Progress in Cardiovascular Diseases

Update on Contemporary Management of Heart Failure

Hector O. Ventura, MD
and Ileana L. Piña, MD, MPH

Guest Editors

Carl J. Lavie, MD
Editor-in-Chief

Christopher J. White, MD
and Hector O. Ventura, MD
Editors
169 Comprehensive Heart Failure Management  
Hector O. Ventura and Ileana L. Piña

171 Is an Admission for Decompensated Heart Failure Inevitable?  
Alexander J. Blood, Ariane M. Fraiche, and Zubin J. Eapen

178 Approach to Acute Heart Failure in the Emergency Department  
Benton R. Hunter, Jennifer Martindale, Osama Abdel-Hafez, and Peter S. Pang

187 Pharmacologic Therapy for Heart Failure With Reduced Ejection Fraction: Closing the Gap Between Clinical Guidelines and Practice  
J. Barr Biglane, Miriam F. Becnel, Hector O. Ventura, and Selim R. Krim

198 Late In-Hospital Management of Patients Hospitalized With Acute Heart Failure  
Nicole B. Cyrille and Snehal R. Patel

205 Changing our Approach to Stage D Heart Failure  
Miriam Becnel, Hector O. Ventura, and Selim R. Krim

215 Palliative Care in Heart Failure: What Triggers Specialist Consultation?  
Mitchell A. Psotka, Kanako Y. McKee, Albert Y. Liu, Giovanni Elia, and Teresa De Marco

226 Heart Failure With Myocardial Recovery - The Patient Whose Heart Failure Has Improved: What Next?  
Petra Nijst, Pieter Martens, and Wilfried Mullens

237 A Blueprint for the Post Discharge Clinic Visit After an Admission for Heart Failure  
Aaron Soufer, Ralph J. Riello, Nihar R. Desai, Jeffrey M. Testani, and Tariq Ahmad

249 Heart Failure Transitions of Care: A Pharmacist-Led Post-Discharge Pilot Experience  
Sherry K. Milfred-LaForest, Julie A. Gee, Adam M. Pugacz, Ileana L. Piña, Danielle M. Hoover, Robert C. Wenzell, Aubrey Felton, Eric Guttenberg, and Jose Ortiz

259 Implementation of a Patient Navigator Program to Reduce 30-day Heart Failure Readmission Rate  
Katherine E. Di Palo, Khusbu Patel, Manaf Assafin, and Ileana L. Piña
Special Article

267  A Review of Cardiac Rehabilitation Delivery Around the World
Ella Pesah, Marta Supervia, Karam Turk-Adawi, and Sherry L. Grace

Editor's Commentary

281  From Heart Failure to Journal Metrics-Making Progress in Cardiovascular Diseases
Carl J. Lavie
Recent Topics

Physical Activity, Exercise and Fitness in Health and Disease
Ulrik Wisloff, PhD, and Carl J. Lavie, MD, Guest Editors

Stroke Prevention and Treatment
Rajan A.G. Patel, MD, and Christopher J. White, MD, Guest Editors

Conceptualizing a New Model for Healthcare: Focus on Healthy Living and Prolonging the Healthspan
Ross Arena, PhD, PT, and Amy McNeil, BA, Guest Editors

A New Renaissance in Pericardial Diseases
Allan L. Klein, MD, and Craig R. Asher, MD, Guest Editors

Controversies in Hypertension
Sripal Bangalore, MD, MHA, and Franz H. Messerli, MD, Guest Editors

New Eyes on Lipids and Lipoproteins
Neil J. Stone, MD, and Conrad B. Blum, MD, Guest Editors

Group 2 Pulmonary Hypertension: From Impaired Left Ventricular Filling to Right Heart Disease
Marco Guazzi, MD, PhD, FESC, FACC, FAHA, and Myung H. Park, MD, FACC, Guest Editors

Using Technology for Cardiovascular Disease Prevention and Treatment
Nina C. Franklin, PhD, MS, and Michael Pratt, MD, MSPE, MPH, Guest Editors

Prevention and Treatment of Cardiovascular Diseases
James J. DiNicolantonio, PharmD, and James H. O’Keefe, MD, FACC, Guest Editors

Emerging Trends and Current Controversies in Heart Failure
Jorge Silva Enciso, MD, and Barry Greenberg, MD, Guest Editors

Advances in Coronary Revascularization in the 21st Century
Sandra Weiss, MD, and William Weintraub, MD, Guest Editors

Advances in Atrial Fibrillation
Daniel P. Morin, MD, MPH, and N.A. Mark Estes III, MD, Guest Editors

Preventive Cardiology Update: Controversy, Consensus, and Future Promise
Jarett D. Berry, MD, MS, Guest Editor

Advances in Myocardial Perfusion Imaging
Sharmila Dorbala, MBBS, MPH, and Vasken Dilsizian, MD, FACC, FAHA, Guest Editors

Why Should We Care About the Coronary, Pulmonary, and Peripheral Vasculature: Perspectives on Pathophysiology, Measurement, and Interventions
Marco Guazzi, MD, and Shane A. Phillips, PhD, Guest Editors

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Comprehensive Heart Failure Management

Scope of heart failure

Epidemiology

Heart failure (HF) is a major public health problem in the United States (US) and across the world.1–3 It is estimated that there are 5.7 million adults in the US living with HF and that there are 1 million hospitalizations for HF yearly.3 Despite a decline in mortality and morbidity from most cardiovascular diseases (CVD), the prevalence of HF has increased worldwide,4,5 whereas the incidence has plateaued.6 Thus, between 1994 and 2003, the prevalence of HF in a US Medicare population increased from 90 to 121 per 1000 subjects.7 The American Heart Association estimates that the prevalence of HF will increase by 46% from 2012 to 2030, which amounts to 8 million people older than 18 years old with a HF diagnosis.5 With the increase in incidence and prevalence, projected cost increases are highly significant.

Hospitalizations

Index hospitalizations and readmissions remain as major issues in CVD, particularly affecting older patients. The Centers of Medicare and Medicaid Services recognize that the older adults with HF are also bringing a minimum of 4–5 comorbidities in each hospitalization.3,8 Furthermore, the natural history of HF is characterized by clinical exacerbations that contribute to a need for hospitalizations. Multiple hospitalizations place a burden on patients, health care systems, and society. It has been reported that hospital discharges for HF has increased by 155% during the last 20 years,9 and the health care costs exceed 30.7 billion dollars annually and will increase to 69.7 billion dollars in 2030.4,9 It is recognized that some hospital readmissions for patients with HF are unavoidable, but many can be prevented.10,11 Factors that are associated with readmission rates for HF include shorter length of stay and multiple emergency room (ER) visits within 6 months of hospitalization. An alarming statistic is that once patients are hospitalized, each admission contributes to an increase in mortality.9,10

Current progress in CVD (PCVD) issue

Because of the complexity of this syndrome as noted above, it is paramount to compile a comprehensive analysis of patients with HF and their associated problems.

In this current issue of PCVD, leaders in the field of HF discuss several aspects of the management of these patients, from ER to chronic care, including treatment of acute, chronic, and advanced HF, as well as patients who achieved myocardial recovery. Palliative care and transitions of care in order to reduce hospitalizations and to improve quality of life of these patients are also discussed.

It has been said, that “Planning is bringing the future into the present so that you can do something about it now”. We sincerely hope that this HF issue of PCVD will guide clinicians to make evidence based choices for their patients. However, where no evidence is available, hopefully this issue helps to at least apply fundamental knowledge and wisdom to their care.

REFERENCES

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Hector O. Ventura, MD*
John Ochsner Heart and Vascular Institute, Ochsner Clinical School
The University of Queensland School of Medicine, Australia

Ileana L. Piña, MD, MPH
Albert Einstein College of Medicine and Montefiore Heart and Vascular Center, Bronx, NY, United States

*Corresponding author at: Ochsner Clinic Foundation
1514 Jefferson Highway, New Orleans, LA 70121, United States
E-mail address: HVentura@ochsner.org

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Is an Admission for Decompensated Heart Failure Inevitable?

Alexander J. Blood, Ariane M. Fraiche, Zubin J. Eapen

Department of Medicine, Duke University Medical Center, Durham, NC, United States

Abstract

Given the high prevalence of heart failure (HF) and the profound impact on morbidity, mortality, and health care costs, strategies to improve outcomes and reduce cost have become progressively more attractive. Reducing HF hospitalizations as a study outcome has gained traction in recent years. The basic hypothesis of these investigations is that HF hospitalizations are preventable and harmful. This article examines advancements in pharmacotherapy, medical devices, and health care delivery techniques targeting reductions in HF hospitalizations and evaluates the role and implications of hospitalization in the natural history of HF.

Keywords: Heart failure, Hospitalizations, Readmission, Transitions of care, Telehealth, Alternative, Payment models

The population affected and health care impact of heart failure (HF) are striking with estimates of roughly 5.7 million adults in the United States (US) living with HF and 1 million hospitalizations for HF in 2000 and in 2010. The American Heart Association (AHA) projects that the prevalence of HF will increase by 46% from 2012 to 2030, which amounts to 8 million people older than 18 years old with a HF diagnosis. The health care costs related to HF exceed 30.7 billion dollars annually, which is estimated to increase by 127% to 69.7 billion dollars in 2030. As a major driver of hospitalizations and health care dollars, HF has become a critical area for health care reform. Contemporary objectives for reform include reducing hospital-
Abbreviations and Acronyms

<table>
<thead>
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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ACEI</td>
<td>Angiotensin converting enzyme inhibitor</td>
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<td>AHA</td>
<td>American Heart Association</td>
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<td>APM</td>
<td>Alternative payment models</td>
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<tr>
<td>BB</td>
<td>Beta blocker</td>
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<tr>
<td>CMS</td>
<td>Centers for Medicare &amp; Medicaid Services</td>
</tr>
<tr>
<td>CRT</td>
<td>Cardiac-resynchronization therapy</td>
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<tr>
<td>CV</td>
<td>Cardiovascular</td>
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<tr>
<td>EF</td>
<td>Ejection fraction</td>
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<tr>
<td>ERR</td>
<td>Excess Readmission Ratios</td>
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<tr>
<td>GWTG</td>
<td>Get with the guidelines</td>
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<td>HF</td>
<td>Heart failure</td>
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<tr>
<td>HRRP</td>
<td>Hospital Readmission Reduction Program</td>
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<tr>
<td>HTN</td>
<td>Hypertension</td>
</tr>
<tr>
<td>ICD</td>
<td>Implantable cardioverter – defibrillator</td>
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<tr>
<td>IPPS</td>
<td>Inpatient Prospective Payment System</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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The most common precipitants for decompensated chronic HF leading to hospitalization include but are not limited to the following: dietary indiscretion (sodium and/or fluid restriction), medication noncompliance, coronary ischemia, uncontrolled hypertension (HTN), infection, arrhythmia and endocrine abnormalities being among the most common.8–10 Fonarow, Abraham, and Albert investigated the frequency of these triggers among patients admitted for HF exacerbation by analyzing a random sample of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry which included 48,612 patients hospitalized for HF at 259 sites in the US.8 The most common etiologies for decompensated HF admission of the 61.3% of patients with precipitant identified included two or more factors in most patients (19.2%), respiratory infection (15.3%), coronary ischemia (14.7%), arrhythmia (13.5%), uncontrolled HTN (10.7%) and medication and dietary nonadherence (8.9% and 5.2%, respectively).7–9 Recently, Wu et al. reviewed all admissions for HF at a tertiary hospital in a 12-month period including 482 patients, and interestingly, the most common trigger that precipitated hospitalization in this cohort was suboptimal medication adherence.11 Contrary to the findings of Wu et al., of the identified causes for HF hospitalization in the OPTIMIZE-HF cohort, sub-optimal medication adherence had one of the weakest associations with HF hospitalization.8 Moreover, Farmer et al. conducted interviews with clinicians, HF patients and caretakers to determine qualitative contributors to hospitalization for HF. Issues with communication between both providers and patients and system-level factors were identified as significant determinants of wellness in patients with HF. Lack of patient education of the disease process and effects of medical therapy, mental health disorders and direct costs to patients were barriers to preventing hospitalizations.12 This diversity of identifiable triggers for HF hospitalization among these studies highlights that it is challenging to identify targets ripe for intervention to reduce HF hospitalizations and suggests that controlling for factors leading to decompensation when there are several simultaneously is a difficult goal.

HF hospitalization as an outcome

Because hospitalizations are associated with increased health care costs and worse patient outcomes in the natural history of HF, reducing hospitalizations is typically included as a primary or secondary outcome in investigations of novel HF therapies.13 For example, an analysis from the Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) shows that patients with an index hospitalization for worsening HF have a 3.5 fold increased risk of mortality at 18 months.14 Yet, research has also shown that although they incur financial penalties, 30-day readmissions do not correlate with mortality.15 Repeated hospitalizations for HF,
Transitions of care and alternative venues for HF care

Regarding transitions of care after HF hospitalization, conclusions from the OPTIMIZE-HF and Get With the Guidelines-Heart Failure (GWTG-HF) registries suggest that higher rates of post-discharge clinic follow-up within 7 days is associated with decreased 30-day readmission rates for hospitals. Determining how to coordinate outpatient care after inpatient hospitalization offers opportunities for quality improvement projects in this key transitional period. Examples of interventions to reach this endpoint include a French study which showed that a more aggressive outpatient management approach with regularly scheduled appointments and higher outpatient diuretic doses was associated with fewer unforeseen appointments and fewer hospitalizations. Al-Damluji et al. propose that communication elements conveyed to primary care providers such as including more elements in discharge documentation such as principal diagnosis, problem list, medication list, transferring physician name and contact information, cognitive status of the patient, test results and pending test results were associated with a lower risk of readmission, further emphasizing the key role of outpatient management to reduce hospitalization.
To complement evidence-based medications and devices, there is a myriad of alternative venues in which a HF patient may be able to receive care. Whellan et al. established a precedent for studying a comprehensive outpatient disease management approach to optimizing HF treatment. This disease management program for patients with HF was able to improve the percentage of patients on optimal medical therapy and decrease hospitalization, all while reducing costs. For example, the use and dose of BB therapy increased after enrollment in the disease management program, which utilized protocols to optimize medical management, frequent visits and telephone encounters with the HF team based on severity of illness and robust patient education materials. Moreover, the median rate of hospitalizations per patient-year decreased from 1.5 hospitalizations per patient-year to 0 for patients enrolled in the program (P < 0.01). Contemporary care model examples include the Duke Same Day Access Clinic and the Brigham and Women’s Hospital’s Ambulatory Cardiac, Triage, Intervention, and Education (ACTIVE) Unit, which provide alternatives to the emergency room for patients needing acute evaluation and management for worsening HF symptoms. During the first three years of operation of the Duke Same Day Access Clinic, the hospital saw an absolute 10.2% reduction in 30-day HF re-admissions. Similarly, an analysis of 60 chronic HF patients treated in the Brigham and Women’s Hospital’s ACTIVE Unit supports the effectiveness of protocolized intravenous diuretics to increase urinary output, achieve weight loss and avoid hospitalization. In addition to improving access to care and extending the arm of clinical care, alternative clinical venues potentially allow hospitals to avoid the penalties associated with hospital readmissions.

In terms of telehealth strategies to reduce hospitalizations related to HF, the data is mixed. A large meta-analysis of 41 peer-reviewed, randomized controlled trials showed a positive impact of a wide range of telehealth methods on HF-related hospitalizations, but the conclusions are limited by the diversity of interventions, size and quality of results. CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION)—a single-blinded, multicenter, randomized controlled trial with 550 patients—included HF hospitalizations as a primary outcome. The 37% decrease in the rate of HF hospitalizations in the treatment group suggests that implantable hemodynamic monitoring devices have a role in reducing HF-related hospitalizations. On the other hand, a recent meta-analysis and systematic review including telemonitoring as an intervention to reduce readmissions in HF patients did not show a statistically significant benefit on all-cause 30-day readmission nor 3 or 6-month all-cause readmission. Diverse and conflicting evidence has hampered efforts to enact telehealth strategies, yet future research encompassing telehealth strategies into alternative payment models and readmission reduction programs may play a role in high value HF care. These creative avenues for HF management are further instruments to prevent hospitalizations for high risk patients that focus on known triggers for decompensation.

Financial considerations of HF readmission

Health care reform that targets reducing hospitalizations in general harvests significant interest in HF hospitalizations. Jencks et al. found that HF was the most common condition at index discharge for patients in the Medicare Fee-For-Service Program readmitted within 30 days with a 26.9% readmission rate, and HF was also the most frequent reason for readmission for patients discharged with HF as condition at index discharge and for all patients readmitted within 30 days. Centers for Medicare & Medicaid Services (CMS) started to publicize 30-day readmission rates for patients hospitalized and discharged with pneumonia, myocardial infarction and HF in 2009. This public reporting began with the aim of increasing transparency, but the reporting itself has not been shown to reduce 30-day readmission rates. The Inpatient Prospective Payment System (IPPS) delivers payments for Medicare beneficiaries who are hospitalized, and since 2012, the IPPS has been used to limit Medicare reimbursements for hospitals with higher than predicted readmission rates. A study analyzing the effect of the Hospital Readmission Reduction Program (HRRP) found that 73% of hospitals in 2014 received penalties for readmissions. Further analysis of the penalties revealed that HF had stronger Excess Readmission Ratios (ERR) than other conditions and had the strongest correlation with the scale of the penalty. In the HRRP CMS defines the ERR as a calculation of a hospital’s readmission rate compared to the national average readmission rate for similar peer hospitals taking care of patients with similar demographic and comorbid conditions. Medicare data from 2009 to 2012 estimates the median risk-standardized 30-day readmission rate for HF as 23.0%. Whether HF hospitalization or all-cause hospitalization is the ideal outcome is a pertinent question. All-cause re-hospitalization, currently the focus of financial penalties, occurs with much greater frequency than HF readmission and captures not only the financial but also the patient-centric aspect of this outcome. In the context of the HRRP, an analysis of Medicare data showed that hospitals subject to penalty had greater reductions in readmission rates, when compared with hospitals not at risk for the penalty.

Advancements in payment and reimbursement models focusing on HF

The Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) was passed with the aim to transition from traditional fee-for-service payment structure to value-based care (Public Law: 114–10). MACRA establishes the Quality Payment Program with two options for Medicare providers to design value-based payment reform including the Merit-based Incentive Payment System and alternative payment models (APMs). Through either of these payment pathways, physicians will receive reimbursements for Medicare patients through measurements related to four core domains—quality activities, clinical improvement activities, advancing care information performance, and cost. Examples of APMs include bundled payments for HF hospitalizations, which fall under APMs built on the fee-for-service architecture with risk and gainsharing and
population-based payments for heart failure care.

The advent of APMs in HF offers opportunities for quality-driven care that encompasses the previously mentioned strategies such as telemonitoring and alternative outpatient management efforts.

Within the APM frameworks, resources will likely shift away from a reactive approach to management to a proactive approach to managing these patients outside of the hospital. Providing the appropriate level of monitoring and therapy for patients at different stages of their illness will likely be critical to reduce hospitalizations. With increasing application of technological advancements using health metrics and monitoring, predictive models to identify HF patients who are at risk of developing adverse events such as hospitalization and death are improving, and there are increasing opportunities to guide resource allotment efficiency. The goal of these reform efforts improve prevention and reduce costs. The hope is that HF hospitalization may be prevented in many if not most cases.

### Turning back to a key question: Hospitalization, morbidity, or mortality?

The knowledge that hospitalization as an event in the natural history of HF portends a poor prognosis has been discussed, and diverse approaches to preventing hospitalizations has been shown to be effective in this assessment. However, some populations have higher risks of hospitalizations offering a potential confounder when assuming hospitalization portends mortality and when determining the inevitability of hospitalization.

Studies have demonstrated that race, ethnicity and socioeconomic states affect hospitalization outcomes in HF patients. Vivo et al. elucidate several noteworthy differences in readmissions and mortality based on race and ethnicity of HF patients using the GWTG-HF registry coupled with Medicare data. A critical finding of this study including 47,149 Medicare patients over age 65 is that even though black and Hispanic patients were more likely to be admitted at 30-day and 1-year follow-up intervals than white patients, mortality was lower in the black and Hispanic population at the same follow-up intervals. When socioeconomic status, patient clinical characteristics and hospital-related variables were added to the multivariable model, the mortality outcome differences among race/ethnicities remained the same, but the groups became more similar regarding readmissions. Black patients still had higher 1-year readmission rates. Similarly, median household income has been shown to be inversely associated with 30-day mortality (OR 0.97, 95% CI 0.95–1.00, P = 0.032). These conclusions highlight an important concept: HF hospitalizations are not associated with higher mortality in all patient populations. As evidence-based methods shift to focus on hospitalization outcomes as described above, mortality-based management and therapeutics are still relevant.

Hospitalization is now featured in many HF trials. As the prevalence of HF continue to increase, the 1 million heart failure hospitalizations in 2000 and 2010 has remained stable. Interventions aimed at reducing hospitalizations may have contributed to reducing the inevitability of HF hospitalization in many cases. But, the natural history of heart failure is one of gradual decline punctuated by acute exacerbations, which in part may be due to non-preventable events. Considering ongoing advances in the development, design and implementation of new HF care, it is important that mortality is not overlooked in favor of hospitalization reduction. Innovation in medical therapies, devices and health care delivery will likely continue to improve access and adeptness of monitoring and management for HF with the added benefit of aiming to reduce hospitalizations. However, while many of these punctuations are preventable and manageable outside of the walls of the hospital, such as tools and systems to ensure medication and dietary compliance, medications to reduce the incidence of coronary ischemia and paroxysms of HTN, these culprits are often not reversible or available within the outpatient setting. These patients are often at risk for rapid and non-reversible clinical decompensation that is not amenable to outpatient management. While we will continue to improve our ability to monitor and prevent HF hospitalizations that are not inevitable, high risk patients will likely continue to experience decompensation that will require inevitable hospitalization.

### Conflict of interest

None.

### References


Approach to Acute Heart Failure in the Emergency Department

Benton R. Hunter\textsuperscript{a}, Jennifer Martindale\textsuperscript{b}, Osama Abdel-Hafez\textsuperscript{a}, Peter S. Pang\textsuperscript{c,⁎, 1}

\textsuperscript{a}Indiana University School of Medicine, Indianapolis, IN, United States
\textsuperscript{b}SUNY Downstate, Brooklyn, NY, United States
\textsuperscript{c}Indiana University School of Medicine, Indianapolis EMS, Indianapolis, IN, United States

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Emergency department

ABSTRACT

Acute heart failure (AHF) patients rarely present complaining of ‘acute heart failure.’ Rather, they initially present to the emergency department (ED) with a myriad of chief complaints, symptoms, and physical exam findings. Such heterogeneity prompts an initially broad differential diagnosis; securing the correct diagnosis can be challenging. Although AHF may be the ultimate diagnosis, the precipitant of decompensation must also be sought and addressed. For those AHF patients who present in respiratory or circulatory failure requiring immediate stabilization, treatment begins even while the diagnosis is uncertain.

The initial diagnostic workup consists of a thorough history and exam (with a particular focus on the cause of decompensation), an EKG, chest X-ray, laboratory testing, and point-of-care ultrasonography performed by a qualified clinician or technologist. We recommend initial treatment be guided by presenting phenotype. Hypertensive patients, particularly those in severe distress and markedly elevated blood pressure, should be treated aggressively with vasodilators, most commonly nitroglycerin. Normotensive patients generally require significant diuresis with intravenous loop diuretics. A small minority of patients present with hypotension or circulatory collapse. These patients are the most difficult to manage and require careful assessment of intra- and extra-vascular volume status. After stabilization, diagnosis, and management, most ED patients with AHF in the United States (US) are admitted. While this is understandable, it may be unnecessary. Ongoing research to improve diagnosis, initial treatment, risk stratification, and disposition may help ease the tremendous public health burden of AHF.
Diagnosis and management begins in the emergency department (ED) for the vast majority of patients hospitalized with acute heart failure (AHF). Unfortunately, the evidence base for ED management is limited. This lack of evidence, combined with the heterogeneity of the AHF patient population, results in tremendous variability in clinical practice. The potential impact of ED management is significant, as diagnostic delay or sub-optimal treatment may have significant downstream consequences. Perhaps the costliest ED management decision is deciding who does or does not require hospitalization, the most expensive resource in healthcare. As epidemiology and pathophysiology of AHF are covered elsewhere, this review focuses on initial ED management.

Obtunded patients with severe respiratory failure will likely require endotracheal intubation and mechanical ventilation. For patients with respiratory distress who are awake and cooperative, early initiation of non-invasive positive pressure ventilation (NIPPV) significantly decreases mortality and need for intubation. NIPPV can be instituted even if the diagnosis of AHF is in doubt, as evidence suggests benefit even in undifferentiated severe dyspnea. The increased intra-thoracic pressure from NIPPV may decrease blood awake and cooperative, early initiation of non-invasive ventilation.

Initial diagnosis and assessment

Fortunately, most AHF patients do not present in extremis. Establishing the diagnosis is the sine qua non of medicine, but is not always easy. It is worth noting the myriad of different patient complaints: Fatigue, dizziness, shortness of breath, chest pain, weakness, exercise intolerance, swelling, and weight gain are all symptoms prompting consideration of AHF as the cause.

The clinical presentation of AHF varies widely, ranging from mildly worsening heart failure, de novo or new onset HF, to overt cardiogenic shock, to hypertensive flash pulmonary edema. Despite the high prevalence of AHF in the ED setting, misdiagnosis occurs in 14–29% of patients. Heterogeneous pathophysiology and phenotypic expression, varied underlying causes and precipitants, and substantial co-morbid burden underlie the challenges of diagnosing this syndrome. Nevertheless, timely and accurate diagnosis of AHF is critical to preventing delays in treatment, which have been associated with increased risk of inpatient mortality and longer length of stay (LOS).

Unfortunately, no single historical variable, symptom, physical exam finding, biomarker, or imaging modality is sensitive enough to sufficiently exclude the diagnosis of AHF. Dyspnea is the most common symptom prompting patients with AHF to seek care, and is most often due to vascular...
congestion. Discriminating AHF from other causes of dyspnea, however, remains challenging, especially for those patients without a preexisting diagnosis of heart failure (HF) and those with comorbidities, such as chronic obstructive pulmonary disease. Symptoms classically associated with HF, such as orthopnea and paroxysmal nocturnal dyspnea are reported by only half of patients with AHF and are <75% specific for the diagnosis. The physical exam finding with the highest likelihood ratio (LR+) is an S3 gallop (LR+ 4.0 [95%CI 2.7–5.9]), but the absence of this finding has minimal effect on changing the pre-test probability of AHF (LR − 0.91 [95%CI 0.89–0.95]). Jugular venous distension and the hepatojugular reflex are more specific, but are insensitive and dependent on the examiner. Despite knowledge that congestion is the primary underlying cause of patient signs and symptoms, measuring congestion with a high degree of intra and interobserver reliability remains challenging.

Natriuretic peptides are the most useful biomarkers for excluding the diagnosis of AHF. Cutoff points of 100 pg/mL and 300 pg/mL for brain natriuretic peptide (BNP) and N-terminal (NT)-proBNP, respectively, substantially reduce the post-test probability of AHF (LR − 0.1) in patients presenting to the ED with dyspnea. Very high BNP values are modestly helpful in ruling in AHF, but intermediate values (100–800 pg/mL for BNP) lack diagnostic specificity. Likelihood ratios associated with even the most elevated NT-proBNP values only modestly favor the diagnosis of AHF. The specificity of these biomarkers above proposed cutoff points are limited by renal dysfunction and advanced age. Other conditions to consider in patients with modestly elevated BNP values are acute respiratory distress syndrome, pulmonary embolism, pulmonary hypertension, and valvular heart disease. While natriuretic peptides provide additive diagnostic value beyond clinical and historical variables, several studies have failed to demonstrate differences in patient-centered clinical outcomes beyond hospital LOS with the addition of diagnostic BNP testing.

In addition to a basic metabolic profile and complete blood count, troponin testing should be considered in AHF patients. Occasionally, troponin testing may uncover occult acute coronary syndrome (ACS), an important precipitant of AHF. Importantly, an elevated troponin does not rule in ACS, as many AHF patients may have troponin release. With the recent approval in the US of higher sensitivity assays, a series found that cardiomegaly alone had moderate sensitivity (79%) and specificity (80%). Lung ultrasound has emerged as a useful point-of-care tool for identifying pulmonary edema and diagnosing AHF. Sonographic detection of pulmonary edema is based on the identification of vertical artifacts called B-lines, which are thought to result from the reverberation of sound waves off of fluid-filled pulmonary interstitium. When distributed diffusely in the proper clinical setting, B-lines represent cardiogenic pulmonary edema. A positive lung ultrasound study, defined as two or more bilateral thoracic zones with ≥3 B-lines, has good discriminatory value with a LR+ of 7.4 (95% CI 4.2–12.8). A negative lung ultrasound study substantially lowers the probability of AHF (LR − 0.16 [95% CI 0.05–0.51]). The extent of pulmonary edema can also be semi-quantitatively measured by the sum of the number of B-lines with high inter-rater reliability. B-line severity has been shown to correlate with other measures of pulmonary congestion and the severity of AHF. The ESC HF guidelines now include lung ultrasound as a recommended diagnostic test to confirm pulmonary congestion.

Point-of-care ultrasound - determined estimates of intravascular volume and right atrial pressures can be made by measuring the diameter of the inferior vena cava (IVC) and percentage change in IVC diameter during the respiratory cycle. An IVC diameter that fails to substantially decrease with inspiration is considered to have a low collapsibility (or caval) index (IVC-CI), reflecting volume overload and highRAP. The diagnostic performance of different cutoff values for IVC collapsibility index, ranging from 20%–50% have been tested in dyspneic patients presenting to the ED. Sensitivities of 80% or greater were achieved in studies that used an IVC-CI cutoff of 33% or greater. Specificities associated with these cut-offs ranged from 81%–87%. Alternative causes of a plethoric IVC include tricuspid regurgitation, pulmonary embolism, pulmonary hypertension, and right ventricular infarction.

Echocardiography is integral to the diagnostic workup of HF. While formal echocardiography is rarely available rapidly in the ED, focused cardiac ultrasound in the hands of trained emergency physicians can be used as a point-of-care tool to assess global systolic dysfunction. Qualitative visual estimations of reduced versus normal ejection fraction (EF) can be made by assessing the inward movement of the interventricular septum and inferior wall of the left ventricle during systole and by observing the degree of excursion of the anterior leaflet of the mitral valve toward the interventricular septum during diastole. These qualitative assessments correlate with more formal, quantitative echocardiographic measures of EF. Reduced EF identified by emergency physicians using focused cardiac ultrasound discriminates AHF from other causes of dyspnea with sensitivities ranging from 77 to 83% and specificities ranging from 74 to 90%. However, sonographic assessments of dyspneic patients limited to this single variable would fail to identify HF patients with preserved EF. Identification of a restrictive pattern of diastolic filling using pulsed Doppler analysis of mitral inflow as a surrogate measure of elevated filling
pressures assist in the diagnosis of AHF (LR+ 8.3 [95% CI 4.0–16.9]). Acquisition and interpretation of mitral inflow and tissue Doppler data are currently beyond the scope of ED physicians who lack formal fellowship training. Diagnostic approaches that integrate lung, cardiac, and IVC assessments increase the specificity of diagnosing AHF in the ED beyond clinical gestalt, biomarkers, and lung ultrasound alone. Further research is needed to help delineate the role of focused cardiac ultrasound in the workup of AHF and how different sonographic assessments can be incorporated into diagnostic algorithms. Importantly, point of care US does not replace formal echocardiography.

**Initial management**

Once the diagnosis is made, presenting phenotype and cause of exacerbation guides initial treatment. As mentioned earlier, first assuring respiratory and hemodynamic stability is paramount (see Table 1 for goals of ED management). While addressing the patient’s respiratory status, the precipitant of AHF should be sought and treated. For example, rapid atrial fibrillation (AF), ACS, pulmonary embolism, underlying infection or dietary indiscretion can all trigger AHF. Often the precipitant is unclear or challenging to identify. Complicating matters, co-morbid conditions may cloud the picture or add challenges to management. A classic example is the patient with both chronic obstructive pulmonary disease and AHF; wheezing may be bronchial or ‘cardiac wheezing’, and one exacerbation may incite the other. While simultaneous treatment frequently occurs clinically, untoward effects (such as inciting AF with beta agonists) may be detrimental.

**Initial classification**

As an initial guide, we recommend grouping patients with suspected AHF by systolic BP (SBP). As evidenced by registries, SBP is often high (> 140 mm Hg) at the time of presentation. We recommend using cutpoints of >140 mm Hg, 100–140 mm Hg, and <100 mm Hg to guide initial selection of pharmacologic therapy. While there is considerable overlap, simple categorization aids the busy clinician. As such, it is reasonable to assume the predominant pathophysiologic derangement in a patient based on presenting SBP. Notably, not all patients present with total volume overload; the prototypical example is the flash pulmonary edema patient. Such patients have also been described as ‘vascular failure’ or ‘volume redistribution’ patients. These patients most commonly present with elevated SBP. Of note, the latest ESC HF guidelines also support dividing patients based on ‘cardiac’ (fluid overload predominates) vs. ‘vascular’ (hypertension predominates) phenotypes.

**Initial therapy**

At the present time, no AHF therapy receives a Level I, Class A recommendation from guidelines, highlighting the lack of robust evidence from randomized studies. Therapies used today are largely the same as those employed 4 decades ago (Table 2). Rotating tourniquets and phlebotomy are no longer used; whether this represents a major advance is debatable. Importantly, lack of high quality evidence from robust, randomized controlled trials does not equate with ineffectiveness in achieving symptom relief, hemodynamic improvement, and decongestion; all important targets of therapies.

**The hypotensive AHF patient**

Shock due solely to worsening HF rarely occurs relative to other types of AHF. Given its relatively uncommon presentation combined with the complexity of these patients’ underlying pathophysiology, precipitant, cardiac structure, function, and resultant hemodynamic status, management can be challenging. Patients with advanced HF may present with alarmingly low SBP. This may, in fact, reflect their baseline SBP. Even when resuscitating shock, a common mistake is attempting to normalize SBP and HR to values seen in those with baseline normal cardiac structure and function. However, for patients with severely reduced EF, a ‘normal’ SBP may be unattainable, and tachycardia may be the key contributor to cardiac output.

For patients with low SBP, administering a fluid bolus is nearly a reflexive action. But in the setting of hypoperfusion secondary to heart failure rather than hypovolemia, this may

---

**Table 1**

Goals of ED management (although written sequentially, steps may occur simultaneously)

1. Ensure stability of Airway, Breathing, and Circulation or resuscitate immediately
2. Identify and treat any other potential life threats (i.e. STEMI, dysrhythmias)
4. Identify the precipitant of AHF and modify treatment if necessary.
5. Consider the potential contribution of other co-morbid conditions and whether they require urgent treatment
6. Re-evaluate patient to ensure improvement in symptoms, hemodynamics, and clinical impression
7. Risk-stratify patient
8. Disposition planning (admission, observation, discharge)

**Table 2 – Therapeutic options for the early treatment of AHF – a historical perspective.**

<table>
<thead>
<tr>
<th>1974</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sit the patient upright</td>
<td>Sit the patient upright</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Oxygen</td>
</tr>
<tr>
<td>Positive pressure ventilation</td>
<td>Positive pressure ventilation</td>
</tr>
<tr>
<td>Morphine</td>
<td>Morphine</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>Intra-aortic balloon pump</td>
</tr>
<tr>
<td>Phlebotomy</td>
<td>Vasodilators/nesiritide</td>
</tr>
</tbody>
</table>
| Rotating tourniquets | }
result in worsening pulmonary edema. On the other hand, infection and overdiuresis are common precipitants that may respond quite well to fluid. At the bedside, assessing volume status is challenging, especially in patients with advanced HF. As noted above, ultrasound may be useful, but response to initial treatment will often be the best guide to subsequent management. Although rarely applied in the ED setting due to concerns of precipitating circulatory failure, AHF patients with low SBP who are congested may require decongestive therapies. Optimizing volume status through diuresis and vasodilation may lead to significant clinical improvement. In some refractory cases, inotropes and vasopressors are required to augment cardiac output and blood pressure.

**Inotropes and vasopressors**

Table 3 shows commonly used inotropes and vasopressors. Although inotropes and vasodilators improve hemodynamics, to date, none are associated with better clinical outcomes. In fact, available inotropes have been associated with harm, though the evidence base is small and inconsistent.68–71 In terms of vasopressors, there is a paucity of robust data to strongly recommend one vasopressor over another. Subgroup analysis from a large randomized trial found increased mortality in patients with cardiogenic shock who were randomized to dopamine compared with those randomized to norepinephrine.72

**The hypertensive patient**

Approximately half of patients admitted with AHF present with hypertension (SBP ≥ 140 mm Hg).15,60 In general, these patients tend to be older, have preserved EF,60 and present with a more acute onset of symptoms, often <24 h. Pulmonary edema in such patients is more likely to be caused by vascular redistribution than by hypervolemia. As such, vasodilators are the mainstay of treatment. Of the guideline-recommended vasodilator options [nitroglycerin (NTG), nitroprusside, or nesiritide], we recommend NTG as first line.73 Clinicians and nurses are familiar with NTG, it can be administered rapidly via sublingual and intravenous routes, and it’s inexpensive. Bolus doses of up to 2–3 mg are well tolerated and effective, though many clinicians are reluctant to give such large doses.74,75 Anecdotally, NTG as an IV drip is often withheld due to the requirement for an intensive care unit (ICU) bed. However, the rapid onset/offset of NTG makes it an ideal titratable drug to initiate before transitioning to topical NTG or alternative therapies.

Nitroprusside and nesiritide are alternatives to NTG. As with NTG, neither nitroprusside nor nesiritide has been shown to decrease mortality or morbidity in AHF.76 However, both are effective vasodilators, with nitroprusside being the more potent. While NTG predominantly acts on the venous circulation until at higher doses, nitroprusside acts rapidly on both the arterial and venous circulation. It may precipitously lower BP; thus careful monitoring is required. Nesiritide is one of the most well studied vasodilators in terms of large randomized controlled trials. After initial concerns regarding safety, a large randomized, controlled trial (ASCEND-HF; n = 7141) found no relative benefit or harm associated with nesiritide in terms of mortality, hospital readmission, or dyspnea.77 It may be a reasonable option if a vasodilator is desired but ICU beds are unavailable.

Despite the lack of compelling evidence supporting acute angiotensin converting enzyme inhibitor (ACEI) use in the ED, these agents are sufficiently used in the setting of AHF to be mentioned in the American College of Emergency Physicians.78 A common misperception: the benefit of ACEI in chronic HF with reduced EF extends to the acute setting. Lack of evidence does not equal a bad therapy; only that sufficiently powered, well-designed trials have not yet been performed.

Morphine’s historic use in AHF continues today. Retrospective observational data suggests an increased risk of death in patients treated with morphine for AHF.79 As it offers no defined benefit, we recommend against routine morphine use in AHF.

**The normotensive patient (SBP 100–140 mm Hg)**

AHF patients presenting with SBP ranging from 100 to 140 mm Hg rarely arrive to the ED in extremis.60 The prototypical patient reports an indolent course over days or even weeks, and may report significant weight gain.

### Table 3

<table>
<thead>
<tr>
<th>Inotrope/Vasodilator</th>
<th>Initial dose</th>
<th>Infusion range</th>
<th>Recommendation class (evidence level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>2–3 ucg/kg/min</td>
<td>2–20 ucg/kg/min</td>
<td>IIB (Level B)</td>
</tr>
<tr>
<td>Milrinone</td>
<td></td>
<td>0.375–0.75 ucg/kg/min</td>
<td>IIB (Level B)</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>0.05–0.2 ucg/kg/min</td>
<td></td>
<td>Not available in US</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2–5 ucg/kg/min</td>
<td>2–50 ucg/kg/min</td>
<td>IIB (Level B)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td>0.2–1.0 ucg/kg/min</td>
<td>IIB (Level B)</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5–20 ucg/min (rapidly titrate to effect)</td>
<td>5–200 ucg/min (rapidly titrate to effect)</td>
<td>IIB (Level A)</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>5–10 mcg/min</td>
<td>0.25 ucg/kg/min–10 ucg/kg/min</td>
<td>IIB (Level A)</td>
</tr>
<tr>
<td>Nesiritide</td>
<td></td>
<td>0.01 ucg/kg/min</td>
<td>IIB (Level A)</td>
</tr>
<tr>
<td>ACE-I (enalaprilat)</td>
<td>1.25–5 mg IV bolus q6 h</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Consider bolus dosing.
Decongestion with intravenous (IV) loop diuretics is the primary therapy. Bolus or continuous infusion diuretic administration makes no difference. A randomized trial comparing IV doses of the patient’s standard oral dose to larger IV doses (2.5 times the standard oral dose) found that larger doses resulted in more diuresis and marginally better dyspnea over the first 72 h, but also increased the likelihood of creatinine elevation. In addition to diuretic therapy, low-dose vasodilators should be considered in normotensive patients.

A Hospitalist’s Perspective in Brief

From the hospitalist perspective, whether so many AHF patients warrant admission is debatable. Nevertheless, at the present time, most AHF patients are hospitalized. Thus, it is worth highlighting the different clinical framework between hospitalists and ED physicians for the management of AHF. While risk overgeneralization, ED physicians work with limited data in a fast-paced environment where rapid disposition and ensured access to short-term follow-up are paramount. Thorough diagnostic evaluation of cardiac structure, function, and AHF etiology are secondary objectives for ED physicians. Hospitalists tend to expect greater diagnostic clarity and institute management plans that address comorbid conditions and the long-term consequences of cardiac remodeling.

In regards to clinical management, the use of diuretics is often a major point of contention between hospitalists and ED physicians. IV loop diuretics are the cornerstone of acute therapy for AHF patients. Nearly 90% of patients hospitalized with AHF receive IV loop diuretics in the ACC/AHA (American College of Cardiology/American Heart Association) and ESC guidelines, though large randomized controlled trials have yet to be performed (and it is doubtful they ever will be). Given the absence of other therapies to readily decongest patients, why IV diuretics are withheld or underdosed appears perplexing. Although retrospective studies suggest harm associated with early aggressive IV loop diuretic use, no prospective evidence supports this hypothesis. Withholding IV diuretics in the ED may be perceived by the inpatient teams as delaying patient care.

If diuretics are given in the ED, they are often underdosed. By their very mechanism of action, loop diuretics must be secreted via active transport in the proximal tubules of the kidney. Rather than minimize doses, especially in patients with impaired renal function, higher doses are required to reach the dose-response threshold.

Disposition and outcomes

Contrary to commonly held belief, most patients who visit the ED are sent home; only 9.3% of the annual 130 million ED visits in the US result in hospitalization. However, nearly all ED patients with AHF are hospitalized. From 2006 to 2011, the annual US hospitalization rate for AHF patients in the ED has consistently been around 85%. Given financial penalties tied to excess re-hospitalization, this admission rate warrants scrutiny.

Administrative data analyses suggest up to 50% of patients with AHF could be discharged or observed briefly and released. AHF is a progressive illness and the short-term prognosis following hospitalization is unacceptably poor. This makes the concept of a low-risk AHF patient difficult for the emergency physician to embrace. Yet within the spectrum of risk, some are lower than others. Identifying patients safe to be sent home from the ED remains challenging, as the majority of risk-stratification work in AHF focuses on defining and characterizing high risk in-patients, making extrapolation to the ED setting challenging. While some risk instruments, such as the AHF Index, EMHRC, STRATIFY, or the Ottawa Heart Failure Index are promising, none have gained widespread acceptance, either due to the need for further validation, differences in patient populations, or limited information on outcomes for discharged patients identified as lower risk. Identifying patients low enough risk for safe discharge from the ED remains a key focus for research.

The absence of high risk features (i.e. low BP, high BNP levels, worsening renal function, elevated troponin, and hyponatremia) does not equal no risk, but it does equate to lower risk. In the future, absence of myocardial injury by high sensitivity troponin assays may help identify low risk patients. As risk-stratification improves, appropriate selection of patients for treatment in observation or short-stay units in AHF may become easier. These units may provide more time to risk stratify patients, gauge response to therapy, provide education, engage case management and social work as needed, reconcile medications, and facilitate close follow up. These tasks are often challenging to complete during a brief ED stay. Furthermore, given the reluctance to discharge lower-risk AHF patients from the ED, the use of observation medicine as a ‘bridge’ may be more clinically feasible and acceptable to ED physicians.

For higher risk patients, hospitalization may offer benefit to improve symptoms, optimize volume status, and ensure initiation of guideline directed chronic medical therapy. AHF pharmacologic therapies, on their own, have not been proven to affect post-discharge outcomes. However, hospitalization may help higher risk patients achieve symptomatic relief, euvolemia/congestion, and medical optimization. Patients with new onset or de novo HF should also be admitted, as potentially reversible or modifiable causes may be identified. These patients will also need education about self-managing their new chronic illness. Overall however, indiscriminate admission is unlikely to translate into patient-centered benefit or justifiable cost. As mentioned previously, identifying who can be safely observed or discharged from the ED remains an unmet need.

Conclusion

The ED management of AHF centers around diagnosis, stabilization, identification of the precipitant of AHF, initial treatment, and risk-stratification. We recommend initial ED treatment be guided by presenting phenotype but treatment
largely centers around diuretics and vasodilators. Although currently available therapies improve symptoms, none definitively improve outcomes. Identification of life saving therapies for the early treatment of AHF remains an unmet need, though whether a short-term treatment can influence longer term post-discharge outcomes remains unclear. As US EDs continue to admit nearly all AHF patients, identifying appropriate low-risk patients for discharge and close follow-up would result in tremendous value to the health care system.

Statement of conflict of interest

Benton Hunter has no conflicts of interest.
Osama Abdel Hafez has no conflicts of interest.
Jennifer Martindale has no conflicts of interest.

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Pharmacologic Therapy for Heart Failure With Reduced Ejection Fraction: Closing the Gap Between Clinical Guidelines and Practice

J. Barr Biglane\textsuperscript{a,b,1}, Miriam F. Becnel\textsuperscript{a,b,1}, Hector O. Ventura\textsuperscript{a,b,c}, Selim R. Krim\textsuperscript{a,b,c,⁎}

\textsuperscript{a}Division of Cardiology, John Ochsner Heart and Vascular Institute, New Orleans, LA, United States
\textsuperscript{b}Section of Cardiomyopathy & Heart Transplantation, John Ochsner Heart and Vascular Institute, Ochsner Clinic Foundation, New Orleans, LA, United States
\textsuperscript{c}The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, LA, United States

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ABSTRACT

Despite the great progress made in the management of heart failure (HF) with reduced ejection fraction (HFrEF), its prevalence continues to rise owing to an aging population and an epidemic of hypertension, obesity and coronary artery disease. For decades, angiotensin converting enzyme inhibitors and beta blockers have been the mainstay of HFrEF therapy. The recent addition of sacubitril/valsartan and ivabradine to the HF armamentarium has the potential to transform our therapeutic approach to HFrEF, while simultaneously raising some questions and uncertainties on their applicability. In this paper, we review the pathophysiology of HFrEF, discuss already established and novel evidenced-based pharmacologic therapies available for these patients. We also share some therapeutic strategies aimed to optimize HF therapy in specific undertreated patient populations including the elderly and patients with chronic kidney disease, while offering insight on how to tailor therapy in the "real-world.”

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Contents

Introduction ............................................................. 188
SNS and RAAS systems: two key HF therapeutic targets ........................................... 188
The good: HF therapy that improves survival ....................................................... 189
   ACEI therapy ............................................................. 189
   ARB therapy ............................................................. 189
   BB therapy ............................................................. 190

Statement of conflict of interest: see page 196.

⁎ Address reprint requests to Selim R. Krim, MD, Section of Cardiomyopathy & Heart Transplantation, John Ochsner Heart and Vascular Institute, Ochsner Clinic Foundation, 1514 Jefferson Highway, New Orleans, LA 70121, United States.
E-mail address: selim.krim@ochsner.org (S.R. Krim).

1 Dr. J. Barr Biglane and Miriam Becnel contributed equally to the article.

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Abbreviations and Acronyms

ACEI = angiotensin converting enzyme inhibitors
ACCF = American College of Cardiology Foundation
AHA = American Heart Association
A-HeFT = African-American Heart Failure Trial
ANP = atrial natriuretic peptide
ARB = angiotensin receptor blocker
ARNI = angiotensin-receptor neprilysin inhibitors
BB = beta blockers
BMP = beats per minute
BNP = brain natriuretic peptide
BP = blood pressure
CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
CIBIS = Cardiac Insufficiency Bisoprolol Study
CIBIS-ELD = Cardiac Insufficiency Bisoprolol Study in Elderly
CKD = chronic kidney disease
CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study
CNP = C-natriuretic peptide
COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Study Group
COR = class of recommendation
CV = cardiovascular
DOSE = Diuretic Optimization Strategies Evaluation
EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
FDA = Food and Drug Administration
GDMT = guideline-directed medical therapy
HF = Heart Failure
HFN-LIFE = Entresto TM In Advanced Heart Failure

Aldosterone antagonist therapy ................................................. 190
Hydralazine and isosorbide dinitrate therapy ............................. 192
The bad: HF therapy for symptom relief .................................. 193
Diuretic therapy ....................................................................... 193
Digoxin .................................................................................... 193
The ugly: inotropic therapy ...................................................... 193
The new kids on the HF block ................................................... 194
Ivabradine therapy .................................................................... 194
Angiotensin receptor-neprilysin inhibitor therapy ....................... 194
Misconceptions, uncertainties and opportunities to optimize GDMT .. 194
Drug selection, initiation and titration ....................................... 194
Patients with CKD ..................................................................... 194
The elderly ................................................................................ 195
Incorporating sacubitril/valsartan into clinical practice ................. 195
Conclusion and future directions ............................................... 195
Financial disclosures .................................................................. 196
Conflict of interest .................................................................... 196
References .................................................................................. 196

Introduction

In the United States (US), 200,000 new cases of heart failure (HF) are diagnosed each year, with a total population exceeding 6 million. This population is only expected to grow in view of our aging population and improving therapies. While data regarding the successful treatment of HF with preserved ejection fraction (HFpEF) are lacking, great progress has been made in the pharmacologic therapy of HF with reduced ejection fraction (HFrEF). Guideline-directed medical therapy (GDMT) has led to significant improvement in both survival and reduction of hospitalization of HFrEF patients. For decades, angiotensin converting enzyme inhibitors (ACEI) and beta blockers (BB) have been the mainstay of HFrEF therapy. These agents target both the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), two major neurohormonal pathways that play a crucial role in the pathogenesis of HF. In the focused update of the HF guidelines published collaboratively by the American College of Cardiology (ACC), the American Heart Association (AHA) and Heart Failure Society of America (HFSA), two new drug classes were added after their approval by the Food and Drug Administration (FDA)—ivabradine and sacubitril/valsartan. The addition of these new agents has the potential to transform the way we approach medical therapy in HFrEF, while simultaneously raising questions and uncertainties on their applicability. This article aims to review the pathophysiology of HFrEF, while discussing established and novel evidenced-based pharmacologic therapies available for these patients. We also discuss some therapeutic strategies aimed to optimize HF therapy in specific undertreated patient populations including the elderly and patients with chronic kidney disease (CKD), while also offering insight on how to tailor therapy in the “real-world”.

SNS and RAAS systems: two key HF therapeutic targets

The SNS, RAAS, vasopressin pathway, and the natriuretic peptides (NP) system have been identified as the key pathophysiological mechanisms leading to the onset and progression of HFrEF. Naturally, these pathways have been the quintessential targets of current HF therapy. Chronic stimulation of the SNS leads to desensitization and down-regulation of the beta-1 receptors in both the myocardium and baroreceptors. Over time, this results in a decreased ability of the myocardium to respond to elevated catecholamine levels. Heart rate variability and baroreceptor dysfunction have consistently been observed in chronic HF patients. Studies have demonstrated that excessive sympathetic activation is associated with cardiac myocyte apoptosis, hypertrophy, and myocardial necrosis.
HFrEF = heart failure with reduced ejection fraction
HFSA = Heart Failure Society of America
LCZ696 = sacubitril-valsartan
LV = Left ventricle or left ventricular
LVEF = Left ventricular ejection fraction
LOE = level of evidence
MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure
NP = Natriuretic peptides
NSR = normal sinus rhythm
NYHA = New York Heart Association
PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PIONEER = ComPartson Of Sacubitril/valsartan Versus Enalapril on Effect on ntpRo-bnp in Patients Stabilized From an Acute Heart Failure Episode
QoL = Quality of Life
RAAS = renin-angiotensin-aldosterone system
RADIANCE = Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme
RALES = Randomized Aldactone Evaluation Study
RCT = randomized controlled trial
SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors
SHIFT = Systolic Heart Failure Treatment with the If inhibitor Ivabradine trial
SNS = sympathetic nervous system
SOLVD = Studies of Left Ventricular Dysfunction

One downstream effect of ongoing sympathetic stimulation is the ensuing chronic over-activation of the RAAS cascade. RAAS stimulation leads to increased concentrations of renin, angiotensin II, aldosterone and vasopressin. The circulation of additional renin triggers the production of angiotensin II. Angiotensin II, one of the most vasoactive peptides, contributes to LV remodeling and may lead to the endothelial dysfunction observed in HF.3 NP have become a new target for future HF therapies. Vasoactive peptides such as NP, bradykinin, and adrenomedullin are degraded by the enzyme neprilysin.2 The neurohormonal overactivation that occurs in HF can be offset by the inhibition of neprilysin, as increased levels of these vasoactive peptides help to prevent the long-term deleterious effects of sodium retention, vasoconstriction, and maladaptive remodeling.5 The most recently approved drug and the angiotensin receptor neprilysin inhibitor (ARNI) focuses on the aforementioned pathway. Fig. 1 summarizes the targets in the RAAS and SNS pathways with their respective therapeutic interventions.

The good: HF therapy that improves survival
Evidence-based medicine obtained through RCTs has remained the catalyst in driving the development and progress made in HF therapy. From the early vasodilator trials10-12 to the most recent ARNI study,7 each trial has been a stepping stone for the next. The major pharmacologic HFrEF trials are outlined in Table 1.

ACEI therapy
ACEI have been a mainstay of treatment for many years given their mortality and morbidity reducing abilities in the HFrEF population. With an ACC/AHA class of recommendation (COR) I and level of evidence (LOE) A recommendation, they are sure to remain a pillar in HFrEF therapy.3-5 Multiple large and multicenter RCT have shown these therapies to improve functional capacity and symptoms, decrease hospitalizations, and most importantly reduce mortality in both ischemic and non-ischemic cardiomyopathy.12,13 The first ACEI trial with favorable results was the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), which studied the effects of enalapril vs. placebo in patients with New York Heart Association (NYHA) class IV HF.12 The enalapril arm exhibited a 40% relative risk reduction in mortality, improvement in NYHA classification, reduction in heart size, and decreased medication requirements when compared to the placebo arm.12 Following the results of the CONSENSUS trial yielded the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial,13 which aimed to further explore the role of ACE-inhibition in NYHA class II and III patients. SOLVD-treatment reinforced the survival benefit and reduction in hospitalizations in these patients with less severe HF.13 Starting and target doses for ACEI is further described in Table 2.

ARB therapy
Following the success of the CONSENSUS12 and SOLVD13 trials prompted the hypothesis that additional inhibition of the RAAS pathway at a different level could be beneficial in chronic HF. The Valsartan HF Trial (Val-HeFT)14 tested the addition of valsartan versus placebo in NYHA class II-IV patients who were already receiving background medical therapy which included ACEI, BB, and aldosterone antagonists. In comparison to ACEI therapy with ACEI, BB, and aldosterone antagonists. In comparison to the findings of Val-HeFT, CHARM found a significant reduction of all-cause mortality, cardiovascular (CV) death and HF hospitalizations in the candesartan arm. Interestingly and
unlike Val-HeFT, concomitant ACEI use did not negate the beneficial effects of candesartan.\textsuperscript{15} ARBs are a reasonable alternative for those patients intolerant of ACE as they antagonize the angiotensin II receptor, thus avoiding kinase inhibition. In turn, this results in a lower incidence of cough and angioedema.\textsuperscript{3}

**BB therapy**

SNS activation is one of the many pathophysiologic abnormalities that leads to chronic HF.\textsuperscript{8} Sympathetic antagonists have been studied and proven to reduce morbidity and mortality in HF.\textsuperscript{16,17} In this regard, several trials have elucidated the beneficial effects of BB, the first being the Cardiac Insufficiency Bisoprolol Study (CIBIS II).\textsuperscript{16} CIBIS II aimed to show that bisoprolol, when compared to placebo, reduced morbidity and mortality in HF. With a significant mortality and morbidity benefit when compared to placebo, the trial was stopped early. Interestingly, while mortality benefit was seen in non-ischemic patients, the greatest effect in CIBIS-II was seen in ischemic cardiomyopathy patients with NYHA class III symptoms.\textsuperscript{16}

The U.S. HF Study Group\textsuperscript{17} compared carvedilol to placebo in patients with chronic HF, primarily NYHA II and III, and was ultimately stopped early given the significant morbidity and survival benefits seen in the treatment group, although not powered to test mortality directly. Several years later, the Carvedilol Prospective Randomized Cumulative Survival Study Group (COPERNICUS) trial\textsuperscript{15} reaffirmed these benefits in moderate-severe HF.

Finally, the Metoprolol CR/XL Randomized Intervention Trial in congestive HF (MERIT-HF)\textsuperscript{19} was a RCT which studied NYHA class II-IV patients assigned either to placebo or metoprolol CR/XL, with a primary endpoint of all-cause mortality. MERIT-HF reduced all-cause mortality and hospitalization for worsening HF, while simultaneously improving NYHA class and QoL.\textsuperscript{19}

As evidenced in the previously mentioned RCTs, metoprolol succinate controlled release/extended release (CR/XL), carvedilol, and bisoprolol are the only approved BB to use in HFrEF. The use of one of these three agents carries a COR I LOE A recommendation and should be initiated in all patients with chronic HFrEF.\textsuperscript{3-5} Patients who are not taking these specific BBs, but qualify for HFrEF diagnosis should be changed to one of the three discussed above.

**Aldosterone antagonist therapy**

Aldosterone plays a considerable role in the pathophysiology of HF and RAAS pathway.\textsuperscript{8} The use of an aldosterone inhibitor was first highlighted in the Randomized Aldactone Evaluation Study (RALES).\textsuperscript{20} Patients with NYHA III-IV symptoms were randomized to receive spironolactone, an aldosterone antagonist, or placebo in addition to an ACEI and loop diuretic.\textsuperscript{20} The trial was discontinued early due to a 30% reduction in the risk of death in the spironolactone group. In addition to mortality benefits, it showed morbidity benefits through symptom improvement and NYHA class regression.\textsuperscript{20} Of note, 10% of male patients who were treated with spironolactone reported gynecomastia or breast pain, a side effect attributed to the nonselective properties of spironolactone that allow the drug to bind to progesterone and androgen receptors.\textsuperscript{20}

Following RALES the Eplerenone in Mild Patients Hospitalization and Survival Study in HF (EMPHASIS-HF),\textsuperscript{21} enrolled
NYHA class II HFrEF patients with an EF of 35% or less and were randomized to receive eplerenone vs. placebo. Eplerenone was found to reduce all-cause morbidity and reduce hospitalizations when added to standard HF therapy. Eplerenone is more selective to the aldosterone receptor than spironolactone, gynecomastia was quite rare and observed in <1% of trial participants. Hyperkalemia was the most common adverse event noted in the treatment arm of the trial.

### Table 1 – Major pharmacologic HFrEF trials.

<table>
<thead>
<tr>
<th>Clinical Trial Acronym</th>
<th>Year</th>
<th>Population Characteristics</th>
<th>HF Background Therapy (&gt;50%)</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Mortality/Morbidity Findings</th>
<th>Mortality Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-HeFT II</td>
<td>1986</td>
<td>Mild to moderate HF</td>
<td>Digoxin, diuretics</td>
<td>Hydralazine</td>
<td>Placebo</td>
<td>↓ in mortality</td>
<td>38%</td>
</tr>
<tr>
<td>CONSENSUS</td>
<td>1987</td>
<td>NYHA IV HF increased heart size</td>
<td>Diuretics, spironolactone, digitalis</td>
<td>Enalapril</td>
<td>Placebo</td>
<td>↑ in mortality</td>
<td>27%</td>
</tr>
<tr>
<td>SOLVD-Treatment</td>
<td>1991</td>
<td>NYHA II, III, IV</td>
<td>Digoxin, diuretics</td>
<td>Enalapril</td>
<td>Placebo</td>
<td>↑ in mortality</td>
<td>16%</td>
</tr>
<tr>
<td>V-HeFT II</td>
<td>1991</td>
<td>NYHA II, IV</td>
<td>Digoxin, diuretics</td>
<td>Enalapril</td>
<td>Placebo</td>
<td>↑ in mortality</td>
<td>N/A</td>
</tr>
<tr>
<td>US Carvedilol HF Study</td>
<td>1996</td>
<td>NYHA II, III, IV</td>
<td>ACEI, digoxin, diuretics</td>
<td>Carvedilol</td>
<td>Placebo</td>
<td>↓ in mortality hospitalizations</td>
<td>65%</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>1999</td>
<td>NYHA III, IV</td>
<td>ACEI, digoxin, diuretics</td>
<td>Bisoprolol</td>
<td>Placebo</td>
<td>↓ in mortality and hospitalizations in bisoprolol group</td>
<td>34%</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>1999</td>
<td>NYHA II, III, IV</td>
<td>ACEI, diuretics</td>
<td>Metoprolol XL</td>
<td>Placebo</td>
<td>↓ in mortality and hospitalizations</td>
<td>39%</td>
</tr>
<tr>
<td>RALES</td>
<td>1999</td>
<td>NYHA III–IV</td>
<td>ACEI, digoxin, diuretics</td>
<td>Spironolactone</td>
<td>Placebo</td>
<td>↓ in mortality</td>
<td>30%</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>2001</td>
<td>NYHA IV</td>
<td>ACEI/ARB, digoxin, diuretics</td>
<td>Carvedilol</td>
<td>Placebo</td>
<td>↑ in mortality</td>
<td>35%</td>
</tr>
<tr>
<td>Val-HeFT</td>
<td>2001</td>
<td>NYHA II, III, IV</td>
<td>ACEI, digoxin, diuretics</td>
<td>Valsartan</td>
<td>Placebo</td>
<td>↑ in mortality and hospitalizations -- all-cause mortality</td>
<td>N/A</td>
</tr>
<tr>
<td>CHARM</td>
<td>2004</td>
<td>NYHA II, III, IV</td>
<td>ACEI, BB, digoxin, diogxin</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>↓ in mortality</td>
<td>33%</td>
</tr>
<tr>
<td>A-HeFT</td>
<td>2004</td>
<td>NYHA III, IV</td>
<td>ACEI, BB, digoxin, diuretics</td>
<td>Hydralazine</td>
<td>Placebo</td>
<td>↓ in mortality and hospitalizations</td>
<td>43%</td>
</tr>
<tr>
<td>SHIFT</td>
<td>2010</td>
<td>NYHA II, III, IV</td>
<td>ACEI, aldosterone antagonist, BB, diuretics</td>
<td>Ivabradine</td>
<td>Placebo</td>
<td>↓ in hospitalizations</td>
<td>N/A</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>2011</td>
<td>NYHA II</td>
<td>ACEI, BB, diuretics</td>
<td>Eplerenone</td>
<td>Placebo</td>
<td>↓ in mortality and hospitalizations</td>
<td>37%</td>
</tr>
<tr>
<td>PARADIGM-HF</td>
<td>2014</td>
<td>NYHA II, III, IV</td>
<td>Aldosterone antagonist, BB, diuretics</td>
<td>LCZ696 (sacubitril/valsartan)</td>
<td>Enalapril</td>
<td>↓ in mortality and hospitalizations</td>
<td>16%</td>
</tr>
</tbody>
</table>

Abbreviations: HFrEF, heart failure with reduced ejection fraction; HF, heart failure; V-HeFT: Vasodilator in Heart Failure Trial; LV, Left ventricle or left ventricular; LVEF, left ventricular ejection fraction; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; NYHA, New York Heart Association; SOLVD, Studies of Left Ventricular Dysfunction; US, United States; ACEI, angiotensin-converting-enzyme inhibitors; CIBIS, Cardiac Insufficiency Bisoprolol Study; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; QOL, quality of life; RALES, Randomized Aldactone Evaluation Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study Group; ARB, angiotensin receptor blockers; Val-HeFT, Valsartan Heart Failure Trial; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; BB, beta blockers; A-HeFT, African-American Heart Failure Trial; SHIFT, Systolic Heart Failure Treatment with the If inhibitor Ivabradine trial; HR, heart rate; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; PARADIGM-HF: Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure.
Candidates for aldosterone receptor antagonist therapy include those with NYHA class II-IV HF with an LVEF of <35% who are already receiving background therapy with a BB and ACEI.

This ACC/AHA COR I LOE A recommendation specifies that in order to deem a NYHA class II HF patient a candidate for aldosterone antagonists they should have been either hospitalized for a CV condition or have elevated plasma NP levels. Additionally, patients with an LVEF of 40% or less following an acute myocardial infarction, who develop HF symptoms or have diabetes mellitus should be initiated on an aldosterone antagonist.

Hydralazine and isosorbide dinitrate therapy

The potential therapeutic benefit in HFrEF patients with combination hydralazine and isosorbide dinitrate was first explored in the Vasodilator-HF Trial (V-HeFT I). In this trial patients with chronic HF already taking digoxin and diuretics were randomized to either placebo, prazosin, or hydralazine plus isosorbide dinitrate therapy. This trial aimed to evaluate if a mortality benefit existed with use of these vasodilator therapies. The group treated with both hydralazine and isosorbide dinitrate showed a statistically significant mortality reduction at two years, in addition to an improvement in LV function.

The approval of ACEI use in HFrEF coincided closely in time to V-HeFT I prompting V-HeFT II. This trial compared enalapril to hydralazine plus isosorbide dinitrate, and found that the ACEI had a more favorable effect on mortality than the vasodilator combination. Upon retrospective analysis of the V-HeFT I and II trials, it was noted that African-Americans were more likely to respond to the combination of hydralazine and isosorbide dinitrate, whereas enalapril only provided a mortality reduction in their Caucasian counterparts. This interesting observation was theorized to be related to a lower bioavailability of nitric oxide and a more active RAAS within the black subgroup.

### Table 2 – Currently available pharmacotherapy for HFrEF.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Maximum Daily Dose</th>
<th>Mean Dose Achieved in Clinical Trials</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I, channel inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>5 mg QD</td>
<td>7.5 mg BID</td>
<td>6.4 mg BID (at 28 days)</td>
<td>II</td>
<td>B-R</td>
</tr>
<tr>
<td>ARNI</td>
<td></td>
<td>6.5 mg BID (at 1 year)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/Valsartan</td>
<td>49/51 mg BID</td>
<td>97/103 mg BID</td>
<td>375 mg QD; target dose: 24/26 mg, 49/51 mg OR 97/103 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg TID</td>
<td>50 mg TID</td>
<td>122.7 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg BID</td>
<td>10–20 mg BID</td>
<td>16.6 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5–10 mg QD</td>
<td>40 mg QD</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5–2.5 mg QD</td>
<td>20–40 mg QD</td>
<td>32.5–35 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25–2.5 mg QD</td>
<td>10 mg QD</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg QD</td>
<td>4 mg QD</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg QD</td>
<td>8–16 mg QD</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg BID</td>
<td>20 mg BID</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4–8 mg QD</td>
<td>32 mg QD</td>
<td>24 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td>25–50 mg QD</td>
<td>50–150 mg QD</td>
<td>129 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valsartan</td>
<td>20–40 mg BID</td>
<td>160 mg BID</td>
<td>254 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 QD</td>
<td>10 mg QD</td>
<td>8.6 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg BID</td>
<td>50 mg BID</td>
<td>37 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg QD</td>
<td>80 mg QD</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol Succinate</td>
<td>12.5–25 mg QD</td>
<td>200 mg QD</td>
<td>159 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5–25 mg QD</td>
<td>25 mg QD or BID</td>
<td>26 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg QD</td>
<td>50 mg QD</td>
<td>42.6 mg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine and isosorbide Dinitrate</td>
<td>37.5 mg hydralazine/20 mg isosorbide dinitrate TID</td>
<td>5 mg hydralazine/40 mg isosorbide dinitrate TID</td>
<td>~175 mg hydralazine/90 mg isosorbide dinitrate QD</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Fixed dose combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine and isosorbide</td>
<td>Hydralazine: 25 to 50 mg, TID or QID and isosorbide dinitrate: 20 to 30 mg TID or QID</td>
<td>Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GDMT, guideline directed medical therapy; HFrEF, heart failure with reduced ejection fraction; mg, milligram; ARNI, angiotensin receptor-neprilysin inhibitor; QD, every day; BID, twice daily; ACE, angiotensin-converting-enzyme inhibitor; TID, three times daily; ARB, angiotensin receptor blocker; BB, beta blocker; CR, controlled release; QID, four times daily.
These striking discoveries prompted further investigation by means of the African-American HF Trial (A-HeFT)\textsuperscript{22} which targeted blacks with NYHA III and IV symptoms and dilated LVs. This landmark study published in 2004 confirmed the previous findings that the addition of a fixed-dose combination of isosorbide dinitrate and hydralazine to standard HF therapy in this population was associated with a significant reduction in all-cause mortality and hospitalizations while also improving QoL.\textsuperscript{22}

Two major recommendations were generated through the gains of these trials. The first endorses the use of combination hydralazine and isosorbide dinitrate to reduce morbidity and mortality in NYHA III and IV African American patients with HF who are already receiving ACEI and BB therapy. The second advises that the same therapy may be useful in reducing mortality and morbidity in this same cohort who are unable to tolerate an ACEI or ARB.\textsuperscript{3 5}

The bad: HF therapy for symptom relief

**Diuretic therapy**

Diuretic therapy has maintained a seat at the table in the management of HF therapy through its symptom relief properties. Bearing in mind that it holds no mortality benefit, diuretics are mainly used for symptom relief in patients who present with acute decompensated HF and fluid retention.\textsuperscript{23} These agents should be used in conjunction with GDMT.

Furosemide, bumetanide, and torsemide are three loop diuretics that are commonly used in clinical practice (Table 3).\textsuperscript{24} Furosemide is the most widely used due to low cost, longevity, and provider familiarity. Nonetheless, both bumetanide and torsemide have better bioavailability and as a result are more efficacious in some situations.\textsuperscript{25} In cases of refractory volume retention, thiazide diuretics may be used in conjunction to loop diuretics.\textsuperscript{26 27} A noteworthy study to consider when managing diuretic therapy is the Diuretic Optimization Strategies Evaluation (DOSE) trial\textsuperscript{28} which showed no difference in outcomes between continuous infusion versus bolus dosing of furosemide in patients hospitalized for HF. In addition, there was no observed difference in the safety and efficacy of bolus injections in comparison to continuous infusions of loop diuretics. However, the higher dose resulted in better diuresis.\textsuperscript{28}

**Digoxin**

Heralded as the oldest known CV drug, digoxin acts by increasing contractility through inhibition of the Na+/K+ ATPase in the myocardium.\textsuperscript{29} Though not effective at reducing mortality, this medication has been shown to decrease hospitalizations and improve functional class.\textsuperscript{30 31} Current guidelines recommend to consider digoxin for HF patients who remain symptomatic despite the use of mortality reducing GDMT.\textsuperscript{3 4} Another utility of digoxin in the HFrEF population is in patients with atrial fibrillation in whom a rate control strategy is preferred, and may be considered for those patients unable to tolerate a BB or who remain inadequately rate controlled on maximum doses of BB.\textsuperscript{3 5}

Owing to a narrow therapeutic range, careful consideration should be given to the side effects and potential toxicity of digoxin prior to initiation. In light of this, digoxin use has significantly decreased, particularly in the era of safer and more proven HFrEF therapies such as BB, ACE and ARNIs. Findings from the Randomized Assessment of Digoxin on Inhibitors of the ANgiotensin Converting Enzyme (RADIANCE)\textsuperscript{32} and Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED)\textsuperscript{33} trials suggest that withdrawal of digoxin in patients with HFrEF can result in worsening clinical symptoms, thus we recommend caution when discontinuing therapy.

The ugly: inotropic therapy

Despite their often controversial presence on the HF scene, continuous inotrope therapy maintains an important role in a few circumstances.\textsuperscript{3 4} The two most commonly used inotropes in HFrEF are dobutamine, a beta-agonist, and milrinone, a phosphodiesterase-3 inhibitor.\textsuperscript{3 4} The net effect of both these inotropes on the myocardium is amplified calcium influx resulting in increased LV contraction. Both agents have the potential to cause peripheral vasodilation and hypotension, but is often more pronounced with milrinone. In addition, providers should be aware of their arrhythmogenic nature.\textsuperscript{3 4}

Data has shown that routine use of these agents for acute decompensated HF without low-output or shock or for long-term treatment of HFrEF increases mortality.\textsuperscript{3 5} Accordingly, current ACC/AHA guidelines urge against this practice.\textsuperscript{4} Clinical scenarios that inotropes may be appropriate is in the setting of cardiogenic shock where inotropes can serve as a bridge-to-decision or as a palliative therapy. When employed as a bridge, the goal should be clearly defined, whether that includes initiation and uptitration of GDMT, addition of cardiac-resynchronization therapy, or advanced HF therapies such as mechanical circulatory support and cardiac transplantation. As a final resort, and in the absence of candidacy for advanced HF therapies, palliative inotropes may be used for symptomatic relief during end of life care.\textsuperscript{4}

---

**Table 3 – Properties of commonly used diuretics in HFrEF.**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Potency</th>
<th>Oral:IV</th>
<th>Duration of effect</th>
<th>Bioavailability</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>1x</td>
<td>2:1</td>
<td>6–8 h</td>
<td>10–100%</td>
<td>2</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>40x</td>
<td>1:1</td>
<td>4–6 h</td>
<td>80–100%</td>
<td>1–1.5</td>
</tr>
<tr>
<td>Torsemide (not available IV)</td>
<td>2x</td>
<td>1:1</td>
<td>6–16 h</td>
<td>80–100%</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Abbreviations: x, times; IV, intravenous; h, hours.
The new kids on the HF block

Ivabradine therapy

Ivabradine was approved for use in the US in 2015 and is a selective inhibitor of the I_f current in the sinoatrial node. The primary therapeutic effect is heart rate reduction and is exclusive of any other effects on the heart or vascular system. The major publication driving drug approval in the US was the Systolic HF treatment with the I_f inhibitor ivabradine Trial (SHIFT) trial.6 This European-based study aimed to assess the benefit of heart rate reduction with ivabradine in moderate to severe HF patients, with the vast majority of the enrollees falling into NYHA class II and III. The composite primary endpoint of CV death or hospital admission for worsening HF showed a relative risk reduction of 18%, but was driven by the reduction in HF hospitalizations.6

Ivabradine carries a class IIa LOE B-R recommendation in the most recent ACCF/AHA/HFSA guidelines, and is indicated to reduce hospitalizations in NYHA II and III patients with symptomatic HFrEF who are receiving GDMT, but most importantly a BB at a maximum tolerated dose. These patients should have a heart rate >70 beats per minute (bpm) at rest and be in normal sinus rhythm (NSR). The adoption of this drug has been slow in the US and more data is needed to evaluate its full benefit in our HFrEF patient population.

Angiotensin receptor-neprilisin inhibitor therapy

The newest agent on the market has the potential to bring new enthusiasm to the treatment of HFrEF. The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF) sought to test the hypothesis that the addition of neurohormonal inhibition to RAAS inhibition via the ARB mechanism may be superior to ACEI alone. This double-blind trial compared a twice daily combination form of the ARB valsartan and the neprilisin-inhibitor sacubitril, otherwise known as LCZ696, to twice daily enalapril (10 mg twice daily) in NYHA class II–IV HF patients. The impressive 20% reduction in the endpoint of CV deaths or hospitalizations for HF in those treated with LCZ696 lead to early trial termination.3

The reduction in mortality and HF hospitalizations observed in this trial prompted the focused update of the ACC/AHA HF guidelines. The COR I LOE B-R recommendation calls for replacement with ARNI in NYHA class II and III patients who are tolerating therapy with an ACEI or ARB to further reduce mortality.5

In regard to the side effect profile, the results were very similar between the two drugs with the exception of a slightly higher rate of non-life threatening angioedema and hypotension in the LCZ696 group. It is important to note that an ACEI should not be co-administered with an ARNI and that, if already taking an ACEI, patients are recommended to discontinue the ACE-inhibitor at least 36 h prior to starting sacubitril/valsartan. More clinical trial data is warranted for additional recommendations including its use in hospitalized patients.

Misconceptions, uncertainties and opportunities to optimize GDMT

Drug selection, initiation and titration

Step-wise initiation and titration of GDMT to efficacious doses as seen in RCTs is imperative to obtain any and all morbidity and mortality benefits in HF patients. Regardless of symptom severity, ACEI therapy remains first-line therapy followed by BB therapy.3-5 We recommend starting at low doses with up titration and frequent clinical assessment during that period. Following ACEI initiation, serum creatinine and potassium levels should be assessed within 1 to 2 weeks.

As previously mentioned, and unlike ACEIs, the benefits obtained with BB therapy are not a class effect, therefore only metoprolol succinate, carvedilol or bisoprolol should be used in HFrEF.3-5 Early initiation of BB therapy is imperative and prescribers need not wait until target doses of ACEI are achieved prior to adding it. This strategy has led to greater improvement in symptoms and reduction in the risk of death when compared to delayed use of BBs until maximal dose ACE is reached. It is acceptable to discontinue BB therapy in the setting of marked hypoperfusion. Moreover, among patients admitted for new onset HF, initiation of BB before discharge has been shown to increase adherence and likelihood to achieve target doses and is recommended in the Guidelines.

When changing from one BB to another, current data suggest starting the new agent at an equivalent dose with close monitoring of clinical status and adverse events. During the up-titration period, the risk of hypotension can be avoided by administering the BB and the ACEI at different times of day. In addition, BB should be titrated to maximally tolerated dose regardless of target heart rate as recent data suggested that titration of BB doses may provide a greater benefit than reduction of heart rate in well treated HFrEF patients.

Patients with CKD

The use of ACEI and aldosterone antagonists in patients with CKD continues to be a conundrum in clinical practice. Data regarding the use of these agents within this population remain scarce, as most HF trials exclude patients with significant renal dysfunction. Hence the conventional wisdom has been to avoid the use of these therapies entirely in patients with impaired renal function. Guidelines recommend the use of these agents with caution in patients with advanced renal impairment and with clear directions in regard to creatinine and potassium levels that would preclude the use of these agents.4,5 Despite the aforementioned, we believe these agents and underused, are potentially safe, and should be used (with caution) as they have the ability to benefit this population.

The element of renal dysfunction that exists in a large majority of HF patients is quite indicative of the struggle clinicians face in the complexities of the cardio-renal relationship. The increased prevalence of CKD in the HFrEF population highlights that ACEI and aldosterone antagonist use may be beneficial in improving renal perfusion and
In several new pharmacologic interventions are now included in landmark HF clinical trials and data suggest survival benefit when used in this patient population. In addition a recent study suggested a strong association between ACEI use and survival in HFpEF patients with severe renal impairment, which may be indicative that ACEI use may be associated with an even higher absolute mortality reduction in this population.

**The elderly**

Elderly patients now represent the largest group of HFrEF patients and paradoxically, limited data exists on the efficacy of GDMT in this population due to their under-representation and frequent exclusion from large clinical trials. Without question, age related physiological changes and drug metabolism in the elderly put them at higher risk for adverse events. Moreover, comorbid conditions such as renal and liver impairment further complicate the elderly’s response to drugs and increase their risk for adverse events such as hypotension and bradycardia. Despite the scarcity of data in the elderly, there are two noteworthy trials. The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) included over 2000 patients over the age of 70 who were randomized to receive either nebivolol or placebo. Treatment with this agent was found to be statistically significant in decreased all-cause mortality and CV hospitalization. Strengths of the trial include the exclusive focus on the older cohort of HF patients and an extensive follow-up of 21 months. Limitations in this trial primarily include the use of nebivolol, a BB that does not carry a HFrEF indication, and the presence of HFpEF patients due to laxity in the inclusion criteria. Nevertheless, the study offered some valuable lessons with regard to tolerability and response to therapy in the elderly. The CIBIS in Elderly (CIBIS-ELD) was another large study that focused on drug specific side effects. This multicenter, double-blind superiority trial of bisoprolol versus carvedilol included 883 elderly HF patients with both HFpEF and HFrEF. Although tolerability was low, no differences between the 2 groups were seen in the primary end point as defined by reaching and maintaining guideline-recommended target doses after 12 weeks of therapy. Intriguingly, adverse events varied among the two drugs in the trial. While bradycardia was more common in the bisoprolol group, pulmonary adverse events were more likely to occur with carvedilol. Despite the above-mentioned studies, many important questions remain unanswered on the efficacy and safety of HF GDMT in the elderly. Large clinical trials and data from national registries are essential to close this knowledge gap.

**Incorporating sacubitril/valsartan into clinical practice**

With a 20% reduction in CV mortality, there is no doubt that sacubitril/valsartan is by far the most efficacious HFrEF therapy developed in the last decade supplanting both ACEI and ARB therapies. Despite this, there has been a very slow adoption of this novel drug in the HF community. Cost may be a factor in the slow implementation of this ANRI into clinical practice, though other concerns exist and have been raised from experts in the field as well as community providers. One of those concerns includes a middle dose of enalapril compared to a higher equivalent dose of valsartan. Often times translating clinical trial results and implementing them to daily practice can be challenging. The reality is patients tend to be older as compared to clinical trials, and frequently possess comorbidities that would be otherwise exclude them from clinical trials. An important limiting factor in prescribing this therapy is low BP. In the PARADIGM-HF study, roughly 1/5 of patients were excluded in the run-in phase due to hypotension in either the sacubitril/valsartan or enalapril group. For this reason, we recommend caution when using this agent in the elderly, in patients with borderline-low BP, or in the advanced HF population. We urge clinicians to use the “start low and titrate slow” approach as it is likely the safest method to avoid such events. Identifying the patient population that will benefit most from this drug can also be arduous. The majority of patients enrolled in PARADIGM-HF were stable patients with NYHA class II patients, which leaves uncertainty in the efficacy and safety of this drug in sicker patients. In a recent study, 84% of HFrEF patients in the US were projected to be good candidates for ARNI therapy highlighting the clear opportunity to expand the use of this drug in patients who would benefit the most. Two additional clinical trials are underway: ComParison Of Sacubitril/valsartan Versus Enalapril on Effect on ntpRo-bnp in Patients Stabilized From an Acute Heart Failure Episode (PIONEER-HF) study and the EntrestoTM In Advanced Heart Failure HFN-LIFE trial. The PIONEER study will be exploring the safety and efficacy of in-hospital initiation of ARNI therapy and its potential role among patients hospitalized for acute decompensated HF. The LIFE trial will focus on the utility of ARNI therapy in patients with advanced HF.

**Conclusion and future directions**

The journey to efficacious pharmacologic therapy in HFrEF has been far from fleeting. Beginning with the V-HeFT trial in 1986 which set the stage by introducing vasodilator therapy in the HF arena, and ending most recently with the PARADIGM-HF trial, major milestones have been met along the way. For decades, ACEI, BB, aldosterone antagonists and combined therapy with hydralazine-isosorbide dinitrate have been the mainstay therapies for HFrEF. With the most recent focused updates to the ACC/AHA Guidelines for the management of HF, several new pharmacologic interventions are now available and may provide superior survival benefits in comparison to established agents. One fundamental take-away message is that provider familiarity with proper patient selection, initiation, maintenance, and adverse events related to the different drug classes is of the utmost importance. Continued collection of data through clinical trials and registries related to this chronic illness is key in ensuring progressive treatment options with a special focus on previously understudied populations in the literature. It is only through this undertaking that we can begin to remedy the HF epidemic.
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Conflict of interest

None.

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Late In-Hospital Management of Patients Hospitalized with Acute Heart Failure

Nicole B. Cyrille, Snehal R. Patel*

Department of Medicine, Division of Cardiology, Montefiore Medical Center-Albert Einstein College of Medicine, Bronx, NY

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ABSTRACT

Acute Heart Failure (AHF) hospitalization presents a significant financial burden and portends a poor prognosis following discharge. As such, there has been significant emphasis on the late inpatient management of patients hospitalized with AHF to ensure successful transition to the outpatient setting and to reduce overall readmission and mortality rates. Thorough discharge planning and a multidisciplinary team approach are essential and as outlined in this review should focus on four key elements: the assessment of patients' readiness for discharge, optimization of goal directed medical therapy and appropriate device therapy, patient education and transition to the outpatient care.

Contents

Assessing readiness for discharge ................................................... 199
- Body weight changes ........................................................... 199
- Biomarkers ............................................................................. 200
- Hemoconcentration .............................................................. 201
- Goal directed medical therapy ................................................. 201
- Device therapies ................................................................. 202
- Patient education ................................................................. 202
- Transition to outpatient care .................................................. 202
- Conclusion ............................................................................ 203
- Statement of conflict of interest ............................................... 203
- References .............................................................................. 203

Acute heart failure (HF; AHF) accounts for about 1 million admissions annually in the United States (US). In 2012, HF expenditure totaled approximately $30.7 billion and is estimated to increase to $69.7 billion by 2030. Hospitalization for AHF is the major contributor to total HF expenditure and accounts for up to 69%. In addition, the prognosis following...
AHF hospitalization remains poor with hospital mortality ranging from 4% to 7%, post-discharge 60 to 90 day mortality as high as 7%–11%, and one year mortality as high as 36%. Re-admission rates are also a significant burden with ≥50% patients re-admitted to the hospital within 6 months of discharge. An analysis of 2007 to 2009 Medicare claims-based data showed that 24.8% of patients admitted with HF were readmitted within 30 days with 35.2% of those readmissions for HF. Further, a 2008 study found that in patients with stage D HF, only 32% were alive and had not been readmitted at one year after discharge for AHF. Reduction in re-admission rates particularly in an effort to reduce cost has been a major focus in pay for performance initiatives resulting in the US Center for Medicare & Medicaid Services requiring public reporting of all-cause re-admission rates after HF hospitalization and the implementation of financial penalties for hospitals with the highest re-admission rates during the first 30 days after discharge. While there has been a significant emphasis on post-discharge follow-up to reduce re-admissions, it is also well established that appropriate pre-discharge care affects outcomes. Therefore, ensuring that HF patients are optimized prior to discharge and developing effective strategies for transition to the outpatient care are of paramount importance and are the focus of this review. In particular, we will emphasize the key management issues that should be addressed in the late stages of the hospitalization. (Fig 1).

### Assessing readiness for discharge

It is well established that the goal of all AHF hospitalizations is to achieve maximal decongestion. What is unclear is how best to determine when this goal has been met and patients can be transitioned to the outpatient setting. In fact, studies have shown that a large proportion of patients are discharged with unresolved symptoms and this may be a major contributor to high re-admission rates. For instance, among the 363 hospitalized patients enrolled in the Initiation Management PredischARGE Process for Assessment of Carvedilol Therapy for Heart Failure (IMPACT-HF) trial, approximately 60% of patients were discharged with continuing symptoms of dyspnea or fatigue. At 60 days after discharge, approximately 45% of these patients experienced worsening HF and 25% required rehospitalization. For this reason, surrogate markers to assess a patient's readiness for discharge are important.

### Body weight changes

A decrease in admission body weight is often used as a surrogate measure for adequate diuresis. In the Acute Decompensated Heart Failure (ADHERE) registry, among 105,358 patients discharged from AHF hospitalization, 52% reported that they were asymptomatic, 37% were improved (but still symptomatic), <1% were unchanged, and <1% were worse. Overall one-third had lost only 0–5 lbs in weight on discharge and 16% had actually gained weight. In the EVEREST registry, among 4172 AHF patients enrolled in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial the median change in body weight during hospitalization was −1.0 kg (interquartile range: −2.1 to 0.0 kg) at 24 h and −2.3 kg (interquartile range: −5.0 to −0.7 kg) by discharge/day 10. After risk adjustment, increasing body weight during hospitalization was associated with a 16% increase per kg in the likelihood of 30-day mortality or HF re-admission for patients showing weight loss ≤1 kg or weight gain during hospitalization (OR per kg increase 1.16, 95% CI: 1.09 to 1.27; p < 0.001). Therefore, the simple but often overlooked metric of reliable daily weights can help guide therapy and assess readiness for discharge. After achievement of pre-admission "dry" weight, patients should ideally be transitioned to oral diuretic therapy during the hospital stay to ensure its effectiveness. A period of 24 h of observation in the hospital after transition to an oral regimen may be required but is often difficult due to external pressures to reduce length of stay. In
proBNP (NT-proBNP), high sensitivity troponin I and galectin-3 (Gal-3) have been studied for their prognostic value in AHF and may be useful in assessing readiness for discharge.14–19 The natriuretic peptides, BNP and NT-proBNP are the best studied and are produced by myocardial stretch. In 1999, one of the earliest studies by Yu et al. showed that in a small prospective cohort of 91 patients admitted with AHF, plasma BNP levels were significantly higher in patients who died of a cardiovascular (CV) cause within 12 months (P < 0.0001) or at 1-month (P < 0.001) after recruitment. By Kaplan–Meier estimated life-table curves, patients with above median plasma ANP or BNP levels had significantly higher 1-year mortality (42.5% vs. 11.6%, both P < 0.005) and by multivariate Cox proportional hazard regression analysis, the plasma BNP level was the most important prognostic factor predicting mortality (chi² = 18.3, P < 0.0001).

More recently in OPTIMIZE-HF, among 7039 patients, median (25th, 75th) admission and discharge BNPs were 832 pg/mL (451, 1660) and 534 pg/mL (281, 1111) respectively. The 1-year mortality and 1-year mortality or rehospitalization rates were 35.2% and 79.4%. In this study the discharge BNP was the most important for predicting 1-year mortality (HR 1.34; 95% CI 1.28–1.40) and 1-year death or rehospitalization (HR 1.15; 95% CI 1.12–1.18). Compared with a clinical variables only model, the discharge BNP model improved risk reclassification and discrimination in predicting each outcome (1-year mortality: NRI 5.5%, P < 0.0001; IDI 0.023, P < 0.0001; 1-year mortality or rehospitalization: NRI 4.2%, P < 0.0001; IDI 0.010, P < 0.0001).19 NT-proBNP has a slower clearance from plasma compared to BNP and shows a correspondingly greater rise in disease which may make it a better marker for prognostication. In 2003, O’Brien et al. measured NT-proBNP at admission in 96 patients hospitalized with AHF. In a subset of 34 patients, NT-proBNP was also measured prior to discharge. On multivariate analysis of the clinical and serological predictors of a combined primary endpoint of death or HF (hospitalization or as an outpatient), admission plasma NT-proBNP was not predictive (OR 1.84 [0.75–4.51], P = 0.185). However, in the 34 patients for whom both admission and pre-discharge NT-proBNP was available, only pre-discharge plasma NT-proBNP (OR 15.30 [95% CI: 1.4–168.9], P = 0.026) was independently predictive of the composite endpoint. The area under the receiver-operator-characteristic curve (AUC ROC) for pre-discharge NT-proBNP was superior to that for admission NT-proBNP for prediction of death or HF (AUC ROC 0.87 cf. 0.70), for death (0.79 cf. 0.66), left ventricular (LV) failure hospitalization (0.78 cf. 0.70) or HF as an outpatient (0.71 cf. 0.61).21 A >30% reduction in natriuretic peptide levels may be used in assessing adequate decongestion prior to discharge based on an analysis of the Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support trial (SURVIVE) trial. The association between changes in BNP levels and all-cause mortality was
assessed among 1038 patients admitted with AHF and random-
ized to levosimendan or dobutamine. A patient was classified as a “responder” if the follow-up BNP level was > or =30% lower than baseline BNP. Responders at days 1, 3, and 5 had lower all-cause mortality compared to nonresponders (p < or = 0.001), with day-5 levels showing superior discriminating value. Short-term (31-day) all-cause mortality risk reduction was 67% in day-5 BNP responders compared with nonresponders, whereas long-term (180-day) risk reduction was 47%.22

Galectin-3 (Gal-3) is a novel biomarker believed to be associated with cardiac macrophage activation of fibroblasts, fibrosis, and ventricular remodeling. The addition of Gal-3 to discharge BNP has been shown to provide significantly improved prediction of 60-day readmission. In addition, Gal-3 alone was found to be a significant predictor of 60-day readmission in patients with preserved LV ejection fraction (LVEF; AUC 0.85, p < 0.001). The net reclassification improvement was 55.2 (p = 0.037). Using multivariate analysis, for every 100 pg/L BNP increase, the probability of readmission increased by approximately 10%, and for every 1-ng/ml Gal-3 increase, the probability further increased 8%. Obtaining both biomarkers at discharge may thus provide additive information in determining likelihood of readmission.8 Gal-3 is now available in a number of commercial laboratories and in the process of being added to many hospital laboratories.

**Hemoconcentration**

Achievement of hemoconcentration may also be used as a surrogate marker of adequate decongestion with restoration of euvolemia leading to a rise in hemoglobin levels. This has been shown to be related to favorable outcomes including a lower risk of mortality and HF rehospitalization.23 In 1684 patients assigned to the placebo arm of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial, 26% of patients had evidence of hemoconcentration (i.e., ≥3% absolute increase in hematocrit). Patients with greater increases in hematocrit tended to have better baseline renal function. Hemoconcentration correlated with greater risk of in-hospital worsening renal function, but renal parameters generally returned to baseline within 4 weeks post-discharge. Patients with hemoconcentration were less likely to have clinical congestion at discharge, and experienced greater in-hospital decreases in body weight and natriuretic peptide levels. After adjustment for baseline clinical risk factors, every 5% increase of in-hospital hematocrit change was associated with a decreased risk of all-cause death [hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.70-0.95]. Hematocrit change was also associated with decreased CV mortality or HF hospitalization at ≤100 days post-randomization [HR 0.73, 95% CI 0.71-0.76].23 Ter Mateen et al. analyzed diuretic response (defined as weight change per 40 mg of furosemide on day 4 after admission) and hemoconcentration (change in hemoglobin at discharge or day 7) to predict the risk of HF and CV rehospitalization 60 days after hospitalization for AHF among patients enrolled in the Pro-BNP Outpatient Tailored CHF Therapy Study (PROTECT) and further validated their findings in EVEREST. The median diuretic response was −0.36 [−0.77 to −0.13] kg/40 mg furosemide (PROTECT) and −0.30 [−0.79 to −0.03] kg/40 mg furosemide (EVEREST). The median hemoconcentration was 0.20 [−0.50 to 0.26] g/dL (PROTECT) and 0.20 [−0.40 to 0.90] (EVEREST), with 58% of patients in PROTECT and 56% of patients in EVEREST displaying a rise in hemoglobin by day 7 or discharge. Patients who displayed both favorable diuretic response (< median kg/40 mg furosemide) and hemoconcentration had a markedly lower risk of rehospitalization for HF in PROTECT (multivariable HR, 0.41; 95% CI, 0.24 to 0.70; P < 0.001) compared with all other patients. This finding was also validated in EVEREST (multivariable HR, 0.52; 95% CI, 0.33 to 0.82; P = 0.004).24

**Goal directed medical therapy**

The presentation of AHF is dependent on the volume and perfusion status of the patient. Patients may be congested (wet) or not congested (dry), adequately perfused (warm) or poorly perfused (cold).25 Irrespective of tailored therapy, which may include diuretics, vasodilators and inotropes, efforts should be made to ensure optimal goal directed medical therapy (GDMT) on discharge. Angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), neprilysin inhibitors and aldosterone antagonists should be continued whenever possible. Though hyperkalemia, acute kidney injury and oliguria may require temporary discontinuation of these drugs, they should be restarted cautiously in the inpatient setting. Continuation of ACEIs or ARBs and beta blockers (BBs) for most patients is well tolerated and results in better outcomes.25-29 The data regarding BB use are particularly strong and discontinuing or reducing BB therapy should be considered only in patients hospitalized after recent initiation or increase in BB therapy, those with marked volume overload or those in a low output state. Among 752 patients enrolled in the 2003 Carvedilol Or Metoprolol European Trial (COMET), 61 patients (8%) had BB treatment withdrawn, 162 (22%) had a dose reduction and 529 (70%) were maintained on the same dose. The risk of death was higher in patients who discontinued BB therapy or those who had their dose reduced with 1 and 2 year cumulative mortality rates of 28.7% and 44.6% for patients whose BB was withdrawn, 37.4% and 51.4% for those with a reduced dosage (NS) and 19.1% and 32.5% for those maintained on the same dose (HR, 1.59; 95%CI, 1.28–1.98; p < 0.001, compared to the other).26 Similar findings were also found on review of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure registry (OPTIMIZE-HF) in which pre-specified 60- to 90-day outcomes at 91 academic and community hospitals throughout the US were analyzed. Among 2373 patients, of which 1350 (56.9%) were receiving BBs before admission and continued on therapy, 632 (26.6%) were newly started, 79 (3.3%) had their therapy withdrawn, and 303 (12.8%) were eligible but not treated. In this cohort, continuation of BBs was associated with a significantly lower risk and propensity adjusted post-discharge death (HR: 0.60; 95% CI: 0.37 to 0.99, p = 0.044) and death or rehospitalization (OR: 0.69; 95% CI: 0.52 to 0.92, p = 0.012) compared with no BBs. In contrast, withdrawal of BBs was associated with a substantially higher adjusted risk for mortality compared with those continued on BBs (HR: 2.3; 95% CI: 1.2 to 4.6, p =
0.013), but with similar risk as HF patients eligible but not treated with BBs.\textsuperscript{27} Patients taking digoxin should also be continued on therapy unless contraindicated since withdrawal may lead to worsening HF.\textsuperscript{30} Lastly, oral therapies should be uptitrated to maximally tolerated doses prior to discharge whenever feasible.\textsuperscript{25}

### Device therapies

Given the increased risk of fatal ventricular tachyarrhythmias appropriate patients may be evaluated for implantable cardioverter-defibrillator (ICD) or chronic resynchronization therapy (CRT) prior to transition to the outpatient care. ICDs may be placed as secondary prevention in patients who have had sustained ventricular tachycardia, ventricular fibrillation, unexplained syncope, or cardiac arrest or prophylactically in select groups of patients who have been on GDMT for a minimum of 3 to 6 months.\textsuperscript{25,31–33} CRT has also been proven to have numerous benefits in HF patients including reductions in rehospitalization and all-cause mortality and is advised for patients who meet criteria.\textsuperscript{34–36} Prior to discharge, eligible patients may be considered for outpatient monitoring with a CardioMicroelectromechanical system (CardioMEMS; St Jude Medical, Inc., Atlanta, GA), which allows pulmonary artery (PA) pressure guided-HF management using a wireless implantable hemodynamic monitoring system. The CardioMicroelectromechanical system (CardioMEMS) Heart Sensor Allows Monitoring of Pressures to Improve Outcomes in New York Heart Association Class III Heart Failure Patients (CHAMPION) trials have shown that implementation of CardioMEMS results in a significant reduction in HF hospitalization rates and a greater reduction in PA pressures, more days alive and outside of the hospital for HF, and an improvement in quality of life when compared with guideline-directed standard of care HF management alone.\textsuperscript{37,38} Moreover, based on the cost-effectiveness thresholds followed by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, with a threshold of <$50,000 indicating highly cost-effective and >$150,000 not cost-effective per quality-adjusted life-years (QALYs) gained,\textsuperscript{39} the CardioMEMS has been shown to be cost-effective compared to usual care in populations similar to the CHAMPION if the trial effectiveness is sustained. CardioMEMS reduced lifetime hospitalizations (2.18 vs. 3.12), increasing quality-adjusted life-years (QALYs) (2.74 vs. 2.46) with increased costs ($176,648 vs. $156,569) yielding a cost of $71,462 per QALY gained and $48,054 per life-year gained. The device was more cost-effective in those with preserved LVEF compared to patients with reduced LVEF ($47,768 vs $82,301 per QALY gained respectively).\textsuperscript{40} Finally, appropriate patients may be evaluated for implantation of a left ventricular assist device (LVAD) which has been shown to improve survival and quality of life in select patients particularly those with NYHA Class IV.\textsuperscript{41,42} The Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) has developed clinical profiles to allow for optimal selection of patients for LVADs. Over the past 5 years, there has been a shift such that the majorities of patients being implanted are INTERMACS profiles 3 and 4 and thus include those who have been stabilized but are inotrope dependent or those who required temporary circulatory support during hospitalization.\textsuperscript{43}

### Patient education

Patient education remains one of the most crucial components of discharge planning. Patients and their families should receive verbal and written discharge instructions in addition to educational material. Thorough discharge planning is associated with improved patient outcomes. Each patient should have a clear understanding of their recommended activity level, diet, discharge medications, follow-up appointment, weight monitoring, and what to do if any recurrent signs and symptoms of decompensation.\textsuperscript{44} Restricting sodium intake to <2 g/d or fluid intake to <2 L/d or <1–1.5 L/d should be underscored when applicable. If deemed safe patients should be encouraged to perform moderate exercise for 30 min at least 5 days/week. Modifiable triggers should be addressed prior to transition to the outpatient setting. Excessive sodium and water intake, medication non-adherence, the use of over the counter drugs such as non-steroidal anti-inflammatory drugs and pseudoephedrine, excessive alcohol intake and illicit drug use may all precipitate AHF. Counseling on smoking cessation, limiting alcohol consumption, and avoidance of precipitating over-the-counter medications should be performed. All patients should be offered influenza and pneumococcal vaccines prior to discharge when appropriate.\textsuperscript{51} Studies have shown that introduction of nurse educator-delivered teaching sessions at the time of hospital discharge may result in improved clinical outcomes, increased self-care and treatment adherence, and reduced cost of care in addition to a lower risk of rehospitalization or death.\textsuperscript{46,47} The incorporation of a pharmacist in discharge counseling has also been shown to be beneficial in reducing 30 day mortality and HF-related readmissions.\textsuperscript{11}

### Transition to outpatient care

Any new diagnostic information or changes in medications during the hospital stay should be communicated clearly and in a timely manner to outpatient clinicians to ensure a proper transition to the outpatient setting. For individual practitioners with heavy patient loads, this is often difficult and needs to be addressed at the institutional level. As mentioned prior, patients and their families should have a clear understanding of what to expect when they leave the hospital and there should be follow-up plans for any outstanding tests. Early outpatient follow-up has been associated with a lower risk of subsequent rehospitalization. A follow-up visit within 7 to 14 days and/or a telephone follow-up within 3 days of hospital discharge are reasonable goals.\textsuperscript{48} Follow up in specialized HF clinics reduces hospitalization, improves medication adherence, increases titration efficacy of goal directed medical therapy and has also been shown to reduce 90 day all-cause mortality.\textsuperscript{11}
Conclusion

Thorough discharge planning is essential to the late management of patients hospitalized with AHF. Several markers may be utilized in assessing patients’ readiness for discharge and predicting poor outcomes such as hospital readmission and mortality. A multidisciplinary approach is beneficial in facilitating a smooth transition to the outpatient setting with early follow-up allowing for improved success.

Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

REFERENCES


Changing our Approach to Stage D Heart Failure

Miriam F. Becnela,b, Hector O. Venturaa,b,c, Selim R. Krima,b,c,⁎

aDivision of Cardiology, John Ochsner Heart and Vascular Institute, New Orleans, LA, United States
bSection of Cardiomyopathy & Heart Transplantation, John Ochsner Heart and Vascular Institute, Ochsner Clinic Foundation, 1514 Jefferson Highway, New Orleans, LA 70121, United States
cThe University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, LA, United States

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Abstract

Despite the tremendous progress made in the management of heart failure (HF), many patients reach advanced stages. This paper aims to present a practical approach to the stage D HF patient who is no longer responding to optimal medical therapy. We discuss all available therapies for this patient population. We also offer some important caveats with regard to identification, risk stratification, evaluation and treatment including early patient referral to a center with an advanced HF program. Given the changing landscape of heart transplantation and an impending change in the allocation system, we also intend to engage a discussion on the need for a paradigm shift towards left ventricular assist device therapy in this population.

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Contents

Early recognition and referral of the stage D HF patient........................................ 206
Risk stratification .......................................................... 206
Clinical risk scores .................................................. 207
Cardiopulmonary exercise testing (CPX) ...................................... 207
Hemodynamic assessment ............................................. 207
Available therapies for stage D HF ............................................... 208
Heart transplantation ................................................ 208
Durable left ventricular assist devices ....................................... 208
Inotrope therapy ................................................... 210
End of life care and palliative therapy ....................................... 210
Mechanical circulatory support for the cardiogenic shock patient.................................. 210
Current heart allocation system and its limitations................................................ 212
Newly proposed heart allocation system and its implications...................................... 212
Durable MCS: What the future holds ............................................... 212
Conclusion ............................................................ 213

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⁎ Corresponding author at: Section of Cardiomyopathy & Heart Transplantation, John Ochsner Heart and Vascular Institute, Ochsner Clinic Foundation, 1514 Jefferson Highway, New Orleans, LA 70121, United States.
E-mail addresses: miriam.becnel@ochsner.org (M.F. Becnel), Hventura@ochsner.org (H.O. Ventura), selim.krim@ochsner.org (S.R. Krim).

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Clinical recognition of when patients reach end-stage HF can be difficult, but identifying patients who need advanced HF therapies is often more challenging. Early patient referral to a center with an advanced HF program is imperative to ensure proper identification, risk stratification, evaluation and treatment. This paper aims to present a practical approach to the stage D HF patient. Given the changing landscape of transplantation and an impending change in the allocation system, we also intend to engage a discussion on the need for a paradigm shift towards LVAD therapy in this population.

**Early recognition and referral of the stage D HF patient**

Timely detection of patient progression from stage C to stage D HF is crucial in relation to treatment. While there are some variations in how different organizations define advanced HF, is it universally accepted that all patients with end-stage HF have become refractory to optimal medical therapy (OMT). It should also be noted that to deem a patient truly refractory to guideline-directed OMT, any other etiologies that may explain their symptomatic decline should be explored. Owing to a growing and aging population, more patients are reaching advanced stages of HF despite tremendous progress in available therapies. Historically, heart transplantation (HT) was the only option for stage D HF. With limited donor supply and a rising need within this population, mechanical circulatory support (MCS) in the form of the left ventricular assist device (LVAD) has emerged as a viable advanced therapy and continues to mature through innovation and invention. LVADs are rapidly becoming standard of care within the field. These devices are being implanted either as a bridge to transplantation (BTT), destination therapy (DT), or in some cases cardiac recovery. Unfortunately not all patients with advanced HF will be candidates for the aforementioned surgical options, and other treatment options include palliative inotropes and hospice care.

<table>
<thead>
<tr>
<th>Abbreviations and Acronyms</th>
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<tbody>
<tr>
<td>ACC = American College of Cardiology</td>
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<tr>
<td>AHA = American Heart Association</td>
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<tr>
<td>BP = blood pressure</td>
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<tr>
<td>BTT = bridge to transplant</td>
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<tr>
<td>CO = cardiac output</td>
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<tr>
<td>CO2 = carbon dioxide</td>
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<tr>
<td>CPX = cardiopulmonary exercise testing</td>
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<tr>
<td>DT = destination therapy</td>
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<tr>
<td>ECMO = extracorporeal membranous oxygenation</td>
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<tr>
<td>HF = heart failure</td>
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<tr>
<td>HFSS = HF Survival Score</td>
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<tr>
<td>HT = heart transplantation</td>
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<tr>
<td>IABP = intra-aortic balloon pump</td>
</tr>
<tr>
<td>ICD = implantable cardioverter-defibrillator</td>
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<tr>
<td>INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support</td>
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<tr>
<td>LBM = lean body mass</td>
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<tr>
<td>LVAD = left ventricular assist device</td>
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<tr>
<td>MCS = mechanical circulatory support</td>
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<tr>
<td>NYHA = New York Heart Association</td>
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<tr>
<td>OMT = optimal medical therapy</td>
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<tr>
<td>RER = respiratory exchange ratio</td>
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<tr>
<td>RHC = right heart catheterization</td>
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<td>SHFM = Seattle HF Model</td>
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<tr>
<td>TAH = total artificial heart</td>
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<td>UNOS = United Network of Organ Sharing</td>
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<td>US = United States</td>
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<tr>
<td>VE = minute ventilation</td>
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<tr>
<td>VO2 = ventilator oxygen uptake</td>
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</tbody>
</table>

References

Conflict of interest
of the SHFM in the advanced HF population. It should be noted that the SHFM tends to overestimate survival in the stage D HF population as it originated from ambulatory patient data.\textsuperscript{10,11}

**Cardiopulmonary exercise testing (CPX)**

Despite not being available in all centers, cardiopulmonary exercise testing (CPX) is a key test in assessing patients for advanced HF therapies.\textsuperscript{12} Two important CPX variables are usually used for risk stratification and prognosis—peak ventilator oxygen uptake (VO\textsubscript{2}) and minute ventilation/carbon dioxide production (VE/VCO\textsubscript{2}) slope. Peak VO\textsubscript{2} has been shown to be a strong predictor of mortality among HF patients evaluated for HT.\textsuperscript{13} A reduced maximal oxygen consumption peak VO\textsubscript{2} of <12 mL/kg/min (or <14 mL/kg/min for patients using beta blockers) signifies advanced HF stage and warrants evaluation for HT. A low peak VO\textsubscript{2} should always be interpreted in the context of adequate effort which is defined as a respiratory exchange ratio (RER) > 1.1.\textsuperscript{12} Owing to significant variability in body composition in our HF population, correcting peak VO\textsubscript{2} for lean body mass (LBM) seems to be a better discriminator of outcome than traditionally reported total weight adjusted values. In this regard, a peak VO\textsubscript{2} corrected for LBM cutoff of 19 mL/kg/min has shown to be a superior discriminator of major cardiac events (death and/or urgent HT) than the total weight-adjusted figure of 14 mL/kg/min in patients with stage D HF.\textsuperscript{12} The VE/VCO\textsubscript{2} slope is another important variable and when abnormal (VE/VCO\textsubscript{2} slope > 34) it provides additional and independent prognostic information. Evaluation of the VE/VCO\textsubscript{2} slope in conjunction with peak VO\textsubscript{2} is recommended to optimize prognostication in patients with HF.\textsuperscript{14–16}

**Hemodynamic assessment**

Right heart catheterization (RHC) is considered the gold standard in evaluating hemodynamics, particularly the cardiac index and pulmonary pressures, when determining the need for HT. A cardiac index value of <2.5 L/min/m\textsuperscript{2} is

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**Table 1 – Signs and symptoms of Stage D HF. Adapted from ACC/AHA guidelines\textsuperscript{6}**

<table>
<thead>
<tr>
<th>Triggers for Advanced HF Referral</th>
</tr>
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<tbody>
<tr>
<td>Frequent (≥2) hospitalizations or ED visits for HF in the past year</td>
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<tr>
<td>Intolerance to ACE inhibitors due to hypotension and/or worsening renal function</td>
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<tr>
<td>Weight loss without other cause (e.g. cardiac cachexia)</td>
</tr>
<tr>
<td>Intolerance to beta blockers due to worsening HF or hypotension</td>
</tr>
<tr>
<td>Frequent systolic blood pressure &lt; 90 mm Hg</td>
</tr>
<tr>
<td>Persistent dyspnea with dressing or bathing requiring rest</td>
</tr>
<tr>
<td>Progressive deterioration in renal function (e.g. rise in BUN and creatinine)</td>
</tr>
<tr>
<td>Progressive decline in serum sodium, usually to &lt;133 mEq/L</td>
</tr>
<tr>
<td>Frequent ICD shocks</td>
</tr>
</tbody>
</table>

**Abbreviations:** HF, heart failure; ED, emergency department; ACE, angiotensin converting enzyme; BUN, blood urea nitrogen; ICD, implantable cardioverter-defibrillator.

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**Table 2 – INTERMACS classification.**

<table>
<thead>
<tr>
<th>INTERMACS Profiles</th>
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<td>Profile 1</td>
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<td>Profile 2</td>
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<td>Profile 3</td>
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<td>Profile 4</td>
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<td>Profile 5</td>
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<td>Profile 6</td>
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<tr>
<td>Profile 7</td>
</tr>
</tbody>
</table>

**Abbreviations:** INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; ADL, activities of daily living; NYHA, New York Heart Association.
suggestive of advanced disease. The use of RHC is key in diagnostic evaluation of pulmonary vascular resistance considering that it precludes HT if found to be elevated and irreversible.  

With regard to LVAD implantation, important hemodynamic parameters identified as strong markers of post-operative right HF, including right atrial pressure > 15 mmHg, right atrial pressure to pulmonary capillary wedge pressure ratio > 0.63, and right ventricular stroke work index \( \leq 0.25 \text{ mm Hg} \times l/m^2 \). 16,19

Available therapies for stage D HF

Heart transplantation

For the last 4 decades, HT has been the panacea for stage D HF. With improved immunosuppressive therapies in addition to 1- and 5-year post-HT survival, HT will likely remain the gold standard treatment for this critically ill patient population. 20

Only 2500 HTs are performed annually in the US, and owing to a meager donor pool this is unlikely to change. As a result, many patients die on the heart transplant list while they wait for a favorable donor. Consideration should be made for HT if OMT and cardiac resynchronization therapy as recommended by current ACC/AHA guidelines have failed to improve patient symptoms and slow disease progression. 5 Assessing for any reversible or surgically amenable cardiac conditions should be addressed before HT or MCS are considered. Table 3 summarizes eligibility criteria for HT. By the same token, a thorough assessment of conditions that may preclude HT should be explored. Examples of absolute and relative contraindications to HT are listed in Table 3. 21,22

Table 3 – Current indications and contraindications of cardiac transplantations.

<table>
<thead>
<tr>
<th>Indications for Cardiac Transplantation</th>
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<tbody>
<tr>
<td>Cardiogenic shock requiring either continuous intravenous inotropic support or MCS with an intraaortic balloon pump counterpulsation device or MCS</td>
</tr>
<tr>
<td>Persistent NYHA class IV congestive HF symptoms refractory to maximal medical therapy (LVEF &lt; 20%; peak VO(_2) &lt; 12 ml/kg/1/min)</td>
</tr>
<tr>
<td>Intractable or severe anginal symptoms in patients with coronary artery disease not amenable to percutaneous or surgical revascularization</td>
</tr>
<tr>
<td>Intractable life-threatening arrhythmias unresponsive to medical therapy, catheter ablation, and/or implantation of implantable cardioverter-defibrillator</td>
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<tr>
<td>End-stage congenital HF with no evidence of pulmonary hypertension</td>
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</table>

<table>
<thead>
<tr>
<th>Absolute Contraindications to Cardiac Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irreversible/fixed pulmonary hypertension with PVR &gt; 3 woods units</td>
</tr>
<tr>
<td>Clinically severe symptomatic cerebrovascular disease</td>
</tr>
<tr>
<td>Severe extra-cardiac amyloid organ dysfunction</td>
</tr>
<tr>
<td>Active substance abuse</td>
</tr>
<tr>
<td>Candidates with a history of primary central nervous system lymphoma and visceral Kaposi sarcoma</td>
</tr>
<tr>
<td>Acute or fulminant HBV/HCV infection</td>
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<tr>
<td>Chronic HBV/HCV with clinical, radiologic or biochemical signs of cirrhosis, portal hypertension, or hepatocellular carcinoma</td>
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<tr>
<td>Severe, irreversible multisystemic disease process</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative Contraindications to Cardiac Transplantation</th>
</tr>
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<tbody>
<tr>
<td>Age &gt; 70 years of age</td>
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<tr>
<td>Obesity with BMI of &gt; 35 kg/m(^2)</td>
</tr>
<tr>
<td>Irreversible renal dysfunction (eGFR &lt; 30 ml/min/1.73 m(^2)) for heart transplant alone</td>
</tr>
<tr>
<td>Peripheral vascular disease that may limit rehabilitation and is not amenable to revascularization</td>
</tr>
<tr>
<td>Diabetes with end organ damage other than non-proliferative retinopathy or persistent poor glycemic control (HbA1C &gt; 7.5% or 58 mmol/mol) despite optimal effort</td>
</tr>
<tr>
<td>Recent substance abuse</td>
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<tr>
<td>Neoplasm (requires individualized assessment)</td>
</tr>
<tr>
<td>Infection (requires individualized assessment)</td>
</tr>
<tr>
<td>Insufficient social support to achieve compliant care in the outpatient setting</td>
</tr>
<tr>
<td>Severe cognitive-behavioral disabilities or dementia (e.g., self-injurious behavior, inability to ever understand and cooperate with medical care)</td>
</tr>
<tr>
<td>Inability to comply with drug therapy on multiple occasions</td>
</tr>
<tr>
<td>Active tobacco smoking</td>
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</tbody>
</table>

**Abbreviations:** MCS, mechanical circulatory support; NYHA, New York Heart Association; HF, heart failure; LVEF, left ventricular ejection fraction; VO\(_2\), ventilator oxygen uptake; PVR, pulmonary vascular resistance; HBV, hepatitis b virus; HCV, hepatitis C virus; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1C.
(Abbott Laboratories, formerly Thoratec Corporation, Abbott Park, IL), in the pivotal 2001 REMATCH trial. 23 This device was approved in 1994 for BTT and in 2003 for DT. 24 Unfortunately, the associated adverse event profile and large pump size led to limited durability with device life averaging only 18 to 30 months. Consequently, pulsatile pumps gave rise to the next generation of continuous-flow LVADs, which include the axial-flow HeartMate II (Abbott Laboratories, Abbott Park, IL) and the centrifugal-flow HVAD (HeartWare Inc., Framingham, MA). 25 The HeartMate II is approved for BTT and DT, whereas the HVAD is only approved for BTT at present. 25–27 The centrifugal-flow HeartMate 3 (Abbott Laboratories, Abbott Park, IL) is the newest device under investigation in the US and is seeking both BTT and DT indications. Additional BTT options include the total artificial heart (TAH) or biventricular ventricular assist devices (Bi-VAD), which are usually only indicated in a select population with biventricular failure or refractory ventricular arrhythmias (Fig. 1). With 1- and 2-year

### Table 4 – Indications and contraindications of LVAD therapy.

#### Indications for LVAD Therapy

- As a bridge to transplantation strategy in patients who are in cardiogenic shock and too sick to wait or who have temporary contraindications for transplant
- As a permanent therapy so called “destination therapy” for patients considered ineligible for cardiac transplantation
- As a bridge to myocardial recovery such as in patients acute myocarditis where recovery is expected
- As bridge-to-decision or “bridge-to-bridge” is used for those patients who present with severe shock or following cardiac arrest and are supported with a temporary support VAD to see if they become candidates for a long-term support device

#### Contraindications to LVAD Therapy

- Potentially reversible cause of heart failure
- Recent or evolving stroke
- Neurological deficits impairing the ability to manage device
- Coexisting terminal condition (e.g., metastatic cancer, cirrhosis)
- Abdominal aortic aneurysm > 5 cm
- Symptomatic right heart failure
- Active systemic infection or major chronic risk for infection
- Severe pulmonary dysfunction (e.g., FEV1 < 1 L)
- Current or impending renal or hepatic failure
- Multisystem organ failure
- Heparin-induced thrombocytopenia
- Significant underlying psychiatric illness or lack of social support

**Abbreviations:** LVAD, left ventricular assist device; VAD, ventricular assist device; FEV1, forced expiratory volume.

Fig. 1 – Proposed algorithm for advanced heart failure therapies. 28 Infiltrative cardiomyopathies (e.g. cardiac amyloidosis, Sarcoidosis, HFpEF with refractory Angina), 28 LVAD complications: pump thrombosis, pump malfunction, pump stop, driveline infection.
survival rates of 80% and 70% respectively, the LVAD population is expected to grow exponentially over the coming years.\textsuperscript{25,26}

**Inotrope therapy**

Positive inotropic agents are frequently used in the setting of acute decompensated HF when evidence of pulmonary congestion and signs of hypoperfusion are present.\textsuperscript{28} Milrinone and dobutamine are the most widely used inotropic agents in the US.\textsuperscript{29} Dobutamine, a $\beta$-adrenergic agonist, is recommended for treatment of patients with low cardiac output (CO) and reduced BP. Concomitant use of $\beta$-blockers with dobutamine is not recommended as it may attenuate the benefit of both agents. Milrinone, a phosphodiesterase inhibitor, is sometimes preferred over dobutamine in the setting of significantly elevated systemic and pulmonary vascular resistance, low CO and hypoperfusion symptoms.\textsuperscript{30} While inotropes have been shown to improve both symptoms and hemodynamics, concerns have been raised with the use of these agents on a long-term continuous basis for patients with refractory HF declined for definitive therapy (HT or MCS).\textsuperscript{31,32} Therefore, long-term continuous or intermittent inotrope infusions should only be recommended as a bridge to decision.

**End of life care and palliative therapy**

Patients with advanced HF unresponsive to OMT who do not qualify for either HT or MCS should be offered palliative measures. After exhausting all standard of care options, hospice should be offered to patients with NYHA class IV symptoms with less than a 6-month life expectancy.\textsuperscript{33–37} These services can be performed at home, in the hospital, or at a specialized hospice center, which can generally provide oral medications and focus on symptom management. Certain hospice programs may provide complex treatments, such as intravenous inotropes or continuous positive airway pressure ventilation.\textsuperscript{33,34} It is only with continued engagement of the clinician and meticulous management of fluid status that quality of life can be fully maximized in hospice care. A noteworthy topic specific to end-of-life within this patient population is ICD deactivation. While this may make for a difficult discussion, thoughtfully counseling patients on deactivation is an essential step for these terminal patients as ICD discharges only exacerbate pain and anxiety.\textsuperscript{38}

**Mechanical circulatory support for the cardiogenic shock patient**

Many patients are too sick upon presentation to undergo HT or durable LVADs. In this regard, temporary MCS may be used as a bridge to more definitive therapy (e.g., bridge to durable LVAD or BTT). INTERMACS profile 1 patients are considered “critical cardiogenic shock” or “crashing and burning” and have held a consistent 15% stake in the total number of patient’s receiving durable LVADs from 2008 to 2014.\textsuperscript{7,39,40} INTERMACS 2 patients are patients with “progressive decline” on inotropic therapy, and accounted for 38% of total implants over the same 6-year time frame.\textsuperscript{7,40} Given the overall instability of profile 1 and the foreseeable deterioration in profile 2 patients, temporizing measures are often pursued. With the aim of reversing end-organ damage, temporary MCS also allows care teams time to explore whether a more definitive therapy can be accomplished. In this case, the use of temporary MCS has been coined “bridge to decision”. While it is still unclear whether reversal of end-organ damage and stabilization via temporary MCS decreases perioperative risk and mortality, there is widespread acceptance and use of these devices. Patient and device selection varies among centers, but ideally should be based on expertise and training, while also being individually tailored to the patient’s hemodynamic and structural profile. Ease of implant differs between devices and method (percutaneous versus surgical)
determines location of implant (cardiac catheterization laboratory or operating room). Optimal timing between temporary device implant and crossover to durable MCS has not been well defined. Additional data including protocols and algorithms are needed to guide providers in selecting the most appropriate device for suitable patients at the right time. Contraindications vary between devices and our proposed algorithm is intended to help guide the selection of support in the cardiogenic shock patient based on their profile (Fig. 2). Table 5 highlights temporary counterpulsation,

| Table 5 – Currently available temporary MCS devices in the US. |
|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Device      | Blood Flow      | Support Type    | Inflow          | Outflow         | Access Type     | Access Approach |
| Counterpulsation | IABP            | 0.5–1 L/min     | LV              | N/A             | Percutaneous    | Axillary or femoral artery |
| Microaxial  | Impella 2.5     | 2.5 L/min       | LV              | AA              | Percutaneous    | Axillary or femoral artery |
|             | Impella CP      | 3.5 L/min       | LV              | AA              | Percutaneous    | Axillary or femoral artery |
|             | Impella 5.0     | 5 L/min         | LV              | AA              | Percutaneous    | Axillary or femoral artery |
| Centrifugal| Impella RP      | 4.4 L/min       | RV              | IVC             | Percutaneous    | Femoral Vein |
|             | Tandemheart     | 5 L/min         | LV              | LA              | Percutaneous    | Transeptal catheterization of left atrium via femoral vein |
|             | Centrimag       | 9.9 L/min       | LV              | LA/LV           | Percutaneous    | Internal jugular vein |
|             | VA-ECMO         | Complete CV bypass | IJV/FV        | FA, SCA, AA     | Peripheral     | Internal jugular vein, femoral vein |
|             |                 |                 | RA/RA/RA/V        | AA               | Surgical (Central) | Median sternotomy |

Abbreviations: IABP, intraaortic balloon pump; LV, left ventricle; RV, right ventricle; AA, ascending aorta; IVC, inferior vena cava; PA, pulmonary artery; FA, femoral artery; RA, right atrium; LA, left atrium; VA, vena arteriosa; ECMO, extracorporeal membrane oxygenation; CV, cardiovascular; IJV, internal jugular vein; FV, femoral vein; SC, subclavian artery; CA, carotid artery.

| Table 6 – New Heart Allocation System. |
| Adapted from Meyer et al.⁴³ |

<table>
<thead>
<tr>
<th>Tiers</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Tier 1</td>
<td>ECMO</td>
</tr>
<tr>
<td></td>
<td>Continuous Mechanical ventilation</td>
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<tr>
<td></td>
<td>Non-dischargeable (surgically implanted) VAD</td>
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<tr>
<td></td>
<td>MCS with life-threatening ventricular arrhythmia</td>
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<tr>
<td>Tier 2</td>
<td>Intra-aortic balloon pump</td>
</tr>
<tr>
<td></td>
<td>Ventricular tachycardia/ventricular fibrillation, mechanical support not required</td>
</tr>
<tr>
<td></td>
<td>MCS with device malfunction/mechanical failure</td>
</tr>
<tr>
<td></td>
<td>Total artificial heart</td>
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<tr>
<td></td>
<td>Dischargeable BiVAD or RVAD</td>
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<tr>
<td></td>
<td>Acute circulatory support</td>
</tr>
<tr>
<td>Tier 3</td>
<td>Dischargeable LVAD for up to 30 days</td>
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<tr>
<td></td>
<td>Multiple inotropes or single high-dose inotropes with continuous hemodynamic monitoring</td>
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<tr>
<td></td>
<td>MCS with device infection</td>
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<td></td>
<td>MCS with hemolysis</td>
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<td></td>
<td>MCS with pump thrombosis</td>
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<td></td>
<td>MCS with right heart failure</td>
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<td>MCS with mucosal bleeding</td>
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<td>MCS with aortic insufficiency</td>
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<tr>
<td>Tier 4</td>
<td>Stable LVAD candidates not using 30 day discretionary period</td>
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<tr>
<td></td>
<td>Inotropes without hemodynamic monitoring</td>
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<tr>
<td></td>
<td>Diagnosis of congenital heart disease</td>
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<td></td>
<td>Diagnosis of ischemic heart disease with intractable angina</td>
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<td></td>
<td>Diagnosis of hypertrophic cardiomyopathy</td>
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<td></td>
<td>Diagnosis of restrictive cardiomyopathy</td>
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<tr>
<td></td>
<td>Diagnosis of amyloidosis</td>
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<tr>
<td></td>
<td>Retransplant</td>
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<tr>
<td>Tier 5</td>
<td>Combined organ transplants</td>
</tr>
<tr>
<td>Tier 6</td>
<td>All remaining active candidates</td>
</tr>
<tr>
<td>Tier 7</td>
<td>Inactive/not transplantable</td>
</tr>
</tbody>
</table>

Abbreviations: ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device; MCS, mechanical circulatory support; BiVAD, biventricular assist device; RVAD, right ventricular assist device; LVAD, left ventricular assist device.
microaxial and centrifugal pumps currently available for use in the US.

Current heart allocation system and its limitations

Established over a decade ago, the current three-tiered heart allocation system has led to tremendous decrease in the rate of waiting list mortality and improvement in post-HT survival. Based on the severity of medical conditions, the United Network of Organ Sharing (UNOS) assigns a status to all patients listed for HT. Those with an expected survival of <1 month are listed 1A, the highest waitlist status. This gravely ill cohort includes those patients either on high doses of inotropic drugs, receiving mechanical ventilation or requiring MCS who meet appropriate criteria (e.g., LVAD 30-day time, temporary LVAD, RVAD, BiVADs, durable devices with complications). The next listing tier is status 1B and is assigned to patients who are stable on lower-dose inotropic therapy or durable mechanical support, and can be inpatient or outpatient. Status 2, the third tier, are stable ambulatory patients who are not on inotropic drugs.

Despite improvement in outcomes after the implementation of the 3-tier system, there are several limitations that remain. For each status within a geographic zone, hearts are allocated to candidates in order of decreasing time spent at that status in addition to blood type-matching. One major drawback of the current system is the lack of clinical differentiation between waitlisted status 1A and 1B candidates. In addition, the rising number of patients listed status 1A and 1B has become a concern and is primarily attributed due to the increased use of durable MCS. This has led experts in the field to question the appropriate designation status of stable LVAD patients. This becomes particularly relevant as recent data has denoted the low risk of adverse events in stable LVAD patients. These events are defined as death or waitlist removal for being too ill to transplant when compared to other status 1A patients (e.g., dual inotropes, paracorporeal VADs, congenital heart disease). It is important to note when a LVAD patient develops a device-related complication that satisfies criteria for 1A listing, they instantly carry a higher waiting list mortality. Consequently, the continued expansion of LVAD therapy as BTT will undoubtedly contribute to an increased number of patients listed UNOS status 1A secondary to device malfunction, thrombosis, and infection. In turn, the present long-term HT outcomes could be negatively impacted.

Newly proposed heart allocation system and its implications

In response to the conundrum of the present-day allocation structure, the UNOS heart subcommittee has proposed a new 6-tier system which aims to 1) improve utilization of the limited supply of donor hearts by modifying geographic distribution and improve overall access to HT; 2) reduce waiting list mortality by prioritizing sicker patients and undeserved groups (congenital heart disease, restrictive cardiomyopathies) without compromising post-HT survival; and 3) decrease the use of exceptions by better accommodating all candidates within the system. The new allocation system is summarized in Table 6.

In a nutshell, the sickest patients under the new system are given top priority in tier 1, including those patients receiving mechanical ventilation and extracorporeal membranous oxygenation (tier 1), and stable LVAD patients will now fall in tier 4—much lower when compared to the current 3-tier system. In view of the recent data revealing low mortality rates among stable LVAD patients, our belief is that these changes will lead to better utilization of available donor hearts and allow sicker patients to receive HT in an expedited fashion. On the other hand, we feel that tier 3 patients with LVAD complications such as pump thrombosis or right HF are at a much higher risk for adverse events and death, and as a result should be given a higher priority. Furthermore, we believe that those patients sick enough to necessitate a higher level of temporary MCS (e.g., Impella, TandemHeart, CentriMag) should certainly be assigned to a higher tier than those only requiring intra-aortic balloon pump support. We also have serious concerns about assigning patients bridged with extracorporeal membranous oxygenation (ECMO) to tier 1 knowing the potential increase in post-HT mortality given their critically ill nature. Lastly, we worry that this newly proposed system may not solve the previous issue of other disadvantaged groups such as congenital heart disease and restrictive cardiomyopathies.

Durable MCS: What the future holds

With the upcoming changes in organ allocation, advancement in durable LVAD technology and management will become more important than ever. With nearly half of LVAD implants performed as destination therapy, continued amelioration of durable devices is imperative to prolong survival on support. Bleeding, infection and device thrombosis are major sources of morbidity and mortality in the present day population. Reduction in the frequency of these adverse events should remain a major driver in the development of better device therapy.

Tunneled drivelines are a major source of infection and are currently used in all durable LVADs. The driveline exits through the skin to connect to an external power source, thus making it prone to mechanical complications. Infection risk is likely to be substantially reduced by way of driveline elimination. A fully implantable system would also allow patients to submerge in water which would increase patient quality of life.

Frequent hospital admissions for LVAD patients with a subtherapeutic international normalized ratio is another important issue. Not only do these unnecessary hospitalizations impact their quality of life, but they also drive the cost-effectiveness of this therapy down. Many centers have adopted strategies for outpatient bridging of anticoagulation with low-molecular weight heparin (e.g., enoxaparin). Validation of the safety and efficacy of such strategies in addition to protocols designed for use in this population need to be tested at a multicenter level in the ambulatory setting.
Integration of hemodynamic monitoring capabilities with LVAD technology could provide a whole new level of care to these patients. Especially true for the centrifugal type-pumps (e.g., HVAD, HeartMate 3), both hypo- and hyper-volemic conditions can trigger LVAD alarms and often the culprit driving the condition is difficult to ascertain. Adding this type of feature to the next generation device would complement the existent resources in evaluation and management of these patients. Ideally, this data would be remotely accessible, which has the potential to decrease hospital readmissions and cost if providers were able to triage and manage patients without necessitating inpatient evaluation.

The most recent device under investigation employs new magnetic levitation and artificial pulse technology in an attempt to mimic native cardiac contractility in hopes of reducing bleeding and thrombosis complications. The future of durable LVADs remains promising, and it is only through experience and refining technology that patient survival will continue to improve.

**Conclusion**

In light of improvement in LVAD outcomes and the continued limited organ supply we propose a paradigm shift in the management of advanced stage D HF patients. First and foremost, we believe that all patients with refractory HF should be promptly referred and evaluated for durable LVADs. Second, only patients deemed to not be candidates for LVAD therapy or those who develop complications post-VAD implant (e.g., gastrointestinal bleeding, driveline infection, pump thrombosis, RV failure) should be offered HT. This approach, albeit controversial, may reduce the current number of patients listed as a status 1A or 1B for HT. It would also allow for sicker and traditionally disadvantaged populations (congenital heart disease, infiltrative cardiomyopathies, refractory arrhythmias) to get transplanted in a timely fashion. Third, although the new allocation system aims to reduce waiting list mortality by prioritizing sicker patients, we have significant concerns with regard to post-HT outcomes in patients receiving ECMO as a BTT given the lack of data in this population. Despite the impressive survival benefit provided by LVAD therapy, the unacceptably high short-and-long term adverse event profile remains a key hindrance. In conclusion, more research is crucial and necessary to better understand and subsequently reduce these events in order to make this technology a viable, permanent and cost-effective alternative to HT.

**Conflict of interest**

None.

**References**


Palliative Care in Heart Failure: What Triggers Specialist Consultation?

Mitchell A. Psotka, Kanako Y. McKee, Albert Y. Liu, Giovanni Elia, Teresa De Marco

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ABSTRACT

Heart failure (HF) continues to cause substantial death and suffering despite the availability of numerous medical, surgical, and technological therapeutic advancements. As a patient-centered holistic discipline focused on improving quality of life and decreasing anguish, palliative care (PC) has a crucial role in the care of HF patients that has been acknowledged by multiple international guidelines. PC can be provided by all members of the HF care team, including but not limited to practitioners with specialty PC training. Unfortunately, despite recommendations to routinely include PC techniques and providers in the care of HF patients, use of general PC strategies as well as expert PC consultation is limited by a dearth of evidence-based interventions in the HF population and knowledge as to when to initiate these interventions, uncertainty regarding patient desires, prognosis, and the respective roles of each member of the care team, and a general shortage of specialist PC providers. This review seeks to provide guidance as to when to employ the limited resource of specialist PC practitioners, in combination with services from other members of the care team, to best tend to HF patients as their disease progresses and eventually overcomes.

Contents

Palliative care defined ................................................. 217
Palliative care needs of heart failure patients .................. 217
Communication ......................................................... 218
Preparedness planning .................................................. 219
Psychosocial and spiritual support ................................. 219
Symptom management ............................................... 220
Evidence supporting palliative care interventions for heart failure patients .................................... 220
When to involve specialized palliative care consultants ...... 221
“We see the patient and family as the focus of our care. We see our role as providing support to the patients and their loved ones for coping with stress, confusion, and the emotional, psychological, spiritual, and social impact of illness.”

[Steven Pantilat, MD]

Heart failure (HF) is a deadly cardiac syndrome commonly manifest by shortness of breath, fatigue, pain and fluid accumulation.\(^1\,^2\) It is a worldwide epidemic with rising international prevalence including more than 5.7 million patients in the United States (US). It occurs more frequently with increasing age and accumulating comorbidities. Despite diverse underlying etiologies, affected patients experience a typical progressive decline in function punctuated by unpredictable acute exacerbations from which there is only partial recovery (Fig 1).\(^3\) The high burden of HF morbidity in this fragile population has spurred development of multiple complicated medical and surgical therapies including implantable cardiac devices to improve survival and quality of life (QoL).\(^4\) Despite these advancements, HF mortality remains high at close to 50% at 5 years, and hospital readmission is frequent at over 50% by one year.\(^5\,^1^3\) In addition, HF therapies successful at preventing mortality can prolong the length of time patients experience serious illness and comorbidities such that they spend more time confronting their symptoms.\(^1\) Because of the burden of HF on families and care systems, and the medical complexities of HF management including the intricate interplay of patient, family, and caregiver decision making, involvement of palliative care (PC) specialists who excel in these domains is imperative.\(6-9\) PC is provided contemporaneously by these specialized multidisciplinary teams and other HF practitioners, limited by local availability, primary provider expertise and desire, and patient inclination. PC intervention strives for adequate symptom management in addition to treating the underlying pathophysiology, counseling and support during shared decision making including the transitions through advanced therapy options, ascertaining the goals and values of patients and families, and changing the focus of care when the time arrives for end of life discussions. These goals are recommended by international HF guidelines and the United States Centers for Medicare & Medicaid services.\(^1^0,^1^1\) This article will

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Fig 1 – Trajectory of Heart Failure Symptoms, Clinical Care, and Potential Triggers for Specialist Palliative Care Involvement. Trajectory of heart failure symptoms and disease progression over time with typical exacerbations and periods of relative stability, eventually leading to consideration for advanced therapies including mechanical circulatory support and heart transplantation versus transition to hospice when symptoms become sufficiently severe. Throughout the clinical course, worsening quality of life or disease progression can trigger specialist palliative care consultation, including but not limited to the initial heart failure diagnosis, consideration for advanced therapies, and transition to hospice care. (Adapted from\(^2^7\).)
describe common sources of suffering and stress experienced by HF patients and caregivers, present the knowledge barriers that currently exist to providing effective PC services to relieve these discomforts, and provide a framework to use when considering involving PC specialists in the management of a HF patient.

Palliative care defined

PC focuses on improving patients’ and their families’ QoL, specifically their psychological, physical, and spiritual well-being, during life-threatening illness and death by using a patient-centered multidisciplinary approach. Although the exact interventions supplied depend on the details of the patient experience, prognosis, and resource availability, PC is a philosophy of care in addition to a specific holistic skill set that is part of a multidimensional practice to relieve pain and discomfort. PC assists patients and families to define their goals and values and plan care so that medical decision-making results in treatment that is aligned with their unique needs. It is complementary to all other medical therapies. The World Health Organization purposefully states that PC is “applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life.” PC is thus ideally integrated into the network of all HF care and should be applied by all involved health care providers across a range of settings including hospitals, outpatient clinics, long-term care facilities, and patients’ homes, by a wide variety of health care workers. PC is also useful to patients of any age and at any stage of a serious illness – from the moment of diagnosis through cure or death – and should be implemented concurrently with aggressive, disease-modifying, or curative treatments aimed at prolonging life.

Unfortunately, the common misconception equating PC with end-of-life care or hospice endures in both patients and providers. Structured qualitative interviews with physicians, nurse practitioners, and physician assistants from cardiology, primary care and palliative care fields demonstrated that these providers had limited knowledge regarding how PC can complement curative therapies, why PC is valuable to patients and care teams, and even what PC entails. Hospice is a specific subset of PC reserved for patients with a life-limiting illness and with a prognosis of 6 months or less to live who wish to focus primarily on QoL and avoid repeated hospitalizations. However, involvement of PC principles and interventions is not limited to the end-of-life, and is useful throughout care because patients who receive early PC concurrent with disease-modifying treatments have better symptom control, improved satisfaction, more focused goals of care, and overall better QoL without accelerated mortality. PC intends neither to hasten nor postpone death, and may even result in longer survival, as evidenced by early PC provided for patients diagnosed with metastatic non-small cell lung cancer.

PC can be explained in part by the services that it incorporates. In general, effective PC interventions fall into a handful of broad domains encompassing communication, preparedness planning, psychosocial and spiritual support, and direct symptom management. Appropriate communication topics include patient prognosis, uncertainty surrounding the expected disease trajectory, anticipated benefits and drawbacks of potential treatments, elicitation of patient and caregiver goals and values, and facilitation of shared decision-making. Preparedness planning includes choices around returning for hospitalization, surrogate decision making, resuscitation orders, coping with the unpredictability of the disease course including the possibility of both sudden and prolonged death, and the consideration of end-of-life options. Psychosocial and spiritual stressors lead to substantial anxiety and depression that should be addressed throughout the disease process. Direct symptom management consists of interventions such as opiates for pain or psychiatric medications for depression and anxiety; however, much of the symptom management in the context of HF is provided by cardiologists and other members of the primary care team until symptoms are refractory.

Specialized PC is that subset of PC ideally provided by a transdisciplinary team of expertly-trained specialty physicians, nurses, social workers, chaplains, pharmacists, and others who work alongside a patient’s typical healthcare practitioners to provide additional comprehensive and integrated symptom management. It involves experience and cultured communication skills above the PC principles practiced by other physicians and healthcare providers – for example, by a patient’s primary care physician or cardiologist. Specialized palliative care consultation is commonly requested by the primary patient care team and often only exists at select secondary and tertiary medical centers worldwide, making it a limited commodity. Because specialized PC providers are a relatively scarce resource in many circumstances, their use may be best restricted to specific high-risk times when PC needs are most likely to remain uncovered or incompletely addressed (Fig 1, Table 1).

Palliative care needs of heart failure patients

PC interventions have a vital role in HF disease management because HF is both deadly and prone to cause suffering worse than many malignant cancers. It is a progressively symptomatic disease with baseline deficits in QoL and symptomatic status associated with more severe worsening over time. Symptom exacerbations lead to expensive hospitalizations and increased care needs that eventually require full time care or lead to death.

Despite these data, PC remains an underused tool in the care of both ambulatory and hospitalized HF patients from both large and small medical systems. While a British primary care database showed that 48% of patients with cancer who died in 2009 were recognized as needing palliative services, only 7% of similarly deceased HF patients were entered onto the same palliative register. Of 40 stage D HF patients that died over a 2 year period at one academic center, less than half received any specialist PC consultation or even hospice services. Of 4474 hospitalized Veterans Affairs patients with severe HF followed from 2007 to 2013, only 7.6% were seen by a specialist PC provider within one year of
hospitalization even though 51.2% died within that same time period. Finally, of 37,270 severe HF patients included in a large US database of 360 hospitals representing 26 health care institutions, only 9.6% were seen by specialist PC within one year, with only mild improvement in usage between 2007 (5.7%) and 2014 (13.4%).

The epidemiology of PC use is similar with HF patients being evaluated for advanced HF therapies; if utilized at all, providers have historically waited until late in the disease process to enlist specialist PC services to aid in patient care. In the case of destination therapy left ventricular assist devices (LVAD), only 15% of patients in one single-center study were enrolled in hospice care at the time of death, and less than half had seen a PC provider within one month preceding death. Close to 80% of these LVAD patients died in the hospital, despite most HF patients preferring to die at home, and data from the oncologic literature demonstrating that patients who die in a hospital (and their caregivers) experience worse QoL compared to those at home with hospice. Part of this discrepancy may be due to the differences between HF patients and the oncology patients many hospices were designed to support: management of LVADs and inotropes is expensive and complicated, and may not be supported by hospice agencies. However, in the case of implantable cardioverter defibrillators (ICD) deactivations at a single center, an inexpensive and straightforward intervention, the median time from PC introduction to death was 7 days, with only half of those discussions leading to specialty PC referral.

Communication

Clear and effective communication between patients and healthcare providers is essential to the provision of high-quality care. Patients and families want open, honest, timely, and accurate information about their chronic or terminal diseases; however, communication about prognoses and care preferences are uncommon. Multiple qualitative studies of New York Heart Association (NYHA) class 3 HF patients have demonstrated similar findings, specifically that HF patients desire to know their prognosis from their physician while they have robust cognitive function, usually at the time of diagnosis, and such a discussion should include the range of potential prognostic possibilities. Nevertheless, this same study showed how patients want these truths balanced with hope for improved quality and quantity of life. Patients and caregivers typically use this information to elaborate their care goals, as in two studies that asked patients to choose between two potential futures: shorter survival time with improved QoL versus longer survival at current QoL. These revealed that patients have strong but polarized preferences and that these desires are malleable over time depending on the symptom burden and prognosis. Additionally, patients and their caregivers often disagree with respect to potential health care decisions. In 100 patient-caregiver pairs from two centers, 47% were incongruent, and incongruent pairs reported greater psychosocial distress.

Unfortunately, HF patients and caregivers frequently remain unaware of the severity of their illness and thus unable to formulate their own goals of care. When effective communication does not take place, patients may not realize that HF is a progressive and life-limiting syndrome. A modern study of 51 stage D HF patients who died within one year asked them to describe their disease and where they saw themselves one year in the future: only 14% believed HF was terminal. Similarly, of experienced caregivers for patients with stage D HF with mean 10 years duration of caregiving, only 67% realized that HF was terminal.

In contrast to the linear and predictable health decline of terminal cancer, prognosticating outcomes in HF is difficult and uncertain, further impeding effective communication. As stated above, patients poorly estimate their own mortality and suffering, and HF progresses differently from cancer and typical aging with regards to the patient experience and rapidity of decline. When compared with the Seattle Heart Failure Model, patients from a single center predicted a mean 40% longer life-expectancy; patients who were younger or
who had more severe disease generated particularly divergent estimates. This may be because model predictions, and thus the likely influential factors leading to death, make use of markers of disease severity not understood by patients when envisioning their own survival. Nonetheless, despite reasonable c-statistics at the population level, none of the multitude of risk models permeating the HF literature reliably predicts whether an individual patient will die, with sensitivities less than 5% for 1-year mortality. Thus, there is confusion during the progression of HF regarding the overall prognosis, the timing of life-changing decompensations requiring hospitalization, sudden cardiac death, shocks if ICDs are implanted, candidacy for advanced therapies including LVADs and heart transplantation (HT), and appropriate timing for hospice referral.

Shared decision making is an extension of appropriate communication. It relies on eloquent description of the medical situation in a manner than can be appropriately digested by patients and caregivers with varied educational backgrounds and medical literacy, as well as elicitation of preferences from patients and their support networks regarding their desires during their HF therapy. Specific patient aims to be addressed include not only end-of-life requests, but also decisions surrounding increasingly risky but high reward therapies including LVADs and HT. For instance, despite a median survival of 14 months following destination therapy LVAD implantation, the inpatient mortality for the surgery approaches 11%. Structured interviews with LVAD candidates, patients, and caregivers showed that many participants made decisions about the LVAD quickly and reflexively, most felt there was no real choice because the alternative was death, and more than half were admitted to the hospital when the potential for LVAD was first expressed to them and thus depended principally on clinicians to decide for them. The relatively late introduction of patients to the concept of receiving an LVAD limited their ability to mentally process the idea, ask reasonable questions, and actively participate in the decision. In contrast, interviews with candidates who initially declined LVAD placement reveal that decision-making, while often initially reflexive, is malleable over time as symptoms worsen and QoL declines, highlighting the need for earlier discussions and perhaps decision aids to assist in this process. Thus, shared decision-making relies on appropriate baseline communication of the clinical situation and further develops the care plan by empowering the patient to incorporate their own individualized care preferences.

Preparedness planning

Preparedness planning encompasses education regarding a wide array of potential future events that HF patients and caregivers should anticipate. While not specific to the HF disease process, the universal goals are to assist patients to communicate their wishes to their families and friends including advanced directives and resuscitation orders. As reported earlier, patients prefer to know their prognosis throughout the HF disease course as best as it can be described. Unfortunately, in a community-based cohort of over 600 HF patients, only 41% had an advance directive in place to document their end-of-life preferences or appoint surrogate decision makers. Other critical issues include the deactivation of implanted cardiac devices around the end of life, including ICDs and LVADs, which can be ethically and emotionally difficult. HF patients implicitly and explicitly weigh the trade-off between improved QoL and decreased survival time to make decisions about resuscitation preferences; however, they can only assess the situation if appropriately informed. The United States Centers for Medicare & Medicaid Services acknowledged these issues by requiring PC involvement in LVAD preparedness counseling.

There are numerous additional end-of-life choices relevant to HF patients that have not been historically well-discussed. One example is location or setting of death. While 46% of cancer patients in a Dutch registry died at home, the same was true for only 21% of HF patients; of the remaining HF patients, 28% died in a hospital, 26% in a skilled nursing facility, and 22% in a care home. Identification and conversation regarding death at home as an end-of-life goal may help to resolve these differences, as patients in one US cohort spent a median of 28% of their final month of life in the hospital. The opportunity to deactivate implanted cardiovascular devices serves as another prime example of how HF patients may be better informed of their medical options. Despite guideline recommendations, no one from a single-center retrospective case review of 44 patients with an ICD who died over a 12-month period was informed of the possibility of device deactivation prior to implantation; furthermore, only 23 (52%) had an end-of-life discussion prior to death and only 16 (36%) had their ICD deactivated prior to death. In a separate investigation, telephone interviews with 278 ICD patients demonstrated that 86% had never considered or been knowingly counseled whether to alter their ICD settings if they were unlikely to survive, though 95% agreed that they should have the opportunity to decide. Willingness to deactivate an ICD varies greatly by patient, with reported prevalence ranging from 12–79%, making conversations on this topic crucial to acting in concordance with patient desires.

Finally, there are largely inevitable implications of the HF disease process that must also be anticipated. Chief among them are the financial implications of HF care, which are often overlooked but can be devastating to patients and families. In one observational cohort of patients within the last week of life, 13% had a family member who had quit work, 16% of families had lost at least one large source of income, and 23% had lost most or all of their family savings due to the patient’s illness. These financial matters are particularly relevant for advanced therapies, both in patient qualification and for their survival afterwards.

Psychosocial and spiritual support

The burdens of HF extend beyond the physical domain and encompass all aspects of patient life. HF patients experience adjustment reactions to progressive losses that lead to growing anxiety and depression. When compared with other common cardiovascular conditions including myocardial infarction and coronary artery bypass grafted patients, HF patients have the highest prevalence of clinical depression (occurring in two-thirds of patients), and the highest level of anxiety. Physical symptoms and loss of function cause
significant life disruption, loss of roles, and social isolation, which in turn engender spiritual distress, loss of stabilizing sense of peace, purpose, meaning, and connections to others. These declines in social, psychological, and spiritual status correlate with physical deterioration.⁵⁰ Additional emotional challenges occur in the setting of the financial stress due to lost ability to work and the high costs of HF treatment including advanced therapies, hospitalizations, and caregiving. Unfortunately, HF patient caregivers report substantial dissatisfaction overall with the current level of emotional support provided by the medical establishment, likely because of a relative lack of screening for these under-recognized non-physical sources of distress and rare referrals to specialists for their treatment.⁵¹

**Symptom management**

Distressing symptoms may arise from HF and its treatments or from coexisting comorbidities. Although HF patients commonly experience shortness of breath, fatigue, pain and edema, this syndrome can elicit diverse symptomatology including nausea, excessive thirst, concentration and memory deficits, weakness, anxiety, and depression.⁵ As the disease progresses, multifactorial pain increases, dyspnea becomes more severe, and depression worsens. Symptoms preceding death from progressive pump failure are often severe. HF patients experience an average of 9–12 symptoms each, with half of patients reporting high symptom-related distress.⁵²,⁵³ Singular symptoms may derive from diverse causes. While 48% of HF patients report pain, most is non-cardiac and may represent neurologic, musculoskeletal, or psychiatric illnesses including depression, each of which may need separate treatment.⁵⁴ As with cancer, the high symptom burden may also include emotional, spiritual and caregiver strain. Each symptom can adversely affect patient well-being and health-related QoL, while improvement in symptoms is associated with better survival and functional status. However, when compared to cancer, HF patients tend to have greater unresolved dyspnea relative to other symptoms of chronic illness, which may be best treated with therapies targeted at the underlying disease process such as diuretics and vasodilators, or advanced therapies such as LVAD and cardiac transplant, until those modalities are no longer effective.⁵⁵ Thus while PC practitioners may have a role in ameliorating some of the symptom distress in advanced and refractory HF, the central symptom of dyspnea typically remains the domain of the other physicians and team members involved until late in HF progression. If common symptoms are unresponsive to or incompletely attenuated by maximally tolerated HF therapies, alternative symptom management strategies can be utilized (Table 2).

**Table 2 – Management strategies for heart failure symptoms unresponsive to optimal standard therapies.**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Potential Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Senna (1st line, 2–10 tab/day), Polyethylene glycol or Lactulose (2nd line), avoid doxucate (no benefit)</td>
</tr>
<tr>
<td>Cough</td>
<td>Address reversible causes (gastroesophageal reflux, pulmonary or laryngeal infection)</td>
</tr>
<tr>
<td></td>
<td>Menthol lozenges, Benzonatate, Guaiifenesin, Opioids</td>
</tr>
<tr>
<td></td>
<td>Consider exchanging ACE-inhibitor for ARB</td>
</tr>
<tr>
<td>Depression/Anxiety</td>
<td>Screen for and treat physical and existential distress, cognitive behavioral therapy</td>
</tr>
<tr>
<td></td>
<td>Antidepressant (SSRI, mirtazapine – also improves appetite and nausea), cautious Benzodiazepines, avoid TCAs/SNRIs</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>Consider changing ACE medications: anticholinergics, sympatholytics, opioids, benzdiazepines</td>
</tr>
<tr>
<td></td>
<td>Salivary gland stimulation (sugarless gum or candy)</td>
</tr>
<tr>
<td></td>
<td>Saliva substitutes (ice chips, mucin-based artificial saliva products)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Optimal oral hygiene, acid avoidance</td>
</tr>
<tr>
<td></td>
<td>Address reversible causes (pleural effusion, pulmonary edema, infection, bronchoconstriction, anxiety)</td>
</tr>
<tr>
<td></td>
<td>Physical therapy, rehabilitation, mindfulness training</td>
</tr>
<tr>
<td></td>
<td>Environmental interventions (fans for air circulation, hospital bed for head elevation)</td>
</tr>
<tr>
<td></td>
<td>Opioids (i.e. Morphine 2.5–5 mg orally q4h as needed or similar, titrated to effect)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Address reversible causes (hypothyroidism, depression, sleep disordered breathing, anemia)</td>
</tr>
<tr>
<td></td>
<td>Physical therapy, rehabilitation, exercise training</td>
</tr>
<tr>
<td></td>
<td>Consider decreased beta-blocker dosing</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Address reversible causes (medication effect, hepatic/gastrointestinal edema, renal failure)</td>
</tr>
<tr>
<td></td>
<td>Ondansetron or Metoclopramide or low-dose Haloperidol (all can prolong QTc), Benzdiazepines</td>
</tr>
<tr>
<td>Pain</td>
<td>Physical therapy, rehabilitation, acupuncture, mindfulness training, cognitive behavioral therapy</td>
</tr>
<tr>
<td></td>
<td>Spinal cord stimulation, transcutaneous nerve stimulation</td>
</tr>
<tr>
<td></td>
<td>Acetaminophen (1st line), Opioids (2nd line), Gabapentin (if neuropathic pain), avoid NSAIDs/TCAs</td>
</tr>
</tbody>
</table>

Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; NSAID = non-steroidal anti-inflammatory drug; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
Although it is hypothesized that combining structured PC techniques with disease-modifying HF therapy should improve QoL and perhaps traditional clinical outcomes including hospital admissions and survival, this has not been well-proven. Many guideline-recommended approaches have been extrapolated from the oncologic literature, but few randomized controlled trials exist in the HF realm and many have significant caveats limiting their interpretation or reproducibility.

Many of the randomized trials of PC interventions that have been performed with HF patients have either utilized additional disease-modifying components, sowing doubt regarding which aspect of the trial caused a change in the outcome, or failed to meet their primary outcome measure. For instance a multidisciplinary intervention in 282 acute HF patients included nurse directed education, diet changes, social work consultation, and intensive follow up with home visits. Although the treatment group had numerically fewer hospitalizations, improved QoL, and lower costs of care, the causality is unknown. The Swedish Palliative Advanced Home Care and Heart Failure Care (PREFER) trial randomized 72 patients to a multidisciplinary team intervention with a person-centered home care component and found no clinically significant change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary scores. There was a suggestion of QoL improvement from less robust scoring methods and from changes in KCCQ sub-scores; however, it remains uncertain whether these were clinically significant improvements or due to the intervention, and which components of the intervention were responsible for any productive changes. The Patient-Centered Disease Management (PCDM) multicenter trial randomized 392 HF patients to multidisciplinary care including nurses, cardiologists, psychiatrists, home telemonitoring, and screening with treatment of depression. There was no significant improvement between treatments groups in the KCCQ summary score, and though there were numerically fewer deaths in the treatment arm, the trial was not powered for this outcome.

Some more simply developed trials have demonstrated benefit for PC involvement in HF care, while others have failed to support typical interventions. A single center trial of 232 patients with acute HF randomized to inpatient specialist PC consultation or standard care demonstrated clinically and statistically significant improvement in QoL after one month as measured by the Minnesota Living with Heart Failure Questionnaire. In contrast, despite the demonstrated association between clinical depression and worse outcomes in HF patients, sizeable randomized controlled trials of the antidepressants escitalopram and sertraline for 12–24 weeks demonstrated no reduction in depression and no benefits in HF morbidity or mortality. Rather, cognitive behavior therapy administered by experienced therapists for 6 months at a single institution to NYHA class 1 through 3 HF patients with clinical depression effectively improved depression scores and clinically significantly increased QoL, as measured by the KCCQ.

Systematic reviews and meta-analyses have sometimes shown improvements in HF QoL, rehospitalizations, and mortality from PC interventions, but they have also demonstrated considerable heterogeneity in design and outcome quantification. One meta-analysis of the association between PC interventions and outcomes for patients and their caregivers, from both the oncologic and HF literature, found statistically and clinically significant benefits for patient QoL. The 14 included HF trials represented 32.5% of the meta-analysis. Notably, there was no association between PC use and survival, and due to the substantial inter-trial heterogeneity, the evidence for all the associations was weak. A separate systematic review of 15 prospective and retrospective interventions in HF patients, only eight of which solely included HF patients with only five of the eight randomized and controlled, found general improvements in QoL and patient satisfaction with PC. However, meta-analysis was limited to only three small studies to show a 42% relative risk reduction in risk of hospitalization. The limited ability to analyze the data again occurred due to substantial intervention and location heterogeneity, including by social workers, nurses, and physicians in inpatients, outpatients, home-based, and hospice settings. The services provided were equally varied, as were the outcomes studied, and overall only 18% of randomized controlled trials investigating PC from 2001 through 2015 utilized HF patients.

Two recently completed randomized clinical trials may add to the PC HF milieu, but results remain tentative. The Palliative Care in Heart Failure (PAL-HF) trial randomized 150 HF patients at increased risk to a multi-dimensional intervention focused on physical symptoms, psychosocial and spiritual well-being, and advanced care planning provided by a nurse practitioner. The treatment group demonstrated a substantial and clinically significant increase in QoL over 24 weeks, with no change in mortality. The Social Worker-Aided Palliative Care Intervention in High Risk Patients with Heart Failure (SWAP-HF) trial randomized 50 hospitalized HF patients to a social worker instituted intervention focused on documentation of advanced care preferences. The treatment arm increased the proportion of medical charts with recorded advanced care preferences from 33% to 65% over 6 months, with improved alignment of care goals between patients and physicians from 26% to 94%. These studies may serve as pilots for larger multi-site trials to hopefully establish feasible and effective PC interventions in the HF population. As this nascent field grows more robust, the methods for providing PC may become more codified with clearer delineation of which services to dispense and how to provide them.

**When to involve specialized palliative care consultants**

There exists no certain unique time to involve specialist PC providers in the care of a HF patient, as the decision depends on the clinical setting, the availability of such specialists, the expertise of the currently involved management team, and the specific characteristics of the interaction between the patient, their providers, and their caregivers. Part of the dearth of experimental evidence for specific PC interventions in HF includes the timing of specialist PC consultation, and the uncertainty regarding a patient’s clinical trajectory makes it difficult to determine when to offer PC services. Thus, while
sensible guidelines can be postulated, it is ultimately the responsibility of HF and PC providers to identify, test, and prove utility of interventions and their appropriate timing. Nevertheless, it is well-accepted that specialty PC consultation is being initiated too late in the HF disease process. In a retrospective chart review from one academic center between 2006 and 2011, the median time from specialist PC consultation to death was 21 days, leaving little time to accomplish many of the tasks set forth in the preceding discussion. This is in spite of data from the oncologic literature that earlier PC consultation is associated with better outcomes and decreased costs.

The local absence of specialty PC resources may constrain utilizing these specialist consultations. For instance, although availability of inpatient PC services has grown substantially from 15% of hospitals over 50 beds in 2001 to 67% of the same hospitals in 2014, there exists considerable regional variability even within the United States. In some areas of the country inpatient consultation is only present in 42% of similarly sized hospitals. Thus, inherent in deciding when to consult PC is to understand the local presence of these services and providers.

Because QoL decreases and symptoms persist throughout the duration of the HF disease process, PC is theorized to ideally be integrated into the multidisciplinary holistic care of HF patients throughout their illness, although robust HF clinical trial data to support this assertion is lacking. The ability to achieve this integration depends on each provider’s skill set and comfort with PC approaches and techniques, and of course the availability of specialized PC resources. Nevertheless, the current shortage of specialist PC practitioners may force members of the primary HF care team into this role. Although there is no clear agreement by patients or providers on which parts of the management team, including the cardiologists, primary care doctors, and PC specialists, should be responsible for advanced care directives and preparedness planning in HF, there is clear onus to provide these resources as part of appropriate patient-centered care. If the involved care team requires assistance completing necessary PC tasks described in the above manuscript, then specialist PC help should be enlisted.

PC must be adaptive to the needs of the patient in their current situation, which requires frequent reassessment given the unpredictability of the disease, the complexity of the management options, and the rational tendency for patients to re-evaluate their preferences as the clinical situation changes. Without systematic consultation with PC specialists there are common opportunities for palliation that reliably occur despite the overall unreliability of disease progression. These periods of elevated risk for unaddressed PC needs include: the first diagnosis of symptomatic or stage C HF, which should be considered akin to a first diagnosis of life-threatening cancer; before implantation of an ICD; during a time of repeated HF hospitalizations or worsening symptoms; upon consideration of advanced HF therapies including LVAD or HT; and when there appears to be no further life-sustaining therapy to be offered and the patient has arrived at the end-of-life with potential transition to hospice care (Table 1). Treating these moments as objective ‘triggers’ to initiate an expert PC consultation can decrease the uncertainty and improve confidence around the referral process; however, the specific events may differ by community and ideally should be agreed upon by local care teams and their associated specialist PC providers.

In order to ease the referral process to specialty PC providers in the above situations, the common understanding of PC should embrace the many levels of support that a PC consultation can offer from diagnosis through death. The palliative care referral process should not worry patients nor practitioners that hope for improvement in the underlying disease is being abandoned. Rather, the goal is to help patients and families live as well as possible for as long as possible by integrating supportive care and coping strategies with ongoing medical and surgical care. At the end of life, patients and providers should be reassured that after accounting for the decline in clinical status, advancing age, and compounding comorbidity, transition to a do-not-resuscitate order does not appear to independently worsen the risk of death.

Conclusions

Even though substantial work remains to be done before the potential benefits of specialty PC for HF patients are realized, currently available data suggest that utilizing specialist PC providers may be helpful to improve symptoms and QoL for these ill and complicated individuals. HF patients have many needs that a PC provider can assist the medical team in meeting, including issues surrounding communication of prognosis and expectations, preparing for medical and social decisions unforeseen by patients, buttressing both the patients and caregivers in times of high stress and emotional fatigue, and at times assisting in managing the cornucopia of symptoms that coalesce with worsening HF. However, many interactions with patients that theoretically fall under the umbrella of PC are typically already provided by HF practitioners but are not labeled ‘PC.’ Thus, the appropriate time for cardiologists and other members of the care team to reach out to specialized PC providers is best tailored to the expertise and comfort of the team members involved, particularly given the relative shortage of highly-trained PC consultants. Evolving expert guidelines along with additional PC training for medical practitioners throughout their education may help them to lead these challenging conversations. At the same time, systematic incorporation of PC conversations and interventions throughout the HF patient journey may improve shared decision-making and assist patients in achieving their desired outcomes. In the meantime, typical triggers for calling specialist PC can be used as guidelines to help patients and caregivers achieve their health care goals during management of chronic HF and ease progression to worsening symptoms, potential advanced therapies, and eventual death.

Statement of conflict of interest

There is no conflict of interest of any of the listed authors.
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Heart failure with Myocardial Recovery - The Patient Whose Heart Failure Has Improved: What Next?

Petra Nijst\textsuperscript{a,b}, Pieter Martens\textsuperscript{a,b}, Wilfried Mullens\textsuperscript{a,c,*}

\textsuperscript{a}Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium
\textsuperscript{b}Doctoral School for Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium
\textsuperscript{c}Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium

\textbf{ARTICLE INFO}

\textbf{ABSTRACT}

In an important number of heart failure (HF) patients substantial or complete myocardial recovery occurs. In the strictest sense, myocardial recovery is a return to both normal structure and function of the heart. HF patients with myocardial recovery or recovered ejection fraction (EF; HFrecEF) are a distinct population of HF patients with different underlying etiologies, demographics, comorbidities, response to therapies and outcomes compared to HF patients with persistent reduced (HFrEF) or preserved ejection fraction (HFpEF). Improvement of left ventricular EF has been systematically linked to improved quality of life, lower rehospitalization rates and mortality. However, mortality and morbidity in HFrecEF patients remain higher than in the normal population. Also, persistent abnormalities in biomarker and gene expression profiles in these patients lends weight to the hypothesis that pathological processes are ongoing. Currently, there remains a lack of data to guide the management of HFrecEF patients. This review will discuss specific characteristics, pathophysiology, clinical implications and future needs for HFrecEF.

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\textbf{Keywords:}

Heart failure with recovered ejection fraction
Myocardial recovery
Reverse remodeling

\textbf{Contents}

Myocardial recovery and definitions .................................................. 227
Myocardial processes associated with reverse remodeling .......................... 227
Improved EF or cured HF? Phenotype versus genotype ........................... 228
Prevalence, predictors and prognosis of myocardial recovery ...................... 228
The contribution of different therapies to LVEF improvement ..................... 229
Neurohumoral blockers ........................................................................... 229
Cardiac resynchronization therapy (CRT) .................................................. 229
VADs ........................................................................................................ 230

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* Address reprint requests to Wilfried Mullens, MD, PhD, Department of Cardiology, Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium.
E-mail address: wilfried.mullens@zol.be (W. Mullens).

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complete myocardial recovery occurs, and it is expected that this number of HF patients will further increase in the future. These patients differ from HF patients with persistent reduced ejection fraction (EF; HFrEF) as well as preserved EF (HFP EF) in underlying mechanisms of cardiac dysfunction, comorbidities and prognosis. In this review we will discuss specific characteristics, pathophysiological and clinical implications and future needs for HF patients with myocardial recovery.

Myocardial processes associated with reverse remodeling

The progression of HF is associated with LV remodeling, which manifests as gradual increases in LV end-diastolic and end-systolic volumes, wall thinning, and a change in chamber geometry to a more spherical, less elongated shape. This process is usually associated with a progressive decline in LVEF. Different triggers can lead to a decline in LVEF and the process of remodeling (Fig 2). The process is influenced by hemodynamic load, neurohumoral activation and other factors. Due to continuous maladaptive remodeling, myocardial dysfunction is usually a progressive condition. In contrast, the biology of myocardial recovery is not well understood. It is likely a spectrum of improvement with (partial) reversal of biological processes which occur in the failing heart. These may be categorized into those that occur in cardiac myocyte versus changes within the extracellular matrix of the myocardium (Fig 2). During the process of reverse remodeling several studies showed that changes
within cardiac myocytes, extracellular matrix but also genetic and proteomic alterations (partly) reverses. Recovery of structure and function probably occurs easier in hearts with fewer pre-existing myocyte and extracellular matrix derangements. Perhaps the purest example is a Takotsubo cardiomyopathy, in which an acute stressor leads to severe regional LV dysfunction with return to normal LV structure and function once the insult resolves.

Improved EF or cured HF? Phenotype versus genotype

Observational studies suggest that improved hearts, even those with normal LVEF (“phenotype”), are not truly normal despite parallel improvements at organ, tissue, and cellular level (“genotype”). As such, HFrecEF patients have higher than normal levels of brain natriuretic protein (BNP), Troponin I, soluble fms-like tyrosine kinase receptor and uric acid, although significantly lower than patients with HFrEF and HfPef. Furthermore, subtle LV systolic changes such as global longitudinal strain often remain decreased despite a recovery in LVEF. This suggests the ongoing of abnormalities in the salt and water homeostasis and abnormal myocyte biology in at least a subset of patients. Moreover, studies using microarrays to profile myocardial gene expression revealed that the reverse-remodeled heart is different from a normal or non-failing heart.

Prevalence, predictors and prognosis of myocardial recovery

Improvement of LVEF has been increasingly observed in a variety of clinical settings over the past 10–15 years. In some etiologies of HF such as acute lymphocytic myocarditis, peripartum cardiomyopathy, some forms of toxic cardiomyopathies (e.g. ethanol or anthracyclines), tachycardia or hyperthyroidism associated cardiomyopathies; recovery and normalization of LV structure and function can occur spontaneously in up to 40-50% of patients. HF with myocardial recovery (defined as a previous LVEF < 40 but ≥40% at the time of study inclusion) was relatively prevalent in a single tertiary HF clinic setting. Within a sample of 358 HF patients, 56 were defined as HFpEF, 181 as HFrEF and 121 (34%) as HFrecEF. Another report on chronic HF patients identified 10% as HFrecEF, however in this study HFrecEF was defined as a LVEF ≥50% and previously <50%.

Patients with myocardial recovery are typically younger than patients with HfPef and HFrEF, and have a lower prevalence of comorbidities such as hypertension, diabetes and atrial fibrillation. Nonischemic origin of HF and no prior myocardial infarction were associated with improvement in

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Table 1 – Overview of definitions of heart failure.

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Criteria</th>
<th>LVEF Cut-off</th>
<th>Definition Adopted by Current Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFrecEF</td>
<td>Recovery is a substantial or complete improvement of left ventricular systolic function</td>
<td>Previous LVEF&lt;40% but currently LVEF ≥40% or Previous LVEF &lt; 40% but currently LVEF ≥ 50%</td>
<td>ACCF/AHA</td>
</tr>
<tr>
<td>HFmrEF</td>
<td>Symptoms and signs of HF + LVEF 40–49% + elevated levels of natriuretic peptides + at least one of the following 1) relevant structural heart disease (left ventricular hypertrophy or left atrial enlargement) 2) diastolic dysfunction</td>
<td>LVEF 40–49%</td>
<td>ESC</td>
</tr>
<tr>
<td>HFpEF</td>
<td>Symptoms and signs of HF + LVEF ≥ 50% + elevated levels of natriuretic peptides + at least one of the following 1) relevant structural heart disease (left ventricular hypertrophy or left atrial enlargement) 2) diastolic dysfunction</td>
<td>LVEF ≥ 50%</td>
<td>ACCF/AHA + ESC</td>
</tr>
<tr>
<td>HFpEF borderline</td>
<td>Symptoms and signs of HF + LVEF ≥ 50% + elevated levels of natriuretic peptides + at least one of the following 1) relevant structural heart disease (left ventricular hypertrophy or left atrial enlargement) 2) diastolic dysfunction</td>
<td>LVEF 41–49%</td>
<td>ACCF/AHA</td>
</tr>
<tr>
<td>HFpEF Improved</td>
<td>Symptoms and signs of HF + LVEF ≥ 50% + elevated levels of natriuretic peptides + at least one of the following 1) relevant structural heart disease (left ventricular hypertrophy or left atrial enlargement) 2) diastolic dysfunction</td>
<td>LVEF ≥ 50%</td>
<td>ACCF/AHA</td>
</tr>
<tr>
<td>HFpEF Improved</td>
<td>Symptoms and signs of HF + LVEF ≥ 50% + elevated levels of natriuretic peptides + at least one of the following 1) relevant structural heart disease (left ventricular hypertrophy or left atrial enlargement) 2) diastolic dysfunction</td>
<td>LVEF ≥ 50%</td>
<td>ACCF/AHA</td>
</tr>
</tbody>
</table>

The acronyms in bold are used throughout the manuscript.
Also, myocardial–39,40 Beta-blockers are the medical therapy addition-35% despite maximally tolerated Moreover, reverse remodeling strategies, Substantial Indeed, the higher the intake of Several trials demonstrat-50%) when compared to HFrEF and HFpEF ≥ Heart failure definitions based on left ventricular ejection fraction and evolution over time. Abbreviations: EF: ejection fraction; HFmrEF: heart failure with mid range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFrecEF: heart failure with recovery ejection fraction.

LVEF in the large IMPROVE-HF cohort, a finding that supports the experience of many HF physicians. Also, myocardial recovery is more likely in patients with a shorter duration and less myocardial fibrosis Improvement of LVEF has been systematically linked to improved quality of life and lower rehospitalization rates and mortality, regardless of how it is achieved. HFrEF patients have often milder symptoms, with patients mainly functioning in New York Heart Association (NYHA) class I or II. All-cause mortality, the need for cardiac transplantation or mechanical circulatory supports are lower in patients with HFrecEF (LVEF ≥ 50%) when compared to HFrEF and HFpEF (HR for HFrEF compared to HF recovered 4.1 (2.4–6.8); HR for HFpEF compared to HF recovered 2.3 (1.2–4.5)). However, patients with myocardial recovery still experienced a significant number of hospitalizations for HF, with approximately 50% of this group being hospitalized by 6 years hinting towards ongoing subclinical alterations driving residual HF morbidity.

**The contribution of different therapies to LVEF improvement**

Renin-angiotensin-aldosterone inhibitors, beta-blockers (BBs), cardiac resynchronization therapy (CRT) and ventricular assist devices (VADs) have the potential to achieve reverse remodeling and to date, every therapy with mortality benefits (except for a cardioverter defibrillator) in HFrEF is capable of inducing reverse remodeling. Moreover, reverse remodeling strategies, whether medical or device-based therapies, seem to exhibit a dose-response relationship. Indeed, the higher the intake of neurohumoral blockers or effective biventricular pacing, the higher the chance of recovery. However, not every patient exposed to these therapies achieves myocardial recovery and reverse remodeling is not always durable.

**Neurohumoral blockers**

Optimal medical therapy appears to be a key component of achieving myocardial recovery. In the IMPROVE-HF (Registry to improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting) study, a large observational cohort of outpatients enrolled in a performance measure intervention, almost one-third of patients experienced meaningful recovery of myocardial function with nearly doubling of LVEF (from 25% to 46%). Beta-blockers are the medical therapy most strongly linked to reverse remodeling. In the magnetic resonance imaging substudy of the MERIT-HF trial, treatment with metoprolol for 6 months significantly increased LVEF by an average of 28%. Animal and human studies have revealed that sustained beta-blocker treatment improves cardiac myocyte contractility, contractile reserve and calcium handling in myopathic hearts. Additionally, even when aldosterone receptor antagonists (AAs) are added to background therapy with ARB/ACEi and BBs, significant beneficial effects on LV volume and function occur. Limited data regarding the reverse remodeling response following Sacubitril/valsartan exists as the PARADIGM-HF trial did not collect follow-up echocardiography data. However, in a rat model of myocardial infarction (MI), 4 weeks of therapy with Sacubitril/valsartan resulted in significant improvement of LVEF and reduction of LV end diastolic diameter. Undoubtedly, data regarding the effect of reverse remodeling and sacubitril/valsartan will arise in the future.

Table 2 summarizes the effect of different pharmacotherapies on LVEF in large randomized trials.

**Cardiac resynchronization therapy (CRT)**

Among HFrEF patients, a very intriguing group are those with improved LVEF after CRT. Indeed, patients eligible for CRT had persistent LVEF ≤ 35% despite maximally tolerated neurohumoral blockers. Yet, systolic function often improves after implantation of a CRT. The average increase in LVEF in the large CRT trials (MIRACLE-ICD, CARE-HF, REVERSE and MADIT-CRT) ranged from +2 to +11% (Table 2). Substantial regression of myocardial dilatation and improvement of ejection fraction is likely the effect of resynchronization which initiates a cascade of positive effects such as improved contractility and filling of the ventricles, reduction of mitral regurgitation, decreased sympathetic nerve activity, and reduction of LV wall stress. Moreover, dog-models of CRT actually indicate that CRT is capable of targeting the molecular underpinnings of progressive LV remodeling, hereby inducing reverse remodeling on a cellular level. CRT has been shown to improve calcium, sodium and potassium channel function, hereby improving calcium cycling and abbreviating action potential duration, with the latter associated with a lower pro-arrhythmicogenic risk. Furthermore, CRT induces mitochondrial genome expression hereby improving myocardial substrate utilization and decreasing apoptotic signaling.
VADs

Since hemodynamic overload is regarded as one of the most prominent stimuli for maladaptive remodeling, VADs are an effective mean to induce reverse remodeling. It has been demonstrated that the powerful mechanical unloading of the LV offered by VADs, accompanied by increments in dosages of HF medication which can then be tolerated by the HF patients, can be a major contribution towards the process of myocardial recovery during mechanical support. A number of reports have demonstrated the effect of VAD therapy on cellular and subcellular reverse remodeling. One prominent feature of reverse remodeling in VAD-supported hearts is regression of myocyte hypertrophy and cell lengths and this was associated with echocardiographically documented reduction in LV dimensions and LV mass. Furthermore, LVADs are capable of enhancing long chain acylcarnitines use in the failing heart, which is indicative of a recovering myocardial metabolism. However, this improvement only allows for successful explanation of the LV-VAD in 1–2% of patients.

Revascularization

There is extensive clinical trial-based evidence supporting the potential for reverse remodeling in patients with chronic HF who have received surgical interventions. Significant improvement in systolic function in the days and weeks after myocardial infarction, as well as the potential for recovery after revascularization for patients with myocardial stunning or hibernation is observed. Both medical and catheter-based revascularization techniques have been associated with significant rates of reverse remodeling following acute myocardial ischemia in patients with chronic ischemic heart disease. More viable myocardial segments indicate a greater likelihood of improved LV function following revascularization.

Life style

Relatively high rates of myocardial recovery and improved LVEF have also been associated with the discontinuation of ethanol. One of the largest series indicated a >50% rate of myocardial recovery following cessation of ethanol use and a 6-fold better survival with abstinence compared with ongoing heavy ethanol use. Additionally, long-term moderate exercise training has been shown to induce reverse remodeling in patients with stable chronic HF.

Additionally, there are indications that several other (less or more experimental) therapies can influence LV remodeling such as mitral clipping, intravenous iron substitution, kidney transplantation, etc.
Current literature on management strategies of patients with HFmrEF

There remains to be a lack of prospective data to guide the management of patients with improved LVEF or myocardial recovery. There is a paucity of evidence on treatment strategies for patients with an LVEF in the grey zone of 40–50% (HFmrEF) or full recovery (LVEF ≥ 50%).

**Pharmacotherapy**

The persistent abnormalities in biomarker profile in these patients lend weight to the hypothesis that HF pharmacotherapy should be continued. However, there are no prospective data to support this approach and data on long-term use of neurohormonal medications in HF recovered patients are lacking. Only small studies studied the effects of withdrawal of medication in stable HF patients with recovered LVEF. Swedberg et al. withdrew BBs from 15 patients whose HF had improved (mean LVEF 46 ± 3%). Echocardiography demonstrated an overall reduction in LVEF from 46 ± 3% to 35 ± 3% (p < 0.01) after a mean of 72 days following beta-blocker withdrawal. Clinical features of HF recurred in 9 of the 15, with 1 sudden death. In a retrospective cohort study of 42 patients with dilated cardiomyopathy and improved LVEF (LVEF ≥ 40%), medication cessation was the only identified predictor of recurrence. A retrospective cohort study of 85 patients with LVEF recovery > 45% evaluated outcome after LV recovery with no changes in baseline medical pharmacotherapy. Thirty-three patients (39%) developed a recurrence of LV systolic dysfunction. When divided by the presence or absence of recurrence of systolic dysfunction, both groups had comparable ACEIs/ARBs but a trend towards lower BBs and AAs. Therefore, in the absence of more robust prospective data, these studies suggest potential benefit of continuation of standard guideline recommended HF medications in patients with HF and myocardial recovery.

**Cardiac device therapy**

Discontinuation of biventricular pacing in patients with improved or even normalized LVEF is contraindicated. One study in patients with mean LVEF 40 ± 15% showed that discontinuation of CRT during 4 weeks resulted in a rapid and progressive decline in LVEF (after 1 week 33 ± 14% and after 4 weeks 30 ± 12%) and increases in LV dimensions. Regarding the indication for CRT implantation, a large gap in evidence exists in patients with an LVEF of 35–50%. One small pilot study looked at the effects of CRT in patients with only mildly reduced LVEF beyond the current indications for CRT (n = 15, LVEF 40 ± 2%). Biventricular pacing resulted in significant increase in LVEF and decrease in dyssynchrony. Patients reported a significant reduction in NYHA class, however, if this results in an improvement of mortality and hospitalization rates is unclear. The MIRACLE EF (clinicaltrials.gov identifier: NCT01735916) and MADIT-ASIA (ClinicalTrials.gov Identifier NCT01872234) trials were designed to address patients with HFmrEF, but both trials have been halted due to difficulties with enrolment. Therefore, up until now, for new implantation of cardiac devices current guidelines should be followed and these exclude HFmrEF with left bundle branch block patients as well as patients with complete myocardial recovery if there is no additional pacing indication.

Patients with complete myocardial recovery after CRT are a specific subset of HFmrEF patients since these patients only demonstrated full recovery after CRT and not under optimal medical therapy. Currently a randomized prospective cohort study is investigating if neurohumoral blockers can safely be withdrawn in CRT patients with fully recovered heart function (clinicaltrial.gov identifier NCT02200822).

Additionally, many HF patients with implantable cardioverter-defibrillator (ICD) have an improved LVEF at the moment of battery change and therefore do not fulfill anymore guideline criteria for an ICD. In one study among 91 patients undergoing ICD generator exchange, 25 had LVEF improvement of at least 10% greater than 35%. The incidence of appropriate ICD shocks was the same between individuals with or without recovery. In a cohort of 231 Veterans affairs patients, 26% no longer met guideline indications for ICD therapy at the time of generator exchange. Subjects without ongoing ICD indication received a smaller number of appropriate ICD therapies than patients with indications (2.8 vs 10.7% annually, p < 0.001), but again, appropriate shocks were delivered in HF patients with myocardial recovery. Other studies report similar observations. However, only a subset of the MADIT-CRT trial investigated the prevalence of arrhythmias in HF patients with myocardial recovery to an LVEF ≥ 50%. The investigators observed that only one ventricular arrhythmia event among 55 subjects occurred and therefore suggested that these patients could be considered for downgrade from CRT-defibrillator to CRT-pacemaker at the time of battery depletion, if the device was placed in
primary prevention and ventricular arrhythmias have not been detected during the life-span of the device.78

Clinical implications and management of patients with myocardial recovery

Many patients with HFrEF have some degree of myocardial recovery or improvement in LVEF. In our daily clinical practice, we will encounter more and more patients with HFrecEF. Although prognosis of these patients is better than HFrEF and HFpEF patients, outcome is not normal and periodic follow up with echocardiographic assessment of LV function remains necessary.67 Until prospective data is available, pharmacotherapy and device therapy as for HFrEF patients should be continued/applied. Should there be a reason to withdraw medication following recovery of function, periodic screening of LV function remains necessary to ensure stability of cardiac function. In case of battery depletion of an ICD, a limited amount of evidence suggests that in patients with a LVEF ≥50% a downgrade is justified if no prior arrhythmias have been detected.

Conclusions

Future research should focus at identifying the best diagnostic and treatment strategies. A one-size-fits-all approach for drug development and management strategies in HF patients, where patients with persistent reduced LVEF and myocardial recovery (HFrecEF) are combined, should be replaced by individualized strategies. Therefore, prospective randomized studies looking at the potential of therapy withdrawal or therapy selection and specific (laboratory or imaging) biomarkers of recovery are urgently warranted.

Statement of Conflict of Interest

None of the authors have any conflicts of interests with regard to this publication.

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A Blueprint for the Post Discharge Clinic Visit after an Admission for Heart Failure

Aaron Soufer, Ralph J. Riello, Nihar R. Desai, Jeffrey M. Testani, Tariq Ahmad

Section of Cardiovascular Medicine, Department of Internal Medicine, Yale New Haven Hospital, Yale University School of Medicine, New Haven, CT, United States

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ABSTRACT

The immense symptom burden and healthcare expenditure associated with heart failure (HF) has resulted in hospital systems, insurance companies, and federal agencies playing close attention to systems of care delivery. In particular, there has been a large extent of focus on decreasing the frequency of HF readmissions through the development of hospital quality measures and the expansion of post discharge services to improve transitions of care from the inpatient to the outpatient setting. The post discharge clinic visit (PDV) serves an important role in this process as it acts as a fulcrum for the multi-disciplinary services available to HF patients, as well as an opportunity to fill any gaps that might have occurred in evidence based care of the patient. The objective of this review is to provide a blueprint for the PDV that will allow clinicians to construct the key elements of the PDV in a patient-centered fashion that is firmly rooted in the guidelines.

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Contents

Background ................................................................................................................................. 238
The Post Discharge Visit ........................................................................................................... 238
Preparing for the PDV ............................................................................................................. 239
History and physical examination ......................................................................................... 239
Comorbidities ......................................................................................................................... 241
Laboratory tests ....................................................................................................................... 241
Imaging ................................................................................................................................... 242
Medication reconciliation and optimization of GDMT .......................................................... 242
Defibrillators/pacemakers ....................................................................................................... 244
Coronary artery and valvular disease ...................................................................................... 244
Lifestyle modification and self-care ....................................................................................... 245
Consideration of advanced therapies ..................................................................................... 246
End of life care ....................................................................................................................... 246

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* Correspondence to: Tariq Ahmad, MD, MPH, Section of Cardiovascular Medicine, Yale School of Medicine, 135 College Street, Suite 230, New Haven, CT 06520, United States.

E-mail address: tariq.ahmad@yale.edu (T. Ahmad).

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Background

As would be readily apparent to most who read this review, heart failure (HF) is a health care issue of enormous proportions, both in terms of patient suffering, and costs to the health care system (HCS). The syndrome we call HF is an amalgam of several disease states, with some commonalities that include dysregulation in several key molecular pathways that lead to impairments in the body’s ability to fulfill its own metabolic demands and maintain euvolemia. This leads to HF patients reaching a physiologic “tipping point” with ease, and being hospitalized for issues such as worsening renal function and volume overload. These are relatively frequent, with published data putting 30 day readmission rates at 26% – 42%, depending on numerous modifiable and fixed risk factors. Due to their enormous impact on the HCS, the metric of HF readmissions is publicly reported by the Centers for Medicare and Medicaid Services (CMS) and included in the Hospital Readmission Reduction Program, which financially penalizes hospitals for excess readmissions, closely measured by entities such as HCS and the CMS. Several programs have been piloted to decrease readmission rates, with one key intervention being the post-discharge follow up visit (PDV).

The PDV is a key point in the transition of care from the inpatient to the outpatient setting and serves as a fulcrum for key multi-disciplinary services available to HF patients. This visit is not only a time slot for patients to be medically optimized, but serves as an opportunity to frame a disease state within the context of an individual patient, and to recalibrate goals of patient care aimed towards alleviation of symptoms, reduction in risk of readmissions, and the improvement of quality of life (QoL) and outcomes. However, as shown in Fig. 1, much can go wrong in the post discharge period for the HF patient, who is particularly susceptible to failed opportunities in management due to complexity of the syndrome. The goal of this review is to serve as guide for physicians and advanced practice providers to construct the key elements of the PDV in a targeted—and importantly patient-centered fashion—by reviewing the currently recommended best practices for this vulnerable patient population. To utilize our blueprint in the clinical setting, we have also created a PDV checklist that can be printed and used to streamline the appointment (Fig. 2).

The Post Discharge Visit

Both the U.S. and European guidelines recommend close follow up after discharge, with a 2-week period considered ideal. These recommendations are based on observational data including a landmark 2010 study by Hernandez and colleagues demonstrating that participation in early discharge follow up programs for HF patients can lead to reductions in 30 day readmission rates. These studies have also noted several issues with the immediate post-discharge care of HF patients, including substantial variations in the timing of follow-up, infrequent involvement by a cardiologist, lack of familiarity with what occurred during the hospitalization, and inadequate involvement of transition care teams. Furthermore, even when appropriate follow up visits are performed, several key interventions that might improve outcomes might be overlooked. This has led to the realization that a somewhat protocolized approach to the post discharge HF patient might be necessary.

Whereas the structure of PDV can vary between medical centers, depending on the resources available, we believe that the following key components should be considered:

- Evaluation by a cardiologist, or an advanced practice provider, under the supervision of a cardiologist (ideally, a HF cardiologist).
- Evaluation by a pharmacist
- Thorough physical examination, with vital signs, blood pressure (BP) measurement, weight, jugular venous pressure assessment, and evaluation for edema.
- Measurement of laboratories including basic metabolic panel, hepatic function testing, and brain natriuretic peptide (BNP) levels.
- Medication education, reconciliation, and uptitrate/add guideline recommended medical therapies as tolerated.
- Review need for device therapies [e.g. implantable cardioverter-defibrillator (ICD)/cardiac resynchronization therapy (CRT)].
- Individualized HF disease education emphasizing self-maintenance, self-monitoring, and self-management.
- Coordination of outpatient health care resources (e.g. social work and home health aides).
- Assessment of need for advanced therapies and goals of care discussion.

With the caveat that HF is a heterogenous syndrome, and each patient’s needs are likely to be unique, we believe that a universal protocol as we present in Fig. 2 can serve as a blueprint for personalized care, and for the purposes of reducing errors or oversights.
Preparing for the PDV

As is the case for any clinic encounter, providers should prepare prior to the PDV by reviewing the patient’s cardiovascular and general medical history, with special attention paid to the hospital course and discharge summary. Although this is the routine for all patients discharged from the hospital for any medical condition, the evaluation of a HF patient ought not to miss key questions:

- Is this a new diagnosis of HF or an exacerbation of a known condition?
- Does the patient have preserved or reduced systolic function?
- What work up has been performed to investigate the etiology of the patient’s cardiomyopathy?
- What precipitated the patient’s HF exacerbation? Have these precipitating factors been addressed?
- Was the patient discharged on an appropriate medical regimen? Are follow up laboratories needed to monitor the safety of these treatments?
- Was the hospital course complicated (i.e., requirement for inotropes, worsening kidney function, extended length of stay (LOS), inability to completely decongest the patient)

Ideally these questions can be answered by review of historical records, but communication with the discharging provider might be helpful if this information is not at hand.

Answering these key questions prior to the visit allows the provider to anticipate the needs of each individual patient, and helps to avoid redundancy in diagnostic workup and therapeutic interventions.

History and physical examination

When evaluating a patient after discharge, the symptoms that initially prompted hospitalization should be explored, and the provider should verify that these symptoms have subsided. Typical symptoms of HF exacerbation include dyspnea, orthopnea, paroxysmal nocturnal dyspnea (PND), lower extremity edema, and weight gain.\(^1\)\(^2\) Every office physical exam should also include assessment of vital signs including weight, and orthostatic vital signs when appropriate. The cardiovascular response to the Valsalva maneuver is a simple, inexpensive, and highly specific bedside test for estimation of volume status and detection of left ventricular (LV) systolic dysfunction in patients with HF. With the blood pressure cuff inflated 15 mm Hg over the systolic pressure, the patient is asked to perform a Valsalva maneuver. A normal response is when Korotkoff sounds are audible only at the onset of straining and at release. In patients with HF and volume overload, Korotkoff sounds can be heard throughout the Valsalva maneuver (the square wave response). In

![Fig. 1 – Prominent factors impeding transition of care in chronic heart failure care.\(^3\)](image-url)
Yale Heart Failure Discharge Follow Up Checklist

**History**
- Discharge summary reviewed
- LVEF quantified (___% on ___/___)
- Etiology of cardiomyopathy identified
- Precipitant of exacerbation identified
- Heart failure symptoms reviewed with patient

**Physical Exam**
- Vital signs
- Weight
- Orthostatic blood pressure (when needed)

**Screen for associated disease states**
- Sleep disordered breathing
- Anemia
- Hypertension
- Diabetes
- Chronic Kidney Disease

**Diagnostic markers**
- JVP estimate
- Pulmonary exam

**Prognostic markers**
- JVP estimate
- "cold/warm” “wet/dry” profile
- S3 present/absent

**Laboratory Tests/Imaging**
- Review and/or obtain when applicable
  - Basic metabolic panel
  - Liver function testing
  - BNP or NT pro BNP
  - CBC with iron studies
  - ECG
  - CXR
  - TTE
  - Left/Right heart catheterization reviewed
  - Consider need for further imaging
  - Follow up LVEF when <35%
    - 40 days post MI
    - 3 months in NICM

**Medical Therapy**
- Medication reconciliation
- Diuretics reviewed/adjusted
- HrEF
- Beta blocker* ARNI, ARB, or ACE-i*
- MRA* HrEF
- Optimize management of hypertension
- ARB or ACE-i*
  - for use in appropriate patients unless medication contraindicated

**Interventional Therapies (when appropriate)**
- ICD
- CRT
- Revascularization
- Valvular intervention

**Multidisciplinary Care**
- 7 day post discharge follow up established
- Discharge follow up telephone call placed
- Ambulatory health monitoring (when needed)
- Medication education
- Dietary education
- Physical activity education

**Referrals (when appropriate)**
- Home health services
- Cardiac rehab referral
- Advanced Heart Failure clinic referral
- Palliative/hospice services

**Communication**
- Communication with PCP

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Fig. 2 – Printable Yale heart failure discharge follow-up checklist.

compensated HF the pattern results in a lack of reappearance of the sounds after release (the absent overshoot response). Other key physical exam maneuvers to assess volume status include estimation of jugular venous pressure (JVP) through neck vein inspection and the abdominojugular reflux test. The third heart sound (or gallop rhythm) is commonly present with tachycardia and volume overload and signifies severe hemodynamic compromise and elevated left-sided filling pressures. It is important to remember that signs of pulmonary congestion such as rales and pulmonary edema may be lacking in patients with chronic HF and elevated pulmonary capillary wedge pressure. Supplemental exam items include general appearance, cardiac auscultation to evaluate for murmurs, S4 and pericardial friction rubs, and evaluation for abdominal ascites. Weight loss is often neglected as a cause of HF, but it can be present due to cardiac cachexia. Lastly, if the etiology of the HF remains unclear, an exam focused on clues as to the underlying cause should be undertaken (e.g. amyloid).

It is widely accepted that the history and physical exam play a central role in evaluating the stability of patients and gauging the appropriateness for diuretics and neurohormonal titration. We should, however, be cognizant of the limitations of this approach for clinical decision making. Several definitive studies have shown that physical exam findings lack profoundly in sensitivity and specificity for the purpose of intravascular volume status appraisal, the sine qua non for management of patients with HF. Furthermore, even right heart catheterization based hemodynamic measurements—mistakenly considered a test for assessment of volume—use intra-cardiac chamber pressures as a surrogate for intravascular volume, a relationship that has repeatedly been demonstrated to be weak, and may partly explain the results of the ESCAPE trial that failed to show the benefit of titration to
hemodynamic goals. As a result, management for patients with volume overload remains heterogeneous and a sizeable percentage of patients are inadequately treated. It is expected that in the future, improved diagnostics will help clinicians measure volume status in a manner that is precise and accurate. Until then, we should interpret exam findings in context of comprehensive data on the individual patient, rather than standalone information.

**Comorbidities**

The PDV serves as an opportunity to identify conditions that are often associated with HF, such as sleep apnea, hypertension, hyperlipidemia, and anemia. Table 1 highlights key comorbid conditions that should be considered while caring for the HF patient, and interventions performed with a clear understanding of the cutting-edge data on their efficacy, as these are constantly changing. For example, while it is reasonable to refer HF patients for a formal sleep study to establish a diagnosis of sleep apnea and to distinguish between a central and obstructive process, data from randomized controlled trials in regards to the most appropriate treatment for sleep apnea in HF have recently cast uncertainty on accepted wisdom, and positive pressure ventilation might not be universally helpful. Other examples include recent findings of intravenous iron replacement being efficacious in HF, but not the per os form, and the new sodium-glucose cotransporter-2 inhibitors (SGLT-2) — novel diabetic therapies — having a potential role in improving HF related outcomes in diabetics.

**Laboratory tests**

Laboratory studies provide a key role in the transition of care from the inpatient to the outpatient setting. Most often this includes a simple “metabolic panel or chem 7” to follow up on renal function and electrolytes when patients are continued on diuretics post discharge, but initial workups should be more thorough, as shown in Table 2. Electrolytes should be checked and replenished in these patients, with specific attention paid to potassium. If patients are on daily diuretics, then standing electrolyte repletion can be considered depending on serum electrolyte levels and medication interactions with potassium sparing agents. Electrolytes should also be checked if patients are started on angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), angiotensin-neprilysin inhibitor (ARNIs) or mineralocorticoid antagonists prior to discharge, as these agents can affect serum potassium concentration and creatinine. Underlying disorders that can cause an exacerbation of HF, and are amenable to monitoring via laboratory testing should be ordered during the PDV (Table 2).

Circulating biomarkers, specifically BNP levels, are central to the diagnosis and prognostication of HF patients in both the inpatient and outpatient settings. Either (BNP) or its precursor N-Terminal (NT)-pro BNP are readily measurable at laboratories within most HCS. During the clinic visit, testing of natriuretic peptides — either BNP or NT-proBNP — are recommended by the American College of Cardiology(ACC)/American Heart Association(AHA) for (a) Support of clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty, (b) For establishing prognosis or disease severity in chronic HF, and (c) To achieve optimal dosing of guideline directed medical therapy (GDMT) in select clinically euvolemic patients followed in a well-structured disease management program. The top line results of GUIDE-IT were recently published and showed no significant difference in outcomes with NT-proBNP guided therapy versus usual care. However, the results do not
definitively address the question the trial sought to address as there were no significant differences in biomarker levels between patients randomized to either strategy.24 Other25 biomarkers of injury (troponin) and fibrosis (serum ST2, galectin-3) can be considered to further fine-tune risk stratification.26

Imaging

All relevant imaging studies from the inpatient admission should be reviewed including electrocardiograms (ECG), echocardiograms, chest radiography, cardiac catheterization data, and nuclear imaging. The role of obtaining new imaging studies during the post discharge follow up is useful in select circumstances. If there was no ECG obtained during hospitalization and the patient has a new diagnosis of heart failure, then an ECG should be obtained during the post discharge follow up (Table 2). A follow up ECG should be obtained at the PDV if there was a notable rhythm disturbance or myocardial infarction during the index hospitalization, or if the patient has any new cardiac complaints in the office. In general, chest radiography should be reviewed from the index hospitalization. Further chest imaging is not necessary unless a patient’s symptoms have worsened and there is suspicion of worsening pulmonary edema, or if there were persistent signs of volume overload on chest radiography prior to discharge, and a repeat study would help to evaluate for stability or improvement of these findings. Transthoracic echocardiography (TTE) should have been obtained for any new diagnosis of HF during the index hospitalization. If a TTE was not performed while in the hospital for a new diagnosis of HF, then one should be obtained in the post discharge follow up visit to assess LV ejection fraction (LVEF), LV wall thickness, LV size, wall motion, right ventricular function, pulmonary pressures, and valvular function. Alternatively, especially in the absence of prior imaging, cardiac magnetic resonance imaging (MRI) can provide superior temporal and contrast resolution, and can serve as an alternate, especially in cases of newly diagnosed cardiomyopathy of unclear etiology. If there is lingering suspicion for ischemic heart disease, stress imaging using TTE, Positron emission tomography (PET), single photon emission computed tomography (SPECT), or cardiac MRI should be pursued, depending on patient and center specific characteristics. Nonetheless, in cases of high pre-test probability for ischemic heart disease, it is reasonable to proceed with coronary angiography.10

Medication reconciliation and optimization of GDMT

Adverse drug reactions are a common complication of preventable medication errors that increase hospital admission rates and prolonged LOS.27 Patients with HF, who are likely to be on multiple medications, and are susceptible to frequent transitions of care, are especially prone to these errors, and may be discharged on inappropriate therapies. In order to prevent this, the Joint Commission incorporated new requirements for safe transitions of care for HF in 2011, updated comprehensive medication management performance standards in 2017, and endorsed national patient safety goals to maintain and communicate accurate patient medication information across continuums of care.28 The initial post discharge encounter is therefore a great opportunity to optimize HF medication management in alignment with regulatory quality of care benchmarks and evidence-based treatment recommendations (Table 3). Performing patient-centered medication reconciliation, as a component of medication therapy management, entails a thorough evaluation of existing and previous medication regimens at each care transition. Prudent medication adjustment to mitigate prescribing errors and assessment of medication compliance is central to thorough reconciliation. The appropriateness of new medication regimen changes should be corroborated with hospital discharge summaries and the latest expert consensus disease state management guidelines; this is especially the case in HF with reduced LVEF, where the pharmacologic armamentarium is broad (Fig. 3). That said, even strong, high quality level of evidence recommendations need to be weighed against individualized patient characteristics. For example, if prescription drug insurance copayments exceed patients’ ability to pay, for example, following recent guideline updates to switch from an ACEI or ARB to an ARNI may require reconsideration.29

Beyond appropriate agent selection and monitoring, optimization of medication dosing is also a critical component of early discharge HF management, an opportunity that is frequently missed in clinical practice.30 This is a point of key importance, as familiarity with guideline-recommended target treatment doses and reasonable up-titration schedules is crucial for HF patients to derive maximal morbidity and mortality benefit (Table 3).31

The PDV also enables a reassessment of fluid status and subsequent adjustment of loop diuretics when indicated. Escalating loop diuretic doses, switching to more potent or better absorbed diuretics, and adjunctive use of thiazide-like diuretics may be necessary to maintain adequate decongestion in the early discharge period, particularly if diuretic resistance or poor dietary compliance has occurred once outside of the hospital environment. Recognizing these patients during the early post-discharge period may prevent an avoidable hospital readmission. Referral to an ambulatory intravenous diuretic infusion clinic rather than hospitalization may also be warranted for patients with worsening HF.32

Patient and caregiver education is also essential to the post-acute care encounter. Teaching common adverse drug effects, proper administration schedules, and self-care technique can improve patient engagement and regimen compliance.33 Improving adherence to HF medications and therapeutic patient education performed by trained pharmacists can decrease hospital readmission rates and reduce mortality.34,35 Studies have supported the premise that pharmacists’ delivery of tailored, health-literacy sensitive counseling and medication reconciliation services can have a meaningful impact on healthcare outcomes in HF.17 Specifically, clinical pharmacists as part of an outpatient HF clinic can perform medication reconciliation, perform therapeutic drug monitoring for agents like digoxin, screen for clinically significant drug-drug interactions, and educate...
<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Causes</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal/kidney impairment (creatinine &gt;150 μmol/L/1.7 mg/dL, eGFR &lt;60 mL/min/1.73 m²)</td>
<td>Renal disease, Renal congestion, ACE-I/ARB/MRA, Dehydration, NSAIDs and other nephrotoxic drugs</td>
<td>Calculate eGFR, Check potassium and BUN, Consider reducing diuretic dose if dehydrated, but if renal congestion more diuresis may help, Review drug therapy, If renal function worsened significantly near RAAS initiation/titration, consider discontinuation or dose reduction</td>
</tr>
<tr>
<td>Anemia (&lt;13 g/dL/8.8 mmol/L in men, &lt;12 g/dL/7.4 mmol/L in women)</td>
<td>Chronic HF, hemodilution, iron loss or poor utilization, renal failure, chronic disease, malignancy</td>
<td>Diagnostic work-up, Consider treatment</td>
</tr>
<tr>
<td>Hyponatremia (&lt;135 mmol/L)</td>
<td>Chronic HF, hemodilution, AVP release, diuretics (especially thiazides) and other drugs</td>
<td>Consider water restriction, adjusting diuretic dosage, Vasopressin antagonist (no good outcome data), Review drug therapy</td>
</tr>
<tr>
<td>Hypokalemia (&lt;3.5 mmol/L)</td>
<td>Diuretics, secondary hyperaldosteronism</td>
<td>Risk of arrhythmia, Consider ACE inhibitor/ARB, MRA, potassium supplements, Review drug therapy</td>
</tr>
<tr>
<td>Hyperkalemia (&gt;5.5 mmol/L)</td>
<td>Renal failure, potassium supplement, renin-angiotensin-aldosterone system blockers</td>
<td>Stop potassium supplements/potassium-sparing diuretic, Consider potassium binding resin, Reduce dose of/stop ACE inhibitor/ARB, MRA, Assess renal function and urine pH, Risk of bradycardia and serious arrhythmias, Evaluate hydration, treat glucose intolerance, SGLT-I</td>
</tr>
<tr>
<td>Hyperglycemia (&gt;6.5 mmol/L/117 mg/dL)</td>
<td>Diabetes, insulin resistance</td>
<td>Evaluate hydration, treat glucose intolerance, SGLT-I</td>
</tr>
<tr>
<td>Hyperuricemia (&gt;500 μmol/L/8.4 mg/dL)</td>
<td>Diuretic treatment, gout, malignancy</td>
<td>Allopurinol, Reduce diuretic dose, SGLT-I</td>
</tr>
<tr>
<td>Albumin low (&lt;30 g/L)</td>
<td>Poor nutrition, renal loss</td>
<td>Diagnostic work-up, Diuresis</td>
</tr>
<tr>
<td>Elevated bilirubin</td>
<td>Liver dysfunction, Liver congestion, Drug toxicity</td>
<td>Diagnostic work-up, Liver congestion, Review drug therapy</td>
</tr>
<tr>
<td>Elevated troponins</td>
<td>Myocyte necrosis, Prolonged ischemia, severe HF, myocarditis, sepsis, renal failure</td>
<td>Evaluate pattern of increase (mild increases common in severe HF), Perfusion/viability studies, Coronary angiography, Evaluation for revascularization, Consider genetic cardiomyopathy (laminopathy, desminopathy, dystrophinopathy), muscular dystrophies, Statin use</td>
</tr>
<tr>
<td>Elevated creatine kinase</td>
<td>Inherited and acquired myopathies (including myositis)</td>
<td>Evaluate pattern of increase (mild increases common in severe HF), Perfusion/viability studies, Coronary angiography, Evaluation for revascularization, Consider genetic cardiomyopathy (laminopathy, desminopathy, dystrophinopathy), muscular dystrophies, Statin use</td>
</tr>
<tr>
<td>Abnormal thyroid tests</td>
<td>Hyper-/-hypothyroidism, Amiodarone</td>
<td>Treat thyroid abnormality, Reconsider amiodarone use</td>
</tr>
<tr>
<td>Urine analysis</td>
<td>Proteinuria, glycosuria, bacteria</td>
<td>Diagnostic work-up, Rule out infection, diabetes</td>
</tr>
<tr>
<td>International normalized ratio &gt; 3.5</td>
<td>Anticoagulant overdose, Liver congestion/disease, Drug interactions</td>
<td>Review anticoagulant dose, Assess liver function, Review drug therapy</td>
</tr>
</tbody>
</table>

(continued on next page)
patients about their medications. Furthermore, they can facilitate prior authorization requirements for third party payers and navigate prescription cost savings programs.

**Defibrillators/pacemakers**

It is important to be mindful of the candidacy for ICD and/or CRT in HF patients. The post discharge follow up visits is an opportunity to determine appropriateness of these therapies on an individual patient basis. Patients with reduced LVEF < 35% are at high risk for sudden cardiac death, and it is crucial to consider the risks and benefits of ICD therapy as primary prevention in these patients. If the index hospitalization was in the setting of myocardial infarction with newly identified LVEF < 35%, then repeat evaluation of LVEF should be performed after 40 days while on of GDMT, and after 3 months in patients with non-ischemic cardiomyopathy. If the LVEF remains <35% after this interval, ICD therapy should be considered in patients with New York Heart Association (NYHA) class II–III symptoms and survival predicted to be >1 year. Wearable external cardiac defibrillators can be considered in high risk patients in the interim period between initial and follow up evaluation of LVEF, but their cost to the patient should be considered prior to prescription.36 Additionally, CRT is another consideration in patients with NYHA class II, III or ambulatory IV HF, LVEF < 35% and left bundle branch morphology QRS complex with duration ≥150 ms.37 We recommend that practitioners download the Guideline Clinical App (https://www.acc.org/tools-and-practice-support/mobile-resources/features/guideline-clinical-app), as it can greatly streamline the evaluation of an individual patient's candidacy for devices and other therapies.

**Coronary artery and valvular disease**

In patients with ischemic cardiomyopathy, revascularization can be considered in select circumstances, including patients with both preserved or reduced LVEF with continued angina while on optimal anti-anginal therapy. Additionally, revascularization should be considered in patients with obstructive coronary artery disease and reduced LVEF, although targeting intervention to regions of viable myocardium remains controversial in light of the STICH trial results.38 The extent of valvular disease should also be considered in patients with worsening HF. Whereas it is beyond the scope of the current review, repair or replacement of the mitral and aortic valves

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Causes</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP &gt;10 mg/L, neutrophil leukocytosis</td>
<td>Infection, inflammation, Decompensated HF, anemia, fever, hyperthyroidism</td>
<td>Diagnostic work-up, Clinical assessment, Laboratory investigation</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>Beta-blockade, digoxin, ivabradine, verapamil, diltiazem, Antiarrhythmics, Hypothyroidism</td>
<td>Slow AV conduction, anticoagulation, pharmacological cardioversion, electrical cardioversion, catheter ablation</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>Hyperthyroidism, infection, mitral valve disease, Decompensated HF, infarction</td>
<td>Laboratory investigation, Exercise test, perfusion/viability studies, coronary angiography, electrophysiology testing, ICD</td>
</tr>
<tr>
<td>Atrial tachycardia/flutter/fibrillation</td>
<td>Hyperthyroidism, infection, mitral valve disease, Decompensated HF, infarction</td>
<td>Echocardiography/CMR</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>Ischemia, infarction, cardiomyopathy, myocarditis, hypokalemia, hypomagnesemia, Digitalis overdose</td>
<td>Echocardiography/CMR, chest x-ray, for amyloidosis consider further testing (CMR, 99mTc-DPD scan) and endomyocardial biopsy</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>Hypertension, aortic valve disease, hypertrophic cardiomyopathy</td>
<td>Echocardiography/CMR, CMD, chest x-ray, for amyloidosis consider further testing (CMR, 99mTc-DPD scan) and endomyocardial biopsy</td>
</tr>
<tr>
<td>Low QRS voltage</td>
<td>Obesity, emphysema, pericardial effusion, amyloidosis</td>
<td>Echocardiography/CMR, CMD, chest x-ray, for amyloidosis consider further testing (CMR, 99mTc-DPD scan) and endomyocardial biopsy</td>
</tr>
<tr>
<td>QRS duration ≥120 ms and LBBB morphology</td>
<td>Electrical and mechanical dyssynchrony</td>
<td>Echocardiography CRT-P, CRT-D</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; AV, atrioventricular; BUN, blood urea nitrogen; CMD, cardiac magnetic resonance; CRP, C-reactive protein; CRT-P, cardiac resynchronization therapy with pacemaker; CRT-D, cardiac resynchronization therapy with defibrillator; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system; SGLT-2, Sodium-glucose co-transporter 2.52
depends on etiology, symptoms, and patient specific conditions; decisions should be made with current guidelines in mind that discuss the nuances of clinical decision making in great detail.39 Of note, remarkable strides in transcatheter valvular interventions are likely to change the landscape of these interventions at a rapid pace.

Lifestyle modification and self-care

Although hospitalization poses a burden to patients and often marks progression of disease, it also provides an educational opportunity that can potentially empower patients to make necessary lifestyle modifications.40 Indeed, patient education is viewed by the ACC and AHA as a necessary aspect of proper transitions of care in HF patients. This may take the form of face to face education led by providers, nurses or pharmacists, but can also take the form of flyers, videos and postings to web based materials.

Topics of lifestyle modifications in HF are broad, but generally focus in on recommendations regarding lifestyle modification including physical activity and diet. In the case of exercise, recommendations for HF patients have evolved from bedrest to supervised graduated exercise programs. Based on the positive results from Heart Failure: a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) that randomized >2300 HF patients with reduced LVEF patients to usual care versus exercise training, the ACC/AHA/European Society of Cardiology guidelines have the highest recommendation of regular aerobic exercise in patients with HF to improve functional capacity and symptoms and to reduce the risk of HF hospitalization. Therefore, patients with HF with reduced LVEF should be referred to cardiac rehabilitation programs during the Post Discharge Visit.41–43

The accepted wisdom about dietary restrictions in HF largely revolves around avoidance of salt. Despite being rooted in outdated data and shaky clinical evidence, it remains a class IIa recommendation by the AHA and ACC. Information to the contrary is emerging; recent data showed that in elderly adults, self-reported sodium restricted diets did not affect mortality, incidence of cardiovascular disease or HF.44 In HF patients admitted with acutely decompensated HF, aggressive sodium and fluid restriction was not associated with any change in weight loss or readmission within 30 days, but was accompanied by increased thirst.45 Furthermore, a sodium restricted diet of <2500 mg per day in HF patients with NYHA class II–III symptoms was associated with higher rate of hospitalization over 36 months.46 Given the lack of definitive data from a clinical trial, for now it is reasonable to discuss sodium intake with patients and consider moderation of sodium intake to <3 g per day in patients with stage C and D heart failure, based on the average sodium intake of 4 g per day.47

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Table 3 – Guideline-directed medical therapy dosing for heart failure.

<table>
<thead>
<tr>
<th>ACEI</th>
<th>Starting dose</th>
<th>Mean daily dose achieved in clinical trials</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg TID</td>
<td>122.7 mg</td>
<td>50 mg TID</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg BID</td>
<td>16.6 mg</td>
<td>10–20 mg BID</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5–5 mg QD</td>
<td>32.5–35 mg</td>
<td>20–40 mg QD</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25–2.5 mg QD</td>
<td>7.7 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 mg QD</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>0.5–1 mg QD</td>
<td>2.5 mg&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4 mg QD</td>
</tr>
<tr>
<td>ARB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4–8 mg QD</td>
<td>24 mg</td>
<td>32 mg QD</td>
</tr>
<tr>
<td>Losartan</td>
<td>50 mg QD</td>
<td>129 mg</td>
<td>150 mg QD</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40 mg BID</td>
<td>254 mg</td>
<td>160 mg BID</td>
</tr>
<tr>
<td>ARNI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>24/26–49/51 mg BID</td>
<td>375 mg</td>
<td>97/103 mg BID</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg QD</td>
<td>8.6 mg</td>
<td>10 mg QD</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg BID</td>
<td>37 mg</td>
<td>25 mg BID</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5–25 mg QD</td>
<td>159 mg</td>
<td>200 mg QD</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>1.25 mg QD</td>
<td>7.7 mg</td>
<td>10 mg QD</td>
</tr>
<tr>
<td>MCR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eperenone</td>
<td>25 mg QD</td>
<td>42.6 mg</td>
<td>50 mg QD</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5–25 mg QD</td>
<td>26 mg</td>
<td>50 mg QD</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine/isosorbide dinitrate</td>
<td>20/37.5 mg TID</td>
<td>175 mg/90 mg</td>
<td>40/75 mg TID</td>
</tr>
<tr>
<td>If channel inhibitor</td>
<td>2.5–5 mg BID</td>
<td>13 mg</td>
<td>7.5 mg BID</td>
</tr>
</tbody>
</table>


<sup>a</sup> 77% of patients tolerated ramipril 5 mg BID in the HOPE trial.

<sup>b</sup> 62% of patients tolerated trandolapril 4 mg QD in the TRACE trial.
Even with teaching from and contact with healthcare professionals, active involvement of patients in the management of their disease is important in ensuring good outcomes. Three different components make up patient self-care: maintenance, monitoring, and management. Maintenance involves adherence to medication and lifestyle changes, while monitoring of the signs and symptoms of HF. Self-care management means responding appropriately to any changes in symptoms—for example, by increasing the dose of medications prescribed for use as needed.

End of life care

HF remains a chronic disease without a cure for the clear majority of patients. Thus, it is imperative for caregivers to discuss goals of care and continued focus on improvement of the QoL for patients. This was highlighted by results of a recent landmark study—Palliative Care in Heart Failure [PAL-HF]—showing that an interdisciplinary palliative care intervention in advanced HF patients consistently led to greater benefits in QoL, anxiety, depression, and spiritual well-being compared with usual care alone. Efforts

**Fig. 3 – Guideline recommendations for patients with HF with reduced ejection fraction, adapted from the ESC guidelines.**

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**Consideration of advanced therapies**

A subset of patients with HF will continue to have symptoms and rapid disease progression despite being on maximally tolerated GDMT, and may even need down titration of neurohormonal blockade. These patients are referred to as having stage D HF and their treatment options are limited to advanced treatment strategies, such as mechanical circulatory support (LV Assist Device), continuous inotropic infusion, cardiac transplantation, and hospice. Objective evidence of end stage HF should be sought in patients suspected to need advanced therapies via right heart catheterization or cardio-pulmonary exercise testing.
should also be made to have honest discussions about the risks and benefits of aggressive medical therapies, especially in circumstances of advanced illness. There will be a time in the disease course of many chronic HF patients where a transition to hospice will be reasonable. However, despite the dire prognosis from HF, and data showing its significant benefit to the patient, referral to palliative care for these patients remains rare. Therefore, we recommend that some discussion related to palliative care be considered during the PDV.

Conclusion

The PDV for the HF patient is a key opportunity to make sure that the highest level of quality and evidence based care is delivered. It can serve as the basis for gauging stability of the patient, filling in any gaps in treatment, and considering additional care. Furthermore, it can be a good time to engage in discussions around goals of care. When executed well, it can ensure that this vulnerable population gets the best care possible.

Statement of conflict of interest

Dr. Ahmad reports receiving research funding from the Heart Failure Society of America and serves as a consultant for Novartis and Amgen; Drs. Riello and Soufer report no relevant disclosures. Dr. Desai is supported by grant K12 HS023000-01 from the Agency for Healthcare Research and Quality; receives research support from Johnson & Johnson through Yale University; and receives funding from CMS. Dr. Testani consults for Boehringer Ingelheim and his research is supported by NIH 2017 K23 HL and NIH 2017 R01 HL.

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Objective To perform a pilot evaluation of a pharmacist-led, multidisciplinary transitional care clinic for heart failure (HF) patients.

Background Transitions of care in HF should include: medication reconciliation, multidisciplinary care, early post-discharge follow-up, and prompt intervention on HF signs and symptoms. We hypothesized that combining these elements with optimization of medications would impact outcomes.

Methods In the SERIOUS HF Medication Reconciliation Transitional Care Clinic (HF MRTCC), patients were seen by a clinical pharmacist trained in HF. The pharmacist performed medication reconciliation, a basic physical exam, and a HF symptom history. Medications were adjusted by the clinical pharmacist or medical provider. Data were retrospectively collected for a quality improvement evaluation of this novel clinic on medication discrepancies, medications optimized, and 30-day readmissions. Descriptive statistics and paired t-tests were used for medication doses.

Results All patients (n = 135) had a diagnosis of HF, 59% were recently discharged. The mean time from discharge to the clinic appointment was 10 ± 6 days, and the 30 day all-cause readmission rate was 9%. Medication discrepancies were detected in 53% of patients. Medications were optimized in 70%, most frequently beta blockers, ace inhibitors, and diuretics. In patients with an ejection fraction ≤40%, significantly higher doses of beta blockers and ace inhibitors were prescribed after the clinic visit.

Conclusion The HF MRTCC identified and corrected numerous medication discrepancies, up-titrated medications, and was associated with a 30-day readmission rate of 9%. These encouraging pilot results are hypothesis-generating and warrant further controlled trials.
After discharge for acute decompensated heart failure (ADHF), patients exhibit variable levels of improvement and self-management skills to maintain symptomatic stability. These factors, coupled with a high incidence of medication errors, demonstrate why early and effective post-discharge follow up has become a strategic intervention impacting readmission rates. In an observational study by Hernandez et al. of 225 hospitals (>30,000 hospitalized patients) participating in Get With the Guidelines (GWTG), the hospitals with the lowest percentage of patients who had follow-up within 7 days had a significantly higher 30-day readmission rate. The Hospital to Home (H2H) initiative, led

### Table 1 – Recommended components of a transitional care program.

- Medication reconciliation
- Very early telephone contact (within 24–72 h)
- Early office follow-up within 7–14 days of discharge
- Clinical assessment (weight, volume status, functional status, symptoms)
- Patient education on symptom recognition and chronic self-care behaviors
- Communication of patient health record with the patient and post-discharge providers
- Integrated interdisciplinary collaboration and coordination
- Framework that ensures education is initiated during hospitalization and continues during initial community care setting
- Screen patients for features that confer a higher risk for poor outcomes (e.g. cognitive impairment, non-English speaking, long travel time to healthcare appointments)
- Ensure that health care providers are adequately trained to provide HF education
- Allot adequate time to deliver complex HF interventions and assess patient/caregiver response
- Use health informatics to assist in program sustainability with patient and provider-centric tools

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**Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin converting enzyme</td>
</tr>
<tr>
<td>ADHF</td>
<td>acute decompensated heart failure</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>CMR</td>
<td>comprehensive medication reconciliation</td>
</tr>
<tr>
<td>CMS</td>
<td>Centers for Medicare and Medicaid</td>
</tr>
<tr>
<td>ED</td>
<td>emergency department</td>
</tr>
<tr>
<td>EF</td>
<td>ejection fraction</td>
</tr>
<tr>
<td>EMR</td>
<td>electronic medical record</td>
</tr>
<tr>
<td>GDMT</td>
<td>guideline-directed medical therapy</td>
</tr>
<tr>
<td>GWTG</td>
<td>Get With the Guidelines</td>
</tr>
<tr>
<td>H2H</td>
<td>Hospital to Home</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>HF MRTCC</td>
<td>Heart Failure Medication Reconciliation Transitional Care Clinic</td>
</tr>
<tr>
<td>HFSA</td>
<td>Heart Failure Society of America</td>
</tr>
<tr>
<td>HFP&lt;sub&gt;E&lt;/sub&gt;</td>
<td>heart failure with a preserved ejection fraction</td>
</tr>
<tr>
<td>HFEF</td>
<td>heart failure with a reduced ejection fraction</td>
</tr>
<tr>
<td>MRA</td>
<td>mineralocorticoid receptor antagonists</td>
</tr>
<tr>
<td>VA</td>
<td>Veterans Affairs</td>
</tr>
</tbody>
</table>

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**Introduction**

Heart failure (HF) continues to burden the Centers for Medicare and Medicaid (CMS) budget. HF hospitalizations for Americans >65 years old are more prevalent than any other medical condition. Due to the aging population and high incidence, the total costs of HF are projected to be 70 billion by 2030. Not only is HF the most prevalent diagnosis for hospitalizations of Medicare recipients, but also the highest diagnosis for potentially preventable 30 day readmissions. Reducing readmission rates by 2% potentially saves more than $100 million a year for the U.S. health care system.

Medication discrepancies are found in 50-60% of all patients who are discharged from the hospital. The Joint Commission National Patient Safety Goals recommend medication reconciliation at all transitions of care. System level and patient-related factors are equally prevalent causes for post-discharge medication discrepancies. Unintentional medication errors account for 30-50% of discrepancies, and post-discharge medication discrepancies are associated with a higher risk of readmission. A best practices model has been developed for discharge counseling in patients with HF that describes optimal processes for comprehensive medication reconciliation (CMR) to overcome these barriers.
by the American College of Cardiology (ACC) and the Institute for Healthcare Improvement, was an initiative to reduce cardiovascular-related hospital readmissions and improve transitional care for individuals hospitalized with cardiovascular disease. Early discharge follow-up, medication reconciliation, and patient recognition of worsening HF symptoms were the targets of this initiative.11 The American Heart Association (AHA)/ACC recently published a scientific statement on transitions in care in HF.12 The recommended components of a transitional care program are detailed in Table 1. Despite these transitional care guidelines, there is no consistent literature on how to develop and execute a transitional care clinic. To address early post-discharge follow-up care in a HF population, we developed an innovative pharmacist-led, multidisciplinary, post-discharge medication reconciliation clinic that encompasses guideline recommendations as well as transitional care.

**Methods**

**Clinic description**

The SERIOUS HF Medication Reconciliation Transitional Care Clinic (HF MRTCC) was a collaborative effort between the departments of pharmacy, cardiology, and the Veterans Affairs (VA) Quality Scholars Program. It was designed as a single visit to combine pharmacist CMR with focused HF transitional care. The primary elements of the clinic are detailed in Table 2. Evaluation of early data determined that one of the crucial aspects of the program was CMR with the patient and their bottles performed by a pharmacist.13 The HF MRTCC visit was an in-person, 60 min appointment. Review of symptoms and CMR were performed by staff pharmacists, supervised by a clinical pharmacist specializing in HF. All pharmacists attended a HF continuing education program created by the clinical pharmacists and a HF nurse practitioner. Based on the patient’s reported symptoms, vital signs, and weight fluctuation since discharge, the pharmacist requested further assessment and physical exam by a nurse practitioner or physician. The patient received HF education and tools to aid in adherence. For those patients unable to attend clinic, a phone interview was performed. If concerning symptoms were identified during the call, the case was reviewed with the medical provider, and appropriate follow-up was arranged.

Upon review of HF discharges from the Cleveland VA Medical Center, patients were contacted to schedule an appointment in the HF MRTCC with a goal follow-up within 7 days of discharge. Patients could also be referred by the discharging medical team, inpatient clinical pharmacists, outpatient primary care, or cardiology providers. Patients not recently hospitalized could be referred for clinical HF deterioration, medication non-adherence, assessment of a patient’s medication use system or additional focused medication education.

A model was developed (SERIOUS model) to standardize the method for CMR, optimization, and communication with the patient and his/her other health care providers (Fig 1).13

<table>
<thead>
<tr>
<th>Table 2 – Primary elements of the SERIOUS HF Medication Reconciliation Transitional Care Clinic (HF MRTCC).</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Perform comprehensive medication reconciliation (CMR) and education following discharge from an admission for ADHF to identify and correct potential medication errors</td>
</tr>
<tr>
<td>• Review patient’s actual medication bottles and/or pill organizer</td>
</tr>
<tr>
<td>• Document and address all medication discrepancies</td>
</tr>
<tr>
<td>• Provide patient-specific education for all medications when discrepancies or patient knowledge deficit identified</td>
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<td></td>
</tr>
<tr>
<td>• Provide early follow-up care including assessment of HF symptoms, vital signs, home weight trends and order/interpret appropriate laboratory testing</td>
</tr>
<tr>
<td>• Evaluate of volume status and adjust medication when clinical instability is suspected</td>
</tr>
<tr>
<td>• Optimize medication regimen based on patient’s clinical status, medication discrepancies, and GDMT</td>
</tr>
<tr>
<td>• Facilitate early up-titration of HF medications</td>
</tr>
<tr>
<td>• Discontinue any inappropriate or obsolete medications</td>
</tr>
<tr>
<td>• Re-enforce HF education provided during the inpatient stay</td>
</tr>
<tr>
<td>• Weight monitoring</td>
</tr>
<tr>
<td>• Sodium intake</td>
</tr>
<tr>
<td>• Medication adherence</td>
</tr>
<tr>
<td>• Patient-specific and tailored to the needs identified at the visit or at discharge</td>
</tr>
<tr>
<td>• Identify and correct any barriers to implementation of the HF plan of care since discharge (including transportation, cognitive impairment)</td>
</tr>
<tr>
<td>• Provide tools for self-management if needed, such as scales, blood pressure monitors, pill organizers, pill cutters, and weight logs</td>
</tr>
<tr>
<td>• Initial fill of pill organizer by pharmacist at clinic visit if needed</td>
</tr>
<tr>
<td>• Facilitate involvement of caregivers, home telemonitoring, or home care nursing, if appropriate</td>
</tr>
<tr>
<td>• Provide patient/caregiver with an updated written medication list at end of visit</td>
</tr>
<tr>
<td>• Ensure that a subsequent appointment with either cardiology or primary care for longitudinal HF care had been scheduled</td>
</tr>
<tr>
<td>• Act as a contact team for the patient between the HF transitional clinic visit and the next point of contact with his/her primary HF provider</td>
</tr>
<tr>
<td>• Provide vigilant follow-up during periods of clinical instability</td>
</tr>
<tr>
<td>• If necessary, schedule additional HF MRTCC visit to assess changes prior to longitudinal primary care or cardiology follow-up</td>
</tr>
<tr>
<td>• Notify primary care and cardiology providers (if appropriate) of the visit findings, plan, and medication changes via electronic notification through the EMR system</td>
</tr>
</tbody>
</table>

Abbreviations: HF—heart failure; ADHF—acute decompensated heart failure; GDMT—guideline-directed medical therapy; EMR—electronic medical record.
Patients were instructed to bring all medication bottles, and a pill organizer if used, to the visit. Each visit included CMR using open-ended questions and a discussion of the patient’s system for home medication use. Medical records, refill patterns, and contents of the bottles were all assessed. Review of symptoms using a standardized approach, vital signs, laboratory values, and recent clinical tests were reviewed and discussed with the clinical pharmacist and/or medical provider. The clinical pharmacists operated under a scope of practice agreement that allowed for titration of HF medications (beta-blockers, angiotensin converting enzyme (ACE) inhibitors, mineralocorticoid receptor antagonists (MRAs), diuretics, etc.). An individualized plan was developed accounting for symptoms, findings during CMR, barriers identified, and collaborative input from the clinical pharmacist and providers.

Methods for clinic assessment
A retrospective quality assurance analysis was performed for patients seen at least once in the HF MRTCC between March 2008 and December 2009. Inclusion criteria were: age > 18 years and a primary or secondary diagnosis of HF. Patients seen more than once during the evaluation period had each visit reviewed separately. Exclusion criteria were: discharge to a long term care facility/nursing home, or hospice service, no active medications, or <30 days following clinic visit to time of chart abstraction. The project was reviewed by the hospital’s IRB and determined to be a quality improvement initiative and, therefore, exempt from review. All data were obtained from medical and pharmacy records through the VA electronic medical record (EMR). Demographic data, dates of clinic visit,
discharge from admission prior to, and admission following the clinic visit were recorded (if applicable). All-cause and HF admissions and mortality within 30 days of the clinic visit were identified. HF with a reduced ejection fraction (HFrEF) was defined as a left ventricular ejection fraction (EF) \(\leq 40\%\). HF with a preserved EF (HFpEF) included patients with an EF > 40%.

Medication discrepancies from the prescribed medication regimen were collected and categorized as duplicate medications or discrepancies between the patient’s reported regimen and the current prescribed list. To compare across drug classes, equivalent doses of the most common agent in the cohort were used: ACE inhibitors were converted to lisinopril equivalents, beta-blockers were converted to metoprolol equivalents, and loop diuretics were converted to furosemide equivalents. All patients receiving an MRA during the study period were prescribed spironolactone. All other medications were recorded without conversion. Patients who were sent to the emergency department (ED) or admitted to the hospital directly from the clinic were counted as having no adjustments. Interventions and tools to aid in adherence were documented in the EMR.

**Statistical analysis**

Descriptive statistics were used for demographic variables as means and standard deviations. Comparisons were made between the doses prescribed prior to and following the clinic visit using Student’s paired t-tests with significance recorded as an alpha of 0.05.

### Table 3 – Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n = 135)</th>
<th>HFrEF (EF ≤ 40%) (n = 71)</th>
<th>Post-ADHF Hospitalization (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± sd)</td>
<td>69 ± 11</td>
<td>65 ± 11</td>
<td>69 ± 11</td>
</tr>
<tr>
<td>Age ≥ 80 years n, (%)</td>
<td>21 (16%)</td>
<td>5 (7%)</td>
<td>13 (16%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>99%</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>Female (%)</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>31%</td>
<td>30%</td>
<td>35%</td>
</tr>
<tr>
<td>African American</td>
<td>65%</td>
<td>65%</td>
<td>64%</td>
</tr>
<tr>
<td>Declined to answer</td>
<td>4%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic Heart Disease (%)</td>
<td>48%</td>
<td>61%</td>
<td>53%</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>94%</td>
<td>93%</td>
<td>95%</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>30%</td>
<td>28%</td>
<td>38%</td>
</tr>
<tr>
<td>History of cerebrovascular accident (%)</td>
<td>16%</td>
<td>13%</td>
<td>16%</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>53%</td>
<td>44%</td>
<td>50%</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease (%)</td>
<td>39%</td>
<td>35%</td>
<td>34%</td>
</tr>
<tr>
<td>Obstructive Sleep Apnea (%)</td>
<td>24%</td>
<td>21%</td>
<td>23%</td>
</tr>
<tr>
<td>Chronic Kidney Disease, Stage IV or V (%)</td>
<td>7%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Estimated Glomerular Filtration Rate (mean ± sd)</td>
<td>62 ± 23</td>
<td>67 ± 21</td>
<td>63 ± 22</td>
</tr>
<tr>
<td>EF &gt; 40% (n, %)</td>
<td>61 (46%)</td>
<td>n/a</td>
<td>37 (46%)</td>
</tr>
<tr>
<td>EF ≤ 40% (n, %)</td>
<td>71 (54%)</td>
<td>71 (100%)</td>
<td>43 (54%)</td>
</tr>
<tr>
<td>Ischemic etiology of HF</td>
<td>n/a</td>
<td>44%</td>
<td>n/a</td>
</tr>
<tr>
<td>Chronic Resynchronization Therapy (% of those with EF ≤ 40%)</td>
<td>n/a</td>
<td>6%</td>
<td>n/a</td>
</tr>
<tr>
<td>Implantable Cardiac Defibrillator (% of those with EF ≤ 40%)</td>
<td>n/a</td>
<td>28%</td>
<td>n/a</td>
</tr>
<tr>
<td>Mortality within 30 days of clinic visit</td>
<td>3 (2.2%)</td>
<td>2 (2.8%)</td>
<td>3 (3.7%)</td>
</tr>
<tr>
<td>Baseline medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor (%)</td>
<td>65%</td>
<td>68%</td>
<td>69%</td>
</tr>
<tr>
<td>mean daily dose (^a)</td>
<td>34 ± 23 mg</td>
<td>30 ± 20 mg</td>
<td>35 ± 23 mg</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>94%</td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td>mean daily dose (^b)</td>
<td>152 ± 110 mg</td>
<td>152 ± 109 mg</td>
<td>132 ± 98 mg</td>
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<tr>
<td>Angiotensin receptor blockers (%)</td>
<td>32%</td>
<td>38%</td>
<td>30%</td>
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<tr>
<td>Loop diuretic (%)</td>
<td>74%</td>
<td>75%</td>
<td>71%</td>
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<tr>
<td>mean daily dose (^c)</td>
<td>60 ± 45 mg</td>
<td>60 ± 48 mg</td>
<td>62 ± 46 mg</td>
</tr>
<tr>
<td>Spironolactone (%)</td>
<td>31%</td>
<td>42%</td>
<td>33%</td>
</tr>
<tr>
<td>mean daily dose</td>
<td>29 ± 30 mg</td>
<td>27 ± 32 mg</td>
<td>30 ± 35 mg</td>
</tr>
<tr>
<td>Hydralazine (%)</td>
<td>33%</td>
<td>38%</td>
<td>33%</td>
</tr>
<tr>
<td>mean daily dose</td>
<td>151 ± 111 mg</td>
<td>144 ± 106 mg</td>
<td>144 ± 111 mg</td>
</tr>
<tr>
<td>Nitrate (%)</td>
<td>50%</td>
<td>58%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Abbreviations: HFrEF—heart failure with reduced ejection fraction; ADHF—acute decompensated heart failure.

Dosages not provided for angiotensin receptor blockers or nitrates as multiple formulations used.

\(^a\) Lisinopril equivalents.

\(^b\) Metoprolol equivalents.

\(^c\) Furosemide equivalents.
Results

On the day prior to the visit, a telephone call reminded patients (n = 135) to bring their medications. Patients (n = 135) with a primary or secondary diagnosis of HF (54% HFrEF, 46% HFpEF) were seen in the HF Medication Reconciliation Transitional Care Clinic (HF MRTCC). Table 3 depicts the baseline characteristics and medications. Eighty patients (59%) were seen following a hospitalization for ADHF; 19 (14%) were seen following a hospitalization for a primary diagnosis other than HF, 11 (8%) were referred following an ED visit for HF. Twenty-seven (20%) were referred by primary care or cardiology providers. Most patients were seen in the clinic only once, however 7% were seen more than once primarily due to having multiple ED or hospital admissions during the 21 month evaluation period. Face to face encounters occurred in 91%, while 9% had a telephone interview due to travel barriers. Of those who attended clinic, 95% brought medication bottles or pill boxes as instructed. Mortality within 30 days of the clinic visit was 2.2% (n = 3) in the entire cohort.

Among the 59% of patients who were seen following a hospitalization for ADHF, 54% had HFrEF. The mean time from discharge to the clinic appointment was 10 ± 6 days, and the 30 day all-cause readmission rate was 9%. The readmitting diagnosis was ADHF for all but one of these patients. Mean time to readmission was 16 ± 6 days (range 5–22 days). In 2007, prior to implementation of the HF MRTCC at the Cleveland VA Medical Center, the 30 day readmission rate of 9% for those who attended. Beta-blockers and ACE inhibitors were the most commonly optimized medications. Among the 71 patients with HFrEF, 77% had medications optimized at the clinic visit. Beta-blockers and ACE inhibitors were the most frequently optimized medications, and MRAs were adjusted more frequently in this group than in the entire cohort. Beta-blocker doses were significantly higher in the entire cohort (152 ± 110 mg/day vs 162 ± 106 mg/day, p = 0.004) and among patients with HFrEF (152 ± 109 mg/day vs 165 ± 108 mg/day, p = 0.005) after the clinic visit. Patients with HFrEF had higher mean ACE inhibitor doses (30 ± 20 mg/day vs 31 ± 19, p = 0.044), with a trend toward a higher hydralazine dose after the clinic visit (Table 5). Angiotensin receptor blockers (ARBs) were prescribed in 38% of patients with HFrEF, however doses were adjusted in only two patients.

<table>
<thead>
<tr>
<th>Patients Receiving Intervention (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient assessment</strong></td>
</tr>
<tr>
<td>Symptom assessment (by staff pharmacist and clinical pharmacist)</td>
</tr>
<tr>
<td>Additional clinical assessment (by nurse practitioner or physician)</td>
</tr>
<tr>
<td><strong>Patient education</strong></td>
</tr>
<tr>
<td>Comprehensive medication reconciliation (CMR)</td>
</tr>
<tr>
<td>Medication education and/or regimen simplification</td>
</tr>
<tr>
<td>Daily weight monitoring, low sodium diet, or HF signs and symptoms</td>
</tr>
<tr>
<td><strong>Self-management tools issued</strong></td>
</tr>
<tr>
<td>Pill boxes</td>
</tr>
<tr>
<td>Pill boxes filled during clinic visit</td>
</tr>
<tr>
<td>Blood pressure cuffs</td>
</tr>
<tr>
<td>Scales</td>
</tr>
</tbody>
</table>

* Regimen simplification: elimination of obsolete, duplicative, or unnecessary medications, consolidation of medication dosing times, creating a medication schedule chart.

Discussion

Our model of a pharmacist-led, multidisciplinary post-discharge transitional care clinic facilitated detection of medication discrepancies and increased the prevalence of guideline-directed medical therapy (GDMT), resulting in a 30 day readmission rate of 9% for those who attended. Appropriate up-titration of GDMT and assessment of clinical stability were performed by clinic staff. Patients and caregivers received counseling on self-management skills. The EMR allowed communication with other providers. The clinic was modeled after the recommendations made by the AHA’s GWTG and the ACC’s H2H program.

Comprehensive medication reconciliation

Medication reconciliation traditionally includes a review of pertinent medications, identifying discrepancies, correcting them according to the prescribed list, and issuing the patient a clean and verified list. The SERIOUS Medication Reconciliation model combined CMR and optimization, patient safety, and guideline-based HF care in a standardized...
multidisciplinary approach. Direct assessment of the patient’s medication system allowed for prompt intervention on errors. This model encourages collaboration and provides a mechanism for other providers to gain additional insight into their patients’ medication use behaviors and proper dosing.

Accurate post-discharge CMR with direct review of medication bottles was a pivotal element in the design of

![Medications Optimized Entire Cohort](image1)

![Medications Optimized Patients with HFrEF (EF ≤ 40%)](image2)

Fig 2 – Medications Optimized. Medications optimized during clinic visit as categorized by drug class. Represented as the entire cohort in part a, and for those patients with HFrEF (EF ≤ 40%) in part b. HFrEF—heart failure with reduced ejection fraction; ACEI/ARB—angiotensin converting enzyme inhibitors or angiotensin receptor blockers; BB—beta-blockers; MRA—mineralocorticoid receptor antagonists; other CV—other cardiovascular medications; EF—left ventricular ejection fraction.

Table 5 – Medication dosages before and after clinic visit.

<table>
<thead>
<tr>
<th></th>
<th>All patients (N = 135)</th>
<th>P Value</th>
<th>HFrEF (EF ≤ 40%) (N = 71)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Visit</td>
<td>Post-Visit</td>
<td>Pre-Visit</td>
<td>Post-Visit</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor * (mg/day)</td>
<td>34 ± 23</td>
<td>34 ± 22</td>
<td>1.0</td>
<td>30 ± 20</td>
</tr>
<tr>
<td>Beta-blocker b (mg/day)</td>
<td>152 ± 110</td>
<td>162 ± 106</td>
<td>0.004</td>
<td>152 ± 109</td>
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<tr>
<td>Loop diuretics c (mg/day)</td>
<td>60 ± 45</td>
<td>59 ± 50</td>
<td>0.547</td>
<td>60 ± 48</td>
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<tr>
<td>Spironolactone (mg/day)</td>
<td>29 ± 30</td>
<td>31 ± 30</td>
<td>0.183</td>
<td>27 ± 32</td>
</tr>
<tr>
<td>Hydralazine (mg/day)</td>
<td>151 ± 111</td>
<td>167 ± 111</td>
<td>0.0130</td>
<td>144 ± 106</td>
</tr>
</tbody>
</table>

a Lisinopril equivalents.
b Metoprolol equivalents.
c Furosemide equivalents.
this clinic. Numerous studies have described medication reconciliation at discharge,\textsuperscript{21-27} and in the outpatient setting.\textsuperscript{21-27} Post-discharge medication discrepancies are highly prevalent, with at least one medication reconciliation discrepancy identified in >50% of discharged patients.\textsuperscript{21,23,35} Direct visualization of the patient’s system and medication supplies are often limited to interventions performed in home care settings. One study compared the medication reconciliation detection rate between a face-to-face in-home encounter versus a verbal report of medication use, and found discrepancies that had been undetected on a telephone interview in 62% of patients.\textsuperscript{72} The frequency of medication discrepancies found in the HF MRTCC was 53%, similar to prior reports using direct review of medication bottles. The SERIOUS model was developed to promote a standardized approach to the CMR process, meeting all components of The Joint Commission’s National Patient Safety Goal\textsuperscript{6} and with the addition of “optimization” of medication therapy. The HF MRTCC made clinically appropriate adjustments of GDMT and diuretics in the early post-discharge period. ACE inhibitor and beta-blocker doses were significantly higher in patients with HFrEF following the clinic visit.

Clinic structure and transitional care

Transitional care interventions have been shown to improve short and long term outcomes in a variety of settings.\textsuperscript{30,31} This clinic model can be easily adapted to meet the recommendations for a transitional care clinic appointment following a HF hospitalization and/or ED visit.\textsuperscript{12,32} This clinic model is appealing to Accountable Care Organizations who seek strategies to decrease acute care utilization and improve outcomes.

The HF MRTCC was not intended to replace longitudinal HF or primary care relationships, rather it was meant to serve as a single clinic visit augmenting longitudinal care. The HF MRTCC clinic pilot experience integrated interdisciplinary collaboration, allotted time to deliver complex HF interventions, and assess patient/caregiver response. These are important components of a transitional care program as referenced in Table 1. The EMR was also utilized as a mechanism for communication and coordination using a templated clinic note that informed providers assuming the next level of care.

Role of the pharmacist

The role of a pharmacist in HF care has been expanded in the past several years to include direct patient care. The existing literature demonstrates conflicting results on the impact of clinical pharmacy services in HF. Several studies have shown a decrease in HF hospitalizations and mortality following interventions including a clinical pharmacist who focused on medication optimization of GDMT, CMR and medication education. These interventions have been demonstrated in longitudinal clinics over several visits,\textsuperscript{33,34} and in single transitional post-discharge home care visits.\textsuperscript{25,27} Other studies have shown neutral effects of pharmacist interventions. The majority of these studies have not been multidisciplinary in nature.\textsuperscript{21,23,35} Most studies did not describe how the pharmacists acted upon discrepancies after performing medication reconciliation other than notifying the provider, nor did they attempt to titrate GDMT. Adequate training of pharmacists providing interventions is important. In previous studies some pharmacists were not clinical pharmacists but were community pharmacists, and may not have had adequate training or access to HF providers.\textsuperscript{21,23} These studies are further limited by patient selection, including only patients with HFrEF,\textsuperscript{23} or “low risk” patients who had not been recently hospitalized.\textsuperscript{35} Outcomes evaluated in some studies were unlikely to be impacted by a single pharmacist visit.\textsuperscript{21,35} The endpoints evaluated in the HF MRTCC pilot program are clinically relevant and were impacted by a single clinic visit. Approximately 45% of patients hospitalized for HF at our institution have HFrEF. Including them in transitional care is important, even though GDMT is limited in this population.

Multidisciplinary interventions targeting patients during periods of clinical instability are more likely to produce a beneficial effect on readmission.\textsuperscript{12} Our pilot program is multidisciplinary, allowing pharmacists to focus on medication management but not to the exclusion of other important aspects of HF management, including clinical assessment by a HF trained medical provider. Furthermore, guideline recommendations for HF are fulfilled by the staff pharmacists performing medication reconciliation, recognizing worsening of HF symptoms, providing patient education, and facilitating care coordination. The clinical pharmacists have scopes of practice which allow prescribing and titration of HF medications, and ordering and evaluation of appropriate laboratory tests. The HF MRTCC team became the patient’s surrogate point of contact until they were seen at the next episode of care.

We recognize that the multidisciplinary nature of the clinic was critical to the observed outcomes. More than half of the patients in this cohort were also seen by a HF nurse practitioner or a physician during the HF MRTCC visit.

The role of a pharmacist on a HF team which highlighted appropriate clinical activities and training for pharmacists in these roles.\textsuperscript{36} The ACC published a health policy statement on the role of cardiovascular team-based care and advanced practice providers, including advanced practice nurses, physician assistants, and clinical pharmacists.\textsuperscript{37} The results of our pilot experience suggest that a scope of practice for the clinical pharmacist is essential in this setting and enables practice of all HF team members at the highest level, improving efficiency and broadening the scope of HF care.

There are limitations to this analysis. It was designed as a quality improvement project to evaluate the impact of a new clinical service (the HF MRTCC), and therefore was non-randomized and did not have a pre-defined control group. Patients with a very large medication burden or with...
a prior history of medication non-adherence may have been more likely to be referred while others may have chosen not to attend at all. Given that a proportion of patients who receive a scheduled follow-up appointment fail to attend, patients who did attend the clinic appointment may have been subject to some degree of bias. We also had no way to report on or control for patients who did not attend the clinic appointment, and therefore the results presented are reflective of patients who were able to attend at least one follow-up appointment.

### Conclusion

The SERIOUS HF MRTCC was developed as a pharmacist-led, multidisciplinary transitional care clinic. This model aimed to improve HF care and “bridge the gap” between hospitalization and routine outpatient care by providing early post-discharge follow-up, CMR with GDMT optimization, prompt medical intervention, and appropriate transitional care. It offers a framework that can easily be adapted by HF care providers to meet organizational goals and achieve enhanced patient-centered outcomes. Numerous medication discrepancies were identified and corrected, GDMT doses were higher at the end of the clinic visit, and patients who attended the clinic had a 30-day all-cause readmission rate of 9%. The AHA/ACC’s Transitional Care in HF Scientific Statement highlights the diverse formats of transitional care interventions, and calls for additional research to evaluate components which may be most beneficial. These encouraging pilot results are hypothesis-generating and warrant further controlled trials to evaluate clinically important endpoints such as health care utilization, medication titration, medication adherence, and patient self-management skills. A collaborative multidisciplinary team approach where clinical pharmacists are utilized as alternative providers offers a future care delivery option for HF patients.

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Sherry Milfred-LaForest—None
Julie Gee—None
Adam Pugacz—None
Ileana Pina—None
Danielle Hoover—None
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There is no conflict of interest of any of the listed authors.

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### REFERENCES

Implementation of a Patient Navigator Program to Reduce 30-day Heart Failure Readmission Rate

Katherine E. Di Palo\textsuperscript{a,*}, Khusbu Patel\textsuperscript{b}, Manaf Assafin\textsuperscript{a}, Ileana L. Piña\textsuperscript{c}

\textsuperscript{a}Montefiore Medical Center, Bronx, NY, United States
\textsuperscript{b}St. John’s University Queens, NY, United States
\textsuperscript{c}Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, United States

A R T I C L E   I N F O
Keywords: Heart failure 30-Day readmissions Pharmacist Nurse

A B S T R A C T
With increasing awareness to provide personalized care our institution applied the American College of Cardiology (ACC) Patient Navigator Program to identify hospitalized heart failure (HF) patients and improve transitions and outcomes. Utilizing a Navigator Team (NT) composed of a nurse and clinical pharmacist, we delivered evidenced-based interventions and hypothesized this approach would improve identification of HF inpatients and reduce the 30-day all-cause readmission rate. Patients were followed from admission to discharge and received at least one intervention, tailored to the patient’s health literacy and social needs. The 30-day all-cause readmission rate was 17.6% for the Patient Navigator Program and 25.6% for the medical center. Compared to the medical center there was a statistically significant increase in education and follow-up. For patients who received specific NT interventions of education and follow-up the readmission rate was 10.3% and 6.1% respectively. Hospital programs can easily embed a NT into existing initiatives to further reduce the readmission rate.

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Contents

Background ............................................................. 260
Methods .............................................................. 261
Patient navigator program ........................................ 261
Navigator team pilot .............................................. 261
Statistical methods ................................................ 262
Results ............................................................... 262
Identification ........................................................ 262
Education and follow-up ......................................... 263
Biomarker monitoring ............................................. 263

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From: Montefiore Medical Center, Bronx, NY.
Supported in part by: American College of Cardiology Patient Navigator Program.
* Corresponding author at: Montefiore Medical Center, 1825 Eastchester Road, Cardiology Administration, Bronx, NY 10461, United States.
E-mail address: kdiпалo@montefiore.org (K.E. Di Palo).

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**Background**

Heart failure (HF) is one of the leading causes of hospital admissions. Data repeatedly show that each hospitalization increases mortality at 6 months and at 1 year.1–2 In the United States, the cost burden of HF is estimated to be 30.7 billion dollars annually.3 This cost can be potentially curtailed as hospital readmissions occur in approximately 1 in 4 patients within 30 days.4 While some readmissions are unavoidable due to barriers in care or concomitant disease states, there are a proportion of patients with preventable causes.5 Health care institutions to curb unplanned readmissions include early identification of patients with HF, improving coordination of care between the care team and education for patients and caregivers.6–8 Stratification of patients with high risk of readmissions can be performed through the use of a 30-day readmission calculator released by the Center for Outcome Research and Evaluation (CORE). Items included on the risk calculator include demographics, presentation at initial hospitalization, medical history, physical exam and diagnostic labs at admission.9

In addition to the risk calculator, an objective marker that is correlated with HF risk is the N-terminal pro-brain natriuretic peptide (NT-proBNP) laboratory test in which a high risk of adverse outcomes is seen with levels above 900 pg/mL.10 A single NT-proBNP reading is a prognostic marker for adverse outcomes; however, additional NT-proBNP testing is also warranted as a trend allows for the identification of clinically significant change in health status.11 Knowledge of the increase in NT-proBNP levels can facilitate beneficial treatment modifications. Despite services provided during the hospitalizations, changes in health status post discharge or barriers to following a plan are among causes that can lead to a readmission. Current evidence identifies drug regimens that prevent HF complications and reduce disease progression yet suboptimal dosing, especially with angiotensin-converting enzyme inhibitors (ACE inhibitor), angiotensin II receptor blockers (ARB), beta-blockers (BB) and mineralocorticoid receptor antagonists (MRA), are still identified as issues that impact patient outcomes.12–13 Furthermore, medication nonadherence is a well-studied factor that leads to readmissions and an increase in morbidity and mortality.14–16 In conjunction with pharmacotherapy, modifications in diet and exercise have also been areas of targeted interventions.17–19 Discharges planning with a timely follow-up with telephone calls, home visits or outpatient providers are needed to provide continuity of care.20 Moreover, follow-up within 7–14 days of a hospitalization has shown to lower readmission rates.21–22

Albert Einstein, the namesake of Montefiore Medical Center’s College of Medicine, highlighted the importance to “learn from yesterday, live for today and hope for tomorrow”. HF as a syndrome, embodies the learning that has occurred from yesterday, the challenge today of Centers for Medicare and Medicaid Services (CMS) penalties for high readmission rates and hope for tomorrow to lower this marker of poor quality. As our institution strives to reduce its readmission rates for HF a simple and fundamental question needed to be answered before looking to future directions. A readmissions reduction program could not be definitively and accurately implemented if patients with the diagnosis of HF could not be...
A heart failure specialist was at discharge – Defined as metoprolol succinate, bisoprolol or carvedilol per ACCF/AHA Heart Failure Guidelines.

American College of Cardiology Patient Navigator Program Metrics.

Table 1 – American College of Cardiology Patient Navigator Program Metrics.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Metric</th>
</tr>
</thead>
</table>
| Outcome | 30-day CMS risk stratified readmission rate  
30-day unadjusted readmission rate |
| Satisfaction | % of patients who reported patient/provider communication was “always good”  
% of patients who reported an understanding of their medications during or after hospitalization  
% of patients who reported an understanding of their signs and symptoms during or after hospitalization |
| Process | % of patients with documentation that LV function was evaluated  
% of patients with an EF <40% prescribed an ACE inhibitor or ARB at discharge  
% of patients with an EF <40% prescribed a guideline beta-blocker* at discharge  
% of patients with documented medication reconciliation performed on admission and discharge  
% of patients that were provided with specific education and documentation on their self-care plan  
% of patients with 7-day follow-up appointment documented on discharge summary  
% of patients receiving community resources for health care services |

Abbreviations: ACE inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CMS, Centers for Medicare and Medicaid Services; EF, ejection fraction.
* Defined as metoprolol succinate, bisoprolol or carvedilol per ACCF/AHA Heart Failure Guidelines.

identified. Hospital Administration and Division of Cardiology asked the question: Can we accurately identify HF patients while they are hospitalized? The answer is critical. Identification of a HF admission is essential to prevent a HF readmission. The primary objective of our study was to manually identify patients admitted with a primary diagnosis of HF in real time. Secondary objectives included optimizing HF treatment based on American College of Cardiology (ACC) Foundation/American Heart Association (AHA) Guideline for the Management of HF, educating patients on diet, exercise and medication, detecting barriers contributing to readmissions and improving access to follow-up care post discharge. The hypotheses were that by studying the processes used to identify HF patients, examining current practices and implementing interventions the goal of reduction in readmission rates could be reached.

Methods

Patient navigator program

The ACC launched the Patient Navigator Program in 2013 to apply a team-based approach for keeping patients at home and healthy after hospital discharge for HF and acute myocardial infarction (AMI). A total of 35 hospitals were selected from across the country to participate in this first of its kind cardiology initiative that applied evidence-based processes to avoid readmissions. The design and implementation of the Patient Navigator Program for each of the participating hospitals was determined at the site level. Our institution elected for a nurse and clinical pharmacist to compose the Navigator Team (NT), as there is robust evidence with these particular disciplines demonstrating a positive impact on HF outcomes. A heart failure specialist was available to the NT for guidance and served as a liaison to the inpatient cardiology and HF services. While other institutions utilized care managers, physicians, nutritionists and physical therapists for their NTs, our pharmacist and nurse team dynamic was unique among participating hospitals.

Quarterly data was submitted from Q1 2015 to Q4 2016 using ACC’s National Cardiovascular Data Registry (NCDR) ACTION Registry-Get With The Guidelines (GWTG). Data measures were broken up into 5 domains: outcomes, patient satisfaction, patient quality of life, efficiency and process. Examples of HF measures specific to each domain are listed in Table 1. Data was collected through a retrospective chart review of 30 patients discharged with a diagnosis of AMI and 30 patients discharged with a diagnosis of HF for a total of 60 patients per quarter. Resources available to participating hospitals included digital scales and pedometers. Quarterly site visits were conducted by the ACC, as well as community webinars and conference calls, to discuss challenges and share best practices.

Navigator team pilot

In alignment with the goals of the institution and the Patient Navigator Program, a pilot was initiated by HF leadership and administration on a cardiac telemetry unit that historically had the highest number of heart failure admissions within the institution and an annual readmission rate above 25%. Data were collected from June to December 2015. The NT primarily implemented the pilot with support from the interdisciplinary team (IDT) composed Care Transitions Clinical Coordinators (CTCCs), staff nurses, physician assistants, cardiologists, social workers, nurse managers and nutritionists. During daily IDT rounds the NT screened patients with particular attention to new admissions. Enrollment into the pilot was based on specific clinical criteria used to diagnose acute decompensated HF (ADHF) and included elevated NT-proBNP defined as >900 pg/mL, presence of HF on imaging such as a chest X-ray or echocardiogram, admitting symptoms of dyspnea or edema and treatment with an intravenous or oral diuretic. The process of the NT is described in Fig. 1. After identification and enrollment, the nurse and pharmacist completed an intake assessment and clinical workup. The intake assessment was a predictive model for readmission which focused on acuity, individual barriers and access to follow-up. The clinical workup contained past medical history, admission medication
reconciliation, daily labs, 30-day readmission risk using CORE calculator and recommendations for guideline-directed medical therapy (GDMT) optimization. HF severity was assessed by New York Heart Association (NYHA) criteria. The NT presented new admissions to the HF consult team who could provide expert assistance on further identification and management.

Providers were encouraged to order NT-proBNP, a biomarker that is a strong predictor for prognosis in ADHF. However, standard of practice on the unit did not include routine monitoring. Under direction of the HF consult team, the Navigator nurse independently ordered NT-proBNP and alerted providers of the results.

The NT focused on providing HF education and obtaining a 14-day follow-up appointment prior to discharge. Baseline Patient Navigator Program data revealed that these two areas needed the most improvement. Deficits in these areas are examined by CMS and signal lack of quality care. As per the Patient Navigator Program process measure, education needed to be documented as HF specific within the medical record. Education was conducted by both the Navigator nurse and pharmacist in multiple sessions throughout the hospitalization for a total of at least 60 min. Education was standardized, tailored to the patient’s health literacy and numeracy and documented in the electronic medical record. The primary teaching resource was an internal booklet created by the Heart Failure Program entitled Living with Heart Failure and included 6 core components: disease state pathogenesis, signs and symptoms, weight monitoring, diet, exercise and medication therapy with focus on adherence. These topics were also available as videos on demand in English and Spanish. Auxiliary resources such as scales, pedometers, pill boxes, weight logs, wallet cards, NT-proBNP logs and shopping lists were distributed by the NT based on patient need. Family members and caregivers were encouraged to participate in education sessions with the patient.

Efforts to obtain a follow-up appointment within 14 days were led by the nurse. The discharge appointment timeline differed from the Patient Navigator Program’s process measure of appointment scheduled within 7 days of discharge. Internal data demonstrated that prior to pilot initiation approximately 50% of patients were discharged with no scheduled appointment. Preferences to office location and coordination of transportation were discussed with the patient and family.

Previous data from the GWTG-HF registry demonstrated poor adherence to GDMT among patients with heart failure with reduced ejection fraction (HFrEF) at our institution. Additionally, process measures from the Patient Navigator Program included percent of patients with an ejection fraction (EF) <40% that were prescribed an ACE inhibitor or ARB or an evidence based BB at discharge. To improve GDMT prescribing patterns, pharmacotherapy notes were written by the pharmacist for patients with frequent admissions or suboptimal therapy. Recommendations for the treatment of chronic HF included personalized therapy, dose targets and monitoring parameters as well as references to pertinent literature to support suggestions. Discharge medication reconciliation was performed by the pharmacist and a final medication list was prepared highlighting prescription changes such as drug initiation, dose titration or discontinuation. A personalized medication schedule with administration times to improve adherence, optimize therapy and minimize side effects was also provided. Finally, the pharmacist and patient discussed a plan to obtain new medications post discharge. Prescription procurement was arranged for bedside delivery prior to discharge for patients with a documented history of nonadherence or upon patient request.

Statistical methods

Descriptive analyses were performed; categorical variables were described by frequencies and percentages and continuous variables were described by means and standard deviations. Interventions with dichotomous outcomes were compared to aggregate medical center data collected annually using a \( \chi^2 \) test. Readmission rates associated with specific interventions were compared to aggregate medical center data collected annually using a one-sample t-test. We assumed a \( p \)-value of <0.05 to be significant.

Results

Identification

The NT enrolled 120 patients during the pilot study period. A HF admission was defined by post discharge coding using Diagnosis Related Groups (DRGs) 291, 292 and 293. These DRGs contained ICD-10 codes that correlated to a principal or index diagnosis of HF. Of the 120 patients enrolled, 51 admissions were confirmed as HF. The remaining 69 admissions identified by the NT were classified as history of HF and excluded from further analysis. The total number of primary
HF admissions on the telemetry unit during the pilot enrollment period was 94. The NT identified and enrolled 51 of these encounters and the accuracy of pilot identification was 54.3%. The 43 primary HF admissions during the study period that were not identified by the NT during inpatient hospitalization, but confirmed post discharge as primary HF by coding, served as a control for analysis (Fig. 2).

Patient demographics of the 94 primary HF admissions are illustrated in Table 2. Baseline characteristics, such as age and gender, were similar among NT and control groups. NYHA functional class was also similar within the two groups; the majority of patients were class III. However, there was a statistically significant difference in average length of stay and average EF. The NT group had a longer length of stay (6.3 days vs. 3.7 days) and lower EF (36.5% vs. 46.3%). The majority of NT patients had HFrEF (68.6%) while the majority of control patients had heart failure with preserved ejection fraction (HFpEF) (51.2%).

**Education and follow-up**

Results for specific NT interventions are described in Table 3. There was a statistically significant difference in HF specific education \( (p = 0.0002); \) documented education increased by 59.0% among the NT group. There were 29 patients (56.8%) that received education by the NT compared to 10 patients (23.3%) that received education by the telemetry nurses. There was also a statistically significant increase in scheduled 14-day follow-up among the NT group \( (p = 0.0044); \) Post discharge appointments, with either a cardiologist or primary care provider, were scheduled within 14 days for 35 patients (68.6%) in the NT group. Conversely, post discharge appointments for the control group were scheduled within 14 days for 17 patients (39.5%). Of the scheduled appointments, Navigator patients were more likely to follow-up with a cardiologist (56.8%) than the control group (18.6%). The utilization of a NT in the discharge process resulted in a 53.2% decrease in the number of patients discharged without a scheduled post discharge follow-up visit.

**Biomarker monitoring**

NT-proBNP was routinely ordered on admission by providers in the emergency department or on the telemetry unit for both Navigator and control groups. Within the Navigator group at least one repeat measurement was attempted prior to discharge and was ordered exclusively by the NT nurse. Repeat orders for the control group were ordered by physician assistants or attending providers. There was a statistically significant increase in the rate of repeat measurement among the NT group \( (p = 0.0002); \) 55.8% of patients in the NT group had at least one repeat NT-proBNP compared to 22.0% of patients in the control group. Repeat measurement is recommended during hospitalization and evidence suggests that a reduction of 30% during admission for ADHF appears to have a favorable prognosis for readmission or cardiovascular (CV) death.\(^{29-31}\) There were more patients in the Navigator group that had a 30% or greater reduction in NT-proBNP. However, this was likely due to the larger sample size of patients who received repeat measurements. NT-proBNP monitoring by the NT nurse did not affect treatment strategies as this was determined by the care team.

**Guideline-directed medical therapy**

Eligibility for GDMT was determined by the clinical pharmacist using the 2013 ACCF/AHA HF guidelines. HFrEF patients were excluded from the analysis. Patients were also excluded if they had a documented contraindication to an ACE inhibitor, ARB or BB, such as hyperkalemia, restrictive lung disease or acute kidney injury at time of discharge. Of the eligible HFrEF patients in the NT group, 85.2% received an ACE inhibitor or an ARB at discharge and 90.9% received a BB at discharge compared to 68.4% and 75.0% of eligible control patients. This trended towards statistical significant \( (p = 0.17, p = 0.12); \) The addition of a clinical pharmacist to the IDT resulted in a 24.6% increase in the number of ACE inhibitor or ARB prescriptions and a 17.5% increase in the number of BB prescriptions.

**Readmissions**

Using the CMS definition of a 30-day readmission, there were 18 all-cause readmissions among patients discharged from the unit during the study period. Among the NT group of 51 patients there were 9 readmissions. The 30-day all-cause readmission rate for the Navigator group was 17.6%. Among the control group of 43 patients there were 9 readmissions.
The 30-day all-cause readmission rate for the control group was 20.9%. During the study period the 30-day all-cause readmission rate for the medical center was 25.6%. The Patient Navigator Program resulted in a 15.8% decrease in the rate of unplanned readmission for HF patients when compared to the readmission rate of the control group and a 31.3% decrease when compared to the medical center. Though readmission penalty is indiscriminate of readmission cause, patients in the NT group were less likely to be readmitted for HF. Of the 9 readmissions in the Navigator group only 2 were readmitted for HF (22.2%) compared to 6 readmissions for HF among the control group (66.6%) which trended towards statistical significance ($p = 0.15$). There is a strong correlation between NT interventions of education and follow-up to readmission rate summarized in Table 4. Among patients who received education by the NT ($n = 35$) the readmission rate was 6.1%. Patients who received both interventions of education and follow-up ($n = 21$) had a readmission rate of 4.8%.

**Discussion**

Our institution’s incentive to reduce readmission rates was not only financial as it relates to penalties imposed by CMS but in alliance with its mission to advance the health of the communities it serves and to practice by evidence-based guidelines and ultimately improve outcomes. Prior to the implementation of the Patient Navigator Program and NT at our institution there was no active, real-time effort to identify patients admitted for ADHF. Utilizing the designated NT increased cognizance of patients admitted with HF. However, identification accuracy was lower than expected. The predominant reason for not identifying an admitted patient with a primary HF diagnosis was inadequate documentation by the attending physician in the patient’s electronic medical record. Other contributing factors included short length of stay, competing diagnoses such as atrial fibrillation, pulmonary hypertension, end-stage renal disease and chronic obstructive pulmonary disease and weekend or holiday admissions. The NT enrolled 69 patients who were actively treated for ADHF but were not coded as an index HF admission and therefore not appropriate for readmission analysis based on CMS rules. Among this group, the final coding trends included other cardiac diagnoses and surgical procedures. Though these chronic HF patients inherently benefited from NT interventions, it may have diluted efforts and contributed to missed acute index admissions.

However, the accurate identification of a HF admission ultimately led to care coordination and enhanced teaching and learning for high risk patients. The impact of nurses and pharmacists as part of an interdisciplinary team on readmissions has been extensively described in literature. Nurses have historically been the most common team leader and have had multiple roles within a team including care coordination, case management and serving as liaisons for patients. The role of the pharmacist in this setting has involved identification of unnecessary medications and clinically significant drug interactions, drug monitoring, medication reconciliation and medication adherence education. The makeup of the health professions involved on a multidisciplinary team may vary especially when there are overlapping scopes, which may consequentially impact the post discharge follow-up arranged by the NT ($n = 35$) the readmission rate was 6.1%. Patients who received both interventions of education and follow-up ($n = 21$) had a readmission rate of 4.8%.

**Table 2 – Baseline demographics and characteristics.**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pilot μ (sd)</th>
<th>Control μ (sd)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
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<td>67.9 (11.2)</td>
<td>0.48</td>
</tr>
<tr>
<td>Gender, n (%)</td>
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<td></td>
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</tr>
<tr>
<td>Female</td>
<td>22 (43.1)</td>
<td>19 (44.2)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (56.9)</td>
<td>24 (55.8)</td>
<td>0.92</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>36.5 (14.6)</td>
<td>46.3 (16.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5 (9.8)</td>
<td>3 (7.0)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>40 (78.4)</td>
<td>37 (86.1)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>6 (11.7)</td>
<td>3 (6.9)</td>
<td></td>
</tr>
<tr>
<td>HFrEF (≤40)</td>
<td>35 (68.6)</td>
<td>20 (46.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>HFrEF (≤50)</td>
<td>14 (27.5)</td>
<td>22 (51.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>HFmrEF (41–49)</td>
<td>2 (3.9)</td>
<td>1 (2.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association.

**Table 3 – Summary of evidence-based interventions provided by Navigator team.**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Patient Navigator Program</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education, %</td>
<td>56.8</td>
<td>23.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>14 day follow-up, %</td>
<td>68.6</td>
<td>39.5</td>
<td>0.0044</td>
</tr>
<tr>
<td>NT-proBNP monitoring, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>82.3</td>
<td>95.1</td>
<td>0.243</td>
</tr>
<tr>
<td>Repeat</td>
<td>58.8</td>
<td>22.0</td>
<td>0.0002</td>
</tr>
<tr>
<td>HFrEF GDMT, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor/ARB at discharge</td>
<td>85.2</td>
<td>68.4</td>
<td>0.17</td>
</tr>
<tr>
<td>Beta-blocker* at discharge</td>
<td>90.9</td>
<td>75.0</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HFrEF, Heart Failure with Reduced Ejection Fraction.

* Defined as metoprolol succinate, bisoprolol or carvedilol per ACCF/AHA Heart Failure Guidelines.

**Table 4 – Comparison of readmission rates by intervention.**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Readmission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Center</td>
<td>25.6%</td>
</tr>
<tr>
<td>Telemetry Unit</td>
<td>20.9%</td>
</tr>
<tr>
<td>Patient Navigator Program</td>
<td>17.6%</td>
</tr>
<tr>
<td>Education intervention</td>
<td>10.3%</td>
</tr>
<tr>
<td>Follow-up intervention</td>
<td>6.1%</td>
</tr>
<tr>
<td>Education &amp; follow-up interven</td>
<td>4.8%</td>
</tr>
</tbody>
</table>


specific roles of each team member. Therefore, specialized training in HF may be more important than provider credentials when HF care transitions are involved. Implementing the NT within the existing IDT created a platform for routine discussion of ADHF admissions during daily rounds and allowed for greater awareness.

Before the Patient Navigator Program, clinical pathways for ADHF management were not standardized and varied by provider team. Prior to deployment of the NT, the primary educators on the unit were telemetry nurses. Pharmacist were not involved in direct patient care activities. Education provided by telemetry nurses was not standardized and did not specify the amount of time spent with a patient or caregiver. The majority of documented counseling points were on diuretic use or low sodium diet. Guidelines for post discharge appointments at our institution’s outpatient cardiology and primary care clinics mandated follow-up within 30 days as opposed to 7 to 14 days. The NT focused on decreasing variance among evidence-based interventions. The resulting standardization of clinical care, education and follow-up decreased the 30-day readmission rate among the NT group. The control group and Medical Center had a higher readmission rate because evidence-based interventions such as routine biomarker monitoring, adherence to GDMT, HF specific education and expedited post discharge follow-up were not standards of practice. Patients were not routinely identified, causes for decompensation were not discussed and strategies to prevent readmission were not addressed prior to discharge.

Most importantly, the provision of services by the NT was tailored to meet patients’ needs and overall risk of adverse outcomes. Greater success occurred when the patient was included as a member of the team. Methods to customize the discharge plan to literacy and social needs increased motivation and adherence. Involving family members and caregivers in post discharge planning and HF management discussions improved disease state awareness. Effective teaching occurred over several sessions to increase attention and retention. Overall a patient and patient-family-centered approach proved critical to prevent readmissions. Efforts to reduce HF readmissions require a high level of vigilance and commitment from a designated team. Our study encouraged continuity of care and allowed team members to collaborate. However, the role of each team member should be clearly defined. From time of admission to hospital unit to discharge we recommend the following:

- Identify HF as primary diagnosis early during hospitalization through daily team discussion
- Confirm HF diagnosis by provider documentation in medical record
- Initiate standardized education in small daily sessions and engage family members or caregivers
- Utilize teach-back method to ensure patient recall
- Accurately reconcile medications at discharge and highlight changes in regimen with patient
- Obtain follow-up appointment prior to discharge within 7-14 days and discuss with patient to ensure transportation

There are several limitations of our study. First, the sample size was small and the study period was during summer and fall. Seasonal trends in HF hospitalizations demonstrate increased admissions and mortality during winter months. The study was conducted on a cardiac telemetry unit which had an IDT composed of health care professionals with extensive HF experience. Results may not be easily reproducible on a non-cardiac telemetry unit with hospitalists and house staff. Because interventions were not blinded or randomized the control group inherently benefited from focused readmissions reductions efforts on the unit despite not being identified or enrolled into the pilot.

**Conclusion**

The results of our study demonstrated that a diligent effort to identify hospitalized HF patients led to evidence-based interventions that improved patient outcomes and ultimately reduced the 30-day readmission rate. A designated NT of a nurse and clinical pharmacist allowed for effective delivery and a patient-centered approach. HRRPs can easily embed a NT into existing initiatives to further reduce the readmission rate.

**Statement of conflict of interest**

None of the authors have any conflicts of interests with regard to this publication.

**REFERENCES**

A Review of Cardiac Rehabilitation Delivery Around the World

Ella Pesah\textsuperscript{a}, Marta Supervia\textsuperscript{b,c}, Karam Turk-Adawi\textsuperscript{d}, Sherry L. Grace\textsuperscript{a,e,⁎}

\textsuperscript{a}School of Kinesiology and Health Science, York University, Canada
\textsuperscript{b}Cardiovascular Rehabilitation Program, Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA
\textsuperscript{c}Miguel Servet Hospital, Zaragoza, Spain
\textsuperscript{d}Department of Public Health, Qatar University, Al-Doha, Qatar
\textsuperscript{e}Cardiovascular Prevention and Rehabilitation Program, University Health Network, University of Toronto, Canada

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ABSTRACT

Herein, 28 publications describing cardiac rehabilitation (CR) delivery in 50 of the 113 countries globally suspected to deliver it are reviewed, to characterize the nature of services. Government funding was the main source of CR reimbursement in most countries (73%), with private and patient funding in about ¼ of cases. Myocardial infarction patients and those having revascularization were commonly served. The main professions delivering CR were physicians, nurses, and physiotherapists. Programs offered a median of 20 sessions, although this varied. Most programs offered the core components of exercise training, patient education and nutrition counseling. Alternative models were not commonly offered. Lack of human and/or financial resources as well as space constraints were reported as the major barriers to delivery. Overall, CR delivery has been characterized in less than half of the countries where it is offered. The nature of services delivered is fairly consistent with major CR guidelines and statements.

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Statement of Conflict of Interest: see page 278.

⁎ Corresponding author at: School of Kinesiology and Health Science, Bethune 368, York University, 4700 Keele Street, Toronto, ON M3J IP3, Canada.

E-mail address: sgrace@yorku.ca (S.L. Grace).

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Introduction

By 2030, it is expected 84 million individuals will be diagnosed with cardiovascular disease (CVD). Moreover, it is among the leading causes of disability around the world, and contributes to 10% of disability-adjusted life years lost world-wide. With improved survival (in high-income countries), clearly there is a great need for secondary prevention, such as is offered in cardiac rehabilitation (CR) programs. Many meta-analyses demonstrate that participation in CR is associated with improved quality of life, as well as decreased morbidity and mortality. CR is also cost-effective. Accordingly, it is a class 1 level A recommendation in clinical practice guidelines for CVD patients.

The International, British and Canadian Associations for Cardiovascular Prevention and Rehabilitation, American Association of Cardiovascular and Pulmonary Rehabilitation, Australian Cardiovascular Health and Rehabilitation Association, and the European Association of Preventive Cardiology, among others, have established guidelines to ensure consistent provision and quality of CR delivery in order to achieve the greatest population health benefits. They all outline the nature of patients indicated for services, and make recommendations regarding the composition of a multi-disciplinary CR team. They also establish the core components such as initial assessment, structured exercise training, nutrition counseling, patient education, risk factor management and psychosocial support.

Recently a review of all CR guidelines was undertaken, which compared recommendations across countries. While some consistencies were noted, much variation was identified, raising questions about the nature of CR services delivered around the globe. There have been few reviews of the nature of CR services on a global scale. However there have been a considerable number of studies reporting on national or regional surveys of CR programs. To our knowledge these have never been reviewed, with an eye to understanding how CR services conform to practice guidelines in different regions of the world. This is important as results of some of these national surveys have shown that services may not meet minimum standards. Therefore, the objectives of this narrative review were to identify these studies, to summarize and evaluate what is known about the nature of CR services.

Methods

Studies reporting results of surveys assessing delivery and/or components of comprehensive phase II CR programs on a national or regional level were sought for this narrative review. Sources were identified by searching MEDLINE, PubMed and Scopus. Examples of search terms included: “cardiac rehabilitation”, “components”, “characteristics”, “survey”, “status” and “inventory”. Articles were also identified by consulting with experts in the field, as well as hand-searching reference lists of CR reviews.

CR characteristics of interest primarily included: capacity and resources, reimbursement sources (i.e., government, social security, private insurance), staff composition (i.e., nurses, cardiologists, physiotherapists), patient diagnoses accepted into CR programs (i.e. myocardial infarction, percutaneous coronary intervention, angina), dose (program duration x session frequency), core components delivered (i.e. physical training, patient education, dietary counseling), alternative model delivery and barriers. All studies reporting results of surveys describing at least one of these characteristics in the English language were included. Studies with English-language abstracts, where the full publications were not available in English, were described but not included in data synthesis.
Studies were classified by world regions according to the World Bank classification (i.e. East Asia and Pacific, Europe and Central Asia, Latin America and the Caribbean, Middle East and North Africa, North America, South Asia and Sub-Saharan Africa). Data was extracted in tabular format and summarized qualitatively.

Results

A total of 35 publications were included, describing CR in 50 (25%) of the 203 countries of the world, or (44%) of the 113 countries (manuscript in preparation) where CR is known to be offered. Forty-two were high-income countries, with the remaining from middle-income countries. Multiple studies were identified in the United Kingdom, Europe (including Portugal), as well as North and South/Latin America. Fig 1 displays the countries with CR where a study was identified.

An additional 10 citations were identified (total = 45). There were 4 English-language abstracts identified describing CR in Chile, Italy, Hong Kong and Mexico, but the full publications were not available in English. There were also 6 papers identified describing CR but they did not report primary data (Germany, Hong Kong, Singapore, Switzerland and Thailand). These publications were summarized in the text only. Two non-English publications were found in Japan and Spain that were excluded. Finally, an issue of Progress in Cardiovascular Diseases was comprised of narrative reviews on CR delivery in Canada, United States, Brazil, Latin America, India and Japan. What primary data could be gleaned from these sources were summarized in the text.

A summary of findings from included studies is shown in Table 1, except those with a specific focus on an aspect of CR delivery (e.g., ventricular assist device patients [VAD]; these are described in text only). No studies were identified in the following regions: Sub-Saharan Africa and South Asia. Thirteen (57%) of the included studies were published since 2010, and hence can be considered fairly current. The response rate across all studies is reported in the Table, with summary statistics for all major elements for each region and overall shown at the bottom. The total number of programs identified by country ranged from a minimum of 1 to a maximum of 1000, with a median of 65. Results not shown in the table are summarized below.

**CR delivery in East Asia and the Pacific**

There have been 6 studies in this region, reporting on CR services in Australia, China, Japan and New Zealand (4 [11%] of 38 countries; 1 [4%] of 23 low and middle-income countries [LMICs]). There were also two descriptive studies found for Germany and Switzerland, and therefore these were not included in Table 1 but are described below.

First, a survey conducted in Australia and New Zealand (NZ) aimed to describe the prevalence of cardiopulmonary resuscitation (CPR) training for patients and their families in CR programs (and hence is not shown in Table 1). Surveys were completed by 253 (47%) phase II programs; 206 (46%) in Australia and 45 (52%) in New Zealand. Findings indicated CPR training was only available in 74 (30%) CR programs. The training was delivered by nurses (82%), physiotherapists (8%), and exercise physiologists (4%). Major barriers to CPR training in CR were lack of resources (50%), awareness (34%) and time (11%).

Two national surveys were conducted in Australia. The first aimed to describe the status of CR in Australia. Findings indicated that the mean exercise session duration was 55 min. In addition to those shown in Table 1, other healthcare professionals on the teams were pharmacists (69%), occupational therapists (61%) and social workers (52%). Psychological counselling (86%), and medication education (86%) were also offered in most programs. The second

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**Fig 1 – World Map depicting countries where surveys of cardiac rehabilitation programs have been undertaken.**
Table 1 – Summary of findings – results from national/regional surveys of CR programs, N = 28.

<table>
<thead>
<tr>
<th>Country (year of publication)</th>
<th>Number of respondents/number of CR centers (response rate %)</th>
<th>Reimbursement Source</th>
<th>Patient diagnoses accepted (% of programs)</th>
<th>Patients Served per program or country per year</th>
<th>Staff composition (% of programs)</th>
<th>Dose (weeks × frequency/week)</th>
<th>Core components delivered (% of programs)</th>
<th>Alternate models (% yes)</th>
<th>Barriers (% of programs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (2015)</td>
<td>225/305 (74%)</td>
<td>Public (68%)</td>
<td>MI (100%) CAGB (100%) PCI (100%)</td>
<td>250</td>
<td>Nurses (88%) Dietitians (82%) Physiotherapists (77%)</td>
<td>11 (7 × 1.6)</td>
<td>ET (100%) PE (98%) NC (88%)</td>
<td>CB (18%) HB (15%)</td>
<td>-</td>
</tr>
<tr>
<td>China (2016)</td>
<td>10/-</td>
<td>PCI (100%)</td>
<td>Physicians (100%) Nurses (85%) Dietitians (46%)</td>
<td>-</td>
<td>IA (100%) PE (100%) NC (100%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Interest in CR (58%) HR (58%) PAW (50%)</td>
</tr>
<tr>
<td>Japan (2007)</td>
<td>52/-</td>
<td>Public (100%)</td>
<td>MI. 96% (96%)</td>
<td>-</td>
<td>-</td>
<td>6 (6 × 1)</td>
<td>ET (100%) RF (100%) NC (100%)</td>
<td>CB (82%) HB (12%)</td>
<td>-</td>
</tr>
<tr>
<td>New Zealand (2016)</td>
<td>34/46 (7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8.6 (8.6)</td>
<td>ET (100%) NC (100%) PE (99%)</td>
<td>CB: 40% (40%) HB: 14% (14%)</td>
<td>HR: 68% (68%)</td>
</tr>
<tr>
<td>Regional summary: mean (median)</td>
<td>74% (74%) Public; 84% (84%) MI. 100% (100%) MI. 96% (96%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8.6 (8.6)</td>
<td>ET (100%) NC (100%) PE (99%)</td>
<td>CB: 40% (40%) HB: 14% (14%)</td>
<td>HR: 68% (68%)</td>
</tr>
<tr>
<td>Europe (2002)-13 countries</td>
<td>252/443 (57%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-(8.4 × [-])</td>
<td>ET (95%) SC (70%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Europe (2010)-28 countries</td>
<td>28/39 (72%)</td>
<td>Public (89%)</td>
<td>CABG (86%) MI (82%) Valv (60%)</td>
<td>-</td>
<td>-</td>
<td>-(9 × [-])</td>
<td>-</td>
<td>HB (28%)</td>
<td>-</td>
</tr>
<tr>
<td>United Kingdom (1998)</td>
<td>263/273 (96%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>England &amp; Wales (1997)</td>
<td>22/25 (86%)</td>
<td>Public (56%)</td>
<td>-</td>
<td>166</td>
<td>Nurses (89%) Physiotherapists (85%) Dietitians (84%)</td>
<td>11 (7 × 1.5)</td>
<td>ET (100%) PE (100%) SM (90%)</td>
<td>CB (4%) HB (4%)</td>
<td>-</td>
</tr>
<tr>
<td>Country</td>
<td>Year</td>
<td>Public (%)</td>
<td>Private (%)</td>
<td>MI (100%)</td>
<td>PCI (100%)</td>
<td>Angina (90%)</td>
<td>Physiotherapists (100%)</td>
<td>Nurses (90%)</td>
<td>Dietitians (89%)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------</td>
<td>------------</td>
<td>-------------</td>
<td>-----------</td>
<td>------------</td>
<td>--------------</td>
<td>-------------------------</td>
<td>---------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Denmark</td>
<td>2005</td>
<td>60/44</td>
<td>-</td>
<td>MI (100%)</td>
<td>PCI (100%)</td>
<td>HF (75%)</td>
<td>Physiotherapists (100%)</td>
<td>Nurses (100%)</td>
<td>Dietitians (89%)</td>
</tr>
<tr>
<td>England</td>
<td>2006</td>
<td>28/28</td>
<td>-</td>
<td>MI (100%)</td>
<td>PCI (100%)</td>
<td>CABG (100%)</td>
<td>-</td>
<td>14 (7 × 2)</td>
<td>-</td>
</tr>
<tr>
<td>Ireland</td>
<td>2001</td>
<td>21/-</td>
<td>Patients (14%)</td>
<td>MI (100%)</td>
<td>PCI (100%)</td>
<td>CABG (100%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>N. Ireland</td>
<td>1997</td>
<td>8/9</td>
<td>-</td>
<td>MI (100%)</td>
<td>PCI (100%)</td>
<td>CABG (88%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Italy</td>
<td>2008</td>
<td>51/65</td>
<td>Public (99%)</td>
<td>MI (100%)</td>
<td>PCI (100%)</td>
<td>CABG (100%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Portugal</td>
<td>2007</td>
<td>12/12</td>
<td>Public (51%)</td>
<td>MI (100%)</td>
<td>PCI (100%)</td>
<td>CABG (100%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Portugal</td>
<td>2010</td>
<td>14/14</td>
<td>Public (82%)</td>
<td>MI (100%)</td>
<td>PCI (100%)</td>
<td>CABG (91%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Portugal</td>
<td>2016</td>
<td>19/19</td>
<td>Public (90%)</td>
<td>MI (100%)</td>
<td>PCI (100%)</td>
<td>CABG (100%)</td>
<td>1,927</td>
<td>25 (10 × 2.5)</td>
<td>-</td>
</tr>
<tr>
<td>Scotland</td>
<td>1996</td>
<td>69/69</td>
<td>Public (50%)</td>
<td>MI (96%)</td>
<td>PCI (81%)</td>
<td>Angina (70%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Spain</td>
<td>2003</td>
<td>11/12</td>
<td>-</td>
<td>MI (100%)</td>
<td>PCI (100%)</td>
<td>CABG (100%)</td>
<td>639</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Summary: mean (median)</td>
<td></td>
<td>89% (96%)</td>
<td>Public: 74%</td>
<td>MI: 96% (100%)</td>
<td>PCI: 91% (90%)</td>
<td>CABG: 91% (90%)</td>
<td>402 (402)</td>
<td>3,573 (3,573)</td>
<td>-</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>2009</td>
<td>33/-</td>
<td>Public (48%)</td>
<td>MI (100%)</td>
<td>PCI (97%)</td>
<td>CABG (97%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>2013</td>
<td>107/-</td>
<td>Mixed (46%)</td>
<td>MI (100%)</td>
<td>PCI (99%)</td>
<td>CABG (97%)</td>
<td>180</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>South America</td>
<td></td>
<td>33/13</td>
<td>Private (24%)</td>
<td>MI (100%)</td>
<td>PCI (97%)</td>
<td>CABG (97%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Country (year of publication)</th>
<th>Number of respondents/number of CR centers (response rate %)</th>
<th>Reimbursement Source</th>
<th>Patient diagnoses accepted (%)</th>
<th>Patients Served per program or country per year</th>
<th>Staff composition (%)</th>
<th>Dose (weeks × frequency/week)</th>
<th>Core components delivered (%)</th>
<th>Alternate models (%) yes</th>
<th>Barriers (%)</th>
<th>Summary mean (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico (2016)</td>
<td>24/24 (100%)</td>
<td>-</td>
<td>IHD (100%)</td>
<td>-</td>
<td>Physicians (100%)</td>
<td>ET (100%)</td>
<td>NC (90%)</td>
<td>HB (37.5%)</td>
<td>FR (83%)</td>
<td>224 (21%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PCI (100%)</td>
<td></td>
<td>Administrative</td>
<td>PE (100%)</td>
<td>IA (80%)</td>
<td>HR (67%)</td>
<td>EQ (46%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HF (92%)</td>
<td></td>
<td>assistants (100%)</td>
<td>ET (80%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MI: 100% (100%)</td>
<td>Physicians: 95% (100%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PCI: 99% (99%)</td>
<td>Dietitians: 81% (81%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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Hospital directors were contacted and 46 responded. Findings indicated programs were value based on approximation from figure. Author contacted to request actual values, but no response.

In the survey conducted in New Zealand, findings indicated that 50% of programs had a session frequency of 1 session per week. In addition to the core components shown in Table 1, stress management (94%), smoking cessation (79%), and weight management (59%) were also included in most CR programs. The survey also assessed support for special populations (i.e. Maori and Pacific peoples). Results showed that 56% of programs provided a specific cultural provider or liaison, but 29% of programs offered no support for these patients.

In the survey in China, findings indicated programs were only available in 8% of hospitals. In addition to providers shown in Table 1, CR teams included clinical educators (31%), exercise physiologists (15%), and psychologists (15%). Dietary counseling and smoking cessation were also offered in all CR programs. In addition to the major diagnoses shown in Table 1, most programs also accepted patients with pacemakers (92%) and post-coronary artery bypass graft surgery (CABG; 69%). Major barriers to establishing CR (specified in this paper in addition to those to delivering CR) were mainly lack of interest (58%), human resources (58%), awareness (50%), and space (47%).

An English-language abstract describing CR in Hong Kong specifically were also identified. The abstract outlined a survey that was completed by 9 phase II CR programs. Results showed that all CR teams include cardiologists, nurses and physiotherapists. The descriptive study outlined phase II CR components that included exercise training, relaxation therapy, and risk factor management.

There were 4 publications in Japan, based on surveys of hospitals (including designated cardiology training centres), regarding their delivery of CR. In the survey conducted in 1999, 76 hospital directors were contacted and 46 responded (61%). Results indicated that 21% of MI patients participated in CR. In the 2007 survey, findings indicated CR programs were only available in 5% of hospitals. Only 6% of facilities were approved for CR. Assuming all patients transferred from phase I CR, phase II programs served an estimated 4,896 patients. Barriers to implementing CR other than those reported in Table 1 included lack of space (23%), and 12% of hospitals believed CR was not necessary. A second publication based on the 2007 survey analyzed patient safety in CR. Findings indicated the rate of adverse events was 12 events/383,096 patient hours. The final publication was based on a 2009 national survey and aimed to examine the CR referral process in Japan. Findings indicated that outpatients were implemented in 18% of hospitals, which was an increase from the previous assessment.

In addition, there was a narrative review comparing CR status between the 2004 survey (described above) and the
2009 survey (published in Japanese).\textsuperscript{40} This reported that public health insurance covers only 70\% of CR costs for patients under 70 years old and 90\% for patients over 70 years old. In terms of CR implementation, rates doubled from 9\% to 21\%, however CR was still only offered in 325 (4\%) of 8,245 hospitals. On average, patients have a longer hospital stay which can explain the in-patient nature of CR in Japan. A major barrier cited was patient referral; there is no system of referral in Japan, and if the patient has not been treated in a facility that offers CR they will not participate in any CR at all. Finally, another national survey was conducted in 2015 (personal communication, Yoichi Goto, October 24, 2016); the results of this survey are greatly awaited.

In the paper describing CR in Singapore\textsuperscript{35}, 3 phase II CR programs were identified. All programs included exercise training and patient education. Phase II programs from 2 centers were described in detail. Program durations were 6 and 12 weeks respectively, with a session frequency of 3 sessions/week. Both centers included nurses and physiotherapists as part of the CR team. The main center accepted patients with myocardial infarction (MI), CABG, percutaneous coronary intervention (PCI), heart transplant, angina, heart failure and valvular disease.

In the paper describing the status of CR in Thailand,\textsuperscript{38} 5 CR programs were identified (phase was not specified). These programs included exercise and lifestyle modification. The barriers to patient participation in CR listed were time constraints, transportation, and lack of a caregiver to take them to sessions.

**CR delivery in Europe and Central Asia**

There have been 15 studies in this region, covering CR in the following 32 countries: Austria, Belarus, Belgium, Croatia, Cyprus, Czech Republic, Denmark, England, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lithuania, Luxembourg, the Netherlands, Norway, Northern Ireland, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Scotland, Spain, Sweden, Switzerland, and Wales (54\% of 59 European/Central Asian countries; 4 [19\%] of 21 regional LMICs). One English language abstract in Italy\textsuperscript{31} and 1 descriptive study in Switzerland\textsuperscript{36} were also identified. Of note, 3 (23.1\%) of these studies noted phase II CR services being provided in a residential setting.

Three regional surveys were conducted in Europe. In the first survey,\textsuperscript{30} findings indicated that most programs offered 20–29 exercise sessions (40\%). In addition to those shown in Table 1 other healthcare professionals on the teams were dietitians, psychologists and social workers. Another core component that was also offered in many phase II programs was smoking cessation.

The second of these studies\textsuperscript{23} was completed by respondents each describing CR delivery in their entire country. Twenty-four (86\%) of these countries were high-income. Results showed that majority of CR programs had a duration ranging between 6–12 weeks. As well as the major diagnoses presented in Table 1, CR programs also accepted patients with heart transplants (46\%). Finally, many countries offered residential phase II programs; 3 (11\%) countries offered only such programs, and 18 (64\%) offered them in addition to other models.

The third and final European survey\textsuperscript{35} aimed to describe the characteristics of programs for VAD patients specifically (and hence is not shown in Table 1). Surveys were completed by 32 phase II programs in VAD centers in 26 countries. Results specified the duration of out-patient CR programs to be between 4 and 12 weeks. CR teams were composed of physiotherapists (73\%), psychologists (51\%), nurses (49\%), specialized cardiologists (49\%) and dietitians (47\%). The exercise component of many programs included exercise training (84\%), respiratory muscle training (55\%), and resistance training (49\%). Alternative models were offered, mostly home-based (9\%).

The survey in Denmark\textsuperscript{60} was completed by 44 phase II CR programs. CR teams were also composed of nurses and physicians. The core component that was also offered in many programs was smoking cessation (71\%).

Two surveys were conducted in Italy. In the first,\textsuperscript{61} in addition to those shown in Table 1, other healthcare professionals on CR teams were psychologists (74\%) and dietitians (62\%). Sixty-eight percent of phase II programs were residential. The mean length of stay for these programs was 18.5 days. Results of the second survey\textsuperscript{58} were reported in an English-language abstract. The survey was completed by 102 phase II programs. Over 75\% of programs were headed by a cardiologist. In terms of alternative models, 8\% offered tele-rehab and 5\% offered home-based CR.

Three surveys were conducted in Portugal. In the first,\textsuperscript{62} in addition to those noted in Table 1, CR teams also included physiatrists (61\%), and psychologists (61\%). In the second,\textsuperscript{63} findings indicated that in addition to the healthcare providers shown in Table 1, again physiatrists (75\%) and psychologists (62\%) were also included as part of the CR team. In the most recent survey,\textsuperscript{64} again physiatrists (74\%) and psychologists (61\%) were also included as part of the CR team. The core components that were also offered in most programs were dietary counseling (96\%), and smoking cessation (96\%).

In the survey conducted in Spain,\textsuperscript{65} in addition to those shown in Table 1, occupational therapy (9\%) was offered as part of the CR program. In addition to the major diagnoses accepted shown in Table 1, patients with valvular surgery (73\%) and with heart failure (64\%) were also included. Barriers to CR creation (not delivery as shown in the Table) included lack of support from administration (72.7\%), lack of patient information/patient skepticism (54.5\%), and lack of staff interest (45.5\%).

Finally, for Europe, 2 descriptive studies were also identified. In the Swiss paper,\textsuperscript{36} 57 phase II CR programs were identified. CR teams were composed of cardiologists, physiotherapists, nurses, dietitians, psychologists, occupational therapists and social workers. In the German paper,\textsuperscript{39} coverage for phase II CR by government for all MI patients, and following CABG and valvular surgeries was described. Phase II programs were delivered in inpatient and outpatient settings, where both are 3 weeks long and are delivered by a multidisciplinary team including physicians, nurses, exercise specialists, physiotherapists and nutritionists.

Six surveys were conducted in the United Kingdom. In the first survey\textsuperscript{66} which was conducted throughout the 4 countries, findings indicated that, in addition to the top 3
healthcare professions shown in Table 1, CR teams also included occupational therapists (40%) and physicians (39%). In the second survey conducted in England and Wales, findings indicated the mean exercise session duration was 55 min. There were 7 major public funding bodies reported which reimbursed CR services, but for 7 (28%) programs funding source was unknown. In addition to the healthcare professionals shown in Table 1, CR teams also included dietitians (8%), psychologists (4%) and exercise physiologists (4%). Counselling (40%) was also offered as a component of CR programs.

In the survey conducted in England only, results showed that the mean exercise session duration was 60 minutes. In addition to those shown in Table 1, other healthcare professionals on the teams were pharmacists, occupational therapists and psychologists.

In the survey conducted in Ireland only, results showed that 21 of 53 (40%) hospitals had a CR program (of which 12 were in the Republic of Ireland, with the remainder in Northern Ireland). Other healthcare professionals delivering CR were physiotherapists and ECG technicians. Other components offered included smoking cessation, medication advice as well as sexual and vocational counselling. In addition, the study in Northern Ireland showed that few centers (13%) accepted patients with valvular disease, heart failure, angina, or PCI.

Finally, for the United Kingdom, a survey was conducted in Scotland. Findings indicated programs were only available in 7% of hospitals. As well as the major diagnoses accepted in CR programs shown in Table 1, patients suffering from heart failure (35%) were also accepted. Another major barrier to patient participation identified was transportation issues (49%).

**CR delivery in Latin America and the Caribbean**

As shown in Table 1, there have been 3 studies in this region, representing CR in the following 11 countries: Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Paraguay, Peru, Uruguay and Venezuela (11 [26%] of 42 countries; 9 [35%] of 26 LMICs in the region). One English-language abstract was identified from Chile.

In the survey conducted in Latin America and the Caribbean, in addition to those shown in Table 1, CR teams were also composed of nurses (52%), psychologists (48%), and social workers (33%). As well as the major diagnoses accepted in CR programs shown in Table 1, patients with valvular conditions (82%), heart failure (73%) and heart transplants (21%) were also accepted.

In the survey in South America, in addition to the healthcare providers listed in Table 1, many CR teams also included psychologists (53%), nurses (50%), and sport physicians (32%). Psychological counseling (68%) and smoking cessation (59%) were also provided as core components in most programs. As well as the major diagnoses accepted in CR programs shown in Table 1, patients with heart failure (97%) and valvular disease (95%) were also accepted. Notably, the main perceived barrier to CR participation was lack of patient referral (70%).

Two surveys were conducted in Mexico. In the first, findings revealed CR teams were also composed of nurses (79%), nutritionists (79%) and psychologists/psychiatrists (71%). In addition to those shown in Table 1, programs also accepted patients with CAGB (87%) and valvular disease (83%). Other barriers to CR cited included lack of space (42%), and a reduction in operating centers (38%).

An English-language abstract was identified from a survey conducted in Chile. The survey was completed by 7 (87%) phase II programs. Findings indicated that CR teams were mainly composed of cardiologists, nurses, physiotherapists and nutritionists. All programs included initial assessment, physical activity counseling, and dietary counseling. The major barrier reported was a lack of patient referral.

There have been 2 narrative reviews in Latin America. The review in Latin America showed that the source of CR funding across this region was highly variable. Only 4 countries offered 100% coverage through the national health system, while patients paid for most programs out-of-pocket. Core components commonly available included exercise training, risk factor management, and patient education. Major barriers described included poor physician referral, distance to CR center, lack of finances and lack of trained personnel.

Finally, the narrative review in Brazil indicated that the duration of Phase II CR was between 3 and 6 months, with many programs allowing patients to stay longer. Exercise sessions were typically offered 3 times/week for 55 min. Most programs were comprised of an interdisciplinary team including physicians, physical educators, physiotherapists, psychologists and nutritionists. The major barrier to CR access was funding, as CR is more available to patients with the means to pay or who have insurance. Another barrier was that CR was mainly located in large urban centers.

**CR delivery in the Middle East and North Africa**

As shown in Table 1, there has been 1 study in this region, reporting on CR services in Bahrain, Egypt, Qatar and the United Arab Emirates (4 [19%] of 21 countries; 1 [8%] of 13 LMICs in the region). The survey was completed by 5 (62%) phase II CR programs. Results indicated that, along with those shown in Table 1, CR teams included social workers (20%), and exercise specialists (20%). Nutrition counselling (80%) and prescription or titration of secondary prevention medications (80%) were also offered in most CR programs. The major barriers (reported on a 5-point scale, with higher scores indicating greater barriers) also included lack of financial resources (3.6) and equipment (3.6).

**CR delivery in North America**

As shown in Table 1, there have been 7 studies in this region, from Canada, its province of Ontario, and the United States, including in the states of New York, North Carolina and Ohio (2 [67%] of 3 countries; all high-income). In the national Canadian study, alongside those presented in Table 1, CR teams also included kinesiologists (35%) and dietitians (12%). All programs also offered nutrition counselling (100%) and
physical activity counseling (100%) as core components of the program. Major barriers (again reported on the same 5-point scale as per above) also included patient referral (3.2), and lack of equipment (2.7). In the provincial survey,\textsuperscript{24} results showed that in addition to those shown in Table 1, 68% of programs also offered psychosocial services. There were also 2 narrative reviews published describing CR status in Canada.\textsuperscript{42,75}

The two surveys conducted in the United States and the 3 surveys conducted in the individual states of New York, North Carolina, and Ohio are shown in Table 1.\textsuperscript{48,76–79} Finally, a narrative review describing CR in the United States\textsuperscript{45} listed lack of patient referral and distance to CR programs as major barriers to CR participation.

**CR delivery in South Asia**

A narrative review was published describing CR in India.\textsuperscript{46} The publication showed that there are less than 50 programs in the entire country. Programs are delivered by physiotherapists, physicians, dietitians and nurses. Alongside exercise training, many programs in India include yoga as component of CR. The major barriers to CR were distance from the CR center and lack of transportation.

**Discussion**

Through this review, the nature of CR services in less than half of countries offering CR around the globe was characterized. This first-ever such study sheds light on variation in quality and nature of CR globally. Clearly evidence-based practices should be applied consistently globally, but tailoring to local health systems and patient needs is required. Arguably many of the recommendations in CR guidelines are consensus rather than evidence-based however. Regardless, the results herein for the first time characterize how CR is delivered in relation to established standards.\textsuperscript{13,14,18,27}

Most programs were funded publicly (73% of studies reporting funding source). This is positive, considering previous research has shown that more sessions are funded where programs are funded publicly.\textsuperscript{86} Regionally, in Europe and Central Asia CR was more commonly reimbursed through a national health service, while in the rest of the world private systems may play a more important role (e.g., United States, Middle East and North Africa). While this review shed light on CR reimbursement and variation in these sources, more information regarding CR delivery costs to the healthcare system and to patients would be informative.

Where reported, MI was the diagnosis most frequently-accepted in Europe and Central Asia, compared to PCI in Eastern Asia and Pacific, as well as Latin America and the Caribbean. Clearly, there is excellent evidence supporting the benefits of CR for acute coronary syndrome and associated revascularization. There is now growing evidence supporting the benefits of CR for arrhythmia patients,\textsuperscript{81,82} those with valve disorders,\textsuperscript{83} and heart failure.\textsuperscript{84–86} With regard to the former, atrial fibrillation was not mentioned as an indication in any study (this could be due to recency of evidence regarding the benefits of exercise in this population), however rhythm devices were stated as an indication in many European countries (i.e., Austria, Belarus, Belgium, Croatia, Cyprus, Czech Republic, Denmark, England, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Lithuania, Luxembourg, the Netherlands, Norway, Northern Ireland, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Scotland, Spain, Sweden, Switzerland, Wales) and also Mexico for example. Valve disorders/procedures were also recognized indications in many European (Austria, Belarus, Belgium, Croatia, Cyprus, Czech Republic, Denmark, England, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Lithuania, Luxembourg, the Netherlands, Norway, Northern Ireland, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Scotland, Spain, Sweden, Switzerland, Wales, Singapore, and Spain) as well as South American (Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Paraguay, Peru, Uruguay, Venezuela) countries. A very similar list of countries also accepted HF patients. Thus, it seems CR programs have the capacity and expertise to adapt to new evidence, and accordingly change their policies regarding patient indications for admission.

In the 7 (30%) studies reporting capacity, the number of patients served per program ranged from 129 to 639, with a median of 202. This appeared higher in Europe than North America. The impact of patient volume on CR care quality appears irrelevant based on early work on this question from the United Kingdom,\textsuperscript{87} but research has suggested higher volume acute cardiac care centres have better outcomes than lower-volume ones.\textsuperscript{88} The number of patients served per country was also reported in some instances, and data confirmed the gross under-capacity established in other work.\textsuperscript{89}

When comparing by region, considerable comparability in CR staff composition was observed. In almost all studies (n = 21, 72%), programs were delivered by a multidisciplinary team. The most common types of healthcare providers were physicians, nurses and physiotherapists. While there is not necessarily an evidence base to support recommendations that CR programs be staffed by an inter-professional team, this certainly supports competent delivery of all recommended core components needed to optimize secondary prevention. Contrary to some (but not all)\textsuperscript{20} guideline recommendations\textsuperscript{15,16,18} that CR be directed by physicians however, these were only among the top three most frequent personnel in the Middle East and North Africa, Latin America and the Caribbean, Europe as well Central Asia (but not in East Asia, the Pacific, and North America). Also interestingly, in some regions physiotherapists were a main part of the team (n = 17 of 21 papers reporting staff composition, e.g., Australia, England, Scotland, Northern Ireland, Wales, Denmark, Italy, Portugal, Spain, Mexico, Bahrain, Egypt, Qatar, UAE and Canada; e.g., \textsuperscript{24,30,61,66}) whereas in others, exercise specialists were more common (i.e., exercise physiologists, kinesiologists; n = 7 of 21 papers reporting staff composition; North America, China and the Middle East; e.g.,\textsuperscript{24,48}). Whether this is a function of availability of training programs and hence staff to hire, reimbursement policies in the healthcare system, costs to programs, or other factors is unknown, as is the impact for patient outcomes (although there is no basis on which to assume different outcomes would be observed).
There is no evidence to our knowledge on which to base clinical practice recommendations regarding number of CR sessions, or dose, to prescribe. A previous review of clinical practice guidelines revealed broad variability in recommendations internationally, as did a review of primary studies by our group. The range of sessions prescribed spanned from a minimum of 16.5 ± 2.1 sessions in France, to a maximum of 142.0 ± 112.4 sessions in Spain. Herein, dose (both program duration and session frequency) was only reported in 12 (41%) studies, and ranged from 6 (New Zealand) to 44 (Canada), with a median of 20. The variability is postulated to be based on reimbursement policies. Clearly, evidence is needed to demarcate minimum dose of CR needed to significantly improve patient quality and quantity of life, with consideration of case-mix, so quality of care in countries/regions not meeting this minimum can be improved.

With regard to core components delivered, exercise training was the most consistently offered one overall, but also in the regions of Europe and Latin America; this is laudable given that the greatest improvements in prognosis are explained by improvements in cardiorespiratory fitness achieved through physical activity. Clearly great efforts are needed to increase CR penetration in healthcare systems across the globe, given these are highly cost-effective strategies. The next most commonly-offered component was patient education, which was delivered particularly often in North America, as well as the Middle East and North Africa. Dietary counseling was particularly common in Eastern Asia and Pacific, which is reflected in the high prevalence of dietitians on their CR teams in this region. Overall results suggest most programs globally offer the main core components, however clearly the results herein are only generalizable to the primarily high-income countries represented (Fig 1).

Due to the challenges of delivering supervised CR in the clinical setting to all patients in need, alternative models such as home-based and community-based programs have been developed, which arguably may have broader reach. They are also shown to be efficacious. The offering of alternative models was first reported in a 1997 publication from England and Wales. The degree of implementation of these alternative models is shown to be incredibly low globally through this review. Where reported, home-based CR was offered by a median of 15% of programs, community-based CR by 24% of programs, and internet or other technologically-based CR by 11% of programs. In the Middle East and North Africa, CR is not available outside a clinical center. Further research on the comprehensiveness and nature of alternative models is needed to understand whether CR standards are being met in non-supervised settings. In addition, we must apply tools from implementation science to ensure these alternative models are available to patients who cannot access, or for whom there is no space, at a supervised program (and arguably even those who only prefer to undertake CR independently, so CR is patient-centered).

On a related note, through this review it was identified that phase II CR is offered in residential settings in the following countries: Austria, Belarus, Croatia, Czech Republic, Finland, France, Germany, Hungary, Iceland, Italy, Lithuania, the Netherlands, Romania, Russia, Serbia, and Spain. Again, it is suspected that this is a function of historic practice and reimbursement policies rather than evidence. To our knowledge, the effect on care quality, patient satisfaction and outcomes as well as long-term maintenance of heart-health behaviors has not been established; this represents an important area for future study.

The most commonly-reported barrier to CR delivery around the globe was lack of resources. This was the most consistent finding across all studies. It continues to be baffling that a Class I, Level A recommendation in applicable clinical practice guidelines around the globe is under-resourced, when compared to other similarly-graded recommendations for the same indications. The cardiac community (including societies, foundations, and governments) must continue to advocate for CR reimbursement.

Indeed, the International Council of Cardiovascular Prevention and Rehabilitation has recently developed and collated resources to achieve this aim (see: http://globalcardiacrehab.com/advocacy/). On a final note, lack of referral was also noted as a significant barrier in many studies.

Through this review, several areas where further research is urgently needed have been identified. First, there is little information on the nature of CR in the following regions, which also have among the highest burdens of CVD: East Asia, the Pacific, the Middle East, North Africa, Sub-Saharan Africa and South Asia (Fig 1). Specifically, in East Asia and the Pacific there are 38 countries, of which we perceive 15 have CR, however services are only characterized in 4 of these countries. There are 21 countries in the Middle East and North Africa, of which we perceive 12 have CR, and services are only characterized in 4. In Sub-Saharan Africa there are 48 countries, of which we perceive 7 have CR, and services have never been characterized. Similarly, South Asia includes 8 countries, of which we perceive 5 have CR, yet CR has also never been characterized there. Second, while number of centers and center capacity was reported in many of the papers, given that this was not reported consistently, the number of countries not represented, the low response rates, and that capacity was not juxtaposed against CVD burden, firm conclusions regarding CR availability and capacity should not be drawn from this work. More comprehensive, but gross, information on this is reported elsewhere. More information on CR density globally is needed. Finally, the way the constructs under investigation in this study were measured was not consistent across studies, and therefore some caution in interpreting the comparisons made across studies herein is warranted. Administering a standardized and validated set of survey items in all countries would address this limitation. Our group is currently performing this.

Caution is warranted in interpreting these results. First, the search was not systematic and only English-language publications were included, so some studies might have been missed, along with grey literature. Second, in many cases, respondents’ estimates of characteristics and delivery of CR programs were reported, and hence values should be interpreted with caution. Finally, generalizability is limited in several ways. Surveys of CR programs have only been
undertaken in half of the countries where it is suspected to be offered. Moreover, better-resourced countries (and perhaps even programs) are represented in the surveys (Fig 1), and thus this characterization of CR services likely reflects higher-quality care than is the norm. As a final point, the response rate was low in some studies (n = 3, 16% <40%), 24,46,76 and not reported in many others (n = 6, 21%), 53,55,60,67,70,71 and hence caution is warranted in generalizing results from those studies in particular.

In conclusion, while the CVD burden and associated death rates are increasing, and CR is recognized as one of the most beneficial and cost-effective mitigation strategies, information about the nature and quality of CR services is only available for about half of countries globally where it is believed to be offered. This review has demonstrated that CR is most often reimbursed by public sources, is most-commonly offered to MI patients with revascularization, with the average program serving ~200 such patients, by a multi-disciplinary team most-frequently comprised of physicians, nurses and physiotherapists. Most programs deliver the major core components, most-commonly exercise training, patient education and nutrition counselling, over a median of 20 sessions (2 sessions/week over 9 weeks). A consequent observation from the review is the lack of CR density, due to lack of human and financial resources as well as space, consistent with previous reviews, but has also for the first time quantified the dearth of delivery of CR in alternate settings globally. This represents an important means to increase reach of CR. Documentation of CR delivery variation can be used to support meeting of minimum standards by all countries.

Statement of conflict of interest

All authors declare that there are no conflicts of interest.

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Editor’s Commentary

From Heart Failure to Journal Metrics-Making Progress in Cardiovascular Diseases

In this issue of Progress in Cardiovascular Diseases (PCVD), my good friend and PCVD Associate Editor, Hector Ventura, MD, along with a major name in the field of heart failure (HF), Ileana Piña, MD, have put together an excellent issue on the contemporary management of patients with severe HF. Our first issue of 2016 was also devoted to HF, with several highly cited papers. Hopefully Dr. Ventura and Piña’s current HF issue will become a major one to help patients and scientists in the field of advanced HF.

As advances are being rapidly made in the field of HF, our PCVD Journal is also making major advances in Journal Metrics. When I took over as Editor in Chief (EIC) of PCVD in January 2014, our first two Impact Factors (IFs) were both 2.4. However, as mentioned previously, our very first January 2014 issue on obesity and the “obesity paradox” produced some of our highest rated papers in PCVD history, largely leading to my first IF in 2015, based on the 2013 papers before I was EIC and my 2014 papers, increasing from 2.4 and ranked 55th of major cardiovascular (CV) journals to 4.635, which gave us a ranking of 21st among major CV journals. We also had many highly ranked papers in 2015, particularly from our January 2015 Physical Activity Issue and Atrial Fibrillation Issue, which have been well-cited, helping to increase our 2016 IF to 8.177, now ranking us 9th of all CV journals (Tables 1 and 2).

There is another Journal Metric that we are also closely following, which is the Elsevier Cite Score. Unlike the 2-year IF which generally follows two years’ worth of papers (e.g. the 2016 IF represents papers published in 2014 and 2015 that are cited in 2016, although there is also a 5-year IF that is also available, but not generally as popular), the Elsevier Cite Score follows papers for three years (e.g. the 2016 Cite Score represents all papers published in 2013, 2014 and 2015 that were cited in 2016.) Unlike the IF, which typically counts all reviews and original investigations but does not count commentaries, editorials or letters to the editor, the Cite Score counts all of these papers in the denominator, which is a disadvantage for journals that have many commentaries and editorials, since these are generally not cited as often as reviews and original papers. Although our #9

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<tr>
<th>Year</th>
<th>Impact Factor</th>
<th>Rank of CV Journals</th>
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<tbody>
<tr>
<td>2016</td>
<td>8.177</td>
<td>9/126</td>
</tr>
<tr>
<td>2015</td>
<td>4.635</td>
<td>21/126</td>
</tr>
<tr>
<td>2014</td>
<td>2.418</td>
<td>55/123</td>
</tr>
<tr>
<td>2013</td>
<td>2.443</td>
<td>57/125</td>
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<tr>
<td>2012</td>
<td>4.0</td>
<td>28/122</td>
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<td>2011</td>
<td>4.931</td>
<td>18/117</td>
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CV = Cardiovascular.

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<th>Journal</th>
<th>Impact Factor</th>
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<tr>
<td>1. Journal of the American College of Cardiology</td>
<td>19.896</td>
</tr>
<tr>
<td>2. European Heart Journal</td>
<td>19.651</td>
</tr>
<tr>
<td>3. Circulation</td>
<td>19.309</td>
</tr>
<tr>
<td>5. Circulation Research</td>
<td>13.965</td>
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<tr>
<td>6. JACC-Cardiovascular Imaging</td>
<td>10.189</td>
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<tr>
<td>7. JACC-Cardiovascular Interventions</td>
<td>8.841</td>
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<tr>
<td>8. JACC-Heart Failure</td>
<td>8.493</td>
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<tr>
<td>9. Progress in Cardiovascular Diseases</td>
<td>8.177</td>
</tr>
<tr>
<td>10. Circulation-Cardiovascular Interventions</td>
<td>7.198</td>
</tr>
<tr>
<td>11. Journal of Heart And Lung Transplantation</td>
<td>7.114</td>
</tr>
<tr>
<td>12. European Journal of Heart Failure</td>
<td>6.968</td>
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<tr>
<td>14. Circulation-Cardiovascular Imaging</td>
<td>6.803</td>
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<tr>
<td>15. Circulation-Heart Failure</td>
<td>6.372</td>
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<tr>
<td>17. Heart</td>
<td>6.059</td>
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<tr>
<td>18. European Heart Journal – Cardiovascular Imaging</td>
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<tr>
<td>19. Cardiovascular Research</td>
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<tr>
<td>20. Journal of Molecular and Cellular Cardiology</td>
<td>5.68</td>
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<tr>
<td>22. Circulation – Arrhythmia and Electrophysiology</td>
<td>5.41</td>
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<tr>
<td>23. Basic Research in Cardiology</td>
<td>5.306</td>
</tr>
<tr>
<td>24. Eurointervention</td>
<td>5.165</td>
</tr>
<tr>
<td>25. Trends in Cardiovascular Medicine</td>
<td>4.964</td>
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ranked 126 CV Journals for the 2016 IF is quite impressive, our Elsevier Cite Score rank of #5 of 328 CV Journals is even more impressive (Table 3).

Going forward, I do not think that our 2016 papers will be cited as highly as our 2014 ones were, although we have a number of 2016 obesity papers, saturated fat and for sugar related to coronary heart disease. Nevertheless, we have a number of topics of interest in 2017, especially last month’s Exercise Issue and including the current HF Issue, so I am very optimistic that the general trend for the PCVD Journal Metrics will be continuing upward for many years to come, which is good news for our Readership, Scientists and authors.

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