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Reassessing Phase II Heart Failure Clinical Trials: Consensus Recommendations

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Abstract

The increasing burden and the continued suboptimal outcomes for patients with heart failure underlines the importance of continued research to develop novel therapeutics for this disorder. This can only be accomplished with successful translation of basic science discoveries into direct human application through effective clinical trial design and execution that results in a substantially improved clinical course and outcomes. In this respect, phase II clinical trials play a pivotal role in determining which of the multitude of potential basic science discoveries should move to the large and expansive registration trials in humans. A critical examination of the phase II trials in heart failure reveals multiple shortcomings in their concept, design, execution, and interpretation. To further a dialogue regarding the challenges and potential for improvement and the role of phase II trials in patients with heart failure, the Food and Drug Administration facilitated a meeting on October 17th 2016 represented by clinicians, researchers, industry members, and regulators. This document summarizes the discussion from this meeting and provides key recommendations for future directions.

Keywords

heart failure; clinical trial; endpoints; trial design; safety

Heart failure (HF) affects 26 million people globally.[1] The approximately 6 million individuals with HF in the United States account for over $30 billion in annual healthcare costs with a projected increase to $77 billion by 2030.[2, 3] Reductions in mortality from chronic HF with reduced ejection fraction (HFrEF) have been shown in trials with drugs primarily targeting neurohormonal dysregulation.[2] Despite these successes, many other

phase III trials with promising agents for HFrEF failed.[4–8] To date, there has been no approved therapy that improves outcomes in patients with worsening heart failure (WHF) in spite of available therapies or those with heart failure and preserved ejection fraction (HFpEF) despite many clinical trials in these populations.[9] A disconnect between the results of phase II and phase III trials of drugs for heart failure is evident (e.g., levosimendan, tezosentan, tolvaptan, rolofylline, and nesiritide programs).[10] This experience with neutral or negative phase III trials for HF, despite enthusiasm from positive *signals* in phase II evaluation, brings into question the utility/role of phase II trials as they are currently designed, conducted and interpreted.[11] A critical examination of previous phase II HF trials reveals opportunities to improve the concept, design, execution, and interpretation of early phase trials to avoid false positive interpretation in the future. Large time and resource intensive phase III trials based on enthusiastic but misleading or misinterpreted phase II evidence negatively impacts the development of therapeutics for HF beyond the obvious financial concerns, and may discourage sponsors from investing in future research.[12]

To better understand the challenges of design, execution, and interpretation of phase II trials in HF drug development, the Food and Drug Administration (FDA) facilitated a meeting on October 17th 2016, which was attended by clinicians, researchers, sponsors, and regulators. The focus of the meeting was to learn from past experiences and provide future recommendation for the conduct and interpretation of phase II trials in HF.

Rationale For Phase II Trials

The evolution of therapeutic agents through the developmental process involves examining the intervention through a series of phases. Phase II studies are intended to provide information on dosing, initial insights into tolerability and gross safety concerns, and potential for efficacy in the target patient population. The phase II trial data help inform researchers and sponsors to estimate the chance of success in achieving mortality and hospitalization risk benefit in the registration trials, targeting drug approval by the regulatory agencies, and bringing the intervention into the market for use by clinicians.

Limitations Of Phase II Trials In Heart Failure

Current approaches to phase II trials in HF present several limitations in all aspects, including dose selection, gaining insights into tolerability, safety, and potential efficacy, exploring subpopulations which may derive particular benefit, and in turn informing phase III program design. One problem is overly enthusiastic interpretation of phase II results that are followed by negative phase III trials. Equally concerning is the discontinued development of potentially promising compounds (e.g., levosimendan, tezosentan, tolvaptan, rolofylline, nesiritide) due to missed primary endpoints in the phase II trials, ignoring the limitations of the predictive ability of a single outcome domain in a phase II setting.[10]

Dose Selection

Dose selection reflects the goals of therapy, which may include improving symptoms, frequency and duration of hospitalization, or prolonging life. Typically, drug development

includes an estimate of a non-effective dose and the highest tolerated dose in a Phase II-a study. The Phase II-b dosing objective is to test doses ranging from a clinically non-effective dose to the highest tolerated dose to determine the dose-response relationship. For drugs with a broad therapeutic window, one hopes to observe similar pharmacodynamic responses at multiple higher doses, facilitating the choice of the lowest dose. It is suboptimal to proceed with the highest tested dose based on limited tolerability taken into phase III, as this does not provide a safety margin. This paradigm is complicated in HF, as drugs tested in phase II are not typically titrated to any specific pharmacodynamic effect targeting a particular physiologic biomarker or pathway, tough secondary assessment of dose on various biomarkers or cardiac functional parameters may be assessed. Also, most therapies tested to date in HF had hemodynamic consequences and dose ranging typically included successively higher doses titrated until intolerance or significant lowering of blood pressure was noted or maximum feasible dose was achieved.

This paradigm is particularly challenging for evaluating drugs that do not have overt acute hemodynamic effects. Unlike other cardiovascular disorders, e.g. dyslipidemia and hypertension, in HF trials there has been a lack of clear biologic response to target with a few exceptions, e.g. ivabradine and heart rate. In part, this lack of pharmacodynamic targeting for dose analysis reflects the complex and heterogeneous within- and between-patient pathophysiology of the HF syndrome, as there is not as direct of a response variable to track as there is using blood pressure for hypertension drugs. Thus dose selection in HF phase II trials may reflect safety concerns more so than potential efficacy. Theoretically it is quite possible that the pharmacodynamic benefits are reached at doses much lower than the highest tolerated dose, in which case patients are unnecessarily exposed to the risks of higher doses. Similarly, it is also possible that minimal pharmacodynamic benefit is achieved at maximum tolerated doses where the chance of success in phase III trials is low.

Safety

Safety assessment in HF phase II trials is currently targeted to detect gross on and off target concerns including end-organ damage or hemodynamic instability, particularly hypotension. Clinical safety can only be assessed with adequately powered long-term studies. This concern is particularly relevant with endpoints for approval for HF including functional capacity or quality of life. Unless adequately powered studies are conducted, smaller studies may demonstrate improvement in patient centered outcomes but miss important safety signals [13] Thus phase II trials may provide useful but limited overall safety information.

Efficacy

Clinical Endpoints

By definition, phase II trials are too small to have the power to show improvement in mortality or hospitalization risk. Thus the stability and reproducibility of clinical endpoint results, either positive or not, in phase II trials can only provide limited confidence. As a result, efficacy assessment in phase II trials by necessity is relegated to surrogate endpoints and translation biomarkers.

Surrogate Endpoints

The surrogate endpoint for HF trials represents several challenges underscoring the main challenge in designing phase II HF trials, i.e. the selection of a phase II endpoint for a disease requiring improved clinical outcomes in phase III.[14] For lipid and blood pressure, phase III approval has traditionally been based on changes in lipid levels or blood pressure allowing use of the same endpoint in phase II and phase III trials. For HF trials, the need for outcomes in phase III requires the use of translational biomarkers in phase II. The uncertainty around the translatability and predictive value of changes in the phase II endpoint to future changes in phase III outcomes is a major issue for researchers and sponsors. An example is the natriuretic peptides. The literature is replete with evidence for the prognostic value of natriuretic peptides in every setting and sub-population of HF patients. Many smaller studies showed improved clinical outcomes for patients who were treated targeting a strategy to lower natriuretic peptide levels.[15] Despite this, in clinical trials, some therapies that reduced natriuretic peptide levels did not improve clinical outcomes. Importantly, recent larger trials failed to show improvement in outcomes for HF patients treated with a strategy targeting lowering of natriuretic peptides.[6]

Heart failure and reduced ejection fraction—There are many data that suggest that while a potential surrogate marker may have a strong observational association with outcomes, they do not necessarily represent a strong correlation with outcomes in a trial setting even if a favorable trend is observed in their trajectory.[16] The most consistent correlation in patients with HFrEF has been left ventricular reverse remodeling and outcomes.[17, 18] However, reverse remodeling has a good positive but not necessarily negative predictive value. Beta-blockers, in a dose dependent manner, result in left ventricular reverse remodeling, a mechanism hypothesized to contribute to the mortality benefit with these agents.[19] However, such remodeling has not been shown with mineralocorticoid receptor antagonists in patients with mild symptoms, despite their association with improved clinical outcomes.[20]

Heart failure with preserved ejection fraction—Concerns remain about traditional surrogates like natriuretic peptides in HFpEF.[21] Left atrial remodeling appears promising[22] and indeed was in part related to the decision to proceed with the Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON) trial.[23] However, the meaning of a 2.3 ml net difference in left atrial volume index between valsartan vs. valsartan/sacubitril arms in the phase II trial remains unclear. Interestingly, though there was a favorable effect on outcomes with spironolactone in the “Americas” subpopulation of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, there was no between-group difference in left atrial volume.[24] Diastolic dysfunction and left ventricular hypertrophy are possible surrogates, but many patients do not have these abnormalities despite the presence of an overt clinical syndrome.[23] Nevertheless considering the HFpEF heterogeneity, structural changes are now required in most HFpEF trials. Blood pressure is a potential target, however, despite lower blood pressure with irbesartan in the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) trial, there was no difference in clinical outcomes.[25] Thus to date there are no biomarkers that can credibly claim to represent a

predictability signal of therapeutic effects on outcomes in HFpEF. This may in part be due to the recognition that the pathophysiology of HFpEF is highly complex. The concept that a single biomarker signal would provide such information, particularly if related to an isolated factor such as natriuretic peptides representing wall stress, may not be possible.[26]

Worsening heart failure—Similar to HFpEF, so far there have been no studies to improve long-term clinical outcomes in patients with WHF and it is not possible to say which surrogate markers are good for WHF.[27] Almost all patients with WHF have congestion that is related to prognosis. Therefore, markers like natriuretic peptides, urine output, and weight may serve as surrogate markers. However, tolvaptan use, despite improving these markers, was unable to show clinical benefit.[7] No difference in all-cause mortality with levosimendan was seen despite a more pronounced reduction in natriuretic peptide levels compared to dobutamine.[5] Nesiritide improved hemodynamics but failed to show an improvement in post discharge readmission or mortality rates.[28]

Targeting poorly understood pathophysiology—In a pilot study, rolofylline prevented worsening renal impairment in WHF.[29] However, the phase III trial failed to demonstrate clinical improvement with rolofylline.[4] Interestingly, only 13.7% developed worsening renal function in the placebo arm of the trial.[30] Importantly however, available data now support the notion that worsening renal function is not necessarily associated with poor outcomes and in some patients may represent better decongestion and potentially improved outcomes.[31]

Path Forward

Recommendations for the Future Conduct of Phase II Trials

Given these challenges, several innovations in phase II trials are proposed to facilitate future drug and device development for HF. (Figure 1) These together may improve the understanding of investigational interventions in phase II trials, leading to a better correlation of early phase data with phase III trial outcomes.

Identifying New Patient and Disease Improvement Markers

For the long-term successful development of therapeutics, close attention needs to be paid to develop novel surrogate markers that inform future trials.[32] This will require embedding new measures into existing phase trials to better understand them. Identifying generic surrogate markers for HF may not be possible and instead, the focus should be to identify markers for subpopulations of patients based on the pathophysiology and the mechanism of action of the agent. *Big data* and machine learning techniques, and personalized medicine approaches using genomics and proteomics applications as well as well as device based real-world, continuous measurement of health status (e.g. wearable and implantable devices) hold promise in this respect.

Tailoring Endpoints Selection to Mechanism of Action

Both HFrEF and HFpEF are syndromes with heterogeneous pathophysiology. Clinical endpoints in phase II and III trials are likely to be affected differently from drugs acting on

different pathways and with different mechanisms of action. This consideration should be linked to the evidence coming from large trials showing that hard endpoints (total mortality, total hospitalizations, major cardiovascular events) in HF patients have causes that are often unrelated to the mechanism of action of the drug. A therapy that improves diastolic function may improve symptoms and have a beneficial impact on HF related hospitalizations, but may not prevent death or hospitalizations due to other underlying conditions such as stroke, myocardial infarction, and non-cardiovascular causes that can represent up to 50% of events in HFpEF. Selecting endpoints and biomarkers that can be mechanistically affected by the studied drug can have a significant impact on the success of a clinical trial and on its size and design. It is important to recognize that curing or controlling HF is a multi-dimensional task, and that different pathways and mechanisms of action will have a different impact on different endpoints. Thus, the path forward to improve HF trials needs the connecting of biological pathways, drug mechanisms of action, and underlying pathophysiology. (Figure 2)

Comprehensive Assessment of Multi-Domain Data

While any individual surrogate and efficacy markers by themselves in phase II may not be sufficient to inform prospects of success in phase III trials, a combination of markers may provide better cumulative information to guide downstream research endeavors. In this respect, the following domains of data represent distinct information relevant to the therapeutic development process. (Table 1)

1. Effect on cardiac structure and function
2. Effect on patient well-being
3. Effect on worsening symptoms and need for changes in standard therapy
4. Effect on cardiac and non-cardiac comorbidities
5. Effect on healthcare resource utilization
6. Effect on biomarkers, both for safety and efficacy

The exact markers included in each domain will vary based on the specific phenotype. It is however recommended that data be collected on select markers representing all of these domains. It is important to move away from over-reliance on a single *primary endpoint,* declaring an entire trial neutral or negative based on it. Thoughtful assessment of numerous important data should allow for the totality of the information to inform subsequent development decisions.

Statistical and Analytical Methods

While a more comprehensive assessment of data representing multiple domains holds promise to improve future development of HF therapeutics, how to assimilate the data may require utilization of analytical methods to aid better understanding of the large quantity of data. These analytic methods will have to be tailored based on the data directionality and stratification, the clinical scenario and patient population, and how to deal with discordant information if that occurs. Several statistical methods may aid in evaluating data from the various domains to give a cumulative assessment of the impact of the intervention.[33–38]

While these methods may provide more power to detect differences in the context of the phase II studies, the main concern is not power but how to understand the multitude of data points to avoid a phase II – III disconnect. In this respect, several aspects need particular attention including selecting and weighing individual components and eventual decision making guidelines.

Developing Guiding Principles

Regardless of the data and the analytic methods, the eventual decision to move from phase II to III trials will involve subjective decision-making. While this cannot be avoided, it can be streamlined, as it is currently widely variable among sponsors and investigators. Developing general guiding principles will help mitigate the variability and help in learning lessons and modifying both the analytic methods as well as guiding principles over time. A dedicated effort to understand how sponsors currently make such decisions and a multi-stakeholder consensus will be needed to develop guiding principles that inform the decisions of whether to stop development of an intervention, move to phase III, or get additional phase II data.

Patient Centeredness

HF is a chronic condition that affects quality of life and functional capacity. It is imperative to keep the patient in the center of research endeavors. Assessing how the patient is feeling and functioning should remain an intricate part of phase II assessment. A patient “well-being” concept is attractive in that it attempts to integrate multiple aspects of the clinical course and to incorporate “the voice of the patient”. It is also a challenging concept in that it potentially includes aspects that are subjective such as symptoms, objective such as functional capacity, and hard outcomes like death or hospitalization. A therapy may not affect all aspects of well-being and individuals may value the various aspects differently. This has led to the proposal to have patients identify which among a defined set of symptoms are most troubling at baseline, and have a study’s end point be based on different aspects of “well-being” in different subjects.[39] This idea has the potential to show small population-based estimates of the treatment effect on a number of symptomatic claims, none of which are particularly compelling, but still have a large effect overall, when considering what each individual participant values most.

The symptomatic claims in HF need to substantial. Small though statistically significant symptomatic benefits are hard to interpret and may not be truly clinically meaningful. A fairly benign safety profile may also be misleading if the background mortality rate is high, because small adverse effects on mortality might be important compared to the benefit. This is not to say that drugs for HF need to show benefits on mortality or hospitalization, but the potential tradeoff needs to be reasonable, and this potential tradeoff needs to incorporate one’s uncertainty around the important outcomes.

Conclusions

The current state of phase II trials for HF drug and device development poses a multitude of challenges and concerns remain regarding all four critical aspects of phase II trials, i.e. surrogate endpoints, totality of data collection, data analysis, and the decision making

process. The heterogeneous nature of HF pathophysiology should be reflected in the selection of endpoints and biomarkers that are more mechanistically related to the drug's mechanism of action. Previous large trials might have suffered from dilution of drug benefits into endpoints unlikely to be affected by the drug. Competing causes for cardiovascular and non-cardiovascular events should be taken into consideration when designing HF trials given the high rates of events often not preventable by a particular drug acting on a specific pathway. Further dialogue to develop a consensus for the data representing these identified domains should be a priority and should involve all of the important stakeholders including academic, sponsors, regulators, payers, and the patients. Such data need to then be tested and validated in ongoing trials to better inform future phase III programs.

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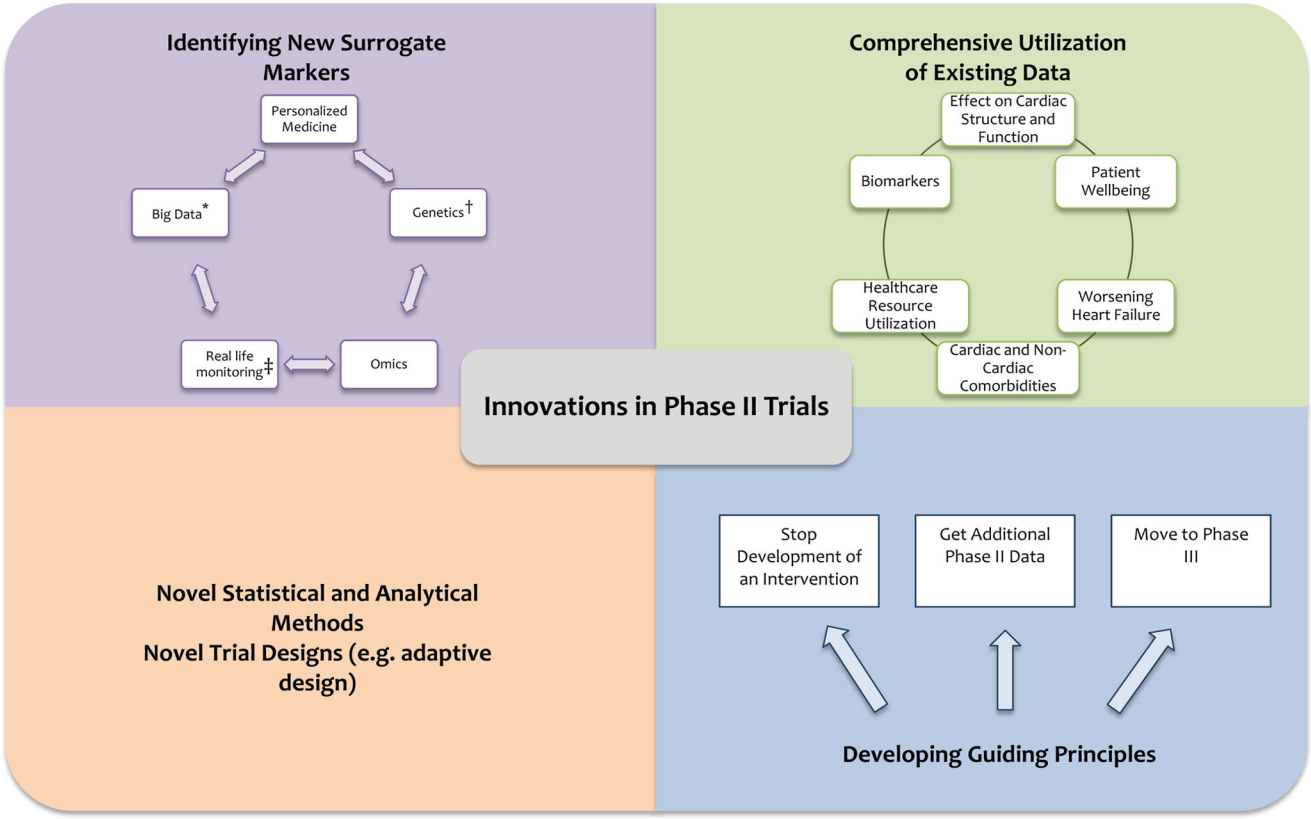

Figure 1. Innovations in Phase II Trials

Innovation in phase II trials should include (1) identifying new surrogate markers, (2) comprehensive utilization of existing data, (3) novel statistical and analytical methods, and (4) developing guiding principles. * Including machine learning, data mining and sharing. † e.g. next generation genome sequencing. ‡ e.g. wearable and implantable devices, smart phone applications.

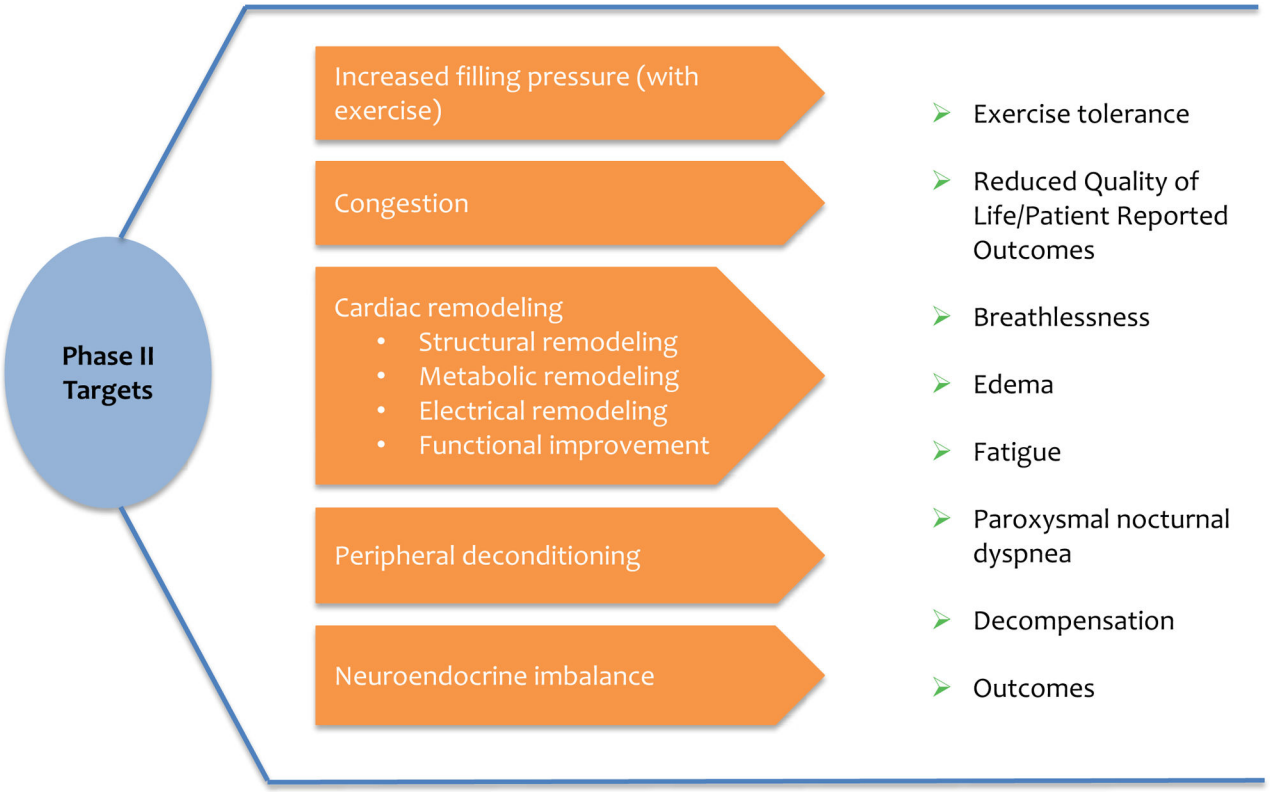

Figure 2. Therapeutic Targets in Phase II Trials

Targets of Phase II Trials should include increased filling pressures, congestion, cardiac remodeling, peripheral deconditioning, and neuroendocrine imbalance

Table 1

Multi-Domain Data for Comprehensive Drug Evaluation in Phase II Trials

Domain	Example
Cardiac Structure and Function	• Structure (myocyte, interstitium, microcirculation) • Function (ejection fraction, filling pressure) • Metabolic abnormalities • Electrical remodeling
Patient Well-Being	• Symptoms (e.g. dyspnea) • Exercise- daily activities • Objective- sings of congestion • Subjective- dyspnea, NYHA
Worsening Heart Failure	• Unexplained outpatient visit • Hospitalization for heart failure • Mortality
Cardiac and Non-Cardiac Comorbidities	• Hypertension • Coronary Artery Disease • Diabetes Mellitus • Renal Disease • Chronic Obstructive Pulmonary Disease • Atrial Fibrillation
Healthcare Resource Utilization	• Test performed (cardiac and non-cardiac) • Overall cost (medications, facility)
Biomarkers	• Efficacy (e.g. biomarkers representing cardiac stress, fibrosis, myocardial and vascular inflammation, mitochondrial dysfunction, oxygen free radial production etc.) • Safety (e.g. troponin, eGFR)