Cardiac Resynchronization Therapy Device-Programmed and Device-Measured Parameters as Predictors of Outcomes in Patients with Heart Failure

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Dedication

For Marta and Nadine – I don't even know where to begin thanking you for your kindness, patience, and support these past years. It has been a long road.

Abstract

Heart failure (HF) is a major public health burden, with over 6.5 million adults in the US suffering from the disease. Moderate to advanced-stage heart failure patients implanted with cardiac resynchronization therapy (CRT) devices suffer from increased mortality risk and frequent inpatient hospitalization. Efforts to reduce mortality and prevent HF-related hospitalizations in this population would be of significant benefit to the patients, as well as to the health care system. In this doctoral dissertation, we present three manuscripts examining associations between CRT device-measured and device-programmed parameters and patient mortality and HF-hospitalization.

In the first manuscript, we examined the device-measured parameter of intrathoracic impedance, and whether an OptiVol® threshold crossing or time above OptiVol® threshold were associated with patient mortality and HF-related hospitalization. We found that patients with >15.1% of their follow-time above threshold had a 4.2 times greater risk of mortality and a 3.2 times greater risk of HF-hospitalization than those patients with <4.1% of follow-up time above threshold. In addition, a single OptiVol® crossing was associated with an 87% higher mortality rate, and a 70% higher HF-hospitalization rate.

In the second manuscript, we examined the device-measured associations between biventricular pacing percentage, AF burden, and heart rate variability on patient mortality and HF-related hospitalization. We found a complex relationship between biventricular pacing percentage, AF, AVN ablation, and HRV where patients with <99% bi-V pacing

percentage had an increased rate of mortality and hospitalization among those with no baseline device-measured atrial fibrillation. In addition, AVN ablation was associated with worse outcomes among those with high baseline HRV, suggesting that the potential loss of benefits of higher HRV must be weighed when performing an AVN ablation procedure.

The third manuscript looked at parameters associated with an increased risk of 30-day HF-related rehospitalization. We found that parameters associated with kidney function to be of critical importance in evaluating the risk of patients at higher risk of rehospitalization within 30 days. Patients with a daily intrathoracic impedance measurement >8Ω less than the reference impedance value on the day of discharge, a diagnosis of chronic kidney disease, no diuretic prescription, male sex, longer duration of heart failure at the time of index hospitalization, and those with a prior CABG procedure to have a higher risk of 30-day rehospitalization. Model AUC, NRI, IDI, and Hosmer-Lemeshow statistics indicated good model discrimination with respect to a previously published model with good calibration.

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1 Introduction to Heart Failure

Heart failure (HF) remains one of the most prevalent and costly cardiovascular diseases to treat in the health care system. Data from the National Health and Nutrition Examination Survey (NHANES) gathered between 2011 and 2014 show that approximately 6.5 million adults in the US have heart failure.[1] Another study projected that the prevalence of heart failure among the US population would increase from 2.4% in 2012 to 3.0% in 2030, representing a 23% increase over 2012 levels. Accounting for the projected growth of the US population over this time period, this represents a 46% increase in the absolute number of Americans living with heart failure by 2030.[2] This projected increase would also come with a corresponding 254% increase in direct medical costs associated with treating and managing the disease, and a further 70% increase in "indirect", or lost productivity costs associated with HF. These costs stand at $20.9 billion and $9.8 billion, respectively, as of 2012. [2] Currently known risk factors for the

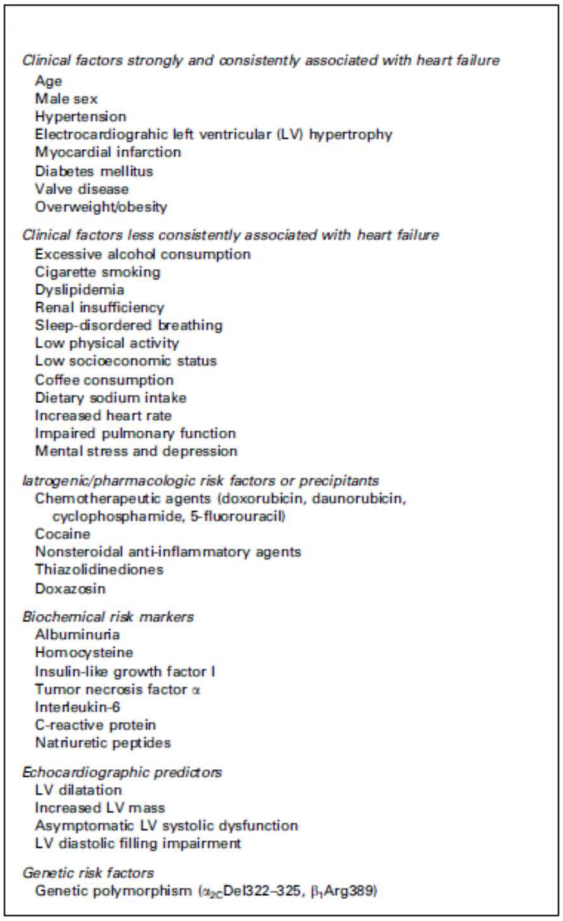


Figure 1. – Risk Factors and Markers for Heart Failure.

Adapted from Kenchaiah S, Narula J, Vasan RS. *Med Clin N Am.* 2004;88:1145-1172.

development of heart failure are listed in Figure 1, and include coronary heart disease (CHD), hypertension, increasing age, male sex, diabetes, valvular disease, and obesity.[3] However, the two factors of CHD and hypertension alone are believed to account for fully three-fourths of all heart failure cases, although interaction with other factors such as race, sex, and age may exacerbate or ameliorate the effects of CHD or hypertension, or both. [4,5] With respect to CHD, it has been proposed that increased survival from myocardial infarction in recent decades have led to a corresponding increase in HF prevalence.[6,7]

1.1 Pathophysiology of Heart Failure

Heart failure itself is a complex, multifaceted disease, and has been broadly defined as a condition where the heart is rendered incapable of ejecting blood supplied to it by the venous system.[8] An important concept to understand in heart failure is that of cardiac output. Cardiac output is combination of both stroke volume (the amount of blood pumped by the left ventricle in a single contraction) as well as heart rate (the number of contractions per minute). Heart failure, importantly, does therefore not include diseases where insufficient blood is supplied to the heart due to blood loss or other impairment of blood return. Heart failure is dichotomized into two main types: heart failure with reduced ejection fraction (or HRrEF, formerly known as systolic heart failure) and heart failure with preserved ejection fraction (or HFpEF, formerly known as diastolic heart failure), both of which affect the left ventricle. HFrEF and HFpEF are both estimated to be equally prevalent at around 50% of heart failure cases, but the dividing line between

the two is of some debate.[9] In general, HFrEF is defined by the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines as a clinical diagnosis of heart failure with a measured ejection fraction <40%.[10] Other definitions may set this distinction at <35% or ≤40%. Similarly, HFpEF is defined as a clinical diagnosis of heart failure with an ejection fraction ≥50%. Patients with ejection fractions in the range of 40% to 50% are therefore technically "in-between" the two categories, but are often treated similarly to those with HFrEF.[10] The most common causes of both HFrEF and HFpEF are hypertension, valvular disease, direct insult due to myocardial infarction (typically associated with HFrEF, specifically), or to ischemic heart disease more generally. HFpEF is generally more difficult to clinically diagnose as there is no evident reduction in ejection fraction in the presence of heart failure symptoms, but still may have clinically relevant LV dysfunction upon evaluation with cardiac catheterization or echocardiography.[11] Valvular disease, in particular mitral valve stenosis, causes heart failure through progressive inability for the left ventricle to fill with blood due to mitral valve dysfunction, increasing backpressure into the pulmonary vein and resulting pulmonary congestion.

A decrease in cardiac output due to any of the above-listed reasons results in activation of two major adaptive responses in the heart: a neurohormonal autonomic response, shown conceptually in Figure 2, and in molecular and morphological changes to the heart. Inability to maintain cardiac output activates the sympathetic nervous system (SNS) with a corresponding decrease in parasympathetic activity. This

sympathetic activity stimulates physiological changes that increase cardiac output either directly by increasing the heart rate, or indirectly by increasing muscle contractility that, in turn, increases the amount of blood pumped from the heart per beat (increased stroke volume). The blood vessels also contract with an increase in SNS activity, which then cause an increase in blood pressure. All of these changes result in a net increase in the cardiac workload, which in turn causes yet more left-ventricular remodeling and dysfunction in the form of molecular and morphological changes such as hypertrophy and dilatation.[8] The cycle then repeats, resulting in a progressive deterioration of cardiac function and its ability to pump blood.

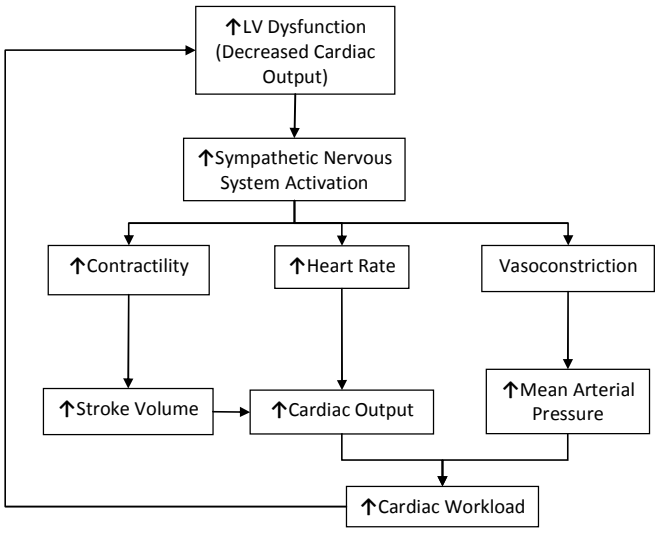


Figure 2. – Theoretical Model of Autonomic Response to Heart Failure

1.2 Classification of Heart Failure

In order to describe and partially quantify the progressive nature of heart failure, two main systems have been established to classify heart failure patients: the New York Heart Association (NYHA) classification scheme, and the American College of Cardiology/ American Heart Association (ACC/AHA) classification guidelines. The

NYHA classification refers primarily to the day-to-day functional capacity of the patient, and is shown in

Table **1**.

Class	**Description**
I	No limitation is experienced in any activities; there are no symptoms from ordinary activities.
II	Slight, mild limitation of activity; the patient is comfortable at rest or with mild exertion.
III	Marked limitation of any activity; the patient is comfortable only at rest.
IV	Any physical activity brings on discomfort and symptoms occur at rest.

Table 1. – NYHA Classification Scheme

Alternately, the ACC/AHA guidelines shown in Table 2, which were developed in 2001 added a “pre-failure” category identifying people at high risk for the disease, but without either clinical or sub-clinical symptoms.

Stage	Description
A	Patients at high risk for developing HF in the future but no functional or structural heart disorder.
B	Structural heart disorder but no symptoms at any stage.
C	Previous or current symptoms of heart failure in the context of an underlying structural heart problem, but managed with medical treatment.
D	Advanced disease requiring hospital-based support, heart transplant or palliative care.

Table 2. – ACC/AHA Classification Guidelines

These measures are subjective, but the classifications (or changes in class over time within patients) are often used as predictors in some studies, and as outcomes in others. It is interesting to note that in the ACC/AHA classification scheme that even those who are not actually diagnosed with heart failure, but are merely *at risk* of developing heart failure are considered to be in Stage A heart failure. Further, it could be construed that after a myocardial infarction of any type or severity, that a patient would be considered in

Stage B heart failure, even though there may be no actual functional physiological impairment.

1.3 Treatments for Heart Failure

Overall, there are three main strategies in treating heart failure. First, pharmaceutical and lifestyle-change strategies are usually the initial approach taken in managing the disease. Lifestyle changes include dietary modifications, quitting smoking, and exercising. Often, though, if lifestyle adaptations have not been adopted at very early stages of the disease they are of very modest effectiveness in treating existing disease alone. Pharmaceutical options at this stage help manage risk factors, such as treating a patient's hypertension, diabetes, or dyslipidemia. In patients that remain or become refractory to medical treatment as the disease progresses, the second option is that of medical device implantation such as cardiac resynchronization therapy (CRT) or, in later stages of the disease, a ventricular assist device (VAD). The third and most drastic treatment for heart failure is that of heart transplantation.[10]

1.3.1 Medications

There are many pharmaceutical options for treating heart failure. In fact, the median number of unique medications a heart failure patient takes for treating HF and other co-morbid conditions is approximately 11, with an interquartile range from 8 to 17 medications.[12] Many of these medications target a specific strategy for addressing the

various autonomic response pathways described in Figure 2. Specifically, the various treatments for treating heart failure fall into the following categories:

1. Vasodilation. These medications attempt to intervene upon vasoconstriction associated with sympathetic nervous system activation. These include angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), isosorbide dinitrate, and hydralazine hydrochloride. Their mechanism of action is either to prevent angiotensin II or aldosterone from being formed, or to block activation of angiotensin II receptors located on smooth muscle cells.[8,13] Both angiotensin II and aldosterone are key components of the renin-angiotensin system, which regulates the body's arterial blood pressure. A recently approved drug therapy combines an ARB (valsartan) with a neprilysin inhibitor (sacubitril). Inhibition of neprilysin increases levels of several vasodilating peptides, such as bradykinin and adrenomedullin.[14]
2. Heart rate control. Sympathetic nervous system activation also results in an increased heart rate through the release of epinephrine and norepinephrine. These compounds bind with β-I adrenergic receptor sites selectively found on cardiac muscle tissue which, in turn, affects heart rate and muscle contractility. Beta-blocker medications compete with epinephrine and norepinephrine for adsorption on these receptor sites, thereby preventing activation, and serving to lower heart rate, reduce contractility, decrease relaxation rate, increase cardiac output, inhibit release of renin, and reduce blood pressure.[13] Other medications for heart rate

control include positive inotropes such as digoxin. Digoxin inhibits sodium-potassium ATP-ase. Inhibiting the function of this enzyme results in a change to the cardiac action potential cycle, and a corresponding increase in intracellular calcium. This elevated calcium then results in a negative chronotropic effect, lowering the heart rate.[13]

3. SNS activity reduction. Beta-blocker medications also treat heart failure through another mechanism by reducing sympathetic nervous system activation in general. The reduction in renin production via beta-blocker uptake leads to reduced aldosterone via the renin-angiotensin-aldosterone system, which in turn, leads to less epinephrine and norepinephrine production and reduced SNS activity.[8,13]
4. Reduce cardiac workload. Diuretics work through two separate mechanisms. First, they work by reducing volume of extracellular fluid via urinary excretion of sodium and water, thereby preventing or reducing edema found in episodes of acute HF decompensation. Further, thiazide-type diuretics provide blood pressure control, decreasing the mean arterial pressure and therefore decreasing cardiac workload.[13] Aldosterone antagonists, such as spironolactone, are another class of drugs which work via a similar mechanism to diuretics. The main effect of aldosterone in the body is to retain sodium and water, resulting in increased intravascular fluid volume. Aldosterone antagonists function as competitors for sites of aldosterone-dependent intracellular sodium channels, thereby increasing excretion of sodium and water which would otherwise be blocked by aldosterone.

Overall, there are many options for pharmacological treatment available to physicians for the management of heart failure. However, adverse effects from these medications need to be carefully monitored and are relatively common, especially considering the sheer number of medications prescribed to the typical heart failure patient. Further, in prescribing a medical regimen for a heart failure patient, the physician must take considerable effort to examine possible interactions between the various medications for each patient and any other potential medications that patient is taking for comorbid conditions.

Management of prescribed medication is also an issue. Many patients have difficulty adhering to their scheduled regimen of prescriptions, which can also have adverse consequences on the patient's outcome. For example, missing a diuretic prescription for a few days in combination with failure to eat a low-salt diet may be enough to trigger an acute decompensation event, and a trip to the emergency room. The cost of heart failure medications can also be a significant burden to the patient, with an estimated annual out-of-pocket expense on heart failure drugs alone estimated at between $750 and $1,626 per person per year.[15]

1.3.2 Medical Devices

If optimal medical therapy proves insufficient in managing a patient's symptoms, other therapies, such as an implanted medical device may also be considered. Such devices meter electrical impulses to either the ventricles or the atria of the heart, or both

in an attempt to correct the mechanical pumping dysfunction of a failing heart by "re-timing" the heart's electrical signals. These impulses are administered by the device in such a way to mimic the natural rhythm of the heart as closely as possible. In heart failure, these devices typically provide electrical stimulation therapy to the left and right ventricles separately, as well as the right atrium, and are called cardiac resynchronization therapy (CRT) devices. When a device paces both the right and left ventricles, it is referred to as "bi-ventricular" pacing. The devices themselves are implanted pectorally under the skin, just inferior to the clavicle. Electrical stimulation is delivered by the device through three insulated, flexible electrical wires, or "leads", to each of the three chambers directly, as shown below in Figure 3.

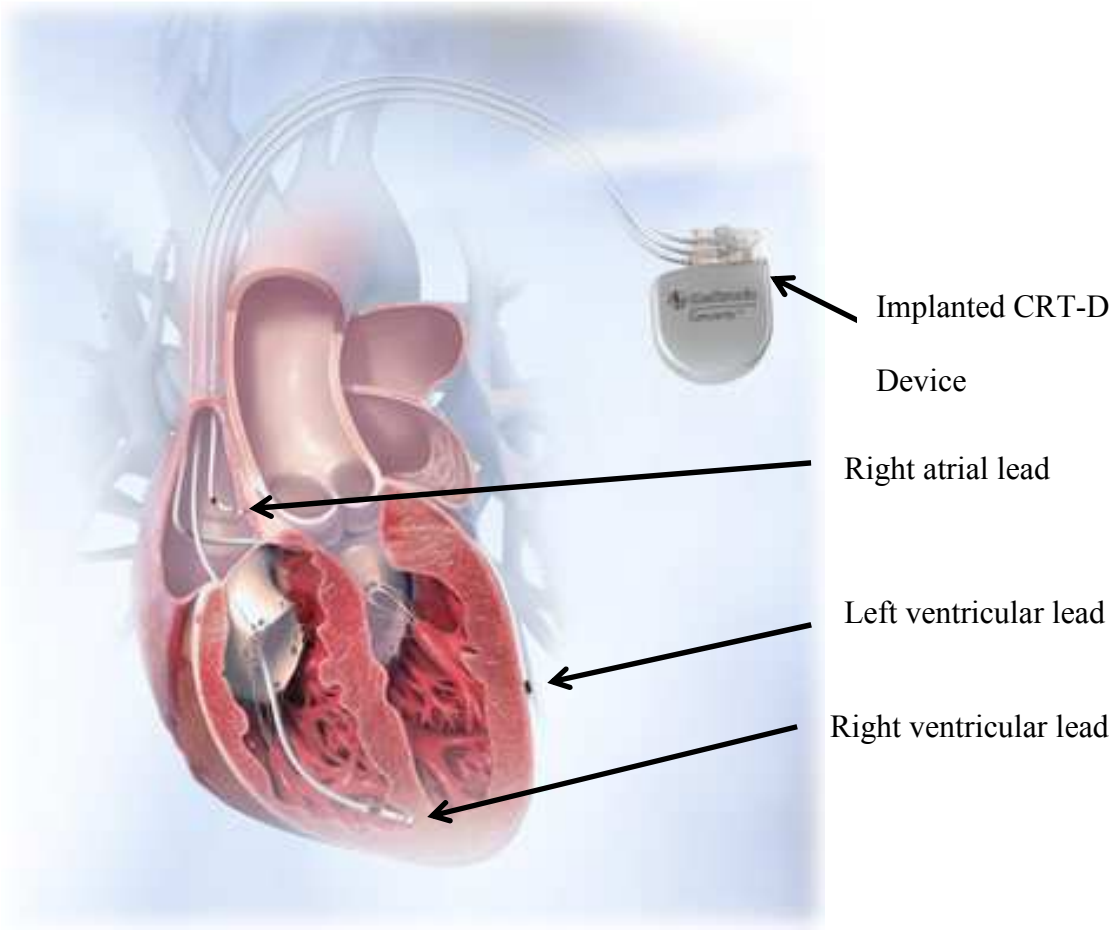


Figure 3. – Cardiac Resynchronization Therapy with Defibrillator (CRT-D) Device and Lead Placement

The leads are each inserted surgically using a catheter, affixed in place, and tested for efficacy. The catheter is then withdrawn, leaving the lead in place. Each lead may provide electrical stimulation separately, and the timing between atrial and ventricular stimulation is often optimized via echocardiography to provide maximal systolic blood flow and diastolic filling volume. Left and right ventricle timing is also programmable, but is only rarely changed from the nominal, simultaneous stimulation setting.

While cardiac resynchronization therapy has been demonstrated to be an effective therapy for treating heart failure patients, there remains the problem that some patients receive no apparent benefit from the device in that their condition either shows no improvement, or continues to worsen. Such "nonresponder" rates can range from 25% to as high as 50% of clinical cohorts.[16-19] However, as CRT implantation carries both patient risks and costs, it is desirable that this therapy be as effective as possible. As mentioned above, if an implanted device fails to improve a patient's condition, there are few options left for treatment, and the costs associated with the device and the associated surgery to implant and potentially explant the device may have been wasted. Since anatomy and physiology differ from patient to patient, it is likely that no single combination of programmed CRT device settings is optimal for all CRT patients. Rather, device programming must be individualized for each patient.

One programmable parameter of these devices which does not treat heart failure directly, but rather can be used as a patient and/or clinician management tool is that of intrathoracic impedance, as it is inversely correlated with left ventricular filling pressure.[20] The devices measure impedance between the tip of the lead in the right ventricular apex and the device itself, implanted just inferior to the clavicle, by sending a known pulse of current through the electrode, and measuring the change in voltage between the lead tip and the metal case of the device. The impedance is then calculated via Ohm's law. The device stores these impedance measurements and accumulates changes in those measurements from a calculated reference value. If this accumulated

impedance measurement, called the OptiVol® fluid index value, drops below the reference value for an extended period of time, indicating that fluid is building up in the lungs, the device can alert the clinician via a home-monitoring network.

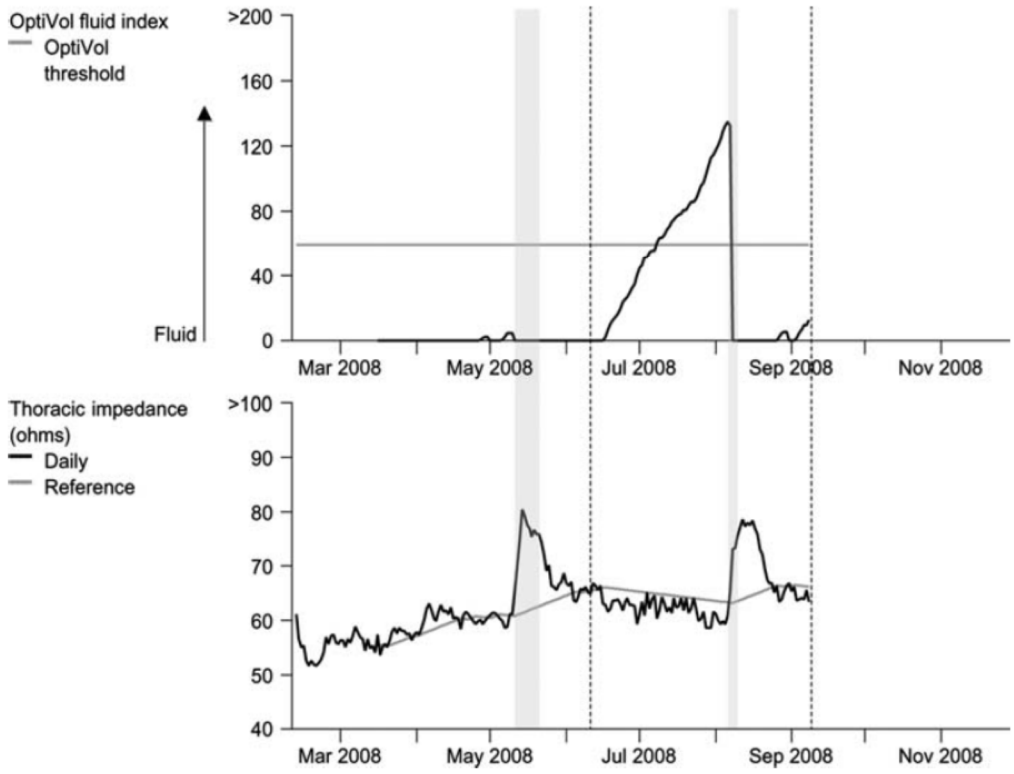


Figure 4. – Example of Patient Intrathoracic Impedance Trends and OptiVol® Threshold Crossing.

From Conraads VM, Tavazzi L, Santini M, Oliva F, Gerritse B, Yu C-M, Cowie MR. *Eur. Heart J.* 2011; 32(18):2266-2273.

In Figure 4, an example patient's impedance measurements began to trend below the reference impedance value in mid-June 2008, resulting in the OptiVol® fluid index value to accumulate over several weeks in June, July and August, with an actual fluid index threshold crossing occurring in early July, and ultimately a hospitalization event occurring in August. Yu, et al. showed that such a threshold crossing was 76.9% sensitive

in predicting hospitalization for fluid overload, with an incidence of 1.5 false positives per patient-year when the nominal programmed threshold value of 60 Ω-days was used.[20] Small, et al., reported that those who had at least three or more 60 Ω-day threshold crossings during an initial 4 month evaluation period after CRT device implant had a significantly higher risk of heart failure hospitalization than those with no threshold crossings (0.76 hospitalizations per year and 0.14 hospitalizations per year, respectively [p-value=0.02]).[21] Ypenburg, et al., reported quite different results for the nominal 60 Ω-day threshold case with nearly 100% sensitivity in predicting a heart failure decompensation event, but with near 0% specificity. After performing a receiver operating characteristic (ROC) analysis they proposed an "optimal" threshold value of 120 Ω -days which offered a sensitivity of 60% and a specificity of 73%.[22] These trials, upon which regulatory approval was based, were very small in nature (33 and 115 patients, respectively) and possibly suffered from the fact that they may not represent typical clinical usage or device management when working with heart failure patients. More recently, Soga, et al., performed a similar ROC analysis on a similarly-sized cohort (n=123), and proposed an optimum threshold value of 114 Ω-days, optimizing the sensitivity at 89.5% and the specificity at 73.0%, with an AUC of 87.1%.[23] They further found that for the default 60 Ω-day programmed threshold setting, the sensitivity and specificity dropped to 83.8% and 28.4%, respectively. Conraads, et al., likewise found very low sensitivity for OptiVol® threshold crossings, but also observed that sensitivity

increased over time from 5.3% during the first 34-63 days to 42.1% for those patients with crossings after 148 days after implant.[24]

A previous study used Medtronic device data along with the Social Security Death Index (SSDI) to look at whether an Optivol® threshold crossing during the initial 6 months after CRT device implantation was predictive of subsequent patient mortality in a large cohort of 21,217 patients.[25] It was found that among those who had an Optivol® threshold crossing during the initial 6 months after CRT device implantation there was a 2.15-fold increased risk of death compared to those who did not have a threshold crossing for both CRT-D and ICD devices (HR 2.15, 95% CI: 1.95-2.38) over the 36 month follow-up period. Further, this association remained significant among only CRT-D devices (HR 2.23, 95% CI: 1.97-2.52), patients which had not experienced a defibrillator shock (HR 2.10, 95% CI: 1.90-2.34), and those without device-detected AF (HR 2.09, 95% CI: 1.86-2.34). This previous study, however, suffers from the fact that no patient covariate information was available other than age and gender to adjust for potential differences between the exposure groups, and as such, the results could have been significantly biased due to confounding. Further, OptiVol® crossings which occurred after the 6-month time window are ignored, which may also have biased their results.

A clinician can examine the OptiVol® data and contact the patient if deemed necessary to determine if the patient has become symptomatic, or has experienced a worsening of heart failure related symptoms and intervene if necessary. The goal is to prevent the symptoms from becoming so severe that they require hospitalization. The threshold at which this alert is triggered is programmed by the clinician and can be set to various values. If the value is set very low, the sensitivity to a true worsening of symptoms will be high, but will likely have a low specificity. Likewise, if the value is set very high, the sensitivity will likely be poor, but the specificity will be high. As shown in Figure 5, intrathoracic impedance monitoring will lead to more frequent clinician interaction, if the impedance monitoring causes the clinician to follow up with the patient in the case of a programmed threshold crossing. This interaction can come in the form of calling the patient to schedule an appointment, or may just be handled over the phone. Such increased clinician interaction may lead to better patient adherence to medications such as diuretics, which directly affect fluid retention. There are several studies which have indicated that heart failure patient adherence to medication is a considerable issue in the management of such patients.[26-28] Increased adherence to medications and/or increased clinician interaction is expected to lead to a decrease in

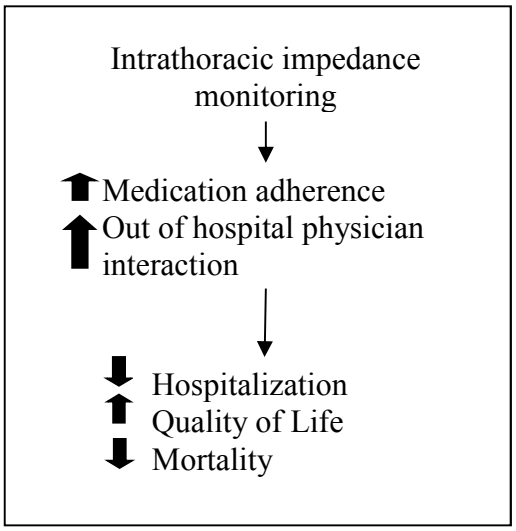


Figure 5. – Theoretical Model of Intrathoracic Impedance Monitoring Intervention

hospitalization due to heart failure-related symptoms, an increase in quality of life, and a decrease in patient mortality.[29]

Lastly, if the electrical intervention of CRT therapy does not provide improvement of a patient's symptoms, a mechanical solution may be considered. These implanted devices are typically mechanical pumps, and are called ventricular assist devices (VADs). There are several types of VADs, left-ventricular assist devices (LVADs), right-ventricular assist devices (RVADs), and bi-ventricular assist devices (bi-VADs). They can be of a continuous flow-type, or a pulsatile-type. The pulsatile-type device is meant to mimic the natural, pulsating flow provided by the intrinsic sinus rhythm of the heart. VAD devices have historically been considered as a "bridge to transplantation" in order to keep a patient alive until a suitable donor heart can be found. More recently, however, VADs have been implanted as "destination therapy". In this case, the device is meant to be permanently implanted throughout the patient's remaining life.

1.3.3 Telemonitoring/Remote Follow-up

Historically, implanted pacemaker and defibrillator-type devices have required in-office follow-up visits to record patient data, and more recently to download device-recorded data from the device. This was typically done via very short range telemetry. A device programming wand, similar in size and shape to a computer mouse was placed over the device, and the device would wirelessly transmit information through the skin to the recording head. More recently, the distance at which the device can transmit

information while in the physician's office has been extended, obviating the need for close patient contact with the programming wand.

Rather than have the patient come into a clinic, another option to conduct patient follow-up is through remote patient monitoring. A patient who receives an implanted Medtronic device in the United States is often eligible to participate in an Internet-based remote monitoring service for patients. The CareLink® network was established in 2002 as a de-identified database containing longitudinal device-programmed and device-measured information on Implantable Cardiac Monitor (ICM), Implantable Pulse Generator (IPG), Implantable Cardioverter-Defibrillator (ICD), and Cardiac Resynchronization Therapy with Defibrillator (CRT-D) devices manufactured by Medtronic in the United States and is still ongoing. A patient is sent home with equipment to interrogate their implanted device while at home or while traveling, and transmit that information to a secure location. The patient's clinician can then log in and pull up a full record of device information as needed, perhaps eliminating the need for some in-office follow-up visits.[30] Both the PREFER study, which compared an older, more primitive version of such a remote monitoring strategy called transtelephonic monitoring (TTM) to the CareLink® network, as well as the CONNECT study showed a significant increase in the number of clinically-actionable events identified with CareLink®, a decrease in the mean time to first diagnosis of such an event, and in the case of the CONNECT study, a reduction in the mean length of a cardiovascular disease-related hospital stay.[31,32] Boriani, et al. recently published the phase 1 results of their

MORE-CARE study, which demonstrated that the time from a device-detected event, such as impedance-threshold crossing, until a clinical decision was made was reduced to 2 days (IQR: 1 to 4 days) among the remote monitored group, compared to 29 days (IQR: 3 to 51 days) among the control group (p=0.004). Further, in-hospital visits were reduced for the remote monitored group (2.0 visits per patients per year) compared to the control group (3.2 visits per patient per year) for a 37.5% relative reduction (p<0.001).[33] Lastly, data from the ALTITUDE survival study have shown that both CRT-D and ICD devices confer a survival benefit (HR 0.67, 95% CI: 0.64-0.69 for CRT-D devices, HR 0.57, 95% CI: 0.55-0.59 for ICD devices) when used with a remote monitoring network compared to those devices when not networked.[34]

Today, enrollment in the CareLink® network is automatic, as patients are pre-enrolled in the program when the device is implanted. However, at the time the Medicare ICD registry was maintained (see below), only 39% of implanted devices utilized the CareLink® network, which significantly affected the number of patients available for study (Medtronic data on file, 2016).

1.3.4 Relationship between Heart Failure, Atrial Fibrillation, Bi-Ventricular Pacing Percentage, and Heart Rate Variability

Atrial fibrillation is the most common sustained heart arrhythmia among adults, currently affecting between 2.7 and 6.1 million people in the US, and is expected to rise to 12.1 million by 2030.[1] Heart failure (HF) and atrial fibrillation (AF) often manifest together. Whether there is a causal relationship or whether this is coincidental due to

their common risk factors (e.g., hypertension, coronary artery disease, diabetes, and advancing patient age) is a subject of debate. However, the clinical treatment of one condition often must consider the other. For the purposes of this dissertation, the focus will be on AF in the context of cardiac resynchronization therapy (CRT) for the treatment of heart failure. Specifically, a reduction in CRT efficacy has previously been found in the presence of AF due to the high prevalence of fusion and pseudo-fusion beats, resulting in poor ventricular capture by the device.[35] This is a non-trivial issue in the treatment of HF via CRT as approximately 25% of patients eligible for CRT also have comorbid AF, even though nearly all previous studies of CRT efficacy have excluded patients with AF.[36,37] Based on a meta-analysis of 23 studies representing 7,495 CRT patients, Wilton, et al., found that CRT effectiveness decreased among those with varying definitions of AF compared to those without. CRT nonresponse was 32% higher in the AF group (RR 1.32, 95% CI: 1.12-1.55), along with 50% higher all-cause mortality (RR 1.50, 95% CI: 1.08-2.09). [38] However, the determination of whether a patient has AF can be difficult, especially in the cases of paroxysmal AF, and sporadic cases of persistent AF. That is, a patient may not be in AF at the time they are examined by a clinician, and therefore cases may be missed during evaluation, yielding an underestimate of the true AF population among CRT patients. CRT devices, however, continually monitor the amount of time a patient spends in AF, and reports it as a percentage of time. This "AF Burden" variable can therefore be very quantitative in measuring and determining the effect of AF on patient outcomes. In a 2012 study, Sarkar, et al. found that CRT patients

with left ventricular dysfunction and CRT device-quantified AF have a higher risk of heart failure hospitalization than those with no AF (HR 2.04, 95% CI: 1.5-2.7).[39] They further found that a single day of high AF burden (more than 6 hours) in the previous 30 days increased risk of HF hospitalization in the following 30 days (HR 3.4, 95% CI: 1.8-6.2), indicating that even transient, potentially asymptomatic AF, which may easily be missed by clinical examination alone and misclassified as "no AF", significantly affects patient outcomes.

One common treatment for persistent, medically refractory AF is atrioventricular (AV) node ablation. The AV node is a feature in the heart that conducts electrical signals from the sinoatrial (SA) node in the atrium, where the signaling of heart muscle contraction begins, to the ventricles. Ablation effectively cuts off communication between the atria and the ventricles, stopping any conducted ventricular beats resulting from a spurious signal from the chaotically contracting atrium as is found in AF. After AV node ablation, a CRT or pacemaker device is then required to maintain heart rhythm, since the sinoatrial node can no longer control ventricular contraction. Many CRT devices can provide electrical stimulation to both ventricles of the heart separately. The frequency at which the device provides bi-ventricular (bi-V) pacing to the heart has also been found to influence patient outcomes, with higher percentages of bi-V pacing leading to fewer hospitalizations and reduced mortality. Koplan, et al., found that a bi-ventricular pacing percentage of greater than 92% led to a 44% reduction in the hazard rate of heart failure hospitalization when compared to those with less than 92% bi-ventricular pacing

(HR 0.56, p-value <0.001).[40] Likewise, Hayes, et al., found that bi-ventricular pacing percentage affected patient outcomes, with those patients in the highest quartile (>99.6% pacing) having a 24% reduction in mortality (HR 0.76, p<0.001) compared to the lowest quartile (paced less than 94.8%).[41]

In this case, knowledge of AV node ablations is essential to provide an appropriate estimate of associations between bi-V pacing percentages and outcomes, since those who have had an AV node ablation are necessarily bi-V paced 100% of the time. Unless AV ablations are accounted for in the results, any observed association between bi-V pacing and hospitalization or death would likely be biased towards the null, as ablations effectively remove the previously reported associations between AF burden and % bi-V pacing. In short, AV node ablation will be presumed to interact with % bi-V pacing in the analysis. Highlighting the importance of knowing AV node ablation status, Gasparini, et al., have recently shown that among AF patients, AV node ablation is more effective in reducing total mortality among CRT patients than drugs alone (HR 1.55, 95% CI: 1.33-1.80) as well as cardiac mortality (HR 1.57, 95% CI: 1.37-1.88). They also found that the rates of both of these events among AV node ablation patients with AF are no greater than for patients in sinus rhythm (p-values=0.79 and 0.95, respectively).[42] Neither the Koplan study, nor the Hayes study stated how they handled patients with AV node ablation.

Lastly, increased atrial heart rate variability (HRV) is also known to improve outcomes of patients with heart failure, including CRT patients.[43,44] CRT, in turn, has

itself also been shown to increase heart rate variability of patients over time. In two studies by Adamson, et al, they found a statistically significant lowering of HRV of 30 milliseconds for those patients implanted with a CRT device, but randomized to "CRT-off" compared to those who had a CRT implanted in the "CRT-on" arm (p-value 0.02). [45] In the second study, lower heart rate variability, as measured by the standard deviation between atrial cycle lengths (SDAAM) averaged over 5 minutes, was found to increase mortality risk--by 320% for low SDAAM values (<50ms) compared to those with high SDAAM values (>100ms).[46] Further, Fantoni, et al., found that a similar measure, SDANN, which measures the standard deviation between intrinsic intervals averaged over a specific period of time also increased by a statistically significant 24 milliseconds three months after CRT implant compared to baseline.[47] Importantly, Sarkar, et al. found that poor ventricular rate control modified the association between AF and outcomes, highlighting the importance of this study to consider the effects of all these variables simultaneously.[39]

1.3.5 Hospitalization Burden in Heart Failure

There is a significant burden to living with heart failure on the part of the patient, and managing such a patient on the part of the clinician, due to the need for frequent patient hospitalization. Many patients experience severe, acute episodes of symptoms including fatigue, dyspnea, edema, sudden weight gain, and chest pain which require immediate treatment and/or hospitalization. Dunlay, et al., found that after HF diagnosis, 83% of patients were hospitalized at least once and 42.6% were hospitalized at least four

times over the follow up period (mean 4.7 years).[48] The need for patient hospitalization is also associated with an increased rate of mortality, as well. After adjusting for potential confounders, Setoguchi, et al., found statistically significant increases in mortality hazard rates for additional hospitalizations beyond the index hospitalization as shown below in Figure 6.

	2 Hospitalizations*		3 Hospitalizations*		4 Hospitalizations*		≥ 5 Hospitalizations*	
Adjustment	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Unadjusted	1.32	(1.25-1.41)	1.51	(1.37-1.67)	1.92	(1.65-2.24)	2.25	(1.87-2.71)
Age and sex adjusted	1.31	(1.23-1.39)	1.51	(1.37-1.67)	1.93	(1.66-2.24)	2.25	(1.87-2.71)
Fully adjusted†	1.22	(1.14-1.30)	1.33	(1.20-1.47)	1.64	(1.40-1.91)	1.84	(1.53-2.23)

HR, Hazard ratio.
*Hazard of deaths compared with the risk after 1 hospitalization.
†Model included age; sex; and history of atrial fibrillation, ventricular arrhythmia/cardiac arrest, chronic kidney diseases, dialysis, diabetes, cancer, chronic pulmonary diseases, rheumatoid arthritis, MI, cerebrovascular attack, hypertension, ischemic heart diseases, and dementia.

Figure 6. – Effect of Number of HF Hospitalizations on Mortality

From Setoguchi S, Stevenson LW, Schneeweiss S. *Am Heart J.* 2007;154:260-6.

There is also a significant cost burden to these hospitalizations, with costs estimated at over $23,000 for each HF-related hospitalization.[49] Managing these costs for patients with HF is particularly challenging, as approximately 20% of patients are rehospitalized within 30 days of initial admission.[50] However, with the advent of a 30-day all-cause readmission penalty by the Centers for Medicare and Medicaid Services (CMS) in 2012, there is added incentive on the part of physicians and hospitals to reduce the frequency of these admissions, as such treatment may not be fully reimbursed.

While several studies have identified device-measured diagnostic data as predictors of impending hospitalization events before an actual, initial hospitalization event[51-54], a result of the institution of the CMS rehospitalization penalty has rather been to focus

efforts on reducing 30-day readmissions for heart failure. Several attempts have been made at identifying those at higher risk of readmission within 30 days based upon demographic, disease state, and device measured information available pre- or post-admission, or at the time of discharge.[55-57]

Whellan, et al., looked at a total of 208 patients from a combination of four studies who were hospitalized for HF-related causes during the follow up period. Of the 166 patients who had more than 30 days of follow-up information after discharge, 27 were hospitalized again within 30 days. Device measured parameters from the first 7 days after discharge were used to generate a model which categorized risk according to intra-thoracic impedance, AF burden, ventricular rate during AF, % bi-V pacing, and night heart rate. This model then stratified patients into "high", "medium", and "low" risk categories based on their score.

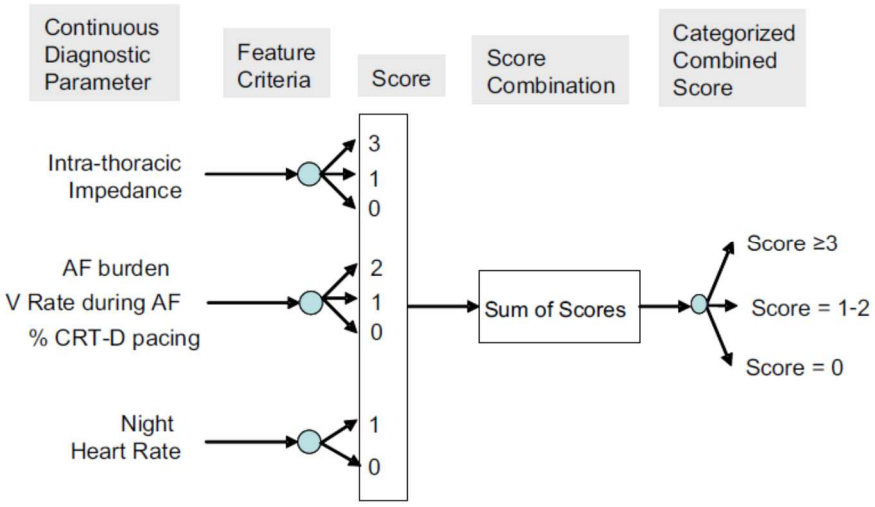


Figure 7. – Risk Stratification Scheme Based on Device Measured Parameters

From Whellan DJ, Sarkar S, Koehler J, Small RS, Boyle A, Warman EN, Abraham WT. *Am J Cardiol.* 2013;111:79-84.

After adjusting for age, gender, and NYHA class, they found statistically significantly elevated hazard ratios for those with scores of 3+ versus those with scores of 0 (HR 22.7, 95% CI: 3.2-161.7) or scores of 1-2 (HR 4.1, 95% CI: 2.0-8.4), indicating that patients who met more of the device-measured diagnostic criteria had significantly higher rates of 30-day rehospitalization.[56]

Small, et al., developed a very similar model, but using device measured information on the day of discharge, as opposed to during the seven days following discharge. Their model used slightly different criteria than the Whellan study, but was very similar in structure. Those patients which met 2 or more of their diagnostic criteria (including intrathoracic impedance value > 8Ω, AF burden > 6 hours, CRT pacing < 90%, and night heart rate > 80 bpm) were found to have a 4.4-fold higher rate of 30-day reshospitalization than those who met none of the diagnostic criteria (HR 4.4, 95% CI: 1.6 – 12.0) and those who met one criterion had a 2.4-fold higher rate than those who met none (HR 2.4, 95% CI: 1.1 – 5.3).[57] Both of these studies predict risk of 30-day rehospitalization after discharge, but are based on relatively small potentially heterogeneous cohorts, and few potential covariates were available when building their rehospitalization model.

2 Data Sources

For the period of January 2005 to April 2006, the Centers for Medicare and Medicaid Services (CMS) maintained a registry of patient information for recipients of new ICD and CRT-D devices from Medicare-reimbursed procedures. This information included clinical characteristics, clinical history, patient demographic information and device-related information. This information has previously been merged with Medicare Provider Analysis and Review (MedPAR) data from the Medicare claims database to examine associations between clinical characteristics and patient outcomes on a population of 14,946 CRT-D patients.[58] The MedPAR data contain information on 100% of Medicare beneficiaries using hospital inpatient services at certified hospitals. However, of note is that hospitalizations occurring for patients with health maintenance organization or managed care organization (HMO or MCO) coverage are not found in the Medicare utilization data. These patients represent approximately 6% of the patients found in the Medicare MedPAR dataset. Two separate analyses were performed for hospitalization outcomes in Manuscript 1 and Manuscript 2, below: one excluding these patients from the analysis, and another keeping these patients in the dataset but adjusting for HMO/MCO status(yes/no), by adding it as another variable in the model. Analyses for the mortality outcome in both Manuscripts 1 and 2 left all patients in the analysis, regardless of HMO/MCO status, as it is unlikely to affect mortality outcomes. In Manuscript 3, all HMO/MCO patients were excluded from the analysis, as we

specifically estimated risk of 30-day rehospitalization, and could significantly underestimate risk for those patients if they were left in the dataset.

These data sources were joined with device information from the Medtronic CareLink® network. The Medtronic CareLink® network contains information from 21,012 unique devices (CRT and ICD devices) implanted during the January 2005 – April 2006 time frame for which CMS maintained records. After removing ICD devices, and removing devices not found in the CareLink® database implanted in this time period, the combined CareLink®-Medicare dataset contained 7,702 Medtronic CRT patients enrolled in the CareLink® network which formed the final population for analysis. Final numbers of patients analyzed varied depending on the analysis performed, the type of devices in the study population, and the features enabled on each device (for example, OptiVol® impedance monitoring is not available on every device).

In order to protect patient privacy, the CMS data was matched on the basis of patient age at implant, patient gender, CRT-D device model, de-identified (3-digit) patient zip code, and date of device implant, rather than on a directly identifiable variable such as patient social security number or device serial number, which is considered protected health information under HIPAA. The data resides at the University of Virginia – Charlottesville School of Medicine pursuant to the Data Use Agreement for the Medicare data. Both the CMS data and Medtronic data were de-identified prior to the joining of the datasets. The study was determined to be exempt from IRB review by the University

of Minnesota IRB under federal guidelines 45 CFR Part 46.101(b) category #4 “existing data; records review; pathological specimens.” (Study number 1505E70742.)

All of the Carelink® data used in this dissertation are by necessity only from Medtronic manufactured devices. Table 3 below compares demographics and clinical characteristics of patients who have received a Medtronic device to those who received a device from another manufacturer. Differences between Medtronic and non-Medtronic CRT patients are small, and are not expected to be of practical significance. We therefore believe that the findings of these manuscripts are extensible to the broader CRT-eligible heart failure population.

Table 3. – Baseline Demographics for Medicare CRT Patients by Device Manufacturer Group

	All Medicare CRT Patients(n=14,902)	Medtronic CRT Patients (n=7,702)	Non- Medtronic CRT Patients (n=7,200)
Age, mean ±SD, y	73.0±10.5	73.1 ±10.3	72.9±10.7
Duration HF, mean ±SD, y	24.7±25.4	25.1±25.4	24.3±25.4
LVEF, mean ±SD, %	23.1±6.3	23.0±6.3	23.3±6.3
QRS duration, mean ±SD, ms	156.8±24.9	157.8±24.7	155.8±25.0
SBP, mean ±SD, mm Hg	126.5±22.4	125.8±21.9	127.3±22.9
DBP, mean ±SD, mm Hg	70.2±13.7	70.0±14.5	70.3±12.9
Heart rate, mean ±SD, bpm	72.0±18.0	72.0±17.8	72.0±18.2
Gender, n(%)			
Female	27.3	27.0	27.7
Male	72.7	73.0	72.3
NYHA class, n(%)			
I	1.2	1.2	1.2
II	11.0	11.0	11.0
III	74.1	74.6	73.7
IV	13.7	13.3	14.1
Ischemic CM, n(%)	69.2	67.9	70.5
Prior CABG, n(%)	42.0	41.7	42.2
Atrial fibrillation, n(%)	34.7	36.1	33.2
Ventricular tachycardia, n(%)	19.6	20.3	18.9
Sudden cardiac arrest, n(%)	1.7	1.8	1.7
Diabetes mellitus, n(%)	35.7	35.3	36.2
Prior MI, n(%)	50.9	49.8	52.0
Smoker Status, n(%)			
Never	42.3	42.4	42.1
Former	48.6	48.9	48.4
Current	9.1	8.7	9.5
Medications, n(%)			
b-blocker	78.9	79.2	78.6
ACEI or ARB	74.3	74.6	73.9
Digoxin	41.7	41.3	42.1
Diuretic	78.7	79.9	77.4
Amiodarone	13.6	13.9	13.3
Warfarin	31.8	33.1	30.4

3 Manuscript 1 – Association of Exceeding Intrathoracic Impedance Threshold on Patient Mortality and Hospitalization

3.1 Overview

Objective: To determine adjusted associations among OptiVol® threshold crossings, long-term survival and hospitalizations among heart failure (HF) patients with Medicare coverage in the United States. **Background:** The long-term prognostic value of OptiVol® crossings on clinical events and mortality in real-world patients with cardiac resynchronization therapy defibrillators (CRT-D) is uncertain. **Methods:** A cohort with OptiVol®-enabled CRT-D devices from the Implantable Cardioverter Defibrillator Registry was linked to both Medicare claims/summary data and Medtronic's CareLink® Network data. An extended multivariable Cox model was used to analyze associations among OptiVol® threshold crossings (treated as time-dependent covariates), mortality, and HF-related hospitalizations (HFH).

Results: We analyzed N= 1,565 patients with OptiVol®-enabled CRT-D devices (mean age 72.8, 28% women). Median follow-up was 6.3 years. Patients with >15.1% of days above OptiVol® threshold (highest quartile) had more than a 4-fold increase in mortality (HR 4.2, 95%CI: 3.3-5.3) and more than a 3-fold increase in HFH (HR 3.2, 95%CI: 2.4-4.2) compared with patients having <4.1% of days above threshold (lowest quartile) after adjustment for key covariates. In addition, a single OptiVol® crossing was associated with

both a significantly increased mortality rate (HR 1.87, 95% CI: 1.27-2.75) and HFH rate (HR 1.70, 95% CI: 1.28-2.27).

Conclusion: In a CRT-D cohort with over 6 years of follow-up, both single OptiVol® crossings and time above OptiVol® threshold were associated with increased rates of mortality and hospitalization, which has important implications for clinical care. This is the first study integrating device data with Medicare outcomes to validate the long-term significance of OptiVol® findings.

3.2 Introduction

Treatment and management of heart failure (HF) in the US remains a major public health burden, with 5.7 million patients suffering from the disease, many of them facing a poor prognosis. These patients are hospitalized over 1 million times a year, and are often hospitalized on multiple occasions throughout their treatment. [1] Therefore, predicting death and future hospitalizations in these patients is a highly desirable goal. One strategy to do so, intrathoracic impedance monitoring, has been shown to be safe and effective for cardiac resynchronization therapy defibrillator (CRT-D) patients in clinical trials.[20-24,59,60] While these trials have shown some predictive power of future adverse events when a pre-programmed threshold value is reached, limitations have included a lack of adjustment for patient characteristics and comorbid conditions, shorter follow-up times, the need for external validation in a real-world cohort, and inclusion of threshold crossings occurring only during the first 6-months of follow-up.[25]

In the current era, the use of intrathoracic impedance monitoring in the clinical setting remains controversial. There remains debate regarding not only which specific clinical actions should be taken in response to device readings in order to avoid adverse outcomes, but also whether device-measured information should be used alone or in combination with an in-person clinical evaluation.[61] Another methods for monitoring HF patients, pulmonary artery pressure monitoring, has shown some promise in preventing decompensation-related hospitalization when guided by a specific management strategy[62], but requires implantation of additional hardware. Additional long-term data demonstrating the independent impact of intrathoracic impedance monitoring on clinical outcomes in a real-world cohort would be of great interest with respect to the value of this strategy. In order to address this unmet need, we examined the impact of OptiVol® threshold crossings and the time above threshold on long-term survival and HF-related hospitalizations after adjusting for key covariates in a large population of patients with Medicare coverage with over 6 years of follow-up.

3.3 Methods

3.3.1 Study Population

For this analysis, we used data from the Medicare Implantable Cardioverter-Defibrillator (ICD) Registry with an OptiVol®-enabled CRT-D device. The Center for Medicare and Medicaid Services (CMS) requires providers who implant ICDs, including CRT-Ds, to record various patient demographic, clinical, and device information. For the

period of January 2005 to April 2006, the registry was maintained by the Iowa Foundation for Medical Care and is available for download from CMS (See https://www.cms.gov/Medicare/Medicare-General-Information/MedicareApprovedFacilitie/Downloads/icdregistry1.pdf for more information). Starting in April 2006, this function was transferred to the American College of Cardiology in the form of the National Cardiovascular Data Registry (NCDR). Therefore, the Medicare registry data used for this analysis were all from this 14-month time period. These registry data were previously linked with MedPAR claims data to ascertain time from device implant until hospitalization and patient death. [58] These data were further linked with Medicare Master Beneficiary Summary File data to determine Medicare enrollment and type of coverage.

We then linked these Medicare data with CareLink® data regarding patient monitoring. The CareLink® network was established in 2002 as a de-identified database containing longitudinal device-programmed and device-measured information on Implantable Cardiac Monitor (ICM), Implantable Pulse Generator (IPG), Implantable Cardioverter-Defibrillator (ICD), and Cardiac Resynchronization Therapy with Defibrillator (CRT-D) devices manufactured by Medtronic in the United States and is still ongoing. To align with the timeframe of available Medicare data, the CareLink® database was queried to find all CRT-D devices equipped with the OptiVol® feature implanted in the US between Jan 1, 2005 and Apr 30, 2006. Some devices equipped with the OptiVol® feature, however, did not actually have the feature "turned-on" in the

device. Information from devices with actual CareLink® transmissions was then linked with the Medicare data on the basis of device implant date (±2 days), patient age at implant (±1 year), patient sex, device model, and de-identified (3-digit) ZIP code. Patient mortality and hospitalization follow-up information was available through December 2011. A pictorial representation of how the data were merged is shown in Figure 8. Patients who had a CRT-D device implanted, but were outside the established indication guidelines at the time to receive such a device (NYHA HF Class III or IV, QRS interval ≥ 120 ms and a left ventricular ejection fraction (LVEF) ≤ 35%) were excluded from the Medicare dataset.[63] In addition to the variables used for linking the two databases, the time until a device experienced an OptiVol® threshold crossing and time above threshold were also taken from the CareLink® registry. Patients were followed up until end of Medicare enrollment or time of the last CareLink® record if they did not experience any threshold crossing. A total of 1,565 patients were matched between the Medicare data and the CareLink® registry.

3.3.2 Endpoint Definition

Heart failure hospitalization in the Medicare dataset was determined by an inpatient admission with a primary ICD-9-CM diagnosis code of 428.x. For mortality endpoints, the available MedPAR data contained only all-cause mortality and not underlying cause of death.

3.3.3 Exposure Definition

The CareLink® database was queried to determine when an OptiVol® threshold was exceeded. The CareLink® database contains information OptiVol® threshold setting and the accumulated fluid index value. These values were examined on a daily basis, and the first instance of the accumulated fluid index value being greater than the programmed OptiVol® threshold value was considered to be the time of threshold crossing. Although the threshold value can be programmed to various values, the time until the first crossing was defined when the OptiVol® fluid index value exceeded the programmed value, independently of the threshold value setting used.

3.3.4 Covariates

Other variables in the Medicare registry that were considered in this analysis included patient age, sex, duration of HF, LVEF, QRS duration, systolic blood pressure, diastolic blood pressure, heart rate, NYHA class, presence of ischemic cardiomyopathy, bundle-branch block morphology, prior coronary artery bypass graft, atrial fibrillation (AF), anticoagulation therapy for AF, presence of ventricular tachycardia, prior sudden cardiac arrest event, diabetes mellitus, prior myocardial infarction, smoking status, chronic kidney disease (CKD), end-stage renal disease (ESRD), and the prescription of beta-blockers, ACE-inhibitors or angiotensin receptor blockers, digoxin, diuretics, amiodarone, and/or warfarin. The diagnosis of chronic kidney disease (CKD) and end-stage renal disease (ESRD) was established based on administrative diagnosis codes from inpatient and outpatient encounters, available in CMS utilization files from the year the

device was implanted. All of the other covariates were input by each patient's provider at the time of implant to the CMS' ICD Abstraction Tool, and were contained in the Medicare ICD registry data.

While the main exposure of interest was time until first threshold crossing, a patient may experience many such events over their follow-up time, or may have extended periods of time above the threshold, indicating a chronic congestive condition. To capture this phenomenon, we counted the number of days an individual patient spent with a fluid index value above the threshold in CareLink® prior to their first clinical endpoint. Days above threshold could be caused by either multiple crossings or by extended periods of time for a single crossing, or both. Patients were then categorized into quartiles based on this parameter.

3.3.5 Statistical Analysis

Extended Cox models were run using PROC PHREG in SAS software, version 9.4 (SAS Institute, Cary, NC) to account for the time-dependent nature of the exposure variable of interest, time to OptiVol® threshold crossing. With increasing follow-up time, patients who experienced a threshold crossing move from the "no crossing" group to the "crossing" group. The extended Cox method accounts for this change in exposure status, adjusting the exposure group sample sizes appropriately at the time of each event.[64] Analyses for hospitalization endpoints were run both with cause-specific models, where all competing outcomes other than hospitalization (namely, patient death) were censored, as well as competing risk (or subdistribution) models, where patients who

died were left in the denominator to estimate actual observable patient hospitalization rates.[65] Models were run first as a minimally-adjusted analysis, only including patient age at implant and patient sex. Where HF-related hospitalization outcomes were examined, we also adjusted for whether the patient had supplemental health maintenance organization (HMO)/ managed care organization (MCO) coverage. Fully adjusted models were then also developed, based on all of the available Medicare ICD Registry variables. Because data on hospitalizations from patients enrolled in HMO or MCO can be incomplete, we performed a sensitivity analysis in which we excluded patients with any indication of HMO or MCO coverage, as determined from Medicare annual summary data. We further explored whether either patient race or sex would modify the association observed between OptiVol® threshold crossing and mortality or HF-related hospitalization by adding interaction terms to each of these models.

For Kaplan-Meier plots based on threshold crossings, we applied the method of Simon and Makuch to account for the time-dependent nature of threshold crossings. Per this method, the data for each individual were split to account for time a patient spent in the "no crossing" group before a threshold crossing occurred. An individual patient's data therefore shows up in both groups, contributing their associated amount of time in each group before an outcome event or censoring occurs.[66,67]

Lastly, we determined the number of days each patient spent above the programmed threshold value, if any, from CareLink®, and calculated the percentage of their follow-up time each individual patient spent above threshold. This could have come in the form of a

single, prolonged crossing event, or through several acute crossing occurrences. Patients were then grouped into quartiles (<4.1%, 4.1-8.3%, 8.3-15.1%, >15.1%) and those in the highest quartile (>15.1% of days above threshold) were compared to those in the lowest quartile.

3.4 Results

Table 4 shows the subset of patients analyzed in this study compared to those in the Medicare dataset who were not examined (those without Medtronic devices, or those who could not be matched in the database). Patient characteristics were similar in those patients who were analyzed versus those who were not analyzed, although some statistically significant differences were obtained because of the large number of patients studied.

In our retrospective cohort study, we linked 1,565 patients between the CareLink® database, Medicare ICD registry, and Medicare claims data. Over the median 6.3 year follow-up period, we observed a mortality rate of 8.8 deaths per 100 person-years (706 deaths/8,037 person-years), and a HF-related hospitalization rate of 9.2 hospitalizations per 100 person-years (608 cases/6,581 person-years). There were a total of 1,514 patients (97%) who experienced an OptiVol® threshold crossing event during follow up, with their distribution over time shown in Figure 9. Median time to threshold crossing was 10.5 months. A threshold crossing value of 60 Ohm-days was programmed in 99.2% of devices.

As shown in Table 5, an OptiVol® threshold crossing at any point in the life of the device was associated with an 87% increase in patient mortality (HR 1.87, 95% CI 1.27-2.75) after adjusting for patient sex, patient age at implant, ischemic cardiomyopathy, CKD, smoking status, and the prescription of digoxin, compared to those patients who have not had a threshold crossing by that same time. Hazard ratios for all statistically significant variables are given in Table 7. We examined the effect of race in this analysis, but it was found not to be a significant predictor of mortality and was therefore dropped from the models. Figure 10 shows that unadjusted Kaplan-Meier survival probabilities comparing mortality between the "Threshold Crossing" group to the "No Crossing" group were statistically significant (log-rank test, p-value < 0.0001). Of note, individual patients contributed follow-up time to both curves if they experienced a threshold crossing: the time until threshold crossing was accounted for in the "no-crossing" group, and any time after such a crossing was accounted in the "crossing" group until either patient death or censoring occurred.

For hospitalization outcomes, the extended Cox model showed that an OptiVol® threshold crossing was associated with a 70% higher rate of HF-related hospitalization (HR 1.70, 95% CI: 1.28-2.27) when adjusting for these same covariates, including whether patients had private health coverage through an HMO or MCO organization, which was added as an additional variable in the model. In the Kaplan-Meier plot shown in Figure 11, the log-rank statistic comparing the "Threshold Crossing" group to the "No Crossing" group was again statistically significant (p-value < 0.0001). When excluding the

HMO/MCO covered patients from the dataset, the association calculated by the extended Cox model was slightly attenuated (HR 1.63, 95% CI: 1.22-2.19). We again examined the effect of race, but it was not found to be a significant predictor of HF-related hospitalizations, and was therefore dropped from the models.

We further explored whether there was any modification of the association between OptiVol® threshold crossing and the outcomes by either race or patient sex. For mortality outcomes, we found no significant interactions between threshold crossing status and either sex (p-value = 0.49) or race when its main effect was left in the model (p-value = 0.99). In contrast, the patient's sex significantly modified the association of threshold crossing with HF-related hospitalization (p-value = 0.01 to 0.03) based on a stronger association between OptiVol® status and HF-related hospitalization in men (regardless of whether HMO/MCO patients were included or excluded, or the survival model used). There was not a significant interaction for race (p-value = 0.90) for hospitalization outcomes when leaving the main effect in the model. The results stratified by sex are presented in Table 6.

Since patients are at risk of experiencing multiple threshold crossings over their follow-up time, we also examined the effect of each individual patient's time above the pre-programmed threshold as a percentage of their total follow up time. These percentages were categorized into quartiles, and their survival plots are shown in Figure 12 and Figure 13, showing significant differences across the quartiles (log-rank test, p-value <0.0001). In a multivariable Cox model with the same covariates as performed above, but removing the threshold crossing variable, the quartile of percent follow-up time above threshold was

statistically significant for both mortality and HF-related hospitalization outcomes (both p-values <0.0001). In this model, patients with > 15.1% of follow-up days above the OptiVol® threshold (highest quartile) had more than a 4-fold increased mortality rate (HR 4.2, 95%CI: 3.3-5.3), and more than a 3-fold rate of HF-related hospitalization (HR 3.2, 95% CI: 2.4-4.2) than those patients in the lowest quartile compared with those in the lowest quartile (< 4.1% of days above threshold).

3.5 Discussion

In this large cohort of patients with CRT devices linked to Medicare data followed for a median of over 6 years, patients who had more than 15.1% of follow-up days above threshold (representing 25% of patients in the entire cohort) had a more than 4-fold increased mortality rate and a more than 3-fold increased HF-related hospitalization rate after adjustment during more than 6 years of follow up compared with the 25% of patients who had <4.1% of days above threshold. In addition, a single OptiVol® threshold crossing was associated with significantly increased rates of both patient mortality (87%) and patient HF-related hospitalization (70%). These results were robust to the statistical analysis used and whether patients with HMO/MCO coverage were excluded. Although the impact of OptiVol® threshold crossing had a clinically significant impact on survival in both genders, we did find that an OptiVol® threshold crossing was associated with an increased rate of HF-related hospitalization in men but not in women. Previous studies either lacked hospitalization outcome information, covariate information, or were insufficiently powered to detect this interaction. However,

this observed difference between the strength of the threshold crossing-hospitalization outcome for men and women is important and likely warrants further study.

The association between OptiVol® threshold crossing, indicating accumulating fluid, and worsening HF is perhaps an obvious one, but has not been validated before in a real-world setting in the context of a large cohort. The present study offers important new findings including associations with long-term clinical outcomes. First, the Medicare data provided data on HF-related hospitalizations in addition to mortality. Second, the Medicare registry data also provided the opportunity to adjust for significant patient covariates and comorbid conditions, which resulted only in small differences in hazard ratio estimates versus the minimally-adjusted analysis. Third, the present study is an improvement on previous work in that it considered Optivol® threshold crossing as a time-dependent variable. Previous publications examined only those patients with an Optivol® threshold crossing during the first six months after device implant, effectively treating a patient with a crossing 1 day after implant as contributing the exact same follow up time to the "crossing" group as a patient with a crossing 6 months after implant.[25]

Our data matching scheme linked about 20.4% of the available 7,670 Medicare CRT patients. This proportion was limited in two major ways: first, few device models implanted in the time frame of the Medicare ICD registry were available with the OptiVol® feature which was introduced beginning in April 2005. As a result, 4,035 (52.6%) devices in our cohort were of a device model which had the OptiVol® feature.

Second, at the time of the Medicare ICD Registry, enrollment in the CareLink® network was not automatic, and is estimated that 39% of Medtronic CRT devices implanted in this timeframe were actually enrolled in the CareLink® network (Medtronic data on file, 2016). We therefore estimate that approximately 1,600 devices of a type with OptiVol® available also enrolled in the CareLink® Network would exist in the available Medicare data. Based on this estimate, our actual linkage (1,565 patients, or 20.4% of available Medicare data) is deemed reasonable.

With respect to the clinical impact of our findings, our data show that both a single OptiVol® crossing and time above OptiVol® threshold are associated with markedly elevated rates of patient mortality and patient hospitalization in real-world practice. Those patients with >15.1% of day above threshold are of particular concern, as these patients have more than 4-fold increased risk of mortality and more than a 3-fold risk of HF-related hospitalization after adjustment during more than 6 years of follow up compared with the 25% of patients who have < 4.1% of days above threshold. These patients, in particular, may benefit from more intensive medical management, including re-assessment of adherence to medical therapy, dietary recommendations, and CRT pacing percentage. The strong association between intrathoracic impedance monitoring and outcomes in this cohort suggests that interventions designed to improve clinical outcomes based on intrathoracic impedance monitoring could be developed and tested in randomized clinical trials with a similar design to that of pulmonary artery pressure monitor trials.[62] In summary, the findings of the present study suggest that OptiVol® has

the clinical predictive value necessary to improve clinical outcomes for HF patients, and that the pressing need is to develop an optimal interventional strategy based on OptiVol® findings.

Limitations of this analysis include our inability to account for what specific clinics do with threshold crossing information. Some clinics may be more likely to actively intervene when a threshold crossing is reached, by using the information to inform management without an actual in-person evaluation, while some may be more likely to hospitalize patients. The net effect of this is that our hazard ratio for hospitalization after a threshold crossing may be biased downwards in clinics with aggressive outpatient management practices, and biased upwards in clinics with aggressive hospitalization practices. Even so, this analysis represents "real-world" usage, and should give a clear, aggregate picture of the effect of a threshold crossing. In addition, the findings with respect to survival reflect a hard endpoint not directly influenced by variation among clinics. Also, recent changes to Medicare reimbursement practices, incentivizing hospitals to treat heart failure in an outpatient setting may affect how current patients are managed versus how they were managed during the follow-up period of this study.

Of note, both the Medicare and CareLink® databases were de-identified prior to our joining them together; however, based on the combination of five variables used to join the data sources together, we have shown that the likelihood of proper Medicare-CareLink® linkage is excellent, since the actual sample size of our cohort matches what

was expected given the constraints of OptiVol® functionality and CareLink® enrollment at the time.

In conclusion, both the occurrence of a single OptiVol® threshold crossing and the time above threshold are very strong predictors of patient survival and HF-related hospitalization after adjustment for key covariates in a large Medicare cohort of CRT-D patients. This represents the first time that these OptiVol® findings have been associated with long-term clinical outcomes including all-cause mortality and HF-related hospitalization after adjustment for a complete range of covariates. Gender-specific associations between OptiVol® findings and HF-related hospitalizations warrant further study.

3.6 Tables and Figures

Table 4. – Baseline Demographics for Medicare CRT Patients by Analysis Cohort

	All Medicare CRT Patients(n=14,935)	Analysis Cohort (n=1,565)	Non- Analyzed Cohort (n=13,370)	p-value*
Age, mean ±SD, y	73.0±10.5	72.8±8.1	73.1±10.7	0.24
Duration HF, mean ±SD, y	24.7±25.4	24.1±24.4	24.8±25.5	0.33
LVEF, mean ±SD, %	23.1±6.3	23.6±6.3	23.1±6.3	0.002
QRS duration, mean ±SD, ms	156.8±24.9	157.8±24.7	156.7±24.9	0.11
SBP, mean ±SD, mm Hg	126.5±22.4	126.1±21.3	126.5±22.5	0.52
DBP, mean ±SD, mm Hg	70.2±13.7	69.9±12.6	70.2±13.8	0.38
Heart rate, mean ±SD, bpm	72.0±18.0	71.3±14.0	72.1±18.4	0.03
Sex, n(%)				
Female	27.3	28.2	27.2	
Male	72.7	71.7	72.8	0.39
NYHA class, n(%)				
I	1.2	1.1	1.2	
II	11.0	10.4	11.1	
III	74.2	77.0	73.8	0.04
IV	13.6	11.6	13.9	
Ischemic CM, n(%)	69.2	62.8	69.9	<0.001
Prior CABG, n(%)	42.0	39.1	42.3	0.02
BBB Morphology, n(%)				
LBBB	69.3	71.4	69.1	
RBBB	11.0	9.7	11.1	0.13
Other IVCD	19.8	18.9	19.8	
Atrial fibrillation, n(%)	34.7	35.2	34.6	0.63
Ventricular tachycardia, n(%)	19.6	17.0	19.9	0.01
Sudden cardiac arrest, n(%)	1.7	1.5	1.7	0.54
Diabetes mellitus, n(%)	35.7	34.9	35.8	0.49
Prior MI, n(%)	50.9	45.8	51.4	<0.001
Chronic Kidney Disease, n(%)	32.0	26.8	32.6	<0.001
End Stage Renal Disease, n(%)	3.1	1.8	3.2	<0.001
Smoker Status, n(%)				
Never	42.3	44.2	42.1	
Former	48.6	47.0	48.8	0.28

Current	9.1	8.9	9.1	
Medications, n(%)				
b-blocker	78.9	80.3	78.7	0.17
ACEI or ARB	74.3	77.8	73.9	<0.001
Digoxin	41.7	40.8	41.8	0.44
Diuretic	78.7	79.9	78.5	0.21
Amiodarone	13.6	10.5	13.9	<0.001
Warfarin	31.8	33.7	31.6	0.09

*p-value comparing analyzed cohort to non-Analyzed cohort.

Table 5. – Associations between OptiVol® Crossing Status and Patient Mortality and Hospitalization

	Minimally Adjusted* Cause-specific HR (95% CI)	Minimally Adjusted* Subdistribution HR (95% CI)	Fully Adjusted† Cause-Specific HR (95% CI)	Fully Adjusted† Subdistribution HR (95% CI)
Mortality	2.03 (1.38-3.00)	N/A	1.87 (1.27-2.75)	N/A
HF related Hospitalization (including HMO/MCO patients)	1.84 (1.38-2.45)	1.86 (1.37-2.52)	1.70 (1.28-2.27)	1.75 (1.30-2.37)
HF-related Hospitalization (excluding HMO/MCO patients)	1.75 (1.31-2.35)	1.77 (1.30-2.42)	1.63 (1.22-2.19)	1.68 (1.24-2.29)

*Adjusted for patient age at implant, sex, and for hospitalization events, any HMO/MCO coverage (Y/N). †Adjusted for patient age at implant, sex, ischemic cardiomyopathy, chronic kidney disease, digoxin, smoking status, and for hospitalization events, any HMO/MCO coverage (Y/N).

Table 6. – Interaction between OptiVol® Crossing Status and Patient Sex

	Fully Adjusted* Cause-specific HR (95% CI)	Fully Adjusted* Overall Interaction p-value	Fully Adjusted* Subdistribution HR (95% CI)	Fully Adjusted* Overall Interaction p-value
Mortality				
Male **Female**	1.76 (1.16-2.66) 2.46 (0.99-6.10)	0.49	N/A	N/A
HF related Hospitalization (including HMO/MCO patients)				
Male **Female**	1.92 (1.42-2.61) 1.18 (0.78-1.77)	0.02	1.96 (1.42-2.70) 1.26 (0.83-1.90)	0.03
HF-related Hospitalization (excluding HMO/MCO patients)				
Male **Female**	1.86 (1.36-2.54) 1.12 (0.74-1.69)	0.01	1.89 (1.36-2.62) 1.20 (0.79-1.82)	0.03

* Adjusted for patient age at implant, sex, ischemic cardiomyopathy, chronic kidney disease, digoxin, smoking status, and for hospitalization events, any HMO/MCO coverage (Y/N).

Table 7. – Hazard Ratios for Patient Mortality and Hospitalization with and without Competing Risks and Patient HMO/MCO Status

	Hazard Ratio for Patient Mortality	Cause-specific Hazard Ratio for Heart Failure-related Hospitalization		Subdistribution Hazard Ratio for Heart Failure-related Hospitalization	
		Including Medicare HMO/MCO Patients	Excluding Medicare HMO/MCO Patients	Including Medicare HMO/MCO Patients	Excluding Medicare HMO/MCO Patients
# of events	705	608	561	607 (327 competing)	561 (276 competing)
Follow up time (person-years)	8,036	6,581	5,825	6,581	5,825
Threshold crossing	1.87 (1.27-2.75)	2.04 (1.49-2.80)	1.93 (1.42-2.68)	1.75 (1.30-2.37)	1.68 (1.24-2.29)
Chronic Kidney Disease (Y vs N)	2.08 (1.78-2.43)	2.38 (2.00-2.78)	2.33 (1.96-2.78)	2.17 (1.85-2.63)	2.17 (1.82-2.56)
Sex (Female)	0.76 (0.63-0.92)	0.91 (0.75-1.11)	0.88 (0.72-1.08)	0.94 (0.77-1.15)	0.91 (0.74-1.12)
Ischemic Cardiomyopathy (N vs Y)	1.33 (1.12-1.59)	1.15 (0.96-1.37)	1.14 (0.93-1.37)	1.10 (0.92-1.32)	1.09 (0.90-1.32)
Age at Implant (years)	1.04 (1.03-1.05)	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.01 (1.00-1.02)	1.01 (1.00-1.02)
Smoking Status					
(Current vs Never)	1.33 (1.01-1.76)	1.31 (0.98-1.76)	1.18 (0.86-1.61)	1.30 (0.96-1.77)	1.17 (0.85-1.62)
(Former vs Never)	1.23 (1.05-1.44)	1.28 (1.08-1.53)	1.19 (1.00-1.42)	1.27 (1.06-1.51)	1.18 (0.98-1.41)
Digoxin (Y vs N)	1.23 (1.06-1.45)	1.19 (1.01-1.41)	1.16 (0.98-1.37)	1.16 (0.98-1.37)	1.14 (0.95-1.35)
Any HMO/MCO coverage (Y vs N)	N/A	0.76 (0.56-1.02)	N/A	0.69 (0.52-0.93)	N/A

Figure 8. – Cohort Selection and Data Merging Scheme

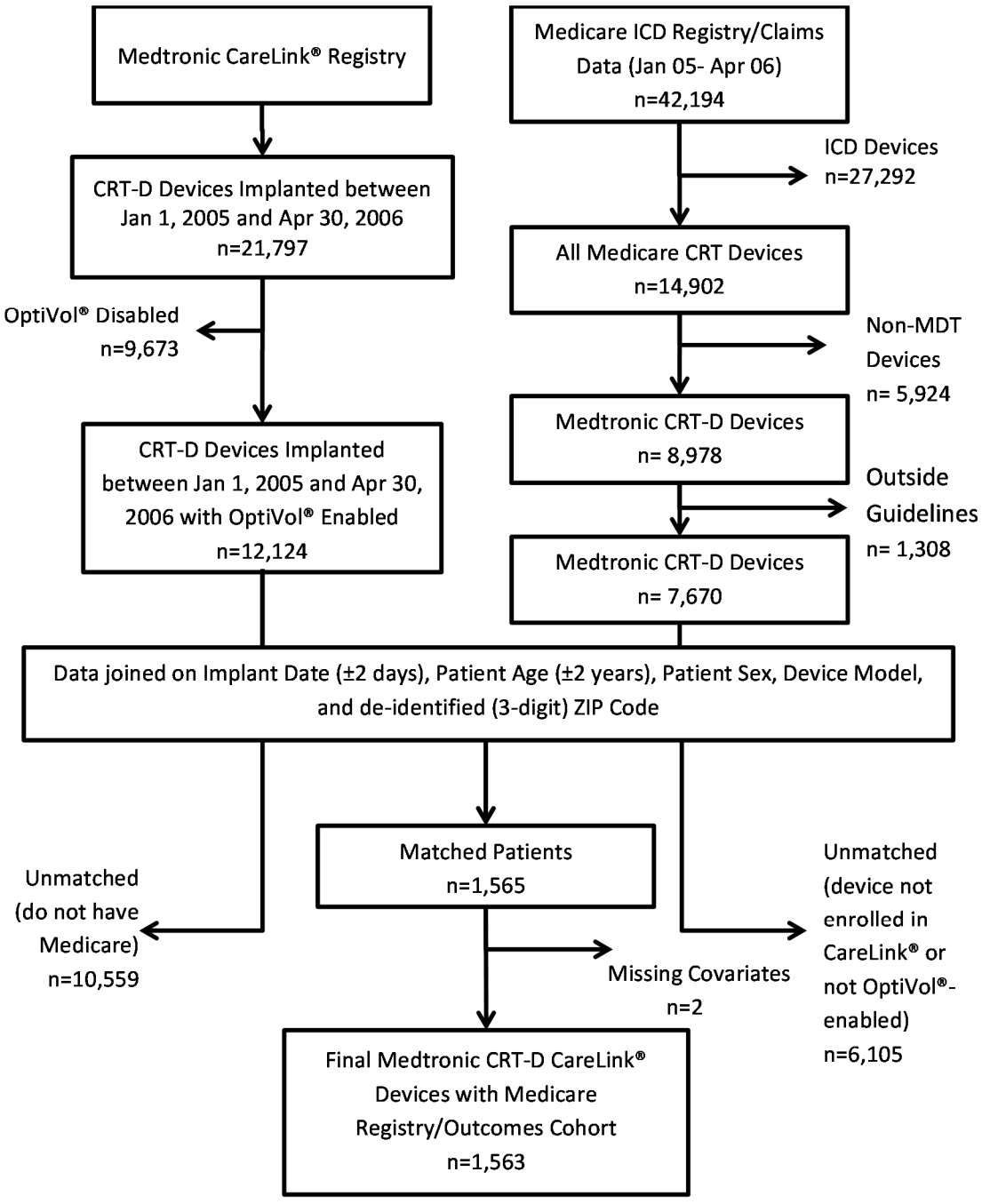


Figure 9. – Kaplan-Meier Plot of Time Until OptiVol® Threshold Crossing

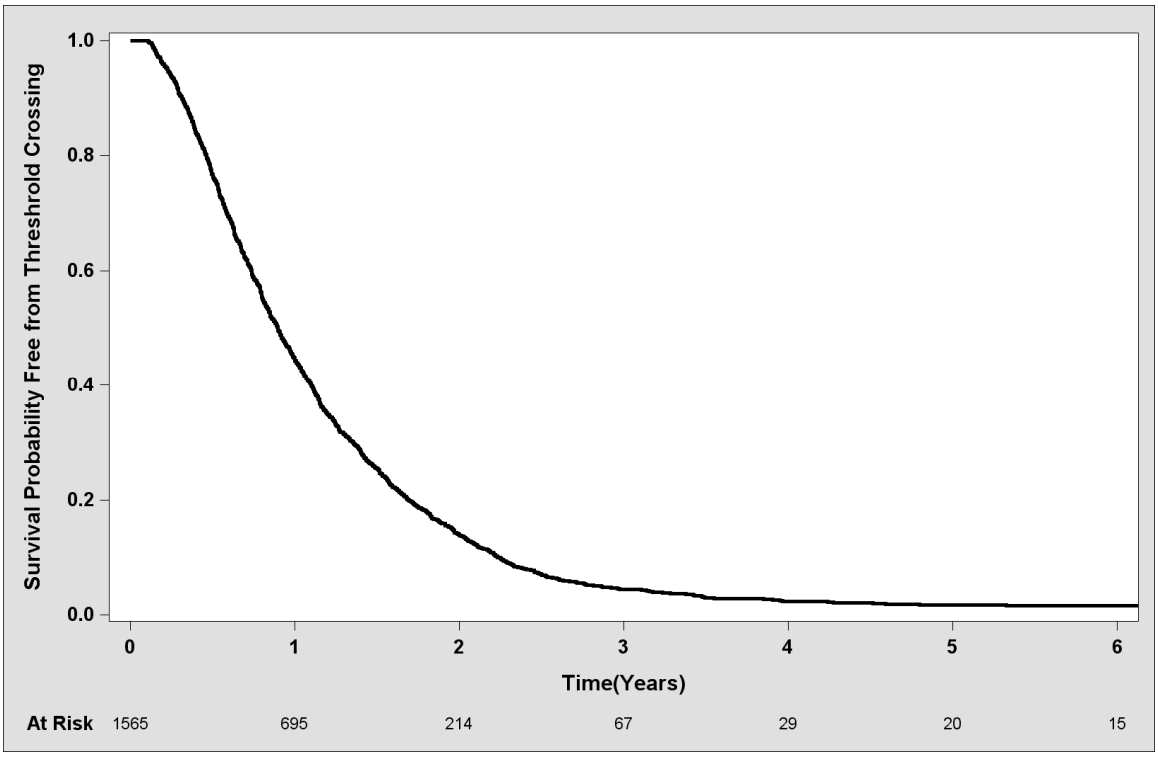


Figure 10. – Kaplan-Meier Plot of Time Until Patient Mortality by Threshold Crossing Status

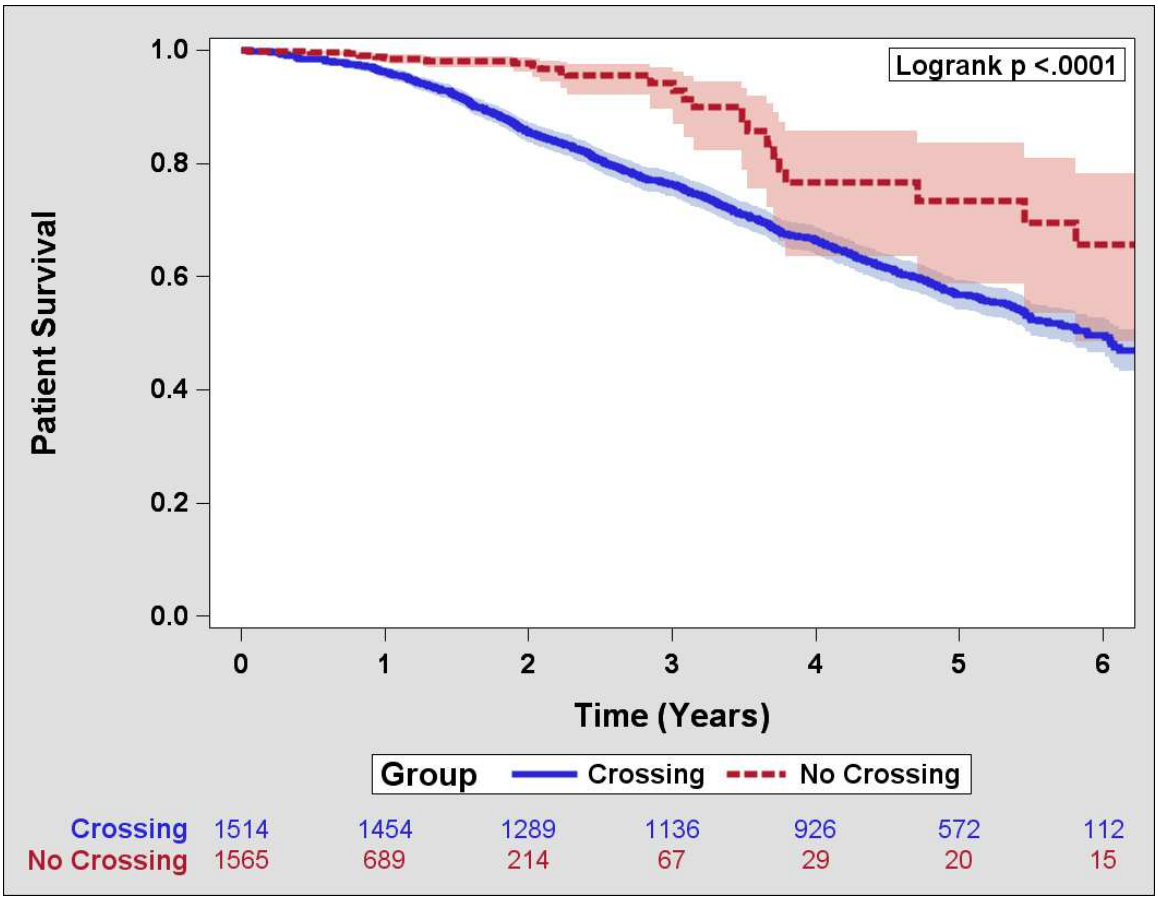


Figure 11. – Kaplan-Meier Plot of Time Until Patient Hospitalization for Heart Failure by Threshold Crossing Status

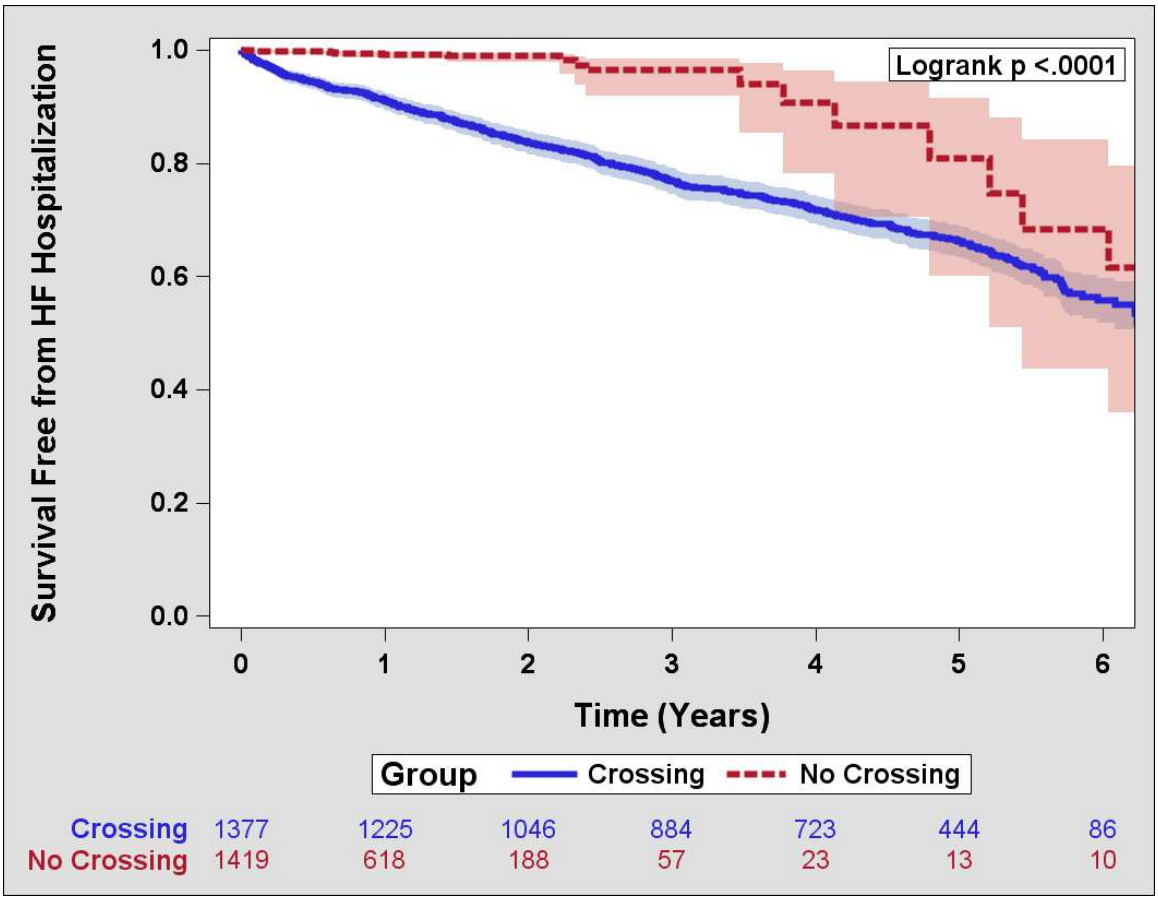


Figure 12. – Kaplan-Meier Plot of Time until Patient Mortality by Percent Follow-up Above Threshold Quartile

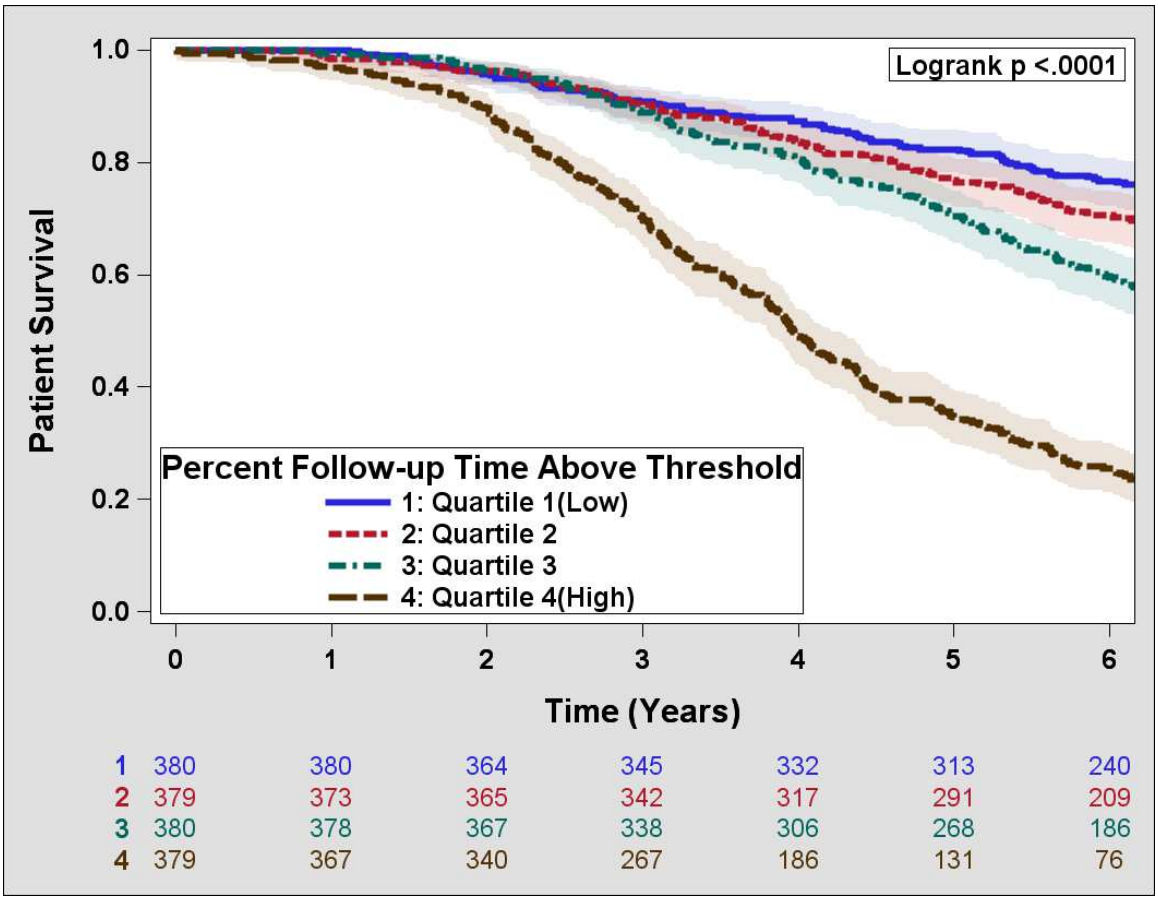
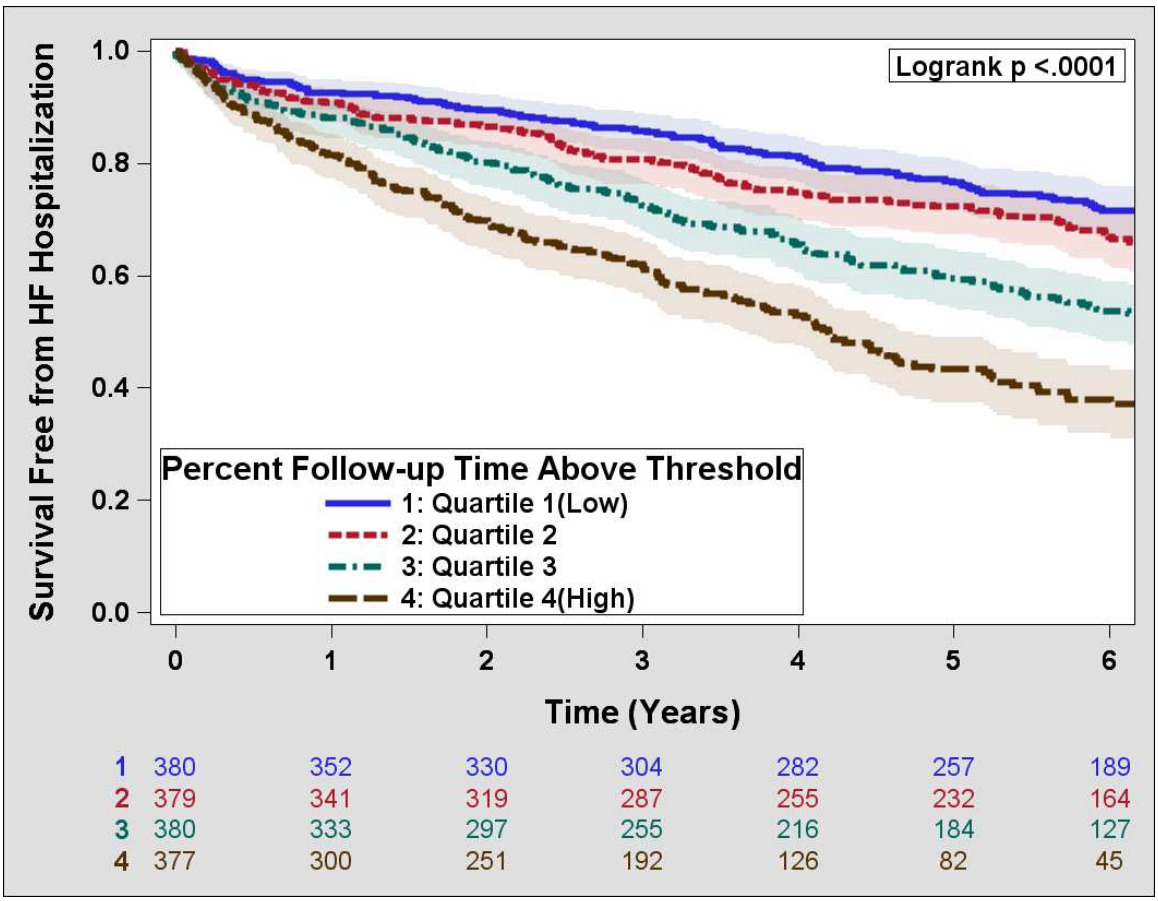


Figure 13. – Kaplan-Meier Plot of Time until HF-related Hospitalization by Percent Follow-up Above Threshold Quartile



4 Manuscript 2 – Association of Baseline Biventricular Pacing Percentage, AF Burden, and Heart Rate Variability with Mortality and Rates of Hospitalization in Patients with HF and CRT

4.1 Overview

Objective: To examine associations of bi-ventricular pacing percentage with time until patient death and HF-related hospitalization after adjusting for AVN ablation status, AF burden, and heart rate variability in CRT-D patients. Further, to determine whether any association of bi-ventricular pacing with the endpoints of interest is modified by AVN ablation status, AF burden or heart rate variability.

Background: Though bi-ventricular pacing percentage, AVN ablation status, AF burden and heart rate variability have previously been associated with outcomes in patients with HF, no studies in real-world practice have investigated them simultaneously or assessed their interactions. **Methods:** A cohort of Medicare CRT-D patients was formed by linking Medtronic CareLink® data with Medicare ICD registry, claims, and beneficiary file data with follow-up of over 6 years. Extended Cox proportional hazards regression models were run to examine the associations of baseline device-measured bi-ventricular pacing, AF burden, heart rate variability, and their interactions, adjusting for a range of clinical covariates with all-cause patient mortality and heart failure-related

hospitalization. **Results:** We analyzed N= 2,625 patients with CRT-D devices (mean age 73.1, 27% women). Median follow-up was 6.4 years. Patients with <99% bi-V pacing had increased rates of mortality and HF-hospitalization compared to those with ≥99% bi-V pacing after multivariable adjustment (HR: 1.28, 95% CI: 1.14-1.45 and HR: 1.27, 95%CI: 1.11-1.43, respectively). However, a complex set of interactions was found between bi-V pacing and AF, as well as HRV and AVN ablation. Across several analytical scenarios, the presence of <99% bi-V pacing was associated with a 33% higher mortality rate compared to those with ≥99% bi-V pacing (HR 1.33, 95%CI: 1.16-1.52) among those without AF, while bi-V pacing was not associated with mortality in those with AF (HR 1.05, 95%CI: 0.81-1.35, comparing <99% to ≥99% bi-V pacing). Findings were similar for heart failure-related hospitalization rates. Also, the association of AVN ablation with outcomes was different across levels of HRV at baseline, with a 3.6-fold higher mortality rate after AVN ablation among those in the highest HRV quartile (HR 3.6, 95%CI: 1.99-6.50), but no increased risk in those with low HRV. **Conclusion:** In a Medicare cohort of CRT patients with over 6 years of follow-up, <99% bi-V pacing percentage was associated with an increased rate of mortality and hospitalization among those with no baseline device-measured atrial fibrillation. In addition, AVN ablation was associated with worse outcomes among those with high baseline HRV, suggesting that the potential loss of benefits of higher HRV must be weighed when performing an AVN ablation procedure. This is the first study integrating device data with Medicare outcomes to validate the long-term significance of these variables together in this population.

4.2 Introduction

An active area of research and controversy in the treatment of heart failure (HF) lies in how CRT patients with AF should be handled, as approximately 20-25% of CRT patients have comorbid AF, and nearly all previous randomized controlled CRT trials have excluded patients with AF.[36,42,68] Device pacing of CRT patients with AF presents challenges due to the occurrence of fusion and pseudo-fusion beats, where the intrinsic cardiac electrical signal and the electrical impulse from the implanted device coincide to alter the QRS morphology. This, in turn, reduces the effective percentage of CRT pacing, and lowers cardiac output. This is of particular concern, as outcomes of CRT patients with AF are worse than for patients without AF, regardless of bi-ventricular (bi-V) pacing percentage.[41] However, patients in AF who undergo an atrioventricular node (AVN) ablation procedure have been shown to experience outcome rates similar to those patients in sinus rhythm, ostensibly mitigating the deleterious effects of AF.[42] One editorial has even advocated that AVN ablations are a "fundamental step" in insuring the best results from CRT.[69]

Heart rate variability (HRV), which is a measure of variability of the intrinsic atrial rhythm of the patient, has also been shown to affect outcomes, with lower HRV being associated with higher mortality.[46] However, measurement of HRV is problematic when a patient experiences persistent AF or experiences atrial pacing from the device most of the time, as there are no clear P-waves to detect and measure atrial rhythm in the former

case, and the measured atrial-atrial cycle length in the latter case is not physiologically meaningful as it is determined by the device, not the patient's intrinsic rhythm.

The objective of this study was to determine the relationship between the variables of bi-V pacing percentage, HRV, AF burden, and their interactions and all-cause patient mortality and HF-related hospitalization. We hypothesized that higher bi-V pacing percentage was associated with lower rates of all-cause mortality, as well as lower HF-related hospitalizations, after adjusting for significant clinical covariates, specifically including baseline AF burden, HRV, and AVN ablation status. In addition, we expected that the association of bi-V pacing percentage with outcomes would be modified by AF burden, HRV, or AVN ablation status.

4.3 Methods

4.3.1 Study Population

Using similar procedures to those used in Manuscript 1 above, we analyzed the Medicare population with Medtronic CRT devices measuring AF burden and heart rate variability, implanted from January 2005 to April 2006, and with at least one CareLink® transmission by the time Medicare follow-up ended in December 2011. A total of 2,625 patients were matched between the Medicare data and the CareLink® registry in this analysis. A pictorial representation of how these data were merged is shown in Figure 14.

4.3.2 Endpoint Definition

As in Manuscript 1, time until first HF hospitalization in the Medicare dataset was determined by an inpatient admission with a primary ICD-9-CM diagnosis code of 428.x. For mortality endpoints, the available MedPAR data contained only all-cause mortality.

4.3.3 Exposure Definition

The main exposure of interest was percentage of bi-V pacing, which was directly measured and reported daily in the CareLink® data. The values of % bi-V pacing, HRV, and AF burden were determined at baseline by calculating the average of the first 30 days of device-reported daily values in the CareLink® database for each of these variables. We dichotomized the baseline bi-V pacing variable (Low/High), with a cutoff at 99% pacing, based on log-likelihood values of model results varying this cutoff value until the lowest log-likelihood value was obtained. Heart rate variability measured by the device is the standard deviation of a 5-minute median atrial sensed interval (SDAAM) over a 24-hour period, and the units are given in milliseconds. Since the SDAAM measurement is based on a patient's intrinsic atrial cycle length, the CRT-D device does not store an HRV value for a given day if the percentage of time the device is pacing the atrium is greater than 80% of the 24-hour period, or if the patient experienced AF for more than 80% of the time during that period. We therefore created a "Missing" value for the HRV variable (presumably patients with >80% atrial pacing, atrial tachycardia (AT), or AF), and grouped the remaining patients into quartiles (<55.8ms, 55.8-67.9ms, 69.0-83.6ms, and >83.6ms). Finally, AV node ablation status at baseline and during follow up, and

procedure date were determined based on a Current Procedure Terminology (CPT) code of 93650 in the Medicare data.

Since the HRV measurement is not only tied to AF burden, but also to atrial pacing percentage, we additionally calculated and included a 30-day baseline atrial pacing percentage variable from available CareLink® data.

4.3.4 Covariates

Other variables available at the time of device implant in the Medicare registry that were considered in this analysis included patient age, duration of HF, LVEF, QRS duration, systolic blood pressure, diastolic blood pressure, heart rate, sex, NYHA class, presence of ischemic cardiomyopathy, bundle-branch block (BBB) morphology, prior coronary artery bypass graft (CABG), AF, anticoagulation therapy for AF, presence of ventricular tachycardia, prior sudden cardiac arrest event, diabetes mellitus, prior myocardial infarction, chronic kidney disease, end-stage renal disease, smoking status, and the prescription of beta-blockers, ACE-inhibitors or angiotensin receptor blockers, digoxin, diuretics, amiodarone, and/or warfarin. The diagnosis of chronic kidney disease (CKD) and end-stage renal disease (ESRD) was established based on administrative diagnosis codes from inpatient and outpatient encounters, available in CMS utilization files from the year the device was implanted.

4.3.5 Statistical Analysis

The associations of bi-V pacing, HRV, and AF burden with the outcomes of hospitalization and death were examined two ways. We first analyzed the data via a Cox regression model using PROC PHREG in SAS, version 9.4 (SAS institute, Cary, NC) with all covariates fixed at their registry-reported baseline values determined, or based on their device-measured average value during the first 30 days after CRT implant. We then ran an extended Cox regression model, adding the time-dependent AVN ablation covariate, with all other variables in the model fixed as before. Both models specifically included the effects of bi-ventricular pacing, AF burden, and heart rate variability as well as the other covariates available in the Medicare ICD registry. We also specifically looked for interactions between variables by adding separate interaction terms to the model between bi-V pacing and AF burden, bi-V pacing and HRV, AF burden and HRV and in the second analysis, AVN ablation status and bi-V pacing, ablation status and HRV, ablation status and AF burden in addition to the other terms listed above. The final set of covariates were selected by stepwise backwards selection, with the specific inclusion of the above-stated interactions, and were further evaluated qualitatively based on known effects of covariates on heart failure survival (e.g., those with diabetes mellitus are expected to experience poorer outcomes).

Analyses for hospitalization endpoints were run both with cause-specific models, where all competing outcomes other than HF hospitalization (specifically, patient death) were censored, as well as competing risk (or subdistribution) models, where patients who

died were left in the denominator to estimate actual observable patient hospitalization rates.[65] Since hospitalizations from patients with HMO/MCO coverage may be missed if they are not billed to Medicare, and are rather billed to the patients HMO/MCO instead, where HF-related hospitalization outcomes were examined we further created two additional models: one model adjusting for whether the patient had supplemental health maintenance organization (HMO)/ managed care organization (MCO) coverage, and another model excluding those patients with and HMO/MCO coverage, as reported in the Medicare data.

4.4 Results

Table 8 shows the subset of patients analyzed in this study compared to those in the Medicare dataset who were not examined (those without Medtronic devices). Patients in the analysis cohort had statistically significantly greater LVEF, QRS interval, proportions of NYHA class I, II, and III patients, BBB morphology, ACE or ARB, and warfarin prescription. They also had lower heart rate, lower proportions of ischemic cardiomyopathy, diabetes mellitus, prior myocardial infarction, chronic kidney disease (CKD), end-stage renal disease (ESRD), and amiodarone prescription than those who were not analyzed. However, these differences were small and not expected to be of practical clinical significance.

In this retrospective cohort study, we linked 2,625 patients between the Medtronic CareLink® database and the Medicare ICD Registry, representing approximately 34.2% of available Medicare patients with a Medtronic CRT device. Over the median follow up

period of 6.4 years, we observed a mortality rate of 8.8 deaths per 100 person-years (1,186 deaths/13,676 person-years) and a HF-related hospitalization rate of 9.4 patients being hospitalized for the first time per 100 person-years (1,050 hospitalizations/11,207 person-years). We examined first HF-related hospitalizations only. Slightly more than half of patients (51.7%) had bi-V pacing percentages over 99%, with a mean of 94.1% bi-V pacing. There were 1,949 patients with no device-measured AF during the first 30 days after implant. Of the remaining 646, the median device-measured AF burden was 3.0%, with a bi-modal distribution towards either high or low values of AF burden as shown in Figure 15. A total of 149 patients (5.7%) in our merged cohort underwent an AVN ablation procedure either prior to or during device implant (57 out of 149) or during their follow-up (92 out of 149). In order to examine whether device-measured AF burden was representative of AF burden over time, we further examined whether their AF burden 30 days prior to the ablation procedure was similar to their baseline AF burden measurement. Of those who experienced an AVN ablation during follow-up, we had device data for 86 patients for the 30 days before the ablation procedure. Those with clinician-diagnosed AF at the time of implant (that is, those with AF noted in the Medicare ICD Registry) had a 4.5 times higher odds of experiencing an AVN ablation (OR 4.5, 95%CI: 3.1-6.5) than those without clinician-diagnosed AF at implant, and Figure 16 shows the pairwise evolution of patients' AF burden values from the first 30 days after implant to the 30 days before an ablation procedure. Only a modest, but still statistically significant, correlation was observed (Pearson's $r = 0.23$, p-value=0.03).

Baseline Main Effects and Interactions – No Time-Dependent Covariates

In the analysis that did not consider the time-dependent AVN ablation status, shown in Table 9, we found that patients with <99% baseline bi-V pacing experienced a 28% higher mortality rate (HR 1.28, 95%CI: 1.14-1.45) and a 27% higher HF-related hospitalization rate (HR 1.27, 95%CI: 1.11-1.43) than those with ≥99% baseline bi-V pacing, after adjustment for baseline AF burden, baseline HRV quartile, ischemic cardiomyopathy, smoking status, age at implant, patient sex, diastolic blood pressure, prior coronary artery bypass graft (CABG) procedure, diabetes mellitus, and prescription of a diuretic, or ACE-inhibitor or ARB. Further, those patients with <55.8ms baseline HRV (lowest quartile) had a 54% greater rate of mortality compared to those patients with >83.6ms baseline HRV (HR 1.54, 95%CI: 1.25-1.90). We likewise found higher mortality rates among those patients in intermediate HRV quartiles (31% and 33% for quartiles 2 and 3 compared to quartile 4, respectively), but no greater hospitalization rates for these patients compared to those in the highest quartile. Those with missing baseline HRV values due to high device-measured AF burden and/or atrial pacing percentages experienced a 38% higher mortality rate compared to those with >83.6ms baseline HRV (HR 1.38, 95%CI: 1.14-1.66) after adjustment for these same covariates. Baseline AF burden was not associated with mortality, but there was a 15% to 17% increase in hospitalization rate, depending on whether HMO/MCO patients were included, and whether the model calculated the cause-specific or competing-risk hospitalization rates.

Baseline Main Effects and Interactions with Time-Varying AVN Ablation Status

Table 10 lists the full results of the analysis including the time-varying AVN ablation status variable, where we found two separate interactions: one between baseline bi-V pacing category and the presence of any device-measured AF at baseline, and another interaction between HRV quartile and AVN ablation status. In the absence of any baseline device-measured AF, patients with bi-V pacing percentage <99% at baseline had a 33% higher mortality rate (HR 1.33, 95%CI: 1.16-1.52) and a 27% higher hospitalization rate (HR 1.27, 95%CI: 1.10-1.47) compared to those with ≥99% bi-V pacing after adjusting for AVN ablation status, baseline AF burden, HRV, ischemic cardiomyopathy, smoking status, patient age at implant, patient sex, diastolic blood pressure, prior CABG procedure, diabetes mellitus, as well as the prescription of a diuretic, ACE-inhibitor or ARB, and in the case of hospitalization outcomes, any HMO/MCO coverage. There was no association observed for <99% bi-V pacing vs ≥99% and mortality for patients with AF (HR 1.05, 95%CI: 0.83-1.23). Consistently, there was little difference between the mortality rates for either bi-V pacing category among those patients with any device-measured AF at baseline (HR 1.31, 95% CI: 1.12-1.54 for <99% bi-V pacing, and HR 1.26, 95% 0.99-1.59 for ≥99% bi-V pacing) compared to those with no AF and ≥99% bi-V pacing (p-value for interaction = 0.10).

Further, in those patients without AVN ablations, lower HRV was associated with worse outcomes, where those with HRV values below 55.8 ms (lowest quartile, Q1) had a 63% greater mortality rate (HR 1.63, 95%CI: 1.31-2.02) and a 47% greater HF-related

hospitalization rate (HR 1.47, 95%CI: 1.18-1.83) compared to patients with HRV values above 83.6 ms (highest quartile, Q4). These beneficial associations between HRV and mortality or HF-related hospitalization disappeared in patients who had undergone AVN ablations (p-value for interaction = 0.07). Missing HRV values due to >80% baseline AF burden and/or atrial pacing percentage were associated with a 41% increased mortality rate (HR 1.41, 95%CI: 1.16-1.72) and a 40% increased rate of HF-related hospitalization (HR 1.40, 95%CI: 1.15-1.71) compared to those in the highest HRV quartile (>83.6ms). However, no association was found between HRV and HF-hospitalization for those with missing HRV values after AVN ablation. AVN ablation itself was indicative of 260% higher mortality rates among those in the highest quartile of HRV values (HR 3.60, 95%CI: 1.99-6.50), as well for those with missing HRV values. However, as shown in Table 10, this effect was not seen for other HRV quartiles, nor was there a consistent effect on hospitalization rates, depending on whether patients with additional HMO/MCO coverage were excluded from the analysis, or whether the cause-specific HR or competing risks (subdistribution) HR was calculated. Other interactions we explored, namely bi-V pacing and HRV, bi-V pacing and AVN ablation status, HRV and baseline AF burden, and baseline AF burden and AVN ablation status were not statistically significant. We also examined the effect of race in this analysis, but it was not found to be a significant predictor of either mortality or hospitalization and was therefore dropped from the models.

4.5 Discussion

There is a complex relationship between biventricular pacing, AF, and HRV in the context of CRT. CRT patients with AF pose a particular challenge, as AF interferes with the positive effects of bi-V pacing. Those patients in our cohort with 99% or greater bi-V pacing experienced lower all-cause mortality and lower hospitalization rates than those with lower bi-V pacing, adding to the growing body of literature supporting that the closer to 100% bi-V pacing the better. Our 99% cutoff value is largely consistent with other studies that have examined bi-V pacing, which have separately reported 92% and 98.7% as optimal bi-V pacing percentages.[40,41]

Unusually, neither clinician-diagnosed AF, nor device-measured baseline AF burden appeared to be statistically significantly associated with study outcomes in any of our models, with the only significant AF-related variable being the time-dependent association of AVN ablation in interaction with other baseline variables. The direction of this association was also unexpected in that AVN ablations were associated with increased mortality and HF-related hospitalization among those in the highest HRV quartile, or even those with missing baseline HRV values, indicating that they likely have high AF burden and/or atrial pacing percentages. Figure 16 shows that the device-recorded baseline AF burden measurement is not particularly representative of future AF burden among those with AVN ablations, with only a very modest correlation between the baseline measured value and the pre-ablation value (Pearson's r=0.24). The finding of higher mortality rates among AVN ablation recipients is therefore likely due to other

factors, including natural progression of their disease, which is not captured in the baseline AF burden metric alone. We believe that the apparent detriment of AVN ablation shown in Table 10 is due to worsening patient health and disease progression necessitating the AVN ablation, which is not captured in either the baseline AF burden metric, the Medicare AF diagnosis, or the "missing" HRV value, rather than the ablation itself. Previous studies examining the effect of AF after AVN ablation in CRT patients did not describe how the diagnosis of AF was determined to compare against our methodology. Further, reasons for performing AVN ablations were not documented during follow-up, so we cannot truly know why an ablation procedure was performed. However, due to the nature of our Medicare cohort, AVN ablation practices in our study should be representative of real-world circumstances, not guided by any formal clinical study protocol.

The observed interaction between baseline HRV and AVN ablation suggests that upon ablation, a patient loses the benefit bestowed by intrinsic atrial rate control. Consistent with previous literature, higher intrinsic atrial rate variability is associated with lower overall mortality, as shown in Table 10. Once an ablation occurs, there is no communication between atria and ventricles, rendering the actual atrial rate moot, and forcing the device to pace the ventricles 100% of the time. Whether the loss of this HRV benefit is outweighed by the prevention of ventricular tachycardia and/or arrhythmia must be considered by the physician when determining whether to perform an AVN ablation.

Our data-matching scheme linked 2,625 patients between the Medicare ICD registry and the Medtronic CareLink® network for this analysis. As noted in Manuscript 1 above, at the time the Medicare Registry was maintained an estimated 39% of Medtronic CRT patients were enrolled in the CareLink® network (Medtronic data on file, 2016), and therefore expect approximately 2,990 of Medicare registry patients to be found in both data sources. Therefore our 34.2% (2,625 patients) match between these two registries seems reasonable.

The limitations of this study include the fact that CRT pacing percentages have been shown to overestimate actual effective pacing percentage. It has been observed that while the CRT-D device reports >90% bi-ventricular pacing, up to 40% of overall paced beats can be fusion and pseudo-fusion beats.[35] However, due to this overreporting of bi-V pacing percentage from the device we would expect the measures of association calculated in this study to underestimate the true effect of high proportions of bi-V pacing. We are also limited by the assumption that baseline HRV, bi-V pacing, and AF burden are indicative of patient characteristics throughout the follow-up period. As we have shown, this is somewhat problematic for the AF burden variable, as our results pertaining to AF differ from previous studies.

In conclusion, baseline bi-ventricular pacing percentages ≥99% were associated with both lower mortality and HF-related hospitalization outcomes in a cohort of Medicare ICD patients after adjusting for key covariates with over 6 years of follow-up. An interaction was noted between missing HRV data, representing high percentages of

AF and/or atrial pacing, in Medtronic's CareLink® data and bi-V pacing, whereby high bi-ventricular pacing was associated with better outcomes in the presence of HRV data (low AF burden and low atrial pacing percentage), but no benefit if HRV data were missing.

4.6 Tables and Figures

Figure 14. – Manuscript 2 Cohort Selection and Data Merging Scheme

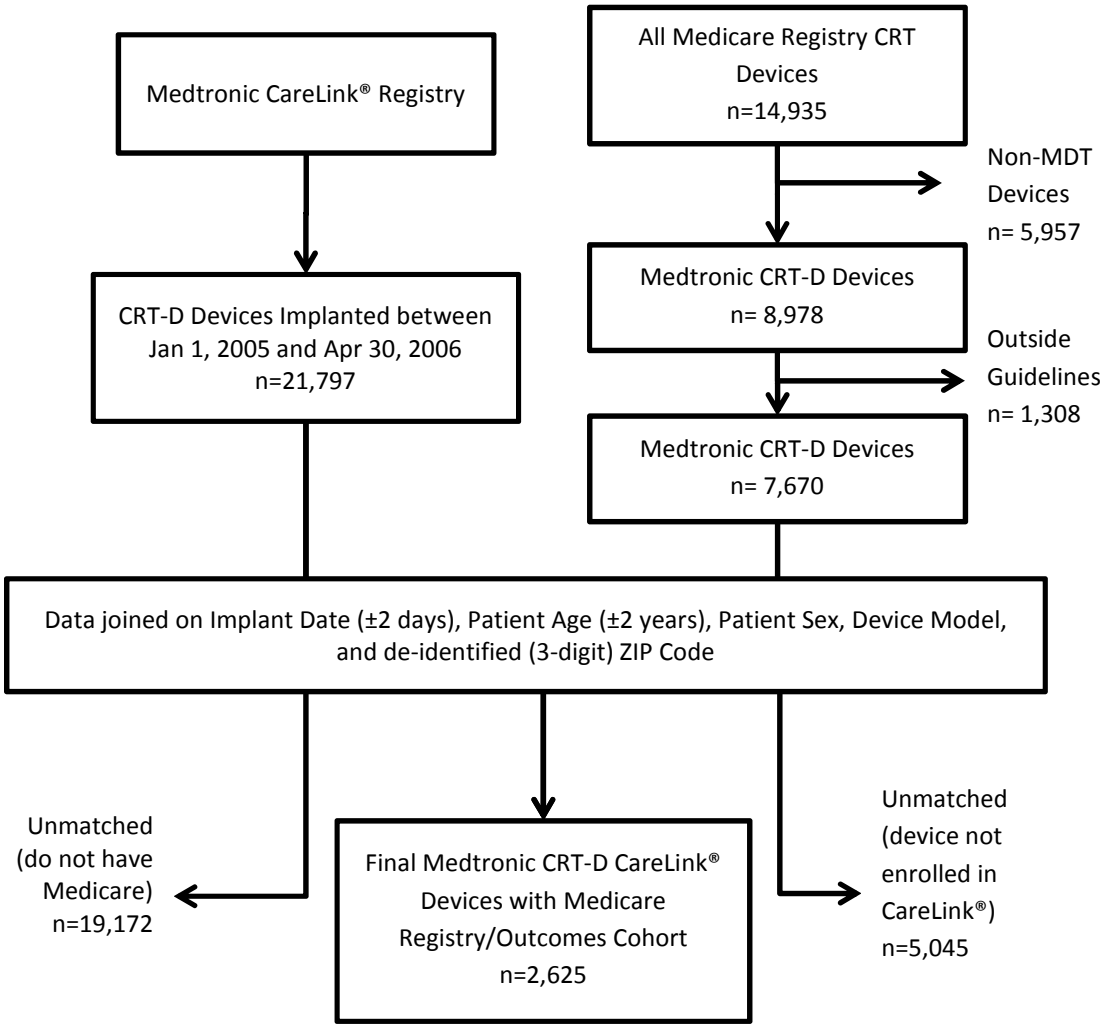


Table 8. – Baseline Demographic and Clinical Characteristics for Medicare CRT Patients by Analysis Cohort

	All Medicare CRT Patients(n=14,935)	Analysis Cohort (n=2,625)	Non- Analyzed Cohort (n=12,310)	p-value*
Age, mean ±SD, y	73.0±10.5	73.1±8.0	73.0 ± 10.9	0.45
Duration HF, mean ±SD, months	24.7±25.4	25.5±25.9	24.5±25.3	0.08
LVEF, mean ±SD, %	23.1±6.3	23.5±6.3	23.0±6.4	<0.001
QRS duration, mean ±SD, ms	156.8±24.9	158.7±24.8	156.4±24.9	<0.001
SBP, mean ±SD, mm Hg	126.5±22.4	126.3±21.4	126.5±22.6	0.67
DBP, mean ±SD, mm Hg	70.2±13.7	70.3±12.4	70.1±14.0	0.56
Heart rate, mean ±SD, bpm	72.0±18.0	71.2±14.4	72.2±18.7	0.003
Sex, n(%)				
Female	27.3	26.7	27.4	
Male	72.7	73.3	72.6	0.44
NYHA class, (%)				
I	1.2	1.3	1.2	
II	11.0	11.3	10.9	
III	74.2	76.8	73.6	<0.001
IV	13.6	10.6	14.3	
Ischemic CM, (%)	69.2	64.8	70.1	<0.001
Prior CABG, (%)				
BBB Morphology, (%)				
LBBB	69.3	71.2	68.9	
RBBB	11.0	9.7	11.2	0.03
Other IVCD	19.8	19.1	19.8	
Atrial fibrillation, (%)	34.7	35.7	34.5	0.24
Ventricular tachycardia, (%)	19.6	18.4	19.8	0.10
Sudden cardiac arrest, (%)	1.7	1.5	1.8	0.39
Diabetes mellitus, (%)	35.7	33.9	36.1	0.04
Prior MI, (%)	50.9	49.0	51.3	0.03
Chronic Kidney Disease, (%)	32.0	25.8	33.3	<0.001
End-Stage Renal Disease, (%)	3.1	1.6	3.4	<0.001
Smoker Status, (%)				
Never	42.3	42.5	42.2	
Former	48.6	49.4	48.5	0.17
Current	9.1	8.2	9.3	
Medications, (%)				
b-blocker	78.9	80.2	78.6	0.07
ACEI or ARB	74.3	77.4	73.6	<0.001
Digoxin	41.7	41.5	41.8	0.83
Diuretic	78.7	79.3	78.5	0.39
Amiodarone	13.6	11.9	13.9	0.004
Warfarin	31.8	34.3	31.3	0.003

*p-value comparing analyzed cohort to non-Analyzed cohort.

Table 9. – Hazard Ratios of Mortality or First HF Hospitalization for Baseline Bi-V Pacing, HRV, and AF Burden. Models include all covariates in the table simultaneously.

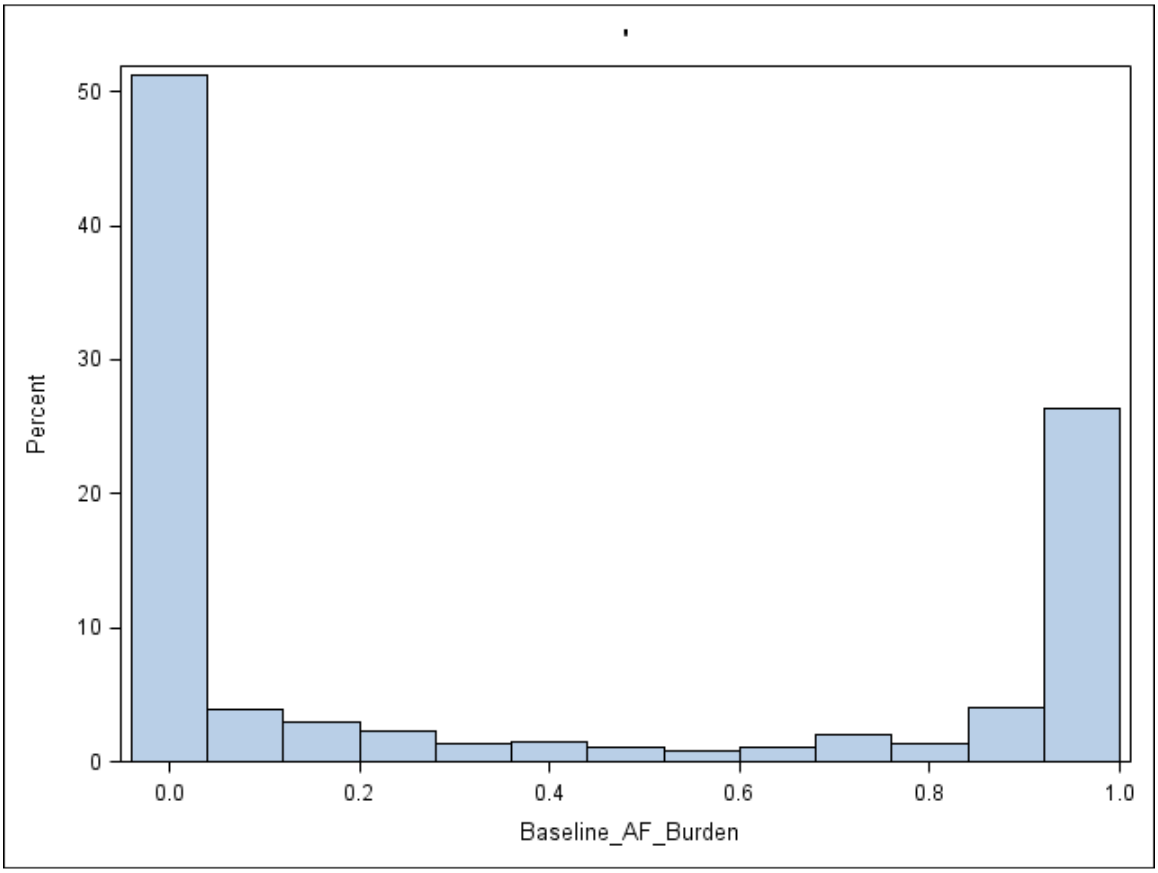
	Hazard Ratio for Patient Mortality	Cause-specific Hazard Ratio for Heart Failure-related Hospitalization		Subdistribution Hazard Ratio for Heart Failure-related Hospitalization	
		Including Medicare HMO/MCO Patients	Excluding Medicare HMO/MCO Patients	Including Medicare HMO/MCO Patients	Excluding Medicare HMO/MCO Patients
# of events	1,186	1,050	980	1,050 (513 competing)	980 (444 competing)
Follow up time (person-years)	13,676	11,207	10,029	11,207	10,029
Baseline Bi-V pacing (<99% vs ≥99%)	1.28 (1.14-1.45)	1.27 (1.11-1.43)	1.23 (1.09-1.41)	1.22 (1.08-1.39)	1.20 (1.05-1.37)
Baseline AF (Any AF vs No AF)	1.08 (0.94-1.24)	1.17 (1.02-1.35)	1.17 (1.01-1.36)	1.16 (1.00-1.34)	1.15 (1.00-1.34)
Baseline HRV					
Q1 vs Q4	1.54 (1.25-1.90)	1.45 (1.16-1.79)	1.40 (1.12-1.76)	1.37 (1.10-1.71)	1.33 (1.06-1.67)
Q2 vs Q4	1.31 (1.06-1.63)	1.10 (0.88-1.38)	1.09 (0.87-1.38)	1.07 (0.86-1.34)	1.06 (0.85-1.33)
Q3 vs Q4	1.33 (1.07-1.65)	1.00 (0.79-1.25)	0.98 (0.77-1.24)	0.95 (0.76-1.19)	0.94 (0.74-1.19)
Missing vs Q4	1.38 (1.14-1.66)	1.38 (1.14-1.68)	1.33 (1.09-1.63)	1.34 (1.11-1.62)	1.29 (1.06-1.57)
Ischemic Cardiomyopathy (Y vs N)	1.22 (1.04-1.41)	1.14 (0.96-1.33)	1.10 (0.93-1.30)	1.10 (0.93-1.28)	1.08 (0.91-1.27)
Smoking Status					
Current vs Never	1.68 (1.36-2.09)	1.44 (1.14-1.82)	1.36 (1.07-1.74)	1.33 (1.05-1.69)	1.27 (0.99-1.63)
Former vs Never	1.17 (1.03-1.32)	1.17 (1.03-1.34)	1.13 (0.99-1.30)	1.15 (1.01-1.31)	1.11 (0.97-1.28)
Age at Implant (per 10 yrs)	1.42 (1.30-1.54)	1.10 (1.01-1.20)	1.11 (1.02-1.22)	1.06 (0.97-1.16)	1.08 (0.98-1.18)
Patient Sex (female)	0.75 (0.64-0.87)	0.95 (0.82-1.11)	0.91 (0.78-1.07)	0.98 (0.84-1.14)	0.93 (0.80-1.10)
Diastolic Blood Pressure (per 10mm Hg)	0.91 (0.87-0.96)	0.93 (0.89-0.98)	0.93 (0.89-0.98)	0.94 (0.89-0.99)	0.94 (0.89-0.99)
Prior CABG (Y vs N)	1.15 (1.00-1.32)	1.15 (1.00-1.33)	1.18 (1.01-1.37)	1.12 (0.97-1.30)	1.14 (0.98-1.33)
Diabetes Mellitus (Y vs N)	1.33 (1.18-1.49)	1.32 (0.67-0.86)	1.30 (1.14-1.47)	1.25 (1.11-1.43)	1.23 (1.08-1.41)
Diuretic (Y vs N)	1.27 (1.09-1.47)	1.52 (1.28-1.79)	1.54 (1.28-1.82)	1.49 (1.27-1.79)	1.52 (1.28-1.82)
ACE or ARB (Y vs N)	0.78 (0.68-0.88)	0.77 (0.67-0.88)	0.76 (0.66-0.88)	0.80 (0.69-0.92)	0.79 (0.68-0.92)
Any HMO/MCO Coverage (Y vs N)	N/A	0.60 (0.47-0.76)	N/A	0.57 (0.45-0.72)	N/A

Table 10. – Adjusted Hazard Ratios for AVN Ablation Status, Baseline Bi-V pacing, AF burden, HRV, and Their Interactions

	Hazard Ratio for Patient Mortality	*Cause-specific Hazard Ratio for Heart Failure-related Hospitalization*		*Subdistribution Hazard Ratio for Heart Failure-related Hospitalization*	
		Including Medicare HMO/MCO Patients	Excluding Medicare HMO/MCO Patients	Including Medicare HMO/MCO Patients	Excluding Medicare HMO/MCO Patients
# of events	1,186	1,050	980	1,050 (513 competing)	980 (444 competing)
Follow up time (person-years)	13,676	11,207	10,029	11,207	10,029
Adjusted* Associations of Baseline Bi-V pacing (>99% vs <99%) by Baseline AF Status (Any vs None)					
<99% bi-V Pacing/Any AF	1.31 (1.12-1.54)	1.47 (1.24-1.73)	1.45 (1.21-1.72)	1.42 (1.20-1.68)	1.40 (1.17-1.65)
<99% bi-V Pacing/No AF	1.33 (1.16-1.52)	1.27 (1.10-1.47)	1.23 (1.06-1.43)	1.23 (1.06-1.42)	1.19 (1.02-1.38)
≥99% bi-V Pacing/Any AF	1.26 (0.99-1.59)	1.20 (0.94-1.55)	1.16 (0.90-1.51)	1.15 (0.89-1.49)	1.11 (0.85-1.45)
≥99% bi-V Pacing/No AF	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Adjusted* Associations of AVN Ablation Status (Y vs N) by Baseline HRV Quartile					
Missing HRV/ Ablation	2.04 (1.47-2.85)	1.39 (0.94-2.06)	1.35 (0.90-2.01)	1.22 (0.79-1.87)	1.18 (0.77-1.83)
Q1 HRV/ Ablation	1.88 (0.95-3.69)	1.36 (0.43-4.30)	1.35 (0.43-4.24)	1.60 (0.42-6.06)	1.58 (0.42-5.97)
Q2 HRV/ Ablation	1.07 (0.58-5.76)	1.11 (0.27-4.52)	1.10 (0.27-4.48)	1.19 (0.30-4.79)	1.18 (0.29-4.72)
Q3 HRV/ Ablation	2.30 (1.07-4.95)	2.18 (0.89-5.35)	2.23 (0.91-5.48)	2.31 (0.86-6.17)	2.34 (0.88-6.24)
Q4 HRV/ Ablation	3.60 (1.99-6.50)	2.13 (0.79-5.78)	2.31(0.85-6.26)	2.10 (0.99-4.47)	2.42 (1.25-4.72)
Missing HRV/ No Ablation	1.41 (1.16-1.72)	1.40 (1.15-1.71)	1.36 (1.11-1.66)	1.37 (1.13-1.67)	1.33 (1.09-1.62)
Q1 HRV/ No Ablation	1.63 (1.31-2.02)	1.47 (1.18-1.83)	1.43 (1.14-1.79)	1.39 (1.12-1.73)	1.35 (1.08-1.70)
Q2 HRV/ No Ablation	1.39 (1.11-1.73)	1.12 (0.89-1.40)	1.11 (0.88-1.40)	1.09 (0.87-1.36)	1.08 (0.86-1.36)
Q3 HRV/ No Ablation	1.39 (1.11-1.73)	0.99 (0.78-1.25)	0.97 (0.76-1.24)	0.94 (0.75-1.19)	0.93 (0.73-1.19)
Q4 HRV/ No Ablation	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)

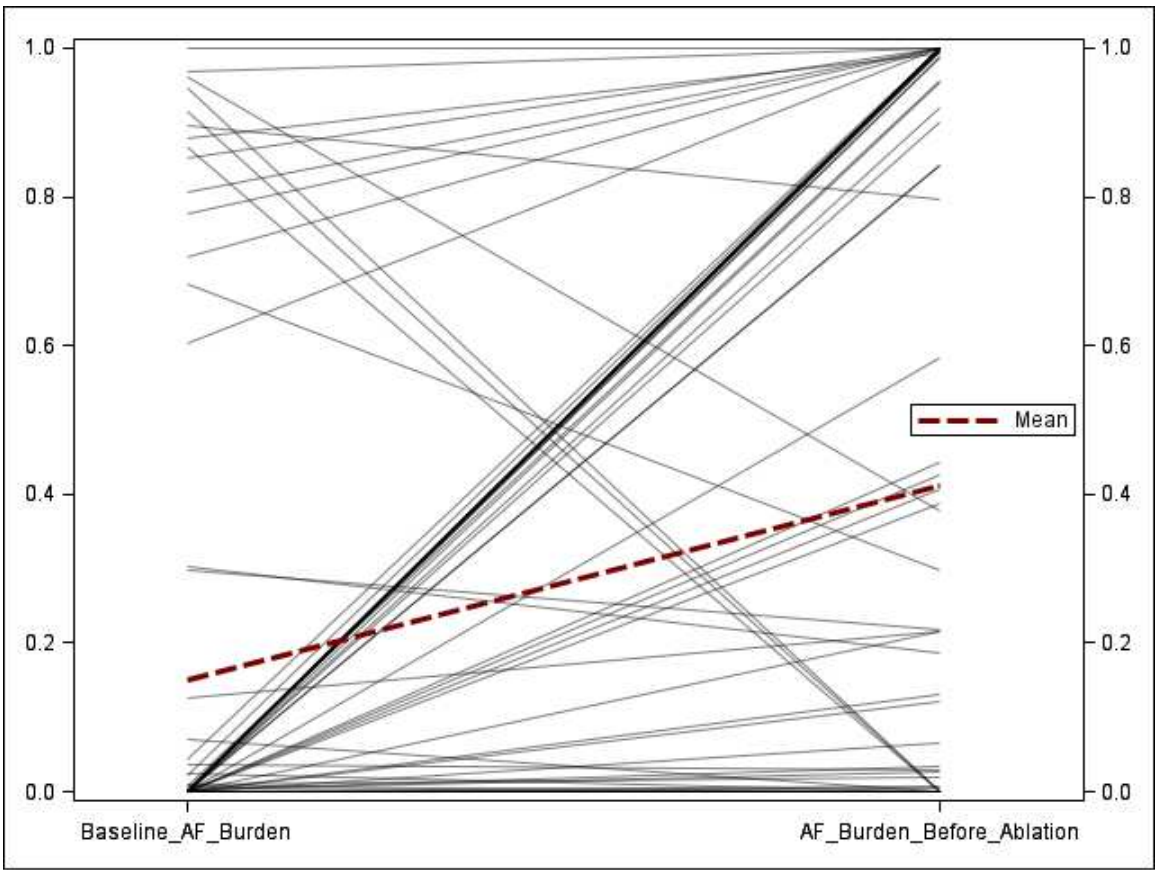
* Adjusted for patient age at implant, sex, ischemic cardiomyopathy, diastolic blood pressure, prior CABG procedure, smoking status, diabetes mellitus, diuretic, ACE or ARB prescription, and for hospitalization events, any HMO/MCO coverage (Y/N).

Figure 15. – Distribution of Baseline AF Burden (% of time patient is in AF) among Patients with Any AF



*Baseline_AF_Burden = proportion of time the patient experiences atrial tachycardia and/or atrial fibrillation (AT/AF)

Figure 16. – Comparison between Baseline AF Burden and AF Burden 30 days Prior to AVN Ablation (n=86, AVN Ablation patients only)



* Lines connect measurements within an individual patient

5 Manuscript 3 – Use of Implantable Device Heart Failure Diagnostics to Predict 30-day HF-Rehospitalization

5.1 Overview

Objective: To improve upon the existing 30-day heart failure hospital readmission prediction model of Small, et al., by the addition of baseline clinical information found in the Medicare registry.

Background: With the advent of the 30-day rehospitalization penalty from the Centers for Medicare and Medicaid Services (CMS), it is imperative to determine which patients may be at risk of imminent rehospitalization. In addition to the poorer outcomes for patients, there is the potential for reduced Medicare payments to providers if their facility experiences higher rates of 30-day rehospitalization. We look to improve existing risk stratification models, which use device-measured data on the day of discharge for HF-hospitalization, by adding patient baseline clinical information. **Methods:** The Cox regression model of Small, et al. (daily impedance >8Ω below reference impedance, AF >6 hrs in previous 24, night heart rate >80 bpm, CRT pacing <90%) was applied to a cohort of Medicare ICD Registry patients with at least one HF-related hospitalization and at least 30 days of follow-up information available in both CareLink® and Medicare claims. Further, a bootstrap variable selection process utilizing both derivation and validation cohorts was performed including the variables of the Small, et al. model. This model then had remaining non-significant variables removed. **Results:** Of 607 index

hospitalizations in our cohort of 1,563 patients, 107 experienced a rehospitalization within 30 days. Those who met one of the device-measured criteria at discharge, which were set forth in the model developed by Small, et al., had a 70% higher rate of 30-day rehospitalization compared to those who met none of the criteria (HR 1.7, 95% CI: 1.1-2.7). Additional device-measured criteria that were met did not further increase risk identification significantly (2+ criteria vs none HR: 1.8, 95%CI 1.1-2.9). The bootstrap selection model indicated that the impedance criterion of Small, et al., was the only criterion of primary importance, as well as the registry variables of diuretic prescription, chronic kidney disease, NYHA class at implant, male sex, prior coronary artery bypass graft (CABG) procedure, and longer duration of heart failure at the time of the index hospitalization. The AUC from our final model in our validation cohort was 0.76 (95%CI: 0.71-0.81), and the model was well calibrated (Hosmer-Lemeshow $\chi^2 = 11.96$, p-value=0.15).

Conclusion: We have derived a model based on device-measured and clinical variables that predicts risk of 30-day HF-related hospitalization. Variables associated with kidney dysfunction at the time of discharge from a HF-related index hospitalization were most strongly predictive of rehospitalization within 30-days.

5.2 Introduction

Frequent hospitalizations place considerable suffering on patients living with HF, as well as burden on clinicians managing these patients.[70] Many HF patients experience

severe, acute episodes of symptoms including fatigue, dyspnea, edema, sudden weight gain, and chest pain, which require immediate treatment and/or hospitalization. While more HF-related hospitalizations themselves have been associated with poorer outcomes[71], there is also an economic burden to the healthcare system in treating these patients. As of 2012, these costs stood at $20.9 billion in direct treatment costs, and a further $9.8 billion in indirect, or lost productivity, costs.[2] In an effort to reduce the frequency of rehospitalizations, the Centers for Medicare and Medicaid Services (CMS) instituted their Hospital Readmissions Reduction Program (HRRP) in 2012, which financially penalizes providers who have excessive 30-day rehospitalization rates (see https://www.cms.gov/medicare/medicare-fee-for-service-payment/acuteinpatientpps/readmissions-reduction-program.html for more information). Therefore, development of interventions or criteria that can identify patients at higher risk of 30-day readmission is of critical importance, such that better interventions or more frequent monitoring strategies can be employed.

Small, et al., have developed a model for predicting HF readmission based on four CRT device-measured criteria on the day of an index HF-hospitalization discharge.[57] These parameters are based on the daily measurement of intrathoracic impedance (>8 Ω below the reference impedance), atrial fibrillation burden (>6 hrs of the past 24), night heart rate (>80 bpm), and CRT pacing percentage (<90% pacing). They reported that those patients who met one of these four criteria on the day of discharge were hospitalized within 30 days at a rate 2.4 times higher than those patients who met none of

these criteria (HR 2.4, 95% CI: 1.1-5.3). Further, those who met two or more criteria were hospitalized at a rate 4.4 times higher than those who met none of the criteria (HR 4.4, 95%CI: 1.6-12.0). This study suffers from the small number of events available(n=36), and the fact that other clinical covariates which may be associated with 30-day readmission were not included in the model. It further was composed of patients from four different clinical studies with differing inclusion and exclusion criteria, as well as case study files, potentially introducing selection bias in the cohort. Therefore, predictive models developed in larger samples that consider more extensive clinical information and use standardized definitions of clinical variables are needed.

We hypothesized that the 30-day HF-rehospitalization model developed by Small, et al., can be improved upon by the inclusion of one or more available clinical covariates as determined by significance testing, AUC (area under the curve) improvement, net reclassification improvement (NRI), or integrated discrimination improvement (IDI) methods.

5.3 Methods

5.3.1 Study Population

Patients who have an OptiVol®-enabled Medtronic CRT-D device implanted from January 2005 to April 2006 with at least one CareLink® transmission and at least one HF-related hospitalization event before Medicare follow-up ended in December 2011 were matched between the Medicare and CareLink® datasets. We excluded those

patients with any HMO/MCO coverage as indicated in the Medicare database since we are specifically looking at hospitalization risk, which may be significantly underestimated in these patients.

5.3.2 Endpoint Definition

A primary ICD-9-CM diagnosis code of 428.x within 30 days of an index hospitalization constituted a 30-day rehospitalization event. Per the CMS guidelines on rehospitalization, any heart failure-related hospitalization event during the follow-up period classified by a primary ICD-9-CM diagnosis code of 428.x for a given patient qualified as an index hospitalization if there were 30 days of device monitoring information available following discharge. Thus, a single patient may have several index hospitalization events, and further, any given rehospitalization event may also count as an index event for the next 30-day interval.

5.3.3 Exposure Definition

Data from the Medtronic CareLink® network from CRT-D devices implanted in the Jan 2005 to Apr 2006 timeframe were queried to determine the values of daily impedance, reference impedance, time in AT/AF, night heart rate, and percent bi-ventricular pacing on the day of discharge from an index hospitalization. The criteria of Small, et al., (daily impedance >8Ω below reference impedance, AF burden >6 hours, CRT pacing <90%, night heart rate >80 bpm) were then applied and coded as indicator

variables for use in modeling outcomes. As per Small's methodology, if device-measured data were missing for a specific diagnostic criterion on the day of discharge, it was considered that that diagnostic criterion was not met.

5.3.4 Covariates

We examined all the available variables in the Medicare ICD registry at the time of device implant, including patient sex, bundle-branch block (BBB) morphology, cardiomyopathy origin (ischemic Y/N), left-ventricular ejection fraction (LVEF), systolic blood pressure (SBP), diastolic blood pressure (DBP), diabetes mellitus, smoking status, chronic kidney disease (CKD), end-stage renal disease (ESRD), and the prescription of digoxin, beta-blockers, diuretic, ACE inhibitor, ARB, amiodarone, or warfarin.

Rather than use the baseline measures of patient age at implant, and duration of HF at implant, we also calculated patient age and duration of HF at the time of the index hospitalization and used those measures in the statistical analysis instead.

5.3.5 Statistical Analysis

For the purposes of directly comparing our model to the original model published by Small, et al., we first performed a proportional hazards regression using PROC PHREG in SAS v9.4 (Cary, NC) using the indicator variables of intrathoracic impedance, AF burden, CRT pacing percentage, and night heart rate based on the criteria set forth by Small, et al., to calculate hazard ratios of a 30-day readmission event for those patients

who met no criteria versus those who met one criterion, and those who met no criteria versus those who met two or more criteria.

To improve upon this model, we employed a Monte-Carlo (or bootstrap) approach of identifying predictors which were associated with a 30-day HF-rehospitalization event.[72] The method involves splitting our cohort into derivation and validation subsets. For the purposes of this analysis, we randomly selected two-thirds of our cohort to derive the model, and held the other third for subsequent validation of the model. We then used PROC MULTTEST in SAS v9.4 to generate 1,000 datasets with the same number of observations as the original dataset, randomly selecting patients for each dataset from our derivation cohort with replacement. As our main interest is specifically whether 30-day rehospitalization events occur, and not other time periods, we shifted our analysis to a logistic regression model using PROC LOGISTIC in SAS using stepwise backwards selection on each of these 1,000 datasets using a p-value threshold of 0.05 to remain in the model. We initially forced the backwards selection process to include the four original indicator variables from the Small model, so that we could compare any potential model improvement directly with that model. Any variable selected in more than 60% of the 1,000 model iterations was then included in our final model. We then removed any remaining non-significant variables from the model, and the final list of parameters was then applied to the remaining validation portion of our cohort.

We formally evaluated improvement to the Small model by examining the change in AUC, NRI, and IDI described by Pencina, et al.[73,74] Reliance on statistics such as

AUC often requires new predictive variables to have enormous effect sizes to provide improvement of the model.[75,76] However, by also examining NRI and IDI measures, they offer insight into the percentage improvement of correctly classifying those patients with events by including another predictor, as well as the changes in sensitivity with the new predictor, given a fixed specificity. To avoid the dilemma of defining meaningful risk categories for NRI calculation, a category-free, or continuous NRI method was employed to calculate NRI, and any change upward or downward in probability of a rehospitalization event for a given patient between models was counted as such.[74] Model calibration was assessed through the Hosmer-Lemeshow χ^2 statistic.

5.4 Results

A total of 607 index hospitalizations were observed in our cohort of 1,563 patients from Manuscript 1 over a mean follow up of 6.3 years (297 patients experienced a single index hospitalization, 69 experienced two, and 45 more than 2). Another hospitalization event occurred within 30 days after 17.6% of index hospitalizations (107 30-day rehospitalizations/607 index hospitalizations). Patient characteristics of those events with and without 30-day rehospitalizations are shown in Table 11. Those who did not experience a HF-related hospitalization event differed from those who did in that they were younger, had HF for a shorter duration before implant, lower LVEF, lower SBP and DBP, less likely to be diagnosed with CKD at baseline, more likely to be prescribed digoxin, warfarin, and diuretics, and also had a different distribution of NYHA class at

baseline. These observed differences in these parameters were all formally tested for statistical significance in the modelling process, described above.

Comparison to Proportional Hazards Model of Small, et al.

A Kaplan-Meier plot of the present analysis based on the model published by Small, et al., containing only the four device-measured criteria is shown in Figure 17. The results from the proportional hazards regression indicated that those patients who met one criterion had a rehospitalization rate 1.7 times higher than those who met none of the four device-measured criteria in the model (HR: 1.7, 95%CI: 1.1-2.7). Further, those who met two or more criteria had a rehospitalization rate 1.8 times higher than those who met no criteria (HR: 1.8, 95%CI: 1.1-2.9). However, there was no significant difference between those who met a single criterion versus those who met two or more (HR 1.0, 95%CI: 0.6-1.7). Hazard ratios of the individual criteria from the Small model were also calculated and compared with the associations observed in the present study, as shown in Table 12. Only the impedance criterion was found to be statistically significant in our cohort (HR 3.3, 95% CI: 2.0-5.8).

Improvement of Small, et al., Model via Inclusion of Clinical Covariates in Logistic Regression Model Setting

The results of our model-building process are summarized in Table 13. Our derivation cohort (n=418) was run through the bootstrap parameter selection process,

where the parameters of diuretic prescription (selected in 91.3% of bootstrap models), diagnosis of CKD (89.5%), NYHA HF class (82.8%), patient sex (77.2%), prior coronary artery bypass graft (CABG) procedure (68.7%), and duration of HF at the time of the index hospitalization (62.9%) were stepwise backwards-selected by more than 60% of the bootstrap model datasets for inclusion into the model. Parameters selected in less than 60% of the bootstrap model datasets did not reach standard statistical significance criteria in either the derivation cohort, and we therefore stopped including parameters below the 60% cutoff. We also included the original four device-measured indicator variables in the model for a direct comparison with the Small model. It should be noted that only the impedance criterion of the original four device-measured variables was found to be statistically significant in this analysis. We then applied the bootstrap-selected set of parameters to our validation cohort (n=189). However, in the validation cohort, the only additional clinical variables which were statistically significant were CKD diagnosis and duration of HF at the time of the index hospitalization, and diuretic prescription, patient sex, NYHA class, and prior CABG procedure were no longer significant.

Model calibration was evaluated via the Hosmer-Lemeshow χ^2 statistic. None of the models showed significant lack of fit, with χ^2 values ranging from 0.89 to 11.96 depending on the exact cohort and model parameters in question. Figure 18 shows the Hosmer-Lemeshow plot of expected probabilities of failure versus observed for the bootstrap-selected model based on the validation cohort, as well as the full cohort.

Also shown in Table 13, the calculated AUC for the logistic model in the validation cohort (n=189) including only the heart rate, daily impedance, AF burden, ventricular pacing, and night heart rate indicator variable criteria – the *de facto* Small, et al., model – was 0.61 (95%CI: 0.51, 0.71). Including baseline diuretic prescription, CKD diagnosis, patient sex, CABG procedure prior to device implant, NYHA class, and duration of HF at the time of the index hospitalization in this same cohort (n=189) increased the AUC metric to between 0.73 and 0.76, depending on the analysis done, and the exact variable set included. This improvement in AUC was significant across all the various models and sets of parameters examined.

Further, the net reclassification improvement (NRI) was 0.76 (95%CI: 0.41-1.10) when comparing the model with the full bootstrap-selected set of parameters to the initial four device-measured criteria model used by Small, et al, with 31% of 30-day rehospitalizations being correctly reclassified from non-events to events, and 44% of non-events being correctly reclassified as non-events from events. The absolute integrated discrimination improvement (IDI) was 0.129(95% CI: 0.066-0.193), and the relative IDI was 2.24. Removal of parameters which were not statistically significant reduced the AUC to 0.73 (95%CI: 0.63-0.83).

We then categorized patients in our full cohort (n=607) into tertiles of risk, based on the predicted probability of a HF-related hospitalization within 30 days as predicted by the reduced bootstrap logistic regression model (low risk < 9.1%, average risk=9.1-18.2%, and high risk >18.2%). A Kaplan-Meier plot showing the survival of the three

risk categories is shown in Figure 19. All pairwise log-rank comparisons between risk categories (Low vs. Average, Low vs. High, Average vs. High) were statistically significant (p-values = 0.0003, <0.0001, and <0.0001, respectively).

5.5 Discussion

Our proportion of HF-hospitalization events (607 total HF-hospitalizations/1,563 patients) was higher than that of Small, et al., (265 total HF-hospitalizations/1,562 patients) even though our initial cohort is nearly identical in size. We believe this is due to the long-term follow-up of our sample. Even though the hospitalization rate we observed was lower than in the study by Small, et al., (the HF-hospitalization rate in the present study was 0.062 HF-hospitalizations per person-year, while Small observed an event rate of approximately 0.166 HF-hospitalizations per person-year), the average follow-up of the Small study was just over one year, while the present study is 6.3 years, allowing for more hospitalizations to occur during follow-up. The proportions of observed 30-day rehospitalizations between our study (17.6%) and theirs (16.6%) were not significantly different (p-value=0.74).

As shown in Figure 17, our model was similar to the previously published model in that if any single criterion of the model was met, it was associated with an increased rehospitalization risk, but that any additional criteria which were met did not significantly increase risk further. Of the four device-measured criteria, the most influential one was the impedance criterion.

The addition of the clinical covariates improved the predictive performance of our model significantly, as indicated not only by observed increases in AUC, but also in NRI and absolute and relative IDI measures. While dependent on the actual AUC value, literature suggests that values of NRI greater than 0.60 indicate strong model improvement from the addition of these new variables.[77,78] Further, our absolute IDI value shows that we increased the difference between average predicted probabilities for events and non-events by 12.9%. Putting this on a relative scale, the observed relative IDI value indicates that we increased this difference in mean predicted probabilities of events and non-events by 224%, a large improvement. Given the smaller sample size in our validation cohort, it is not surprising that some variables lost significance; rather, examining the AUC between the derivation and validation cohorts (0.78 and 0.76, respectively) indicates that the model in our validation cohort was still strong in predicting outcomes relative to the derivation cohort. Further, our Hosmer-Lemeshow statistics for the derivation and validation cohorts were 9.65 (p-value=0.29) and 11.96 (p-value=0.15), respectively, indicating no gross lack-of-fit.

Reducing the model further in our validation cohort by removing parameters which were not statistically significant resulted in a non-significant reduction in AUC (p-value=0.26). However, reductions in both NRI and IDI measures comparing the reduced model to the full bootstrap model in the validation cohort indicated significant reductions in model discrimination, and we therefore left all of the terms selected in by the bootstrap process in the derivation sample in the model.

The most robust measures from model to model that predicted 30-day HF-related rehospitalization were associated with kidney function, namely: the prescription of a diuretic, intrathoracic impedance criterion (daily impedance more than 8Ω below the reference impedance), and diagnosis of CKD, indicating the critical role that kidney function plays in the rehospitalization risk of heart failure patients. These factors show the potential to develop monitoring or interventional strategies guided by these factors to reduce 30-day rehospitalizations in CRT patients.

While the addition of baseline clinical measures significantly improved the previous model, it should be noted that these variables were qualitative in nature, and were not updated over the follow-up period. Specifically, we do not know diuretic dosage, for example, or if a patient was still prescribed a diuretic at the time of discharge from the index hospitalization. We further lacked quantitative measures of kidney function, such as serum creatinine, glomerular filtration rate (GFR), and blood urea nitrogen (BUN), which may provide additional criteria or risk stratification refinement or a basis upon which to develop interventions. Further study is warranted to determine whether the device-measured intrathoracic impedance criterion provides incremental predictive value over and above these other quantitative measures of kidney function.

We did not consider patient death to be a competing risk in this analysis, as the 30-day time frame for patient mortality to compete with an index hospitalization is very short, and is not expected to meaningfully affect observed associations since the observed mortality rate in our initial cohort is 0.007 deaths per month (705 deaths/ 96,432 person-

months). We also did not reevaluate the threshold value for meeting the impedance criterion at hospital discharge (daily impedance value >8Ω below reference impedance), as we desired a direct comparison with previous literature.

In addition, our treatment of multiple hospitalizations from a patient did not consider that each index event might be correlated with prior index hospitalization. That is, the probability of a rehospitalization within a 30-day interval might depend on prior hospitalizations a patient experienced. Future work in this area could calculate NRI and IDI accounting for the within-patient correlation of hospitalization, and determine 95% confidence intervals via a bootstrap methodology.

In summary, we have derived a model based on device-measured and clinical parameters on the day of discharge for a HF-related hospitalization which predicts risk of rehospitalization within 30 days. We have shown this model to be an improvement over an existing model, with better discrimination between events and non-events. Several variables in the model were related to kidney function, indicating the critical nature of maintaining kidney function in preventing rehospitalization of heart failure patients.

5.6 Tables and Figures

Table 11. – Demographic and Clinical Characteristics of Medicare Registry CRT-D Patients with and without 30-day Readmission

	All Hospitalizations (n=607)	Hospitalizations without 30-Day Readmission (n=500)	Hospitalizations with 30-Day Readmission (n=107)	p-value*
Age, mean ±SD, y	74.0±8.1	73.6±7.9	75.8±8.4	0.01
Duration HF, mean ±SD, months	30.5±29.7	29.2±29.0	36.5±32.2	0.02
LVEF, mean ±SD, %	23.1±6.4	22.7±6.5	25.1±5.9	<0.01
QRS duration, mean ±SD, ms	156.1±23.6	155.9±23.9	156.7±22.6	0.75
SBP, mean ±SD, mm Hg	124.8±22.4	123.9±21.9	129.0±24.4	0.03
DBP, mean ±SD, mm Hg	69.8±12.4	69.3±12.1	72.0±13.8	0.04
Heart rate, mean ±SD, bpm	70.9±13.7	71.3±14.0	68.9±11.8	0.07
Sex, n(%)				
Female	28.0	27.0	33.7	0.23
Male	72.0	73.0	67.3	
NYHA class, (%)				
I	1.7	1.2	3.7	
II	11.0	10.2	15.0	
III	72.5	72.0	74.8	0.01
IV	14.8	16.6	6.5	
Ischemic CM, (%)	65.7	65.4	67.3	0.71
Prior CABG, (%)	45.3	44.4	49.5	0.33
BBB Morphology, (%)				
LBBB	71.7	70.2	78.5	
RBBB	9.9	9.8	10.3	0.10
Other IVCD	18.5	20.0	11.2	
Atrial fibrillation, (%)	37.4	36.4	42.1	0.27
Ventricular tachycardia, (%)	18.3	18.4	17.8	0.88
Sudden cardiac arrest, (%)	2.0	2.0	1.9	0.93
Diabetes mellitus, (%)	39.5	39.6	39.3	0.95
Prior MI, (%)	48.1	46.4	56.1	0.07
Chronic Kidney Disease, (%)	45.3	42.0	60.8	<0.01
End-Stage Renal Disease, (%)	1.5	1.4	1.9	0.74
Smoker Status, (%)				
Never	42.3	42.0	43.9	
Former	49.1	48.8	50.5	0.48
Current	8.6	9.2	5.6	
Medications, (%)				
b-blocker	78.9	78.2	82.2	0.36
ACEI or ARB	74.1	75.2	69.2	0.20
Digoxin	40.5	42.6	30.8	0.02
Diuretic	82.4	84.8	71.0	<0.01
Amiodarone	11.7	12.4	8.4	0.20
Warfarin	32.3	34.4	22.4	0.01

Figure 17. – Survival Free from HF-Hospitalization after Index HF Hospitalization by Number of Device-Measured Criteria Met on Day of Discharge

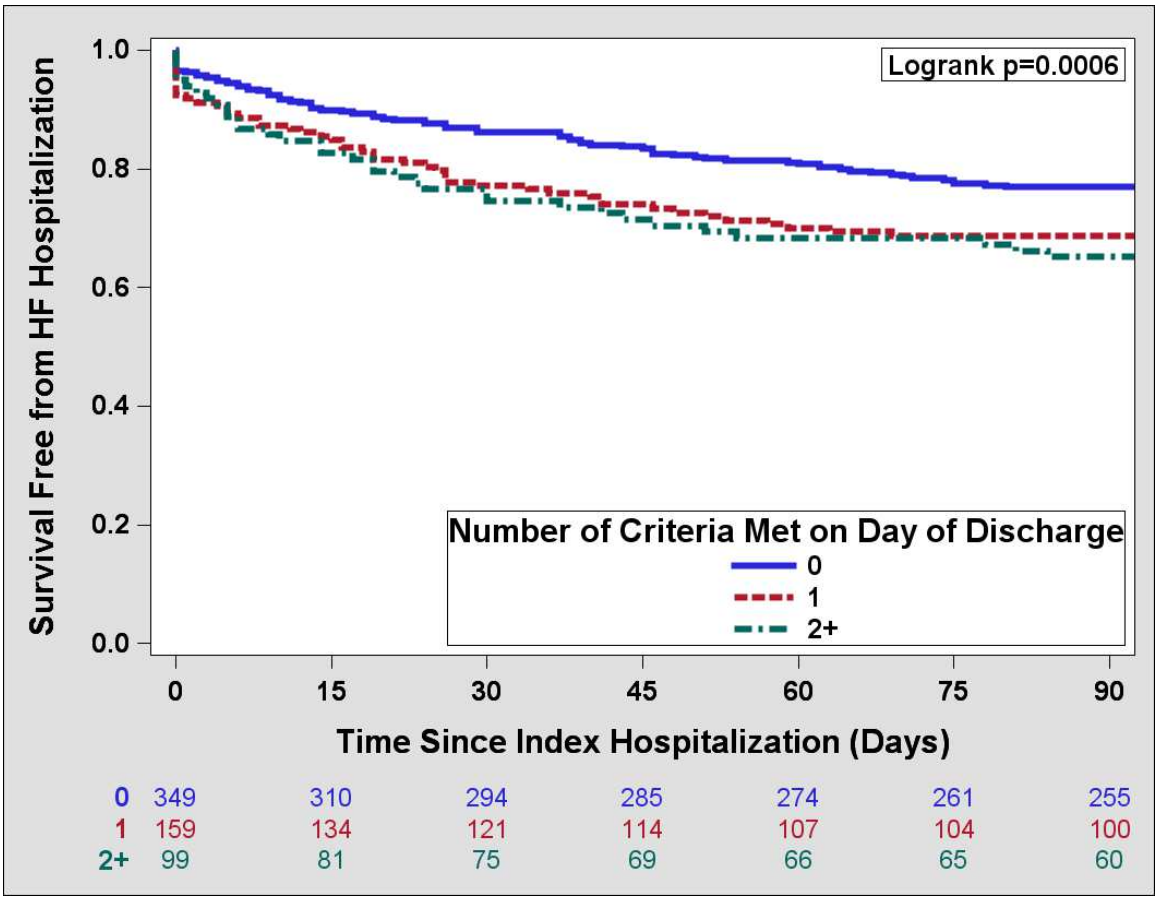


Table 12. – Hazard Ratios for Rates of 30-day Rehospitalization from Proportional Hazards Regression Modeling

	Small, et al. Reported[57] Cohort, n=265		*CareLink®- Medicare Cohort, n=607*	
	Proportion Meeting Criterion, n(%)	Hazard Ratios (95% CI)	Proportion Meeting Criterion, n(%)	Hazard Ratios (95%CI)
Model Variables				
Reference Impedance - Daily Impedance > 8Ω	7 (28%)	**2.6 (1.2,5.6)**	38 (6.3%)	**3.3 (2.0,5.8)**
AF Burden > 6h	9 (20.5%)	1.7(0.6,5.1)	103 (17.0%)	0.9 (0.5,1.6)
CRT Pacing < 90%	14 (28.6%)	**3.1 (1.4,6.8)**	120 (19.8%)	1.2 (0.7,2.0)
Night Heart Rate > 80 bpm	12 (17.1%)	1.4 (0.7,2.7)	109 (18.0%)	1.1 (0.6,1.7)

Table 13. – Odds Ratios and Model Performance Metrics for Probability of 30-day Rehospitalization from Logistic Regression Modeling

	Derivation Sample (n=418)	*Small, et al. Model, Validation Sample (n=189)*	*Bootstrap Model, Validation Sample (n=189)*	*Reduced Bootstrap Model, Validation Sample (n=189)*	*Small, et al. Model, Full Cohort (n=607)*	*Bootstrap Model, Full Cohort (n=607)*
Model Variables						
Reference Impedance - Daily Impedance > 8Ω	**4.37 (1.59,11.97)**	**5.10 (1.64,15.86)**	**5.34 (1.54,18.50)**	**4.10 (1.41,11.96)**	**4.06 (2.03,8.11)**	**4.27 (2.01,9.04)**
AF Burden > 6h	1.10 (0.46,2.61)	1.24 (0.40,3.84)	0.84 (0.24,2.98)	n/a	0.90 (0.47,1.72)	1.08 (0.54,2.16)
CRT Pacing < 90%	1.43 (0.68,3.00)	0.63 (0.20,2.02)	0.65 (0.19,2.20)	n/a	1.26 (0.71,2.25)	1.16 (0.63,2.15)
Night Heart Rate > 80 bpm	1.55 (0.76,3.18)	1.21 (0.42,3.51)	1.27 (0.40,4.03)	n/a	1.15 (0.66,1.98)	1.38 (0.76,2.50)
Diuretic (Y/N)	**0.30 (0.15,0.60)**	n/a	0.50 (0.18,1.43)	n/a	n/a	**0.34 (0.20,0.60)**
Patient Sex (M/F)	**3.82 (1.94,7.51)**	n/a	0.81 (0.30,2.17)	n/a	n/a	**2.35 (1.37,4.01)**
Chronic Kidney Disease (Y/N)	**2.89 (1.59,5.26)**	n/a	**2.35 (1.02,5.42)**	**2.27 (1.02,5.08)**	n/a	**2.63 (1.63,4.24)**
NYHA Class						
I	Ref.		Ref.			Ref.
II	0.28 (0.04,1.81)	n/a	1.94 (0.11,34.98)	n/a	n/a	0.52 (0.12, 2.30)
III	0.24 (0.04,1.35)		1.39 (0.09,20.75)			0.47 (0.12,1.86)
IV	0.08 (0.01,0.54)		0.61 (0.03,12.78)			0.17 (0.04,0.79)
Duration of HF at Index Hospitalization (years)	**1.12 (1.02,1.23)**	n/a	**1.27 (1.10,1.46)**	**1.26 (1.10,1.44)**	n/a	**1.16 (1.07, 1.24)**
Prior CABG Procedure	**1.89 (1.03,3.48)**	n/a	1.61 (0.68,3.82)	n/a	n/a	**1.64 (1.01,2.64)**
Discrimination						
AUC	0.78 (0.72,0.83)	0.61 (0.51,0.71)	0.76 (0.66,0.86)	0.73 (0.63,0.83)	0.59 (0.53,0.65)	0.77 (0.72,0.81)
NRI	n/a	n/a	0.76 (0.41,1.10)†	-0.39 (-0.74,-0.04)‡	n/a	0.69 (0.50,0.89)†
Absolute IDI	n/a	n/a	0.129 (0.066,0.193)†	-0.043 (-0.074,-0.0125)‡	n/a	0.097 (0.071,0.124)†
Relative IDI	n/a	n/a	2.24†	-0.23‡	n/a	2.78
Calibration						
Hosmer-Lemeshow χ^2 (p-value)	9.65 (0.29)	0.89 (0.93)	11.96 (0.15)	4.60 (0.80)	2.12 (0.98)	9.33 (0.32)

*Equation from the bootstrap model in the derivation cohort is given by:

$$\begin{aligned} ln\ \text{odds(30-day Rehospitalization=1)} = &-2.55 + 1.47 * [\text{Impedance Criterion} = 1] + 0.09 * [\text{AF Criterion} = 1] + 0.35 * [\text{Pacing Criteron} = 1] + 0.44 * [\text{HR Criterion} = 1] \\ &- 1.20 * [\text{Diuretic=1}] + 0.04 * [\text{NYHA class} = 2] - 0.11 * [\text{NYHA class} = 3] - 1.25 * [\text{NYHA class} = 4] + 1.06 * [CKD = 1] \\ &+ 1.34 * [\text{Male sex}] + 0.01 * [\text{Duration of HF at index hospitalization(months)}] + 0.64 * [\text{Prior CABG} = 1] \end{aligned}$$

†Comparing Bootstrap model to Small, et al., model.

‡Comparing Reduced Bootstrap Model to Bootstrap Model

Figure 18. – Hosmer-Lemeshow Calibration Plot of Small Model, Bootstrap Model, and Reduced Bootstrap Model

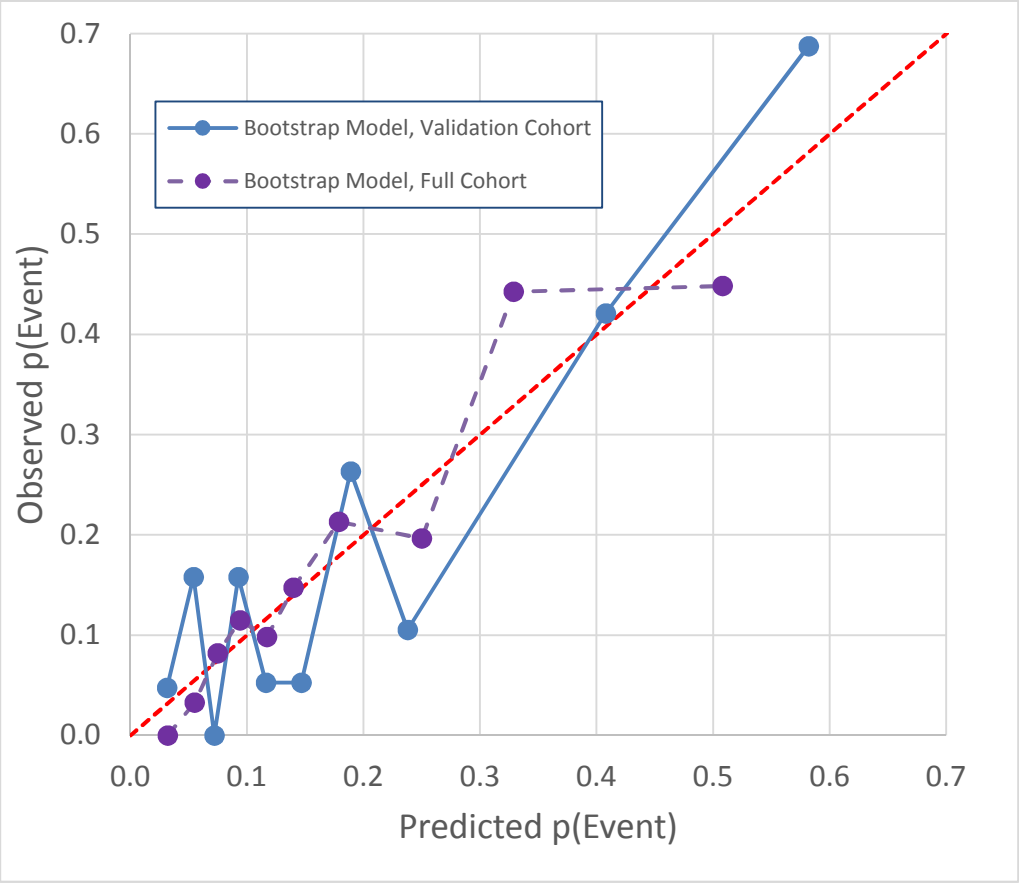
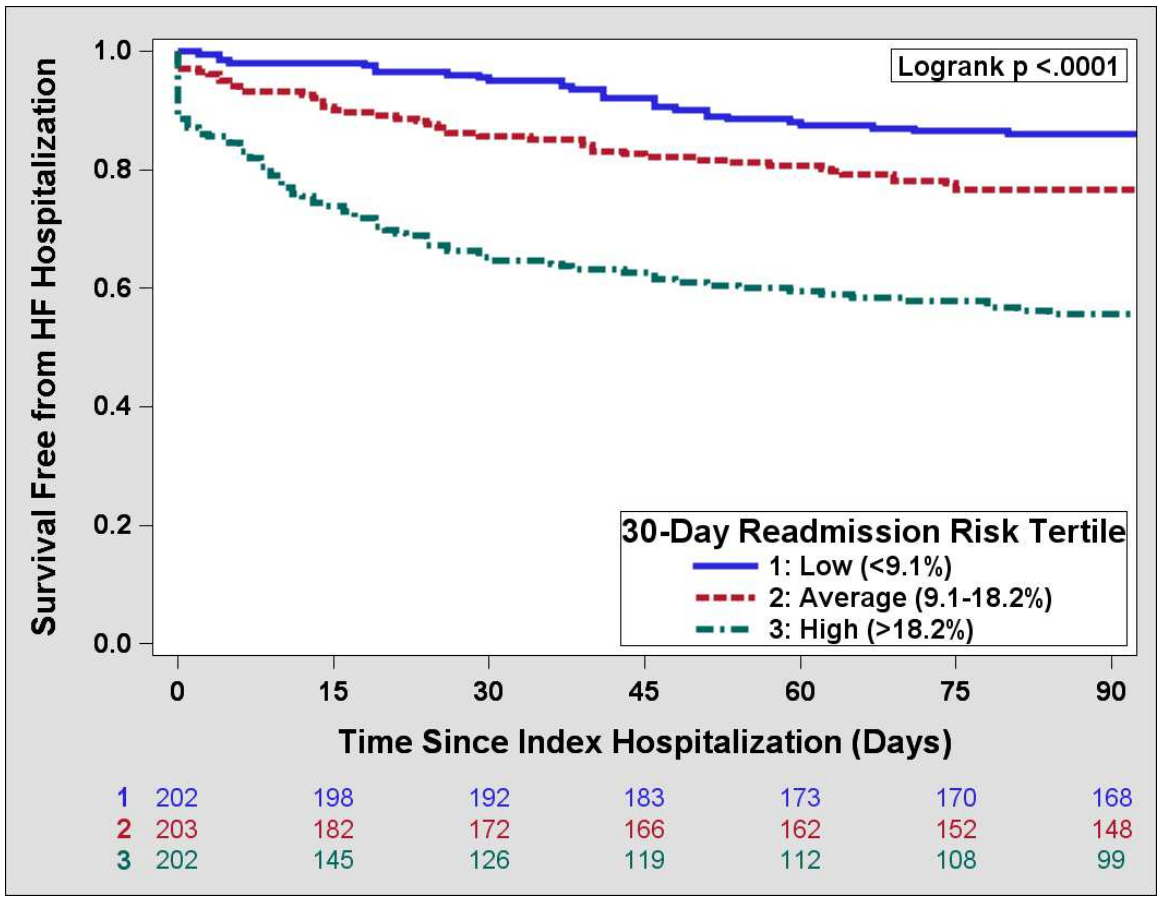


Figure 19. – Kaplan-Meier Plot of 30-Day HF-Rehospitalization Risk based on Tertile of Reduced Bootstrap Model-Predicted Risk



6 Summary

The objectives in this dissertation were to examine associations between OptiVol® threshold crossings, bi-ventricular pacing percentage, heart rate variability, AF burden and overall patient mortality and HF-related hospitalization in a population of Medicare patients with over 6 years of follow-up. Additionally, we sought to improve risk stratification models for HF-related rehospitalizations within 30-days, which are penalized by the Centers for Medicare and Medicaid Services.

The first manuscript sought to determine associations between OptiVol® threshold crossings and overall patient mortality and HF-related hospitalizations. Patients with >15.1% of days above OptiVol® threshold (highest quartile) had a more than 4-fold increase in all-cause mortality rate and a more than 3-fold increase in HF-related hospitalization rate compared with patients having <4.1% of days above threshold (lowest quartile). In addition, a single OptiVol® crossing was associated with significantly increased rates of both mortality and HF-related hospitalization.

In manuscript 2, we explored the complex relationship between bi-ventricular pacing, atrial fibrillation, and heart rate variability and overall patient mortality and HF-related hospitalization in CRT-D patients. Our main finding was that high levels of bi-ventricular pacing and higher heart rate variability were associated with both lower rates of patient mortality as well as hospitalization. However, we also found a complex interaction between AF burden and bi-V pacing, as well as a patient's AVN ablation status, suggesting that a patient may lose the protective effect of high HRV after an

ablation, and that patients with AF also do not benefit from high levels of bi-ventricular pacing. This is complicated further by the fact that some device-measured information is either not available, or not meaningful in patients with persistent or permanent AF.

Manuscript 3 sought to stratify risk of HF-related rehospitalization within 30 days of a prior HF-related hospitalization. We examined the applicability of a prior risk-stratification model to our cohort of CRT patients with Medicare coverage, and further examined whether baseline patient demographic and clinical characteristics would improve the prediction of 30-day rehospitalization risk. We found variables associated with kidney function to be of key importance in predicting 30-day HF-rehospitalization, in addition to other covariates.

In this thesis we have, for the first time, combined device-measured data via Medtronic's CareLink® network with registry data for Medicare beneficiaries. This unique linkage has allowed us to create a large cohort of CRT-D patients with a long follow-up period to examine three clinically important questions on the management of heart failure patients implanted with CRT devices: 1.) management of patients based on intrathoracic impedance findings, 2.) understanding and management of patients based on atrial fibrillation and AVN ablation status, and 3.) identifying patients at high risk of 30-day rehospitalization on the day of discharge through device-measured and baseline clinical variables. We were restricted, however, to the use of Medicare administrative claims data, and only have clinical information at the time of device implant, with no further information on time-dependent clinical covariates.

This thesis has provided insight into how device-measured data can be added to in-person clinical evaluation to better treat heart failure patients implanted with a CRT device. We propose that specific intervention strategies be developed and evaluated based on the measures identified here for the future benefit of patients.

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