Systolic Heart Failure: Knowledge Gaps, Misconceptions, and Future Directions

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ABSTRACT

Background: Systolic heart failure is the final manifestation of several cardiovascular conditions. The 2001 American College of Cardiology/American Heart Association guidelines depicting the progression of heart failure (HF) from stage A through stage D are aimed at the early treatment of risk factors. However, treatment is often delayed until stage C, and as a result HF continues to impose a major burden on our healthcare industry.

Methods: We conducted an extensive literature review of the MEDLINE/PubMed database with the purpose of elucidating knowledge gaps and misconceptions regarding systolic HF.

Results: Long-term beta adrenergic blocking is the only pharmacologic intervention that reverses left ventricular remodeling. Whether beta adrenergic blocking prevents or delays left ventricular remodeling in patients at risk of HF is presently unknown. A knowledge gap also exists regarding the phenotype of patients that derive a mortality benefit from implantable cardioverter defibrillator therapy. Acute decompenated HF is a misnomer because patients with chronic HF are known to be deteriorating in the weeks preceding hospitalization. Functional class and ejection fraction are not closely correlated. Advanced HF therapies such as heart transplantation and mechanical circulatory support are available to an extremely small fraction of patients with systolic HF.

Conclusion: Concentrating efforts on the early stages of the disease process with optimal management of risk factors for HF is critical to having a significant impact on this ongoing pandemic.

INTRODUCTION

Hospital administrators and the pharmaceutical and medical device industries have spearheaded the growth of heart failure (HF) as an independent discipline since the late 1970s. Because HF is the most common cause of hospitalizations in elderly patients, hospital administrators became interested in curtailing the financial burden of lengthy hospitalizations for symptomatic deterioration of HF. The pharmaceutical industry recognized HF early as a new market for existing medications (beta adrenergic blockers) and newly developed medications (angiotensin-converting enzyme inhibitors), while device companies viewed HF as an untapped opportunity. In 2010, advanced HF and transplant cardiology became a full-fledged, American Board of Internal Medicine-accredited subspecialty.

Traditionally, HF has been described as a clinical condition rather than an organ dysfunction. Patients are usually assessed by the severity of symptoms that range from New York Heart Association (NYHA) functional class I to IV. In most instances, HF is diagnosed late in the course of the syndrome when patients present with NYHA functional class III-IV symptoms.

In 2001, the 4 stages of the American College of Cardiology/American Heart Association (ACC/AHA) HF classification—from stage A (risk factors for HF) to stage D (low cardiac output/end organ hypoperfusion)—underlined that HF is the final manifestation of most cardiovascular conditions. The ACC/AHA classification clearly recommended the aggressive treatment of risk factors to prevent or delay the development of clinical HF. However, in routine clinical practice, the treatment of HF begins in stage C of the ACC/AHA classification when most of the left ventricular (LV) remodeling has already occurred, and symptoms start to interfere with daily activities.
This review focuses exclusively on HF because of LV systolic dysfunction. We discuss knowledge gaps that may be responsible for the initiation of treatment late in the progression of HF rather than early, review common misconceptions in the current management of HF, and consider future directions for the management of HF.

KNOWLEDGE GAPS
Prevention of Heart Failure

The high yield of prevention compared to treatment is best illustrated by comparing beta adrenergic blocking and cardiac transplantation (CT) with days saved and cost as endpoints. Of the approximately 500,000 Americans diagnosed with HF in 2013, half had systolic HF. Half of these patients (250,000) were likely to have responded to beta adrenergic blockers. Assuming that 125,000 responders have their lives prolonged by 4 years, beta adrenergic blocking amounts to 182 million days saved. In the same year, 2,127 American adults underwent CT (United Network for Organ Sharing statistics). Assuming that each patient’s life is prolonged by 12 years, CT amounts to 9 million days saved (Figure 1). The cost of beta blocking is $60 million (carvedilol at $4/month), and the cost of CT is $2 billion (approximately $900,000 per transplant in 2011 according to the Milliman report).

The 2001 ACC/AHA classification emphasized prevention and early treatment of HF. However, by setting apart risk factors without structural heart damage (class A) from risk factors with structural heart damage (class B), the ACC/AHA classification may have undermined its aim by delaying the initiation of pharmacologic interventions that may prevent structural heart damage. Many patients with risk factors and without overt LV remodeling revealed by routine echocardiography have evidence for functional, structural, or both abnormalities with more sophisticated imaging techniques than routine echocardiography. Thus, splitting risk factors into class A and B may be a therapeutic step back.

Forecasting HF in stage A patients has been attempted using risk models such as the Health ABC study’s risk score and the Atherosclerosis Risk in Communities (ARIC) HF risk score. The Health ABC study was limited to patients aged 70-79 years and had a mediocre c statistic (0.72), while the ARIC study c statistic was slightly better (0.77). However, the validity of the c statistic in assessing models that predict future risk or stratify individuals into risk categories is not optimal, and as such the generalizability of these models is questionable.

Long-term beta adrenergic blocking with carvedilol, metoprolol succinate, or bisoprolol is the only pharmacologic intervention that reverses LV remodeling. Angiotensin-converting enzyme inhibition may enhance LV ejection fraction (LVEF) by lowering cardiac loading conditions, but it has no enduring impact on LV remodeling. Experience with beta adrenergic blocking at the stage of LV remodeling showed that the sooner beta adrenergic blocking is initiated, the more complete is the reversal of LV remodeling. Whether long-term beta adrenergic blocking with agents found to reverse LV remodeling will prevent or delay LV remodeling in patients with risk factors for HF has not been investigated. Such an investigation should require a lengthy follow-up period to acquire enough events and should have LV remodeling as a primary endpoint. Because the pharmaceutical industry and the academic community are unlikely to embark on an investigation with a protracted follow-up, federal agencies with an interest in prevention and healthcare cost reduction may need to step in and fund a study of HF prevention at risk factors class A and B.

A similar knowledge gap and need for investigation exist regarding coronary revascularization in patients with coronary artery disease (CAD) and normal LV systolic function. The Surgical Treatment for Ischemic Heart Failure (STICH) trial showed that coronary artery bypass surgery does not prolong life in patients with CAD and LVEF ≤35% compared to medical therapy alone. Whether percutaneous or surgical revascularization in patients with a high SYNTAX (Synergy Between PCI with TAXUS and Cardiac Surgery) score prevents or delays LV remodeling in patients with stable CAD and preserved LVEF needs to be evaluated in randomized trials of sufficient duration. Steady improvement in coronary stent designs and knowledge that coronary revascularization is of no benefit to patients who have a substantial amount of LV damage may lead federal agencies to fund such trials rather than leaving...
percutaneous coronary revascularization to the physician’s discretion in the absence of refractory angina.

An important aspect of prevention is projection. Although the progression rate of risk factors is impossible to predict, progression undoubtedly occurs. Thus, at any stage of the syndrome one must prepare for the next stage. The appropriate time to consider CT and mechanical circulatory support is stage C and not stage D as is customary. Similarly, optimal management of risk factors and prompt use of interventions known to reverse LV remodeling are preferred to prevent or delay the transition of risk factors to clinical HF. Underutilization of these therapies is common among primary care physicians and internists who frequently are the first contact for patients in stages A and B. Continued emphasis on early screening and referral of patients with risk factors, adherence to guideline-directed medical therapy (GDMT), and an understanding of patients’ perceptions based on targeted education of community practitioners are of utmost importance.

In summary, the scarcity of evidence-based medicine in the early stages of HF contrasts with the availability of evidence-based therapy in the late stages. This scarcity is to a large extent responsible for the current lack of emphasis on HF prevention. Planning ahead, which involves prevention and projection, is crucial for efficient HF management.

**Implantable Cardioverter Defibrillators**

Current guidelines recommend an implantable cardioverter defibrillator (ICD) for patients with LVEF \( \leq 35\% \) after GDMT for at least 3 months and with life expectancy greater than 1 year. Among patients with primary prevention ICDs, 1 in 5 patients was shocked for ventricular arrhythmias at 3-5 years, while mortality in controls was half this rate. Thus, only 10% of patients with ICDs received life-saving therapy, and 90% of patients were subjected to the unnecessary risks and costs associated with ICD implantation. The phenotype of patients that derives a mortality benefit from ICD therapy among the large population of patients with LVEF \( \leq 35\% \) eligible for ICD remains unknown, and fear of a malpractice claim rather than true patient benefit continues to drive ICD implantation rates.

The patient population in the pivotal ICD trials was younger and more frequently male and had fewer comorbidities and HF symptoms. A recent metaanalysis of ICD trial subgroups showed that 47% of the trial population was comprised of patients \( \geq 65 \) years, while the National Cardiovascular Data Registry ICD registry had \( > 60\% \) of patients \( > 65 \) years. Similarly, in a Medicare cohort, mortality following implantation of a primary prevention ICD was 30% at 3 years compared to the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and the Second Multicenter Automated Defibrillator Implantation Trial (MADIT-II) populations that had a mortality of 16% and 22%, respectively. Initial reports showed that elderly patients did not benefit from ICD therapy, but further studies showed that they do in fact benefit from ICD therapy. Despite strategically delayed programming, the rates of appropriate shocks were similar to the rates of appropriate shocks given to younger patients. Sex-based differences in outcomes have been explored, with initial studies showing no benefit to all-cause mortality and significantly lower appropriate shocks in women. The risk for sudden cardiac death in women is lower than in men, and several mechanisms resulting in sex-based differences in arrhythmia susceptibility have been proposed. However, a recent metaanalysis failed to show any difference between men and women in all-cause mortality from ICD therapy. In severe chronic kidney disease (CKD) (stage 4 or higher, glomerular filtration rate \( < 30 \) mL/min/kg), primary prevention ICD was not shown to have any survival benefit. This lack of survival benefit is likely related to the higher risk of device-related infections, increased defibrillation thresholds, inadequate response to defibrillation, and higher noncardiac death compared to other ICD recipients.

Now that ICDs are approved for patients with LVEF \( \leq 35\% \), it may be difficult to enroll patients in new trials that with more stringent inclusion criteria aim to define the phenotype of patients that truly benefit from ICD. However, careful analysis of national ICD registries may help refine the indications for ICD in the framework of primary prevention by defining the phenotype of patients with improved LVEF \( > 35\% \) in the months after ICD implantation and the phenotype of patients without ICD shocks for \( \geq 5 \) years after ICD implantation.

Meanwhile, because LVEF is more likely to improve in patients with nonischemic cardiomyopathy rather than in patients with ischemic cardiomyopathy, and the full effect of beta adrenergic blocking on LV systolic function may only be observed after 12 months of therapy, a longer duration of GDMT (\( > 3-6 \) months) appears rational for patients with nonischemic cardiomyopathy. A wearable cardiac defibrillator (WCD) such as LifeVest (ZOLL Medical Corporation) could be used in patients who have not experienced an optimal beta blocker response at 3 months. In fact, the US Food and Drug Administration–approved LifeVest and Subcutaneous-ICD are attractive alternatives for patients with severe CKD, structural heart disease, or
peripartum-cardiomyopathy and for patients with a
time-limited indication, including awaiting a heart
transplant, having myocarditis, or having suffered a
myocardial infarction. During patient selection, an
important consideration is that these devices currently
do not offer bradycardia and antitachycardia pacing
therapies.

In summary, the indication for ICD in the frame-
work of primary prevention needs to be refined to
avoid implantation of unnecessary devices and to
curtail ICD-related financial burden. Because the
device industry has no motivation for refining the
indications for ICD, it is up to federal agencies to
underwrite the efforts that may define the phenotype
of patients that truly benefits from ICD in the
framework of primary prevention. Until then, alterna-
tive primary prevention strategies such as the non-
intravascular WCD or Subcutaneous-ICD should be
actively considered for patient groups in which a
knowledge gap exists.

COMMON MISCONCEPTIONS

Acute Decompensated Heart Failure

The term acute decompensated heart failure
(ADHF) is used to describe the clinical course of
patients with chronic heart failure (CHF) who are
hospitalized for symptomatic deterioration. However,
implantable hemodynamic monitoring devices have
shown that estimated pulmonary artery pressure
keeps rising for many days before patients are
hospitalized or seen in an emergency department
for HF decompensation. Similarly, the monitoring
of thoracic impedance (an index of pulmonary
congestion) indicates that thoracic impedance starts
decreasing on average 2 weeks before hospitalization
for HF decompensation. Body weight was first
reported to increase steadily in the 2 weeks preceding
hospitalization for HF decompensation. However,
close monitoring of body weight does not appear to
be a reliable index of symptomatic deterioration, as
many patients are hospitalized for HF without expe-
rencing weight gain in the days that precede hospitalization.

Because clinical and hemodynamic parameters are deteriorating for several days/weeks
before patients seek medical attention, telemonitoring
was expected to prevent hospitalizations and improve
outcomes in patients with CHF. However, telemoni-
toring was not found useful in preventing hospitaliza-
tions and improving outcomes. The failure of
telemonitoring to improve outcomes is not well
understood.

It seems that a plethora of electrical, hemody-
namic, and clinical data does not match the diagnos-
tic accuracy of a clinic visit with an HF physician who
is familiar with the patient. In contrast to the lack of a
relationship between the intensity of telemo-

toring and improvement in patient outcomes, frequent clinic
visits with adjustment of the loop diuretic regimen are
essential to keep patients with CHF from being
hospitalized. Whether internet-based clinical inter-
views can match the diagnostic accuracy of real clinic
visits for patients who are out of reach of specialized
HF centers needs to be thoroughly investigated.

In summary, ADHF is a misnomer. Patients with
CHF who are hospitalized for symptomatic deteriora-
tion have in most instances been deteriorating in the
weeks preceding hospitalization. Development and
implementation of efficient and flexible programs for
the follow-up of patients with CHF may reduce the
need for hospitalizations and thereby the bulk of HF-
related expenses.

Ejection Fraction and Functional Capacity

The dissociation between LVEF and functional
capacity before therapeutic interventions is well
recognized. Patients with LVEF ≤20% with aero-
bic capacity >20 mL/kg/min may have no symp-
toms of HF (NYHA class I). Conversely, patients with
moderately reduced LVEF (<30%) may present with
severe functional intolerance (NYHA class III-IV).
Overall, LVEF declines well before the occurrence of
symptoms (Figure 2).

Patients with CHF and LVEF ≤35% who were not
receiving therapy for HF were enrolled in the
asymptomatic arm of the Study of LV Dysfunction
(SOLVD) trial. Their aerobic capacity averaged 22
mL/kg/min, more than needed to perform daily
activities without any symptoms. Of therapeutic
importance, the disconnect between LVEF and
functional capacity persists during pharmacologic or
device interventions except in patients with extremely
reduced cardiac output at rest when enhancement of
LV systolic function immediately results in improved
functional capacity.
Functional intolerance happens in part because of skeletal muscle disuse, as exertional symptoms prompt HF patients to curtail physical activities. Consequently, interventions that improve LVEF need to reverse skeletal muscle disuse to improve functional intolerance. Interventions that improve LV systolic performance and alleviate symptoms enhance functional capacity when patients taking advantage of lesser symptoms are becoming more physically active. Thus, interventions that enhance LV systolic performance do not automatically improve functional capacity. In summary, functional capacity and especially aerobic capacity are therapeutic endpoints that are largely patient dependent.

FUTURE DIRECTIONS

During the past decade, the treatment of HF has focused on the use of mechanical circulatory support with LV assist devices for advanced HF. Management of advanced HF is challenging, as patients are commonly unaware of their poor prognosis and wholly unprepared to consider the palliative care that is overwhelmingly the only available option. To be successful, mechanical circulatory support requires as strong an emotional support from the caregiver as CT does. Moreover, the caregiver must be technically savvy. Because mean survival is around 50% at 2 years, mechanical circulatory support for destination therapy may be viewed as an active form of palliative care. Except for CT that affects an infinitesimal fraction of the HF population, intervening before the LV remodeling process is underway may be the only rational approach to meaningfully impact life expectancy and quality in patients with HF. However, the dire lack of evidence-based medicine at the early stages of HF is the major barrier to a preventive approach. Another concern is the lack of a cost-effective and reliable method for identifying structural heart disease in stages A or B. The development of novel imaging techniques would help earlier identification and treatment of these patients and should reduce the healthcare expenditure on patients diagnosed in stages C and D who currently comprise the major proportion of the financial burden of HF.

Frequent hospitalization is part of the HF syndrome continuum, and despite extensive research initiatives, frequent hospitalization for HF will continue to occur and probably worsen, given our rapidly aging population. In spite of the mean hospital stay decreasing from 8.8 to 6.3 days during the past decade, rehospitalization rates remain unchanged, with the 30-day all-cause readmission rate approaching 25% (ie, 1 in 4 patients). Meanwhile, a worthy aim is to curtail the cost of hospitalizations for ADHF. The majority of patients who are hospitalized for ADHF receive intravenous loop diuretic therapy with daily determinations of hematologic and chemistry blood parameters. Although hospitalizations for ADHF require a modest manpower and minimal technical apparatus, they cost several thousands of dollars. Patients with ADHF and ICD could be treated at a significantly lower cost in specialized facilities that without the huge overhead of regular hospitals could be set up to accommodate ADHF patients.

CONCLUSION

HF is the final manifestation of many cardiovascular conditions. Current treatment of HF focuses on alleviating symptoms in the late stages of the process. Notwithstanding its inordinate cost, treatment of HF when the heart is severely damaged is arduous and of limited benefit. Switching focus to the early stages of the process with optimal management of risk factors for HF is the rational approach to meaningfully impact the final manifestation of many cardiovascular conditions.

REFERENCES


