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Early readmission for heart failure: An avoidable or ineluctable debacle?

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ABSTRACT

Early hospital readmission after an episode of Acute Decompensated Heart Failure (ADHF) is an emerging issue that is causing a relevant clinical and economic burden. Although there might be several reasons for early readmissions, in many cases these might be effectively prevented by a more adequate post-discharge management, including recommendations on lifestyle and rehabilitation programs. However, almost half of hospitalizations are unrelated to specific cardiac causes and thus increases the difficulty in analyzing risks prediction. Many episodes are related to social environment, poor familiar assistance and inadequate followup program. In addition, the national and insurance companies constantly quest for a reduction of costs that could lead to inappropriately shortened hospital stays. Therefore, the suitability of early re-hospitalization as a correct target for good medical practice is highly debated. Nevertheless, the post-discharge phase after episodes of ADHF remains poorly analyzed in clinical trials and specific investigations should be considered during the transition period from acute to chronic status. A validated program, which focuses on an appropriate risk algorithm including cardiac and extracardiac precipitating factors is lacking. This is a necessary and it should become one of the most important targets to aim for in HF management and strategy.

1. Introduction

Despite traditional and innovative therapies in Heart failure (HF) which has led to a significant reduction of mortality, currently one quarter of patients discharged from hospitalization for HF are usually readmitted within the first 30–90 days [1]. Data from larger clinical registries demonstrated that the early re-hospitalization rate is superior with respect to patients affected by myocardial infarction or neoplastic diseases [2]. Increasing interest regarding the necessity to reduce readmissions is justified by the need to improve the quality of care and to reduce public and private costs. An official statement from the ACC/AHA article on task force in CMS reimbursement, has established a 30-day readmission after HF hospitalization as an acceptable target to stimulate public and private hospitals, insurance companies and medical organizations to invest financial resources to reduce hospitalization for HF and to implement related solutions [3–5]. Because hospitalization represents around 70% of the total cost related to HF management, it was estimated that the total expense will at least double within the next twenty years [6,7]. In addition, it was shown that the numbers of hospitalization ultimately increase the risk of fatal events [8,9]. Data from the Enhanced Feedback For Effective Cardiac Treatment (EFFECT) study have shown that readmissions for worsening HF occurred most often in the early months of post-discharge or in the late months before death. Similar trend occurs in patients affected by HF with reduced ejection fraction (HFrEF) and those with preserved ejection fraction (HFpEF) [10]. Finally, as recently reported by the ARNO database, the subjects affected by HF showed a higher prevalence of non-cardiac comorbidities, advanced age and suboptimal treatment compared to subjects commonly enrolled in interventional clinical Trials [11]. Consequently, almost half of hospitalizations are unrelated to specific cardiac causes, which leads to further difficulties in events prediction. In this context, an important role is due to the burden of comorbidities and the condition severity could widely change and tends to be less than in clinical practice. Recently, a specific meta-analysis failed to recognize a precise statistical model able to identify the higher risk population [12]. This is probably due to the different risk profile of each population as well as different precipitating factors and associated conditions in HFrEF and HFpEF that are not accounted in the most risk

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algorithm models. Therefore, patients related factors such as socio economic condition, familiar context, medical and nursing support driving to inadequate followup, may be recognized. All these concerns lead to undetectable prediction of early hospitalization after an acute HF episode.

This data provides a daily practice scenario and it could stimulate alternative strategies for optimizing risk management before discharge, new methods for monitoring the post-discharge period, and stimulating a precision model care in terms of clinical condition and socio-economic status that would be much more tailored to each subject.

2. The post-discharge vulnerable phase

Discharge from hospitalization due to HF is followed by a readmission rate ranging from 20 to 30% within the first 30 days [13,14]. This vulnerable phase represents the period in which patients elapse from a sub-acute to a more stabilized chronic phase [1]. Epidemiological data on patients hospitalized for HFpEF demonstrated that re-hospitalization and mortality rates were similar with respect to HFrEF, but the mechanisms leading to destabilization as well as risk profile are quite different [15]. Even though the readmissions during the early post-discharge period are attributed to cardiac reasons by at least 50%, the EVEREST Trial clearly demonstrated that one-third of all hospitalizations are due to non-related HF causes. Another one-third are attributed to ischemic or arrhythmic reasons, and the remaining are due to effective decompensation. Around 25% of readmissions occurred within the first 30 days, and followed by a plateau period between 31 and 60 days that provided a peak of readmission after 2 months [16]. The same trend was described by Chun et al. in a community cohort population study after the first hospital admission [10]. Gheorghiade et al. made a descriptive analysis of the baseline, in-hospital and post discharge clinical, laboratory, and neurohormonal characteristics of patients hospitalized for HF. The detailed clinical profile of patients may facilitate whom to target for early post-discharge follow-up. Low systolic blood pressure, low serum sodium, decreased renal function, higher heart rate, worsening orthopnea, increased levels of neurohormones such as antidiuretic hormone and aldosterone, and lower albumin levels might be used for a rapid risk stratification in routine clinical practice [17]. Apart epidemiological explanations, other determinants could be involved to explain early re-hospitalization: although most of the HF patients are admitted for pulmonary and systemic congestion. They're not commonly categorized according to admission and discharge clinical profile and are often discharged without complete decongestion. Moreover, a comprehensive assessment is not performed and patients receive a suboptimal titration of life-saving drugs [18]. Therefore, during the vulnerable phase, patients often do not have access to an adequate follow-up program and their compliance is influenced by their psychosocial and socioeconomic status [19]. The lack of an accurate approach for each subtype is probably the first cause of inconclusive data in reducing this trend of recurrent hospitalizations (Fig. 1). A specific schedule including clinical parameter, hemodynamic profile, presence of comorbidities, and serial laboratory measurements together with therapeutic optimization, could be applied more extensively to avoid further events.

3. Comorbidities relevance

Identifying patients at risk for readmission might possibly be accomplished by using clinical and laboratory parameters but the impact of comorbidities must be accounted. Since around half of events are due to non-HF related causes and particularly in elderly patients, the impairment of associated conditions could lead to new admission. Therefore, a recent trial revealed that in common practice, the prevalence of comorbidity burden is high and often the same subjects had more than one associated disease [11]. Comorbidities could be divided into cardiovascular related diseases (atrial fibrillation, hypertension and coronary artery

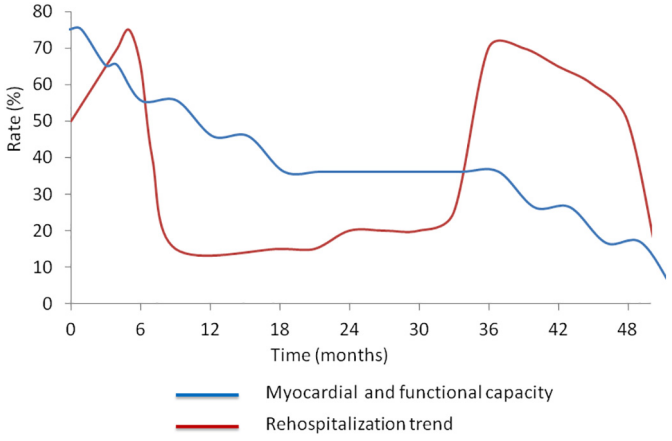

Fig. 1. The vulnerable phase of HF: high episodes can be observed during early post discharge phase and over the late phase before expire.

disease-CAD) [20,21]. Systemic conditions such as anemia, renal dysfunction, lung diseases, diabetes mellitus, depression, nutritional and metabolic disorders and sleep apnea syndrome, all create a negatively influenced outcome. Non-cardiac associated diseases affect patients with more advanced HF and higher disability suggesting a causal relation to HF severity. Unfortunately, AHA and ESC Guidelines provide only generic recommendations regarding comorbidities management. The prognostic impact of comorbidities has been recently analyzed during a long follow-up period showed its burden was strictly related to short and long-term mortality and hospitalization [22] (Table 1). Ather et al. revealed that comorbidities affect both HFrEF and HFpEF patients with similar impacts on mortality in both groups. However a higher number of comorbidities are associated with a more elevated risk of hospitalization for non-cardiac causes in HFpEF [23]. Unfortunately, current analysis did not take into account neoplastic diseases that are often "a priori" excluded conditions from clinical trials and cannot be achieved. However patients with HF and associated neoplastic disease, could be hospitalized independently from its cardiocirculatory status. The episode could occur as for deterioration of oncologic status as for the needing of chemotherapy or palliative care. Some authors propose a prolonged hospital stay as a good strategy in avoiding future events in "frequent flayers" subjects, and this hypothesis is confirmed by the post hoc ASCEND data concluding each additional day of hospitalization was independently correlated with a lower risk of combined end point of death and re-hospitalization [24]. Unfortunately, these findings have been partially contradicted by a meta-analysis that also showed many discrepancies in terms of hospital management, permanence, and costs in different geographical areas [25].

4. Prognostic factors

Despite progresses in chronic HF therapy, patients are still at a high risk for mortality and re-hospitalization for decompensated HF after their initial hospital discharge. Several reports evaluated the prognostic value of many clinical and laboratory factors: ESCAPE, OPTIMIZE-HF and ADHERE Trials. In these studies, the authors conducted an analysis to identify clinical models that could be used as a predictive tool for mortality or re-hospitalization in patients discharged for HF. They developed an algorithm to distinguish patients from low to high risk, and to identify who may benefit from a closer monitoring and aggressive evidence-based treatment. Features that are used in predicting an early postdischarge mortality include increased age, elevated serum creatinine, lower systolic blood pressure, lower serum sodium, elevated blood urea nitrogen, lower admission weight, BNP levels, New York Heart Association functional class IV. Therefore, the same registries identified the potential benefit of using betablockers, Renin-Angiotensin-Aldosterone system (RAAS) inhibitors, lipid-lowering therapy at discharge and

Table 1
Clinical factors and systemic causes of re-hospitalization.

Parameters	Prevalence in/of HF	Reasons
Demographic variables		
Age	~1–2% > adult ~10% > 70 years	Aging and related diseases reduce cardiac performance and increase HF exacerbation.
Gender	Male ~30–40% Female ~25–30%	Women are more frequently rehospitalized with respect to man because of aging and increased comorbidities burden. Otherwise, men present higher mortality rate.
Race	Black race ~20%	The Black race is characterized by a high prevalence of risk factors such as diabetes mellitus, obesity, and HTN. HF in the black is more prevalent, occurs at an early age, and has a more severe course than in whites. Moreover it is associated with increased HF hospitalization, and reduced response to Ace-Inhibitors.
Social environment	~10–15%	Familiar condition and socio economic status may play an important role during the post discharge phase. Those patients living alone are much more prone to be rehospitalized because of therapy discontinuation or lack of check-up. Conversely patients with better education and familiar context tend to follows advices more rigorously and to have better lifestyle
Clinical variables		
Heart rate	HR > 90 beats/min ~15–30%	Heart rate variability is a marker of sympathetic overdrive and reduced contractility. High heart rate, by shortening of diastolic filling time, increases rehospitalization rate.
BP	HTN ~50–70%	HTN increases the risk of development of HF. Hypertensive attacks impairs the hemodynamic status producing HF symptoms and signs development and consequent rehospitalization. Lower BP values are related to more impaired hemodynamic status, reduced cardiac output and systemic vasoconstriction.
NYHA class	NYHA III/IV ~50–80%	Higher NYHA classes are associated with more advanced HF and consequent rehospitalization index.
Clinical congestion evaluation	~90%	Pulmonary and systemic congestion are the mirror of decompensated HF. Hemodynamic derangements proceeding from impaired systo/diastolic performance, increased left ventricular pressure, vascular pulmonary redistribution up to right size dysfunction that ultimately drain into pulmonary edema and systemic congestion
CAD	~50–60%	The presence of CAD has been shown to be independently associated with a worsened long-term outcome. Patients with associated ACS and significant troponin increase at admission, are prone to major myocardial tissue damage and consequently to high risk for both in-hospital and post-discharge mortality.
AF	~30–40%	High ventricular rate in permanent AF or new onset AF deteriorate haemodynamic increasing HF related symptoms and signs through reduced cardiac output.
Previous HF hospitalization	~50–70%	Hospitalization for acute HF is associated with high rates of subsequent mortality and readmission. Half of rehospitalization is attributed to cardiovascular causes. Independently of EF, the rates of cardiovascular death and HF hospitalization are higher in patients who have been previously hospitalized for HF.
Comorbidities		
Renal dysfunction	~25–40%	Most patients with HF display mild or moderate renal dysfunction. This is due to several causes such as chronic renal parenchymal disease, renal congestion and concomitant hypoperfusion, neuroendocrine activation and finally for HF treatment. This comorbidity promotes diuretic resistance and consequent reduced diuresis.
COPD	~15–30%	COPD is an important comorbidity in HF patients and consistently represents an independent predictor of hospitalization. The COPD exacerbation is the main reason of rehospitalization in these patients.
Anemia	~10–40%	Anemia is found in about one-third of all cases of congestive HF, mostly associated with chronic diseases (i.e. CKD) and, less frequently, to iron deficiency, nutritional deficiencies and other causes. This common comorbidity leads to an increased oxygen request and consequent cardiac overload.
Diabetes mellitus	~25–40%	Diabetes may play an important role in the pathogenesis, prognosis and response to treatment of HF. Diabetes leads to HF rehospitalization through the development of renal dysfunction, the increased rate of infections due to uncontrolled glucose serum levels.
Peripheral vascular disease	~10–25%	PAD in patients with HF is associated with increased risk of death and hospitalization, predominantly due to atherosclerotic disease and acute peripheral arteries ischemia.
Depression/anxiety	~10–35%	Depression and anxiety strongly impact the quality of life of patients with HF. They are an important determinant of patient adherence to HF treatment and appropriate life-style. Depression is an important and independent predictor of outcome among HF patients, while anxiety does not appear to have a strong effect in HF outcome.
Hyponatremia	~25%	Hyponatremia is a frequent occurrence in HF patients and it is related to several mechanisms such as neuroendocrine overdrive, and particularly the increased release of AVP. Lower serum sodium levels are often associated with poor diuretic response.
Neoplastic diseases	~20–35%	The contemporary presence of any type of neoplastic disease could worsen the clinical status and prognosis independently from HF status. General condition could be impaired by the presence of primitive or secondary lesions and re-hospitalization could occur because of chemotherapy or palliative care related to the oncologic aspect.
Cachexia	~10%	In HF patients, cardiac cachexia may represent a the reflection of a vicious circle strictly related to worse prognosis; in particular malabsorption, pro-inflammatory cytokines expression, neuro-hormonal overdrive, fluid overload and diuretic resistance which promotes worsening heart failure and consequent rehospitalization.

Abbreviations: acute coronary syndrome (ACS), atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD), blood pressure (BP), systolic blood pressure (SBP), diastolic blood pressure (DBP), coronary artery disease (CAD), heart failure (HF), hypertension (HTN), peripheral arterial disease (PAD), Renin-Angiotensin-Aldosterone system (RAAS), vasopressin (AVP), New York Heart Association (NYHA), ejection fraction (EF), chronic kidney disease (CKD), haemoglobin (Hb).

implantable cardioverter defibrillator during hospitalization. However, the use of a high loop diuretic amount appeared to be associated with an increased risk of re-hospitalization [26–29]. Several studies and registries have demonstrated the importance of an elevated blood urea nitrogen (BUN) and a decreased renal function in predicting outcome [29,30]. It is well established that BUN is mostly a marker of kidney perfusion and its increase is very much related to the high venous pressure, while creatinine is a marker of kidney function that can be more sensitive

to variables change such as age, gender, medical therapy, circulating volume, engaged nephron population Because BUN can reflect the rate of plasma refill during the process of diuresis, the rise in BUN in the setting of little change in serum creatinine can be valuable to understand when a relative intravascular volume reduction is taking place in a patient with congestive status [31]. In chronic condition BUN could reflects an increased prevalence of unfavorable condition such as CAD, atrial fibrillation and CKD stage. Overall, it is difficult to recognize the main driver or kidney function deterioration and a ratio including BUN and creatinine has been proposed to include all the potential variables. The renal function deterioration is very common and it affects around 40% of hospitalized patients [32]. Nevertheless, the exact role on worsening renal function (WRF) is currently under debate: a metanalysis showed that WRF occurrence during hospitalization is comparable to chronic kidney disease (CKD). Patients would then have a worse hemodynamic status and deteriorated systemic and metabolic conditions [33]. Conversely, other studies did not reveal a specific prognostic role of WRF occurring during hospitalization because it is simply related to aggressive decongestion [29,33–36].

The most studied biomarkers in the HF setting are natriuretic peptides (N-terminal pro B-type natriuretic peptide [NTpro BNP] and B-type natriuretic peptide [BNP]). Natriuretic peptides (NP) entered the current guidelines for HF diagnosis and management because of their high specificity, high sensibility and their serial changes demonstrated an interesting role in risk stratification. NP synthesized in the cardiac myocyte as a reaction to ventricular and atrial wall distension due to increased Left Ventricular (LV) pressure. These peptides convey a multitude of actions at the cardiac and renal levels including vascular smooth muscle cell relaxation, promotion of natriuresis and diuresis, direct neurohormonal antagonism on the RAAS [37,38]. Nevertheless, their variation in the plasma is significantly affected by non-cardiac factors such as age, gender, obesity, renal function and other systemic conditions. In the ASTRONAUT study, patients with high levels and a subsequent decrease >50% before the discharge level, had a similar prognosis when compared to those with low admission levels [39]. Accordingly, in the OPTIMIZE-HF Cox model including several clinical variables, the BNP value at discharge was the most important predictor of one-year mortality and re-hospitalization [40]. In a prospective multicentre cohort, high levels of NT-proBNP were significantly associated with poor outcomes and it was the most important prognostic factor in both HFpEF and HFrEF [41]. In ambulatory patients with CHF, a BNP-guided strategy reduced the risk of CHF-related death or readmission by about 50% [42]. Cardiac troponins are integral parts of the cardiac muscle infrastructure and play critical roles in excitation–contraction coupling. The release of intracellular proteins from the damaged cardiomyocytes into the bloodstream is the basis for estimating extent of cardiac damage through the assay of circulating molecules and for the diagnosis of acute myocardial infarction [38]. A significant increase of hsTnT is not only related to the presence of significant CAD and myocyte necrosis, but it is also an expression of several underlying processes. This includes an increase in oxidative stress endothelial dysfunction, elevated wall stress neurohormonal activation, myocardial fibers degradation and apoptosis [43]. Although most studies demonstrated a high prevalence of hsTnT elevation and a strict association with early mortality [44–46], some reports showed that baseline and change hs-cTnT were associated with worse outcomes during a mid-follow-up period [47–49].

Recently, a novel biomarker, soluble ST-2, a member of interleukin-1 receptor family formally known as interleukin-1 receptor like 1 (IL1RL-1), demonstrated greater prognostic power with respect to traditional biomarkers in patients with HF. Soluble ST-2 has been identified as the ligand for interleukin-33 (IL-33) and it exists in two isoforms: a transmembrane and a soluble variety. IL-33/ST-2 signalling control cardiomyocyte hypertrophy and cardiac fibrosis. Thus, it was demonstrated that eliminating IL-33/ST-2 signalling leads to hypertrophy and fibrosis; these mechanisms are related to poor prognosis in HF patients [50,51]. Different studies evaluated ST-2 both in chronic and acute HF. In the acute setting, an analysis of PROTECT trial showed that soluble ST-2 level at discharge were much more elevated in patients who experienced cardiovascular events at 30 days [52]. Similarly, RELAX-AHF trial demonstrated that measurement of ST-2 until 60 days from enrollment gave more precise prognostic information together with cardiac troponin and BNP [53]. In the chronic setting, a post-hoc analysis of CORONA trial showed that soluble ST2 was related to adverse outcomes in older patients with systolic, ischaemic HF and it was independently associated with worsening HF. In this sense, Januzzi et al. evaluated ST-2 changes according to HF therapy adjustment [54]. They found that ST-2 concentrations may predict benefit from specific HF therapy changes. Thus, a cut-off of 35 ng/ml in serial testing for chronic HF patients appeared useful [55].

Tumor marker antigen carbohydrate 125 (CA125) is a glycoprotein synthesized by epithelial serous cells. Although CA125 is widely used for ovarian cancer therapy monitoring, high serum levels have also been observed in other malignant and nonmalignant diseases (HF, nephrotic syndrome, liver cirrhosis, tuberculosis, or pelvic inflammatory disease, among others) [56]. In particular, in HF patients CA125 was increased in presence of pleural and pericardial effusion, in ascites and peripheral congestion. Thus, several authors demonstrated that CA125 guided therapy in acute HF was related to lower rate of death and rehospitalization [56,57]. In this sense Nunez et al. showed that CA125 gave prognostic information, in particular after serial determinations; moreover, CA125 together with BNP measurement increased the accuracy of each biomarker for outcome prediction in acute HF patients [58]. In a recent trial (CHANCE-HF) standard of care was compared with CA125 guided therapy in acute HF; the result of this trial showed that HF therapy guided by CA125 was superior to standard of care in reducing rehospitalization and death at 1 year [59] (Table 2).

A multi-modality biomarkers strategy including traditional and new laboratory parameters has been recently validated to help better predict outcomes in ADHF patients. However, the building of a biomarkers model able to identify high risk HF patients is quite difficult. All risk model based on biomarkers were used in different population (such as acute and chronic HF, HFpEF, HFrEF, ischemic heart disease) and for this reason they cannot universally validated. It should be useful to distinguish biomarkers model involved in risk prediction in acute HF patients evaluating their temporal trends (NP, ST-2 and CA125); differently, other biomarkers should be used to predict prognosis in chronic setting according to LVEF and comorbidities [38,51–55,58,60]. Therefore it could be of limited significance because risk model are currently applied in specific cohort selected for the preliminary generated hypothesis, his could result of scarce significance in a general population and in different HF settings.

Overall, the risk stratification of patients hospitalized for ADHF may be easily assessed by applying a categorical scheme including some clinical variables, patients' history and risk factors and the burden of associated diseases. Laboratory tools should be a part of this algorithm and need to be contextualized looking at all these variables. A similar model could be prospectively employed to help in outcome recognition (Fig. 2).

5. Current inadequate targets

In patients hospitalized for ADHF the first immediate objective remains unchanged over the last 15 years: a rapid resolution of symptoms and congestion. Medications such as diuretics and inotropes have proven effective in achieving this goal despite not improving the prognosis. Nevertheless, pharmacological trials in the context of ADHF have given negative or only marginally positive results in the last years. In particular, any phase 3 study has demonstrated an improvement in survival and/or re-hospitalization during the follow-up. This does not include inotropes (milrinone, levosimendan, dopamine) [61–63], BNP recombinant (nesiritide) [64,65], antagonist receptors of vasopressin [66], and adenosine antagonist [67,68]. In addition to the treatment of symptoms

Table 2
Current biomarkers flow chart and specific Trials measuring their potential prognostic power for risk stratification in HF.

Biomarkers	Main author	Study name	HF setting	Follow-up	Timing measurement	Main findings
BNP	Kociol RD et al. [42]	OPTIMIZE-HF	AHF HFrEF and HFpEF	1 year	At discharge[a]	Discharge BNP model improved risk reclassification for 1-year mortality or rehospitalization.
BNP	Jourdain P et al. [44]	STARS-BNP	CHF LVEF < 45%	15 months	Every 3 months[b]	BNP-guided strategy reduced the risk of CHF-related death or hospital stay for CHF.
NT-proBNP	Greene SJ et al. [41]	ASTRONAUT	AHF LVEF < 40%	11.3 months	5 days[a] 1 month[b]	NT-proBNP change from baseline to 1 month was predictive of increased cardiovascular mortality or HHF.
NT-proBNP	Kang SH et al. [43]	KorHF registry	AHF LVEF ≥ 50% or ≤40%	1 year	At admission[a]	NT-proBNP is the most powerful prognostic factor for all-cause death or HF hospitalization in both LVEF ≥ 50% and ≤40%.
Troponin T Hs troponin T	Latini R et al. [46]	Val-HeFT	CHF LVEF < 40%	24 months	At baseline[b] At 4 months[b]	TnT was associated with all cause of death and first hospitalization for HF; addition of hsTnT improved prognostic discrimination for both outcome.
Hs troponin T	Felker GM et al. [49]	RELAX-AHF	AHF LVEF ≥ 40% or <40%	60–180 days	At baseline[a] Day 2 or day 5[a] Day 14[ab] Day 60[b]	Higher baseline or peak hs TnT and greater peak change were associated with cardiovascular death, or HF/renal hospitalization to 60 days and cardiovascular mortality to 180 days.
Troponin T	O'Connor CM et al. [51]	PROTECT	AHF LVEF not assessed	60 days	At baseline[a] Days 2,3,4 and 7[a]	Positive troponin at baseline, and conversion to positive levels, were associated with cardiovascular/renal rehospitalization or death at 60 days.
sST-2	Bayes-Genis A et al.	/	CHF LVEF ≤ 50%	4.2 ± 2.1 years	At baseline[b] 3 months[b] Every 6 months[b]	sST2 provides valuable long-term risk stratification information in HF considering 5-year all-cause and cardiovascular mortality, and the combined all-cause death/HHF.
sST-2	Demissei BG et al. [54]	PROTECT	AHF LVEF not assessed	30 days	At baseline[a] Day 6[a] Days 7 and 14[ab]	Median sST-2 was higher in patients' experienced death or heart failure rehospitalization at 30 day.
sST-2	Demissei BG et al. [55]	RELAX-AHF	AHF LVEF ≥ 40% or <40%	60–180 days	At baseline[a] Day 14[ab] Day 60[b]	sST-2 levels were associated to cardiovascular mortality at 180 days and improved biomarkers model for risk prediction in AHF.
sST-2	Broch K et al. [56]	CORONA	CHF LVEF ≤ 40% LVEF ≤ 35% if NYHA II	36 months	6 weeks[b] 3 months[b] Every 6 months[b]	Soluble ST2 is associated with cardiovascular death, non-fatal MI and rehospitalization in older patients with systolic, ischaemic HF.
CA125	Núñez J et al. [60]	/	AHF and CHF Both HFrEF and HFpEF	Day 30 until death, CT or to the last date they were contacted alive.	At discharge[a] 31 days[b]	In patients discharged for AHF, CA125 modeled as a pre-post categorical change together with BNP resulted in the best marker combination for predicting all-cause mortality.
CA125	Núñez J et al. [61]	CHANCE-HF	CHF Both HFrEF and HFpEF	1 year	1, 6, 12 months[b]	The CA125 strategy was superior to the SOC in terms of reducing the risk of the composite of 1-year death or AHF readmission. The effect was driven by significantly reducing rehospitalizations but not mortality.

Abbreviations: acute heart failure (AHF); B-type natriuretic peptide (BNP); carbohydrate antigen-125 (CA125); chronic heart failure (CHF); cardiac transplantation (CT); heart failure with preserved ejection fraction (HFpEF); heart failure with reduced ejection fraction (HFrEF); heart failure hospitalization (HHF); high sensitivity troponin T (Hs TnT); left ventricular ejection fraction (LVEF); N-terminal pro B-type natriuretic peptide (NT-proBNP); standard of care (SOC); soluble ST-2 (sST-2); troponin T (TnT).
[a] During hospitalization.
[b] After discharge.

in the acute phase, the other priority is to minimize the damage to the cardiac organ by avoiding hypoxia and hypoperfusion. Focusing on the effectiveness of treatment in reducing congestion and dyspnea has been widely shown to be insufficient because many patients clinically worsen, despite a progressive relief of signs and symptoms after admission. The apparent amelioration cannot be translated in a substantial prognostic benefit and it requires intensifying therapies that often result in higher doses of diuretics and inotropes [69].

Numerous studies have shown that the worsening heart failure (WHF) is a powerful predictor of mortality in short and long term hospitalization [70,71]. Recently, serelaxin significantly reduced the WHF although long term data did not show significant long-term benefits [72]. The only trial revealing a good trend reducing neurohormonal overdrive and the diuretic amount is PARADYGM, which tested sacubitril/valsartan [73]. Despite favourable data, its use is currently limited to stable outpatients with HFrEF. Use of this drug in acute setting prior to discharge, and in HFpEF, could became of pivotal relevance to ascertain its tolerability and prognostic value.

WHF is an event that probably corresponds to the activation of multiple mechanisms that include peripheral hypoperfusion, parenchymal renal damage, inflammation and neurohormonal hyperactivity. Whether all these items could be considered as primary endpoints and important targets after discharge, remains to be seen. Whereas most targets are focused just on dyspnea relief that does not mind an effective congestion status solution. Therefore physicians could distinguish between central cardiac congestion and peripheral retention by using different methods and evaluation. Therefore different features need to be contemplated during the post discharge phase evaluation: 1) Around half of recurrent hospitalizations are not up-to-date on specific cardiac and hemodynamic destabilization and other comorbidities that should be taken into consideration. 2) The readmission rate is similar in both patients affected by HFrEF and HFpEF, even though the events following HFpEF are more related to associated conditions rather than to specific cardiac impairment. 3) The trend over time of readmission is applicable only for “de novo” HF subjects, which represent only 20% of the total HF population. 4) Patients with multiple recurrent admissions are more prone to reduced functional capacity and low quality of life. Thus a recurrent episode could not be related to effective worsening in cardiac functions.

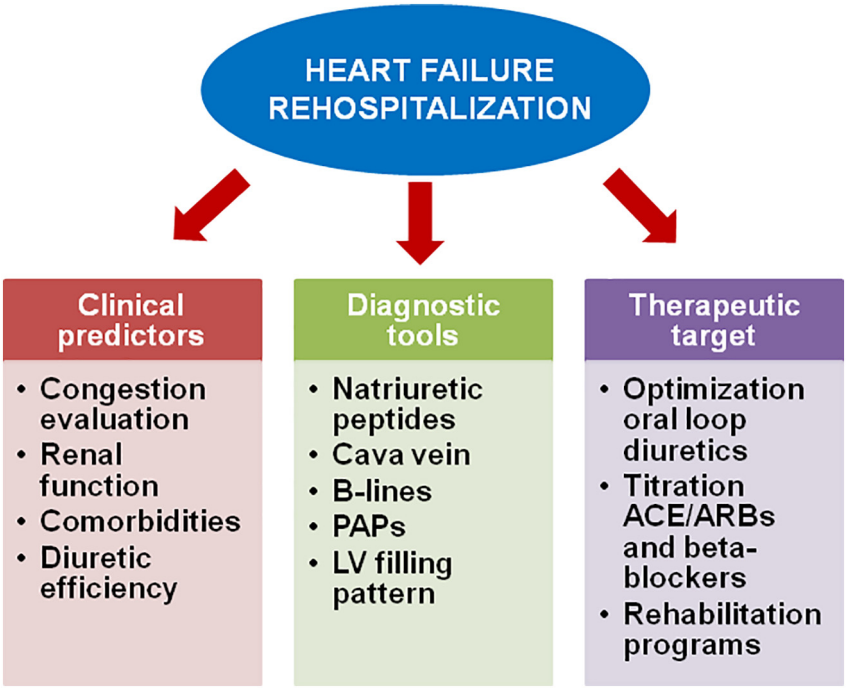

Fig. 2. Clinical laboratory and therapeutic management to minimize re-hospitalization.

6. Role of palliative care and quality initiatives

The improvement of drug treatment and the use of devices have increased the survival of patients with chronic HF [73]. Improved survival does not always correspond to a better quality of life and currently, patients with advanced HF who are destined to die are gradually increasing, despite optimal medical therapy. In the USA, less than half of patients (46.7%) with cardiopulmonary end-stage diseases (HF or chronic obstructive pulmonary disorder) received a palliative care consultation compared with more than three quarters of patients suffering from cancer [74]. In a family report retrospective analysis, the quality of life in the HF subjects was significantly worse compared to patients with cancer and other chronic illnesses. An early identification of end-stage HF items should become strategic in referring those patients to palliative care [75,76]. A position statement from the palliative care workshop of the HF Association of the European Society of Cardiology describes five clinical criteria to define end-stage HF:

1) >1 episode of decompensation/6 months despite optimal tolerated therapy
2) the need for frequent or continual i.v. support
3) chronic poor quality of life with NYHA IV symptoms
4) signs of cardiac cachexia
5) clinically judged to be close to the end of life [77].

The application of multidisciplinary protocols for palliative care in end-stage HF is mandatory, and recently the European guidelines for treatment of HF have emphasized multidisciplinary strategies including nursing management, psychological support and communication strategy between patients and their family members. Palliative care, as defined by the World Health Organization (WHO), is an approach that improves the quality of life of patients who are suffering from fatal diseases [78]. Palliative care is an active, holistic, multidisciplinary model, which represents a passive approach finalized only to reduce symptoms and suffering [79]. The first objective affects the cardiologist who has to accept that the end-stage HF is a malignant disease with a similar evolution to cancer. This awareness must also be transmitted to the patient and his family acknowledging that the primary goal of palliative care is to improve the quality of life. A palliative care staff should alleviate symptoms and depression and improve quality of life in outpatients with end-stage HF [80]. Indeed, the PAL-HF (Palliative Care in Heart Failure) trial to evaluate the impact of an interdisciplinary palliative care intervention combined with usual HF management, revealed an improvement in psychosocial and quality-of-life status [81]. General recommendations for a palliative care approach are summarized in Supplementary Table 3. New research regarding the identification of evidenced-based strategies to improve palliative care in HF patients are still needed.

7. Potential strategies to reduce re-hospitalization rate

Although international trials taught the community about the principal concerns associated with re-hospitalization, they do not represent the real HF world because of the recruitment criteria that do not afford an effective picture of these patients. Thus, data taken by International registries remain inconclusive regarding the post-discharge time course and management program, which is different in relation to the respective geographic areas and National Health Systems. There is an effective need to assess the specific management considering the post-discharge phase, and its related social and medical issues. Although several programs during the last decade have been proposed, only limited strategies currently exist to reduce post-discharge events. Most reports are single-center studies with a small sample size and with heterogeneous interventional programs based on direct checkups or telemonitoring [82–84]. Only one metanalysis including pooled-data about home visit programs, revealed this model was associated with a significant reduction in mortality and re-hospitalization at 6 months [85]. The inconsistent results can be attributed to different follow up criteria, rate of post-discharge evaluation, and accounted parameters. Worsening of congestion status is the major reason for hospital readmission. Regrettably, in most cases congestion is evaluated only through clinical signs that do not perfectly reflect the effective idrosaline retention status. Indeed, congestion is preceded by several hemodynamic derangements emerging from an impaired systo/diastolic performance, increased left ventricular pressure, vascular pulmonary redistribution up to right size dysfunction. In patients with advanced HF, pulmonary capillary

wedge pressure and right atrial pressure are stronger predictors of post-discharge outcomes compared to cardiac index, encouraging the use of hemodynamic evaluation in that setting; however, invasive monitoring cannot be performed extensively, and it should be reserved to specific high-risk population during hospitalization. However, a detailed dyspnea and congestion score at discharge is able to discern 30-day hospitalization and mortality events after an adjustment for risk factors such as EF blood pressure, natriuretic peptide, and diuretics. Application of a model accounting clinical congestion NP measurement and echocardiographic monitoring with non-invasive pulmonary pressure and LV filling pressure estimation, could partially avoid HF related events [86,87] (Fig. 2). Therefore a recent techniques evaluating water status by echo lung ultrasound scan demonstrated a good accuracy in the pulmonary congestion assessment in either HFrEF or HFpEF acute patients: specifically a significant decrease of B-lines over observational period was related to a better outcome with respect to patients experiencing unchanged or increased number [88,89]. Application of a model accounting clinical congestion, NP measurement, and echocardiographic monitoring with non-invasive pulmonary pressure and LV filling pressure estimation, could partially avoid HF related events.

Unplanned readmissions also have a heavy financial burden and associated costs. A US policy intervention Hospital Readmission Reduction Program (HRRP) applying financial penalties to those hospitals with higher readmissions. This showed a reduction in 30-days and 1-year risk-adjusted readmissions rate, despite an increase of 30-day and 1-year mortality. Therefore, incentives to reduce readmissions can potentially encourage inappropriate care strategies and may adversely affect patient outcomes [90].

Another algorithm was based on admission risk stratification and categorization: patients at low risk will be observed for a short period and then admitted with a new evaluation at 30 days after the episode. Whereas, subjects with a higher risk should be admitted and observed for a longer period and carefully monitored during the first month [91].

A specific investigation should be considered during the dynamic post-discharge period, which is the transition from the acute to the CHF. Specific trials designed for therapies initiated soon after discharge and pursued in the outpatient setting should be planned and investigated [92,93]. In this sense, Gayate et al. emphasized the importance of early introduction of betablockers and renin–angiotensin system inhibitors to achieve better outcomes, regardless of LVEF or the presence of co-morbidities [94]. Similarly, a recent meta-analysis showed that a discontinuation of betablockers in patients with AHF was associated with significantly increased in-hospital mortality and short-term mortality [95].

Beyond the traditional treatment and hospitalization environment (ICU, clinically dedicated HF in-hospital Unit), the patients course just before discharge could be organized in a multidisciplinary setting including different professionalisms such as geriatric, pneumologist, nephrologist, physiotherapist and psychological support. Last but not least, the general primary care that may enter as an active part of the domiciliary program. A self-monitoring evaluation mediated by a specific nurse, is also useful and patients could gain confidence with daily physical activity, diuresis and body weight measurement, avoidance of excessive food, salt and liquid intake [96]. Obviously, all these initiatives depend on the patients' capacity and self-management, their social and scholastic level, and on the stage and severity of the disease. In relation to different conditions, the management target could be changed ranging from mortality and hospitalization reduction, to quality of life improvement and finally to palliative care during the end of life. While several parameters of HF severity may possibly predict future events, a robust and actionable risk model for early readmission is lacking. This is due partially to the dynamic nature and to the variable trend of HF in which the clinical. Haemodynamic, and neurohormonal profiles are continuously changing [16,97]; secondly, to the absence of rigorous methodological studies aimed to evaluate recurrent hospitalization causes as a primary endpoint [96]. Several questions are still arising about the suitability of early re-hospitalization as a correct target for good medical practice. The hospitalization rate reduction cannot be necessarily translated in an overall mortality reduction; many admissions are due to non-specific causes of worsening HF particularly in elderly and frail people. An increase in re-hospitalization could simply reflect a more advanced HF stage with increased comorbidities burden. Finally, an elevated re-hospitalization rate can be related to mortality reduction and increased life expectancy [98]. All these items may be contemplated when the scientific community discuss the causes of early re-hospitalization, its relative costs and admission modalities.

8. Conclusions

Early re-hospitalization for ADHF is one of the most notable concerns related to HF. It has several socio-economic implications and its reduction could become a future target in HF management. The early post-discharge period also called “vulnerable phase”, is a crucial time in which many clinical haemodynamic and therapeutic changes occur. Identifying the precipitant causes of re-hospitalization is challenging because they could depend on the dynamic process of disease or on non-cardiac conditions deterioration. Therefore, criteria for admission discharge and hospital stay may vary on the national health system, geographic area, and physicians' background. Interventional studies should be focused on this peculiar changing period and its relative risk assessment on which the future events and early readmission could depend. In this direction, specific trials focusing on the post-discharge vulnerable period and the relative risk assessment should be encouraged.

Despite these recognized processes, a comprehensive program based on randomized clinical data is an unmet need and an appropriate risk algorithm should be designed to recognize potential precipitating factors. The temporal evaluation of a multi-disciplinary integrated algorithm after the discharge period could lead to the identification and possibly to the prevention of future events. Moreover the traditionally measured 30-days risk adjustment model suffers of two main shortcomings: a) it is not possible to recognize differences across hospitals in health outcome by the simple count of patients who died, as the methods assume that resources employed for those who survived are the same than for dead or readmitted people. b) Readmission rates could be paradoxically reduced by the competing risk of death, as patients who die during the index episode of care obviously can never be readmitted. Finally, readmission is a process reflecting a poor territorial coordination and services, inadequate follow up access, and lack of a specific care program [98–100]. For these reasons, re-hospitalization should be entered in the future endpoints and contextualized with careful analysis including patients' conditions, social environment, and comorbidities. However, an increased rate of events does not automatically imply bad clinical practice because it could be simply the reflection of more frailty: indeed an increased in hospitalization rate would be associated with lower 30 days adjusted mortality risk. Only by taking into account all these items together, will it be possible to achieve efficacious programs. Distinguishing early readmissions due to avoidable events that are related to bad clinical management.

> “**Not everything that count can be counted, and not everything that can be counted counts**.”
>
> [(A. Einstein)]

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Conflict of interests

None declared.

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