IDENTIFYING DISPARITIES: RURAL-URBAN COMPARISON IN MECHANICAL CIRCULATORY SUPPORT

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By
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Abstract

Heart failure (HF) is one of the most prevalent diseases worldwide and the number of people living with advanced or stage D HF is rising. In many cases, advanced HF is refractory to medical treatment and requires the use of more advanced treatments like heart transplantation or ventricular assist device (VAD) therapy. Patients with advanced HF from all metropolitan statuses are being implanted with VADs, yet the impact of different metropolitan statuses has not been adequately explored in the literature. This study aimed to identify and examine outcome disparities between VAD therapy recipients and metropolitan status by comparing rural and urban VAD recipient outcomes in the first twelve months after implantation. Secondary analysis of institutional data maintained by the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) was completed. VAD recipients were designated as rural or urban using county level data from the U.S. 2010 Census. Kaplan-Meier and Cox proportional hazards models were used to identify differences in hazards between rural and urban VAD recipients. Event counts were analyzed using negative binomial regression. The sample included 158 VAD recipients that were discharged from the hospital following VAD implantation. Twenty-two recipients died in the first twelve months after receiving their device. Nearly 81% of all recipients experienced at least one adverse event during the study period. Although none of the Cox proportional hazards models achieved statistical significance, the Kaplan-Meier event curves seem to suggest rural patients may be at a disadvantage in terms of some adverse events associated with VAD implantation. Until further research with more robust samples of VAD recipients is conducted, these findings seem to indicate no difference in VAD outcomes related to metropolitan status. However, the VAD recipients in this study experienced many adverse events and hospitalizations that may impact HRQoL for VAD recipients irrespective of metropolitan status. Management of complications is an ongoing concern for nurses caring for
VAD recipients. New strategies to prevent VAD-related adverse events and poor outcomes are needed. Nursing clinicians and researchers are in a prime position to develop and test these new interventional strategies.
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List of Abbreviations

APN – Advanced Practice Nurse
BTR – Bridge-to-decision
BTT – Bridge-to-transplant
DT – Destination therapy
HF – Heart failure
MCS – Mechanical circulatory support
VAD – Ventricular assist device
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Dedication

This dissertation is dedicated to my 3 beautiful, smart, and funny children, Trevor, Pearce, and Natalie. You are my inspiration. You can be whatever you want to be. Be brave.
Chapter 1

Introduction

Heart Failure (HF) contributes to one in nine deaths and accounts for almost twenty-five billion dollars of healthcare spending annually nationwide (Mozaffarian et al., 2015). These figures place HF among the costliest and deadliest diseases in the United States, and as such, a top public health priority (Mozaffarian et al., 2015). The number of new HF diagnoses in the U.S. exceeded 850,000 in 2014 and is steadily rising despite enhanced prevention strategies (Heart Failure Society of America, 2014; Mozaffarian et al., 2015). Over 8 million individuals with HF are expected in the U.S. by 2030 related to the growing aging population, the increased prevalence of predisposing risk factors, and the steady progress in post-myocardial infarction survival (Heidenreich et al., 2013). Heart transplantation is the most promising treatment for advanced HF, yet the number of patients awaiting donor hearts far exceeds the number of available organs and many do not meet the minimum eligibility standards for transplantation (Deng, 2004; Miller, 2011; Radovancevic & Frazier, 2000; Westaby, 2004). This supply and demand imbalance led to the development of alternative treatment strategies such as ventricular assist device (VAD) therapy. VAD therapy provides mechanical circulatory support (MCS) to one or both ventricles and is becoming a popular treatment choice for patients with advanced HF as the therapy has shown promise in improving quality of life and decreasing frequent hospital admissions (Grady et al., 2015; Kirklin et al., 2015; Prinz von Bayern, Caderias & Deng, 2007; Savage, 2003; Wissman et al., 2012).

In 1994, the first VAD patient was discharged from the hospital with a portable, long-term version of the device, also referred to as durable mechanical circulatory support (MCS), and use of the technology has flourished since that time (Patient Care Profile, 2004; Rojas et al.,
The number of VAD implantations in the U.S. is increasing as the technology continues to mature and the number of implanting centers grows (Kirklin et al., 2015; Katz et al., 2015). A map representing the current VAD implanting centers in the U.S. is shown in Figure 1.1.

Figure 1.1 Map representing U.S. VAD Centers in 2013

There are a greater number of VAD-implanting centers in the eastern U.S. when compared to central and western regions. This could be related to population density and the number of larger metropolitan areas along the eastern seaboard. Some regional differences have been noted in VAD outcomes with those patients residing in the southern U.S. having significantly lower survival rates beyond the one-year post implantation time point (Krim et al., 2015).

In 2015, the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) contained the records of over 15,000 VAD patients throughout the country with over 2000 implantations in 2014 alone (Kirklin et al., 2015). However, not all VAD-implanting
centers are required to participate in INTERMACS and patient participation in the registry is voluntary. Nevertheless, the frequency of VAD implantation has increased since FDA approval of the device and as Medicare/Medicaid and private insurances provide coverage for implantation and necessary follow-up care under the diagnosis-related group used for heart transplantation (Centers for Medicare and Medicaid Services, 2015; Miller, Guglin, & Rogers, 2013).

Although there has been an increase in VAD implantations and VAD implanting centers in recent years, not all hospitals are equipped to manage VAD patients (Bellumkonda & Jacoby, 2013; Katz et al., 2015). Timely access to emergency VAD services and routine follow up care is critical in maintaining patient health given the life-sustaining nature of VAD therapy for advanced HF patients and the complexity of the device itself. For this reason, patients may choose to relocate to a residence in closer proximity to the VAD hospital or a larger, regional medical center that is better equipped to manage their care. However, relocation is not feasible for all patients and many will choose to remain in their homes without access to the VAD implanting center despite potential challenges to managing their VAD therapy and the potential for increased risk of adverse events.

Patients undergoing VAD therapy that reside in rural areas face unique challenges and circumstances that may increase their risk of complications or negative outcomes. These concerns include: cultural attitudes in rural areas that may limit the use of routine or preventive health services or influence health-seeking behaviors in times of medical need (Long et al., 1989), lower likelihood that a family caregiver will be available for assistance with routine VAD care and social support (Jurkowski & DeWolfe, 2015; National Advisory Committee on Rural Health and Human Services, 2010), less access to emergency medical personnel with training in
the physiological nuances of patients with VADs (Schweiger et al., 2012), and lastly, potentially longer distances to reach VAD-supporting centers which has been shown to have a relationship to poor outcomes in other medically fragile populations such as organ transplantation (Axelrod et al., 2010). These circumstances amplify the concern that rurality may increase risk of poor outcomes for VAD patients and are discussed in more detail in Chapter 2. Despite the great potential of rurality to influence VAD outcomes, there is insufficient knowledge about the influence of geographic residence on clinical VAD outcomes and patient-reported health-related quality of life (HRQoL) in rural and urban VAD patients reported in the literature. Therefore, this study addressed the following specific aims:

Aim 1: To determine the relationship of metropolitan status (rural versus urban) and clinical VAD outcomes in the first year following device implantation.

Sub-Aim 1.1: To examine the relationship of metropolitan status (rural versus urban) and VAD-related mortality in the first year following device implantation.

Sub-Aim 1.2: To examine the relationship of metropolitan status (rural versus urban) and VAD-related hospital admissions in the first year following device implantation.

Sub-Aim 1.3: To examine the relationship of metropolitan status (rural versus urban) and the most common VAD-related adverse events including infection, bleeding, neurological dysfunction, device malfunction, and cardiac arrhythmias in the first year following device implantation.

Aim 2: To determine the relationship between metropolitan status (rural versus urban) and patient-reported health-related quality of life (HRQoL) in the first year following device implantation.

The time-frame of one year was selected for analysis for the following reasons:
1. Health-related quality of life has been found to reach a point of stabilization in the VAD patient trajectory over the first year following implantation (Grady et al., 2004).

2. Although many patients survive beyond the one-year milestone, reports indicate that 13-30% die in the first year (Kirklin et al., 2015; Tsiouris et al., 2015). However, these numbers may be significantly higher in coming years as the prevalence of advanced HF increases and the number of donor organs for transplant remains consistent (Mozafarian et al., 2015). These two factors could significantly impact mortality in the first year after implantation and increase the importance of this time frame for study.

3. The post-implantation period requires intensive follow-up care. Therefore, the examination of longitudinal data over the critical first year will produce a robust evaluation of differences in outcomes between rural and urban dwelling VAD patients.

4. The study was limited to a one-year time frame to enhance feasibility.

**Conceptual Framework**

The framework for this study was developed through a theory-integration of Bruce Link and Jo Phelan’s theory of fundamental social causes of health disparities (Phelan et al., 2004) and Ronald Andersen’s behavioral model of health services use (Andersen & Newman, 1973; Andersen, 1995; Andersen, 2008).

**Link and Phelan’s Theory of Fundamental Social Causes of Health Disparities**

The theory of fundamental social causes of health disparities, also referred to as fundamental cause theory (FCT), was developed in the mid-1990s by Bruce Link and Jo Phelan (Link & Phelan, 1995). The theory postulates that socioeconomic status is a “fundamental cause” of health disparities (Link & Phelan, 1995). To be defined as a “fundamental cause” an entity must exhibit the following features (Phelan et al., 2004):
1. The ability to exert influence over multiple disease outcomes,
2. Disease outcomes are influenced through multiple associated risk factors,
3. The link between the “fundamental cause” and disparate outcomes persists over time regardless of intervention,
4. “Fundamental causes” are associated with inadequate access to resources.

This study will investigate metropolitan status as a “fundamental cause” of disparate outcomes for patients undergoing VAD therapy. More detail of FCT and examples of how metropolitan status was examined as a “fundamental cause” in this study are provided in Chapter 2.

**Ronald Andersen’s Behavioral Model of Health Services Use**

The goal of Andersen’s behavioral model of health services use, which was originally developed in the 1970s, is to define and measure the dimensions of access to care (Andersen, 2008). The model incorporates predisposing, enabling, and need factors and considers not only individual health determinants, but also societal (Andersen & Newman, 1973). Predisposing factors are those features of an individual that make them likely to utilize health services (Andersen, 1995). These include things such as demographic characteristics, social structures, and health beliefs (Andersen, 1995). Social structures are a comprehensive category that includes an individual’s social support, availability and use of resources, and more generally speaks to the individual’s status in the community (Andersen, 1995). Examples of social structures include educational attainment and occupation (Andersen, 1995). Health beliefs include “attitudes, values, and knowledge that people have about health and health services that might influence their subsequent perceptions of need and use of health services” (Andersen, 1995, p. 2). Enabling factors either enhance or impede the use of health services (Andersen,
Andersen (1995) considers needs factors to be those that influence the need for health services use (Andersen, 1995).

Individual predisposing factors include characteristics like demographics (e.g. race, gender), social structures (e.g. education level, occupation), and personal health beliefs that may provide a predisposition to utilize health services (Andersen & Newman, 1973; Andersen, 1995; Andersen, 2008). Individual need factors include perceived health or how the individual views their health and evaluated health which includes illness severity and the presence of comorbid conditions as determined through formal medical evaluation (Andersen & Newman, 1973; Andersen, 1995; Andersen, 2008). In 2008, the model established contextual characteristics as potential predisposing, enabling or needs factors and incorporated health outcomes; this updated model will be utilized in this study.

Andersen (2008) considered contextual characteristics to be those measured as an aggregate and may include characteristics of the health organization and community. Andersen (2008) combines compositional factors that collectively describe a community like demographics and contextual factors like health care supply into the contextual characteristics shown in the model. Contextual characteristics are subdivided into those characteristics that may predispose, enable, or suggest the need for healthcare utilization (Andersen, 2008). Predisposing contextual characteristics (demographic, social structures, and health beliefs) are similar to individual predisposing characteristics, but measured as a collective. Enabling contextual characteristics include health policy (local, state, and federal), financing or the overall financial resources of a community including rates of the uninsured and community affluence, and organization which refers to health service availability including distribution of services, physician density, and number of specialists (Andersen & Davidson, 2001; Babitsch et al., 2012). Contextual level
need factors include environmental or those collective conditions of the community environment including indices like regional environmental health hazards (e.g. air pollution) (Babitsch et al., 2012) and population health indices like regional mortality rates. Health behaviors addressed in the model include: personal health practices, the process of medical care, and the use of health services. Three outcomes are included: perceived health, evaluated health and consumer satisfaction.

This study investigated metropolitan status as a contextual barrier to enabling resources. Andersen (2008) considers access to be inequitable in situations where enabling resources, social structure, and health beliefs determine utilization. Patients living in some locations while undergoing VAD therapy may be at a disadvantage to access important health services like routine follow up care and treatment during times of medical need (Douthit et al., 2015; Li, 2006; Myers et al., 2013). This dissertation study aimed to identify metropolitan status as a contextual dis(en)abling factor that may influence clinical outcomes (evaluated health) (Aim 1) and HRQoL (perceived health) (Aim 2) in rural VAD patients (Andersen, 2008). In addition, VAD recipients may have predisposing health beliefs (Andersen, 2008) that include delayed health seeking in periods of decline related to self-reliance and distrust of outsiders (Long et al., 1989; Sethares et al., 2014) related to their metropolitan status. The integrated framework that guided this study is depicted in Figure 1.2.
Figure 1.2 Integration of Andersen’s behavioral model of health services use and the theory of fundamental social causes of health disparities (Andersen, 2008; Link & Phelan, 1995). The circles indicate those facets of the behavioral model that are investigated in this study. Metropolitan status is the examined as a fundamental cause and the overarching contextual characteristic.
Research Questions

The following research questions guided this study:

1. Are there differences in mortality risk in the first year following VAD implantation based on metropolitan status (rural vs. urban)?

2. Are there differences in hospital admissions in the first year following VAD implantation based on metropolitan status (rural vs. urban)?

3. Are there differences in the number of adverse events experienced by VAD recipients based on metropolitan status?

4. Are there differences in HRQoL for VAD recipients based on metropolitan status in the first year following device implantation?

5. Does HRQoL in VAD recipients change over the first year post-implantation in relation to the recipient’s metropolitan status?

Definitions

Advanced heart failure: Patients that experience symptoms that are refractory to maximal medical support, classified as Stage D by the American Heart Association (AHA) or New York Heart Association (NYHA) class III or IV (Criteria Committee, NYHA, 1994; Yancy et al., 2013).

Health-related quality of life: Patient-reported quality of life as determined using the Euro-QOL 5 Dimension Scale (Rabin & Di Charro, 2001).

Device Strategy

Bridge-to-decision: Indefinite-term implantation of durable MCS while patients and/or providers come to a decision about the plan of care. Includes patients that are not actively listed for potential transplant, but that could be considered in the future (AHA, 2015).
**Bridge-to-transplant:** Indefinite-term implantation of MCS in those patients that are awaiting a donor heart (AHA, 2015).

**Destination Therapy:** Permanent, long-term implantation of a MCS/VAD to improve quality of life in advanced heart failure patients that are ineligible for heart transplantation (AHA, 2015).

**Durable Mechanical Circulatory Support (MCS):** A mechanical pump that is implanted in the right ventricle, left ventricle or both ventricles to augment the pumping ability of the ventricle(s) in patients with advanced heart failure (AHA, 2015). Mechanical circulatory support will be used interchangeably with ventricular assist device throughout. A differentiation is made that the focus of this study was durable MCS as opposed to non-durable (temporary) MCS, such as extracorporeal membrane oxygenation (ECMO) or intra-aortic balloon pump (IABP).

**Metropolitan status:** Classification of recipients as rural or urban based on county population density. Any county with a population density of less than 284 people per square mile is considered rural as per the Center for Rural Pennsylvania (Center for Rural Pennsylvania, 2014)

**Ventricular assist device (VAD):** See definition for durable mechanical circulatory support above. These terms will be used interchangeably throughout.

**Assumptions**

This study assumes:

1. Patients that live in rural counties have access to a community hospital
2. Patients that live in urban counties have access to an academic medical center or larger, regional health system.
3. Participants responded honestly to EQ5D-3L self-reported health-related quality of life measures

**Significance to Nursing**

As the largest group of health care professionals in the United States, nurses are in a prime position to significantly impact the perceived and evaluated health outcomes of VAD recipients irrespective of metropolitan status. However, due to the complexity of VAD care and the life-sustaining nature of the device it is important for nurses to know if metropolitan status could be a concern for VAD recipients. Examining the impact of metropolitan status on VAD recipient outcomes will raise awareness of the events, complications, and issues that may by most likely to arise in a VAD recipient related to where they live. Specific protocols could be developed to address the needs of VAD recipients and caregivers based on their metropolitan status. In addition, this study could identify time points where adverse events related to metropolitan status are most likely. These findings could be used by nurses as specific target time periods where more frequent recipient evaluations are necessary. More detail on the significance of this study to nursing research, policy, and practice can be found in Chapter 5.

**Chapter Summary**

As HF reaches epidemic proportions in the coming years, the need for sophisticated treatments such as durable MCS will undoubtedly increase. These inevitable increases in VAD therapy will result in larger numbers of patients being implanted with devices across all levels of metropolitan status. The health disparities already present across the gradient of metropolitan statuses (rural vs. urban) in HF care make the risk of poor outcomes for VAD recipients in disparate areas seem unavoidable. Outcome disparities related to metropolitan status should be identified with the goal of addressing and eliminating as many disparate outcomes as possible.
That was the objective of this dissertation study. Identifying outcome disparities is the first step to inform the development of targeted strategies to ensure equitable access to the quality of life improvements and longer lifespan that is afforded to patients with advanced HF through VAD therapy regardless of metropolitan status.
Chapter 2

Review of the Literature

Introduction

Heart failure (HF) is a growing problem worldwide. In 2016, in the U.S. alone, there were nearly six million HF patients, and this number is expected to reach eight million by 2030 (Heidenreich et al., 2013; Mozaffarian et al., 2016). Half of those newly diagnosed with HF are expected to die within five years of diagnosis without a life-sustaining intervention like heart transplantation or durable mechanical circulatory support (MCS)/ventricular assist device (VAD) therapy (Alraies & Eckman, 2014; Mozaffarian et al., 2016). Although heart transplantation is the most promising option for treating advanced HF, the number of potential recipients far exceeds the number of donor organs available and many patients with advanced HF are not eligible for transplant based on their age, comorbid conditions, or health behaviors (Alraies & Eckman, 2014). This imbalance has resulted in more patients receiving durable MCS devices (VADs) including patients living in rural and urban areas.

VADs have evolved and are approaching a status as standard of care for advanced HF patients awaiting transplant or as a life-sustaining therapy in those ineligible to receive a donor heart (Mehra & Domanski, 2012). However, these devices are not implanted without consideration given to serious risks of potential life-threatening and life-altering complications and the arduous regimen of care required for successful therapy (Owens & Jessup, 2012). These troubling factors may be compounded in certain contexts where patients are at a disadvantage in terms of access to specialty VAD care related to metropolitan status, but also in regards to attaining formal and informal caregiver support (Jurkowski & DeWolfe, 2015; National Advisory Committee on Rural Health and Human Services, 2010) and the availability of properly trained providers of emergency care (Schweiger et al., 2012). Poor clinical outcomes
including increased risk of mortality, adverse events, and hospital admissions, as well as poor patient-reported health-related quality of life (HRQoL) may be a reality for VAD recipients based on their metropolitan status. Yet, to date, these issues have not been adequately explored. Therefore, this study was necessary to identify differences in clinical and patient-reported outcomes in a sample of VAD patients categorized as rural or urban based on the location of their primary residence.

The purpose of this chapter is to review the literature relevant to the impact of metropolitan status on VAD outcomes. The chapter begins with a review of the HF literature including a discussion of treatment guidelines and how they have evolved in recent years. The role of durable MCS or VADs in HF also will be explored. The evolution of the VAD is discussed including landmark trials and the role of INTERMACS leading to approval of VADs by the Centers for Medicare and Medicaid. This is followed by an examination of health disparities and a more focused discussion of rural and urban health disparities, which will lay the groundwork for a presentation of the state of the science of metropolitan status and heart failure. This section specifically addresses the known implications of metropolitan status on HF outcomes, management, and specialist access. Metropolitan status will be discussed as a fundamental cause and then linked to Andersen’s behavioral model of health service utilization through a broad review of the study framework in the context of VAD outcomes. Finally, this chapter will culminate with a discussion of knowledge gaps related to VAD outcomes and metropolitan status and how metropolitan status could impact clinical and patient-reported VAD outcomes.

A comprehensive database search was the cornerstone for this chapter. Databases included were: PubMed, CINAHL, ProQuest Nursing and Allied Health, Web of Science, and
Google Scholar. Searches were conducted with the following key terms in a variety of combinations:

- Heart failure related terms: heart failure, HF, advanced heart failure, congestive heart failure
- Metropolitan status-related terms: rural, rurality, urban, urbanicity, remote, residency status, location, distance, travel time, travel distance, metropolitan status
- VAD therapy-related terms: ventricular assist device, VAD, mechanical circulatory support, MCS, durable MCS, left-ventricular assist device, LVAD, cardiac support, cardiac device, INTERMACS
- Health-related quality of life terms: health related quality of life, quality of life, patient-reported outcomes.

**Heart Failure (HF)**

Heart failure (HF) is a chronic and incurable condition that involves weakening of the heart muscle over time (National Heart, Lung and Blood Institute (NHLBI), 2015). This progressive deterioration can result in insufficient filling of the heart, inadequate contractility, which interferes with the ability of the heart to effectively pump blood around the body, or both (NHLBI, 2015). HF most commonly impacts both sides of the heart muscle, but can also be focused on the left-side or the right-side (NHLBI, 2015). The side of the heart most affected will determine which symptoms of HF are most prominent in a patient (NHLBI, 2015). For example, right-sided HF often results in lower extremity edema and ascites whereas left-sided more commonly presents with shortness of breath or fatigue (NHLBI, 2015). The type of HF is often classified based on left ventricular ejection fraction (LVEF) (Nicoara & Jones-Haywood, 2015). LVEF is a measure of the ability of the left ventricle to empty with each contraction of the heart.
muscle (Yancy et al, 2013). In some patients, the ability of the heart to contract is minimally impacted, despite the presence of the structural abnormalities associated with HF (Nicoara & Jones-Haywood, 2015). These patients have a LVEF greater than 50% and their HF is referred to as HF with preserved ejection fraction or diastolic HF (Nicoara & Jones-Haywood, 2015). Half of all HF patients have diastolic HF (Nicoara & Jones-Haywood, 2015). In the other half of HF patients, LVEF is reduced to less than 50% as shown by echocardiography or cardiac catheterization (Nicoara & Jones-Haywood, 2015). This is referred to as systolic HF or heart failure with reduced ejection fraction (Givertz, 2011; Henes & Rosenberger, 2016). Patients with systolic (left) heart failure are most often the recipients of VAD therapy; however, VAD therapy does have some use in diastolic HF patients as well (Givertz, 2011). HF is caused by several cardiovascular diseases including hypertension, coronary artery disease, and diabetes (NHLBI, 2015).

Although HF most commonly impacts older adults with other comorbid conditions like diabetes (Kannel, Hjortland & Castelli, 1974), it can also impact children with congenital abnormalities or following a cardiac infection (NHLBI, 2015). However, device implantations for pediatric patients are not included in the INTERMACS registry. These implantations are recorded in a separate database, the Pediatric Interagency Registry for Mechanically Assisted Circulatory Support (PediMACS) (Blume et al., 2016). Therefore, pediatric patients were excluded from this study and the literature presented in this chapter focuses on HF in adults.

HF severity is most commonly ranked based on classification systems developed by NYHA and AHA. The NYHA classification system assesses subjective, functional capacity and assigns classes ranging from Class I (no functional deficit, asymptomatic) to Class IV (most functional deficit, symptoms at rest) (The Criteria Committee of the New York Heart
The American Heart Association (AHA) has also established a staging system based on objective measures of disease (Hunt et al., 2005). AHA staging classifies patients from Stages A and B which represent those patients without evidence of structural abnormality that are asymptomatic (A) and those with mild structural abnormality, but not symptoms of HF (B) to the most severe HF, Stage D (Hunt et al., 2005). Stages A and B are requisite stages in which the patient has not been given a diagnosis of HF (Yancy et al., 2013). Stage D is characterized by objective evidence of severe disease that has resulted in major structural changes with symptoms present at rest despite maximal medical treatment (Hunt et al., 2005). Stage D patients are often candidates for VAD therapy or heart transplantation (Jessup et al., 2009).

The course of HF is unpredictable for most patients. Figure 2-1 represents a trajectory with outpatient, medical management and a steady decline until death that was adapted from Field and Cassel (1997). However, advanced HF patients are often treated with life-prolonging treatments like durable MCS/VADs or heart transplantation, which alter the trajectory to appear as that shown in Figure 2-2.

![Figure 2.1. Heart failure trajectory for patients with medical management (Adapted from Field & Cassel, 1997, p. 29).](image-url)
Advanced Heart Failure

An estimated one to ten percent of HF patients have reached an advanced stage of disease (Bjork et al., 2016). This broad variation in estimates is the result of an unclear definition of advanced HF in clinical trials. Bjork et al., (2016) recently reported many definitions of advanced HF cited by clinical trials designed for those HF patients nearing the end of the disease trajectory. The Heart Failure Society of America defines advanced HF as “…the presence of severe signs and symptoms of heart failure despite optimized medical, surgical and device therapy” (Fang et al., 2015, p. 519). The AHA/American College of Cardiology Foundation definition is: “patients with truly refractory HF who might be eligible for specialized, advanced treatment strategies, such as MCS, procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation or other innovative or experimental surgical procedures, or for end-of-life care, such as hospice” (Yancy et al., 2013, p. e281). These subjective definitions are left to the interpretation of the investigator and lend themselves to heterogeneous definitions of advanced HF across studies.

The large number of symptoms experienced by advanced HF patients, including those that may or may not be attributable to other comorbid conditions, make using symptomatology in defining advanced stage HF difficult and ambiguous (Norton et al., 2011). In addition, patients or
providers may be contributing to symptom severity by lack of adherence to prescribed medication regimens on the part of the patient or failure to follow treatment guidelines on the part of the providers (Norton et al., 2011). Further, as mentioned above, the HF trajectory is variable, with periods of decline followed by periods of stability. In general, patients do not reach a precise point where the advanced stage begins, which adds to the ambiguity of defining advanced HF (Norton et al., 2011). Some agencies, namely the European Society of Cardiology (ESC) and INTERMACS have developed objective criteria for defining advanced HF. These criteria are discussed below.

The ESC established the following criteria that may be used to define advanced HF:

1. Significant symptom burden and shortness of breath or fatigue at rest or with minimal exertion,
2. Fluid retention of any kind and/or evidence of decreased cardiac output,
3. Objective clinical findings suggestive of severe cardiac dysfunction (one or more of the following: a LVEF less than 30%, an abnormal mitral inflow pattern, mean pulmonary wedge pressure greater than 16mmHg or a high plasma level of natriuretic peptide in the absence of non-cardiac etiology),
4. Severely limited functional capacity evidenced by an inability to exercise, a 6-minute walk test distance of less than 300 meters or a peak VO\textsubscript{2} less than 12-14mL/kg/min,
5. Hospitalization history of one or more admissions in the previous 6 months, and
6. All issues named above are present while in the context of optimized treatments (Metra et al., 2007).

INTERMACS criteria are divided into seven profiles for stratification of advanced HF. These profiles are summarized in Table 2-1 and will be referred to again in Chapter 3.
Table 2.1 INTERMACS Patient Profiles (INTERMACS, n.d.)

<table>
<thead>
<tr>
<th>Profile</th>
<th>Description</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cardiogenic Shock</td>
<td>Life-threatening hypotension and rapidly escalating inotropic/pressor support, with critical organ hypoperfusion often confirmed by worsening acidosis and lactate levels.</td>
</tr>
<tr>
<td>2</td>
<td>Progressive Decline</td>
<td>“Dependent” on inotropic support but nonetheless shows signs of continuing deterioration in nutrition, renal function, fluid retention, or other major status indicator. Can also apply to a patient with refractory volume overload, perhaps with evidence of impaired perfusion, in whom inotropic infusions cannot be maintained due to tachyarrhythmias, clinical ischemia, or other intolerance.</td>
</tr>
<tr>
<td>3</td>
<td>Stable, but inotrope dependent</td>
<td>Clinically stable on mild-moderate doses of intravenous inotropes (or has a temporary circulatory support device) after repeated documentation of failure to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction (usually renal).</td>
</tr>
<tr>
<td>4</td>
<td>Resting symptoms on oral therapy at home</td>
<td>Patient who is at home on oral therapy but frequently has symptoms of congestion at rest or with activities of daily living (dressing or bathing). He or she may have orthopnea, shortness of breath during dressing or bathing, gastrointestinal symptoms (abdominal discomfort, nausea, and poor appetite), disabling ascites, or severe lower-extremity edema.</td>
</tr>
<tr>
<td>5</td>
<td>Exertion intolerant</td>
<td>Patient who is comfortable at rest but unable to engage in any activity, living predominantly within the house or housebound.</td>
</tr>
<tr>
<td>6</td>
<td>Exertion limited</td>
<td>Patient who is comfortable at rest without evidence of fluid overload but who is able to do some mild activity. Activities of daily living are comfortable and minor activities outside the home such as visiting friends or going to a restaurant can be performed, but fatigue results within a few minutes or with any meaningful physical exertion.</td>
</tr>
<tr>
<td>#</td>
<td>Advanced NYHA Class III</td>
<td>Patient who is clinically stable with a reasonable level of comfortable activity, despite a history of previous decompensation that is not recent. This patient is usually able to walk more than a block. Any decompensation requiring intravenous diuretics or hospitalization within the previous month should make this person a Patient Profile 6 or lower.</td>
</tr>
</tbody>
</table>

Findings from Bjork and colleagues (2016) suggest that investigators have trended in recent years toward defining advanced HF using measures like NYHA function class or left ventricular ejection fraction (LVEF). For the purposes of this study, advanced HF will be considered as occurring in those patients with NYHA functional class III or IV or AHA Stage D as these guidelines are complimentary and recommended by AHA and the American College of Cardiology Foundation guidelines for the treatment of HF (Yancy et al., 2013). HF diagnosis and treatment recommendations vary based on individual needs and tolerability. Current diagnosis and treatment guidelines will be summarized in the subsequent section.

**Diagnosis and Treatment of Heart Failure**

HF diagnosis and treatment plans vary based on the unique HF presentation of each patient. However, AHA in collaboration with the American College of Cardiology Foundation (ACCF), produces guidelines every three years with updates of significant changes published annually. The most recent guidelines were published in 2013 with a focused update for pharmacological HF treatments published in 2016. This section will outline recommendations for the diagnosis of HF followed by a summary of recommended HF management strategies.

**Diagnosis**

The diagnosis of HF requires assessment of many patient attributes including physical symptoms, biomarkers, and other objective assessments of cardiac function. The recommendations for the diagnosis of HF that were designated Class I diagnostics, meaning they
have been established as being effective by a large body of evidence were: measuring natriuretic peptides, biomarkers of myocardial injury as well as myocardial fibrosis (Yancy et al., 2013).

Class I non-invasive imaging recommendations included chest x-ray, two-dimensional echocardiogram with Doppler and repeated measurements of LVEF (limited to times of change in clinical status, significant treatment modification or when considering device implantation) (Yancy et al., 2013). The only invasive monitoring that was given a Class I recommendation was pulmonary artery catheter monitoring, but this procedure was limited to patients presenting with respiratory distress or perfusion impairment (Yancy et al., 2013).

**Treatment**

For patients considered AHA Stage A, who have not yet received a diagnosis of HF, it is recommended that hypertension be identified and controlled, and any contributing comorbid conditions be avoided or managed (Yancy et al., 2013). Non-invasive, non-pharmacologic recommendations included: self-care education, exercise training, cardiac rehabilitation, and management of sleep apnea (Yancy et al., 2013). Fluid restriction is recommended for patients that reach a Stage D severity (Yancy et al., 2013). Table 2-2 below summarizes the Class I pharmacologic recommendations for Stages B through D (Yancy et al., 2016).

Table 2.2 Class I pharmacological recommendations for HF treatment

<table>
<thead>
<tr>
<th>Stage B (Non-symptomatic HF)</th>
<th>Stage C (Symptomatic HF)</th>
<th>Stage D (Advanced HF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) to prevent symptomatic HF</td>
<td>Diuretics</td>
<td>Intravenous inotropes for stabilization in cardiogenic shock situations (Class I Recommendation*)</td>
</tr>
<tr>
<td>Beta blockers to lower risk of mortality</td>
<td>Aldosterone receptor antagonists (NYHA Class II-IV with LVEF &lt;=35% or post-MI with reduced LVEF and HF symptoms or diabetes)</td>
<td></td>
</tr>
<tr>
<td>Statins (for patients with recent myocardial infarction or acute coronary syndrome) to prevent HF symptoms and additional cardiac events</td>
<td>Hydralazine and isosorbide dinitrate for African Americans or those unable to receive ACE inhibitors or ARBs.</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Anticoagulants for patients with concomitant atrial fibrillation (AF) with other risk factors for stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD placement recommended in Stage B, Class IIa patients and beyond</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: *Short-term intravenous inotrope therapy recommended in patients awaiting MCS, transplant or as a palliative measure (Class II Recommendations)*

Recommendations are also provided for device therapy in Stage C HF and beyond. Stage C, Class I recommendations included internal cardioverter-defibrillator (ICD) placement to prevent sudden cardiac death and cardiac resynchronization therapy (CRT) (Yancy et al., 2013). Both non-durable (temporary) and durable mechanical circulatory support are recommended by the AHA/ACCF provided patients are “carefully selected” (Yancy et al, 2013, p. e283). Yancy et al. (2013) point out that indications for durable MCS are the subject of ongoing investigation; however, indications that should prompt consideration for durable MCS implantation are a LVEF less than 25% and NYHA Class III or IV despite optimal treatment in accordance with the guidelines. Durable MCS (VAD) technology is continually evolving. Recent device redesigns have been done to minimize complications and have demonstrated promise in increasing survival time (Rogers et al., 2017; Rojas et al., 2016).

**Durable Mechanical Circulatory Support**

Durable mechanical circulatory support (MCS) in the form of a ventricular assist device (VAD) is a promising treatment option for individuals living with advanced HF. Most VADs are partially implanted devices that augment cardiac output by supporting ventricular function (National Heart, Lung, and Blood Institute (NHLBI), 2016). The internal pump is connected to
an external control unit and power source via the device driveline that exits the recipient through a hole in the abdomen (National Library of Medicine, 2017). Care of the VAD is complex and requires the recipient and a caregiver to maintain frequent dressing changes, upkeep of the power source, and anticoagulation along with frequent follow up visits to VAD specialists.

VAD implantation strategies are defined based on the goals of care to be either rescue therapy, bridge-to-recovery, bridge-to-transplant, bridge-to-decision, or destination therapy. Rescue therapy and bridge-to-recovery recipients are recovering from an acute incident and ventricular recovery is expected (Al-Adhami et al., 2014; Drakos et al., 2012). Recipients categorized as bridge-to-transplant are those that are listed on the transplant waiting list and are active candidates for heart transplantation. Bridge-to-decision recipients are those that are not actively listed on the transplant waiting list, but are pending evaluation and may eventually become eligible. Those recipients who will never be listed for transplant and have been implanted with a VAD as a palliative therapy are considered destination therapy where the destination is end of life. The last category, destination therapy, was only recently approved by the FDA as a device strategy for advanced HF. This decision instigated a subsequent decision by the Centers for Medicare and Medicaid Services (CMS) to require that implanting centers belong to a nationwide VAD registry as a stipulation to receive reimbursement for VAD implantations for destination therapy (CMS, 2010). This registry is INTERMACS and will be discussed in the following section.

**Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)**

INTERMACS is a collective registry of clinical and demographic data of patients with VADs implanted at participating institutions in the U.S. and now world-wide with the recent introduction of the International Society for Heart and Lung Transplantation Registry for
Mechanically Assisted Circulatory Support (IMACS) (Kirklin et al., 2016). The 2015 INTERMACS summary reported the database contained the records of over 15,000 adult patients that have received a VAD for durable MCS (Kirklin et al., 2015). The number of patients receiving devices and the number of hospitals performing implantations are steadily rising with over 2,000 new patients added to the database in 2015 from 163 participating centers nationwide (Kirklin et al., 2015). According to the 7th annual INTERMACS report, most patients in the registry were an INTERMACS Patient Profile of two (progressive decline) or three (stable but inotrope dependent) at the time of implant (Kirklin et al., 2015). Destination therapy recipients account for half of the implantations in the INTERMACS registry (Kirklin et al., 2015).

**Landmark VAD Trials**

VAD therapy is a promising treatment for patients with advanced HF that has decreased HF-related mortality and improved patient quality of life (Dembitsky et al. 2004; Grady et al., 2014; Khazanie et al., 2014; Ozalp et al., 2014; Rose et al., 2001). In 1999, a landmark randomized controlled trial, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH), reported a 48% reduction in the risk of death for destination therapy (ineligible for transplant) VAD patients compared to control patients that received optimal medical management (Dembitsky et al., 2004; Rose et al., 2001). These findings were recently duplicated in a prospective, observational study, Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) which reported improved survival for VAD patients when compared to similar medically managed patients (Starling et al., 2016). Since REMATCH, survival rates for patients implanted with VADs have been reported as high as 75% at 1 year post-implantation (Khazanie et al., 2014) and mortality rates continue to trend
downward (Kirklin et al., 2015). VADs have shown promise by decreasing the total number of inpatient days experienced by patients with advanced HF (Whittier et al., 2013) and through improving health-related quality of life (Estep et al., 2015; Whittier et al., 2013) when compared to patients with optimal medical management (Estep et al., 2015). Nevertheless, patients with VADs do often experience frequent hospitalizations and recent studies reported stagnation in all-cause readmission rates over time despite breakthroughs in device mechanics and features (Forest et al., 2013; Hasin et al., 2013; Hernandez et al., 2015). Frequent adverse events and hospital admissions have the potential to negatively impact patients’ HRQoL despite the symptom relief commonly experienced by VAD recipients. This and other considerations in the HRQoL of durable MCS patients will be considered in the subsequent section.

**Health-related Quality of Life (HRQoL) in VAD therapy**

Advanced HF is accompanied by many disturbing physical symptoms including shortness of breath, activity intolerance, and severe fatigue that influence HRQoL in these patients (Nesbit et al., 2014). VAD implantation has resulted in improved HRQoL in advanced HF patients over time especially when compared to pre-VAD assessments and when compared to medical treatment alone (Dembitsky et al., 2004; Estep et al., 2015; Grady et al., 2004; Grady et al., 2014; Whittier et al., 2013). These results are not surprising given the significant improvement in HF-related symptoms commonly experienced post-implantation (Ottenberg et al., 2014). However, it is crucial to note that VAD care is complex and requires the assistance of a family caregiver, significant lifestyle modifications, and a commitment to an arduous regimen of routine care (Dembitsky et al., 2004).

**Clinical VAD Outcomes**

Although VAD therapy may improve HRQoL and functional status in advanced HF the therapy is not without risk (Estep et al., 2015; Whittier et al., 2013). VAD patients commonly
experience adverse events including: heart failure, right ventricular failure, cardiac arrhythmias, gastrointestinal (GI) bleeding, stroke, and infection (Singh et al., 2015; Stulak et al., 2015; Tsiouris et al., 2015; van der Bergh et al., 2015). GI bleeding is the most common adverse event reported with 18-40% of patients experiencing a GI bleed during VAD therapy (Harvey, Holley & John, 2014; Lampropulos et al., 2014). Hospitalizations for adverse events are common with the literature reporting 72-81% of VAD recipients experiencing at least one device-related admission post-implantation (Hasin et al., 2013; Hernandez et al., 2015). Stroke is the leading cause of VAD-related death in the first year following device implantation (Kirklin et al., 2015).

As mentioned above, heart failure management guidelines are revisited every four years with extensive reliance on the scientific literature for changes to the management of HF. Although the guidelines are comprehensive in nature, they cannot address the nuances of healthcare delivery in various contexts, including rural and urban areas. The following section will broadly address disparities in health related to metropolitan status, specifically rural and urban statuses.

Health Disparities and Metropolitan Status

According to the National Institutes of Health (NIH) (n.d.), health disparities are “differences in the incidence, prevalence, morbidity, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups in the United States.” Health disparities exist for several characteristics of the U.S. population with multi-faceted influences and interactions between characteristics. For example, there are known disparities in health based on race, ethnicity, gender, sexual identity, socioeconomic status and geography (NIH, n.d.) and the influence of these characteristics may not be in isolation from the others (e.g. geography and socioeconomic status).
Addressing health inequalities is a priority for many institutions and organizations across the country including the NIH, the Centers for Disease Control and Prevention (CDC), the American Medical Association, the Robert Wood Johnson Foundation, and the Henry J. Kaiser Family Foundation. The CDC reports that health disparities have persisted and worsened, in some cases, despite receiving national attention (CDC, 2013). The 2013 CDC Health Disparities and Inequalities Report (CHDIR) suggests health disparities exist across many dimensions of health care including social determinants: education and income, access to a healthy food retailer and unemployment; environmental hazards: access to a major highway & air pollution and work-related injuries; screening and preventive services: colorectal cancer screening, health insurances, and flu vaccination; behavioral risks: adolescent pregnancy, binge drinking, and smoking; morbidity outcomes: chronic conditions with limited physical activity, asthma, diabetes, health related quality of life, HIV, obesity, periodontitis, preterm birth, preventable hospitalizations, hypertension, tuberculosis; mortality: heart disease and stroke, drug-induced, homicides, infant deaths, motor vehicle related deaths, and suicides. The CHDIR report examined many of the population characteristics mentioned above including the influence of metropolitan status (rural vs. urban) on health disparities. The following subsections will discuss urban and rural health disparities in more detail.

**Urban Health**

Half of the world’s population and 2/3 of the U.S. population reside in urban areas (Vlahov et al., 2007). Thus urban health has been increasingly recognized as a distinct enterprise with focus paid to the influence of the urban environment on population health (Galea & Vlahov, 2005). Galea and Vlahov (2005) suggested that as the populations continue to urbanize, the study of urban health will become important as the urban context “…promises both to shape
health directly and indirectly to affect what we typically consider risk factors or determinants of population health” (p. 341).

Several facets of the urban context influence the impact of urbanity on health. These include the physical environment, the social environment, and health and social services (Galea & Vlahov, 2005). The physical and social environments include things like exposure to pollution and social capital, respectively. Health and social services include factors such as number of health care providers in the area and availability of high quality care. Although in general there are more providers available in urban areas compared to nonurban, access is not guaranteed and is dependent on other socioeconomic factors including insurance status and neighborhood wealth (Fiscella & Williams, 2004; Galea & Vlahov, 2005). In addition, urban contexts are more likely to be the home of marginalized populations like the homeless, immigrants, or former inmates (Galea & Vlahov, 2005). A positive correlation was reported between urbanization and likelihood of living within 150 meters of a major highway and greater exposure to vehicular air pollution (Boehmer et al., 2013).

The literature was searched for instances where urban patients experienced disparate health outcomes when compared to rural counterparts. This search identified two studies where urban residents fared worse than rural residents: one found urban residents more likely to be diagnosed with colorectal cancers at later stages when compared to rural residents (Paquette & Finlayson, 2007) and the other, by Wu and colleagues (2010), found urban HF patients to be more likely to die from HF than rural HF patients. The results from Wu et al. (2010) contrast with many HF outcome studies. A discussion of this study can be found below.

When examining the impact of metropolitan status, the literature frequently reports a rural-urban dichotomy. However, there are some health outcomes that are the worst in the most
rural and most urban areas when compared to suburban counterparts (Eberhardt & Pamuk, 2004). For example, infant mortality is highest in the most rural and most urban counties when compared to suburban counties that are nearby a large metropolitan area (Eberhardt & Pamuk, 2004). These disparities may be related to other variables that have been shown to increase morbidity and mortality like socioeconomic status and race (Fiscella & Williams, 2004). That being said, Singh and Siahpush (2014) and Pathak and Forsyth (2016) recently reported broadening of the rural-urban outcome gap for heart disease related deaths and all-cause mortality even after considering socioeconomic status and race as covariates. Additional rural health disparities will be discussed in the section below.

**Rural Health**

In the U.S., rural residents often suffer worse health outcomes compared to urban residents (Hartley, 2004; Singh & Siahpush, 2014). People living in rural areas are more likely to be diagnosed with a chronic disease like HF (Eberhardt & Pamuk, 2004) or diabetes (Bennett, Olatosi, & Probst, 2008). Mortality related to ischemic cardiovascular disease is highest in rural counties compared to urban or suburban counties, particularly in the southern U.S. (Eberhardt & Pamuk, 2004; Meit et al., 2014). In addition, rural African Americans have a significantly higher risk of cardiovascular death (Taylor, Hughes & Garrison, 2002). Rural residents have worse mental health and higher rates of suicide, especially among youth populations, compared to urban and suburban counterparts (Fontanella et al., 2015; Meit et al., 2014) and rural adolescents are at greater risk of prescription opioid misuse (Monnat & Rigg, 2015). Also, there is evidence in the literature that disparities in HRQoL exist between people residing in rural locations compared to urban locations (Weeks et al., 2006)

Health-seeking and health-maintenance behaviors in rural areas have been shown to be inconsistent and may lead to poorer results in some outcomes. For instance, the odds of a late-
stage breast cancer diagnosis were found to be significantly greater in women residing in non-metropolitan areas (Williams & Thompson, 2016). Rural residents are less likely to seek preventive services like colorectal cancer screening (Andersen et al., 2013) and report more alcohol consumption, more tobacco use and more difficulties maintaining a healthy weight and achieving recommended physical activity targets when compared to residents of urban counties (Matthews et al., 2017; Meit et al., 2014). Lack of insurance has been reported by rural residents as a reason to delay or avoid seeking care (Spleen et al., 2014) and when compared to urban counterparts, rural residents are less likely to be insured (Meit et al., 2014). Income was shown to be related to insurance status with those in lowest income brackets also the least likely to have health insurance (Meit et al., 2014). In addition, income can impact the ability to access healthy food choices for rural residents who are already at a disadvantage in terms of access to healthy food retailers (Drewnowski & Eichelsdoerfer, 2010). Rural census tracts were nearly four times less likely to have access to healthier food retailers when compared to urban census tracts (Grimm, Moore, & Scanlon, 2013).

Health literacy is a skill that is important for patients to “obtain, process and understand basic health information and services that they need to make important health decisions” (Zahnd, Scaife & Francis, 2009, p. 550). Unfortunately, rural patients have lower health literacy than their urban peers (Jurkowski & DeWolfe, 2015; Montalto & Spiegler, 2001; Zahnd et al., 2009). Wood (2005) reported that rural males have lower health literacy compared to rural females. These health literacy findings are important considering the impact health literacy may have on health outcomes in relation to the health outcomes of a complex medical device, like a VAD, that is more commonly received by male patients.
Additionally, rural patients seem to have specific definitions for what constitutes health when compared to urban patients (Gessert et al., 2013). Definitions of good health centered on the ability of patients to remain productive and independent (Gessert et al., 2013). The contribution of rural milieu to overall health is not a new concept. In fact, it was introduced by Long and Weinert in 1989 as part of the rural nursing theory.

**Metropolitan Status and the Affordable Care Act**

Much of the data supporting health disparities related to metropolitan status was collected prior to implementation of the Affordable Care Act (ACA). The ACA aims to address health disparities through the following provisions: *Community Transformation Grants*, *Understanding Health Disparities – Data Collection and Analysis*, and the *Prevention and Public Health Fund*. The community transformation grants focus on the community-at-large by building community capacity to make healthy changes and as support to implement said changes (National Advisory Committee on Rural Health and Human Services, 2011). The ACA provision for data collection is, as it sounds, a support mechanism to enhance the data collected and analyzed on health disparities (National Advisory Committee on Rural Health and Human Services, 2011). The prevention and public health fund provision of the ACA encourages the Centers for Disease Control to utilize public health funds in a manner consistent with helping rural people despite the lesser number of people residing in rural areas (National Advisory Committee on Rural Health and Human Services, 2011). The ACA is also poised to impact the ability of urban public health departments to deliver more effective, promising population health interventions to urban areas (Leider et al., 2015). With recent discussion of repeals of the ACA the ongoing impact is unknown; however, repeals may result in millions of rural and urban residents losing their health insurance (Blumberg, Buettgens, & Holahan, 2016).
Comparing Heart Failure Outcomes: Rural versus Urban

Patients residing in rural locations comprise a significant percentage (up to 30%) of patients with new HF diagnoses (Barnett & Halverson, 2000; Barnett et al., 2000; Klug & Muus, 2012) and have been found to be significantly more likely to experience negative health outcomes, such as hospital admission and death, compared to patients in urban locations (Gamble et al., 2011; Jin et al., 2003; Joshi, O’Souza & Madhavan, 2004; Joynt et al., 2011a; Joynt et al., 2011b; Singh & Siahpush, 2014; Taubert et al., 2001). However, two studies reported no difference in outcomes when comparing rural and urban patients (Hornberger, 1999; Ross et al., 2008), and one study reported finding rural HF patients to be at an advantage in terms of outcomes compared to similar urban counterparts (Wu et al., 2010). Wu and colleagues (2010) found rural patients to experience longer event-free survival and be more likely to be adherent to prescribed medication regimens when compared to urban counterparts. Only one rural patient and one urban patient died over the course of the study which may suggest that illness severity differed when comparing these results to other studies of rural HF patients. Incongruence between findings of Wu and colleagues (2010) study with previous findings were not fully explained.

Several investigators have examined rural residency as a moderator of poor HF outcomes in the context of medical management alone (Gamble et al., 2011; Jin et al., 2003; Joshi, O’Souza & Madhavan, 2004; Joynt et al., 2011a; Joynt et al., 2011b; Taubert et al., 2001). When compared to urban patients with HF and similar comorbidities, medically managed rural patients with HF have been found to be significantly more likely to visit the emergency department, be admitted to the hospital, or die (Gamble et al., 2011; Jin et al., 2003; Joshi, O’Souza & Madhavan, 2004; Joynt et al., 2011a; Joynt et al., 2011b; Taubert et al., 2001). Taubert and colleagues (2001) reported that mean survival time for urban-dwelling patients with HF was
greater than that of rural-dwelling patients with HF at 13.4 and 7.7 months, respectively. There are a variety of potential explanations for the disparities seen in HF outcomes between rural- and urban-dwelling patients. The subsequent section will address heart failure management differences that may be contributing to geographic HF outcome imbalances.

**Geographic Heart Failure Management Differences: Rural versus Urban**

The ACCF) and AHA provide guidelines for healthcare providers for the prevention and treatment of HF including an evidence-based regimen of maintenance medications and assessment techniques (Yancy et al., 2013). However, these organizations have a task-force that reviews literature on an ongoing basis and meets bi-annually to keep up to date with new and important research findings in the treatment of HF (Jessup et al., 2009). This has resulted in the availability of “focused updates” to clinical guidelines allowing clinicians access to best practice standards (Jessup et al., 2009). Although these updates are widely available, timely access may be an issue for rural providers that are at a distance to educational resource centers or with limited access to internet services.

Evidence suggests that rural patients may not always be receiving standardized therapies for the management of HF and assessment of left ventricular function (an important indicator in the treatment decision-tree) with echocardiography upon HF admission when compared to urban counterparts (Sanborn, Manuel & Cichanska, 2008). Despite clear recommendations in the ACCF/AHA guidelines from 2002, 2005, 2008, 2011 and most recently, 2014, rural-dwelling patients were significantly less likely than their urban counterparts to be prescribed evidence-based medications like ACE inhibitors and beta blockers (Gamble et al., 2011; Joynt et al., 2011b; Lutfiyya et al., 2007; Murphy, 2013; Sanborn et al., 2008; Taubert et al., 2001) and in some cases, patients that were prescribed recommended drugs were receiving suboptimal
dosages (Sanborn et al., 2008). The reasons for this failure to follow recommendations are unclear and are likely rooted in a complex web of many issues.

Rural patients with HF are frequently managed by primary care physicians due to decreased access to specialists compared to urban patients with access to HF specialized cardiologists readily available (Sanborn et al., 2008). Improving access to HF specialists via the primary care provider has been the goal of several interventional studies in recent years (Fonarow et al., 2010; Lee et al., 2005, Mejhert & Kahan, 2015). These studies aimed to improve care for patients with HF by taking a team approach that was supervised by cardiology and managed by primary care providers who are available to follow up with their patients on a more frequent basis. Not surprisingly, routine follow up in HF care has been shown to decrease readmission tendencies (Kociol et al., 2011; Muus et al., 2010). Yet, rural-dwelling patients with HF have remained less likely to benefit from follow up care after hospital discharge (Gamble et al., 2011; Kociol et al., 2011; Muus et al., 2010).

**The Impact of Distance and Access to Heart Failure Specialists**

Rural patients may be at a disadvantage accessing HF specialists due to long travel distances and the limited number of HF specialists in rural locations. According to multiple studies, increased traveling distance to the hospital was a predictor of HF admission rates (Harris, Aboueissa & Hartley, 2008; Hornberger, 1999). However, in a study of urban residents with HF, closer travel distance to the implanting center was associated more with unplanned readmissions (Hernandez et al., 2015). Pierce (2007) found that the average distance to a cardiac specialist in rural upstate New York was reported at 32.6 miles. The increased distance to a healthcare facility could contribute to what some cardiac nurse specialists described as rural HF patients arriving to the emergency department in a more decompensated state in comparison to urban patients (Wagnild et al., 2004). These issues are especially concerning when considering VAD therapy in the rural
context given the complexity of VADs and VAD care. The next section contains a brief discussion of the literature connecting metropolitan status and VAD outcomes.

**Metropolitan Status and VAD Outcomes**

Some VAD recipients, those in healthcare professional shortage areas in particular, may have difficulty achieving the level of support required to maintain health with a VAD. These deficits are related to limited access to services including primary care providers that are knowledgeable in HF management and VAD care, cardiologists and VAD specialists, emergency care, and informal caregivers (Douthit et al., 2015; Li, 2006; Myers et al., 2013). Metropolitan status is likely to exert influence over a patient’s ability to adapt to living with a VAD and in turn, impact HRQoL. Investigating HRQoL in the context of metropolitan status in VAD recipients is important as VAD implantation becomes a common treatment in advanced HF and more patients, including those living in rural and urban areas, are implanted as a result (Grady et al., 2004; Nesbitt et al., 2014). HRQoL has not been investigated across metropolitan status in VAD recipients to date.

VAD-related adverse events can be expected to occur irrespective of metropolitan status; however, limited access to services, as mentioned above, may place some VAD recipients at increased risk of these life-threatening complications. The impact of metropolitan status on health outcomes in HF has been clearly documented; yet, very little is known about the influence of metropolitan status on clinical VAD outcomes including adverse events, hospital admissions, and mortality (Gamble et al., 2011; Jin et al., 2003; Joshi, O’Souza & Madhavan, 2004; Joynt et al., 2011a; Joynt et al., 2011b; Taubert et al., 2001). Two previous studies found no significant relationships between metropolitan status (rural vs. urban) and transplants, adverse outcomes and/or mortality in a sample of VAD patients; however, these results were taken from conference abstracts with limited methodological details (Rajagopalan et al., 2016; Vader et al., 2013).
Aside from these abstracts, no full-length publications have been located that specifically addressed VAD recipient outcomes in the context of metropolitan status. Vader et al. do not intend to seek publication of their results (J. Vader, personal communication, November 20, 2015). An inquiry sent to Rajagopalan has not been returned. The paucity of evidence reported in the literature suggests more research is necessary to discover specific clinical outcome differences in divergent groups of VAD recipients.

Conceptual Framework

The framework for the proposed study incorporates concepts from the theory of fundamental social causes of health disparities or fundamental cause theory (FCT) (Link & Phelan, 1995) and Ronald Andersen’s behavioral model of health services use (Andersen & Newman, 1973; Andersen, 1995; Andersen, 2008). This section will discuss these frameworks in detail and describe their intended use in this study.

Link and Phelan’s Theory of Fundamental Social Causes

In 1995, Bruce Link and Jo Phelan introduced the theory of fundamental social causes, also referred to as fundamental cause theory (FCT). Link and Phelan (1995) highlighted the tendency of the scientific community to focus on the proximal risk factors for disease rather than more distal factors like context. In their words, “…what puts people at risk of risks…” (Link & Phelan, 1995, p. 80). The context that Link and Phelan (1995) described was that of social factors including socioeconomic status (SES) and social support that may increase the risk of acquiring risk factors for subsequent diseases. FCT contends that SES is a “fundamental cause” of disease as it affects access to health services, service utilization, health behaviors, and health risk exposures. According to FCT, to be considered a “fundamental cause” of disease, a factor must demonstrate the following features (Phelan et al., 2004):

1. The ability to exert influence over multiple disease outcomes,
2. Influence over outcomes through multiple associated risk factors,

3. A link between the “fundamental cause” and disparate outcomes that persists over time regardless of intervention, and

4. An association with inadequate access to resources.

As Link and Phelan (1995) pointed out, the link between social conditions and health has long been established. Yet, the disparities in health between the wealthy and the poor have remained intact (Link & Phelan, 1995; Naimi, 2016). This is the result of socioeconomic status being a “fundamental cause” of health inequalities. Per Link and Phelan (1995), what defines a cause as “fundamental” lies in the inability to improve health outcomes associated with the cause even when the mechanisms that link the cause to disease have been addressed. In other words, as interventions are developed to successfully address one risk factor that links low SES to disease, another risk factor emerges (Link & Phelan, 1995). This persistence is related to access to resources (Link & Phelan, 1995). According to FCT, higher SES individuals are in a better position to utilize resources that would allow them to mediate their own health risk factors (Link & Phelan, 1995). These resources, which are persistently and intimately connected to overall health and disease risk, include “…money, knowledge, power, prestige…” and “…social connectedness…” (Link & Phelan, 1995, p. 87).

SES has been examined as a “fundamental cause” of differences in morbidity and mortality outcomes across a plethora of diseases including: cancer (Rubin, 2014), cholesterol levels, (Chang & Lauderdale, 2009) human papillomavirus vaccination, (Polonijo & Carpiano, 2013) and malaria (Dickinson et al., 2012). FCT generalizes populations as either having social resources (higher SES) or not having social resources (lower SES) (Diez Roux, 2012). Included in this generalization is that those with high social resource availability are more motivated to
pursue health (Diez Rouz, 2012). According to Phelan et al. (2004), intention to utilize health services is a key factor that links SES and outcomes such as mortality; the deliberate use of healthcare resources is the connection between SES and mortality (Phelan et al., 2004). In this study, recipients of VAD therapy may experience disparate outcomes related to their metropolitan status. The health-seeking behaviors inherent in rural culture may increase risk of adverse outcomes for these VAD recipients.

FCT acknowledges that additional sociological and demographic structures feature the characteristics of “fundamental causes” of health disparities, including race/ethnicity and gender (Link & Phelan, 1995). This study advances the literature in this area by examining metropolitan status as a “fundamental cause” of outcomes for VAD recipients. Although metropolitan status, in and of itself, cannot be changed, interventions and policies can be developed that lessen the health burden imparted as a result of residing in a particular area. Metropolitan status was incorporated as a fundamental cause and the overarching context in Andersen’s behavioral model of health services use. Andersen’s model is discussed in detail below.

**Andersen’s Behavioral Model of Health Services Use**

The goal of the behavioral model of health services use, which was originally developed in the 1970s by Ronald Andersen, was to define and measure the dimensions of access to care (Andersen, 2008). The model has gone through several iterations with revisions by Andersen and colleagues. The model was most recently revised in 2008, which is shown in Figure 2-1 (Andersen, 2008). This updated model added health outcomes and established the importance of contextual characteristics (Andersen, 2008).
Figure 2.3 Andersen’s behavioral model of health services use (Andersen, 2008).
According to Andersen’s model, the propensity toward health service utilization is influenced by predisposing, enabling and needs based factors that occur at both contextual and individual levels and influence health behaviors and subsequent health outcomes (Andersen & Newman, 1973; Andersen, 1995; Andersen, 2008). Andersen considered contextual characteristics to be those measured as an aggregate and may include characteristics of the health organization and/or the collective community (Andersen, 2008). Individual characteristics are those specific to the individual. Individual predisposing factors include characteristics like demographics (e.g. race, gender), social structures (e.g. education level, occupation), and personal health beliefs that may predispose an individual to utilize health services (Andersen & Newman, 1973; Andersen, 1995; Andersen, 2008). Individual need factors relate to illness severity and comorbid conditions (Andersen & Newman, 1973; Andersen, 1995; Andersen, 2008). Andersen considers access to be inequitable in situations where enabling resources, social structure, and health beliefs determine utilization (Andersen, 2008). Some VAD recipients may be at a disadvantage to access important health services like routine follow up care and treatment during times of medical need based on their metropolitan status (Douthit et al., 2015; Li, 2006; Myers et al., 2013). This study aimed to identify metropolitan status as a contextual dis(en)abling factor that may influence clinical outcomes (evaluated health) (Aim 1) and HRQoL (perceived health) (Aim 2) VAD patients.

Andersen’s model has been used extensively in the literature since the model’s original development. The revised model from 1995 is the model most commonly cited (Babitsch et al., 2012). However, the 2008 revision is also a popular choice and was utilized for this study (Babitsch et al., 2012). The contextual utility of the model is broad and ranges from mental health services to primary care (Dhingra et al., 2010; Hammond, Matthews, & Corbie-Smith,
Many studies that utilized Andersen’s model were secondary data analyses like this study (Babitsch et al., 2012). The model crosses study designs and has been utilized in quantitative (Dhingra et al., 2010; Hammond et al., 2010; Hochhausen et al., 2011) and qualitative studies (Insaf et al., 2010).

**Theory Integration**

To gain a comprehensive understanding of the nature of the influence of metropolitan status on outcomes in VAD therapy, an integration of these two models is necessary. Distal influence over resource access and subsequent health is common between the two frameworks and served as the overarching context of the proposed study. Initially FCT was developed to establish socioeconomic status as a fundamental cause of diseases (Link & Phelan, 1995). Since then, several other social conditions have been investigated as potential fundamental causes including: stigma (Hatzenbuehler, Phelan & Link, 2013), educational attainment (Mackenbach et al., 2015; Masters et al., 2014), sexual orientation (Branstrom et al., 2016), and racism (Phelan & Link, 2015). Although the FCT has not previously been used to investigate metropolitan status, it serves as a fitting model for such a study which will be discussed below.

Evidence suggests that metropolitan status exhibits the features of a fundamental cause. Metropolitan status has influenced multiple disease outcomes including: heart disease, chronic obstructive pulmonary disease, and mental illnesses (Fiscella & Williams, 2004; Galea & Vlahov, 2005; Meit et al., 2014) and through multiple risk factors including rates of smoking, alcohol consumption, obesity, lack of physical exercise, and exposure to air pollution (Fiscella & Williams, 2004; Galea & Vlahov, 2005; Matthews et al., 2017; Meit et al., 2014). Metropolitan status has been an ongoing source of health disparities throughout much of history despite the development of the Office of Rural Health Policy in 1987 (Hartley, 2004) and ongoing efforts to address the impacts of urban living on health (Galea & Vlahov, 2005). Efforts to reduce
disparities through various interventions including technology, like telehealth, and increased incentives for clinicians to practice in underserved settings, like loan repayment and other financial incentive programs have been employed with limited success (Albert et al., 2016; Hartley, 2004). Lastly, it is widely known that metropolitan status can impact income, educational attainment, social power, prestige, and connectedness that would allow disease risk to be avoided or high quality disease management to be established (Hartley, 2004). The emergence of a fundamental cause is dependent on changes across time in disease risks, knowledge of risks, emergence of new disease treatments or changes in the diseases themselves (Link & Phelan, 1995). These milestones are occurring in advanced HF as knowledge of new risk factors emerge and are studied, and as VAD therapy is improved. Identifying metropolitan status as a fundamental cause of VAD outcome disparities now, before the technology reaches maturity, provides the foresight necessary to improve the care and outcomes of rural-dwelling VAD patients. Although metropolitan status cannot be changed per se, the health consequences associated with it may be minimized or even eliminated for VAD recipients.

From the time of the conception of Andersen’s behavioral model, the framework was noted to be potentially useful to examining health disparities and equitable access to health services (Andersen & Newman, 1973). Andersen’s model has been adapted to many disease processes and health behaviors. In past research the behavioral model has served as the framework for studies ranging from examining health-seeking and screening behaviors (Ogunsanya et al., 2014; Roh et al., 2014) to predicting service utilization (Kim & Lee, 2016), hospital admissions (Rieke et al., 2015), hospice use (Conner, 2012), and self-care (Porteous et al., 2015). Access is considered equitable when the variance in service use can be accounted for by considering predisposing demographics and levels of need for care. In contrast, per
Andersen’s model, inequitable access occurs when service utilization is determined by predisposing social structures, health beliefs and/or the presence of enabling resources (Andersen, 2008). This study utilized Andersen’s notion of equity to examine the factors associated with metropolitan status in rural vs. urban areas as contextual enabling (or disabling) influences on VAD outcomes. Predisposing demographic variables and needs factors were considered as covariates since there was a hypothesized likelihood that they influence the relationship between geographic residence and VAD outcomes.

Although many of the concepts in the behavioral model and the FCT are compatible, the frameworks are not identical. The strengths of the FCT relate to its unwavering distal focus, and attention to the “fundamental cause’s” influences on access to care, attitudes toward health, health behaviors, and exposure to health risk factors. The FCT was intended to capture the tendency of culture and behavior to exert influence over health outcomes. In this case, FCT frames the exploration of how the composition and contexts of where VAD recipients reside could influence health disparities and treatment outcomes. Alternatively, Andersen’s model of 2008 focuses on health services utilization and subsequent health outcomes while considering contextual and individual characteristics. Framework integration allowed the comprehensive assessment of the relationships between metropolitan status, individual factors, service utilization, and VAD outcomes.

**Competing Framework**

**Conceptual Model of Health-related Quality of Life in MCS Patients**

Recently a conceptual framework was introduced in the literature that models the pathway to adjustment and health-related quality of life (HRQoL) in MCS patients (Grady et al., 2015). The impetus for the development of this model was the lack of a device-specific tool to measure HRQoL in patients undergoing device support (Grady et al., 2015). Tools are available
to assess HRQoL in HF; however, these tools fail to incorporate the unique needs of the MCS patient (Grady et al., 2015). Grady and colleagues (2015) developed the model based on qualitative interviews with VAD patients, advanced HF patients awaiting device implantation, and clinicians that were VAD experts. The concepts that emerged from these interviews were: “the effect of disease and treatment,” “resources,” and “implant strategy” (Grady et al., 2015, p. 1292). The model links implant strategy, availability of resources and disease impact to the dimensions of HRQoL (Grady et al., 2015). The “impact of disease and treatment” concept includes the sub-concepts of patient satisfaction, symptoms of HF and MCS, and self-efficacy in the care of the device (Grady et al., 2015, p. 1296). This model was considered for the framework for this dissertation study due to its connection to the study population and one of the major study outcomes. Although the concepts included in the model follow a logical flow based on what is known about living with a VAD and the potential link to HRQoL is clearly established, the constructs in the model are not directly tested in the proposed study in relation to HRQoL. The model may be important for future work with rural-dwelling MCS patients when items like patient satisfaction, symptomology and self-care are assessed. However, at this time, FCT incorporated with Andersen’s behavioral model of health services use were deemed more appropriate and Grady’s model was excluded.

**Chapter Summary**

Outcome disparities in HF related to metropolitan status are not an unfamiliar target of nursing research. Numerous studies have found relationships between metropolitan status and HF-related events like hospitalizations and death (Gamble et al., 2011; Jin et al., 2003; Joshi, O’Souza & Madhavan, 2004; Joynt et al., 2011a; Joynt et al., 2011b; Taubert et al., 2001, Wu et al., 2010). Further compounding these disparities may be reduced access to specialist cardiology care in some areas leading to an onus being placed directly on the patient to access such care.
This is accompanied by evidence that primary care providers in some areas may not follow recommended HF management guidelines (Gamble et al., 2011; Joynt et al., 2011b; Lutifiyya et al., 2007; Murphy, 2013; Sanborn et al., 2008; Taubert et al., 2001). The web of interconnected issues faced by medically managed HF patients likely extend to those advanced HF patients receiving a VAD. The complexity of VAD care makes this possibility particularly concerning. Yet, the relationship of metropolitan status to clinical and patient-reported VAD outcomes is largely unknown.
Chapter 3

Methods

Introduction

This study is a secondary analysis of data collected from the Penn State Hershey Medical Center (PSHMC) maintained by the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS). This chapter will begin by describing INTERMACS followed by a discussion of the methods utilized in this study including: study variables, human VAD recipients’ protection measures, data analysis methods, and study limitations.

INTERMACS

INTERMACS is a registry of FDA-approved, durable mechanical circulatory support (MCS) devices from 165 participating centers in the United States (163) and Canada (2) (Holman, 2012; Kirklin et al., 2015). Excluded from the registry are any devices awaiting FDA approval or short-term MCS such as extracorporeal membrane oxygenation (Holman, 2012). The registry has been supported by grant funding from the NHLBI of the National Institutes of Health (NIH) since its inception in June of 2006. Although participation in the INTERMACS registry is not required for all MCS implanting centers, involvement in a recognized multi-institution registry is a requirement for reimbursement from the Centers for Medicare and Medicaid Services when implantation is indicated as destination therapy (Holman, 2012).

INTERMACS was chosen for this study for several reasons: it is a comprehensive database that includes over 500 input parameters, including clinical outcomes and health-related quality of life (HRQoL) that are collected longitudinally throughout the patient’s trajectory with durable MCS, data standards are monitored, and INTERMACS is the only nationwide registry of its kind. Data quality is certainly a concern with such a large, multi-site operation; however, INTERMACS sets the expectation that reporting sites collect and maintain high quality data.
through regular auditing of sites and a series of ramifications for nonadherence to quality standards including site exclusion from the registry if necessary (Holman, 2012). Only a small subset of INTERMACS variables were used for this study. Study variables are highlighted in Table 3-1.

**Sample**

This study was a secondary analysis that incorporates data from PSHMC data maintained by INTERMACS. INTERMACS is supported by the NHLBI, the NIH, and the Department of Health and Human Services (HHS) under Contract Number HHSN268201100025C. Patients are added to the PSHMC INTERMACS registry as they receive ventricular assist device support at the medical center. At the time of this study, the PSHMC INTERMACS contained the records of 188 patients collected from 2006 to the time of query in November, 2016.

**Measures**

Data collected by INTERMACS including adverse events (bleeding, cardiac arrhythmias, death, device exchanges, device malfunctions, hospitalizations, infections, neurological events, and renal dysfunction) and transplants were used for this study. Demographic and pre-implantation clinical data were also used including age, gender, race, ethnicity, pre-implant NYHA, LVEF, device strategy, INR, blood type, and year of implantation. Distance and travel time from the implanting center were calculated based on address of primary residence from the recipient chart.

HRQoL data were collected by INTERMACS using the European Quality of Life 5-Dimension, 3-point Likert (EQ-5D-3L) routinely at pre-implantation and the 3, 6 and 12 month follow up time points. The EQ-5D is a generic, non-disease specific instrument measuring health-related quality of life variables including mobility, self-care, usual activities,
pain/discomfort and anxiety/depression (Rabin & de Charro, 2001). Each dimension requires the patient to select a response formatted in a 3-point Likert-scale. Responses range from no problems to some or moderate problems to extreme problems. Although the EQ-5D is not widely reported in studies of HRQoL in VAD recipients outside of those using INTERMACS it has been shown to be a reliable and valid measure in cardiovascular disease (Dyer et al., 2010). Test-retest reliability of the EQ-5D has been previously tested (van Agt et al., 1994). van Agt and colleagues (1994) surveyed 896 households in Rotterdam, the Netherlands, in the early 1990s via the Rotterdam Survey which included the EQ-5D. Of the 896 households that initially responded, 398 consented to receive a second questionnaire (retest) of the EQ-5D of which 302 were returned (van Agt et al., 1994). Analysis included the assessment of variance related to three sources: person, time, and health state in a generalizability study (G-study) (van Agt et al. 1994). The G-study confirmed that variance between the two tests could be attributed to changes in “health state” scores that occurred between the time points by testing interactions between person and time, person and health state, person, time and health state and time and health state (van Agt et al., 1994). The time and time by person and health state interactions were reported to make up 11% of the variability which suggests some change in the results over time (van Agt et al., 1994).

**Protection of Human VAD recipients**

Human VAD recipients were not directly involved in this study. The sample was drawn from the PSHMC’s INTERMACS database. To be included in this study, VAD recipients must have consented to be part of the INTERMACS. All VAD recipients in the database were considered for enrollment. VAD recipients were excluded from the proposed study if they were unable to be discharged from the hospital following ventricular assist device (VAD) implantation or if their enrollment date does not fall within the proposed study period. In addition, any subject
that received a total artificial heart for MCS were excluded. Figure 3.1 shows the exclusion flowchart. One additional patient was excluded due to their age (16 years old) at time of implant. Children were excluded from this study.

Figure 3.1 Exclusion Flowchart

The VAD recipients were minimally exposed to potential risks which are detailed below along with the plan used to mitigate these risks. The following sections include a detailed plan for the Protection of Human VAD recipients in this dissertation study. A copy of the Penn State Hershey Institutional Review Board approval for this study can be found in the Appendix.

Sources of Materials

This study used previously collected data from PSHMC that is maintained in the INTERMACS registry. These data included demographic information, such as age, race,
ethnicity, gender, rural/urban classification via geocoding, clinical information and patient survey at specified time points including prior to implantation, 3, 6, and 12 months post-implantation as well as any readmission or adverse event recorded over the same time period. No further contact with VAD recipients was required for this study.

Data were collected for research purposes only. Data coding preserved the confidentiality of the VAD recipients and findings will be reported as an aggregate to avoid identification of VAD recipients or the institution. A more detailed description of the plan used to ensure subject confidentiality and anonymity is included in the section below, Protection against Risk.

**Potential Risks**

This study posed a risk to VAD recipients’ anonymity and right to confidentiality. These risks were directly related to the use of address of primary residence to determine rural or urban status. The PI, sponsor, and advisory committee of this study recognized these risks and thus developed this plan to mitigate breeches in subject anonymity and confidentiality.

**Recruitment and Informed Consent**

Enrollment in INTERMACS is not mandatory of all VAD patients and informed consent is gained prior to device implantation and registry enrollment by a specially trained nurse VAD coordinator. Every effort is made to ensure subject autonomy is protected and consent to enroll is informed. The PSHMC institutional review board approved all procedures associated with the PSHMC INTERMACS database.

**Protection against Risk**

Subject confidentiality was maintained throughout data analyses which will continue through reporting of results. All VAD recipients were coded so that identification from raw data was not possible, including addresses of primary residence. Address information was used to
determine zip code of primary residence which was then converted to rural or urban based on definitions from the Center for Rural Pennsylvania (2014) for this study. Once rural-urban status was assigned to each subject all address information was purged from the data files.

Raw data were stored electronically in the Penn State Hershey Secure File Transfer (SFT) data center. This secure data center is available to Penn State Hershey faculty, staff, and students to securely send and receive large data files including protected health information and raw research data. The SFT is password protected by means of the Penn State Hershey ePass system. Only the PI of this study, the dissertation committee chair, and statistician were permitted to access the SFT site for this study.

After data were stratified as rural or urban data was analyzed using SAS statistical software (SAS Institute Incorporated, 2014). This required downloads of de-identified files to a desktop computer accessible only via the Penn State University web access system. This system required two-factor authentication that assured the security of the data once stored on a University desktop for analyses. The desktop computer used for analysis is in a locked office in Dr. Hupcey’s (dissertation chair) research suite at the Penn State Hershey College of Nursing office. Only the study’s PI (Alonso) and Dr. Hupcey had access to this office.

Data Analysis

INTERMACS data was converted to SAS format (SAS Institute Incorporated, 2014) without identifying patient information. Addresses of primary residences were retrieved from the PSHMC electronic medical record for geocoding and subsequently transformed to rural or urban codes by county in SAS. Longitudinal data has been collected by the PSHMC INTERMACS on continual basis since 2006. PSHMC data included all consented patients implanted with ventricular assist devices (VADs) from pre-implantation and at 1 week post-implantation, 1
month post-implantation and every 3 to 6 months thereafter. Additionally, data collection occurred with any hospital admission to PSHMC and/or device-related adverse event. For this study, the 1-week time point was not utilized as patients had not been discharged from the hospital prior to this assessment. The comprehensive INTERMACS database included specific information related to morbidity and mortality as well as patient reported quality of life indicators. At the time of analysis, the PSHMC database held the records of 188 patients.

Study Variables

This study examined demographic information including age, gender, race and ethnicity at baseline. Patients pre-implant cardiac health status was determined using New York Heart Association classes, INTERMACS Patient Profile designations and device strategy. Prior to implantation patients were categorized with an INTERMACS Patient Profile Level from 1-7 with level 1 indicating most severe status (Miller, Ulisney & Baldwin, 2010). Analysis included stratification of these levels to eliminate potential confounding effects of pre-implantation illness severity. Device strategies included: bridge to transplant, bridge to decision, bridge to recovery, and destination therapy. Those patients designated bridge-to-transplant were listed on the transplant waiting list. A bridge-to-decision designation included all patients who may possibly be considered transplants candidates, but had not been listed at the time of VAD implantation. Bridge to recovery is an uncommon strategy reserved for those occasions were VADs are implanted temporarily with anticipation of ventricular recovery. Lastly, the destination therapy designation included all patients who did not meet criteria for transplant and were not expected to ever meet the criteria. Destination therapy devices are implanted as a palliative measure for advance HF. The INTERMACS Patient Profile Level, NYHA class and device strategy designations address the individual needs factors suggested by Andersen’s behavioral model.
Additional confounding variables were analyzed as noted in the analysis below. Outcome variables included hospital admissions, adverse events including exchanges, transplant and death in the 12 months following implantation. Patient-reported health related quality of life was collected pre-implantation and at 3, 6 and 12 months after implantation using the EQ-5D-3L. Each of the study variables and the time points of data collection are included in Table 3.1.

Table 3.1 Variables and collection time points

<table>
<thead>
<tr>
<th>Variable</th>
<th>Collection Time Point</th>
<th>Type of Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics (Predisposing Factors)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Baseline</td>
<td>Continuous</td>
<td>Range 22-80</td>
</tr>
<tr>
<td>Gender</td>
<td>Baseline</td>
<td>Dichotomous</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>Race</td>
<td>Baseline</td>
<td>Nominal</td>
<td>Caucasian/White</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>African American/ Black</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Asian</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Baseline</td>
<td>Dichotomous</td>
<td>Hispanic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Hispanic</td>
</tr>
<tr>
<td>Metropolitan Status</td>
<td>Baseline</td>
<td>Dichotomous</td>
<td>Rural</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urban</td>
</tr>
<tr>
<td>Distance to VAD Center (Miles)</td>
<td>Baseline</td>
<td>Continuous</td>
<td>Range 0-200</td>
</tr>
<tr>
<td>Travel time to VAD Center (Minutes)</td>
<td>Baseline</td>
<td>Continuous</td>
<td>Range 2-300</td>
</tr>
<tr>
<td><strong>Health Status (Individual Need Factors)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA Classification</td>
<td>Baseline</td>
<td>Ordinal</td>
<td>Range Class I – Class IV</td>
</tr>
<tr>
<td>INTERMACS Patient Profile</td>
<td>Baseline</td>
<td>Ordinal</td>
<td>Range Levels 1-7</td>
</tr>
<tr>
<td>Indication for Placement</td>
<td>Baseline</td>
<td>Nominal</td>
<td>BTT - Bridge to transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BTD - Bridge to decision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BTR - Bridge to recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DT - Destination therapy</td>
</tr>
<tr>
<td><strong>Aim 1 (Evaluated Health Outcomes)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>At event</td>
<td>Ordinal</td>
<td>0-30</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>At event</td>
<td>Ordinal</td>
<td>0-30</td>
</tr>
</tbody>
</table>
Defining Rural

Consistently defining rural was essential to the success of this study. As there is no universally accepted definition of rural (Pennsylvania Office of Rural Health, 2014), the definition identified as most appropriate for this study and available data was selected. Address of primary residence was used to determine zip codes which were then used to determine county of residence. VAD recipients were then classified as rural or urban based on rural/urban county designations as reported by the Center for Rural Pennsylvania which is based on data from the 2010 U.S. Census (Center for Rural Pennsylvania, 2014). A map of rural and urban Pennsylvania counties is shown in Figure 3.2.

<table>
<thead>
<tr>
<th>Aim 2 (Perceived Health Outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exchange</strong></td>
</tr>
<tr>
<td><strong>Transplant</strong></td>
</tr>
<tr>
<td><strong>Death</strong></td>
</tr>
<tr>
<td><strong>Health-related quality of Life (EQ-5D-3L)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Note: VAD- ventricular assist device, INTERMACS- Interagency Registry of Mechanically Assisted Circulatory Support, NYHA- New York Heart Association, EQ-5D-3L – European Quality of Life, 5 Dimensions, 3-point Likert
Figure 3.2 Map of Pennsylvania, Rural/Urban designation by county (Center for Rural Pennsylvania, 2014)

Data Analysis Plan

Table 3.2 summarizes the proposed analytical plan by aim and outcome. The SAS® Edition 9.4 software was utilized for data analysis (SAS Institute Incorporated, 2014).

Table 3.2 Project Outcomes and Analytic Plan by Study Objective

<table>
<thead>
<tr>
<th>Study Objective</th>
<th>Outcomes</th>
<th>Analytic Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Preparation</td>
<td>Classification of metropolitan status</td>
<td>Identification of county of residence via address of primary residence and subsequent definition as rural or urban based on the definition utilized by the Center for Rural Pennsylvania</td>
</tr>
</tbody>
</table>
Examination of demographics across metropolitan status

Identify missing data rates and patterns

Establish influential covariates (age, gender, race, device flow, years from implant, NYHA class, INTERMACS patient profile, placement indication and device type)

**Aim 1**
Identify group difference (rural vs. urban) in outcomes: death, transplant, hospital admissions, VAD-associated adverse events

**Aim 2**
Identify group differences (rural vs. urban) in HRQoL via composite scores from EQ5D-3L

**Data Preparation**

Data preparation began with the identification of each subject as either rural or urban using geocoding followed by subsequent county classification as described above. Next, a comparison of the demographics by rural or urban county was undertaken to ensure comparability. Chi-square analysis was used to determine comparability of categorical variables. (See Table 3.1) T tests were used to analyzed continuous variables. (See Table 3.1) To further prepare the data for analysis, missing data was assessed for rates and patterns. This was accomplished through descriptive analysis as well as t-test and Chi-square to compare those with missing data against those without. Descriptive statistics and correlations were used to examine
the distribution of all covariates to determine which were influential in the proposed statistical model. Unadjusted models were fit first to ensure enough change over time in the variables.

**Missing Data**

The assessment of missing data was accomplished through manual review and utilization of PROC FREQ in SAS that could account for variables and the counts of missing data for each variable. Missing data was found to be not missing at random which is a violation of the assumptions required for imputation or modeling via full information maximum likelihood (Little & Rubin, 2002). In addition, greater than 50% of the data would have been imputed for many study variables. Therefore, the data analysis approaches were adapted and any variables found to be related to missingness were included in all models as covariates regardless of their relationship to other study variables whenever possible.

**Analysis by Aim**

SAS® Edition 9.4 software was utilized for data analysis (SAS Institute Incorporated, 2014). Descriptive statistics were completed using PROC MEANS, PROC TTEST, and PROC FREQ with expected Chi-square analysis options. Analysis of Aim 1 was achieved using PROC GENMOD and PROC PHREG. Aim 2 was examined using PROC Mixed

**Aim 1**

Aim 1 examined the longitudinal relationship of metropolitan status (rural vs. urban) to VAD-related clinical outcomes including: mortality, hospitalizations, adverse events including: exchanges, cardiac arrhythmias, bleeding events, neurological dysfunction, infections, and renal dysfunction, and transplant as a treatment endpoint. Each of these outcomes was analyzed individually. The interaction of time and metropolitan status (rural vs. urban) was the primary target for the models described in this analysis. To begin, descriptive statistics including
frequencies, means and standard deviations were calculated to examine the distribution of variables. Initially, Poisson regression models were fit to model the adverse event and transplant counts data. However, over-dispersion, or excess variance beyond the mean, necessitated the use of negative binomial models (Berk & MacDonald, 2008). Negative binomial regression allows counts to be modeled as a function of covariates while also accounting for over-dispersion (The Pennsylvania State University, 2016). In this case, counts of hospital admissions, transplants, and adverse events were examined as they related to study covariates. Covariates included: implant age, gender, race, year of implant, number of inpatient days during hospitalizations, INTERMACS patient profile at time of implant, pre-implant and bleeding INR, pre-implant NYHA class, distance to the implanting center in miles, and travel time to the implanting center. Any models that did not meet the Hessian convergence criteria of 0.0001 were not included in the analysis.

Survival and event curve plots were achieved using the Kaplan-Meier (K-M) method as K-M graphically models time dependent hazard functions (Bewick, Cheek, & Ball, 2004). Plots were modeled as cumulative proportions of those patients that had survived or not experienced an adverse event or been transplanted in their first 365 days post device implantation. Cox regression modeling was then utilized to account for covariates and calculate hazard ratios which provide an estimation of the hazard rates between two groups (Spruance et al., 2004). Cox proportional hazards modeling is the gold standard to examine time to an event as it relates to certain risk factors or covariates (Bewick, Cheek, & Ball 2004). Therefore, Cox proportional hazard models were utilized to examine the time to study outcomes including: adverse events, hospital admissions, transplant, and death. Hazard ratios that were statistically significant but
with lower limits of the confidence limits less than one were not interpreted. Notations are made in the text where this was an issue.

This study expected death, hospitalizations and adverse events hazards to be greater over time for those recipients living in rural areas when compared to urban. Time to first event was also expected to be less for rural recipients. Explant due to transplantation was hypothesized to be more likely for urban patients. In addition, time to transplant was expected to be longer in those patients residing in rural locations.

Aim 2

The second aim of the proposed study examined the relationship of metropolitan (rural vs. urban) to health-related quality of life (HRQoL) in VAD patients in the first twelve months following device implantation. Mixed linear maximum likelihood analysis was used to examine differences in composite EQ5D-3L scores between those patients in rural counties compared to those in urban counties. It was expected that overall urban patients would report increased EQ5D-3L scores in comparison to rural counterparts.

Chapter Summary

Study methods included initial data cleaning and preparation including the assessment of missing data and categorization of VAD recipients as rural or urban metropolitan status. Initial analyses centered on descriptive statistics including t-tests and $X^2$ analysis. Correlation analysis was completed to examine the relationships between dependent variables and covariates. Kaplan-Meier survival curves and Cox proportional hazards models were fitted for all primary endpoints. Negative binomial models were fit for count data. Logistic regression was completed on the limited HRQoL data available.
Chapter 4

Results

The following chapter discusses the dissertation study findings by aim. Aim 1 was addressed using Kaplan-Meier survival and event curves and Cox proportional hazards models to investigate differences in time to events or death experienced by VAD recipients based on metropolitan status (rural vs. urban) as the primary predictor, with additional covariates added based on clinical and statistical relevance. Additionally, negative binomial models were fit to examine data that was compiled as counts, for example, counts of the number of hospitalizations experienced by the sample. Metropolitan status was the primary predictor with additional covariates added as appropriate.

Linear maximum likelihood modeling was used to examine available HRQoL data and address Aim 2. Although no models showed statistical significance the Kaplan-Meier curves for any event, bleeding events, death, hospitalizations, and transplants seemed to suggest shorter times to event (longer for transplant) for rural VAD recipients. HRQoL composite scores were not different for rural and urban VAD recipients.

Sample

The total sample after exclusion of ineligible recipients was 158. A flowchart demonstrating recipient inclusion/exclusion is shown above in Figure 3.1. Demographics for those selected for the study can be found in Table 4.1. The sample was 57 years old on average, ranging from twenty-two to eighty years. The sample was mostly male (81%), Caucasian/white (89%) and married (67%). Six percent self-identified as Hispanic. VAD recipients lived an average of 55 miles ($SD=34$) from the implanting center, which translated to a 66-minute mean travel time ($SD=35$).
Clinical characteristics of the sample are shown in Table 4.2. From a clinical standpoint, most patients were classified as NYHA class III or IV prior to implant (98%). Primary cardiac diagnosis was over two years prior to implantation (74%). The most common primary diagnoses were dilated cardiomyopathy (80%) and coronary artery disease (15%). The sample was split nearly in half in terms of device strategy at implant with 45% and 41% of patients listed as bridge-to-decision and destination therapy, respectively. Device strategy changed over their course of the first year after implantation for 45 patients (28%). Twenty-three had upward
mobility, moving from bridge-to-decision to bridge-to-transplant, or destination therapy to a bridge status. The other twenty-two experienced downward status changes from a bridge status to destination therapy. Most patients (61%) had a pre-implantation left-ventricular ejection fraction of less than 20%. All INTERMACS patient profiles were represented in the sample with many patients stratified as 1-critical cardiogenic shock, 2-progressive decline, or 4-resting symptoms.
Table 4.2 Pre-implant clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Descriptive Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-implant NYHA</strong></td>
<td></td>
</tr>
<tr>
<td>Class I or II</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Class III or IV</td>
<td>155 (98)</td>
</tr>
<tr>
<td><strong>Device Strategy at Implant</strong></td>
<td></td>
</tr>
<tr>
<td>Bridge to Decision</td>
<td>69 (45)</td>
</tr>
<tr>
<td>Bridge to Transplant</td>
<td>22 (13)</td>
</tr>
<tr>
<td>Destination Therapy</td>
<td>63 (14)</td>
</tr>
<tr>
<td>Bridge to Recovery</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Unknown/Missing</td>
<td>3 (1)</td>
</tr>
<tr>
<td><strong>Time since 1st Cardiac Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>15 (10)</td>
</tr>
<tr>
<td>1 month – 1 year</td>
<td>14 (8)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>6 (4)</td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>117 (74)</td>
</tr>
<tr>
<td><strong>Pre-implant LVEF</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>90 (61)</td>
</tr>
<tr>
<td>20-29</td>
<td>35 (24)</td>
</tr>
<tr>
<td>30-39</td>
<td>16 (11)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
</tr>
<tr>
<td><strong>INTERMACS Patient Profile at Implant</strong></td>
<td></td>
</tr>
<tr>
<td>1 Critical Cardiogenic Shock</td>
<td>44 (29)</td>
</tr>
<tr>
<td>2 Progressive Decline</td>
<td>44 (29)</td>
</tr>
<tr>
<td>3 Stable, Inotrope Dependent</td>
<td>17 (11)</td>
</tr>
<tr>
<td>4 Resting Symptoms, 5 Exertion Intolerant, 6 Exertion Limited</td>
<td>48 (31)</td>
</tr>
<tr>
<td><strong>Primary Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>126 (80)</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>23 (15)</td>
</tr>
<tr>
<td>Hypertrophic Cardiomyopathy</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Valvular Heart Disease</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td><strong>Pre-implant INR</strong></td>
<td>Mean (SD), Range</td>
</tr>
<tr>
<td></td>
<td>1.38 (0.34), 0.9-3.1</td>
</tr>
</tbody>
</table>
Sample demographics and pre-implant clinical characteristics by metropolitan status

The sample contained 57 rural VAD recipients and 101 urban VAD recipients as assigned based on county of residence. Demographics were examined to determine differences between the two groups. These findings are shown in Table 4.3. Rural and urban VAD recipients were similar across most demographic characteristics apart from race and distance and time to the implanting center. There were significantly more (p=0.009) non-white VAD recipients in the urban group compared to the rural group. Also, distance and travel time to the implanting center were significantly longer for the rural VAD recipients (p<0.001). Pre-implant clinical characteristics were also similar across metropolitan status and reflected the characteristics of the complete sample. These findings are shown in Table 4.4
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rural (n=57)</th>
<th>Urban (n=101)</th>
<th>Test of Significance (Rural vs. Urban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant Age (years)</td>
<td>Mean (SD), Range</td>
<td>Mean (SD), Range</td>
<td>t (156)= 1.16, p=0.25</td>
</tr>
<tr>
<td></td>
<td>58.8 (10.9), 22-80</td>
<td>56.6 (11.7), 26-75</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>N (%)</td>
<td>N (%)</td>
<td>X²=0.57, p=0.45</td>
</tr>
<tr>
<td>Female</td>
<td>13 (23)</td>
<td>18 (18)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44 (77)</td>
<td>83 (83)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>N (%)</td>
<td>N (%)</td>
<td>X²=6.87, p=0.009</td>
</tr>
<tr>
<td>Caucasian/White</td>
<td>56 (99)</td>
<td>86 (85)</td>
<td></td>
</tr>
<tr>
<td>African American/Black</td>
<td>1 (&lt;1)</td>
<td>7 (7)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>9 (9)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>N (%)</td>
<td>N (%)</td>
<td>X²=3.52, p=0.06</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>6 (6)</td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td>N (%)</td>
<td>N (%)</td>
<td>X²=3.94, p=0.14</td>
</tr>
<tr>
<td>In a relationship (Includes:</td>
<td>44 (77)</td>
<td>64 (63)</td>
<td></td>
</tr>
<tr>
<td>Married, Domestic partners)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>7 (12)</td>
<td>17 (17)</td>
<td></td>
</tr>
<tr>
<td>Divorced/Widowed</td>
<td>5 (8)</td>
<td>19 (19)</td>
<td></td>
</tr>
<tr>
<td>Distance from Implanting Centera</td>
<td>Mean (SD), Range</td>
<td>Mean (SD), Range</td>
<td>t(158)=6.6, p=&lt;.001</td>
</tr>
<tr>
<td>(miles)</td>
<td>74 (29), 20-148</td>
<td>42 (30), 2-138</td>
<td></td>
</tr>
<tr>
<td>Travel time from Implanting Centera (minutes)</td>
<td>Mean (SD), Range</td>
<td>Mean (SD), Range</td>
<td>t(158)=6.99, p=&lt;.001</td>
</tr>
<tr>
<td></td>
<td>86 (31), 28-166</td>
<td>51 (29), 8-142</td>
<td></td>
</tr>
</tbody>
</table>

*Distance from implanting center and travel time to implanting center are collinear (see Figure 4.12)*

Note: Significant p-values (<0.05) are highlighted in **bold** type
Table 4.4 Clinical characteristics by metropolitan status with tests of significance

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Rural (n=57)</th>
<th>Urban (n=101)</th>
<th>Test of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-implant NYHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I or II</td>
<td>N (%)</td>
<td>N (%)</td>
<td>$X^2=3.65, p=0.056$</td>
</tr>
<tr>
<td>Class III or IV</td>
<td>2 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Class III or IV</td>
<td>54 (95)</td>
<td>101 (100)</td>
<td></td>
</tr>
<tr>
<td>Device Strategy at Implant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bridge to Decision</td>
<td>N (%)</td>
<td>N (%)</td>
<td>$X^2=1.65, p=0.65$</td>
</tr>
<tr>
<td>Bridge to Transplant</td>
<td>23 (40)</td>
<td>46 (46)</td>
<td></td>
</tr>
<tr>
<td>Bridge to Transplant</td>
<td>10 (17)</td>
<td>12 (12)</td>
<td></td>
</tr>
<tr>
<td>Bridge to Recovery</td>
<td>22 (39)</td>
<td>41 (41)</td>
<td></td>
</tr>
<tr>
<td>Bridge to Recovery</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Time since 1st Cardiac Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>7 (12)</td>
<td>8 (8)</td>
<td></td>
</tr>
<tr>
<td>1 month – 1 year</td>
<td>2 (3)</td>
<td>12 (12)</td>
<td></td>
</tr>
<tr>
<td>1-2 years</td>
<td>3 (4)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>44 (77)</td>
<td>73 (72)</td>
<td></td>
</tr>
<tr>
<td>Pre-implant LVEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>36 (63)</td>
<td>54 (53)</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>12 (21)</td>
<td>23 (23)</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>3 (4)</td>
<td>13 (12)</td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>0</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>INTERMACS Patient Profile at Implant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Critical Cardiogenic Shock</td>
<td>16 (28)</td>
<td>28 (28)</td>
<td></td>
</tr>
<tr>
<td>2 Progressive Decline</td>
<td>16 (28)</td>
<td>28 (28)</td>
<td></td>
</tr>
<tr>
<td>3 Stable, Inotrope Dependent</td>
<td>6 (10)</td>
<td>11 (11)</td>
<td></td>
</tr>
<tr>
<td>4 Resting Symptoms, 5 Exertion Intolerant, 6 Exertion Limited</td>
<td>16 (28)</td>
<td>32 (32)</td>
<td></td>
</tr>
<tr>
<td>Primary Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated Cardiomyopathy</td>
<td>49 (86)</td>
<td>77 (76)</td>
<td></td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>6 (10)</td>
<td>17 (17)</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic Cardiomyopathy</td>
<td>0</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>Valvular Heart Disease</td>
<td>1 (&lt;1)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Pre-implant INR</td>
<td>Mean (SD), Range</td>
<td>Mean (SD), Range</td>
<td>$t(144)=1.17, p=0.24$</td>
</tr>
<tr>
<td></td>
<td>1.36 (0.38), 0.9-3.1</td>
<td>1.29 (0.31), 0.9-2.8</td>
<td></td>
</tr>
</tbody>
</table>
Results by Aim

**Aim 1**

Sub-Aim 1.1 was to examine the relationship of metropolitan status (rural vs. urban) and VAD-related mortality in the first year following device implantation. The findings did not indicate a statistically significant relationship between VAD-related mortality and metropolitan status. Survival curves suggested rural VAD recipients may fare worse in terms of survival time; however, statistical significance was not achieved. Therefore, it cannot be ruled out that these apparent differences in the curves were simply due to chance.

Sub-aim 1.2 was to examine the relationship of metropolitan status (rural vs. urban) and hospitalizations in the first year following device implantation. The findings did not indicate a statistically significant relationship between hospitalizations experienced by VAD recipients and metropolitan status. Event curves suggest that rural recipients may experience shorter time to hospitalization, but again this may have been due to chance.

Sub-aim 1.3 was to examine the relationship of metropolitan status (rural vs. urban) and VAD-related adverse events in the first year following device implantation. The findings did not indicate a statistically significant relationship between any of the adverse events of interest (any event, bleeding, cardiac arrhythmias, device exchange, device malfunction, infection, neurological events and renal dysfunction). However, event curves suggested that rural recipients experienced a shorter time to event on the following outcomes: any event, bleeding, cardiac arrhythmias, device exchanges, device malfunctions, and neurological events. It cannot be ruled out that these were due to chance since statistical significance was not achieved.

**Aim 2**

Aim 2 was to determine the relationship between metropolitan status and patient-reported HRQoL in the first year following device implantation. Due to missing data HRQoL analyses
could not be performed as planned. Mixed linear regression modeling of composite scores irrespective of time of collection did not indicate a statistically significant relationship between metropolitan status and HRQoL.

**Event Findings**

Events examined included: bleeds, cardiac arrhythmias, device exchanges, device malfunctions, death, hospitalizations, infections, neurological events, renal dysfunction, and transplant. Summary data for these events is included in Table 4.5. When all adverse events (bleeding, cardiac arrhythmias, device exchanges, device malfunctions, deaths, infections, neurological events and renal dysfunction) were considered together, 126/158 (79%) of VAD recipients experienced at least one adverse event in the first twelve months after implantation. Twenty percent of the sample experienced at least one episode of bleeding. The most common bleeding source was gastrointestinal (27%) followed by mediastinal bleeding (18%) Nearly half of the sample experienced at least one infection in the first-year post-implantation. The device driveline was the most common site of infection. Twenty-one percent of the patients experienced at least one neurologic event in the first year of therapy. Neurological events were associated with seven of the twenty-two deaths (32%) in the sample. Cardiac arrhythmias, device malfunctions, and renal dysfunction were the least common adverse events with 20%, 19%, and 17% of all recipients having at least one event, respectively. Other adverse events were considered for examination including hepatic events, psychiatric episodes, the need for pericardial drains, and respiratory failure. These adverse events occurred in less than 15% of the VAD recipients and were therefore excluded from further analysis.

Twenty-two (15%) VAD recipients died during the first year following device implantation. Of these, nine were destination therapy, nine were bridge to decision and four were
bridge to transplant at implantation. Causes of death included: neurological dysfunction (32%), circulatory (includes heart failure and cardiomyopathy) (16%), major infection (14%), withdrawal of support (14%), and major bleeding (9%). Less common causes were hepatic dysfunction, respiratory failure, renal failure and multiple system organ failure. Twenty-three (16%) VAD recipients received heart transplants during the first year after their VAD was implanted.

Table 4.5 Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Count n (% total sample)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any event</strong></td>
<td></td>
</tr>
<tr>
<td>1 – 40 (25)</td>
<td></td>
</tr>
<tr>
<td>2 – 24 (15)</td>
<td></td>
</tr>
<tr>
<td>3 – 21 (13)</td>
<td></td>
</tr>
<tr>
<td>4 or more – 41(26)</td>
<td></td>
</tr>
<tr>
<td>Total – 126 (79)</td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
</tr>
<tr>
<td>1 – 31 (20)</td>
<td></td>
</tr>
<tr>
<td>2 – 18 (11)</td>
<td></td>
</tr>
<tr>
<td>3 or more – 18 (11)</td>
<td></td>
</tr>
<tr>
<td>Total – 67 (42)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Arrhythmia</strong></td>
<td></td>
</tr>
<tr>
<td>1 – 27 (17)</td>
<td></td>
</tr>
<tr>
<td>2 – 5 (3)</td>
<td></td>
</tr>
<tr>
<td>Total – 32 (20)</td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
</tr>
<tr>
<td>22 (14)</td>
<td></td>
</tr>
<tr>
<td><strong>Device Malfunction</strong></td>
<td></td>
</tr>
<tr>
<td>1 – 23 (14)</td>
<td></td>
</tr>
<tr>
<td>2 or more – 8 (5)</td>
<td></td>
</tr>
<tr>
<td>Total – 31 (19)</td>
<td></td>
</tr>
<tr>
<td><strong>Hospitalizations</strong></td>
<td></td>
</tr>
<tr>
<td>1 – 31 (19)</td>
<td></td>
</tr>
<tr>
<td>2 – 24 (15)</td>
<td></td>
</tr>
<tr>
<td>3 – 26 (16)</td>
<td></td>
</tr>
<tr>
<td>4 – 9 (6)</td>
<td></td>
</tr>
<tr>
<td>5 – 12 (8)</td>
<td></td>
</tr>
<tr>
<td>6 or more – 14 (9)</td>
<td></td>
</tr>
<tr>
<td>Total – 116 (73)</td>
<td></td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
</tr>
<tr>
<td>1 – 39 (62)</td>
<td></td>
</tr>
<tr>
<td>2 – 17 (27)</td>
<td></td>
</tr>
<tr>
<td>3 or more – 7 (10)</td>
<td></td>
</tr>
<tr>
<td>Total – 63 (40)</td>
<td></td>
</tr>
</tbody>
</table>
Events by metropolitan status

Comparisons were made for each event by metropolitan status (rural vs. urban) using Chi-square analysis. Each of these comparisons is shown in Table 4.6 with bold type indicating values that were statistically significant at an alpha =0.05. The only significant event difference between rural and urban VAD recipients was device malfunction (p=0.01). Rural VAD recipients were more likely to experience a device malfunction compared to urban counterparts (15/57 vs. 16/101). Of the 22 patients who died, seven (32%) were residing in rural counties. Fifteen (65%) of the transplant recipients resided in an urban county.

Table 4.6 Events by Metropolitan Status

<table>
<thead>
<tr>
<th>Event</th>
<th>Count by Metropolitan Status (% total metropolitan status)</th>
<th>Test of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rural (n=57)</td>
<td>Urban (n=101)</td>
</tr>
<tr>
<td>Any event</td>
<td>46 (80)</td>
<td>80 (80)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>24 (42)</td>
<td>43 (43)</td>
</tr>
<tr>
<td>Cardiac Arrhythmia</td>
<td>12 (21)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Death</td>
<td>7 (12)</td>
<td>15 (14)</td>
</tr>
<tr>
<td>Device Malfunction</td>
<td>15 (26)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>46 (80)</td>
<td>70 (70)</td>
</tr>
<tr>
<td>Infection</td>
<td>20 (35)</td>
<td>43 (43)</td>
</tr>
<tr>
<td>Neurological Event</td>
<td>9 (16)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>8 (14)</td>
<td>19 (19)</td>
</tr>
<tr>
<td>Transplant</td>
<td>8 (14)</td>
<td>15 (14)</td>
</tr>
</tbody>
</table>

Unadjusted Survival Curves and Cox Proportional Hazards Models

Unadjusted survival and event curves and Cox proportional hazards regressions were modeled for each of the events of interest by metropolitan status.
**Unadjusted survival curves**

Event and survival curves were modeled for each of the events reported in Table 4.5 by metropolitan status alone. These unadjusted survival curves are shown below in Figures 4.1 – 4.11. Rural VAD recipients had shorter times to events when compared to urban VAD recipients for any event (Figure 4.1), bleeding events (Figure 4.2), cardiac arrhythmias (Figure 4.3), device malfunctions (Figure 4.4), device exchanges (Figure 4.5), hospitalizations (Figure 4.6), infections (Figure 4.7), and neurological events (Figure 4.8). Rural recipients experienced a longer time to event compared to urban counterparts when examining renal dysfunction (Figure 4.9). Survival curves indicated that rural patients experience a shorter survival time following implantation (Figure 4.10). Interestingly, all recipients (n=22) in the sample that died in the first year following implantation did so in the first one hundred days following implantation, irrespective of metropolitan status. Transplant event data indicated that rural patients experience a longer time to transplant compared to urban VAD recipients (Figure 4.11). Cox proportional hazards regressions indicated that the differences between rural and urban events/survival were not statistically significant in unadjusted models. Those results are reported in the next section and summarized in Table 4.7.

**Unadjusted Cox proportional hazards models**

Unadjusted Cox proportional hazards models were fit for each of the events of interest by metropolitan status. None of these models reached statistical significance (See Table 4.7). Although some hazard ratios were greater than one, none of the lower limits of the 95% confidence limits was also greater than one which is required to make an interpretation of the events hazards (Spruance et al., 2004).
Adjusted Survival Curves and Cox Proportional Hazards Models

Adjusted Event and Survival Curves

Kaplan-Meier survival curves were fitted for models accounting for covariates. Covariates were divided into categorical sets: demographics (included gender, race, marital status, age at time of implant), distance (travel time), and cardiac health markers (pre-implant INTERMACS patient profile, pre-implant LVEF, pre-implant INR). Models were fitted with covariates simultaneously as degrees of freedom allowed. Adjusted models plotted similarly to unadjusted with rural VAD recipients appearing to have shorter time to adverse events and longer time to transplant. These figures were excluded due to their similarity to unadjusted models and because the cox proportional hazards were not significantly different based on metropolitan status.

Adjusted Cox proportional hazards models

Adjusted Cox proportional hazards models were completed for each of the events of interest with covariates added to the models. Race, travel time and distance to the implanting center were found to be significantly different in models comparing metropolitan status alone. Race was recategorized as a dichotomous variable (Caucasian/white and Non-white) for analyses due to lack of racial diversity in the sample. Non-white included those patients identifying as African American/Black, Asian and other. Travel time and distance were found to be collinear in this sample (See Figure 4.12). Therefore, only travel time was used as a covariate. Other covariates included: gender, marital status, INTERMACS patient profile at time of implant, age at time of implant, implant year, pre-implant INR, pre-implant device strategy, number of inpatient days during unplanned hospital admissions, blood type, device flow, and INR at bleeding events. Additional variables were considered and not added to the models for the
following reasons: pre-implant NYHA class – not enough variance in sample, 98% NYHA Class III or IV on implantation, pre-implant left ventricular diastolic diameter, pre-implant cardiac output, number of hospital admissions in the twelve months prior to implantation, and educational attainment—data 50% or more missing.

**Demographic Covariates**

Models adjusted for demographic covariates are shown in Tables 4.8 and 4.9 with statistically significant hazard ratios highlighted by bold print. Cox proportional hazards for device malfunction indicated the hazard was significantly different for age at the time of implant (p=0.0010, HR 0.951). However, the hazards based on metropolitan status remained insignificant. Other covariates did not reach significance as shown in Table 4.8. Cox proportional hazards for infection reached significance for patients that were divorced or widowed and by age at time of implant as shown in Table 4.9. However, metropolitan status hazards remained insignificant. None of the other event models with demographic covariates showed statistically significant hazards for the covariates or metropolitan status as the primary predictor.

**Travel time**

Travel time to the implanting center was assessed as a covariate for all events of interest in survival curves and Cox proportional hazards models. Findings from Cox proportional hazards adjusted for travel time are shown in Tables 4.10 and 4.11. Travel time was not a significant predictor of any of the outcomes of interest and hazards for metropolitan status were unchanged with the addition of travel time to the models.

**Cardiac health covariates**

Cardiac health covariates were examined individually with the clinically relevant endpoints. The cardiac health covariates included: pre-implant left ventricular ejection fraction
(LVEF), INTERMACS patient profile at time of implant, pre-implant INR, and pre-implant device strategy.

**Pre-implant LVEF**

Cox proportional hazards models adjusted for pre-implant LVEF are shown in Tables 4.12 and 4.13. The model for any event reached significance for a normal to mildly compromised pre-implant ejection fraction compared to severely compromised with those with severely compromised pre-implant LVEF being twice as likely to experience an event (p=0.001, HR=2.47) as shown in Table 4.12. However, the metropolitan status hazard remained insignificant. Also shown in Table 4.12 is the Cox proportional hazard for bleeding which reached significance for a moderately compromised pre-implant ejection fraction (p=0.02, HR=0.28) and normal to mildly compromised pre-implant ejection fraction (p=0.01, HR=2.62). Recipients with a severely compromised (<20) LVEF were over two and half times as likely to have a bleeding event. As with any event, metropolitan status hazards for bleeding remained insignificant. The hazard ratio for device exchanges was significant for pre-implant LVEF of 30-39 (moderately compromised) (p=0.01, HR=0.42). Again with those with severe compromise being less likely than those with mild compromise to experience a device exchange. Metropolitan status remained insignificant as in unadjusted models as shown in Table 4.12. Shown in Table 4.13, Cox proportional hazards for hospitalizations reached significance for a moderate to severely (20-29) compromised pre-implant ejection fraction (p=0.04 HR=1.31) and normal to mildly compromised pre-implant ejection fraction (p=0.004, HR=2.49) when compared to severely compromised (<20). As with other models adjusted for pre-implant LVEF metropolitan status hazards remained insignificant.
INTERMACS patient profile at time of implant

INTERMACS patient profile at time of implant was considered as a covariate for the following events: any event, death, hospitalizations, renal dysfunction, and transplant. Cox proportional hazards for hospitalizations reached significance for INTERMACS patient profiles of two (progressive decline) \( p=0.0192, \text{HR}=1.414 \) and three (stable but inotrope dependent) \( p=0.0429, \text{HR}=1.405 \) compared to patient profile one (cardiogenic shock) as shown in Table 4.14. Metropolitan status remained insignificant as in unadjusted models.

INR

Pre-implant INR was examined as a covariate in models of cardiac arrhythmias, bleeding events, death, device exchanges, device malfunctions, hospitalizations and neurological events. These findings are shown in Tables 4.15 and 4.16. INR was also recorded in VAD recipients at the time of bleeding event. This INR was considered a separate covariate for bleeding events. However, this model did not reach significance and is shown in Table 4.17. Cox proportional hazards for any event reached significance for pre-implant INR \( p=0.002, \text{HR}=1.61 \) as shown in Table 4.15. Metropolitan status remained insignificant as in unadjusted models for any event. Cox proportional hazards for bleeding events reached significance for pre-implant INR \( p=0.018, \text{HR}=1.85 \) as shown in Table 4.15. Cox proportional hazards for death reached significance for pre-implant INR \( p=0.04, \text{HR}=2.97 \) as shown in Table 4.15. Additionally, Cox proportional hazards for hospitalizations reached significance for pre-implant INR \( p=0.0164, \text{HR}=1.537 \) as shown in Table 4.16. Metropolitan status remained insignificant for all models adjusted for pre-implant INR.

Pre-implant Strategy

Pre-implant device strategy was also examined as a covariate for death, hospitalizations, and transplants. Cox proportional hazards for transplants reached significance for pre-implant
device strategies bridge-to-decision (p=0.021, HR=0.37) and destination therapy (p=0.0007, HR=0.03) compared to bridge to transplant as shown in Table 4.18. Despite significance the hazard ratios were relatively miniscule. Metropolitan status remained an insignificant primary predictor as in unadjusted models.

**Additional Covariates**

Additional covariates were considered as they were clinically relevant to the events of interest. These additional covariates included the number of inpatient days spent per admission, the year of transplant, and blood type. Cox proportional hazards for hospitalizations reached significance for inpatient days (p=0.004, HR=1.01) as shown in Table 4.19. None of the other covariates influenced metropolitan status as a primary predictor in any of the other models. These findings are shown in Tables 4.20 - 4.22.

**Unadjusted negative binomial regression models**

Count data for all events was calculated and then modeled using negative binomial regression models to account for over-dispersion of some variables. Estimated beta values and standard errors for unadjusted negative binomial models is shown in Table 4.23 for any event, bleeding events, death, hospitalizations, neurological events, and transplants. Cardiac arrhythmias, device exchanges, device malfunctions, infections, and renal dysfunction negative binomial models were excluded because these count outcomes did not reach the criteria required for model convergence.

**Any Event**

The any event variable included: bleeding events, cardiac arrhythmias, death, device exchange, device malfunction, infection, neurological events and renal dysfunction. When modeling any event as the outcome variable the estimated effect for rural compared to urban was
-0.0594. This did not reach statistical significance. On average the estimated count for rural (3.2391; 95% CI: 2.59, 4.05) was approximately equal to urban (3.4375; 95% CI: 2.90, 4.06).

**Bleeding Events**

When modeling bleeding events, the estimated effect for rural compared to urban was -0.0403. This did not reach statistical significance. On average the estimated count for rural (2.2558; 95% CI: 1.61, 2.92) was approximately equal to urban (2.1667; 95% CI: 1.81, 2.81).

**Death**

When modeling death as the outcome variable, the estimated effect for rural compared to urban was -0.1901. This did not reach statistical significance. On average the estimated count for rural (0.1228; 95% CI: 0.06, 0.26) was approximately equal to urban (0.1485; 95% CI: 0.09, 0.25).

**Hospitalizations**

The estimated effect for rural compared to urban was 0.0452 when modeling hospitalizations as the outcome variable. This did not reach statistical significance. On average the estimated count for rural (3.1087; 95% CI: 2.59, 3.74) was approximately equal to urban (2.9714; 95% CI: 2.55, 3.46).

**Neurological Events**

When modeling neurological events as the outcome variable, the estimated effect for rural compared to urban was 0.0910. This did not reach statistical significance. On average the estimated count for rural (1.3333; 95% CI: 0.76, 2.35) was approximately equal to urban (1.2174; 95% CI: 0.84, 1.76).
Transplants

The estimated effect for rural compared to urban was -0.0565 when modeling transplants as the outcome variable. This did not reach statistical significance. On average the estimated count for rural (0.1404; 95% CI: 0.07, 0.28) was approximately equal to urban (0.1404; 95% CI: 0.09, 0.25).

Adjusted Negative Binomial Models

Only those events that met convergence criteria were adjusted for covariates. Covariates were added to the models by set as above. Demographic covariates were considered first. Followed by travel time to the implanting center, INTERMACS patient profile at time of implant and then additional analyses with clinical relevance. These are described in more detail below.

Models adjusted with demographic covariates

Chi-square analysis showed significant differences in the sample across gender and race. Therefore, gender and race were considered as demographic covariates in adjust negative binomial models. Table 4.24 shows the results of demographic covariate analysis for any event, bleeding events, hospitalizations, neurological events, and transplants. Other outcome variable models did not reach convergence.

Any event

When considering any event as an outcome variable, the estimated effect for rural compared to urban was -0.0862, non-white compared to white was -0.1105, and female to male was 0.3082. These did not reach statistical significance. On average the estimated count for rural (3.3197; 95% CI: 2.45, 4.51) was approximately equal to urban (3.6184; 95% CI: 2.86, 4.58).
**Bleeding events**

The estimated effect for rural compared to urban was -0.0225, non-white compared to white was 0.0046, and female to male was -0.1374 when the outcome variable was bleeding events. These did not reach statistical significance. On average the estimated count of bleeding events for rural (2.1188; 95% CI: 1.43, 3.14) was approximately equal to urban (2.1671; 95% CI: 1.61, 2.92).

**Hospitalizations**

When modeling hospitalizations as the outcome variable, the estimated effect for rural compared to urban was 0.0510, non-white compared to white was 0.0652, and female to male was 0.0236. These did not reach statistical significance. On average the estimated hospitalization count for rural (3.2239; 95% CI: 2.48, 4.20) was approximately equal to urban (3.0636; 95% CI: 2.47, 3.80).

**Neurological events**

The estimated effect for rural compared to urban was -0.0290, non-white compared to white was -0.3897, and female to male was 0.4290 when modeling neurological events as the outcome variable. These did not reach statistical significance. On average the estimated count for neurological events for rural VAD recipients (1.1537; 95% CI: 0.53, 2.52) was approximately equal to urban (1.1877; 0.70, 2.02).

**Transplants**

When modeling transplants as the outcome variable, the estimated effect for rural compared to urban was -0.0401, non-white compared to white was -0.0346, and female to male was -0.4773. These did not reach statistical significance. On average the estimated count for rural (0.1190; 95% CI: 0.04, 0.33) was approximately equal to urban (0.1239; 95% CI: 0.05, 0.28).
When demographic covariates were added to the death event as a set model convergence criteria were not met. A statistically significant relationship between race and metropolitan status was described above with X² analysis therefore race was kept in the model and gender was removed. An alternative model was run with gender as a covariate and race removed. Neither of these models of death as the outcome variable met convergence criteria.

Models with travel time covariate

Travel time was modeled as a covariate in negative binomial regression models to fit any event, bleeding events, hospitalizations, and neurological events. These findings are shown in Table 4.25. Other adverse events did not meet convergence criteria. For these negative binomial models travel time was converted to a binary variable where travel time was assessed as being less than or equal to 60 minutes or greater than 60 minutes from the implanting center. Under these conditions more rural VAD recipients (61%) were greater than sixty minutes travel time when compared to urban VAD recipients (39%) and vice versa.

Any event

When modeling any event as the outcome variable, the estimated effect for rural compared to urban was -0.1170, and travel time over sixty minutes compared to under sixty minutes was 0.0991. These did not reach statistical significance. On average the estimated count for rural (3.1325; 95% CI:2.44, 4.02) was approximately equal to urban (3.5214; 95% CI:2.93, 4.24) for any event.

Bleeding events

Models with bleeding events as the outcome variable showed the estimated effect for rural compared to urban was -0.1830, and travel time over sixty minutes compared to under sixty minutes was 0.3023. These did not reach statistical significance. On average the estimated count
of bleeding events for rural (1.9906; 95% CI: 1.45, 2.73) was approximately equal to urban (2.3902; 95% CI: 1.91, 2.99).

**Hospitalizations**

When modeling hospitalizations as the outcome variable, the estimated effect for rural compared to urban was -0.0364, and travel time over sixty minutes compared to under sixty minutes was 0.1709. These did not reach statistical significance. On average the estimated hospitalization count for rural (2.9509; 95% CI: 2.42, 3.61) was approximately equal to urban (3.0604; 95% CI: 2.62, 3.58).

**Neurological events**

Models for neurological events as the outcome variable showed the estimated effect for rural compared to urban was 0.2877, and travel time over sixty minutes compared to under sixty minutes was -0.2578. These did not reach statistical significance. On average the estimated count for rural (1.5168; 95% CI: 0.74, 3.13) was approximately equal to urban 1.1376; 95% CI: 0.72, 1.79).

Death and transplant were modeled via negative binomial regression with metropolitan status as the primary predictor and travel time as a covariate. However, these models did not meet the convergence criteria and were therefore omitted.

**Pre-implant LVEF**

Pre-implant left ventricular ejection fraction was also considered as a covariate in negative binomial regression models for any event, death, hospitalizations, and transplants. Death and transplant models did not meet convergence criteria and were omitted. Results from models of any event and hospitalizations are reported in Table 4.26; all models failed to reach statistical significance.
Any event

When any event was considered as an outcome variable, the estimated effect for rural compared to urban was -0.0520, and pre-implant LVEF less than 20 was 0.1794, 20-29 was 0.4240, and 30-39 was 0.2679 compared to those with mild compromise and normal LVEF. These did not reach statistical significance. On average the estimated count for any event for rural VAD recipients (3.4357; 95% CI: 2.50, 4.73) was approximately equal to urban (3.6192; 95% CI: 2.88, 4.55).

Hospitalizations

When modeling hospitalizations as the outcome variable, the estimated effect for rural compared to urban was 0.0445, and pre-implant LVEF less than 20 was 0.0805, 20-29 was 0.1418, and 30-39 was 0.0101 compared to those with mild compromise and normal LVEF. These did not reach statistical significance. On average the estimated hospitalization count for rural recipients (3.0317; 95% CI: 2.29, 3.99) was approximately equal to urban (2.8998; 95% CI: 2.34, 3.59).

INTERMACS Patient Profile at Time of Implant

INTERMACS patient profile at time of implant was also considered as a covariate in negative binomial regression models for any event, death, hospitalizations, and transplants. Death and transplant models did not meet convergence criteria and were omitted. Results from models of any event and hospitalizations are reported in Table 4.27

Any event

When modeling any event as the outcome variable with pre-implant INTERMACS patient profile as a covariate, the estimated effect for rural compared to urban was -0.0012, and patient profile 1 (cardiogenic shock) was 0.1054, patient profile 2 (progressive decline) was -
0.4462, and patient profile 3 (stable, but inotrope dependent) was -0.2539. Profiles 1 and 3 did not reach statistical significance. Profile 2 (progressive decline) was significantly different than the reference; however, this did not impact the significance of metropolitan status. This estimate is highlighted in bold type in Table 4.27 On average the estimated count for any event for rural recipients (3.2293; 95% CI: 2.55, 4.09) was approximately equal to urban (3.2332; 95% CI: 2.69, 3.89).

**Hospitalizations**

The estimated effect for rural compared to urban was 0.0869, and patient profile 1 (cardiogenic shock) was -0.1233, patient profile 2 (progressive decline) was -0.0481, and patient profile 3 (stable, but inotrope dependent) was -0.1145 when modeling hospitalizations as the outcome variable. These did not reach statistical significance. On average the estimated count for rural (3.2037; 95% CI: 2.64, 3.89) was approximately equal to urban (2.9371; 95% CI: 2.49, 3.46).

**Device Flow**

Device flow (pulsatile vs. continuous) was also considered as a covariate in negative binomial regression models for any event, bleeding events, death, device malfunction, device exchange, hospitalizations, neurological events, renal dysfunction and transplants. Device exchanges, device malfunctions, hospitalizations, neurological events, and renal dysfunction models did not meet convergence criteria and were omitted. Results from models of any event, bleeding events, death, and transplants are reported in Table 4.28; all models failed to reach statistical significance.
Any event

When any event was considered as an outcome variable, the estimated effect for rural compared to urban was -0.4388, and continuous flow was 0.0885. These did not reach statistical significance. On average the estimated count for rural (2.6260; 95% CI: 1.40, 4.92) was approximately equal to urban (4.0726; 95% CI: 2.98, 5.58).

Bleeding events

The estimated effect for rural compared to urban was -0.6813, and continuous flow was -0.4173 when bleeding events were modeled as an outcome with a device flow covariate. These did not reach statistical significance. On average the estimated count for rural (1.54; 95% CI: 0.62, 3.88) was approximately equal to urban (3.0438; 95% CI: 2.27, 4.09).

Death

When death was modeled as the outcome variable, the estimated effect for rural compared to urban was -0.4322, and continuous flow was 0.4322. These did not reach statistical significance. On average the estimated count for rural deaths (0.1212; 95% CI: 0.01, 1.02) was approximately equal to urban (0.1867; 95% CI: 0.06, 0.56).

Transplant

When transplant was modeled as the outcome of interest, the estimated effect for rural compared to urban was 0.0926, and continuous flow was -0.9876. These did not reach statistical significance. On average the estimated count for rural (0.1887; 95% CI: 0.03, 1.38) was approximately equal to urban (0.1720; 95% CI: 0.06, 0.46).
Other Covariate Models

Blood type and pre-implant strategy were both considered as covariates in models of metropolitan status and transplant; however due to the small number of transplants in the sample (23), neither of these models met convergence criteria and were omitted.

HRQoL

Of the 158 VAD recipients included in this study, twenty-seven completed the EQ5D-3L at the time of implantation. Twenty-two completed the EQ-5D at three months, twenty-three at six months and fifteen at twelve months for a total of eighty-seven composite scores. Seventy-one percent (62/87) of the EQ-5D-3Ls were collected from urban recipients compared to rural. Ten recipients had greater than one time point collected. Therefore, the analysis to achieve Aim 2 was not completed as anticipated. No information was provided on the reasons for missingness and too little data existed to determine missing-at-random conditions necessary for imputation techniques. All composite EQ-5D-3L scores were compiled and analyzed via mixed linear maximum likelihood models irrespective of time of collection. Mean EQ-5D composite score was 2.88 (SD=2.12). Statistical significance was not achieved when rural and urban metropolitan status were compared. These findings are shown in Table 4.29. Due to the small number of VAD recipients with complete HRQoL data points models were not fitted with covariates.

Chapter Summary

Kaplan-Meier event or survival analyses, Cox proportional hazards models and negative binomial models for analyzing variable counts did not show significant differences in VAD outcomes based on metropolitan status in unadjusted or models adjusted with covariates. Survival and event Kaplan-Meier curves suggest there may be longer times to events based on metropolitan status; however, these did not reach statistical significance. HRQoL data was
incomplete and did not allow a robust analysis of this data. From the data that was available a
composite score was calculated and analyzed irrespective of visit of completion. Results did not
indicate a significant relationship between composite EQ-5D-3L scores and metropolitan status.
### Table 4.7 Unadjusted Cox proportional hazards models by event

<table>
<thead>
<tr>
<th>Events</th>
<th>Hazard Ratios for Events of Interest (95% Wald Robust Confidence Limits)</th>
<th>Test of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>1.0 (0.79, 1.29)</td>
<td>$X^2 = 0.003, p=0.95$</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.91 (0.54, 1.54)</td>
<td>$X^2 = 0.13, p=0.72$</td>
</tr>
<tr>
<td>Cardiac Arrhythmias</td>
<td>1.17 (0.56, 2.4)</td>
<td>$X^2 = 0.17, p=0.68$</td>
</tr>
<tr>
<td>Death</td>
<td>0.77 (0.31, 1.88)</td>
<td>$X^2 = 0.33, p=0.56$</td>
</tr>
<tr>
<td>Device Malfunctions</td>
<td>1.62 (0.79, 3.36)</td>
<td>$X^2 = 2.83, p=0.09$</td>
</tr>
<tr>
<td>Exchanges</td>
<td>1.17 (0.53, 2.14)</td>
<td>$X^2 = 0.27, p=0.60$</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>1.10 (0.88, 1.39)</td>
<td>$X^2 = 0.39, p=0.53$</td>
</tr>
<tr>
<td>Infection</td>
<td>0.79 (0.50, 1.23)</td>
<td>$X^2 = 1.18, p=0.28$</td>
</tr>
<tr>
<td>Neurological</td>
<td>0.79 (0.35, 1.78)</td>
<td>$X^2 = 0.43, p=0.51$</td>
</tr>
<tr>
<td>Renal</td>
<td>0.53 (0.21, 1.25)</td>
<td>$X^2 = 2.13, p=0.14$</td>
</tr>
<tr>
<td>Transplants</td>
<td>0.68 (0.27, 1.72)</td>
<td>$X^2 = 0.66, p=0.43$</td>
</tr>
</tbody>
</table>
Table 4.8 Cox proportional hazards models for any event, bleeding events, cardiac arrhythmias, death, device exchange, and device malfunctions with metropolitan status as the primary predictor and adjusted for demographic covariates

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Any event, Hazard ratio (95% CL)</th>
<th>Bleeding, Hazard ratio (95% CL)</th>
<th>Cardiac Arrhythmias, Hazard ratio (95% CL)</th>
<th>Death, Hazard ratio (95% CL)</th>
<th>Device Exchange, Hazard ratio (95% CL)</th>
<th>Device Malfunction, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>0.97 (0.75, 1.26)</td>
<td>0.92 (0.53, 1.56)</td>
<td>1.38 (0.59, 3.2)</td>
<td>0.58 (0.2, 1.65)</td>
<td>0.92 (0.4, 2.08)</td>
<td>1.45 (0.69, 3.05)</td>
</tr>
<tr>
<td>Gender</td>
<td>0.99 (0.75, 1.33)</td>
<td>1.03 (0.62, 1.73)</td>
<td>0.35 (0.11, 1.15)</td>
<td>1.53 (0.47, 5.02)</td>
<td>0.57 (0.21, 1.5)</td>
<td>1.07 (0.53, 2.12)</td>
</tr>
<tr>
<td>Race</td>
<td>0.99 (0.63, 1.55)</td>
<td>1.08 (0.55, 2.14)</td>
<td>2.38 (0.79, 7.13)</td>
<td>0.73 (0.11, 4.97)</td>
<td>3.69 (1.08, 12.55)</td>
<td>0.38 (0.09, 1.53)</td>
</tr>
<tr>
<td>Marital Status</td>
<td>0.97 (0.69, 1.53)</td>
<td>1.48 (0.81, 2.71)</td>
<td>1.25 (0.23, 2.83)</td>
<td>1.97 (0.11, 2.32)</td>
<td>3.04 (0.11, 3.97)</td>
<td>0.38 (0.14, 0.98)</td>
</tr>
<tr>
<td>Single</td>
<td>0.96 (0.69, 1.57)</td>
<td>1.52 (0.84, 2.78)</td>
<td>1.77 (0.25, 1.28)</td>
<td>0.40 (0.29, 20.8)</td>
<td>.</td>
<td>0.79 (0.26, 2.41)</td>
</tr>
<tr>
<td>Widowed/Divorced</td>
<td>0.99 (0.98, 1.0)</td>
<td>1.01 (0.99, 1.03)</td>
<td>1.0 (0.97, 1.04)</td>
<td>1.02 (0.97, 1.08)</td>
<td>0.99 (0.95, 1.03)</td>
<td>0.951 (0.93, 0.98)</td>
</tr>
<tr>
<td>Implant Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status, male gender, Caucasian/white race, and marital status married were used as reference groups.

Note: Hazard ratios in **bold** type were statistically significant at an alpha=0.05.
Table 4.9 Cox proportional hazards models for hospitalizations, infections, neurological events, renal dysfunction and transplants with metropolitan status as the primary predictor and adjusted for demographic covariates

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hospitalizations, Hazard ratio (95% CL)</th>
<th>Infections, Hazard ratio (95% CL)</th>
<th>Neurological events, Hazard ratio (95% CL)</th>
<th>Renal dysfunction, Hazard ratio (95% CL)</th>
<th>Transplants, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>1.07 (0.83, 1.37)</td>
<td>0.74 (0.48, 1.15)</td>
<td>0.68 (0.32, 1.44)</td>
<td>0.55 (0.22, 1.39)</td>
<td>0.82 (0.32, 2.07)</td>
</tr>
<tr>
<td>Gender</td>
<td>0.95 (0.69, 1.31)</td>
<td>0.98 (0.55, 1.74)</td>
<td>1.99 (0.83, 4.77)</td>
<td>1.11 (0.49, 2.5)</td>
<td>0.42 (0.11, 1.63)</td>
</tr>
<tr>
<td>Race</td>
<td>1.19 (0.68, 2.07)</td>
<td>1.05 (0.56, 1.97)</td>
<td>1.27 (0.32, 5.1)</td>
<td>0.61 (0.19, 1.89)</td>
<td>0.61 (0.13, 2.94)</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>1.16 (0.75, 1.78)</td>
<td>0.54 (0.24, 1.19)</td>
<td>0.32 (0.06, 1.72)</td>
<td>1.3 (0.41, 4.1)</td>
<td>1.66 (0.49, 5.7)</td>
</tr>
<tr>
<td>Widowed/Divorced</td>
<td>0.80 (0.49, 1.29)</td>
<td><strong>0.45 (0.21, 0.95)</strong></td>
<td>0.36 (0.09, 1.47)</td>
<td>2.03 (0.73, 5.63)</td>
<td>1.22 (0.37, 4.03)</td>
</tr>
<tr>
<td>Implant Age</td>
<td>1.01 (0.99, 1.02)</td>
<td><strong>0.98 (0.96, 1.01)</strong></td>
<td>1.01 (0.97, 1.06)</td>
<td>0.98 (0.94, 1.03)</td>
<td>0.97 (0.94, 1.01)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status, male gender, Caucasian/white race, and marital status married were used as reference groups. Hazard ratios in **bold** type were statistically significant at an alpha=0.05.

Table 4.10 Cox proportional hazards models for any event, bleeding, cardiac arrhythmias, death, device exchange and device malfunction with metropolitan status as the primary predictor and adjusted for a travel time covariate

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Any event, Hazard ratio (95% CL)</th>
<th>Bleeding, Hazard ratio (95% CL)</th>
<th>Cardiac Arrhythmias, Hazard ratio (95% CL)</th>
<th>Death, Hazard ratio (95% CL)</th>
<th>Device Exchange, Hazard ratio (95% CL)</th>
<th>Device Malfunction, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>1.03 (0.77, 1.36)</td>
<td>0.82 (0.43, 1.58)</td>
<td>1.34 (0.64, 2.81)</td>
<td>0.97 (0.32, 2.97)</td>
<td>0.81 (0.38, 1.72)</td>
<td>1.84 (0.82, 4.12)</td>
</tr>
<tr>
<td>Travel time</td>
<td>0.99 (0.99, 1.00)</td>
<td>1.00 (0.99, 1.01)</td>
<td>0.99 (0.99, 1.00)</td>
<td>0.99 (0.98, 1.00)</td>
<td>1.01 (0.99, 1.02)</td>
<td>0.99 (0.99, 1.01)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status was used as a reference group.
Table 4.11 Cox proportional hazards models for hospitalizations, infections, neurological events, renal dysfunction and transplants with metropolitan status as the primary predictor and adjusted for a travel time covariate

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hospitalizations, Hazard ratio (95% CL)</th>
<th>Infections, Hazard ratio (95% CL)</th>
<th>Neurological events, Hazard ratio (95% CL)</th>
<th>Renal Dysfunction, Hazard ratio (95% CL)</th>
<th>Transplants, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>1.06 (0.81, 1.39)</td>
<td>0.89 (0.57, 1.39)</td>
<td>0.90 (0.40, 2.03)</td>
<td>0.68 (0.29, 1.63)</td>
<td>0.77 (0.22, 2.66)</td>
</tr>
<tr>
<td>Travel time</td>
<td>1.00 (0.99, 1.00)</td>
<td>0.99 (0.99, 1.00)</td>
<td>0.99 (0.99, 1.00)</td>
<td>0.99 (0.98, 1.00)</td>
<td>0.99 (0.98, 1.01)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status was used as a reference group.

Table 4.12 Cox proportional hazards models for any event, bleeding, cardiac arrhythmias, death, device exchange and device malfunction with metropolitan status as the primary predictor and adjusted for pre-implant left ventricular ejection fraction (LVEF)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Any event, Hazard ratio (95% CL)</th>
<th>Bleeding, Hazard ratio (95% CL)</th>
<th>Cardiac Arrhythmias, Hazard ratio (95% CL)</th>
<th>Death, Hazard ratio (95% CL)</th>
<th>Device Exchange, Hazard ratio (95% CL)</th>
<th>Device Malfunction, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>1.09 (0.85, 1.4)</td>
<td>0.85 (0.49, 1.47)</td>
<td>1.54 (0.68, 3.47)</td>
<td>0.66 (0.21, 2.02)</td>
<td>1.09 (0.58, 2.04)</td>
<td>1.58 (0.75, 3.32)</td>
</tr>
<tr>
<td>Pre-implant LVEF 20-29</td>
<td>1.18 (0.88, 1.58)</td>
<td>1.06 (0.63, 1.79)</td>
<td>0.64 (0.22, 1.82)</td>
<td>0.69 (0.18, 2.64)</td>
<td>1.03 (0.36, 2.94)</td>
<td>0.5 (0.22, 1.14)</td>
</tr>
<tr>
<td>30-39</td>
<td>1.11 (0.75, 1.65)</td>
<td><strong>0.28 (0.09, 0.88)</strong></td>
<td>1.81 (0.62, 5.26)</td>
<td>1.81 (0.54, 6.06)</td>
<td><strong>0.42 (0.22, 0.82)</strong></td>
<td>0.59 (0.17, 1.99)</td>
</tr>
<tr>
<td>&gt;40</td>
<td><strong>2.47 (1.88, 3.24)</strong></td>
<td><strong>2.62 (0.99, 6.92)</strong></td>
<td>4.2 (0.72, 24.4)</td>
<td>1.69 (0.28, 10.0)</td>
<td>2.01 (1.09, 3.7)</td>
<td>1.38 (0.17, 11.2)</td>
</tr>
</tbody>
</table>

Note: Hazard ratios in **bold** type were statistically significant at an alpha=0.05.
Note: Urban metropolitan status and pre-implant LVEF <20 were reference groups.
Table 4.13 Cox proportional hazards models for hospitalizations, infections, neurological events, renal dysfunction and transplants with metropolitan status as the primary predictor and adjusted for pre-implant LVEF

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hospitalizations, Hazard ratio (95% CL)</th>
<th>Infections, Hazard ratio (95% CL)</th>
<th>Neurological events, Hazard ratio (95% CL)</th>
<th>Renal dysfunction, Hazard ratio (95% CL)</th>
<th>Transplants, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>1.15 (0.89, 1.47)</td>
<td>0.79 (0.51, 1.24)</td>
<td>0.95 (0.44, 2.07)</td>
<td>0.61 (0.24, 1.51)</td>
<td>1.12 (0.45, 2.77)</td>
</tr>
<tr>
<td>Pre-implant LVEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td><strong>1.31 (0.99, 1.72)</strong></td>
<td>0.84 (0.47, 1.48)</td>
<td>1.1 (0.45, 2.73)</td>
<td>1.16 (0.48, 2.78)</td>
<td>0.85 (0.27, 2.67)</td>
</tr>
<tr>
<td>30-39</td>
<td>0.98 (0.63, 1.52)</td>
<td>1.03 (0.55, 1.91)</td>
<td>1.74 (0.59, 5.13)</td>
<td>1.65 (0.61, 4.45)</td>
<td>1.46 (0.45, 4.76)</td>
</tr>
<tr>
<td>&gt;40</td>
<td><strong>2.5 (1.33, 4.7)</strong></td>
<td>1.07 (0.43, 2.68)</td>
<td>2.73 (0.88, 8.47)</td>
<td>2.2 (0.68, 7.19)</td>
<td>1.98 (0.25, 15.81)</td>
</tr>
</tbody>
</table>

Note: Hazard ratios in **bold** type were statistically significant at an alpha=0.05.
Note: Urban metropolitan status and pre-implant LVEF <20 were reference groups.
Table 4.14 Cox proportional hazards models for any event, death, hospitalizations, renal dysfunction and transplants with metropolitan status as the primary predictor and adjusted for pre-implant INTERMACS patient profile (LVEF)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Any event, Hazard ratio (95% CL)</th>
<th>Death, Hazard ratio (95% CL)</th>
<th>Hospitalizations, Hazard ratio (95% CL)</th>
<th>Renal dysfunction, Hazard ratio (95% CL)</th>
<th>Transplants, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>1.04 (0.84, 1.29)</td>
<td>1.04 (0.27, 1.71)</td>
<td>1.09 (0.86, 1.39)</td>
<td>0.56 (0.24, 1.34)</td>
<td>0.77 (0.34, 1.75)</td>
</tr>
<tr>
<td>Pre-implant INTERMACS Profile 2 – Progressive Decline</td>
<td>0.85 (0.65, 1.12)</td>
<td>0.85 (0.17, 1.64)</td>
<td><strong>1.41 (1.01, 1.96)</strong></td>
<td>0.48 (0.16, 1.68)</td>
<td>2.06 (0.84, 5.08)</td>
</tr>
<tr>
<td>3 Stable, Inotrope Dependent</td>
<td>1.13 (0.77, 1.65)</td>
<td>1.13 (0.05, 3.05)</td>
<td><strong>1.41 (1.01, 1.93)</strong></td>
<td>0.65 (0.12, 3.62)</td>
<td>0.93 (0.22, 4.02)</td>
</tr>
<tr>
<td>4, 5, 6 Resting Symptoms/ Difficulties with Exertion</td>
<td>0.82 (0.63, 1.07)</td>
<td>0.82 (0.28, 1.84)</td>
<td>1.17 (0.83, 1.62)</td>
<td>1.19 (0.55, 2.56)</td>
<td>0.26 (0.05, 1.25)</td>
</tr>
</tbody>
</table>

Note: Hazard ratios in **bold** type were statistically significant at an alpha=0.05.
Note: Urban metropolitan status and pre-implant INTERMACS profile of 1 – cardiogenic shock were reference groups.
Table 4.15 Cox proportional hazards models for any event, bleeding, cardiac arrhythmias, death, device exchange, and device malfunction with metropolitan status as the primary predictor and adjusted for pre-implant INR

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Any event, Hazard ratio (95% CL)</th>
<th>Bleeding, Hazard ratio (95% CL)</th>
<th>Cardiac Arrhythmias, Hazard ratio (95% CL)</th>
<th>Death, Hazard ratio (95% CL)</th>
<th>Device Exchange, Hazard ratio (95% CL)</th>
<th>Device Malfunction, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>1.02 (0.79, 1.32)</td>
<td>0.95 (0.57, 1.6)</td>
<td>1.36 (0.62, 2.97)</td>
<td>0.79 (0.31, 2.05)</td>
<td>1.21 (0.68, 2.15)</td>
<td>1.61 (0.79, 3.28)</td>
</tr>
<tr>
<td>Pre-implant INR</td>
<td><strong>1.61 (1.19, 2.18)</strong></td>
<td><strong>1.85 (0.97, 3.54)</strong></td>
<td>1.46 (0.51, 4.22)</td>
<td><strong>2.97 (1.04, 8.44)</strong></td>
<td>0.70 (0.12, 3.97)</td>
<td>0.71 (0.24, 2.07)</td>
</tr>
</tbody>
</table>

Note: Hazard ratios in **bold** type were statistically significant at an alpha=0.05.
Note: Urban metropolitan status was the reference group.

Table 4.16 Cox proportional hazards models for hospitalizations and neurological events with metropolitan status as the primary predictor and adjusted for pre-implant INR

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hospitalizations, Hazard ratio (95% CL)</th>
<th>Neurological Events, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>1.07 (0.85, 1.35)</td>
<td>0.82 (0.36, 1.87)</td>
</tr>
<tr>
<td>Pre-implant INR</td>
<td><strong>1.54 (1.05, 2.26)</strong></td>
<td>0.82 (0.34, 1.97)</td>
</tr>
</tbody>
</table>

Note: Hazard ratios in **bold** type were statistically significant at an alpha=0.05.
Note: Urban metropolitan status was the reference group.
Table 4.17 Cox proportional hazards model of bleeding events with metropolitan status as the primary predictor and adjusted for INR at the time of bleeding event

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Bleeding, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>1.12 (0.78, 1.59)</td>
</tr>
<tr>
<td>INR at time of Bleeding Event</td>
<td>0.84 (0.68, 1.05)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status was the reference group

Table 4.18 Cox proportional hazards models for hospitalizations and neurological events with metropolitan status as the primary predictor and adjusted for pre-implant device implantation strategy

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Death, Hazard ratio (95% CL)</th>
<th>Hospitalizations, Hazard ratio (95% CL)</th>
<th>Transplants, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>0.64 (0.25, 1.62)</td>
<td>1.10 (0.86, 1.4)</td>
<td>0.68 (0.31, 1.52)</td>
</tr>
<tr>
<td>Pre-implant Strategy</td>
<td>0.58 (0.2, 1.69)</td>
<td>0.99 (0.65, 1.48)</td>
<td>0.37 (0.16, 0.81)</td>
</tr>
<tr>
<td>Bridge-to-Transplant</td>
<td>0.51 (0.17, 1.51)</td>
<td>0.92 (0.6, 1.41)</td>
<td>0.03 (0.004, 0.21)</td>
</tr>
</tbody>
</table>

Note: Hazard ratios in **bold** type were statistically significant at an alpha=0.05.
Note: Urban metropolitan status and pre-implant strategy bridge-to-transplant were the reference groups

Table 4.19 Cox proportional hazards model of hospitalizations with metropolitan status as the primary predictor and adjusted for number of inpatient days during last prior hospitalization

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hospitalizations, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>0.95 (0.76, 1.19)</td>
</tr>
<tr>
<td>Inpatient days last prior hospitalization</td>
<td>1.01 (1.003, 1.01)</td>
</tr>
</tbody>
</table>

Note: Hazard ratios in **bold** type were statistically significant at an alpha=0.05
Note: Urban metropolitan status was the reference group
Table 4.20 Cox proportional hazards model of hospitalizations with metropolitan status as the primary predictor and adjusted for year of implant

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Hospitalizations, Hazard ratio (95% CL)</th>
<th>Device Malfunction, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>1.09 (0.86, 1.39)</td>
<td>1.64 (0.79, 3.4)</td>
</tr>
<tr>
<td>Year of implant</td>
<td>0.98 (0.93, 1.03)</td>
<td>0.97 (0.84, 1.12)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status was the reference group

Table 4.21 Cox proportional hazards model of any event with metropolitan status as the primary predictor and adjusted for device flow (pulsatile vs. continuous)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Any event, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>1.02 (0.79, 1.3)</td>
</tr>
<tr>
<td>Device flow - Pulsatile</td>
<td>1.15 (0.53, 1.45)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status and continuous flow were the reference groups

Table 4.22 Cox proportional hazards models for transplants with metropolitan status as the primary predictor and adjusted for recipient blood type

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Transplants, Hazard ratio (95% CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>0.79 (0.3, 2.04)</td>
</tr>
<tr>
<td>Blood Type A</td>
<td>0.71 (0.29, 1.72)</td>
</tr>
<tr>
<td>AB</td>
<td>0.76 (0.09, 6.45)</td>
</tr>
<tr>
<td>B</td>
<td>1.39 (0.41, 4.77)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status and blood type - O were the reference groups
Table 4.23 Unadjusted negative binomial models of metropolitan status for the outcomes any event, bleeding, death, hospitalizations, neurological events, and transplants

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Any event, (\beta) (SE)</th>
<th>Bleeding, (\beta) (SE)</th>
<th>Death, (\beta) (SE)</th>
<th>Hospitalizations, (\beta) (SE)</th>
<th>Neurological events, (\beta) (SE)</th>
<th>Transplants, (\beta) (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>-0.06 (0.14)</td>
<td>-0.04 (0.19)</td>
<td>-0.19 (0.46)</td>
<td>0.09 (0.12)</td>
<td>0.09 (0.34)</td>
<td>-0.06 (0.44)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status served as the reference group

Table 4.24 Negative binomial models of metropolitan status adjusted for demographic covariates (gender, race) for the outcomes any event, bleeding, hospitalizations, neurological events, and transplants

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Any event, (\beta) (SE)</th>
<th>Bleeding, (\beta) (SE)</th>
<th>Hospitalizations, (\beta) (SE)</th>
<th>Neurological events, (\beta) (SE)</th>
<th>Transplants, (\beta) (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>-0.09 (0.14)</td>
<td>-0.02 (0.19)</td>
<td>0.05 (0.13)</td>
<td>-0.03 (0.36)</td>
<td>-0.04 (0.45)</td>
</tr>
<tr>
<td>Gender</td>
<td>0.31 (0.17)</td>
<td>-0.14 (0.31)</td>
<td>0.02 (0.21)</td>
<td>0.43 (0.35)</td>
<td>-0.48 (0.78)</td>
</tr>
<tr>
<td>Race</td>
<td>-0.11 (0.23)</td>
<td>0.004 (0.23)</td>
<td>0.07 (0.15)</td>
<td>-0.39 (0.56)</td>
<td>-0.03 (0.64)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status, male gender, and white race served as reference groups

Table 4.25 Negative binomial models of metropolitan status adjusted for travel time covariate for the outcomes any event, bleeding, hospitalizations, and neurological events.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Any event, (\beta) (SE)</th>
<th>Bleeding, (\beta) (SE)</th>
<th>Hospitalizations, (\beta) (SE)</th>
<th>Neurological events, (\beta) (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>-0.12 (0.17)</td>
<td>-0.18 (0.21)</td>
<td>-0.036 (0.14)</td>
<td>0.29 (0.50)</td>
</tr>
<tr>
<td>Travel time</td>
<td>0.10 (0.17)</td>
<td>0.30 (0.20)</td>
<td>0.18 (0.13)</td>
<td>-0.26 (0.46)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status and less than 60 minutes from the implanting center served as reference groups
Table 4.26 Negative binomial models of metropolitan status adjusted for pre-implant left-ventricular ejection fraction (LVEF) covariate for the outcomes any event and hospitalizations.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Any event, $\beta$ (SE)</th>
<th>Hospitalizations, $\beta$ (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>-0.05 (0.15)</td>
<td>0.04 (0.13)</td>
</tr>
<tr>
<td>Pre-implant LVEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 (severe)</td>
<td>-0.18 (0.37)</td>
<td>0.08 (0.35)</td>
</tr>
<tr>
<td>20-29 (severe-moderate)</td>
<td>-0.42 (0.38)</td>
<td>0.14 (0.36)</td>
</tr>
<tr>
<td>30-39 (moderate)</td>
<td>-0.27 (0.39)</td>
<td>-0.01 (0.41)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status and normal LVEF served as reference groups, LVEF – left ventricular ejection fraction

Table 4.27 Negative binomial models of metropolitan status adjusted for pre-implant INTERMACS patient profile covariate

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Any event, $\beta$ (SE)</th>
<th>Hospitalizations, $\beta$ (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>-0.001 (0.14)</td>
<td>0.09 (0.12)</td>
</tr>
<tr>
<td>Pre-implant INTERMACS Patient Profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Critical Cardiogenic Shock</td>
<td>0.10 (0.16)</td>
<td>-0.12 (0.16)</td>
</tr>
<tr>
<td>2 Progressive Decline</td>
<td>-0.45 (0.18)</td>
<td>-0.05 (0.15)</td>
</tr>
<tr>
<td>3 Stable but Inotrope Dependent</td>
<td>-0.25 (0.26)</td>
<td>-0.11 (0.21)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status and INTERMACS patient profile 4 served as reference groups.

Note: **Bold** type indicates p-value <0.05

Table 4.28 Negative binomial models of metropolitan status adjusted for device flow (continuous vs. pulsatile) covariate

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Any event, $\beta$ (SE)</th>
<th>Bleeding, $\beta$ (SE)</th>
<th>Death, $\beta$ (SE)</th>
<th>Transplants, $\beta$ (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>-0.44 (0.33)</td>
<td>-0.68 (0.47)</td>
<td>-0.43 (1.09)</td>
<td>0.09 (1.12)</td>
</tr>
<tr>
<td>Device flow</td>
<td>0.09 (0.31)</td>
<td>-0.42 (0.30)</td>
<td>0.43 (1.08)</td>
<td>-0.99 (0.92)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status and pulsatile flow served as reference groups
Table 4.29 Fixed effects for linear models of EQ5D-3L Composite Scores by Metropolitan Status

<table>
<thead>
<tr>
<th>Predictor</th>
<th>EQ5D-3L, $\beta$ (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metropolitan Status</td>
<td>-0.21 (0.50)</td>
</tr>
</tbody>
</table>

Note: Urban metropolitan status served as reference group

Figures

Unadjusted Survival Curves

Figure 4.1 Unadjusted Kaplan-Meier Event Curve for All Events by Metropolitan Status
Note: Events included: cardiac arrhythmias, bleeds, death, device malfunction, exchanges, infections, neurological events, renal dysfunction and hospitalizations
Figure 4.2 Unadjusted Kaplan-Meier Event Curve for Bleeding Events by Metropolitan Status.
Figure 4.3 Unadjusted Kaplan-Meier Event Curve for Cardiac Arrhythmias by Metropolitan Status
Figure 4.4 Unadjusted Kaplan-Meier Event Curve for Device Malfunctions by Metropolitan Status
Figure 4.5 Unadjusted Kaplan-Meier Event Curve for Device Exchanges by Metropolitan Status
Figure 4.6 Unadjusted Kaplan-Meier Event Curve for Hospitalizations by Metropolitan Status
Figure 4.7 Unadjusted Kaplan-Meier Event Curve for Infections by Metropolitan Status
Figure 4.8 Unadjusted Kaplan-Meier Event Curve for Neurological Events by Metropolitan Status.

Note: Neurological events included: Stroke, transient ischemic attack (TIA), seizure or encephalopathy.
Figure 4.9 Unadjusted Kaplan-Meier Event Curve for Renal Dysfunction by Metropolitan Status
Figure 4.10 Unadjusted Survival Curve by Metropolitan Status
Figure 4.11 Unadjusted Kaplan-Meier Event Curve for Transplants by Metropolitan Status
Figure 4.12 Fit plot showing collinearity of travel time and distance to the implanting center
Chapter 5

Discussion

This study aimed to determine the relationship of metropolitan status to clinical and patient-reported outcomes for patients with advanced HF that were recipients of VAD therapy. Statistical models including Cox proportional hazards, negative binomial regression and linear maximum likelihood did not show statistically significant differences for any of the study outcomes when comparing those VAD recipients of a rural metropolitan status to those VAD recipients with an urban metropolitan status. The addition of covariates to these models did not change these findings. Kaplan-Meier survival curves for any event, bleeding events, cardiac arrhythmias, death, device malfunction, device exchange, neurological events and transplants suggested that rural VAD recipients may experience shorter time to adverse events and shorter survival time.

This section will discuss how this sample aligns similarly with other VAD populations on needs, predisposing characteristics and outcomes from the Andersen behavioral model of health services uses, discussion of results in the context of the current available literature, and lastly, the study limitations and directions for future research.

Comparison of sample and event data to the current literature

The predisposing characteristics of this sample were similar between metropolitan statuses. Overall, the patient sample in this study was slightly younger (mean age at implant=57.3 years) than previous larger reports where average age at implant ranged from 59-71 years (Lampropulos et al., 2014; Tsiouris et al., 2015). Race (white vs. non-white) was the only predisposing demographic characteristic with a significant difference ($X^2=6.87$, $p=0.008$) between rural and urban VAD recipients. Racial and gender homogeneity existed with over 80% of the sample identifying as Caucasian/white and male, particularly in the rural recipients where
98% self-identified as Caucasian/white and 77% were male. Similar trends have been reported in other studies (Beaty et al., 2013; Lampropulos et al., 2014; Stulak, et al., 2013; Tsiouris et al., 2015; van Meetern et al., 2017). Most VAD recipients (66%) reported being in a relationship (either married or with a domestic partner). This was slightly less than other reports which indicated over 75% of their samples were married (Wright et al., 2015). Reports have suggested that marital status may have a relationship to device-related adverse events with unmarried recipients faring worse than married (Vader et al., 2012).

Needs factors assessed in study analyses included: pre-implant LVEF, INTERMACS patient profile at time of implant, and number of hospitalizations in the year prior to implantation. Seventy-three percent (116/158) of VAD recipients had at least one hospitalization in the first year following device implantation. This is consistent with the literature where 72% and 81% had readmissions in other single-center samples (Hasin et al., 2013; Hernandez et al., 2015). According to the 7th annual INTERMACS report, most patients in the registry were an INTERMACS Patient Profile of two (progressive decline) or three (stable but inotrope dependent) at the time of implant (Kirklin et al., 2015). In this study, patient profiles were mostly one, cardiogenic shock followed by two, progressive decline, which could represent the preferences of implanting surgeons for VADs as a last resort or patient/family preferences.

The most common adverse events reported in the literature are gastrointestinal bleeding (21-29%), heart failure, right ventricular failure (19-22.5%), and stroke (15%) (Morgan et al., 2016; Tsiouris et al., 2015). In this study, right ventricular failure was reported in less than 15% of the VAD recipients. This could be the result of less occurrences of this event at PSHMC, related to the small sample size or missed reporting of events of right ventricular failure. The most common event among VAD recipients in this study were bleeding events with 42% of all
recipients in the sample experiencing at least one event in the first year following device implantation. GI bleeds were the most common which is consistent with the literature (Morgan et al., 2016; Tsiouris et al., 2015).

Device strategy at implant was divided nearly evenly with 45% of recipients designated as bridge-to-decision and 40% as destination therapy. Destination therapy patients make up about half of the implantations in the INTERMACS registry (Kirklin et al., 2015). Only 14% of the sample was designated as a bridge-to-transplant at the time of implantation. For some, device strategy did change throughout the first year of the VAD trajectory.

Sixteen percent of the sample received a heart transplant in the year following VAD implantation. This was higher than other reports which reported 9% of their sample received transplants in the first year (Lampropulos et al., 2014), but slightly less than the 20% of the bridge to decision patients that were transplanted and 31% of bridge to transplant patients that received hearts reported in the 7th annual INTERMACS summary (Kirklin et al., 2015).

Eighty-six percent of recipients survived beyond the first year following device implantation. This is consistent with other reports where nearly 75% of recipients survived for twelve months (Khazanie et al., 2014). The most common causes of death were neurological dysfunction (32%), circulatory (includes heart failure and cardiomyopathy) (16%), major infection (14%), withdrawal of support (14%), and major bleeding (9%). Neurologic events are the most common cause of death in the first year of the VAD therapy trajectory in the cumulative INTERMACS registry (Kirklin et al., 2015).

**Outcome Differences by Metropolitan Status**

Aim 1 investigated the relationship between metropolitan status (rural vs. urban) and clinical VAD outcomes (mortality, hospitalizations, transplants, and adverse events) in the first
year following device implantation. It was anticipated that rural VAD recipients would experience a shorter time to adverse events, shorter survival time and longer time to transplant compared to urban counterparts. Additionally, it was expected that the number of adverse events to be greater for rural VAD recipients compared to urban. The data did not support these hypotheses. Statistically significant differences between rural and urban VAD recipients were not found for any of the outcomes of interest in unadjusted or adjusted models. These results were consistent with the two previous studies of the impact of metropolitan status on VAD recipient mortality and risk for adverse events (Rajagopalan, et al. 2016; Vader et al., 2013). These results were different from previous studies in that Kaplan-Meier survival curves and event curves for any event, bleeding events, cardiac arrhythmias, death, device malfunction, device exchange, neurological events and transplants showed evidence of a trend for rural patients to fare worse than urban patients. However, since statistical significance was not reached we cannot rule out that these differences were due to chance.

Aim 2 investigated the relationship of metropolitan status and patient-reported HRQoL. HRQoL was measured using the EQ-5D-3L at intervals throughout the first year following implantation. Data limitations led to examination of all composite EQ-5D scores in a single linear maximum likelihood model comparing rural and urban VAD recipients. This model did not reach statistical significance. However, mean EQ-5D composite scores were 2.88 (SD=2.12). Scores can range from 0-10 with lower scores indicating better HRQoL.

Metropolitan status was evaluated as a fundamental cause of VAD recipient outcome differences using the features of a fundamental cause as defined by Link and Phelan (2004). Previous studies suggest that metropolitan status does impact multiple disease outcomes through multiple associated risk factors. Examples of disease outcomes include the increased likelihood
of rural residents dying from cardiovascular disease and the increased likelihood of urban residents receiving a late-stage colorectal cancer diagnosis (Meit et al., 2014; Paquette & Finlayson, 2007). Differences in metropolitan status can impact the exposure risk of rural and urban residents and thus the risk factors associated with rural or urban living can differ substantially. For instance, urban residents are more likely to reside nearby a highway where exposure to vehicle-produced air pollution is likely and could eventually lead to lung disease (Boehmer et al., 2013) Rural residents may not be exposed to as much air pollution; however they face the burden of limited access to HF specialty care which may lead to poorer HF outcomes (Gamble et al., 2011). This study specifically tested how metropolitan status impacts adverse events over time for VAD recipients. Although no significant difference was found between rural and urban VAD recipients, the Kaplan-Meier event curves seem to suggest that rural VAD recipients fare worse than urban VAD recipients. Future work will need to look at a longer time period to see if these discrepancies continue to the end of the VAD trajectory, whether that be death of the recipient, transplant or another endpoint. This data did not contain variables to assess the adequacy of resource access. However, this could be determined through qualitative interviews with VAD recipients in concert with chart review and geographic assessment of resource availability.

Limitations and Future Directions

This study had several important limitations in the following categories: data-related, metropolitan status designation, HRQoL, and underlying mechanisms of influence. Suggestions for how these limitations could be addressed in future research are included below.
**Data-related limitations**

This study was a secondary analysis of previously existing data. Missing data significantly limited the analytic approaches and calls into question the quality of the data that was collected. Missing data included: potential covariates for comorbid conditions, educational attainment, nutritional status and others which were greater than 50% missing or not collected. For most variables, there was not enough complete data to determine if missingness was random, which hampered the utilization of maximum likelihood imputation strategies. Had there been enough data to impute some values a more robust, multi-level longitudinal analysis would have been possible. Without this data, this study was required to rely heavily on survival/event analysis and counts to make any determinations about the influence of metropolitan status in VAD outcomes.

In addition, some values were either misreported or entered erroneously. For example, some VAD recipients weighed less than fifty pounds at implant. HRQoL assessment was nearly entirely missing for the dataset. Hospitalizations were only captured for those VAD recipients admitted to the PSHMC. No data was available for admissions that may have occurred outside the PSHMC system. Lastly, the sample utilized in this study was relatively homogenous with most VAD recipients being white males. However, these demographics are representative of many VAD recipients across the United States.

**Metropolitan status designation**

Metropolitan status can be assessed using several different strategies like RUCA codes, by municipality or by county as in this study. Limitations of the sample necessitated the use of rural-urban county designations which may not have truly reflected the metropolitan status of the recipients. Also, rural-urban county designations were provided by the Center for Rural
Pennsylvania, a political institution that is most interested in providing resources to rural Pennsylvanians. These designations could be inherently biased by the mission of the Center. The sample contained relatively few rural VAD recipients even with the broad rural-urban county designation. Future studies should compare rural and urban based on different classification schemes to determine how different definitions of metropolitan status impact results and incorporate a greater number of rural VAD recipients.

In addition, the addresses used in this study were reported by the VAD recipients during their most recent hospital encounter. It is possible that some participants may have moved into or out of a rural and urban county during their time in the study. There was no way to reliably track this information for all VAD recipients, therefore the decision was made to establish rurality or urbanity based on a one-time medical chart review.

Although the literature does not report interactions between distance to the transplant center and transplant outcomes specific for heart transplantation, other organ systems have been studied. Further distance to the implanting center was related to decreased access to deceased donor kidneys and associated with a greater risk of post-transplantation mortality (Axelrod et al., 2010). Axelrod and colleagues also found an association between socioeconomic status and better access to donor kidneys. This study was not able to account for differences in SES by metropolitan status due to limitations in the data; however, future studies should account for various indicators of SES including income, insurance status, and educational attainment as this may differ across metropolitan status.

The relationships between metropolitan status and VAD outcomes is undoubtedly complex. This study accounted for as many contextually relevant features as possible within the limits of the available data; however, a more robust analysis would incorporate additional
measures to account for disparities between rural and urban VAD recipients including variables representing socioeconomics, culture, and neighborhood-level or contextual characteristics

Furthermore, this study did not explore the mechanisms that may underlie any differences in VAD outcomes based on metropolitan status. A comprehensive assessment of the differences between rural and urban outcomes should include other measures such as socioeconomic variables, social support, and contextual characteristics as suggested by the theory of fundamental social causes of health disparities and Andersen’s behavioral model (Andersen & Newman, 1973; Phelan et al., 2004). This may be accomplished using a database and data visualization tool like Social Explorer (Social Explorer, 2017) that allows the development of customizable reports of community level demographic data and data from the American Community Survey which contains other community level measures like household income and education.

In addition, contextual characteristics that may be unique to rural or urban metropolitan statuses should be explored. For example, access to transportation could be an issue for rural or urban VAD recipients but with different instigating circumstances. Rural VAD recipients may need to travel a long distance to the implanting center or urban VAD recipients may be multiple types of public transportation away despite close proximity to the implanting center.

HRQoL limitations

Due to limitations in the data the HRQoL analyses was unable to completed as anticipated. Only ten VAD recipients had more than one point of collection of the EQ-5D-3L. However, since it is known that patients with advanced HF in rural areas often report poorer HRQoL compared to urban counterparts (Nesbitt et al., 2014), these differences should be
explored in future work with a more robust dataset. HRQoL may be more sensitive to differences in metropolitan status as suggested by Grady and colleagues (2014).

The EQ-5D test-retest study by van Agt and colleagues (1994) showed little change in the instrument scores over time (11% variability in time interactions). However, this may be alleviated by measurement at additional time points. In addition, the EQ-5D-3L was administered at multiple clinic visits by a variety of trained research assistants or VAD coordinators. The EQ-5D is a generic HRQoL instrument that may not address the HRQoL issues inherent in VAD therapy. A VAD specific HRQoL instrument is currently being developed and may be more appropriate in future HRQoL assessment of VAD recipients (Grady et al., 2015).

**Study Assumptions**

This study assumed that VAD recipients in rural counties have access to a local, community hospital and that VAD recipients in urban counties would have access to a larger, academic or regional health system. These assumptions were not validated. Access is a multi-faceted issue for VAD recipients irrespective of metropolitan status that could not be comprehensively examined with the current data. Rather than assuming access in general, future studies should explore operational measures of access. For example, insurance status, distance to the health center, availability of viable transportation, and SES may all be considered measures that indicate accessibility of health care.

This study also assumed that recipients were honest when responding to the EQ-5D-3L. This study silently assumed that the EQ-5D data would be complete for most follow up encounters with the VAD recipients. However, missing HRQoL data was a major limitation. Prior to initiating future longitudinal assessments of HRQoL in VAD recipients, a more reliable
collection method would be instituted. Prospective HRQoL data collection by trained research nurses is warranted in this population.

Implications for Nursing

Research

This study has brought to the forefront a significant amount of work for nurse researchers to investigate in future studies. This study scratched the surface of the variables contained in the integrated framework. Andersen’s behavioral model has many other variables of interest for VAD recipients that should be addressed in future research. In addition, as mentioned above, this study did not address the fourth feature of a fundamental cause, access to resources.

Although none of the models reached statistical significance, recipients in rural counties did seem to have poorer outcomes on most events compared to urban counterparts. This warrants further investigation, particularly as the number of VAD recipients continues to rise and the devices become more commonplace in the treatment of HF. This study should be repeated with a larger, more robust sample that can incorporate covariates representing additional concepts in Andersen’s behavioral model and more variety across metropolitan statuses. Additional classifications of rural and urban and metropolitan and non-metropolitan should be investigated. The selection of differentiation measures for determine geographic variables like metropolitan status can impact study results (Krieger et al., 2012). Furthermore, distance to the implanting center and distances to any health center in general should be considered.

Qualitative analysis will be important in the future to determine how VAD recipients see their metropolitan status influencing their outcomes. The insights of VAD center staff including implanting surgeons, cardiologists, mid-level providers, advanced practice nurses (APNs), nursing, and VAD coordinators could be valuable in ascertaining true barriers to VAD care
based on metropolitan status. Lastly, nurse researchers should search for novel intervention strategies associated with telehealth or mobile health technologies to improve outcomes for VAD recipients (Bhuyan et al., 2016). Recent literature suggests that online health communities may provide a supportive environment across metropolitan status (Mein Goh et al., 2016). Similar initiatives may provide access to informal social support for VAD recipients and caregivers.

**Policy**

Reich (2016) suggests that addressing a fundamental cause of health disparities requires a “fundamental intervention” (p. 189). Overarching policies to support VAD recipients of all metropolitan statuses could serve as this type of intervention. For instance, policies could be instituted that require hospitals to provide transportation to and from clinic visits for any recipients with difficulty traveling, whether these difficulties have arisen from metropolitan status, access to reliable transportation, or any other cause. The opportunity for telehealth communication between VAD specialists and recipients with limited access to the VAD center could be made available through policies that improve existing infrastructure in low technology areas (Reich et al., 2016; Slifkin, 2002). Additionally, local, regional, state and federal policies could be instituted to provide more funds for community-based education for emergency responders, law enforcement agencies and the public. Efforts to provide community-based education to reduce cardiovascular risk factors in rural areas have been successful (Record et al., 2015) as well as community engagement in urban areas through “neighborhood-engaged care” (Alicea-Alvarez et al., 2016).

**Practice**

Nursing is the largest healthcare subspecialty with nearly 2.6 million nurses actively employed in nursing in the U.S. (Health Resources and Services Administration, 2010). Nurses
make up a large proportion of the staff in heart failure clinics across the country (Jessup et al., 2011). In this role, nurses can serve as sounding boards for concerns voiced by VAD recipients and their caregivers in relation to everyday care of their devices. Nurses in the outpatient setting, particularly those in the VAD coordinator role, may be the first point of contact for a VAD recipient or caregiver when questions or problems arise. Appropriate nurse triage, with consideration given to the recipient’s metropolitan status, could help to prevent a VAD-related hospital admission or complication. Alternatively, nurses triaging VAD recipients could help to save the recipient and caregiver time and financial resources by considering metropolitan status and distance to the health center prior to advising that they be examined in clinic.

Advanced practice nurses can also serve an important role in maintaining the health of the VAD recipient. Consistent with the position statement from the Heart Failure Society of America and American Association of Heart Failure Nurses (Lee et al., 2015) APNs should play an active role in the holistic care of VAD recipients. The most recent report suggests mid-level providers are utilized less often by heart failure clinics when compared to physicians and nurse coordinators (Jessup et al., 2011). In the future APNs could provide a stop-gap for VAD recipients in the inpatient and outpatient settings, especially those residing in rural areas without a VAD center nearby. In-home visits by APNs have been successful in reducing 30-day readmissions, total hospitalizations, and emergency department visits in a group of homebound heart failure patients and may be a good option for VAD care in the future (Echeverry, Lamb, & Miller, 2015).

**Conclusions**

In rural VAD recipients it appeared that death, bleeding, infection, cardiac arrhythmias, and neurological events happened sooner but these events were not significantly different from
urban VAD recipients in this sample. Future studies should incorporate a larger, more robust sample, to examine if these differences are more apparent and reach significance. Although this study did not reach significant conclusions, it was imperative that outcome disparities between rural and urban patients undergoing VAD therapy be examined based on trends that suggest less favorable outcomes for rural residents with HF. This study will serve as a springboard to a larger study with collection of important covariates to more comprehensively assess the impact of metropolitan status on ventricular assist device outcomes.
References


Grady, K., Naftel, D., Stevenson, L., Dew, M., Weidner, G,…Young, J. (2014). Overall quality of life improves to similar levels after mechanical circulatory support regardless of


Patient care profile. (2004). Texas LVAD patient is first to await new heart at home: patient care profile...left ventricular assist device (LVAD). *Case Management Advisor*, 5(9), 120-122.


**APPROVAL OF SUBMISSION**

**Date:** October 6, 2016

**From:** Daniel McBride, IRB Analyst

**To:** Windy Alonso

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<tr>
<th><strong>Type of Submission:</strong></th>
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<td>Rural-Urban Comparison of Ventricular Assist Device Outcomes</td>
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<td><strong>Principal Investigator:</strong></td>
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| **Documents Approved:** | • HRP-596_Alonso,W. (9.01), Category: IRB Protocol  
• HRP-598 Alonso_NRSA/Dissertation (9/23/16), Category: IRB Protocol |
On 10/6/2016, the IRB approved the above-referenced Modification. This approval is effective through 8/24/2017 inclusive. You must submit a continuing review form with all required explanations for this study at least 45 days before the study’s approval end date. You can submit a continuing review by navigating to the active study and clicking ‘Create Modification / CR’.

If continuing review approval is not granted before 8/24/2017, approval of this study expires on that date.

In conducting this study, you are required to follow the requirements listed in the Investigator Manual (HRP-103), which can be found by navigating to the IRB Library within CATS IRB (http://irb.psu.edu). These requirements include, but are not limited to:

- Documenting consent
- Requesting modification(s)
- Requesting continuing review
- Closing a study
- Reporting new information about a study
- Registering an applicable clinical trial
- Maintaining research records

This correspondence should be maintained with your records.
VITA
Windy Williams Alonso

EDUCATION

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SELECTED PUBLICATIONS


HONORS AND AWARDS

2016 NIH/NINR F31 Ruth L. Kirschstein National Research Service Award, Predoctoral Fellowship (F31NR016895)

2013 Center for Integrated Healthcare Delivery Systems Scholar