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EFFECTIVENESS OF CRT-D THERAPY
IN HEART FAILURE PATIENTS AT EMORY

BY

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Degree to be awarded: M.P.H.
Career MPH

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# EFFECTIVENESS OF CRT-D THERAPY IN HEART FAILURE PATIENTS AT EMORY

BY

Louise Pelletier Savoye
M.P.H., Emory University, 2010
M.D., University of Lyon I, 1998

Special Studies Project Committee Chair: Kimberly Rask, MD, PhD

An abstract of
A Special Studies Project submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Master of Public Health in the Career MPH program
2010

**Abstract**

EFFECTIVENESS OF CRT-D THERAPY
IN HEART FAILURE PATIENTS AT EMORY

BY
Louise Pelletier Savoye

**Purpose:** The efficacy of cardiac resynchronization therapy combined with defibrillator devices (CRT-D) for the reduction of mortality in heart failure patients has been demonstrated through randomized clinical trials but accounts of the "real-world" effectiveness of CRT-D devices are much more limited. The purpose of this study is to explore the effectiveness of CRT-D therapy in a general hospital population cohort and to examine the factors that are associated with survival outcomes in these patients.

**Hypothesis**: Patient survival outcomes in a general hospital population would differ from those in a clinical trial setting.

**Methods:** A retrospective, cohort study was conducted of 228 patients who received an initial CRT-D device between January 2004 and December 2005 according to guideline-based indications. Primary endpoint was the composite outcome of death, cardiac transplantation, or left ventricular assist device(LVAD) implantation. Data was collected on baseline characteristics, clinical outcomes and participation status in an observational trial or registry. A multivariate model was constructed to determine factors associated with time to event for the primary endpoint.

**Results:** Mean age of patients was 62.5 +/-13.7 years; 70.2% were men, 69.9% were Caucasian 29.1% were black. Median follow-up time was 3.8 years. During this period, 93 patients (40.8%) experienced the composite endpoint ; 86 patients died, 6 underwent transplantation and 1 received LVAD. Survival at 6, 12, 18, and 24 months was 95%, 89%, 86%, and 81% respectively. These outcomes are comparable with the CRT-D arm of the COMPANION trial (6 month survival: 95%; 12 month survival 88%) and the CRT-D arm of CARE-HF (12 month survival 90%). Increased creatinine level and digitalis use were associated with a higher HR for the death outcome, in the multivariate model (HR= 1.238 and 1.605 respectively). Increasing EF was associated with a lower HR (.833) as was participation in an observational registry (HR= .477).

**Conclusion**: Despite the broader clinical characteristics of this hospital cohort compared to clinical trial cohorts enrolled according to inclusion/exclusion criteria, the clinical outcomes for survival are very similar to those observed in major RCTs such as COMPANION and CARE-HF.

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# Chapter I: Introduction

*Introduction and Rationale*

Heart failure is a serious, chronic condition that affects a growing number of people each year. Recent figures estimate the prevalence of heart failure at over 5.7 million people in the United States, with incidence that is greater than 670,000 new cases per year (Albert, Fonarow et al. 2010). It is a complex condition with multiple etiologies and a natural evolution towards progressive worsening, impacting quality of life and decreasing productivity. Economically, heart failure is responsible for enormous medical and hospitalization costs and is one of the most frequent causes of hospitalization, particularly among elderly patients (Kalogeropoulos, Georgiopoulou et al. 2009).

Treatment options for heart failure consist of sodium and fluid management with diet guidelines, medications (beta-blockers, ACE or ARB, diuretics, digoxin) and device therapy. CRT-D devices are implanted at the moderate to severe stages to improve symptoms and hopefully reduce the number subsequent hospitalizations due to acute exacerbation (WRITING COMMITTEE MEMBERS, Hunt et al. 2009).

*Problem Statement*

Since the advent of CRT in the early 1990's there have been numerous clinical trials to study the effects of this therapy on the clinical outcomes of heart failure patients. These trials, which included some fairly large randomized trials, have repeatedly shown the efficacy of CRT therapy in reducing heart failure mortality and hospitalization (Young, Abraham et al. 2003; Bristow, Saxon et al. 2004; Cleland, Daubert et al. 2005).

Certain trials were more focused on functional capacity endpoints (quality of life scores, 6 minute hall-walk tests, NYHA classification, and peak oxygen consumption) and demonstrated improvement of these measurements with CRT-D (Linde, Leclercq et al. 2002).

In spite of the fact that CRT-D has been established as a valid therapeutic option through positive trial results, there is still ongoing discussion about patient selection for this therapy. One reason that patient selection is topic of discussion is the fact that about 30% of patients are "non-responders" to CRT (Nagueh 2008). The precise reason(s) for this lack of improvement are unknown but may be related to the underlying cause of heart disease or other characteristics of these patients (Diaz-Infante, Mont et al. 2005). There are many different ways to define improvement after CRT implantation and the measurements used to define success in the various clinical trials vary greatly (Packer 2001; Yu, Bleeker et al. 2005). Longer survival does not always mean better quality of life during the additional lifespan, and patients may see functional improvement during a short trial but longer-term survival may not improve.

Another question that arises when considering the results of CRT trials is whether or not participation in a clinical trial has an impact on the clinical outcomes of the study subjects. It is conceivable that the added scrutiny of regular study visits with subjective and objective data collection may lead to earlier intervention and possibly better patient compliance with diet and medications. There may also be other differences between patients who volunteer to be part of a trial and those who don't, other than just the

inclusion and exclusion criteria. These differences may be related to gender, ethnicity, attitudes about health, socio-economic status, insurance coverage, etc.

Also, randomized clinical trials have inclusion and exclusion criteria that do not reflect a more general patient population. For example, older patients and those with co-morbidities such as renal insufficiency or cancer are often excluded from trial participation.

Combined with the uncertainty of how to define CRT "response" vs. "non-response", this raises the question of the effectiveness of CRT therapy in a general heart failure patient population. Based on the different points mentioned above, the results obtained in clinical trials may be overly optimistic and the reduction of mortality and morbidity observed in clinical trials may not be reproducible outside of that context. It is therefore imperative to obtain more insight into the applicability of current scientific knowledge about CRT-D to a more heterogeneous population.

*Purpose Statement*

The purpose of this study is to provide information about effectiveness of CRT-D devices in a general hospital population. The main clinical outcome that will be examined is survival rate after CRT implant. Within the study cohort, patients who were enrolled in a registry or in a randomized clinical trial will be compared with those who were not to look for differences in outcomes but also in baseline characteristics. The

study data will also be compared to that of the major CRT-D trials. In this manner, the analysis should provide more insight into the effectiveness of CRT-D devices.

*Research Questions*

1) How do survival rates in CRT-D patients at Emory compare to those observed in RCTs and what do they tell us about the effectiveness of CRT-D therapy?

2) Are there specific factors (demographic or clinical characteristics, insurance coverage, medications, participation in a clinical trial or observational registry) that influence survival rates in CRT-D recipients at Emory and how do they compare with the outcome predictors most frequently presented in the CRT-D literature?

3) Are there significant differences between patients who participate in registries or clinical trials and those who do not in terms of demographics, insurance coverage, and/or clinical characteristics?

*Significance Statement*

CRT-D devices represent a useful tool for the treatment of chronic heart failure.

While the efficacy of CRT-D device therapy has been well demonstrated, the device implant remains a costly, surgical procedure that needs proper guidelines in order to be a successful therapeutic option. Current guidelines are based on trial data and should be complemented by more information from "real-world" device experience, i.e. clinical effectiveness. This study will hopefully provide some insight into the use of CRT-D outside of the somewhat artificial context of the clinical trial. Studies such as this one provide external validity (i.e., generalizability) to the findings of controlled trials.

*Definition of Terms*

*CRT-D:* Cardiac Resynchronization Therapy-Defibrillator. CRT is also known as biventricular pacing. Cardiac resynchronization therapy (CRT) is a proven treatment for selected patients with heart failure-induced conduction disturbances and ventricular dyssynchrony. When used in combination with stable, optimal medical therapy, CRT is designed to reduce symptoms and improve cardiac function by restoring the mechanical sequence of ventricular activation and contraction. The D (Defibrillator) component of CRT-D consists of delivering a therapeutic dose of electrical energy to the affected heart in order to treat rapid, life-threatening abnormal heart rhythms (arrhythmias). This depolarizes a critical mass of the heart muscle, terminates the arrhythmia, and allows normal sinus rhythm to be reestablished by the sinoatrial node.

NYHA: New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

RCT: Randomized Clinical Trial. A type of scientific experiment in which the participants are assigned randomly (by chance alone) to different treatments (pharmaceuticals, medical devices, or surgery).

# Chapter II: Review of the Literature

The literature review was conducted using PubMed as a search engine to find manuscripts, summaries and reviews that were pertinent to the study topic. The search was centered on documents that would provide information on previous research related to the main research questions of this study. CRT-D device efficacy and effectiveness were key search terms. Articles that address the patient characteristics and clinical outcomes of both randomized clinical trial and observational cohort study populations were collected. Finally, articles pertaining to specific factors that influence clinical outcomes were also retrieved.

## CRT-D EFFICACY IN CLINICAL TRIALS

It appeared logical to begin this literature review by summarizing the findings of major CRT-D clinical trials as well as those of the few observational studies available in the literature. Several trials have shown that CRT-D reduces morbidity and mortality in patients with moderate to severe chronic heart failure (NYHA III or IV) , left ventricular ejection fraction (EF) $\leq$ 35% and QRS duration $\geq$ 120 ms (Albouaini, Egred et al. 2008).

The COMPANION trial (Bristow, Saxon et al. 2004) included 1520 patients and compared optimal medical therapy to CRT-P (CRT + pacemaker) and CRT-D in a 1:2:2 randomization. Median follow-up duration was 14 months. In the results, both groups

with CRT had a 20% reduction in the primary endpoint of all-cause mortality or hospitalization ($p < 0.01$). For the secondary endpoint of all-cause mortality, only CRT-D demonstrated a significant risk reduction of 36% ($p = 0.003$).

CARE-HF (Cleland, Daubert et al. 2005) was another major CRT-D trial that followed 813 patients randomly assigned to optimal medical therapy or CRT for an average duration of 29.4 months. The results showed a 37% relative risk reduction ($p<0.001$) in the composite primary endpoint of death from any cause or hospitalization for a major cardiovascular event and a 36% reduction in the secondary endpoint which was risk of death from any cause.

The MIRACLE ICD trial (Young, Abraham et al. 2003) followed 369 CRT-D patients (randomized to CRT-on or CRT-off) for a 6 month period. The CRT-on group showed significant improvement in quality of life scores, peak oxygen consumption and NYHA class; however, there was no significant change in 6-minute hall walk distance, hospitalization rates or left ventricular function and size.

MUSTIC (Linde, Leclercq et al. 2002) was a small, randomized, cross-over study involving 131 patients followed up over a period of 12 months. Secondary analyses were conducted based on whether subjects were in normal sinus rhythm or atrial fibrillation. Overall, patients showed significant improvement in functional endpoints: six minute hall walk, NYHA functional class and quality of life. Heart failure hospitalizations were recorded during the follow-up and the number of HF hospitalizations was 7 times less with CRT for the sinus rhythm group and 4 times less in the atrial fibrillation group.

CRT OUTCOMES IN OBSERVATIONAL STUDIES

None of the observational, non-randomized studies in the published literature described a purely CRT-D cohort. Rather, they were comparing CRT-P (CRT-pacemaker) and CRT-D patients for different outcomes, mainly for survival rates.

Among observational, non-randomized studies, the MILOS group (Auricchio, Metra et al. 2007) described a longitudinal study (median follow-up of 34 months) of CRT alone and CRT-D recipients at 4 European centers. The main endpoint was a composite endpoint of death from any cause, urgent transplantation, or implantation of a left ventricular assist device. Patients with a combined device (CRT-D) had an event rate of 8.3 per 100 patient years, compared to 8.7 with CRT alone. At multivariate analysis, CRT-D was associated with a nonsignificant 20% decrease in risk of the combined event.

The InSync / InSync ICD Italian Registry (Gasparini, Lunati et al. 2006) followed a cohort of 316 CRT alone (76% of patients) and CRT-D patients (24% of study population) for 36 months. The study showed an overall mortality rate of 10% per year. Mortality was higher among patients with ischemic heart disease ($p=0.002$) and NYHA class IV patients ($p=0.014$).

Another study of 233 consecutive implants (Stabile, Solimene et al. 2009) with 117 CRT-P and 116 CRT-D patients, conducted over a mean follow-up period of 58 +/- 15 months, did not find a significant difference in the mortality rate between the two groups. This contradicts the findings of a larger observational cohort of 542 patients (CRT-P n=147 and CRT-D n=395) in which all-cause mortality was significantly lower in CRT-D patients at 18.5% vs. 38.8% (BAI, BIASE et al. 2008).

## PATIENT CHARACTERISTICS

Demographic, clinical and echocardiographic characteristics of clinical trial and observational cohort patients were also derived from the literature and these aspects are summarized in **Tables 1 and 2 (APPENDIX A).**

## CRT-D OUTCOME PREDICTORS

### *Clinical Factors*

With a complex disease such as heart failure, there are many possible factors which may affect the outcomes in patients who receive a CRT-D device. In most of the studies reviewed, the authors have tried to identify one or more predictors of response to CRT therapy, especially since about one-third of recipients do not see significant improvement and identifying these predictors might help physicians understand the lack of positive response in certain patients.

Among the different factors that could potentially influence CRT-D patient outcomes, age does not appear to be a significant factor based on the literature. The subgroup analysis from the COMPANION and CARE-HF trials found a similar benefit in terms of decreased risk of death or hospitalization and improvement in quality of life and functional capacity for patients above and below the age of 65 and 66.4 years respectively (Grimm 2008). These results were by a study of 170 CRT-D recipients which compared the clinical and echocardiographic outcomes of the elderly patients (age 70+ years) with the younger patients (<70 years) and found that both groups had similar improvements in functional status as well as in their echocardiographic parameters (Bleeker, Schalij et al. 2005) .

The concept of a gender difference in the response to CRT-D therapy is widely explored in the literature. Whereas the major RCTs did not find a significant difference in hazard ratio for clinical events between the genders (Yarnoz and Curtis 2006), male gender was associated with a higher risk of combined endpoint (death or urgent transplantation or implantation of a left ventricular assist device) after CRT-D implant (HR 1.97, $p = 0.002$) in one large observational trial (Auricchio, Metra et al. 2007). The gender difference was more pronounced in another trial (Stabile, Solimene et al. 2009) that found a HR=3.62 ($p=0.0075$) for males, which they attributed to a lesser degree of LV remodeling after CRT-D implantation in men than in women. It is interesting to note that according to two large studies based on national registry data between 2002 and 2004, hospitalizations for congestive heart failure are consistently higher in women yet

women are significantly less likely to receive a CRT-D device than men (El-Chami, Hanna et al. 2007; Alaeddini, Wood et al. 2008).

The NYHA classification, which is a measure of the functional impact of heart failure and severity of its symptoms, has been often identified as a reliable predictor of CRT-D outcomes in the literature. Several authors have found that patients who are NYHA class IV have worse survival outcomes than other CRT-D recipients (Gasparini, Lunati et al. 2006; Saxon, Bristow et al. 2006; Stabile, Solimene et al. 2009).

In regards to associated comorbidities, chronic renal failure appears to be the disease most consistently associated with poor clinical outcomes after implant of a CRT-D device. A retrospective study of 330 CRT recipients (Shalaby, El-Saed et al. 2008), divided into tertiles by serum creatinine levels and followed for 19.7 +/- 9 months, found that an increase of 0.1 mg/dL in creatinine level was associated with an 11 % increase in mortality risk and a 7% increase in the combined endpoint of mortality or heart failure hospitalization. In the analysis of the COMPANION trial data, renal dysfunction was associated with an increased risk of sudden cardiac death (HR = 1.69, p=0.03) in that study population(Saxon, Bristow et al. 2006). One study isolated 3 comorbidities that seemed to be associated with higher risk of death: chronic renal failure (HR=4.885, p =0.005), diabetes mellitus (HR =4.130, p=0.003), and atrial fibrillation (HR=1.473, p=0.036) (BAI, BIASE et al. 2008).

One theory has been that patients who have heart failure due to ischemic heart disease are less likely to benefit from CRT-D therapy than patients with idiopathic, non-ischemic heart disease, possibly due to the presence of scar tissue in the myocardium which could interfere with the proper conduction of the resynchronization impulse (Diaz-Infante, Mont et al. 2005). A secondary analysis of the data from CARE-HF (Wikstrom, Blomström-Lundqvist et al. 2009) did not support this theory. Their analysis suggested that the clinical and survival outcomes were quite similar between patients with or without ischemic heart disease. A third small scale study of 74 patients followed for 2 years also did not find a significant different in outcomes based on heart failure etiology (Molhoek, Bax et al. 2004).

*Echocardiographic Factors*

Echocardiography plays a key role in the attempt to determine prognosis in CRT-D device recipients. At the stage when device therapy is simply being considered as a therapeutic option for a patient with advanced heart failure, risk prediction can be improved by including echocardiographic parameters to clinical assessments (Agha, Kalogeropoulos et al. 2009). One of the ways in which response to CRT is measured is by observing changes in the LVEDV (left ventricular end diastolic volume), which are indicative of the remodeling process within the heart muscle. Severe mitral regurgitation, which mediates the ventricular volume overload, has been associated with more modest remodeling in two different studies (Cappola, Harsch et al. 2006; Ypenburg, van Bommel et al. 2009) There is further debate within the literature as to whether or not reverse remodeling is the most accurate measure of outcome after the device is implanted, mainly

because the clinical outcomes do not always correspond to the improvement measured with echocardiography (Foley, Leyva et al. 2009).

Ventricular dyssynchrony is a factor that has been shown to be an independent predictor of the benefit of CRT therapy (Jessup 2009). The QRS width on the ECG is the most widely used indicator of dyssynchrony, perhaps because of the relative ease in obtaining an ECG, but the correlation between QRS duration on the surface ECG and the degree of mechanical dyssynchrony is considered to be poor based on a recent study (r correlation <0.30) (Cesario, Turner et al. 2007) Certain authors suggest that a normal QRS may exist in certain patients who nonetheless have dyssynchrony that would be discovered through echocardiographic assessment and that ideally, ECG and echocardiography should be used together to detect dyssynchrony (Albouaini, Egred et al. 2008).

The current body of knowledge about CRT- D therapy strongly supports the use of these devices as an effective treatment in patients with advanced heart failure. Randomized clinical trials have supplied solid evidence in favor of CRT-D therapy for survival and functional endpoints that vary slightly between the various trials and for study populations that may not be entirely representative of the heart failure patient population.

Although there are a few references available from non-RCT cohorts, the data on CRT-D effectiveness is relatively scarce. There are still many unanswered questions about the number of heart failure patients that might actually benefit from CRT and which patients

are most likely to benefit based on their clinical characteristics. These interrogations, combined with the growing concern for cost-effectiveness, underscore the need for more research about CRT-D outcomes outside of the clinical trial setting.

# Chapter III: Methodology

*Introduction*

A retrospective cohort study was undertaken to collect data on patient characteristics and clinical outcomes in CRT-D device recipients at Emory University Hospital in order to obtain answers to the research questions outlined in Chapter 1.

*Population and Sample*

All patients who received an initial CRT-D implant between January 2004 and December 2005 were included in the cohort. CRT-D recipients were identified from the list of patients systematically registered with the pacemaker clinic after implant of a cardiac device at Emory. Patients were included regardless of whether or not they fulfilled traditional CRT selection criteria (NYHA III or IV, LVEF < 35%, QRS duration >120 ms and left bundle branch block morphology). Only patients who were hospitalized for replacement of a previous CRT-D device were excluded because of the previous CRT-D therapy obtained and its potential effect on the interpretation of outcomes.

*Research Design*

The cohort study was conducted as retrospective chart review of both electronic and paper medical records. Institutional Review Board permission for chart review was

obtained prior to the study. Patients whose records were included in the cohort were not contacted.

The baseline characteristics that were recorded are listed in **Table 3**.

The main composite outcome endpoint studied in this cohort is a combined end point comprised of death from any cause, urgent heart transplantation, or left ventricular assist device implantation (LVAD). This outcome has been used in previous studies in patients with advanced heart failure (Levy, Mozaffarian et al. 2006; Kalogeropoulos, Georgiopoulou et al. 2009).

The date and reason for hospitalization was collected for all hospitalizations in the medical record after the CRT-D implant date. Data concerning patient deaths was derived from the electronic medical records and confirmed using the SSDI (Social Security Death Index) database.

*Procedures and Instruments*

The electronic medical record was consulted first for all patients identified as having received a CRT-D during the study period. Baseline was defined as +/- 3 months from the date of implant if values were not available for the day of implant. Paper medical records were consulted if necessary to complete the data set for each patient. Patient data sets were de-identified by using patient first and last initial and assigning a consecutive case number to each data set. The de-identified data sets were entered into an Excel spreadsheet and transferred to SPSS for statistical analysis.

*Plans for Data Analysis*

Descriptive statistics were computed as means +/- standard deviation for continuous variables and as relative frequencies for categorical data expressed as percentages. The Mann-Whitney test and Pearson's chi-square test were used to compare the quantitative and categorical variables between groups, respectively.

Univariate Cox proportional hazards regression was used to evaluate the association of baseline characteristics with time to event for the primary and secondary endpoints. All variables associated with the endpoint at the $p < 0.2$ level were entered into a multivariate Cox regression model. Independent variables were selected with a stepwise backwards elimination approach, using a threshold of $p < 0.05$ to retain a variable in the final model.

A P value $< 0.05$ was considered significant for all tests. All statistical analyses were performed using SPSS software (SPSS for Windows, version 18.0, SPSS Inc., Chicago, IL, USA).

*Limitations and Delimitations*

One of the potential limitations for this study mainly involves the electronic and paper medical records which were used as the data source. For some patients, certain data elements were not available for the implant +/- 3 month period and therefore had to be considered as missing. Every effort was made to complete missing data elements by reviewing paper charts to look for documents that may not have been uploaded to the

digital system. Although the main demographic and clinical elements were available for the majority of patients, missing data elements for other variables can potentially lead to biases in the data analysis.

Another limitation is that the data analysis is based solely on implant and hospitalization records from Emory's medical records. It is impossible to collect data on hospitalizations that may have occurred outside of the Emory system and therefore to determine if additional heart failure or device related hospitalizations took place for the patients in this cohort. Likewise, the cause of death is not always available for patients who were identified as deceased during the study period.

Information on co-morbidities, medications, and laboratory values was collected at the baseline date and may have evolved for individual patients during the course of the data collection period for hospitalization events, leading to regression dilution bias. However, this bias is more pronounced in very long follow-up periods (Clarke, Shipley et al. 1999).

The study cohort included patients having received a CRT-D device at Emory University Hospital between January 2004 and December 2005. This time period was selected to have sufficient follow-up time for analysis and corresponds to the approximate start of the transition to electronic medical records which facilitated data collection.

Data collection was limited to demographic and clinical data elements that are readily available in medical charts for heart failure device recipients. The study did not

collect functional information (quality of life, 6-min walk test, etc.) or detailed echocardiographic data which is beyond the scope of this study. The data points collected were delimited to those necessary for an accurate demographic and clinical profile of this patient population at baseline (implant) and to evaluate outcomes in terms of hospitalization and mortality.

# Chapter IV: Results

*Introduction*

This study observed the characteristics of a cohort of 228 patients who received a CRT-D device implant at Emory University Hospital between January 2004 and December 2005. The results included baseline characteristics such as demographics and clinical data, as well as analyses of differences in survival rates based on different patient characteristics. Data regarding patient participation in different registries and randomized trials was also collected and analyzed to detect differences between study participants and non-participants. Finally, some of the data collected on the hospitalizations that occurred at Emory was also included in the results.

*Findings*

***Patient Characteristics***

A total of 228 patients were included in the cohort. Their baseline characteristics of the cohort are summarized in **Table 4**. Within the cohort, approximately 70% were males. Information pertaining to the subject's race was available for 206 of the 228 patients, and 144 (69.9%) of the patients for whom the data was available were Caucasian. African-Americans represented about 29 % of the cohort.

The average age at implant was 62.5 +/- 13.7 years. About two-thirds of patients had private medical insurance alone or in combination with Medicare coverage, twenty-

one percent (21%) had Medicare coverage alone and about thirteen percent (12.7%) had Medicaid or Medicaid and Medicare combined. Insurance data was missing for four of the patients implanted with a CRT-D device. Eighty-nine subjects (39%) signed a consent form to be in a study or an observational registry.

The majority of the patients were class III (75.9%) and class IV (14.5%) NYHA, which corresponds to severity of heart failure symptoms. The average LVEF (left ventricular ejection fraction) was 20% +/- 9.3. Ischemic cardiomyopathy was identified as the causal factor in 45.8% of the subjects, 44.4% were considered to have idiopathic cardiomyopathy, and the other 10 % had heart failure due to various other cardiac diseases. Hypertension was the most commonly associated comorbid condition (46.7%), followed by atrial arrhythmias (31.7%) and diabetes (27.8%). It is important to note that chronic renal disease was present in almost 20% of patient histories and that the average serum creatinine level was 1.4 +/- 0.8 mg/dl.

***Survival***

Of the 228 patients included in the cohort, 93 (40.8%) experienced a primary composite endpoint event; 86 patients died, 6 underwent an urgent cardiac transplantation, and 1 patient received and LVAD. The median follow-up time was 3.8 years ($25^{th}$ percentile, 1.6 years; $75^{th}$ percentile, 4.6 years). **(Figure 1).** The total time at risk was 712 patient-years (average 3.1 years per patient). The annual rate of the

primary endpoint was 13.1% (95% CI, 10.7%-16%). At 12 months post-implant 89% of patients had survived, at 24 months, the survival rate was 81%.

**Table 5** summarizes survival rates for the first 24 months.

Baseline characteristics of patients who survived vs. patients who reached the composite endpoint are summarized in the right-hand columns of **Table 4**.

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Patients who had a negative survival outcome (death/ LVAD/ transplant) had significantly lower ejection fraction values (18.0 +/- 8.6% vs. 21.4+/-9.6 %) than those who did not reach the composite endpoint (p= .006). In regression analysis, a 5% increase in ejection fraction was significantly associated with a 0.15 decrease (HR=.855, 95% CI = .756-.966, p=.012) in the hazard ratio of negative survival outcome.

Univariate proportional hazards regression showed significant results in time to event for private health insurance coverage +/- Medicare and for Medicaid +/- Medicare. For patients with private health insurance (with or without Medicare coverage associated), the HR for the composite death/ LVAD/ transplant event was significantly lower (HR=.590, 95% CI = .378- .920, p= .019). Inversely, Medicaid patients (with or without Medicare coverage), presented a significantly higher risk of the negative outcome ( HR=2.003, 95% CI = 1.117- 3.591, p= .017).

Participation in a registry or in a clinical trial (vs. non-participation) was associated with a lower hazard ratio for the negative survival outcome (HR=.570, 95% CI =.365-.891, p=.012). When the variable was divided into 3 categories: no registry or clinical trial, registry or clinical trial, participating in observational registry was associated with a lower risk of reaching the primary endpoint (HR=-.568, 95% CI .341-.941, p=.026). Participating in a clinical trial did not have a significant impact on survival outcomes.

The 93 patients who met the primary endpoint of death/ LVAD/ transplant also had significantly higher serum creatinine levels (1.5+/- 0.84 vs. 1.3+/- 0.78) (p=.001). Univariate time to event analysis did not differ significantly based on creatinine levels (p=0.09). There were no significant differences between the two groups for age, gender, race, NYHA class, comorbidity, heart failure etiology, ECG profile, vital signs, and medications.

***Multivariate analysis of Survival***

Several univariate analyses were conducted for the composite outcome to determine if there were differences in time to event between groups for baseline characteristics. These results are summarized in the top portion of **Table 6**. Because these analyses offer useful but limited information about the determination of a complex

outcome such as survival, a multivariate model were constructed to assess the impact of these different factors.

The model was constructed using variables that were associated with the composite endpoint at the $p<0.2$ level in univariate analysis. These variables were: gender, race, type of insurance, participation in a trial, quantitative ejection fraction, history of renal disease, history of previous device, loop diuretic use, digitalis use, and creatinine level. Age and history of diabetes were two additional variables that were added to the model because they could plausibly be associated with heart failure outcomes but no significant effect was found so they were not retained in the final model.

The significant ($p<0.05$) multivariate baseline variables found to be associated with the composite outcome of death/ LVAD/ transplant are presented in the bottom portion of **Table 6**. Ejection fraction, which is the standard measure of left ventricular function, was a strong negative predictor of the death outcome. According to the model, a 5% increase in ejection fraction corresponded to about a 17% decrease (.167) in the risk of the death outcome. Participation in an observational registry was associated with a lower risk of the death/ LVAD/transplant outcome (HR=-.740, 95% CI= .280-.813, p=.007). On the other hand, increased creatinine level and digitalis use were both found to be associated with a higher risk for the negative outcome.

***Clinical Trial and Observational Study Participation***

Among the 228 patients, 89 patients signed consent to participate in a study. Eighteen patients were enrolled in a randomized trial and 71 were enrolled in one of various observational studies that were ongoing during the time period in which data collection took place. Patients who signed consent for any type of study were compared to those who did not, and a second, finer analysis was done by breaking down the study patient group into randomized trial patients and observational registry patients.

There were no significant differences between patients who gave consent to be in a study and those who did not for the following characteristics: age, gender, race, ejection fraction, NYHA, insurance, heart failure etiology, use of beta blockers, digitalis, ACE inhibitors or angiotensin receptor blockers. When study participants were separated into sub-groups (no study, observational registry or randomized trial), the only difference between the three groups was a significant difference with regards to insurance coverage ($p=.021$).

When the distribution of patients in each type of study was examined separately, patients with private insurance +/- Medicare were significantly more numerous than expected to have participated in observational registries ($p=.004$) but the same was not true for randomized clinical trials ($p=.198$). Patients with Medicaid +/- Medicare were more numerous than expected in the randomized trial group and participated less frequently in registries but these findings were not statistically significant.

***Other Findings***

The admission date and reason for the hospitalization of the 228 patients were collected for hospitalizations during the data collection period of this study. Unfortunately, this data, although it constitutes a large quantity of information about post-implant hospitalizations at Emory, does not include any hospitalizations that may have occurred elsewhere. For this reason, it could not be used to accurately predict a generalized hospitalization outcome for this CRT-D recipient cohort.

The data described in this section does however give a complete picture of the heart failure hospitalizations that took place at Emory after CRT-D implant. At 6 months after implant, 15% of patients had been hospitalized at Emory for heart failure, and at one year, 21% had been hospitalized. (**Table 7)** Further analyses compared groups for a composite endpoint of death/ LVAD/transplant or heart failure hospitalization. The patients who reached the composite endpoint of death/ LVAD/ transplant or heart failure hospitalization at Emory were significantly more likely to be African-American. They were also more likely to have a higher creatinine level and a lower ejection fraction than those who did not reach this endpoint, and they were more likely to be taking digitalis. (**Table 8)**

# Chapter V

## Conclusions, Implications, and Recommendations

### *Introduction*

Abundant evidence is available from clinical trials to support the efficacy of CRT-D therapy as a therapeutic option for the reduction of morbidity and mortality in chronic heart failure. This study provides a real world comparison to verify if knowledge obtained from clinical trials with regards to CRT-D outcomes and the factors that influence these outcomes translates to general patient populations. The study also attempts to identify differences in survival rates and baseline characteristics between the small number of patients who were involved in a RCT, those who consented to one of many observational registries that were ongoing at the time of their implant, and the larger proportion of patients who received their device without participating in any sort of trial.

### *Summary and Conclusions of the Study*

The results of this retrospective analysis are in favor of the effectiveness of CRT-D devices outside of the RCT setting based on the survival rates observed after CRT-D

implant for this cohort of 228 patients. The 6-month survival rate of 95% and the 12-month survival rate of 89% were very similar to those of the major randomized trials in the bottom rows of Table 1. This supports the effectiveness of CRT-D therapy by demonstrating survival rates comparable to those of clinical trials in a more diverse population of CRT-D recipients. Although it could be argued that the cohort did include some randomized trial patients, they comprised less than 8% of the total population, and the largest proportion of patients in the cohort were not study patients. While our population was slightly younger than the major trial populations, the patients in this cohort presented with various comorbidities such as recent myocardial infarction, severe COPD or renal disease, or atrial fibrillation that would have disqualified them from most major clinical trials. The presence of a much broader spectrum of clinical profiles in our cohort with comparable survival outcomes supports the effectiveness of CRT-D therapy, The results are in favor of the effectiveness of CRT-D therapy because the survival rates are very similar in this population even though many of these patients have complex medical histories that would have excluded them from clinical trial participation at the time of their implant.

It is interesting to note that the average LVEF was slightly lower in the Emory cohort compared to the study cohorts, whereas there were almost 10% of NYHA class II patients in the Emory cohort and none in the large clinical trial groups used for comparison. This may be due to the data collection process that considered baseline to be the time period encompassing implant date +/- 3 months, or it may also simply reflect variation in physician evaluation of a given patient due to the more subjective nature of

NYHA assessment. These observations reflect the greater heterogeneity in the Emory cohort which is to be expected in the absence of inclusion/ exclusion criteria such as those applied for patient selection in a randomized clinical trial.

Age and gender were not associated with the survival outcome in this cohort. This is consistent with the existent body of medical literature concerning CRT-D outcomes, since age and gender have not been shown to be predictors of outcome in most major studies of CRT-D device use.

The etiology of the underlying heart failure was not found to be a significant factor in determining the survival outcome in the Emory cohort. Again, this finding is consistent with the secondary analyses of major clinical trials that determined that the presence of ischemic heart disease did not reduce the benefits of CRT-D therapy in device recipients as was originally thought.

Serum creatinine levels were found to be a significant predictor of the negative composite outcome of death/LVAD/transplant. This was true at both the univariate ($p=.001$) and multivariate ($p=.03$) levels. This result is not surprising because kidney function is frequently cited throughout the literature as having a close association with survival outcomes in CRT-D patients. Diabetes and atrial fibrillation, which have been identified along with chronic renal disease as significant risk factors for higher mortality in CRT-D patients (BAI, BIASE et al. 2008), were not predictors of survival in this cohort.

Ejection fraction was a negative predictor of the death outcome in the cohort. It was an independent predictor in univariate analysis and also one of the factors retained in the multivariate model. This result could mean that the patients who died may have been more likely to have an extremely low ejection fraction going into the procedure and therefore have still succumbed to heart failure despite having a device, or inversely, survivors were patients who benefited from the device because they were more likely to have had conserved a bigger portion of intrinsic heart function at baseline. The case by case reality is much more complex and factors such as the morphology of the heart, the presence of scar tissue, valvular disease and ventricular dyssynchrony should be taken into account when attempting to predict the success of CRT-D therapy. Interestingly, QRS width, which is a commonly used but somewhat controversial indicator of ventricular dyssynchrony, was not associated with the survival outcome in this cohort. A more in-depth analysis of cardiac parameters has been suggested as a better predictive tool (Agha, Kalogeropoulos et al. 2009) but this would require more complete echocardiographic data collection at baseline and at different points during the follow-up period and was beyond the scope of this particular study. Ejection fraction remains however the most common parameter used to assess heart function and results such as the ones obtained in this study can be informative as to the timing of the CRT-D implant in the natural course of a heart failure patient's disease.

In the multivariate model, digoxin use was associated with the negative outcome of death/ LVAD/ urgent transplant after controlling for several other factors such as

creatinine levels, ejection fraction and previous device history (p=.042). There did not appear to be confounding between ejection fraction and digitalis use since the distribution of the two variables was independent within the cohort. Although digoxin has been utilized to reduce clinical symptoms of heart failure for many years, recent studies have begun to raise questions with regards to its usefulness and have warned clinicians that digoxin may actually be detrimental in certain cases. Our findings concur with those of a recent study that found that patients with advanced heart failure on optimal therapy plus digoxin were twice as likely to experience a composite outcome of death / LVAD/ transplant than those who were not taking digoxin (Georgiopoulou, Kalogeropoulos et al. 2009). This study concerned heart failure patients in general, with about 38% of the study population comprised of CRT-D recipients.

The other therapeutic classes (beta blockers, angiotensin receptor blockers, ACE inhibitors, aldosterone antagonists, diuretics) did not have a significant impact on the survival outcome in this cohort, including loop diuretics which were added to but not retained in the multivariate model. This finding contradicts recent study results (Voigt, Shalaby et al. 2010) which found the absence beta-blockers to be independently associated with poor outcomes in 177 CRT-D recipients followed for an average of 19.9+/-9.2 months. There was no significant difference in beta blocker use within the Emory cohort with regards to the death outcome. There was also a higher proportion of beta-blocker use in the Emory cohort (79.7% vs. 73% for the population of the study). In

general, there are very few studies on the effects of cardiac medications on mortality and hospitalization outcomes conducted solely in CRT-D patients in current literature.

According to the multivariate model derived from the data for this cohort, participation in an observational registry was found to be a negative predictor of the composite outcome of death/ LVAD/ or urgent transplant. Most attempts to identify a trial effect have been based on randomized cancer trials and have not been conclusive. (Braunholtz, Edwards et al. 2001)

While participation in clinical trials has not been shown to be detrimental to patient outcomes, the question of a the intrinsic benefit of trial participation is very difficult to analyze empirically and there is very little solid evidence to show that there is substantial benefit to a patient from participating in a clinical trial other than the therapeutic benefits of the trial treatment itself, which was the same for all of the patients in this cohort. Patients in clinical trials often get additional office visits and phone calls from the study staff based on the requirements of the protocol. They may have extra testing such as echocardiographic exams at close intervals to collect study data. All of this extra attention for the study could contribute to early intervention in case of worsening heart failure. Even if the study is a registry, the extra data collection via phone calls or visits can potentially improve medication compliance. The willingness to participate may also reflect a patient's attitude towards their illness and its treatment, as was demonstrated by one study that found a better prognosis in heart failure patients who were simply willing to eventually participate in a trial, whether or not they ever did (Clark, Lammiman et al.

2009). These positive effects should also have influenced survival rates for the randomized trial participants, but participation in a randomized trial was not associated with better survival outcomes.

The explanation for the association between participation in an observational registry and better survival outcomes may be related to the third research question which explored the differences between trial participants and non-participants. The only significant difference between study/ registry participant participants and non-participants was insurance coverage. This was actually rather surprising considering the solid evidence in the literature to indicate that women, minorities, and elderly persons are generally less willing to give consent to participate in clinical trials or registries, yet none of these differences were present in this cohort.

In the Emory cohort, patients who participated in observational registries were significantly more likely to have private insurance +/- Medicare coverage. Insurance coverage is often used as a surrogate variable for estimating socio-economic status (SES), with private insurance coverage associated with higher SES and Medicaid associated with lower SES (Cohen 2007). Medicare is based on age and therefore not directly related to socio-economic status. Patients who enrolled in registries tended to have better survival rates and were also had significantly higher levels of private insurance coverage, which would tend to indicate a higher SES. Socio-economic status has been found to be correlated with health outcomes because of the relationship between income

level and factors such as access to health care, health behaviors, education level and health literacy. The results of our cohort are in line with those of recent studies that show SES to be an independent determinant from race and gender with regards to its effect on outcomes (Karlamangla, Merkin et al. 2010; Koch, Li et al. 2010). Factors such as age, gender and race did not differ between study participants and non-participants in our cohort and they were not determinants of the survival outcome in the multivariate model.

Although the distribution of Medicaid patients among the different options of study participation was not statistically significant, Medicaid patients were more numerous than expected in the randomized trial group. Randomized trial participation was not associated with better survival outcomes in the survival analysis. Some authors (Unger, Coltman et al. 2006) have suggested that patients with Medicare and private insurance were more likely to participate in clinical trials because any coinsurance costs from the trial would be covered by the private insurance. This was not the case in the Emory cohort, since private insurance patients were less numerous than expected in the clinical trial group.

The data presented in Tables 7 and 8 can be the object of limited discussion because of the fact that it only represents hospitalization data from Emory and does not reflect hospitalizations that may have occurred at outlying centers. While taking into account the potential bias generated by this limited data source, it is still interesting to compare our results with those of the COMPANION trial. At the 12 month point, the

Emory cohort had a 79% event free survival rate vs. 71% for the COMPANION trial. It is likely that if our data had taken into account events at outlying centers the event-free survival would have been comparable.

The factors that differentiated patients based on event-free survival included ejection fraction, creatinine and digitalis use as with the survival variable, but this time African Americans were more likely to be experience the endpoint of death / LVAD/ transplant or hospitalization and insurance was no longer a significant factor. Again, if insurance is used as a surrogate for SES, it would then appear, based on the cohort results, that lower SES has less of an effect on access to hospital care and perhaps more impact on aspects such as the economic burden such as office visits, prescriptions or health behaviors, social support systems, etc.

***Implications***

This study provides support to the idea that the efficacy of CRT-D devices that has been repeatedly demonstrated in various randomized trials is generalizable to a non-trial, clinical practice setting. The information derived from this cohort will add to the relatively limited body of knowledge concerning CRT-D use in routine practice. The similar survival rates to those of RCTs in this more diverse patient population (in terms of comorbidity) is a strong argument for the effectiveness of CRT-D therapy in heart failure patients. This type of observational trial can be used to better understand which patients will truly benefit from CRT-D, besides those who fit RCT inclusion/exclusion

criteria. It may also generate more questions and more research, for example, with regards to the timing of the CRT-D implant in the evolution of the heart failure disease, considering the importance of kidney function as a predictor of outcomes.

The discovery of better outcomes for the observational registry patients was more of a statement about their socio-economic status than a potential trial result from taking part in the registry and underscores the importance of taking in account about the relationship between socio-economic status and health outcomes. The results of this study demonstrate that there is no "typical" study participant, and that the factors that motivate or prevent patients from participating are not necessarily the same from one patient to another since none of the classic disparities in research participation were found in this cohort.

***Recommendations***

A major limitation in this retroactive chart review was the absence of consent to obtain outside medical records which limited data analysis to the data available in Emory medical records. Ideally, it would be preferable to obtain access to outside hospitalization records as hospitalization is an important endpoint to analyze in heart failure. This was not feasible in the scope of this chart review but could certainly be done in a registry study design.

This study focused on baseline and clinical data such as medical history but it might be useful to do a similar study of patient outcomes with a greater focus on echocardiographic data as well as data from cardiac MRI, which will probably play a role in answering the questions surrounding the 30% non-responder rate to CRT-D therapy. Cohort studies should be conducted for as many RCT-validated devices and drugs as possible because they provide clinicians with a real-world account of the outcomes with a more diverse patient population than the usual set of patients encountered in a randomized trial. Similar studies should be done in other clinical settings to have different clinical experiences for comparison. In this sense they have a definite place in the hierarchy of evidence of evidence-based medicine.

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# APPENDIX

| Characteristic | COMPANION | CARE-HF | MIRACLE ICD | MUSTIC (sinus rhythm arm) | MUSTIC (atrial fibrillation arm) |
|---|---|---|---|---|---|
| **Age *** | 66 | 67 | 66.6 (11.3) | 63 (10) | 65 (9) |
| **% Male** | 67 | 74 | 75.9 | 75 | 81 |
| **LVEF %** | 22 | 25 | 24.2 (6.5) | 22 (8) | 26 (10) |
| **QRS width** | 160 | 160 | 165 (22) | 176 (19) | 206 (19) |
| **Ischemic Cardiomyopathy (%)** | 55 | 40 | 64 | 37 | 27 |
| **% Diabetic (%)** | 41 | - | - | - | - |
| **% NYHA III** | 86 | 94 | 88.2 | 100 | 100 |
| **% NYHA IV** | 14 | 6 | 11.8 | - | - |
| **% Beta Blocker therapy** | 68 | 70 | 62 | 28 | 22 |
| **% ACE or ARB therapy** | 90 | 95 | 92.5 | 96 | 100 |
| | | | | | |
| **Survival Rates for CRT-d sub-groups** | | | | | |
| **At 6 months** | 95% | | 92% | | |
| **At 12 months** | 88% | 90% | | 83% (global rate) | 83% (global rate) |

**Table 1: Patient Characteristics of CRT Trial Patients**

*Median values were provided for continuous variables in Companion and Care-HF.

Source:(Linde, Leclercq et al. 2002; Young, Abraham et al. 2003; Bristow, Saxon et al. 2004; Cleland, Daubert et al. 2005)

| Observational Cohort Studies | | | | | |
|---|---|---|---|---|---|
| | Stabile et al, 2009 | Bai et al, 2008 | Auricchio et al, 2007 | Molhoek et al, 2004 | Shalaby et al, 2008 |
| Characteristic | | | | | |
| | | | | | |
| Age * | 68.2 (+/- 9) | 66(+/-11.6) | 64 (+/- 9) | 65 (+/-11) | 67.3 (+/-11.3) |
| % Male | 81 | 79.7 | 83 | 78 | 81.8 |
| LVEF % | 25 (+/-6.5) | 19.9 (+/-7.7) | 25 (+/-7) | 23(+/-13) IC 21(+/-9) IDC | 22.4 (+/-9.3) |
| QRS width | - | 160.5 (+/-24.5) | 169 (+/- 30) | 177 (+/-29) | 156.5 (+/-29.4) |
| Ischemic Cardiomyopathy (%) | 56 | 68.6 | 55 | 46 | 63.6 |
| % Diabetic (%) | - | 10.4 | - | - | - |
| % NYHA III | 72 | 81.3 | 78 | 85 | Mean NYHA 3.0 +/-.03- |
| % NYHA IV | 16 | 18.7 | 15 | 15 | |
| % Beta Blocker therapy | - | 70.1 | - | 60 | 77.2 |
| % ACE or ARB therapy | - | 80.5 | - | 85 | 79.6 |

**Table 2 : Patient Characteristics in Observational Cohort Studies** Source: (Molhoek, Bax et al. 2004; Auricchio, Metra et al. 2007; BAI, BIASE et al. 2008; Shalaby, El-Saed et al. 2008; Stabile, Solimene et al. 2009)

| Demographics | |
|---|---|
| Date of birth | |
| Date of implant | |
| Gender | |
| Zip code | |
| Race | |
| Insurance coverage | |
| Participation in a registry | |
| | |
| **Clinical Data** | **Laboratory Data** |
| Height and Weight | Glucose and Hb A1c |
| Systolic and diastolic blood pressure | TSH |
| Heart rate | BUN |
| Respiration rate | Creatinine |
| NYHA classification | Lipid panel |
| LVEF | BNP |
| QRS width | Sodium, Potassium, calcium |
| ECG rhythm | INR |
| | |
| **Medical History** | **Medical treatment** |
| | |
| Smoking history | Aldosterone antagonists |
| Alcohol abuse | ACE inhibitors |
| Hypertension | Angiotensin receptor blockers |
| Dyslipidemia | Calcium channel blockers |
| Thyroid disorders | Digitalis |
| Diabetes | Diuretics |
| Stroke | Nitrates |
| Ischemic heart disease | Anti-arrhythmic drugs |
| Peripheral arterial disease | Statins and lipid lowering drugs |
| Asthma | Aspirin and anti-coagulant agents |
| COPD | Oral diabetic drugs and insulin |
| Renal insufficiency | Anti-depressants |
| Dementia | Hormone replacement therapy |
| Depression | Bronchodilators |
| HIV status | Non-steroidal anti-inflammatory drugs |
| Toxicity from chemotherapy or radiotherapy | |
| Previous implant of a pacemaker or defibrillator | |

**Table 3: Data Collection: Baseline Characteristics**

**Table 4 : Baseline Characteristics : Total Cohort and by Survival (Death or LVAD or Transplant)**

| | Total Cohort | Survived without LVAD /transplant | Death/ transplant / LVAD | p* |
|---|---|---|---|---|
| | n=228 | n=135 | n=93 | |
| | | | | |
| | | | | |
| **Age (x +/- SD)** | 62.5 (+/- 13.7 years) | 61.6 (+/- 12.5 years) | 63.8 (+/- 15.3 years) | **0.142** |
| | | | | |
| **Male, n (%)** | 160 (70.2) | 89 (66) | 71 (76) | **0.106** |
| **Female, n(%)** | 68 (29.8) | 46 (34) | 22 (24) | |
| | | | | |
| **Race, n (%) *( n=206)*** | | | | **.118** |
| **Caucasian** | 144 (69.9) | 92 (68) | 52 (56) | |
| **African American** | 60 (29.1) | 31 (23) | 29 (31) | |
| **Missing** | 22 (9.6) | 11 (4.8) | 11 (4.8) | |
| **Other** | 2 (1) | 1 (.004) | 1 (.004) | |
| | | | | |
| **Insurance n (%) *(n=224)*** | | | | **.181** |
| **Private Insurance +/- Medicare** | 146 (64) | 93 (69) | 53 (57) | |
| **Medicare Alone** | 49 (21.6) | 26 (19.2) | 23 (25) | |
| **Medicaid +/- Medicare** | 29 (12.7) | 14 (10.1) | 15 (16) | |
| **Missing / self pay** | 4 (0.2) | 2 (1.5) | 2 (2) | |
| | | | | |
| **RCT / registry participation, n (%) (n=228)** | | | | **.053** |
| **Consented to registry or RCT** | 89 (39) | 60 (44) | 29 (31) | |
| **Did not give consent** | 139 (61) | 75 (56) | 64 (69) | |
| | | | | |
| **NYHA, n (%) *(n=228)*** | | | | **0.391** |
| **II** | 22 (9.6) | 13 (10) | 9 (10) | |
| **III** | 173 (75.9) | 106 (78) | 67 (72) | |
| **IV** | 33 (14.5) | 16 (12) | 17 (18) | |
| | | | | |
| **LVEF (x +/- SD)** | 20 (+/- 9.3) | 21.4 (+/-9.6) | 18.0 (+/- 8.6) | **0.006** |

| | Total Cohort | Survived without LVAD /transplant | Death/ transplant / LVAD | p* |
|---|---|---|---|---|
| | | | | |
| **LVEF qualitative, n (%) (n=226)** | | | | **0.121** |
| **normal** | 3 (1.3) | 3 (2) | 0 | |
| **mild** | 7 (3.1) | 4 (3) | 3 (3) | |
| **moderate** | 37 (16.4) | 27 (20) | 10 (11) | |
| **severe** | 179 (79.2) | 100 (74) | 79 (85) | |
| | | | | |
| **Cormorbidities, n (%)** ***(n=227)*** | | | | |
| **Diabetes** | 67 (27.8) | 37 (27) | 26 (28) | **0.927** |
| **Hypertension** | 106 (46.7) | 65 (48) | 41 (44) | **0.685** |
| **Myocardial Infarction** | 44 (19.4) | 25 (19) | 19 (20) | **0.734** |
| **Peripheral Arterial Disease** | 14 (6.2) | 8 (6) | 6 (6.5) | **1** |
| **CVA/ TIA** | 18 (7.9) | 12 (9) | 6 (6.5) | **0.305** |
| **Atrial arrhythmia** | 72 (31.7) | 42 (31) | 30 (32) | **0.944** |
| **Ventricular arrhythmia** | 32 (14.1) | 16 (12) | 16 (17) | **0.165** |
| **Renal disease** | 45 (19.8) | 21 (16) | 24 (26) | **0.062** |
| **Previous device (IPG/ ICD)** | 41 (19.1) | 27 (20) | 14 (15) | **0.086** |
| **COPD** | 29 (12.8) | 14 (10) | 15 (16) | **0.226** |
| | | | | |
| **Type of Cardiomyopathy, n (%)** ***(n=227)*** | | | | |
| **Ischemic** | 104 (45.8) | 58 (43) | 46 (49) | **0.343** |
| **Idiopathic** | 101 (44.4) | 64 (47) | 37 (40) | **0.341** |
| | | | | |
| **ECG rhythm, n (%)** ***(n=225)*** | | | | **0.468** |
| **Sinus rhythm** | 138 (61.3) | 80 (59) | 58 (62) | |
| **AF** | 47 (20.9) | 26 (19) | 21 (23) | |
| **Paced or other rhythm** | 40 (17.8) | 27 (20) | 13 (14) | |
| | | | | |
| **QRS width, n (%) (n=226)** | | | | **0.466** |
| **<120 ms** | 58 (25.7) | 33 (24) | 25 (27) | |
| **121-150** | 80 (35.4) | 45 (33) | 35 (38) | |
| **>150** | 88 (38.9) | 57 (42) | 31 (33) | |
| | | | | |
| **Bundle Branch Block, n (%) (n=225)** | | | | **0.232** |

| | Total Cohort | Survived without LVAD /transplant | Death/ transplant / LVAD | p* |
|---|---|---|---|---|
| **No BBB** | 117 (52) | 70 (52) | 47 (51) | |
| **LBBB** | 87 (38.7) | 55 (41) | 32 (34) | |
| **RBBB** | 21 (9.3) | 9 (7) | 12 (13) | |
| | | | | |
| | | | | |
| **Systolic Blood Pressure (x +/- SD)** | 119.8 (+/-20.8) | 121.2 (+/-20.2) | 117.6 (+/-21.6) | **0.402** |
| **Diastolic Blood Pressure (x +/- SD)** | 73 (+/-11.8) | 72.8 (+/- 11.8) | 73.2 (+/- 11.9) | **0.933** |
| | | | | |
| **Heart rate (x +/- SD)** | 78.1 (+/- 15.3) | 78.8 (+/- 16.3) | 77.2 (+/- 13.9) | **0.798** |
| | | | | |
| **Serum creatinine (x +/- SD)** | 1.4 (+/- .8) | 1.3 (+/- .78) | 1.5 (+/-.84) | **0.001** |
| | | | | |
| **Medications n (%) (n=227)** | | | | |
| **Aldosterone antagonists** | 73 (32.2) | 39 (29) | 34 (37) | **0.247** |
| **ACE inhibitors** | 144 (63.4) | 83 (61) | 61 (66) | **0.485** |
| **Angiotensin Receptor Blockers** | 52 (22.9) | 35 (26) | 17 (18) | **0.202** |
| **Beta Blockers** | 181 (79.7) | 106 (79) | 75 (81) | **0.618** |
| **Loop Diuretics** | 174 (76.7) | 98 (73) | 76 (82) | **0.109** |
| **Digoxin** | 112 (49.3) | 61 (45) | 51 (55) | **0.139** |
| | | | | |
| | | | | |
| | | | | |

*missing values were not taken into account for the calculation of p values

**Figure 1: Survival estimate: total cohort**

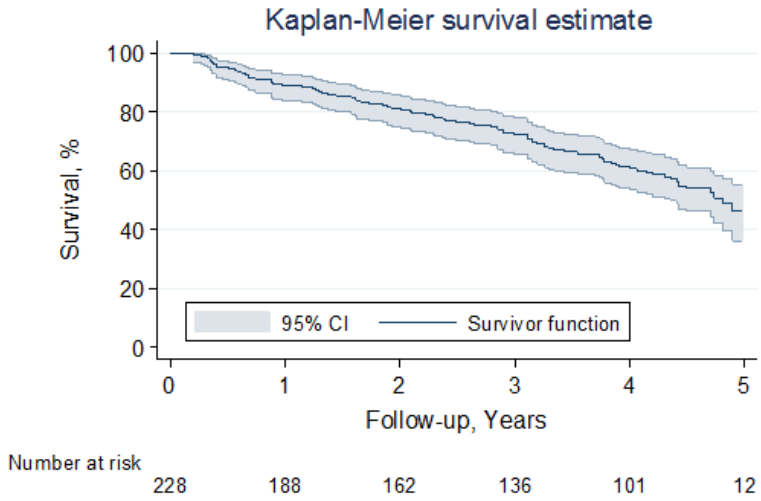

**Table 5: Emory University Hospital Cohort: Survival at 6, 12, 18 and 24 months**

| Time (mo) | Survival | Lower 95% CI | Upper 95% CI |
|---|---|---|---|
| 6 | 95% | 91% | 97% |
| 12 | 89% | 84% | 92% |
| 18 | 86% | 80% | 90% |
| 24 | 81% | 75% | 86% |

**Table 6: Factors Associated With Composite Outcome (Death / Transplant/ LVAD)**

| | β | HR | 95% CI | Significance |
|---|---|---|---|---|
| ***Univariate*** | | | | |
| Age less than 65 years | -.171 | .843 | .560-1.269 | .413 |
| Male gender | .391 | 1.478 | .908-2.407 | .116 |
| African American | .429 | 1.536 | .973-2.427 | .066 |
| Medicaid +/- Medicare | .694 | 2.003 | 1.117-3.591 | .018 |
| Participating in Observational Study | -.568 | .567 | .341-.941 | .026 |
| Ejection Fraction (per 5% increase) | -.157 | .855 | .756-.966 | .012 |
| History of Renal Disease | .450 | 1.568 | .983-2.501 | .059 |
| History of previous pacemaker | -1.009 | .365 | .133-.999 | .050 |
| Creatinine | .147 | 1.158 | .978-1.372 | .090 |
| Use of loop diuretics | .418 | 1.519 | .884-2.611 | .130 |
| Use of digitalis | .384 | 1.468 | .970-2.223 | .070 |
| ***Multivariate*** | | | | |
| Ejection Fraction (per 5% increase) | -.183 | .833 | .721-.962 | .013 |
| Digitalis use | .473 | 1.605 | 1.018-2.533 | .042 |
| Participation in an Observational Registry | -.740 | .477 | .280-.813 | .007 |
| Increase in creatinine level | .213 | 1.238 | 1.020-1.502 | .030 |

**Table 7: Heart Failure Hospitalization Rates at Emory in CRT-D Patients**

**Survival rate without a heart failure hospitalization at Emory at 6, 12, 18, and 24 months was as follows**:

Louise Savoye 9/28/10 6:25 PM
**Deleted:** .

| Time (months) | Survival | Lower 95% CI | Upper 95% CI |
|---|---|---|---|
| 6 | 85% | 80% | 89% |
| 12 | 79% | 73% | 84% |
| 18 | 73% | 66% | 78% |
| 24 | 67% | 61% | 73% |

**Table 8: Baseline Characteristics and Endpoint of Death or Heart Failure Hospitalization**

| Variables | Survived without HF Hospitalization | Death/LVAD/ Tx Or HF Hospitalization | p |
|---|---|---|---|
| Age , x age | 62.34 | 62.65 | .865 |
| Male Gender , n (%) | 70 (65) | 90 (74) | .150 |
| African American, n (%) | 18 (19) | 42 (39) | .002 |
| Insurance | | | .125 |
| Medicaid+/- Medicare, n (%) | 9 (8) | 20 (17) | |
| Medicare only, n (%) | 22 (21) | 27 (23) | |
| Private insurance +/- Medicare, n (%) | 75(71) | 71 (60) | |
| Ejection Fraction (%) | 21.9 | 18.3 | .004 |
| Creatinine (mg/dl) | 1.23 | 1.48 | .000 |
| Regtype (type of study Participation) | | | .350 |
| No study, n (%) | 60 (56) | 79 (65) | |
| Observational study, n (%) | 38 (36) | 33 (27) | |
| Randomized trial, n (%) | 9(8.4) | 9 (7.4) | |
| Digitalis use | 52 (43) | 68 (57) | .024 |