Worsening Heart Failure: What is it and Why is it Important?

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Conflict of Interest Disclosures

- **Grants/research support**: Servier, Vifor, Novartis
- **Consulting fees**: Boehringer Ingelheim

Learning Objectives

- Learn how to identify and define worsening heart failure
- Review clinical trial and registry data addressing this patient population
- Review guideline's recommendations for the management of WHF

HF hospitalization and HF progression

Recognizing Hospitalized Heart Failure as an Entity and Developing New Therapies to Improve Outcomes

Academics', Clinicians', Industry's, Regulators', and Payers' Perspectives

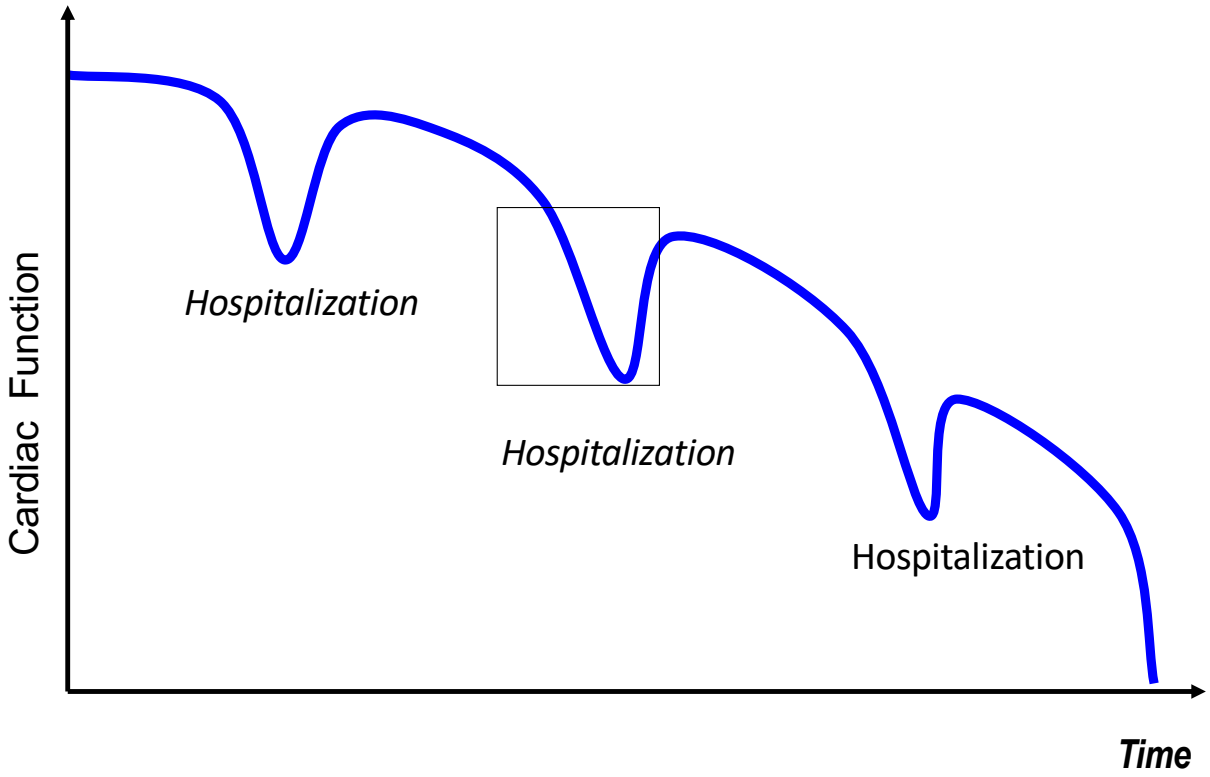
Mihai Gheorghiade, MD[a,*], Ami N. Shah, MD[a], Muthiah Vaduganathan, MD, MPH[b], Javed Butler, MD, MPH[c], Robert O. Bonow, MD, MS[a], Giuseppe M.C. Rosano, MD, PhD[d], Scott Taylor, RPh, MBA[e], Stuart Kupfer, MD[f], Frank Misselwitz, MD, PhD[g], Arjun Sharma, MD[h], Gregg C. Fonarow, MD[i]

KEYWORDS

• Hospitalized heart failure • Heart failure • Postdischarge mortality

KEY POINTS

- Hospitalized heart failure (HHF) is associated with unacceptably high postdischarge mortality and rehospitalization rates.
- This heterogeneous group of patients, however, is still treated with standard, homogenous therapies that are not preventing their rapid deterioration.
- The costs associated with HHF have added demands from society, government, and payers to improve outcomes.
- It is important to consider that once HHF patients are stabilized by discharge, the majority of them should be considered to be in a chronic heart failure state at a significantly high risk for adverse outcomes. Delaying initiation of potentially effective therapies for weeks to months post discharge risks unabated high risk for adverse events in the meantime. Initiating therapies in patients who are stabilized in the hospital and continued long term provides a potent option to improve long-term clinical outcomes.
- With coordinated and committed efforts in the development of new therapies, improvements may be seen in outcomes for patients with HHF.
- This article summarizes concepts in developing therapies for HHF discussed during a multidisciplinary panel at the Heart Failure Society of America's Annual Scientific Meeting, September 2012.



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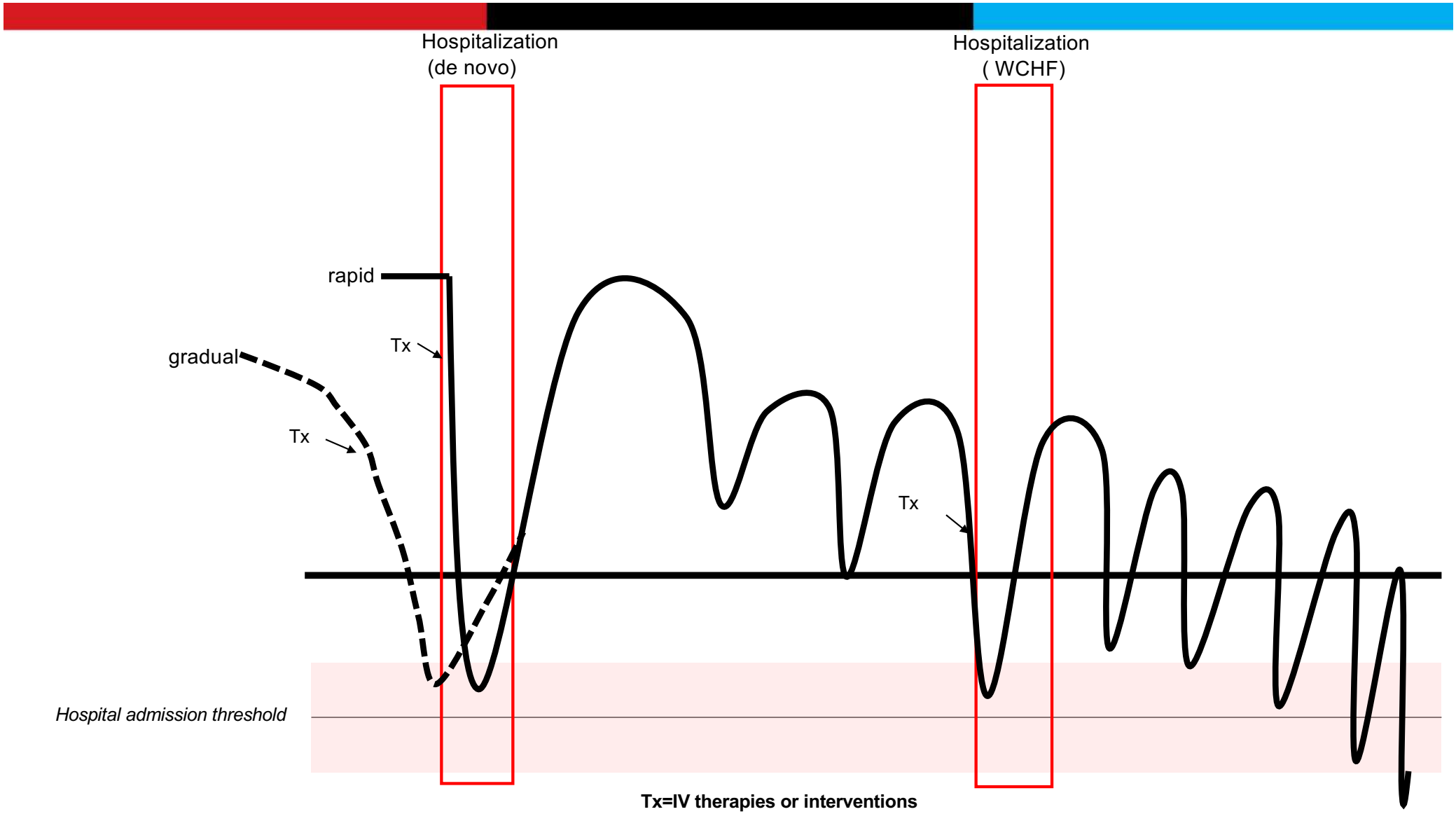
HF is a multi event disease

Hospitalization is a key event in the progression of HF

Hospitalization is an unique opportunity to assess CV and nonCV substrate and to optimize treatment

Initiating therapies in patients who are stabilized in the hospital and continued long term provides a potent option to improve long-term clinical outcomes

The risk extends beyond hospitalization


Hospitalization
(de novo)
Hospitalization
(WCHF)
rapid
gradual
Tx
Tx
Tx
Hospital admission threshold
Tx=IV therapies or interventions

European Journal of Heart Failure (2014) 16, 560–565
doi:10.1002/ejhf.71

Prognosis and response to therapy of first inpatient and outpatient heart failure event in a heart failure clinical trial: MADIT-CRT

Hicham Skali[1]*, Edward M. Dwyer[2], Robert Goldstein[3], Mark Haigney[3], Ronald Krone[4], Marrick Kukin[5], Edgar Lichstein[6], Scott McNitt[7], Arthur J. Moss[7], Marc A. Pfeffer[1], and Scott D. Solomon[1]

[1]Harvard Medical School, Brigham and Women's Hospital, Cardiovascular Division, Boston, MA, USA; [2]New Jersey Medical School, Newark, NJ, USA; [3]Uniformed Services University, Bethesda, MD, USA; [4]Washington University Saint Louis, MO, USA; [5]St. Luke's Roosevelt Hospital, Columbia University College of Physicians & Surgeons, New York,

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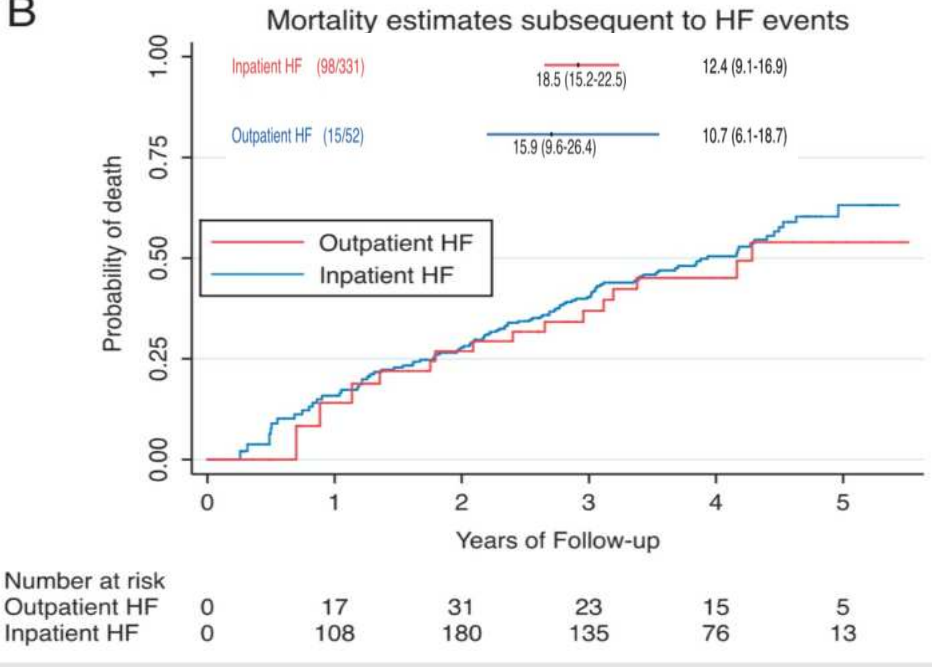


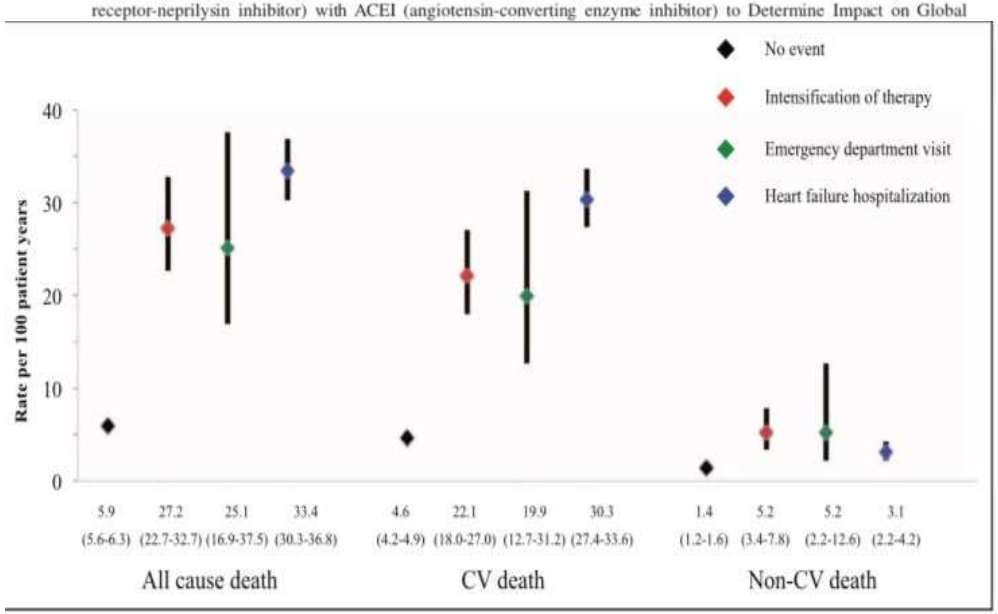
Heart Failure

Importance of Clinical Worsening of Heart Failure Treated in the Outpatient Setting

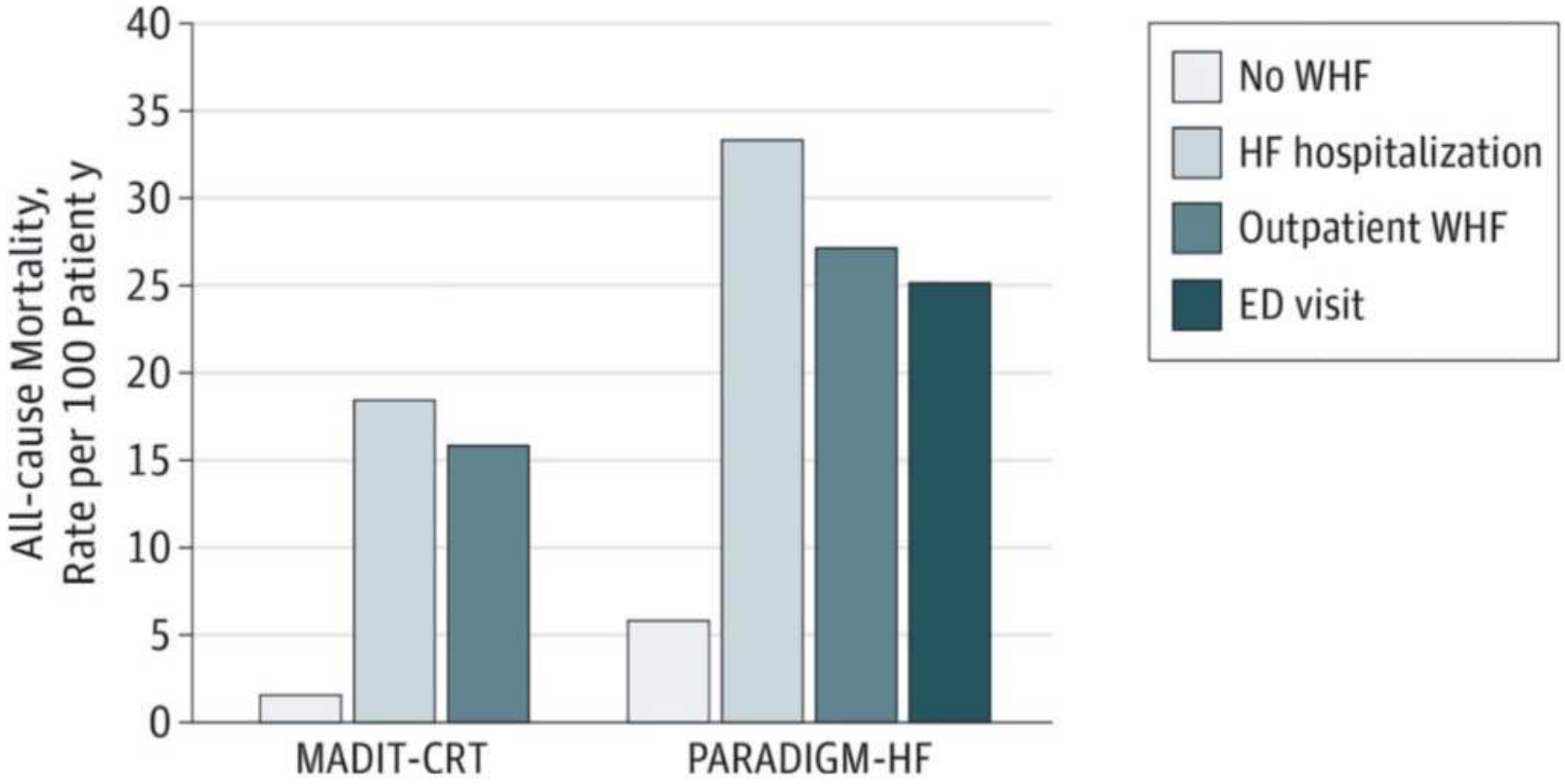
Evidence From the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF)

Naoki Okumura, MD, PhD; Pardeep S. Jhund, MBChB, MSc, PhD; Jianjian Gong, MD; Martin P. Lefkowitz, MD; Adel R. Rizkala, PharmD; Jean L. Rouleau, MD; Victor C. Shi, MD; Karl Swedberg, MD; Michael R. Zile, MD; Scott D. Solomon, MD; Milton Packer, MD; John J.V. McMurray, MD; PARADIGM-HF Investigators and Committees*

Background—Many episodes of worsening of heart failure (HF) are treated by increasing oral therapy or temporary intravenous treatment in the community or emergency department (ED), without hospital admission. We studied the frequency and prognostic importance of these episodes of worsening in the Prospective Comparison of ARNI (angiotensin-receptor-neprilysin inhibitor) with ACEI (angiotensin-converting enzyme inhibitor) to Determine Impact on Global



Worsening HF is associated with a high subsequent risk of death, irrespective of treatment as an outpatient, inpatient, or in the emergency department (ED)



ESC European Society of Cardiology

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doi:10.1002/ejhf.1323

RESEARCH ARTICLE

Heart failure in the outpatient versus inpatient setting: findings from the BIOSTAT-CHF study

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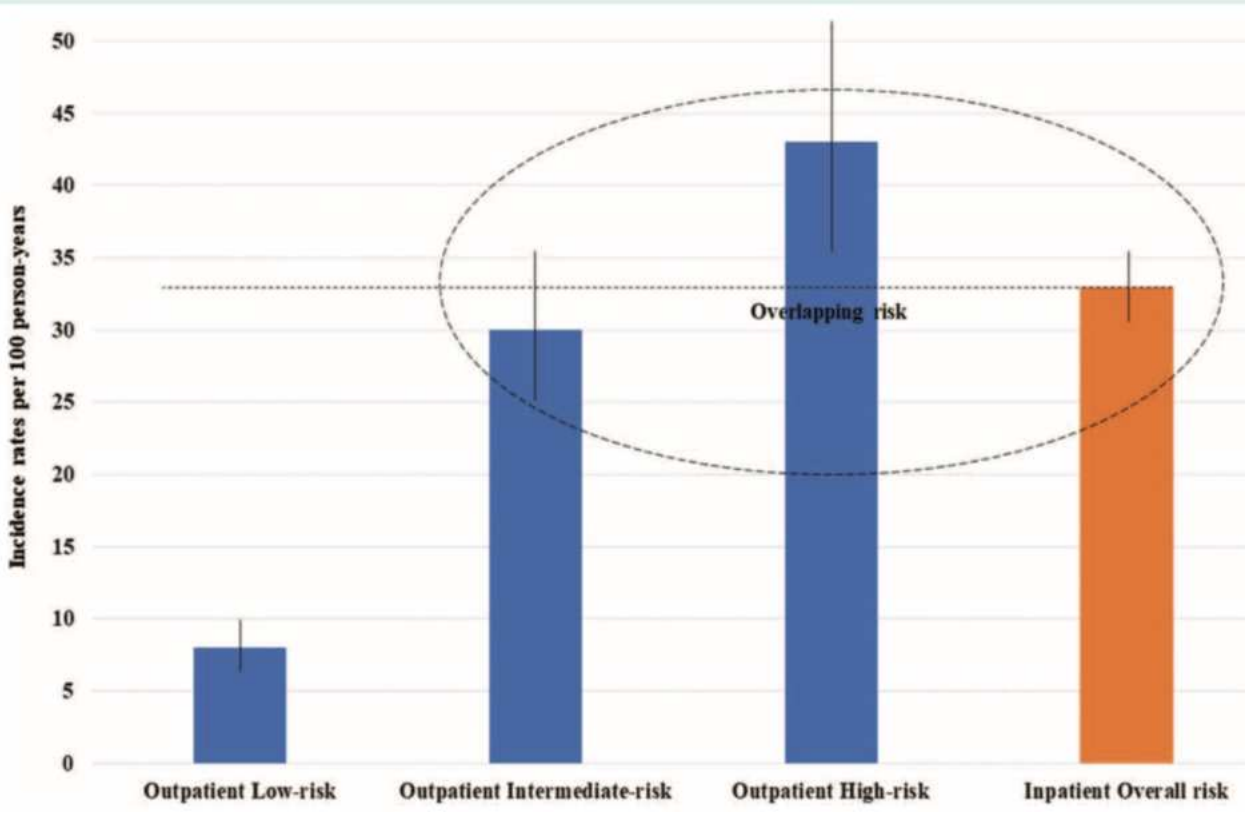
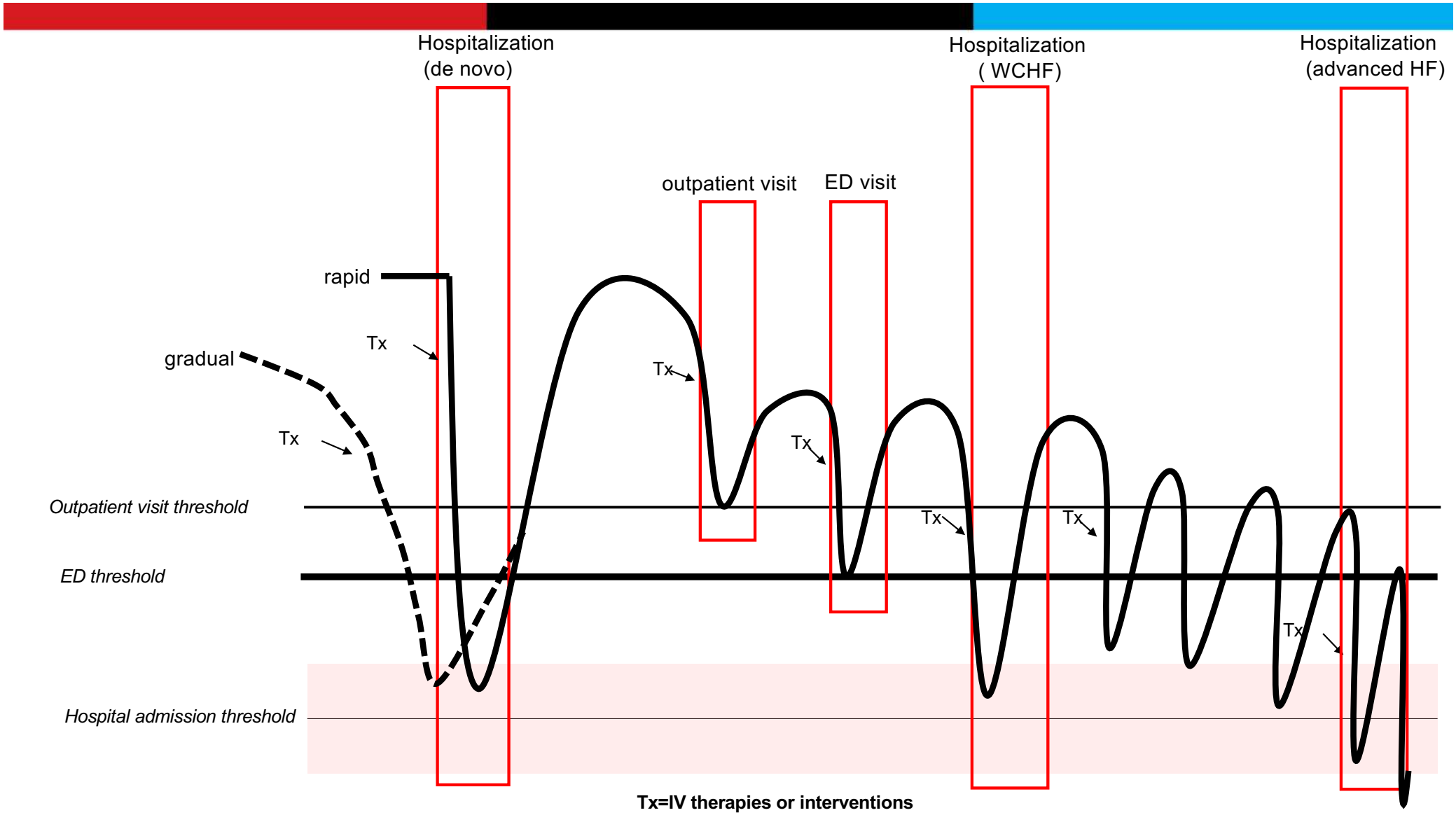
Introduction Patients with symptomatic heart failure (HF) require additive therapies and have a poor prognosis. However, patient characteristics and clinical outcome between HF patients treated in the outpatient setting vs. those who are hospitalized remain scarce.

Methods and results The BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) included 2516 patients with symptoms and/or signs of HF: 1694 as inpatients and 822 as outpatients. Compared to ambulatory HF patients, inpatients had higher heart rate, urea, N-terminal pro-brain natriuretic peptide, lower blood pressure, lower estimated glomerular filtration rate, sodium, potassium, high-density lipoprotein cholesterol, had more often peripheral oedema, diabetes, anaemia, and were less often treated with beta-blockers and angiotensin-converting enzyme inhibitors (ACEi). Outpatients had a more frequent history of HF hospitalization and received more frequently beta-blockers and/or ACEi/angiotensin receptor blockers up-titrated to target doses ($P < 0.001$). Inpatients had higher rates of the primary outcome of death or HF hospitalization: incidence rate per 100 person-years of 33.4 [95% confidence interval (CI) 31.1–35.9] for inpatients vs. 18.5 (95% CI 16.4–21.0) for outpatients; adjusted hazard ratio 1.24 (95% CI 1.07–1.43). Subdividing patients into low, intermediate and high-risk categories, the primary outcome event rates were 14.3 (95% CI 12.3–16.7), 36.6 (95% CI 32.2–41.5), and 71.3 (95% CI 64.4–79.0) for inpatients vs. 8.4 (95% CI 6.6–10.6), 29.8 (95% CI 24.5–36.2), and 43.3 (95% CI 34.7–54.0) for outpatients, respectively. These findings were externally replicated.

Conclusions Marked differences were observed between inpatients and outpatients with HF. Overall, inpatients were sicker and had higher event rates. However, a substantial proportion of outpatients had similar or higher event rates compared to inpatients. These findings suggest that HF outpatients also have poor prognosis and may be the focus of future trials.

Keywords Heart failure • Trials • Entry criteria • Risk levels




Hospitalization
(de novo)
Hospitalization
(WCHF)
Hospitalization
(advanced HF)
outpatient visit
ED visit
rapid
gradual
Tx
Tx
Tx
Tx
Tx
Tx
Tx
Outpatient visit threshold
ED threshold
Hospital admission threshold
Tx=IV therapies or interventions

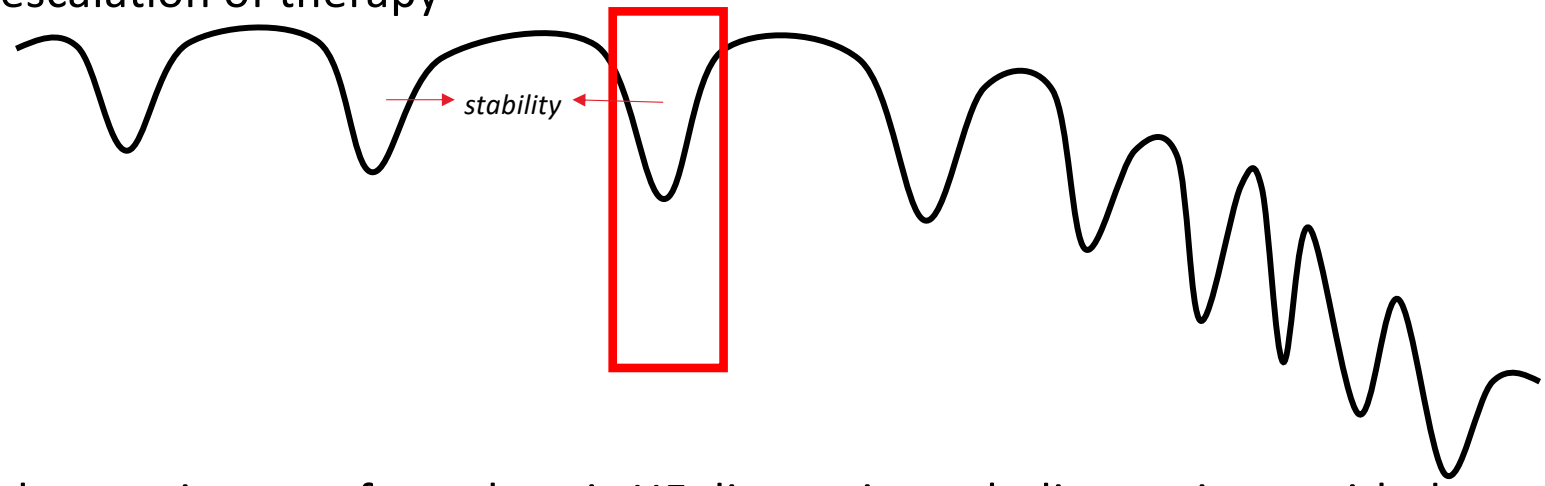
2021 HF Guidelines: AHF Definition

Acute HF (AHF) refers to rapid or gradual onset of symptoms and/or signs of HF, severe enough for the patient to seek urgent medical attention, leading to an unplanned hospital admission or an emergency department visit. Patients with AHF require urgent evaluation with subsequent **initiation or intensification of treatment**, including *IV therapies or procedures*. Compared to patients with acutely decompensated CHF, those with new onset HF may have a higher in-hospital mortality but have lower post-discharge mortality and rehospitalization.

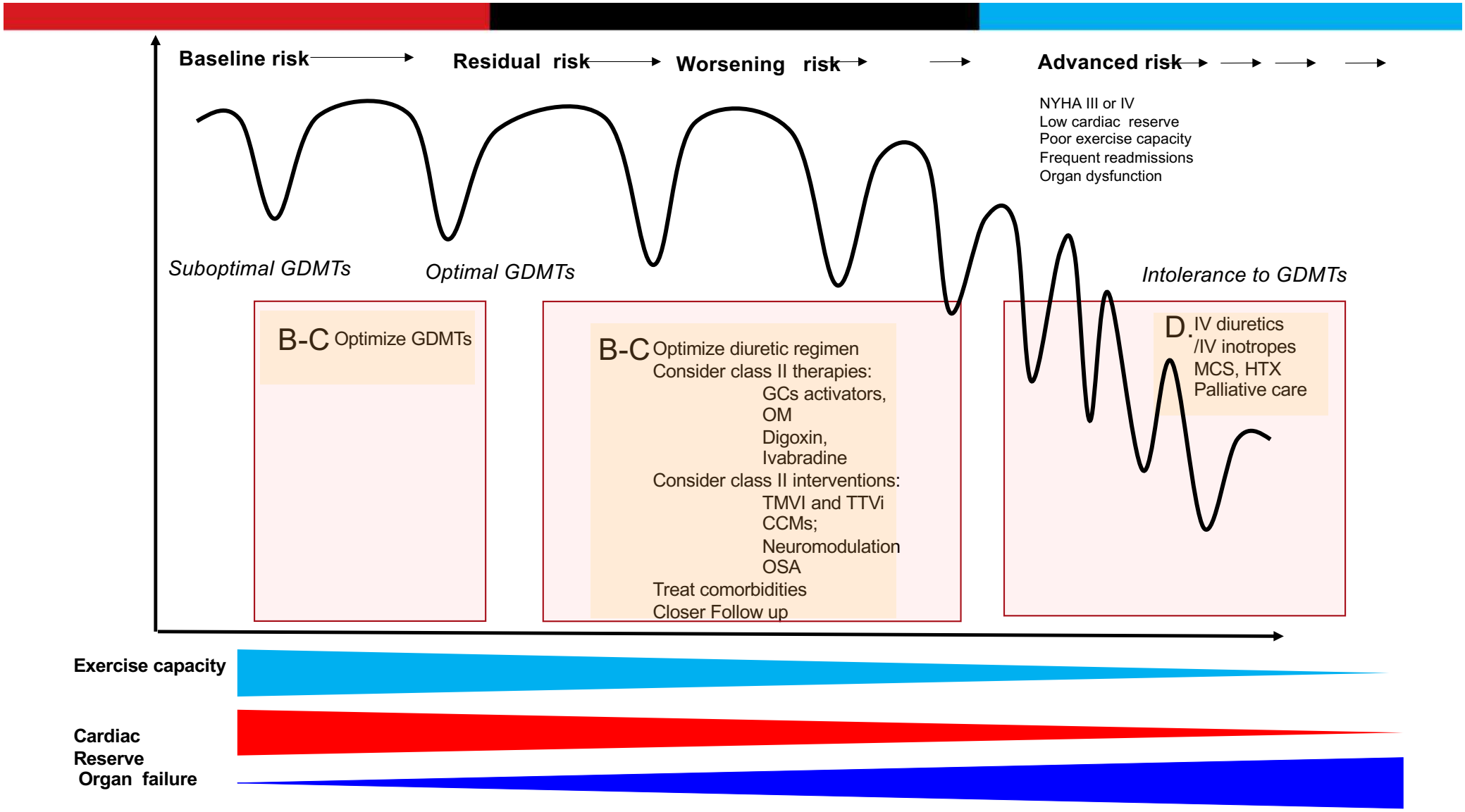
2005	2008	2012	2016
Acute heart failure is defined as the **rapid onset** of symptoms and signs secondary to abnormal cardiac function. It may occur with or without previous cardiac disease. The **cardiac dysfunction** can be related to systolic or diastolic dysfunction, to abnormalities in cardiac rhythm, or to preload and afterload mismatch. It is often life threatening and requires **urgent treatment.** AHF can present itself as acute *de novo* (new onset of acute heart failure in a patient without previously known cardiac dysfunction) or acute decompensation of chronic HF.	Acute heart failure (AHF) is defined as a **rapid onset or change** in the signs and symptoms of HF, resulting in the need for **urgent therapy**. AHF may be either *new HF or worsening* of pre-existing chronic HF. Patients may present as a medical emergency such as acute pulmonary oedema. The **cardiac dysfunction** may be related to ischaemia, abnormalities in cardiac rhythm, valvular dysfunction, pericardial disease, increased filling pressures or elevated systemic resistance.	Acute heart failure (AHF) is the term used to describe the **rapid onset of, or change** in, symptoms and signs of HF. It is a **life- threatening** condition that requires immediate medical attention and usually leads to **urgent admission to hospital**. In most cases, AHF arises as a result of deterioration in patients with a previous diagnosis of HF (either HF-REF or HF-PEF), and all of the aspects of chronic management described in these guidelines apply fully to these patients. AHF may also be the first presentation of HF *('de novo' AHF)*.	AHF refers to **rapid onset or worsening** of symptoms and/or signs of HF. It is a **life-threatening** medical condition requiring **urgent** evaluation and treatment, typically leading to **urgent hospital admission**. AHF may present as a first occurrence (*de novo*) or, more frequently, as a consequence of acute decompensation of chronic HF, and may be caused by primary **cardiac dysfunctio**n or precipitated by extrinsic factors, often in patients with chronic HF.

Definition of WHF

- deterioration of HF signs and symptoms after a period of stability that requires escalation of therapy



- the requirement for a chronic HF diagnosis, excluding patients with de novo or recently diagnosed HF.
- Irrespective of venue of care


Baseline risk
Residual risk
Worsening risk
Advanced risk
NYHA III or IV
Low cardiac reserve
Poor exercise capacity
Frequent readmissions
Organ dysfunction
Suboptimal GDMTs
Optimal GDMTs
Intolerance to GDMTs
B-C Optimize GDMTs
B-C Optimize diuretic regimen
Consider class II therapies:
GCs activators, OM
Digoxin, Ivabradine
Consider class II interventions:
TMVI and TTVi
CCMs;
Neuromodulation
OSA
Treat comorbidities
Closer Follow up
D. IV diuretics /IV inotropes
MCS, HTX
Palliative care
Exercise capacity
Cardiac Reserve
Organ failure

Definition of WHF

- Deterioration of HF signs and symptoms after a period of stability that requires escalation of therapy
- the requirement for a chronic HF diagnosis, excluding patients with de novo or recently diagnosed HF.
- Irrespective of venue of care: outpatient, ED or hospitalization
- **Hospitalization for HF is a sentinel event that signals worse prognosis but also provides key opportunities to redirect the disease trajectory**

Multicenter Prospective Observational Study on Acute and Chronic Heart Failure

One-Year Follow-up Results of IN-HF (Italian Network on Heart Failure) Outcome Registry

Luigi Tavazzi, MD; Michele Senni, MD; Marco Metra, MD; Marco Gorini, MS; Giuseppe Cacciatore, MD; Alessandra Chinaglia, MD; Andrea Di Lenarda, MD; Andrea Mortara, MD; Fabrizio Oliva, MD; Aldo P. Maggioni, MD; on the behalf of IN-HF (Italian Network on Heart Failure) Outcome Investigators*

Background—Clinical observational studies on heart failure (HF) deal mostly with hospitalized patients, few with chronic outpatients, all with no or limited longitudinal observation.

Methods and Results—This is a multicenter, nationwide, prospective observational trial on a population of 5610 patients, 1855 hospitalized for acute HF (AHF) and 3755 outpatients with chronic HF (CHF), followed up for 1 year. The cumulative total mortality rate at 1 year was 24% in AHF (19.2% in 797 patients with de novo HF and 27.7% in 1058 with worsening HF) and 5.9% in CHF. Cardiovascular deaths accounted for 73.1% and 65.3% and HF deaths for 42.4% and 40.5% of total deaths in AHF and CHF patients, respectively. One-year hospitalization rates were 30.7% in AHF and 22.7% in CHF patients. Among the independent predictors of 1-year all-cause death, age, low systolic blood pressure, anemia, and renal dysfunction were identified in both acute and chronic patients. A few additional variables were significant only in AHF (signs of cerebral hypoperfusion, low serum sodium, chronic obstructive pulmonary disease, and acute pulmonary edema), whereas others were observed only in CHF patients (lower body mass index, higher heart rate, New York Heart Association class, large QRS, and severe mitral regurgitation).

Conclusions—In this contemporary data set, patients with CHF had a relatively low mortality rate compared with those with AHF. Rates of adverse outcomes in patients admitted for AHF remain very high either in-hospital or after discharge. Most deaths were cardiovascular in origin and ≈40% of deaths were directly related to HF. (***Circ Heart Fail.*** **2013;6:473-481.**)

Key Words: epidemiology ■ heart failure ■ prognosis

During the last decades, the interest in observational research by medical societies, health authorities, and drug or device companies has been rising for several reasons, including monitoring the incorporation of new diagnostic–therapeutic processes, and guidelines' recommendations, need of awareness of met and unmet clinical needs, and use of the observational data as platform for continuous medical education and health authorities' policy and strategy.

Clinical Perspective on p 481

Several studies have been conducted in patients with heart failure (HF), particularly in those with acute HF (AHF), with rather inconsistent results.[1–14] For instance, the in-hospital mortality rate ranged from <3%[1] to >20%.[3] Moreover, most studies had a transversal design with no or limited longitudinal observation, and no previous registry included cohorts of patients with AHF and chronic HF (CHF) enrolled in the same setting.

In Italy, through the series of the large cooperative GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) randomized trials and nationwide observational studies, a vast experience on pragmatic clinical research has been achieved by cardiology centers, and an expert trial coordinating center has been developed. In consideration of the numerous limitations of available surveys and registries on HF mentioned above and the availability of an expert national clinical research structure, a nationwide registry was performed with the following main characteristics and

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From the GVM Hospitals of Care and Research, Ettore Sansavini Health Science Foundation, Cotignola, Italy (L.T.); USC Cardiovascular Medicine, Papa Giovanni XXIII Hospital, Bergamo, Italy (M.S.); Department of Cardiology, University and Spedali Civili, Brescia, Italy (M.M.); ANMCO Research Center, Florence, Italy (M.G., A.P.M.); Department of Cardiology, San Giovanni—Addolorata Hospital, Rome, Italy (G.C.); Cardiology Department, Maria Vittoria Hospital, Torino, Italy (A.C.); Cardiovascular Center, Azienda Servizi Sanitari n. 1 Triestina, Trieste, Italy (A.D.L.); Department of Clinical Cardiology and Heart Failure, Policlinico di Monza, Monza, Italy (A.M.); and Cardiologia 2-Heart Failure and Heart Transplant Program, "A. De Gasperis" Cardiovascular Department, Niguarda Hospital, Milan, Italy (F.O.).

*A list of participating centers and investigators is given in the Appendix.

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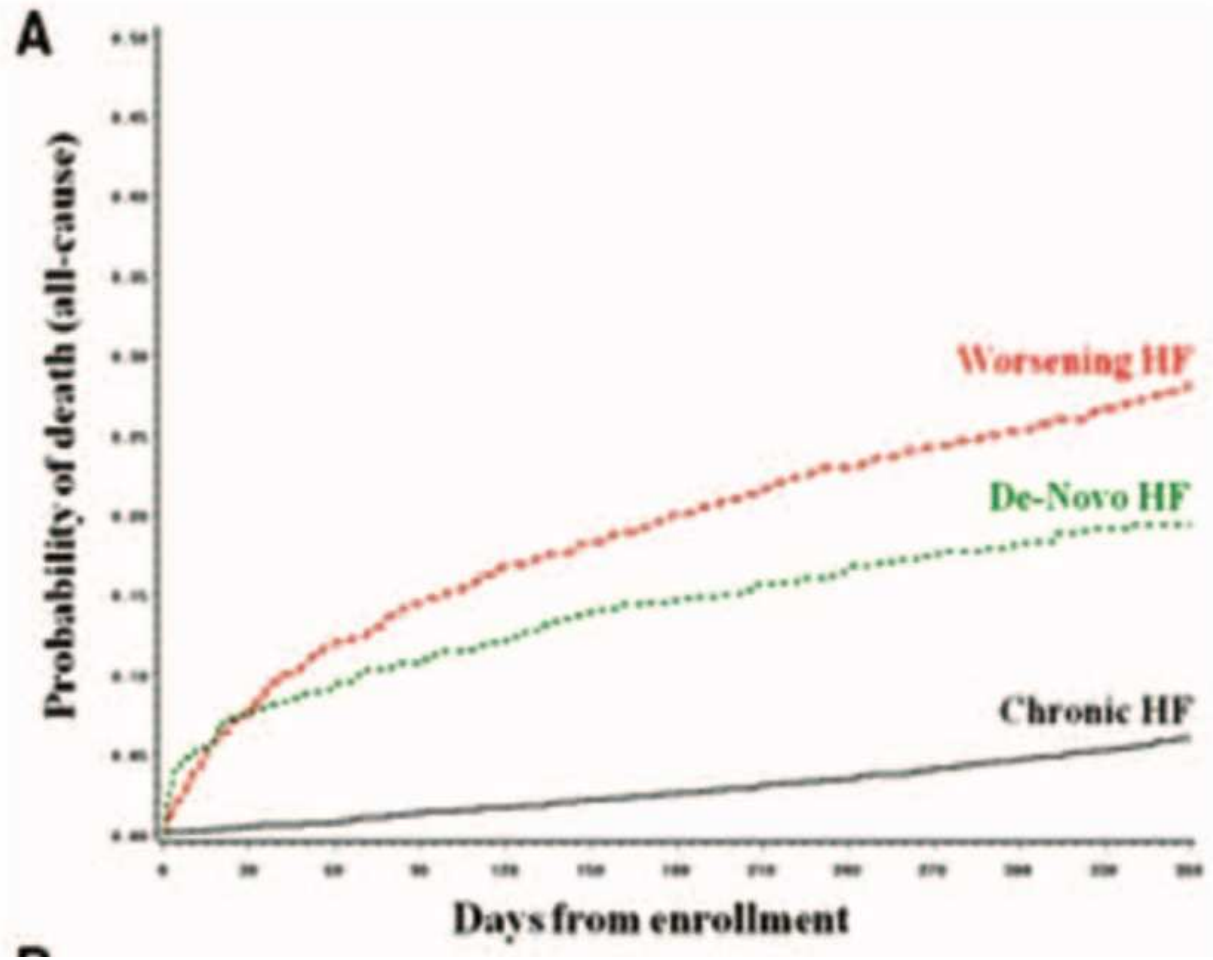


Hospitalization for Recently Diagnosed Versus Worsening Chronic Heart Failure

From the ASCEND-HF Trial

Stephen J. Greene, MD,[a,b] Adrian F. Hernandez, MD, MHS,[a,b] Allison Dunning, MS,[a] Andrew P. Ambrosy, MD,[a,b] Paul W. Armstrong, MD,[c] Javed Butler, MD, MPH, MBA,[d] Lukasz P. Cerbin, MD,[e] Adrian Coles, PhD,[a] Justin A. Ezekowitz, MBBCh, MSc,[c] Marco Metra, MD,[f] Randall C. Starling, MD, MPH,[g] John R. Teerlink, MD,[h] Adriaan A. Voors, MD, PhD,[i] Christopher M. O'Connor, MD,[j] Robert J. Mentz, MD[a,b]

ABSTRACT

BACKGROUND It is unclear how patients hospitalized for acute heart failure (HF) who are long-term chronic HF survivors differ from those with more recent HF diagnoses.

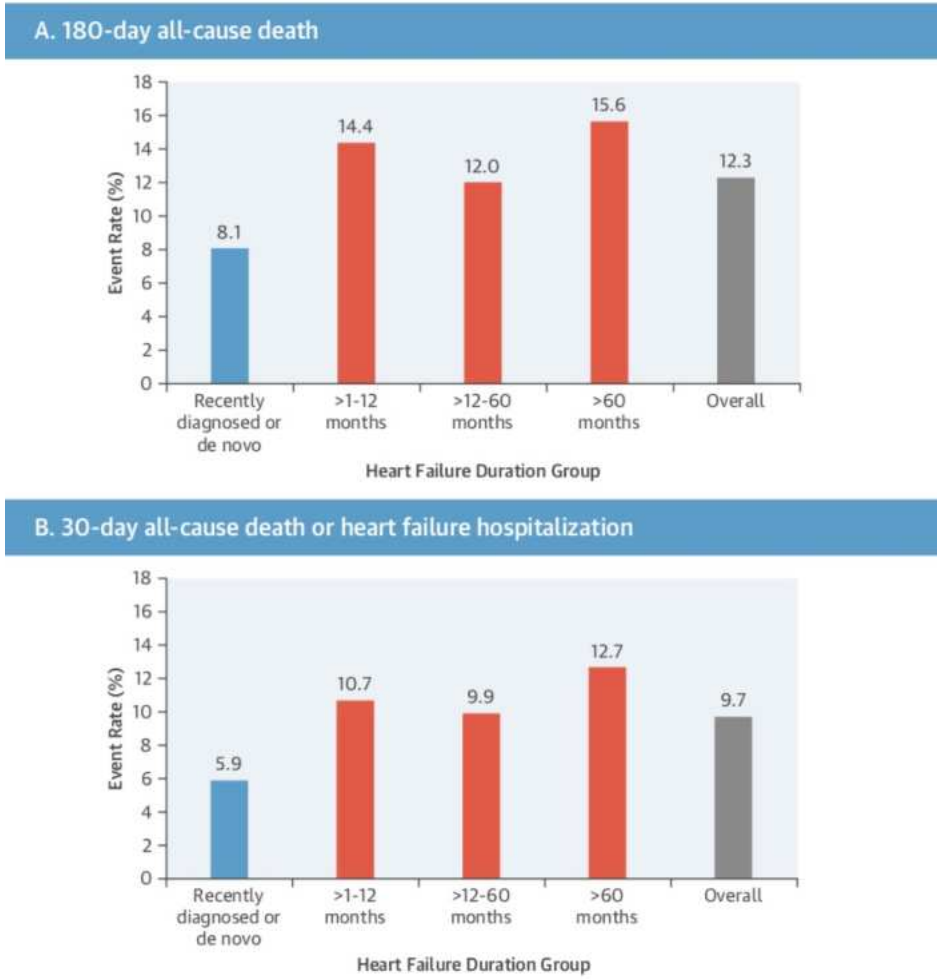
OBJECTIVES The goal of this study was to evaluate the influence of HF chronicity on acute HF patient profiles and outcomes.

METHODS The ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial randomized 7,141 hospitalized patients with acute HF with reduced or preserved ejection fraction (EF) to receive nesiritide or placebo in addition to standard care. The present analysis compared patients according to duration of HF diagnosis before index hospitalization by using pre-specified cutoffs (0 to 1 month [i.e., "recently diagnosed"], >1 to 12 months, >12 to 60 months, and >60 months).

RESULTS Overall, 5,741 (80.4%) patients had documentation of duration of HF diagnosis (recently diagnosed, n = 1,536; >1 to 12 months, n = 1,020; >12 to 60 months, n = 1,653; and >60 months, n = 1,532). Across HF duration groups, mean age ranged from 64 to 66 years, and mean ejection fraction ranged from 29% to 32%. Compared with patients with longer HF duration, recently diagnosed patients were more likely to be women with nonischemic HF etiology, higher baseline blood pressure, better baseline renal function, and fewer comorbidities. After adjustment, compared with recently diagnosed patients, patients with longer HF duration were associated with more persistent dyspnea at 24 h (>1 to 12 months, odds ratio [OR]: 1.20; 95% confidence interval [CI]: 0.97 to 1.48; >12 to 60 months, OR: 1.34; 95% CI: 1.11 to 1.62; and >60 months, OR: 1.31; 95% CI: 1.08 to 1.60) and increased 180-day mortality (>1 to 12 months, hazard ratio [HR]: 1.89; 95% CI: 1.35 to 2.65; >12 to 60 months, HR: 1.82; 95% CI: 1.33 to 2.48; and >60 months, HR: 2.02; 95% CI: 1.47 to 2.77). The influence of HF duration on mortality was potentially more pronounced among female patients (interaction p = 0.05), but did not differ according to age, race, prior ischemic heart disease, or ejection fraction (all interactions, p ≥ 0.23).

CONCLUSIONS In this acute HF trial, patient profile differed according to duration of the HF diagnosis. A diagnosis of HF for ≤1 month before hospitalization was independently associated with greater early dyspnea relief and improved post-discharge survival compared to patients with chronic HF diagnoses. The distinction between de novo or recently diagnosed HF and worsening chronic HF should be considered in the design of future acute HF trials. (A Study Testing the Effectiveness of Nesiritide in Patients With Acute Decompensated Heart Failure; NCT00475852) (J Am Coll Cardiol 2017;69:3029–39)

CENTRAL ILLUSTRATION **Hospitalization for De Novo or Recently Diagnosed HF Versus Worsening Chronic HF: Distinct Patient Populations**



Greene, S.J. et al. J Am Coll Cardiol. 2017;69(25):3029–39.

ESC European Society of Cardiology

European Journal of Heart Failure (2020)
doi:10.1002/ejhf.1800

RESEARCH ARTICL

Readmission and death in patients admitted with new-onset versus worsening of chronic heart failure: insights from a nationwide cohort

Jawad H. Butt[1,2]*, Emil L. Fosbøl[1], Thomas A. Gerds[3,4], Charlotte Andersson[5], John J.V. McMurray[6], Mark C. Petrie[6], Finn Gustafsson[1], Christian Madelaire[5], Søren Lund Kristensen[5], Gunnar H. Gislason[4,5,7], Christian Torp-Pedersen[8], Lars Køber[1,7], and Morten Schou[2,7]

[1]Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [2]Department of Cardiology, Herlev and Gentofte University Hospital, Herlev, Denmark; [3]Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark; [4]The Danish Heart Foundation, Copenhagen, Denmark; [5]Department of Cardiology, Herlev and Gentofte University Hospital, Gentofte, Denmark; [6]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [7]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; and [8]Department of Cardiology, Nordsjællands Hospital, Hillerød, Denmark

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Aim To examine the rates of all-cause mortality and heart failure (HF) readmission in patients hospitalized with decompensated HF according to HF duration – new-onset HF and worsening of chronic HF.

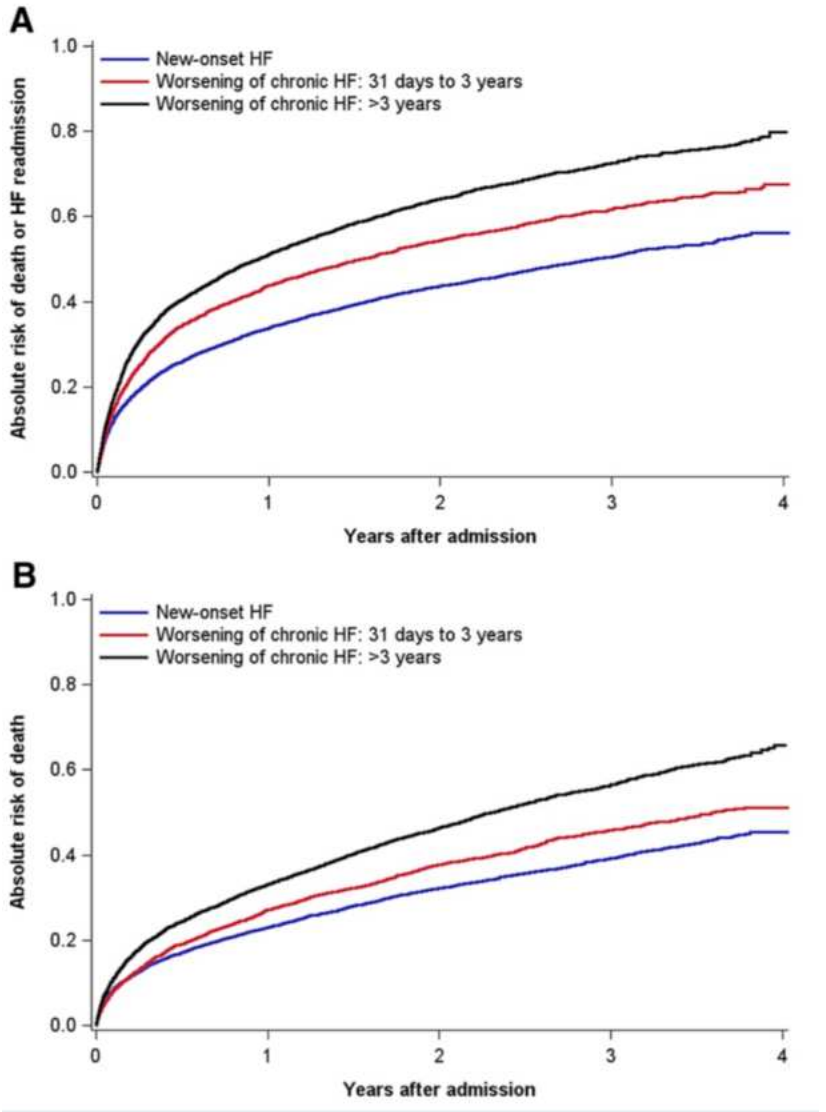
Methods and results In this nationwide observational cohort study, 17 176 patients were included at first hospital admission for HF in the period 2013–2015 using data from Danish nationwide registries. In total, 8860 (51.6%) patients were admitted with new-onset HF and 8316 (48.4%) with worsening of chronic HF. Patients with worsening of chronic HF were characterized by a greater comorbidity burden compared with patients with new-onset HF. The rates of outcomes

Danish nationwide registry; 17 176 patients

the rate of the composite endpoint was lower in patients with AF compared with those without (HR 0.91, 95% CI 0.85–0.96) (*P*-value for interaction <0.001).

Conclusions Among patients hospitalized with decompensated HF, worsening of chronic HF was associated with poorer outcomes compared with new-onset HF.

Keywords Acute heart failure • New-onset heart failure • Worsening of chronic heart failure • Heart failure readmission • All-cause mortality • Epidemiology



Congestive Heart Failure

Repeated hospitalizations predict mortality in the community population with heart failure

Soko Setoguchi, MD, DrPH,[a] Lynne Warner Stevenson, MD,[b] and Sebastian Schneeweiss, MD, ScD[a] *Boston, MA*

Background Identification of patients at high risk of death is critical for appropriate management of patients and health care resources. The impact of repeated heart failure (HF) hospitalization on mortality has not been studied for a large community population with HF. We aimed to characterize survival of patients in relation to the number of HF hospitalizations.

Method Using the health care utilization databases, we identified a cohort of patients with a first hospitalization for HF among all residents of British Columbia between 2000 and 2004. Survival time was measured after patients' first and each subsequent HF hospitalization. Kaplan-Meier cumulative mortality curves were constructed after each subsequent HF hospitalization. Hazard ratios for the number of HF hospitalizations were estimated using a multivariate Cox regression adjusting for major comorbidities.

Results Of 14374 patients hospitalized for HF, 7401 died during the 24766 person-years of follow-up. Mortality significantly increased after each HF hospitalization. After adjusting for age, sex, and major comorbidities, the number of HF hospitalizations was a strong predictor of all-cause death. Median survival after the first, second, third, and fourth hospitalization was 2.4, 1.4, 1.0, and 0.6 years. Advanced age, renal disease, and history of cardiac arrest attenuated the impact of the number of HF hospitalizations.

Conclusions The number of HF hospitalizations is a strong predictor of mortality in community HF patients. This simple predictor of mortality in HF patients should help triage management and resources for HF and trigger patient planning for prognosis. (Am Heart J 2007;154:260-6.)

The prevalence and economic burden of heart failure (HF) have been increasing during the past several decades,[1,2] with an estimated 5 million people currently diagnosed.[3] The number of hospitalizations with HF as the first listed diagnosis has increased steadily over the last 3 decade
2003.[4] Heart
readmission
Heart failur
1-year mortal
after the first
new manage
implantable

14374 patients

assist devices, and transplantation, have improved survival[5] and quality of life for selected patients with HF, health care systems face difficult decisions regarding the allocation of these and other limited resources within the broader community. Health care staffs need guid-
ne discussions with individual patients and
out prognosis and plans for the end of life.
dies examining predictors of survival in HF
ingle-center experiences or trial populations
exclusions that limit enrollment of older
ith HF.[7,9-11] A recent study suggested that one
IF hospitalization is a predictor of death.[9]
in the community population, the first HF hospitalization is often the time of first HF diagnosis, after which evaluation and treatment are initiated. The mortality of patients with HF in relation to the number of additional HF hospitalizations has not been studied in a community population. The aim of the current study is to characterize the mortality of HF patients with repeated hospitalizations.

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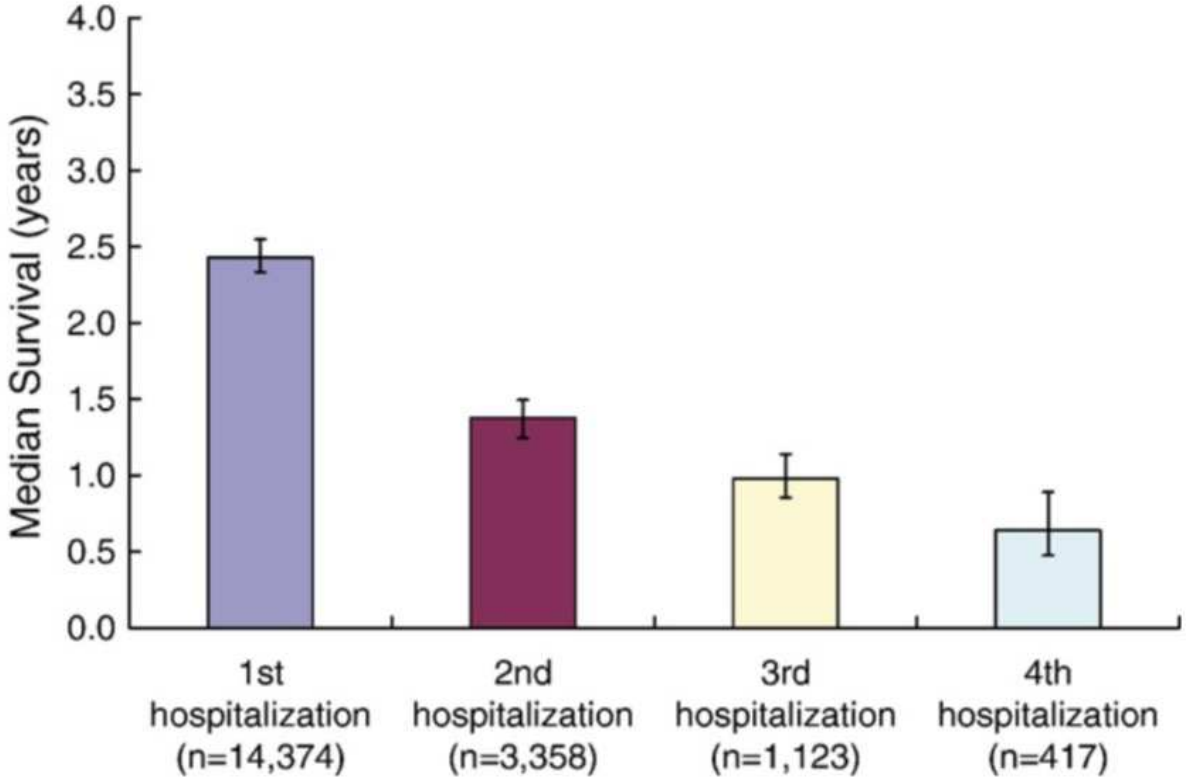
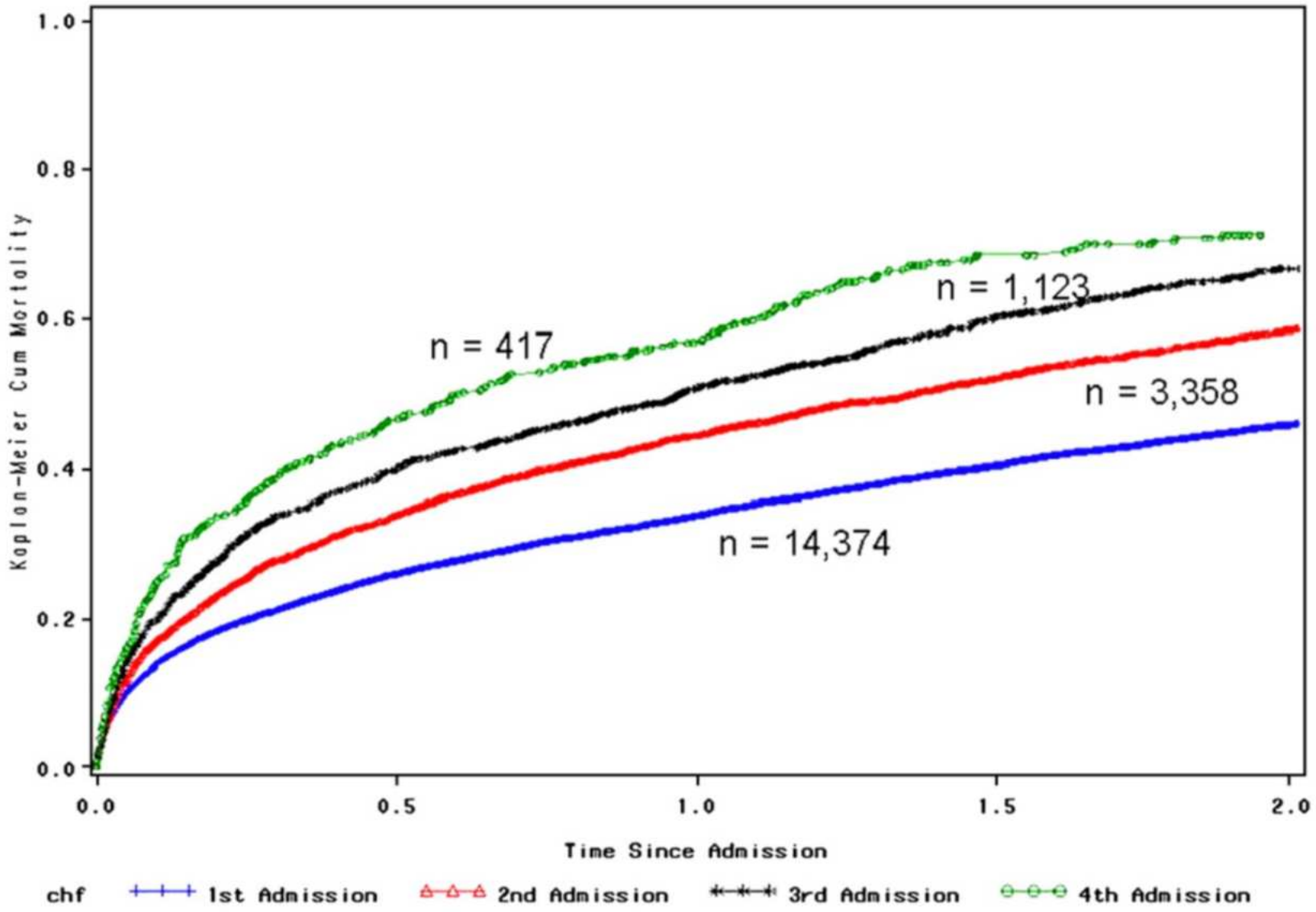
Methods

Data sources

We used health care utilization databases that contain information on discharge abstract, outpatient diagnoses, and



Median survival (50% mortality) and 95% confidence limits in patients with HF after each HF hospitalization.


1.0
0.8
0.6
0.4
0.2
0.0
Koplon-Meier Cum Mortolity
n = 417
n = 1,123
n = 3,358
n = 14,374
0.0
0.5
1.0
1.5
2.0
Time Since Admission
chf
1st Admission
2nd Admission
3rd Admission
4th Admission

ESC European Society of Cardiology

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RESEARCH ARTICL

Defining a 'frequent admitter' phenotype among patients with repeat heart failure admissions

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Aims We aimed to identify a 'frequent admitter' phenotype among patients admitted for acute decompensated heart failure (HF).

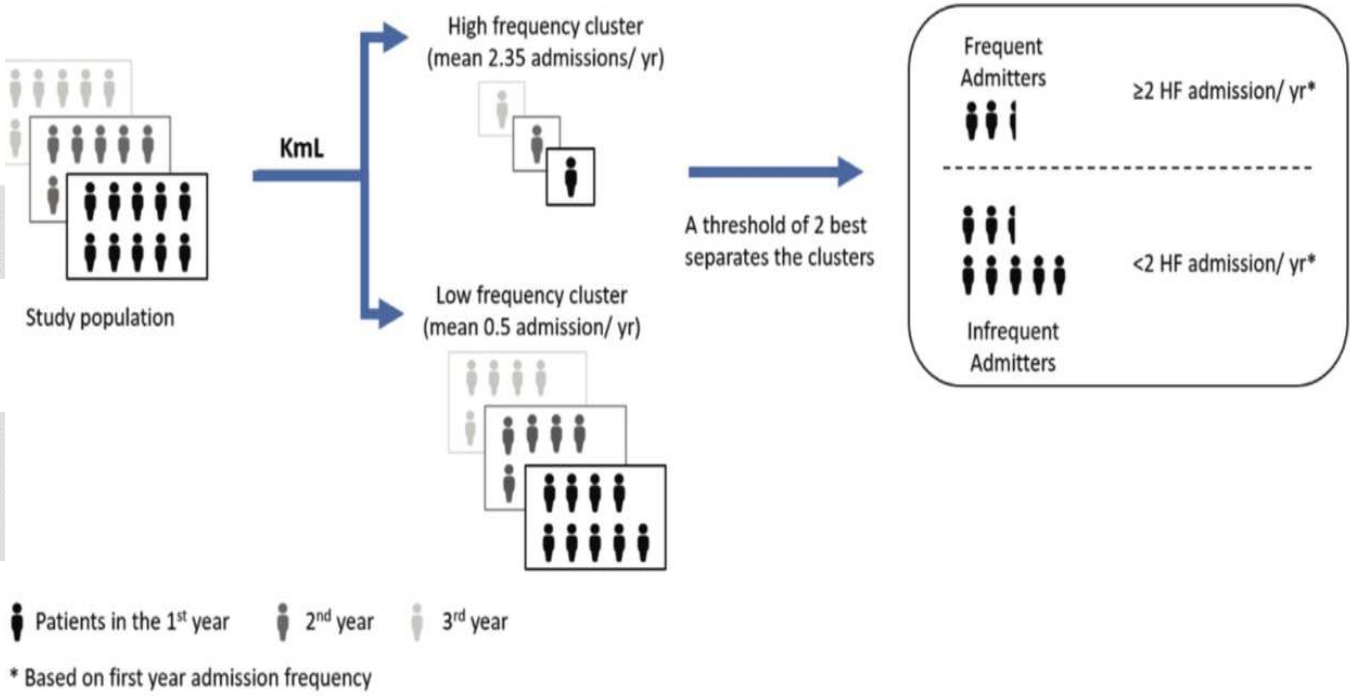
Methods and results We studied 10 363 patients in a population-based prospective HF registry (2008–2012), segregated into clusters based on their 3-year HF readmission frequency trajectories. Using receiver-operating characteristic analysis, we

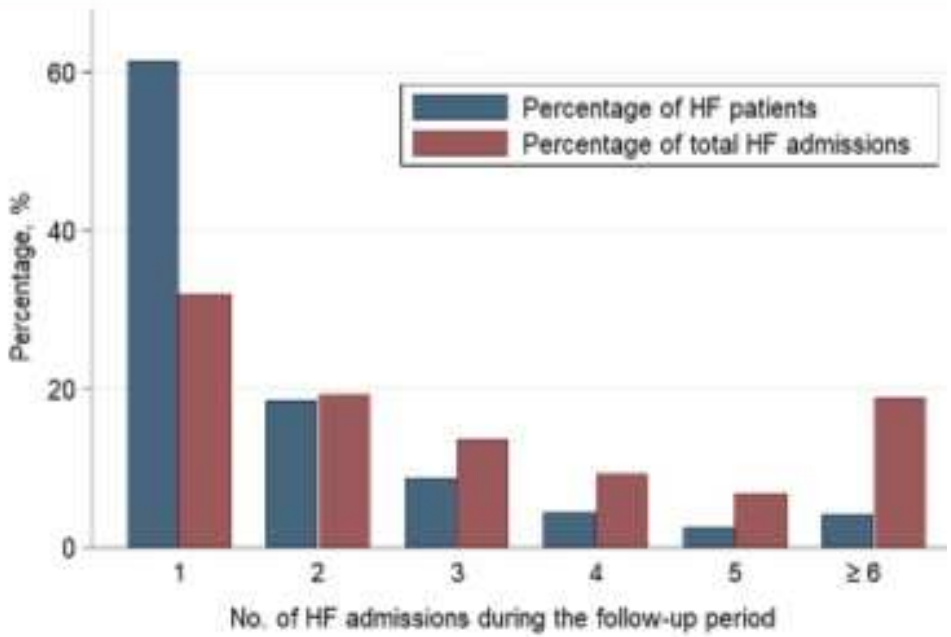
rates of advanced care utilization, frequent admitters had longer length of stay (median 4.3 vs. 4.0 days), higher annual inpatient costs (€ 7015 vs. € 2967) and higher all-cause mortality at 3 years compared to the non-frequent admitters (adjusted odds ratio 2.33, 95% confidence interval 2.11–2.58; $P < 0.001$).

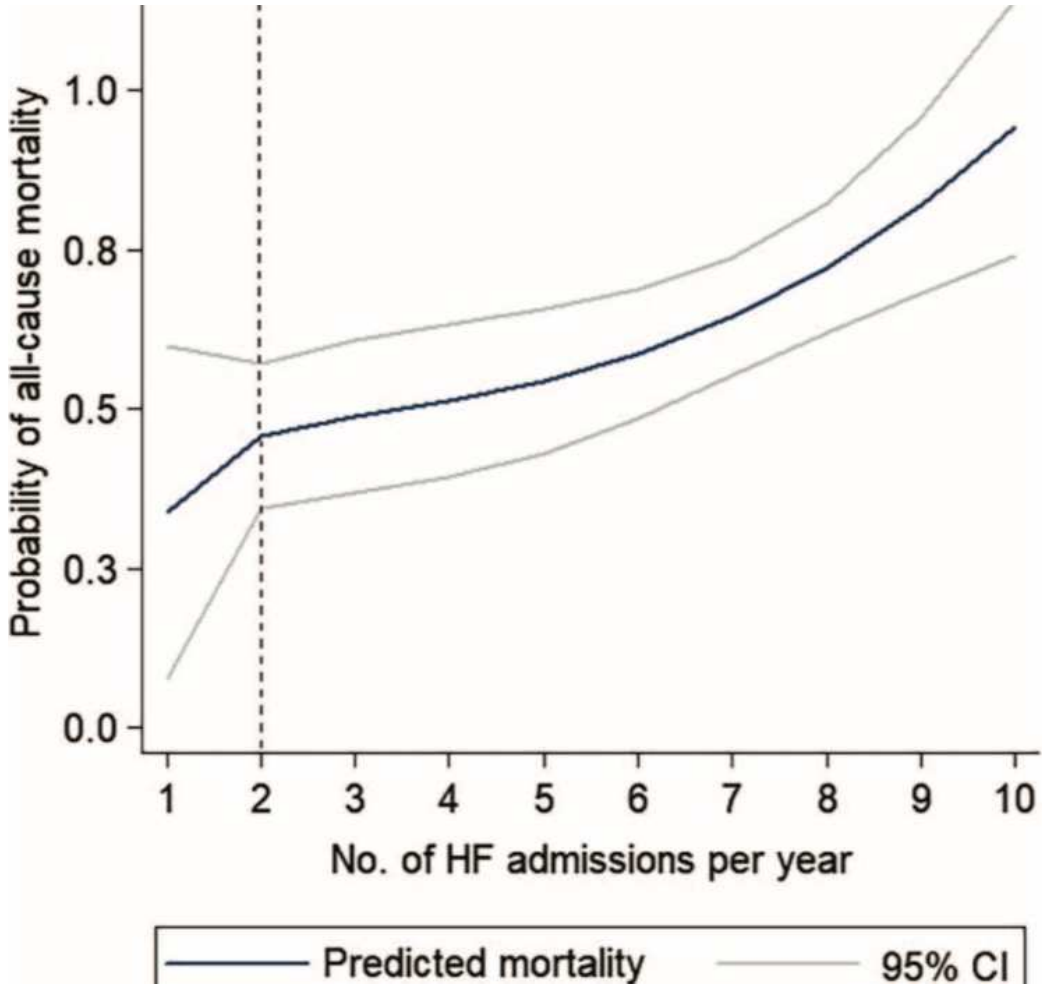
Conclusion 'Frequent admitters' have distinct clinical characteristics and worse outcomes compared to non-frequent admitters. This study may provide a means of anticipating the HF readmission burden and thereby aid in healthcare resource distribution relative to the HF admission frequency phenotype.

Keywords Acute heart failure • Readmission • Frequent admitter • Longitudinal clustering

10363 patients in a prospective HF registry




Percentage of HF patients
Percentage of total HF admissions
Percentage, %
60
40
20
0
1
2
3
4
5
≥6
No. of HF admissions during the follow-up period


Probability of all-cause mortality
1.0
0.8
0.5
0.3
0.0
1
2
3
4
5
6
7
8
9
10
No. of HF admissions per year
Predicted mortality
95% CI

Adv Ther (2020) 37:4015–4032
https://doi.org/10.1007/s12325-020-01456-1

ORIGINAL RESEARCH

Clinical and Economic Burden of Chronic Heart Failure and Reduced Ejection Fraction Following a Worsening Heart Failure Event

Javed Butler · Laurence M. Djatche · Baanie Sawhney · Sreya Chakladar · Lingfeng Yang · Joanne E. Brady · Mei Yang

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ABSTRACT

Introduction: A worsening heart failure event (WHFE) is defined as progressively escalating heart failure signs/symptoms requiring intravenous diuretic treatment or hospitalization. No studies have compared the burden of chronic heart failure with reduced ejection fraction (HFrEF) following a WHFE versus stable disease to inform healthcare decision makers.

Methods: A retrospective study using the IBM® MarketScan® Commercial Database included patients younger than 65 years of age with HFrEF (one inpatient or two outpatient claims of systolic HF or one outpatient claim of systolic HF plus one outpatient claim of any HF). The first claim for HFrEF during 2016 was the index date. Patients were followed for the first 12 months after the index date (the worsening assessment period) to identify a WHFE, and for an additional 12 months or until the end of continuous enrollment (the post-worsening assessment period). Mean per patient per month (PPPM) health care resource use (HCRU) and costs were compared between patients following a WHFE and stable patients during the two periods using generalized linear models adjusting for patient characteristics.

Results: Of 16,646 patients with chronic HFrEF, 26.8% developed a WHFE. Adjusted all-cause hospitalizations (0.16 vs. 0.02 PPPM, $P < 0.0001$), outpatient visits (3.54 vs. 2.73 PPPM, $P < 0.0001$), and emergency department visits (0.25 vs. 0.06 PPPM, $P < 0.0001$) were higher in patients following a WHFE than stable patients during the worsening assessment period. Similar differences in HCRU were observed between the two cohorts during the post-worsening assessment period. Mean total adjusted cost of care PPPM was $8657 in patients with HFrEF following a WHFE versus $2195 in stable patients during the worsening assessment period, and $6809 versus $2849, respectively, during the post-worsening assessment period.

Conclusion: HCRU and costs were significantly greater in patients with chronic HFrEF following a WHFE compared to those who remained

Digital Features To view digital features for this article go to https://doi.org/10.6084/m9.figshare.12689600.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12325-020-01456-1) contains supplementary material, which is available to authorized users.

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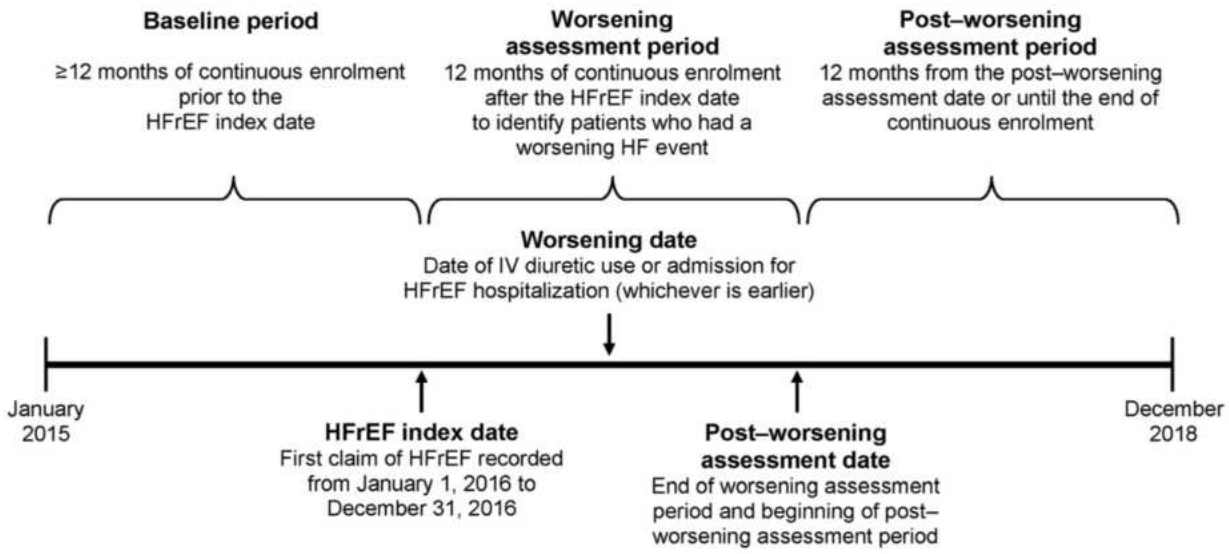
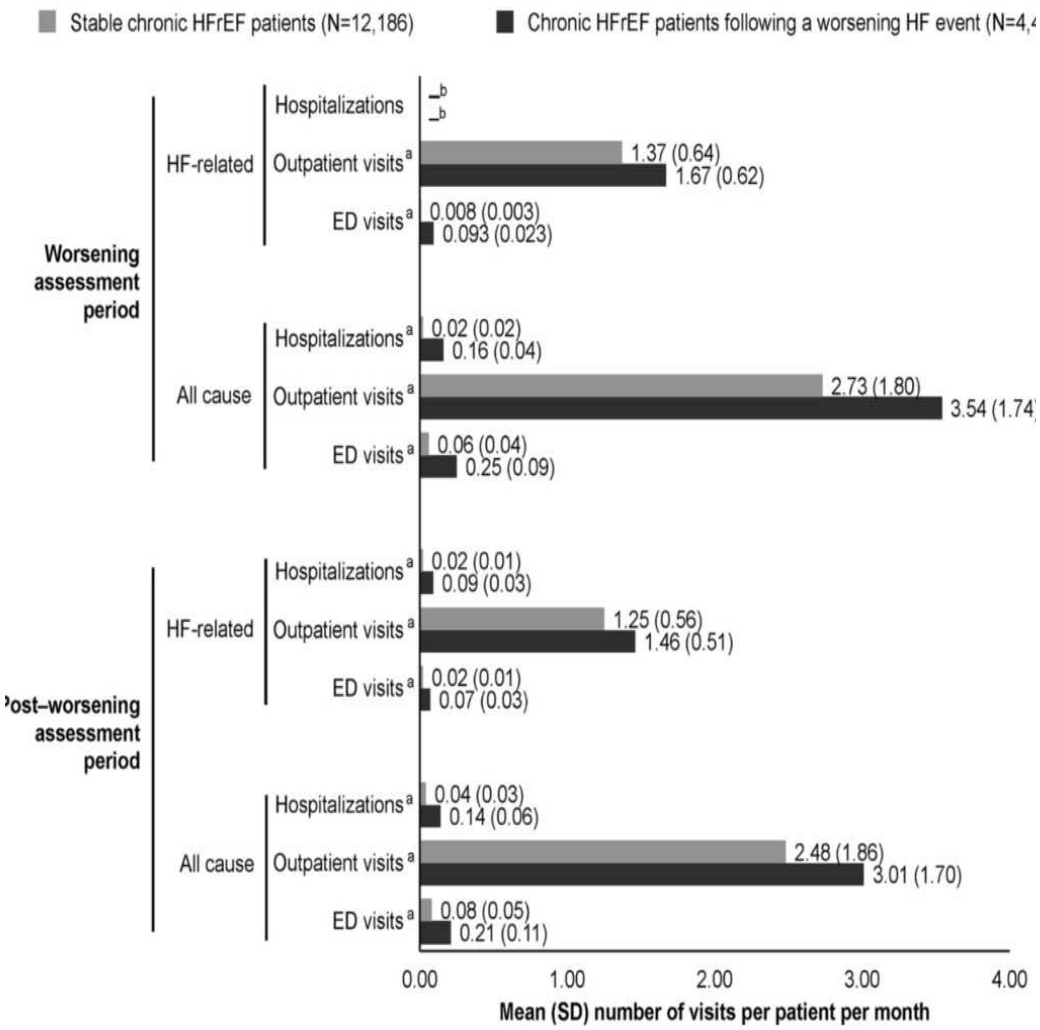
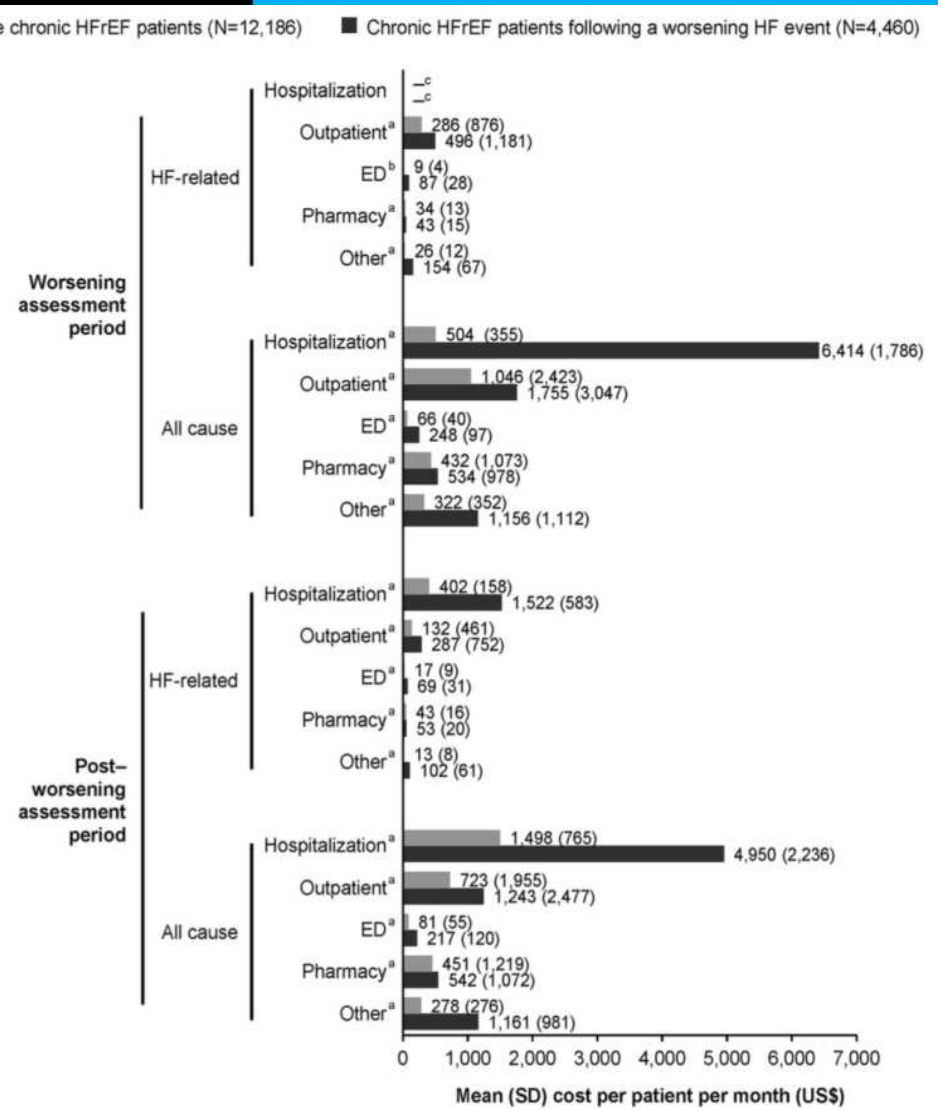
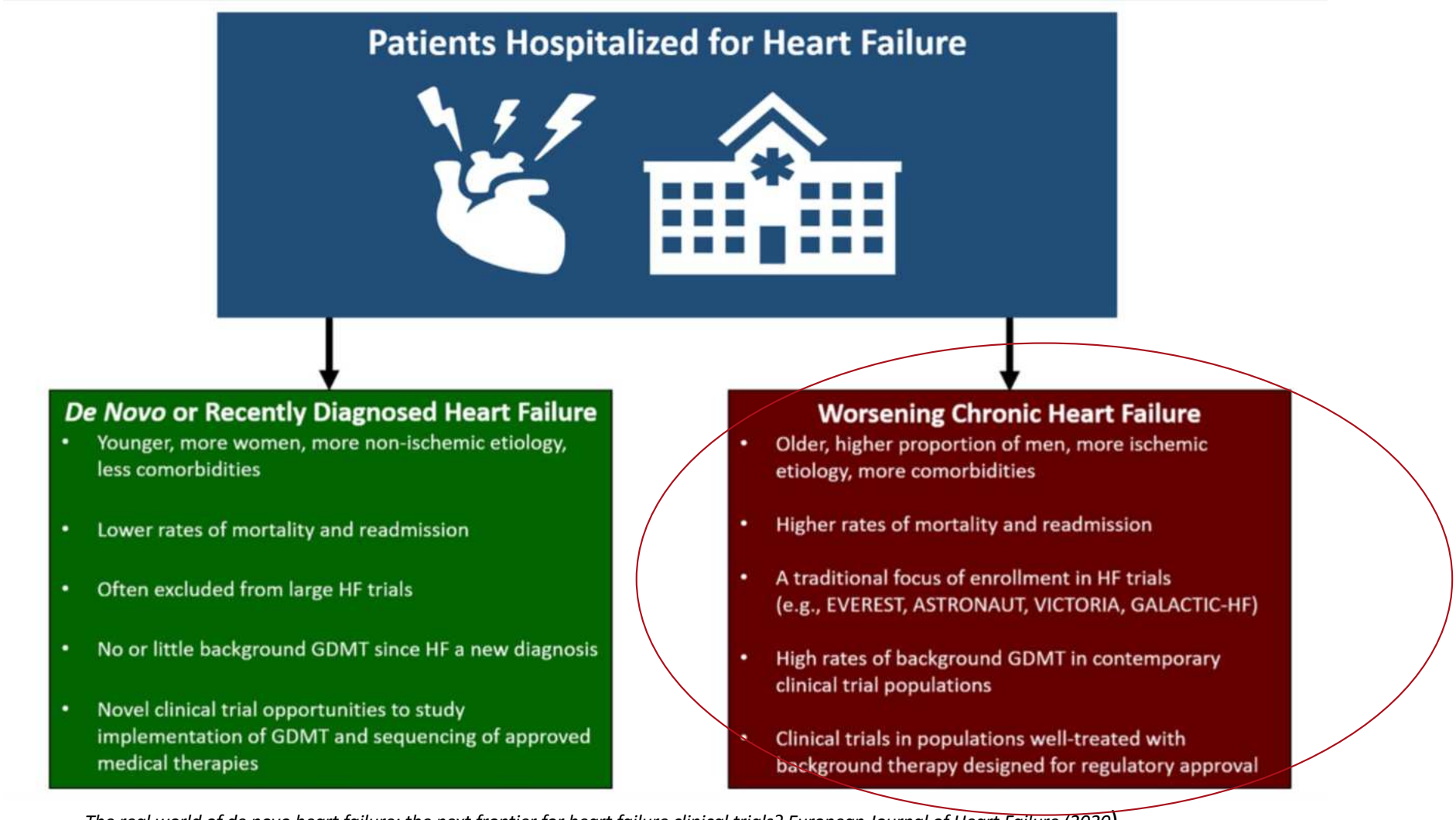



Stable chronic HFrEF patients (N=12,186)
Chronic HFrEF patients following a worsening HF event (N=4,
Worsening assessment period
Post–worsening assessment period
HF-related
All cause
Hospitalizations
Outpatient visits
ED visits
1.37 (0.64)
1.67 (0.62)
0.008 (0.003)
0.093 (0.023)
0.02 (0.02)
0.16 (0.04)
2.73 (1.80)
3.54 (1.74
0.06 (0.04)
0.25 (0.09)
0.02 (0.01)
0.09 (0.03)
1.25 (0.56)
1.46 (0.51)
0.02 (0.01)
0.07 (0.03)
0.04 (0.03)
0.14 (0.06)
2.48 (1.86)
3.01 (1.70)
0.08 (0.05)
0.21 (0.11)
0.00
1.00
2.00
3.00
4.00
Mean (SD) number of visits per patient per month


Stable chronic HFrEF patients (N=12,186)
Chronic HFrEF patients following a worsening HF event (N=4,460)
Worsening assessment period
Post–worsening assessment period
HF-related
All cause
Hospitalization
Outpatient
ED
Pharmacy
Other
286 (876)
496 (1,181)
9 (4)
87 (28)
34 (13)
43 (15)
26 (12)
154 (67)
504 (355)
6,414 (1,786)
1,046 (2,423)
1,755 (3,047)
66 (40)
248 (97)
432 (1,073)
534 (978)
322 (352)
1,156 (1,112)
402 (158)
1,522 (583)
132 (461)
287 (752)
17 (9)
69 (31)
43 (16)
53 (20)
13 (8)
102 (61)
1,498 (765)
4,950 (2,236)
723 (1,955)
1,243 (2,477)
81 (55)
217 (120)
451 (1,219)
542 (1,072)
278 (276)
1,161 (981)
0
1,000
2,000
3,000
4,000
5,000
6,000
7,000
Mean (SD) cost per patient per month (US$)



The real world of de novo heart failure: the next frontier for heart failure clinical trials? European Journal of Heart Failure (2020)

Epidemiology of Heart Failure in Europe

Aldo Pietro Maggioni, MD

KEYWORDS

• Heart failure • Epidemiology • Prognosis • Guidelines

KEY POINTS

- Heart failure (HF) is a major public health problem. Patients admitted for acute heart failure (AHF) generally present with severe clinical characteristics and have a high in-hospital mortality rate as well as a prolonged length of stay, with, as a consequence, a strong socioeconomic impact.
- For this clinical condition, therapeutic developments have been scarce in the past decades. For this reason, current guidelines are not including recommendations based on solid evidences from randomized clinical trials. Prospective studies focused on different AHF phenotypes to identify new treatment strategies are necessary to positively influence the poor outcomes of these patients.
- In contrast to AHF, chronic HF was the object of several successful controlled studies conducted in the past 30 years, which encouraged the use of drugs and devices able to improve the outcomes of ambulatory patients. In this clinical setting, the efforts should be focused on the appropriate and widespread application of the treatments recommended by the current international guidelines in the real clinical practice.
- For both patients with AHF and chronic HF, observational research remains an important research tool to confirm the results of the controlled trials in the real world, to collect periodic reports, and to assess the quality-of-care indicators.

Table 1
IN-HF Outcome Registry: clinical characteristics

	Total (n = 1855)	WHF (n = 1058)	DN-HF (n = 797)	*P*
Age (y), mean ± SD	72 ± 12	72 ± 11	72 ± 13	.14
Age ≥70 (y), %	64.4	65.8	62.6	.16
Females, %	39.8	37.2	43.2	.01
Ischemic etiology, %	42.3	45.3	38.4	.003
BMI (kg/m^2), mean ± SD	28 ± 5	28 ± 6	28 ± 5	.32
BMI ≥30 (kg/m^2), %	29.0	29.0	29.0	.78
Systolic BP (mm Hg), mean ± SD	134 ± 33	129 ± 30	141 ± 34	<.0001
Systolic BP < 110 (mm Hg), %	20.2	24.0	15.2	<.0001
Heart rate (bpm), median [IQR]	90 [73–110]	82 [70–100]	95 [80–116]	<.0001
Clinical History				
Treated hypertension, %	57.8	55.7	60.7	.03
Diabetes mellitus, %	40.4	43.0	36.9	.008
COPD, %	30.1	32.9	26.5	.003
Renal dysfunction, %	32.5	39.1	23.6	<.0001
History of atrial fibrillation, %	37.7	43.3	30.4	<.0001
Previous stroke, %	5.2	5.3	5.1	.89
Peripheral artery disease, %	19.8	21.8	17.1	.01
ICD in situ, %	9.5	14.8	2.4	<.0001
CRT-D in situ, %	3.8	6.2	0.5	<.0001
CRT-P in situ, %	1.6	2.3	0.6	.005
Signs/Symptoms at Presentation				
Pulmonary congestion, %	78.2	75.8	81.4	.004
Peripheral congestion, %	56.1	61.3	49.1	<.0001
Pulmonary and/or peripheral congestion, %	88.4	87.8	89.1	.40
Peripheral hypoperfusion, %	12.0	12.4	11.4	.53
Cold, %	10.8	11.1	10.4	.66
Somnolent, confused, sedated, %	11.5	9.6	14.1	.003

Lessons from RCTs

European Heart Journal Supplements (2016) 18(Supplement G), G19-G32
The Heart of the Matter
doi:10.1093/eurheartj/suw045

The bumpy road to drug development for acute heart failure

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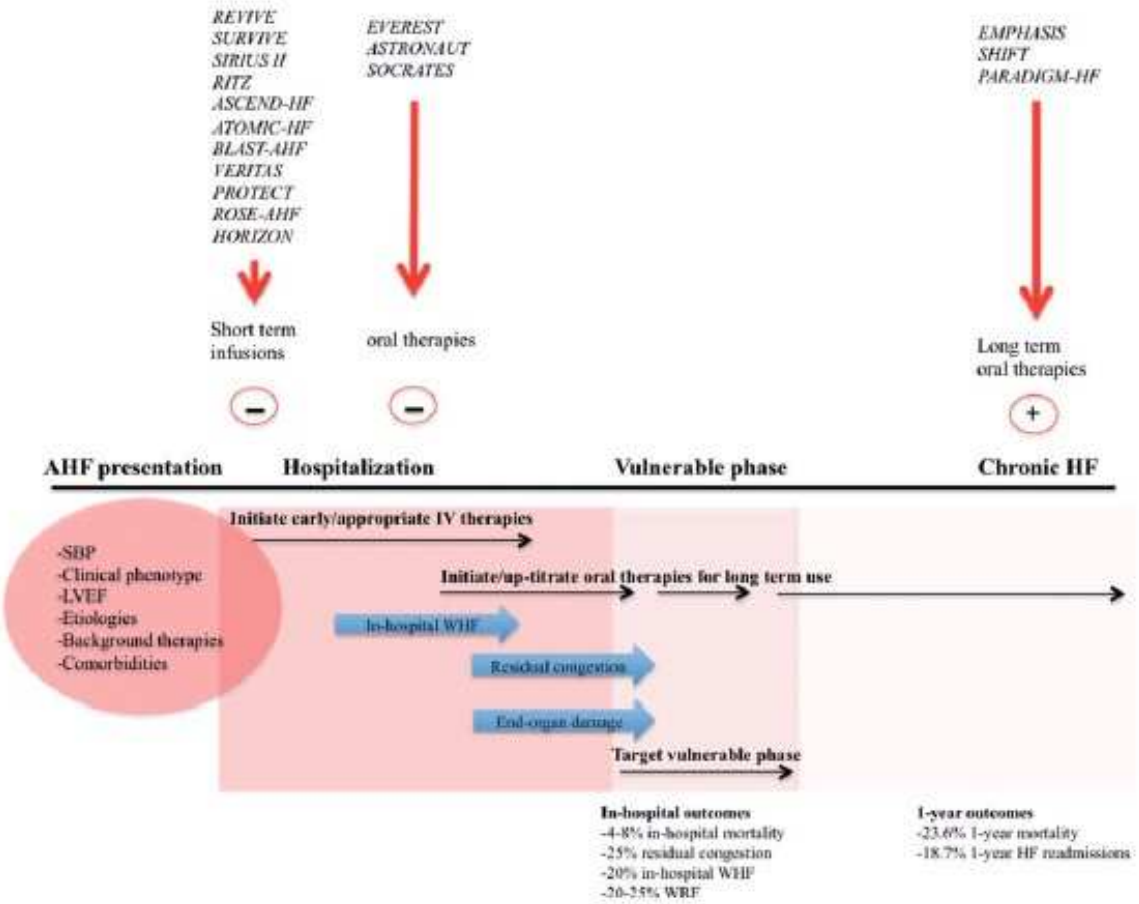
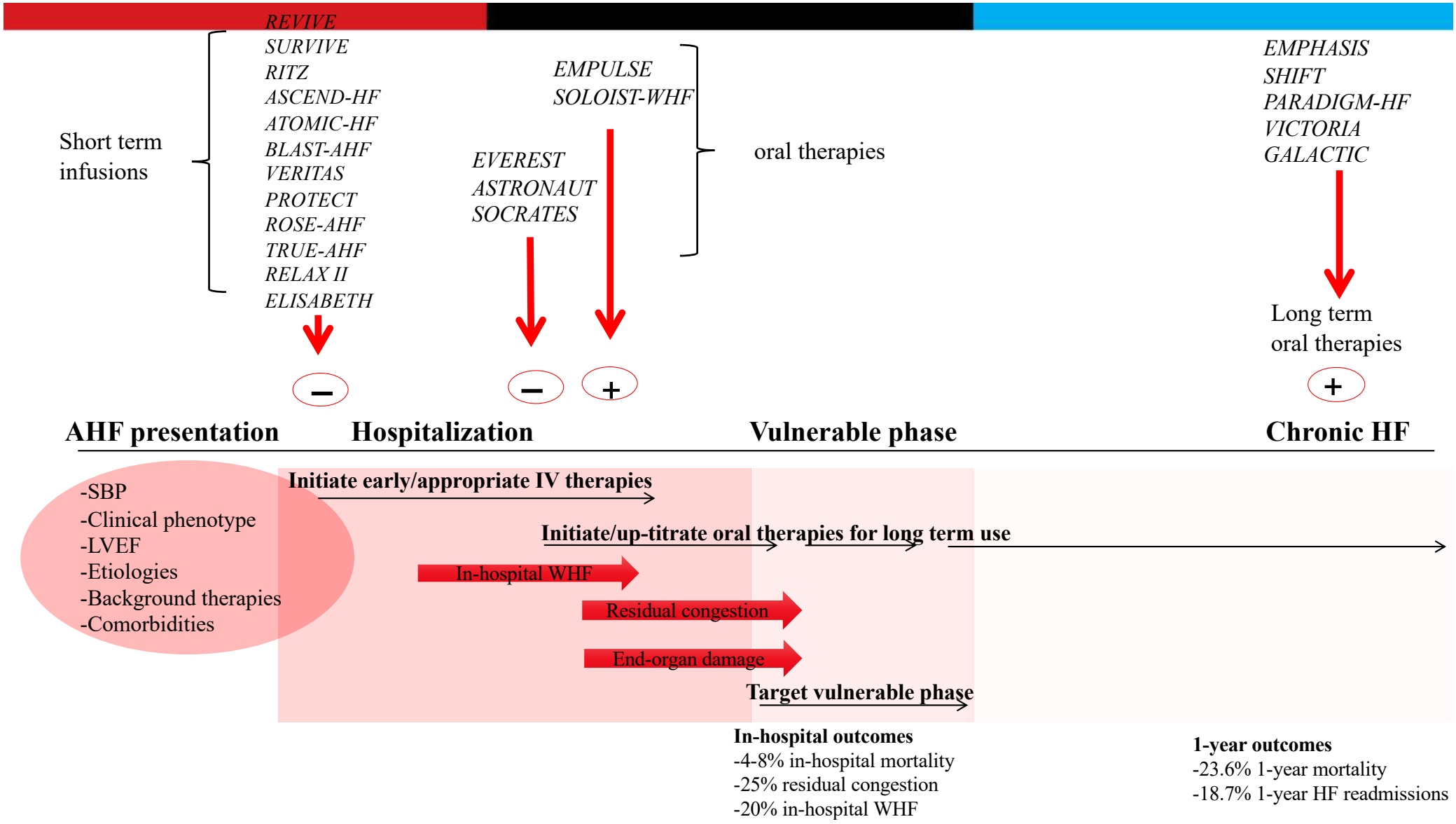
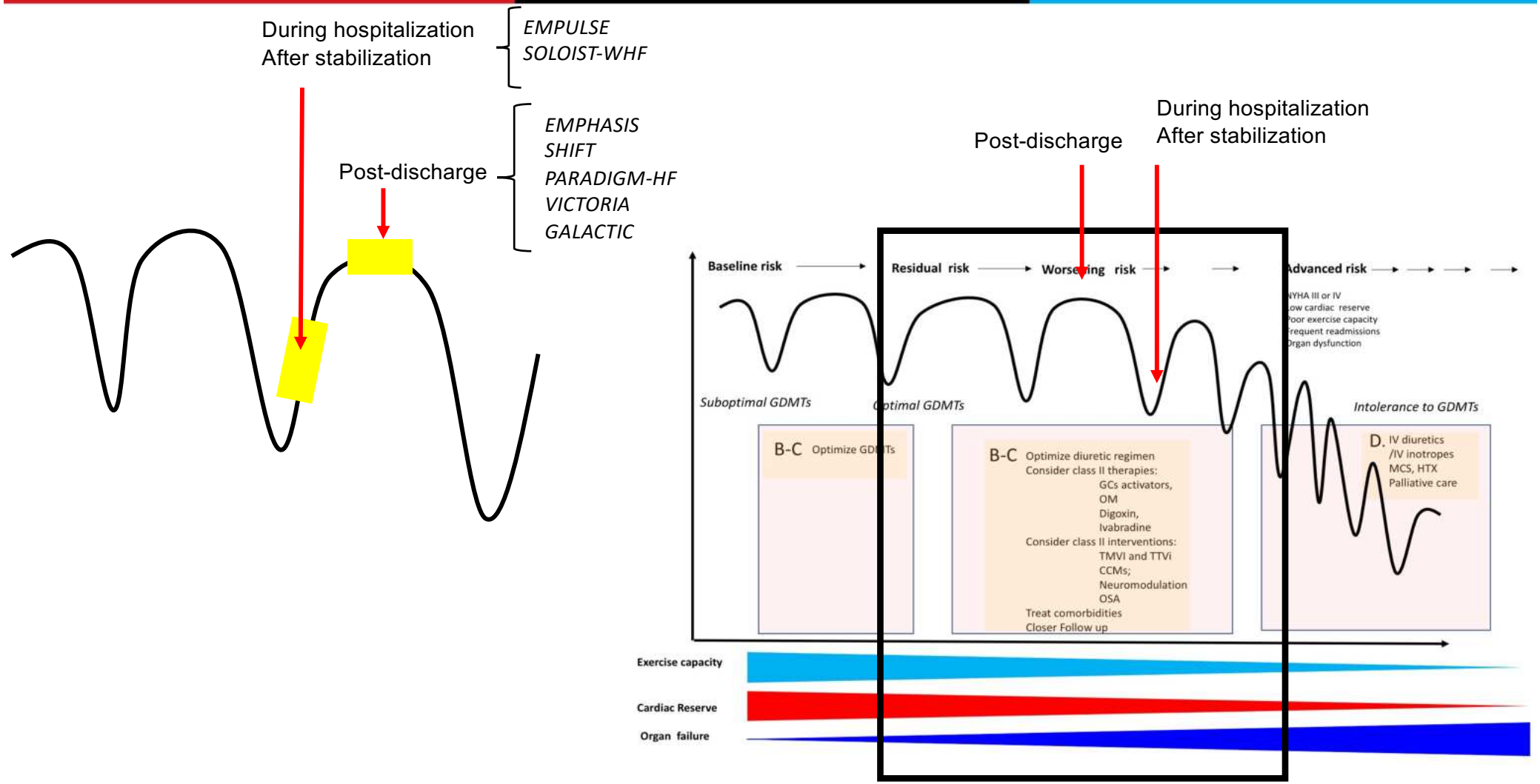
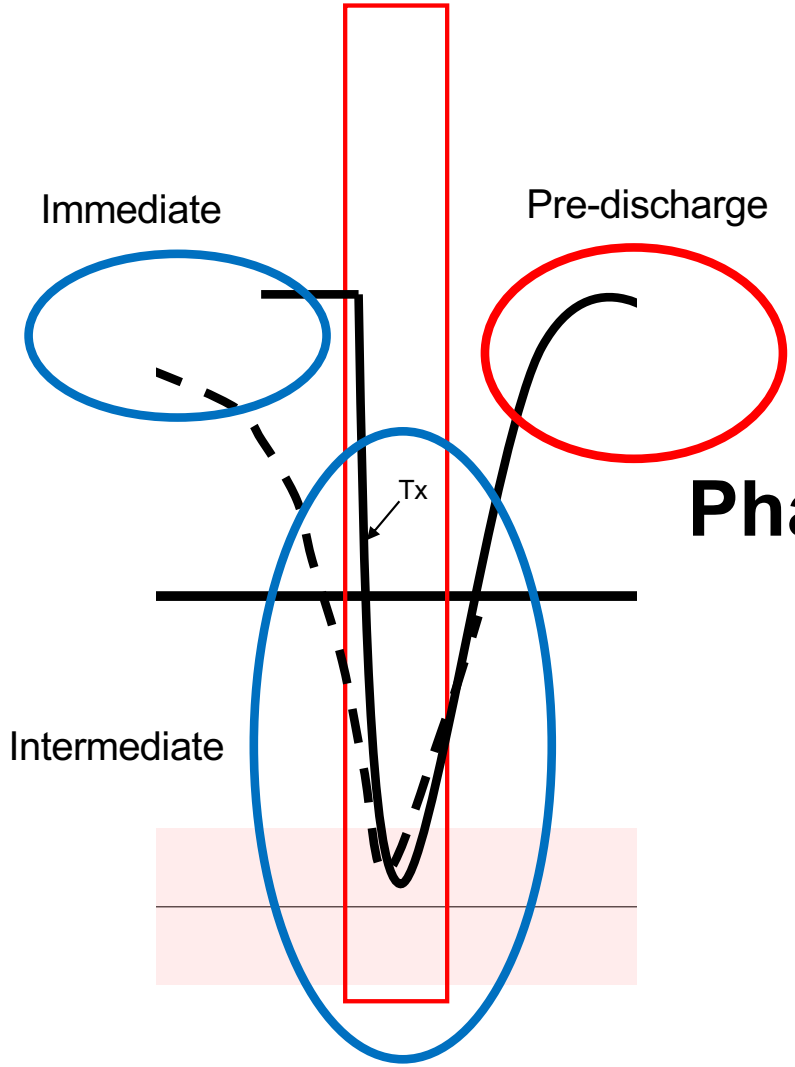
KEYWORDS
Worsening chronic heart failure;
Clinical trials;
Drug development

The prevalence of heart failure (HF) continues to grow, in large part attributed to the aging population. Parallel to this trend is the increasing burden of hospitalization for worsening HF, which accounts for the majority of the very high societal burden of costs of care for these patients. These hospitalizations represent a change in the trajectory of the disease process and are associated with a significantly higher risk of adverse outcomes, a trend that has not changed over the past two decades. Although short-term readmissions are due to haemodynamic congestion, long-term prognosis and mortality are the result of the continuous deterioration of cardiac substrate, worsening of comorbidities, and progression of HF. Thus, when planning a new therapeutic intervention in acute HF, it is essential to have insight into the mechanism and temporal distribution of adverse outcomes. Furthermore, as acute HF patients die or are readmitted due to multiple reasons it is important to match the mechanism of action of the intervention to the mechanism of the adverse event. Despite many clinical trials to date in these patients, there currently is not a single agent that is known to improve post-discharge mortality risk in these patients. A variety of reasons have been offered to account for the lack of success in these clinical trials. A careful review of these previous experiences offers some significant insights into lessons learned and provides guidance for future novel intervention development for this growing patient population.




REVIVE
SURVIVE
RITZ
ASCEND-HF
ATOMIC-HF
BLAST-AHF
VERITAS
PROTECT
ROSE-AHF
TRUE-AHF
RELAX II
ELISABETH
Short term infusions
EMPULSE
SOLOIST-WHF
EVEREST
ASTRONAUT
SOCRATES
oral therapies
EMPHASIS
SHIFT
PARADIGM-HF
VICTORIA
GALACTIC
Long term oral therapies
−
−
+
+
AHF presentation
Hospitalization
Vulnerable phase
Chronic HF
-SBP
-Clinical phenotype
-LVEF
-Etiologies
-Background therapies
-Comorbidities
Initiate early/appropriate IV therapies
Initiate/up-titrate oral therapies for long term use
In-hospital WHF
Residual congestion
End-organ damage
Target vulnerable phase
In-hospital outcomes
-4-8% in-hospital mortality
-25% residual congestion
-20% in-hospital WHF
1-year outcomes
-23.6% 1-year mortality
-18.7% 1-year HF readmissions


During hospitalization
After stabilization
EMPULSE
SOLOIST-WHF
Post-discharge
EMPHASIS
SHIFT
PARADIGM-HF
VICTORIA
GALACTIC
Post-discharge
During hospitalization
After stabilization
Baseline risk
Residual risk
Worsening risk
Advanced risk
NYHA III or IV
Low cardiac reserve
Poor exercise capacity
Frequent readmissions
Organ dysfunction
Suboptimal GDMTs
Optimal GDMTs
Intolerance to GDMTs
B-C Optimize GDMTs
B-C Optimize diuretic regimen
Consider class II therapies:
GCs activators,
OM
Digoxin,
Ivabradine
Consider class II interventions:
TMVI and TTVi
CCMs;
Neuromodulation
OSA
Treat comorbidities
Closer Follow up
D. IV diuretics
/IV inotropes
MCS, HTX
Palliative care
Exercise capacity
Cardiac Reserve
Organ failure

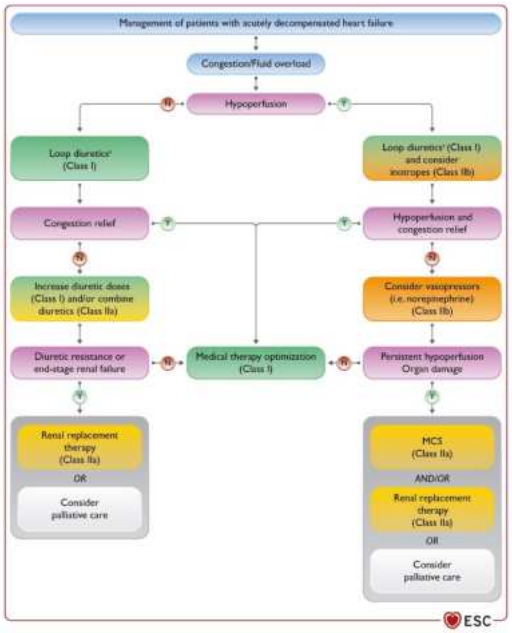


Phases of AHF management

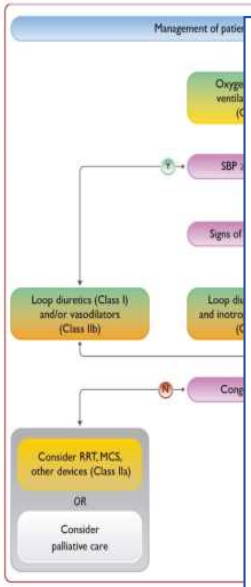
2021 AHF Management

Clinical phenotypes

Decompensated HF

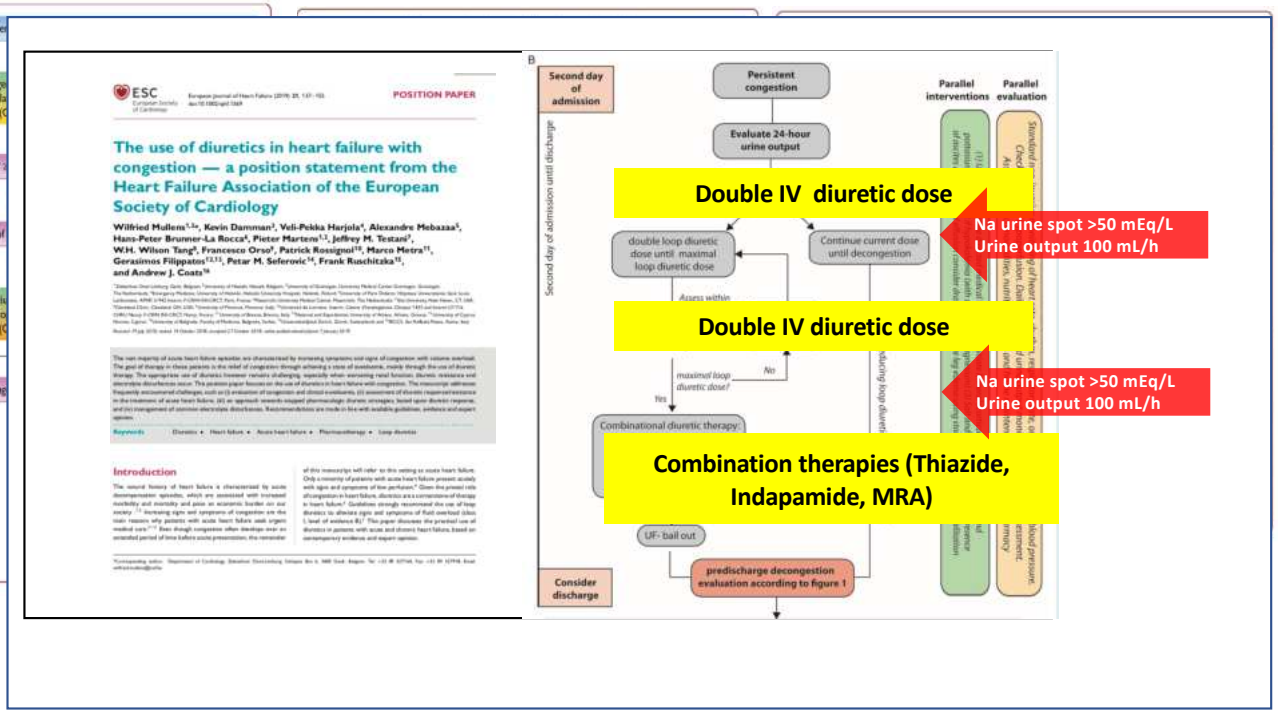


Acute Pulmonary Oedema

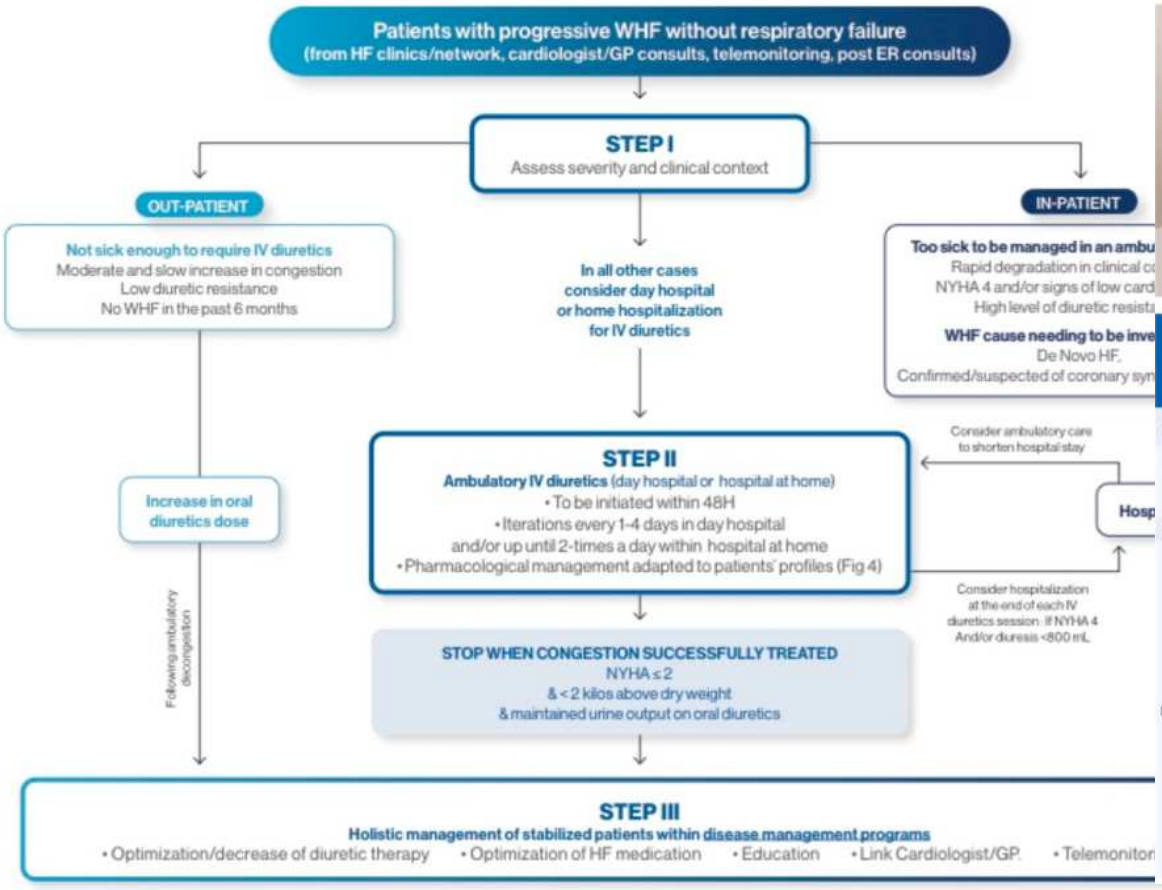


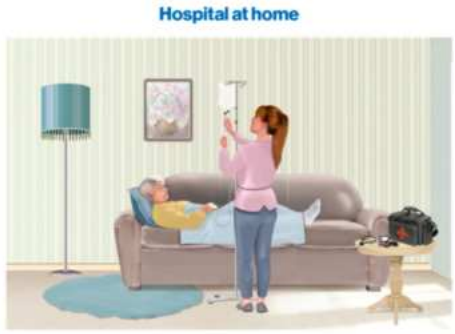
Acute Right HF

Cardiogenic Shock



Practical outpatient management of Worsening Chronic Heart Failure





Category	Maintenance furosemide equivalent dose (mg)*	IV Furosemide dose		SC Furosemide infusion dose	If inadequate urine output (<500ml) after 90 min of infusion	Oral potassium supplement during the furosemide infusion	Parallel Intervention	Monitoring
		Bolus mg**	Infusion mg/hr During 2 to 3 hours***					
Low dose	≤ 40	20	20	40 mg over 5 hours	Additional 200 mg bolus of furosemide and/or (thiazide diuretic† or 100 mg potassium canrenoate)	**K⁺> 4 mmol/l**, No potassium supplement **K⁺ 3.7 to 4.0**, 20 mEq**** if creatinine <20 mg/L **K⁺ 3.4 to 3.6**, 40 mEq if creatinine <20 mg/L, 20 mEq if creatinine 20-28, 10 mEq if creatinine >28 **K⁺ 3.1 to 3.3** 40 mEq if creatinine <20 mg/L, 30 mEq if creatinine 20-28, 20 mEq if creatinine >28 **If K⁺ <3.1**, achieve potassium >3.1 before diuretic infusion.	Continue guideline directed medical therapy (RAASi/ SGLT2i /ARNi) Consider increasing / initiating MRAs and/or thiazide in case of diuretic resistance	**Day hospital setting** • Monitor HR & BP, every hour • Quantify diuresis and natriuresis **At-home hospitalization setting** • Monitoring 2 to 3 times a day • Monitor HR & BP prior and 5 minutes after the bolus **Following the infusion** • After the IV diuretic session, in all patients, monitor creatinine and potassium levels within 7 days of IV diuretics infusion
Standard dose	41-160	Numeric equivalent of maintenance diuretic dose	20	2/3 of numeric equivalent + 40 mg				
High dose	161-300	200	20	160 mg				
Mega dose	≥ 301	200	20	160 mg				

Girerd N.Practical outpatient management of worsening chronic heart failure. European Journal of Heart Failure (2022)

Time to diuretics vs Time to decongestion

Time to Diuretics

Relation of Decongestion and Time to Diuretics to Biomarker Changes and Outcomes in Acute Heart Failure

Yu Horiuchi, MD[a,b], Nicholas Wettersten, MD[c], Dirk J. van Veldhuisen, MD[c], Christian Mueller, MD[d], Gerasimos Filippatos, MD[e], Richard Nowak, MD[f], Christopher Hogan, MD[g], Michael C. Kontos, MD[h], Chad M. Cannon, MD[i], Gerhard A. Müeller, MD, PhD[j], Robert Birkhahn, MD[k], Pam Taub, MD[c], Gary M. Vilke, MD[l], Olga Barnett, MD[m], Kenneth McDonald, MD[n,o], Niall Mahon, MD[n,p], Julio Nuñez, MD[q,r], Carlo Briguori, MD, PhD[s], Claudio Passino, MD[t], Alan Maisel, MD[u], and Patrick T. Murray, MD[n,o]

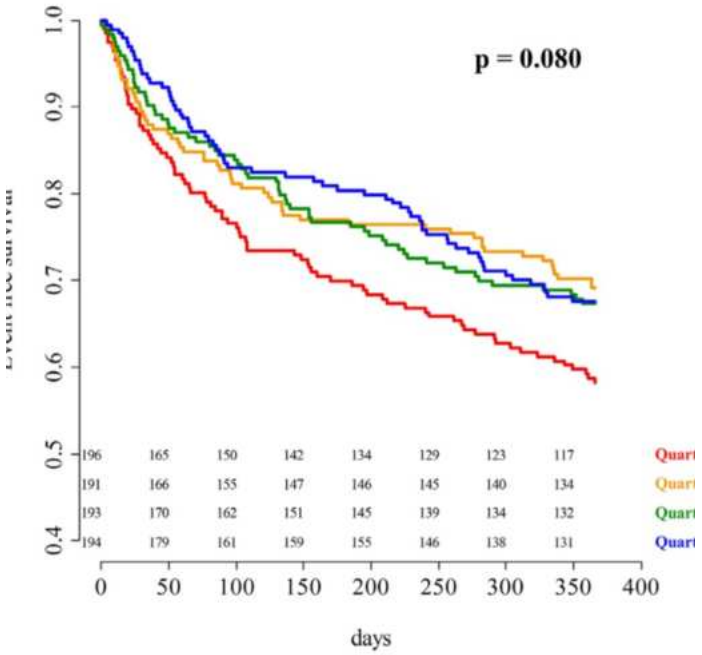
Prompt treatment may mitigate the adverse effects of congestion in the early phase of heart failure (HF) hospitalization, which may lead to improved outcomes. We analyzed 814 acute HF patients for the relationships between time to first intravenous loop diuretics, changes in biomarkers of congestion and multiorgan dysfunction, and 1-year composite end point of death or HF hospitalization. B-type natriuretic peptide (BNP), high sensitivity cardiac troponin I (hscTnI), urine and serum neutrophil gelatinase–associated lipocalin, and galectin 3 were measured at hospital admission, hospital day 1, 2, 3 and discharge. Time to diuretics was not correlated with the timing of decongestion defined as BNP decrease ≥ 30% compared with admission. Earlier BNP decreases but not time to diuretics were associated with earlier and greater decreases in hscTnI and urine neutrophil gelatinase–associated lipocalin, and lower incidence of the composite end point. After adjustment for confounders, only no BNP decrease at discharge was significantly associated with mortality but not the composite end point (p = 0.006 and p = 0.062, respectively). In conclusion, earlier time to decongestion but not the time to diuretics was associated with better biomarker trajectories. Residual congestion at discharge rather than the timing of decongestion predicted a worse prognosis. **(Am J Cardiol 2021;147:70–79)**

In patients with acute heart failure (AHF), prompt initiation of decongestive therapy may help mitigate the adverse effects of congestion and multi-organ injury in the early phase of hospitalization and result in improved outcomes. Several studies have examined the relationship between early initiation of diuretics and/or vasoactive agents and clinical outcomes.[1–5] However, a pathophysiologic link between early treatment, decongestion, organ damage and clinical outcomes has not been fully assessed, especially from the viewpoint of biomarker trajectories. B-type natriuretic peptide (BNP) is a well-established biomarker of congestion and the timing of BNP decrease can serve as an objective surrogate for time to decongestion.[3] In this subanalysis of the Acute Kidney Injury Neutrophil gelatinase–associated lipocalin (NGAL) Evaluation of Symptomatic heart failure Study (AKINESIS), we investigated whether

[a]Division of Cardiovascular Medicine, University of California San Diego, La Jolla, California; [b]Division of Cardiology, Mitsui Memorial Hospital, Tokyo, Japan; [c]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [d]Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland; [e]Department of Cardiology, Athens University Hospital Attikon, University of Athens, Athens, Greece; [f]Department of Emergency Medicine, Henry Ford Hospital System, Detroit, Michigan; [g]Division of Emergency Medicine and Acute Care Surgical Services, VCU Medical Center, Virginia Commonwealth University, Richmond, Virginia; [h]Division of Cardiology, VCU Medical Center, Virginia Commonwealth University, Richmond, Virginia; [i]Department of Emergency Medicine, University of Kansas Medical Center, Kansas City, Kansas; [j]Department of Nephrology and Rheumatology, University Medical Centre Göttingen, University of Göttingen, Göttingen, Germany; [k]Department of Emergency Medicine, New York Methodist Hospital, New York, New York; [l]Department of Emergency Medicine, University of California San Diego, La Jolla, California; [m]Division of Cardiology, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine; [n]Department of Cardiology, School of Medicine, University College Dublin, Dublin, Ireland; [o]Department of Cardiology, St Vincent's University Hospital, Dublin, Ireland; [p]Department of Cardiology, Mater Misericordiae University Hospital, Dublin, Ireland; [q]Department of Cardiology, Valencia University Hospital, INCLIVA, Valencia, Spain; [r]Centro de Investigación Biomédica en Red (CIBER) in Cardiovascular Diseases, Madrid, Spain; [s]Department of Cardiology, Mediterranea Cardiocentro, Naples, Italy; [t]Department of Cardiology and Cardiovascular Medicine, Fondazione Gabriele Monasterio, Pisa, Italy; and [u]Department of Medicine, School of Medicine, University College Dublin, Dublin, Ireland. Manuscript received November 28, 2020; revised manuscript received and accepted January 22, 2021.

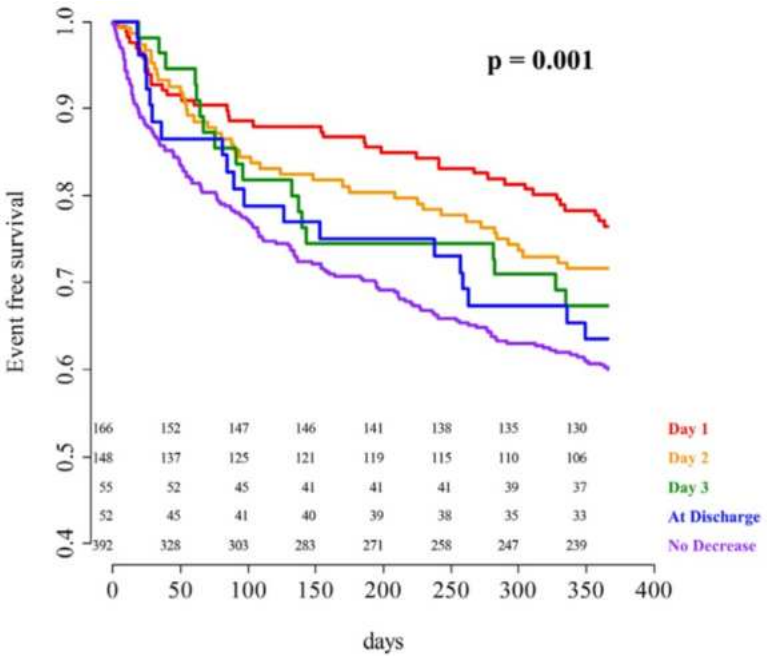
*Corresponding author: Tel: (353) 1-716-4564
E-mail address: patrick.murray@ucd.ie (P.T. Murray).

One-year Composite of Death or Heart Failure Hospitalization

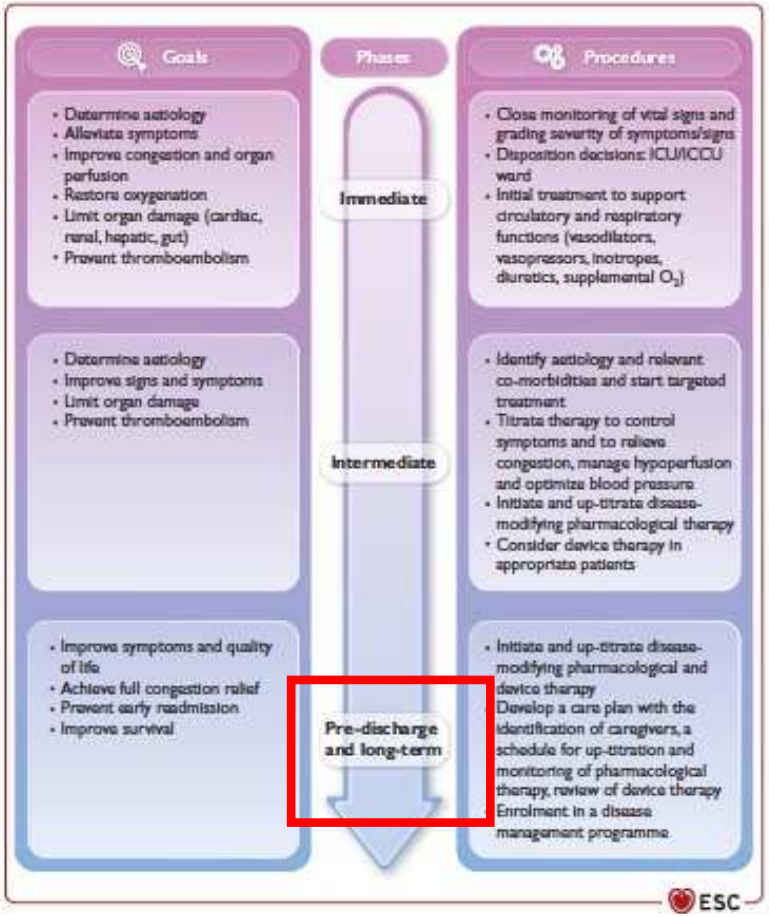


Time to NP decrease

One-year Composite of Death or Heart Failure Hospitalization



Pre-discharge phase : opportunity to improve long term prognosis



Recommendations for pre-discharge and early post-discharge follow-up of patients hospitalized for acute heart failure 2021

Recommendations	Class[a]	Level[b]
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.[433, 479]	I	C
It is recommended that evidence based oral medical treatment be administered before discharge[6, 7]	I	C
An early follow-up visit is recommended at 1-2 weeks after discharge to assess signs of congestion, drugs' tolerance and start and/or uptitrate evidence-based therapy.[8, 9]	I	C
Ferric carboxymaltose should be considered for iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100-299 ng/mL with TSAT <20%, to improve symptoms and reduce rehospitalizations.[519]	IIa	B

1/3 of AHF patients are discharged with residual congestion

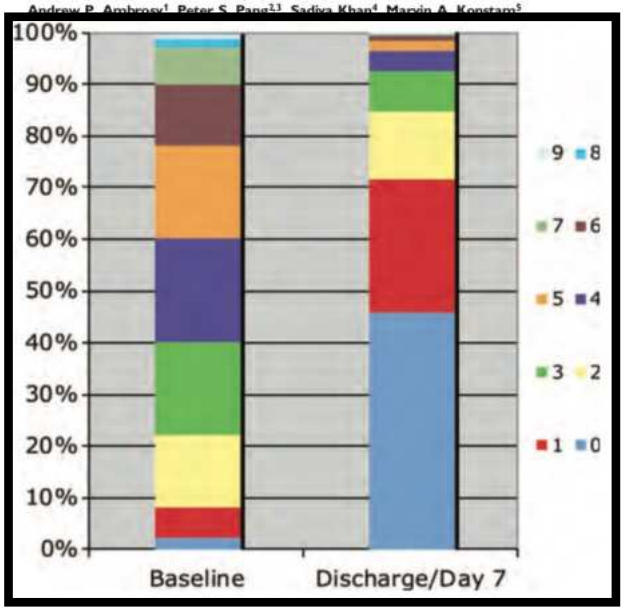
EVEREST

European Heart Journal (2013) 34, 835–843
doi:10.1093/eurheartj/ehs444

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial†

Andrew P. Ambrosy[1], Peter S. Pang[2,3], Sadiya Khan[4], Marvin A. Konstam[5]

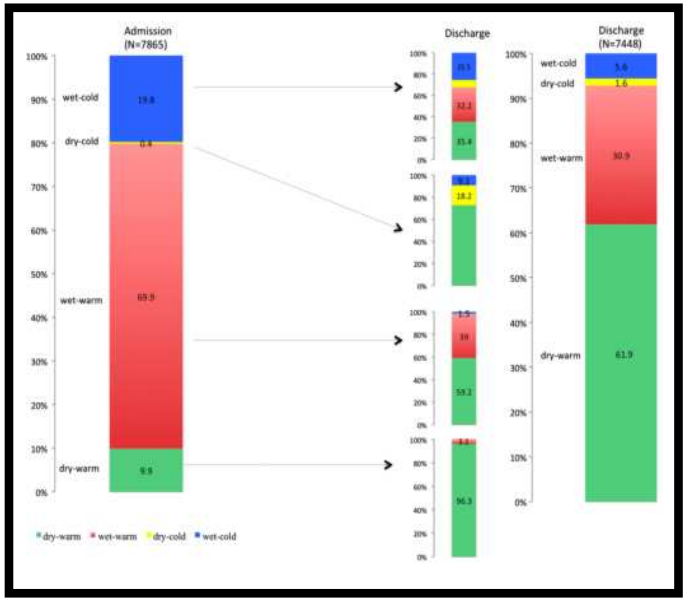


ESC HF LT registry

ESC European Society of Cardiology
European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1492

RESEARCH ARTICL

Acute heart failure congestion and perfusion status – impact of the clinical classification on in-hospital and long-term outcomes; insights from the ESC-EORP-HFA Heart Failure Long-Term Registry

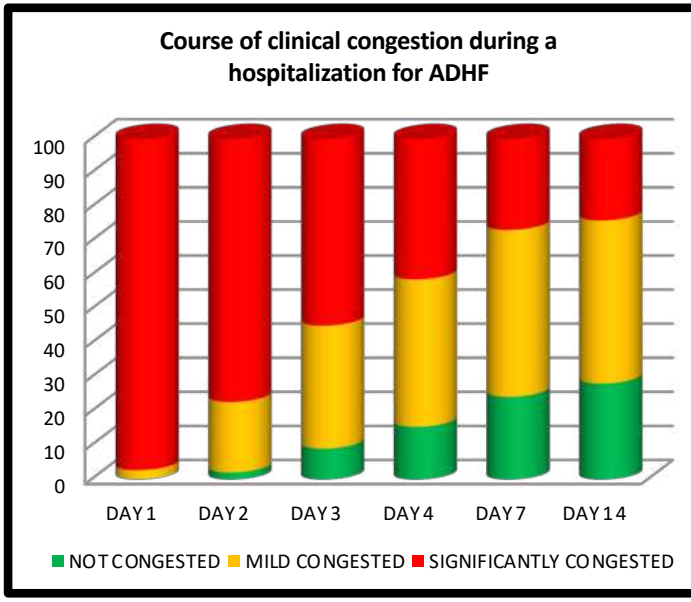


PROTECT

International Journal of Cardiology 258 (2018) 185–191
Contents lists available at ScienceDirect
International Journal of Cardiology
journal homepage: www.elsevier.com/locate/ijcard

Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure

Jorge Rubio-Gracia[a,b,c], Biniyam G. Demissei[c], Jozine M. ter Maaten[c], John G. Cleland[d], Christopher M. O'Connor[e], Marco Metra[f], Piotr Ponikowski[g], John R. Teerlink[h], Gad Cotter[i], Beth A. Davison[i],



Residual congestion at discharge is associated to a poor prognosis

EVEREST

European Heart Journal (2013) 34, 835–843
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Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial†

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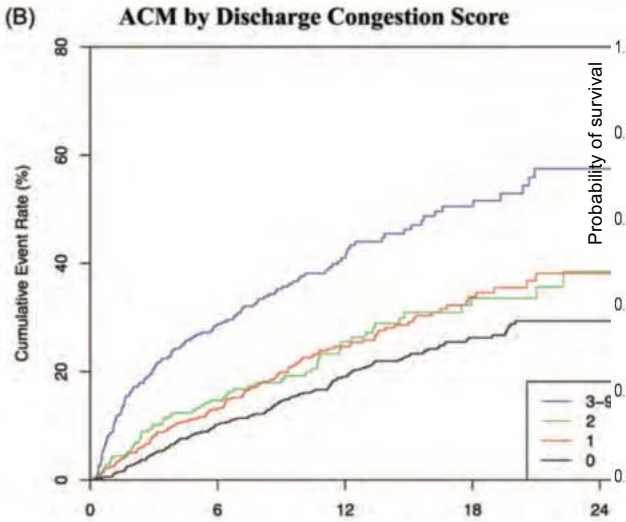

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RESEARCH ARTICL

Acute heart failure congestion and perfusion status – impact of the clinical classification on in-hospital and long-term outcomes; insights from the ESC-EORP-HFA Heart Failure Long-Term Registry

Ovidiu Chioncel[1]*, Alexandre Mebazaa[2], Aldo P. Maggioni[3,4], Veli-Pekka Harjola[5], Giuseppe Rosano[6,7], Cecile Laroche[8], Massimo F. Piepoli[9], Maria G. Crespo-Leiro[10], Mitja Lainscak[11], Pio
Frank Ruschitzka[16], I
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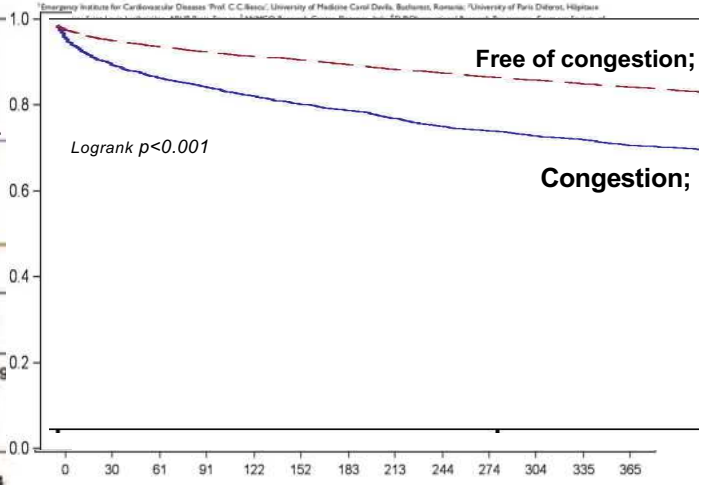

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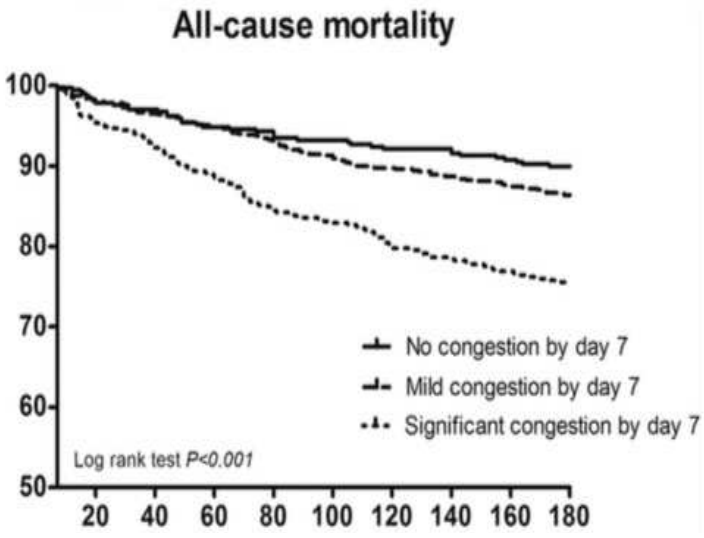
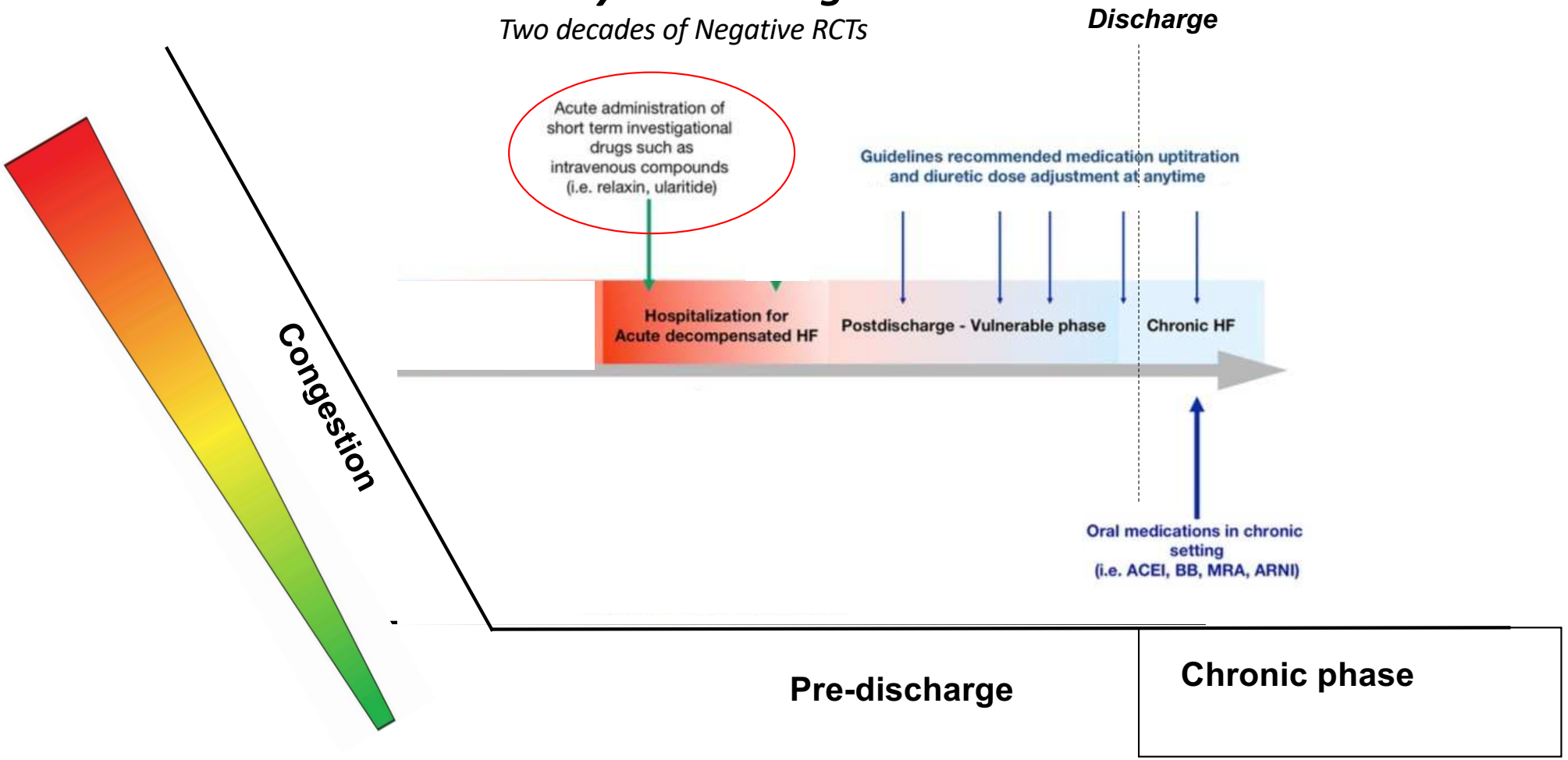
Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure

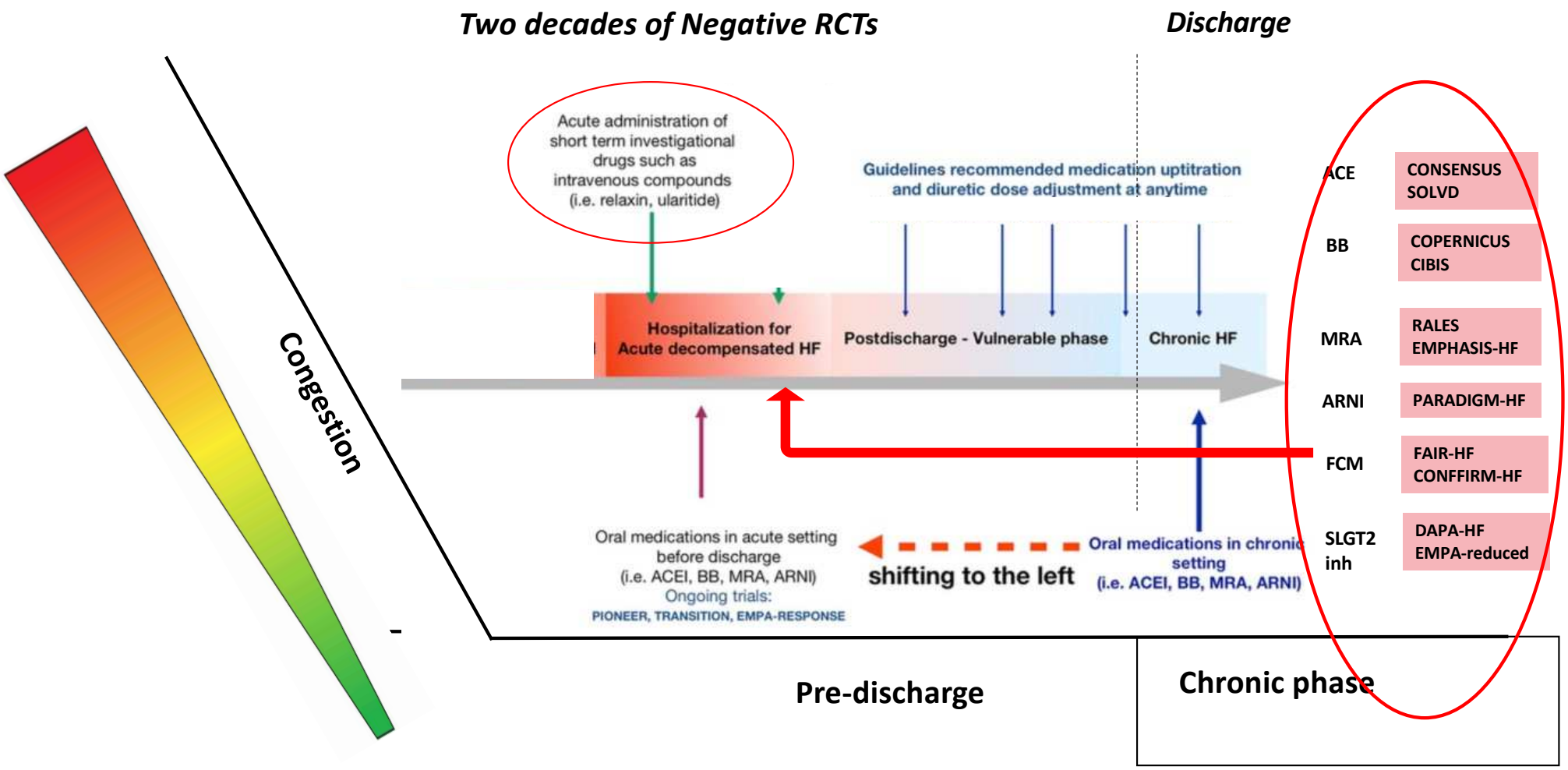
Jorge Rubio-Gracia[a,b,c], Biniyam G. Demissei[c], Jozine M. ter Maaten[c], John G. Cleland[d], Christopher M. O'Connor[e], Marco Metra[f], Piotr Ponikowski[g], John R. Teerlink[h], Gad Cotter[i], Beth A. Davison[i], Michael M. Givertz[j], Daniel M. Bloomfield[k], Howard Dittrich[l], Kevin Damman[c], Juan I. Pérez-Calvo[a,b], Adriaan A. Voors[c,*]



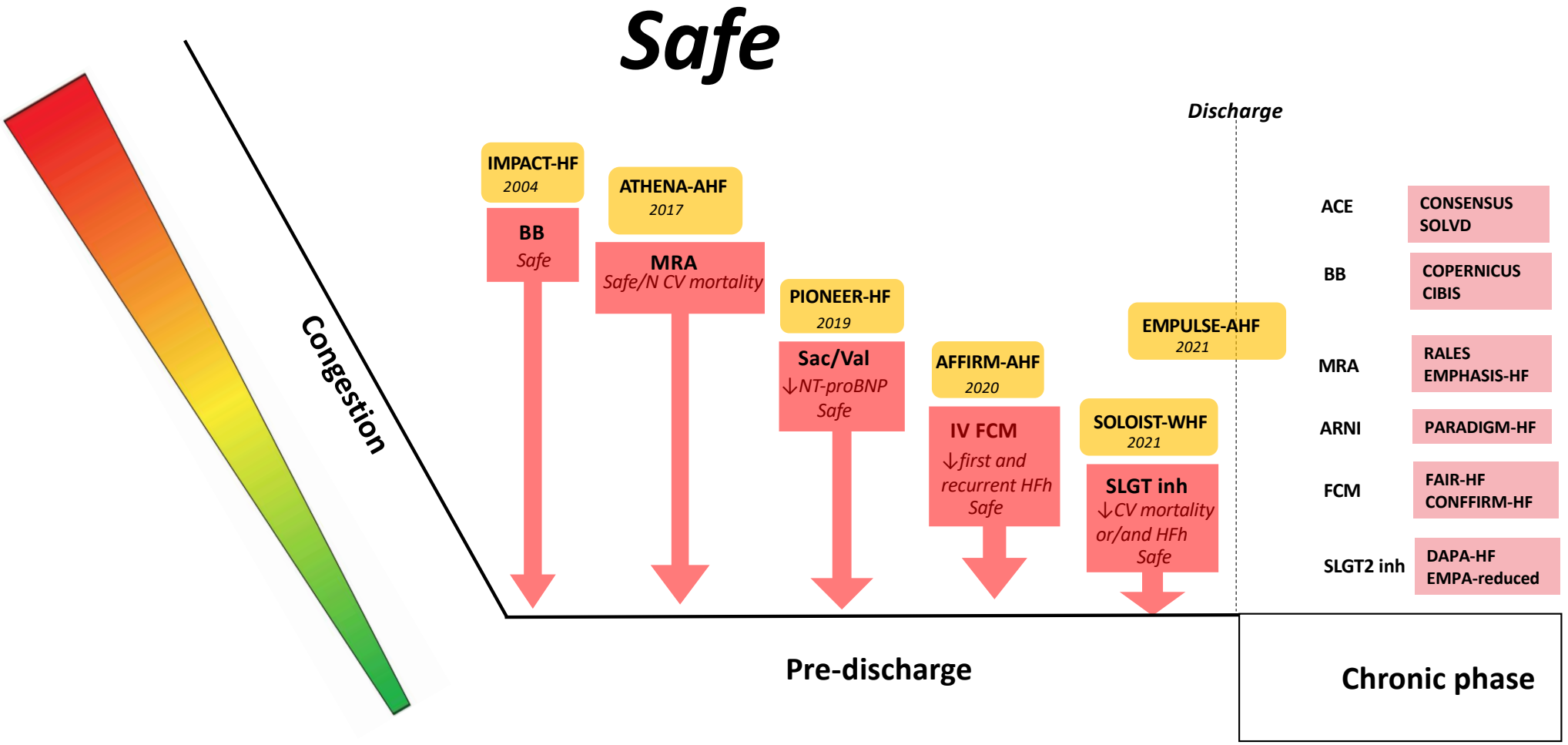
What beyond decongestion?

Two decades of Negative RCTs




Two decades of Negative RCTs
Discharge
Congestion
Acute administration of short term investigational drugs such as intravenous compounds (i.e. relaxin, ularitide)
Guidelines recommended medication uptitration and diuretic dose adjustment at anytime
Hospitalization for Acute decompensated HF
Postdischarge - Vulnerable phase
Chronic HF
Oral medications in acute setting before discharge (i.e. ACEI, BB, MRA, ARNI)
Ongoing trials:
PIONEER, TRANSITION, EMPA-RESPONSE
shifting to the left
Oral medications in chronic setting (i.e. ACEI, BB, MRA, ARNI)
ACE
CONSENSUS SOLVD
BB
COPERNICUS CIBIS
MRA
RALES EMPHASIS-HF
ARNI
PARADIGM-HF
FCM
FAIR-HF CONFFIRM-HF
SLGT2 inh
DAPA-HF EMPA-reduced
Pre-discharge
Chronic phase

Initiation of oral therapies during hospitalization



European Journal of Heart Failure (2018) 20, 345–354
doi:10.1002/ejhf.932

RESEARCH ARTICLE

Heart failure oral therapies at discharge are associated with better outcome in acute heart failure: a propensity-score matched study

Etienne Gayat[1,†*], Mattia Arrigo[1,2†], Simona Littnerova[3], Naoki Sato[4], Jiri Parenica[5], Shiro Ishihara[4], Jindrich Spinar[5], Christian Müller[6], Veli-Pekka Harjola[7], Johan Lassus[8], Òscar Miró[9], Aldo P. Maggioni[10], Khalid F. AlHabib[11], Dong-Ju Choi[12], Jin Joo Park[12], Yuhui Zhang[13], Jian Zhang[13], James L. Januzzi Jr[14], Katsuya Kajimoto[15], Alain Cohen-Solal[16], and Alexandre Mebazaa[1], on behalf of the GREAT Network

[1]Department of Anesthesiology and Critical Care, APHP – Saint Louis Lariboisière University Hospitals, University Paris Diderot and INSERM UMR-S 942, Paris, France; [2]Division of Cardiology, University Heart Center, University Hospital Zurich, Zurich, Switzerland; [3]Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic; [4]Division of Cardiology and Intensive Care Unit, Nippon Medical School Musashi-Kosugi Hospital, Kawasaki, Japan; [5]Department of Cardiology, University Hospital Brno and Medical Faculty, Masaryk University, Brno, Czech Republic; [6]Cardiovascular Research Institute Basel and Department of Cardiology, University Hospital Basel, Basel, Switzerland; [7]Emergency Medicine, Helsinki University and Helsinki University Hospital, Helsinki, Finland; [8]Division of Cardiology, Heart and Lung Center, Helsinki University and Helsinki University Hospital, Helsinki, Finland; [9]Emergency Department, Hospital Clinic and 'Emergencies: Processes and Pathologies' Research Group, IDIBAPS, University of Barcelona, Barcelona, Spain; [10]ANMCO Research Center, Florence, Italy; [11]Department of Cardiac Sciences, King Fahad Cardiac Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [12]Division Cardiology, Cardiovascular Center, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, South Korea; [13]Heart Failure Center Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [14]Division of Cardiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [15]Division of Cardiology, Sekikawa Hospital, Tokyo, Japan; and [16]Department of Cardiology, APHP – Lariboisière University Hospital, and INSERM UMR-S 942, Paris, France

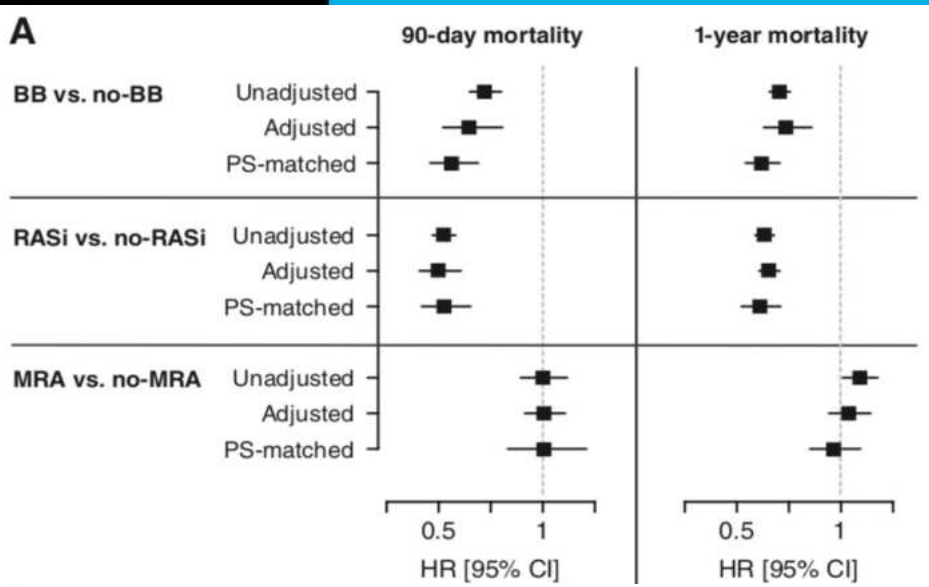
Received 22 November 2016; revised 26 May 2017; accepted 5 June 2017; online publish-ahead-of-print 28 August 2017

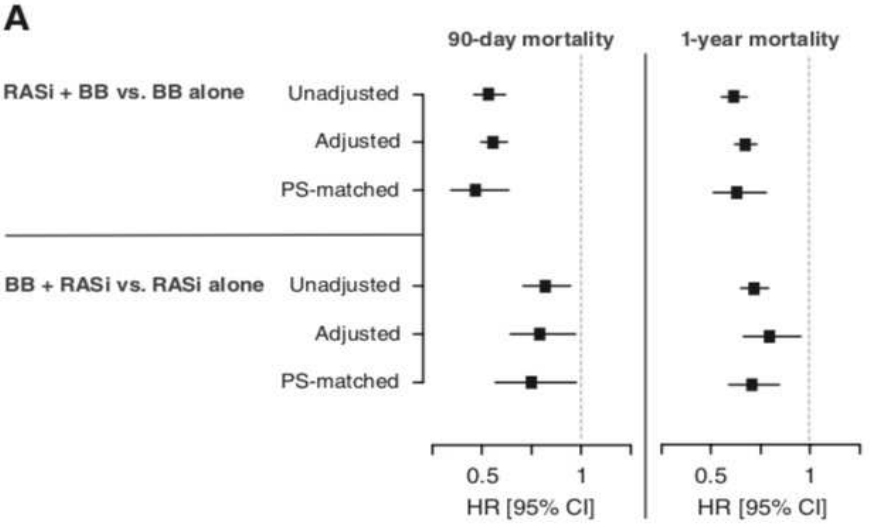
Aims Heart failure oral therapies (HFOTs), including beta-blockers (BB), renin–angiotensin system inhibitors (RASi) and mineralocorticoid receptor antagonists, administered before hospital discharge after acute heart failure (AHF) might improve outcome. However, concerns have been raised because early administration of HFOTs may worsen patient's condition. We hypothesized that HFOTs at hospital discharge might be associated with better post-discharge survival.

Methods and results The study population was composed of 19 980 AHF patients from the GREAT registry. The primary and secondary outcomes were 90-day and 1-year all-cause mortality, respectively. Survival was estimated with univariate and covariate-adjusted Cox proportional hazards regression models for the whole population and after propensity-score matching. HFOTs at discharge were consistently associated with no excess mortality in the unadjusted and adjusted analyses of the whole and matched cohorts. In the matched cohort, BB and RASi at discharge were associated with lower 90-day mortality risks compared to the respective untreated groups [hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.46–0.69; and HR 0.53, 95% CI 0.42–0.66, respectively]. The favourable associations of BB and RASi at discharge with 90-day mortality were present in many subgroups including patients with reduced or preserved left ventricular ejection fraction and persisted up to 1 year after discharge. The combination of RASi and BB was associated with an even lower risk of death than RASi or BB alone.

Conclusions Administration of HFOTs at hospital discharge is associated with better survival of AHF patients.

Keywords Acute heart failure • Prognosis • Oral therapy





Lessons from ESC-HF-LT registry

Postponing the initiation of optimal medical therapy in the hospital-based setting often leads to failure to initiate medication in the outpatient setting.

Table 3 Oral treatments of hospitalized heart failure patients ($n = 5039$) prior to hospitalization and at discharge

	Prior to hospitalization ($n = 5039$)	At discharge ($n = 5039$)	*P*-value
ACE-I/ARBs, %	64.3	77.0	<0.0001
Beta-blockers, %	54.8	71.8	<0.0001
MRAs, %	33.9	55.3	<0.0001
Diuretics, %	65.3	83.6	<0.0001
Digitalis, %	19.5	26.4	<0.0001
Statins, %	42.6	58.4	<0.0001
Antiplatelets, %	49.2	61.9	<0.0001
OAC,			<0.0001
Amioc			<0.0001
Ivabra			<0.0001
Nitrat			<0.0001
Calciu			0.59
blockers, %			

Substantial increase during hospitalization

Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12 440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2013;15:1173–1184.

Table 9 Pharmacological treatment of acute heart failure patients at discharge and at 1 year

	At discharge	At 1 year	*P*-value
ACEI/ARBs, %	77.0	79.1	0.0003
Beta-blockers, %	72.6	77.8	0.1211
MRAs, %	53.9	56.5	0.0416
Diuretics, %	83.9	86.4	0.1735
Digitalis, %	25.9	23.6	<0.0001
Statins, %	57.8	62.1	0.1579
Antiplatelet, %	60.8	60.5	<0.0001
OAC, %	42.7	40.7	0.0014

No changes

medical inertia, diversity of medical providers, absence of FU

European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. European Journal of Heart Failure (2016) 18, 613–625

Foundational therapy for heart failure :

reduce CV death and/or all-cause mortality;

and has a major effect to reduce the risk of hospitalizations for HF

BB **ACEinh** **ARBs** **ARNI** **MRAs** **SLGT2 inh**

Therapeutic targets

↓ ↓ neurohormonal activation

↓ ↓ cardiac and vascular remodelling

↓ All cause deaths HF hospitalization

↓ All cause deaths ↓ HF hospitalization

↓ CV deaths and/or HF hospitalization

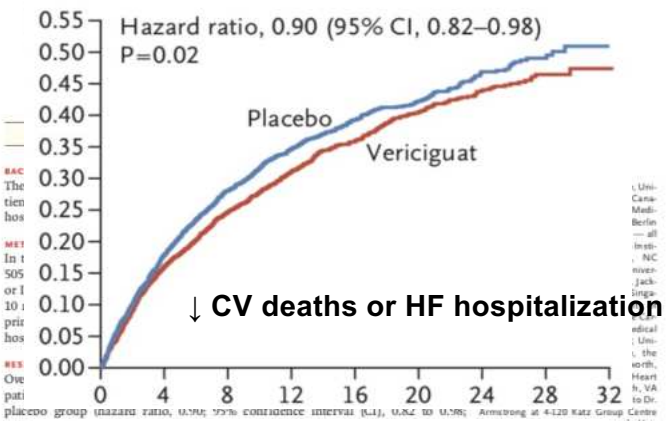
↓ CV deaths ↓ All cause deaths ↓ HF hospitalization

VICTORIA

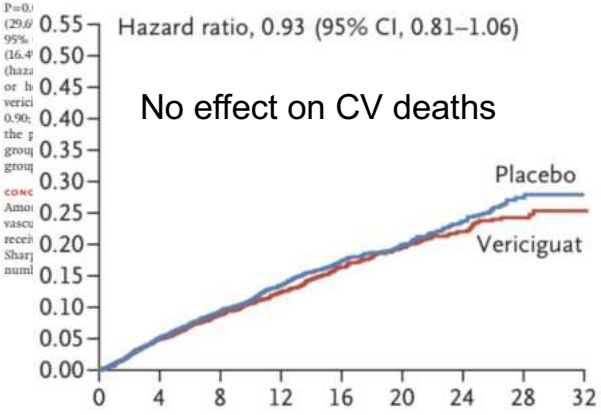
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction



↓ CV deaths or HF hospitalization



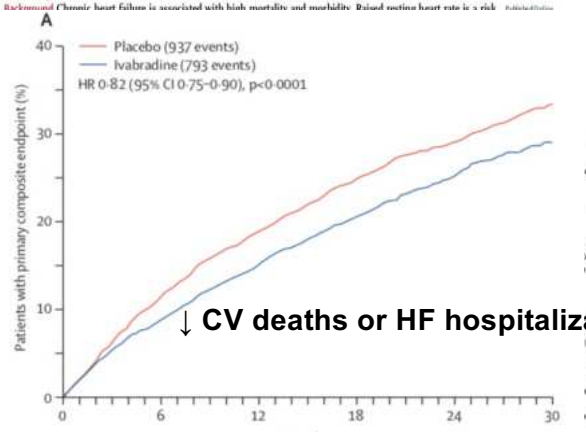
No effect on CV deaths

SHIFT

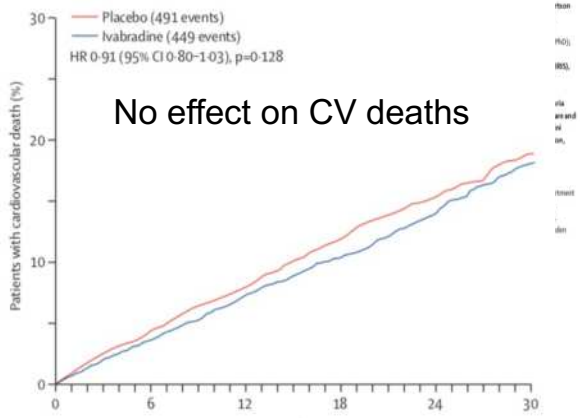
Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators*

Summary



↓ CV deaths or HF hospitalization

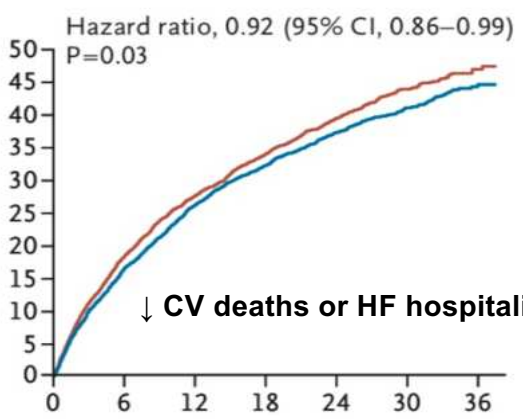


No effect on CV deaths

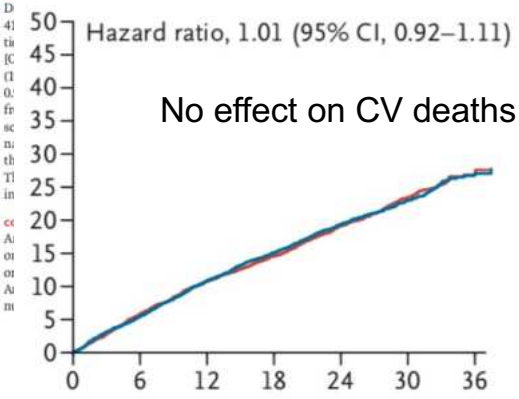
GALACTIC

ORIGINAL ARTICLE

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure

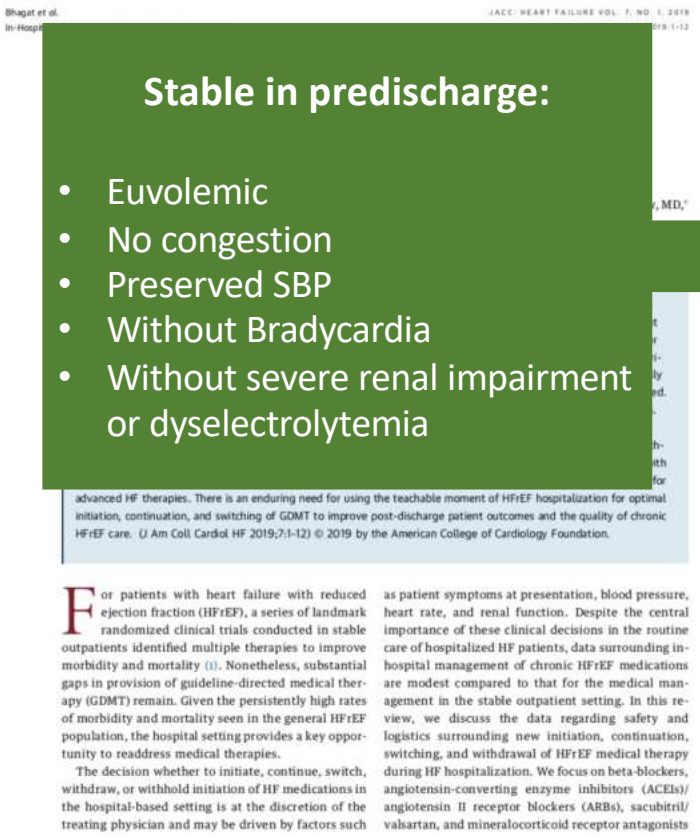


↓ CV deaths or HF hospitalization



No effect on CV deaths

Initiation, Switching, Continuation, and Withdrawal of GDMT During Hospitalization for HF



advanced HF therapies. There is an enduring need for using the teachable moment of HFrEF hospitalization for optimal initiation, continuation, and switching of GDMT to improve post-discharge patient outcomes and the quality of chronic HFrEF care. (J Am Coll Cardiol HF 2019;7:1-12) © 2019 by the American College of Cardiology Foundation.

For patients with heart failure with reduced ejection fraction (HFrEF), a series of landmark randomized clinical trials conducted in stable outpatients identified multiple therapies to improve morbidity and mortality (1). Nonetheless, substantial gaps in provision of guideline-directed medical therapy (GDMT) remain. Given the persistently high rates of morbidity and mortality seen in the general HFrEF population, the hospital setting provides a key opportunity to readdress medical therapies.

The decision whether to initiate, continue, switch, withdraw, or withhold initiation of HF medications in the hospital-based setting is at the discretion of the treating physician and may be driven by factors such as patient symptoms at presentation, blood pressure, heart rate, and renal function. Despite the central importance of these clinical decisions in the routine care of hospitalized HF patients, data surrounding in-hospital management of chronic HFrEF medications are modest compared to that for the medical management in the stable outpatient setting. In this review, we discuss the data regarding safety and logistics surrounding new initiation, continuation, switching, and withdrawal of HFrEF medical therapy during HF hospitalization. We focus on beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs), sacubitril/valsartan, and mineralocorticoid receptor antagonists

Stable in predischarge:

- Euvolemic
- No congestion
- Preserved SBP
- Without Bradycardia
- Without severe renal impairment or dyselectrolytemia

Type II DM

SLGT inh

Continue GDMT

Initiate or switch GDMT

Tolerance of GDMT and Optimization

- Tolerability includes documentation of the absence of postural hypotension and the administration of all doses as scheduled, without any being held for hypotension or dizziness
- Medicine reconciliation
- Reassess NCCs

postdischarge follow-up

36h ACEI washout required prior to switching to ARNI

Withdraw/ dose-reduction of GDMT

Hemodynamic intolerance, borderline perfusion, cardiogenic shock, concomitant vasopressor or inotrope requirement

Hemodynamic intolerance, substantial renal dysfunction, allergy (i.e., angioedema)

Hemodynamic intolerance, substantial renal dysfunction, or hyperkalemia

Risks Associated with Failure to Continue/Initiate/Switch GDMT During Hospitalization

- ↑ risk of readmission & short-, intermediate-, and long-term mortality
- ↓ medication adherence and ↓ medication persistence
- Substantially ↑ likelihood of never being initiated or switched to GDMT as outpatient
- Missing out on the teachable moment during hospitalization

Bhagat, A.A. et al. J Am Coll Cardiol HF. 2019;7(1):1-12.

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Position Paper

Patients profiling in Heart Failure for tailoring medical therapy A consensus document of the Heart Failure Association of the European Society of Cardiology

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REVIEW

Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction

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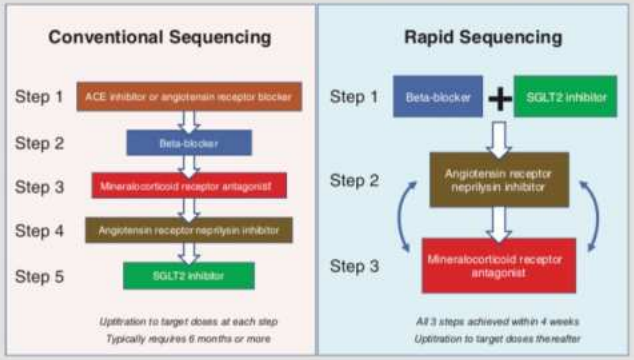
Foundational therapy for heart failure and a reduced ejection fraction consists of a combination of an angiotensin receptor–neprilysin inhibitor, a beta-blocker, a mineralocorticoid receptor antagonist and a sodium–glucose co-transporter 2 (SGLT2) inhibitor. However, the conventional approach to the implementation is based on a historically-driven sequence that is not strongly evidence-based, typically requires ≥6 months, and frequently leads to major gaps in treatment. We propose a rapid sequencing strategy that is based on four principles. First, since drugs act rapidly to reduce morbidity and mortality, patients should be started on all four foundational treatments within 2–4 weeks. Second, since the efficacy of each foundational therapy is independent of treatment with the other drugs, priority can be determined by considerations of relative efficacy, safety and ease-of-use. Third, low starting doses of foundational drugs have substantial therapeutic benefits, and achievement of low doses of all four classes of drugs should take precedence over up-titration to target doses. Fourth, since drugs can influence the tolerability of other foundational agents, sequencing can be based on whether agents started earlier can enhance the safety of agents started simultaneously or later in the sequence. We propose an accelerated three-step approach, which consists of the simultaneous initiation of a beta-blocker and an SGLT2 inhibitor, followed 1–2 weeks later by the initiation of sacubitril/valsartan, and 1–2 weeks later by a mineralocorticoid receptor antagonist. The latter two steps can be re-ordered or compressed depending on patient circumstances. Rapid sequencing is a novel evidence-based strategy that has the potential to dramatically improve the implementation of treatments that reduce the morbidity and mortality of patients with heart failure and a reduced ejection fraction.

Graphical Abstract



Take home messages:

- WHF represents worsening of signs and symptoms occurring after a period of stability, that requires escalation of the therapies
- WHF is an unplanned event
- Venue of care is not a biological threshold and clinical deterioration may lead to intensification of therapy in outpatient settings, ED or may lead to hospital admission; prognostic is similar
- New definition is important from epidemiological, research and regulatory perspective
- Hospitalization for HF is a sentinel event that signals worse prognosis but also provides key opportunities to redirect the disease trajectory
- Irrespective of clinical settings the treatment requires phenotipization
- Focus on pre-discharge phase