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A rationale for dedicated trials of combination therapy in heart failure

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As heart failure (HF) enters a new era with high level of evidence supporting the use of individual drug therapies, we put forth a rationale for the need for dedicated investigation of the safety, tolerability, and practicalities associated with combination medical therapy. Being able to tailor therapies via combination approaches might offer a way to maximize benefits of available therapies and also facilitate compliance. The evidentiary bar to support multi-drug regimens should be raised in HF for a variety of reasons: (1) Pivotal HF randomized controlled trials (RCTs) to date have not traditionally tested and proven safety and efficacy of drug combinations, (2) HF patients have variable disease trajectories, (3) There is hesitancy by clinicians and patients to using multiple drugs and such trials may build confidence in their use, and (4) HF therapies have overlapping side effects. Similar to combination therapies being developed and tested in adjacent fields of medicine, HF care too would greatly benefit from dedicated investigations of combination treatment approaches. Personalizing precision medicine with combination therapies has the potential to further improve outcomes and facilitate optimal implementation of disease-modifying therapies in HF.

Introduction

Since chronic illnesses are often driven by complex pathophysiological processes, targeting multiple therapeutic pathways may lead to a more effective way of disrupting mechanisms leading to disease progression. Combination therapy has become critical in developing prevention and treatment strategies across many medical disciplines, as drug combinations have the potential to improve treatment response, minimize development of resistance, allow lower doses of component therapies, or reduce adverse events. Combination of pegylated interferon-alpha and ribavirin, two drugs that alone demonstrated very minimal benefit, provides synergistic actions in chronic hepatitis C virus.[1] Combination antiretroviral therapy has become the standard for human immunodeficiency virus infections to reduce the likelihood of drug resistance.[1,2] Combination therapy with several drugs is also the preferred approach in some cardiorenal metabolic diseases. Combination of low doses of multiple antihypertensive therapies represents a highly effective blood pressure-lowering strategy, while minimizing treatment attendant adverse events seen at higher doses.[3] Multi-drug regimens are strongly recommended to attenuate early risk after acute myocardial infarction.[4] In chronic kidney disease, the use of a sodium-glucose co-transporter 2 inhibitor (SGLT2i) may mitigate hyperkalaemia risks facilitating ongoing use of mineralocorticoid receptor antagonists (MRAs).[5]

Combination therapy in heart failure

In 2022, heart failure (HF) with reduced ejection fraction has reached a critical juncture with quadruple therapy [a combination of angiotensin receptor-neprilysin inhibitor (ARNI), β-blockers, MRA, and SGLT2i] estimated to reduce clinical events and extend survival when compared with conventional therapy.[6] While using each of these therapies

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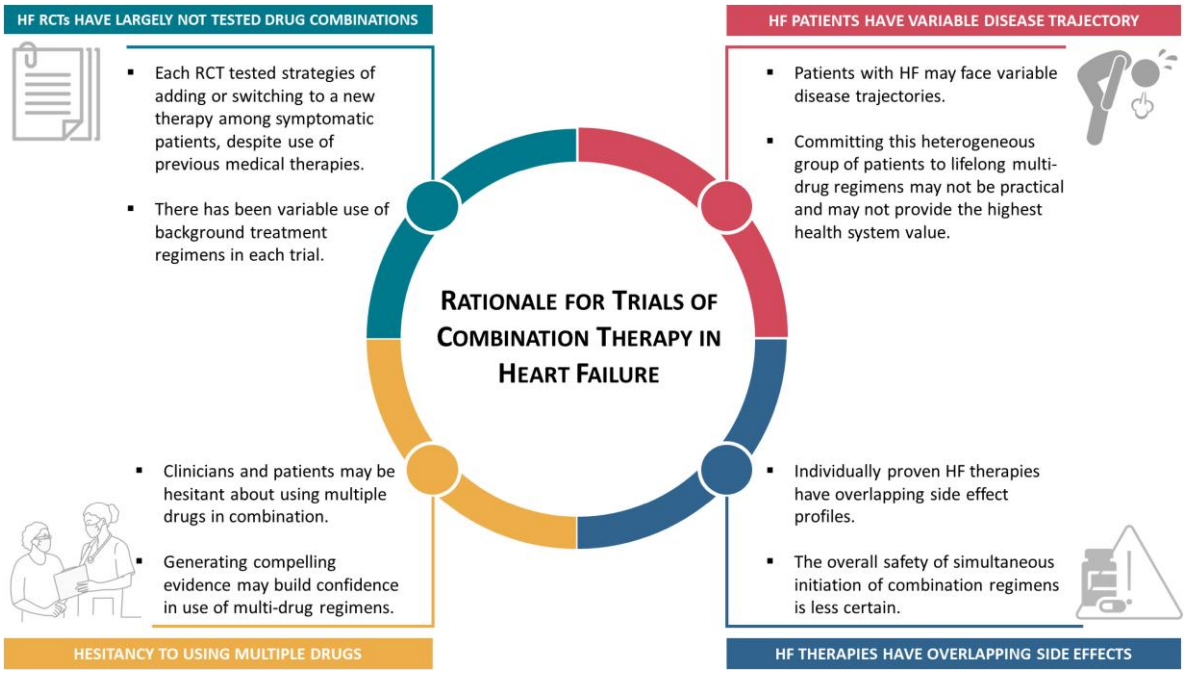

Figure 1 Rationale for trials of combination therapy in heart failure. The evidentiary bar to support multi-drug regimens should be raised in heart failure for a variety of reasons: (i) pivotal heart failure randomized controlled trials to date have not traditionally tested and proved safety and efficacy of drug combinations, (ii) heart failure patients have variable disease trajectory, (iii) there is hesitancy by clinicians and patients in using multiple drugs, and (iv) heart failure therapies have overlapping side effects.

in combination may theoretically yield additive treatment responses,[7,8] appropriately identifying which drug combinations (and at what doses) are safe and effective, which populations may derive the greatest benefit, and when in the disease course they should be integrated remain central treatment priorities. Furthermore, while guideline-based therapies have proved to improve outcomes, adherence to guidelines and implementation barriers have been widely described.[9] As HF enters a new era, we put forth a rationale for the need for dedicated investigation of the safety, tolerability, and practicalities associated with combination medical therapy in HF. Being able to tailor therapies via combination approaches might offer a way to maximize benefits of available therapies and also facilitate compliance.

Raising the evidentiary bar for combination treatment strategies

We believe the evidentiary bar to support multi-drug regimens should be raised in HF for a variety of reasons (*Figure 1*). First, the pivotal randomized clinical trials that have supported current standard of care therapies were largely not designed to test their use in combination. Indeed, each trial tested strategies of adding or switching to a new therapy among individuals with HF who remained symptomatic and at high clinical risk (e.g. elevated natriuretic peptide levels), despite use of previous medical therapies. While best available therapies were encouraged, these suggestions were not mandated, yielding variable use of background treatment regimens in each trial. Second, patients with HF, especially those with mildly reduced or preserved left ventricular ejection fraction, may face variable disease trajectories. Committing this heterogeneous group of patients uniformly to lifelong multi-drug regimens may not be practical in all treatment settings and may not provide the highest health system value. Third, clinicians and patients may be hesitant about using multiple drugs in combination, especially early in disease course. Generating compelling evidence for their additive benefits and safe combination may build confidence in multi-drug regimens. At present, even clinical practice guidelines for HF support individual drug therapies with high level of evidence, but are more vague and less prescriptive with respect to timing of initiation and their use in combination. Lastly, many individually proved HF therapies have overlapping side-effect profiles. While trials have shown that these therapies have been generally safe and clinicians have gained familiarity with managing practicalities and adverse effects of individual therapies, the overall safety of simultaneous initiation of combination regimens is less certain. For instance, as renin angiotensin system inhibitors, MRA, and SGLT2i each result in an early, acute decline in estimated glomerular filtration rate, what would be the expected impact if they were started simultaneously? Similarly, multiple HF drug therapies are haemodynamically active and simultaneous initiation may result in excess blood pressure lowering.

Would a trial of combination therapy be feasible and ethical in heart failure?

There has been limited precedent for dedicated combination trials in HF outside of select examples such as the

experience with the ARNI sacubitril/valsartan. In cancer care, where combination regimens are common, dedicated regulatory guidance is in place to guide sponsors and trialists in investigating combination regimens. Indeed, nearly half of all combination therapy trials are conducted in oncology, and a quarter of oncology trials use combination therapies.[2] The US Food and Drug Administration released formal guidance for trial sponsors in consideration of combination therapy in oncology: (i) the combination should be intended to treat a serious disease or condition, (ii) there should be a strong biological rationale for use of the combination, (iii) a full nonclinical or a short-term clinical study should suggest the combination is superior to the individual agents, and (iv) there is a compelling reason why the new investigational drugs cannot be developed independently.[10]

The critical challenge to design an HF combination trial should be to assess rational combinations efficiently and effectively, and have a mechanistic understanding of the contribution of each drug to the treatment effect. Trials of combination therapies in HF face many challenges. First, generating high-quality evidence for combination therapies may lead to increases in costs and time of drug development, and discourage overall investment in the therapeutic area. To date, most novel early phase combination trials in oncology have failed to demonstrate sufficient safety and efficacy to advance to later phases of development.[11] However, combination drug regimens have important regulatory and patent implications. New combination therapies have the potential to be marketed separately and may afford extension of licensing rights, which may incentivize their development. Second, the number of combinations and sequences of drug therapies in HF may be considered infeasible to test in a rigorous manner. Leveraging platform trials can represent a potentially useful approach and have the advantage of creating an efficient trial infrastructure that can help address critical clinical questions as the evidence evolves.[12] Third, powering these trials for clinical outcomes (as is commonplace in HF) would be challenging to conduct and fund due to the necessary sample size. While combination treatment trials in adjacent disease states such as chronic kidney disease use well-validated surrogate markers of disease progression (such as urine albumin to creatinine ratio), an open question would be whether use of markers such as natriuretic peptides or improvement in left ventricular ejection fraction may be sufficient to rapidly test combination strategies in HF. Finally, we recognize that trialing HF patients on less than quadruple therapy can introduce equipoise concern. However, while guidelines support the general strategy of use of these therapies together, the specific timeline and sequence of their use is not well delineated. Furthermore, short- or medium-term trials would still be informative to understand the initial tolerability, safety, and feasibility of a given combination therapy approach, while not exposing patients to substantial or excessive delays in HF care.

Ongoing trials of combination therapies across cardiorenal metabolism

In all, the design and conduct of combination clinical trials pose distinct challenges for clinicians, industry, and regulatory bodies, but can offer very promising management alternatives and new insights into disease therapeutics. Ongoing trials in adjacent disciplines in cardiorenal metabolism are evaluating the incremental role of combination use of drug therapies. In chronic kidney disease, the combination use of an SGLT2i and an MRA is being studied (NCT05254002). In type 2 diabetes, the combination of an SGLT2i and a glucagon-like peptide-1 receptor antagonist is being evaluated.[13] In obesity, a dual glucose-dependent insulinotropic polypeptide receptor agonist and GLP-1RA is being tested against a GLP-1RA alone on long-term cardiovascular outcomes (NCT04255433). We believe that HF care would greatly benefit from similar dedicated investigations of combination treatment approaches. Personalizing precision medicine with combination therapies has the potential to further improve outcomes and facilitate optimal implementation of disease-modifying therapies in HF.

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Data availability

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