

Development of Therapeutics for Heart Failure: Expedited Commentary

Transforming Drug Development in Heart Failure Navigating the Regulatory Crossroads

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Based on favorable hemodynamic data, flosequinan, an oral vasodilator, received marketing approval in Europe in September 1992 and in the United States in March 1993 for use in chronic heart failure (HF). Later, a phase III trial signaled increased mortality, prompting its withdrawal from the market. Oral milrinone was initially used for refractory HF but was later shown to increase adverse events when tested in late-phase trials. More recently, in 2002, the Food and Drug Administration (FDA) approved nesiritide for dyspnea improvement in patients with worsening HF,¹ but a subsequent phase III trial showed that it did not influence mortality or readmission risk.² These examples reinforce the enduring need for large, randomized trials with clinically meaningful end points and the role of regulatory authorities in protecting public health.

Contradicting results between early-phase data and outcomes in registration trials in HF have raised the global regulatory bar for new drug approvals and have introduced regulatory uncertainty³ into the current drug development model. In 2016, candidate compounds are tested in sequential phases, terminating in trials in global, heterogeneous populations,⁴ mostly targeting neurohormonal pathways that may contribute to adverse remodeling. Surrogate end points are used in early-phase trials, whereas an adequate margin of safety (often assessed by risk of mortality or hospitalization) is required in registration trials.⁵ Placebo-controlled designs have been the standard, although active-controlled protocols have been used.⁶ Sponsors, few academic collaborators, and academic or contract research organizations guide the process and ultimately present the data to regulatory authorities. This paradigm has unfortunately been met with high operating costs of contemporary HF drug development programs, which has translated into fewer new drug applications and approvals by the FDA.³ This underscores the need for new approaches that will match increasingly scarce resources with high-yield trial propositions aimed at improving outcomes. A critical aspect to achieve this goal is to leverage partnership with the regulatory authorities in optimizing trial design and the drug development process.

Early Regulatory Collaboration

Regulatory uncertainty presents a major barrier to drug development. Steering committees add layers of complexity to trial design, increasing data collection and costs, to maximize

chances of drug approval.⁷ Early, transparent, and substantive regulatory integration may help guide study leaders at multiple levels of planning and execution.

Study Planning and Protocol Development

In the initial phases of trial planning, regulatory input may help shape protocol development. Early discussions with regulatory authorities may inform key aspects of the study, including optimal drug dosing, end point selection, blinding strategy, extent of adjudication, and the roles and responsibilities of study personnel. These efforts, on the one hand, may identify aspects that can be omitted or abbreviated, rendering trial conduct more efficient and less costly and, on the other hand, may identify important and relevant additions that may have a major impact on study conduct and results. Early regulatory oversight can ensure that end points are patient-centric, clinically relevant, and importantly, if met, sufficient for drug approval.

Data Analyses and Trial Designs

Upfront discussion may clarify planned statistical approaches and timeline for primary and interim analyses, especially when novel end points or adaptive trial designs are introduced into HF drug development.⁸ Study sponsors and leadership will be required to provide transparent and clear rationale for choice of trial design, offer validated statistical approaches, and establish an independent external data and safety monitoring committee with definitive decision rules at each interim analytic juncture.

Global Clinical Trial Conduct

Regulatory authorities may be key mediators in navigating challenges inherent to the conduct of global clinical trials. Regional heterogeneity in HF trials may have important implications on the ability of a drug to show benefit.⁹ Based on their collective formidable trial experience, regulators may be helpful in identifying high-quality sites in regions that have been underrepresented in prior global trials. Regulators may ensure consistent and comprehensive data collection across global sites. Regional regulatory authorities may further delineate local requirements for marketing applications pursued in global programs.

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Overall Drug Development Process

Large-scale confirmatory trials are a tremendous resource investment. Beyond input regarding individual trials, regulators may have insight into the appropriateness of terminating the drug development process, application of seamless phase 2 to 3 designs, or advancing to later phases of investigation. When safety concerns are raised based on early data collection or from parallel trial programs evaluating the same drug or intervention, limited appropriate interaction between trialists, regulators, and sponsors during the progress of the trial may collaboratively ensure patient safety.^{10–12}

Identifying Unmet Clinical Needs in HF

The cases of flosequinan, milrinone, and nesiritide typify the short-lived enthusiasm for many agents that enter clinical practice in HF. However, with select recent exceptions, the drug armamentarium for chronic HF with reduced ejection fraction has remained relatively stagnant for over a decade, and to date, despite many trials, no drug has been approved for HF with preserved ejection fraction and for worsening chronic HF. The FDA has created pathways like priority review, accelerated approval, and fast track to expedite the process of bringing therapies to market, but only a minority of new cardiovascular drug applications use these pathways. Many cancers have similarly dismal event rates as HF, but a substantially higher proportion of oncological drugs are brought to market via these programs.

We think that this discrepancy may be related to the underestimation of risk associated with HF and the lack of validated surrogate end points in HF. Given the ready improvement in dyspnea, the major symptom requiring acute care, with diuretics alone, many stakeholders underestimate the impact of HF beyond symptoms and assign it a lower priority as an unmet clinical need. The pathophysiologic drivers of HF are complex, and the patient population is heterogeneous and suboptimally phenotyped. As such, surrogates consistently linked to clinical outcomes sufficient to support drug approval in HF are lacking.⁵ This is in contrast to oncology, where the biology underlying pharmacological targets is better understood, and many drug approvals are based on improvements in surrogate markers.

However, there may be circumstances where early drug approval and patient access should be considered even in the absence of definitive outcome data, for example, advanced HF with symptom-limiting functional status. Patient-centered outcomes, such as quality of life and clinical stabilization or improvements in symptoms, should be leveraged in this high-risk cohort, typically refractory to traditional therapies. This framework would necessitate frequent communication with regulators, postmarketing pharmacovigilance, and mechanisms to withdraw agents or limit indications if safety signals emerge.

Sharing Clinical Trial Data

There have been several negative or neutral HF trials that remain unpublished, at least in a timely manner. A recent survey of 4347 interventional clinical trials registered on ClinicalTrials.gov completed between October 2007 and September

2010 reported that only 66% of trials disseminated findings in total, of which just over half completed reporting within 24 months.¹³ Another aggregate trial-level study corroborated these findings that less than two thirds of extramural randomized cardiovascular clinical trials supported by the National Heart, Lung, and Blood Institute were published within 30 months of study completion.¹⁴ A similar historical experience of failure or significant delays in trial publication and disclosure has been observed in HF. One example was REVIVE II (Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy II), a large, prospective, randomized clinical trial evaluating the role of the calcium sensitizer, levosimendan, in hospitalized patients with acute HF. Although the primary trial results were presented at a Late-Breaking Clinical Trial Session at the American Heart Association Scientific Sessions in 2005, the study was formally published by the Dead Letter Office¹⁵ of *JACC: Heart Failure* in April 2013.¹⁶ Similarly, PRAISE-2 (Prospective Randomized Amlodipine Survival Evaluation 2) failed to demonstrate clinical benefit of amlodipine on all-cause mortality in patients with nonischemic advanced functional class chronic HF, a clinical subgroup that had experienced apparent favorable drug effects in PRAISE-1. Although the trial was presented at the American College of Cardiology Scientific Sessions in 2000, it was subsequently published in August 2013.¹⁷ These trial experiences reinforce the enduring need for early results dissemination and data disclosure, especially for agents that are in active clinical use with potentially untoward effects.

For those that are published, many of the databases are accessible only to a few trialists or sponsors after protocol completion. This year, the International Committee of Medical Journal Editors released formal statements endorsing sharing of clinical trial data.¹⁸ The recently formed ACCESS CV consortium (Academic Research Organization Consortium for Continuing Evaluation of Scientific Studies—Cardiovascular) represents a practical platform to execute this planned data-sharing proposal.¹⁹ Teaming with regulatory authorities may facilitate timely registration, disclosure, and data release. This would not only fulfill responsibilities to participants, but also allow researchers to learn from even negative or neutral resource-intensive trials.²⁰ This investment and upfront commitment may provide a more in-depth understanding of the HF patient population and, in turn, improve the yield of future trials in this area.

Conclusions

The rising global economic and clinical burden of HF has outpaced the introduction of new drugs and research investment, fueling their development. The prevalence of HF will continue to rise with the aging population. Transparent partnership bridging academia, industry, and regulators and their respective interests may increase the sustainability and productivity of the current drug development model. FDA representatives in a recent cardiovascular working group have corroborated interest in pursuing this collaborative model in future trial design.³ Regulatory involvement and collaboration during the progress of the trial must be carefully balanced with maintenance of blinded data integrity and the independence of the data monitoring committees. The specific delineation of roles and responsibilities of

regulatory authorities in HF clinical trials has become a topic of active discussion, in light of the recent regulatory experience with the direct renin inhibitor, aliskiren.^{10–12} The overarching goal will be to streamline and expedite the overall process from target identification to patient access, while simultaneously maintaining rigorous standards for review. This paradigm shift may ultimately transform the role of regulation in drug development from a burden to an opportunity. Decisions regarding the design of phase II trials and transition to phase III studies should be reached by consensus, aligning the perspectives of all involved stakeholders including industry, government sponsors, trialists, opinion leaders, and regulators.

Disclosures

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