Timing and Duration of Interventions in Clinical Trials for Patients With Hospitalized Heart Failure

Catherine N. Marti, MD, MSc; Gregg C. Fonarow, MD; Mihai Gheorghiade, MD; Javed Butler, MD, MPH

There are more than a million hospitalizations for heart failure (HHF) annually in the United States[1] and >80% of them occur in patients with known chronic heart failure (HF).[2,3] These patients have a combined mortality and readmission rate of 35% to 40% within 90 days, a readmission rate of 25% within 30 days, and a mortality rate of 30% within a year after discharge.[1] Many trials have been conducted on these patients and yet there are no approved therapies for these patients with proven efficacy for reducing mortality or readmission.[4–12] There are many reasons for this,[13] including the lack of consensus on therapeutic targets and aims. Most trials have focused on short-term dyspnea, but the rapid response to conventional therapy may indicate that dyspnea relief is a largely a met need. These trials have generally intervened by infusing investigational drugs for 2 to 3 days early in the hospital course signifying a philosophy that HHF represents an acute disease with distinct pathophysiology, like acute myocardial infarction, where short-term interventions can improve outcomes[13] (Figure 1). Myocardial infarction, however, represents a truly acute onset of a distinct pathophysiology (ie, plaque rupture and thrombus formation). Whether HHF is an acute disease representing a distinct pathophysiology is uncertain. The selection of timing and duration of novel intervention among patients with HHF is rooted on fundamental concepts on the acuity of the disease process, its pathophysiology, the timing of adverse events, and past experience.

Subacute Symptom Onset

Some episodes of HHF are truly acute; however, many of these are related to secondary conditions (eg, acute coronary syndrome, rapid atrial fibrillation, or infections). The majority of HHF reflects subacute, progressively worsening congestion.[1,13] Changes occur 12.4±1.4 days before admission for edema, 11.3±1.6 days for weight gain, and 8.4±0.9 days for dyspnea.[14] Changes in weight frequently begin at least a week before admission.[15,16] Defibrillators and cardiac resynchronization devices can assess thoracic impedance that may correlate with fluid status and predict worsening HF before symptom onset. Ninety percent of the detected alerts for changes in impedance were followed by a hospital evaluation for HF within 30 days in 1 study.[17] In another, 53 alert and HF deteriorations were identified in 43 subjects; 83% showed evidence of fluid accumulation several days before the event.[18] In 1 study with ambulatory hemodynamic monitoring, elevated pulmonary artery diastolic pressure correlating with HF events began rising on average 29±22 days before the event[19] (Figure 2). Data with implanted sensors demonstrate that left atrial pressures are most commonly elevated during the 30 days before HF events.[20] Many patients do not have acute symptoms when admitted but present on the basis of availability of caregiver, lack of ad hoc outpatient appointment, reaching a threshold of slowly worsening symptoms, or other social issues; some are hospitalized for worsening HF detected during routine clinic visits.

No Distinct Pathophysiology

The abnormalities that have been described in patients with HHF, although exacerbated, mirror those seen in chronic stable patients with HF (Table). If indeed a ruptured plaque HHF pathophysiology is identified, it will forestall a new era of intervention development; however, no such insights have been gained to date. Patients with HHF have a cardiac structure and function that is similar to chronic HF with varying left[21,22] and right ventricular function,[23] left atrial enlargement, mitral regurgitation, and other abnormalities.[24] Both HHF and stable patients show a wide range of hemodynamics ranging from altered filling pressures, afterload, and cardiac output; however, these tend to be worse during hospitalization.[25] Neurohormonal activation (plasma renin activity, norepinephrine, vasopressin, copeptin, and adrenomedullin)[26–29]; myocyte damage (troponin)[30,31]; inflammation (tumor necrosis factor,[32] C-reactive protein,[33] interleukin-6,[34] and ST-2)[35]; oxidative stress (isoprostane, aminothiols, uric acid, and myeloperoxidases)[36–39]; extracellular matrix (matrix metalloproteinases and their inhibitor, galactin-3)[40,41]; myocardial stress (natriuretic peptides) [42,43]; and renal function (blood urea nitrogen, creatinine, Cystatin C, neutrophil gelatinase-associated lipocalin, and kidney injury molecule)[44–48] alterations have all been shown in both patients with HHF and chronic stable HF.

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From the Division of Cardiology, Emory University, Atlanta, GA (C.N.M., J.B.); Division of Cardiology, University of California, Los Angeles (G.C.F.); and Center of Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, IL (M.G.).

Correspondence to Javed Butler, MD, MPH, Division of Cardiology, Emory Clinical Cardiovascular Research Institute, 1462 Clifton Rd, NE, Suite 504, Atlanta, GA 30322. E-mail javed.butler@emory.edu

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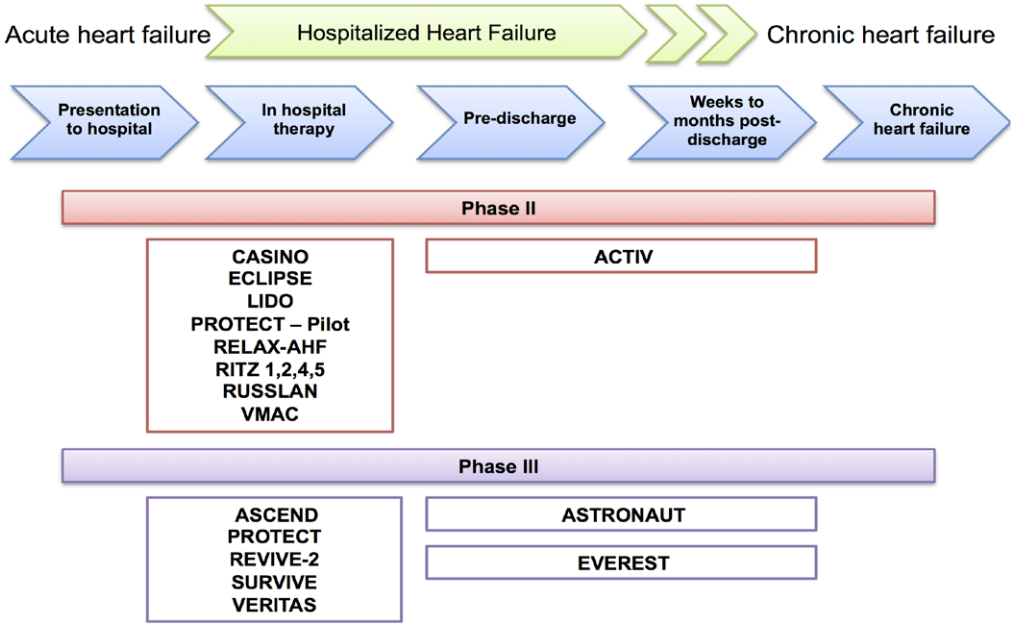

Figure 1. Clinical trials in patients hospitalized for heart failure. Most trials initiated and terminated novel therapies during the acute stages of management. ACTIV indicates Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure; ASCEND, Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; ASTRONAUT, Aliskiren Therapy on Top of Standard Therapy, on Morbidity and Mortality in Patients With Acute Decompensated Heart Failure; CASINO, Calcium Sensitizer or Inotrope or None in Low-Output Heart Failure; ECLIPSE, Effect of Tolvaptan on HemodynamIc Parameters in Subjects with Heart failure; EVEREST, Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure; LIDO, Efficacy and Safety of Intravenous Levosimendan Compared with Dobutamine in Severe Low-Output Heart Failure; PROTECT, Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function; RELAX-AHF, Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure; REVIVE, Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy Versus Placebo in the Short-Term Treatment of Decompensated Heart Failure; RITZ, Randomized Intravenous Tezosentan; RUSSLAN, Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct; SURVIVE, Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support; VERITAS, Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Studies; and VMAC, Vasodilation in the Management of Acute Congestive Heart Failure.

Postdischarge Risk

Current data suggest that patients with HHF have lower in-hospital but higher postdischarge risk for adverse events compared with patients with acute myocardial infarction. The patients with HHF are at a substantially higher risk for death and readmissions compared with stable outpatients with a recent HHF being one of the strongest and most consistent predictors of poor outcomes. Each successive readmission is associated with incrementally higher risk of mortality. The risk for death or readmission is highest within 30 days, and the observed risk decreases significantly within 3 to 6 months. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial, odds for mortality after discharge following HHF declined from 6-fold in the first month after discharge to 2-fold over time (Figure 3).[49] Similar data from registries showed a period of increased risk within the first 6 months after discharge.[50,51] Whether HHF identifies patients at higher risk (a marker) or there are discrete pathophysiologic processes in patients with HHF that contribute the adverse outcomes (a mediator) has not been fully elucidated.

Impact of Short-Term Interventions

The current standard of HHF care, that is, intravenous diuretics, nitrates, and other vasodilators, and in select cases, inotropes are all short-term interventions to improve symptoms and signs, but none has been shown to improve outcomes after discharge. Most HHF clinical trials have also focused on short-term intravenous infusions and none has improved postdischarge outcomes, barring 1 trial. Seralaxin in the Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) trial showed improved 6-month mortality but not the readmission rate or the composite end point of cardiovascular death or readmission to the hospital for HF or renal failure. The results of RELAX-AHF are promising but require confirmation. Therapies that improve postdischarge HHF outcomes are those that affect HF with reduced ejection fraction pathophysiology, and using HHF as an opportunity to optimize care, are initiated in-hospital and continued after discharge (eg, angiotensin-converting-enzyme inhibitors or β-blockers).[52–55] Drugs targeting dyspnea and hemodynamics are usually given intravenously at doses aiming to reverse pulmonary pressures rapidly. Such doses may not be needed for disease modification over long term and may lead to adverse effects (eg, angiotensin-converting-enzyme inhibitor was related to hypotension when given acutely intravenously for patients with acute myocardial infarction, whereas chronic oral use improves outcomes).[56]

Approaches to Future Clinical Trials

If HHF mostly represents worsening chronic HF with no entirely distinct pathophysiologic targets beyond those operative in

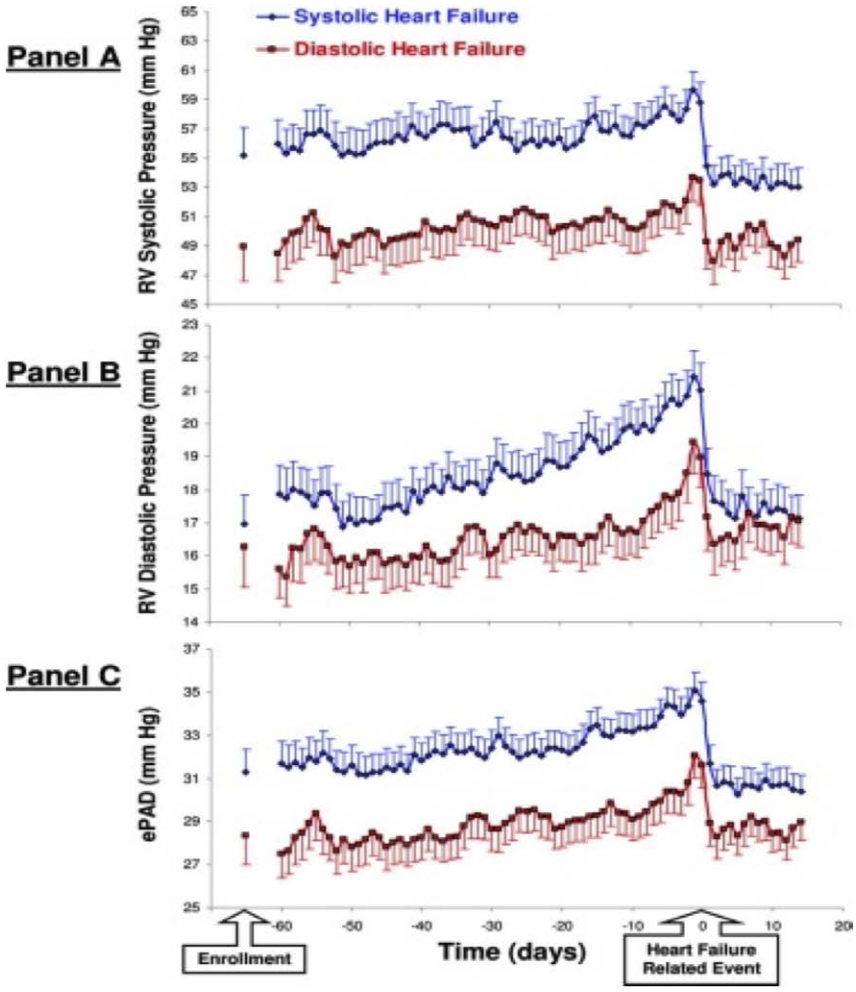

Figure 2. Daily implantable hemodynamic monitor-derived pressures in patients with heart failure (HF). Trends in daily median implantable monitor-derived pressures are shown beginning 60 days before a hypervolemic HF-related event and continuing for 14 days after. Open blue circles represent low ejection fraction and closed red squares preserved ejection fraction patients with HF. Right ventricular systolic pressure (**A**) and diastolic pressure (**B**), and an estimate of pulmonary artery diastolic pressure (**C**) are shown. In both group of patients, an increase was found preceding the event in all 3 pressures, which returned to baseline after treatment. ePAD indicates estimated pulmonary artery diastolic pressure; and RV, right ventricle. Reprinted from Zile et al[19] with permission of the publisher. © 2008, *Circulation*. 118:1433–1441.

chronic HF known, and that the highest risk for adverse events are after discharge among these patients, these facts then have important implications for trial design in HHF. Moving forward, based on the current pathophysiologic understanding and the past experiences with clinical trials, there are several possibilities for study design for patients with HHF (Figure 4).

In-Hospital Short-Term Infusions

This most commonly applied approach has failed with many drugs, raising the possibility that short-term infusions that do not affect the fundamental disease pathway but affects its secondary manifestation will not be successful. However, pulmonary pressures are associated with outcomes in HHF and it is also possible this approach might be effective with a given particular drug and whether this approach is matched with the most appropriate patient population. In addition, if a short-term infusion facilitated improved initiation, continuation, and titration of guideline-directed medical therapy after discharge, outcomes could be benefited. A short-term infusion of therapy, if efficacious for reducing mortality and readmission, has the distinct advantage of limiting duration of drug exposure and potentially side effects, as well as costs. Seralaxin has revived interest in this respect but is an early experience needing validation. It is humbling to note that multiple prior attempts with drugs tested on the basis of sound physiological promise and positive preliminary data failed to improve clinical outcomes or were harmful with this approach.

In-Hospital Short-Term Infusions but Initiate Earlier

It is plausible that the strategy employing short-term infusion will improve outcomes if initiated earlier. It is argued that delay in initiating therapies leads to worsening ongoing myocardial and renal damage. Some observational studies have suggested that earlier initiation of intravenous diuretic and vasoactive medications is associated with better outcomes, whereas other studies have not.[57,58] Secondary analysis of the RELAX-AHF data showed that seralaxin infusion was associated with improved natriuretic peptide, liver function, and cardiac troponin levels at 72 hours. Interestingly, RELAX-AHF trial started infusion at ≈12 hours after hospital presentation, which is earlier than other HHF trials. The ongoing Trial to Evaluate the Efficacy and Safety of Ularitide Intravenous Infusion in Patients Suffering From Acute Decompensated Heart Failure (TRUE-AHF) is planning to enroll patients within 6 hours.[59] It has also argued that intravenous diuretics worsen neurohormonal activation, and earlier investigational therapy may prevent iatrogenic complications of loop diuretics. However, it has been demonstrated that adverse physiological changes in patients with HHF occur days to weeks before admission. It is not clear that a few hours

Table. Reported Pathophysiologic Abnormalities in Patients With Chronic and Hospitalized Heart Failure

Pathophysiology	Chronic Heart Failure	Heart Failure Hospitalization
Hemodynamics		
Central venous pressure, pulmonary artery pressure	↑	↔↑↑↑
Pulmonary capillary wedge pressure, systemic vascular resistance	↑	↔↑↑↑
Cardiac output	↔↓	↔↓
Neurohormonal activation		
Sympathetic nervous system	↔↑	↔↑↑↑
Renin–angiotensin–aldosterone system	↔↑	↔↑↑↑
Arginine vasopressin	↔↑	↔↑↑↑
Endothelin	↔↑	↔↑↑↑
Adrenomedullin	↔↑	↔↑↑↑
Myocyte damage		
Troponin	↔↑	↔↑↑
Inflammation		
C-Reactive protein, interleukin-6, tumor necrosis factor, ST-2	↔↑	↔↑↑↑
Oxidative stress		
Myeloperoxidases, uric acid	↔↑	↔↑↑
Extracellular matrix regulation		
Matrix metalloproteinase, tissue inhibitor of metalloproteinase, galactin-3	↔↑	↔↑↑↑
Natriuretic peptide		
B-type natriuretic peptide, N-terminal prohormone of B-type natriuretic peptide	↔↑	↔↑↑↑
Renal function and injury		
Blood urea nitrogen and creatinine	↔↑	↔↑↑
Cystatin C	↔↑	↔↑↑
Neutrophil gelatinase-associated lipocalin, kidney injury molecule-1	↔↑	↔↑↑
Endothelial function	↔↓	↔↓↓

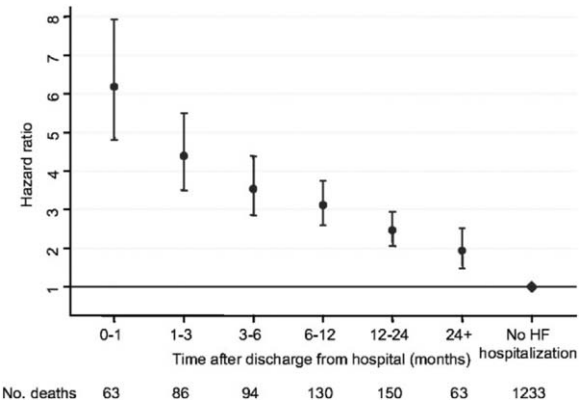

Figure 3. Changes in risk profile after hospitalization. Hazard ratios and 95% confidence intervals of all-cause mortality after discharge from hospital for first hospitalization for heart failure (HF) at various time intervals after discharge adjusted for other baseline predictors. Reprinted from Solomon et al[49] with permission of the publisher. © 2007, *Circulation*. 116:1482–1487.

difference in initiation of novel therapies in patients already receiving otherwise medications for congestion relieve can have a pronounced impact on long-term outcomes. However, it is conceivable that if an early infusion can avoid cardiorenal or other end-organ damage, or limit its extent, then this approach can be beneficial. The degree to which decompensated HF leads to permanent organ damage, however, is not clear.

Target the Immediate Postdischarge Phase

Because the postdischarge risk among patients with HHF seems to be primarily within the first few weeks to months after discharge, 1 options is to target this vulnerable phase when patients are at the highest risk. The use of subcutaneous natriuretic peptide in patients with HHF after discharge for 8 weeks has been showed to improve cardiac function and quality of life scores.[60] Another trial with this strategy that is currently enrolling patients is the Functional Impact of GLP-1 (glucagon-like peptide-1) for Heart Failure Treatment (FIGHT) trial testing 3 months of subcutaneous GLP-1 agonist initiated at the time of discharge among patients with HHF. Targeting the vulnerable phase after discharge makes intuitive sense; however, the vulnerable phase hypothesis has not been proven. An alternate explanation to the observed highest risk in the immediate postdischarge phase that seems to decrease over time is that the highest risk patients die earlier after discharge leaving behind a population of patients with lower absolute risk translating into changes in observed risk over time. Giving long-term injections is challenging and even with oral drugs, limiting effective therapy to a short time assuming that the targeted abnormality is normalized, is unlikely. Indeed, some of these abnormalities may improve over time, but without fundamentally changing the HF state, they are unlikely to completely reverse, and limiting therapy rather than long-term continuation, waiting for another exacerbation to use them, is less appealing. However, if this approach allows patients to be bridged to achieve optimal initiation and titration of guideline-directed medical and device therapy as indicated over the ensuing months after discharge, this may be an attractive and ultimately successful approach.

Initiate Therapies During Hospitalization for Long-Term Use

Another approach is to consider HHF as a marker of high-risk patients with HF and using admission as an opportunity to initiate effective long-term therapies. Indeed, initiation of angiotensin-converting enzyme inhibitors or β-blockers during HHF has been associated with improved outcomes in patients with HF and reduced ejection faction.[52–55] Any pathway that is effectively targeted in patients with HHF is unlikely to be completely reversed in any short time frame to allow for safe discontinuation of therapy. This approach permits long-term exposure of effective therapies, possibly at lower doses that may be safer and still effective, without the intent of using higher intravenous doses to acutely reverse hemodynamic abnormalities. Although promising, 2 trials using this approach did not improve postdischarge outcomes, including the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST)[6] and

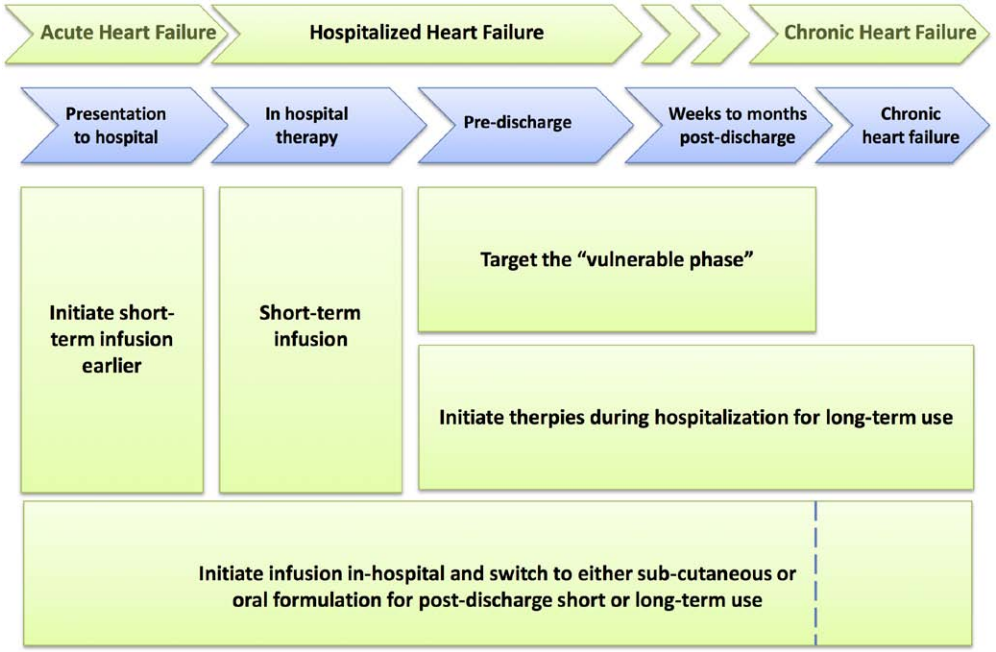

Figure 4. Options for targeting therapy at various stages during hospitalization.

Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT).[61] Whether this failure to demonstrate efficacy was related to the drugs that were tested or the patient population chosen can be debated. However, both EVEREST and ASTRONAUT were successful in enrolling patients with sufficient event risk where the effect on primary outcomes could be readily determined, which is a significant additional benefit of this design.

In-Hospital Infusion Followed by Postdischarge Administration

Potentially one can combine several options listed above. For example, a novel therapy may be available in both intravenous infusion form for early in-hospital use but may be continued after discharge for short term or long term in the form of subcutaneous injections or an oral formulation. One example of such an approach potentially under current development is omecamtiv mecarbil, with which a phase II short-term intravenous use trial just completed enrollment, the Study to Evaluate the Safety and Efficacy of IV Infusion Treatment With Omecamtiv Mecarbil in Subjects With Left Ventricular Systolic Dysfunction Hospitalized for Acute Heart Failure (ATOMIC-AHF), whereas another trial with an oral formulation, the Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF), is under way. If any particular drug does show benefit with this approach, it has the obvious significant benefit of bridging the acute early phase to more chronic use with an effective agent.

Conclusions

The HHF population is currently a significant health and healthcare burden to the society. Even if the hospitalization rates fall, with the growing elderly population and the increasing prevalence of HF, the actual numbers of HHF are projected to grow. There are no targeted therapies for these patients that can reduce the risk of mortality or readmissions after discharge. Many trials have attempted to alter the outcomes of these patients with novel therapies, but the results have been disappointing. It is possible that this lack of success may partially be related to trial design and execution. In this respect, there are multiple options for testing the timing and duration for new drugs for patients with HHF, but all have their pros and cons. Clinical trials should consider these opportunities and challenges carefully, as besides the pharmacological properties of the drugs, these factors may well determine the fate of the intervention. These options should also be taken into the context of the clinical scenario and the patient substrate, (eg, there may be a differential benefit of earlier treatment if it is instituted before a possible cardiorenal injury, as opposed to once the injury has taken place). Future research leading to better understanding of HHF triggers, and pathophysiology may make the selection from the possible choices more obvious.

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