "tissue capital" is minimal at the point of failure.

**Point 3. A potential path for a greater probability of translational success involves an early T1 mechanistic phase**

This is a two-step approach of demonstrating benefit in animal followed by testing of a hypothesis and agent in small "mechanistic clinical models" termed T1 trials investigating mechanism-function relationships using imaging and other biomarkers. *Reverse remodeling* should go beyond structural to include functional remodeling, including myocyte function effects on contractility, interstitial effects on contractility and relaxation, microcirculation, and metabolic and mitochondrial abnormalities. Irrespective of the models and analytical methods used, demonstration that target and pathway engagement by a hypothesized therapeutic intervention translates into reversing cardiac/pump functional deficit in small, early T1 trials would build scientific, clinical, and regulatory confidence in the intervention under investigation, and thus promote advanced investigation in broader populations of heart failure patients.

**Point 4. Advanced imaging may be very useful in proof-of-mechanism studies for novel interventions**

Novel imaging can detect relevant anatomical and functional features upon which many diverse pathophysiological pathways converge. Whether a drug targets calcium signaling, microcirculation, mitochondrial function, substrate shifts, or myocardial regeneration, clinically relevant biomarkers should 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 in heart failure patients must continue**

Identifying homogeneous patients whose disease is clearly or more likely to be driven by the mechanisms of action involved in the therapeutic hypotheses to be tested with new agents is challenging but not limiting. Currently it is challenging to segment patients into subsets whose worsening state is driven by a particular mechanism. However, given the unmet need in WCHF and HFpEF, the testing of novel hypotheses for saving and extending healthy life in heart failure patients must continue aggressively.

WCHF = worsening chronic heart failure; HFpEF = heart failure with preserved ejection fraction; RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system

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

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- **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
      - Electrical
      - Mechanical
      - Atrioventricular, interventricular, intraventricular
    - RV function
  - **Metabolism**
    - Glucose utilization
    - Mitochondrial function
    - Calcium handling
  - **Vascular coupling**
    - Venous/arterial interactions
    - Pulmonary/systemic interactions
    - Ventricular-vascular coupling
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