Patient-Caregiver Dyadic Dynamics in Heart Failure and Ventricular Assist Device Therapy

By

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Abstract

Background: Heart failure (HF) is a source of significant burden to patients and families. While patients experience distressing symptoms, compromised quality of life, and poor clinical outcomes, family caregivers often experience strain and compromised physical and mental health. Although HF influences patients and caregivers alike, little is known about how patients and caregivers experience HF together across the spectrum of illness severity. **Objective:** The purpose of this dissertation research is to characterize the impact of the patient-caregiver dyadic relationship on clinical and person-oriented outcomes in HF dyads in general and ventricular assist device (VAD) dyads in particular. **Methods:** This manuscript-style dissertation utilizes multiple data sources and methods to address three major goals. First, a meta-analysis of peer-reviewed publications and a primary latent growth analysis of data from VAD patients and caregivers are used to describe relationships between patient and caregiver outcomes in HF and VAD (Aims 1 and 2). Second, a secondary analysis of data from Italian HF dyads using Cox proportional hazards modeling and a primary analysis of data from VAD dyads using growth curve modeling are used to predict individual outcomes using interpersonal factors (Aims 3 and 4). Third, a secondary analysis of data from Italian HF dyads and a primary analysis of data from VAD dyads, both utilizing dyadic multilevel modeling, are used to predict patient-caregiver outcomes within a dyadic context (Aims 5 and 6). **Conclusions:** Collectively, this work advances the science by providing researchers and clinicians with knowledge to support patients and caregivers together towards better clinical and person-oriented outcomes.

MeSH Keywords: Heart Failure, Ventricular Assist Device, Caregivers

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Introduction

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Chapter 1: Introduction

Background and Significance

Heart failure (HF) is the fastest growing cardiovascular disorder, currently affecting nearly 6 million adults in the United States (Heidenreich et al., 2013; Mozaffarian et al., 2016). Patients with HF experience distressing symptoms, compromised quality of life (QOL), and increased risk of clinical events (Lesman-Leegte et al., 2009; Mozaffarian et al., 2016; Zambroski, Moser, Bhat, & Ziegler, 2005). At the same time, caregivers of persons with HF face substantial risks of compromised physical and mental health and significant strain related to their caregiving role, which is itself associated with greater mortality (Pinquart & Sorensen, 2003; Schulz & Beach, 1999; Vitaliano, Strachan, Dansie, Goldberg, & Buchwald, 2014). Despite the fact that HF is commonly a shared experience between patients and their informal caregivers (Chung et al., 2014; Hwang, Fleischmann, Howie-Esquivel, Stotts, & Dracup, 2011), few studies examine how patients and caregivers experience and manage HF together. This program of research seeks to fill this gap, providing foundational information on how the patient-caregiver dyadic relationship impacts clinical and person-oriented outcomes for patients and their caregivers across the HF spectrum: from stable HF to advanced HF requiring ventricular assist device (VAD) therapy.

The Clinical Syndrome of Heart Failure

Heart failure is a rapidly growing epidemic, both nationally and globally. In the United States, 5.7 million adults currently have HF (Mozaffarian et al., 2016), and in the developed world as a whole, HF affects 1-2% of the general adult population and ≥10% of adults over 70 years of age (McMurray et al., 2012). HF is of particular concern because it is substantially burdensome from a personal, clinical, and societal perspective. From a personal perspective, the

HF syndrome is characterized by a preponderance of distressing physical and affective symptoms, cognitive disruptions, activity limitations, and poor QOL (Lesman-Leegte et al., 2009; Mozaffarian et al., 2016; Vogels, Scheltens, Schroeder-Tanka, & Weinstein, 2007; Zambroski et al., 2005). From a clinical perspective, HF is associated with substantial risk of hospitalization, re-hospitalization, and premature death (Alter et al., 2012; Jencks, Williams, & Coleman, 2009; Liu, 2011). Although not often presented to patients and families as a terminal illness, HF has a worse prognosis than most terminal cancers, and its unstable trajectory is notoriously hard to predict, making clinical management and decision-making for patients and families incredibly challenging (L. A. Allen et al., 2012; Stewart, MacIntyre, Hole, Capewell, & McMurray, 2001). Furthermore, when HF becomes advanced, limited treatment options exist, and most patients are not eligible for or will not survive long enough to receive the gold standard of treatment: transplant (Mehra et al., 2016; Russell, Miller, & Pagani, 2008). From a societal perspective, compounding our current HF crisis is a rapid expansion in prevalence that is projected to triple our already-burgeoning national HF cost burden to $70 billion dollars annually by 2030 (Heidenreich et al., 2013). Thus, there is an imminent need for research in HF to improve person-oriented and costly clinical outcomes, both for the current, large population of HF patients and families, and the rapidly growing future population.

Burden of Heart Failure on the Patient

Patient-oriented outcomes. Most patients with HF experience substantial clinical and personal burden related to their illness. In particular, the HF syndrome is associated with distressing physical and affective symptoms. Physical symptoms are diverse and typically include fatigue, breathlessness, sleep disturbances, loss of functional capacity, edema, pain, and others (McMurray et al., 2012; Shah et al., 2013; Yancy et al., 2013). Less widely examined but similarly distressing are affective and cognitive symptoms, which include depression and anxiety – likely compounded by the realities of coping with life-threatening chronic illness – and cognitive impairment (Rutledge, Reis, Linke, Greenberg, & Mills, 2006; Vogels et al., 2007; Yohannes, Willgoss, Baldwin, & Connolly, 2010). Moreover, as HF is a chronic, progressive, and heterogeneous syndrome, physical and psychological symptoms worsen over time, necessitating personalized adjustments to medical therapy and increased efforts to manage and respond to symptoms appropriately (McMurray et al., 2012; Riegel et al., 2009; Yancy et al., 2013). Concomitant with distressing symptoms, patients with HF typically report compromised QOL (Bekelman et al., 2007; Lesman-Leegte et al., 2009; Zambroski et al., 2005). QOL is an important person-oriented outcome in chronic illness in general and in HF in particular (Yancy et al., 2013). As HF progresses, QOL typically worsens, and for patients with advanced HF, QOL is particularly poor (L. A. Allen et al., 2012).

Clinical outcomes. In addition to the daily interference and activity limitations from symptoms, the syndrome of HF is also associated with poor clinical outcomes: in particular, HF patients are at high risk for hospitalization, re-hospitalization, and premature death. In terms of mortality, half of HF patients will die with 5 years of diagnosis (Mozaffarian et al., 2016), and for patients with advanced HF, the outlook is particularly grim, with a projected life expectancy of less than 2 years (Hunt et al., 2009). In terms of hospitalization, HF is the primary reason for hospitalization and re-hospitalization of older adults (Jencks et al., 2009; Liu, 2011). Furthermore, an index (first) hospitalization for acute HF is often not an independent event, but a harbinger of progressive decline, additional hospitalization, and increased risk of death: the average patient lifespan after index hospitalization is 5 years, and 27% of patients will die within one year (L. A. Allen et al., 2012; Alter et al., 2012; Jencks et al., 2009). Despite substantial efforts to model and predict risk, there remains substantial unexplained variability in clinical outcomes in HF (Rahimi et al., 2014; Russell et al., 2008), and lack of precision in our ability to predict risk and estimate prognosis is a key barrier to effective decision making for providers and for patients and their families (L. A. Allen et al., 2012).

Disease management. In order to maintain clinical stability and prevent worsening of symptoms and QOL, patients with HF must adequately manage their disease (Lee, Moser, Lennie, & Riegel, 2011; Riegel et al., 2009). From a clinical perspective, disease management for HF involves a combination of pharmacological and non-pharmacological interventions. Pharmacological interventions are tailored based on patient stage and response to therapy, but typically involve medications such as diuretics, beta-blockers, angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers, and often other drugs (e.g. aldosterone receptor antagonists, digoxin, hydralazine, isosorbide dinitrate, antiarrythmic agents, etc.; Yancy et al., 2013). Device therapy (e.g. implantable cardioverter-defibrillator for primary or secondary prevention, cardiac resynchronization therapy) may also be indicated for some patients (Yancy et al., 2013). Non-pharmacological interventions typically include: 1) basic health promotion behaviors (e.g. physical activity, nutrition, maintaining a healthy weight, good primary care, avoiding infectious illness, etc.); 2) HF education, including restricting dietary sodium intake, understanding medications, and recognizing and responding to symptoms quickly; 3) maintaining good social support, particularly given its correlation with reductions in clinical event-risk (Luttik, Jaarsma, Moser, Sanderman, & van Veldhuisen, 2005); and 4) managing comorbid conditions, as concomitant comorbid burden is particularly high in HF patients (Wong, Chaudhry, Desai, & Krumholz, 2011; Yancy et al., 2013). Importantly, the success of disease management overall largely rests on the patient and his/her ability to maintain health and manage

HF in accordance with provider instructions and current guidelines. This is commonly referred to as “HF self-care.”

HF self-care involves engagement in daily maintenance behaviors (e.g. medication adherence, restricting dietary sodium, exercising), recognition of HF symptoms when they occur (HF symptom perception), and timely and appropriate response to symptoms (self-care management) (Riegel, Dickson, & Faulkner, 2015; Riegel et al., 2009). As HF progresses and self-care becomes increasingly critical for maintaining clinical stability, aspects of the HF syndrome (e.g. cognitive impairment, psychological symptoms, sleep disturbances) impede patients’ ability to adequately engage in self-care (Riegel, Lee, & Dickson, 2011). Thus, there is an imminent need for research to better understand and support patients to successfully engage in HF self-care, particularly in terms of difficulties related to psychological symptoms, which may be modifiable.

Advanced heart failure and therapies. HF is a progressive disorder, and will eventually result in poor clinical and person-oriented outcomes despite optimal self-care and disease management. When symptoms continue to worsen and no longer respond to optimal medical therapy, the patient has progressed to advanced HF – a stage of illness with a particularly high level of symptom burden and limited treatment options (Russell et al., 2008). Although heart transplant remains the gold standard of treatment for advanced HF, most patients are not eligible for transplant, and, for those that are eligible, the limited availability of donor organs is a major barrier (Mehra et al., 2016). For many advanced HF patients that are not transplant-eligible or cannot survive protracted transplant wait times, VAD therapy has become a primary therapeutic option (Feldman et al., 2013; Kirklin et al., 2015; Peura et al., 2012). Although VAD therapy is associated with substantial QOL improvements, as with symptoms, there is significant heterogeneity in responses to VAD (Grady et al., 2014; Grady et al., 2015). Similarly, although VAD is associated with a reduced risk for death as compared with optimal medical management (Fang, 2009; Slaughter et al., 2009), there is substantial heterogeneity in response to VAD therapy: over 50% will be re-hospitalized within a year, and approximately 20% will die, 10% will have a stroke, and 20% will have a serious device-related infection (McIlvennan et al., 2014). Thus, in order to advance the science and improve clinical and person-oriented outcomes for HF patients across the spectrum of illness, we need research that elucidates determinants of clinical event-risk and non-response to both medical and VAD therapies.

Burden of HF on the Caregiver

Caregiver contributions to disease management. HF caregivers frequently assist patients with HF self-care behaviors, but this contribution is rarely quantified (Buck et al., 2015; Clark et al., 2014). Importantly, clinicians often interact with caregivers as though they were members of the healthcare team, relying on them to assist the patient with health behaviors, medication adherence, and symptom monitoring (Grady et al., 2000). However, we know little about determinants of caregiver contributions to self-care, or how the patient and caregiver work together to manage illness. This lack of knowledge is particularly pronounced in advanced HF with VAD therapy, where caregivers are mandatory and expected to be available to provide round-the-clock care to patients in the early postoperative period or longer (Blumenthal-Barby et al., 2015; Feldman et al., 2013; Kirkpatrick et al., 2015; Peura et al., 2012). Given the prevalence of strain and psychological distress in HF caregivers and the clinical expectation that caregivers assist patients in disease management, it is concerning that psychological distress in caregivers has been associated with reduced ability to provide patient care (Buck, Mogle, Riegel, McMillan, & Bakitas, 2015; Foebel, Hirdes, & Heckman, 2012). Thus, further research across the spectrum of HF is needed to quantify caregiver contributions to HF self-care and identify caregivers who need additional support to assist the patient in managing illness successfully while maintaining their own health and well-being.

Caregiver strain. Caregiver strain (sometimes termed “burden”) is a common and concerning phenomenon in caregivers of patients with chronic illness. Most notably, caregivers who report strain are at greater risk for increased mortality and morbidity when compared to caregivers without strain or non-caregivers (Beach, Schulz, Yee, & Jackson, 2000; Schulz & Beach, 1999). Notably, care strain in HF has also been associated with compromised caregiver mental health and QOL (Barnes et al., 2006; Chung, Pressler, Dunbar, Lennie, & Moser, 2010). In chronic illness in general and in HF in particular, strain often increases with the natural progression of disease (e.g. worsening patient symptoms and subsequent increases in caregiving intensity) (Agren, Evangelista, & Stromberg, 2010; Chung et al., 2010; Hwang et al., 2011; J. G. Lyons, Cauley, & Fredman, 2015). There are also aspects of the HF syndrome and experience that may place HF caregivers at particular risk for strain. The uncertain trajectory of HF with its unpredictable exacerbations – any of which could lead to emergent intervention (e.g. urgent transplant or mechanical support) or fatal decline – may be particularly stressful for family members, who may remain at heightened levels of anxiety about the future even in times of apparent stability (L. A. Allen et al., 2012; Kirkpatrick et al., 2015). Furthermore, despite the difficulties of caregiving in chronic HF, HF caregivers report receiving less supportive services than other chronic illness caregivers (e.g. cancer), and palliative care utilization in for families with end-stage HF is particularly poor (Burton et al., 2012; Garlo et al., 2010; McGonigal, 2013). Additionally, the limited treatment options for patients with advanced HF is likely a source of distress for patients and families as HF advances, and the only potentially life-extending treatments for end-stage HF (transplant and VAD therapy) rely heavily on informal caregivers in order to be successful (Blumenthal-Barby et al., 2015; Mehra et al., 2016; Peura et al., 2012). Thus, given the distressing aspects of chronic illness caregiving in general and HF caregiving in particular, and the concerning sequelae of caregiver strain, we are in need of research that identifies HF caregivers that are at particular risk for strain so we can more effectively target supportive interventions.

Physical and mental health and quality of life. The risks of comprised physical/mental health and QOL related to caregiving have been well-documented, both in the broader caregiving literature (Beach et al., 2000; Pinquart & Sorensen, 2003; Vitaliano et al., 2014; Vitaliano, Zhang, & Scanlan, 2003) and in HF in particular (Agren, Evangelista, Davidson, & Stromberg, 2011; Chung et al., 2014). Importantly, caregiver physical and mental health and QOL have been associated with multiple patient characteristics in HF, including patient depression, QOL, and clinical event-risk (Chung et al., 2014; Hooley, Butler, & Howlett, 2005; Rohrbaugh, Shoham, Cleary, Berman, & Ewy, 2009). When the progression of HF necessitates advanced therapies such as VAD, less is known quantitatively about sequelae for caregivers. However, several qualitative studies of VAD caregivers have documented substantial psychological distress and compromised physical health as a result of their caregiving role (Baker, Flattery, Salyer, Haugh, & Maltby, 2010; Kaan, Young, Cockell, & Mackay, 2010; Marcuccilli, Casida, Bakas, & Pagani, 2014). Thus, given the potential negative impact of caregiving on mental and physical health and QOL for caregivers across the spectrum of HF, there is a pressing need for research that identifies and supports caregivers at particular risk for poor outcomes.

Heart Failure and the Patient-Caregiver Dyad

There is consensus from broader chronic illness caregiving literature that patient and caregiver outcomes are interdependent, and that the caregiving dyad is transactional in nature (e.g. the characteristics and experiences of one member of the dyad influence the other member, and vice versa) (Berg & Upchurch, 2007; Klinedinst et al., 2009; Rayens & Svavarsdottir, 2003). In the context of HF, there are substantial gaps in our understanding of which patients and caregivers are at risk for poor outcomes, and what factors might be amenable to intervention. Examining the transactional nature of the caregiving dyad by integrating dyad-focused aims and methods into HF research opens up new avenues for solving problems in clinical management that individual-level research methods have been unable to fully elucidate. Fortunately, as with the broader chronic illness context, there is evidence from within the HF literature that the HF patient-caregiver dyad is also transactional in nature. For example, as patient HF symptoms worsen, caregiver strain also increases (Rohrbaugh et al., 2009). Caregiver strain also increases concomitantly with decreases in patient QOL (Agren et al., 2010), and both caregiver strain and psychological distress have been linked with patient-clinical event-risk (Hooley et al., 2005; Hwang et al., 2011; Saunders, 2008; Schwarz & Elman, 2003). In the context of HF self-care, caregiver psychological distress has been associated with both reduced caregiver and reduced patient contributions to self-care (Buck, Mogle, et al., 2015; Foebel et al., 2012), and although dyadic research is limited in HF, there is evidence that dyads work together to manage HF (Buck, Mogle, et al., 2015; Lee et al., 2015; K. S. Lyons et al., 2015; Vellone et al., 2014). Furthermore, early self-care interventions taking a family-based approach have been successful in HF (Chung, Lennie, Mudd-Martin, & Moser, 2015; Dunbar et al., 2013).

Although these observed relationships between HF patients and caregivers provide foundational support for investment in dyadic studies to improve outcomes for HF patients and their caregivers, it is important to note that almost all research involving HF patients and caregivers is conducted at the individual, rather than the dyadic, level. Patient-centered caregiving research in HF tends to emphasize the outcomes of the patient, and characterize the caregiver as a care asset or liability to the patient's health. Caregiver-centered caregiving research in HF tends to emphasize the outcomes and preferences of the caregiver, and characterize the patient and illness as a source of stress. Both of these perspectives have value, but are individual-level perspectives, and by definition, research questions and analyses conducted at the level of the individual cannot be generalized to the level of the relationship (Thompson & Walker, 1982). Thus, in order to improve outcomes for HF patients and caregivers *together*, there is an imminent need for research questions and approaches that are focused on the dyadic relationship, rather than one member of the dyad or the other.

Theoretical Framework

The theoretical framework for this program of research is the Developmental-Contextual Model of Couples Coping with Chronic Illness Across the Adult Life Span (Berg & Upchurch, 2007) (**Figure 1)**. The model was developed from the broader caregiving, dyadic and family literature using a developmental and contextual framework. Although the Developmental-Contextual Model is not specific to HF, it is based on commonalities across multiple chronic illness contexts, including chronic cardiovascular disease. The three primary concepts in the model are dyadic appraisal, coping and adjustment: 1) *dyadic appraisal* refers to how patients and caregivers appraise the illness in terms of illness representation (controllable, consequences), ownership, and specific stressors; 2) *dyadic coping* refers to the varied patterns of couple interactions as they deal with stressors (uninvolvement, support, collaboration, control, protective buffering); and 3) *dyadic adjustment* refers to how patients and caregivers adjust to illness (psychosocial, relational, or physical health outcomes).

In the Developmental-Contextual Model, interactions among appraisal, coping and adjustment occur within a larger sociocultural context and the dyad-specific proximal context. For example, how a dyad functions is influenced by culture and gender, as well as relationship quality and characteristics of the illness. Interactions among appraisal, coping, and adjustment also occur within the context of time (both lifespan developmental stages and the progression of illness over time). A critical aspect of the Developmental-Contextual Model is a “transactional” phenomenon wherein patients and caregivers influence each other and their experiences with key concepts in the model (appraisal, coping and adjustment), which may occur continuously, both in and out of order. For example, the way a dyad appraises HF may influence coping strategies used by the dyad, which may in turn influence appraisal and adjustment, which may in turn influence coping and so on.

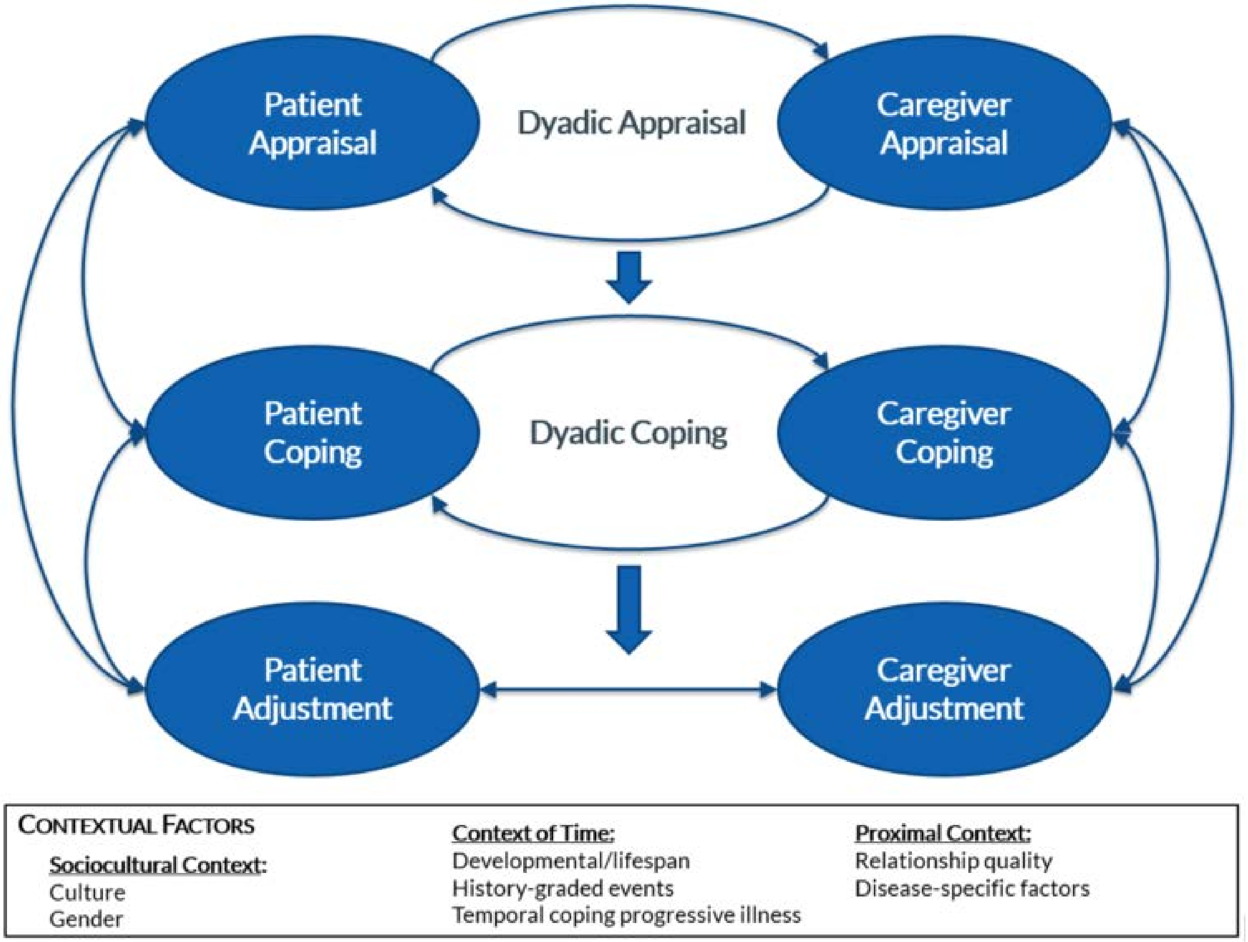

Figure 1: The Developmental-Contextual Model of Couples Coping with Chronic Illness, adapted from Berg & Upchurch (2007).

The rationale for utilizing the Developmental-Contextual Model as a guiding theoretical framework for research in HF family care dyads is that the model is explicitly dyadic, in contrast to most theories of caregiving or illness that are focused on the individual. Instead of placing either the patient or caregiver as the endpoint or reducing the patient to a stressor or the caregiver to a therapeutic asset/liability, the Developmental-Contextual Model gives even weight to patient and caregiver outcomes. Furthermore, the relationship between patient and caregiver is central and nested within important sociocultural and proximal contexts over the trajectory of the illness and the lifespan. Thus, the Developmental-Contextual Model provides a theoretical basis for a broad spectrum of dyadic research questions with the capacity to improve the health and well-being of patients and caregivers together. Given that some of the specific concepts within the model (appraisal, coping, adjustment) do not necessarily align with the most pressing clinical and research issues in HF, however, this program of research rests on an adapted interpretation of the model. Specifically, by reframing HF-specific concepts within the broader constructs of appraisal, coping and adjustment, the Developmental-Contextual Model becomes more informative in improving clinical care and outcomes in HF in particular. For example, as previously noted, HF self-care behaviors are key in maintaining clinical stability, and are one way in which patients and caregivers work together to manage and cope with illness. Thus, we can consider patient and caregiver contributions to self-care to be aspects of *dyadic coping.* In this way, the Developmental Contextual Model of Couples Coping with Chronic Illness Across the Adult Lifespan becomes an appropriate framework for guiding the study of patient-caregiver dyads in HF in general and for this program of research in particular.

Purpose and Specific Aims

The overall purpose of this program of research is to characterize the influence of the patient-caregiver relationship on clinical and person-oriented outcomes in HF dyads in general and VAD dyads in particular. To accomplish this purpose, six specific aims are proposed and addressed in six data-based manuscripts (Table 1). Each aim is described in brief in the sections following the table, and collectively they form a body of work that utilizes a variety of data sources and analytic methods in a stepwise manner: from describing how individual patient and caregiver outcomes are related, to predicting individual outcomes using interpersonal (cross-partner and dyadic) factors, to predicting outcomes for both patients and caregivers within the context of the dyadic relationship.

Table 1: Overall Purpose and Specific Aims

Overall Purpose: Characterize the influence of the patient-caregiver dyadic relationship on clinical and person-oriented outcomes in HF dyads in general and VAD dyads in particular.

		Research Question	**Aim/Hypotheses**	**Manuscript**
HEART FAILURE	DESCRIBE interplay between patients and caregivers	Synthesizing extant literature, how are patient and caregiver outcomes related in heart failure?	Aim 1: Summarize known relationships between person-oriented and clinical outcomes within patient-caregiver dyads in heart failure. *Hypothesis: Better caregiver well-being (lower strain and psychological distress) will be associated with better patient outcomes.*	*Caregiver well-being and patient outcomes in heart failure: A meta-analysis* In Press: The Journal of Cardiovascular Nursing
VAD THERAPY		How do HF patients and caregivers respond to VAD therapy over time? Do their individual outcomes covary over time?	Aim 2: Describe changes in person-oriented outcomes for HF patients and caregivers in response to VAD therapy, and quantify relationships between patient and caregiver outcomes. *Hypothesis 1: Changes in patient outcomes in response to VAD therapy will be early and substantial, while caregiver outcomes will remain relatively stable over time.* *Hypothesis 2: There will be strong relationships between patient and caregiver outcomes in response to VAD therapy*	*Quality of Life, Depression, and Anxiety in Ventricular Assist Device Therapy: Longitudinal Outcomes for Patients and Caregivers* Target Journal: The Journal of Cardiovascular Nursing (under review)
HEART FAILURE	PREDICT individual outcomes using interpersonal factors	How do characteristics of the patient, caregiver, and their relationship to one another help us understand patient clinical event-risk in HF?	Aim 3: In patient-caregiver dyads with heart failure, quantify the impact of individual and dyadic characteristics on patient clinical event-risk. *Hypothesis: Individual-level and dyad-level determinants of patient clinical event-risk will be identified.*	*Interpersonal determinants of patient clinical event risk in patient-caregiver dyads in heart failure* Target Journal: European Journal of Cardiovascular Nursing (under internal review)

VAD THERAPY		How do characteristics of the patient, caregiver, and their relationship to one another help us understand how patients and caregivers individually respond to VAD therapy?	Aim 4: In VAD patient-caregiver dyads, identify individual- and dyad-level determinants of change in patient HF-specific quality of life and caregiver strain. *Hypothesis: Both individual and dyadic determinants of change in patient HF-specific QOL and caregiver strain will be identified.*	*Individual and interpersonal determinants of HF-specific quality of life and caregiver strain in ventricular assist device therapy* Target Journal: The Journal of Heart and Lung Transplantation (ready for internal review at final defense)
HEART FAILURE	PREDICT patient-caregiver outcomes within a dyadic context	Across caregiving dyads, how do characteristics of the patient, caregiver, and their relationship to one another help us understand how engaged patients and caregivers are in managing heart failure?	Aim 5: In patients and caregivers with heart failure, identify individual- and dyad-level determinants of HF self-care within a dyadic context. *Hypothesis: Across dyads, both individual and dyadic determinants of patient and caregiver self-care behaviors will be identified.*	*Determinants of heart failure self-care maintenance and management in patients and caregivers: A dyadic analysis* Published: Research in Nursing & Health (October 2015)
VAD THERAPY		Across caregiving dyads, how do characteristics of the patient, caregiver, and their relationship to one another help us to better understand how patients and caregivers will respond to VAD therapy together?	Aim 6: Identify individual and dyad-level determinants of change over time in psychological symptoms and quality-of-life within a dyadic context *Hypothesis: Across dyads, both individual and dyadic determinants of change in patient and caregiver psychological symptoms and quality-of-life will be identified.*	*Determinants of quality of life and psychological symptom trajectories in patient-caregiver dyads in ventricular assist device therapy* Target Journal: Journal of Cardiac Failure (ready for internal review at final defense)

Aims 1 and 2: Describing Interplay between Patient and Caregiver Outcomes

Aim 1. The first aim is to summarize known relationships between person-oriented and clinical outcomes within patient-caregiver dyads in HF. This aim is accomplished through a series of random-effects meta-analyses of observed relationships between HF patients and caregivers on key outcomes within the existing HF caregiving literature. In particular, we examine relationships between caregiver well-being (strain and psychological distress) and patient clinical and person-oriented outcomes (HF symptoms, QOL, and clinical event-risk). This work advances the science by demonstrating that patient and caregiver outcomes in HF are transactional, providing foundational evidence for examining HF patients and caregivers together within a dyadic context.

Aim 2. The second aim is to describe changes in person oriented outcomes for HF patients and caregivers in response to VAD therapy, and to quantify relationships between patient and caregiver outcomes. This aim is accomplished through two prospective, longitudinal studies: parent study PREMISE-HF (PI Lee), which enrolls patients receiving VAD therapy for advanced HF (Lee et al., 2014) and ancillary study PREMISE-CG (PI Lee/Bidwell), which enrolls the caregivers of patients enrolled in PREMISE-HF. After merging data from both studies to form a dyadic dataset, latent growth modeling with parallel processing is used to model trajectories of change for patients and caregivers from pre-implant to 3 months post-implant on person-oriented outcomes of interest (QOL, depression, anxiety). This work advances the science by being the first quantitative study in VAD to describe change in person-oriented outcomes from pre- to post-implant in patients and caregivers, and by quantifying previously unknown relationships between VAD patient and caregiver outcomes.

Aims 3 and 4: Predicting Individual Outcomes Using Interpersonal Factors

Aim 3. The third aim is to quantify the impact of interpersonal characteristics on patient clinical event-risk in HF. This aim is accomplished with a secondary analysis of data utilizing Cox proportional hazards modeling with a sample of Italian community-dwelling HF patients and their informal caregivers. In particular, we examine the influence of baseline patient and caregiver characteristics on patient clinical event-risk (all-cause mortality or hospitalization/ED visit for HF) over a median of 15 months' follow-up. This work advances the science by demonstrating that understudied interpersonal characteristics are related to a primary clinical endpoint in HF.

Aim 4. The fourth aim is to identify individual- and dyad-level determinants of change in patient HF-specific QOL and caregiver strain in VAD patient-caregiver dyads. This aim is accomplished with a primary analysis of data from the aforementioned PREMISE studies. In particular, we use two individual growth curve models to describe and predict change over time in patient HF-specific QOL and caregiver strain. Similar to Aim 2, this aim advances the science by being the first quantitative study of VAD patient-caregiver dyads to examine change over time from pre-implant through post-implant, and by identifying determinants of key person-oriented outcomes for both dyad members.

Aims 5 and 6: Predicting Patient-Caregiver Outcomes within a Dyadic Context

Aim 5. The fifth aim is to identify individual- and dyad-level determinants of HF self-care within a dyadic context. This aim is accomplished with a secondary analysis of data from a sample of Italian HF patients and their informal caregivers. In particular, we use multilevel modeling to identify determinants of patient and caregiver contributions to HF self-care in the context of the caregiving dyad. This aim advances the science by providing insight into the complex nature of the patient-caregiver relationship and its influence on HF self-care, potentially leading to more effective ways to intervene to improve self-care and subsequently maximize outcomes.

Aim 6. The sixth aim is to identify individual- and dyad-level determinants of change in psychological symptoms and QOL within a dyadic context. As with aims 2 and 4, this aim is accomplished with a primary analysis of data from the PREMISE studies of VAD patients and their caregivers. In particular, we utilize longitudinal dyadic multilevel modeling to describe and predict change over time in anxiety, depression, and QOL for patients and caregivers within the context of the caregiving dyad. This aim advances the science by being the first known analysis of change in VAD patients and caregivers that concomitantly quantifies and controls for dyadic interdependence in person-oriented outcomes. As such, this analysis provides much-needed insight into how patients and caregiver respond to VAD therapy together, and which dyads may need additional support.

Implications for Research and Practice

Collectively, the results of this program of research carry multiple implications for clinical practice and research. First, the combined work of Aims 1 and 2 in quantifying relationships between patients and caregivers on important HF and VAD outcomes make foundational contributions to the nascent field of dyadic research in HF. Without quantitative support for the hypothesis that the patient-caregiver relationship is transactional in HF and that interpersonal factors have an important impact on patient and caregiver outcomes, it is challenging to justify dyadic approaches to clinical care and research. Second, the cumulative work of Aims 3 and 4 to predict 1) clinical event-risk for HF patients and 2) caregiver strain and patient HF-specific QOL in VAD, provides important information on how interpersonal factors (dyad characteristics and cross-partner effects) assist in quantifying previously unexplained variability in critical person-oriented and clinical outcomes. This adds to the foundation built with Aims 1 and 2, providing insight into which patients and caregivers may be at greater risk and which patient, caregiver, or dyadic factors may be appropriate targets for intervention to support better outcomes. Third, the collective work of Aims 5 and 6 to predict self-care in HF dyads and person-oriented outcomes in VAD dyads builds on the work of the previous aims to provide additional support for a dyadic approach to clinical practice and research. In particular, our analysis of self-care gives greater insight into how patients and caregivers work together to manage illness, and what individual, cross-partner, and dyadic factors may be promising targets for intervention. Our analysis of person-oriented outcomes over time within the context of the VAD patient and caregiver dyad will be the first to quantitatively examine how patients and caregivers respond to VAD therapy together over time. As such, it provides critical information for researchers and clinicians working to support better outcomes for both members of the VAD caregiving dyad.

Summary

In summary, this program of research provides important foundational information on how patient and caregiver outcomes are related in HF and VAD, how interpersonal characteristics predict important clinical and person-oriented outcomes across the spectrum of disease, and how patients and caregivers together manage HF and respond to VAD therapy within a dyadic context. Collectively, through examining interdependence between patients and caregivers in HF and VAD, these interpersonal and dyadic research aims provide new means for addressing issues in clinical management that individual-level approaches have been unable to fully elucidate. Thus, this work advances the science by providing researchers and clinicians with new knowledge to support patients and caregivers together towards better clinical and person-oriented outcomes.

Chapter II

Caregiver Well-Being and Patient Outcomes in Heart Failure: A Meta-Analysis

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This manuscript replaces portions of the literature review, methods, results, and discussion sections of the traditional dissertation. Ms. Bidwell was the primary author on this paper, and Dr. Lee was the senior author on this paper. Ms. Bidwell completed the meta-analysis and manuscript preparation under the supervision of Dr. Lee. This article was submitted for publication to the Journal of Cardiovascular Nursing in October 2015. The Journal of Cardiovascular Nursing is an indexed and peer-reviewed journal with an impact factor of 2.172. The main readership for this journal is healthcare personnel, particularly nurses and advanced practice nurses, interested in the physiologic, psychologic, and social needs of cardiovascular patients. This manuscript is in final state and is currently in press.

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Declaration of Conflicting Interests

None Declared

Abstract

Background: Despite evidence from the broader caregiving literature about the interdependent nature of the caregiving dyad, few studies in heart failure (HF) have examined associations between caregiver and patient characteristics. **Objective**: Quantitatively synthesize relationships between caregiver well-being and patient outcomes. **Methods**: MEDLINE, PsycINFO, and CINAHL databases were searched for studies of adult HF patients and informal caregivers that tested the relationship between caregiver well-being (perceived strain and psychological distress) and patient outcomes of interest. Summary effects across studies were estimated using random effects meta-analysis following the PRISMA guidelines. **Results:** 15 articles meeting inclusion criteria were included in the meta-analysis. Taking into account differences across studies, higher caregiver strain was associated significantly with greater patient symptoms (Fisher's $z = 0.22$, $p < 0.001$) and higher caregiver strain was associated significantly with lower patient quality of life (Fisher's $z = -0.36$, $p < 0.001$). Relationships between caregiver psychological distress and both patient symptoms and quality of life were not significant. Although individual studies largely found significant relationships between worse caregiver well-being and higher patient clinical event-risk, these studies were not amenable to meta-analysis due to substantial variation in event-risk measures. **Conclusions:** Clinical management and research approaches that acknowledge the interdependent nature of the caregiving dyad hold great potential to benefit both patients and caregivers.

Keywords: Heart Failure, Meta-Analysis, Caregivers

Caregiver well-being and patient outcomes in heart failure: A meta-analysis

Introduction

Heart failure (HF) is a rapidly growing health concern affecting nearly 6 million patients and families in the United States (US) alone (Heidenreich et al., 2013; Mozaffarian et al., 2015). From a health systems perspective, HF is the primary reason for hospitalization and rehospitalization among older adults in the US (Jencks, Williams, & Coleman, 2009; Liu, 2011) and comes with exorbitant health expenditures (Heidenreich et al., 2013). Persons with HF also live with poor quality of life (QOL) and disabling symptoms, and 50% of patients will die within 5 years of diagnosis (Mozaffarian et al., 2015; Zambroski, Moser, Bhat, & Ziegler, 2005). Although patients are the focus of the vast majority of research in HF, living with HF is typically a shared experience, and there are considerable implications for caregiver well-being (Joo, Fang, Losby, & Wang, 2015; Gure, Kabeto, Blaum, & Langa, 2008). For example, informal caregivers of patients with HF experience significant strain (Hwang, Luttik, Dracup, & Jaarsma, 2010; Luttik et al., 2007) and depression related to caregiving (Agren, Evangelista, Davidson, & Stromberg, 2011; Pinquart & Sorenson, 2003). Higher caregiver strain is especially concerning because of the link between strain and caregiver morbidity/mortality (Beach, Schulz, Yee, & Jackson, 2000; Schulz & Beach, 1999). Hence, there is increasing interest in examining both caregiver- and patient-level factors associated with HF and the treatment thereof.

Although HF patient and caregiver characteristics are often studied at the individual level rather than in the context of a dyadic relationship, there is evidence from the broader caregiving literature that the patient-caregiver dyad is transactional in nature (i.e. bi-directional influence of one member on the other; Berg & Upchurch, 2007; Chung et al., 2014). Quantifying these important transactional influences in HF fills an important gap for researchers and clinicians who are interested in supporting the health of patients, caregivers, and the caregiving dyad. A meta-analytic approach is a particularly rigorous way to advance the science of caregiving dyads by synthesizing effects observed across multiple studies and providing insight into the design of future dyadic research (Borenstein, Hedges, Higgins, & Rothstein, 2009). Accordingly, the purpose of this meta-analysis was to synthesize the results of HF studies focused on relationships between caregiver well-being and patient-oriented and clinical outcomes.

Methods

Study selection and data extraction

This study was a random-effects meta-analysis of published observational studies, conducted in accordance with PRISMA and MOOSE guidelines (Liberati et al., 2009; Stroup, Berlin, & Morton, 2000). Studies were considered eligible for inclusion if they met the following characteristics: 1) the sample consisted of adult HF patients and their informal caregivers, 2) data on measures of interest were collected on both members of the dyad, and 3) the results included tests of association between patient and caregiver measures of interest. We did not exclude studies based on date of publication. Non-English language studies were excluded. MEDLINE, CINAHL, and PsycInfo databases were searched for eligible studies; full search strategies are presented within the PRISMA flow diagram (**Figure 1**). The original search was conducted in November 2013 and was updated in March 2015 to ensure no new studies met inclusion criteria.

Study screening and evaluation for eligibility and inclusion into the meta-analysis was conducted by the first author with guidance from the senior author. Data were extracted into Excel format, then re-extracted, compared, and corrected for any errors. For each study, the following variables were collected: 1) study authors, 2) date of publication, 3) journal/source of publication, 4) funding source, 5) number of patient-caregiver dyads in sample, 6) patient-caregiver dyad relationship type, 7) demographic characteristics of patients and caregiver (age, gender, race), 8) instrument used to measure outcomes of interest, 9) analytic approach used to test the association between patient and caregiver outcomes, 10) result of statistical test of association for given relationships of interest. If clarification on published findings was needed, this was requested from the corresponding author, who was also queried about other available data in accordance with current guidelines.

Analysis

A random-effects meta-analytic approach was selected for this analysis because of substantial differences across studies in terms of measurement and sampled populations. In random-effects meta-analysis, it is not assumed that there is one true effect size across all studies. Rather, the effect sizes of the observed studies are considered to be a random sample of all possible effect sizes (DerSimonian & Laird, 1986; Hedges & Vevea, 1998). Under this assumption, the summary effect is the weighted average of all studies, with the weight of each study being the inverse of variance within each study plus the variance between studies. As this was a meta-analysis of correlations from observational studies, the summary effect was estimated in the metric of Fisher's *z*; Pearson's *r* are also provided for ease of interpretation.

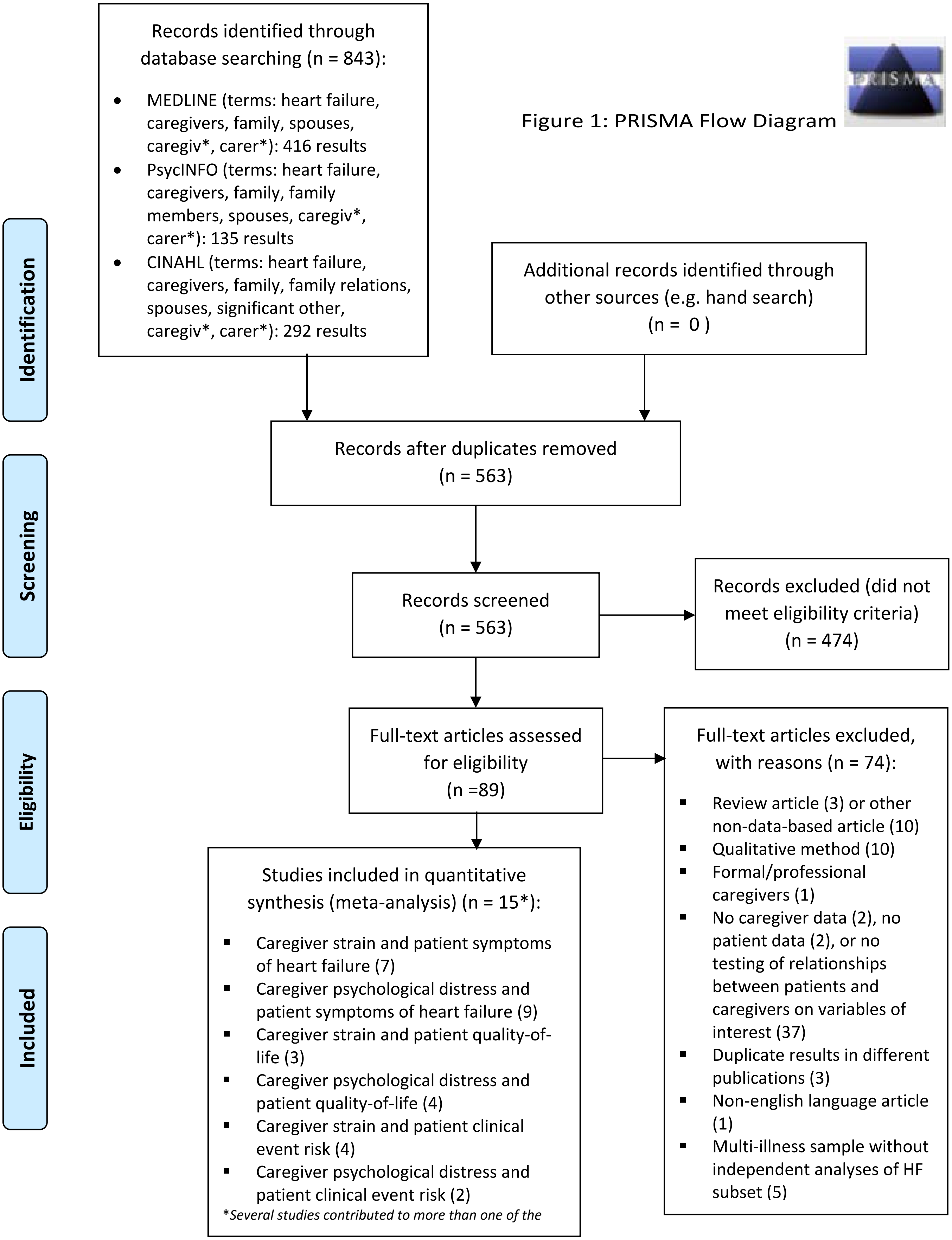
Significant heterogeneity across studies can reduce precision in meta-analyses. In this analysis, heterogeneity in effect sizes was examined using the Q and I^2 statistics. A significant Q indicates excess dispersion in effect sizes across studies. The I^2 is a "signal-to-noise" ratio of excess dispersion to total dispersion, and therefore indicates the proportion of heterogeneity that is concerning and warrants additional investigation (signal), versus "spurious" heterogeneity that is due to chance (noise). Typically, an I^2 of <25% is considered a low amount of "real" heterogeneity and is not considered problematic, while I^2 values of 50% or 75% are considered moderate and high amounts of “real” heterogeneity, respectively, and should be investigated further to identify the source (Higgins, Thompson, Deeks, & Altman, 2003). In the instance of concurrent significant Q and I^2 greater than 25%, subgroup analysis can be conducted in an effort to explain sources of heterogeneity, provided the *n* (number of studies included) is adequate.

Publication bias (bias in the summary effect due to unpublished studies) was assessed visually using funnel plots. Additionally, bias from small-study effects (bias in the summary effect due to studies that have a very large effect, but a very small *n*) was assessed using Egger’s test; a non-significant Egger’s test indicates limited concern of bias from small-study effects.

Results

Results from the process of study identification, screening, eligibility, and inclusion are outlined in the flow diagram (**Figure 1**). As a whole, a total of 15 articles were included across the six meta-analyses we conducted (**Table 1**). However, most studies contributed to more than one individual meta-analysis, as shown in **Table 2** (Luttik et al., 2007; Agren, Evangelista, & Stromberg, 2010; Barnes et al., 2006; Chung, Moser, Lennie, & Rayens, 2009; Chung, Pressler, Dunbar, Lennie, & Moser, 2010; Hooley, Butler, & Howlett, 2005; Hwang, Fleischmann, Howie-Esquivel, Stotts, & Dracup, 2011; Martensson, Dracup, Canary, & Fridlund, 2003; Pihl, Jacobsson, Fridlund, Stromberg, & Martensson, 2005; Pressler et al., 2013; Rohrbaugh et al., 2002; Rohrbaugh, Shoham, Cleary, Berman, & Ewy, 2009; Saunders, 2008; Schwarz & Elman, 2003; Trivedi, Piette, Fihn, & Edelman, 2012)**.**

Figure 1: PRISMA Flow Diagram



Records identified through database searching (n = 843):

- MEDLINE (terms: heart failure, caregivers, family, spouses, caregiv*, carer*): 416 results
- PsycINFO (terms: heart failure, caregivers, family, family members, spouses, caregiv*, carer*): 135 results
- CINAHL (terms: heart failure, caregivers, family, family relations, spouses, significant other, caregiv*, carer*): 292 results

Additional records identified through other sources (e.g. hand search) (n = 0)

Records after duplicates removed (n = 563)

Records screened (n = 563)

Records excluded (did not meet eligibility criteria) (n = 474)

Full-text articles assessed for eligibility (n =89)

Full-text articles excluded, with reasons (n = 74):

- Review article (3) or other non-data-based article (10)
- Qualitative method (10)
- Formal/professional caregivers (1)
- No caregiver data (2), no patient data (2), or no testing of relationships between patients and caregivers on variables of interest (37)
- Duplicate results in different publications (3)
- Non-english language article (1)
- Multi-illness sample without independent analyses of HF subset (5)

Studies included in quantitative synthesis (meta-analysis) (n = 15*):

- Caregiver strain and patient symptoms of heart failure (7)
- Caregiver psychological distress and patient symptoms of heart failure (9)
- Caregiver strain and patient quality-of-life (3)
- Caregiver psychological distress and patient quality-of-life (4)
- Caregiver strain and patient clinical event risk (4)
- Caregiver psychological distress and patient clinical event risk (2)

**Several studies contributed to more than one of the*

Table 1: Study Characteristics

Author, Date	Journal	Funding	Dyad *n* and Relationship Type	Caregiver Characteristics	Patient Characteristics
Agren, 2010	Eur J Cardiovasc Nurs	Linköping University; Swedish Institute for Health Sciences; Sweden; Swedish Research Council; Vårdal Foundation	*n*=135 100% Spousal	Age 69±12 75% Female Race not reported	Age 71±12 25% Female Race not reported
Barnes, 2006	Int J Palliat Nurs	UK Department of Health	*n*=213 73% Spousal	70% > 60 years 76% Female Race not reported	100% > 60 years 36% Female Race not reported
Chung, 2009	J Psychosom Res	NIH/NINR; University of Kentucky	*n*=58 100% Spousal	Age 58±12 Gender not reported Race not reported	Age 62±13 26% Female 93% White
Chung, 2010	J of Cardiovasc Nurs	University of Kentucky; NIH/NINR	*n*=109 79% Spousal	Age 57±13 75% Female 94% White	Age 61±12 40% Female Race not reported
Hooley, 2005	Congest Heart Fail	Undergraduate Internal Medicine Research Foundation, Dalhousie University	*n*=50 66% Spousal	Age 61±14 80% Female Race not reported	Age 72±11 28% Female Race not reported
Hwang, 2011	Am J Crit Care	University of California, San Francisco	*n*=76 74% Spousal	Age 53±16 71% Female 63% White	Age 54±14 45% Female 66% White
Luttik, 2007	Eur J Heart Fail	Netherlands Heart Foundation	*n*=357 100% Spousal	Age 67±12 75% Female Race not reported	Age 68±11 25% Female Race not reported
Martensson,	J Heart Lung	Research Council of	*n*=48	Age 57±10	Age 61±9

2003	Transplant	Southeastern Sweden; Swedish Heart and Lung Foundation; AHA	100% Spousal	100% Female 83% White	0% Female 77% White
Pihl, 2005	Eur J Heart Fail	Funding source not reported	*n*=47 100% Spousal	Age 75±7 72% Female Race not reported	Age 78±5 28% Female Race not reported
Pressler, 2013	J Cardiovasc Nurs	Indiana University; NIH/NINR	*n*=63 68% Spousal	Age 60±15 76% Female 84% White	Age 69±13 46% Female 81% White
Rohrbaugh, 2002	J Fam Psych	NIH	*n*=181 100% Spousal	Age 52±11 Gender not reported 83% White*	Age 53±10 27% Female 83% White*
Rohrbaugh, 2009	Heart Lung	AHA	*n*=60 100% Spousal	Age 66±11 72% Female Race not reported	Age 67 ±12 28% Female 85% White
Saunders, 2008	Home Healthc Nurse	Funding source not reported	*n*=41 46% Adult child of patient, 46% Spousal	Age 59±15 85% Female 68% White	Age 78±10 51% Female 85% White
Schwarz, 2003	Heart Lung	Funding source not reported	*n*=128 61.7% Spousal, 27.3% Adult child of patient	Age 65±15 74% Female 89% White	Age 77±6 50% Female 89% White
Trivedi, 2012	J Cardiovasc Nurs	VA Puget Sound; Durham VA	*n*=23 100% Spousal	Age not reported 100% Female Race not reported	Age 66±7 100% Male 61% White

*This publication reported race for the whole sample (patients and caregivers together), rather than for patients and caregivers separately

All journal abbreviations per National Library of Medicine; Age reported as Mean±SD; UK: United Kingdom; NIH: National Institutes of Health; NINR: National Institute of Nursing Research; AHA: American Heart Association; VA: Veterans Affairs

Table 2: Study Measures by Meta-Analysis Aim

Author, Date	Caregiver Strain and Patient HF Symptoms	Caregiver Psychological Distress and Patient HF Symptoms	Caregiver Strain and Patient QOL	Caregiver Psychological Distress and Patient QOL	Caregiver Strain and Patient Clinical Event Risk	Caregiver Psychological Distress and Patient Clinical Event Risk
Agren, 2010	CG: CBS (Swedish) Pt: NYHA		CG: CBS (Swedish) Pt: SF-36 PCS			
Barnes, 2006	CG: CSI (dichotomized) Pt: NYHA (dichotomized)					
Chung, 2009				CG: BSI – Depression Pt: MLHFQ		
Chung, 2010		CG: BDI-II Pt: NYHA				
Hooley, 2005	CG: ZBI (dichotomized) Pt: NYHA (dichotomized)	CG: BDI-II (dichotomized) Pt: NYHA (dichotomized)	CG: ZBI Pt: MLHFQ		CG: ZBI (dichotomized) Pt: hospitalization or death 6 months after enrollment	CG: BDI-II Pt: hospitalization or death 6 months after enrollment
Hwang, 2011	CG: CRA (schedule) Pt: NYHA				CG: CRA (physical health) Pt: days since last hospital discharge	
Luttik, 2007			CG: CRA (schedule) Pt: RAND-36 PF			
Martensson, 2003		CG: BDI Pt: NYHA		CG: BDI Pt: SF-12 PCS		
Pihl, 2005		CG: Zung Pt: NYHA		CG: Zung Pt: SF-12 PCS		
Pressler,	CG: OCBS	CG: PHQ-8				

2013	Pt: NYHA (dichotomized)	Pt: NYHA (dichotomized)				
Rohrbaugh, 2002		CG: HSC-25				
		Pt: NYHA				
Rohrbaugh, 2009		CG: HSC-25		CG: HSC-25		
		Pt: NYHA		Pt: SF-36 composite PCS/MCS		
Saunders, 2008	CG: CRA (schedule)	CG: CES-D			CG: CRA (family)	
	Pt: NYHA (caregiver evaluated)	Pt: NYHA			Pt: Number of hospitalizations past 12 months	
Schwarz, 2003					CG: PSS	CG: CES-D
					Pt: Hospitalization or death 3 months after enrollment	Pt: Hospitalization or death 3 months after enrollment
Trivedi, 2012	CG: ZBI	CG: CES-D				
	Pt: HCS (HF-specific)	Pt: HCS (HF-specific)				

CG: Caregiver; Pt: Patient; CBS (Swedish): Swedish Caregiver Burden Scale; NYHA: New York Heart Association Classification; SF-12/36 PCS/MCS: Short Form-12/36 Physical Component Summary/Mental Component Summary; CSI: Carer Strain Index; BSI: Brief Symptom Inventory; MLHFQ: Minnesota Living with Heart Failure Questionnaire; BDI: Beck Depression Inventory; ZBI: Zarit Burden Interview; CRA: Caregiver Reaction Assessment; RAND-36 PF: RAND version of the SF-36, Physical Function subscale; Zung: Zung Depression Scale; OCBS: Oberst Caregiving Burden Scale; PHQ-8: Patient Health Questionnaire-8; HSC-25: Hopkins Symptom Checklist-25; CES-D: Center for Epidemiologic Studies Depression Scale; PSS: Perceived Stress Scale; HCS: Health Complaints Scale

Caregiver Well-being and Patient Heart Failure Symptoms

Seven studies tested the relationship between caregiver strain and patient HF symptoms (**Table 2**). Selected strain measures across studies were variable, while HF symptom measures were fairly consistent with most studies reporting New York Heart Association (NYHA) Class. Higher caregiver strain was significantly associated with worse HF patient symptoms across studies (**Figure 2**). There was limited between-study heterogeneity (Q = 7.16, p = 0.306) and minimal small sample bias.

Nine studies tested the relationship between caregiver psychological distress and patient

HF symptoms (**Table 2**). For caregiver pyschological distress, depression instruments were the most commonly used measures. Measures of patient HF symptoms were consistent (largely NYHA Class). Overall, there was significant heterogeneity across studies (*Q* = 16.96, *p* = 0.031, I^2 = 52.8%) and no precise estimate of the relationship between caregiver psychological distress and patient HF symptoms could be quantified. We conducted a four-subgroup analysis of studies by measure (Hopkins Symptom Checklist, Beck Depression Inventory, Center for Epidemiologic Studies Depression Scale, and remaining depression measures) (**Figure 3**). Greater caregiver psychological distress was associated with worse patient symptoms across studies that used the Hopkins Symptom Checklist; otherwise, there was no significant relationship between caregiver psychological distress and patient HF symptoms.

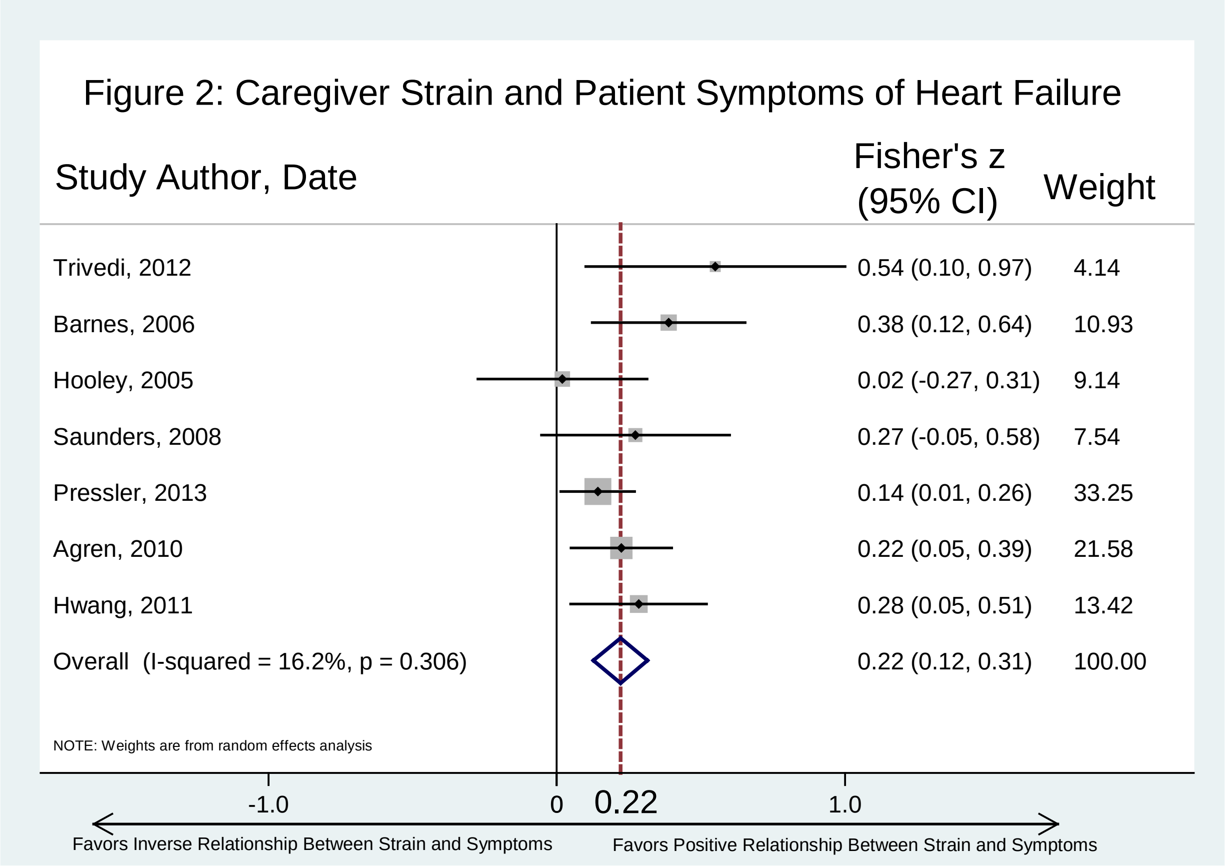


Figure 2: Random effects meta-analysis of relationship between caregiver strain and patient symptoms of HF. Note: Fisher's z converted to metric of Pearson's *r* = 0.213. Egger's test for bias of small study effects: t = 1.60, *p* = 0.170.

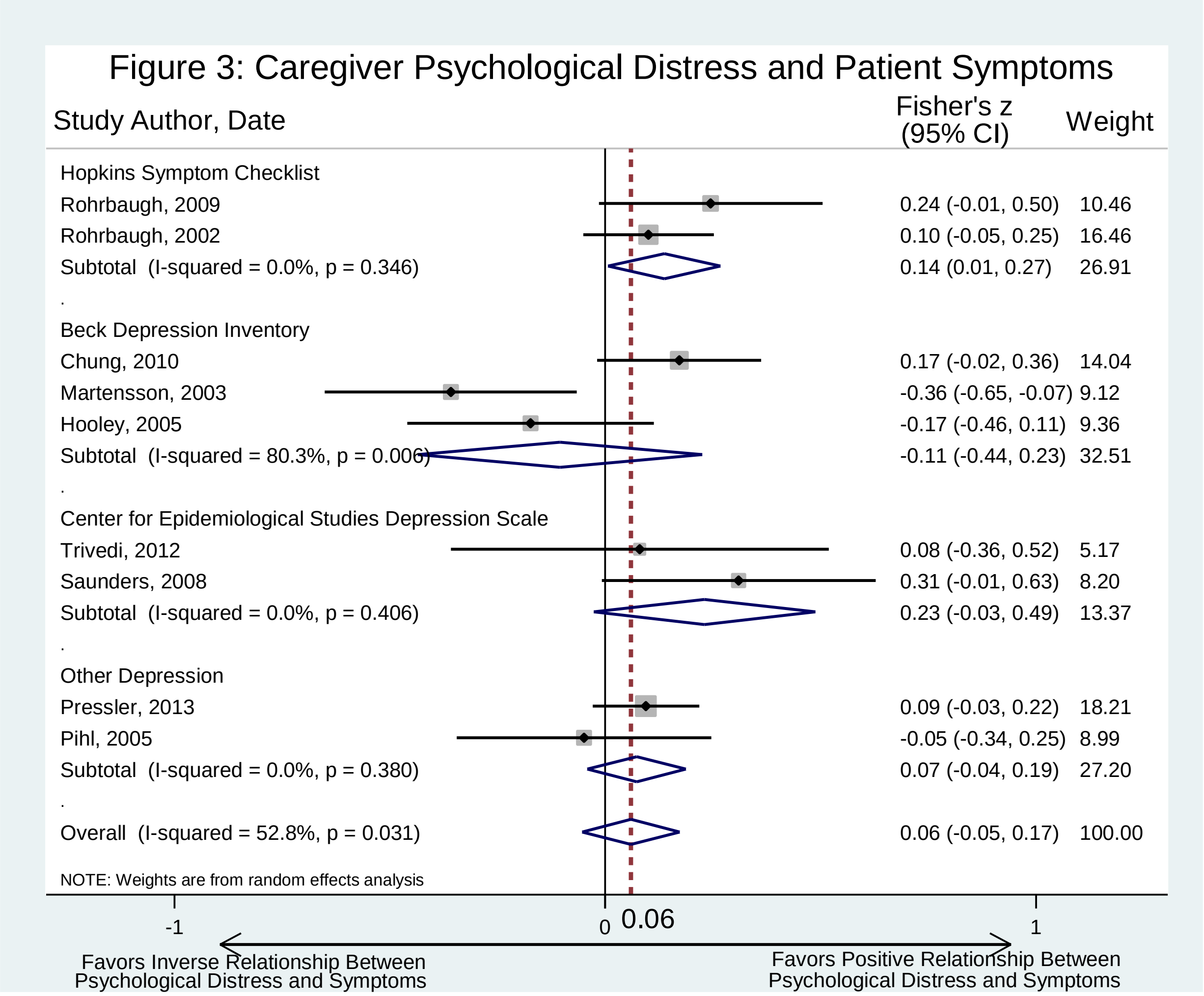


Figure 3: Random effects meta-analysis of relationship between caregiver psychological distress and patient symptoms of HF. Note: Fisher's Z converts to the metric of Pearson's *r* as follows: for HSC summary effect r = 0.136; for BDI summary effect r = -0.105; for CES-D summary effect r = 0.226; for Other Depression summary effect r = 0.073; for Overall summary effect r = 0.060. Egger's test for bias of small study effects: t = -0.71, p =0.502.

Caregiver Well-being and Patient Quality-of-Life

Three studies tested the relationship between caregiver strain and patient QOL **(Table 2)**. Across studies, three different measures of caregiver strain and three different measures of QOL were utilized. One study was not amenable for inclusion in the analysis due to missing data, leaving two studies appropriate for synthesis. There was a significant relationship between higher caregiver strain and worse patient QOL (Fisher's $z = -0.356 \pm 0.08$, z-score = 4.76, $p <$ 0.001); however, results from this analysis are limited by the small number of included studies.

Four studies tested the relationship between caregiver psychological distress and patient QOL **(Table 2)**. Across studies, there was substantial variability in both the selection of caregiver and patient measures and in study design. This substantial between-study heterogeneity ($Q = 13.15$, $p = 0.004$, $I^2 = 77.2\%$) prevented a precise estimation of effect size (Fisher’s $z = -0.08 \pm 0.15$, z-score = 0.53, $p = 0.595$) (**Figure 4**). Due to the small number of identified studies testing this relationship it was not possible to run additional analyses by measure subgroups.

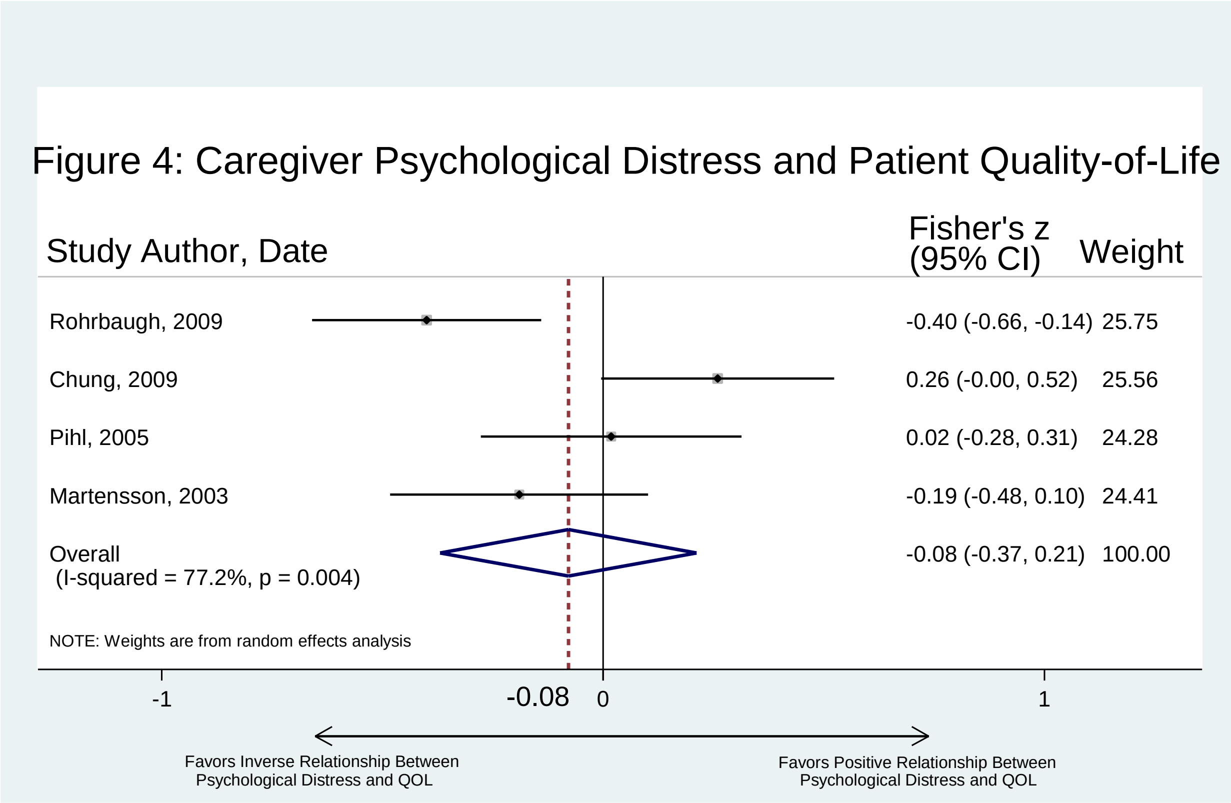


Figure 4: Random-effects meta-analysis of relationship between caregiver psychological distress and patient QOL. Note: Fisher’s Z when converted to metric of Pearson’s $r = -0.079$. Egger’s test for bias of small study effects: t = 0.15, $p = 0.898$.

Caregiver Well-being and Patient Clinical Event Risk

Four studies tested the relationship between caregiver strain and patient clinical event risk (**Table 2**). Across studies there was substantial variability in measures of caregiver strain and definitions of clinical event risk. Although the number of studies was adequate for attempting meta-analysis, the variation in type of event (hospitalization only, mortality only, combined hospitalization/mortality) and time-to-event (days since last event, number of events in past year, event occurrence within 6 months post-enrollment, event occurrence within 3 months post-enrollment) made the examination of this relationship non-conducive to meta-analysis. Of these four studies, all found a significant relationship between greater caregiver strain and clinical events, regardless of how those events were quantified or modeled in the original papers **(Table 2)**. In order to estimate a summary effect for this relationship, however, studies with congruent type of event and time-to-event measures are needed.

Two studies tested the relationship between caregiver psychological distress and patient clinical event risk (**Table 2**). As with the examination of strain and clinical events, differences in type of event and time-to-event made the examination of this relationship inappropriate for meta-analysis. Both studies found a significant relationship between worse caregiver psychological distress and higher clinical event risk. However, in order to estimate an accurate and informative summary effect, congruence in type of event and time-to-event in future studies are needed.

Discussion

Although a small body of literature has examined relationships between caregiver well-being and patient outcomes in HF, this analysis is the first to combine existing quantitative knowledge in this domain using meta-analytic methods. In accordance with sections 24-26 of the PRISMA guidelines (Liberati et al., 2009), this discussion will summarize the main findings of each meta-analysis, consider relevance and implications of each to clinical practice, health policy, and research, and discuss study limitations.

Caregiver Well-Being and Patient HF Symptoms. In this meta-analysis, we found that higher caregiver strain was significantly associated with worse patient symptoms. Strengthening our confidence in this finding, there was no evidence of excess heterogeneity (despite differences in measures) or small study effects. This is not surprising, given that similar relationships between strain and disease severity have been observed in other illness contexts (Ornstein & Gaugler, 2012; Mioshi et al., 2013; Burke, Elamin, Galvin, Hardiman, & Pender, 2015). In contrast, we observed no significant association between caregiver psychological distress and patient symptoms in HF. Given that a positive association has been demonstrated between patient symptoms and caregiver depression in cancer, Parkinson's, and dementia dyads (Carter et al., 2008; Given, Wyatt, & Given, 2004; Ornstein et al., 2012), this lack of significant finding was somewhat unexpected.

In terms of measurement of patient symptoms, it is possible that differences in cancer/ Parkinson's/ dementia symptoms or the utilization of NYHA Classification – a global measure of symptom severity – as a proxy for more nuanced HF symptom measures may explain both the variability in study results and the lack of a significant summary effect. Although NYHA Class quantifies severity of symptoms in general, we have no way of quantifying types of symptoms in particular or the degree to which those symptoms are bothersome to the patient – both aspects of HF symptomatology that may be pertinent to the caregiver experience. For example, there may be particular symptoms or clusters of symptoms (e.g. breathlessness) that are particularly distressing to family members.

In terms of measurement of caregiver psychological distress, it is notable that our subgroup analysis by caregiver measures found significant associations between the HSC (which measures both depression and anxiety) and patient symptoms, but not between patient symptoms and depression-only measures of caregiver distress. Congruent with our findings, the landmark Caregiver Health Effects Study reported that increases in patient physical impairment were associated with increases in caregiver anxiety, but not depression, over time (Beach et al., 2000).

Similarly, within the context of HF, several qualitative studies have identified caregiver anxiety as a major theme of the caregiving experience and a common response to increasing patient symptoms (Kang, Li, & Nolan, 2011). Thus, there may be particular utility in adding measures of anxiety to future studies involving patient-caregiver dyads.

Caregiver Well-Being and Patient Quality of Life. We found that higher caregiver strain was significantly associated with worse patient QOL. However, our analysis was constrained by sample size, as few studies examined this relationship. Thus, our confidence in this finding is somewhat limited by our inability to adequately test for bias. In contrast, we observed no significant association between caregiver psychological distress and patient QOL, but again, relatively few studies exist that test this relationship. Moreover, the substantial amount of between-study heterogeneity – possibly related to a high degree of variability in measuring both caregiver psychological distress and patient QOL across studies – precluded identification of a summary effect. Thus, there may indeed be a significant relationship between caregiver psychological distress and patient QOL that is otherwise obscured by differences in measurement or sampling across studies, as well as the relative paucity of studies. As QOL becomes an increasingly important outcome in HF (Yancy et al., 2013), it is essential to understand the important role caregiver factors may have on patient QOL. Furthermore, given that patients with HF often report substantial QOL impairment (Lesman-Leegte et al., 2009), it is important to support caregivers who may experience associated increases in strain or psychological distress.

Caregiver Well-Being and Patient Clinical Event Risk. Although there were multiple studies that tested the relationship between caregiver strain and caregiver psychological distress and patient clinical event risk, we were unable to summarize them using meta-analytic methods. With substantial variation in type and time-to-event, a summary effect would be uninterpretable.

However, it should be emphasized that this does not mean that no relationship between caregiver well-being and patient clinical event risk exists. To the contrary, these were the only relationships in this analysis in which *all* studies reported significant positive findings between worse caregiver well-being and higher patient clinical event-risk. This level of consensus on such critical outcomes – hospitalization and death – clearly warrants continuing investigation, ideally utilizing more congruent measures of clinical event risk.

Implications for Clinical Practice, Health Policy, and Research. There are several notable clinical, research, and policy implications from these findings. As HF symptoms worsen and patient QOL declines, caregivers may be at increased risk of strain and its sequelae, namely, increased morbidity and mortality (Beach et al., 2000; Schulz et al., 1999). However, because the synthesis of cross-sectional observational studies precludes conclusions about directionality/causality of relationships, it might also be said that assessment of increased strain in caregivers may signal higher patient symptom burden or QOL impairment. In either case, this first meta-analysis of patient-caregiver relationships in HF demonstrates that the experiences of patient and caregiver are clearly transactional, providing support for dyadic approaches to research and clinical management. For example, researchers and clinicians interested in studying and supporting self-care in HF patients recognize that caregiver strain may have a negative impact on self-care behaviors (Foebel, Hirdes, & Heckman, 2012). This is particularly concerning if caregiver strain increases commensurate with patient symptoms, since caregivers may be less able to assist advanced HF patients who are at greatest risk for exacerbation if self-care is compromised. Therefore, the patient and caregiver as a *dyad* may benefit jointly from research, clinical care, and health policies that recognize and support the health and well-being of both members of the caregiving dyad, rather than focusing solely on either patient or caregiver.

This is reflected in the recent interventions in HF that have successfully integrated patients and caregivers together to improve outcomes for both members of the dyad (Dunbar et al., 2013; Chung, Lennie, Mudd-Martin, & Moser, 2015). However, our ability to make definitive clinical recommendations for managing patient-caregiver dyads together is hindered by the current state of the literature in HF, which consists largely of analyses conceptualized and conducted at the individual level (e.g. individual patient/caregiver endpoints and limited examination of within-dyad interdependence). Thus, although this meta-analysis provides important information on how individual caregiver and patient outcomes are related on average, we are almost completely bereft of insight into how patients and caregivers experience and manage HF together within the context of their relationship to one another. Therefore, in order to better support patients and caregivers together within a dyadic context, we must expand research in HF to include studies that conceptualize and analyze research questions at the level of the dyad.

Dyadic research approaches may also contribute to a more holistic understanding of clinical event-risk. Despite emphasis on reducing hospitalizations (Lindenauer et al., 2007), HF-associated hospitalizations in the United States have not declined (Blecker, Paul, Taksler, Ogedegbe, & Katz, 2013), and there is some concern that over-avoidance of hospitalization may sacrifice potentially associated survival benefits (Heidenreich, Sahay, Kapoor, Pham, & Massie, 2010). Most nursing interventions that aim to reduce clinical event risk do not include the caregiver or take a dyadic approach, and almost half have no success in reducing hospitalization or death (Allen & Dennison, 2010). Furthermore, most risk prediction models in HF do not include social support variables (Rahimi et al., 2014). Although we were not able to statistically synthesize relationships between caregiver well-being and patient clinical event risk due to variation in event risk measures, all the studies we identified found significant positive relationships between worse caregiver well-being and patient clinical events. Given the clinical and research gaps in explaining variability in HF risk, it may be useful to examine caregiver factors as potential predictors of patient clinical event risk. However, the limitations of the cross-sectional nature of these studies cannot be understated. It is equally, if not more, plausible that the directionality of the relationship runs opposite – namely, that higher odds of patient clinical events influences higher strain in caregivers. Regardless, this is clearly a relationship that warrants further investigation, as both event-risk in patients and strain in caregivers are important clinical outcomes (Schulz et al., 1999; Yancy et al., 2013). Thus, developing a better understanding of the patient-caregiver dyad as a whole in HF may assist researchers in designing more efficacious models and interventions, guide clinicians in providing care that is more closely aligned with the real-world context of caregiving relationships in outpatient settings, and help policy makers to develop policies that support better outcomes for *both* patients and caregivers.

Limitations and Future Recommendations. The findings of this study have several limitations. Firstly, this analysis required integrating studies that used differing measures (e.g. strain, psychological distress, clinical event risk). In some instances this did not appear problematic (e.g. strain and patient symptoms), but in other cases this contributed to substantial heterogeneity in the analysis (e.g. caregiver psychological distress) or precluded analysis entirely (patient clinical event risk). Secondly, in the meta-analyses involving patient symptoms, although we used NYHA Class as a proxy for symptom severity, it is not a robust symptom measure; however, this is a readily available clinical characteristic frequently collected on patients in studies of HF caregivers. This is a reflection of the current state of the literature in HF, which predominantly consists of studies whose central focus is either patients *or* caregivers, rather than *both* members of the dyad. That is to say, although studies may include measures of both patient and caregiver characteristics, typically only one member is extensively measured and few characteristics of the other member are included. Thus, there is an opportunity to advance the science by explicitly acknowledging and examining the transactional nature of the patient-caregiver dyad, collecting robust data on clinical- and person-oriented measures (ideally using the same measure for patient and caregiver to facilitate dyadic analysis) from *both* members of the dyad, and using appropriate dyadic methods in future study designs and analysis. Thirdly, some of our analyses were hindered by the size and number of available studies. Although a minimum of two studies is required for meta-analysis, our confidence in the summary effect is strengthened when the sample size is adequate for rigorous tests of bias. Again, the lack of studies examining the interrelationship of patients and caregivers in HF is an important limitation of the current state of the science in HF. As more research is done at the level of the dyad, dyadic interdependence, covarying outcomes, and dyadic archetypes can be more fully elucidated. Furthermore, when more studies are available for synthesis, techniques such as meta-regression can be utilized to more rigorously examine relationships of interest. And finally, although every effort was made to ensure inclusion of all available studies in this meta-analysis, there is always a possibility of bias from missed studies.

Conclusions

In this meta-analysis, higher caregiver strain was associated with worse patient symptoms and worse patient QOL. Although we found no significant relationship between caregiver psychological distress and patient symptoms or QOL, substantial heterogeneity was present in both analyses. Finally, studies examining relationships between caregiver well-being and patient clinical events were not amenable to meta-analysis due to variations in event-risk estimation. Future research involving patients and caregivers should include robust measures of clinical- and person-oriented outcomes from both members of the dyad. In particular, measures of psychological (anxiety and depression) and physical health and QOL should be included, as well as comprehensive measures of patient HF symptoms and caregiver strain. Most importantly, in order to better address the needs of patients and caregivers together, we must advance the science through research that is conceptualized and conducted at the level of the dyad.

Chapter III

Quality of Life, Depression, and Anxiety in Ventricular Assist Device Therapy: Longitudinal Outcomes for Patients and Caregivers

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This manuscript replaces a portion of the research design, methods, results, and discussion sections of the traditional dissertation. Ms. Bidwell will be the primary author on this paper; Dr. Lee will be the senior author on this paper. Ms. Bidwell will conduct the study and perform the statistical analyses under the supervision of Dr. Lee. This article is under review at the Journal of Cardiovascular Nursing. The Journal of Cardiovascular Nursing is an indexed and peer-reviewed journal with an impact factor of 2.172. The main readership for this journal is healthcare personnel, particularly nurses and advanced practice nurses, interested in the physiologic, psychologic, and social needs of cardiovascular patients. This manuscript will be revised in accordance with peer review (pending).

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Declaration of Conflicting Interests

None Declared

Abstract

Background: Person-oriented outcomes in ventricular assist device (VAD) therapy are of interest to clinicians and researchers, as well as patients and caregivers. The purpose of this study was to characterize changes in person-oriented outcomes (quality of life, QOL; depression; and anxiety) for VAD patients and caregivers from pre-implantation to 3 months post-implantation. **Methods:** This was a formal interim analysis from an ongoing prospective study of VAD patients and caregivers. Data on person-oriented outcomes (depression: Patient Health Questionnaire-8, anxiety: Brief Symptom Inventory, patient QOL: Kansas City Cardiomyopathy Questionnaire, caregiver QOL: Short Form-36 Physical Component Summary) were collected at three time points (median of 5 days prior to implantation, and at 1 and 3 months post-implantation). Trajectories of change for patients and caregivers on each outcome of interest were estimated using latent growth modeling with parallel processes. **Results:** Pre-implant depression and anxiety for both patients and caregivers were high, but while patients improved dramatically post-implant, caregivers did not change. Similarly, there were no changes in caregiver QOL over time, while patients' QOL improved significantly. Person-oriented outcomes for patients and caregivers became increasingly correlated over time, and there was substantial variability in change for both patients and caregivers. **Conclusions:** This is the first quantitative study of VAD patient-caregiver dyads in modern devices that describes change from pre- to post-implant. This work supports the need for future studies that account for the interdependent nature of the patient-caregiver dyad and examines heterogeneity in individual and dyadic responses to VAD therapy.

Keywords: Heart Failure, Ventricular Assist Device, Caregivers, Quality of Life, Depression, Anxiety

Quality of Life, Depression, and Anxiety in Ventricular Assist Device Therapy: Longitudinal Outcomes for Patients and Caregivers

Introduction

Along with the increasing prevalence of heart failure (HF) (Roger, 2013), the use of ventricular assist device (VAD) therapy for advanced HF has risen dramatically (Kirklin et al., 2015). Continuous-flow VAD therapy is used to both extend and improve life; hence, understanding person-oriented outcomes (e.g. quality of life, depression and anxiety) is important (Brouwers et al., 2011; Grady et al., 2012). Caregivers of patients undergoing VAD implantation play an important role in most aspects of post-implant care (Blumenthal-Barby et al., 2015). In fact, the absence of an appropriate caregiver is a relative contraindication to VAD implantation (Feldman et al., 2013; Peura et al., 2012). Early and sustained improvements in patient quality of life (QOL) after VAD implantation are well known (J. G. Allen et al., 2010), and patient anxiety and depression also generally decrease (Brouwers et al., 2011; Grady et al., 2014). In contrast, there is qualitative evidence that caregivers of VAD patients are at risk for compromised QOL and high anxiety and depression post-implant (Dahlrup, Ekstrom, Nordell, & Elmstahl, 2015; Kirkpatrick et al., 2015; Kitko, Hupcey, Gilchrist, & Boehmer, 2013). Importantly, person-oriented outcomes of patients and their caregivers are typically interdependent – meaning that the outcomes for one member of the caregiving dyad typically influence the other – both in the context of chronic illness in general (Berg & Upchurch, 2007), as well as in the context of HF (Rohrbaugh, Shoham, Cleary, Berman, & Ewy, 2009; Trivedi, Piette, Fihn, & Edelman, 2012) and VAD implantation (Brouwers, Denollet, et al., 2015) in particular. The inherent interrelatedness of person-oriented outcomes of both members of a patient-caregiver dyad has important implications for research design and interpretation. Specifically, research that examines patients and their caregivers together can better approximate the context in which patients and caregivers experience and manage illness (Berg & Upchurch, 2007), providing critical information to help clinicians support patients and families to cope with and manage HF and VAD therapy together. Thus, the purpose of this study was to characterize changes for both members of the VAD dyad on important person-oriented outcomes (QOL, depression, and anxiety) from pre-implantation to 3 months post-implantation.

Methods

Design and Population

This was a formal interim analysis of data from an ongoing prospective study of VAD patients and their family caregivers, modeled after the dyadic framework proposed by Berg and Upchurch (2007). A primary aim of this study is to examine concurrent change in person-oriented outcomes among VAD patients and their caregivers. Data were collected over two years of enrollment (2013-2015) from a sample recruited from an academic medical center in the Northwestern United States. Patients were part of a federally-sponsored study on biobehavioral responses to VAD implantation; the design and recruitment procedures have been published previously (Lee et al., 2014). Patients were included if they were ≥21 years of age and excluded for previous VAD/heart transplant or if they were unable to complete study requirements (e.g. concomitant terminal illness, major psychiatric illness, major cognitive impairment). Caregivers were eligible if they were the adult (≥21 years of age) primary caregiver of the enrolled patient, as identified by the patient and agreed upon by the caregiver and the advanced HF team. The center’s Institutional Review Board reviewed and approved all procedures and all patient and caregiver participants provided written informed consent.

Data for this analysis were collected at three time points: a median of 5 days prior to VAD implantation, and again at 1 and 3 months post-implantation. Data on patient comorbid conditions (Charlson, Pompei, Ales, & MacKenzie, 1987), etiology and duration of HF, New York Heart Association Class, ejection fraction, and implant strategy were abstracted from the medical record. Both patients and caregivers completed surveys which included demographic data (age, gender, race/ethnicity, education, employment, and relationship to one another) and study instruments as described below. Caregivers self-reported their own comorbid conditions using a validated instrument (Chaudhry, Jin, & Meltzer, 2005).

Measures

QOL in patients and caregivers was measured using the EuroQol 5 Dimensions Visual Analogue Scale (EQ-5D VAS). The EQ-5D VAS is a standard vertical visual analogue scale, on which participants rate their current health-related QOL from 0 (“worst imaginable health state”) to 100 (“best imaginable health state”). The EQ-5D is widely used in both healthy and chronically ill populations, and has been recommended in VAD populations in particular for its reliability, validity and utility in quantifying general health-related QOL (Grady et al., 2012; Maciver & Ross, 2012).

Depression in patients and caregivers was measured using the Patient Health Questionnaire (PHQ-8), an 8-item depression screen (Kroenke & Spitzer, 2002). Participants respond on a 0-3 Likert scale; scores were summed to produce a total score ranging from 0-24 with higher scores indicating greater depressive symptoms. The PHQ-8 is appropriate for self-administration; scores greater than 5, 10, 15, or 20 indicate mild, moderate, moderately severe, or severe depression, respectively (Kroenke & Spitzer, 2002). In this sample, Cronbach’s α for patients and caregivers at all time points ranged from 0.84 to 0.90.

Anxiety in patients and caregivers was measured using the anxiety subscale of the Brief Symptom Inventory (Derogatis & Melisaratos, 1983). The anxiety subscale contains 6 items on a

0-4 Likert scale. The mean of responses produces a total score ranging from 0-4 with higher scores indicating greater anxiety (Derogatis & Melisaratos, 1983). In this sample, Cronbach's α for patients and caregivers at all time points ranged from 0.78 to 0.90.

Analysis

The sample was described using means and standard deviations for continuous data and frequency and percentages for categorical data. Trajectories of change for patients and caregivers on each variable of interest were estimated using latent growth modeling with parallel processes (Willett & Sayer, 1994). Growth modeling with parallel processes allows for joint analysis of two interdependent processes (e.g. concurrent change in patient and caregiver depression), providing an estimation of the intercept (pre-implant assessment) and slope (change over time) for each member of the dyad, as well as how each process is correlated (Willett & Sayer, 1996). Importantly, this approach includes random effects between intercepts and slopes of both members of the dyad while controlling for the dependent nature of these data, allowing us to characterize changes in person-oriented outcomes for both members of the VAD patient-caregiver dyad. We generated three separate growth models with parallel processes: one for QOL, depression, and anxiety respectively. Changes in person-oriented outcomes were quantified in the metric of Hedges *g* (standardized mean difference with a correction factor for small samples) (Hedges, 1981). Missing data were handled using full information maximum likelihood estimation (Muthen, Kaplan, & Hollis, 1987). Descriptive statistics were conducted using Stata 14; parallel process models were generated using MPlus 7.

Results

Characteristics of the sample (*n* = 41 dyads) are presented in **Table 1**. Patients and caregivers were in their mid-fifties on average. Most patients were male and most caregivers were female, and the majority of patient and caregiver participants were Caucasian/non-Hispanic. Most caregivers were the patients' spouse; the next most common caregiver relationship was parental. The average length of relationship was 27.5 years (median 28.3, interquartile range 16.0 – 39.0). The majority of patients received VAD therapy as a bridge to transplant, and the duration of HF at baseline was 7.9 years on average (median 5.2, interquartile range 2.5 – 10.5). Patients were primarily INTERMACS Class 3 or higher at time of implant. There was a small amount of attrition due to patient death (*n* = 2) and dissolution of the caregiving relationship (*n* =2). Data on patient and caregiver QOL, depression, and anxiety are presented in **Table 2**.

Table 1: Characteristics of the Sample (n=41 dyads)

	Patient Mean ± SD or *n*(%)	Caregiver Mean ± SD or *n*(%)
Age	53.8±14.2	54.7±11.4
Gender (Female)	6(14.6)	33(80.5)
Caucasian	35(85.4)	37(90.2)
Non-Hispanic	40(97.6)	39(95.1)
Relationship		
Spouse	-	30(73.2)
Parent of Patient	-	7(17.1)
Employment		
Full-time	3(7.5)	16(39.0)
Part-time	1(2.5)	6(14.6)
Unemployed/Retired	21(51.2)	17(41.5)
Quit due to health	13(32.5)	1(2.4)
Education		
High School or Less	19(46.3)	17(41.5)
Bachelors or Some College	21(51.2)	20(48.8)
Masters/Professional	1(2.4)	4(9.8)
CCI Score*	2.4±1.5	1.1±1.4
Idiopathic Etiology of HF	25(61.0)	-
Duration of HF (Months)†	94.9±95.4	-
NYHA Class		
III	21(51.2)	-
IV	16(39.0)	-
Ejection Fraction (%)	20.3±2.5	-
VAD Therapy		
Bridge to Transplant	25(62.5)	-

Destination Therapy	12(30.0)	-
Bridge to Decision	3(7.5)	-

*Charlson Comorbidity Index Score[17] (self-report Charlson used in Caregivers[18])
†Median duration of HF = 62.5 months

Table 2: Study Measures

Measure	Patient (Mean ± SD)	Caregiver (Mean ± SD)	Correlation*
Quality of Life[†]			
Pre-Implant	26.7 ± 20.8	52.9 ± 8.2	0.06
1-Month	49.3 ± 23.7	51.5 ± 9.3	0.10
3-Months	61.0 ± 20.1	49.8 ± 10.5	-0.16
Depression[‡]			
Pre-Implant	10.2 ± 5.8	5.6 ± 4.9	0.02
1-Month	6.8 ± 5.2	5.1 ± 4.7	0.40[b]
3-Months	4.4 ± 4.2	6.3 ± 5.5	0.31[a]
Anxiety[§]			
Pre-Implant	1.0 ± 0.8	0.7 ± 0.6	-0.08
1-Month	0.5 ± 0.7	0.6 ± 0.7	0.07
3-Months	0.3 ± 0.4	0.6 ± 0.7	0.55[c]

Note: Data collected pre-implant and at 1 and 3 months post-implant.
*Model-based Pearson's correlations; [a]p<0.05, [b]p<0.01, [c]p<0.001
[†]EuroQol Visual Analogue Scale
[‡]Patient Health Questionnaire-8
[§]Brief Symptoms Inventory-Anxiety Subscale

Quality of Life

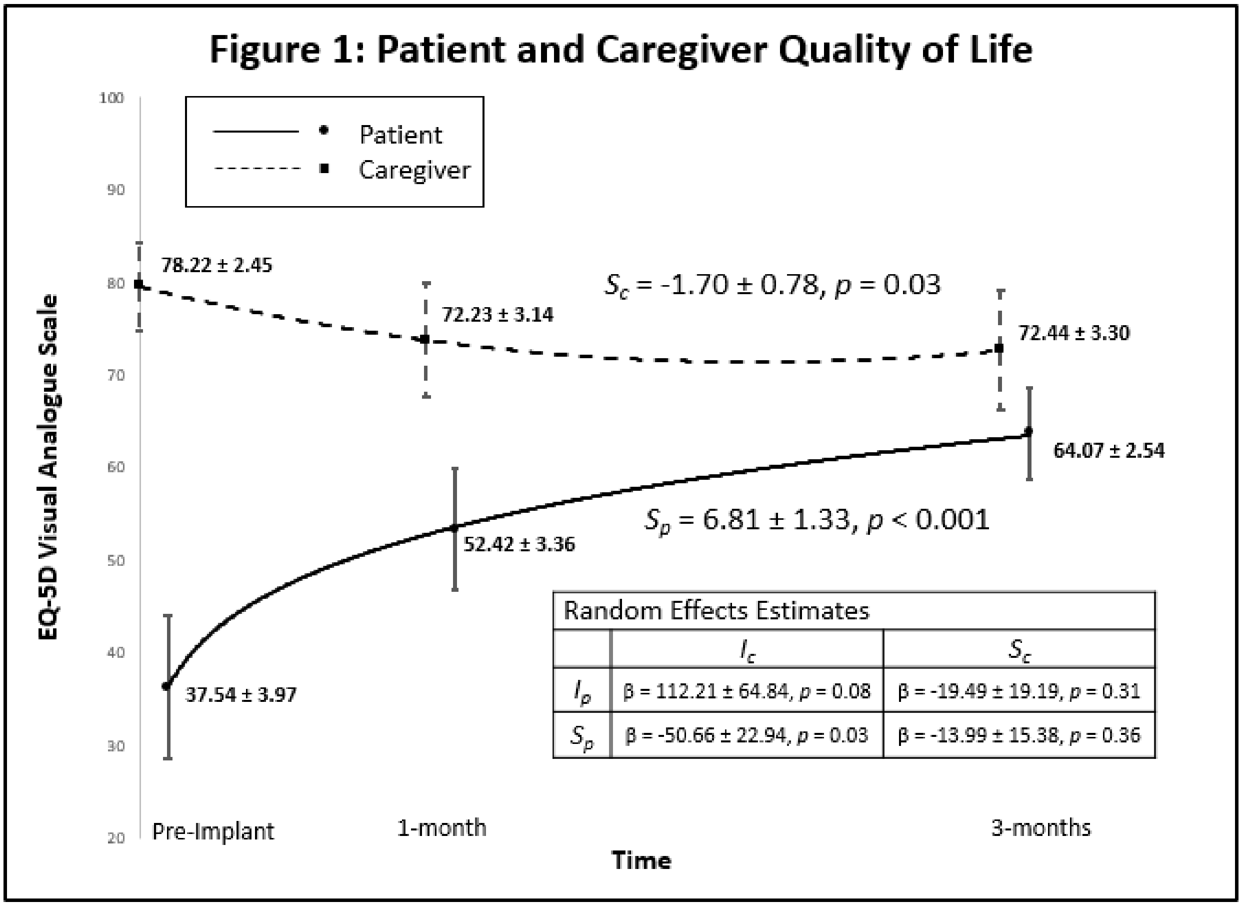
Patient and caregiver QOL was not correlated prior to implant or at 1 or 3 months post-implant. On average, patients had large, statistically significant improvements in QOL from pre- to post-implant **(Figure 1)**. In contrast, caregiver QOL significantly worsened from pre- to post-implant. Based on the random effects modeling, worse caregiver QOL at baseline was correlated with greater improvements in patient QOL in response to VAD.

Depression

There was no significant correlation between patient and caregiver depressive symptoms prior to implant, but worse depression in patients was correlated with worse depression in caregivers at both 1 and 3 months post-implant (and vice versa). In response to VAD implantation, patients had large, statistically significant improvements in depressive symptoms from pre- to post-implant **(Figure 2)**. In contrast, caregiver depressive symptoms remained relatively stable from pre- to post-implant; there was a small numerical increase (worsening depression) at 3 months that was not statistically significant. Finally, based on the random effects analysis there were no significant associations among pre-implant values or change over time in depression between patients and their caregivers.

Anxiety

Patient and caregiver anxiety were not correlated prior to implant or at 1 month post-implant, but worse anxiety in patients was correlated with worse anxiety in caregivers at 3 months post-implant (and vice versa). On average, patients had moderate-to-large, statistically significant improvements in anxiety from pre- to post-implant **(Figure 3)**. In comparison, caregiver anxiety remained relatively stable over time, as there was no statistical change from pre- to post-implant. Based on the random effects modeling, patients with worse anxiety pre-implant tended to have caregivers who reported less anxiety and vice-versa. Additionally, worse caregiver anxiety at baseline was associated with less reduction in patient anxiety in response to VAD.



Random Effects Estimates		
	I_c	S_c
I_p	β = 112.21 ± 64.84, p = 0.08	β = -19.49 ± 19.19, p = 0.31
S_p	β = -50.66 ± 22.94, p = 0.03	β = -13.99 ± 15.38, p = 0.36

Figure 1: Change in patient and caregiver quality of life. Means and 95% confidence intervals are displayed for patients and caregivers at each time point. Note: I_p: patient intercept, S_p: patient slope (β ± SE), I_c: caregiver intercept, S_c: caregiver slope (β ± SE). Effect sizes for patient and caregiver slope in the metric of Hedges *g* were 0.80 and 0.34, respectively.

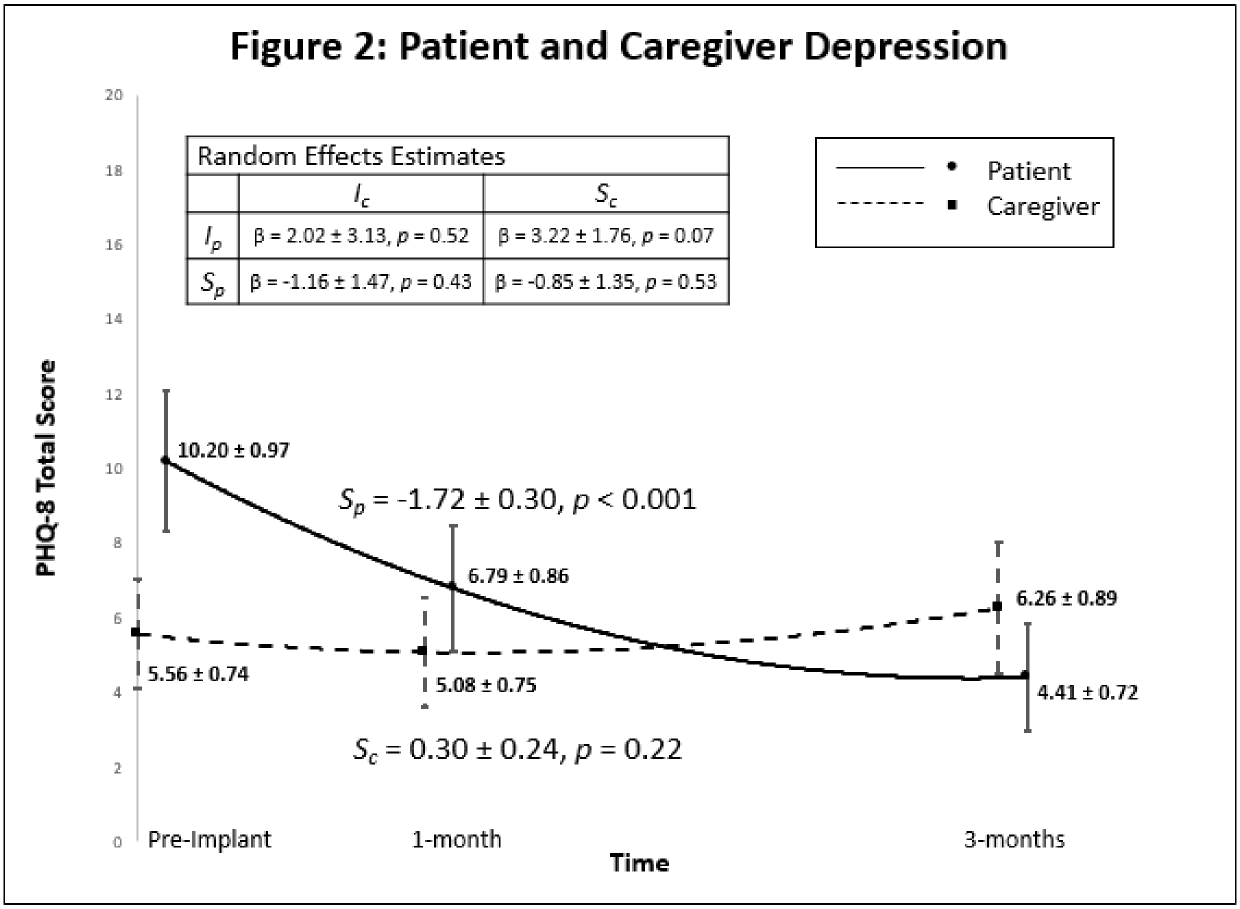


Figure 2: Patient and Caregiver Depression

Random Effects Estimates		
	I_c	S_c
I_p	β = 2.02 ± 3.13, $p = 0.52$	β = 3.22 ± 1.76, $p = 0.07$
S_p	β = -1.16 ± 1.47, $p = 0.43$	β = -0.85 ± 1.35, $p = 0.53$

Figure 2: Change in patient and caregiver depression. Means and 95% confidence intervals are displayed for patients and caregivers at each time point. Note: Ip: patient intercept, Sp: patient slope (β ± SE), Ic: caregiver intercept, Sc: caregiver slope (β ± SE). Effect sizes for patient and caregiver slope in the metric of Hedges g were 0.87 and 0.19, respectively.

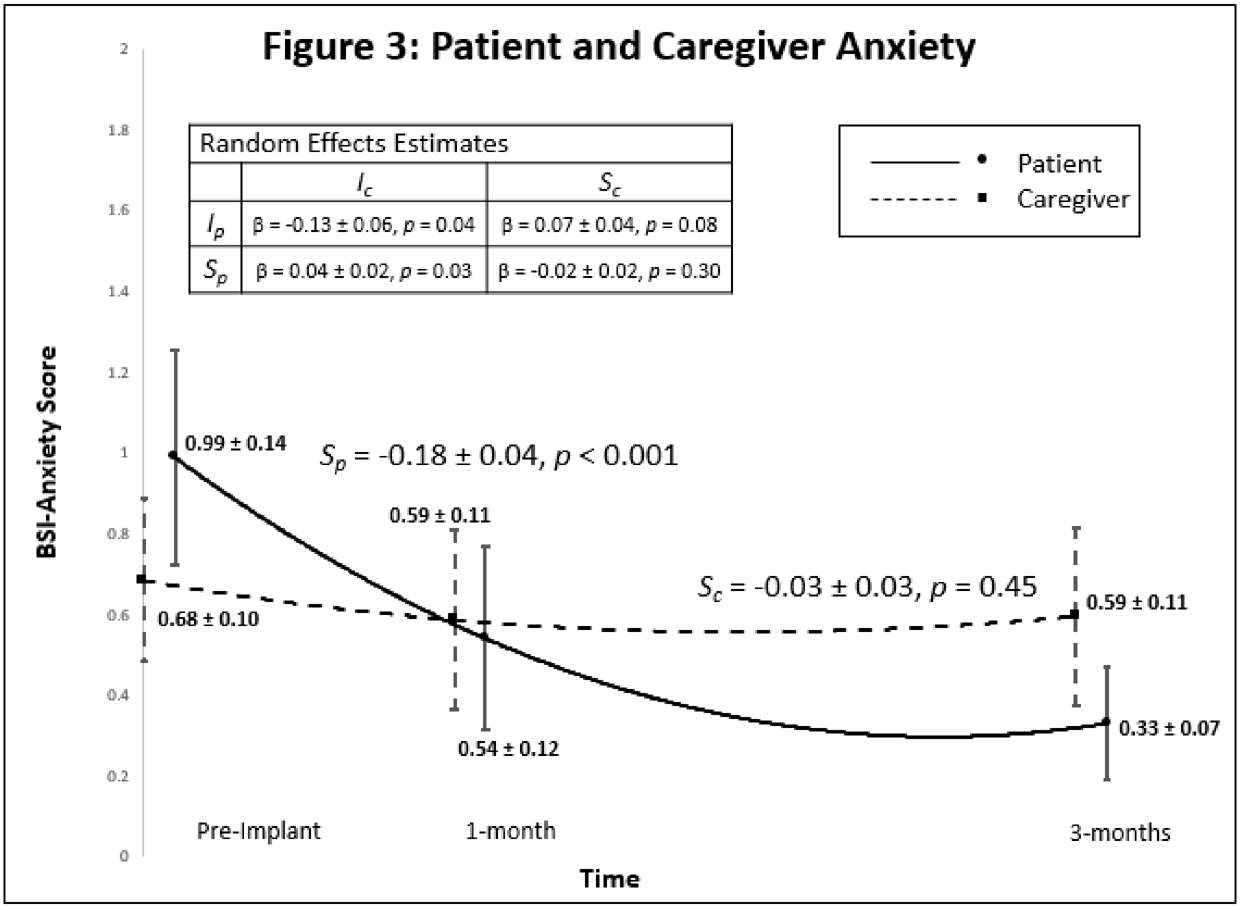


Figure 3: Patient and Caregiver Anxiety

Random Effects Estimates		
	I_c	S_c
I_p	β = -0.13 ± 0.06, $p = 0.04$	β = 0.07 ± 0.04, $p = 0.08$
S_p	β = 0.04 ± 0.02, $p = 0.03$	β = -0.02 ± 0.02, $p = 0.30$

Figure 3: Change in patient and caregiver anxiety. Means and 95% confidence intervals are displayed for patients and caregivers at each time point. Note: I_p: patient intercept, S_p: patient slope (β ± SE), I_c: caregiver intercept, S_c: caregiver slope (β ± SE). Effect sizes for patient and caregiver slope in the metric of Hedges *g* were 0.68 and 0.12, respectively.

Discussion

In this sample of 41 patients undergoing VAD therapy and their caregivers, we observed improvement in person-oriented outcomes of QOL, depression, and anxiety among patients from pre- to post-VAD. Concurrently, patients' caregivers experienced worsening QOL, but relative stability in depression and anxiety. In this section, we discuss initial levels, change, and interdependence in person-oriented outcomes for patients and caregivers; implications for clinical practice and research; and study limitations.

While our findings of QOL improvement for VAD patients are consistent with the existing literature (J. G. Allen et al., 2010; Grady et al., 2014), this study adds novel quantitative information on how QOL changes for VAD caregivers from pre- to post-implantation. Pre-implant, caregivers in our sample had QOL scores that were equivalent to national norms (Szende, Janssen, & Cabases, 2014). Over time, however, caregiver QOL significantly worsened, and at 1 and 3 months post-implant, average QOL scores were worse than healthy population averages (Szende et al., 2014). While we do not have an EQ-5D VAS comparator in HF caregiving, QOL scores in our sample were worse than those reported in stroke caregivers (McCullagh, Brigstocke, Donaldson, & Kalra, 2005). Given that psychological distress is associated with poor QOL (Pinquart & Sorensen, 2007), it is possible that sustained depression and anxiety in our sample is a driver of compromised caregiver QOL. Additionally, substantial gains in VAD patient QOL alongside losses in caregiver QOL may signal a potential trade-off in patient and caregiver QOL post-VAD. In particular, our quantitative findings are consistent with qualitative reports of caregivers sacrificing their own health to care for the VAD patient (Baker, Flattery, Salyer, Haugh, & Maltby, 2010), possibly as a mechanism for coping with elevated emotional distress post-VAD (Egerod & Overgaard, 2012).

Findings from this study are also consistent with what little has been published on depression and anxiety for VAD patients and caregivers. For example, patient depression and anxiety improve post-implantation (Brouwers, Denollet, et al., 2015; Brouwers et al., 2011; Grady et al., 2014), and similarly, we found substantial improvements for patients from pre- to post-VAD. For caregivers, VAD caregiving is characterized by high levels of anxiety from the point of decision onwards, and many caregivers report persistent fear of clinical events and uncertainty for the future (i.e. transplant potentiality or device failure) (Akbarin & Aarts, 2013; Kaan, Young, Cockell, & Mackay, 2010; Kirkpatrick et al., 2015; Kitko et al., 2013; Marcuccilli, Casida, Bakas, & Pagani, 2014). Hence, it not surprising that we observed caregiver depression and anxiety that were substantially worse than national norms and published averages in HF caregiving samples (Chung, Moser, Lennie, & Rayens, 2009; Hwang, Fleischmann, Howie-Esquivel, Stotts, & Dracup, 2011; Kocalevent, Hinz, & Brahler, 2013; Pressler et al., 2013). Furthermore, at 3 months post-VAD, caregiver depression and anxiety were numerically worse than patient depression and anxiety on average – a finding which is consistent with previous work in VAD (Brouwers, Denollet, et al., 2015; Bunzel, Laederach-Hofmann, Wieselthaler, Roethy, & Wolner, 2007). Additionally, we observed worse caregiver anxiety pre-implant correlated with less improvement in patient anxiety over time, and increasing correlations between patient and caregiver depression and anxiety. Given the large proportion of spousal dyads in our sample, this may be a function of a sharing of psychological distress between individuals in close relationship, a phenomenon called *emotional contagion* (Hatfield, Cacioppo, & Rapson, 1994) that has also been observed in stroke dyads (McCarthy, Lyons, & Powers, 2011). In sum, our results demonstrate that the experience and outcomes of one member of the caregiving dyad also influence the other member, and vice versa, supporting a need to examine

VAD patients and caregivers within the context of the caregiving relationship (Berg & Upchurch, 2007; Bidwell, Lyons, & Lee, [in press]).

This is the first study in continuous-flow devices to quantify change over time in caregiver person-oriented outcomes from pre-implant through post-implant. Given the dramatic changes in patient outcomes, it is important to discuss the contrasting finding of relative stability in caregivers. First, VAD caregivers typically transition into VAD caregiving with a substantial amount of HF caregiving experience (Baker et al., 2010), and have described VAD caregiving as different but equally challenging (Kitko et al., 2013). Furthermore, caregivers have characterized the VAD experience as a “24/7” role even months after implant (Marcuccilli & Casida, 2011) and report distress at *all* phases (from pre-implant evaluation through support) (Kaan et al., 2010). This may explain both the burden of depression and anxiety at baseline and lack of change over time. It is also important to note that “no average change” is not equivalent to “no change,” given that substantial variability in change impeded our ability to precisely estimate slope coefficients for caregiver depression and anxiety. In particular, we observed substantial variability in caregiver anxiety, depression, and QOL at each time point and over time, as evidenced by large standard deviations and wide 95% confidence intervals. Furthermore, it is important to note that, while the patient underwent a major clinical intervention (VAD), the caregiver did not; thus, we would not expect consistent caregiver response in a therapeutic direction. Rather, our findings of interdependence and variability in change for patients and caregivers provides support for examining and quantifying potential subgroups of dyads that respond well or poorly to VAD therapy together, in order to identify dyads that may be at particularly high risk for poor outcomes.

Implications

This study has several clinical and research implications. First, variability in responses to VAD implant limit our ability to provide anticipatory guidance to patients in general and family caregivers in particular. There remains an imminent need for research that provides clarity on which patients and caregivers are at highest risk, and how they can be supported together to optimize person-oriented outcomes. Second, we observed correlations in person-oriented outcomes within dyads over time. Given that VAD therapy is often a long-term intervention, research is needed that examines patients and caregivers together to inform clinical strategies that best approximate the real-world context in which patients and caregivers jointly manage the device. Third, we observed a substantial burden of emotional distress for caregivers and a significant decline in QOL. Lack of preparation for the psychological burden of caregiving and the necessity of support systems for caregivers and patients are well-documented (Akbarin & Aarts, 2013; Blumenthal-Barby et al., 2015; Kirkpatrick et al., 2015), however, little is known about how support should be structured or potential costs/benefits. Importantly, despite difficulties, most patients and caregivers have minimal decisional regret (Kitko et al., 2013; McIlvennan et al., 2015). Thus, in order to advance the science towards supporting patients and caregivers together and identifying when and for whom psychosocial and dyadic interventions are most appropriate, we need investment in research that includes both patients and caregivers, and that employs robust methods to handle dyadic data.

Limitations

This study has limitations. First, this was a relatively small, single-site sample of primarily middle-aged, white male patients and female caregivers, almost all of whom were couples. Future work with analyses by age, gender, relationship type, and more diverse racial and ethnic backgrounds is needed. Second, out of necessity we excluded a small number of patients who did not have a primary caregiver at the time of implant; thus, these findings may not be generalizable to rare situations where a VAD is placed without clear caregiving support. Finally, this current analysis followed patients and caregivers through 3 months post-implant; our future work will contain follow-up through 6 months.

Conclusions

In this study of person-oriented outcomes in VAD patients and caregivers, we found that VAD caregiver QOL worsened from pre- to post-implant, while patient QOL improved significantly. VAD patient depression and anxiety also improved, while caregivers reported substantial depression and anxiety pre-implant that did not improve over time. Given the morbidity and mortality associated with end-stage HF and VAD, it is likely normative for patients and caregivers to feel anxious and/or depressed prior to implant. For patients, these symptoms will most likely improve post-implantation, but for caregivers, it is reasonable to recommend supportive therapy (e.g. psychological services) across the spectrum of VAD support to manage persistent anxiety and depression and potentially mitigate compromises to QOL. Furthermore, given the relationships between patient and caregiver outcomes and the transactional nature of the caregiving dyad, there may be particular benefit to referring patients and caregivers together for supportive services (e.g. joint patient-caregiver counseling). However, in order to better identify and support patients and caregivers who are at greatest risk for poor outcomes, future research is needed that examines how patients and caregivers respond to VAD therapy together, within the context of the caregiving dyad.

Chapter IV

Interpersonal Determinants of Patient Clinical Event Risk in Heart Failure

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This manuscript replaces portions of the methods, results, and discussion sections of the traditional dissertation. Ms. Bidwell will be the primary author on this paper; Dr. Lee will be the senior author on this paper. Ms. Bidwell will conduct the analysis under the supervision of Dr. Lee and Dr. Lyons. This paper will be submitted to the European Journal of Cardiovascular Nursing, which is an indexed and peer-reviewed journal with an impact factor of 2.491. The readership for this journal includes cardiovascular nurse researchers, educators, and clinicians. This manuscript is currently under internal review.

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Declaration of Conflicting Interests

None Declared

Abstract

Background: Preventing hospitalization and improving event-free survival are primary goals of heart failure (HF) treatment according to current European Society of Cardiology guidelines; however, substantial uncertainty remains in our ability to predict risk and improve outcomes. Although caregivers often assist HF patients to manage their disease, little is known about their influence on clinical outcomes. **Objective:** To quantify the influence of interpersonal characteristics on patient clinical-event risk in HF. **Methods:** This was a secondary analysis of data using a sample of Italian adults with HF and their informal caregivers. HF patients were followed-up over a median of 15 months for the following clinical events: hospitalization for HF, emergency room visit for HF or all-cause mortality. Influence of caregiver, as well as patient, factors on patient risk of death or hospitalization/emergency room use was quantified using Cox proportional hazards regression. **Results:** Over the course of follow-up, 32.8% of patients had died, 19.7% had been hospitalized for HF and 10.4% had visited the emergency room. Higher caregiver strain, better caregiver mental health status and greater caregiver contributions to HF self-care maintenance at baseline were associated with significantly better event-free survival. Higher patient NYHA Class and greater caregiver contributions to patient self-care management at baseline were associated with significantly worse patient event-free survival. **Conclusions:** Considering caregiving factors together with patient factors significantly increases our understanding of patient clinical event-risk in HF.

MeSH Keywords: Heart Failure, Hospitalization, Mortality, Caregivers

Interpersonal Determinants of Patient Clinical Event Risk in Heart Failure

Introduction

A rapidly increasing number of adults are being diagnosed with heart failure (HF), a disorder characterized by significant symptom burden, poor quality of life (QOL) and premature mortality (Heidenreich et al., 2013; McMurray et al., 2012). Frequent hospitalization and premature death are particularly distressing for patients and families and costly to healthcare systems. As such, preventing hospitalization and improving event-free survival are primary goals of treatment according to current European Society of Cardiology guidelines (McMurray et al., 2012). Despite this, the burden of hospitalization and mortality remains high. Over half of patients admitted for HF will be readmitted within a year (Avaldi et al., 2015), and 27% will die during that time (Alter et al., 2012). The prognosis for HF is worse than most cancers (Stewart, MacIntyre, Hole, Capewell, & McMurray, 2001), and for patients with advanced HF, mortality risk increases, with most dying within 2 years (Hunt et al., 2009; Russell, Miller, & Pagani, 2008). Despite a heavy burden of events, there remains a substantial amount of uncertainty around our ability to predict clinical event-risk in HF (Rahimi et al., 2014; Russell et al., 2008), and half of nursing interventions that aim to reduce hospitalization or death are unsuccessful (J. K. Allen & Dennison, 2010). Thus, there is an imminent need to improve our capacity to predict and ameliorate clinical-event risk in HF.

Despite the fact that HF patients often have informal (unpaid) caregivers to assist them in managing their disease (Hwang, Luttik, Dracup, & Jaarsma, 2010), caregiver factors are rarely included in risk models or interventions (J. K. Allen & Dennison, 2010; Rahimi et al., 2014). Including interpersonal factors may be one promising avenue for elucidating unexplained variability in clinical event-risk in HF: patient and caregiver outcomes have been shown to be transactional (e.g. one member's characteristics influencing the other member and vice versa) in HF and other chronic illness contexts (Berg & Upchurch, 2007; Bidwell et al., [in press]; Dunbar, Clark, Quinn, Gary, & Kaslow, 2008), and clinical event-risk in particular has been associated with caregiver characteristics in HF (Hooley, Butler, & Howlett, 2005; Saunders, 2008; Schwarz & Elman, 2003). Thus, the objective of this analysis is to quantify the impact of interpersonal characteristics on patient clinical-event risk in HF.

Methods

Study Design

This was a secondary analysis of a subset of data from a multi-site observational study of Italian community-dwelling HF patients and their informal caregivers. The study methods have been described previously (Cocchieri et al., 2015; Vellone et al., 2014). In essence, patients were enrolled from outpatient cardiovascular clinics across 28 Italian provinces, and were eligible if: 1) they were at the clinic for a routine HF appointment; 2) they had an echocardiogram-confirmed diagnosis of HF; 3) clinical evidence of HF was present, as outlined by current European Society of Cardiology guidelines (McMurray et al., 2012) and 4) they were willing and able to provide informed consent. Patients less than or equal to 18 years of age were excluded, as were those with a recent (≤ 3 months prior) acute coronary event or clear evidence of dementia. If the patient's adult primary informal caregiver had accompanied them to the appointment, the caregiver was offered enrollment as well. For the cross-sectional parent study, data was collected at the time of enrollment. Data for this analysis is derived from a subset of data from an ancillary study, in which patients and caregivers provided additional consent for patient clinical events follow-up over the course of approximately one year.

Ethical Approval

This investigation conformed with the principles outlined in the Declaration of Helsinki, ethics committees at each site approved the research protocol and written informed consent was obtained from all participants. Data for this analysis was appropriately de-identified and the Institutional Review Board of the first and senior authors approved this analysis as being exempt from human subjects review.

Measurement

Demographics and clinical characteristics. Demographic data (age, gender, marital status, education level, employment and how patient and caregiver were related) were collected from patients and caregivers using self-report questionnaires. Self-report questionnaires also included several study instruments; those germane to this analysis are described in the following section. Questionnaires were administered in a private space at the clinic at the time of enrollment by trained research nurses. The patient's medical record was also abstracted for clinical characteristics (left ventricular ejection fraction, New York Heart Association (NYHA) Class, duration of HF, hospitalizations within the past year, number of medications, serum sodium, serum hemoglobin, home oxygen use and comorbid conditions (Charlson et al., 1987)).

Clinical events. The clinical events of interest in this study were as follows: all-cause mortality and hospitalizations and/or emergency room visits due to HF exacerbation. Clinical events data were collected via phone interviews with participants. If the participant could not be reached at the time of follow-up, the caregiver was contacted.

Patient cognitive impairment. Cognitive impairment was measured using the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). The MMSE is designed for brief cognitive evaluation in the clinical setting, and involves questions and activities that collectively test orientation, memory, attention and calculation and language.

Scores on each portion of the exam are summed for a total possible score of 30, with higher scores indicating better cognition. The MMSE is one of the most widely used instruments for testing cognition, and has been validated for use in an Italian population (Grigoletto, Zappala, Anderson, & Lebowitz, 1999).

Caregiver strain. The Caregiver Burden Inventory (Novak & Guest, 1989) was used to asses strain in caregivers. It is a multidimensional instrument with 24 items and 5 subscales. This instrument has been validated for use in an Italian population (Marvardi et al., 2005). The summed Physical and Developmental subscales were used for this analysis. Within an Italian population, the 9 items from these two subscales load together in psychometric analysis (Marvardi et al., 2005), providing cumulative information on strain related to caregiving in terms of physical stress and feelings of being “off time” in life expectations and hopes. Together, this combined subscale includes items such as: “I wish I could escape from this situation,” My social life has suffered,” “I feel emotionally drained due to caring for my care receiver” and “My health has suffered.” Scores for this subscale range from 0-36, with higher scores indicating greater strain; subscale reliability in this sample was good (Cronbach’s $\alpha = 0.93$).

Caregiver mental health status. The mental component summary scale of the Short Form-12 (Ware, Kosinski, & Keller, 1996) was used to assess caregiver mental health status. Scores are normed and standardized to range from 0-100, with higher scores indicating better mental-health status. The SF-12 has been validated for use in Italy, has good reliability (Cronbach’s $\alpha > 0.90$) and has been widely used in caregiving research in general and HF caregiving research in particular (Evangelista et al., 2002; Gandek et al., 1998; Martensson, Dracup, Canary, & Fridlund, 2003; Ware et al., 1996). To examine the comparative difference in survival by caregiver mental health status, tertiles of caregiver mental health were generated and modeled as categorical predictors.

Patient and caregiver contributions to heart failure self-care. HF self-care is conceptualized as the daily maintenance (e.g. adhering to medications, exercise, restricting sodium, monitoring for HF symptoms) and symptom management (i.e. timely and appropriate response to HF symptoms when they occur) behaviors that patients must engage in in order to maintain clinical stability (Lee, Moser, Lennie, & Riegel, 2011; Riegel, Lee, & Dickson, 2011). Caregivers often assist patients with both maintenance and management behaviors (Buck et al., 2015; Lee et al., 2015). Patient and caregiver contributions to HF self-care were assessed using the validated Italian Self-Care of HF Index version 6.2 (SCHFI) and the parallel caregiver contributions version (CC-SCHFI), respectively (Vellone, Riegel, Cocchieri, Barbaranelli, D'Agostino, Antonetti, et al., 2013; Vellone, Riegel, Cocchieri, Barbaranelli, D'Agostino, Glaser, et al., 2013). The SCHFI and CC-SCHFI have separate subscales for self-care maintenance and management behaviors, with varied item response scales. Scores for each subscale are standardized to range from 0-100, with higher scores indicating better self-care. While the SCHFI (patient version) asks the respondent how often they engage in their own care, the CC-SCHFI (caregiver version) asks how often the respondent recommends that the patient engages in care (or does the behavior for the patient if the patient is unable) on the same items. Factor score determinancy reliability coefficients were acceptable (0.78 – 0.90).

Analysis

Standard descriptive statistics (Means and standard deviations or *n* and proportions) were used to describe the sample. Cox proportional hazards modeling was used to quantify clinical event risk (all-cause mortality, hospitalization for HF or emergency room visit for HF). Due to limitations in sample size, a modified backwards stepwise approach was used to select covariates for a parsimonious model with a goal of no more than 10 predictors. First, patient HF-related clinical covariates identified in a previous event-risk analysis using a larger subset of this data (Lee et al., [under review]) were entered into a backward stepwise Cox regression. Entered covariates included NYHA class (III/IV versus I/II), hospitalization in the past year (yes/no), number of medications, left ventricular ejection fraction, serum sodium, serum hemoglobin, home oxygen use (yes/no), HF-specific QOL (Minnesota Living with Heart Failure Physical and Emotional subscales (Rector, Kubo, & Cohn, 1987)), duration of HF (months) and patient cognition. NYHA Class and patient cognition were retained in the model ($p < 0.20$ retention). Next, patient and caregiver controls and caregiver/dyadic variables of interest were entered into the model: patient/caregiver age, gender, education and employment; patient comorbidities; dyad relationship type (spousal/non-spousal); caregiver perceived social support (subscale of the Carers of Older People in Europe Index (Balducci et al., 2008)); caregiver strain; caregiver mental and physical health status (SF-12 mental and physical component summary scores (Ware et al., 1996)) and patient and caregiver contributions to HF self-care maintenance and management. Variables without significant individual or global effect were removed to arrive at a parsimonious model. There was no evidence of multicollinearity among final model covariates. Global and individual covariate tests using Schoenfeld residuals were non-significant, and were graphically confirmed to verify that the proportional hazards assumption had not been violated (Schoenfeld, 1981). All analyses were performed using Stata MPv14 (College Station, TX); results from the proportional hazards model are reported using hazard ratios (HR) and 95% confidence intervals (CI).

Results

Of the 575 patients who agreed to participate in clinical events follow-up, 183 also had caregivers who participated in baseline data collection for the parent study. Characteristics of these 183 patient-caregiver dyads are presented in **Table 1**. In short, patients were older, on average, than caregivers, and a slight majority of patients were male, while caregivers were largely female. Most commonly, caregivers were adult children of patients, and the second most common relationship was spousal. A little over half of patients were NYHA Class III or IV at baseline and had been hospitalized in the year prior to enrollment. Over the course of a median follow up period of 15 months, approximately one-third of patients had died, one-fifth had been hospitalized for HF, and one-tenth had visited the emergency room for HF.

Table 1: Characteristics of the Sample

	Patients Mean ± SD or *n* (%)	Caregivers Mean ± SD or *n* (%)
Age (years)	75.6 ± 11.7	57.2 ± 14.3
Gender (female)	85 (46.5%)	107 (67.3%)
Education[a]	46 (25.1%)	87 (51.2%)
Employed	23 (12.6%)	89 (52.1%)
Spousal Caregiver	-	51 (32.5%)
NYHA Class III/IV	94 (51.4%)	-
EF (%)	43.9 ± 12.4	-
HF Duration (months)	60.7 ± 49.4	-
Prior hospitalization[b]	100 (54.6%)	-
Comorbidities[c]	3.18 ± 1.4	-
Cognition (MMSE)	22.8 ± 7.1	-
Caregiver Strain	-	10.2 ± 9.5
Mental Health Status[d]	-	48.5 ± 9.4
Highest Tertile		58.1 ± 2.2
Middle Tertile		49.6 ± 2.6
Lowest Tertile		38.0 ± 6.9
Physical Health Status	-	46.4 ± 8.8
Self-Care Maintenance	56.7 ± 16.5	58.5 ± 19.2
Self-Care Management	50.0 ± 21.6	56.7 ± 19.8
Clinical Events Distribution:		
Alive Without Event	68 (37.2%)	-
Death (All-Cause)	60 (32.8%)	-
HF Hospitalization	36 (19.7%)	-
HF ED Visit	19 (10.4%)	-

[a] Education: High School, Professional School, or University versus not

[b] Hospitalization (yes/no) in year prior to enrollment

[c] Comorbidities: Charlson Comorbidity Index score

[d] Participants in the highest and lowest tertiles reported the best and worst mental health status, respectively

NYHA Class: New York Heart Association Class; EF: ejection fraction; HF: heart failure; MMSE: Mini Mental State Exam; ED: emergency department

Results from the Cox proportional hazards model are displayed in **Table 2**. The final model included patient and caregiver age, patient NYHA Class (III/IV versus I/II), patient cognition, patient comorbidities, caregiving relationship type (non-spousal versus spousal), caregiver strain, caregiver mental health status and caregiver contributions to self-care maintenance and management. Higher caregiver strain, better caregiver mental health status and greater caregiver contributions to HF self-care maintenance (daily adherence behaviors) at baseline were associated with significantly lower risk of patient death or hospitalization during follow-up. In contrast, higher patient NYHA Class and greater caregiver contributions to patient self-care management (response to HF symptoms when they occur) at baseline were associated with significantly higher patient clinical event-risk during follow up. Patients with caregivers in the highest tertile of self-reported mental health (as opposed to the lowest tertile) had significantly lower hazard of clinical events over time (**Figure 1**).

Table 2: Determinants of Patient Clinical Event-Risk

	HR	95% CI	*p* - value
Patient Age	1.00	0.98 – 1.03	0.83
Caregiver Age	1.00	0.98 – 1.03	0.86
Patient NYHA Class III/IV	2.10	1.26 – 3.49	<0.01
Patient Cognition (MMSE)	0.98	0.94 – 1.02	0.24
Patient Comorbidities (Charlson)	1.07	0.91 – 1.26	0.41
Non-Spousal Caregiver	0.70	0.31 – 1.57	0.39
Caregiver Strain	0.94	0.91 – 0.97	<0.001
Caregiver Mental Health Status			
Moderate versus lowest mental health	0.65	0.35 – 1.21	0.17
Highest versus lowest mental health	0.41	0.20 – 0.84	0.01
Caregiver Contribution to Self-Care Maintenance	0.99	0.97 – 0.99	0.04
Caregiver Contributions to Self-Care Management	1.01	1.00 – 1.03	0.04

HR: hazards ratio; CI: confidence interval; NYHA: New York Heart Association; MMSE: Mini-Mental State Exam

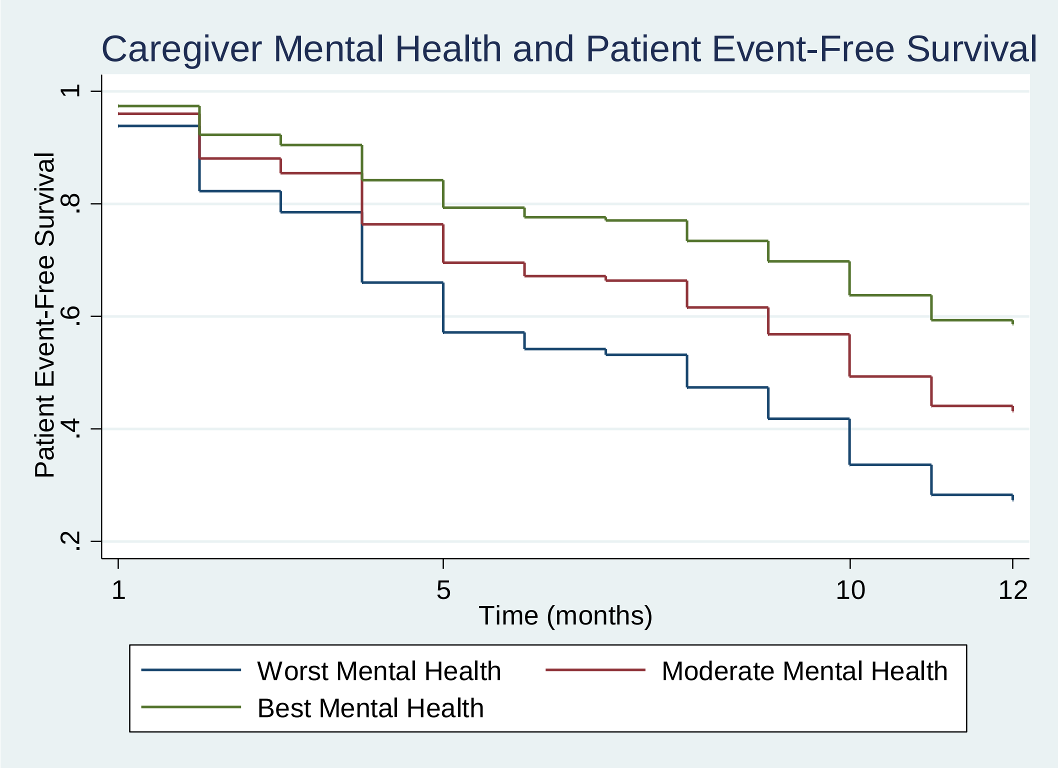

Figure 1: Comparative difference in event-free survival by tertiles of caregiver self-reported mental health status, reported as hazard ratios (95% confidence intervals). Highest tertile (best mental health status) versus lowest tertile (worst mental health status): 0.41 (0.20 – 0.84), *p* = 0.01; middle tertile versus lowest tertile: 0.64 (0.35 – 1.21), *p* = 0.17.

Discussion

In this analysis of HF patients and their informal caregivers, we found that, in addition to patient functional class, multiple caregiver factors predicted patient clinical event-risk. We will focus our discussion on the significant caregiver determinants identified in the model, namely, caregiver strain, caregiver mental health and caregiver contributions to HF self-care. We will then discuss implications for research and practice and address study limitations.

Caregiver Strain

We found that higher caregiver strain was significantly associated with lower patient clinical event-risk, meaning patients with better event-free survival had caregivers who reported more strain at baseline. Given that two previous studies in HF caregiving have identified associations between higher caregiving strain and more patient clinical events over time (Hooley et al., 2005; Schwarz & Elman, 2003), we were somewhat surprised by this finding. These results may be explained, in part, by patients' prior clinical course at time of enrollment; namely, that existing studies almost exclusively consisted of patients who were hospitalized or previously hospitalized at time of enrollment. Given that prior hospitalization has been associated with greater strain in HF caregivers (Hwang et al., 2011; Saunders, 2008), it is not surprising that our sample of solely community-dwelling patients, nearly half of whom had no prior hospitalization, would yield different results. Thus, for caregivers of relatively stable outpatients, our findings demonstrate a potential trade-off between patient and caregiver clinical event risk, given that caregiver strain is itself an independent predictor of caregiver morbidity and mortality (Beach, Schulz, Yee, & Jackson, 2000; Schulz & Beach, 1999). This may be indicative of caregivers sacrificing their own health and well-being to provide care for the HF patient, a phenomenon that has been observed in advanced HF patients receiving VAD therapy (Baker et al., 2010), as well as more broadly across chronic illness contexts (Wolff, Spillman, Freedman, & Kasper, 2016).

Caregiver Mental Health

We found that better self-reported caregiver mental health status was associated with lower patient clinical event risk, or conversely, worse caregiver mental health was associated with worse patient event-free survival. This is consistent with previous work, which has found associations between greater caregiver depression at baseline and higher HF patient clinical event-risk over time (Hooley et al., 2005). It is possible that caregivers experience psychological distress as a function of caring for a patient that they perceive to be clinically worsening; thus, caregivers may be an early litmus test for impending loss of patient clinical stability. It is also possible that caregivers with worse mental health are impaired in their ability to provide care, resulting in higher patient event-risk. For example, feelings of distress, anger or depression in caregivers has been associated with significantly worse HF patient medication adherence (Foebel, Hirdes, & Heckman, 2012). In either case, there may be value in including caregivers in regular clinic visits, as they may provide additional information to assist in patient clinical events prognostication, and identification and intervention on caregiver psychological distress may have dual patient-caregiver benefit.

Caregiver Assistance with Heart Failure Self-Care

We found that higher caregiver contributions to self-care maintenance were associated with better patient event-free survival, while higher caregiver contributions to self-care management were associated with worse patient event-free survival. To our knowledge, this is the first study in HF to demonstrate an association between caregiver engagement in HF self-care behaviors and patient clinical event-risk. This was a statistically significant but small effect, which may be a function of the relatively small sample size and/or generally low levels of self-care contributions on average. Interestingly, patient self-care contributions had no individual or global effect in our model. This is contrary to previous work done in a North American population (Lee et al., 2011), which may be evidence of cultural effects (i.e. Italian versus American) or modeling effects (i.e. individual patient contributions become less significant when caregiver factors are controlled). From recent observational and interventional research, we know that caregivers play a major role in HF self-care (Buck et al., 2015), that the patient-caregiver relationship influences self-care engagement (Bidwell et al., 2015; Buck, Kitko, & Hupcey, 2013; Lee et al., 2015) and that dyadic interventions to improve self-care may be more efficacious than individual approaches (Chung, Lennie, Mudd-Martin, & Moser, 2015; Dunbar et al., 2013). Thus, it is not surprising that caregiver self-care contributions significantly predicted patient event-free survival in this analysis. Specifically, our analysis demonstrates that that caregiver engagement in the day-to-day adherence behaviors required to maintain clinical stability (self-care maintenance) may be protective against clinical events for patients, while greater caregiver engagement in symptom response behaviors (self-care management) may be a signal of increasing frequency of HF symptoms and impending decompensation.

Implications

This study has several implications for research and practice. Broadly, from both a research and clinical perspective, this analysis provides evidence that caregivers have a substantial impact on patient clinical event-risk in HF. Considering patients that are otherwise similar (age, functional class, cognition, comorbid burden), caregiver factors may provide additional information to refine our ability to predict clinical events. For example, caregiver psychological distress may be a sign that a patient is deteriorating, and similarly, increasing caregiver investment in self-care management behaviors may signal increasing or poorly controlled symptoms that require timely adjustment to medical management. Furthermore, our analysis demonstrates that the support caregivers provide in terms of assistance with daily adherence behaviors (self-care maintenance) and investment in other caregiving activities that may result in caregiver strain have a measurable influence on patient clinical outcomes.

Our analysis also demonstrates that there may be trade-offs between caregiver and patient outcomes. Higher caregiver strain predicting better patient event-free survival is particularly concerning, given the increased risk of morbidity and mortality that comes with caregiver strain. Thus, there may be both ethical and clinical rationale for providing supportive services to caregivers. From an ethical perspective, healthcare systems rely on informal caregivers to assist patients with disease management in the community setting, which may subsequently make family members vulnerable to adverse outcomes as a result of assuming a caregiving role

(Schulz & Beach, 1999; Wolff et al., 2016). From a clinical perspective, supporting caregivers has the potential to improve both patient and caregiver outcomes. If caregiver factors impact patient clinical outcomes, as our analysis and others have demonstrated (Hooley et al., 2005; Schwarz & Elman, 2003), it may be beneficial to consider including caregivers (if patient and caregiver consent) in regular clinic visits. Caregivers may detect physical declines that the patient is not perceiving (e.g. due to compromised somatic perception or mild cognitive impairment related to HF (Jurgens, 2006; Lee et al., 2013)) and thus may be able to provide additional insight to how the patient is progressing clinically in the community setting. This may also be a time that providers can identify and refer caregivers that may need extra support, given that struggling caregivers may not readily advocate for themselves (Wolff et al., 2016).

Limitations

This analysis has limitations. Ideally, our model would control for all patient-level factors that are known predictors of clinical event-risk, before adding caregiver factors, however, our relatively small sample size limited the number of covariates we could include. Larger samples are needed to further examine the relationships we identified. Second, clinical events were measured by self-report, as the study personnel did not have long term access to patients' medical records. Third, given that this was a single-country sample, results may not be generalizable outside of Italy; replication in other regions is needed.

Conclusions

We identified multiple caregiver factors at baseline that significantly predicted patient clinical event risk over one year. In particular, higher caregiver strain and greater caregiver contributions to day-to-day HF self-care maintenance behaviors were associated with better patient event-free survival. Additionally, worse caregiver mental health status and greater caregiver engagement in HF symptom-response behaviors (self-care management) were associated with higher risk of patient clinical events. This analysis demonstrates that caregivers have a measurable impact on patient event-risk, and that concerning trade-offs may exist between patient and caregiver clinical outcomes. Future work is needed in larger samples and other regions to further examine the relationships identified in this study, and to test potential interventions to optimize clinical outcomes for patients and caregivers together.

Chapter V

Individual and Interpersonal Determinants of Heart Failure-Specific Quality of Life and Caregiver Strain in Ventricular Assist Device Therapy

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This manuscript replaces a portion of the methods, results, and discussion sections of the traditional dissertation. Ms. Bidwell will be the primary author on this paper; Dr. Lee will be the senior author on this paper. Ms. Bidwell will conduct the study and perform the statistical analyses under the supervision of Dr. Lee. This article will be submitted for publication to The Journal of Heart and Lung Transplantation (JHLT). JHLT is an indexed and peer-reviewed journal with an impact factor of 6.650. The readership for this journal includes both clinicians and researchers and is one of the primary journals for those who work with mechanical circulatory support. This manuscript is ready for internal review prior to submission to JHLT.

Citation:

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Declaration of Conflicting Interests

None Declared

Abstract

Background: Although current mechanical circulatory support (MCS) guidelines emphasize the importance of social support to the success of ventricular assist device (VAD) therapy, few studies examine the influence of caregivers on patient outcomes, or quantify the impact of MCS caregiving on the caregiver. **Objective:** To identify individual and interpersonal determinants of change in patient HF-specific quality of life (QOL) and caregiver strain in MCS. **Methods:** Data on MCS patients and caregivers was prospectively collected pre-implantation and 1, 3, and 6 months post-implantation. Trajectories of change in patient HF-specific QOL (Kansas City Cardiomyopathy Questionnaire) and caregiver strain (Multidimensional Caregiver Strain Index) were quantified and predicted using piecewise growth curve modeling. **Results:** Patients experienced substantial initial QOL improvement in response to MCS, followed by gradual improvement and stabilization. Caregivers experienced significant initial worsening of strain in response to MCS, followed by gradual reduction back to baseline levels. Across both models, worse patient HF symptoms adversely impacted both patient and caregiver, while relationship quality was a protective factor for both members of the dyad. There were also significant differences in both patient QOL and caregiver strain by caregiving relationship type.
Conclusions: A combination of individual and dyadic characteristics predict how patients and caregivers respond to MCS therapy in terms of patient QOL and caregiver strain. Including caregiver and interpersonal factors in future studies in MCS may provide important information to support patient and caregiver outcomes together.

MeSH Keywords: Heart Failure, Ventricular Assist Device, Caregivers, Quality of Life

Individual and Interpersonal Determinants of Heart Failure-Specific Quality of Life and Caregiver Strain in Ventricular Assist Device Therapy

Introduction

Patients with advanced heart failure (HF) have limited treatment options (Russell et al., 2008): many advanced HF patients are not eligible for the gold standard of treatment, transplant, or cannot survive protracted organ wait times (L. A. Allen et al., 2012; Russell et al., 2008). Thus, mechanical circulatory support (MCS) with a ventricular assist device (VAD) has become a primary therapeutic option for patients ineligible for transplant who need permanent support (destination therapy; DT) and for patients who require a bridge to transplantation (BTT) (L. A. Allen et al., 2012; Kirklin et al., 2015). In order for MCS to be successful, current guidelines recommend that patients have strong social support, and most centers require that patients have a designated informal (unpaid family member or friend) caregiver to assist them in managing the device (Ben Gal & Jaarsma, 2012; Blumenthal-Barby et al., 2015; Feldman et al., 2013; Peura et al., 2012). Despite this, few quantitative studies in MCS examine the influence of these informal caregivers on patient outcomes, or quantify the impact of MCS caregiving on the caregiver.

Quality of life (QOL) is a major outcome of interest in MCS (Grady et al., 2012), and although MCS is associated on average with improvements in QOL, there is still substantial variability in QOL outcomes post-implantation (J. G. Allen et al., 2010; Brouwers et al., 2011; Grady et al., 2014). As such, there is a current need for research in MCS that elucidates determinants of QOL and identifies potential intervention targets, particularly for DT patients who will permanently live with the device (Rich et al., 2016). Similarly, there is a current call for more research on caregivers in MCS, about whom little is known quantitatively, but who may be at particularly high risk for strain (burden) – a known predictor of increased morbidity and mortality in caregivers (Beach et al., 2000; Rich et al., 2016; Schulz & Beach, 1999). Furthermore, caregiver and patient outcomes are transactional, both in chronic illness in general and HF in particular (Berg & Upchurch, 2007; Bidwell et al., [in press]), supporting quantitative approaches in MCS that examine patient and caregiver outcomes together. Thus, the purpose of this analysis of patient-caregiver dyads in MCS is to identify both individual and interpersonal determinants of change in patient HF-specific quality of life and caregiver strain.

Methods

Study Design and Population

This was a prospective longitudinal study of patients receiving MCS and their informal caregivers, the details of which have been published previously (Bidwell et al., [under review]; Lee et al., 2014). In brief, this was a collaboration between two federally sponsored studies: a parent study on biobehavioral responses in patients receiving MCS, and an ancillary study on patients' informal caregivers. Patients were eligible for enrollment if they were 21 years of age or older, eligible and likely to receive a VAD, and without previous heart transplant. Patients were excluded if they were unable to complete study requirements (e.g. concomitant terminal illness, major psychiatric illness/cognitive impairment). Adult (21 years of age or older) caregivers were eligible if they were the primary caregiver of a patient enrolled in the parent study (as agreed upon by the patient, the caregiver, and the advanced HF team). Data in both studies were collected at four time points: prior (median of 5 days) to implantation and 1 month, 3 months, and 6 months post-implantation. Patient data included clinical data abstracted from the medical record, as well as data on demographic and person-oriented outcomes collected via survey. For caregivers, demographic and person-oriented outcomes data were collected via survey. Study measures are described in detail below. Data from patients and their associated caregivers were merged to create a dyadic (patient and caregiver) dataset. All procedures for both parent and ancillary studies were reviewed and approved by the Institutional Review Board at the study site (single center), and all participants (patients and caregivers) provided informed consent to participate.

Measurement

Demographic and clinical characteristics. Patients and caregivers self-reported their own demographic information (age, gender, race/ethnicity, marital status, education, employment), and caregivers provided information about the nature of their relationship to the patient (relationship type, duration). Clinical characteristics of the patient (etiology and duration of HF, NYHA Class, EF, VAD therapy type, and comorbid conditions as measured by the Charlson Comorbidity Index; Charlson et al., 1987) were abstracted from the patient's medical record at baseline. No caregiver clinical characteristics were collected, as we did not have access to their medical records. However, caregivers did report their own comorbidity history using a validated self-report measure (Chaudhry et al., 2005).

Patient heart failure specific quality of life. The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to measure patient QOL (Green et al., 2000). The KCCQ is a multidimensional measure; the 3-item QOL subscale was selected for this analysis. Patients respond on a 1-5 Likert scale, and scores are normed to a potential range of 0-100 with higher scores indicating better QOL (Green et al., 2000). Reliability in this sample was low-to-acceptable (Cronbach's α across all time points ranged from 0.67 – 0.77).

Caregiver strain. The Multidimensional Caregiver Strain Index (MCSI) was used to measure caregiver strain (Stull, 1996). The MCSI is a multidimensional measure of strain with an 18-item total strain score. Items ask how frequently caregivers feel strained in terms of a particular aspect of caregiving, and responses are on a 5-point Likert scale (from "never" to "all of the time"). Scores are summed to for a potential range of 18-90, with higher scores indicating more strain. Reliability in this sample was acceptable (Cronbach's α across all time points ranged from 0.92 – 0.94).

Physical Symptoms. Patient physical symptoms of HF (e.g. fatigue, weight gain, orthopnea, dyspnea) at baseline (pre-implant) were measured using the Heart Failure Somatic Perception Scale (HFSPS; Jurgens, Fain, & Riegel, 2006). The 18-item HFSPS asks patients about how bothersome symptoms are on a six-point (0-5) Likert scale, with 0 indicating the patient did not have the symptom, and 1 to 5 indicating the symptom was not at all bothersome to extremely bothersome, respectively. Scores on the HFSPS are summed to range from 0 to 90, with higher scores indicating worse perceived symptom severity. The reliability of the HFSPS in this sample was acceptable (Cronbach's α of 0.88).

Relationship Quality. Caregiver-perceived relationship quality at baseline (pre-implant) was measured using the 15-item Mutuality Scale (Archbold, Stewart, Greenlick, & Harvath, 1990), which measures positive dimensions of relationship quality. Each item is rated on a 5-point Likert scale from 0 (not at all) to 4 (a great deal). Individual item scores are averaged to derive a summary score ranging from 0-4, with higher scores indicating greater relationship quality. Reliability for the Mutuality Scale in this sample was acceptable (Cronbach's α of 0.95).

Analysis

Standard descriptive statistics (means and standard deviations for continuous variables, *n* and percentage for dichotomous/categorical variables) were used to describe patients and their caregivers at baseline. To quantify and predict change in patient HF-specific QOL and caregiver strain, two individual latent growth curve models were estimated. Growth curve models are an extension of random coefficient models where time is treated as a quantitative variable with a random coefficient. The main advantage of this approach to modeling longitudinal data is that it allows for estimation of both intra-individual (within-person) trajectories of change (fixed effects) and estimation of the inter-individual (between-person) variability in change (random effects). Thus, growth curve models provide information on how the sample population as a whole changes over time, to what degree individuals within that sample deviate from the mean trajectory, and how predictor variables explain this inter-individual variability in change (Bollen & Curran, 2005; Curran, Obeidat, & Losardo, 2010). Given that changes in QOL and functional status in response to VAD therapy are typically early and sustained (Maciver & Ross, 2012; Rogers et al., 2010), and both patient QOL and caregiver strain in this sample had average trajectories that mirrored this pattern, a piecewise (spline) approach was appropriate for modeling this data. In piecewise growth modeling, multiple growth curves are simultaneously estimated to best reflect the differing rates of growth over time. In this analysis, we modeled separate linear slopes for change from pre-implant through 1 month post-implant (the span of time across which both patients and caregiver experienced the largest magnitude in change), and from 1 month to 6 months post-implant (during which patients and caregivers experienced more gradual change) (Bollen & Curran, 2005). Model covariates were selected using the dyadic Berg and Upchurch Developmental-Contextual Model (2007) as a guiding theoretical framework. Therapy type (DT versus BTT) and caregiving relationship type were retained in both models as necessary controls. Additional variables matching the theoretical framework and with significant individual or global effect on the model were retained, with a limit of 5 variables per model (given *n* = 50). To facilitate early identification of at-risk patients and caregivers, only baseline (pre-implant) variables were considered in model selection. All analyses were conducted in

MPlus7 (Los Angeles, CA).

Results

Characteristics of the sample are presented in **Table 1**. Patients and caregivers were on average 54.6 and 54.7 years of age, respectively. Patients were largely male, while caregivers were largely female, and most identified as Caucasian/non-Hispanic. The most common type of caregiving relationship was spousal, and the next most common relationship was parental. Approximately three-quarters of patients received VAD therapy as BTT or bridge to decision (as compared to DT).

Table 1: Characteristics of the Sample (*n* = 50 dyads)

	Patient mean±SD or *n*(%)	Caregiver mean±SD or *n*(%)
Age	54.6±13.9	54.7±12.5
Gender (male)	42(84.0%)	9(18.0%)
White/Non-Hispanic	42(84.0%)	46(92.0%)
Relationship type		
Spousal		38(76.0%)
Parental		7(14.0%)
Relationship duration[a]		318.7±182.8
Relationship Quality[b]		3.3±0.6
Education (> high school)	27(54.0%)	33(66.0%)
Employed	5(10%)	28(56.0%)
Comorbidity Index Score[c]	1.02±1.3	2.5±1.5
Ischemic HF Etiology	19(38.0%)	
Duration of HF[a]	101.4±94.1	
Ejection Fraction (%)	20.8±3.5	
NYHA Class IV	20(40.0%)	
HF Symptoms[d]	39.4±17.5	
On Inotropes Pre-implant	26(52.0%)	
Destination Therapy[e]	14(28.0%)	

Note: HF: heart failure; NYHA Class: New York Heart Association Functional Class; QOL: Quality of Life; mo: month; mos: months.

[b] Mutuality Index score

[c] Charlson Comorbidity Index for patients, self-report version for caregivers

[d] Heart Failure Somatic Perception Scale total score

[e] Therapeutic strategy at time of implant; as opposed to Bridge to Transplant or Bridge to Decision

Patient heart failure-specific quality of life. The mean intercept and growth curve trajectories for patient HF-specific QOL are presented in **Figure 1**. In general, patients experienced substantial improvement in QOL from immediately pre-implant (intercept) through 1 month post-implant (initial change), followed by gradual improvement and stabilization between 1 and 6 months post-implant (long-term change). Initial change was significantly associated with pre-implant QOL, such that better QOL pre-implant was associated with less dramatic improvements in QOL within the first month following implant. There was significant variability between patients' pre-implant QOL ($p < 0.001$) and in initial response to MCS ($p = 0.01$), but long-term responses to MCS did not vary significantly ($p = 0.10$). The final model is presented in **Table 2.** Patients with greater symptoms at baseline had significantly worse pre-implant QOL, but also had significantly greater initial QOL improvements in response to MCS. Patients with caregivers who reported better relationship quality prior to implant had significantly greater initial improvements in QOL. Patients with non-spousal caregivers had significant losses, rather than improvements, in QOL from 1 month to 6 months post-implant. Patients with non-ischemic etiology of HF had significantly greater improvements in QOL from 1 month to 6 months post-implant.

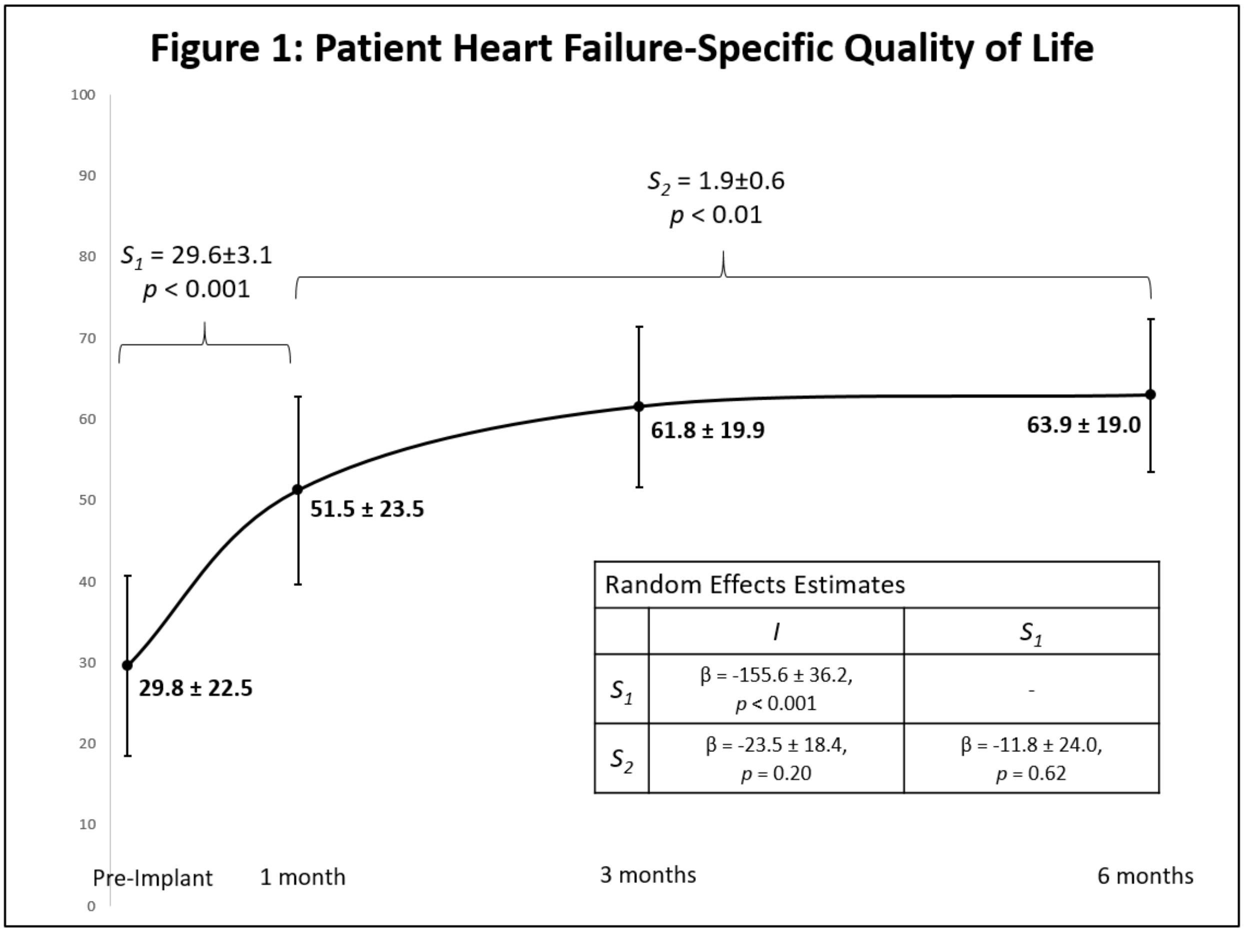
Figure 1: Patient Heart Failure-Specific Quality of Life

Random Effects Estimates

	I	S_1
S_1	β = -155.6 ± 36.2, p < 0.001	-
S_2	β = -23.5 ± 18.4, p = 0.20	β = -11.8 ± 24.0, p = 0.62

Figure 1: Growth curve trajectories and random effects estimates for patient heart failure-specific quality of life. Means and 95% confidence intervals are displayed at each time point. Note: *I*: intercept, S_1: linear growth from pre-implant through 1 month post-implant, S_2: linear growth from 1 month through 6 months post-implant.

Table 2: Determinants of Patient Pre-Implant HF-Specific QOL and Change Over Time

	Pre-Implant QOL (intercept) β±SE, *p*-value	Initial Change[a] in QOL (slope 1) β±SE, *p*-value	Long-Term[b] Change in QOL (slope 2) β±SE, *p*-value
Unadjusted model	29.62±3.15, *p*<0.001	23.22±3.76, *p*<0.001	1.90±0.64, *p*<0.01
Non-spousal Caregiver[c]	4.18±6.89, *p*=0.54	0.58±9.28, *p*=0.95	**-3.70±1.62, *p*=0.02**
Destination Therapy[d]	-6.61±6.32, *p*=0.30	3.10±7.39, *p*=0.68	1.97±1.60, *p*=0.22

Relationship Quality[e]	-7.15±5.13, *p*=0.16	**14.39±5.85, *p*=0.01**	-0.72±1.40, *p*=0.61
Patient HF Symptoms[f]	**-0.62±0.18, *p*<0.001**	**0.53±0.19, *p*<0.01**	-0.01±0.04, *p*=0.87
Non-Ischemic Etiology[e]	-3.24±7.10, *p*=0.65	-8.82±7.74, *p*=0.25	**4.31±1.52, *p*<0.01**

Note: QOL: Quality of Life; SE: standard error; HF: heart failure

[a] Change from pre-implant through 1 month post-implant

[b] Change from 1 month post-implant through 6 months post-implant

[c] Caregiving relationship type: non-spousal versus spousal caregiver

[d] VAD therapy type: Destination Therapy versus Bridge to Transplant/Decision

[e] Mutuality Scale score

[f] Heart Failure Somatic Perception Scale total score

Caregiver strain. The mean intercept and growth curve trajectories for caregiver strain are presented in **Figure 2**. In general, caregivers experienced significant increases in strain from immediately pre-implant (intercept) through 1 month post-implant (initial change), followed by gradual reduction back to baseline levels between 1 and 6 months post-implant (long-term change). There were no significant associations between pre-implant caregiver strain and either initial or long-term change over time. There was significant variability between caregivers' pre-implant strain (p < 0.001) but initial and long-term responses did not vary significantly (p = 0.11 and 0.50, respectively). The final model is presented in **Table 3.** Caregivers who reported better relationship quality with the patient at baseline had significantly less strain pre-implant, as did non-spousal caregivers. Caregivers of patients with more severe HF symptoms prior to implant had significantly greater worsening of strain between implant and 1 month post-implant. Long-term (between 1 and 6 months post-implant), female caregivers had significantly greater improvements (reductions) in strain as compared to male caregivers.

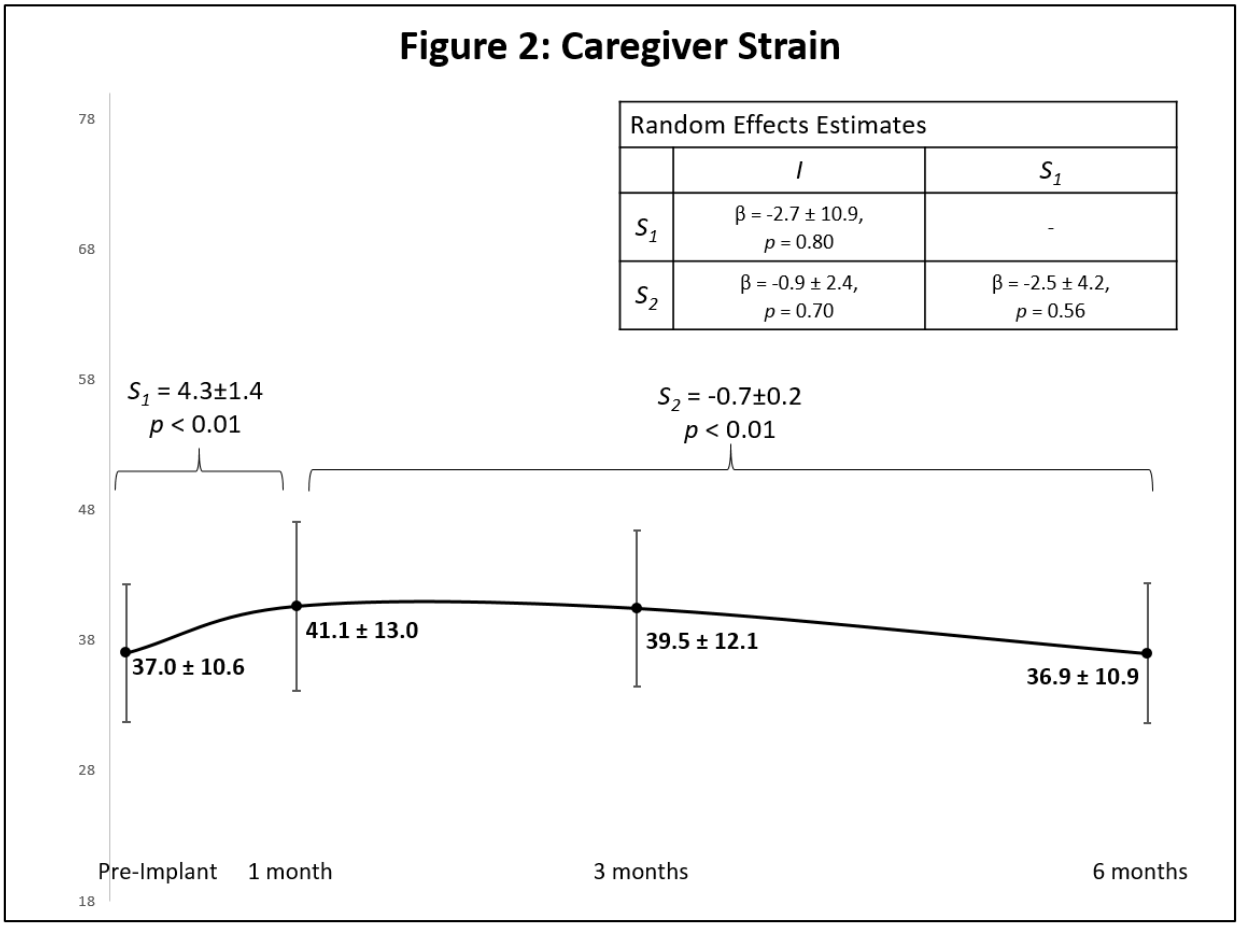

Figure 2: Growth curve trajectories and random effects estimates for caregiver strain. Means and 95% confidence intervals are displayed at each time point. Note: *I*: intercept, S_1: linear growth from pre-implant through 1 month post-implant, S_2: linear growth from 1 month through 6 months post-implant.

Table 3: Determinants of Caregiver Pre-Implant Strain and Change Over Time

	Pre-Implant Strain (intercept) β±SE, *p*-value	Initial Change[a] in Strain (slope 1) β±SE, *p*-value	Long-term Change[b] in Strain (slope 2) β±SE, *p*-value
Unadjusted model	37.03±1.50, *p*<0.001	4.30±1.42, *p*<0.01	-0.71±0.23, *p*<0.01
Non-spousal Caregiver[c]	**-8.60±3.10, *p*=0.01**	5.48±3.17, *p*=0.08	-0.34±0.59, *p*=0.56
Destination Therapy[d]	-0.32±2.33, *p*=0.89	0.22±3.07, *p*=0.94	-0.04±0.49, *p*=0.94

Relationship Quality[e]	**-9.31±2.28, $p<0.001$**	0.23±2.61, $p=0.93$	0.08±0.42, $p=0.84$
Patient HF Symptoms[f]	-0.03±0.07, $p=0.65$	**0.15±0.07, $p=0.04$**	-0.01±0.01, $p=0.50$
Caregiver Gender (Female)	2.32±3.35, $p=0.50$	3.04±2.58, $p=0.24$	**-0.98±0.46, $p=0.03$**

Note: SE: standard error; HF: heart failure

[a] Change from pre-implant through 1 month post-implant

[b] Change from 1 month post-implant through 6 months post-implant

[c] Caregiving relationship type: non-spousal versus spousal caregiver

[d] VAD therapy type: Destination Therapy versus Bridge to Transplant/Decision

[e] Mutuality Scale score

[f] Heart Failure Somatic Perception Scale total score

Discussion

In this study of MCS patients and their caregivers, we observed significant changes from pre-implantation through 6 months post-implantation in patient HF-specific QOL and caregiver strain. The discussion of results will center on particularly notable aspects of our findings, namely, the nature of trajectories of change for patients and caregivers and variables that were significant in both models, specifically, the effect of HF symptoms and dyadic characteristics (caregiving relationship type and quality) on patient HFQOL and caregiver strain. We will conclude with a summary of research and practice implications, study limitations, and future directions for research.

Trajectories of Change in HF-Specific QOL and Caregiver Strain

We observed dramatic initial improvements (between pre-implantation and 1 month post-implantation) in patients’ HF-specific QOL in response to MCS, followed by stabilization and gradual improvement over the remaining 5 months of study follow-up. This is consistent with previous studies in MCS patients, which have also demonstrated early and sustained patterns of improvement in both QOL and functional status over time (Maciver & Ross, 2012; Rogers et al., 2010). We also observed significant variability in both pre-implant levels of QOL and in patients' initial (1 month) change in QOL, but no significant variability in long term (between 1 and 6 months) change in QOL. This is notable, as it demonstrates that although initial QOL responses in MCS are highly variable, once the patient has reached 1 month post-implant, patients on average will no longer experience further dramatic improvement. Thus, factors that predict robust, positive responses to MCS therapy within the first month post-implant, particularly modifiable factors, may be promising targets for intervention or risk prognostication.

In terms of change in caregiver strain, this is the first study to quantify strain in MCS caregivers from pre- to post-implantation. Although previous qualitative studies have demonstrated that the MCS caregiving experience can be characterized as emotionally distressing at all stages of support (Akbarin & Aarts, 2013; Kaan et al., 2010; Kirkpatrick et al., 2015; Kitko et al., 2013), it is not possible to derive information about the trajectory of change from these studies, or identify specific points in the trajectory when the caregiver is at highest risk for strain. However, in other chronic illness contexts that involve major patient clinical intervention (e.g. bone marrow transplant, heart transplant), strain or distress in caregivers is at its highest immediately pre-intervention, followed by improvement over time (Applebaum et al., 2016; Canning, Dew, & Davidson, 1996). It is therefore possible that our observed trajectory of early worsening of strain, followed by a return to baseline (and no improvement) over 6 months may be unique to the MCS caregiving experience. However, it should also be noted that the initial increase in caregiver strain in this sample of VAD caregivers, though statistically significant, was not particularly large (less than half the standard deviation of the population average). Thus, characteristics that predict pre-implant levels of caregiver strain, from which caregivers will not deviate substantially from on average, may have particular value in identifying at-risk caregivers. Notably, in our sample of VAD caregivers, pre-implant strain was more than twice as high as was observed in a recent study of Parkinson's caregivers using the same instrument (Oyama et al., 2014), and approximately 10 points higher than HF caregivers in one of our ongoing studies of community-dwelling HF patient-caregiver dyads [unpublished data].

Influence of HF Symptoms

Heart failure symptoms were a significant determinant of both patient HF-specific QOL and caregiver strain in our analysis, demonstrating that the HF symptom experience – a hallmark of the HF syndrome – does not exclusively effect patients, but also adversely impacts caregivers. In MCS patients, we observed greater symptoms were associated with worse pre-implant QOL, a finding that is consistent with the existing HF literature (Lum et al., 2016). Interestingly, we also observed that greater symptoms pre-implant predicted greater initial QOL improvements in response to MCS, possibly meaning that more symptomatic HF patients have more to gain from VAD therapy. In MCS caregivers, we observed that greater HF symptoms in patients predicted greater worsening of strain in the first month after MCS implantation. Given that greater severity of HF has been associated with greater strain in caregivers (Bidwell et al., [in press]), it is possible that distress related to greater severity of symptoms pre-implant has an lagged effect on caregivers' ability to cope with caregiving immediately post-implant. Alternatively, patients with worse symptoms pre-implant may have more difficult post-implant courses, although our finding of greater pre-implant symptoms predicting more dramatic gains in QOL somewhat contradicts this hypothesis. Either way, the influence of pre-implant HF symptoms on both patient and caregiver outcomes underlines the important role that symptoms play for both patients and caregivers, and suggests that the patient experience of HF symptoms is a shared, transactional experience with their caregiver.

Influence of Dyadic Characteristics

Relationship quality. In this analysis, relationship quality was a significant protective factor in patient HF-specific QOL and caregiver strain. In particular, better relationship quality between patient and caregiver predicted greater improvements in patient QOL during the first month post-implant, and less caregiver strain at baseline. This is notable, as these are the most clinically meaningful points in the patient and caregiver trajectories, respectively, given that any gains the patient makes in QOL in the first month are sustained on average over time, and caregiver strain changes significantly, but not substantially, from baseline. Importantly, relationship quality is a measurable, modifiable factor that is potentially amenable to intervention and has established benefit across chronic illness and HF contexts. In chronic illness in general, relationship quality has been associated with better caregiver emotional health outcomes (Park & Schumacher, 2014). In HF dyads in particular, relationship quality is a known determinant of better patient and caregiver HF self-care behaviors (whether patients and caregivers comply with daily adherence behaviors and respond appropriately to symptoms) (Bidwell et al., 2015) and is protective against patient and caregiver psychological distress (Rohrbaugh et al., 2002). Although this is the first study in VAD dyads to demonstrate that patient-caregiver relationship quality may have a positive impact on patients and caregivers alike, its known protective benefits in similar populations suggest that it may be a promising factor in future observational and interventional research.

Relationship type. In this analysis, caregiving relationship type – whether the caregiver was a spouse or non-spouse – was a determinant of both long-term change in HF-specific QOL for patients and baseline strain for caregivers. Specifically, patients with nonspousal caregivers had significant declines, rather than gains, in QOL from 1 to 6 months post-VAD, and spousal caregivers had greater baseline strain. Many studies in HF focus on spouses, which was the majority of dyads in our sample. However, there is a significant proportion of caregivers in HF and VAD who are not spouses, and there are likely differences in caregiving dynamics and outcomes by relationship type. It is not surprising that spousal caregivers had significantly higher strain pre-implant than nonspousal caregivers, as similar results have been demonstrated previously in caregivers of older adults (Neal, Ingersoll-Dayton, & Starrels, 1997). The finding of worsening QOL in patients of nonspousal caregivers, however, is novel. It may be that the physical and emotional proximity of spousal caregiving holds benefits and drawbacks to patients and caregivers alike. For caregivers, distress pre-implant may be heightened by the potential threat of losing a life partner, and/or the added workload associated with having to care for a spouse who was previously able to share in financial, practical, and instrumental household responsibilities. For patients, long-term QOL may suffer as nonspousal caregivers, who may not live with the patient, possibly reduce their caregiving contributions for practical or emotional reasons. Alternatively, previous research has demonstrated that, over time, nonspousal, rather than spousal, caregivers may actually be at greatest risk for emotional distress (Kim, Baker, & Spillers, 2007; Neal et al., 1997; Young & Kahana, 1989), which may in turn affect the patient. Either way, our study demonstrates that the type of caregiving relationship influences MCS patient and caregiver outcomes. In future studies, relationship type should be further examined (or at minimum, controlled), or authors should be explicit about the generalizability limitations of spousal only studies.

Implications for Research and Practice

Overall, this study demonstrates that the MCS patient-caregiver dyad is transactional. In particular, we observed that a combination of individual and dyadic characteristics predicted key patient and caregiver outcomes. In order to better understand and leverage the dynamic relationship context in which patients and caregivers experience and manage VAD therapy over time, we need research and clinical approaches that examine and treat patients and caregivers together as a dyad. Second, our findings underline the importance of the HF symptom experience for both patient and caregiver outcomes. Continued symptom management research from a dyadic perspective is needed, particularly given that symptoms affect both dyad members, and symptom management is a critical component of good HF self-care (Buck et al., 2015; Clark et al., 2014). Finally, we identified relationship quality as a potentially protective – and importantly, modifiable – factor for both dyad members. Research to better understand relationship quality and clinical approaches that support healthy relationships between patients and caregivers may be a promising avenue for improving the health and well-being of MCS patients, caregivers, and the dyad overall. Relationship quality should be measured in both members, studied at the dyadic level, and, given the dearth of dyadic MCS research, we must pool information across disciplines and chronic illness contexts to better understand how to support healthy relationships in patient-caregiver dyads throughout the course of advanced HF and MCS.

Study Limitations

This study has limitations. Although this is the largest quantitative sample of patient-caregiver dyads in continuous flow devices, it is still relatively small. Subsequently, we encountered modeling limitations that should be acknowledged; specifically, we were unable to control for all known predictors of strain or HF-specific QOL in our models, and there is also a potential lack of power to detect significant effects. Second, this study is from a single center and contains mostly female caregivers, mostly male patients, and mostly Caucasian/non-Hispanic participants. Future multi-site studies with more diverse demographics are needed, particularly to investigate potential differences in outcomes by region, gender, and race/ethnicity.

Finally, generalizability is limited to the six-month period following implantation. For patients, the majority of known change occurs within this initial six-month period, and thus the length of follow-up in this study is likely appropriate. However, given the dearth of longitudinal quantitative research on MCS caregivers, it is impossible to determine if the most important phenomena are captured within six months, or if additional change occurs beyond six months. As MCS is typically a long term therapeutic strategy, particularly in DT patients, longer term dyadic research in VAD caregivers is warranted.

Conclusions

In summary, we observed significant changes in patient HF-specific QOL and caregiver strain in response to VAD, with the most substantial changes occurring in the first month after implantation. Specifically, patient QOL improved dramatically in the first month post-implant, followed by gradual improvement and stabilization over the remaining six months of follow-up. For caregivers, strain increased significantly in the first month post implant, followed by gradual reduction back to baseline levels over the remaining 6 months. Importantly, a combination of individual and dyadic characteristics predicted patient QOL and caregiver strain. In particular, worse HF symptoms adversely impacted both patients and caregivers, while better relationship quality seemed to be protective for both dyad members. There were also significant differences in both patient QOL and caregiver strain by relationship type. Overall, this study demonstrates that the transactional nature of the caregiving dyad has a measurable impact on key patient and caregiver outcomes in VAD therapy, and that future dyadic research in this population is warranted.

Chapter VI

Determinants of Heart Failure Self-Care Maintenance and Management in Patients and Caregivers: A Dyadic Analysis

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Declaration of Conflicting Interests

None Declared

Abstract

Background: Disease self-management is a critical component of maintaining clinical stability for patients with chronic illness. This is particularly evident in the context of heart failure (HF), which is the leading cause of hospitalization for older adults. HF self- management, commonly known as HF self-care, is often performed with the support of informal caregivers. However, little is known about how HF dyads manage the patient's care together. **Objective:** The purpose of this study was to identify determinants of patient and caregiver contributions to HF self-care maintenance (i.e., daily adherence and symptom monitoring) and management (i.e., appropriate recognition & response to symptoms), utilizing an approach that controls for dyadic interdependence. **Methods:** This was a secondary analysis of cross-sectional data from 364 Italian HF patients and caregivers. Multilevel modeling was used to identify determinants of HF self-care within patient-caregiver dyads. Patients were 76.2 (*SD*=10.7) years, a slight majority (56.9%) was male, while caregivers were 57.4 (*SD*=14.6) years, and fewer than half (48.1%) were male. Most caregivers were adult children (48.4%) or spouses (32.7%) of patients. Both patients and caregivers reported low levels of HF maintenance and management behaviors. Several significant individual and dyadic determinants of self-care maintenance and self-care management were identified, including gender, quality of life, comorbid burden, impaired ADLs, cognition, hospitalizations, HF duration, relationship type, relationship quality, and social support. **Conclusions:** These comprehensive dyadic models assist in elucidating the complex nature of patient-caregiver relationships and their influence on HF self-care, leading to more effective ways to intervene and maximize outcomes.

Keywords: heart failure; self-care; caregivers; dyad; disease management

Determinants of Heart Failure Self-Care Maintenance and Management in Patients and Caregivers: A Dyadic Analysis

Introduction

Appropriate disease self-management in the outpatient setting is an essential component of successful overall management of chronic illness in adults. In many contexts, community-dwelling individuals with chronic illnesses rely on informal caregivers – spouses, adult children, siblings, or other family members or friends – to help with daily adherence behaviors or to appropriately respond to symptoms of illness as they occur. In the United States, upwards of $450 billion worth of unpaid care is provided by informal caregivers each year (Feinberg, Reinhard, Houser, & Choula, 2011). Clinicians often interact with caregivers as though they were members of the healthcare team, relying on them to assist the patient with health behaviors, medication adherence, and symptom monitoring (Grady et al., 2000); heart failure (HF) is no exception.

A rapidly increasing number of adults are being diagnosed with HF (Heidenreich et al., 2013), a disorder that is marked by significant symptom burden, poor quality of life (QOL), and premature mortality (McMurray et al., 2012). In order to prevent exacerbation and progression of disease and reduce the risk of hospitalization and death, patients with HF must engage in a series of self-care behaviors to maintain clinical stability (self-care maintenance) and manage symptoms when they occur (self-care management) (Riegel et al., 2009). Not surprisingly, informal caregivers play a critical role in the effective management of HF in the outpatient setting (Dunbar, Clark, Quinn, Gary, & Kaslow, 2008; Gallagher, Luttik, & Jaarsma, 2011; Salyer, Schubert, & Chiaranai, 2012). Yet, despite awareness that both patients and caregivers contribute to self-care and that patient and caregiver outcomes are often interdependent (Berg &

Upchurch, 2007; Kim, Reed, Hayward, Kang, & Koenig, 2011; Klinedinst et al., 2009; Rayens & Svavarsdottir, 2003), there is a paucity of knowledge on the determinants of self-care maintenance and management behaviors within this dyadic (patient and caregiver) context. This gap in knowledge poses a major barrier to clinicians' ability to identify and intervene in cases of low levels of self-care, and hampers researchers' ability to appropriately conceptualize HF self-care and develop effective interventions that benefit both the patient and caregiver.

HF Self-Care

At an individual (patient) level, HF self-care has been conceptualized as a naturalistic decision-making process with two components: self-care maintenance and self-care management (Riegel & Dickson, 2008). Self-care maintenance refers to daily behaviors that a patient must do to maintain clinical stability, such as taking medications as prescribed, adhering to a low sodium diet, and monitoring for HF symptoms. Self-care management refers to behaviors in which a patient must engage when symptoms of HF occur, namely, recognizing the symptom as being related to HF, engaging in appropriate treatment (e.g. taking an extra diuretic, etc.), and evaluating whether the treatment adequately resolved the symptom (Dickson, Buck, & Riegel, 2011; Riegel & Dickson, 2008). Effective self-care has been recognized as a critical component of overall HF management (Jurgens, Hoke, Byrnes, & Riegel, 2009) and has been associated with reduced clinical event risk for HF patients (Lee, Moser, Lennie, & Riegel, 2011).

Determinants of HF Self-Care

In patients, self-care is often impaired by multiple sequelae that characterize the complex syndrome of HF, such as depression (Holzapfel et al., 2009), sleep disturbances (Riegel, Moelter, et al., 2011), impaired cognition (Cameron et al., 2010; Harkness et al., 2013; Lee et al., 2012), high comorbid burden (Dickson et al., 2011), and decreased perception of declines in health

(Gravely-Witte, Jurgens, Tamim, & Grace, 2010; Jurgens et al., 2009). Patient self-care management has also been shown to be associated with such factors as patient age (Holzapfel et al., 2009; Jurgens et al., 2009; Riegel, Lee, & Dickson, 2011; Seto et al., 2011), patient gender (Jurgens et al., 2009), HF duration (Jurgens et al., 2009; Oosterom-Calo et al., 2012; Riegel, Lee, et al., 2011), hospitalizations (Jurgens et al., 2009), general QOL (Lee, Suwanno, & Riegel, 2009), and HF-specific QOL or symptom burden (Altice & Madigan, 2012; Jurgens et al., 2009; Peters-Klimm et al., 2013; Riegel, Lee, et al., 2011; Seto et al., 2011).

Dyadic approaches to studying HF self-care hold great promise for elucidating key determinants of patient maintenance and management behaviors, and understanding caregiver contributions to those behaviors. Caregiver contributions to patient self-care can be conceptualized as the caregiver doing the behavior for the patient (e.g. the caregiver calling a healthcare provider for the patient when symptoms occur) or prompting the patient to do the behavior (e.g. the caregiver telling the patient to call a healthcare provider when symptoms occur) (Vellone, Riegel, Cocchieri, Barbaranelli, D'Agostino, Glaser, et al., 2013). Relatively little is known about caregiver or dyadic determinants of HF self-care, despite the important role caregivers play in HF patient outcomes. However good relationship quality and social support are considered key factors in better patient self-care (Dunbar et al., 2008; Graven & Grant, 2014; Riegel, Lee, et al., 2011; Riegel et al., 2009; Salyer et al., 2012; Stromberg, 2013). In addition, previous dyadic work on a subset of spousal dyads from the data used in this study provided evidence of significant actor and partner relationships between self-care and quality of life across dyads (Vellone et al., 2014). The current study expands upon this work by examining determinants of self-care in a larger sample of both spouse and non-spouse dyads using more comprehensive dyadic models.

Analyzing the HF Dyad

Most research on chronic disease management is undertaken at the level of the individual (i.e., patient or caregiver only). In order to better inform theory and develop a solid base of evidence for interacting with patients and caregivers in clinical practice, there is a clear and pressing need to acknowledge this interdependence and examine patients and caregivers within the context of the dyad. Such studies require appropriate methodologies that control for the interdependent nature of the data, as traditional analytic approaches are often unsuitable for handling responses from patients and caregivers within the same dyad (Lyons & Sayer, 2005). In particular, traditional approaches often require aggregating and comparing data on patients and caregivers, thereby ignoring the relational aspect of the dyad and making it impossible to examine within and between dyadic effects.

Multilevel modeling has several advantages over traditional approaches to dyadic data, as within-dyad interdependence can be controlled, and between-dyad variability can be examined. Multilevel modeling also allows for the examination of actor effects (one’s own characteristics predicting one’s own outcomes) and partner effects (one’s own characteristics predicting the outcomes of the partner) across dyads (Lyons, Sayer, Archbold, Hornbrook, & Stewart, 2007; Rayens & Svavarsdottir, 2003). Accordingly, the goal of this multilevel dyadic analysis was to 1) characterize HF maintenance and management behaviors within a dyadic context, and 2) identify individual- and dyad- level determinants of both patient and caregiver contributions to HF self-care maintenance and management behaviors.

Methods

Study Design

This was a secondary analysis of data from a multi-site, cross-sectional descriptive study of HF self-care behaviors conducted on a large cohort of patients and primary informal caregivers in Italy. The primary aims and detailed study procedures have been published previously (Cocchieri et al., 2014; Vellone et al., 2014). In short, HF patients from ambulatory cardiovascular clinics in 28 different Italian provinces were screened and offered enrollment by trained research nurses. Patients were eligible for enrollment if they: 1) were being seen at the clinic for a routine HF appointment, 2) had a diagnosis of HF confirmed by echocardiogram, 3) had clinical evidence of HF as outlined by European Society of Cardiology guidelines (McMurray et al., 2012), and 4) were willing and able to provide informed consent. Patients were excluded if they were less than or equal to 18 years of age, had an acute coronary event in the three months prior to enrollment, or had clear evidence of dementia. If the primary informal caregiver of an enrolled patient was present at the appointment, he or she was also offered enrollment in the study.

Ethical Approval

The parent study complied with the Declaration of Helsinki, ethics committees at each site approved the research protocol, and informed consent was obtained from all participants. This secondary analysis also was reviewed and approved by our institutional review board.

Data Sources

Demographics and clinical characteristics. Patients and caregivers completed self-report questionnaires that included basic demographic data (age, gender, marital status, education level, employment, income, and how patient and caregiver were related) and the study instruments described in the sections that follow. Clinical HF characteristics (ejection fraction, New York Heart Association (NYHA) Class, duration of HF, hospitalizations, medications) and comorbid conditions as assessed by the Charlson Comorbidity Index (Charlson, Pompei, Ales, &

MacKenzie, 1987) were abstracted from the patient’s medical record.

Caregiver and patient quality of life. Physical and mental QOL for both patients and caregivers were assessed using the physical and mental component summary scales of the Short Form-12 (SF-12) (Ware, Kosinski, & Keller, 1996); standardized scores range from 0-100 with higher scores indicating better QOL. The SF-12 is a health status measure that has been widely used in caregiving research and has been validated for use in Italy (Gandek et al., 1998). HF-specific physical and emotional QOL for patients was assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (Rector, Kubo, & Cohn, 1987), a 21-item measure of the impact of symptoms of HF on patient QOL; physical and emotional summary scores were computed with higher values indicating worse QOL.

Patient impairment in activities of daily living. The Barthel Index (Mahoney & Barthel, 1965) was used to evaluate patient impairment in 10 activities of daily living (ADLs). Response categories for each item vary; but, scores were standardized to range from 0-100, with higher scores indicating less impairment.

Patient cognition. Patient cognition was assessed using the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), an 11-item clinical assessment tool. Item scores vary depending on the question or task, and item scores are summed to produce a score ranging from 0 to 30, with higher scores indicating better cognition. The commonly-used cutoff of ≤ 24 was used to indicate cognitive dysfunction (Mitchell, 2009).

Caregiver strain. Caregiver strain was assessed using the Caregiver Burden Inventory (CBI) (Novak & Guest, 1989), a 24-item instrument that measures strain on multiple dimensions. The total score for the CBI was used in this analysis. The item-response scale is a five-point Likert scale ranging from 0 to 4, and scores are summed, with higher scores indicating greater strain. The CBI was selected for this study because it is the only measure of caregiver strain that has been shown to be valid and reliable in an Italian population (Marvardi et al., 2005).

Caregiver perceived social support. Caregiver perceived social support was assessed using a subscale of the Carers of Older People in Europe Index (COPE Index) (Balducci et al., 2008). The COPE Index is a 15-item instrument that measures the positive and negative impacts of caregiving as well as the quality of social support received. It was developed and validated in multiple European languages and countries (Balducci et al., 2008; McKee et al., 2003) and was used to study caregiving of elderly people in Italy (Vellone et al., 2011). The 4-item perceived caregiving social support subscale was used in this analysis. The item-response scale for the COPE Index is a 4-point Likert scale ranging from 1 to 4; scores are summed with higher scores indicating greater perceived support (possible range 4-16).

Perceived quality of the relationship between patient and caregiver. Perceived quality of the relationship between patient and caregiver was assessed using a single item. Patients responded to an item designed by the research team, “How do you judge your relationship with your caregiver?” (Likert scale ranging from 1 to 5, with higher scores indicating greater perceived relationship quality). Caregivers responded to an item from the COPE Index, “Do you have a good relationship with the person you care for?” (Likert scale ranging from 1 to 4, with higher scores indicating greater perceived relationship quality).

Patient and caregiver contributions to HF self-care maintenance and management. Patient-reported contributions to HF self-care maintenance and management were assessed using the Italian version of the Self-Care of HF Index version 6.2 (SCHFI) (Vellone, Riegel, Cocchieri, Barbaranelli, D'Agostino, Antonetti, et al., 2013), a 22-item instrument that measures self-care maintenance (daily behaviors such as medication and dietary adherence, physical activity, symptom monitoring, etc.) and self-care management behaviors (recognizing and responding appropriately to symptoms of HF when they occur). Item response scales vary, and scores are standardized to range from 0 to 100, with higher scores indicating better self-care; the cutoff for “adequate” self-care is 70 or above (Jurgens et al., 2009). Caregiver-reported contributions to patient HF self-care maintenance and management behaviors were assessed using the Italian version of the Caregiver Contribution to Self-Care of HF Index (CC-SCHFI) (Vellone, Riegel, Cocchieri, Barbaranelli, D'Agostino, Antonetti, et al., 2013), a parallel version of the SCHFI designed for administration to caregivers. The items on the CC-SCHFI mirror the items on the SCHFI; however, instead of asking how often the respondent engages in their own self-care, the items ask how often the caregiver recommends that the patient engage in the given behavior, or how often the caregiver does the behavior for the patient if they are unable.

Statistical Analysis

The sample was described using means and standard deviations for continuous variables and *n* and frequency for binary or categorical variables. Two dyadic cross-sectional multivariate outcomes models were constructed using HLM 7 (Raudenbush, Bryk, & Congdon, 2011). The advantages of using this analytic approach with dyadic data include: 1) the patient-caregiver dyad (rather than the individual patient or caregiver) is the unit of analysis, 2) within-dyad interdependence is controlled, and 3) both actor effects (e.g. patient characteristics predicting patient outcomes) and partner effects (e.g. patient characteristics predicting caregiver outcomes) can be examined across dyads (Sayer & Klute, 2005) .

The cross-sectional dyadic multivariate outcomes model used in this analysis is a two-level hierarchical linear model that allowed for simultaneous estimation of regression coefficients for both patients and caregivers while controlling for interdependence within dyads.

Two models (one for self-care maintenance & one for self-care management) were examined. In the Level 1 model, scores for self-care maintenance or management were estimated for patients and caregivers as a function of observed responses and measurement error. The Level 1 (within-dyad) equation for the self-care maintenance model is as follows:

$$\text{SCMaintenance}_{ij} = \beta_{1j}\,(\text{PATIENT}_{ij}) + \beta_{2j}\,(\text{CAREGIVER}_{ij}) + r_{ij}$$

In this equation, $\text{SCMaintenance}_{ij}$ represents the self-care maintenance score i ($i = 1, \ldots k$ responses per dyad) for dyad j. PATIENT and CAREGIVER are indicator variables that take on the value of 0 or 1 depending on whether the response is from the patient or the caregiver (e.g. if the response was obtained from a patient, the PATIENT variable would take on a value of 1 and the CAREGIVER variable would take on a value of 0), making β_{1j} the latent self-care maintenance score for the patient, and β_{2j} the latent self-care maintenance score for the caregiver. The error term in the equation is represented by r_{ij}. A similar model is run for self-care management.

Before proceeding to Level 2, a chi-square test was used to confirm that the variability around the average scores for self-care maintenance or management were significantly different from zero. If this was the case, then the variability around those averages was predicted in Level 2 models by adding independent variables. Thus, at Level 2 (between-dyad), β_{1j} and β_{2j} become the dependent variables in two separate simultaneous regression models: one simultaneous regression for self-care maintenance and one simultaneous regression for self-care management. A combined theoretico-empirical approach was used for the selection of independent determinants for the models. In addition to the theoretical factors of age, gender, general QOL, comorbid illness burden, cognition, duration of HF, hospitalizations, HF-specific QOL, relationship quality, and social support (as reviewed in the introduction), we included additional factors identified in a priori testing within the sample (correlated with self-care maintenance or management at $p \leq 0.1$). This resulted in the inclusion of ADL impairment, relationship type, and caregiver strain in the models. Selected independent variables were divided into three categories (patient non-HF characteristics, patient HF characteristics, and relationship/caregiving variables) and added to predictive models in blocks to facilitate the evaluation of model fit (deviance, χ^2) by variable category.

Results

The characteristics of the sample (*n*=364 dyads) are presented in Table 1. On average, patients were approximately 20 years older than caregivers, and although there was a slightly higher proportion of male as opposed to female patients, the gender proportions for caregivers were nearly equivalent. The majority of patients and caregivers were married, but not necessarily to one another, as the majority of caregivers were adult children. Caregivers were more educated than patients, and most caregivers were employed. In general, both members of the dyad rated the quality of their relationship with the other member as good. Most patients had NYHA Class II or III HF, and the duration of HF was highly variable, ranging from 1 month to 20 years.

Table 1*: Characteristics of the Sample (n=364 dyads)*

	Patient		**Caregiver**	
	mean (SD) or n (%)		**mean (SD) or n (%)**	
Age	76.26	(10.72)	57.44	(14.63)
Female	157	(43.13%)	189	(51.92%)
Married	198	(54.40%)	253	(69.51%)
High School Ed	96	(26.37%)	193	(53.02%)
Employed	45	(12.36%)	177	(48.63%)
Caregiver Relationship to Patient				
Spouse			119	(32.69%)
Adult Child			176	(48.35%)
Other			69	(18.96%)

RQ[a]	4.19	(1.12)	3.13	(0.90)
CBI			29.71	(23.56)
COPE			10.60	(2.51)
Comorbidities	3.09	(1.31)		
MMSE	23.79	(6.61)		
SF-12 PCS	34.93	(9.97)	45.29	(8.96)
SF-12 MCS	42.25	(9.82)	47.38	(9.74)
NYHA Class				
I/II	205	(56.32%)		
III/IV	156	(42.86%)		
EF (%)	44.31	(10.94)		
HF Duration (mos)	59.65	(48.61)		
Hospitalizations	0.75	(0.84)		
MLHFQ Physical	22.04	(8.38)		
MLHFQ Emot	11.42	(5.57)		
Self-Care Maint	53.40	(15.68)	54.78	(18.58)
Self-Care Mgmt	49.07	(19.55)	53.98	(18.23)

Note: High School Ed: attained High School education or beyond; RQ: Relationship Quality; CBI: Caregiver Burden Inventory; COPE: Caregiver perceived social support subscale of the COPE Inventory; Comorbidities: Charlson Comorbidity Index; MMSE: Mini-Mental State Examination; SF-12 PCS: Physical Component Summary of the SF-12; SF-12 MCS: Mental Component Summary of the SF-12; NYHA Class: New York Heart Association Functional Class; EF: Ejection Fraction; HF Duration (mos): Duration of heart failure in months; Hospitalizations: Hospitalizations within the past year; MLHFQ Physical and MLHFQ Emot: Minnesota Living with Heart Failure Questionnaire Physical and Emotional Subscales; Self-Care Maint: Self-Care Maintenance; Self-Care Mgmt: Self-Care Management

[a] Relationship Quality instrument uses a different scale for patients vs. caregivers: Patient possible range is 1-5, Caregiver possible range is 1-4

Determinants of Self-Care Maintenance

Level 1 results revealed that patient HF self-care maintenance and caregiver contributions to patient HF self-care maintenance were generally low on average (patient: 51.77 ± 0.76, $p < 0.001$; caregiver: 54.48 ± 0.92, $p < 0.001$), and were significantly variable across dyads (patient: $\chi^2 = 487.97$, $p < 0.001$; caregiver: $\chi^2 = 700.77$, $p < 0.001$). Determinants of patient self-care maintenance and caregiver contributions to self-care (Level 2 results) are presented in Table 2. Patient HF-specific emotional QOL was the only significant factor to influence the self-care maintenance of both patients and the contributions of caregivers. Other significant factors only influenced the self-care maintenance of either the patient (patient physical QOL, comorbidities, ADL impairment, cognition, number of hospitalizations, and patient-reported relationship quality, as well as caregiver gender and perceived social support), or the contributions of the caregiver (duration of HF). Each block of variables (patient non-HF characteristics, patient HF characteristics, and caregiver/relationship characteristics) resulted in a significant improvement in model fit at $p < 0.001$ or lower.

Determinants of Self-Care Management

Level 1 results revealed that patient HF self-care management and caregiver contributions to patient HF self-care management were also low (patient: 48.20 ± 0.97, $p < 0.001$; caregiver: 53.61 ± 0.97, $p < 0.001$) and highly variable across dyads (patient: $\chi^2 = 626.80$, $p < 0.001$; caregiver: $\chi^2 = 633.11$, $p < 0.001$). The significant determinants of self-care management and caregiver contributions to self-care management (Level 2 results) were distinct for patients and their caregivers (Table 2). For patients, male gender and higher caregiver physical QOL were associated with worse self-care management, and better cognition and patient-reported relationship quality were associated with better self-care management. For caregivers, greater patient comorbid illness burden was associated with fewer contributions to patient self-care management, while nonspousal relationship, higher frequency of patient hospitalization, better caregiver-reported relationship quality, and better caregiver perceived social support were all significantly associated with more contributions to patient self-care management. When independent variables were added in blocks, blocks of patient non-HF characteristics and relationship/caregiving variables resulted in a significant improvement in model fit over the previous blocks at $p < 0.01$ or lower, while the block containing patient HF characteristics did not ($p = 0.12$).

Table 2: Multilevel Models Predicting HF Maintenance and Management (n=364 dyads)

	Maintenance Model				**Management Model**			
	Patient		**Caregiver**		**Patient**		**Caregiver**	
Independent Variables	**β**	**(SE)**	**β**	**(SE)**	**β**	**(SE)**	**β**	**(SE)**
Patient Non-HF Characteristics								
Patient Age	0.01	(0.07)	-0.12	(0.12)	0.01	(0.10)	0.08	(0.10)
Patient Gender (Male)	-2.55	(1.46)	0.47	(1.96)	**-4.71***	**(1.99)**	-0.34	(2.03)
Patient Physical QOL	**-0.27***	**(0.10)**	-0.13	(0.12)	0.15	(0.14)	**0.43***	**(0.13)**
Patient Mental QOL	-0.03	(0.09)	0.02	(0.12)	-0.05	(0.12)	-0.15	(0.12)
Patient Comorbidities	**1.26***	**(0.64)**	0.56	(0.64)	-0.70	(0.81)	**-2.31***	**(0.77)**
Patient ADL Impairment	**0.13***	**(0.05)**	0.01	(0.06)	0.02	(0.06)	-0.04	(0.07)
Patient Cognition	**0.30***	**(0.14)**	0.35	(0.19)	**0.38***	**(0.19)**	-0.06	(0.19)
Patient HF Characteristics								
HF Duration (Months)	0.03	(0.02)	**0.05***	**(0.02)**	0.03	(0.02)	0.03	(0.02)
Hospitalizations	**-2.03***	**(0.89)**	0.69	(1.11)	1.16	(1.28)	**3.12***	**(1.40)**
HF-Specific Phys QOL	-0.10	(0.14)	-0.08	(0.17)	0.12	(0.18)	0.21	(0.18)
HF-Specific Emot QOL	**0.42***	**(0.21)**	**1.04***	**(0.23)**	0.08	(0.25)	0.14	(0.22)
Caregiver/Relationship Characteristics								
CG Gender (Female)	**3.45***	**(1.40)**	2.76	(1.73)	0.40	(1.90)	-2.78	(1.91)
Non-spousal Relationship	-1.52	(1.56)	0.47	(1.87)	3.07	(2.07)	**6.72***	**(1.96)**
Caregiver Physical QOL	-0.12	(0.09)	-0.20	(0.11)	**-0.42***	**(0.12)**	-0.16	(0.13)
Caregiver Mental QOL	0.08	(0.08)	0.16	(0.10)	0.03	(0.11)	0.09	(0.10)
Patient-reported RQ	**1.87***	**(0.75)**	1.79	(0.95)	**2.28***	**(0.92)**	0.34	(0.77)
Caregiver-reported RQ	0.40	(0.84)	0.32	(1.13)	2.00	(1.19)	**2.23***	**(1.06)**
Caregiver Strain	-0.06	(0.04)	-0.06	(0.05)	-0.04	(0.05)	-0.05	(0.05)
Caregiver Social Support	**0.65***	**(0.31)**	0.53	(0.37)	0.51	(0.40)	**1.17***	**(0.42)**
Explained Variance	75.91%		33.76%		26.56%		29.04%	
(Cohen's f^2)	(3.15)		(0.51)		(0.36)		(0.41)	

Note: QOL: Quality of Life; HF-Specific Phys QOL: HF-Specific Physical Quality of Life; HF-Specific Emot QOL: HF-Specific Emotional Quality of Life; CG Gender: Caregiver Gender; RQ: Relationship Quality

*$p < .05$

Discussion

In this secondary analysis of data from 364 Italian patient-caregiver dyads in HF, significant determinants for patient HF self-care and caregiver contributions to patient self-care were identified. Importantly, both individual and dyadic effects were identified in models predicting patient and caregiver contributions to maintenance and management. Furthermore, several of these identified determinants were partner effects (e.g., patient's physical QOL on caregiver contributions to patient self-care management). Together, these findings underline the need to examine HF self-care maintenance and management in the context of the patient-caregiver dyad in order to better understand these critical behaviors and the transactional nature of disease management within HF dyads. Several of our findings are particularly noteworthy. Namely, the role of patient and caregiver gender, cognition, HF-specific QOL, relationship type and relationship quality, and the role of caregiver strain and perceived social support will frame this discussion.

Gender and Self-Care

Given that there was no gender difference in HF self-care management in previous and large cross-national samples (Lee et al., 2011), our finding that patient gender (male) was a significant determinant of (worse) patient self-care management was somewhat surprising. There is evidence, however, of a gender difference in symptom recognition (Jurgens et al., 2009), which is the first and essential component of self-care management. Thus, it is possible that the worse self-care management observed among men in this sample is a function, at least in part, of worse symptom recognition. The specific sociocultural context in which this study was conducted (Italian patients and caregivers) may also explain discordance of our findings with prior published work, or it may be that gender becomes significant for patients when we consider the dyadic context of self-care by controlling for the influence of the caregivers.

Very little is known about the influence of caregiver gender on HF self-care. In this sample, it was caregiver gender (female) that was a significant determinant of patient (better) self-care maintenance. In the broader caregiving literature there is evidence that female caregivers report greater investment of time in caregiving (Pinquart & Sorensen, 2006) and tend to provide more social and emotional support to the care recipient than male caregivers (Neal, Ingersoll-Dayton, & Starrels, 1997). It is possible that this additional emotional support from female caregivers motivates patients to engage in better self-care, or that it is protective against some of the aspects of the heart failure syndrome that are associated with lower levels of self-care (e.g. depression). It is also possible that there may be differences in quality or type of care provided depending on whether the caregiver is the daughter of the patient versus a female partner. Although this analysis examined relationship type (spousal or nonspousal) as a determinant of self-care (discussed in a following section), the interplay between gender and relationship type is complex, and likely also includes interactions with age. Thus, there is an opportunity to examine this important relationship – about which very little is currently known – in future research.

Cognition and Self-Care

In alignment with previous findings that even mild cognitive impairment can have a substantial impact on self-care (Lee et al., 2012), we observed a relationship between cognitive dysfunction and low levels of patient self-care maintenance and management. It should be noted that, on average, the degree of cognitive dysfunction in the sample was fairly low and thus potentially undetectable by caregivers. In fact, perhaps reflecting caregivers' inability to recognize mild cognitive dysfunction in their care recipients, patient cognition was not a significant predictor of caregiver contributions to patient self-care. On the other hand, the lack of a significant relationship between patient cognitive dysfunction and caregiver contributions to patient HF self-care may be reflective of caregivers' desire to support or promote the autonomy and independence of the older adult, particularly in situations of adult-child caregivers where the dyad does not cohabitate.

HF-Specific QOL and Self-Care

There is mounting evidence that symptoms of HF are related to self-care. In this analysis, QOL related to physical symptoms of HF was not a determinant of patient self-care or caregiver contributions to patient self-care. This may be a function of a generally poor ability to recognize physical symptoms in this sample overall (Cocchieri et al., 2014). In contrast, QOL related to emotional symptoms of HF was a significant determinant of better self-care maintenance for patients and higher contributions to patient self-care maintenance from caregivers. It is possible that the emotional symptoms of HF are particularly evident and distressing for patients and caregivers, and thus serve as a motivator or reminder of the severity of disease and the need to attend to routine behaviors in an effort to prevent hospitalization. One might expect to see a similar relationship between greater HF specific emotional QOL and better self-care management that we did not observe in this sample; but, emotional symptoms may not be readily linked to HF by patients and caregivers, and thus may not trigger engagement in HF-specific self-care management behaviors. It is important to educate patients and families that engagement in effective self-care maintenance is necessary even in situations where physical symptoms are well-controlled but emotional symptoms are pervasive. It should be noted that this observed effect is not an argument to leave emotional symptoms of HF unaddressed, but rather suggests that emotional distress related to HF may be particularly burdensome for both patients and caregivers. It should be noted that a previous analysis of a subgroup of spousal dyads from this dataset (n=138) focusing on general physical and mental QOL as an outcome (Vellone et al., 2014) had somewhat contrasting findings. It is possible that relationships with QOL in patient-caregiver dyads change when the QOL construct examined is specific to symptoms of HF, rather than exclusively general QOL. It is also possible that the additional examination of nonspousal dyads and the adjustment for multiple confounders in the model contributes to different findings.

Relationship Type and Quality and Self-Care

To our knowledge, this is the first study to examine the association between *type* of relationship and HF self-care, and we observed that non-spousal relationship type was a significant determinant of higher caregiver contributions to patient self-care management. Nonspousal caregivers are more likely to live away from the patient and have competing demands (e.g., young children, jobs), and thus the actions that they take to help patients manage their symptoms may require travel and/or communication by phone. That is, symptom management does not occur in the course of normal interactions within a household, and it may be easier to recognize problem-based interactions as being contributions to the patient's HF self-care management. It is also possible that caregivers who do not live with the patient may feel pressure to be particularly diligent in helping patients manage symptoms, as they are not able to be physically present to respond to declines in patient health.

It also appears that better relationship quality is associated with better patient self-care and caregiver contributions to patient self-care, although it is the individual's own perception of the quality of the relationship that was important. Social support is considered a major determinant of expertise in self-care behaviors (Dickson et al., 2011), and the relationship that the patient has with their primary caregiver is arguably the most influential supportive relationship in the patient's life. If the patient perceives that the quality of that relationship is good, they may feel more supported in attending to their own health. This is a particularly promising finding, as the quality of the relationship between two known, accessible individuals in a caregiving dyad (e.g. a husband and wife) may be more feasibly targeted for intervention than a patient's overall social network. Furthermore, in the context of self-care management, better caregiver-reported relationship quality predicted higher contributions to patient self-care from the caregiver. Thus, interventions tailored to relationship quality may have an added advantage of improving self-care in the dyad overall, in addition to its known protective benefits for caregivers (Park & Schumacher, 2014).

Caregiver Strain and Perceived Social Support and Self-Care

Caregiver strain was not a significant determinant of either patient self-care or caregiver contributions to patient self-care. One possible explanation is that the caregivers in this sample reported very low levels of strain on average, and that the measure used in this study (the only validated measure of caregiver strain available in Italian) was designed for dementia caregiving and had not been previously utilized in the study of HF. Alternatively, in multivariate models that adjust for relationship quality, strain may not retain significance in the model due to relationship quality being a known protective factor against strain (Lyons, Stewart, Archbold, & Carter, 2009).

Social support is thought to be important in HF; but ours is the first report of perceived caregiver social support as a determinant of both patient and caregiver contributions to self-care. It is reasonable that patients may perceive their caregiver's social supports as an extension of their own existing support, and/or patients (particularly family members) may share many of the same supportive relationships as their caregivers. The influence of perceived social support on caregiver management may reflect caregivers' particular need to rely on family and/or friends when responding to patient symptoms, which can arise quickly and without warning. Additionally, caregivers with less external support may have less capacity to urgently step away from everyday commitments to assist a patient with an exacerbation of symptoms.

Strengths and Limitations

This study has several notable strengths. In particular, the sample of dyads utilized in this analysis is much larger than typical dyadic studies in HF, which allows for the implementation of more complex multivariate models that included patient, caregiver and dyad characteristics. Additionally, the statistical approach used allows for the prediction of self-care maintenance and management behaviors for both patient and caregiver while controlling for dyadic interdependence; this is not possible using most traditional approaches which assume independence of observations. The analysis of such a large sample using methods that are robust and appropriate for patient-caregiver dyads provides information that enhances understanding of these behaviors in a real-world, dyadic context.

This study also has some important limitations. First, this is an analysis of cross-sectional data, which precludes conclusions about directionality or cause of the identified relationships. Second, the sample is limited to a single European country, and thus there may be sociocultural influences unique to this population that may limit applicability in other countries. Third, this study enrolled caregivers who accompanied patients to appointments, and did not pursue caregivers who were not present at the time the patient was enrolled. It is difficult to surmise whether there might be differences in these two groups, although this may also be considered a strength, given that providers will likely only have opportunities to interact with caregivers if they are present with the patient at a clinical encounter. Finally, the wording of the CC-SCHFI does not allow for distinction between caregivers providing verbal recommendation to patients to do self-care behaviors and caregivers who are actively doing self-care for the patient. However these two aspects are consistent with the definition of caregiver contributions underpinning the

CC-SCHFI. It should also be noted that the Situation-Specific Theory of Heart Failure Self-Care was recently updated (Riegel, Dickson, & Faulkner, 2015). In addition to other revisions, this updated theory explicitly includes influences of “multiple players” (e.g. family or friends) on patient self-care. Our understanding of self-care in patient-caregiver dyads can be further expanded in future research using instruments based on this revised model.

Conclusions

In this analysis of 364 patient-caregiver dyads in HF, we identified multiple determinants of patient HF self-care maintenance and management behaviors and caregiver contributions to those behaviors. Although the traditional emphasis in studies of HF self-care is on individual patient models that include limited caregiver and relationship variables, this analysis showed that a combination of patient, caregiver, and dyadic characteristics predicted both patient self-care and caregiver contributions to patient self-care. Because the majority of HF patients have informal caregivers to assist them with disease management, utilizing robust analytic approaches to dyadic data in this context holds great promise for elucidating the complex nature of these relationships and their influence on HF self-care.

Chapter VII

Determinants of Quality of Life and Psychological Symptom Trajectories in Patient-Caregiver Dyads in Ventricular Assist Device Therapy

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This manuscript replaces a portion of the methods, results, and discussion sections of the traditional dissertation. Ms. Bidwell will be the primary author on this paper; Dr. Lee will be the senior author on this paper. Ms. Bidwell will conduct the study and perform the statistical analyses under the supervision of Drs. Lee and Lyons. This article will be submitted for publication to the Journal of Cardiac Failure (JCF). JCF is an indexed and peer-reviewed journal with an impact factor of 3.051. The readership for this journal is clinicians and researchers in the field of heart failure and related disciplines. This paper is ready for internal review prior to submission to JCF.

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Declaration of Conflicting Interests

None Declared

Abstract

Background: Providers often interface with mechanical circulatory support (MCS) patients and caregivers in tandem, however, little is known quantitatively about the impact of ventricular assist device (VAD) therapy on the patient and caregiver together as a dyad, particularly in terms of person-oriented outcomes. **Objective:** The purpose of this study is to use dyadic analytic methods to identify individual and dyad-level determinants of change over time in psychological symptoms and quality-of-life (QOL) in MCS patients and their caregivers. **Methods:** This was a prospective, longitudinal study of MCS patients and their primary informal caregivers. Data was collected pre-implantation and at 1, 3, and 6 months post-implantation. Multilevel modeling was used to quantify and predict change in patient and caregiver QOL (European QOL 5 Dimensions Visual Analogue Scale) and psychological symptoms (depression: Patient Health Questionnaire-8; anxiety: Brief Symptom Inventory, Anxiety Subscale) within a dyadic context. **Results:** We observed substantial improvement in patient QOL, depression, and anxiety over time, but significant worsening of caregiver QOL and substantial caregiver depression and anxiety that did not improve after implantation. A combination of patient, caregiver, and dyadic characteristics predicted both patient and caregiver outcomes, including patient illness severity, appraisal of controllability of illness, caregiver strain, caregiving relationship type, and social support for caregivers. **Conclusions:** Dyadic approaches to studying MCS improve our understanding of how patients and caregivers respond together to therapy, providing much-needed insights for clinical management and potential intervention targets.

Keywords: Heart Failure, Ventricular Assist Device, Caregivers, Quality of Life, Anxiety, Depression

Determinants of Quality of Life and Psychological Symptom Trajectories in Patient-Caregiver Dyads in Ventricular Assist Device Therapy

Introduction

Although the population of HF patients is rapidly increasing, the number of donor organs available for heart transplant – the current gold standard of treatment – remains relatively stable (Heidenreich et al., 2013; Peura et al., 2012). Thus, an increasing number of patients are receiving mechanical circulatory support (MCS) with a ventricular assist device (VAD) for advanced heart failure (HF) (Kirklin et al., 2015). Commensurate with improvements in MCS technology and the progressive increase of MCS implantation for permanent (destination) therapy, the use of MCS is likely to continue to expand with time (Feldman et al., 2013; Kirklin et al., 2015; Peura et al., 2012). Although the body of research used to guide clinical care in MCS has also expanded, most studies in MCS are designed at the individual (patient) level. However, VAD therapy is unique in that social support is an integral part of pre-implant evaluation and post-implant management, and most centers require an informal caregiver to help the patient manage their device (Feldman et al., 2013; Peura et al., 2012). Thus, although care teams often interface with the patient and caregiver in tandem (Kirkpatrick et al., 2015; Widmar, Dietrich, & Minnick, 2014), little is known quantitatively about the impact of the VAD caregiving relationship on the patient or the caregiver themselves, particularly in terms of person-oriented outcomes (Rich et al., 2016). As the patient-caregiver dyad has been shown to be transactional in nature (e.g. experiences of one member influence the other member and vice versa) in chronic illness in general and HF in particular (Berg & Upchurch, 2007; Bidwell et al., [in press]), dyadic research approaches are especially well-positioned to provide important insight into how characteristics of the patient, caregiver, and their relationship to one another can influence how patients and caregivers respond together to MCS therapy (K. S. Lyons & Sayer, 2005). Thus, the purpose of this study is to use dyadic analytic methods to identify individual and dyad-level determinants of change over time in person-oriented outcomes (psychological symptoms and QOL) in VAD patients and their caregivers.

Methods

Study Design and Population

This was a collaborative partnership between two federally sponsored studies in MCS: 1) a parent study of adult biobehavioral responses to MCS therapy over time and 2) an ancillary study of psychosocial outcomes in MCS caregivers. The methods and procedures for both studies have been published previously (Bidwell et al., [under review]; Lee et al., 2014). In short, adult (≥ 21 years of age) patients and caregivers were enrolled prior to patient MCS implantation. In order to be eligible for enrollment, patients had to be eligible to receive a VAD, could not have received a previous heart transplant, and must be free of concomitant conditions that would preclude their completion of study requirements (e.g. terminal illness, major psychiatric illness, major cognitive impairment). Caregivers of enrolled patients were eligible if they were the primary informal MCS caregiver, as agreed upon by the patient, the caregiver, and the advanced HF team. Study data were collected at four time points: immediately prior to implantation, and post-implantation at 1, 3, and 6 months. Both patients and caregivers completed surveys at each time point that included demographic data and all study instruments. Additionally, patient clinical characteristics were abstracted from the medical record.

Measurement

Demographic and clinical data. Patients and caregivers filled out surveys reporting their age, gender, race/ethnicity, marital status, education, and employment information. Caregivers answered questions about how they were related to the patient (e.g. spouse, parent, child, etc.) and the duration of their relationship. Caregivers also reported their own comorbidity history using the validated self-report version of the Charlson Comorbidity Index (Chaudhry et al., 2005), and caregiver comorbidity scores were derived using weights developed by Chaudry and colleagues (2005). The patient's medical record was accessed by trained cardiovascular research nurses for relevant clinical characteristics (etiology and duration of HF, NYHA Class, ejection fraction, inotropic therapy prior to implantation, VAD therapy type and device) and comorbid conditions. Comorbid conditions were entered into the Charlson Comorbidity Index (Charlson et al., 1987) to derive weighted comorbidity scores.

Patient and caregiver quality of life. Patient and caregiver QOL was measured using the European Quality of Life 5 Dimensions instrument (EQ5D; *EQ-5D Value Sets: Inventory, Comparative Review and User Guide*, 2007), specifically the Visual Analogue Scale (EQ-5D VAS). Participants rate their health-related QOL on a standard vertical visual analogue scale, from 0 ("worst imaginable health state") to 100 ("best imaginable health state"). The EQ5D is a well-validated and widely used measure, with extensive use in VAD and caregiving studies across multiple illness contexts. It is recommended in VAD patients for its utility in quantifying general health-related QOL, and for its reliability and validity (Grady et al., 2012; Maciver & Ross, 2012).

Patient and caregiver depression. Patient and caregiver depression was measured using the first 8 items of the Patient Health Questionnaire-9 (PHQ9; Kroenke et al., 2001). The PHQ8 omits the PHQ9 item on suicidal ideation, and has been recommended for use in clinical research that involves questionnaires that are self-administered (Kroenke & Spitzer, 2002). The PHQ8 has been evaluated comparatively with the PHQ9, with demonstrated near-identical sensitivity, specificity, and predictive validity as the 9-item version (Kroenke & Spitzer, 2002). The PHQ8 scores each of the 8 related DSM-IV criteria on a four-point Likert scale, ranging from 0 (not at all) to 3 (nearly every day). Respectively, scores of greater than 5, 10, 15, and 20 are indicative of mild, moderate, moderately severe, and severe depression (Kroenke et al., 2001). The reliabilities of the PHQ8 for patients and caregivers across all time points in this sample were acceptable (Cronbach's α range from 0.74 to 0.90).

Patient and caregiver anxiety. Patient and caregiver anxiety was measured using the 6-item anxiety subscale of the Brief Symptom Inventory (BSI; Derogatis & Melisaratos, 1983), which asks about frequency of feelings of anxiety on a five-point Likert scale from 0 (no) to 4 (extreme). Subscale scores are calculated by adding the ratings and dividing the total by the number of items in the subscale, with higher scores indicating greater anxiety. The reliabilities of the anxiety subscale of the BSI for patients and caregivers across all time points in this sample were acceptable (Cronbach's α range from 0.70 to 0.88) with the exception of patients' at 6 months, which was low (Cronbach's α = 0.62).

Patient physical symptoms of heart failure. Patient symptoms of HF (e.g. fatigue, weight gain, orthopnea, dyspnea) were measured using the multidimensional Heart Failure Somatic Perception Scale (HFSPS; Jurgens et al., 2006). The 18-item HFSPS asks patients how bothersome symptoms are on a six-point (0-5) Likert scale, with 0 indicating the patient did not have the symptom, and 1 to 5 indicating the symptom was not at all bothersome or extremely bothersome, respectively. Total scores on the HFSPS are summed to range from 0 to 90, with higher scores indicating worse perceived symptom severity. The HFSPS also has a 7-item "early and subtle" subscale that consists of items that ask about common and burdensome symptoms that may not be readily perceived by patients as symptoms of HF (e.g. fatigue, sleep disturbances, cough, digestive problems/lack of appetite). The reliabilities of the HFSPS total score and early and subtle subscale in this sample were acceptable (Cronbach's α 0.88 and 0.77, respectively).

Controllability of illness. The patient and family versions of the Control Attitudes Scale – Revised (CAS-R) was used to measure patient and caregiver appraisal of the controllability of the patients HF, respectively (Moser et al., 2009). The CAS-R is an 8-item instrument that asks patients and caregivers how well they are able to manage and cope with the patient's HF (e.g. "If I do all the right things, I can successfully/I can help my family member successfully manage my/his/her heart condition," "I have considerable ability to control/help my family member control my/his/her symptoms"). Participants respond on a 5-point Likert scale (from "strongly disagree" to "strongly agree"). Scores are summed to generate a total score with a range of 8-40, with higher scores indicating greater perceived control. The reliabilities of the CAS-R for both patients and caregivers in this sample was acceptable (Cronbach's α of 0.81 and 0.82, respectively).

Caregiver strain. The Multidimensional Caregiver Strain Index (MCSI) was used to measure caregiver strain (Stull, 1996). The MCSI is an 18-item instrument that asks how frequently caregivers feel strained in terms of a particular aspect of caregiving. Participants respond on a 5-point Likert scale (from "never" to "all of the time"). Scores are summed to generate a total score with a potential range of 18-80, with higher scores indicating more strain. The MCSI also includes a 3-item subscale that captures physical strain related to caregiving (e.g. "I feel physically strained because of caring for the patient," "I feel I have less energy now that I am caring for the patient."). Reliabilities for the MCSI total score and physical strain subscale in this sample were acceptable (Cronbach's α of 0.92 and 0.83, respectively).

Caregiver perceived social support. Perceived social support was measured using the 4 item family support subscale of the Multidimensional Scale of Perceived Social Support (MSPSS; Dahlem et al., 1991; Zimet et al., 1990). Each item (e.g. “My family really tries to help me,” “I get the emotional help and support I need from my family”) is rated on a 7-point Likert scale from 1 (very strongly agree) to 7 (very strongly disagree). Subscale scores range from 4-28, with higher scores indicating greater perceived social support from family. The reliability of the MSPSS in in this sample was acceptable (Cronbach’s $\alpha = 0.94$).

Analysis

The sample was described using means and standard deviations for continuous variables, and *n* and percentage for dichotomous/categorical variables. Changes in quality of life and affective symptoms within the context of the patient-caregiver dyad were described and predicted using three separate multilevel models: one for quality of life, one for depression, and one for anxiety, respectively. Specifically, we utilized the longitudinal dyadic multivariate multilevel modeling approach, which is unique from traditional multilevel modeling in that the model is structured to model within-dyad interdependence while adjusting for the correlation in repeated measures over time (K. S. Lyons & Sayer, 2005; Raudenbush, Brennan, & Barnett, 1995). This approach also allows for flexibility in the spacing and number of data collection points across time and across dyads and a robust means for handling missing data on one or both dyad members (full maximum likelihood estimation).

The specific structure for dyadic multilevel models in general (K. S. Lyons & Sayer, 2005; Sayer & Klute, 2005) and the dyadic multivariate longitudinal model in particular (K. S. Lyons & Sayer, 2005) have been well-described previously. In short, models are constructed in steps. First, a within-dyad (Level 1) model is constructed that estimates growth parameters for patient and caregiver outcomes as a function of repeated measures across time, providing estimates of the population averages and associated variance for each parameter. Second, a between-dyad (Level 2) model is constructed, adding predictors to explain variability in trajectories for each dyad member. From this process, we get the following information: 1) unadjusted estimates of growth parameters (intercept, slope) for patients and caregivers, an estimate of the interdependence between patient and caregiver parameters (τ correlations), 2) an estimate of unexplained variance in each growth parameter and whether the amount of unexplained variance is significant (χ^2); 3) adjusted estimates of growth parameters within a conditional model that includes predictors (with beta coefficients and robust standard errors for each predictor); 4) adjusted variance in each growth parameter based on the conditional model, which can be used to calculate variance explained by model predictors. Potential model covariates were selected using the dyadic Berg and Upchurch Developmental-Contextual Model (2007) as a guiding theoretical framework, although caregiving relationship type and VAD therapy type (e.g. Destination Therapy versus Bridge to Transplant or Bridge to Decision) were retained in all models as necessary controls. Given the collinearity between VAD therapy type and age, caregiver and/or patient age were precluded from entry into the models. Additional variables that mirrored concepts within the Berg and Upchurch framework and with significant individual or global effect were retained in the final models. Models were limited to a maximum of 5 variables each (given $n = 50$ dyads). Although the theoretical framework is longitudinal, in order to support early identification of at-risk patients and caregivers, only baseline (pre-implant) characteristics were included in the model selection process. Descriptive statistics were estimated using StataMPv14 (College Station, TX); dyadic multilevel models were estimated using HLM 7 (Skokie, IL).

Results

Patient and caregiver characteristics are presented in **Table 1**. On average, patients and caregivers were approximately 55 years of age, and were Caucasian/non-Hispanic. The majority of patients were male, while the majority of caregivers were female. Most caregivers were the patients' spouses, while the second most common type of caregiver was parent to the (adult child) patient. The remainder were friends/neighbors or other family members (e.g. siblings, adult children of the patient). Therapy type was largely Bridge to Transplant or Bridge to Decision, as opposed to Destination Therapy. Average patient and caregiver QOL, depression, and anxiety from pre-implant through 6 months post-implant are presented in **Table 2**.

Table 1: Characteristics of the Sample (*n* = 50 dyads)

	Patient mean±SD or *n*(%)	Caregiver mean±SD or *n*(%)
Age	54.6±13.9	54.7±12.5
Gender (female)	8(16.0%)	41(82.0%)
White/Non-Hispanic	42(84.0%)	46(92.0%)
Education (> high school)	27(54.0%)	33(66.0%)
Employed	5(10%)	28(56.0%)
Relationship Type		
Spousal		38(76.0%)
Parental		7(14.0%)
Relationship Duration[a]		26.6±15.2
Comorbidity Index Score[b]	1.02±1.3	2.5±1.5
Ischemic HF Etiology	19(38.0%)	
Duration of HF[a]	8.5±7.8	
Ejection Fraction (%)	20.8±3.5	
NYHA Class IV	20(40.0%)	
Inotropes Prior to Implant	26(52.0%)	
Bridge to Transplant/Decision[c]	36(72.0%)	
HF Symptoms, Total	39.4±17.5	
HF Symptoms, Early and Subtle	17.2±7.4	
Controllability of Illness	24.7±5.9	29.3±5.3
Caregiver Strain, Total		37.0±10.6
Caregiver Strain, Physical		5.9±2.3
Caregiver Perceived Social Support		23.3±5.2

Note: HF: heart failure; NYHA Class: New York Heart Association Functional Class; QOL: Quality of Life; mo: month; mos: months.

[a] years

[b] Charlson Comorbidity Index for patients, self-report version for caregivers

[c] Therapeutic strategy at time of implant; as opposed to Destination Therapy

Table 2: Patient and Caregiver Quality of Life, Depression, and Anxiety

	Patient mean±SD	Caregiver mean±SD
Quality of Life		
Pre-Implant	39.2±23.6	79.2±16.3
1 Month Post-Implant	53.9±22.2	74.9±18.8
3 Months Post-Implant	64.4±15.4	72.9±19.8
6 Months Post-Implant	64.8±16.5	71.2±19.7
Depression		
Pre-Implant	10.4±6.0	5.8±5.0
1 Month Post-Implant	6.5±5.0	5.2±4.6
3 Months Post-Implant	4.3±4.0	6.3±5.6
6 Months Post-Implant	3.8±3.4	5.2±4.2
Anxiety		
Pre-Implant	0.94±0.77	0.70±0.65
1 Month Post-Implant	0.52±0.66	0.59±0.69
3 Months Post-Implant	0.31±0.40	0.57±0.64
6 Months Post-Implant	0.29±0.37	0.59±0.57

Note: SD: standard deviation

Quality of life. Unadjusted growth parameters for patient and caregiver trajectories of change in QOL and the relationship between the two are presented in **Table 3.** Patient QOL significantly improved over time, while caregiver QOL significantly worsened. Patient and caregiver trajectories differed significantly from one another (χ^2=97.52, *p*<0.001). Baseline patient and caregiver QOL and change in patient and caregiver QOL were weakly correlated (τ=0.22 and τ=0.11, respectively), as were baseline patient QOL and caregiver change in QOL (τ=-0.18). Baseline caregiver QOL and patient change in QOL were moderately inversely correlated (τ=-0.46, e.g. worse caregiver QOL at baseline was associated with greater improvements in patient QOL over time). The final model predicting pre-implant QOL and change in QOL for patients and caregivers is presented in **Table 3**. Patients experienced better initial QOL but slower improvements in QOL post-VAD if they appraised the controllability of their HF at baseline as “high.” Caregivers experienced better initial QOL if they reported less caregiving strain at baseline, and if the patient had fewer HF symptoms prior to VAD.

Table 3: Dyadic Multilevel Model for Patient and Caregiver Quality of Life

Unadjusted Estimates (Level 1); β±SE, p-value		
	Patient Baseline QOL	**Caregiver Baseline QOL**
	45.90±2.7, *p*<0.001	77.42±2.40, *p*<0.001
	Patient Δ in QOL	**Caregiver Δ in QOL**
	3.86±0.59, *p*<0.001	-1.00±0.30, *p*=0<0.01
Final Model with Determinants (Level 2); β±SE, p-value		
	Patient Initial QOL	**Caregiver Initial QOL**
Non-spousal caregiver	3.97±6.50, *p*=0.55	1.78±4.69, *p*=0.71
Destination therapy	-8.27±5.41, *p*=0.13	-7.16±4.86, *p*=0.15
Caregiver strain (physical)	-0.21±1.22, *p*=0.86	**-2.69±0.98, *p*<0.01**
Patient controllability of HF	**12.19±2.41, *p*<0.001**	-1.03±2.24, *p*=0.65
Patient HF symptoms (E/S)	-0.09±0.33, *p*=0.77	**-0.91±0.28, *p*<0.01**
	Patient Δ in QOL	**Caregiver Δ in QOL**
Non-spousal caregiver	-1.37±1.32, *p*=0.31	0.85±0.90, *p*=0.35
Destination therapy	0.44±1.24, *p*=0.73	0.66±0.80, *p*=0.41
Caregiver strain (physical)	0.18±0.22, *p*=0.42	-0.13±0.15, *p*=0.39
Patient controllability of HF	**-2.39±0.70, *p*<0.01**	-0.58±0.45, *p*=0.20
Patient HF symptoms (E/S)	0.05±0.08, *p*=0.51	-0.05±0.05, *p*=0.26

Note: SE: standard error, QOL: quality of life, HF: heart failure, E/S: early and subtle subscale of the Heart Failure Somatic Perception Scale

Depression. Unadjusted growth parameters for patient and caregiver trajectories of change in depression and the relationship between the two are presented in **Table 4.** Patient depression improved significantly over time, while caregiver depression did not significantly change. Patient and caregiver trajectories differed significantly from one another (χ^2=24.74, *p*<0.001). Baseline patient and caregiver depression and change in patient and caregiver depression were weakly correlated (τ=0.17 and τ=-0.10, respectively), as were baseline caregiver depression and patient change in depression (τ=-0.16). Baseline patient depression and caregiver change in depression were moderately correlated (τ=0.44, e.g. more patient depression at baseline was associated with greater worsening of caregiver depression over time). The final model predicting pre-implant depression and change in depression for patients and caregivers is presented in **Table 4**. Patients experienced lower initial levels of depression when they had less overall burden of HF symptoms at baseline. Patients experienced faster improvements in depressive symptoms when they had spousal caregivers. Caregivers experienced lower initial levels of depression when they reported less baseline caregiving strain, and when the patient did not require inotropes prior to VAD. On average, nonspousal caregivers had greater worsening of depression over time as compared to spousal caregivers.

Table 4: Dyadic Multilevel Model for Patient and Caregiver Depression

Unadjusted Estimates (Level 1); β±SE, p-value		
	Patient Baseline Depression	**Caregiver Baseline Depression**
	8.93±0.72, *p*<0.001	5.88±0.67, *p*<0.001
	Patient Δ in Depression	**Caregiver Δ in Depression**
	-0.99±0.14, *p*<0.001	-0.05±0.11, *p*=0.65
Final Model with Determinants (Level 2); β±SE, p-value		
	Patient Baseline Depression	**Caregiver Baseline Depression**
Non-spousal caregiver	-0.51±1.57, *p*=0.75	-0.67±1.20, *p*=0.58
Destination therapy	1.22±1.46, *p*=0.41	0.77±1.02, *p*=0.45
Caregiver strain (tot)	0.07±0.07, *p*=0.35	**0.25±0.05, *p*<0.001**
Pre-implant inotropes	-0.73±1.35, *p*=0.59	**2.61±1.03, *p*=0.02**
Patient HF symptoms (tot)	**0.09±0.04, *p*=0.02**	-0.00±0.03, *p*=0.97
	Patient Δ in Depression	**Caregiver Δ in Depression**
Non-spousal caregiver	**0.70±0.28, *p*=0.02**	**0.35±0.18, *p*=0.04**
Destination therapy	-0.02±0.33, *p*=0.96	-0.18±0.25, *p*=0.45
Caregiver strain (tot)	-0.01±0.02, *p*=0.57	-0.01±0.01, *p*=0.35
Pre-implant inotropes	-0.19±0.29, *p*=0.50	-0.33±0.18, *p*=0.07
Patient HF symptoms (tot)	-0.01±0.01, *p*=0.41	0.01±0.00, *p*=0.07

Note: SE: standard error, QOL: quality of life, HF: heart failure, tot: total score

Anxiety. Unadjusted growth parameters for patient and caregiver trajectories of change in anxiety and the relationship between the two are presented in **Table 5.** Patient anxiety improved significantly over time, while caregiver anxiety did not significantly change. Patient and caregiver trajectories differed significantly from one another (χ^2=22.19, *p*<0.001). Baseline patient and caregiver depression and change in patient and caregiver depression were not correlated (τ=-0.03 and τ=0.03, respectively), as were baseline patient anxiety and caregiver change in anxiety and baseline caregiver anxiety and patient change in anxiety (τ=0.14 and τ=-0.02). The final model predicting pre-implant anxiety and change in anxiety for patients and caregivers is presented in **Table 5**. Patients experienced lower initial levels of anxiety but slower improvements in anxiety symptoms when caregivers appraised the controllability of HF as "high" at baseline. Caregivers experienced lower initial levels of anxiety if they were nonspousal caregivers, if the patient did not require inotropic therapy prior to VAD, if they perceived high pre-implant levels of support from family, and if they appraised the controllability of the patient's HF as "high" at baseline.

Table 5: Dyadic Multilevel Model for Patient and Caregiver Anxiety

Unadjusted Estimates (Level 1); β±SE, p-value		
	Patient Baseline Anxiety	**Caregiver Baseline Anxiety**
	0.76±0.09, *p*<0.001	0.65±0.09, *p*<0.001
	Patient Δ in Anxiety	**Caregiver Δ in Anxiety**
	-0.10±0.02, *p*<0.001	-0.02±0.02, *p*=0.33
Final Model with Determinants (Level 2); β±SE, p-value		
	Patient Initial Anxiety	**Caregiver Initial Anxiety**
Non-spousal caregiver	0.10±0.23, *p*=0.68	**-0.41±0.11, *p*<0.001**
Destination therapy	0.02±0.21, *p*=0.91	0.25±0.15, *p*=0.10
Caregiver social support	-0.02±0.02, *p*=0.33	**-0.04±0.01, *p*<0.001**
Caregiver controllability of HF	**-0.30±0.14, *p*=0.03**	**-0.26±0.11, *p*=0.02**
Pre-implant inotropes	-0.13±0.17, *p*=0.47	**0.30±0.12, *p*=0.02**
	Patient Δ in Anxiety	**Caregiver Δ in Anxiety**
Non-spousal caregiver	-0.00±0.04, *p*=0.97	0.01±0.03, *p*=0.59
Destination therapy	-0.03±0.04, *p*=0.42	-0.05±0.04, *p*=0.17
Caregiver social support	-0.00±0.00, *p*=0.73	0.00±0.00, *p*=0.21
Caregiver controllability of HF	**0.06±0.02, *p*=0.02**	0.04±0.03, *p*=0.18
Pre-implant inotropes	-0.00±0.03, *p*=0.90	-0.02±0.04, *p*=0.53

Note: SE: standard error, HF: heart failure, E/S: early and subtle subscale of the Heart Failure Somatic Perception Scale

Discussion

In this longitudinal study of MCS patients and caregivers, we examined change and determinants of change in patient and caregiver QOL, depression, and anxiety within a dyadic context. This discussion of findings will focus on the identified trajectories (characteristics and relationships between patients and caregivers) and significant factors within our dyadic models (patient illness severity, controllability of illness, caregiver strain, relationship type, and social support). We will conclude with a summary of study limitations and future opportunities for research.

Trajectories of Change in Patient and Caregiver Quality of Life, Depression, and Anxiety

Consistent with previous literature, we observed significant improvements in patient QOL, depression, and anxiety from pre-implant through 6 months post-implant (J. G. Allen et al., 2010; Brouwers, Denollet, et al., 2015; Brouwers et al., 2011; Grady et al., 2014). Conversely, we observed significant declines in caregiver QOL, and substantial depression and anxiety pre-implantation that did not change significantly post-implant. Although there is limited quantitative research on MCS caregivers, and no previous studies that include pre-implant caregiver measures, existing quantitative and qualitative work demonstrates the presence of emotional distress and potential compromised health in MCS caregivers (Akbarin & Aarts, 2013; Baker et al., 2010; Brouwers, Caliskan, et al., 2015; Brouwers, Denollet, et al., 2015; Kaan et al., 2010; Kirkpatrick et al., 2015). Interestingly, there were minimal correlations between patient and caregiver baseline levels of QOL, depression, and anxiety, and change; and patient and caregiver trajectories were significantly different. Although patient and caregiver outcomes are frequently interdependent (Berg & Upchurch, 2007; Rayens & Svavarsdottir, 2003), the patient and caregiver experience of QOL, depression, and anxiety in response to MCS may be unique.

This is not particularly surprising, given that the trajectory of MCS therapy involves the patient receiving a major clinical intervention that typically results in dramatic QOL improvements in over a relatively short period of time (typically 1 to 3 months) (Grady et al., 2014). Although the caregivers are not the recipients of a major clinical intervention, they appear to be at least somewhat affected by the patient's experience of the intervention and/or their caregiving role, as demonstrated by caregiver worsening QOL post-implantation.

Significant Determinants of Quality of Life, Depression, or Anxiety

Patient severity of illness. Severity of illness (pre-implant symptoms of HF or need for inotropes prior to MCS) was a significant determinant of both patient and caregiver outcomes pre-implantation. In particular, worse patient HF symptoms predicted lower caregiver QOL and higher patient depression, and inotrope requirement predicted higher caregiver depression and anxiety. These findings are important because they demonstrate that symptoms and illness severity impacts caregivers as well as patients – a phenomenon that has been previously demonstrated in HF patients, but has not been quantified in MCS (Bidwell et al., [in press]). Given that caregivers' QOL worsened on average, and depression and anxiety tended to remain at pre-implant levels, understanding what impacts caregivers' pre-implant levels of QOL and psychological symptoms is valuable. In our sample, if the patient was highly symptomatic and required inotropes before implantation, their caregiver was at risk for compromised QOL and a high burden of psychological symptoms – poor outcomes that are not likely to improve within 6 months post-implant.

Controllability of illness. Patient and caregiver appraisal of the controllability of HF was a significant predictor of both patient and caregiver outcomes at baseline, and patient change over time. Specifically, if the patient and caregiver perceived the patient's HF to be more controllable, this was associated with better patient pre-implant QOL and less anxiety, respectively, but less improvement over time. Additionally, if the patient perceived their HF to be more controllable, this was associated with less pre-implant anxiety for caregivers. Although there are multiple theoretical frameworks describing perceived control of illness, and substantial variability in the literature in definitions of perceived control, there is consensus that perceived control is an important determinant of well-being (Jacelon, 2007). In particular, perceived control has been shown to be a significant contributor to health and well-being of both patients and caregivers in the context of Parkinson's Disease (Wallhagen & Brod, 1997) and cancer (Vallerand, Saunders, & Anthony, 2007), as well as in HF (Hwang et al., 2011; Moser et al., 2009) and heart transplant (Conway et al., 2013). In the Berg and Upchurch model (2007), appraisal of illness – of which controllability is one important aspect – is a major component of dyadic outcomes. Our study is the first to show that perceived control – both of patients and their caregivers – is also an important determinant of patient and caregiver outcomes within MCS dyads. Interestingly, we also found that higher levels of control were associated with more moderate improvements over time in patients, which may be a function of baseline values of QOL and anxiety, as patients with the worst initial QOL and anxiety may have the most to gain from the device. Although perceived control may not be in itself a modifiable factor, in HF there has been some early work to identify factors that may improve perceived control, such as removing barriers to complying with daily HF maintenance behaviors and improving social support (Heo et al., 2015). Overall, perceived control of HF in MCS patients and caregivers – which can be quickly and reliably measured during the pre-implant evaluation process – may be one way of identifying patients and caregivers who are at risk for poor QOL and high anxiety. And although perceived control did not have a positive impact on outcomes for patients or caregivers over time in response to MCS, understanding determinants of pre-implant anxiety for caregivers has particular value, as anxiety and emotional distress – which may have long-term negative impacts on QOL – are a hallmark of the MCS caregiving experience (Kaan et al., 2010; Kirkpatrick et al., 2015), and caregiver anxiety remains at pre-implant levels long after implant.

Caregiver strain. Caregiver strain was a predictor of caregiver, but not patient, outcomes in this analysis. In particular, higher caregiver strain pre-implant predicted worse initial caregiver QOL and depression. Given that depressed caregivers tended to stay depressed, and caregiver QOL tended to decline from baseline, caregivers who are strained prior to implant are at risk for sustained depressive symptoms and additional losses of already-compromised QOL, in addition to being at risk for known sequelae of strain (increased morbidity and mortality) (Beach et al., 2000; Schulz & Beach, 1999). This is the first study to demonstrate that strain is associated with higher depression and worse QOL in MCS caregivers. Together, these analyses provides support for including measures of caregiver strain in future studies of MCS caregivers, particularly in studies where QOL and psychological symptoms are primary outcome variables.

Relationship type. Whether the caregiving relationship was spousal or nonspousal was a significant predictor of both patient and caregiver outcomes in this analysis. Interestingly, nonspousal caregivers had less pre-implant anxiety, but substantially worse depressive symptoms over time, and patients of nonspousal caregivers had less improvement in depressive symptoms in response to MCS. To our knowledge, relationship type has not been previously examined as a determinant of either patient or caregiver outcomes in MCS therapy, and as such, these findings are novel. However, there are some parallels to previous research in other caregiving contexts, which have found that nonspousal caregivers are at higher risk for long term distress as a result of caregiving (Young & Kahana, 1989), although there may be gender effects, with female nonspousal caregivers at highest risk (Kim et al., 2007). In our sample there may also be some contribution of caregiver age (nonspousal caregivers tended to be younger on average), but the inclusion of MCS therapy type in our models (bridge to transplant versus destination therapy) is highly correlated with age and thus somewhat controls for the influence of developmental stage in predicting patient and caregiver outcomes. It is possible that the risks to nonspousal dyads in our analysis is evidence of a relationship-level effect, in which patients and caregivers in a spousal relationship are more protected against depressive symptoms. Given that patients enjoy substantial improvements in depression in response to MCS, in spousal relationships, closer physical and emotional proximity may drive the cross-partner sharing of this therapeutic effect (Hatfield et al., 1994). Meaning, improvements in patient depressive symptoms as a result of VAD may impact the closer spousal caregiving group such that patient improvement is perceived by and reciprocally impacts the caregiver, providing dual-benefit for patient and caregiver together. It is also interesting that spouses, rather than nonspouses, have greater pre-implant anxiety, which may be related to the uncertainty and implications of potentially losing one’s close partner to life-threatening chronic illness. Although more research is needed to elucidate the underpinnings of these important effects, our study demonstrates that nonspousal dyads in particular are at substantial risk for depression post-MCS, and spousal dyads are at risk for sustained anxiety. Both groups may need additional, but different, psychological support.

Caregivers’ social support from family. Caregiver perceived social support from other family members significantly predicted lower baseline caregiver anxiety. This is novel, but not surprising, given that caregiver perceived social support is a known correlate of caregiver distress in HF (Hwang et al., 2011). Social support (in the form of a mandatory caregiver) has been a longstanding aspect of eligibility criteria for MCS and transplant in advanced HF

(Feldman et al., 2013; Peura et al., 2012), but assisting these mandatory caregivers to leverage their own social support networks to assist them in caregiving is not part of current guidelines. This analysis provides evidence that additional family support matters in reducing anxiety for caregivers prior to implant, which is important given that anxiety does not significantly change for caregivers over time. Furthermore, caregivers may not independently pursue additional avenues for support (e.g. asking other family members for physical or emotional support) without intervention – a phenomenon observed in dementia dyads (Whitlatch, Judge, Zarit, & Femia, 2006). Thus, this analysis demonstrates that there may be value in helping caregivers identify additional sources of support during the pre-implant evaluation and education period, but more research is needed.

Study Limitations and Future Research Opportunities

This study has limitations. First, although this is the largest known longitudinal sample of patient caregiver dyads in continuous flow MCS, the limited number of dyads prevented us from including all potential theoretical and known determinants of patient and caregiver QOL, depression, and anxiety. As such, additional research is needed to develop more comprehensive models. It is also possible, given the relatively small *n*, that there are significant individual and dyadic effects that we were unable to detect due to insufficient power. Second, there are demographic and regional biases in this analysis, given our single-site sample of relatively homogeneous dyads (mostly female caregivers and male patients, mostly spouses, mostly Caucasian/non-Hispanic). Thus, there is an opportunity to advance the science by collecting data from larger samples of patients and caregivers, from multiple sites, with more diverse demographics. This is critical for developing our understanding of patient-caregiver dynamics in MCS, and particularly for examining the complex interplay that likely exists between gender, age, culture, relationship type, and MCS therapy type. Understanding this interplay is a particularly important step in understanding and identifying which dyads will be at greatest risk for poor outcomes with MCS therapy. Larger samples would also provide the power necessary to more fully examine non-linear change within a dyadic framework – our analysis was limited to the examination of linear change over time.

Conclusions

This analysis examined trajectories of change for patients and caregivers together within a dyadic framework, providing insight into how dyads' QOL, depression, and anxiety change over time in response to MCS. This is the first study in MCS to examine changes in patients and caregivers together from pre- to post-implant, within the context of the caregiving dyad. We observed substantial improvement in patient QOL, depression, and anxiety over time, but significant worsening of caregiver QOL and substantial caregiver depression and anxiety that did not improve after implantation. Importantly, a combination of patient, caregiver, and dyadic characteristics predicted both patient and caregiver outcomes, including patient illness severity, appraisal of controllability of illness, caregiver strain, caregiving relationship type, and additional social support for caregivers. Overall, this first dyadic study of MCS patients and caregivers supports the theory that the MCS patient-caregiver dyad is transactional and provides a foundation for future dyadic work in this high-risk population.

Chapter 8:

Cumulative Discussion and Implications

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Chapter 8: Cumulative Discussion and Implications

The overall purpose of this program of research is to characterize the influence of the patient-caregiver dyadic relationship on clinical and person-oriented outcomes in HF dyads in general and VAD dyads in particular. We utilized a variety of data sources and methods in a stepwise manner to collectively form a single, cohesive body of work that: 1) describes how individual patient and caregiver outcomes are related, 2) predicts individual outcomes using interpersonal (cross-partner and dyadic) factors, and 3) predicts outcomes for both patients and caregivers within the context of the dyadic relationship. This final section of the dissertation will present the primary research findings from each of the six manuscripts within the context of the existing literature; summarize the overall strengths and limitations of the work; and discuss how the research as a whole advances the science in terms of implications for theory, clinical practice, and future research.

Discussion

In order to address the overall goal of this program of research, six specific aims and associated manuscripts were proposed. **Table 1** presents the major findings from each study by specific aim. Following the table, major findings will be discussed by concept. In particular, this discussion will focus on findings pertaining to HF symptoms, affective symptoms and mental health, controllability of illness, HF self-care, social support, caregiver strain, caregiving relationship type, and relationship quality.

Table 1: Major Findings by Specific Aim

		Aim	**Findings**
HEART FAILURE	DESCRIBE interplay between patients and caregivers	Aim 1: Summarize known relationships between person-oriented and clinical outcomes within patient-caregiver dyads in heart failure.	• Higher caregiver strain is significantly associated with worse patient symptoms of HF • Higher caregiver strain is significantly associated with worse patient quality of life • We found no significant relationship between caregiver psychological distress and patient symptoms or quality of life; however, substantial heterogeneity was present in both analyses • Worse caregiver strain and psychological distress are likely associated with worse patient clinical event-risk, but there is substantial variability in the way clinical events are quantified in the existing literature
VAD THERAPY		Aim 2: Describe changes in person-oriented outcomes for HF patients and caregivers in response to VAD therapy, and quantify relationships between patient and caregiver outcomes.	• VAD patients had large, statistically significant improvements in quality of life from pre- to 3 months post-implant**,** while caregiver quality of life significantly worsened • VAD patients had large, statistically significant improvements in depression and anxiety from pre- to 3 months post-implant, while caregivers had substantial depression and anxiety pre-implant that did not improve over time • Worse caregiver anxiety pre-implant correlated with less improvement in patient anxiety in response to VAD, and patient and caregiver depression and anxiety became increasingly correlated over time
HEART FAILURE	PREDICT individual outcomes using interpersonal factors	Aim 3: In patient-caregiver dyads with heart failure, quantify the impact of individual and interpersonal characteristics on patient clinical event-risk.	• Higher patient New York Heart Association functional class at baseline was associated with higher patient clinical event-risk during follow-up (1 year) • Higher caregiver strain and better caregiver mental health status at baseline were associated with lower patient clinical event-risk • Greater caregiver contributions to HF self-care maintenance and fewer caregiver contributions to HF self-care management at baseline were associated with lower patient clinical event-risk

VAD THERAPY		Aim 4: In VAD patient-caregiver dyads, identify individual- and dyad-level determinants of change in patient HF-specific quality of life and caregiver strain.	• Patients experienced substantial quality of life improvement from immediately pre-implant through 1 month post-implant (initial), followed by gradual improvement and stabilization between 1 and 6 months post-implant (long-term) • Caregivers experienced significant increases in strain from immediately pre-implant through 1 month post-implant (initial), followed by gradual reduction back to baseline levels between 1 and 6 months post-implant (long term) • Worse patient HF symptoms pre-implant predicted significantly worse patient pre-implant quality of life, greater initial patient quality of life improvements, and greater initial worsening of caregiver strain • Better relationship quality pre-implant predicted significantly greater initial patient quality of life improvements and less caregiver strain prior to implant • Non-spousal caregiving relationship predicted significant long-term worsening of patient quality of life, and less caregiver strain prior to implant
HEART FAILURE	PREDICT patient-caregiver outcomes within a dyadic context	Aim 5: In patients and caregivers with heart failure, identify individual- and dyad-level determinants of HF self-care within a dyadic context.	• Many significant determinants of patient and caregiver contributions to HF self-care were identified. Importantly, many of the identified effects were partner (e.g. patient characteristics predicting caregiver contributions) or relationship (relationship characteristics predicting patient or caregiver contributions) effects. In particular: o Patient duration of HF, HF-specific and general physical quality of life, comorbidities, and hospitalizations were all significantly associated with caregiver contributions to self-care o Caregiver gender, social support, and general physical quality of life were all significantly associated with patient contributions to self-care o Relationship quality was associated with both patient and caregiver contributions to self-care, and relationship type was associated with caregiver contributions to self-care

VAD THERAPY		Aim 6: Identify individual and dyad-level determinants of change over time in psychological symptoms and quality-of-life within a dyadic context	• Patient QOL significantly improved from pre-implant through 6 months post-implant, while caregiver QOL significantly worsened • Patient depression and anxiety improved significantly from pre-implant through 6 months post-implant, while caregiver depression and anxiety were substantial at baseline and did not significantly change • Patient severity of illness was a significant determinant of worse pre-implant quality of life and greater psychological symptoms in patients and caregivers • Patient and caregiver appraisal of controllability of illness was a significant determinant of less pre-implant anxiety for patients and caregivers and better pre-implant patient quality of life, but less improvement over time for patients • Nonspousal relationship was a significant determinant of better (less) caregiver anxiety pre-implant, but less improvement in patient depression and greater worsening of caregiver depression over time

Symptoms and Severity of Heart Failure

Across multiple aims, we found that HF symptoms and/or severity of illness were significant determinants of both patient and caregiver outcomes. For HF patients, we found that HF severity (NYHA functional class), predicted greater hazard of clinical events over 1 year; a finding that is consistent with the existing literature (Rahimi et al., 2014). In the context of HF with VAD therapy, we found that worse HF symptoms prior to implant correlated with worse patient pre-implant HF-specific QOL and depression, but also greater QOL improvements over the first month of therapy. In caregivers of HF patients, we found that worse patient symptoms were associated with higher caregiver strain across existing studies that examined this relationship, a phenomenon also observed in other chronic illness contexts (Burke, Elamin, Galvin, Hardiman, & Pender, 2015; Ornstein & Gaugler, 2012).

Similarly, in caregivers of VAD patients, worse patient symptoms pre-implant predicted greater worsening of caregiver strain in the first month after implantation. Additionally, VAD caregivers of patients with worse pre-implant symptoms had greater worsening of QOL across six months of post-implant caregiving, and that worse patient HF severity pre-implant (as measured by inotrope requirement) was associated with worse caregiver depression and anxiety. Our findings in relation to VAD patients in particular are novel, as quantitative research of this kind in VAD caregivers has not previously been conducted. However, given that severity of patient illness is consistently associated with caregiver strain in HF caregivers in general, it is not surprising that severity of HF is also associated with worse caregiver outcomes in VAD. Overall, our findings demonstrate that HF symptoms and severity of illness are not an experience that is limited to the patient. Rather, symptoms and severity appear to adversely impact both patients and their caregivers together across the spectrum of illness: from stable HF to advanced HF with VAD therapy.

Affective Symptoms and Mental Health Status

We examined affective symptoms (i.e. depression and anxiety) and mental health status both as person-oriented outcomes, but also as predictors across the several analyses we conducted. This is in alignment with our chosen theoretical framework, the Developmental-Contextual Model (Berg & Upchurch, 2007), where patient, caregiver, and dyadic adjustment (outcomes) are not a definitive endpoint, but rather go on to further impact appraisal and/or coping in a cycle that continues across the experience of chronic illness over the lifespan (**Figure 1**). In this section, however, we will limit our discussion to analyses where affective symptoms or mental health status were examined as predictors of other critical outcomes, or where affective symptoms between patients and caregivers were examined in relationship to one another.

Overall, the main finding across this body of work was that affective symptoms and mental health status are transactional in patient-caregiver dyads, both in the context of HF in general and in VAD in particular. For example, in HF dyads, we found that better caregiver mental health status was a predictor of lower hazard of clinical events (all-cause mortality or emergency room visit/hospitalization for HF). This was consistent with what we observed in our meta-analysis of caregiver well-being and patient outcomes in HF (Bidwell, Lyons, & Lee, [in press]), although we were unable to estimate a summary effect due to heterogeneity in event-risk measurement. In contrast, in that same article, we observed that HF caregiver psychological distress (measures of depression, depression and anxiety combined, or mental health status) was not significantly associated with patient outcomes (QOL and HF severity), although both of those analyses were limited by significant heterogeneity. It is possible, therefore, that given adequate numbers of studies to further examine these important relationships (e.g. with meta-regression techniques) that a significant effect may indeed exist, as is the case in other chronic illness contexts (Carter, Stewart, Lyons, & Archbold, 2008; Ornstein & Gaugler, 2012).

In VAD patient-caregiver dyads, we did not examine affective symptoms or mental health status as predictors of patient or caregiver outcomes, but we did examine trajectories of change in depression and anxiety for patients and caregivers in response to VAD therapy, and correlations between trajectories and at each individual time point. In general, we found that caregiver depression and anxiety were substantial prior to patient VAD implantation, and did not improve over time, while patients' depression and anxiety improved dramatically. Not surprisingly, these significantly different patient and caregiver trajectories in response to VAD were not well correlated over time, although in our preliminary analysis we found moderate correlations between patient and caregiver anxiety at 3 months post-VAD, and weak-to-moderate correlations between patient and caregiver depression at 1 and 3 months post-VAD. We also found correlations between patients' initial levels of depression and caregivers' change in depression, and between caregivers' initial levels of anxiety and patients' change in anxiety. Although our findings in VAD dyads are novel, one previous study (without pre-implant data) also found correlations between patients and caregivers (Brouwers et al., 2015). Together, these findings demonstrate the transactional nature of the caregiving dyad in terms of mental health and affective symptoms across the spectrum of HF and advanced therapies, and provide an important foundation for future dyadic research.

Controllability of Illness

Controllability of illness is an important aspect of chronic illness management (Jacelon, 2007), and is nested within the "appraisal" concept of the Developmental-Contextual Model

(Berg & Upchurch, 2007). In dyads, how patients and caregivers appraise the controllability of illness (e.g. “Can I do something about my/my family member’s HF?”) theoretically influences how dyads cope and eventually adjust to living with a chronic disease. In HF, controllability is often measured with a cardiovascular disease-specific instrument, the Control Attitudes Scale – Revised (CAS-R) (Moser et al., 2009), and has been associated with better health and well-being in HF and heart transplant patients and caregivers alike (Conway et al., 2013; Hwang, Fleischmann, Howie-Esquivel, Stotts, & Dracup, 2011; Moser et al., 2009). Although we did not examine perceived control in our analyses of HF patients and caregivers (it was not measured in the samples available to us for secondary analysis), in accordance with the Developmental-Contextual Model, we did include the CAS-R in our study of VAD dyads. This is the first time perceived control has been measured in the VAD population, and we found perceived control to be a significant determinant of both patient and caregiver outcomes. In particular, if the patient and caregiver felt that they had more control over the patient’s HF, this was associated with better QOL and less anxiety for patients immediately before they received the VAD. Similarly, for caregivers, less pre-implant anxiety was observed when caregivers felt that they had better control of the patient’s HF. In sum, we observed that perceived control was associated with similar protective benefits that have been observed in other chronic illness contexts (Vallerand, Saunders, & Anthony, 2007; Wallhagen & Brod, 1997), and also impacted patients and caregivers in a transactional way (e.g. caregiver perceptions influencing patient outcomes). Thus, taken together with the existing evidence for perceived control in the HF literature, our findings suggest that perceived control plays an important role in patient and caregiver outcomes together across the spectrum of HF and VAD therapy, and may be a promising intervention target for future dyadic research.

Contributions to Heart Failure Self-Care Behaviors

HF self-care behaviors are critical for maintaining clinical stability (Lee, Moser, Lennie, & Riegel, 2011; Riegel, Lee, & Dickson, 2011; Yancy et al., 2013), and although they are typically studied as individual patient behaviors, there is mounting evidence that caregivers contribute significantly to patient self-care, and that it may be informative to study self-care as a dyadic process (Buck et al., 2015; Lee et al., 2015). Although we did not examine self-care within the context of VAD therapy, this program of research does provide novel insights into interpersonal and dyadic self-care in the general HF context. From an interpersonal perspective, we examined caregiver determinants of patient clinical event-risk, and demonstrated for the first time that caregiver contributions to HF self-care predict clinical events over one year. In particular, if the caregiver was more engaged in helping the patient with day-to-day self-care maintenance behaviors (e.g. helping patients with medication adherence, compliance with dietary and physical activity recommendations, etc.), this predicted lower patient event-risk over one year. Conversely, if the caregiver reported high engagement in helping the patient with self-care management behaviors (responding to HF symptoms when they occur), this predicted higher patient event-risk over one year. In summary, this analysis showed that caregiver engagement in daily HF adherence behaviors was protective for patients, but also that high caregiver engagement in symptom response behaviors was a red flag for higher hazard of event-risk, potentially because expertise in HF symptom response may, in part, be a function of helping patients manage HF that is increasingly uncontrolled. In both cases, this analysis provides foundational evidence for studying caregiver engagement in self-care, and potentially including caregivers in clinical visits or future dyadic self-care interventions.

Because we demonstrated that caregiver self-care contributions impacted a major clinical endpoint in HF (event-risk), and thus, that self-care is transactional and potentially dyadic in nature, we also examined self-care contributions as an outcome variable within the context of the patient-caregiver dyad. In particular, we predicted both patient and caregiver self-care maintenance and self-care management behaviors within two dyadic multilevel models. Using this approach, we identified both individual and dyadic effects predicting patient and caregiver contributions to these critical HF self-care behaviors. Importantly, many of the determinants we identified were partner effects (e.g. patient characteristics predicting caregiver self-care and vice versa). The full list of partner effects are summarized in **Table 1**, but the overarching scientific contribution of this analysis is that HF self-care maintenance and management are transactional, and that dyadic models are useful in helping us better understand how patients and caregivers manage illness together in a real-world, dyadic context.

Social Support

Social support for patients is an explicit part of clinical guidelines for both HF management and VAD eligibility (Feldman et al., 2013; Peura et al., 2012; Yancy et al., 2013), but few studies examine the relationships patients have with the family members and/or friends that provide that support. In particular, caregiving and dyadic research in HF and VAD is particularly limited as compared with other chronic illness contexts, hence the need for this program of research. In order to better identify at-risk caregiver-patient dyads in HF and VAD therapy, the focus of these dissertation manuscripts was on the caregiving relationship specifically, rather than the broader concept of social support. However, we did include caregiver-perceived social support (“who cares for the caregiver”) as an independent variable in our dyadic analyses in HF and VAD, and found it to be a significant determinant of both patient and caregiver outcomes. In particular, we found that more social support for the caregiver from family members was a significant determinant of less pre-implant caregiver anxiety, which is important, as we found pre-implant anxiety levels for caregivers are maintained, on average, post-implant. In HF patients, we examined caregiver-perceived social support as a determinant of patient and caregiver self-care, and found that better caregiver social support predicted better patient engagement in self-care maintenance, and better caregiver engagement in self-care management. These findings in both HF and VAD dyads are novel, as social support has not previously been examined in a dyadic context in these populations, although social support has been shown to be protective for both HF patients and caregivers in individual models (Heo, Moser, Chung, & Lennie, 2012; Hwang et al., 2011). Thus, taken together with the existing literature, these analyses demonstrate that leveraging social support for caregivers may be one avenue for improving both patient and caregiver outcomes.

Caregiver Strain

Caregiver strain (sometimes termed “burden”) is an important concept in caregiving research because of its known sequelae of increased morbidity and mortality for caregivers (Beach, Schulz, Yee, & Jackson, 2000; Schulz & Beach, 1999). As such, we included caregiving strain in several of our analyses of HF and VAD caregiving dyads. In addition to the finding that worse caregiver strain is associated with worse symptoms of HF (discussed in previous section), we found in our meta-analyses that worse caregiver strain was associated with worse patient QOL. Furthermore, we found that worse caregiver strain was consistently associated with worse patient clinical-event risk across existing studies in HF caregiving (Hooley, Butler, & Howlett, 2005; Schwarz & Elman, 2003), although we were not able to derive a summary effect due to variation in clinical event-risk measures. In our own secondary analysis, we found a contrasting effect, with worse caregiver strain predicting lower hazard of patient clinical events (all-cause mortality, emergency room visit/hospitalization for HF). However, our sample of HF patients was notably different from previous research, both culturally (Italian sample versus largely North American) and clinically (no previous hospitalizations on average versus hospitalized at enrollment or ≥1 previous hospitalization on average), which may explain our different findings. Thus, in HF dyads there does appear to be consistent relationships between caregiver strain and patient outcomes, with worse strain generally associated with worse patient outcomes. The notable exception, however, being patient clinical-event risk, for which there may be a “tipping point” at which the direction of the relationship between caregiver strain and event-risk transitions from negative to positive.

Given the relationships we observed in HF caregiving dyads, we felt it was important to examine strain within the context of VAD caregiving, which, by definition, involves caregiving for patients with greater severity of illness and a typical history of multiple hospitalizations and/or emergency room visits within the year prior to implant. We therefore included a multidimensional measure of strain in our study of VAD caregivers, and our findings represent the first quantification of strain in this at-risk caregiving population. On average, we found that strain for VAD caregivers significantly worsened in the first month post-implant, followed by a gradual return to pre-implant levels (numerically higher than other populations utilizing this measure) over the remaining five months of follow up. These findings of both worsening and persistent strain over time are in alignment with the qualitative VAD caregiving literature (Kaan, Young, Cockell, & Mackay, 2010; Kirkpatrick et al., 2015), but somewhat contrasting with similar chronic illness contexts (e.g. bone marrow transplant, heart transplant) in which strain is at its worst prior to intervention, and then consistently improves over time (Applebaum et al., 2016; Canning, Dew, & Davidson, 1996). We also observed both caregiver- and patient-level factors that were associated with caregiver strain in our sample of VAD dyads (discussed in other sections). Therefore, across both HF and VAD caregiving dyads, this program of research demonstrates that HF and VAD caregivers are at risk for strain (and therefore increased morbidity and mortality), and that caregiver strain is transactional with patient outcomes. More research is needed both to examine caregiver strain within the context of the caregiving dyad, and to identify potential interventions to reduce strain and subsequently improve both caregiver and patient outcomes.

Relationship Type

The type of relationship between the patient and the caregiver (e.g. spousal, child-parent, sibling, etc.) is rarely examined in the few existing studies of HF caregivers. To our knowledge, our studies are the first to examine relationship type as a predictor of patient or caregiver outcomes in HF or VAD, and as such, our findings are novel and important. In HF, we found that nonspousal caregivers perceived significantly greater engagement in helping the patient with HF self-care management (responding to HF symptoms when they occur). It is possible that nonspousal caregivers – who are more likely to live apart from the patient – are more aware of actions they take to assist the patient in managing symptoms, as they do not take place within the context of their own household and likely require travel or phone communication. Additionally or alternatively, nonspousal caregivers may feel a need for greater proactivity in symptom management, since they are unlikely to be constantly present to natively observe and respond to symptoms. Either way, this study is the first to demonstrate a difference in self-care engagement by relationship type in HF.

In VAD therapy, we found that relationship type was a significant determinant of multiple outcomes, including patient QOL, caregiver strain, caregiver anxiety, and caregiver and patient depression. In particular, in our individual models, patients with nonspousal caregivers experienced worsening, rather than improvement, in HF-specific QOL from 1 through 5 months post-implant, while nonspousal caregivers experienced less pre-implant strain. Within our dyadic models examining anxiety and depression for patients and caregivers, we found that nonspousal caregivers also had less pre-implant anxiety; however, for both patients and caregivers in nonspousal relationships, there seemed to be concerning implications for depressive symptoms. Specifically, patients with nonspousal caregivers had less improvement in depression in response to VAD, while caregivers had worsening, rather than stable, depressive symptoms over time. It is possible that nonspousal dyads, while somewhat protected from initial adverse outcomes related to VAD, may also be prevented from enjoying the potential full benefits of VAD therapy over time. This may be a function of proximity, given that they may live apart from the patient after the patient becomes more independent (Hatfield, Cacioppo, & Rapson, 1994). It is also possible that there may be some lifespan/developmental factors involved, as nonspousal caregivers in our sample were mostly parents of adult child patients. Either way, our findings across the spectrum of HF and VAD therapy demonstrate that relationship type is a determinant of patient and caregiver outcomes, and should be examined further in future research.

Relationship Quality

The quality of the relationship between patient and caregiver is another factor that is rarely examined in HF caregiving research, despite its known protective benefits in the broader chronic illness caregiving context (Park & Schumacher, 2014). We examined relationship quality in our analyses of both HF and VAD dyads, and found it to be a significant determinant of patient and caregiver outcomes in both contexts. In particular, we found that in HF, patient and caregiver perceived relationship quality was a predictor of better patient and caregiver engagement in HF self-care behaviors, respectively, and in VAD dyads, we found that caregiver perceived relationship quality was a determinant of less caregiver strain pre-implant and greater patient improvement in HF-specific QOL over the first month post-implant. Our VAD findings are particularly notable, as they are the first to show the importance of relationship quality in VAD dyads. Overall, our findings relating to relationship quality across the spectrum of HF are promising, as they demonstrate that good relationship quality has benefits for both patient and caregiver (in addition to known protective benefits for the dyad as a whole), and that targeting relationship quality may be an effective means of improving patient and caregiver outcomes together. Future observational and interventional research is needed to examine relationship quality in HF and VAD, and particularly to determine what aspects of relationship quality may be most beneficial in these contexts.

Limitations and Strengths

Limitations

This research has limitations. First, our sample size for the analyses of all aims (with the exception of Aim 5) were somewhat limited in terms of modeling (e.g. number of covariates) and power to detect significant effects. In our meta-analyses (Aim 1), the small sample size was a function of the limited number of studies in HF that examine interrelationship of patients and caregivers, which is an important limitation of the current overall state of the science in HF. In our prospective study of VAD patients and caregivers (Aims 2, 4, and 6), although the sample size was relatively small, it is also currently the largest known quantitative sample of patient-caregiver dyads in VAD. This is also an important limitation of the current state of the science in

VAD, which, despite its dependence on informal caregivers for success of therapy, does not have an established body of caregiving or dyadic literature. Furthermore, despite this sample size limitation, we were still able to identify significant interpersonal effects across studies. Second, relative homogeneity of samples across our analyses limits generalizability, and represents an important avenue for future research. In particular, our meta-analyses and VAD studies all largely involved female caregivers of male patients, mostly white, and mostly spousal. It is difficult to examine complex gender, cultural, and relationship-type effects with limited sample diversity. Additionally, our analyses of patient clinical event-risk and dyadic self-care involved Italian patients and caregivers, whose experiences may not be generalizable outside of that geographic region. Replication is needed in other populations to better understand the relationships we identified. Third, our VAD and Italian analyses had some interesting limitations related to caregiver enrollment. In particular, our Italian colleagues enrolled patients at regular HF clinic visits, and only enrolled caregivers if they were at the visit with the patient. Thus, our findings in those analyses can only be generalized to dyads in which the caregiver and patient attend clinic visits together. In our VAD study, out of necessity, we had to exclude a small number of patients who did not have a primary caregiver at time of implant. In both cases, from a clinical perspective, this may actually be useful, as providers will not be able to evaluate patients and caregivers together, either in the context of regular clinical care, or in the context of pre-VAD evaluation, if the caregiver is not physically present. Fourth, some of our analyses or aspects of our analyses were cross-sectional (meta-analyses, dyadic self-care, pre-implant characteristics predicting pre-implant outcomes in Aims 4 and 6), which, importantly, precludes any conclusions about directionality or cause of the identified relationships.

Strengths

This dissertation research also has several notable strengths. First, our meta-analysis of relationships between patients and caregivers in HF, which provided an initial foundation of evidence for examining HF patients and caregivers together, is a particularly rigorous analytic approach for synthesizing effects observed across multiple studies. Second, our prospective study of VAD patients and caregivers is the first known study to examine patients and caregivers together from pre- to post-VAD implantation, and the largest quantitative sample to date of patient-caregiver dyads. It is also the first study to quantify and predict caregiver strain over time, as well as examine VAD patients and caregivers within the real-world dyadic context in which they manage the device. Third, our interpersonal examination of patient clinical event-risk is the first to demonstrate that caregiver contributions to self-care behaviors influence event-risk, and overall is one of the few studies to demonstrate that caregivers have a quantifiable impact on one of the most important outcomes in HF clinical management. And finally, our dyadic analysis of patient and caregiver self-care behaviors was one of the few quantitative studies to examine self-care within a dyadic context, and our identification of multiple partner- and relationship-effects provides strong support for continuing examination of self-care as a dyadic process. In conclusion, this program of research was both robust and limited, providing findings to guide clinical care in HF and VAD caregiving, as well as pointing to important next steps in advancing the science.

Implications

Implications for Theory

In Chapter 1, the theoretical framework that underpins this program of research – the Developmental-Contextual Model of Couples Coping with Chronic Illness over the Adult Lifespan, presented in **Figure 1** – was described in detail (Berg & Upchurch, 2007). In short, the

Developmental-Contextual Model was derived from the broader caregiving, dyadic and family literature in chronic illness, and includes three primary concepts: appraisal, coping and adjustment. Appraisal refers to how patients and caregivers appraise the illness in terms of illness representation (controllable, consequences), ownership, and specific stressors. Coping refers to the varied patterns of couple interactions as they deal with stressors (uninvolvement, support, collaboration, control, protective buffering). Adjustment refers to how patients and caregivers adjust to illness (psychosocial, relational, or physical health outcomes). Additionally, interactions among these three primary concepts occur within a larger sociocultural context, dyad-specific proximal context, and across time. A central aspect of the model is a “transactional” phenomenon, in which patients and caregivers influence each other within context of the dyad and also influence their own experiences with other key concepts in the model as a continuous, non-linear process. The rationale for utilizing the Developmental-Contextual Model in this program of research was the dyadic nature of the model, which provides a strong theoretical framework for understanding and improving the health and well-being of patients and caregivers together.

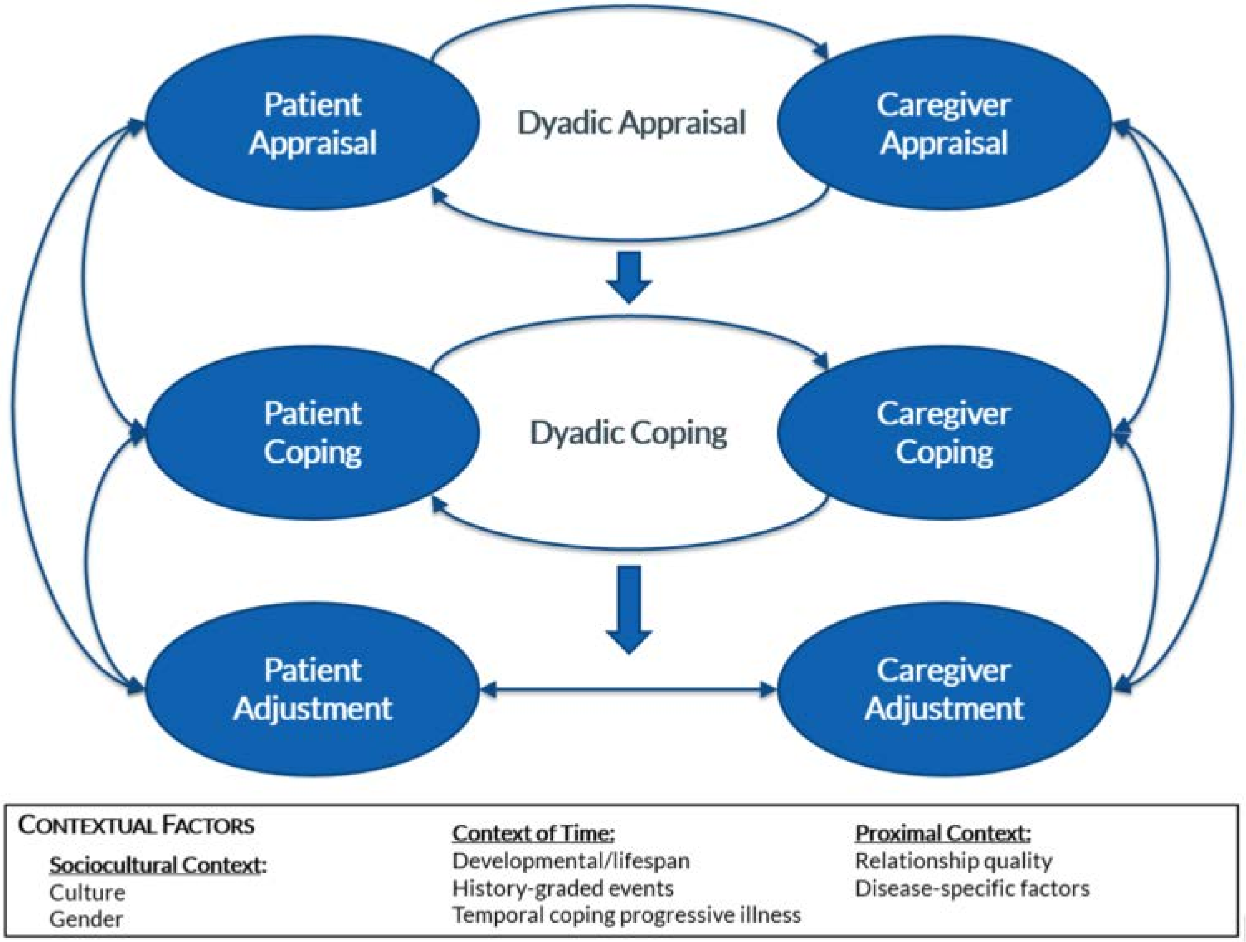

Figure 1: The Developmental-Contextual Model of Couples Coping with Chronic Illness, adapted from Berg & Upchurch (2007).

Despite limited contribution from the HF literature (and no contribution from the VAD literature) in the initial development of the Developmental-Contextual Model (due to few existing studies at the time), we found the model to be generally very informative and in relatively good alignment with what we observed and modeled in our analyses of HF and VAD patients and their caregivers. However, there were some notable exceptions, and it may be useful to consider slight adjustments to the model to better fit this unique population of patient-caregiver dyads. In particular, we found that changes to contextual factors and movement of certain contextual factors into main model concepts, may bring the theory into closer alignment with the experiences of HF and VAD dyads. We discuss these proposed changes below, and present a potential revised framework (**Figure 2)** that may be more appropriate for guiding research in HF and VAD dyads.

Sociocultural context. Culture and gender are important factors to consider in the study of dyads in chronic illness. Although we did not conduct analyses by culture, this was largely due to relative homogeneity of our samples, and thus, examining cultural differences in the HF and VAD patient-caregiver experience remains a promising and important avenue for future research. In terms of gender, we observed gender effects in caregiver strain in VAD dyads (female caregivers experienced greater strain) and in self-care in HF dyads (female caregiver was a determinant of better patient self-care, and male patient was a determinant of worse patient self-care). Additionally, because there are likely complex, potentially interacting, relationships between culture, gender, and several other contextual factors within the proposed model (developmental/lifespan stage, caregiving relationship type, and eligibility/therapeutic strategy in advanced HF), we have also added a notation (*) to the proposed model figure to emphasize the likely interplay between these factors. Future research is needed in larger, more diverse samples to examine these contextual factors together. This is an important aspect of advancing the science and improving understanding of how these key individual and dyadic characteristics influence patient, caregiver, and dyadic outcomes.

Context of time: Developmental/lifespan effects. HF is largely a disease of older adults, although the advanced HF population in our samples tended to be younger on average, and HF broadly affects individuals across all developmental/lifespan stages. In HF, however, age and lifespan take on additional meaning, as age is one of the primary determinants of eligibility and therapeutic strategy when HF becomes advanced (i.e. transplant, bridge to transplant VAD, destination VAD, hospice). Although age was not a significant determinant in our models, or was not included due to modeling limitations or multicollinearity concerns (therapeutic strategy and age in VAD patients are highly associated) future research examining age and/or developmental lifespan variables is warranted, and thus should remain in the theoretical model, particularly since our findings related to relationship type in VAD therapy may have an age component, given that parent caregivers of adult children tended to be younger on average than the spousal caregivers in our sample.

Context of time: Temporal coping with progressive illness. In the original model, this is a recurring process that involves anticipatory coping, symptom identification, coping with treatment, and daily management. In our analyses, we observed transactional relationships between patients and caregivers involving HF symptom experience and engagement in HF self-care: two major aspects of this process. Furthermore, both of these factors directly influenced adjustment in our analyses, suggesting that, in HF, these processes may be more appropriately reframed under the main concepts of the model, rather than as contextual factors. In particular, we propose that symptom experience – since our work demonstrates that it is a transactional process – become part of patient, caregiver, and dyadic *appraisal*, and that self-care in HF (daily maintenance and management behaviors) be considered as part of how patients, caregivers, and the dyad together *cope* with disease and manage distressing symptoms. Specifically, these proposed changes are supported by our findings that symptoms impacted important adjustment outcomes, such as QOL and depression for both patients and caregivers, as well as caregiver strain. Additionally, within a dyadic context, the burden of emotional symptoms of HF for patients was a significant determinant of self-care engagement for both patients and caregivers, which may support self-care engagement as a potential coping strategy in response to symptoms or other aspects of illness appraisal.

Pursuant to these conceptual changes, we propose that the previously mentioned "temporal coping" contextual time factor be changed to "Progression of Illness," since this is a time-graded process that may dramatically impact all of the main model concepts. We found in multiple analyses that clinical markers of illness progression were associated with patient and caregiver outcomes. For example, we found functional class to be a significant predictor of patient clinical event-risk, and inotrope requirement to be a significant predictor of pre-implant anxiety for VAD caregivers. Overall, our findings support that mild and stable HF is a different experience for caregiving dyads than unstable HF with frequent, unpredictable exacerbations, supporting this proposed change.

Proximal context. We also propose minor changes to the proximal contextual factors in the model, perhaps most notably, the addition of caregiving relationship type. In the original model, only the spousal caregiving experience was considered, but caregiving in general and HF caregiving in particular is not exclusive to spouses. Although the majority of caregivers in our samples were spousal caregivers, there were also substantial proportions of nonspousal caregivers, and the effects of spousal versus nonspousal caregiving were notably different in several of our analyses. For example, in HF dyads, nonspousal caregivers perceived greater engagement in self-care management behaviors, and in VAD dyads, nonspousal dyads were somewhat protected from adverse outcomes pre-implant (e.g. strain, anxiety) but were more susceptible to depressive symptoms after implantation. If nonspousal caregivers are to be included in future research, relationship type should be, at minimum, controlled, and ideally, further studied. Relationship quality was also an important protective factor in multiple analyses, as was controllability of illness under the main *appraisal* concept. As such, both relationship quality and controllability of illness are therefore original model factors that should be retained and studied further as a promising modifiable, protective factors for patients and caregivers. In summary, although the main framework of the model remains, we have suggested some revisions to contextual factors and main model concepts in light of this program of research and additional aspects of the HF syndrome in general and the experience of VAD therapy in particular. The proposed adjusted model is presented in **Figure 2**, with alterations from the original model highlighted in red.

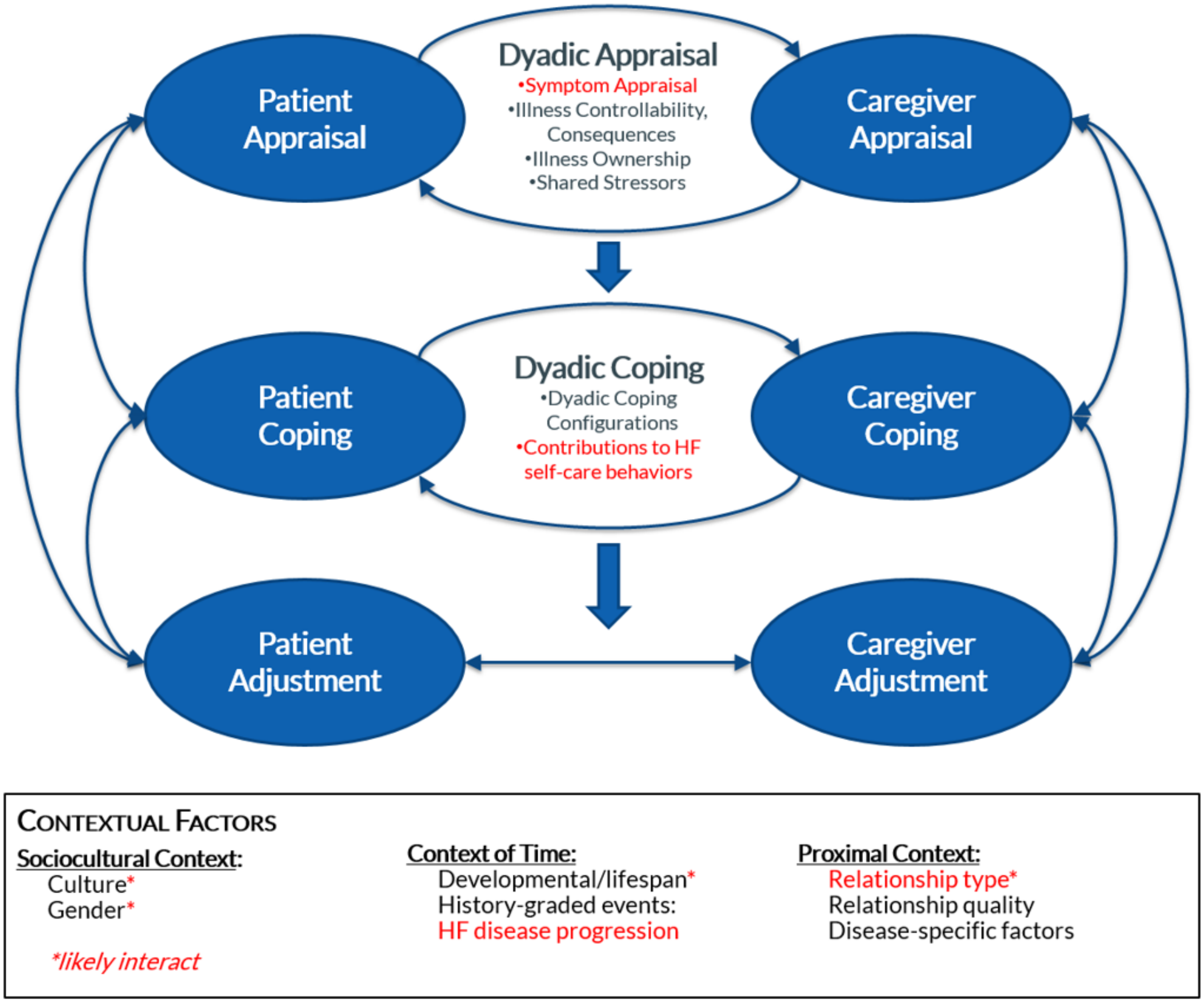

Figure 1: The Developmental-Contextual Model of Couples Coping with Chronic Illness, adapted for heart failure and mechanical circulatory support from Berg & Upchurch (2007); changes from original theory noted in red. Note: HF: heart failure.

Implications for Practice and Future Research

Implications for practice and future study based on this program of research are summarized in **Table 2.** Importantly, all implications across this cohesive work can be tied back to its overarching consensus, namely, that the patient-caregiver dyad in HF and VAD therapy is transactional in nature. Therefore clinical and research approaches that are dyadic or interpersonal may be more beneficial and informative than individual approaches in jointly improving outcomes for patients and caregivers.

Table 2: Implications for Practice and Future Research
Consensus Statement: The overarching consensus of this program of research is that the patient-caregiver dyad in HF and VAD therapy is *transactional* in nature (patients and caregivers influence one another bi-directionally). Clinical and research approaches that treat and examine patients and caregivers as a dyad are greatly needed, as they may be more beneficial and informative than individual approaches (the current state of the science) in improving outcomes for patients and caregivers together.
Implications for Clinical Practice
• In HF in general, it may be beneficial to include caregivers in regular clinic visits, as: o They may provide information to refine patient event-risk prognostication o Identifying/supporting distressed caregivers may have dual patient-caregiver benefit • Relationship quality is an important protective factor in both HF and VAD. Supportive services to promote a healthy patient-caregiver relationship in the face of illness may have multifaceted patient and caregiver benefits across the spectrum of HF. • Patient HF symptoms adversely impact both patients and caregivers. As HF worsens, patients and caregivers may benefit from joint support to cope with progression of illness. • We observed trade-offs in HF and VAD patient and caregiver outcomes (e.g. strain and event-risk; simultaneous improvement/decline in post-VAD QOL). There may be ethical and clinical rationale for providing supportive services to caregivers, and referring patients and caregivers together for supportive services may benefit both dyad members. • The caregiving experience in HF and VAD is different for nonspousal versus spousal caregivers. In VAD in particular, nonspousal dyads may need additional support.
Implications for Future Research
• Our ability to make recommendations for dyadic clinical management is hindered by the current individual-level state of the science, which can be advanced by: o Conceptualizing research questions and designing studies at the level of the dyad o Collecting robust data from both dyad members and analyzing at the level of the dyad • The symptom experience is a hallmark of HF and impacts both patient and caregiver. We need dyadic studies of HF symptom appraisal and response to better understand and support patients and caregivers together to manage and cope with symptoms. • Caregiver contributions to HF self-care have a measurable impact on patient outcomes, and a combination of individual, partner, and dyadic effects predict both patient and caregiver

self-care. Dyadic research in HF self-care maintenance and management is warranted.

- Given our findings and the gaps in HF event-risk prognostication, it may be informative to further examine caregiver and dyadic factors as predictors of patient clinical event risk.
- The interplay of age, gender, and relationship type within HF and VAD dyads is complex and warrants further study in larger, more diverse samples.
- Appraisal of the controllability of illness matters for patients and caregivers in VAD as well as HF. Research is needed to better understand this phenomenon and determine if it can be leveraged to improve patient and caregiver outcomes.
- Social support that the caregiver receives from sources outside the patient-caregiver relationship may be important in both HF and VAD, and warrants further study.

Implications for practice. We identified multiple clinical implications across studies, all of which warrant further investigation**.** First, we observed that caregiver and relationship factors were significant determinants of patient clinical and person-oriented outcomes across our analyses. Perhaps most notably, we identified multiple caregiver factors that predicted patient clinical event-risk over one year of follow-up. Therefore, it may be mutually beneficial to include caregivers in regular clinic visits. Caregivers may be able to detect declines in health that the patient cannot perceive, giving providers additional insight into clinical progression of illness or alerting them to potential instability. Furthermore, given that the patient and caregiver influence one another bi-directionally, this may be an opportunity for providers to identify caregivers that may need extra support. Assisting caregivers to cope with their caregiving role likely has dual benefit for both dyad members, as well as the health of the dyad overall. Second, relationship quality was a significant protective factor in our HF and VAD analyses. Supporting healthy patient-caregiver relationships across the spectrum of HF (e.g. joint referral to a family psychologist or counselor) may improve clinical and person-oriented outcomes for both members of the dyad. Third, HF symptoms and increasing severity of illness were consistent determinants of not only patient, but caregiver outcomes in our analysis. Given that the experience and management of HF largely centers on symptoms, it is not surprising that symptoms impact both members of the dyad. Evaluating severity of HF symptoms from the perspective of patients and caregivers together may be valuable in clinical management and maximization of person-oriented outcomes for patients and families. Addtionally, as HF becomes increasingly severe and symptoms become pervasive, patients and caregivers alike may need additional supportive services to cope with the progression of illness. Fourth, we observed some potential trade-offs in patient and caregiver outcomes, with higher caregiver strain predicting lower patient clinical event-risk, and patient improvement concurrent with caregiver decline in QOL in response to VAD. More research is needed to better understand this phenomenon, but there may be adequate ethical and clinical rationale now to ensure that caregivers have the support they need to manage HF and/or VAD without undue exposure to the concerning sequelae of caregiver strain or compromises to health-related QOL. Finally, we did not restrict our research to spousal caregivers, and, in doing so, found significant differences in patient and caregiver outcomes by relationship type. Although this phenomenon also warrants further research, nonspousal dyads in VAD in particular (both patients and caregivers) may be at particular risk for depression, and may therefore need additional psychological support services.

Implications for research. Our primary recommendation for future research is grounded in the current state of the literature in HF, which is largely at the individual level. As such, it is difficult to make strong clinical recommendations for how to manage patients and caregivers together as a dyad. Therefore, in order to advance both science and practice in HF and VAD caregiving, it is critical that future research involves: 1) a strong foundation in dyadic theory and the existing HF-specific *and* broader chronic illness caregiving literatures, 2) research questions and associated studies that are conceptualized and designed at the level of the dyad, 3) studies that collect robust data (ideally utilizing like measures for patients and caregivers when possible) on both members of the dyad, and 4) studies that analyze data at the level of the relationship. Second, we observed a significant influence of HF symptoms on both patient and caregiver outcomes. There is a dearth of dyadic research on symptom appraisal and symptom response in HF. This is a critical gap given the impact of symptoms on dyadic adjustment in our research, and the broader role that symptoms play in HF self-care behaviors. Third, we identified multiple partner and dyadic characteristics that were determinants of both patient and caregiver HF self-care contributions, and that caregiver self-care contributions in particular were significant predictors of patient clinical event-risk. Continued research examining self-care as a dyadic process is necessary for advancing the science of self-care and improving associated patient outcomes. Fourth, there remain major gaps in our ability to predict clinical event-risk for HF patients; however, our findings support additional examination of caregiver and dyadic factors as potentially valuable prognostic indicators or possible intervention targets for refining or reducing risk. Fifth, we were unable to comprehensively examine the effects of age, gender, and relationship type (and VAD therapeutic strategy) on patient and caregiver outcomes. These factors likely interact, and require further study in samples that are larger and less homogeneous. Elucidating these complex relationships are a critical next step in identifying which patient-caregiver dyads may be at particular risk for poor outcomes. Sixth, we identified perceived controllability of illness as an important protective factor, a finding that is consistent with other chronic illness caregiving contexts. In HF in general and VAD in particular, measures of patient- and caregiver-perceived controllability of illness should be included in future research, particularly to investigate whether it can be modified or otherwise leveraged to improve dyad outcomes. And finally, social support as perceived by the caregiver appears to be an important protective factor in both HF and VAD. Future research is needed, both to determine the nature of this effect, what types of support are most valuable, and whether this is a potentially modifiable (e.g. assisting caregivers to identify potential additional sources of support) factor that can be used to improve patient, caregiver, and dyadic outcomes.

Conclusions

The overarching conclusion of this program of research is that the patient-caregiver dyad in HF and VAD therapy is transactional in nature, with the experiences and characteristics of one member of the dyad influencing the other member and vice versa. In addition to this overall result, specific findings from each of the manuscripts contained in this body of work individually and collectively represent significant advances in the science of HF and VAD caregiving, and suggest notable implications for theory, future research, and clinical practice. Although future research is needed to further examine the relationships identified in these studies, this program of research fills critical gaps in our understanding of patient-caregiver dyadic dynamics in HF and VAD therapy, and provides foundational evidence for the feasibility and value of future dyadic observational and interventional work in this unique population of patients and caregivers.

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