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"Therapeutic Advances in the Management of Acute decompensated Heart Failure"

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Abstract

Background: Acute decompensated heart failure (ADHF) is the most common presenting phenotype of acute heart failure (AHF). The main goal of the present manuscript is to review the contemporary management strategies in these patients, and to describe how future clinical trials may address unmet clinical needs.

Areas of Uncertainty: The current pathophysiologic understanding of AHF is incomplete. The guideline recommendations for the management of ADHF is based only on algorithms provided by expert consensus guided by blood pressure and/or clinical signs of congestion or hypoperfusion. The lack of adequately conducted trials to address the unmet need for evidence-therapy in AHF has not yet been surpassed, and at this time, there is no evidence-based strategy for targeted decongestive therapy to improve outcomes. The precise time point for initiation of guidelines directed medical therapies (GDMTs), as respect to moment of decompensation is also unknown.

Data Sources: The available data informing current management of patients with ADHF patients is based on RCTs, observational studies and administrative databases.

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Therapeutic Advances: A major step-forward in the management of ADHF patients is recognizing congestion, either clinical or hemodynamic, as major trigger for HF hospitalization and most important target for therapy. However, a strategy based exclusively on congestion is not sufficient, and at present comprehensive assessment during hospitalization of cardiac and non-cardiovascular substrate with identification of potential therapeutic targets, represents "the corner-stone" of ADHF management. In the last years, substantial data has emerged to support the continuation of GDMTs during hospitalization for HF decompensation. Recently, several clinical trials raised hypothesis of "moving to the left" concept that argues for very early implementation of GDMTs as potential strategy to improve outcomes.

Conclusions: The management of ADHF is still based on expert consensus documents. Further research is required to identify novel therapeutic targets, to establish the precise time-point to initiate GDMTs and to identify patients at risk of recurrent hospitalization.

Keywords

congestion; hospitalization; heart failure; therapies; outcomes

Background

Acute decompensation of chronic heart failure (ADHF) accounts for roughly 60–70% of hospitalizations for acute heart failure (AHF) and predominantly affects patients with reduced ejection fraction (rEF) (1–3). It is the most common phenotype of the AHF spectrum and was initially introduced by the 2005 and 2008 European Society of Cardiology (ESC) guidelines as one of the 5 proposed presentation phenotypes (Table 1) (4, 5). Currently it is defined as the worsening (gradual or rapid) of HF signs and symptoms with evidence of pulmonary and/or peripheral congestion that requires therapy and results in hospitalization (1). However, substantial overlap exists among the clinical phenotypes, making sometime difficult the distinction of any specific clinical phenotype.

In-hospital mortality varies between 3 to 7% and seems to be stable over the past 10 years (6). After discharge, these patients are at high-risk of adverse events (either death, or repeated hospitalization). In the first 60 days this may be as high as 25%, and at one-year 40–45% (6) (7) (8). Each hospitalization carries an additional short- and long-term mortality risk. Furthermore, a previous history of HF is an independent predictor of long-term mortality (HR=1.8; 95% CI=1.4–2.2; for 5-year mortality) (9), for both HFrEF and HFpEF.

Mechanisms that cause worsening of a stable chronic condition, are not adequately understood. Although, the main driver for clinical worsening leading to hospitalization is congestion, HF represents a complex interplay among cardio-vascular dysfunctions and non-cardiac comorbidities (NCC).

Two simplified profiles have been proposed to describe the mechanisms responsible for the vast majority of ADHF patients: 1) cardiac profile - patients with overt fluid overload and progressive symptomatic deterioration; and the 2) vascular profile – a state characterized by redistribution of fluids in the vascular bed (usually to the lungs) with rapid occurrence of symptoms (10, 11). Majority of patients who underwent decompensation had little or no

weight gain in the days preceding hospitalization for worsening of chronic HF, but instead, all patients had elevated diastolic pressures and this is a mechanistic reason for the transition to a decompensated state (12). This finding is present, across the full spectrum of EFs and the full spectrum of morphological cardiac dysfunctions (valvular, myocardial, pericardial) (12).

The clinical presentation of patients is heterogenous and varies widely across the spectrum of severity. Current guideline recommended classification uses the initial clinical assessment according to the presence of congestion and/or hypoperfusion (13). Each category portends outcomes, even in the most severe of patients, as shown in a more recent analysis of the ESC Heart Failure Long-Term Registry (2, 14). The congested and hypoperfused ("cold and wet") patients have the worst outcomes with long-term event rates of cumulative HF hospitalization and all cause death approaching 50% at 1 year (2).

Areas of Uncertainty

The current pathophysiologic understanding of AHF is incomplete. Complex interaction between initial insult as result of diverse precipitants, progressive deterioration of cardiac substrate and worsening of NCC produce heterogeneity of clinical presentations. While *de novo* HF is often a consequence of primary severe myocardial injury, decompensation of chronic symptoms may be more related to the different mechanisms that induce vascular decompensation or worsening of NCC.

Given the phenotypic diversity of ADHF patients, appropriate risk stratification remains an unmet need. Although a multitude of prognostic markers have been identified in registries and trials, only a few represent targets for treatment (such as QRS duration, congestion, the presence of NCC, heart rate). Probably the most notable, derived form a large cohort of ADHF patients, is the *ADHERE risk tree,* which employs blood urea nitrogen (BUN), serum creatinine and systolic blood pressure as powerful risk markers for in hospital mortality (15). Although post-hoc analysis of recent RCTs such as PROTECT and RELAX-AHF proposed risk-scores for post-discharge mortality (16), these a prognostic models have not been prospectively validated and remain only informative in the clinical decision-making process regarding (17).

In spite of more than 20 billion dollars spent in the research and development for the new drugs, RCTs performed in the last two decades have failed to provide convincing results in the treatment of AHF and the acute phase therapies has largely remained unchanged and comprising intravenous (iv.) loop diuretics and iv. nitrates.

The guideline recommendations for the management of ADHF is based only on algorithms derived on expert consensus guided by blood pressure and clinical signs of congestion or hypoperfusion, and no any strategy has been validated in clinical trials (13).

The main goal during a patient's hospitalization is complete decongestion - which occurs in only 50–60% of patients (24). There is still no consensus on the optimal decongestive strategy (regimen or dose) as none of the available therapies (medications or renal replacement therapies - ultrafiltration) have shown any improvement of outcomes in trials.

The lack of adequately conducted trials to address the unmet need for evidence-therapy in AHF has not been surpassed (18). Some of the studies that tried to address this lack of knowledge (such as DOSE and ROSE) were mostly underpowered and their results should not be considere d as definitive (18–20).

Device therapy is an important step in the HF management, which significantly changes prognosis. Although some of the beneficial effects of CRT devices are immediate, with the potential to improve HF clinical status shortly after implant, so far all studies were conducted in ambulatory settings. At present, hospitalization is considered only as an opportunity to screen eligible patients for device therapies.

The precise time point for initiation of guidelines directed medical therapies (GDMTs), as respect to moment of decompensation is also unknown. Although indirect evidence suggests that non-use of angiotensin converting enzyme inhibitors and beta blockers (BB) during hospitalization for AD HF is an independent factor for repeated hospitalization and a marker for dismal prognosis (21–23), there are very few studies to investigate directly this hypothesis. An important uncertainty is related to the rate of real life use of GDMTs, since divergent information are provided by registries and RCTs. All the major RCTs (such as EVEREST, ASTRONAUT) report high rates of use of BB and ACEI, more than 70% and 80% respectively (24, 25). Contemporary data derived from registries reveal significantly lower rates - no more than 50% (26).

Also, the recent change in paradigm considering inflammation the main pathophysiological pathway for HFpEF has not translated into clinical implications (27).

Data Sources

The available data informing current management of patients with ADHF patients is based on RCTs, observational studies and administrative databases (such as Medicare reports, and the ARNO database) (28, 29).

Although, rigorously collected, data from RCTs can be difficult to generalize due to highly selected patients, where very severe patients, or patients with severe comorbidities or those with coexisting organ dysfunction are often excluded. This contrasts with observational registries where the entire spectrum of patients is captured, reflecting real-world practice. There are several high quality prospective registries with very low proportion of missing data and long term follow-up which have been conducted in different regions or continents. These registries have greatly enriched the knowledge regarding HF epidemiology, in-hospital management, long-term outcomes, and even geographical disparities (8, 30). Administrative databases based on discharge documents or recorded visits offer the possibility of studying large populations in the real-world setting, with systematic collection of data over time, being readily available at low cost (56). Nonetheless, although attractive, there are concerns about data validity, lack of detailed information, limited ability to control confounding, and properly defining clinical conditions (57).

Therapeutic Advances

Pathophysiology—Most patients present with congestive symptoms, due to either fluid overload or to fluid redistribution, and in both instances intra-cardiac filling pressures are increased (12). Given the fact that in the majority of cases the body weight variation (one of the most important components of patient self-monitoring status) is rather insignificant before an acute decompensation, monitoring of intra-cardiac pressures/pulmonary artery pressures in addition to change in body weight is more sensitive for acute decompensation (12) (31).

Although overall fluid overload is a common trigger and best understood pathophysiological mechanism, the redistribution of fluids is equally important. When the latter mechanism is involved, changes occur fast and are poorly tolerated.

The myocardium in patients with HF have abnormal pressure-volume loops and act on exhausted preload reserve. Any sympathetic-mediated vasoconstriction on the venous capacitance vessels may cause a shift of blood volume from the splanchnic venous reservoir to the dynamic component and hereby immediately increasing preload and filling pressures, even in the absence of absolute volume overload (32). Cotter et al. proposed the sympathetically mediated systemic vasoconstriction and increased afterload as a mechanism for redistribution (10). Shift of fluid from peripheral and splanchnic to central circulation and increased permeability of membranes allowing fluid to transudate mostly to lungs are essential for the pathophysiology of ADHF as a systemic disorder(32).

Given this recognized imbalance of the sympathetic nervous system controls, a recent in man hypothesis-generating study (SPLANCHNIC-HF) investigating the hemodynamic and hormonal effects of splanchnic nerve block showed a significant reduction in intra-cardiac filling pressures and of systemic vascular resistance (33).

There has been a shift on the understanding of the pathophysiology of organ injury in ADHF as data has accumulated supporting that the main driver for worsening renal or hepatic function is congestion and less frequently hypoperfusion (34). Increased central venous pressure is the main determinant for congestion and further organ injury (34, 35).

Congestion.—The standard assessment of congestion is important, and scoring systems have been developed such as the clinical congestion score from the EVEREST trial (36). This can aid in the decision-making process regarding the need for further treatment during hospitalization. At this time, there is no evidence-based strategy for targeted decongestive therapy to improve outcomes. However, a more individualized strategy, such as reduction in NPs by 30% during the hospital stay, hemoconcentration-targeted diuresis with avoiding hypotension, and using spot urine sodium to guide natriuresis may be considered (37, 38). CHAMPION trial showed benefit in terms of re-hospitalizations, from guiding decongestive therapies (frequent change of diuretic together with ACEI doses) using pulmonary artery pressure measurements (31).

To note, ultrafiltration did not provide superior survival benefits compared with fixed dose loop diuretics, as shown by UNLOAD trial and CARRESS-HF trials (39, 40).

At least one fifth of AHF patients are discharged with persistent signs/symptoms of congestion and/or minimal or no weight loss and even more with relief of congestive signs but with persistently high left ventricular filling pressures (2, 41). As patients who maintain normal filling pressures have better survival, treating beyond clinical congestion should be an essential target (42). Markers of residual congestion include: elevated natriuretic peptides (NPs), low discharge serum osmolality, provoked orthopnea, paradoxical changes of SBP in orthostasis or at Valsalva maneuver and a poor 6MWT. (43–47).

Triage—A consensus document published in 2015 by the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine gives a framework for the triage of patients starting with the initial emergency department evaluation(48). Wise clinical evaluation for signs of hypoperfusion, hemodynamic instability and respiratory distress identifies those patients who require the most advanced level of care and admission to an Intensive Care Unit/Intensive Coronary Care Unit (48). These patients have high risk of in-hospital mortality - up to 18.4% in one registry (49).Among the predictors that predict the need for ICU admission, age, unstable vital signs, especially low systolic blood pressure, and hyponatremia remain most relevant.

Risk stratification—Several risk scores have been proposed to assess the risk of in hospital mortality and post-discharge outcomes. Developing risk models would aid in targeting limiting resources to the appropriate patients. Even if the phenotypic heterogeneity of AHF patients makes it difficult to find a risk model suitable for all patients, some parameters recur in many models (17). Most models were derived from demographic, clinical and biological data collected at admission and only a few used discharge data. The current available models do not include the use of devices, which may carry a strong impact on long-term prognosis (17). Actually, risk stratification by scoring methods remains only informative in the clinical decision-making process. A recent analysis showed that the MAGGIC risk score showed the best overall accuracy (area under the curve [AUC] = 0.743) for the long-term risk estimation (50). Further data is required to establish whether use of risk prediction models in clinical practice can alter prognosis and improve mortality.

Acute phase IV therapies—No medication tested in a prospective RCT in AHF patients (Table 2) has shown a consistent and reproducible benefit in phase III so far, although preliminary efficacy measures were positive in phase II.

Early treatment - the “golden hour” may be important and may improve outcomes. A retrospective analysis of ADHERE showed that every 6 hour delay for the initiation of intravenous therapy increases mortality (51). The investigation of intravenous infusion of novel therapies such as serelaxin or ularitide (administred in the first few hours after admission) relies on this concept, but translating short-term hemodynamic benefits into a long-term outcome benefit probably requires more profound myocardial and/or systemic alterations.

In hospital worsening HF (IH-WHF) is an appealing concept and was proposed as mediator of 180-day mortality in RELAX I trial. However, the definitions used so far have largely

varied, limiting the appropriate understanding and clinical applicability (71). Current definitions of worsening HF are based on worsening HF symptoms and signs, intensification to and/or failure to respond to HF therapy during hospitalization (71). The hypothesis that IH-WHF, as in-hospital outcome, would mediate long term outcomes has been investigated in RELAX II but with disappointing results, highlighting the disconnection between short and long term outcomes and the disconnection between the mechanism of action of the drug and targeted pathophysiology.

None of the innovative medications studied in trials in the past two decades have proven any benefit in AHF patients, although the underlying mechanisms were promising. Many positive phase II studies have failed to translate to successful outcome in phase III, including the latest investigated drug - serelaxin - that has failed to meet the primary end-point in RELAX-AHF 2 trial (65). However, subgroup analysis showed that patients with organ injury (myocardial, liver and renal injury) may benefit from serelaxin therapy (72). Given the obvious limitations in interpreting subgroup analysis in a negative trial, use of serelaxin may still hold promise for benefit in AHF patients. The publication of ongoing studies such as RELAX AHF-ASIA and RELAX AHF-EU will allow the analysis of almost 12,000 patients and probably will give relevant information about the net clinical benefit of the drug.

Again, conducting adequate trials is an unresolved issue in AHF as it remains a complex disease without a simple objective definition, with phenotypical variability, with no unique causal factor and with incomplete understanding of the pathophysiology making it difficult for the investigator/clinician to distinguish between congestion and non-HF related precipitants.

Guideline directed medical therapies (GDMTs)—Consistent data has accumulated that support the continuation of GDMTs during hospitalization for HF decompensation. Thus, the “moving to the left” concept (Figure 1) that argues for very early (before discharge) implementation of GDMTs becomes relevant in acute setting.

The evidence base to inform providers about continuing ACEI or BB is based on retrospective analysis or secondary analysis of RCTs, and this is the basis for the current practice of continuing BB and ACEI even in hospitalized decompensated HF patients.

The IMPACT-HF trial demonstrated the safety of pre-discharge initiation of carvedilol in stabilized patients hospitalized for HF (73). Another analysis of the OPTIMIZE-HF study supports these results and even suggests an early mortality benefit (74). Analysis of Medicare patients with HFrEF who were prescribed BB during the hospitalization, showed improved long-term prognosis: at 4-year follow-up, those in the beta-blocker group had lower mortality (HR 0.81; 95% CI, 0.67–0.98) and combined outcome of all-cause mortality or all-cause readmission (HR 0.87; 95% CI, 0.74–0.97) (75).

Similar to BB, the withdrawal of ACEI during hospitalization may increase mortality while prescription may improve outcome on short term and even longer at 1year (76, 77). Also, a retrospective analysis of worsening heart failure patients enrolled in DOSE-HF, CARRESS-

HF and ROSE-AHF trials identified ACEI prescribing during hospitalization, among the predictive factors for less re-hospitalizations/death (23).

Use of mineralocorticoid receptor antagonists in high doses (100mg spironolactone) was tested in the ATHENA-HF trial, in acute decompensated HF patients, with overt signs of systemic congestion. Although safe and well-tolerated, this strategy has not been associated to outcome improvement (70). However, it remains a relevant treatment option in patients with diuretic resistance, or in patients with the most severe hemodynamic profile - “the wet and cold”, where the vasoactive medications such as BB and ACEI cannot be implemented/or continued.

PARADIGM-HF trial showed improved survival in ambulatory HF patients with sacubitril/valsartan relative to enalapril who had a recent decompensation. (78) Further analysis revealed that the timing after hospitalization for acute decompensation does not influence the benefit from sacubitril/valsartan (79). The ongoing PIONEER trial will provide new evidence about the safety and tolerability and efficiency of initiating sacubitril/valsartan early after hemodynamic stabilization before discharge (80).

Another ongoing TRANSITION trial will assess the adequate timing to initiate sacubitril/valsartan before discharge vs. immediately after (1 to 14 days) (81).

Ivabradine was tested for safety in ADHF patients. In one study ivabradine was administered as mono therapy in the first 24 hours without significant side effects and was effective in lowering heart rate (82). Another small study (ETHIC-HF) randomized ADHF patients either to combined therapy with BB vs. BB alone, also administered early. This study suggested ivabradine was safe and effective (83). Another ongoing study is PRIME-HF (Predischarge Initiation of Ivabradine in the Management of Heart Failure) which randomizes AHF patients with low EF and high heart rate (>70bpm) to either predischarge initiation of ivabradine vs. usual care (84).

Digoxin is among the recommended agents that are most underused, with a significant decrease in prescription rates to about 20% in contemporary data (8). There is still controversy surrounding the safety of digoxin in current clinical practice, although the DIG trial showed a neutral mortality effect (85). At the same time, withdrawing digoxin therapy leads to an increased risk of HF (86). Further analysis on Medicare beneficiaries with HFrEF showed that prescribing digoxin reduced 30-day and 1-year hospitalizations and not at at the expense of increased mortality (87); reduced re-admission rates were still present even in patients who had received BB (88). Dosing of the agent should be in line with the recommendations derived from the post-hoc analysis of the DIG trial, identifying a higher serum concentration to increase the risk for sudden cardiac death (89).

Current therapies have mainly addressed hemodynamics, neurohormonal modulation, and electrophysiological aspects of HF. There is no available strategy that targets the metabolic needs of the failing heart (i.e. substrate utilization switches from mostly fatty acids to glucose with decreased high-energy phosphate content, alteration of the mitochondrial respiratory chain) (90).

There are currently no drugs that directly target cardiac metabolism for the treatment of HF (91).

Although, trimetazidine ameliorated symptoms and echocardiographic endpoints in a small trial in chronic HF, there is no evidence for its using during hospitalization for HF (92). Also, CoQ 10 deficiency may be a rational target for clinical trials.

Identification and treatment of noncardiac comorbidities—Given that following a HF hospitalization, 40% of all deaths and rehospitalizations are due to non-cardiac comorbidities, identification and treatment of NCC, as well as interaction with non-HF specific medications become relevant (7).

ADHF is associated with worsening of insulin resistance (93) and because insulin causes fluid retention, management of glucose control in ADHF may be challenging.

The only medications proved not to cause harm are metformin and empaglifozine. The latter was shown to provide a survival benefit in patients with type 2 DM and established HF in the EMPAREG trial (94). At this point it is not considered a class effect, although the CANVAS trial investigating canagliflozin also reported improved outcomes by decreasing hospitalization rates for HF (95). Glitazones, on the other hand, increase the risk of HF decompensation (96). The presumed mechanism of action as a ‘smart’ diuretic of empaglifozine has set the basis for an ongoing study investigating its effect when initiated during a hospitalization for AHF - the EMPA-RESPONSE trial (Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure - ClinicalTrials.gov Identifier: NCT03200860).

Chronic obstructive pulmonary disease (COPD) is present in approximately 10%−15% of hospitalized patients for AHF and increases by 30% the risk for new hospitalization in the subsequent year (97). The use for BB is not a contraindication in COPD (especially for cardioselective BB), and unjustified lack of use for BB may alter the prognosis of these patients,

Iron deficiency (ID) negatively impacts exercise capacity, quality of life and functional status in HF patients. In a recent study enrolling patients with AHF, the reported prevalence of ID was 68.6% in men and even higher (75.3%) in women (98). The FERIC-RO registry will further explore the prevalence and prognostic impact of ID in the specific setting of ADHF (99). Intravenous iron administration during hospitalization was shown to be well-tolerated in ADHF patients from Asia, but without impact on clinical endpoints, (100).

Patient adherence—Non-adherence to GDMTs (ACEI, BB, MRA, ivabradine) as defined by less than 80% use, is a common finding and was associated with an increased risk of all-cause mortality and cardiovascular hospitalizations in a HF population (101). Several interventions to improve adherence were tested in studies such as regular follow-up visits and teaching patients strategies to mitigate symptoms. A meta-analysis of the conducted studies, unsurprisingly showed interventions to improve medication adherence among HF patients have significantly reduce readmissions and mortality rates (102).

Advanced HF—Repeated hospitalizations for AHF are a marker of advanced HF. Only a minority of patients represent true end-stage HF, and even in these patients the prognosis can be changed. Adequate selection for heart transplantation or ventricular assist devices offers the premises for improved survival. The REMATCH study showed long term survival benefits in patients who received left ventricular assist devices as destination therapy as compared to medical therapy (103). However, for those patients who do not qualify for destination therapy, adjusting their goals for care and palliative care involvement may be beneficial for their days alive and out of hospital and quality of life. (104).

Performance measures—Raising standards to improve acute HF care has proved to be troublesome. Re-hospitalizations remain relevant as a measurable cost and as a marker for disease severity and prognosis. But a very rigid approach to penalize for recurrent HF hospitalization has paradoxically increased mortality and shifted care patterns with increased ED visits (105)(106).

Other metrics, recently considered, such as planning early post-discharge follow-up for high risk patients and including them in multidisciplinary care programs, although intuitive as a surrogate for quality, need prospective validation (107).

Conclusions

In spite of large-scale clinical trials performed during hospitalization for AHF, the management of ADHF is still based on expert consensus documents. Although in hospital mortality is modest and has changed little recently, the rate of post-discharge events remains unacceptably high. Further research is required to establish the precise time-point to initiate evidence based chronic HF medications and to identify and regularly follow patients at risk of recurrent hospitalization.

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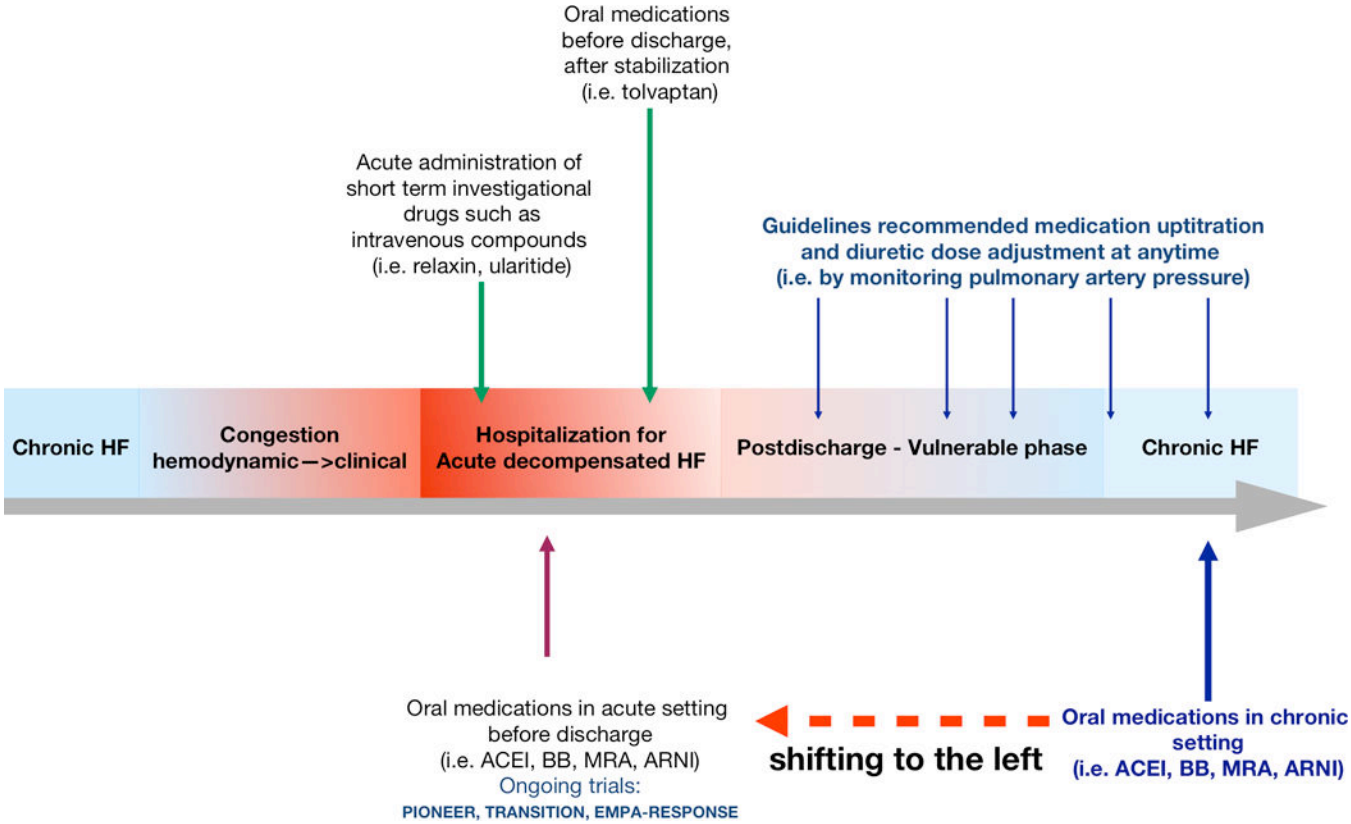

Figure. 1.

The timing of administration of different treatment strategies along the continuum of HF evolution. HF heart failure, ACEI angiotensin converting enzyme inhibitor, BB beta blocker, MRA mineralocorticoid antagonist, ARNI angiotensin receptor - neprilysin inhibitor, PIONEER Comparison of Saocubitril/valsartaN Versus Enalapril on Effect on ntpRo-bnp in Patients Stabilized From an Acute Heart Failure Episode, TRANSITION Pre-discharge and posT-discharge tReatment initiation with sacubitril/valsartan in heArt failure patieNtS with reduced ejectIon-fracTion hospItalised for an acute decOmpensation eveNtpre-discharge and posT-discharge tReatment initiation with sacubitril/valsartan in heArt failure patieNtS with reduced ejectIon-fracTion hospItalised for an acute decOmpensation eveNt.

Table 1.

Classification of AHF phenotypes according to the 2005 and 2008 ESC guidelines * (4,5).

Presentation phenotypes	Prevalence **	Main characteristics
Acute decompensated HF	60–70%	de novo or decompensation of chronic HF; evidence of clinical signs of systemic and pulmonary congestion; symptoms are moderate to severe
Right HF	3–7%	Evidence of RV dysfunction and raised jugular venous pressure, edema, increased liver size, hypotension; no signs of pulmonary congestion
Hypertensive HF	3–6%	signs and symptoms of HF and high blood pressure (usually>180mmHg), with preserved left ventricular systolic function
Pulmonary Oedema	12–25%	severe respiratory distress accompanied by alveolar or interstitial edema verified by chest X-ray and with oxygen saturation 90% or higher on room air
Cardiogenic Shock	2.5–5%	signs of tissue hypoperfusion after correction of preload and (systolic blood pressure <90 mmHg or a drop of mean arterial pressure >30 mmHg);oliguria or anuria

* the 2005 ESC Guidelines on the diagnosis and treatment of acute heart failure initially proposed a 6 clinical phenotypes classification, including 'high cardiac output HF' no longer recognized in the subsequent guidelines and classification

** Prevalence of each profile was derived from analysis of the European registries (2,26,30)

Table 2.

Randomized control trials with medications investigated in acute decompensated heart failure.

Investigated drug	RCT
Milrinone	OPTIME-CHF[52]
Levosimendan	SURVIVE[53] REVIVE[54]
Tolvaptan	EVEREST[24] ECLIPSE [55]
Tezosentan	VERITAS[56]
Rolofylline	REACH UP[57] PROTECT[58]
Nesiritide	ASCEND-HF[59]
Aliskiren	ASTRONAUT[25]
TRV027	BLAST-HF[60]
Istaroxime	HORIZON[61]
Omecamtiv mecarbil	ATOMIC-AHF[62]
Serelaxin	PRE-RELAX[63] RELAX-AHF[64] RELAX-AHF-2[65] RELAX-AHF-ASIA[66] RELAX EU[67]
Ularitide	SIRIUS II[68] TRUE-HF[69]
Spironolactone	ATHENA-HF[70]
Furosemide	DOSE-HF[19]

RCT randomized controlled trial