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Advanced Heart Failure in Older Women with Heart Failure and Preserved Systolic Function

by

Bonita Louise Huiskes, RN, PhD(c)

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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by
Bonita Louise Huiskes, RN, FNP, PhD(c)

Dedication

But yield who will to their separation,
My object in living is to unite
My avocation and my vocation
As my two eyes make one in sight.
Only where love and need are one,
And the work is play for mortal stakes,
Is the deed ever really done
For Heaven and the future's sakes.

Two Tramps in Mud Time
Robert Frost

Soli Deo Gloria

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Advanced Heart Failure with Preserved Systolic Function in Older Women

Bonita L. Huiskes

Abstract

Heart failure with preserved systolic function (HFPSF) accounts for approximately half of all heart failure (HF) patients, a majority of whom are older women. Little is known about this HF subgroup since they have not been included in most HF clinical trials and other research studies. Moreover, the characteristics of those who have advanced disease have not been well described.

The primary aims of this dissertation were 1) to use a cross-sectional design to describe the characteristics of older women with advanced HFPSF and 2) to examine potential factors influencing their quality of life (QOL). The variables included were demographic, clinical, symptom, comfort, and functional capacity.

Sixty women (76 ± 7.7 years; 86.7% Caucasian) with New York Heart Association Class III HFPSF were recruited from two outpatient HF clinics. The women had high symptom prevalence (13.2 ± 6.4) and burden (2.1 ± 0.43 on a 0-4 scale), impaired functional capacity (mean 6-minute walk distance: 201.4 ± 117.1 meters) and multiple co-morbidities (4.65 ± 1.55). Co-morbid medical conditions associated with increased mortality and morbidity risk in HFPSF included pulmonary hypertension (76%), compromised renal function (73%), atrial fibrillation (66.7%), coronary artery disease (45%), and diabetes (40%).

Using a multiple linear regression model to control for disease severity, clinical status, and functional capacity, age ($p = .023$), comfort ($p = .002$) and symptom burden ($p = .001$) were significantly associated with QOL. The final overall model explained 66%

of the variance in QOL ($p < .001$). Age explained 4% of the variance ($p = 0.023$), total symptom burden explained 14% of the variance ($p = < .001$), and comfort explained 7% of the variance ($p = 0.002$) in QOL.

Interventions reducing symptom burden and enhancing comfort for older women with advanced HFPSF may result in improved QOL. Addressing factors germane to QOL is congruent with palliative care in advanced chronic illness, since QOL enhancement is a palliative care goal.

The unrecognized palliative need of advanced HFPSF patients, a group comprised largely of older women, must be addressed. This segment of our aging society deserves better quality in the last phase of their life journey.

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Chapter 1

Introduction

Heart failure (HF) is a unique chronic illness in many respects. One important distinguishing feature is the remarkable changes of the past two decades. No other chronic illness has seen such dramatic shifts in the understanding of the condition's pathophysiology, such rapid alteration in treatment paradigms and patient outcomes, and such promising growth in options for advanced stages. The nomenclature has also changed, from *congestive heart failure* to *heart failure* or *chronic heart failure* as effective options for managing (or preventing) volume overload and the resulting congestion-based symptoms have become commonplace.

Importantly, the changes have also brought an increase in the number of patients who survive to advanced stages of HF, and who live with considerable symptom burden. Little research attention has focused on the plight of those patients, and limited management direction for advanced and end-stage disease exists in published HF guidelines. As a clinician for more than a decade in an outpatient HF clinic, I observed and worked at alleviating the progressive suffering of patients with advanced HF. As I accompanied them, I came to understand that they required the same level of careful management for palliation as patients earlier in the disease trajectory needed for treatment of acute and chronic HF. But I looked in vain for guidance in an uncharted territory.

An Unaddressed Group with Palliative Care Need

One group of patients with heart failure is particularly challenging for clinicians. Patients with HF and a preserved (normal) ejection fraction (previously known as

diastolic heart failure), represent a growing percentage of the overall HF population; one-half of the patients in a large national registry of hospital discharges had HF with preserved systolic function (HFPSF) (Yancy et al., 2006). The challenge of managing these patients is largely due to the paucity of clinical trials addressing HFPSF and the relative absence of evidence-based management guidelines for this HF subgroup. Of note, older women with HFPSF are a largely invisible group, since women (and older persons of both genders) have not been included in HF clinical trials and since there has been a lack of research on HFPSF. Little is known about the characteristics of older women with disease progression to an advanced stage. Furthermore, no treatment direction exists, since symptomatic HFPSF has not been addressed in the limited discussions to date about palliation in advanced HF. The challenges clinicians (and their patients) face when the condition worsens are compounded by this dearth of knowledge concerning treatment.

Therefore, the purpose of this dissertation research was to describe the characteristics of a sample of community-dwelling older women with advanced (symptomatic) HFPSF. The specific aims of the cross-sectional study were to 1) describe the sociodemographic and clinical characteristics of older women with advanced HFPSF, 2) measure the functional capacity of the women, 3) describe the physical and emotional symptoms, comfort and quality of life (QOL) of older women with HFPSF and 4) identify sociodemographic, clinical, symptom, comfort and functional capacity factors associated with QOL in older women with HFPSF.

Background

The chronic illness of HF has considerable significance for healthcare because it is the only cardiovascular disease increasing in prevalence (Mather & Konstam, 2007). In the United States, HF prevalence is an estimated 5.7 million adults, with a direct and indirect cost of 37.2 billion dollars projected in 2009 (American Heart Association [AHA], 2009). Hospitalization is a significant driver of the cost (and societal burden) of HF, with more than 1 million inpatient stays/year in the United States (AHA, 2009).

Pharmacologic therapies for HF are well-established, with a strong evidence base developed over the past two decades. Device-based treatment of HF has gained a place in evidence-based guidelines more recently. Core medical management strategies for HF are clearly articulated in national guidelines and are applied regularly in clinical practice. As a result of the implementation of treatment advances, patients in the current era of HF care are less likely to die suddenly, and are more likely to live for extended periods with advanced (and often refractory) symptoms and reduced functional status (Stevenson, 2005; Teuteberg et al., 2006).

However, the body of evidence lacks guidance for clinicians who treat HF when disease progression brings patients to an advanced or end stage since palliation of the multiple symptoms of advanced HF has not been studied (Goodlin et al., 2004). The wide range of symptoms beyond the familiar dyspnea, fatigue and swelling requires treatment approaches that go beyond the familiar IV diuretics, opioids and intravenous inotropes. The expertise for managing a wide range of symptoms at end of life has been well-developed in palliative and hospice care for malignant disease; evidence-based treatment for the multiple symptoms in advanced HF are needed as well.

Little is known about how to best integrate a palliative approach and hospice into HF management at the end of life. Small studies and diverse approaches characterize current research, limiting conclusions about end-stage care design. Not surprisingly, the number of HF patients who receive hospice care is small, representing just 11.8% of persons receiving hospice care in 2007 (National Hospice and Palliative Care Organization [NHPCO], 2009). Since the number of patients in the United States with advanced, symptomatic HF is between 300,000 to 800,000 (Stevenson & Rose, 2003), the current knowledge gap around palliation has considerable import and must be addressed if the attendant personal suffering and societal burden are to be ameliorated.

In an earlier era of HF management, palliative care and hospice for advanced and end-stage disease would have been unnecessary. Now, the approaching tsunami of increasing numbers of adults with advanced and end-stage HF (with either reduced or preserved systolic function) in an aging population mandates attention.

Theoretical Framework

The *Chronic Illness Trajectory Theory* developed by Julie Corbin and Anselm Strauss (Corbin & Strauss, 1991) provides the theoretical framework for the dissertation. The concept that chronic conditions have a course (trajectory) which varies and changes over time is key to understanding the life impact and adaptive requirements of each phase of the chronic illness of HF. One of the nine identified chronic illness trajectory phases (Corbin & Strauss, 1991; Corbin, 1998), the downward phase, is characterized by greater patient disability and difficulty controlling symptoms, an apt description of advanced HF both in the more well-known systolic heart failure and in HFPSF.

Dissertation Chapters

Chapter 1 provides an introduction to the dissertation, presents the research questions, a brief background, the theoretical framework and an overview of the content of each chapter.

Chapter 2 is divided into two parts. Part 1 is a review of the literature concerning palliative and hospice care in advanced HF. Part 2 is a paper prepared for publication which traces the development of palliative care content in the major HF guidelines, from 1994 to the present. These documents, developed to promote evidence-based treatment of HF, have only recently begun to devote greater attention to the management of end-stage disease. Unfortunately, the attention to end-stage disease primarily concerns systolic HF, since so little is known about HFPSF treatment in any stage.

Chapter 3 presents the theoretical background for the dissertation. This chapter addresses an unintended consequence of the remarkable advances in the treatment of systolic HF – that of facing death twice. The treatment advances are the precursor of a new type of “comeback” phase in HF, and this development is analyzed within the context of Corbin and Strauss’ *Chronic Illness Trajectory Theory*. The absence of remarkable advances in the treatment of HFPSF and the inapplicability of a “comeback phase” for this subgroup are also noted.

Chapter 4 covers the methodology utilized in the dissertation research study of older women diagnosed with advanced HFPSF, including sample inclusion and exclusion criteria, methods of measurement, data analysis and human subject protection.

In Chapter 5, two papers prepared for publication report the findings of the cross-sectional research study on older women with advanced HFPSF. The first highlights the

unrecognized and unaddressed palliative need in this subgroup of HF patients, as evidenced by their multiple co-morbidities, symptom prevalence and burden, cardiac dysfunction despite medical treatment, limited functional capacity and high morbidity and mortality risk. In the second paper, the results of a multiple linear regression analysis of factors associated with QOL in the group of older women with HFPSF are analyzed within the context of what is currently known about QOL in HF.

Chapter 6 summarizes the findings of the research study on older women with advanced HFPSF. The chapter concludes with implications for clinical practice and health policy development, as well as recommendations for future research direction.

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ADHERE Scientific Advisory Committee and Investigators. (2006). Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: A report from the Acute Decompensated Heart Failure National Registry (ADHERE) database. *Journal of the American College of Cardiology*, 47, 76-84.

Chapter 2 Part 1

Introduction

The treatment of heart failure (HF) has undergone tremendous change over the past two decades, as pharmacologic and device therapies have altered the natural history of the syndrome. The nomenclature has also changed, from *congestive heart failure* to the more frequently-used *heart failure* (HF) or *chronic heart failure*, as effective options for managing volume overload and the resulting congestion-based symptoms are now commonplace.

Although significant strides have been made in the management of acute and chronic HF, little is known about the care of advanced HF patients, and no national guidelines exist to guide treatment of end-stage disease. Prior to the present era of HF management, consideration of palliative care and hospice for advanced and end-stage HF would have been unnecessary, as patients usually died suddenly as the disease progressed, and few lived with refractory Class IV symptoms (Stevenson, 2005). Currently, HF patients may live for months or years with advanced symptoms and reduced functional status, as medical therapies are adjusted and other cardiac interventions are performed (Teuteberg et al., 2006).

Palliation of advanced HF symptoms has not been studied (Goodlin et al., 2004). As the prevalence of HF approaches 6 million (AHA, 2009), addressing the significant societal responsibility for the increasing numbers of patients with advanced and end-stage disease is critical. Developing evidence-based interventions and providing comfort for the individual suffering represented in the significant symptom burden of advanced HF is

also imperative. In addition, reducing the personal and societal cost of unnecessary (and often ineffective) treatment for this condition at end of life requires widespread attention.

The focus of this two-part literature review is palliative and hospice care for patients with advanced HF. Part 1 of the review begins with a definition of HF and a summary of HF pathophysiology, followed by an overview of advanced HF. The particular case of patients with advanced and end-stage heart failure with preserved systolic function (HFPSF), previously known as diastolic HF, is addressed, as even less is known about palliative needs in this population. Next, the literature review covers therapeutic options for advanced HF, the challenge of establishing prognosis, symptoms at end-stage, palliative care and hospice for HF, and the integration of palliative and hospice care into standard care for HF. The conclusion provides a summary of what is known about palliative care and hospice in HF, the areas of knowledge which have had some research development, and the current gaps in the literature. Part 2 extends the literature review with a specific focus, that of end-of-life content in the major HF guidelines. The relative absence of content concerning HFPSF palliative needs in the majority of those documents is noted as well.

Heart Failure

HF is defined as a complex clinical syndrome resulting from a range of cardiac disorders and characterized by limitation in the ability of the ventricle to fill with or eject blood (Hunt et al., 2005). The chronic illness of HF has an estimated prevalence of 5.7 million persons in the United States and is the diagnosis for more than a million hospital discharges per year. The direct and indirect cost of HF is projected to be 37.2 billion in 2009 (AHA, 2009).

Heart Failure Pathophysiology

Heart failure was once thought to be a fairly straightforward problem, but it is now understood to be a complex clinical syndrome (Francis, 2001), usually preceded by an initiating cardiovascular event (Piano, 2004). Early disease models posited that HF resulted from abnormalities of renal blood flow which caused salt and water retention (the cardiorenal model) and, in a subsequent conception, that a reduced cardiac output and excessive peripheral vasoconstriction (the hemodynamic model) were associated with HF (Mann & Bristow, 2005). In the late 1980s and early 1990s, the neurohormonal model developed, as data from both experimental models and clinical trials provided evidence that angiotensin converting enzyme inhibitors and beta-adrenergic blockers might effect the biology of the failing heart and prevent or reverse the progression of cardiac dysfunction (Mann & Bristow, 2005). More recently, the notion of a biomechanical model extends the concept of a neurohormonal model, asserting that “heart failure develops and progresses as a result of the deleterious changes in cardiac function and cardiac remodeling that occur as a result of sustained neurohormonal activation” (Mann & Bristow, 2005, p. 2844). Current pathophysiologic understanding of HF also includes the cardiorenal syndrome, a term describing the mechanisms of the interdependence of the heart and kidney in HF (Obialo, 2007; Rea & Dunlap, 2008).

Cardiac remodeling, a hallmark of HF (Kaye, Hoshijima, & Chien, 2008), refers to the multiple adaptive alterations within the myocardium (Mann & Bristow, 2005) and includes molecular, cellular, biochemical and structural changes (Birks et al., 2006). Pathophysiologic processes contributing to remodeling of the ventricle include the loss of myocytes from necrosis or apoptosis (cell death), alteration in the geometry of the heart

(e.g. cell hypertrophy and development of a spherical cardiac shape), myocardial fibrosis, and reduction in myocardial contractility (Kaye et al., 2008).

While medical and device therapy for HF have significantly impacted the processes of left ventricular (LV) remodeling, the biomechanical model “predicts that at some point HF will progress independently of the neurohormonal status of the patient” (Mann & Bristow, 2005, p. 2844). One contributing factor may be that fibrotic changes in the myocardium have not been shown to be completely reversible. In addition, once the adverse changes of cardiac remodeling are well-advanced, they become self-sustaining and are able to maintain disease progression independent of neurohormonal status (Mann & Bristow, 2005). Disease progression eventually results in advanced and end-stage HF.

Advanced Heart Failure

Advanced HF, defined as the presence of persistent symptoms limiting daily life despite optimized, evidence-based medical therapy, is an important subset of the syndrome of HF (Adams & Zannad, 1998), numbering approximately 300,000-800,000 patients in the United States (Stevenson & Rose, 2003). Patients with advanced disease are described functionally as New York Heart Association Class III (symptomatic with less than ordinary activity) or Class IV (symptomatic with any activity, and may be symptomatic at rest) (Goldman, 2000). The American College of Cardiology/American Heart Association (ACC/AHA) (Hunt et al., 2005) guideline classification places these patients in Stage D, a designation for patients with refractory HF who have marked symptoms at rest despite maximal medical therapy. Stage D patients may be eligible for specialized, advanced treatment strategies or may be appropriately referred for end-of-life

care (Hunt et al., 2005), as they have an expected one-year mortality in the range of 30-50% (Stevenson, 2005). The somewhat arbitrary distinction between the advanced HF terminology of *refractory* and *end-stage* lies in the degree of reversibility which may be present in a *refractory* condition but not in *end-stage* (Metra et al., 2007).

Patients with advanced disease are frequently hospitalized for decompensated HF, and many require assistance with activities of daily living (ADLs) (Goodlin et al., 2004). Despite the high symptom burden and high mortality, little is known about how to manage the symptoms of advanced HF, about how to design care processes to meet patients' needs, or about the experience of HF patients as they approach the end of life.

Clinical management of advanced HF presents several challenges. When compared to patients with milder limitations in an outpatient prospective cohort study, those with advanced HF had greater variability in health status, suggesting a need for frequent clinical follow-up (Hauptman et al., 2004). Although data from randomized clinical trials (RCTs) and information from published guidelines address the care of patients with advanced HF, many questions remain unanswered, such as whether to use certain therapies or how to use them in particular patients. In addition, researchers have not included measures addressing symptoms and quality of life in clinical trials, two critical endpoints as patients become older and more compromised. Since patients must evaluate therapies that offer both substantial benefit and significant risks (Shah & Stevenson, 2004), the need for more data about the quality of life impact of the therapies is all the more urgent.

Advanced and End-Stage Heart Failure with Preserved Systolic Function

An estimated 20-60% of HF patients have normal (or near normal) left ventricular ejection fraction (LVEF) (Hunt et al., 2005). This type of HF, once known as diastolic HF, is now more commonly referred to as HF with preserved systolic function (HFPSF). Patients with HFPSF are older, more likely to be women, have high rates of hospitalization and similar, or slightly lower, mortality when compared to those with systolic dysfunction (Lenzen et al., 2004).

Half of patients reviewed in a large national study of hospitalizations for decompensated HF had preserved systolic function (PSF); nearly two-thirds of the group with PSF had a prior history of HF. Compared to those with systolic HF, patients with HFPSF had lower in-hospital mortality, were more likely to be older, female, hypertensive, have atrial fibrillation and lower extremity edema, and less likely to be receiving standard HF therapies. Similarities between the two groups indicating the presence of advanced disease included the level of renal impairment, presence of dyspnea at rest (34%), and frequency of hospital discharge with mild-moderately symptomatic HF (Yancy et al., 2006).

Overall patient management, unlike that for systolic HF, lacks an evidence base and comprehensive national guidelines. Two recent large randomized clinical trials of angiotensin receptor blockers failed to show a mortality advantage with treatment (Massie et al., 2008; Yusuf et al., 2003). The very recent (2008) addition of *diastolic heart failure* as a separate U.S. National Library of Medicine MeSH subject heading is evidence of the emergent state of research on the topic.

The relative lack of information concerning HFPSF extends to advanced and end-stage disease, as a computerized search of the PubMed and CINAHL data bases using the terms *diastolic heart failure* and *palliative care* returned no entries. Guidelines for referral to hospice apply to patients with systolic dysfunction only (Stuart, 2007), and recommendations for integrating palliative care into HF care excluded HFPSF due to prognostic uncertainty regarding this patient group (Hauptman & Havranek, 2005). Moreover, many advanced therapeutic options do not apply to those with HFPSF, as they include the criterion of a reduced ejection fraction. In general, advanced therapies have been developed for advanced systolic HF.

Advanced Therapies in Advanced Heart Failure

Several options exist for patients who continue to experience HF symptoms despite maximal evidence-based therapy. Advanced therapies range from the minimally invasive treatment of continuous intravenous (IV) inotrope infusions, to more invasive device therapies (biventricular pacemakers and implantable defibrillators), to left ventricular assist devices and, lastly, to cardiac transplantation. Each is described in the following section.

Chronic Inotropic Therapy

The IV administration of a positive inotropic agent on an intermittent or continuous basis is a treatment option for symptomatic advanced HF. Commonly used IV inotropic drugs (dopamine, dobutamine and milrinone) increase the concentration of intracellular cyclic adenosine monophosphate (c-AMP), either by augmenting its synthesis (beta-adrenergic agonists) or inhibiting its degradation (phosphodiesterase [PDE] inhibitors) (Rapezzi, Bracchetti, Branzi, & Magnani, 2000). These agents, long

used in the treatment of decompensated HF, enhance cardiac contractility and produce short-term improvement in hemodynamic parameters and cardiac output (Fonarow, 2002). Intermittent outpatient infusions of dobutamine appeared promising in the 1970s and early 1980s (Levine, 2000) as an option for patients with advanced HF, but concerns about associated high mortality (Applefeld et al., 1987; Krell et al., 1986) limited widespread acceptance of the treatment. Current AHA/ACC guidelines do not support intermittent inotropic infusions in any setting (Hunt et al., 2005).

Few research studies have addressed IV inotrope infusions in patients with end-stage HF; five small heterogeneous studies since 2000 provide limited data about the therapy. These five studies will be briefly reviewed.

In the first, the only study employing continuous infusions at home, Hershberger and colleagues (2003) followed inotrope-dependent HF patients ($n=36$, mean age 55.4 ± 9.5) discharged from the hospital between 1993 and 2001. In this descriptive study, the median duration of continuous outpatient support with inotropes (COSI) was 3.4 months (mean 4.7 ± 5.6) with a range of 0.2-26.3 months. The majority of patients (20; 55.6%) died at home, most often from worsening HF (28; 80%), with only 5 (14%) experiencing sudden death. (One patient was not included in the analysis due to aortic valve replacement.) Of note, home health agencies delivered the care as hospice providers were unwilling to take inotrope-dependent patients.

In another small study ($n=73$, 69 ± 12 years) of inotropes in end-stage HF, Lopez-Candales and colleagues (2004) provided a retrospective review of their experience with intermittent outpatient infusions over a 49-month period. Nearly half of the patients (35; 48%) met hospice criteria, but were offered (and accepted) the

alternative of inotrope infusions instead. More than half (44; 61%) were discharged from the infusion program due to significant symptomatic improvement. Eighteen patients (25%) died, seven of whom required hospice or palliative care. Lopez-Candales included a group of 29 patients in this retrospective review from a previously reported clinical trial (2002) in which participants were randomized to receive intermittent infusions of dobutamine, milrinone or placebo. During the trial, multiple cross-over assignments among groups occurred. One dobutamine patient was moved to the milrinone group, one milrinone patient entered the placebo group, four placebo patients were crossed-over to dobutamine, and two placebo patients were crossed over to milrinone. Symptomatic and functional improvements were noted in the patients in the two inotrope groups when compared to the placebo group in the 2002 trial, which was industry-supported.

Researchers conducting two small studies in Greece (Nanas et al., 2001; Nanas et al., 2004) combined oral amiodarone administration with dobutamine infusions, with the intent of ameliorating the proarrhythmic effect of dobutamine. The 2001 clinical trial assigned the first 11 refractory HF patients (53 ± 10.8 years; all males) to intermittent dobutamine infusions (Group 1) and the second 11 patients (52 ± 11.5 years; all males) to intermittent dobutamine infusions and daily oral amiodarone (Group 2). While the dobutamine dose was identical for both groups and there were no baseline demographic or clinical differences, the frequency and length of infusions varied considerably between them (Group 1 – every 16 days for 12-48 hours; Group 2 – every 7 days for 8 hours). At 12 months, only one patient was alive in Group 1, while 6 were alive in Group 2. Small sample sizes and differences in infusion schedules limit the reviewer's ability to draw

conclusions about the striking difference in mortality between the groups, as well about the role of amiodarone for patients receiving dobutamine infusions.

In the second study reported by Nanas et al. (2004), 30 patients were randomized to receive dobutamine infusions ($n = 16$; 64 ± 9.9 years) or placebo ($n = 14$; 61 ± 8.2 years); all received daily oral amiodarone (400 mg), initiated 2 weeks before randomization. Patients with an ICD in place (number of patients not provided) were given twice the dose of amiodarone (800 mg). Biweekly infusions for both groups continued until 4 patients (at separate timepoints) from the placebo group crossed over to dobutamine infusions due to clinical deterioration; likewise, therapy for 4 patients (at separate timepoints) with clinical deterioration in the dobutamine group was intensified to weekly infusions. The one-year survival rate for patients in the dobutamine group was 69% and 28% for those in the placebo infusion group.

Articulating a summary of findings across the five reviewed studies or meaningful comparisons among them is limited by the two diverse approaches (intermittent infusions in 4, continuous infusions in 1) and varying sample ages, with younger patients (55.4 ± 9.5 – Hersherberger et al.; 53 ± 10.8 and 52 ± 11.5 - Nanas et al. 2001) in two of the studies and older patients (64 ± 9.9 years and 61 ± 8.2 – Nanas et al. 2004; 69 ± 12 years – Lopez-Canales) in the others. Additionally, the samples appear to differ among the studies in the degree of true inotrope dependency. In some studies patients could be weaned from inotropes, and in others some participants experienced a level of functional improvement which allowed discharge from the infusion program. Patients in the Hersherberger et al. study, however, were defined by their inability to wean from inotropes despite the efforts of experienced providers.

Important design concerns in the Nanas et al. 2001 clinical trial were the non-randomization of groups and the difference between the two groups in frequency and length of infusions. Methodological issues in the second Nanas et al. study (2004) included the crossover from placebo to treatment groups, intensification of therapy for some subjects in the treatment group, absence of data concerning the number of patients with ICDs, higher amiodarone dosage for the ICD patients, and lack of discussion (and data) concerning the impact of the ICDs on mode of death. The earlier Lopez-Candales et al. (2002) study was not well-conducted, with multiple cross-overs among the three infusion groups, rendering meaningful comparison of the outcomes among treatment and placebo groups impossible. Inclusion of those study data in the Lopez-Candales et al. 2004 retrospective review of 73 infusion patients precludes confidence in the validity of those findings as well.

Sample sizes were small in all five of the studies, an issue of particular concern in those that compared the treatment effect between two groups, as they lack adequate power to detect differences in outcomes between them. These study findings do not provide evidence to support inotrope infusions as a treatment strategy in advanced and end-stage HF. However, they do raise awareness of the palliative need for symptomatic relief and highlight the inherent challenges in inotrope infusions therapy, such as limited hospice support and the trade-off between symptom control and increased mortality.

The only large study ($n=331$, 69.1 ± 11.3 years) of palliative inotropes in advanced HF was a retrospective review of the mortality impact and cost of the therapy in a 17-state Medicare region from 1995 to 2002 (Hauptman et al., 2006). The majority of the infusions were continuous (89.7%), with the remainder (10.3%) receiving intermittent

inotropes. Hospitalizations declined following inotrope initiation at three time points: 30, 60, and 180 days; however, mortality was high at 6 and 12 months (42.6% and 56.8% respectively). Despite limitations common to retrospective reviews (no researcher control over study design, missing or incomplete data), this study's findings provide supportive evidence for the symptomatic relief inotropes provide (inferred from declining number of hospitalizations) in advanced HF as well as for the high mortality associated with inotrope infusions.

Although the AHA/ACC Practice Guidelines (Hunt et al., 2005) strongly discourage the use of intermittent inotrope infusions, they do support consideration of the palliative use of continuous inotrope infusions in patients with refractory end-stage HF. This treatment strategy is particularly warranted as an element of an overall plan focused on patient comfort in a home setting. Hospice use is limited, however, by three factors: individual program philosophies excluding invasive procedures, cost considerations (e.g., drugs, supplies), and hospice staff unfamiliarity with inotrope infusions (Rich & Shore, 2003).

Inotropes as "Bridge" Therapy

Inotropes are also used as "bridge" therapy, supporting patients until further advanced therapies can be applied. Continuous infusion at home is an option for patients awaiting cardiac transplantation, usually with an implantable defibrillator in place (Stevenson, 2003). According to Stevenson (2004), continuous inotropic therapy is increasingly utilized for patients who survive to develop refractory symptoms and end-stage failure. This trend is illustrated by the overwhelming majority (71%) of the 129 patients randomized to left ventricular assist device (LVAD) or optimal medical

management in the REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure) trial who required continuous inotropic therapy (Rose et al., 2001).

Cardiac Resynchronization Therapy

Patients with HF may develop delays in the cardiac conduction system propagation of the electrical impulse between the atria and the ventricles and delays between the ventricles. Electrical impulse delay between the ventricles results in a mechanical delay between the contraction of the left and right ventricles. The resulting dyssynchrony leads to worsening ventricular function (Gura & Foreman, 2004) and worsening HF. For a predicted 15-20% of patients with advanced HF and reduced LVEF, cardiac resynchronization therapy (CRT) can improve clinical status (Stevenson, 2003). Current selection criteria for CRT include severe HF (New York Heart Association functional class III or IV), left ventricular ejection fraction <35%, and a wide (> 120 ms) QRS complex (Epstein et al., 2008).

CRT is the electrical activation of the right and left ventricles in a synchronized manner with a biventricular pacemaker (Hunt et al., 2005). In patients with advanced and end-stage HF (NYHA Class III-IV), CRT has been shown to prevent (or defer) the need for cardiac transplantation (Greenberg et al., 2003; Vanderheyden et al., 2006), decrease the risk of death or hospitalization (Bristow et al., 2004), improve functional capacity (De Marco et al., 2008; Higgins et al., 2003; Molhoek et al., 2002; Vanderheyden et al., 2006), improve quality of life, reduce HF hospitalizations, improve left ventricular ejection fraction (Molhoek et al., 2002), and allow weaning from inotropic support with subsequent hospital discharge (Cowburn, Patel, Jolliffe, Wald, & Parker, 2005).

Unresolved issues regarding the application of CRT in advanced HF include the value of the therapy when the QRS complex is normal (Bax et al., 2005b); when a right bundle branch block (RBBB) type of conduction delay exists; if atrial fibrillation has developed (McAlister et al., 2007); or when combining CRT therapy with an ICD (Bax et al., 2005b; Lehmann & Aaronson, 2006). Long-term term effects of CRT are not known (Hunt et al., 2005), and greater understanding of the differences between CRT responders and the 20-30% who are non-responders is needed (Bax et al., 2005a). In addition, the CRT implantation procedure is not without potential complications, including lead dislodgement, coronary sinus dissection, phrenic nerve stimulation (Bax et al., 2005b), infection, and device malfunction.

Left Ventricular Assist Devices

Left ventricular assist devices (LVADs) provide hemodynamic circulatory support. Some have short-term application in acute states (myocardial infarction, myocarditis, open heart surgery); others are designed for longer-term use, most commonly to augment left ventricular function. These mechanical devices are surgically placed in the left upper quadrant of the abdomen, have a tunneled driveline site which exits on the right side of the abdomen and connects either to a console at the bedside or to a battery pack worn in a vest. Devices are of two main types: pulsatile and the smaller continuous flow device (Stahovich, Chillcott, & Dembitsky, 2007; Stevenson & Shekar, 2005).

Left ventricular assist devices (LVADs) are an option for patients who require mechanical circulatory support while awaiting heart transplantation (Rogers et al., 2007), permitting survival until a suitable donor heart is found (Miller et al., 2007). This “bridge

to transplant” LVAD role differs from that of implantation as “destination therapy” (DT) for patients who do not meet transplant criteria, since DT is a permanent alternative to cardiac transplant (Lietz et al., 2007). A third LVAD role, that of “bridge to recovery,” appears promising, as myocardial function improves with the mechanical support of the LVAD (Stevenson & Rose, 2003), but experience to date involves only small numbers of patients (Birks et al., 2006; Simon et al., 2005). “Bridge to transplant eligibility,” is an emerging LVAD role, as reversal of secondary organ dysfunction, pulmonary hypertension, or other clinical improvement attributable to mechanical circulatory support changes patients’ potential for inclusion on transplant waiting lists (Hunt, 2007; Rogers et al., 2007).

The Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure (REMATCH) trial established the superiority of LVAD destination therapy over medical therapy for end-stage, transplant-ineligible HF patients (Rose et al., 2001); one-year survival in the device group was 52% but only 25% in the control group (medical therapy). In a subsequent (2002-2005) follow-up of 280 device patients enrolled in the US Destination Therapy Registry, survival was 56% at one year (Lietz et al., 2007).

While survival results are encouraging, this therapeutic option for advanced HF must be weighed along with its significant associated morbidity, including complications of bleeding, thromboembolic events, infection and device failure (Delgado & Radovancevic, 2007). Other important factors which must be considered are the cost of the therapy, the relatively small target population (currently estimated at 5,000-10,000 patients), and the societal challenge of providing equitable access to this technology

(Stevenson & Rose, 2003). In addition, timing of implantation for compromised HF patients is challenging, as judging the point at which survival benefit would be greatest and surgical risk lowest has high importance (Lietz et al., 2007). Lastly, this treatment option is available only at specialized centers, requires careful follow-up and intense patient education in self-management, and engenders a requirement for careful end-of-life planning (Stahovich et al., 2007).

Destination therapy becomes end-of-life therapy if reverse remodeling does not occur, raising complex ethical issues around deactivation or the less-likely option of device explantation (Dudzinski, 2006). While the ethical principle that withdrawal of a mechanical device providing life support is ethically equivalent to withholding the therapy is well established (Rubenfeld, 2004), LVAD withdrawal presents a special case. Disabling an LVAD results in disruption of the heart's contractility (the device is cannulated to the apex), regurgitant blood flow in and out of the device, and the potential for pooling in the device with thrombus formation. Unlike permitting death by withdrawing a ventilator, disabling an LVAD appears to contribute causally to the death (Bramstedt & Wenger, 2001). Thus, advance care planning with informed decision making is an essential preparatory component of destination therapy initiation (Dudzinski, 2006).

Cardiac Transplantation

Cardiac transplantation, the only established surgical approach for HF refractory to standard treatment, is limited by the supply of donor hearts (Hunt et al., 2005). In 2005, only 2126 cardiac transplants were performed in the United States (2006 OPTN/SRTR

Annual Report), a small number when compared to the estimated 100,000 refractory HF patients who might meet criteria for transplant (Stevenson & Rose, 2003).

Cardiac transplantation, though life-saving and life-prolonging, is not without significant challenges. A number of relative (i.e. diabetes in poor control) and absolute (i.e. fixed pulmonary hypertension) contraindications limit the field of potential candidates (Mehra et al., 2006). For patients who are listed, waiting times are often lengthy, with a median of 130 days time to transplant in 2005 (2006 OPTN/SRTR Annual Report). Waiting times vary by blood type, with Type O patients experiencing the longest number of days to transplant according to Scandinavian (Rexius, Nilsson, & Jeppsson, 2002), United Kingdom (Hussey, Parameshwar, Banner et al., 2007) and United States (Bove et al., 2006) reports.

Post-transplant, recipients may experience the complications of perioperative graft failure, infection and rejection during the first post transplant year, and allograft vasculopathy and various malignancies in later years (Kirklin, Pambukian, McGiffin, & Benza, 2004). In addition, patients must be vigilant for the remainder of their lives about medication adherence and other aspects of self-care; careful monitoring and follow-up in specialized transplant centers is likewise essential.

Survival rates after transplantation have increased over the past two decades as a result of improved patient selection, surgical techniques, organ preservation and postoperative management (Leibundgut & Brunner-La Rocca, 2007). One-year survival is 88%, and five-year survival is 74% (2006 OPTN/SRTR Annual Report). However, for the more stable Status 2 candidates on standard medical therapy, one-year survival (89.4%) now approximates the one-year outcome of cardiac transplant patients, raising

questions about whether early listing of Status 2 patients is justified (Lietz & Miller, 2007). As treatment advances continue to improve the health status of candidates awaiting transplant, and as other end-stage options become available, the role of transplant (of a limited number of donor hearts) in advanced HF is likely to continue to undergo evaluation.

Implantable Cardioverter Defibrillators

Implantable cardioverter defibrillators (ICDs) are indicated for the primary and secondary prevention of ventricular arrhythmias and sudden cardiac death (SCD) in patients with HF and reduced LVEF, since they are at high risk for those events (Whang et al., 2004). Data from two large clinical trials (Bardy et al., 2005; Moss et al., 2002) established that ICDs provide a mortality benefit for HF patients with reduced LVEF who meet implantation criteria .

Although ICD implantation is not indicated for HF patients with refractory Stage D symptoms (Hunt et al., 2005) unless they are awaiting cardiac transplant (Epstein et al., 2008), Nazarian et al. (2005) found that 21% of the 438 patients hospitalized for advanced HF already had an ICD present on admission, and 37% of the 160 HF deaths reviewed by Teuteberg et al. (2006) were in patients with ICDs. As HF prevalence grows and evidence-based guidelines for management increasingly inform treatment decisions, many more patients are likely to have ICDs implanted. As the number of HF patients with ICDs increases, fewer of them are likely to die suddenly, thus increasing the number who will survive to die of progressive HF (Stevenson & Desai, 2006).

As a result of this altered trajectory, the issue of device deactivation assumes greater salience as greater numbers of HF patients approach end of life with an ICD in

place. Anecdotal reports (Stein, 2006), case studies (Nambisan & Chao, 2004) and research data (Goldstein, Lampert, Bradley, Lynn, & Krumholz, 2004) describe significant patient and family distress when repeated shocks from an ICD accompany the dying process. The Goldstein et al. (2004) retrospective cohort study of 100 family members of ICD patients who died is the only larger-scale investigation of the end-of-life experience with the device. However, the phone surveys took place up to 4.6 years after the death (median 2.3 years), limiting the reliability of recall for the older aged (median 76.2 years; range 49-91) next of kin. Despite that limitation, the findings serve to highlight the considerable impact of provider inattention to an important source of actual and potential suffering at end of life.

A number of factors contribute to this disturbing scenario in end-stage disease. These include the following: 1) lack of patient understanding regarding the risks as well as benefits of ICDs (Stevenson & Desai, 2006), 2) infrequent discussions with health care providers about the option of deactivation, even when patients are near death (Goldstein et al., 2004), 3) historical lack of direction from national guidelines for healthcare providers (Sears et al., 2006), 4) patient and family misperception that the device provides life support and that disabling it will result in immediate death (Stevenson & Desai, 2006), 5) lack of clear understanding that deactivation is consistent with the established ethical principle and legal right of treatment withdrawal (Braun, Hagen, Hatfield, & Wyse, 1999; Mueller, Hook, & Hayes, 2003), and 6) lack of ICD deactivation information in standard advance directive forms (Berger, Gorski, & Cohen, 2006; Goldstein et al., 2004). Thus, the issue is less likely to be addressed by patients, families and providers.

Two recent qualitative studies, one of physician barriers to ICD deactivation (Goldstein, Mehta, Teitelbaum, Bradley, & Morrison, 2008) and the other examining patients' attitudes (Goldstein, Mehta, Siddiqui, Teitelbaum, Zeidman, Singson, et al., 2008), add to the limited knowledge base concerning this highly-charged subject. In the first study, Goldstein and colleagues used grounded theory methodology to conduct individual open-ended interviews with twelve physicians (4 electrophysiologists, 4 cardiologists, and 4 generalists [internists and geriatricians]). Nearly all of the physicians agreed that conversations about ICD deactivation should occur but indicated that they found the concept of deactivation conversations with patients challenging and rarely had them. Reasons for the avoidance included aspects of the ICD itself, which made the device inherently different from other treatment modalities. ICDs were seen as life-saving devices, internal and thus easy to overlook; turning off an ICD was seen as a stark finality, one which turned off hope as well.

In the second qualitative study, fifteen patients with ICDs were stratified to 3 focus groups based on the length of time since device implantation and whether or not they had received a shock. During the facilitated discussions, no patients recalled discussing deactivation with their physicians, and none were aware of this ICD option. Misunderstandings about the role the ICD played in their health and the reasons for device implantation were common. Participants were not open to discussing possible future scenarios when they might consider deactivation (which one participant described as an act of suicide), preferring to leave such decisions to their physicians. They appeared to have complex relationships with their ICDs, describing them only in beneficial terms.

These two qualitative studies provide examples of 1) carefully designed qualitative research with clear descriptions of the methodology and presentation of the findings and 2) the value of interpretive research in important, but relatively unstudied, aspects of medical care. The work of Goldstein et al. contributes significantly to our very limited understanding of the complex issues surrounding provider and patient conceptions of device deactivation.

Establishing Prognosis in Advanced Heart Failure

The determination of prognosis in HF is the estimation of the nature and length of the chronic illness trajectory, based on studies of the effect of identified factors (or combination of factors) and development of predictive models in specified population subsets over a particular period of time. In advanced and end-stage HF, prognosis estimation concerns the length, character and slope of the downward trajectory phase of this progressive chronic illness. Mortality and the inverse, survival, are closely related concepts, as prognosis is concerned with predicting their likelihood.

Prognostic information is important for providers in selecting and advising appropriate candidates for advanced therapies as well as for considering referral to hospice (Goodlin et al., 2004) and palliative care (Fonarow, 2008). And while national HF guidelines, from the earliest (Konstam, Dracup, Baker et al., 1994) to the most recent (Adams et al., 2006; Hunt et al., 2005) recommend that clinicians discuss prognosis with patients and families, such conversations require reliable prognostic information.

For many reasons, currently available empirical data about prognosis is of limited utility when applied to individual advanced HF patients in the clinical setting (Frankel et al., 2006; Lehman, 2006b). Estimates of HF prognosis continue to change, in part due to

the considerable impact of pharmaceuticals and devices on the syndrome's natural history.

As a result of advances in medical therapy, some cardiomyopathy patients recover normal ventricular function (Binkley et al., 2008). But the treatment advances also mean that patients in the current era (Teuteberg et al., 2006) are less likely to die suddenly and more likely to survive for extended periods with advanced symptoms, with at least one hospitalization in the 6 months prior to death. For some who reach an advanced disease stage, however, remarkable improvement with resynchronization therapy or dramatic rescue with an LVAD or cardiac transplantation can reconfigure the expected short-term trajectory, with new possibilities for longer-term stability. Thus, treatment advances limit our confidence in the contemporary applicability of prognostic estimates derived from previous eras of HF therapy to current patients, including those reaching advanced stages.

Moreover, considerable heterogeneity exists in the multiple sources for HF prognostic information, adding to the interpretive complexity. Major inputs for the derivation of prognostic indicators and models include community-based studies of HF patients (Cowie et al., 2000; Goldberg, Ciampa, Lessard, Meyer, & Spencer, 2007; Jong, Vowinckel, Liu, Gong, & Tu, 2002; Lee et al., 2003; Mosterd et al., 2001), follow-up of patients hospitalized for HF, data from large interventional HF clinical trials, and studies of patients referred for cardiac transplantation.

Hospitalization for HF has strong negative prognostic significance and has been researched extensively as a predictor of mortality. Retrospective study samples vary in size, from 282 elderly patients (Huynh, Rovner, & Rich, 2006), to moderate-sized groups of 2445 (Goldberg et al., 2007) and 4031 (Lee et al., 2003) and larger groups of more

than 14,000 (Setoguchi, Stevenson, & Schneeweiss, 2007) and nearly 39,000 (Jong et al., 2002) community-based patients.

Solomon et al. (2007) assessed the influence of nonfatal HF hospitalization on subsequent mortality in a substudy of a large clinical trial ($n = 7599$) of a new pharmacologic agent. The 1455 (19% of the parent study sample) patients with a hospitalization for HF had an estimated hazard for all-cause mortality of 3.15 times that of those not hospitalized for HF (95% CI 2.83-3.50). This study also illustrates both the benefit and limitations of a subanalysis of an existing data set from a clinical trial. In terms of benefit, the availability of a data set of considerable size, including HF with reduced EF and HFPSF patients, provided the opportunity for an inquiry such as the one reported here, which adds to our understanding of the prognostic importance of HF hospitalization in both groups. However, subanalysis limitations include a restriction to variables included in the original study; the inability to update co-morbidity data (such as the development of diabetes) over the course of an extended clinical trial (clinical characteristics were available only as baseline data); the unknown impact of a proprietary sponsor; and the potential for variation in the sample selection, treatment of patients, and data collection in multiple locations (618 sites in 26 countries in the parent trial) (Solomon et al., 2007).

Findings in this substudy and the other studies listed above underscore the vulnerability of the early discharge period (Solomon et al., 2007) and the mortality import of repeated hospitalizations (Setoguchi et al., 2007). The findings also highlight the independent predictive role of multiple other factors, including advancing age, presence of comorbidities, and elevated serum urea nitrogen levels during hospitalization.

The Heart Failure Survival Score (HFSS), a risk stratification tool developed to predict survival in patients referred for cardiac transplant (Aaronson et al., 1997), uses seven clinical characteristics (including peak oxygen consumption) in a multivariable model to compare survival estimates with outcomes from cardiac transplantation (Koelling, Joseph, & Aaronson, 2004). Koelling et al (2004) addressed contemporary application of the tool in patients treated with beta blockers and found that the HFSS provided effective risk stratification in evaluation for transplant. Constraints to utility include the limited availability of metabolic exercise testing (Frankel et al., 2006) and inconsistent predictive accuracy across validation data sets (Levy et al., 2006).

The Seattle Heart Failure Model (SHFM) (Levy et al., 2006) yields a risk score using 24 clinical, pharmacological, device, and laboratory characteristics to predict 1-, 2- and 3-year survival. The SHFM was developed from a HF clinical trial data base (n = 1125) from the early 1990s and validated in 5 other cohorts (3 - clinical trials, 2 - general population; total n = 9942) in the subsequent decade. Not surprisingly, beta blocker use varied from non-existent in the first cohort to 72% in the most recent patient group. As in other data bases largely derived from clinical trials, the patients were younger (mean age 63 years) and predominantly male (range 69%-80%). However, the development and validation of the model of clinical and laboratory variables, HF medications, and devices in a large number of patients from 6 cohorts establishes a foundation for confidence in its prognostic ability. The study finding of an overall receiver operating characteristic area under the curve of 0.729 (95% CI, 0.714 – 0.744) provides strong support for the utility of the SHFM.

Recently, May et al. (2007) validated the SHFM in a non-clinical trial hospital cohort of HF patients (n = 4077; 67 [range 19-96] years; 61.4% male) undergoing angiography, finding similar 1-year area under the curve of 0.70 (95% CI 0.68-0.72), with increased predictive ability (+ 0.05) when BNP levels were added to the model. Further validation in older, more representative (particularly with respect to gender) HF patient samples would add greatly to the utility of this promising model in community-based settings.

A separate body of literature addresses the prognostic role of psychosocial factors, which have received comparatively little attention in clinical practice despite their demonstrated predictive ability in HF patients (Moser, 2002). Researchers have demonstrated that reduced quality of life (Konstam et al., 1996), lack of emotional support (Krumholz et al., 1998), greater social isolation (Murberg, 2004), lower marital quality (Rohrbaugh, Shoham, & Coyne, 2006), and the presence of depression (Jiang et al., 2004; Junger et al., 2005; Murberg, Bru, Svebak, Tveteras, & Aarsland, 1999; Sherwood et al., 2007; Sullivan, Levy, Crane, Russo, & Spertus, 2004) are positive predictors of mortality in cardiac disease.

Likewise, HF patients' perspectives on their health, assessed with summary (self-report) health status measures, had prognostic significance in a study of 142 outpatients (53.2 ± 10 years; 77.5% male) with advanced HF followed over 3 years (Sullivan, Levy, Russo, Crane, & Spertus, 2007). In unadjusted analysis using a Cox proportional hazards model, a lower total summary score (indicating worse QOL) on a disease-specific HRQOL measure, the Kansas City Cardiomyopathy Questionnaire (KCCQ), was significantly associated ($p = 0.002$) with time to the combined endpoint of cardiac

transplant or death. When clinical variables were added to the model, lower health utility scores on the Standard Gamble instrument (indicating greater willingness to accept the risk of death to escape a current health state) were significantly associated ($p = 0.007$) with time to the combined endpoint. The study was small, with a predominantly younger, male sample with few comorbidities (i.e., 26 [18%] with diabetes) followed in a tertiary referral center HF clinic. Despite these limitations to the generalizability of study results, the finding of the prognostic significance of patient self-assessment provides important direction for further inquiry with larger, more representative HF patient samples.

The sources and many variables included in the above-reviewed research studies concerning prognosis in HF and the predictive models derived from them are diverse. Considerable variation exists in the size of the populations studied, length of patient follow-up, years included in the analysis, diagnostic criteria for HF, etiology of HF, age and gender of the samples, and the period of time for which mortality risk was predicted. In addition, more than one hundred factors (Lehman, 2006b) are identified in the literature as predictors of mortality, including variables easily obtainable in community clinical practice and those limited to specialized programs and centers. The availability of simple clinical criteria (age, presence of diabetes, serum creatinine, blood urea nitrogen) and an objective measure of cardiac function (ejection fraction difference over 6 months $\geq 15\%$ vs. $< 15\%$) favors their prognostic use in a HF clinic and other outpatient settings (Heywood, Elatre, Pai, Fabbri, & Huiskes, 2005).

No one predictive model or single prognostic marker applies without caveat to current advanced HF patients. The marked heterogeneity in sources, study design and predictors, as well as the largely unknown effects of contemporary therapy on survival,

make it difficult to draw substantive conclusions about the estimation of prognosis.

Adding to the challenge is the observation that, at the end of life, some predictors such as New York Heart Association functional class and decreasing left ventricular function lose their ability to discriminate (Frankel et al., 2006) as less variation exists in those parameters in advanced disease. Thus, clinicians are limited both in evaluating the appropriateness of advanced therapeutic options for advanced HF patients and in addressing HF patient and family inquiries about prognosis.

Though not tested empirically, one practical prognostic question suggested for clinicians treating HF patients is, “Would I be surprised if this patient were to die within the next year, and should I adopt a palliative care approach?” (Lehman, 2006b). This approach may have important utility in individual patient encounters, particularly when considered within the context of concurrently assessed known predictors of HF mortality (such as repeated hospitalization, declining renal function, lower serum sodium, and worsened functional status) and informed by nuanced clinician knowledge of that patient – and that patient’s trajectory.

Symptoms in Advanced and End-Stage in Heart Failure

HF patients have a wide range of symptoms at end of life (Goodlin et al., 2004), but assessment and treatment of symptoms is not an integral component of current care in advanced disease. Neither cardiology (Mehta et al., 2001), with a focus on acute care and interventional procedures, nor hospice and palliative care services, with a historical focus on cancer (Solano, Gomes, & Higginson, 2006), have devoted significant attention to the symptom burden and distress of HF patients at end of life. While the small body of literature addressing advanced HF symptoms has grown in the past few years, much work

remains to be done.

Researchers have employed a variety of methods to assess the nature and extent of advanced HF symptoms. Methods include the following: (1) retrospective medical record review (McMillan, Dunbar, & Zhang, 2007; Nordgren & Sorensen, 2003; Zambroski, Moser, Roser, Heo, & Chung, 2005); researcher-developed patient survey (Anderson et al., 2001); (3) various symptom assessment tools (Blinderman, Homel, Billings, Portenoy, & Tennstedt, 2008; O'Leary, Tiernan, & McDonald, 2006; Walke et al., 2007; Zambroski, Moser, Bhat, & Ziegler, 2005); (4) symptom assessment tool plus interview (Barnes et al., 2006); (5) qualitative interviews (Boyd et al., 2004; Ekman, Ehnfors, & Norberg, 2000; Horne & Payne, 2004; Rogers et al., 2002); (6) combined qualitative interviews of patients, informal caregivers and healthcare providers (Aldred, Gott, & Gariballa, 2005b; Boyd et al., 2004); (7) mixed-methods study of patients, caregivers and providers (Fitzsimons et al., 2007); (8) post-mortem surrogate interviews (Sullivan & O'Meara, 2006; Sullivan & O'Meara, 2006); and (9) combination of patient interview, surrogate interview and chart abstraction (Levenson, McCarthy, Lynn, Davis, & Phillips, 2000). In one symptom assessment study of seriously ill patients nearing end of life, those with HF were grouped with other chronic or life-limiting illnesses (COPD and cirrhosis) and compared to cancer patients with respect to symptom experience (Tranmer et al., 2003). Walke et al. (2007) documented the range and severity of seven symptoms over time (every 4 months for up to 2 years) for COPD and HF patients.

Advanced heart HF patients experience multiple symptoms, with a mean of 6.2 (O'Leary et al., 2006), 6.7 (Nordgren & Sorensen, 2003), 11.9 (McMillan et al., 2007), and 15.1 symptoms (Zambroski, Moser, Bhat et al., 2005) per patient in recent studies.

Research documenting the multidimensional nature of HF symptoms adds breadth and depth to current understanding, assessing symptom frequency, severity, distress and the resulting overall symptom burden (Zambroski, Moser, Bhat et al., 2005).

Study findings include documentation of the expected symptoms of dyspnea, fatigue and swelling, but also a wide range of other symptoms: anorexia, cough, orthopnea, weight loss, poor concentration, chest pain/pressure, other pain, anxiety, insomnia, depression, dysphagia, dry mouth, dizziness, drowsiness, irritability, nervousness, worrying, numbness and tingling of the hands and feet, pruritis, constipation, tremors, palpitations, headache, indigestion, nausea, vomiting, incontinence, confusion, sexual problems, and sweats (McMillan et al., 2007; Nordgren & Sorensen, 2003; Zambroski, Moser, Bhat et al., 2005). The symptom of pain other than chest pain (Levenson et al., 2000; Nordgren & Sorensen, 2003; Zambroski, Moser, Bhat et al., 2005) in advanced HF is prevalent but not well understood; in one study, the percentage of patients reporting moderate or severe (undifferentiated) pain doubled (from 20% to 40%; $p = 0.02$) over the time of follow-up (Walke et al., 2007).

The prevalence of HF symptoms in six studies published between 2003 and 2008 is presented in Table 1. The studies are widely diverse in design, with three retrospective record reviews (McMillan et al., 2007; Nordgren & Sorensen, 2003; Zambroski, Moser, Roser et al., 2005; Zambroski, Moser, Roser et al., 2005); a descriptive cross-sectional design (Zambroski, Moser, Bhat et al., 2005); mixed-methods (Barnes et al., 2006); and prospective observational design (Blinderman et al., 2008). Sample sizes varied as well, from 80 participants (Nordgren & Sorensen, 2003) to 542 (Barnes et al., 2006); five of the six studies had 103 or fewer participants. Patients ranged

in age from a mean of 55.5 years to a mean of 85.7 years, and only one study (McMillan et al., 2007) had nearly equal representation of males and females. In the 3 studies with NYHA Class information, marked differences in functional status existed among the study samples; the greatest contrast is between the Barnes et al. study (61% Class I and II; 39% Class III and IV) and the Zambroski et al. study (23% Class II; 57% Class III; 21% Class IV).

The functional status difference between the patients in these two studies is likely related to the settings from which they were drawn. Patients in the Barnes et al. study were recruited from community general practices, while those included in the Zambroski et al. study were recruited from a single HF clinic. Patients managed in a specialty HF clinic are generally younger, more seriously ill, more often cardiac transplantation candidates, and thus more functionally limited than those in general practices. Moreover, general practice physicians often refer HF patients to specialty clinics for consideration of advanced therapeutic options when HF clinical management becomes more complex.

The wide diversity in design, sample size and functional status limits meaningful summary of symptom prevalence across the studies presented in Table 1. However, general observations about the high prevalence of expected and unexpected symptoms underscore the presence of significant burden and suffering in advanced HF. The expected symptoms of dyspnea and fatigue were experienced by more than half of participants in all of the studies reviewed, with dyspnea prevalence as high as 88% in one hospice record review. Incontinence is not a surprising finding in more than a third in one of the hospice studies since HF patients tend to be referred to hospice late in the

Table 1 Heart Failure Symptom Prevalence in Selected Research Studies

Nordgren & Sorensen, 2003* n = 80		Zambroski et al. 2005 n = 90	Zambroski et al., 2005 n = 53	Barnes et al. 2006 n = 542	McMillan et al. 2007 n = 51	Blinderman et al., 2008**** n = 103
Symptoms						
Dyspnea	88%	60%	85.2%	54%**	76.5% (exertion) 52.9% (at rest)	56.3%
Fatigue	69%		84.9%	53%**	82.4%	66%
Swelling	44% (ankle)	43%	47.2% (arms/legs)	34%*** (legs)	56.9%	32% (arms/legs)
Orthopnea	19%		57.7%	28%***		
Waking breathless			48.1%			
Cough/Wheezing	35%		57.4%		45.1%	40.8%/18.6%
Anorexia	41%		30.2%		49%	31.1%
Food taste change			18.9%			15.5%
Dysphagia					27.2%	11.7%

Symptoms	Nordgren & Sorensen 2003 n = 80	Zambroski et al. 2005 n = 90	Zambroski et al. 2005 n = 53	Barnes et al. 2006 n = 542	McMillan et al. 2007 n = 51	Blinderman et al. 2008*** n = 103
Nausea	48%		41.5%			14.6%
Vomiting			24.1%		5.9% (nausea or vomiting)	2.9%
Dry mouth/thirst	9% (thirst)		74.1%		25.5%	62.1%
Feeling bloated			51.9%			28.2%
Constipation	42%		26.4%		13.7%	25.2%
Diarrhea			22.2%			9.8%
Weight loss			32.1%		41.2%	19.4%
Weight gain			34.6%			
Chest pain/pressure		3%	53.7%		37.3%/25.5%	29.1%
Palpitations	5%		48.1%		9.8%	
Dizziness	21%		51.9%		15.7%	27.2%
Pain (unspecified)	75%	20%	57.4%			37.9%

Symptoms	Nordgren & Sorensen 2003 n = 80	Zambroski et al. 2005 n = 90	Zambroski et al. 2005 n = 53	Barnes et al. 2006 n = 542	McMillan et al. 2007 n = 51	Blinderman et al. 2008*** n = 103
Insomnia	36%		64.2%		31.4%	44.1%
Drowsiness			67.9%			52.4%
Anxiety	49%				35.3%	
Fearfulness					17.6%	17.5%
Depression	9%				29.4% depression/ sadness	
Feeling sad			54.7%			42.7%
Poor concentration			50%		39.2%	33%
Confusion	29%	48%				
Irritability			53.7%		13.7%	33%
Nervousness			53.7%			35.9%
Worrying			61.5%			43.7%

	Nordgren & Sorensen 2003 n = 80	Zambroski et al. 2005 n = 90	Zambroski et al. 2005 n = 53	Barnes et al. 2006 n = 542	McMillan et al. 2007 n = 51	Blinderman et al. 2008*** n = 103
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Symptoms

Numbness/tingling of hands/feet			46.2%			48.5%
Headaches					7.8%	24.5%
Tremors					11.8%	
Incontinence	20% (urinary)	37% (bowel +/or bladder)				
Urination problems	4% (nocturia)		24.1%			26.2%
Sexual problems			46.3%			26%
Pruritis	12%		43.4%			34.3%
Sweats			53.7%			21.4%

*symptom not listed: limitation in physical activity (assessed functional status rather than a specific symptom)

**at least once a day

***at least once a week

****symptoms not listed: "I don't look like myself" (25.2%), change in skin (19.4%), mouth sores (10.7%), and hair loss (10.7%)

disease trajectory; neither is the 46.3% of the younger (mean age 55.5 years) participants reporting sexual problems unexpected. But the significant prevalence of unspecified pain (20% to 75%) is unanticipated in HF and is the subject of a current research study (Goodlin, Wingate, Pressler, Teerlink, & Storey, 2008). All major body systems except the musculoskeletal system are represented in the HF symptom list: neurological (i.e. confusion, headache), pulmonary (i.e. dyspnea, wheezing, cough), cardiac (i.e. palpitations, chest pain), gastrointestinal (i.e. anorexia, abdominal bloating, constipation), genitourinary (i.e. problems with urination, sexual problems) and integumentary (i.e. swelling, prurities). Emotional symptoms are prevalent as well, with anxiety and feeling sad commonly reported.

One of the symptoms included in the lists is swelling, but no symptom lists or studies address the pain and discomfort associated with the skin breakdown which may occur when lower extremity edema is significant. The weeping, ulcerated lower extremity lesions can be extensive in end-stage HF, particularly in bed-bound patients who may also be cachectic. Patients nearer death are more likely to experience this complex symptom and, as a result, their input is not included in currently available research. In addition, hospice symptom checklists designed for cancer patients may not include skin breakdown due to massive lower extremity edema. Thus, both prospective and retrospective research may not capture this symptom complex.

Qualitative interview studies addressing the symptom experience of advanced HF patients add the patient's perspective to the findings of quantitative research. For example, patients described a range of breathlessness experiences, from "everyday" breathlessness, to "worsening," to "uncontrollable" (Edmonds et al., 2005). They

expressed difficulty in distinguishing between medication side effects and symptoms (Edmonds et al., 2005); linked the effects of symptoms to activity of daily living limitations (Horne & Payne, 2004); expressed related feelings of uselessness (Barnes et al., 2006); described the panic and terror of severe dyspnea (Boyd et al., 2004; Murray et al., 2002); and detailed how they felt trapped by their symptoms (Ekman et al., 2000).

HF symptoms and their associated distress are clearly important to patients and are vital considerations in the management of advanced disease, as they are related to impaired quality of life, reduced psychological well-being, and declining functional status (Blinderman et al., 2008), and they lead to social isolation for patients and caregivers (Aldred, Gott, & Gariballa, 2005). Symptom stability is also a key criterion for discharge readiness when advanced HF patients are hospitalized for decompensation (Nohria, Lewis, & Stevenson, 2002). Moreover, advanced HF symptoms, when defined operationally as NYHA Class III or IV functional status, were an independent predictor of the time to first inappropriate ICD shock (Hreybe et al., 2006). The individual symptoms of fatigue and breathlessness were found to have long-term prognostic implications (Ekman et al., 2005) as well.

Although end-stage HF symptoms are prevalent and often severe, research findings revealed a common theme of inadequate treatment. Symptoms reported at hospice admission were unchanged on the day of death (Zambroski, Moser, Roser et al., 2005). Patients were rarely referred to specialist HF teams (Horne & Payne, 2004). Measures to control symptoms were provided sparingly (Nordgren & Sorensen, 2003). Furthermore, utilization of a palliative care approach was rare (Boyd et al., 2004). An issue with important implications for symptom management uncovered in the retrospective hospice

record review by Zambroski et al. (2005) is that standard HF medications were discontinued following admission to hospice care. While HF medications are disease-modifying, they also control HF symptoms and thus are essential in a palliative approach to end of life.

The current body of research addressing symptoms in advanced and end-stage HF has produced findings with a wide range of evidence quality and generalizability. Data derived from studies using retrospective designs to investigate symptoms documented in deceased hospice or hospitalized patient records (McMillan et al., 2007; Nordgren & Sorensen, 2003; Zambroski, Moser, Roser et al., 2005) have played an important role in raising awareness of the multiple, undertreated symptoms at end of life in HF. However, numerous threats to validity of the retrospective findings exist. Threats include the relatively small sample sizes, sample inclusion limited to patients enrolled in hospice programs or hospitalized with end-stage HF, the unknown quality of the records and the absence of the patient voice. For the studies of hospice patients, threats to validity also include that of unknown provider skill in assessing the symptoms of less-familiar, non-cancer patients.

Limitations to the reliability of the data in other symptom studies include the use of proxy informants in post-mortem interviews to explore deceased Cardiovascular Health Study (CHS) participants' experiences (including symptoms) prior to death (Sullivan & O'Meara, 2006). More than half of the informants for the elderly decedents (mean age 75.8 years) were spouses who were likely to be older themselves and may have had difficulty with recall over the unspecified time period since the death. Another limitation in this research is the lack of clarity in the definition of HF. Two groups of HF patients

were identified: 1) those with definite HF, diagnosed at least one year before death during the CHS follow-up period; and, 2) those with prevalent HF (present at the CHS study baseline) and those with probable HF (lacking complete diagnostic data). As a result, the analysis and presentation of the findings comparing the definite and prevalent/probable groups to subjects without HF is complicated and confusing. Moreover, the inclusion of subjects with incomplete HF diagnostic data (the probables) reduces confidence in the findings regarding symptoms at end of life.

Two other studies illustrate some of the contributions and limitations in HF symptom research. First, the study combining HF patients and other non-cancer patients (Tranmer et al., 2003) and comparing them as a group to cancer patients provides important data. Study findings highlight the differences in particular physical symptom prevalence between cancer and non-cancer patients as well as the similarities in the prevalence of psychological symptoms in both groups. However, the distinctions between HF and the COPD and end-stage liver disease patients are absent in the grouped findings. A second study (Ekman et al., 2005) has both the benefits and limitations inherent in a secondary data analysis of a large clinical trial. The large sample ($n = 3029$), with symptom data available for further analysis, provides a potentially rich source of research material. However, the predominantly male (79.8%) sample was younger (mean age 62 years) and less limited functionally (48% NYHA Class II) than HF patients seen in clinical practice. The sample characteristics thus limit generalizability to the wider population of HF patients. In addition, the data were limited to three HF symptoms (breathlessness, fatigue and orthopnea) and were collected using a non-validated instrument.

Findings from the Zambroski et al. (2005) study represent the upper boundary of the range of evidence quality in HF symptom research. The study's major strength is in the methodology, specifically the instrument used for symptom assessment. The Memorial Symptom Assessment Scale – Heart Failure (MSAS-HF), an instrument based on a known multidimensional cancer symptom assessment tool, was adapted for HF. The psychometric properties were evaluated in a pilot study and found to be adequate (Zambroski, Lennie, Chung, Heo, & Ziegler, 2004). The instrument covers a wide range of symptoms, includes symptom dimensions, and replaces five symptoms more commonly associated with cancer, such as mouth sores, with those HF patients experience. The MSAS-HF is the only currently available instrument for assessing multiple symptoms (and their dimensions) in HF.

Further evaluation of the body of HF symptom research literature requires attention to semantic and definitional issues. Expanding the scope of research from the conceptualization of HF symptoms as unidimensional to multidimensional is complicated by the absence of standard assessment tools and by a lack of definitional clarity for some symptoms and terms. For instance, anxiety, fearfulness, and worrying appear in symptom lists, and depression and feeling sad are separated in one instrument and combined in a retrospective record review. Chest pain and chest pressure are combined or presented separately. How patients interpret the differences in meaning among potentially subtle distinctions is not known. In another example, dry mouth and thirst may both express one physiological phenomenon or overlapping dimensions of local factors and overall fluid volume status.

An additional illustration of lack of clarity is presented in Table 2, comparing the

terms used to characterize the aspects of the symptom experience in the Theory of Unpleasant Symptoms (Lenz, Pugh, Milligan, Gift, & Suppe, 1997) with those used in three symptom instruments. While the MSAS-HF follows the Lenz et al. theoretical dimensions of frequency, severity, and distress (bothersomeness), the Kansas City Cardiomyopathy Questionnaire (KCCQ) equates severity with bothersomeness.

Burden in the MSAS-HF is computed by summing the mean of the frequency, severity and distress scores for each symptom to arrive at a burden score for that symptom. The overall mean for all the symptoms is the total burden score. In another application of the term, the Barnes et al. (2006) study uses *burden* for the bothersomeness (severity) component of the symptom experience. Although this research used the KCCQ, no reference to burden was found in the instrument development and evaluation publication (Green, Porter, Bresnahan, & Spertus, 2000). However, the KCCQ symptom score does address the overall impact of symptoms in that it combines symptom prevalence and symptom severity for three symptoms: lower extremity swelling, fatigue and breathlessness. In a final example of the diverse use of the term, Walke et al. (2007) created a composite measure of symptom burden from the sum of the severity ratings for seven symptoms evaluated with an adaptation of the Edmonton Symptom Assessment Scale (ESAS).

In summary, symptom research in advanced and end-stage HF is at a beginning stage of development. Available evidence suggests that symptoms are highly prevalent, multiple, and under-treated. They are associated with great burden, declining functional status, social isolation, and reduced psychological well-being. Further research is required, using validated instruments, to assess a wide range of symptoms in sample

Table 2 Symptom Dimension Terminology

	Theory of Unpleasant Symptoms (Lenz et al., 1997)	MSAS-HF*	KCCQ**	ESAS*** (Adapted by Walke et al., 2007)
Dimension	Frequency	Frequency	Frequency	Prevalence
	Intensity = Strength or Severity	Severity	Severity = Bothersomeness	Severity
	Distress = Bothersomeness	Distress		
Symptom Burden	Burden not defined	Burden = mean of frequency, severity + distress for each symptom. Total Burden Score = overall mean for all symptoms.	Burden = bothersomeness (Barnes et al., 2006) KCCQ Symptom Score = mean symptom frequency score + mean symptom severity score	Burden = sum of severity ratings for 7 symptoms

* Memorial Symptom Assessment Scale – Heart Failure

** Kansas City Cardiomyopathy Questionnaire

***Edmonton Symptom Assessment Scale

groups similar to those encountered in clinical practice. Establishing definitional clarity for symptom dimension terminology is also an important need in order that researchers might use the same language to describe the concepts they study. The palliation of

suffering in symptomatic HF patients requires a substantive research evidence base regarding the extent and characteristics of the symptoms they experience.

Palliative Care in Heart Failure

Palliative care developed within and from the hospice movement, according to Dame Cicely Saunders (2006), the founder of the first modern hospice (Dame Cicely Saunders, 2005). Palliative care, an approach first known as ‘terminal care,’ is defined by the World Health Organization (WHO) as that which “improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” (Davies & Higginson, 2004, p. 14). Although palliative care expertise developed in the field of oncology, the principles are now extending to other diseases and into other settings (Ferrell & Coyle, 2006).

More than four decades ago, Hinton (1963) recognized the symptom burden of end-stage HF in a case-control study of 102 dying patients (matched with 102 ill, but not dying patients) in an acute hospital. The number of dying HF patients (14) was small, but physical distress (defined as pain, nausea, vomiting, severe malaise or persistent cough) at end of life was greater in those dying from HF or renal failure, or both, than in the 82 patients dying from terminal cancer. While twenty-one (26%) of the cancer patients failed to get relief from physical distress, more than half (8 patients; 57%) of the heart or renal failure patients did not experience relief. The time period for relief assessment appears to have been the week of the first interview, but is not clearly defined in the research report (Hinton, 1963).

Advanced HF symptoms clearly require palliation and an approach which addresses the attendant physical, psychosocial and spiritual problems. However, early published commentary provided a negative evaluation of this non-cancer use of palliative care. Jones (1995) described a survey of 10 English hospices that showed little to no demand for terminal HF palliative care in a *British Medical Journal* letter, decrying the neglect of the subject and recommending exploratory research (Jones, 1995). Responses to the letter included concern that terminal cardiac failure patients might make considerable demands on community palliative care services, although the need was reluctantly acknowledged (Beattie, Murray, Brittle, & Catanheira, 1995). Another response stated with certainty that hospices could not fill this role and predicted that broadening the scope of palliative medicine would slow the specialty's progress (Gannon, 1995). The context of the historical association of palliative care in the United Kingdom with cancer and its dependence on charitable funding (Lehman, 2006a) facilitates an understanding of those responses to the prospect of HF patients in palliative care.

While the appropriateness of palliative and hospice care for advanced HF was debated, advances in the medical management of HF were altering the natural history of the condition. The first national clinical practice guideline (Konstam et al., 1994) was pivotal in promoting both the disease-modifying neurohormonal blockade of angiotensin-converting enzyme inhibitor (ACEI) medications and the comprehensive care of HF patients, ushering in an era of remarkable progress in care. The development of device-based approaches to the management of advanced HF followed the neurohormonal blockade era, with an emphasis on targeting hemodynamic and mechanical pathophysiological abnormalities (Mancini & Burkhoff, 2005). As a result of these

advances, HF progression has been delayed, sudden death rates decreased, and potential survival with chronic left ventricular dysfunction and advanced symptoms lengthened (Teuteberg et al., 2006).

Palliative approaches to advanced HF, however, have received little research attention. A survey study with the goal of identifying difficult, unanswered questions in advanced HF medical management (Shah & Stevenson, 2004) illustrates this lack. Of the 318 questions raised on inpatient cardiomyopathy service rounds concerning whether to use a treatment ($n = 73$) or how to use a therapy ($n = 242$) for hospitalized patients with advanced disease, only three could be characterized as relating to end of life in HF.

Further contrasts are evident in research showing more frequent use of aggressive treatments for inpatients who died of HF than for those who died of cancer (Tanvetyanon & Leighton, 2003). Haydar et al. (2004) published similar findings, demonstrating that dementia patient care was more likely to focus on symptom relief and anticipation of dying, while the focus for advanced HF was disease-modifying treatment. Surprisingly, HF disease management, a comprehensive approach with an extensive body of research literature, does not include the component of palliative care (Taylor et al., 2005).

However, the current growing recognition of palliative needs in HF seen in the literature crosses disciplines and specialties to include palliative medicine (Stuart, 2007), cardiology (Hauptman, 2006; Ward, 2002), palliative medicine/cardiology (Gibbs, McCoy, Gibbs, Rogers, & Addington-Hall, 2002; Pantilat & Steimle, 2004), internal medicine (Goodlin, 2005), geriatrics/internal medicine (Liao & Arnold, 2007), nursing (Brush, Zambroski, & Rasmusson, 2006; Flowers, 2003), nursing/cardiology (Stewart &

McMurray, 2002), and collaborative nursing/palliative medicine/cardiology authorship (Albert, Davis, & Young, 2002) among others.

Evidence is mounting for HF palliative care knowledge gaps in medicine and nursing. Hauptman et al. (2008) conducted a national survey of cardiologists, geriatricians and family practice/internal medicine physicians and found little experience with hospice referral. Sixty-four percent of cardiologists, 45% of geriatricians and 44% of internal medicine/family practice physicians cited uncertainty about timing of referral as one factor which limited wider use of this end-of-life option. Survey researchers also found that physician conversations with patients and families concerning defibrillator deactivation were infrequent, as 59.8% of cardiologists, 88% of geriatricians, and 95% of internal medicine/family practice physicians reported two or fewer discussions about this option. Other limitations in end-stage HF knowledge and practice were also noted in the survey results.

Cardiologists participating in palliative care focus groups indicated that they perceived patient death as a failure and that they made the switch to a palliative approach late in the illness (Hanratty et al., 2002). Reigel et al. (2006) surveyed HF specialists about nonpharmacologic aspects of care and found that 67% of HF specialists (50.3% physicians, 90.4% of whom were cardiologists) had not referred any patients to palliative care in the prior 6 months.

In two studies, acute care and palliative care nurses identified the limited role of palliative care in chronic illness, noting that it is often initiated late in the case of HF, and speaking of their own discomfort dealing with death and dying (Davidson et al., 2003; Wotton, Borbasi, & Redden, 2005). Not surprisingly, hospice nurses are limited in HF

knowledge, while HF nurses lack palliative care knowledge (Goodlin, Trupp, Bernhardt, Grady, & Dracup, 2007).

Palliative need for advanced HF has also received attention from other sources. A group of HF experts published a consensus statement on palliative and supportive care in advanced HF, identifying gaps in knowledge and proposing a research agenda to address them (Goodlin et al., 2004). The Institute of Medicine identified end of life with advanced organ failure (with a focus on HF and chronic obstructive pulmonary disease) as one of twenty priority areas for health care improvement (Adams & Corrigan, 2003). In addition, the population identified as appropriate for palliative care by the National Consensus Project for Palliative Care includes all patients who are living with life-threatening or debilitating illness (National Consensus Project, 2008).

HF patients have considerable palliative needs in advanced and end-stages, needs which are gaining attention in medical, nursing and national arenas. As an *approach* to end of life, palliative care is distinct from a hospice *program*, though hospice embodies the approach, and is a defined, structured vehicle for delivering palliative care.

Hospice – Delivering Palliative Care

The hospice movement in the United States began in the 1970s, with a primary focus on cancer patients at end of life (NHPCO, 2008). The Medicare Hospice Benefit, enacted in 1982, extended the end-of-life approach to Medicare beneficiaries meeting defined criteria (Pyenson, Connor, Fitch, & Kinzbrunner, 2004). Hospice referral patterns have shifted over the past several years and, by 2006, when hospices provided care to an estimated 1.3 million patients, more than half had non-cancer diagnoses. While heart disease is currently the most common non-cancer hospice diagnosis, comprising 11.8 %

of the total patients served in 2007 (NHPCO, 2008), there is a paucity of research addressing hospice care for advanced and end-stage HF.

Data from two small retrospective reviews of hospice medical records for 90 (Zambroski, Moser, Roser et al., 2005) and 50 (McMillan et al., 2007) deceased HF patients were similar with respect to the patients' reduced functional status on admission to hospice, with mean Palliative Performance Scale (PPS) scores of 32 and 34.7, respectively (score range 10-50 for both studies). PPS scores range from 100% (normal activity with no evidence of disease) to 0% (indicating death) (Anderson, Downing, Hill, Casorso, & Lerch, 1996). In addition, Zambroski et al. (2005) found that more than half of the patients were essentially bed-bound, and 9% were actively dying on admission to hospice care.

Patients were older in both the Zambroski and McMillan reviews, with similar ages (81 ± 8 years; 80.3 ± 9.8 years) reported. Wide variation in hospice length of stay (LOS) was evident in both reports, with a considerably shorter LOS in the Zambroski study (37 ± 56 days; range 1-314) than in the McMillan study (127.5 ± 216.5 days; range 1-915). Nearly 37% of the hospice patients in the Zambroski et al. review were admitted in the last week of life. McMillan et al. reported a symptom prevalence of 11.9 ± 5.96 , and the Zambroski et al. review identified two important issues regarding symptoms. They noted that a symptom checklist developed primarily for cancer was used to record HF symptoms, and that there was no difference between symptoms on admission and on the day of death for the HF patients in hospice care.

The two reviews of hospice records have the limitations inherent in a retrospective design, as they are limited to available data and not open to researcher

planning or control. In addition, both samples are small and derived from two geographic regions, limiting wide generalizability of the research findings. Despite these limitations, the studies contribute potentially valuable insights regarding the relatively unstudied topic of hospice care in advanced and end-stage HF. For example, the wide range of hospice LOS may be the result of both late referrals to hospice (a conclusion supported by the low functional status and the number of patients actively dying on admission) and of the prognostic uncertainty which characterizes advanced HF. Issues including the number of symptoms patients experience, the inadequate methods for tracking them, and the evidence of undertreatment serve to focus the attention of researchers, providers, administrators and policy-makers on the significant concerns of the growing population of HF patients at end of life.

Targeting another source of information regarding hospice care for HF, Goodlin, Kutner & Connor et al. (2005) conducted a survey of hospice medical directors (n = 70). Medical directors reported an average of 9% (range 2-30%) of patients with a primary diagnosis of HF in their hospice programs, with a mean LOS of 60 days (range 15-150). Few hospices provided IV inotropes and, for some, inotropic or other IV therapy precluded admission if the hospice was expected to cover the cost. While a majority (94%) of the programs accepted patients with ICDs, less than one-third of them (27%) had policies and procedures addressing device deactivation. Findings of this survey study add confirmatory evidence regarding the low referral rate and wide range of LOS for HF patients in hospice care, as well as the important issues surrounding IV inotropes and ICD deactivation. The authors correctly acknowledge the preliminary nature of these pilot data, an appropriate caveat given the potential for bias introduced by the low

response rate of 45%. In addition, the sampling frame of the membership of a hospice professional organization (with announcements in publications of other hospice-related groups), overlooked the considerably larger potential target population of the medical directors of the more than 3000 hospices in the US. Unknown, but important, differences might exist in the data regarding HF patient utilization other hospice medical directors would provide.

In the first of three reviewed research studies utilizing Medicare claims data, admission assessments for nursing home residents receiving hospice care (21% of whom had HF) revealed that half of the patients experienced pain daily and, for nearly one-third, pain was horrible or excruciating. Living wills were infrequent (27%), and cognitive impairment and physical dependency were common among those admitted for hospice care (Buchanan, Choi, Wang, & Huang, 2002). In another study of Medicare beneficiaries, HF patients in hospice incurred lower costs and survived longer than non-hospice HF patients (Pyenson et al., 2004). Lastly, of the cohort of Medicare beneficiaries in the third study, HF patients who died used hospice infrequently, with only 8.3% of men and 7.9% of women receiving this type of care at end of life (Iwashyna, Zhang, & Christakis, 2002).

Hauptman et al (2007) reviewed data from a large database of HF hospital admissions, the Acute Decompensated Heart Failure Registry (ADHERE). Researchers found that patients referred for hospice care ($n = 3010$) had a mean age of 80.2 (± 10.8) years, were nearly evenly divided by gender (54% female), and had a considerable number of comorbidities (atrial fibrillation – 39.6%, hypertension – 66.5%, renal insufficiency – 43.5%, diabetes - 37.9%, and COPD – 36%). Forty-five percent had been

hospitalized for HF in the prior 6 months. Over the course of data collection, the hospice referral median rate showed a small (non-significant) increase, from 0.8% in 2001 to 1.3% in 2005 (Hauptman et al., 2007). This study derives from a large registry developed in a contemporary HF treatment era (2001-2005), with wide representation throughout the US, adding interpretive relevance to the findings. One limitation is that the parent study sample of hospitalized patients restricted the inquiry to HF patients who experienced an acute decompensation, excluding the unknown number of others referred to hospice from clinic settings or home.

Diverse research approaches have addressed the relatively unstudied subject of HF hospice care. A composite summary of important findings from them provides a limited description of patient characteristics and identifies some of the issues impacting the evolving role of hospice in end-stage HF. Patients tend to be older, to have multiple co-morbidities, and to have a considerable, often unrelieved, symptom burden. The wide range of LOS for these patients may reflect at one end of the range the late referrals of very ill, often dying, patients to hospice, and at the other end, the trend toward longer life with advanced symptoms in a chronic illness population with known prognostic uncertainty.

Both the AHA/ACC (Hunt, 2005) and Heart Failure Society of America (Adams et al., 2006) guidelines support hospice referral as an option for HF patients at end of life. Challenges encountered in following this recommendation include the uncertainties inherent in estimating a prognosis of 6 months of life or less (Hauptman & Havranek, 2005). This is especially important, given the finding that the recommended prognostic criteria, as tested in the Study to Understand Prognoses and Preferences for Outcomes

and Risks of Treatment (SUPPORT) were ineffective in identifying patients unlikely to survive for that period (Fox et al., 1999). Other considerations are the unpredictable disease trajectory of HF (Levenson et al., 2000), pharmacologic treatment of HF which is at once both disease-modifying and palliative (Zambroski, Moser, Roser et al., 2005), hospice provider unfamiliarity with HF symptoms and treatment, and physician orientation toward treatment modalities improving survival and their resulting perception of hospice referral as failure (Bekelman & Havranek, 2008). In addition, for inotrope-dependent patients, the current (2007) hospice per diem rate of \$130.79 (Home Health Interactive, n.d.) precludes all but the largest hospice programs from accepting their referral (Goodlin et al., 2005).

Integration of Palliative Care and Hospice into Standard Heart Failure Care

HF palliative care consensus guidelines (Goodlin et al., 2004) recommend research concerning appropriate systems of care for advanced HF patients. Patients at end of life require both exquisite management of their advanced HF and simultaneous, experienced palliative attention to the multiple symptoms they experience. This dual challenge requires the expertise of providers from both cardiology and palliative care. How the integration of these diverse medical and nursing specialties is best accomplished is not yet clear, but is the focus of pioneering efforts and beginning research attention in various settings. The integration efforts include an outpatient palliative care consultation service (Rabow, Dibble, Pantilat, & McPhee, 2004), palliative home care (Brannstrom, Ekman, Norberg, Boman, & Strandberg, 2006), joint patient management between a hospice clinical nurse specialist and a community HF nurse specialist (Pooler, Yates, & Ellison, 2007), and community-based HF nurse specialists and existing specialist

palliative care services (Daley, Matthews, & Williams, 2006). These and other approaches, while not yet empirically tested, stress integration, collaboration and partnership and hold great promise for improving the care of advanced and end-stage HF patients.

Conclusion

This review of the literature in palliative and hospice care for advanced HF patients includes content areas with considerable knowledge development, those with beginning to moderate levels of knowledge development, and those with very little or no information in the literature. For some topics, such as advanced therapies in advanced HF, various dimensions of the subject have differing levels of development maturity.

Pharmacologic therapy for HF is well-established, with a strong evidence base developed over the past two decades. While ongoing research aims to refine current approaches to medical therapy and to develop new pharmacologic agents, the core medical management strategies for HF are clearly articulated in national guidelines and widely applied in clinical practice. Likewise, the basic pathophysiologic processes responsible for disease progression in HF are known, though research continues to elucidate the precise mechanisms involved.

Prognosis determination in HF remains a critical area for development. A significant body of research has developed around establishing prognosis in HF, both by identifying a large number of factors shown to be predictive of mortality and combining factors in various predictive models. However, a clinically useful and valid prognostic model for advanced and end-stage disease is not yet available. Such a tool would have particular relevance for patient care, as decisions about advanced therapies, discussions

with patients and families around end-of-life issues, and referrals to hospice require mortality estimation.

The technology for HF devices (ICDs, CRT, LVAD) has had considerable research development, and researchers have examined outcomes for each of these advanced therapies in large-scale, randomized clinical trials. However, the elements of eventual end-of-life care for patients with devices have not been addressed. For example, how to best insure that patients and families make informed decisions around the option of deactivating or disabling ICDs at end-stage is not known. Likewise, the issues surrounding LVAD withdrawal are yet to be elucidated.

Content areas with rudimentary levels of knowledge development include the widely-accepted downward trajectory depiction of advanced and end-stage HF, which makes intuitive clinical sense but is not evidence-based. In addition, the dramatic rescues and remarkable improvements in functional status (and physiologic measures) which can result from application of advanced therapies (or maximal application of standard therapies) are not accounted for in the downward trajectory depiction. Redrawing the trajectory requires the addition of upturns connected to plateaus (of various lengths), essentially reversing the trajectory direction – for a time. One unintended result of such reversal is that patients may be consigned to experience HF's end stage more than once. The potential for increased suffering in this paradox has not been addressed.

Palliation of the multiple symptoms of advanced HF symptoms has not been studied. The wide range of symptoms requires treatment approaches that go beyond the familiar opioids, IV diuretics, and inotropes. The expertise for managing a wide range of symptoms at end of life has been well-developed in palliative and hospice care for

malignant disease; research addressing specific application to the multiple symptoms in advanced HF is needed. In addition, the symptom burden for patients who are non-responders to CRT, who do not meet transplant criteria, or who die while hospitalized after LVAD implantation has not been described.

Very little is known about how to best integrate a palliative approach and hospice into HF management at end of life. Small studies and diverse approaches characterize current research, limiting conclusions about end-stage care design. Further research is needed to identify the design elements which most effectively meet patient and family needs as function declines and end-stage is reached.

The final content area concerns the growing group of elderly HF patients with preserved systolic function (HFPSF). This “other” HF type has been largely neglected, and frequently dismissed as not well understood. With the beginning development of an evidence base and management guidelines for HFPSF, attention to symptom palliation and unique needs of this sub-group of HF patients in advanced and end-stage disease is a necessary parallel development. A first step is research exploring the characteristics and symptom experience of advanced HFPSF patients, as no currently available studies specifically target this population.

Advancing nursing science in chronic illness end-of-life care must include attention to the rapidly growing population of advanced HF patients. Research in palliative and hospice care for this population is vital, in order that those who have benefited from the remarkable advances in treatment over the past two decades are not abandoned in the last patch of their journey.

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Chapter 2 Part 2

Background

Despite increasing death rates from CHF, palliative cardiology remains undefined. (Sullivan & O'Meara, 2006)

The past two decades of rapid, dramatic changes in heart failure (HF) treatment have presented extraordinary challenges to HF guideline writing committees. In 1994, the Agency for Health Care Policy and Research (AHCPR) published the first major United States (US) guideline (Konstam, Dracup, Baker, et al., 1994); this guideline highlighted just one new HF medication class, and provided a wealth of assessment and management direction for HF patient care. Current North American and European HF guidelines provide a striking contrast to the earliest document. Guidelines written in the past 5 years combine evidence-based assessment of multiple pharmacologic and device options along with numerous other topics, including co-morbid conditions, elderly patients, disease management, and considerations in the treatment of the growing number of patients with HF and preserved systolic function.

One important topic, end-of-life and palliative care for advanced and end-stage HF patients, is an emerging subject area in current HF guidelines. Prior to the era of advances in HF treatment, such guideline content would have been unnecessary, as patients were more likely to die suddenly. Now, patients more commonly experience lengthy survival with advanced symptoms and at least one hospitalization in the 6 months prior to death (Teuteberg et al., 2006).

However, few chronic illness clinical guidelines, including those addressing HF management, have significant palliative content for advanced and end-stage disease (Mast, Salama, Silverman, & Arnold, 2004). Since clinical guidelines reflect the state of

knowledge (Konstam et al., 1994), and are a key tool for translating that knowledge into clinical practice (Adams, 2001), they have an important role in chronic illness diagnosis and treatment. The relative absence of treatment direction at end of life in the chronic illness of HF has important implications for providers, patients, families, and ultimately for society.

McMurray and Swedberg (2006) compared chronic HF treatment recommendations in four major guidelines and Brush, Zambroski and Rasmusson (2006) compared HF end-of-life content in two US guidelines, but no comprehensive review exists of palliative and end-of-life content in all major HF guidelines. Therefore, we conducted a review of the evolution and development of palliative care and end-of life content in ten North American and European heart failure guidelines between 1994 and the present.

Methods

A literature search was performed using Medline and CINAHL databases. We identified all heart failure guideline documents published by major North American and European cardiology or HF organizations from 1994 to the present (see Table 1). We assessed the guidelines for inclusion of end-of-life/palliative content, categorizing the content in ten domains (see Table 2) which emerged from the content analysis: prognosis, advance directives, identification of end-stage status, provider/patient/family communication, inotropes, symptom palliation, and device deactivation, family/caregiver issues, hospice/palliative care, and advanced therapies (when included in end-of-life material). Two heart failure specialists reviewed the domain list for adequacy. One author

Table 1 Organization/Agency Sources of Included Guidelines with Year[s] of Publication

Agency for Health Care Policy and Research (AHCPR)	1994
American College of Cardiology/American Heart Association (AHA/ACC)	1995, 2001, 2005
European Society of Cardiology (ESC)	1997, 2001, 2005, 2008
Heart Failure Society of America (HFSA)	2006
Canadian Cardiovascular Society (CCS)	2006

reviewed each heart failure guideline for palliative and end-of-life content, with validation and feedback from a second author.

Six guidelines published by the above-named organizations were not included in the review. The 1999 Heart Failure Society of America (HFSA) guideline did not include end-of-life content, as it focused entirely on pharmacological approaches to HF management (Heart Failure, 1999). Likewise, the CCS guidelines of 2001 (Liu et al., 2001) and 2002/2003 (Liu et al., 2003) cover diagnostic and management topics, but do not address end of life. The CCS guideline updates of 2007 (Arnold et al., 2007) and 2008 (Malcom et al., 2008) provide supplemental material to the original 2006 document (e.g., care of HF with inter-current illness and transitioning care to and from HF specialists), but do not update palliative care or other content. The ACCF/AHA 2009 update of the ACC/AHA 2005 guideline (Jessup et al., 2009) focused primarily on three topics 1) management of the hospitalized HF patients 2) clarification of the 2005 guideline ICD recommendations and 3) management of atrial fibrillation in the setting of HF.

Table 2 End-of-life Domains in Major North American and European Heart Failure Guidelines

Domain	Description
Prognosis	Estimation of survival and likely course of disease process for an individual HF patient
Provider/Family/ Patient Communication	Discussions between provider/patient/family related to advanced and end-stage HF
Advance Directives	Recommendations for written documentation of patient wishes concerning treatment options
Identification of End-Stage HF	Information describing patient characteristics, treatment considerations associated with advanced/end-stage HF
Symptom Palliation	Identification of end-stage HF symptoms and options for symptom relief/control
Inotropes/Vasodilators	Recommendations for IV pharmacologic agents in advanced and end-stage HF
Device Deactivation	Consideration of disabling implanted technology (i.e. ICD) at end of life
Family/Caregiver Support	Specific recommendations concerning support other than informational for those involved in the care of an end-stage patient
Palliative Care/Hospice	Provision for goals of care directed toward comfort rather than life prolongation at end-stage
Advanced Therapies	Specialized, more invasive treatment focus for advanced and end-stage HF patients

Results

Table 3 summarizes the results of the review of the ten guidelines for content in the ten domains. Further development of each of the content domains follows:

Prognosis

Major HF guidelines, from the earliest (AHCPR, 1994) to the more recent (Arnold et al., 2006; Adams, et al., 2006; Hunt et al., 2005) recommend that clinicians discuss prognosis with patients and, in most instances, with families as well. Such conversations require reliable prognostic information to guide discussion around advanced therapies or referral to palliative care (Fonarow, 2008) or hospice (Goodlin et al., 2004). While guideline authors acknowledge the challenge of prognosis estimation for the individual HF patient, all but one guideline (European Society of Cardiology [ESC], 1997) with end-of-life content recommends establishing and/or communicating prognosis.

In 1994, prior to advanced treatment availability, the rationale for providing prognostic information was to allow patients to make decisions and plans for the future (Konstam et al., 1994). Prognosis is one of the essential elements of educational content for patients and families in the ACC/AHA 1995 (Guidelines, 1995) and 2001 (Hunt et al., 2001) guidelines, although the 2001 document substitutes the phrase *the expected or anticipated course of illness* for *prognosis*, listing it along with *final treatment options*. The ACC/AHA 2005 document encourages providers to attempt prognostication in HF and communicate the information to patients and families.

Table 3 End-of-life Content in Major North American and European Heart Failure Guidelines

Entity	Year	Prognosis	Provider/ Pt/Family Communication	Advance Directives	Identification End-Stage	Symptom Palliation	Inotropes	Device Deactivation	Family/Care- giver Support	Palliative Care/Hospice	Advanced Therapies
AHCPR	1994	X	X	X					X		
ACC/ AHA	1995	X	X	X							
ESC	1997					X	X			X	X
ACC/ AHA	2001	X	X	X	X	X	X	X		X	
ESC	2001	X				X	X			X	X
ACC/ AHA	2005	X	X	X	X	X	X	X		X	X
ESC	2005	X				X	X			X	X
CCS	2006	X	X	X	X	X		X	X	X	
HFSA	2006	X	X	X	X	X	X	X		X	
ESC	2008	X	X	X	X	X			X	X	

The ESC 1997 (The Treatment of Heart Failure, 1997) guideline does not address prognosis, but the ESC 2001 (Remme, et al., 2001) guideline lists estimating prognosis in an outline of heart failure management, as does the ESC 2005 (Swedberg, et al., 2005) guideline, the latter adding a table of risk stratification predictors. The ESC 2001 and ESC 2008 (Task Force, 2008) documents list prognosis with other general subjects to be discussed with patients and families. The ESC 2005 guideline places prognostication in a

paragraph at the end of the HF diagnosis section, but does not include prognosis content in the section of general counseling of patients and families.

The CCS (Arnold et al., 2006) guideline suggests that providers approach heart failure patients regarding their prognosis. In the HFSA 2006 guideline, the recommendation of patient and caregiver discussion around prognosis is included with the topic of quality of life; these discussions are considered part of the disease management of HF.

The challenge and complexity of estimating prognosis for individual patients are acknowledged in several of the guidelines (ACC/AHA 2005; ESC 2005; CCS 2006); discussing the prognosis with patients is also noted to be difficult (ESC 2008) and likely to be avoided (HFSA 2006). The implicit recognition that prognosis estimation may be difficult for patients to hear as well as for providers to communicate is evident in the ESC 2008 advice that patients seek psychosocial support if appropriate. Recommended self-care behaviors related to prognosis (understanding important prognostic factors and making realistic decisions) may prompt the need for that support.

Although the estimation and discussion of HF prognosis are challenging, the guidelines underscore their importance for the following reasons: 1) to motivate patient adherence to treatment (ESC 2008), 2) to help patients and families plan for the future and make realistic and informed decisions regarding treatment (ESC 2008), 3) to identify appropriate candidates for advanced therapies (ACC/AHA 2001; ACC/AHA 2005), and 4) to provide 6-month survival estimates so that patients can be referred for hospice care (ACC/AHA 2001). The ACC/AHA 2001 document offers two caveats: 1) the considerable uncertainty surrounding prognosis estimates are unlikely to facilitate patient

planning for the future and 2) six-month prognosis estimates for hospice care are unreliable.

When should the discussion about prognosis take place? Guidelines recommend that physicians broach the topic early in the disease process (CCS 2006), before the patient becomes too ill to participate in such discussions (ACC/AHA 2001; HFSA 2006). Ongoing reassessment and discussion should occur throughout the course of the disease, given the nature of the HF trajectory (ACC/AHA 2005; HFSA 2006).

Provider/Patient/Family Communication

Guideline content reflects involvement of patients and families from the earliest guidelines to the present. Communication topics identified include: 1) advance directives (ACC/AHA 1995, 2001, 2005; HFSA 2006), 2) expected or anticipated course of illness and treatment options (ACC/AHA 2001), 3) treatment preferences (ACC/AHA 1995, 2001, 2005), 4) disease progression and change in treatment emphasis (ESC 2008), 5) family/caregiver response to cardiopulmonary arrest when patients do not wish CPR (HFSA 2006).

Important discussions should be individualized (HFSA 2006) and should take place before patients are too ill to participate in decision making (ACC/AHA 2001). Good listening and open communication are key elements of end-of-life care (HFSA 2006), with the dual purposes of 1) ensuring care consistent with patient preferences and 2) avoiding conflict among patients, family and clinicians (CCS 2006).

Advance Directives

All but three of the 10 guidelines reviewed advise encouraging patients to complete advance directives. The 1995 ACC/AHA document strongly encourages

patients to complete written advance directives about their future care, and the ACC/AHA 2005 and CCS 2006 guidelines add the recommendation that patients designate a surrogate for health care decisions. The ESC 2008 guideline lists establishing an advanced care plan as one of the steps in the process of providing palliative care. These should be designed along with the patient and a family member, reviewed regularly and include patient future treatment preferences.

The HFSA 2006 guideline underscores the importance of advance directives given the high mortality of HF. The CCS 2006 advises early incorporation of advance directives so that patient wishes can be upheld throughout the disease course. Importantly, they suggest that decisions be reviewed regularly, particularly after a change in the patient's condition. One helpful feature in the CCS guideline is a list of the available advance directive formats in the various Canadian provinces. One caution noted in the ACC/AHA 2005 guideline is that mandated consideration of advance directive decisions at the time of admission for worsening HF may heighten patient anxiety.

Identification of End-Stage in Heart Failure

The ACC/AHA 2001 and 2005 guidelines describe end-stage patient characteristics, and recommend consideration of advanced treatment strategies, which include both advanced therapy options such as mechanical circulatory support and hospice care. The 2005 guideline adds the caveat that options for end-of-life care should be discussed when further therapies are no longer appropriate. In addition, the guideline notes that decisions about the likelihood of end-of-life patient status involve a “complex interaction between objective information and subjective information, emotions, and patient and family readiness” (Hunt et al., 2005, p. 55).

The HFSA 2006 guideline describes another type of indicator. When destination therapy with a ventricular assist device is considered, or intermittent or continuous inotropic support is required for patients with persistent HF symptoms at rest (despite optimal treatment), end-of-life care may be appropriate.

In the end-of-life section of the CCS 2006 guideline, the authors describe the shift in focus from quantity to quality of life that should occur as patients become end-stage. At this point, palliative care consultation should be considered. The content does not include indicators or characteristics of end-stage status in HF, however. In a contrasting approach, the ESC 2008 guideline provides a list of characteristics found in patients appropriate for palliative care. At the same time, the guideline acknowledges the challenge of identifying the timing for palliative care and emphasizes the importance of ensuring that all treatment options have been explored before determining end-stage status.

Symptom Palliation

Eight of the ten reviewed guidelines with end-of-life content address symptom palliation in advanced stages of HF. The two earliest guidelines, AHCPR 1994 and ACC/AHA 1995, do not include symptom management for end-stage patients.

The ESC guidelines of 1997, 2001, and 2005 advise opiates for symptom relief. Goals identified in the ESC 2008's new palliative care section include symptom management, which requires ongoing assessment of patients' physical, psychological, social and spiritual needs, as well as consideration of patients' multiple co-morbidities.

Both the ACC/AHA 2001 and 2005 guidelines recommend IV inotropes for symptom palliation in end-stage patients, as this therapy may allow patients to die with

comfort at home. End-of-life considerations for symptom relief in these guidelines also include the use of IV diuretics, sleeping medications, anxiolytics and narcotics. The 2005 guideline also calls for increased research on comfort provision (including pain and dyspnea relief) at end of life in HF.

The CCS 2006 guideline identifies pain and other symptom control as one of the elements of quality end-of-life care. The guideline highlights the potential suffering associated with dyspnea, noting that it may require narcotics as well as diuretics for symptom control.

End-of-life strategies advised in the HFSA 2006 guideline include effective symptom management. In addition, clinicians are advised to maintain standard HF therapies as part of end-of-life care, since they may also ease symptoms.

Intravenous Inotropes/Vasodilators

Considerable heterogeneity exists among the guidelines with respect to intravenous (IV) inotropes, which may reflect the changing philosophy of clinicians as more evidence about their effectiveness and efficacy has been published (Hauptman et al., 2006). This treatment option is mentioned in six of the ten reviewed guidelines; two of the guidelines include therapy with intravenous peripheral vasodilators. The therapy is further defined (see Table 4) as intermittent or continuous, with either a bridging or palliative function.

Table 4 Intravenous Inotropes and Vasodilators in Advanced and End-stage Heart Failure

Entity	Year	Intermittent	Continuous	Bridge	Palliation	IV Vasodilator
AHCPR	1994			Not addressed		
ACC/AHA	1995			Not addressed		
ESC	1997	X		X		
ACC/AHA	2001	Strongly discouraged	X		X	
ESC	2001	X		X		
ACC/AHA	2005	Recommend against	X		X	X
ESC	2005	<i>Temporary</i> inotropic support - not defined		X	X	
CCS	2006		Not addressed in palliative care section			
HFSA	2006	X	X		X	X
ESC	2008		Not addressed in palliative care section			

The ACC/AHA 2001 and 2005 guidelines list continuous inotrope infusions as one of the specialized treatment strategies Stage D (end-stage) patients may require. The authors of these guidelines note that palliative infusions increase family and healthcare system burden, as well as hasten death, and they advise against the use of intermittent inotrope infusions for end-stage patients. They suggest that when palliative infusions are utilized, they should be part of a comprehensive plan, allowing the patient to die with comfort at home.

The potential bridging function of inotrope infusions is described in both the ESC 1997 and 2001 guidelines: “Intermittent intravenous inotropes can be used in end-stage HF, but should always be considered as an interim approach to further treatment which provides benefit to the patient” (ESC, 1997, p. 749). The 2005 ESC document uses nearly identical language. The ESC 2008 guideline moved discussion of inotropes as a bridge to more definitive therapy to the *organization of acute heart failure treatment* section and omitted inotropes in a new *palliative care for patients with heart failure* section.

The HFSA 2006 guideline acknowledges the temporary symptomatic improvement vasodilator or inotrope infusions offer at end of life, but adds a number of caveats, particularly regarding inotropes. These include: 1) potential for reduced survival, which should be communicated to patients, 2) management by experienced HF clinicians necessary, 3) only employed when other evidence-based treatment options exhausted, 4) reevaluation of intermittent or continuous infusions important, particularly because patient quality of life may be negatively impacted by the intensity of the therapy.

Device Deactivation

The topic of implantable cardioverter-defibrillators (ICDs) deactivation in advanced and end-stage HF patients first appeared in the ACC/AHA 2001 guideline and then in three subsequent guidelines: ACC/AHA 2005, CCS 2006 and HFSA 2006. The ACC/AHA 2001 guideline includes one statement regarding deactivation, noting that decisions against resuscitation should lead to possible deactivation of an implanted defibrillation device. ICD therapy has in-depth coverage in the ACC/AHA 2005 guideline, including the recommendation that discussion of the potential rationale and process for deactivation should occur before an advanced stage of HF is reached. The

recommendation for discussing the option of ICD deactivation is repeated in the section addressing refractory, end-stage HF and again in the end-of-life section.

The 2006 CCS guideline advises a comprehensive process for device deactivation, noting the likelihood that end-stage patients with ICDs will increase and that deactivation has implications with respect to mode of death. The 2006 HFSA guideline states that deactivation of implantable defibrillators should be discussed with patients and families/caregivers. No major North American or European guidelines to date have addressed an emerging end-of-life issue for a small group of HF patients, i.e., if and when ventricular assist devices should be disabled.

Family/Caregiver Support

The majority of HF guidelines include content describing provider/family education and communication, but only a minority address family and caregiver needs for instrumental and/or emotional support, particularly around end-of-life issues. The AHCPR 1994 guideline recognizes the potential for emotional trauma for family members learning cardiopulmonary resuscitation (CPR) and recommends they receive psychosocial support if indicated.

In the end-of-life section, the CCS 2006 guideline advises routine re-evaluation of a patient's home supports and their need for respite care. Moreover, caregivers should be evaluated for coping and degree of caregiver burden, since they experience emotional distress and loneliness and carry increased risk for morbidity and mortality. One of three critical elements of quality end-of-life care identified in the section is support of dying patients and their families.

The ESC 2008 guideline recognizes the sensitive nature of advanced and end-of-life discussions for both patients and families with the recommendation that addressing disease progression and changing treatment emphases should be undertaken with care.

Palliative Care/Hospice

All except the initial two (AHCPR 1994; ACC/AHA 1995) guidelines recommend palliative care and/or hospice for patients at end of life. The ACC/AHA 2001 guideline was the first to advise consideration of hospice for symptom relief, noting its recent extension to patients dying from non-cancer diagnoses. Discussion of the unique palliative considerations for HF and the challenging requirement of establishing HF prognosis for hospice referral accompanied this recommendation.

The ACC/AHA 2001 guideline was also the first to introduce a HF staging system, from Stage A (at risk for heart failure) to Stage D (end-stage heart failure). In the 2001 guideline diagram depicting the stages and recommended therapy by stage, hospice care is listed last under stage D therapies. However, in the ACC/AHA 2005 guideline stage diagram, compassionate end-of-life care/hospice was moved to the top of the list of therapy options for patients with Stage D HF.

The ESC documents of 2001 and 2005 place a palliative care recommendation for terminal patients at the close of the end-stage HF section which advises transplant re-evaluation and interim left-ventricular assist device support. The ESC 2008 guideline moves expanded palliative and end-of-life content to a separate section, listing the goals and steps of the palliative care process. While the guideline acknowledges the challenge of identifying the point at which palliative care treatment should be instituted, it also

notes that the essential components of palliative care programs are not that different from those of HF management programs.

The HFSA 2006 guideline provides coverage of a number of issues related to hospice. Topics addressed include the rationale and timing for appropriate referral, the potential for patient misconceptions about hospice or their prognosis, a description of the Medicare hospice benefit, and the clarification that hospice is not so much a defined place as a method of palliative care delivery.

The section of *Ethical and end-of-life issues* in the CCS 2006 guideline covers a broad range of palliative care content and advises palliative care consultation along with revisiting goals of therapy as patients approach end of life. The document also includes the option of hospice referral in a table of suggested end-stage care domains.

Advanced Therapies

The end-stage sections of the ESC 1997, ESC 2001 and ESC 2005 guidelines begin with the recommendation to (re)consider heart transplantation and the potential need for bridging procedures (i.e. intra-aortic balloon pumping, ventricular assist devices) for those on heart transplant waiting lists. No advanced therapy recommendations appear in ESC 2008 new guideline section *Palliative care for patients with heart failure*.

The *Patients with Refractory End-Stage HF (Stage D)* section of the AHA/ACC 2005 guideline provides recommendations for cardiac transplant referral for potentially eligible patients and for consideration of a left ventricular assist device (LVAD) as destination (permanent) therapy. The recommendations in this section also include referring refractory patients to specialty HF management programs, providing patients and families with information about end-of-life care, informing ICD patients about the

option of deactivation, and considering inotrope infusions for symptom palliation. The *End-of-Life Considerations* section of this guideline does not include recommendations for implementing advanced therapies, but does underscore the importance of clear provider communication regarding procedures done at end of life which may not promote recovery or enhance quality of life.

Discussion

The major North American and European heart failure guidelines demonstrate a remarkable evolution of end-of-life and palliative care content over the past 15 years, much of which can be explained by the temporal sequence of their development. The first US guideline was published by the AHCPR in 1994, as treatment with the first targeted therapy began to alter the natural history of congestive heart failure. At this early stage, content did not include end-of-life considerations, since patients were more likely to die suddenly from arrhythmic, ischemic or embolic events (Teuteberg et al., 2006). The rapid acceleration of change in pharmacologic management of HF in the mid-1990's gave rise to a guideline (HFSA 1999) exclusively devoted to the application of the evidence-based therapies. The ACC/AHA 2001 guideline introduced the categorization of HF in 4 stages, with Stage D representing end-stage. The recognition of advanced, potentially refractory and end-stage disease as a distinct entity was an important factor in the development of greatly expanded guideline content in that document and others to follow. In the ensuing years, as results of clinical trials of advanced therapies such as CRT, ICD, LVAD became available, recommendations concerning their application were incorporated into guideline updates. The competing goals of saving life and easing death became increasingly evident as the question of which patients were truly refractory

emerged; the need to identify end-stage became more urgent as new therapies for Stage D patients were adopted into clinical practice.

Recently, the growing awareness of extended patient survival in advanced HF, despite application of appropriate therapies, has produced a growing presence of end-of-life material in the guidelines. Not only are more content domains included, but palliative and end-of-life care now has its own section in a majority of the guidelines, separate from acute treatment and advanced therapies.

Still, the practice of HF palliative care is in its infancy. This is not surprising, since the subject has been largely absent from medical training, cardiology texts and cardiology journals (Mehta et al., 2001; Rabow, McPhee, Fair, & Hardie, 1999; Rabow & McPhee, 2002). The emergent nature of the field is also evident in a recent survey of US cardiologists, geriatricians and family practice/internal medicine physicians. Hauptman et al. (2008) found little experience with hospice referral. Sixty-four percent of surveyed cardiologists cited uncertainty about referral timing as one factor which limited wider use of this end-of-life option and nearly sixty percent reported two or fewer discussions with patients and families about the option of defibrillator deactivation.

Thus, the low referral rate to specialist palliative care in European countries (ESC 2008) and the relatively small (though increasing) percentage of patients referred to hospice in the US (Hauptman, 2006) may be largely due to unfamiliarity and inexperience with palliative cardiology, in addition to the acknowledged uncertainty inherent in estimating prognosis for advanced HF patients. The relative absence of palliative content in earlier guidelines reflects and confirms the undeveloped state of knowledge.

There may be other important influences on palliative and hospice referrals, as well. For instance, cardiologists participating in palliative care focus groups indicated that they perceived patient death as a failure (Hanratty et al., 2002), a view with important implications for palliative care referral. As Chatoo and Atkin (2009) elucidate, negotiating the tensions between a focus on living with and managing heart failure, which is often espoused by cardiologists, and a focus on dying with heart failure challenges the integration of the two views in both policy and clinical practice.

Instituting a palliative approach to symptom management at the beginning of treatment with evidence-based therapies and devices (Bekelman, Hutt, Masoudi, Kutner, & Rumsfeld, 2008; Goodlin et al., 2004) is one answer to the dilemma of when to refer to palliative/hospice care. Symptom palliation can be titrated according to individual need, a process familiar to HF clinicians in pharmacologic management. Importantly, further research is needed for a range of unanswered questions around palliative care in HF. Both the Consensus Conference of 2004 (Goodlin et al., 2004) and the recent position statement from the palliative care workshop of the Heart Failure Association of the European Society of Cardiology (Jaarsma et al., 2009) detail important avenues for further inquiry.

Three overall principles about treatment at end of life are evident in the HF guidelines. The first is to insure adequate treatment, i.e., that all potentially lifesaving therapies, both standard and advanced, have been employed, ideally by providers familiar with the complex management of HF patients. Secondly, the guidelines caution against unproven therapies such as intermittent IV inotrope infusions, inappropriately aggressive treatment with advanced device therapies, or unwarranted advanced life support at end of

life in HF. Lastly, guideline authors recommend implicitly and explicitly that end of life treatment in HF have the goal of comfort. Still, the notable absence of an evidence-base to guide end-of-life decisions and management poses great challenge to the providers, patients and families who must function within this knowledge gap.

Conclusion

Physicians – and patients and families as well – face unexplored territory as advanced HF becomes end of life with HF. The uncertain nature of the HF illness trajectory, the promise of advanced therapies, the imprecision inherent in prognosis estimation, provider unfamiliarity with complex symptom management, and numerous other difficulties are vital issues confronting all who are involved.

The considerable growth and development of end-of-life content in major HF guidelines in Europe and the US is a promising step in acknowledging and addressing these challenges. As the field continues to evolve, and as research yields evidence to guide clinical practice at end of life, palliation in cardiology will then have clear definition, and clear purpose, as HF patients experience greater comfort in this last stage of the illness journey.

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Chapter 3

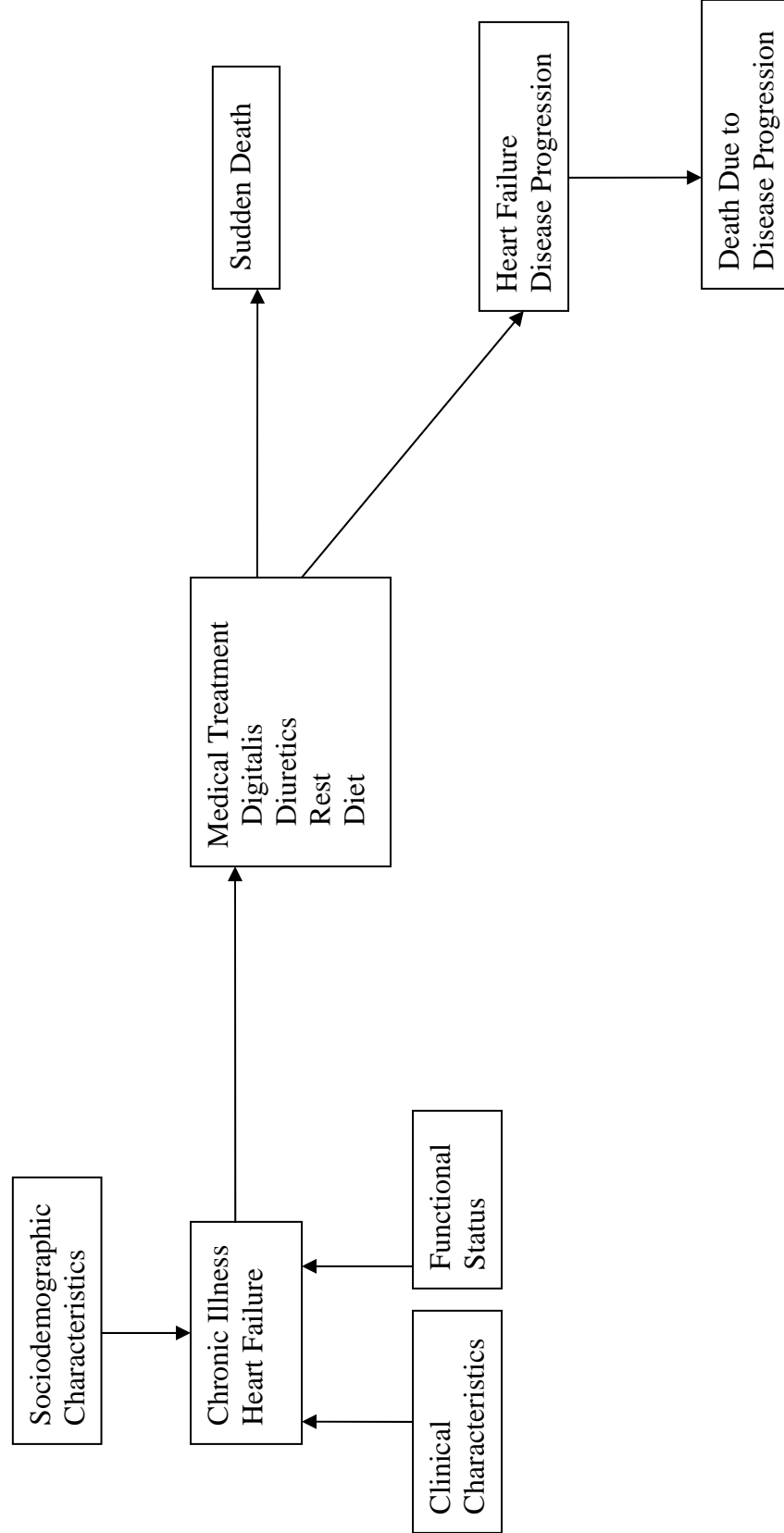
Background

Heart failure (HF) is a condition once known as *dropsy* and treated with bleeding and purges (Stevenson & Kormos, 2001). This complex clinical syndrome results from a range of cardiac disorders and is characterized by limitation in the ability of the ventricle to fill with or eject blood (Hunt et al., 2005). Prior to the late 1980s, treatment was limited to digitalis and diuretics, along with rest and dietary restrictions. Sudden death was common, and few patients lived for extended periods with progressive disease (see Figure 1). Clinical management of HF has undergone tremendous change over the past two decades, as pharmacologic and device therapies have altered the natural history of the syndrome, bringing unprecedented improvements in heart function. The nomenclature has also undergone change, from *congestive heart failure* to the more frequently-used *heart failure* (HF) or *chronic heart failure*, as effective options for managing volume overload and the resulting congestion-based symptoms are now commonplace.

HF is the only cardiovascular disease increasing in prevalence (Mather & Konstam, 2007), a result of a significant decline in coronary heart disease mortality (Ford et al., 2007), increased survival after the onset of HF (Levy et al., 2002; Roger et al., 2004), the ageing of the population (Aging Stats, 2008) and a reduction in sudden cardiac death due to implantable defibrillators (Rose et al., 2001). Thus, as HF survival improves and sudden death incidence declines, patients who die in the current era are likely to have lived with symptoms of advanced disease for an extended period (Teuteberg et al., 2006).

The purpose of this paper is to describe the emergence of a new comeback phase in advanced HF within the theoretical framework of the Corbin and Strauss Chronic

Figure 1 Heart Failure Trajectory Prior to the Neurohormonal Era of Treatment



Illness Trajectory Theory and to integrate aspects of comfort and quality of life (QOL). The Corbin and Strauss Theory does include a comeback phase, but it is more suited to an earlier era of HF care, when patients were likely to die suddenly and few lived for long periods with advanced illness. In the new comeback phase, seriously ill patients may experience remarkable recoveries, only to face end-stage HF and death a second time. A central aim of the paper is to consider the implications of the new comeback phase in advanced HF and the attendant palliative concerns, including the particular challenge of facing death twice.

Factors Affecting the Person with Advanced Heart Failure

In addition to the symptoms resulting from the pathophysiologic processes of advanced disease, sociodemographic factors are important considerations affecting physical functioning among chronically ill persons (Mackenbach, Borsboom, Nusselder, Looman, & Schrijvers, 2001). These include age, gender, race/ethnicity, economic status, living situation and social support. Psychosocial factors and clinical characteristics also have significant impact on advanced HF patients.

Age

Epidemiologic data are not available for advanced HF patients, but hospitalized patient characteristics are most likely to be representative (Metra et al., 2007) since inpatient stays are common in this group. Mean age in two recent, large hospitalized HF patient registries in the United States was 72.4 years (Adams et al., 2005) and 73.1 years (Fonarow et al., 2007), reflecting the high prevalence of HF in older adults (American Heart Association [AHA], 2009). In a survey of HF admissions in England, Wales and Northern Ireland, Nicol et al. (2008) found that patients were somewhat older (mean age

of 77 years) than those in the US registries. All hospitalized HF patients are considerably older, however, than the patients typically enrolled in HF clinical trials. The mean age of clinical trial participants was 64 years in the late 1990s (Heiat, Gross, & Krumholz, 2002), limiting generalizability of findings from RCTs to all HF patients.

Gender

Half of patients hospitalized for HF are female (Adams et al., 2005; Fonarow et al., 2007). As in the case of patient age, the equal gender division is not characteristic of HF clinical trials, as the average number of women enrolled in studies since 1985 is only 22% (Heiat et al., 2002).

Race/Ethnicity

In the two largest registries of hospitalizations (Adams et al., 2005; Fonarow et al., 2007), patients were predominantly Caucasian (72%, 74.1%), with African-Americans comprising 20% and 17.7% of the samples, respectively. US population prevalence data show that in males 3.1 % of Caucasian adults, 4.2 % of Black adults, and 2.1% of Mexican-American adults have HF. For females, 1.8 % of Caucasian adults, 4.2 % of Black adults, and 1.4 % of Mexican-American adults have HF (AHA, 2009). African-American females have the highest (3.5%) mortality (Miller, 2008).

Sociodemographic Factors

Few sociodemographic data are available for advanced HF patients, but sociodemographic factors deserve research attention. For example, in the overall US population, low socioeconomic status is associated with lower reported health status and higher mortality (Franks, Gold, & Fiscella, 2003) and may have considerable impact on older, advanced HF patients with multiple co-morbidities and few economic resources.

Moreover, while little is known about the living situation of this group with advanced disease, social isolation has been shown to be a predictor of mortality in HF patients (Murberg, 2004). Greater social support is associated with higher health-related QOL (Clark, Tu, Weiner, & Murray, 2003), and marital quality (Rohrbaugh, Shoham, & Coyne, 2006) has prognostic importance in cardiac disease.

Psychosocial Factors

Psychosocial factors are assessed and treated infrequently in HF patients (MacMahon & Lip, 2002; Moser, 2002) but have important implications for short and long-term outcomes. Researchers have demonstrated that anxiety (Moser & Dracup, 1996) and depression (Jiang et al., 2004; Jiang et al., 2007; Junger et al., 2005; Murberg, Bru, Svebak, Tvetas, & Aarsland, 1999; Sherwood et al., 2007; Sullivan, Levy, Crane, Russo, & Spertus, 2004) are positive predictors of morbidity and mortality. Furthermore, HF patients' perspectives on their health, assessed with summary (self-report) health status measures (Kansas City Cardiomyopathy Questionnaire and Standard Gamble instrument), were significant prognostic indicators in a study of 142 outpatients with advanced HF (Sullivan, Levy, Russo, Crane, & Spertus, 2007).

Clinical Characteristics

Relevant clinical characteristics in advanced HF include disease severity assessment, measurement of cardiac function, comorbidities, previous HF history, and physiologic measurements such as blood pressure. Data from one registry of hospitalized HF patients showed that 44% were dyspneic at rest (Fonarow et al., 2007), a finding which correlates with New York Association (NYHA) Class IV functional assessment (symptomatic at rest). Of the patients with NYHA Class data in the second large registry

(Adams et al., 2005), 32% were Class IV and 44% were Class III (symptomatic with minimal activity).

The mean left ventricular ejection fraction (EF), an assessment of cardiac pumping function obtained with echocardiography, was 39% (normal range 55-70%) (Beers, Jones, Berkwits, Kaplan, & Porter, 2004) in the first-mentioned registry. In the patients with available EF data in the second registry, 54% had an EF at or below 40%, meeting the widely-used, but arbitrary definition of left ventricular systolic dysfunction (Definition, n.d.). Thus, a significant proportion of patients had higher EFs, an indication of HF with preserved systolic function (HFPSF). Much less is known about the management of HFPSF, a condition previously known as diastolic HF.

Comorbidities were common in the hospitalized HF patients and included diabetes, hypertension, and renal insufficiency. Mean systolic blood pressure was just above 140 mmHg in both registries. (Adams et al., 2005; Fonarow et al., 2007). The majority of patients had a prior HF diagnosis in one of the registries (Fonarow et al., 2007), and patients had an average of one HF admission in the previous 6 months in the second registry (Adams et al., 2005). Advanced HF patients currently live with their decline for extended periods, as they are less likely to die suddenly than patients in earlier eras of HF therapy.

In summary, an overview of the characteristics of this patient group indicates that the extended life for the largely older individuals includes comorbidities, significant HF symptoms, functional limitations, and frequent hospital admissions for worsening HF. The significant proportion of patients with higher EFs, indicating HFPSF, may be related to the demographic of half women in the large registries of hospitalized patients, as this

type of HF is more common in females. Little is known about socioeconomic factors such as living situations or about levels of social support, issues of vital importance as these patients approach end of life.

Advanced Heart Failure

The increased survival in HF over the past two decades is largely the result of pharmacologic and device therapies altering the natural history of the syndrome. The development of the new pharmacologic therapies has both been the result of and a contributor to significant advances in our understanding of the pathophysiology of HF. The emergence of the new comeback phase in HF would not have occurred without that understanding. Although remarkable improvement for extended periods is now possible for many patients, disease progression eventually results in advanced and end-stage HF.

When the chronic illness of HF progresses to an advanced stage, its trajectory corresponds to the that of the downward phase in the Corbin and Strauss framework (Corbin & Strauss, 1991). Advanced HF, defined as persistent symptoms limiting daily life despite optimized, evidence-based medical therapy, (Adams & Zannad, 1998) affects approximately 300,000-800,000 patients in the United States (Stevenson & Rose, 2003). Patients with advanced disease are described functionally as New York Heart Association Class III or IV, and classified as Stage D in the American College of Cardiology/American Heart Association (Hunt et al., 2005) guidelines. Stage D is considered end-stage, identifying patients who require additional, often advanced, treatment strategies (Hunt et al., 2005), and who have an expected one-year mortality in the range of 30-50% (Stevenson, 2005). Hospitalization is common for decompensated HF, and patients often require assistance with activities of daily living (ADLs) (Goodlin et al., 2004).

The Corbin and Strauss Chronic Illness Trajectory Theory

HF is a quintessential chronic illness: long-term rather than episodic, rarely cured, associated with symptoms, treatments, and significant patient involvement in the treatment process (Holman, 2004). Other key chronic illness characteristics found in HF are the uncertain prognosis, the significant effort required for symptom palliation, and the intrusiveness into patients' and families' lives (Corbin & Strauss, 1988). Overall, the chronic illness of HF exerts "profound influence on the lives of the sufferers" (Scambler, 2003, p.80). The concepts of trajectory and trajectory phases place that profound influence within a framework, facilitating greater understanding on the part of patients, families and providers.

The concept of *trajectory* is a useful one to depict or describe a process or typical course of a phenomenon. This concept has been used to characterize the dying patterns of hospitalized patients and the related organization of hospital work (Glaser & Strauss, 1968); the differences between the dying patterns of cancer and the patterns of the other four major causes of death (HF, diabetes mellitus, cerebral vascular accident and chronic obstructive pulmonary disease) in the US (Teno, Weitzen, Fennell, & Mor, 2001); functional decline in older adults in the year before death (Lunney, Lynn, Foley, Lipson, & Guralnik, 2003); and social, psychological and spiritual decline in advanced illness (Murray et al., 2007). While these trajectories depict dying and decline patterns, Corbin and Strauss applied the notion of trajectory to the totality of chronic illness.

Background

The trajectory framework developed by Julie Corbin and Anselm Strauss evolved in the 1960s from chronic illness research and narratives of nurses caring for persons with

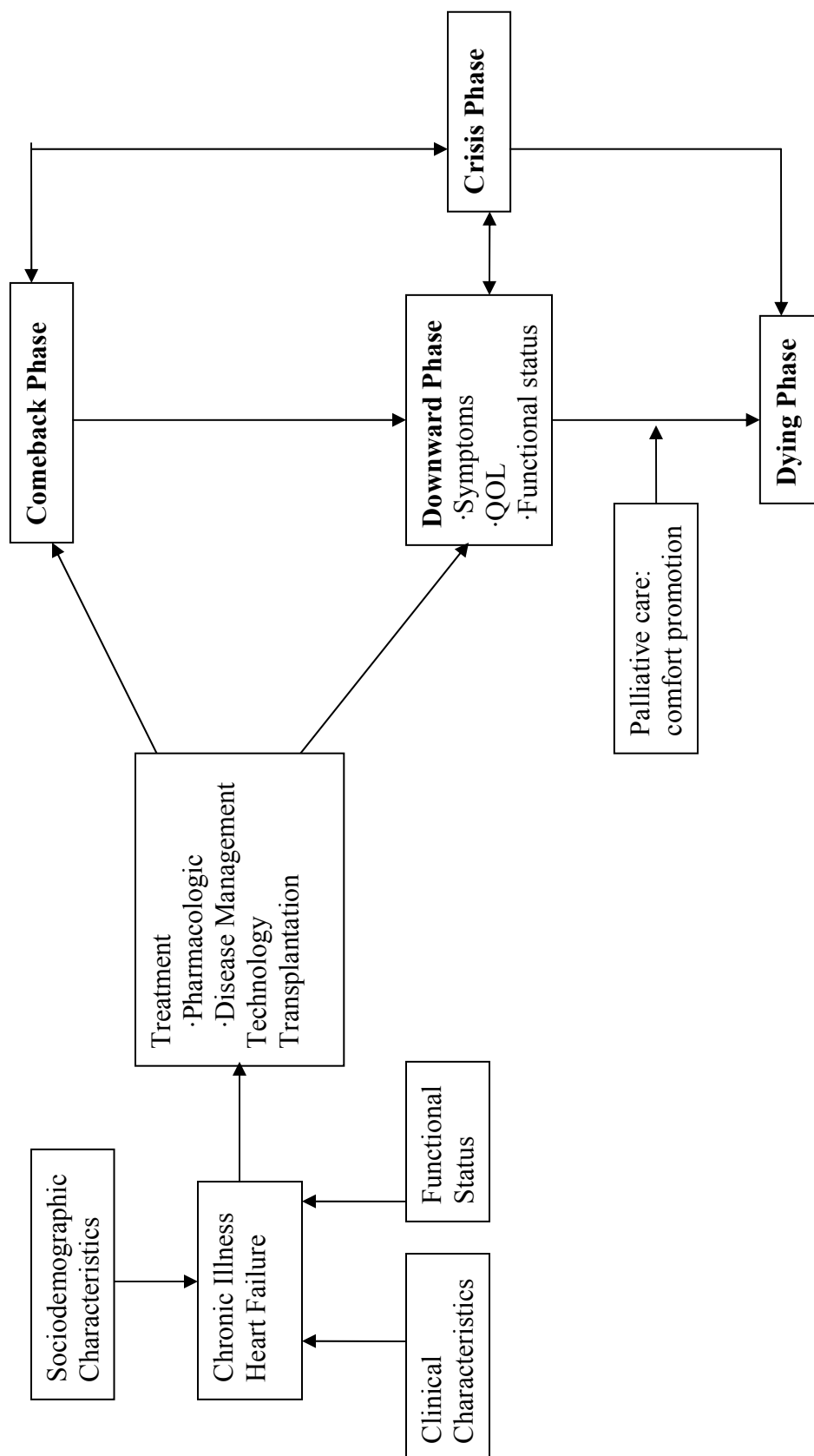
a variety of chronic illnesses. A central concept is that chronic conditions have a course (trajectory) which varies and changes over time, and which includes the following dimensions: 1) the physiological unfolding of the condition, 2) the organization of the work required throughout the illness course, and 3) the impact on all involved in that work (Strauss et al., 1984). The five trajectory phases Corbin and Strauss identified in 1988 expanded into eight phases three years later: pre-trajectory, trajectory onset, crisis, acute, stable, unstable, downward and dying (Corbin & Strauss, 1991), with a comeback phase added in a later revision (Corbin, 1998). Each phase requires different types and amounts of “work;” i.e., the management tasks the illness requires (Strauss & Corbin, 1988).

Four phases have particular relevance for advanced HF: crisis, downward, comeback and dying (See Figure 2). As a result of the expanded therapeutic options currently available for HF (discussed in subsequent sections), the illness trajectory possibilities for individual patients are far more complex than those depicted in Figure 1.

Crisis Phase

The goal of management in a crisis phase (critical or life-threatening situation) is to remove the life threat. Emergency treatment is required, and all of everyday life activity is suspended until the crisis is resolved (Corbin, 1998). In advanced HF, acute pulmonary edema (lung congestion) and cardiogenic shock are two such potential life-threatening situations requiring immediate action. Patients may enter the crisis phase (see Figure 2) from a downward phase, with worsening HF suddenly becoming an acute illness. Or, relatively stable comeback phase patients may experience an acute event, such as a myocardial infarction, and become critically ill. One of three outcomes of the

Figure 2 Heart Failure Trajectory Phases in Current Treatment Era



crisis phase is possible: 1) resuming the more gradual downward phase, 2) coming back; i.e., recovering significantly with the aid of current therapeutic options, or 3) entering the dying phase.

Downward Phase

The downward phase, known as the deterioration phase in an earlier publication (Strauss & Corbin, 1988), is characterized by a rapid or gradual decline in the chronic illness course with the result of increasing disability and difficulty controlling symptoms. These changes, common to advanced HF, alter daily life and require ongoing adaptation by the ill and those close to them. Patients enter the downward phase (see Figure 2) when they do not respond to therapeutic interventions such as pharmacologic treatment, technological interventions, or cardiac transplant. Other patients, who did respond to the therapies and entered a comeback phase (see below), enter the downward phase when disease progression recurs. Two outcomes are possible: 1) continuing slow decline into the dying phase or 2) rapid deterioration into the crisis phase.

Comeback Phase

The comeback trajectory phase, inadvertently omitted from Corbin and Strauss' 1993 presentation of the theory, describes a "gradual return to an acceptable way of life within limits imposed by disability or illness" (Corbin, 1998, p. 36). Four components of the phase were identified: 1) physical healing, 2) rehabilitation 3) psychosocial adaptation and 4) biographical reengagement with adjustments in everyday activities (Corbin, 1998). In 1988, when there were only five phases in the chronic illness trajectory, the comeback phase followed the acute phase, but moved to follow the crisis phase in 1998. Figure 2 depicts the new comeback phase, which is the result of treatment advances and is

characterized by an unprecedented degree of recovery in HF. This new type of comeback is further developed in a subsequent section.

Dying Phase

The downward phase eventually leads to the dying phase, which covers the final days or weeks before death (Corbin, 1998). The four subphases of the dying phase are: immediate, proximate, farther in the future, and far away but still inevitable (or gradually happening) (Strauss & Corbin, 1988). Patients enter the dying phase (see Figure 2) gradually from the downward phase or more acutely from a crisis phase. The goal of palliative care is the provision of comfort along that path between the downward and dying phase, with continuation in the dying phase.

Therapeutic Advances in Advanced Heart Failure: The Promise of Comeback

Improved HF survival is largely due to advances in pharmacologic therapies, device technology and cardiac transplantation over the past two decades. These advances have made the emergence of the new type of comeback phase in advanced HF possible.

Pharmacologic Advances

An example of the therapeutic advances is the application of evidence-based pharmacologic therapy (primarily angiotensin-converting enzyme inhibitors and beta blockers), which often results in gradual improvement in cardiac structure and function (Cioffi et al., 2005; Hunt et al., 2005). One caveat is that titration of these therapies to optimum levels requires personnel experienced in HF management, skilled in patient coaching, and endowed with patience, as the process may take many months.

Technological Advances

In addition to pharmacologic therapy, technological advances in device therapies and improved survival following cardiac transplantation provide expanded options for advanced HF patients and may usher in the new comeback phase. Technology has moved to the forefront of HF treatment in the past decade with the use of three device types: biventricular pacemaker implantation (also known as cardiac resynchronization therapy [CRT]), implantable cardioverter defibrillators (ICDs), and left ventricular assist devices (LVADs). Large-scale randomized clinical trials (RCTs) have tested the application of each of the devices to advanced HF patients. None of the therapies are without potential complications, however, and not all patients respond with improved cardiac function. Furthermore, not all patients meet the particular criteria for use of each of the devices.

Cardiac resynchronization therapy. When HF patients develop delays in the cardiac conduction system propagation of the electrical impulse between the atria and ventricles and between the ventricles, mechanical delay between the contraction of the right and left ventricles follows. The resulting dyssynchrony leads to worsening ventricular function (Gura & Foreman, 2004) and worsening HF. CRT restores more normal electrical activation with the result of a more synchronous ventricular function in patients with advanced HF. Use of resynchronization therapy has been shown to prevent (or defer) the need for cardiac transplantation (Greenberg et al., 2003; Vanderheyden et al., 2006), decrease the risk of death or hospitalization (Bristow et al., 2004), improve functional capacity (De Marco et al., 2008; Higgins et al., 2003; Molhoek et al., 2002; Vanderheyden et al., 2006), improve QOL, reduce HF hospitalizations, improve left ventricular ejection fraction (LVEF) (Molhoek et al., 2002), and allow weaning from

inotropic support with subsequent hospital discharge (Cowburn, Patel, Jolliffe, Wald, & Parker, 2005).

Implantable cardioverter defibrillators. Despite treatment with current evidence-based therapies, HF patients may die suddenly and unpredictably from arrhythmias (Bardy et al., 2005). Implantable cardioverter defibrillators (ICDs) are indicated for the primary and secondary prevention of ventricular arrhythmias and sudden cardiac death (SCD) in patients with HF and reduced LVEF, since they are at high risk for these events (Whang et al., 2004). Data from two large clinical trials (Bardy et al., 2005; Moss et al., 2002) established that ICDs provide a mortality benefit for HF patients with reduced LVEF who meet implantation criteria. As HF prevalence grows and evidence-based guidelines for management increasingly inform treatment decisions, many more patients are likely to have ICDs implanted. As the number of HF patients with ICDs increases, fewer of them are likely to die suddenly, thus increasing the number who will survive to die of progressive HF (Stevenson & Desai, 2006), often with an ICD in place.

As a result of this altered trajectory, the issue of device deactivation assumes greater salience, as greater numbers of HF patients approach end of life with an ICD in place. Anecdotal reports (Stein, 2006), case studies (Nambisan & Chao, 2004) and research data (Goldstein, Lampert, Bradley, Lynn, & Krumholz, 2004) describe significant patient and family distress when repeated shocks from an ICD accompany the dying process. Factors contributing to this disturbing scenario at end of life include those attributable to patient understanding and attitudes (Goldstein et al., 2008; Stevenson & Desai, 2006), health care provider barriers and knowledge deficits (Braun, Hagen, Hatfield, & Wyse, 1999; Goldstein et al., 2004; Goldstein, Mehta, Teitelbaum, Bradley,

& Morrison, 2008; Mueller, Hook, & Hayes, 2003), deficiencies in national guidelines (Sears et al., 2006), family misperceptions (Stevenson & Desai, 2006), and deficiencies in standard advance directive forms (Berger, Gorski, & Cohen, 2006; Goldstein et al., 2004).

Left ventricular assist devices. Left ventricular assist devices (LVADs) provide hemodynamic circulatory support. Some LVADs have short-term application for acute cardiac dysfunction, while others are designed for longer-term use. These mechanical devices are surgically placed in the left upper quadrant of the abdomen, and have a tunneled driveline site which exits on the right side of the abdomen and connects either to a console at the bedside or to a battery pack worn in a vest (Stahovich, Chillcott, & Dembitsky, 2007; Stevenson & Shekar, 2005).

Left ventricular assist devices (LVADs) are an option for patients who require mechanical circulatory support while awaiting heart transplantation (Rogers et al., 2007). This “bridge to transplant” LVAD role differs from that of implantation as “destination therapy” (DT) for patients who do not meet transplant criteria in that the bridge is a temporary measure and DT is a permanent alternative to cardiac transplant (Lietz et al., 2007). A third LVAD role, “bridge to recovery,” appears promising, as myocardial function improves with the mechanical support of the LVAD (Stevenson & Rose, 2003). “Bridge to transplant eligibility,” is an emerging LVAD role, as physiologic improvements attributable to mechanical circulatory support change patients’ potential for inclusion on transplant waiting lists (Hunt, 2007; Rogers et al., 2007).

Cardiac transplantation. Cardiac transplantation remains the gold standard for treatment of end-stage HF, with a one-year survival of 88% and five year survival of 74%

(OPTN/SRTR 2006 Annual Report). However, the limited availability of donor hearts, the requirement of lifelong immunosuppression, and the potential for serious complications post-transplant are important considerations in evaluating this advanced option. For the future, beyond cardiac transplant and current device therapies, new pharmacologic therapies, cell-based and gene therapies show considerable promise in treating advanced HF (Mudd & Kass, 2007).

Therapeutic Advances and the New Comeback Phase

An unanticipated consequence of the progress in treatment, technology and transplant is the creation of a new type of *comeback phase* in advanced HF, with unique characteristics depending on the type of therapy. When medical (pharmacologic) treatment is employed, the return to prior function is usually gradual, depending on the response to medications and clinical challenges encountered in titrating to evidence-based dosage levels.

Device technology has dramatic rescue potential with an LVAD, as patients near death in critical care units have circulatory function restored following assist device implantation. Cardiac resynchronization therapy (CRT) with a biventricular pacemaker provides both short and long-term improvement potential in functional status. Rescue from instances of a sudden (arrhythmic) death trajectory is possible for patients with ICDs, but these defibrillators do not change the overall downward disease trajectory in advanced HF. Patients who receive cardiac transplants have the potential for longer-term survival, with extended plateaus of relative stability characterizing the trajectory. Transplanted patients, who may have been hospitalized and dependent on intravenous (IV) medications (inotropes) to maintain their circulation, are in many cases able to

resume productive lives when they receive a new heart. Figure 2 depicts the comeback phase, which patients enter when they respond to the current HF therapies or when they experience significant recovery from a crisis phase. Little is known about the time frame of the new comeback, with the exception of the documented length of survival after heart transplantation.

The new comeback phase provides a striking contrast to the original comeback phase Corbin and Strauss described, as that original phase was characterized by *stabilization* and *modest improvement* in the chronic illness patient's functional status through rehabilitative and other efforts *within the limits of their condition*. In the new comeback phase, advanced HF patients may experience dramatic rescues, remarkable improvement in function (exceeding the previous limits of their condition) and, in some cases, a return to normal or near-normal life. The new comeback phase in a chronic illness is unique to HF, as this trajectory phase is not found in other chronic illnesses such as chronic obstructive pulmonary disease (COPD) (personal communication, P. Gold, MD, 4/16/08).

The new type of comeback phase is distinct from recovery following a crisis phase in HF or other chronic illnesses. HF decompensation is characterized by severe shortness of breath (dyspnea) and swelling (edema) and frequently requires hospitalization for treatment with IV diuretics and other therapies to restore fluid balance (i.e., a "crisis"). Recovery returns the patient to the downward trajectory, albeit to a somewhat lower point than pre-crisis. Other chronic illnesses also have crises: diabetic coma or pneumonia requiring intubation and mechanical ventilation for a COPD patient. However, their recovery does no more than return them to (or near) their pre-crisis state.

The new comeback phase is also distinct from cure and is more closely akin to remission in malignant disease, with a decrease or disappearance of the signs and symptoms of cancer. Remission may be complete or partial (depending on the extent of the disappearance of signs and symptoms), and does not exclude the possibility that cancer is still present in the body (National Cancer Institute, n.d.).

An unintended but significant result of the therapeutic advances and the new comeback phase is that advanced and end-stage HF patients may be consigned to experience the downward trajectory phase and end of life more than once. Although rescue or other more gradual (“comeback”) improvements may return them to a near-normal quality of life (QOL), HF progression will resume at some point in the illness course. This potential for increased suffering for advanced HF patients and their families as they encounter recurrent decline has not been studied systematically, and palliative needs have not been described.

Palliative Care: Adding Comfort to the Downward and Dying Phases

The need for palliative care in the downward and dying phases of HF is evident from the symptoms patients experience and the impact of advanced disease on QOL. The symptom burden is considerable, and symptoms negatively impact patients’ functional status. QOL suffers as a result of the disease process, but also may decline as a consequence of the advanced therapies. While advanced therapies and cardiac transplantation move many patients out of the downward and dying phases into a comeback phase with markedly improved QOL, complications related to the therapies themselves are a potential source of suffering. At some point, disease progression will recur and, with it, the need for palliation and comfort.

The Downward Phase: Symptoms

HF symptoms define the downward phase in advanced HF, as patients experienced a mean of 6.2 (O'Leary, Tiernan, & McDonald, 2006), 11.9 (McMillan, Dunbar, & Zhang, 2007), and 15.1 symptoms (Zambroski, Moser, Bhat, & Ziegler, 2005) according to recent studies. Study findings included the expected symptoms of dyspnea, fatigue and swelling. They also included a wide range of other symptoms: anorexia, cough, orthopnea, weight loss, poor concentration, chest pain/pressure, other pain, anxiety, insomnia, depression, dysphagia, dry mouth, dizziness, drowsiness, irritability, nervousness, worrying, numbness and tingling of the hands and feet, pruritis, constipation, tremors, palpitations, headache, indigestion, nausea, vomiting, incontinence, confusion, sexual problems, sweats (McMillan et al., 2007; Nordgren & Sorensen, 2003; Zambroski, Moser, Bhat et al., 2005) The symptom of pain (Nordgren & Sorensen, 2003; Zambroski, Moser, Bhat et al., 2005) in advanced HF is prevalent but not well understood; in one study, reported pain doubled among subjects over time (Walke et al., 2007).

Qualitative interview studies addressing the symptom experience of advanced HF patients add their perspective to the findings from quantitative research. For example, patients described a range of breathlessness experiences: from “everyday” breathlessness, to “worsening,” to “uncontrollable” (Edmonds et al., 2005). They expressed difficulty in distinguishing between medication side effects and symptoms (Edmonds et al., 2005); linked the effects of symptoms to ADL limitations (Horne & Payne, 2004); expressed related feelings of uselessness (Barnes et al., 2006); described the panic and terror of severe dyspnea (Boyd et al., 2004; Murray et al., 2002); and detailed how they felt

trapped by their symptoms (Ekman, Ehnfors, & Norberg, 2000).

HF symptoms and their associated distress are clearly important to patients and are vital considerations in the management of advanced disease, since they are related to impaired QOL, reduced psychological well-being, and declining functional status (Blinderman, Homel, Billings, Portenoy, & Tennstedt, 2008), and they lead to social isolation for patients and caregivers (Aldred, Gott, & Gariballa, 2005). Symptom stability is also a key criterion for discharge readiness when advanced HF patients are hospitalized for decompensation (Nohria, Lewis, & Stevenson, 2002). Moreover, advanced HF symptoms, when defined operationally as NYHA Class III or IV functional status, were independent predictors of the time to first inappropriate ICD shock (Hreybe et al., 2006). Individual symptoms of fatigue and breathlessness were found to have long-term prognostic implications as well (Ekman et al., 2005).

Although end-stage HF symptoms are prevalent and often severe, research findings revealed a common theme of their inadequate treatment. Symptoms reported at hospice admission were unchanged on the day of death (Zambroski, Moser, Roser, Heo, & Chung, 2005); patients were rarely referred to specialist HF teams (Horne & Payne, 2004); measures to alleviate symptoms were provided sparingly (Nordgren & Sorensen, 2003); and utilization of a palliative care approach was rare (Boyd et al., 2004). An issue with important implications for symptom management uncovered in the retrospective hospice record review by Zambroski et al. (2005) is that standard HF medications were discontinued following admission to hospice care. While these evidence-based therapies are disease-modifying, they are also essential for palliation in advanced HF, since they reduce symptoms such as breathlessness and swelling.

Symptom Impact on Daily Life: Functional Status

Symptoms are an important determinant of functional status (Wilson, Rayos, Yeoh, Gothard, & Bak, 1995) and are commonly considered an indicator of the impact of a disease on capacity and ability to perform (Coyne & Allen, 1998). Conceptual clarity regarding the term functional status is limited, however, as it has been used as a synonym for functional ability, disability, health status, ability to perform activities of daily living, and QOL (Miller-Davis, Marden, & Leidy, 2006). Coyne and Allen (1998) provide a useful clarification of functional status, referencing Leidy's (1994) description of four dimensions: functional capacity, functional performance, functional reserve, and functional ability utilization. Functional capacity describes maximal potential to perform daily activities, while function performance concerns the daily activities people do as they meet their basic needs, fill their roles and maintain health and well being. Functional reserve describes the difference between capacity and performance. The definition of functional capacity utilization is less clear, as it describes the degree of functional potential used in a certain level of performance (Leidy, 1994). The dimensions with the greatest utility for chronic illness assessment are functional performance (i.e., what is the person doing on a daily basis?) and functional capacity (i.e., what could they do when tested at a level commensurate with the energy expenditure of daily activities?).

Exercise-based functional measures assess physical capacity (Coyne & Allen, 1998), now understood to be more closely related to skeletal muscle pathophysiology in HF (Witte, Notarius, Ivanov, & Floras, 2008) than to abnormal cardiac hemodynamics (Wilson et al., 1995). However, both subjective and objective measures figure in the assessment of functional status in HF.

The subjective, provider-assessed New York Heart Association (NYHA) classification system provides “an overall cardiac appraisal of the status of a patient with heart disease” (Miller-Davis et al., 2006, p. 217) and assesses functional performance (Coyne & Allen, 1998). Symptoms experienced with various levels of activity are the basis for the determination of the NYHA class, ranging from I (no symptoms with ordinary activity) to Class IV (symptomatic at rest) (Miller-Davis et al., 2006). This measure of functional status, commonly used by clinicians and researchers (Shively & Wilson, 2001), has limitations of interobserver variability and insensitivity to changes in exercise capacity (Hunt et al., 2005). Patient self-report of symptoms or general (global) health perception (Shively & Wilson, 2001) are other subjective methods of functional status assessment commonly used by clinicians.

An objective performance measure, the 6-minute Walk Test (6MWT), assesses patient physical capabilities at a submaximal level, as patients choose their own exercise intensity and stop to rest as needed. This test provides information about functional limitations since most activities of daily living are performed at a submaximal level of exertion (ATS, 2002). Measurement of peak oxygen uptake during cardiopulmonary exercise testing provides another objective assessment of functional status. This form of exercise testing is used in cardiac transplant evaluation, disability determination, and in formulating exercise prescriptions (Hunt et al., 2005).

Advanced HF patients are characterized by severe symptoms which impact daily life activities (NYHA Class III-IV) and by a considerable reduction in exercise capacity when measured objectively with a 6MWT or peak oxygen uptake (Metra et al., 2007).

Moreover, patients with advanced disease show greater short-term variability in functional status than those with milder limitations (Hauptman et al., 2004).

Quality of Life

The goal of trajectory management in the Corbin and Strauss theoretical chronic illness framework is QOL (Corbin & Strauss, 1991). Patients themselves have a central role in achieving this goal (Corbin, 1993), and healthcare providers have a role in supporting them. Physicians “must pay considerable attention to developing the types of treatment plans that will ensure patients and their families quality as well as quantity of life” (Corbin & Strauss, 1988, p. 36). For nursing, the highest goal in caring for patients with chronic illness is to help them shape the illness course while also maintaining QOL (Corbin & Strauss, 1991).

The concept of QOL, defined with elegant simplicity as “satisfaction in areas of life deemed important to the individual” (Bredow, Peterson, & Sandau, 2009, p.273), includes consideration of “physical symptoms, psychological problems, iatrogenic adverse effects and curtailment in social activities” (Berry & McMurray, 1999, p. 248). A subset of the broader concept of QOL is health-related quality of life (HRQOL). This subjective, multidimensional and temporal concept has been described as “representing satisfaction in areas of life likely to be affected by health status” (Bredow et al., 2009, p. 273). However, the distinction between the broader concept of QOL and the more specific HRQOL is not always clear in the HF literature (Johansson, Dahlstrom, & Brostrom, 2006), and the terms are often used interchangeably.

Generic QOL instruments are designed for the assessment of general aspects of health and can be used for a variety of conditions, while disease-specific instruments are

used for a particular disease or disorder (Bennett et al., 2003). Examples of generic instruments include the Short Form Health Survey (SF-36) (Ware & Sherbourne, 1992) and the Sickness Impact Profile (SIP) (Bergner, Bobbitt, Pollard, Martin, & Gilson, 1976). Instruments specific to HF include the Chronic Heart Failure Questionnaire (CHQ) (Guyatt et al., 1989), the Minnesota Living with Heart Failure Questionnaire (MLHF) (Rector, Kubo, & Cohn, 1993), and the Kansas City Cardiomyopathy Questionnaire (KCCQ) (Green, Porter, Bresnahan, & Spertus, 2000).

Patients in the downward trajectory phase of HF, i.e., those with advanced disease, have significantly compromised QOL (Dracup, Walden, Stevenson, & Brecht, 1992). Researchers observed that the higher the NYHA Class (greater HF severity), the greater the difference in QOL (across all domains of the SF36 questionnaire) when HF patients were compared to the general population (Hobbs et al., 2002). In a study of community-dwelling patients with NYHA Class III-IV HF, impaired QOL was significantly associated with high symptom distress ($p = 0.002$), poorer psychological well-being ($p = 0.002$), and functional impairment ($p = 0.002$) (Blinderman et al., 2008). Appropriately, a group of HF experts (Goodlin et al., 2004) identified QOL in advanced HF as a key research focus, both in discovering and testing interventions to optimize QOL and in identifying outcome measures best suited for assessing QOL in advanced HF patients.

Advanced Therapies and QOL

For those who meet criteria for advanced HF therapies, the impact on QOL has considerable variability. For example, researchers found that ICD recipients who have experienced shocks from the device have decreased QOL (Carroll & Hamilton, 2005;

Schron et al., 2002), but others report little relationship between ICD shocks and QOL (Duru et al., 2001; Kamphuis, de Leeuw, Derksen, Hauer, & Winnubst, 2003; Sears, Lewis, Kuhl, & Conti, 2005). Relatively small sample size and lack of a consistently used QOL instrument use across studies limit the generalizability of these research findings.

In a study of twenty-two LVAD patients, those who had a device in place showed a trend toward poorer QOL than those who had received a transplant or been explanted (had the device removed) (Wray, Hallas, & Banner, 2007). In another study, patients randomized to destination LVAD therapy (n = 24) had significantly better SF-36 scores at one year than the medical therapy group (n = 11), in both physical function and emotional role subscales; however, device patients were more than twice as likely as those receiving medical therapy only to have an adverse event such as sepsis, device failure, or stroke (Rose et al., 2001).

Birks et al. (2006) combined LVAD implantation and pharmacologic therapy to promote reversal of HF in inotrope-dependent patients. With this approach, heart function recovery allowed device explantation in 11 of the 15 patients; the other four patients required cardiac transplantation. The eight survivors (2 deaths, 1 cardiac transplant) of the eleven who were explanted had QOL scores in a near-normal range at 3 years after device removal. The QOL of the four potential study candidates who were in cardiogenic shock at the time of LVAD implantation, the four who died in the perioperative period, and the patient with severe abdominal complications on post-operative day eight is unknown. Of note, the patient with abdominal complications lived for 138 days and died of disseminated sepsis.

CRT patients also can experience considerable change in QOL as a result of the therapy. When compared to patients randomized to medical therapy alone, those randomized to CRT therapy plus medical therapy had significantly greater improvement in QOL scores at 3 months and 6 months post device implantation (De Marco et al., 2008). This finding is consistent with other researchers' findings of improved QOL for HF patients who meet criteria for CRT implantation (Abraham et al., 2002; Auricchio et al., 2002; Cazeau et al., 2001; Cleland et al., 2005). QOL for advanced HF patients who do not meet criteria for CRT implantation has not been studied specifically, but advanced HF patients in general are known to have poor quality of life (Blinderman et al., 2008; Dracup et al., 1992).

During evaluation for cardiac transplant, patients and caregivers identified hope for a good QOL as their most important educational and counseling need (Walden et al., 2001). Cardiac transplant recipients report improvement in QOL following transplantation (Grady, Jalowiec, & White-Williams, 1996; Molzahn et al., 1997). However, they may experience continued challenges to QOL such as limited exercise capacity (Myers et al., 2003) and their awareness of vulnerability to complications associated with transplant (Dew et al., 1997).

Palliative Care

More than four decades ago, Hinton (1963) recognized the symptom burden of end-stage HF in a case-control study of 102 dying patients (matched with 102 ill, but not dying, patients) in an acute hospital. The number of dying HF patients (14) was small, but physical distress at end of life was greater in those dying from HF or renal failure, or both, than in the 82 patients dying from terminal cancer. While twenty-one (26%) of the

cancer patients failed to get relief from physical distress, more than half (8 patients, 57%) of the heart or renal failure patients did not experience relief. Currently, although HF patients may live for months or years with advanced symptoms and reduced functional status (Teuteberg et al., 2006), palliation of advanced HF symptoms has not been studied (Goodlin et al., 2004).

Palliative care, an approach first known as ‘terminal care,’ is defined by the World Health Organization as that which “improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” (WHO, n.d.). The population identified as appropriate for palliative care by the National Consensus Project for Palliative Care includes all patients who are living with life-threatening or debilitating illness (National Consensus Project, n.d.), and palliative principles and expertise developed in the field of oncology are now extending to other diseases (Ferrell & Coyle, 2006).

Palliative approaches to advanced HF, however, have received little attention. Research identifying the difficult, unanswered questions in advanced HF medical management (Shah & Stevenson, 2004) illustrates this lack, as only three of the 318 questions about treatment of hospitalized patients with advanced disease could be characterized as relating to palliation. Further contrasts are evident in research that shows more frequent use of aggressive treatments for inpatients who died of HF than for those who died of cancer (Tanvetyanon & Leighton, 2003). In another study illustrating the contrast in treatment, Haydar et al. (2004) found that dementia patient care was more

likely to focus on symptom relief and anticipation of dying, while the focus for advanced HF was disease-modifying treatment.

Evidence is mounting for the existence of significant HF palliative care knowledge gaps. Hauptman et al. (2008) conducted a national survey of cardiologists, geriatricians and family practice/internal medicine physicians and found little experience with hospice referral. Survey results showed that 64% of cardiologists, 45% of geriatricians and 44% of internal medicine/family practice physicians cited uncertainty about timing of referral as one factor limiting wider use of this end-of-life option. The survey researchers also found that physician conversations with patients and families concerning defibrillator deactivation were infrequent, as 59.8% of cardiologists, 88% of geriatricians and 95% of internal medicine/family practice physicians reported two or fewer discussions about this option.

Cardiologists participating in palliative care focus groups indicated that they perceived patient death as a failure and that they made the switch to a palliative approach in HF late in the illness (Hanratty et al., 2006). Reigel et al. (2006) surveyed HF specialists about nonpharmacologic aspects of care and found that 67% of HF specialists (50.3% physicians, 90.4% of whom were cardiologists) had not referred any patients to palliative care in the prior 6 months.

Palliative need for advanced HF patients has received recent attention from a group of HF experts who published a consensus statement on palliative and supportive care in advanced HF, identified gaps in knowledge, and proposed a research agenda to address the gaps (Goodlin et al., 2004). In addition, the Institute of Medicine has identified end of life with advanced organ failure (with a focus on HF and chronic

obstructive pulmonary disease) as one of twenty priority areas for health care improvement (Adams & Corrigan, 2003).

Comfort

According to von Gunten (2002), the goals of palliative care are comfort and QOL. Comfort work is one of the types of work sick persons and their families must undertake to manage the various key problems of chronic illness (Strauss et al., 1984). The primary focus of comfort work, according to Corbin and Strauss, is the relief of the physical discomforts associated with chronic illness in both hospital and home settings. However, in discussing the needs and concerns of the dying, they note that “the support of an appropriately trained nurse or professional can bring physical and emotional comfort” (Corbin & Strauss, 1988, p. 287).

Comfort has long been associated with the care of the sick. Development of the concept includes Kolcaba’s (1991) analysis of comfort in which she identified three types of comfort needs: ease, relief and transcendence. According to the Theory of Comfort (Kolcaba, 2009), each type of comfort need can be met in four possible contexts of holistic experience: physical (bodily sensations); psychospiritual (awareness of self [esteem, sexuality and meaning in one’s life] and relationship to a higher order or being); sociocultural (interpersonal, family, cultural traditions and societal relationships); and environmental (external background of human experience). Kolcaba also developed instruments to measure comfort and tested them in various populations including patients with breast cancer (Kolcaba & Fox, 1999), those with urinary incontinence (Dowd, Kolcaba, & Steiner, 2000), preoperative patients (Wagner, Byrne, & Kolcaba, 2006),

nursing home residents (Kolcaba, Schirm, & Steiner, 2006), and patients at end of life (Novak, Kolcaba, Steiner, & Dowd, 2001).

Comfort has not been studied in advanced and end-stage HF, although end-of-life care for these patients includes the recommendation of comfort. Various sources advise comfort, comfort measures or comfort care, including national guidelines (HFSA, 2006; Hunt et al., 2005), and journal articles (Albert, Davis, & Young, 2002; Lewis et al., 2006; Riegel et al., 2006). Despite the absence of definition, more than half of the seriously ill hospitalized patients (including those with HF) in the Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatments (SUPPORT) indicated that they preferred comfort care to treatment focused on extending life (Teno, Fisher, Hamel, Coppola, & Dawson, 2002). However, as Stevenson (2003) notes, cardiology is behind oncology in efforts to establish systems promising comfort both in and out of the hospital for patients who reach the end of life.

Analysis of the Chronic Illness Trajectory Theory in Advanced Heart Failure

The Corbin and Strauss Chronic Illness Trajectory Theory has several distinct characteristics when compared to other trajectory depictions. First, the model covers the entirety of a chronic illness, from pre-diagnosis to death, while the majority of the other trajectories (Glaser & Strauss, 1968; Lunney et al., 2003; Teno et al., 2001) address types of death or functional decline periods alone. In addition, the specific focus in the Corbin and Strauss model is chronic illness, whereas a more recent trajectory (Lunney et al., 2003) includes the broader category of frailty. Lastly, the chronic illness trajectory conceptualization moves beyond the linear metric of ADL performance representing functional status, to consider the wider breadth of the illness experience, in particular the

management work required in each stage and the impact on all those involved in that work.

The Strauss and Corbin trajectory model was developed in an era when reverse remodeling (improvements at a cellular level) in HF was unknown, when sudden death was common in HF, and before the development of disease-modifying therapies and technologies for HF. Then, improvement of a chronic illness such as HF was more predictable, its boundaries more circumscribed by the constraints of the specific pathophysiology. Now, technology, while not the only force involved, is in the forefront of the creation of the new comeback phase in HF, eclipsing the less dramatic palliative needs of advanced HF patients. The implications, including practical considerations, ethical concerns and economic challenges, remain largely unaddressed.

Maintaining QOL, the goal of trajectory management in Strauss and Corbin's model, carries significant challenge in the new comeback trajectory phase for providers, advanced HF patients and their families. Improvement in life quality has been shown to result from the application of advanced therapies within the comeback phases they initiate, but the therapies themselves may present significant new challenges to QOL. In addition, little attention has been given to the transition period when the new comeback phase begins to slide into a downward trajectory phase as the inevitable disease progression recurs. Here, the Corbin and Strauss trajectory framework has particular salience, as it provides a clear reminder that QOL is not a static concept, to be measured once in a particular phase and then assumed to reflect life quality for the remainder of the illness course.

As the downward trajectory resumes (or in some cases, continues), palliative care and the provision of comfort assume greater importance for patients and families. The concept of palliative care emerged after the development of the Corbin and Strauss trajectory theory, but the theory's clear emphasis on issues such as symptom management and the impact of chronic illness on patients and families is congruent with palliative care principles. While the Corbin and Strauss concept of comfort work is almost entirely concerned with physical discomforts, Kolcaba's multidimensional Comfort Theory supplements that more narrowly focused concept with other areas of comfort need. Combining the concept of a chronic illness trajectory and phase-specific requirements with the concept of comfort in many dimensions has potential for fruitful inquiry in advanced and end-stage HF.

One researcher cited in this review called attention to trajectories other than the physical, such as the spiritual. The concept of a spiritual aspect is not addressed in Corbin and Strauss' framework and is combined with psychological issues (psychospiritual) in Kolcaba's comfort theory. Spiritual issues have received little attention in advanced and end-stage HF but may represent an area of importance to patients as they face mortality, in some cases, a second time.

Conclusion

The emergence of the new comeback phase in advanced HF illustrates our preference in medicine and in the culture for "restitution" stories, narratives in which ill persons have health restored, often through the auspices of high-tech medicine (Frank, 1995). A disproportional focus on the dramatic rescue potential of new technology and treatment for some patients overlooks the significant suffering and palliative needs of the

many who are left behind, who do not meet criteria, who do not respond to new therapies, who have serious complications, or who have device malfunctions. An important unrecognized group with palliative need is that of patients with HFPSF. Not only does basic medical treatment for this HF subgroup lack an evidence base, but options for management in advanced disease do not include device therapies, since HFPSF patients do not meet criteria for these treatments. Thus, they lack even the opportunity for entering the comeback phase which is possible with the application of current therapies in systolic HF.

In summary, tremendous progress in the management of heart failure, particularly systolic heart failure, has brought both great benefit to many patients and significant challenge for others. In particular, patients who do not come back to any measure of their previous function do not figure in the favored narratives of restoration and cure. They must not be abandoned as we continue to develop new comeback-fostering therapies. Moreover, we cannot fail to acknowledge, accompany and provide comfort for those patients and families who, as the result of our successes, must face the challenge of end of life in advanced HF more than once.

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Chapter 4

This chapter presents the research design, setting and sample, data collection methods, procedures and data analysis for a cross-sectional study of older women with advanced HFPSF. Advanced HFPSF was defined for the study as persistent HFPSF symptoms despite medical treatment.

Methods

Research Design

An exploratory, cross-sectional design was used in this study of older women with advanced HFPSF. Exploratory designs move beyond the description of a phenomenon, as they investigate related factors, thus providing more in-depth results (Polit & Beck, 2004). In a cross-sectional study, measurement of all of the variables occurs at a single time point, with no follow-up period. Cross-sectional studies are a good fit for defining the demographic and clinical characteristics of a group of interest, and they are time-efficient and economical. Although cross-sectional studies are useful for examining associations, causal relationships cannot be determined from data gathered at one time point (Hulley, Cummings, Browner, Grady, & Newman, 2007).

Research Setting

Outpatients were recruited from two specialty HF clinics in Southern California, one in Loma Linda and one in La Jolla. The Loma Linda International Heart Institute's Cardiomyopathy Clinic, located in the Schuman Pavilion of the Loma Linda University Medical Center, follows approximately 850 HF patients (D. Petersen, personal communication, 7/10/08). The La Jolla-based Scripps Clinic Heart Failure Recovery and Research Center, located in the Anderson Outpatient Pavilion of the Scripps Green

Hospital, has a patient base of approximately 500-600; more than 80 of the patients followed there have HFPSF (T. Heywood, personal communication 7/1/08). Patients in both clinics are managed collaboratively by cardiologists and nurse practitioners who are HF specialists.

Sample

The convenience sample consisted of sixty older women. Older women were defined as those aged 60 years and older. The term *older women* is consistent with the descriptor *Older Adult* used for a population aged 60 years or older by the American Association of Retired Persons' (AARP) *Thesaurus of Aging Terminology* (Rimkus & Melinchok, 2005) and is the term used in current research with patients aged 60 and older by other researchers (Fried & Bradley, 2003; Fried, Bradley, & O'Leary, 2006).

The following criteria were used for sample selection:

Inclusion criteria. Patients included in the sample were:

- female
- aged 60 or older
- identified by medical providers as having advanced HFPSF with an ejection fraction of $\geq 50\%$
- classified functionally as New Heart Association Class III-IIIb
- English speaking
- community-dwelling (i.e., not receiving care in an institution)

Exclusion criteria. Those deemed not appropriate for study inclusion were:

- currently hospitalized
- physically or cognitively unable to complete questionnaires or

participate in a low-level walk test

- diagnosed with other serious cardiac problems (e.g. severe valve disease, infiltrative myocardial disease or constrictive pericarditis)
- diagnosed with other serious medical conditions resulting in life expectancy < 1 year (as determined by medical record review and physician consultation).

Human Subjects Assurance

The Committee on Human Research (CHR) at the University of California, San Francisco, the Institutional Review Board at Loma Linda University and the Scripps Health Human Subjects Committee reviewed and gave approval to the study. No participant contact took place before these approvals were granted.

Data Collection Methods

The study utilized a cognitive screening tool (Mini-Cog), a sociodemographic data sheet, three quantitative measures (Memorial Symptom Assessment-HF, General Comfort Questionnaire, and Minnesota Living with Heart Failure Questionnaire) an objective measure of functional capacity, the Six Minute Walk Test, and medical record review in order to provide a comprehensive depiction of an unstudied population. This portion of the chapter includes a rationale for the measurement of cognitive function, symptoms in advanced HF, comfort, quality of life (QOL), and functional capacity. The instruments and the functional capacity test will be described and the psychometric properties of each reviewed.

Sociodemographic data. The sociodemographic data sheet requested information from the women on race/ethnicity, marital status, living situation, relationship and health of other person (if not living alone), and hospitalization for HF in the previous year.

Clinical characteristics. The following clinical data and pertinent medical/surgical history elements were collected or calculated from information in the patient's medical record: age, the most recently entered systolic and diastolic blood pressure, weight, height, New York Heart Association (NYHA) functional class, body mass index (BMI), echocardiographic data, laboratory test results, glomerular filtration rate, comorbidities and current medications.

BMI is the relationship of height and weight (kg/m^2) and provides an estimate of body fat. A BMI of $\geq 25 \text{ kg/m}^2$ is considered overweight and $\geq 30 \text{ kg/m}^2$ is considered obese (National Institutes of Health, 1998). Methods of body composition estimation (such as the BMI) may not be accurate across all ethnic groups, since the methods have been developed primarily in Caucasians (Deurenberg & Deurenberg-Yap, 2003).

The NYHA functional classification is a subjective determination based on functional capacity and cardiac symptoms; providers assign a score between I and IV, with higher scores indicating worse functional status. NYHA Class III patients with HF are symptomatic (fatigue, palpitations, dyspnea) with less than ordinary physical activity. In male and female outpatients with systolic or diastolic HF, NYHA functional classification is a marker of hospitalization, disease progression and mortality (Ahmed, 2007; Radford et al., 2005).

Echocardiographic data consisted of: ejection fraction (EF), E/A ratio (ratio of early [E] to late [A] mitral valve flow velocity), E/E' (early mitral valve flow velocity/early tissue Doppler lengthening velocity), left atrial volume index (LAVI), left ventricular mass index (LVMI), (Paulus et al., 2007), right atrial (RA) pressure and estimated pulmonary artery (PA) pressure.

EF is a measure of systolic left ventricular function, as it represents the percentage of the end-diastolic volume ejected during systole (Hosenpud & Greenberg, 2000). The present study uses the EF cutoff of 50% for normal or mildly abnormal systolic left ventricular function (Paulus et al., 2007). Table 2 presents the normal/cutoff ranges or values for E/A ratio, E/E', LAVI, LVMI, estimated RA pressure and estimated PA systolic pressure (PASP).

Table 1 Echocardiographic Data Reference Ranges*

Data	Reference Range	Other Range Information
E/A ratio	0.7-3.1	0.5-1.7 – elderly
E/E'	> 15 = high LV filling pressure	< 8 = low LV filling pressure
LAVI (ml/m ²)	**22 ± 6 - female	Mildly abnormal 29-33 - female Moderately abnormal 34-39 - female Severely abnormal ≥ 40 - female
LVMI (gm/m ²)	44-88 - female	Mildly abnormal 89-100 - female Moderately abnormal 101-112 - female Severely abnormal ≥ 113 - female
RA pressure	10 mmHg	Elevated ≥ 15 mmHg
PASP	< 30 mmHg, but varies with age and BMI	Pulmonary HTN = PASP > 35 mmHg

*(Lam et al., 2009; Lang et al., 2005; McQuillan, Picard, Leavitt, & Weyman, 2001;

Paulus et al., 2007; Rimington & Chambers, 2007)

** female ranges provided in table where gender differences exist

Echocardiogram reports at the Scripps La Jolla clinic included the calculated LAVI and LVMI values, but were calculated from information on the echocardiogram report and/or initial work sheet at the Loma Linda clinic. The following formulas were used for the LVMI and LAVI:

$$\text{LV mass} = 0.83 \times [(\text{LVDD} + \text{IVS} + \text{PW})^3 - \text{LVDD}^3]$$

$$\text{LVMI} = \text{LV mass} / \text{BSA} \text{ (g/m}^2\text{)}$$

Left atrial volume, indexed to the body surface area (BSA), was calculated by dividing the sum of the echocardiographic apical 4-chamber and 2-chamber measurements by 2 and then dividing by the BSA (personal communication, R. Bansal, 2008).

The most recent laboratory values for the following were abstracted from the medical record: blood urea nitrogen (BUN), serum creatinine (Cr), hemoglobin (Hgb), serum albumin. The preceding laboratory values are among those recommended in the HFSA national guideline (Adams, et al., 2006) for routine evaluation of HF patients. The levels of NT-proBNP (N-terminal pro-brain natriuretic peptide) or BNP (brain natriuretic peptide) were also abstracted from the medical record (see subsequent paragraph for further discussion).

The estimated glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) Study equation (Levey et al., 1999). The commonly used 4-variable MDRD equation estimates GFR using the variables of serum creatinine, age, race, and gender (National Kidney Foundation, 2002). This study used the original MDRD equation, which adds the variables of blood urea nitrogen and serum albumin:

$$\text{MDRD GFR (ml/min/1.73 m}^2\text{)} = 170 \times [\text{PCr}]^{-0.176} \times [0.762 \text{ if patient is female}] \times [1.180 \text{ if patient is black}] \times [\text{BUN}]^{-0.170} \times [\text{Alb}]^{+0.318}$$

(Levey et al., 1999)

Individual subject variables abstracted from the medical record were entered into a medical formula program (using the original MDRD equation) on the researcher's personal digital assistant (PDA), which calculated the estimated GFR.

One laboratory value, the blood level of the natriuretic peptide and NT-proBNP and BNP, differed between the two data collection sites. The Loma Linda site laboratory used the NT-proBNP assay and at Scripps La Jolla, the laboratory reported the BNP value. NT-proBNP and BNP are circulating forms of natriuretic peptides; BNP is the biologically active form and NT-proBNP the inactive amino-terminal fragment. Both are elevated in HF and are used in clinical settings for diagnosis, monitoring therapy and estimating prognosis (Daniels & Maisel, 2007). Elevated levels of both NT-proBNP and BNP are correlated with the severity of diastolic heart failure (Maisel et al., 2008). However, NT-proBNP and BNP have important differences (see Table 2) and blood level values are not interchangeable.

Comorbidities are the diseases that exist along with the condition under study (the index disease) (de Groot, Beckerman, Lankhorst, & Bouter, 2003). The simple disease count method was considered most likely to yield the appropriate level of information for this exploratory, cross-sectional study of older women with advanced HFPSF. Areas of the medical record reviewed to obtain the information included the problem list, progress notes, history and physical, and discharge summaries. The list of included comorbidities was based on HF literature review, investigator clinical experience, and consultation with two heart failure experts (a PhD nurse researcher and a cardiologist).

Table 2 Comparison of BNP and NT-proBNP*

	BNP	NT-proBNP
Biological Role	Natriuretic and diuretic hormone	Not well understood
Biological Half-life	~ 20 minutes	70 minutes
Main clearance mechanism	Neutral endopeptidases and specific receptors	Renal excretion
Clinical range (pg/ml)	0-5,000	0-35,000
Suggested cutoff to rule out HF in acute dyspnea	< 100 pg/ml	< 300 pg/ml
Rule in HF cut-points**	> 400 pg/ml	50-75 years 900 pg/ml > 75 years 1800 pg/ml

*adapted from Daniels & Maisel, 2007; Maisel et al., 2008; Masson et al., 2006

**evaluated along with consideration of other conditions causing elevation, renal function, time from symptom onset, and obesity

This researcher abstracted information about the following comorbidities and surgical history from the medical record: hypertension, diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease (COPD), asthma, coronary artery disease (CAD) (as indicated by one or more of the following: myocardial infarction, cardiac revascularization, or coronary stent placement), hyperlipidemia, thyroid disease, cerebral vascular accident (CVA), transient ischemic attack (TIA), arthritis, depression, pacemaker placement (and pacemaker type), and hemodialysis.

This researcher also reviewed the medication sheet in the outpatient medical record for current use of the following medications: angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), beta blocker, digoxin, calcium channel blocker, aldosterone blocker, diuretic (loop, thiazide), lipid-lowering medication, amiodarone, aspirin, warfarin, non-steroidal anti-inflammatory drugs (NSAIDs), and depression or anxiety meds.

Instruments/Functional Capacity Test

Mini-Cog. The Mini-Cog instrument (Borson, Scanlan, Brush, Vitaliano, & Dokmak, 2000) is a brief (3 minute) assessment of cognitive function. The tool addresses the following cognitive domains: memory (semantic and short-term), visuospatial/constructional praxis, frontal/executive, and attention/calculation (Woodford & George, 2007).

The Mini-Cog uses an uncued three-item recall test with a clock drawing test (CDT), and requires only pen and paper for completion. Subjects are asked to repeat 3 unrelated words and then draw the face of a clock displaying a requested time of ten minutes after 11:00 o'clock; following that task, they are asked to recall the three words. Those who recall all of the words are classified as non-demented, and those who recall one or two words are classified based on the CDT (abnormal = demented, and normal = non-demented). Normal CDT depictions have the numbers correctly spaced around the circle and the minute hand pointing to the number 2, rather than to the 10 (Borson et al., 2000; Woodford & George, 2007). For the present study, women who recalled three words, and those with a one-two word recall and a normal CDT were classified as non-demented.

When the Mini-Mental State Exam (MMSE), Cognitive Abilities Screening Instrument (CASI), and Mini-Cog were administered to a diverse (gender, language, education) group of elders (n = 249) (with and without probable dementia), the Mini-Cog had the highest sensitivity (99%) of the three tests and a specificity of 93% (Borson, Scanlan, Watanabe, Tu, & Lessig, 2005).

Memorial Symptom Assessment Scale-Heart Failure. The Memorial Symptom Assessment Scale (MSAS), originally developed to assess cancer patient symptoms (Portenoy et al., 1994), has been modified to assess physical and emotional symptoms in HF patients. The resulting Memorial Symptom Assessment Scale – Heart Failure (MSAS-HF) is a 32-item questionnaire which includes three subscales: physical symptoms (PHYS), psychological symptoms (PSYCH), and HF symptoms (HFS). One symptom listed in the MSAS, “pain,” was modified to “other pain” in the MSAS-HF, as “chest pain” was one of the added HF symptoms. The other four added HF symptoms are: “palpitations,” “waking up breathless at night,” “difficulty breathing while lying flat,” and “weight gain.” The following five MSAS items with low prevalence in HF were eliminated in the MSAS-HF: “Don’t look like myself,” “Mouth sores,” “Hair loss,” “Difficulty swallowing,” and “Changes in skin” (Zambroski, Lennie, Chung, Heo, & Ziegler, 2004).

The MSAS-HF asks participants to indicate which of 32 symptoms have been experienced in the previous 7 days and then to rate the selected symptoms on frequency using a 1 to 4 scale (rarely to almost constantly) for 26 of the symptoms, severity on a 1 to 4 scale (mild to very severe) for 32 symptoms and distress on a 0 to 4 scale (not at all to very severe) for 32 symptoms. Higher numbers indicate higher frequency (range 0 –

104), severity (range 0-128) and distress (range 0-128). The sum of the symptoms present is the total prevalence score, with a 0-32 range. Symptom burden scores are determined by summing the mean of the frequency, severity and distress of each symptom. For the six symptoms without a frequency response option (e.g. constipation), burden is calculated from the mean of the severity and distress scores. The symptom scores are combined into the following subscale scores: PSYCH, PHYS and HFS (HF symptoms); the total symptom burden score (TOT Burden) is the mean of the symptom burden scores for all 32 of the symptoms (Portenoy et al., 1994; Zambroski, Moser, Bhat, & Ziegler, 2005).

Zambroski et al. (2004) evaluated the psychometric properties of the MSAS-HF in a pilot study of patients with NYHA Class II-IV HF ($n = 83$) and healthy elders ($n = 122$). Symptom prevalence was significantly different ($p < 0.001$) in HF patients (14.1 ± 8.0) compared to healthy elders (4.1 ± 4.9). Cronbach's alpha coefficient for the HF patients tested was: 0.92 TOT score, 0.83 PSYCH subscale, 0.87 PHYS subscale and 0.73 HF subscale; values for the healthy elders were: 0.88 TOT, 0.76 PSYCH, 0.82 PHYS, and 0.54 HFS. Content validity was supported by the review of two advanced practice nurses.

General Comfort Questionnaire. The General Comfort Questionnaire (GCQ) is a generic instrument that contains 48 self-report items concerning comfort (Kolcaba, 1992). The measure's four subscales correspond to the four theoretical contexts of comfort: physical, psychospiritual, environmental and sociocultural. The current response scale has 6 choices with endpoints labeled *Strongly Disagree* (1) and *Strongly Agree* (6). Responses pertain to comfort at the moment one is answering the questions. An example

of a negative item in the GCQ is “No one understands me,” and an example of a positive item is “My body is relaxed right now.” Instruction is given to reverse code negatively worded items and sum the total score. The possible total score range is 48-288 with the current 6-choice response scale, with higher scores indicating higher comfort.

Reliability testing in the original GCQ instrumentation study (Kolcaba, 1992) resulted in a Cronbach’s alpha of .88, but subscale results were not provided. The author then removed 13 items from the instrument, and the revised subscale reliabilities were (a) physical .70, (b) psychospiritual .78, (c) environment .80, and (d) sociocultural .66. The range of correlations between the subscales was .51 to .62, with the strongest relationships occurring between the psychospiritual subscale and the other three subscales. High correlations between the subscales would not be expected, since each subscale is measuring a different concept. For the 35-item instrument revision, Cronbach’s alpha increased to .90.

While the 48-item GCQ reliability score is high, other psychometric data are incomplete or missing. Despite this limitation, the instrument was included in the assessment of the older women, as no other general questionnaire measuring comfort exists. This research study used the original GCQ, but removed the items clearly identified as belonging to the environmental subscale as it pertains to hospitalized patients only. The score range for the modified 35-item GCQ instrument is 35-210.

Partial guidance exists for subscale item inclusion in the GCQ (Kolcaba, 2003). Written commentary from Dr. Kolcaba in response to an e-mail regarding three items not easily categorized provided some clarification, with decisions about two of the items left to this researcher’s discretion.

One open-ended question, “How would you define comfort?” was added to the end of the GCS.

Minnesota Living with Heart Failure Questionnaire. Defined simply as satisfaction in the areas of life an individual considers important (Bredow, Peterson, & Sandau, 2009), quality of life (QOL) includes components of symptom experience, functional capacity and individual perception (i.e. general health status and level of well-being) (Wenger, Mattson, Furberg, & Elinson, 1984). The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is the most commonly used QOL instrument in HF research (Heo, Moser, Riegel, Hall, & Christman, 2005). This 21-item self-administered instrument uses a 6-point Likert response scale ranging from 0 (no impact on QOL) to 5 (most severe impact on QOL). Participants answer the stem question, “Did your HF prevent you from living as you wanted during the past month by...” as it relates to items such as “swelling in the ankles” and “feeling a burden to family or friends.” Item scores are added, yielding a possible total score range of 0 to 105, with lower scores indicating better QOL. Instrument scoring also yields two subscores: physical (8 items) and emotional (5 items) (Heo et al., 2005; Riegel et al., 2002); eight additional items are incorporated in the total score, but not included in a subscale (Bennett et al., 2003).

Heo et al. (2005) conducted a comprehensive analysis of the psychometric properties of the MLHFQ. The researchers used data from 638 HF patients (49% female) enrolled in four studies (three randomized, controlled trials of community-based HF disease management and a randomized, controlled trial of a biofeedback-relaxation intervention). Mean age was 57 ± 12 years; 28% of the patients were age 60 or older. The majority of patients (80%) were NYHA Class III or IV.

Cronbach's alpha was .91 for the total instrument score, .91 for the physical subscale and .85 for the emotional subscale. Previous researchers have shown a Cronbach's alpha greater than .80 for the total score and two subscales (Bennett et al., 2003; Middel et al., 2001; Rector & Cohn, 1992; Riegel et al., 2002).

Six Minute Walk Test. The widely used Six Minute Walk Test (6MWT) provides an objective assessment of functional capacity by measuring the distance an individual can walk on a flat, hard surface in a six minute period. In chronic heart failure, the 6MWT has been used in studies of exercise capacity, randomized clinical trials (RCTs) of new therapeutic agents, quality of life, exercise training, and in prognostic stratification (Opasich et al., 2001).

Patients walk in a marked corridor, choosing their own exercise intensity and stopping to rest as needed. The American Thoracic Society guidelines provide a standardized approach for performing the 6MWT (ATS, 2002).

The findings of investigators who used the 6MWT in older HF patients (Enright et al., 2003; Peeters & Mets, 1996; Zi, Carmichael, & Lye, 2003) suggest that it is a suitable tool to measure functional capacity in an older, chronic illness population.

Procedures

Following the process of informed consent at either of the two clinic sites, I administered the Mini-Cog instrument to patients in a private clinic room to assess mental status and ability to complete the data form and questionnaires. Completion of the Mini-Cog screen required approximately 3-5 minutes. Women classified as normal (non-demented) based on the Mini-Cog screen participated in the study.

Participants completed the sociodemographic form and the three questionnaires: MSAS-HF, GCQ and MLHFQ, requiring 20 to 45 minutes. The participant was accompanied to a marked hallway in the clinic for completion of the 6MWT. Blood pressure, heart rate and pulse oximetry were obtained. Participants were instructed to walk at their own pace, and to stop and rest as needed throughout the six minute test period. They were allowed to use their usual ambulation aid (cane, walker, pushing wheelchair) during the 6MWT. Distance walked was calculated by counting the number of laps walked and multiplying that number by the meters/lap. Partially completed laps were measured with a measuring tape and that number was added to the lap total. Completion of the 6MWT required approximately 30 minutes.

Data Analysis

The sample size was selected based on power analysis for the multiple regression used in the data analysis for the fourth study aim. For a multiple linear regression model which includes 6 covariates with a squared multiple correlation (R^2) of 0.13, a sample size of 60 will have 80% power to detect at $\alpha = 0.05$ an increase in R^2 of 0.10 when one additional covariate is included in the model. This effect size was determined to be in the small to medium range (0.02 – 0.13) (Cohen, 1988).

Data were analyzed using SPSS for Windows (version 15.0; SPSS, Inc., Chicago, IL). The conduct of data analysis related to each of the study aims follows:

Aim 1: Describe the sociodemographic and clinical characteristics of older women with advanced HFPSF.

Analysis: The women's sociodemographic data (race/ethnicity, marital status, living situation, and hospitalization for HF in past 12 months) and clinical characteristics

were analyzed using descriptive statistics (frequencies and percentages, means and standard deviation, or medians depending on the level of measurement). For the NT-Scripps La Jolla clinic were analyzed separately.

Aim 2: Measure the functional status of older women with advanced HFPSF.

Analysis: Measured distances (in meters) traversed in 6 minutes by each of the participants were summed and a mean, median, and standard deviation for the total sample of women was computed.

Aim 3: Describe the emotional and physical symptoms, comfort and quality of life of older women with advanced HFPSF.

Analysis: The total and three subscale (physical symptoms, psychological symptoms and HF symptoms) scores of the Memorial Symptom Assessment Scale – Heart Failure (MSAS-HF) were calculated. The mean of the frequency, severity and distress of each symptom were used to determine symptom burden.

The General Comfort Questionnaire (GCQ) total and subscale (physical, psychospiritual, and sociocultural) scores were calculated to provide an assessment of self-rated comfort; means and standard deviations of these scores were calculated for the sample of older women.

Analysis of the answers to the single open-ended question asking the women's definition of comfort used the method of content analysis, a process of organization and integration of qualitative information according to emerging concepts and themes (Polit & Beck, 2004). The results of the content analysis were reviewed with an experienced qualitative researcher and dissertation committee member, Dr. Elizabeth Davies.

For the assessment of QOL, the total score and two subscale (physical and emotional) scores were calculated for the Minnesota Living with Heart Failure (MLWHF) questionnaire. The mean and standard deviation of total and subscale scores were calculated. Subscale scores of the three scales were examined for any issues of collinearity.

Aim 4: Identify sociodemographic, clinical, functional status, symptom status, comfort and factors associated with QOL.

Analysis: Univariate analyses were conducted to assess the impact of sociodemographic, clinical, symptom status, comfort, and functional status factors on QOL. A correlation matrix was developed using the variables of interest. Scatterplots of each candidate variable with QOL (as represented by the total MLHF score) were created to assess whether or not the associations were linear.

Multiple regression analyses were conducted to identify which combination of variables provided the strongest association with overall QOL. Variables associated by themselves at $p < 0.10$ were considered candidate variables for the regression model. Candidate variables included: sociodemographic characteristics, clinical characteristics, NYHA functional class, mean distance walked on the 6MWT, echocardiographic variables, laboratory values, comorbidities, medications, the total symptom prevalence score, the symptom prevalence score for each of the subscales (PSYCH, PHYS and HFS), the total symptom burden score, the total comfort score and the score for each the three comfort subscales (physical, psychospiritual and sociocultural). Statistical significance was set at $p < 0.05$.

Conclusion

Advanced HFPSF in older women is an unstudied phenomenon, albeit one with great significance, as the aging of the population and improved HF survival continue to increase the prevalence of this group of seriously chronically ill persons. Moreover, as little is known about the management of HFPSF before it reaches the advanced stage, the challenges providers and patients face when the condition worsens are compounded.

Measurement issues related to the instruments and test which were utilized in the research study have been addressed in this chapter. The Mini-Cog's high sensitivity, specificity and brevity made it an appropriate and useful screening tool for dementia. The MSAS-HF has had adequate psychometric testing, with findings of strong evidence for reliability and validity. The inclusion of both "chest pain" and "pain" in this instrument was important, as the symptom of pain in HF is not well understood. The GCQ, although not an optimal instrument for the reasons given in the body of the paper, is a beginning point for exploring comfort in this population of advanced chronic illness patients. Content analysis of the women's comfort definitions adds an important dimension to the discussion of comfort questionnaire results. Finally, the MLHFQ has well-described psychometric properties and is the most commonly used instrument in HF research, including a recent large clinical trial of a new pharmacologic agent for HFPSF.

The 6MWT has been used in studies of older adults, patients with HF, and women with HFPSF and demonstrates good correlation with both objective (metabolic exercise test) and subjective (NYHA classification) measures of functional capacity. Those with more advanced HF and limited functional capacity (NYHA Class III) have been successfully tested with the 6MWT. While metabolic exercise testing is the

cardiovascular gold standard for testing functional capacity, it would have added significant burden to research participation for this patient group.

Advanced chronic illness is multifaceted; this is particularly true of advanced HFPSF in older women. The measurement of demographics, clinical characteristics, comorbidities, medications, symptoms, comfort, QOL and functional capacity using the methods described in this chapter provides a comprehensive exploration of important aspects of this rapidly expanding patient group.

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Chapter 5 - Part 1

Introduction

New heart failure (HF) cases number more than 600,000 per year in adults age 45 and older (AHA, 2009). Approximately half of HF patients have preserved systolic function (HFPSF) (Paulus et al., 2007). Less is known about treatment in this subgroup, since HF clinical trials have historically included few patients with HFPSF (Smith, Masoudi, Vaccarino, Radford, & Krumholz, 2003), and two recent large randomized clinical trials of angiotensin receptor blockers failed to show a mortality advantage with treatment (Massie et al., 2008; Yusuf et al., 2003). Patients with HFPSF are more commonly older women (Lenzen et al., 2004), who are at risk of declining physical function and loss of independence (Gary et al., 2004). Moreover, HFPSF patients have frequent readmissions for HF (Hogg, Swedberg, & McMurray, 2004), a high mortality rate (Fitzgibbons, Meyer, & Aurigemma, 2009), and represent considerable societal economic burden (Liao et al., 2006).

Pharmacological trials have helped characterize the clinical attributes of this population, but little is known about their symptom burden and functional status. Symptoms are known to be common and burdensome (Bekelman et al., 2007; Zambroski, Moser, Bhat, & Ziegler, 2005) in all HF patients, similar in number and distress to those experienced by patients with cancer (Bekelman et al., 2009). However, the characteristics and symptom burden of a HF subgroup with high prevalence, that of older women with advanced HFPSF, have received little research attention.

The relative lack of information concerning HFPSF extends to palliative and supportive treatment in advanced and end-stage disease, as a computerized search of the

PubMed and CINAHL data bases using the terms *diastolic heart failure* and *palliative care* returned no entries. Guidelines for referral of HF patients to hospice apply to those with systolic dysfunction only (Stuart, 2007), and recommendations for integrating palliative care into HF care exclude HFPSF due to prognostic uncertainty (Hauptman & Havranek, 2005) and a lack of knowledge about the symptom burden of this patient group.

The purpose of this exploratory, cross-sectional study was to describe the characteristics of a sample of community-dwelling older women with advanced (symptomatic) HFPSF. The specific aims were to 1) describe the sociodemographic and clinical characteristics of older women with advanced HFPSF, 2) describe the women's physical and emotional symptoms and 3) measure their functional capacity.

Methods

The institutional review boards at participating sites reviewed and gave approval to conduct the study. All patients gave written informed consent.

Study Population

Participants were recruited from two specialty HF clinics in Southern California between October, 2008 and May, 2009. Eligible study participants (1) had a diagnosis of New York Heart Association Class III HF with an EF of $\geq 50\%$, 2) were English-speaking and community-dwelling, 3) were female and aged 60 or older. Patients were excluded if they were 1) currently hospitalized, 2) physically or cognitively unable to complete questionnaires or participate in a low-level walk test, 3) diagnosed with other serious cardiac problems (e.g. severe valve disease, infiltrative myocardial disease or constrictive pericarditis), or 4) diagnosed with other serious medical conditions with life

expectancy < 1 year (as determined by medical record review and physician consultation).

Measurements

After eligible patients gave informed consent, the principal investigator administered the Mini-Cog cognitive screening tool. The psychometric properties of the Mini-Cog have not been evaluated in HF patients, but the instrument is one of three recommended by psychiatrists for general practitioners screening for cognitive impairment in their practices (Brodaty, Low, Gibson, & Burns, 2006). The Mini-Cog uses an uncued three-item recall test with a clock drawing test (CDT). Subjects are asked to repeat 3 unrelated words and then complete the face of a clock displaying a requested time of ten minutes after 11:00 o'clock; following that task, they are asked to recall the three words. Those who recall all of the words are classified as non-demented, and those who recall one or two words are classified based on the CDT result (abnormal = demented, and normal = non-demented). Normal CDT depictions have the numbers correctly spaced around the circle and the minute hand pointing to the number 2 (Borson, Scanlan, Brush, Vitaliano, & Dokmak, 2000; Woodford & George, 2007). For the present study, women who recalled three words, and those with a one-two word recall and a normal CDT were classified as non-demented.

The women then completed a sociodemographic data sheet and the questionnaire in a private clinic room. Following questionnaire completion, the 6-Minute Walk Test (6MWT) was conducted in a marked hallway. Demographic data and clinical characteristics were obtained from patient self-report and the medical record.

Symptoms were measured using the Memorial Symptom Assessment Scale – Heart Failure (MSAS-HF), a modification of the Memorial Symptom Assessment Scale (MSAS), a cancer symptom instrument (Portenoy et al., 1994). Five MSAS items with low prevalence in HF were eliminated in the modification, and five heart failure symptoms were added to complete the MSAS-HF instrument. The MSAS-HF assesses physical and emotional symptoms in a 32-item questionnaire which includes three subscales: physical symptoms (PHYS), psychological symptoms (PSYCH), and HF symptoms (HFS) (Zambroski, Lennie, Chung, Heo, & Ziegler, 2004).

The MSAS-HF asks participants to indicate which of 32 symptoms have been experienced in the previous 7 days and then to rate the selected symptoms on frequency using a 1 to 4 scale (rarely to almost constantly) for 26 of the symptoms, severity on a 1 to 4 scale (mild to very severe) for 32 symptoms and distress on a 0 to 4 scale (not at all to very severe) for 32 symptoms. Higher numbers indicate higher frequency (range 0 – 104), severity (range 0-128) and distress (range 0-128). The sum of the symptoms present is the total prevalence (TOTPREV) score, with a 0-32 range. Symptom burden scores are determined by summing the mean of the frequency, severity and distress of each symptom. For the six symptoms without a frequency response option (e.g. constipation), burden is calculated from the mean of the severity and distress scores. The symptom scores are combined into the following subscale scores: PHYS, PSYCH and HFS; the total symptom burden score (TOT Burden) is the mean of the symptom burden scores for all 32 of the symptoms ((Portenoy et al., 1994; Zambroski et al., 2005). In the current study, the Cronbach alpha coefficients for the total and PHYS, PSYCH and HFS subscales were .86, .80, .73 and .56, respectively.

The Six Minute Walk Test (6MWT) measures the distance an individual can walk on a flat surface in a six minute period, providing an objective assessment of functional capacity. The 6MWT is easier to complete than an exercise stress test (Steele, 1996), since it assesses the submaximal level of functional capacity, the level at which most activities of daily living are performed. Validity and reliability of the 6MWT have been previously reported (Demers, McKelvie, Negassa, Yusuf, et al., 2001; Hamilton & Haennel, 2000). A number of studies have used the 6MWT safely in elderly subjects, including those with and without known cardiac disease, with systolic dysfunction (with and without HF) and with HFPSF (Enright et al., 2003; Ingle et al., 2007; Peeters & Mets, 1996; Zi, Carmichael, & Lye, 2003).

Study participants walked in a marked corridor in each of the clinics, covering as much distance as possible during the allotted time. They were allowed to walk with their accustomed ambulation aids, to rest as needed, and were instructed to stop if they experienced serious symptoms (angina, dizziness, severe dyspnea, severe fatigue, or musculoskeletal pain). Distance covered was expressed in meters.

Statistical Analysis

Descriptive statistics were applied as appropriate according to the distribution of variables. Data were reported as mean \pm standard deviation (SD) for continuous variables; frequencies and percentages summarize categorical variables. All statistical calculations were carried out using SPSS for Windows (Version 15.0, SPSS, Inc., Chicago, IL).

Results

Eighty-nine patients met the clinical criteria for study entry. Fourteen patients meeting all other criteria could not be enrolled because they did not speak or understand English. Eleven patients declined participation, primarily due to transportation issues. Four consented patients were not enrolled due to abnormal Mini-Cog screen results. Two of the four patients were subsequently retested at the request of their medical providers after they had improved clinically. Both were classified as non-demented based on the repeat Mini-Cog screen, and were enrolled in the study. Another patient became fatigued midway through the questionnaires and did not complete them; she was not able to return for a follow-up appointment due to worsened medical status. One potential subject declined further study participation during the process of informed consent. Sixty patients completed the study.

Demographics

The mean age of study participants was 76 ± 7.7 years (Table 1). The women were older on average than HFPSF patients enrolled in the following recent clinical trials: I-PRESERVE (mean age - 72), DIG-PEF (mean age - 67), CHARM-preserved (mean age - 67), and PEP-CHF (mean age - 75) (McMurray et al., 2008).

The majority of the women (86.7%) were Caucasian, with other race/ethnicity reported as Hispanic/Latino (1 [1.7%]), African American (4 [6.7%]), Asian (1 [1.7%]) and American Indian/Alaskan Native (2 [3.3%]). Less than half of the women (45%) were married, and more than a third (35%) had been widowed. However, the majority (67%) lived with another person (spouse, son, daughter, other relative). Of the women

Table 1 Demographic and Clinical Characteristics* N=60

Mean age, y		76.8 \pm 7.7
Caucasian		52 (86.7 %)
Married		27 (45.0 %)
Living with other persons		40 (66.7 %)
Hospitalized in past 12 months for HF		22 (36.7 %)
Clinical characteristics		
Systolic blood pressure (mmHg)		131.1 \pm 21.1
Diastolic blood pressure (mmHg)		70.0 \pm 10.7
Body mass index (kg/ m ²)		1.2 \pm 7.9
Ejection fraction %		64.5 \pm 9.4
Left atrial volume index (mL/m ²)	<i>n</i> = 48	41.9 \pm 20.2
Left ventricular mass index (g/m ²)	<i>n</i> = 52	112.8 \pm 32.3
RAP (mmHg)	<i>n</i> = 50	8.9 \pm 4.8
PASP (mmHg)	<i>n</i> = 50	47.6 \pm 13.6
Hemoglobin (gm/dL)		12.0 \pm 1.4
NT-proBNP (pg/mL)	<i>n</i> = 22	1577.2 \pm 2191.3
BNP (pg/mL)	<i>n</i> = 28	329.8 \pm 196.2
Glomerular filtration rate (mL/min/1.73 m ²)		51.7 \pm 20.3
6 minute walk distance (meters)		201.4 \pm 117.1

*Data are presented as patient number (%) or mean \pm SD.

RAP, right atrial pressure; PASP, pulmonary artery systolic pressure; NT-proBNP,

N-terminal pro-brain natriuretic peptide; BNP, brain natriuretic peptide.

who were married, more than half (54%) rated their spouse's health as fair or poor. More than a third (37 %) reported hospitalization for HF in the previous 12 months.

Clinical Characteristics

Mean systolic/diastolic blood pressure (BP) was 131/70 mmHg (Table 1). This BP reading is within the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Seventh Report (JNC-7) category of pre-hypertension (120-139/80-89). However, systolic BP readings reflected a wide range of control, with 32% in the JNC-7 normal (<120) range, 35% in the pre-hypertension (120-139) range, 23% in the Stage I hypertension (140-159) range and 10% with Stage II hypertension (≥ 160). The majority (82%) had a diastolic BP in the normal (<80) range, with 13% categorized as pre-hypertension (80-89) and one patient each in Stage I (90-99) and Stage II (≥ 100) diastolic hypertension ranges (Chobanian et al., 2003).

The average study participant had a body mass index (BMI) of 31.2 ± 7.9 . Twenty percent of the women were at normal weight (BMI 18.5-24.9), 32 percent were overweight (BMI 25-29.9), 33 percent were obese (BMI 30-39.9) and 15 percent were extremely obese (BMI ≥ 40) (National Institutes of Health, 1998).

The mean ejection fraction percentage was 64.5 ± 9.4 , with an inter-quartile range of 56-70 %. Left atrial volume index (LAVI) was 41.9 ± 20.15 (mL/m²). The reference range is 22 ± 6 mL/m² for females, with ≥ 40 being severely abnormal (Lang et al., 2005). More than half (52%) of the women had LAVI values ≥ 40 . Left ventricular mass index (LVMI) (g/m²) was 112.8 ± 32.3 . The LVMI reference range for females is 44-88 g/m², with ≥ 113 being severely abnormal (Lang et al., 2005). Half (51%) of the women had LVMI values ≥ 113 .

Mean estimated right atrial (RA) pressure (mmHg) was 8.9 ± 4.8 with a range of 5-20 mmHg. The RA pressure was estimated from the diameter of the vena cava and response to respiratory change on echocardiogram, with 10 mmHg considered normal (Kircher, Himelman, & Schiller, 1990). The mean estimated pulmonary artery systolic pressure (PASP) (mmHg) was 47.6 ± 13.6 with a range of 23-84 mmHg. Pulmonary hypertension is defined as $\text{PASP} > 35$ mmHg (Lam et al., 2009).

Natriuretic peptide clinical laboratory assays differed by clinic site. At Site 1 ($n = 22$), the mean (SD) NT-proBNP (pg/mL) value was 1577.2 ± 2191.3 , with an inter-quartile range of 406.83 – 1419.25. At Site 2 ($n = 28$) the mean (SD) BNP (pg/mL) value was 329.8 ± 196.2 , with an inter-quartile range of 192.5-467. Elevated levels of both of these natriuretic peptides have been shown to be strongly predictive of adverse outcomes in patients with HFPSF (Grewal et al., 2008).

The sample of older women had considerable reduction in renal function with a mean estimated glomerular filtration rate (GFR) of 51.7 ± 20.3 mL/min/1.73 m². The majority (73 %) had a GFR below 60 mL/min/1.73 m², meeting the diagnostic criterion for chronic kidney disease (CKD) (if persistent for three months or more) (National Kidney Foundation, 2002). More than half (63%) of the participants had Stage 3 CKD (GFR 30-59 mL/min/1.73 m²), 8 % had Stage 4 (GFR 15-29 mL/min/1.73 m²) and one patient, who was receiving peritoneal dialysis, was in Stage 5 (GFR < 15 mL/min/1.73 m²).

The mean hemoglobin value was 12 gm/dL ± 1.4 . Forty-two percent of the women had hemoglobin levels below 12 gm/dL, consistent with the World Health Organization (1968) definition of anemia in females.

The mean distance walked in the 6MWT was 201.4 + 117.1 meters (range of 6.7-408 meters). Four of the participants used oxygen during the walk test, and one-third used their accustomed ambulation aid (5 – cane, 10 – walker, 5 – pushed wheelchair).

Comorbidities

Hypertension (n = 60, 100%), hyperlipidemia (n = 46, 76.7%), atrial fibrillation (n = 40, 66.7%), coronary artery disease (n = 26, 45%), diabetes (n = 24, 40%) and respiratory disease (COPD or asthma) (n = 24, 40%) were common comorbid conditions. More than a third (n = 22, 36.7%) had thyroid disorders. Arthritis (n = 13, 21.7%) and depression (n = 12, 20%) were less frequently noted. Overall, study participants had a mean 4.65 ± 1.55 of the 12 possible comorbid conditions.

Pharmacologic Treatment

Medications commonly associated with HF treatment included angiotensin converting enzyme inhibitor (ACEI) (n = 24, 40%), angiotensin receptor blocker (ARB) (n = 25, 41.7%), beta blocker (n = 46, 76.7%), and diuretic (n = 57, 95%); digoxin (n = 9, 15%) and aldosterone blockers (n = 12, 20%) were prescribed less frequently. Other cardiovascular medications included calcium channel blocker (n = 28, 46.7%), lipid lowering agent (n = 45, 75%), and aspirin (n = 29, 48.3%). More than a third (n = 22, 36.7%) of the participants were taking an antidepressant or anxiolytic medication. A non-steroidal anti-inflammatory drug (NSAID) was listed on only one clinic medication record.

Although atrial fibrillation was present in two-thirds of the subjects, less than half (n = 28; 46.7%) were prescribed warfarin. However, data concerning current cardiac

rhythm and the presence or absence of contraindications to anticoagulation were not collected.

Symptoms and Symptom Burden

Older women with advanced HFPSF reported a mean of 13.2 ± 6.4 (range 4-30) of a possible 32 symptoms. The most common symptoms (Table 2) were lack of energy (88.3%), shortness of breath (83.3 %) and pain other than chest pain (73.3 %). If participants experienced pain, they were asked to indicate the pain site; Table 4 presents a summary of the diverse pain sites they reported. Other common symptoms included feeling drowsy (67.8%), dry mouth (59.3%), numbness/tingling in hands/feet (55%), swelling of arms or legs (51.7%), cough (50%) and worrying (50%).

Table 2 Symptoms with Highest Prevalence N = 60

Symptom	n	(%)
Lack of energy	53	88.3
Shortness of breath	50	83.3
Pain (other than chest pain)	44	73.3
Feeling drowsy	40	67.8
Dry mouth	35	59.3
Numbness/tingling in hands/feet	33	55.0
Swelling of arms or legs	31	51.7
Cough	30	50.0
Worrying	30	50.0

Individual symptom burden scores were computed from the mean of each symptom frequency, severity and bother (severity and bother for the six symptoms without a frequency dimension). Overall mean symptom burden (for all 32 symptoms) was 2.10 ± 0.43 . The most burdensome symptom (Table 3), while reported by only 7 (11.7%) of the women, was that of problems with sexual interest or activity (mean 2.73 ± 1.1). Other high burden symptoms were lack of energy (88.3%), shortness of breath (83.3%), pain other than chest pain (73.3%), dry mouth (59.3%), difficulty breathing when lying flat (46.7%) and difficulty sleeping (46.7%).

Table 3 Symptoms with Highest Burden N = 60

Symptom	n	%	*Symptom Burden
Sexual problems	7	11.7 %	2.73 ± 1.1
Difficulty sleeping	28	46.7 %	2.65 ± 0.7
Pain (other than chest pain)	44	73.3 %	2.62 ± 0.7
Lack of energy	53	88.3 %	2.43 ± 0.8
Shortness of breath	50	83.3 %	2.40 ± 0.7
Difficulty breathing - lying flat	28	46.7%	2.34 ± 1.0
Dry mouth	35	59.3%	2.34 ± 0.8
Waking up breathless at night	11	18.3 %	2.32 ± 0.9
Worrying	30	50.0%	2.30 ± 0.7

*Data presented as mean \pm SD. Overall mean symptom burden 2.10 ± 0.43

Discussion

Older women with advanced HFPSF have significant unrecognized and unaddressed palliative need. They are not unlike patients with advanced systolic HF (Metra et al., 2007), since the findings of this study demonstrate persistent severe symptoms, functional limitation and evidence of cardiac dysfunction despite medical treatment. Moreover, the women's multiple comorbidities add complexity and challenge to their clinical care and the various indicators of increased mortality and morbidity risk in the women further underscore their truly advanced HF status.

Palliative Need in Advanced HFPSF

Palliative care was defined in 2002 by the World Health Organization as that which "improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" (Davies & Higginson, 2004, p. 14).

Palliative care developed within and from the hospice movement (Saunders, 2006), and emerged in the United States during the late 1980's (Fadul et al., 2009). While palliative care expertise developed in the field of oncology, the principles are now extending to other diseases and into other settings (Ferrell & Coyle, 2006). Articulating the application of this approach beyond end-stage disease, the National Consensus Project for Palliative Care places those who are living with life-threatening or debilitating illness in the category of palliative need (National Consensus Project, 2004).

Palliative care is a relatively new concept for HF providers, since it was unnecessary in earlier eras of HF management when patients were more likely to die

suddenly than to live for extended periods with significant symptom burden (Stevenson, 2005). Responding to the needs of the growing number of patients with advanced HF in the current era, a group of heart failure, palliative care and other experts from related fields convened to address the issues in 2002. They reviewed the literature on advanced HF and established a research agenda for supportive and palliative care. An important, related concept highlighted in the subsequently published consensus statement was that of supportive care, with a focus on symptom management and reduction of the burden of illness on patients and families. Thus, the concurrent application of supportive care for palliation and HF disease management has merit at any point in the trajectory of illness (Goodlin et al., 2004).

The recent comprehensive position statement on palliative care in HF from the Heart Failure Association of the European Society of Cardiology corroborates the principle of early palliative care integration, reviews the challenges of symptomatic HF and provides an overview of the essential components of palliation. Important recommendations include the integration of palliative care throughout the entire trajectory of HF, rather than reserving the relief of suffering for the end of life (Jaarsma et al., 2009).

The findings of the present study of older women provide clear evidence of palliative need in HF. Persistent severe symptoms, functional limitation, cardiac dysfunction, multiple comorbidities, mortality and morbidity risk in the older women identify them as appropriate for this complement to standard HF care.

Persistent Severe Symptoms

Symptoms such as lack of energy, shortness of breath, pain other than chest pain, dry mouth, swelling in arms or legs and worrying were prevalent in half or more of the women and associated with high burden. Other symptoms such as difficulty sleeping, difficulty breathing when lying flat and waking up breathless at night were reported less frequently but also had high burden ratings. While symptoms such as fatigue, dyspnea and swelling are expected in HF, the unrelieved burden of those and other diverse symptoms is a compelling finding.

Symptom prevalence in the older women with HFPSF was similar to that of a sample of younger, mostly male systolic HF patients (13.2 ± 6.4 [range 4-30] vs. 15.1 ± 8.0 [range 0-30], respectively) (Zambroski et al., 2005). The most prevalent symptoms were similar in the two groups, although pain other than chest pain was reported less frequently in the systolic HF patients (57.4%) than in the older, female HFPSF patients (73.3%).

Other researchers have also demonstrated considerable symptom burden in studies of advanced HF patients. Indeed, the challenge of multiple symptoms in HF may exceed or be similar to that of malignant disease. Bekelman et al. (2009) found that older HF patients (classification as systolic or HFPSF not provided) ($n = 60$; median age 75; 36.7% female) reported a mean of 13.2 physical symptoms, significantly higher than the 8.6 symptoms ($p = 0.03$) found in the comparison group of advanced cancer patients ($n = 30$; mean age 64, 60% female). Symptom burden was also shown to be similar for the two conditions in another study comparing patients with systolic HF ($n = 50$; median age 76.5) to cancer patients ($n = 50$; median age 75.0). Mean symptom distress level

(measured with the Edmonton Symptom Assessment Scale) was 33.1 ± 13.17 in HF patients and 31.0 ± 13.34 in cancer patients, despite less agreement in individual symptom prevalence and intensity across the two groups. Of interest, the HF patients in this study were drawn from a specialty HF unit and were receiving the careful management associated with such programs (O'Leary, Murphy, O'Loughlin, Tiernan, & McDonald, 2009).

In the present study, pain was a frequent and burdensome symptom. Although this symptom has had little attention in HF patients historically, a growing body of evidence validates the common occurrence of pain other than chest pain in the HF population (Evangelista, Sackett, & Dracup, 2009; Goebel et al., 2009; Goodlin et al., 2008; Levenson, McCarthy, Lynn, Davis, & Phillips, 2000; Walke et al., 2007; Zambroski et al., 2005). Goodlin et al. (2008) surveyed advanced HF patients in various outpatient settings ($n = 349$; 65.9 ± 15.6 years; 64.2 % male) at two time points concerning the nature, location and severity of pain in HF. They found a 53.9 % prevalence of pain at baseline, with 20% of subjects reporting severe pain and significant associations with a number of comorbidities such as degenerative joint disease ($p < .001$) and peripheral vascular disease ($p = .032$). At the follow-up time point, pain prevalence remained high at 51.0%.

The older women noted a variety of pain locations (Table 4), affecting upper body, lower body, and in some cases, the entire body. The presence and severity of pain in these already functionally impaired older women is likely to further reduce their ability to walk, perform ADLs and maintain independence. The causes of pain, including those attributable to one or more of the women's multiple comorbidities, were not explored.

Table 4 Pain Locations (Other Than Chest Pain)

Location	n
Neck/shoulders/arm	5
Wrist/hand/fingers	4
Back	15
Hip	2
Knee	9
Ankles/feet	4
Generalized/arthritis/fibromyalgia	5
Other (pelvic area, left side, side of/under breast, throat)	6

Although only seven of the participants reported sexual problems as carrying the highest symptom burden, the finding is unique to this study. The small number of existing studies concerning sexuality in HF have included fewer women than men (Jaarsma, Dracup, Walden, & Stevenson, 1996; Jaarsma, 2002; Schwarz et al., 2008; Steinke, Wright, Chung, & Moser, 2008; Westlake, Dracup, Walden, & Fonarow, 1999) and no studies have explored the sexual concerns of older women with HFPSF. Previously unrecognized sexual concerns in this HF subgroup warrant further research to determine the prevalence and elucidate the nature of the sexual issues.

Functional Limitation

The women were able, on average, to walk less than 300 meters in six minutes, an indication of severe impairment in functional capacity (Metra et al., 2007). This reduction of basic mobility is similar to the functional limitation seen in advanced systolic HF (Shah et al., 2001).

Cardiac Dysfunction Despite Medical Therapy

Guideline recommendations for this subset of HF patients (Adams et al., 2006; Hunt et al., 2005), while not evidence-based, include treatment with standard heart failure medications, diuretics for symptom management, and blood pressure control. The majority of women in this study were on either an ACEI or an ARB (three were taking both medications), and more than three-fourths had been prescribed beta blockers. Nearly all (95%) had been prescribed diuretics. Blood pressure control, while not optimal, was on average in the JNC-7 range of pre-hypertension.

Despite medical therapy, evidence for cardiac dysfunction includes pulmonary hypertension (PASP > 35 mmHg in 76% of the women), elevated levels of natriuretic peptides, and severely limited functional capacity. Moreover, cardiac structural abnormalities, with measurement values in the severely abnormal range for both left atrial size and left ventricular mass were present in a majority (52%, 51%, respectively) of the women.

Multiple Comorbidities

Additional chronic illnesses commonly accompany HF in older persons. In a survey of community-dwelling adults aged 77 and older (n = 1,099; 70% female), Marengoni et al. (2009) found that of the 194 persons with HF, only 2.1% had no

comorbidities. The remainder of the HF cases had a mean of 2.6 ± 1.2 coexistent conditions. Women in the present study had an average of nearly twice (4.65 ± 1.55) that number of comorbidities. Similarly, in a study of hospitalized HF patients, fewer of those with HFPSF had no comorbidities than those with reduced systolic function (18% vs. 31%; $p = 0.003$) (Berry et al., 2005).

Mortality and Morbidity Risk

Findings in this study of older women include the high prevalence of a number of conditions which are associated with increased morbidity and mortality risk in HFPSF, including chronic kidney disease (Ahmed et al., 2007), atrial fibrillation (Parkash, Maisel, Toca, & Stevenson, 2005), anemia (O'Meara et al., 2006; Young et al., 2008) and diabetes (Tribouilloy et al., 2008). Further evidence of mortality risk is found in a subset of 50 women with echocardiographic measurement of the PASP. Pulmonary hypertension, defined as PASP > 35 mmHg and present in 76% of the subset of women, is strongly predictive of mortality in HFPSF (Lam et al., 2009).

Another risk factor, coronary artery disease (CAD), was present in 45% of the women. Eight women had a history of myocardial infarction (MI), eight had undergone coronary artery bypass graft (CABG) surgery, and fifteen had coronary artery stents placed. Of those with cardiovascular event and intervention history, one-third had one or more events/interventions (i.e. MI and stent placement; MI, stent and CABG). Attention to the risk factor of hyperlipidemia, present in the majority (76.7%) of the women, was evident in that all but one (45 out of 46) of those with high lipids were treated with lipid lowering agents.

The obesity paradox of lower mortality in obese HF patients than those who are not obese (Lavie, Mehra, & Milani, 2005) has been described in patients with HFPSF as well (Lavie et al., 2007). However, when researchers analyzed just the cohort of obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) patients with HFPSF, they identified higher BMI as a strong independent predictor of greater mortality (Lavie et al., 2007). Not only are the nearly half (48%) of the present study's participants with a $\text{BMI} \geq 30 \text{ kg/m}^2$ at increased mortality risk, but they are also at increased risk of functional impairment (Jenkins, 2004) and greater reduction in QOL (Evangelista et al., 2006; Lewis et al., 2007).

Lastly, the symptom of drowsiness, experienced by more than two-thirds (67.8%) of the women, was recently shown to be associated with increased risk of cardiovascular mortality in older, community-dwelling persons, sixty percent of whom were women (Empana et al., 2009). The relationship to sleepiness, another symptom with the finding of high burden, was not explored in the present study. Likewise, the prevalence of sleep apnea or other sleep pattern disturbance was not addressed in the women.

Study Limitations

Limitations of the present study include the small sample size, and the specialty HF clinic enrollment sources, which may not be representative of older women with HFPSF in other outpatient care settings. The study sample was largely Caucasian and did not allow for exploration of important differences among older women from various ethnic and racial groups.

Information concerning the comorbidity of arthritis was obtained from the medical record, which may not have provided complete information. The limited walk distance and incidence and sites of reported pain suggest that arthritis may be more

prevalent than clinic records would indicate. A related concern is that NSAID use is likely to be underreported, with only one medication record entry of this medication.

Conclusion

Older women with advanced HFPSF have unaddressed palliative need, evident in their multiple comorbidities, striking symptom prevalence and burden, significant reduction in functional capacity and high morbidity and mortality risk. A palliative approach to the multifaceted challenges older women with advanced HFPSF face does not entail prognosis estimation or abandonment of standard HF care, but does require recognition and intervention targeting the sources of the considerable palliative need. Multidisciplinary attention to the suffering in this growing subgroup of HF patients is vital for the reduction of significant personal and societal burden.

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Chapter 5 Part 2

Introduction

“All my favorite things are gone...”
(older woman with NYHA Class III HFPSF)

Heart failure (HF) is a quintessential chronic illness: long-term rather than episodic, rarely cured, associated with symptoms, treatments, and significant patient involvement in the treatment process (Holman, 2004). The characteristics of uncertain prognosis, challenging symptom palliation, and intrusiveness into daily life (Corbin & Strauss, 1988) contribute considerable challenge as well. The prevalence of HF continues to increase worldwide, as pharmacologic and device treatment advances extend patients' lives, as populations age, and as the epidemics of obesity, hypertension and diabetes contribute growing numbers of those at risk for the development of this chronic illness.

The prevalence of patients with the less-well known HF and preserved systolic function (HFPSF) is also increasing (Bhatia et al., 2006; Owan et al., 2006). Approximately one-half of patients have this type of HF, previously known as diastolic heart failure (Hogg, Swedberg, & McMurray, 2004; Paulus et al., 2007). Patients with HFPSF are older, more commonly women, and more likely to have a hypertensive etiology than those with reduced systolic function (Lenzen et al., 2004; McMurray et al., 2008).

The growing number of individuals with reduced or relatively preserved systolic function are at risk for experiencing the negative impact of HF on their quality of life (QOL) (Dracup, Walden, Stevenson, & Brecht, 1992; Hobbs et al., 2002). Defined simply as satisfaction in the areas of life an individual considers important (Bredow, Peterson, & Sandau, 2009), QOL includes components of symptom experience,

functional capacity and individual perception (i.e. general health status and level of well-being) (Wenger, Mattson, Furberg, & Elinson, 1984). To date, the majority of QOL research in HF has addressed patients with systolic dysfunction, and, as a result, limited data exist concerning the impact of HFPSF on QOL (Lewis et al., 2007).

A number of researchers have shown that women's QOL is more adversely affected by HF than men's (Cline, Willenheimer, Erhardt, Wiklund, & Israelsson, 1999; Lesman-Leegte et al., 2009; Riedinger et al., 2001), while others have found minimal (Riegel et al., 2003) or no (Zambroski, Moser, Bhat, & Ziegler, 2005) gender difference in QOL. Conflicting results may be related to the differential impact of factors such as physical symptom status and depression on men and women's QOL (Heo, Moser, & Widener, 2007). Little is known about the impact of advanced HFPSF on QOL in older women, including their symptom experience, functional capacity and individual perception.

Symptoms are known to be highly prevalent in advanced HF (Moser, Doering, & Chung, 2005; Walke, Gallo, Tinetti, & Fried, 2004). However, the multidimensional assessment of the symptom experience, expressed as symptom burden (Cleeland, 2007; Gapstur, 2007), has received less research attention than symptom prevalence. Moreover, little is known about the relationships among symptoms and symptom burden, functional capacity and QOL.

Comfort, a concept historically associated with medicine (von Gunten, 2002) and nursing (McIlveen & Morse, 1995), is recommended for advanced HF patients (Albert, Davis, & Young, 2002; Hunt et al., 2005; Adams et al., 2006; Lewis et al., 2006; Riegel, Moser, Powell, Rector, & Havranek, 2006). While lacking definitional clarity,

researchers have described comfort variously as a state of well-being (Morse, 1992) or as the satisfaction of human needs for relief, ease or transcendence within healthcare situations (Kolcaba, 1994). However, what patients perceive regarding comfort in advanced HF is not known, since no studies have assessed individual comfort in this complex chronic illness.

The purpose of this cross-sectional study was to identify sociodemographic and clinical factors associated with QOL in older women outpatients with advanced HFPSF.

Methods

Participants and Setting

Women were recruited from two specialty heart failure clinics in Southern California. Eligible study participants (1) had a diagnosis of NYHA Class III HF with an EF of $\geq 50\%$, 2) were English-speaking and community-dwelling, and 3) were aged 60 or older. Patients were excluded if they were 1) currently hospitalized, 2) physically or cognitively unable to complete questionnaires or participate in a low-level walk test, 3) diagnosed with other serious cardiac problems (e.g. severe valve disease, infiltrative myocardial disease or constrictive pericarditis), or 4) diagnosed with other serious medical conditions with life expectancy < 1 year (as determined by medical record review and physician consultation).

Measurement of Variables

Cognitive screen. After eligible patients gave informed consent, the principal investigator administered the Mini-Cog cognitive screening tool. The Mini-Cog uses an uncued three-item recall test with a clock drawing test (CDT). Subjects are asked to repeat 3 unrelated words and then complete the face of a clock displaying a requested

time of ten minutes after 11:00 o'clock; following that task, they are asked to recall the three words. Those who recall all of the words are classified as non-demented, and those who recall one or two words are classified based on the CDT result (abnormal = demented, and normal = non-demented). Normal CDT depictions have the numbers correctly spaced around the circle and the minute hand pointing to the number 2 (Borson, Scanlan, Brush, Vitaliano, & Dokmak, 2000; Woodford & George, 2007).

Demographic and clinical characteristics. Data on age, ethnic/racial category, marital status, living situation and history of hospitalization for HF in the past year were obtained from patient self-report (demographic questionnaire) and medical record review. Clinical characteristics obtained from medical record review included blood pressure, height, weight, echocardiogram data, laboratory results (i.e. blood urea nitrogen [BUN], creatinine [Cr.], hemoglobin [Hgb], albumin, NT-proBNP [N-terminal pro-brain natriuretic peptide] or BNP [brain natriuretic peptide]), comorbidities and current medications. Body mass index (BMI) and the estimated glomerular filtration rate (GFR) were calculated from the relevant clinical values.

Symptom prevalence and burden. Two mean summary scores from the Memorial Symptom Assessment – Heart Failure (MSAS-HF) instrument were used to represent HF symptom prevalence and HF symptom burden. The MSAS-HF, a 32-item modification of the Memorial Symptom Assessment Scale (MSAS) for cancer symptoms (Portenoy et al., 1994), asks if a symptom has been experienced in the previous 7 days, and then for a rating of the symptom on the dimensions of frequency, severity and bother. The sum of the symptoms present is the total prevalence (TOTPREV) score, with a 0-32 range. Symptom burden scores are determined by summing the mean of the frequency, severity

and distress of each symptom. The total symptom burden score (TOT Burden) is the mean of the symptom burden scores for all 32 symptoms (Portenoy et al., 1994; Zambroski et al., 2005).

Functional capacity. The Six Minute Walk Test (6MWT) measures the distance an individual can walk on a flat, hard surface in a six minute period, providing an objective assessment of functional capacity. The 6MWT is easier to complete than an exercise stress test (Steele, 1996), since it assesses the submaximal level of functional capacity, the level at which most activities of daily living are performed. Validity and reliability of the 6MWT have been previously reported (Demers, McKelvie, Negassa, Yusuf, et al., 2001; Hamilton & Haennel, 2000). A number of studies have used the 6MWT safely in elderly subjects, including those with and without known cardiac disease, with systolic dysfunction (with and without HF) and with HFPSF (Enright et al., 2003; Ingle et al., 2007; Peeters & Mets, 1996; Zi, Carmichael, & Lye, 2003).

Study participants walked in a marked corridor in each of the clinics, covering as much distance as possible during the allotted time. They were allowed to walk with their accustomed ambulation aids, to rest as needed, and were instructed to stop if they experienced serious symptoms (angina, dizziness, severe dyspnea, severe fatigue, or musculoskeletal pain). Distance covered was expressed in meters.

Comfort. Comfort was measured with an adaptation of the General Comfort Questionnaire (GCQ). This generic instrument contains 48 self-report items concerning comfort (Kolcaba, 1992) and has been widely adapted for use in diverse patient groups, such as post-coronary angiogram patients, those with urinary incontinence, and those

undergoing radiation therapy for breast cancer (Kolcaba, 2003). The GCQ has not been used previously in patients with HF.

The GCQ has four subscales: Physical – 12 items, Psychospiritual – 13 items, Sociocultural – 9 items, and Environmental – 14 items. The Environmental subscale was removed for the present study since it applies solely to hospitalized patients. The possible total score range for the resulting 35-item instrument is 35-210, with higher scores indicating greater comfort.

Reliability testing in the original 48-item GCQ instrumentation study resulted in a Cronbach's alpha of .88; no subscale results were provided (Kolcaba, 1992). In the present study, the Cronbach alpha coefficients for the 35-item total instrument and subscales (physical, psychospiritual, sociocultural) were .86, .64, .79, .67, respectively.

Quality of life. Quality of life (QOL) was measured using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), the most commonly used QOL instrument in HF research (Heo, Moser, Riegel, Hall, & Christman, 2005). This 21-item self-administered instrument uses a 6-point response scale, from 0 (no impact on QOL) to 5 (most severe impact on QOL). The score range is from 0 to 105, with lower scores indicating better QOL. Instrument scoring also yields two subscores: physical (8 items) and emotional (5 items). Eight additional items are incorporated into the total score but not included in a subscale (Bennett et al., 2003).

Validity and reliability of the MLHFQ have been established (Rector & Cohn, 1992; Rector, Kubo, & Cohn, 1993) and reliability confirmed in subsequent studies, with a Cronbach's alpha greater than .80 for the total score and two subscales (Bennett et al., 2003; Middel et al., 2001; Riegel et al., 2002). In the current study, the Cronbach alpha

coefficients for the total, physical and emotional subscales were .92, .92, .85, respectively.

Statistical Analysis

Statistical calculations were carried out using SPSS for Windows (Version 15.0, SPSS, Inc., Chicago, IL). Data were reported as mean \pm standard deviation (SD) for continuous variables; frequencies and percentages summarize categorical variables.

One-way analyses of variance and Chi-squared analyses were performed to evaluate differences in QOL scores using selected demographic (i.e. marital status, living situation) and disease-specific characteristics including history of hospitalization (yes/no), laboratory values (i.e., hemoglobin) and different comorbidities (i.e., diabetes). To determine variables to include in the multiple regression analyses, correlation coefficients were calculated between the total MLHFQ score and selected sociodemographic, clinical, and comorbidity characteristics, as well as MSAS-HF and GCQ scores.

Multiple regression analyses were then used to identify which combination of variables provided the greatest explanation of the variance in QOL. Variables significant at $\alpha < .10$ by themselves were entered into the regression model simultaneously. The final model was based on an n of 60. For all tests, a p value of <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

Table 1 presents the demographic and clinical characteristics of the 60 women recruited from two specialty HF clinics between October 2008 and May 2009. The

majority of the older women were Caucasian (86.7%), with ages ranging from 61-90. Of those who were married (45%), more than half (54%) rated their spouse's health as fair or poor. Clinical characteristics reflective of the women's medical complexity and overall vulnerability include a mean BMI in the obese range (30-39.9) (National Institutes of Health, 2000), multi-morbidity and compromised renal function, with the GFR of the majority (73%) falling below 60 mL/min/1.73 m². This level of renal function is consistent with the diagnosis of chronic kidney disease when persistent for three months or more (National Kidney Foundation, 2002). In addition, the average woman had a pulmonary artery systolic pressure meeting criteria (> 35 mmHg) for pulmonary hypertension (Lam et al., 2009). Forty-two percent were anemic (Hgb < 12 gm/dL) (World Health Organization, 1968), and more than a third (37%) had been hospitalized for HF in the past year. Considerable limitation in functional capacity characterizes the women in the sample, as they could walk, on average, less than 300 meters in six minutes.

Symptoms, Symptom Burden, Comfort and Quality of Life

Study participants reported (Table 2) high symptom prevalence, with the most common symptoms being lack of energy (88.3%), shortness of breath (83.3 %) and pain other than chest pain (73.3 %). The symptom burden (combined frequency, severity and bother) rating of $2.1 \pm .43$ was at the midpoint of the 0-4 possible score range. Table 2 also presents possible ranges, and total and subscales scores for the GCQ and MLHFQ. The median score for the MLHFQ was 44.5, with an inter-quartile range of 20.3-58.8.

Table 1 Demographic and Clinical Characteristics* N = 60

Mean age, y	76.8 ± 7.7
Race/ethnicity	
Caucasian	52 (86.7)
Hispanic/Latino	1 (1.7)
African American	4 (6.7)
Asian	1 (1.7)
American Indian/Alaskan Native	2 (3.3)
Marital status	
Married	27 (45)
Single	3 (5)
Divorced/separated	9 (15)
Widowed	21 (35)
Living situation	
Live alone	20 (33.3)
Live with other persons	40 (66.7)
Hospitalized in past 12 months for HF	22 (36.7)
Clinical Characteristics	
Systolic blood pressure (mmHg)	131.1 ± 21.0
Diastolic blood pressure (mmHg)	70.0 ± 10.7
Body mass index (kg/ m ²)	31.2 ± 7.9
Ejection fraction (%)	64.5 ± 9.4
RAP (mmHg) n = 50	8.9 ± 4.8

PASP (mmHg)	<i>n</i> = 50	47.6 ± 13.6
NT-proBNP (pg/mL)	<i>n</i> = 22	1577.2 ± 2191.3
BNP (pg/mL)	<i>n</i> = 28	329.8 ± 196.2
Hemoglobin (gm/dL)		12.0 ± 1.4
Glomerular filtration rate (mL/min/1.73 m ²)		51.7 ± 20.3
Number of comorbid conditions		4.7 ± 1.6
6 minute walk distance (meters)		201.4 ± 117.1

*Data are presented as patient number (%) or mean ± SD.

RAP, right atrial pressure; PASP, pulmonary artery systolic pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; BNP, brain natriuretic peptide.

Association of Selected Demographic and Disease Specific Characteristics, Symptom Status, and Comfort with Quality of Life

Table 3 lists the correlations between the total score on the MLHFQ and selected demographic and disease-specific, symptom prevalence and burden and GCQ (comfort) scores. Based on these correlational analyses, multiple regression analyses were performed, testing the association of demographic, clinical, symptom burden and comfort factors with QOL.

As shown in Table 4, the final overall model explained 66% of the variance in QOL, using the total score from the MLHFQ as the dependent variable ($p < .001$). In terms of unique contributions, age explained 4% of the variance ($p = 0.023$), total symptom burden explained 14% of the variance ($p < .001$), and comfort explained 7% of the variance ($p = 0.002$) in QOL. Hospitalization for HF, a marker of disease severity,

Table 2 Symptoms and Symptom Burden, Comfort and Quality of Life N = 60

	Range	Mean \pm SD	Median
MSAS-HF			
Symptom total	0-32	13.2 \pm 6.4	12
Total burden	0-4	2.1 \pm 0.43	2.1
GCQ - comfort			
Physical	12-72	51.7 \pm 9.6	51.0
Psychospiritual	13-78	61.8 \pm 10.3	63.5
Sociocultural	9-54	42.0 \pm 8.1	42.8
Total comfort score	35-210	160.3 \pm 24.5	162.5
MLHFQ - QOL			
Physical subscale	0-40	22.3 \pm 10.9	22.5
Emotional subscale	0-25	7.8 \pm 6.5	6.0
Total MLHFQ score	0-105	42.3 \pm 21.8	44.5

Table 3 Correlations Between MLHFQ Total Score and Selected Demographic, Clinical, Functional Capacity, Symptom and Comfort Characteristics N = 60

	<u>MLHFQ Total Score</u>	
	Correlation r	p-value
<i>Demographic Characteristics</i>		
Age	-.323	.012
Caucasian	-.164	.209
Married	.199	.128
Living situation	.180	.168

Clinical Characteristics

BMI	.151	.251
GFR	-.172	.190
Number of comorbidities	.302	.019
6MWT distance (meters)	-.402	.001
HF hospitalization in past yr.	.224	.086

Symptoms, Symptom Burden and Comfort

MSAS-HF Total Symptom Prevalence	.546	.000
MSAS-HF Total Symptom Burden	.681	.000
GCQ Total Score	-.657	.000

**Table 4 Factors Associated with QOL in Older Women with Advanced HFPSF:
Results of Multiple Linear Regression Model**

	R ²	<u>Regression Coefficients</u>		R ² Δ	P-value
		Unstandardized (B)	(SE)		
Overall Model	0.655				0.001
Age		-0.549	0.25	0.04	0.023
GFR		0.020	0.101	0.0003	0.842
6MWT distance		-0.017	0.020	0.005	0.406
HF hospitalization		7.189	3.670	0.025	0.055
MSAS-HF Total Burden		22.145	4.786	0.14	0.001
GCQ Total Comfort Score		-0.304	0.095	0.07	0.002

showed a trend toward significance ($p = 0.055$). Neither the distance walked in the 6MWT nor the GFR made a significant unique contribution to QOL.

Discussion

The older women with advanced HFPSF in this study reported poor QOL (MLHFQ median total score 44.5), not unlike that reported in two recent large randomized controlled trials (RCTs) of pharmaceuticals in HFPSF. The MLHFQ median total score of 45.0 for women in the HF-Preserved EF arm ($n = 1097$; 66.6 ± 11.4 years; 42.8% female; 48% Class III) of the CHARM study (Lewis et al., 2007) was higher than that of males (median 35) and like that of females (median 44) in the HF-Low EF CHARM group. In the second large RCT ($n = 4128$; 60% female; 72 ± 7 years; > 75% Class III), median total score on the MLHFQ was 42 for the combined samples of men and women in both placebo and intervention groups (Massie et al., 2008).

The findings of the present study contrast with those of a small study of HFPSF patients ($n = 150$; 62 % female; mean age 74; > 70% NYHA Class II) randomized to one of three pharmacologic treatment arms (Yip et al., 2008). At baseline, mean MLHFQ total scores for each of the 3 groups were 20 ± 1.8 , 19 ± 2.1 and 23 ± 2.3 , with declining scores in all three groups over the 52 week study. The marked difference in mean MLHFQ scores between the clinical trial by Yip and colleagues and the findings of the present study is likely due to the higher functional status of the patients in the former study. The majority of the sample was NYHA Class II, and the three groups (in combination) had a baseline mean 6MWT distance of nearly 100 meters further than the older women in the present study (297 meters vs. 201 meters).

Both QOL and functional capacity of the older women in the present study are similar to the baseline characteristics of an intervention group ($n = 16$; 62.5 % NYHA Class III) in a small exercise study of older women with HFPSF ($n = 32$; mean age 68 years) (Gary et al., 2004). Total MLHFQ score for the intervention group was 41 ± 26 at baseline and the baseline 6MWT distance was 256 ± 112 meters. When baseline walk results for women classified as NYHA Class III in both intervention and control groups were combined, the distance traveled (200 ± 94 meters) was nearly identical to that of the women in the present study (201 ± 117 meters).

Age and Quality of Life

Another finding consistent with other studies (Clark, Tu, Weiner, & Murray, 2003; Hou et al., 2004; Jaarsma et al., 2000; Lewis et al., 2007; Zambroski et al., 2005) is that older age is associated with better QOL than that of younger persons with HF. Interestingly, the relationship between older age and better QOL holds true even in this sample of women 60 years and older. It may be that older persons make accommodations to illness over time and expect to have some limitations. Thus, they may be better able to adapt to the realities of disease-related disability than younger persons, whose expectations of life are at considerable variance with the boundaries serious chronic illness defines.

However, one of the findings from a study (Masoudi et al., 2004) comparing functional status and QOL in younger ($n = 328$; 52 ± 8.2 years; 25% female) and older patients ($n = 218$; 74 ± 6.2 years; 22% female) with systolic HF provides an important age-related caveat with clinical and research relevance. While the QOL in older HF patients was better at baseline than that of younger patients ($p = .005$), older patients who

had a reduction in functional status at follow-up had a significant decline in their QOL score when compared to younger patients ($p = .0003$). Providers should consider opportunities to preserve or improve functional capacity in older women with HFPSF, since they may also be at risk for considerable decrement in QOL if they have continued functional decline. Additionally, further study of age-related factors associated with QOL in advanced HF (with reduced or preserved systolic function) is warranted.

Symptom Burden and Quality of Life

The findings are similar to those from a study of advanced (NYHA Class III/IV) systolic HF patients ($n = 103$; 28% female; $EF 22.3 \pm 6.8 \%$; 67.1 ± 12.1 years) that used the original MSAS with one added symptom (chest pain) and calculated a global symptom distress (GDI) summary score (derived from selected MSAS psychological and physical symptoms). Impairment in QOL, measured with the Mutidimensional Index of Life Quality (MILQ), was significantly related to high symptom distress in a model which also included psychological well-being and functional mobility ($R^2 = 0.67$; $p = 0.002$) (Blinderman, Homel, Billings, Portenoy, & Tennstedt, 2008).

In another study with comparable findings in systolic HF patients, researchers (Zambroski et al., 2005) used the MSAS-HF and MLHFQ to examine the impact of symptoms and symptom burden on QOL ($N = 53$; 55.5 ± 9.6 years; 34% female; $EF 23.7 \pm 14.5 \%$; 77% NYHA Class III/IV). Greater symptom prevalence and higher symptom burden, along with lower age and worse NYHA functional class, explained 67% of the variance in QOL in a younger, mostly male sample with systolic dysfunction.

Comfort and Quality of Life

The current study is the first to identify a significant role for the individual perception of comfort in QOL for a sample of older women with advanced HFPSF. In a model which includes older age, symptom burden, GFR, and HF hospitalization history, self-reported comfort explained 7% of the variance in QOL ($p = 0.002$). Comfort may be one of the positive psychological factors that improve QOL, but is not addressed in either disease-specific or generic QOL instruments used in HF (Heo, Lennie, Okoli, & Moser, 2009).

Limitations

Limitations in the study include the small sample size, which may have lacked sufficient power to detect other relationships that exist among the variables examined in the study. For instance, expected associations between renal function (GFR), anemia (Hgb level) or functional capacity (6MWT distance) and QOL were not observed. Moreover, the women in the study were not ethnically or racially diverse; important distinctions in symptom prevalence and burden, comfort and QOL may exist in a more diverse sample.

The sample of older women was recruited from two specialty HF clinics, and may not be representative of the population of older women with HFPSF receiving care in other outpatient settings. In addition, the cross-sectional study design limits conclusions that can be drawn with regard to the causal mechanisms underlying the observed associations.

Conclusion

Symptom burden had the greatest association with QOL in older women with advanced HFPSF. The individual perception of comfort and age were also important factors impacting QOL. An indicator of disease severity, hospitalization for HF in the past year, showed a trend toward being a significant factor by worsening QOL. These findings suggest that targeting interventions to reduce the women's symptom burden and to maximize their experience of comfort, while identifying concerns unique to those of younger age, may improve the QOL of this largely unaddressed, growing group of HF patients.

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Chapter 6

Summary

The overall purpose of this dissertation was to describe a growing, but unaddressed group of advanced HF patients. Older women with advanced HF and preserved systolic function (HFPSF) have received little research attention to date. This oversight may be due in part to relative unfamiliarity with HFPSF, previously known as *diastolic heart failure*. The first data based paper from the dissertation describes the characteristics of a sample of older women with advanced HFPSF. Evidence of significant palliative need in the women includes findings of high symptom burden, marked functional limitation and multiple comorbidities. The purpose of the cross-sectional study reported in the second data based paper was to identify sociodemographic, clinical, symptom and comfort factors associated with QOL in the older women. While controlling for disease severity (represented by HF hospitalization), clinical status (represented by estimated renal function), and functional capacity, factors independently associated with better QOL in the older women with advanced HFPSF were younger age, lower symptom burden and higher comfort.

Findings from this dissertation have implications for clinical practice, both in specialty HF clinics and in other settings providing medical care to HFPSF patients. The theoretical implications of applying the Chronic Illness Trajectory Model to HFPSF are as yet unexplored, since little is known about the natural history of patients with this type of HF. Results of the study may also serve as an impetus to develop policy initiatives regarding these vulnerable elders and may stimulate further research concerning this relatively unaddressed HF patient subgroup.

Clinical Implications

Symptom Burden

The symptoms of fatigue, dyspnea and swelling are the usual focus of HF management, but the present study of HFPSF and other studies of HF patients (Blinderman, Homel, Billings, Portenoy, & Tennstedt, 2008; Zambroski, Moser, Bhat, & Ziegler, 2005) demonstrate that patients experience many more symptoms than these. Both the number of symptoms and the associated burden negatively impact QOL. Providers should inquire about troublesome symptoms, and should seek to identify precipitating factors, as well as those which worsen or improve the symptom (Goodlin, 2009). Realistically, decreasing the severity or distress of the most burdensome symptoms may be a more reachable goal than alleviating the symptom completely (Zambroski et al., 2005). Since multiple co-morbidities may contribute to symptom prevalence and burden, collaboration with primary providers is needed to optimize management of the other conditions.

Obesity

Obesity is a major public health issue in the United States (Ogden et al., 2006), with more than one-third categorized as obese (Kuczmarski & Flegal, 2000). One-third of the older women in the present study were obese, fifteen percent were extremely obese, with a minority were at normal weight. This level of body weight places them at risk for continued decline in functional status (Jenkins, 2004), which has troubling implications. For older women with already impaired functional capacity (6MWT distance < 300 meters), further reduction may adversely impact their ability to care for themselves and ultimately, their ability to live independently. Other negative effects of obesity they might

experience include increased insulin resistance, hypertension, dyslipidemia, coronary artery disease, and obstructive sleep apnea (Lavie, Milani, & Ventura, 2009).

Lavie et al. (2007) found that a higher BMI was a strong independent predictor of greater mortality in a cohort of obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) HFPSF patients. Thus, it may be that the so-called obesity paradox in HF (Lavie, Mehra, & Milani, 2005) has diminished relevance after a certain weight threshold is reached. Providers should focus their efforts toward encouraging small increases in activity and realistic dietary modification for HFPSF patients in the obese and extremely obese weight ranges.

Functional Capacity

Regular assessment of the functional capacity of older women with advanced HFPSF has great importance, since they are at risk of further reduction of function. Evidence from a recent small study of older women with HFPSF (Gary et al., 2004) suggests that a home-based exercise intervention improves functional capacity and QOL. However, limited data exists concerning about this type of intervention since exercise trials in HF have excluded older patients with HFPSF (Haykowsky, Ezekowitz, & Armstrong, 2004) and no current guideline addresses exercise training in patients with diastolic dysfunction (Barmeyer, Mullerleile, Mortensen, & Meinertz, 2009).

Providers who recommend increased activity for women with HFPSF must consider multiple factors, including the medical stability of HF and co-morbid conditions, transportation availability, living situation, social support, and need for ambulation aids. In addition, the prevalence of the multi-site pain documented in this study may require diagnostic and treatment collaboration with primary providers and other specialists before older women are able to comfortably increase their activity levels.

Social Support

Providers tend to focus on applying disease-modifying treatments and monitoring patient response during clinic visits for HF. Other issues such as the level of social support and current living situation are easily overlooked. Furthermore, little research evidence concerning social support and HF (Luttik, Jaarsma, Moser, Sanderman, & van Veldhuisen, 2005) exists to guide providers who might address broader patient concerns.

More than two-thirds of the older women in this study reported living with another person. What is unknown is whether these arrangements mean that the women have high levels of social support or that they exhibit dependence in some activities of daily living. Moreover, the low ratings of spousal health from a majority of the married women in the study has great potential impact on both social support and living situation as both partners must negotiate the constraints of a marriage in which two persons need support simultaneously.

Professionals caring for older women with advanced HFPSF should remain alert to these extraordinary vulnerabilities of increased burden and loss of independence. Assessment of living situation and available support should accompany assessment of fluid volume level and other physiologic variables. Although the absence of an evidence base must be acknowledged, a multidisciplinary team approach should be employed whenever possible in caring for these patients with complex needs.

Theoretical Implications

The chronic illness trajectory of systolic HF in advanced stages, with the potential for a comeback phase, has been described in Chapter 3 of this manuscript. This extension of the Corbin and Strauss Chronic Illness Theory was feasible because considerable

research and clinical experience has developed around advanced systolic HF. No such theoretical development is possible with regard to HFPSF because so little is known about the natural history of the condition, particularly the usual course of advanced stages and outcomes. Although half of patients hospitalized with HF have a normal EF (Yancy et al., 2006), relatively few ambulatory patients with diastolic dysfunction (impaired left ventricular relaxation and compliance) in community datasets have symptomatic HF (Thohan & Patel, 2009). This scarcity of patients with advanced HFPSF in the community datasets is not likely to be the result of high in-patient mortality. Recent large-scale studies have shown lower (Fonarow et al., 2007; Yancy et al., 2006) in-hospital mortality when HFPSF patients were compared to those with systolic HF.

Older women with advanced HFPSF did not figure prominently in long-term follow-up of patients hospitalized with acute HF, either. Costanzo et al. (2008) analyzed data from the a nationwide registry following chronic Stage D (persistent symptoms, high hospitalization risk) HF patients, and found that the majority (65%) were males (mean age 69.6 ± 13.2 years) with reduced systolic function (mean EF 29.5 ± 14.1 %). These findings contrast with data from the earlier registry of acute decompensated HF, in which patients were older (mean age 72.8 ± 14.3 years), nearly evenly divided by gender (49% male), and with a higher mean EF (38.9 ± 17.4 %). Lastly, the finding of reduced systolic function (mean \pm SD $33.4\% \pm 17.4\%$) in a study of patients referred to hospice following a HF hospitalization (Hauptman et al., 2007) does not provide information regarding the trajectory and destination of advanced HFPSF patients.

Thus, much remains to be elucidated concerning the characteristics and disease trajectory (and living situation) of advanced HFPSF patients. The findings of the present

study suggest that the older, functionally limited, multimorbid, symptomatic women are at extraordinary risk of further decline and of losing their independence. The number of women (11) who declined study participation, primarily due to transportation difficulties, also underscores their vulnerability. It may be that many older persons with advanced HFPSF reside in assisted living or long-term care facilities, but this conjecture requires investigation.

Policy Implications

Older adults have considerable vulnerability following a HF hospitalization (Moser, Doering, & Chung, 2005; Naylor et al., 2004). Transitional care, defined by Naylor as intervention in the post-discharge period at home with master's-prepared nurses directing comprehensive management, is associated with reductions in re-hospitalization and overall health care costs for elders with HF and multiple co-morbidities (Roundtable, 2009). Reframing payment structures to include transitional care has demonstrated potential to reduce societal burden and to improve outcomes for a growing segment of the older adult population with chronic illnesses. For older women with advanced HFPSF, comprehensive intervention following hospitalization may help reduce their symptom burden, manage their co-morbidities and support assessment and appropriate referral regarding their living situation and social support.

A related issue with policy implications is that of preventing the loss of independence for older adults with HF and multiple co-morbid illnesses. If the personal and societal cost of institutionalization can be delayed or avoided with early assessment and intervention such as that described above in the transitional care model, great potential tangible (and intangible) benefit is possible.

Palliative care delivery in the end stages of HF is closely allied with the mechanism of hospice referral. However, the historical development of hospice is associated with malignant disease, and policy around prognosis estimation, referral and reimbursement continues to be tied to a disease trajectory unlike that characterizing end of life in HF. Until hospice referral criteria consider the unique needs of advanced HF patients (including those with preserved systolic function), a disproportionate few will receive the benefit preferentially targeting cancer patients. Of note, the disparity in hospice enrollment is particularly striking since heart disease continues to be the leading cause of death in the United States. (Stuart, 2007).

Although palliative care is underutilized, the treatment imperative across the continuum of HF is well-funded (Stuart, 2007). Since reimbursement is procedure-driven, and since cardiac interventions beget further cardiac interventions, (Shim, Russ, & Kaufman, 2008), cardiac procedures and devices such as defibrillators are increasingly common in older patients (Shim, Russ, & Kaufman, 2006). Policy initiatives which regard the provision of comfort as worthy a goal as procedure-based life extension are needed to offer the alternative of palliative care and hospice to HF patients at end of life.

Finally, greater attention must be given to the prevention of the highly prevalent conditions associated with the development of HFPSF. Greater public (and provider) awareness of the long-term risks of hypertension, diabetes and obesity has clear implication for the health of the nation's current and future older adults.

Future Studies

Although HFPSF is more common in older women, future studies should include older men. In addition, since the present study sample was predominantly Caucasian,

future studies of HFPSF should include greater representation from other racial and ethnic groups.

Evidence from the review of literature in Chapter 2 and from the present study of older women reveals substantial symptom burden in advanced systolic HF and HFPSF. Although the need is clear, palliative care has had limited integration into HF management (Stuart, 2007). Research is needed to determine how best to implement a palliative care in a manner which is congruent with the World Health Organization (WHO) definition (WHO, 2002). The WHO conceptualization describes concurrent application of a palliative approach along with disease-modifying therapies beginning early in an illness (WHO, 2002). Early application of palliation HF will also require research establishing an evidence base for the management of individual HF symptoms.

Little is known about how patients, including those with advanced HF, define comfort. The finding of the association of patient-rated comfort with QOL in this study prompts further questions about factors which influence an individual HF patient's comfort positively or negatively. A related research direction would be testing a modification of the GCQ to address comfort specifically in HF patients. Would a comfort tool have relevance for HF management, for example, in predicting HF hospitalization?

Conclusion

Increasing numbers of advanced systolic HF patients now reach the later stages of the disease, as remarkable advances in treatment and overall management strategies have altered the trajectory. Growing interest in palliative and hospice care for this population is an important development, since the symptom burden is considerable and the psychosocial challenges are myriad. However, one patient group, older women with

advanced HFPSF has grown in relative obscurity. Fewer research studies have addressed HFPSF, and fewer women and older persons have been included in HF clinical trials. Furthermore, they have not been included in the current discussions about palliative care in advanced HF.

Greater research attention, appropriate policy development, and increased provider awareness related to the needs of older patients with HFPSF is vital for the health of an ageing society. The particular vulnerabilities and suffering of patients who reach advanced stages cannot be ignored. The consequences of evidence-based, targeted interventions, on the other hand, may include reduction of the burden of multiple symptoms, enhancement of comfort and betterment of the quality of life in the last stage of the journey.

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