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Getting ahead of the game: in-hospital initiation of HFrEF therapies

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Hospitalizations for heart failure (HF) have become a global problem worldwide. Each episode of HF decompensation may lead to deleterious short- and long- term consequences, but on the other hand is an unique opportunity to adjust the heart failure pharmacotherapy. Thus, in-hospital and an early post-discharge period comprise an optimal timing for initiation and optimization of the comprehensive management of HF. This timeframe affords clinicians an opportunity to up titrate and adjust guideline-directed medical therapies (GDMT) to potentially mitigate poor outcomes associated post-discharge and longer-term. This review will cover this timely concept, present the data of utilization of GDMT in HF populations, discuss recent evidence for in-hospital initiation and up-titration of GDMT with a need for post-discharge follow-up and implementation this into clinical practice in patients with heart failure and reduced ejection fraction.

Introduction

Heart failure (HF) has become a global problem and the leading cause of death and hospitalizations worldwide.[1-4] Each episode of HF decompensation often referred to as acute HF has deleterious short- and long- term consequences. With each episode of acute HF, a dysfunction of the vital organs may develop or progress, which translates into worse outcome.[5-8] Although risk of in-hospital death for patients with acute HF is still high, remaining in the range of 3–5%, the early post-discharge phase has been consistently proven as particularly vulnerable resulting in readmission or mortality in 30–40% of HF patients within the first 3–6 months after hospital discharge.[9] Thus, in-hospital and an early post-discharge period comprise an optimal timing for initiation and optimization of the comprehensive management of HF. This window affords clinicians an opportunity to up titrate guideline-directed medical therapies (GDMTs) to potentially mitigate poor outcomes associated post-discharge and longer term. This review will discuss this timely concept, present recent evidence for in-hospital initiation and up-titration of GDMT with a need for post-discharge follow-up, and implement this into clinical practice in patients with heart failure and reduced ejection fraction (HFrEF).

Underuse and under-dosing of GDMT in HFrEF patients: real-world evidence

In the last decades, we have seen significant strides in the understanding of the underlying pathophysiology and advancement in the management of this clinical syndrome. The early concept of neurohormonal blockade with beta-blockers, angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB), and mineralocorticoid receptor antagonist (MRA) recently has been updated with the evidence of the beneficial effects of angiotensin receptor–neprilysin inhibitor (ARNI) on mortality and morbidity in patients with HFrEF.[10-14] The results of trials with sodium-glucose cotransporter 2 (SGLT2) inhibitors have revolutionized the landscape of HF

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pharmacological management and further improved the patients' quality of life and prognosis.[15-20] Thus, recent ESC (European Society of Cardiology)[21], Heart Failure Society of America (HFSA) and ACC (American College of Cardiology)/AHA (American Heart Association) guidelines[22] recommend the combination of all four drugs from these classes—ARNI/ACEi/ARB, beta-blocker (β-blocker), MRA, and SGLT2 inhibitor—as the core of GDMT in HFrEF.

Unfortunately, despite such overwhelming evidence for benefit and consensus among the experts, only a minority of patients with HFrEF are prescribed GDMT. The data reported in large registries illustrating real-life scenarios have uniformly confirmed such undesirable gap between evidence-based guideline recommendations derived from randomized clinical trials and the real-world use of GDMT in clinical practice.

The US-based CHAMP-HF registry included data from more than 150 cardiology practices across the USA and included more than 5000 ambulatory HFrEF patients who received at least one oral HF medication at the time of enrolment.[23] Overall, 30% of eligible patients were not on an ACEi/ARB/ARNI or beta-blocker, and two-thirds were not receiving MRA.[23] Even fewer patients were on more novel GDMT, only 14% of HFrEF patients were prescribed ARNI. Additionally, there was significant underdosing of GDMT: 82.5% for ACEi/ARB, 72.5% for beta-blockers, 23% for MRA, and 86% for ARNI, respectively. However, the most alarming message reported by Greene al.[23] was that less than 25% of eligible HFrEF patients were receiving a combination of ACEi/ARB/ARNI, beta-blocker, MRA and 1% at guideline-recommended optimal dosing. The other US outpatient registry—PINNACLE (Practice Innovation and Clinical Excellence)—which included over 6 million patients, reported in 2017 that among 700 000 HFrEF patients, 75% were at least receiving a β-blocker, 78% were at least receiving an ACEI/ARB/ARNI, and only 73% were receiving both a β-blocker and an ACEI/ARB/ARNI.[24] Data from European and Asian registries demonstrate the same pattern of underuse and under-dosing of GDMT in HFrEF patients. In the recent report from the ESC-HFA EORP (EURObservational Research Programme of the ESC) Heart Failure Long-Term Registry among all eligible patients, 68% received ACEi/ARB/ARNI, 72% β-blocker and 60% MRA.[25] In the Multinational ASIAN-HF registry, which enrolled HF patients between 2012 and 2015 reported that ACEi/ARB were prescribed to 77% of patients, β-blocker to 79% and MRA to 58% with substantial regional variation.[26] Recommended doses of GDMT were achieved in only 17% for ACEi/ARB, 13% for beta-blockers, and 29% for MRA.[26]

Clinical inertia related to a lack of longitudinal up-titration/optimization and discontinuation of GDMT is a relevant barrier particularly in the real-world clinical setting. Recently Savarese *et al.*[27] have reported the analysis of healthcare databases from the USA, UK, and Sweden from 2016–2019. The inclusion criterion for the analysis was a recent HF hospitalization triggering the initiation of GDMT. Among newly diagnosed patients with HF after 12 months, target doses of GDMT were achieved in 15%, 10%, 12%, 30%, and discontinuation was 55%, 33%, 24%, and 27% for ACEi, ARB, beta-blockers, and ARNI, respectively.[27]

Taken together, data from all these registries suggest a massive therapeutic gap in the optimal management of patients with HFrEF. Up to one-third of these patients are not on individual components of GDMT, with only a minority receiving optimal dosing (*Figure 1*).

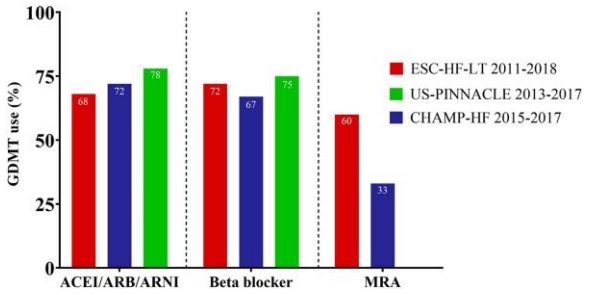

Figure 1 Use of guideline directed medical therapy in heart failure stratified by 3 seminal analyses.

These findings are even more alarming given the overwhelming evidence that GDMT leads to significant improvement in morbidity and mortality.[28-30] Vaduganathan *et al.*[31] compared treatment effects of GDMT based on all four recently recommended components (ARNI, beta-blocker, MRA, and SGLT2 inhibitor) with 'conventional' therapy comprising only ACEi/ARB and beta-blocker in patients with chronic HFrEF. The benefit of GDMT with all 4 foundational therapies was seen across all analysed endpoints [cardiovascular death or hospital admission for HF: hazard ratio (HR) = 0.38; cardiovascular death alone: HR 0.50, hospital admission for HF alone: HR = 0.32, and all-cause mortality: HR = 0.53]. In this study, optimal GDMT compared to conventional therapy predicted an improved survival resulting in an additional 1.4 years for an 80-year-old to 6.3 years for a 55-year-old with HFrEF.[31] Similar finds have been reported by Tromp *et al.*[32] who found that a combination of ARNi, beta-blocker, MRA, and SGLT2 inhibitor was most effective in reducing all-cause death (HR = 0.39) followed by ARNi, beta-blocker, MRA, and vericiguat (HR = 0.41) and ARNi, beta-blocker and MRA (HR = 0.44) vs. no treatment. The estimated additional number of life-years gained for a 70-year-old patient on ARNi, beta-blocker, MRA, and SGLT2 inhibitor was 5.0 years (2.5–7.5 years) compared with no treatment in secondary analyses.[32]

In-hospital initiation and optimization of GDMT: the emerging solution to improve GDMT implementation

There is a clear need to improve the devastating poor implementation of GDMT and adherence in the chronic care of HFrEF patents. There are numerous reports on the main barriers for non-prescription of GDMT in HF, which in principle tend to identify factors related to the systems of medical care (system-related), socioeconomic, patient-related and/or physicians-related factors.[33-35] A detailed discussion would be beyond the scope of this review. Thus, we will briefly focus on selected patient-/physician-related factors.

Several elements of the patient clinical characteristic may constitute well-known factors which affect physicians' decisions on implementation/optimization of GDMT. These concerns are mainly related to safety

Table 1 Goals of treatment in acute heart failure and peri-discharge phase (adopted from ESC HF guidelines 2016)

Phase of the disease	Major goals
Immediate (in hospital in the acute setting)	Improve haemodynamics and organ perfusion. Alleviate symptoms. Limit cardiac, renal and multiorgan damage. Ensure safe and effective decongestion. Prevent thromboembolic events.
Intermediate (in hospital)	Initiate and up-titrate guidelines directed medical therapy (GDMT). Identify heart failure aetiology and relevant co-morbidities. Adjust the therapy to control symptoms, congestion and optimize control of comorbidities. Consider and plan device therapy in appropriate patients.
Peri-discharge and longer-term management	Prevent early readmission. Improve symptoms, quality of life and survival. Further careful up-titration and monitoring of pharmacological therapy (GDMT). Schedule a review for device therapy. Enroll in disease management programme, educate, and initiate appropriate lifestyle adjustments.

including but not limited to hypotension, impaired renal function, hyperkalaemia, uncontrollable heart rate, frequent comorbidities requiring additional treatment, and increased frailty associated with older age.[33-35] Clinicians may simply not see clear indications for prescribing certain therapies or simply forget to prescribe them. GDMT up titration is also time-consuming for both patients and clinicians requiring close follow up and frequent visits.[33-35]

Historical recommendations (from previous guidelines) of sequential, step-wise initiation of consecutive drugs (ACEi/ARB, beta-blockers, MRA, ARNI) with an adjustment of the doses are major practical challenges, which result in poor implementation of GDMT requiring a minimum of 3–6 months for optimization.[33,34,36] Also the period of 3–6 months is currently seen as too long deprivation of HFrEF patient from the benefits of novel therapies[33,34,36] as the clinical benefit associated with SGLT2 inhibitors is seen as early as during initial weeks of therapy.[37-39]

Thus, the concept of concurrent initiation of more than one drug with relatively rapid up-titration has become an appealing solution.[36,40] Different algorithms have been proposed (although none has been yet tested in clinical practice—please see below), and it appears that rapid initiation of currently recommended quadruple HFrEF therapy may be fully implemented within 6–8 weeks in selected uncomplicated cases.[36,40] However, it needs to be remembered that such alternative approaches of GDMT optimization should not compromise patient safety. Hospitalization for HF appears to be an optimal moment to consider and undertake such a decision.

We propose framing hospitalization for HF needs as the four phases (*Table 1*)[13]: (i) acute phase starting at the emergency department (with a patient typically in unstable clinical conditions) followed by (ii) early in-hospital (iii) intermediate phase, and (iv) pre-discharge. Once the patient is stabilized, clinicians should initiate GDMT and take an advantage of access to laboratory testing and regular clinical assessments in the inpatient setting. Side effects related to GDMT may include worsening renal function, hypotension, hyper-/hypokalaemia, bradycardia, fatigue, angioedema, hypoglycaemia, genitourinary infection, cough, all can be identified and managed early, which may lead in higher compliance in a post-discharge period. GDMT needs to be adjusted according to organ function (i.e. kidney), blood pressure, and laboratory tests, all can substantially vary during the in-hospital stay and post-discharge follow-up.

Despite a common belief that time to initiation of optimal GDMT in HFrEF matters, a clinician needs to remember the potential risk of adverse events in this vulnerable, high-risk population. There are no well-defined, prospectively evaluated criteria defining the stability of the AHF patient, which would allow early identification readiness for immediate initiation of all GDMT. However, following clinical experience and inclusion/exclusion criteria from previous clinical trials the following conditions need to be carefully assessed[41,42]:

(1) Haemodynamic stability, i.e. stable blood pressure, with no clinical symptoms of hypotension, and no need for intravenous vasoactive therapy.
(2) Stability of key laboratory tests (reflecting stable and preserved function of vital organs).
(3) Stability of diuretic response with no need for an increase of intravenous diuretic dose within last 24 hours, with clinically satisfactory diuresis and natriuresis; all patients need careful monitoring of volume status in order to achieve euvolaemia.

Careful analysis of patient-profile/phenotype is mandatory for optimal GDMT planning, can be applied during in-hospital, pre-discharge period with subsequent planning of follow-up appointments with further optimization of the comprehensive HF management. It should cover a holistic implementation of HF guidelines as well as integration of HF care.[21,22]

In-hospital initiation and optimization of GDMT: existing evidence-based care

There are data from clinical trials, and vast clinical experience confirming that initiation of ACEi/ARB, and beta-

blockers prior to hospital discharge is safe and related to post-discharge benefits in patients with HFrEF.[43] In patients already taking ACEi/ARB or beta-blockers prior to hospitalization, it is recommended to continue the therapy, except hemodynamic instability, deterioration in renal function and hyperkalaemia.[21,22,43] In such cases modification of doses (or temporary discontinuation) may be required based on clinical in-hospital course with careful dose re-adjustment (or re-initiation) after stabilization. In-hospital treatment initiation is also strongly associated with improved adherence in the post-discharge period.[43]

In clinical practice, MRAs are less often initiated in hospitalized HFrEF patients[43] and tend to be discontinued in the post-discharge phase due to concerns mainly related to worsening renal function and hyperkalaemia.[44] There are reports that in-hospital initiation of MRA is safe, associated with improved outcome and better post-discharge adherence, and failure to maintain therapy with MRA may be associated with higher risk mortality and morbidity.[45,46] Of note, it needs to be recognized that findings proving the benefits from MRA therapy initiated during hospital stay are not consistent. Only recently, the Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure trial compared initiation of high-dose spironolactone 100 mg daily plus usual care vs. usual care alone among patients hospitalized for HF. While the findings of this study showed no significant difference between groups in 30-day all-cause mortality/HF hospitalization rate, in-hospital initiation of MRA is safe, associated improved post-discharge adherence.[45–47]

The benefits of ARNI (sacubitril/valsartan) added to standard medical therapy in the inpatient setting have been assessed in the The Comparison of Sacubitril/Valsartan vs. Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode. This trial was designed to test the safety and efficacy of ARNi among patients who were hospitalized for acute HF.[42] After hemodynamic stabilization (defined by a systolic blood pressure ≥110 mg Hg for the preceding 24 hours, stable diuretic dose, no intravenous vasoactive treatment), patients were randomized to sacubitril/valsartan or enalapril. The primary efficacy outcome of the study of time-averaged reduction in the NT-proBNP concentration was significantly greater in the sacubitril/valsartan group than in the enalapril group. Moreover, the initiation of ARNi during hospitalization was safe as patients had similar rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema in the control and intervention groups.[42] Similar findings were noted in the safety-driven TRANSITION (Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event) trial, where patients treated for acute HF were randomized to ARNI initiation either prior to hospital discharge or within first 14 days after discharge. There was no difference in the safety endpoints between both strategies.[48]

Although, SGLT-2 inhibitors have consistently shown positive, multidirectional impact on natural course and prognosis in HF, the data related to safety and efficacy in acute HF setting has been recently established. The SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Participants With Type 2 Diabetes Post Worsening Heart Failure) trial was a phase 3, double-blind, randomized, placebo-controlled trial that enrolled more than 1200 hospitalized for HF patients with type 2 diabetes mellitus to receive sotagliflozin (SGLT-1 and SGLT-2 inhibitor) or placebo.[19] The first dose of the study drug was administrated shortly pre- (49%) or post- (51%) discharge. Despite early termination (due to the sponsor decision), the trial was able to demonstrate that patients allocated to sotagliflozin experienced a significant reduction in primary endpoint, which was composed of death from cardiovascular causes or hospitalization for HF.[19] Moreover, sotagliflozin significantly reduced the incidence of secondary endpoint: hospitalizations and urgent visits for HF.[19]

The EMPagliflozin in patients hospitalized with acUte heart faiLure who have been StabilizEd trial was a multicentre, randomized, double-blind trial designed to test the safety and clinical benefit of early initiation of empagliflozin (SGLT-2 inhibitor) in the individuals hospitalized for AHF.[41] In the study, patients admitted to the hospital for acute HF after initial stabilization were randomized to receive either 10 mg empagliflozin or placebo on top on standard care for 90 days. The median time from admission to stabilization and subsequent randomization was 3 days. The study was designed to assess the clinical benefit expressed by the win ratio, which allows prioritization of clinically relevant endpoints. The use of win ratio allows to compare different types of endpoints, which also takes into account the clinical importance and timing of the outcomes. The importance of the outcome is represented by the hierarchy of the analysed components. Patients from competing groups are compared with each other and the winner-looser pairs are found, which are later used to calculate the final win ratio of the group. The components and the hierarchy of the study endpoints were: time to all-cause death, number of HF events, time to first HF event, and an improvement in quality of life after 90 days of treatment. The in-hospital initiation of empagliflozin was safe and associated with significant clinical benefit assessed at the end of the trial.[41,49] Moreover, patients on SGLT-2 inhibitor experienced early (evident already at day 15), consistent (across all analysed indexes of decongestion) and sustainable (till the end of study) decongestion when compared to placebo group.[50]

Beyond foundational GDMT therapeutics in the inpatient setting

Targeting mechanisms unrelated to hemodynamics to improve exercise tolerance such as iron deficiency has also been critical in patients with HFrEF. Iron supplementation can improve oxygen uptake, oxidative metabolism and improved erythropoiesis which has translated clinically with improvement in symptoms, quality of life and exercise tolerance in chronic HFrEF and iron deficiency.[51] The A Randomized, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalizations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure (AFFIRM-AHF) trial highlighted that therapy with ferric carboxymaltose in iron deficient patients hospitalized for acute HF at discharge from the hospital was safe and associated with a lower risk of repeated HF hospitalizations.[52] The primary endpoint included a composite of cardiovascular death and recurrent hospitalizations related to HF up to 52 weeks after randomization.[52] The AFFIRM-AHF trial is a perfect exemplification of the fact that even a single

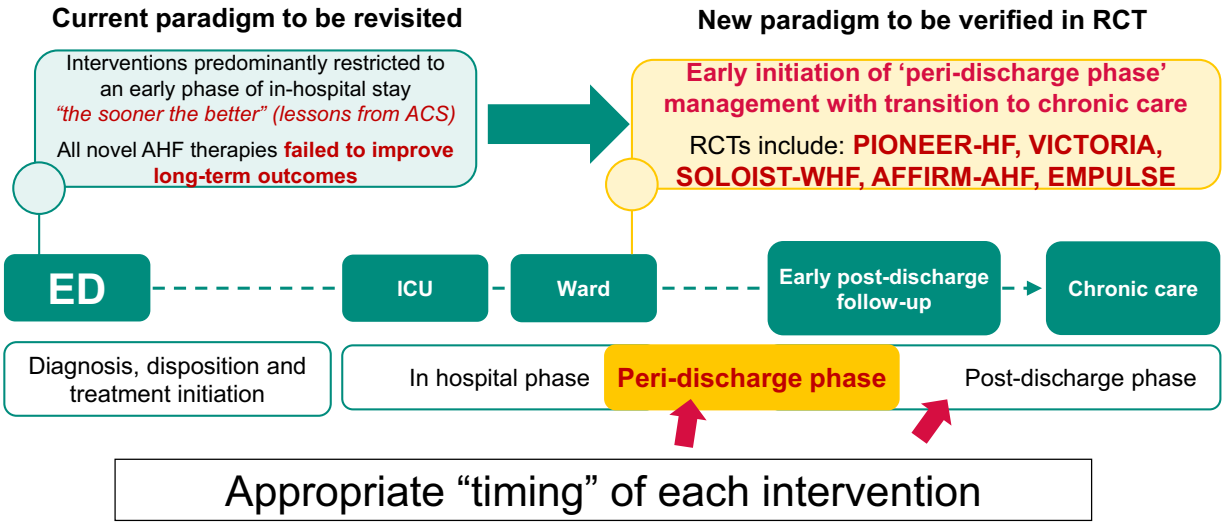

Figure 2 Targeting 'peri-discharge' phase of in-hospital stay in order to improve long-term outcomes.

intervention that efficiently interferes with pathophysiology of HF may translate to clinical benefit.

Cardiac myosin activators are a new class of medications that selectively increase cardiac sarcomere function. In the GALACTIC-HF study, omecamtiv mecarbil improved reverse remodelling in patients with HFrEF (EF < 35%).[53] Among 8256 patients enrolled, eligibility for study inclusion required either current hospitalization (~25% of the cohort) or needed an urgent visit or hospitalization for HF within 1 year prior to screening. Treatment with omecamtiv mecarbil resulted in a lower incidence of a composite of a HF events or death from cardiovascular causes when compared to placebo.[53] The subgroup analysis did not reveal any significant difference in the study outcome based on time of the study initiation in-hospital vs. out of hospital.

Vericiguat, a novel oral soluble guanylate cyclase stimulator, was recently studied in the VICTORIA trial (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction). This was a multinational, randomized, double-blind, placebo-controlled trial, which recruited stable, ambulatory chronic HFrEF (EF < 45%), NYHA class II–IV patients who had recently been hospitalized or had received intravenous diuretic therapy.[54] The drug was not initiated during the hospitalization, but most patients were hospitalized for HF or received intravenous diuretics within 3 months prior to randomization. The incidence of death from cardiovascular causes or hospitalization for HF was significantly lower in patients who received vericiguat than among those who received placebo. The initiation of vericiguat in those vulnerable patients was also safe as the risk of hypotension and syncope did not differ significantly between both study groups.[54]

Post-discharge: safely transitioning to the ambulatory setting to reduce clinical deterioration

According to the current HF guidelines[21,22] GDMT should be continued in the inpatient setting for patients with decompensated HF, in the absence of contraindications (e.g. hemodynamic instability, bradycardia, renal dysfunction, electrolytes abnormalities). After stabilization, GDMT should to be re-instituted optimized before discharge. For those with de-novo acute HF, naïve to GDMT, such therapies should be initiated after clinical stabilization.

Despite growing evidence (and recommendations) that GDMT can be safely initiated after clinical stabilization, in practice several questions will appear.[55] They will comprise a uncertainty about safety of rapid sequencing of multiple therapies, an optimal order of therapies, timing of dose up-titration (one vs. multiple drugs), optimal mode of a patient evaluation, possible chance of hospital stay prolongation—just to name a few.[55]

The sequence of 4 foundational therapies has not been prospectively evaluated and the decision should be based on patient clinical and laboratory profile. In patients with no hemodynamic compromise, not requiring intravenous therapies with preserved renal function, multidrug GDMT can be safely initiated. Further modification/optimization should be performed in the early post discharge phase according to patient clinical status. Thus, a follow-up visit (optimally within first 2 weeks after discharge) should be planned, in order to evaluate clinical status, euvolaemia, symptoms, and basic laboratory indices (renal function, creatinine).

The transition from inpatient to outpatient care is particularly vulnerable period, associated with a high risk of decompensation and re-admission. This is mainly due to residual risk of progression of the disease (despite GDMT), multiple comorbidities, and the complexity of medical regimens. Multidisciplinary systems of care that promote improved communication between health care professionals, systematic use and monitoring of GDMT, medication reconciliation, and consistent documentation are examples of patient safety standards that should be ensured for all patients with HF transitioning out of the hospital.[13,14,21,22]

Conclusions

In light of the unacceptably high risk of morbidity and mortality in patients admitted with acute HF, our primary clinical task needs to be directed towards further

improvement of the long-term post-discharge outcome. There is a new found urgency of initiating GDMT, with interventions targeted in the earliest phase of in-hospital stay (being initiated already at the emergency department or in the intensive care unit) as soon as there is clinical stability. There is mounting evidence for early initiation of GDMT in the 'peri-discharge' phase (comprising pre- and early post-discharge vulnerable period), with a well-planned transition to chronic care, which may favourably modify an ominous prognosis in acute HF. This approach has now been tested in recent randomized clinical trials with promising results (*Figure 2*).

Hospitalization for HF affords clinicians with an ideal window to initiate and adjust the GDMT (with rapid concurrent administration of medications, rather than conventional step-wise approach) as well as plan non-pharmacological interventions. It is only when we can embrace this early period as an opportunity to optimize GDMT that **'we are getting ahead of the game in management of patients with HFrEF'**.

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Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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