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The Morbidity & Mortality of Prevalent Heart Failure

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THE MORBIDITY & MORTALITY OF PREVALENT HEART FAILURE

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Each person whose signature appears below certifies that this dissertation, in his/her opinion, is adequate in the quality as a dissertation for the degree Doctor of Public Health.

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ABSTRACT

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The first study population included 292 unselected consecutive patients from the LLUMC heart failure clinic who were enrolled in the study from January to July 2006 and were followed up through the end of December 2010. The treatment policy at the clinic was to uptitrate dosages of beta-adrenergic blockade (β-blockers), angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) to the most tolerable levels in order to reach target dosages, as recommended by the Heart Failure Society of America (HFSA). Patients were classified into systolic heart failure (ejection fraction (EF) <40%) or diastolic heart failure (EF≥40%). All dosages of β-blockers, ACEi and ARB were extracted through chart reviews and were used as the main predictors of the patients' survival. Results from analyses showed that reaching target dosages of β-blockers and ACEi/ARB may increase survival when compared to not reaching target among the systolic HF population ($HR_{\beta\text{-blockers}}$= 0.64, 95% CI 0.26-1.56 and $HR_{ACEi/ARB}$=0.50, 95% CI 0.22-1.14). Similarly, the HR of 0.48 (95% CI 0.13-1.81) for β-blocker therapy and HR of 0.21 (95% CI 0.04-1.07) for ACEi/ARB therapy

suggests improvements in survival with these drug regiments among the diastolic HF population. Unfortunately, the study lacked power to make the observations statistically significant. A larger sample size is needed to adequately address the possible benefits of these drugs for heart failure patients.

The second study is comprised of a random, representative sample of 200 cases of self-reported congestive health failure (CHF) and 260 non-cases from the Adventist Health Study-2 (AHS-2). A total of 67 cases and 147 non-cases were successfully contacted or contacted through proxy and their consents were obtained for medical record review. Consenting participants' medical records were retrieved and examined for the validity of self-reported heart failure. The sensitivity of self-reported CHF was calculated as 97.4% and the specificity was 83.4%. The positive predictive value was 56.7% and the negative predictive value was 99.3 %. Total agreement (accuracy) between presence of self-reported heart failure and obtained physician-diagnosed heart failure from medical records was 86.0%. Further study with a larger sample is necessary to obtain reliable measures of validity of self-reported CHF in this population.

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CHAPTER 1

INTRODUCTION

The significance of heart failure in the realm of health care is substantial due to its high prevalence and incidence. The subsequent excessive rates of heart failure-related hospitalizations and its poor prognosis is a great public health concern. Continued research is essential in order to find effective treatment for patients with heart failure and more importantly, to work towards effective prevention.

Randomized clinical trials have shown that drug therapies at recommended dosages significantly improve heart failure survival, but application of the recommended dosages in clinical practice has not been extensively studied.

Large epidemiological studies are fundamental in investigating preventative measures of heart failure. And with heart failure data collected from large cohorts, it is important to estimate the validation of self-reported heart failure in order to ensure reliability when using such self-reported health outcomes in analysis.

Aims

This dissertation has two main aims:

1. To analyze the association between drug therapies and the survival of an out-patient population at the heart failure clinic in Loma Linda University Medical Center.
2. To validate self-reported, physician-diagnosed congestive heart failure among the Adventist Health Study-2 population.

CHAPTER 2

LITERATURE REVIEW

A. Pathology

Heart failure (HF) is a chronic condition where the body is unable to receive adequate oxygen and nutrients because of the inadequate pumping of the heart due to ventricular dysfunction. The American College of Cardiology/American Heart Association (ACC/AHA) Task Force guidelines define chronic HF as a complex clinical syndrome, a result of cardiac dysfunction that impairs the ability of the ventricle to fill and eject blood.[1] It is initiated by injury or stress on the myocardium, but it is a progressive disease that manifests after multiple complications have further damaged or weakened the heart, such as other cardiovascular diseases or even alcohol abuse.

Heart failure can be classified into left-sided and right-sided heart failure. Right-sided heart failure refers to systemic congestion and left heart failure refers to congestion of the pulmonary veins. As the right ventricle fails to effectively pump the deoxygenated blood into the left side of the heart, the blood starts backing up in the body's veins. This leads to the collection of fluid in the lower extremities and eventually in the abdomen. The weight gain that accompanies the fluid retention can be used to measure the amount of fluid congestion. With left-sided heart failure, the left ventricle is unable to pump the newly oxygenated blood out to the body and the lungs become congested with blood as a result. Right-sided heart failure will often occur as a result of left-sided heart failure.

Left-sided heart failure can be further differentiated into systolic and diastolic heart failure. Systolic heart failure is characterized by the dysfunction of the left ventricle. A clinical measurement of the left ventricular pumping capacity is the ejection fraction (EF), a calculation of the proportion of the blood in the ventricle that is ejected with each contraction of the left ventricle.

An EF of <40% is typically used to diagnose systolic heart failure. In heart failure with preserved ejection fraction, or diastolic heart failure, the heart may contract normally, but the left ventricle is unable to fill fully because it is stiff, therefore less compliant to relax. This malfunction impedes the blood flow into the heart from the lungs and produces backup in the lungs.

1. Remodeling & reverse remodeling

A major clinical marker of progressive heart failure is changes to the heart on the cellular and molecular level. The changes that result in modification of the heart size, shape and function define cardiac remodeling.[2] Cardiac remodeling can also occur after myocardial infarction, inflammatory heart muscle disease and other etiologies.

The pathogenic mechanisms that lead to cardiac remodeling are unclear, but the stress induced on the myocardial wall from persistent ventricular dilation may stimulate the pathogenesis toward remodeling. The pathophysiologic changes in response to cardiac injury include oxygen free radical formation which causes oxidative stress. Increased levels of norepinephrine and continued activation of neurohormonal systems lead to excessive vasoconstriction, volume expansion and left ventricular remodeling. On a cellular level, myocyte hypertrophy, necrosis, apoptosis, fibrosis, increased fibrillar

collagen, proliferation of fibroblast and the increased circulation of angiotensin II are involved. The usually elliptical-shaped heart becomes more spherical as the remodeling progresses, with increases in ventricular mass, composition and volume.

The presence of major remodeling in heart failure patients is an indicator of poor prognosis. The morphological change, initiated as a compensatory process, eventually impedes the function of the heart and further becomes a maladaptive one. Changes in the heart's size and shape can be measured to detect remodeling using several methods. Measuring wall thickness or myocardial mass can give clues to changes in overall cardiac structure. Left ventricular volume, ejection fraction, linear dimensions and functional shortening can be measured to assess the extent of cardiac remodeling.

Reverse remodeling is a terminology used to describe the process in which the heart is restoring back to its original state in function and structure. Clinical trials have shown that reverse remodeling may be possible through certain drug therapies and this will be discussed later. Improvements in ejection fraction read from echocardiograms (echo) can detect presence of reverse remodeling.[3]

B. Classifications

The degree of heart failure progression can be classified in several different ways. The most commonly used classification is the New York Heart Association (NYHA) Functional Classification. The NYHA classifications are based on symptoms in relation to physical activity. For example, there is no symptom limitation with ordinary physical activity in NYHA Class I while Class IV indicates dyspnea at rest or with very little exertion. Another HF classification system that is used is the American College of Cardiology (ACC) and American Heart Association's stages A through D. Stage A

denotes an absence of functional or structural heart disorder whereas Stage D indicates advanced disease.[3]

C. Diagnosis

The criteria for heart failure diagnosis have historically been ambiguous because of its varying definitions, which may have further led to heart failure being either misdiagnosed or even overlooked in clinical settings. The clinical manifestations among HF patients include multiple symptoms such as dyspnea when lying down or active, persistent coughing or wheezing, edema in the lower extremities, fatigue, decreased appetite, nausea, impaired thinking and increased heart rate. The ACC/AHA task force asserts that heart failure is a symptomatic disorder.[3] Initial assessment of patients with HF usually involves difficulty with exercise tolerance due to dyspnea or fatigue, fluid retention in their abdomen or legs, or the presence of another disorder, cardiac or otherwise.

There is no one specific test for the diagnosis of heart failure, but there are several tools used for a clinical diagnosis. A stress test on a treadmill may be used while measuring the blood oxygen saturation or more invasive hemodynamic measurements may also be used to isolate the cause for decreased exercise tolerance. Chest X-ray can be used to detect buildup of fluid in the lungs or see any enlargements of the heart. Electrocardiogram (ECG) results may be normal in HF, but can identify rhythm disorders or other heart problems that are usually antecedent to heart failure. Levels of sodium, potassium and other electrolytes can be measured to detect kidney disease, a major risk factor for heart failure. Multiple-gated acquisition scanning (MUGA) can be

done to assess the pumping performance of the ventricles by tracking the path of the radioactive dye through the heart.

Elevated levels of cardiac hormones can be used to diagnose HF because of the disease's activation of the endocrine systems. The stretching of the ventricular wall, due to volume and pressure overload, triggers the cardiac hormone system. Injury to the heart increases the synthesis of atrial natriuretic peptide (ANP) and B-type natriuretic peptide BNP and its release from atrial and ventricular myocardium.[4] Cardiac troponin in the serum may also be indicative of cardiac injury.[5] Patients can be tested for elevated plasma concentrations of ANP, BNP and cardiac troponins and their pro-hormones. However, age and gender must be taken into consideration in combination with hormone levels for a heart failure diagnosis to be determined due to the nondiscriminatory outcome of cardiac hormone changes.

Echocardiograms are most useful to look at various cardiac structures to determine whether there are abnormalities of the myocardium, heart valves, or pericardium. Ejection fraction, ventricular dimension, volume, wall thickness, chamber geometry and regional wall motion are measured in echos. Left ventricular ejection fraction (LVEF) is used to differentiate between diastolic or systolic heart failure diagnoses.

D. Treatment

Treatments for heart failure range from lifestyle adjustments to drug therapy. Heart failure patients are often advised to take on lifestyle changes including reduction in sodium intake, smoking cessation and if necessary, weight loss. Diuretics are prescribed to treat water retention. Effective drug therapies include beta-adrenergic

blockade (β-blocker), angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB). The dosages of drug treatment for HF have not been standardized until recently. The Heart Failure Society of America (HFSA) published new guidelines in 2010 that recommended initial and target doses of β-blockers, ACEi and ARB to improve HF prognosis. The recommended target dosages are based on successful outcomes of clinical trials and compliance of the recommended target dosages that may enhance overall survival.

1. Clinical trials

Numerous clinical trials have established that β-blockers increase survival and improve prognosis of patients with HF. The MOCHA (multicenter oral carvedilol heart failure assessment) study found that subjects treated with carvedilol, a β-blocker, experienced a reduction in all-cause mortality risk by 73% ($p<.001$) and a decrease in hospitalization rate from 64% to 58% ($p=0.10$) compared to patients in the control group.[6] Another clinic trial of carvedilol found that there was a 65% attributable risk reduction in mortality with β-blocker usage ($p<.001$).[7] It also found that carvedilol therapy was associated with a 27% risk reduction in cardiovascular-related hospitalizations (19.6 % vs. 14.1%, $p=0.036$) when compared with placebo. The Cardiac Insufficiency Bisoprolol Study (CIBIS), a European, multicenter double-blind, randomized placebo-controlled trial, was stopped early because bisoprolol significantly lowered all-cause mortality (HR=0.66, 95% CI 0.54-0.81).[8] Very recent results from the HF-ACTION (Heart Failure: A controlled Trial Investigating Outcomes of Exercise Training) trial demonstrated that there was an inverse relationship between β-blockers

and all-cause mortality among systolic HF patients receiving up to 50mg of β-blockers per day.[9]

Studies have shown that reverse remodeling may also be achieved through β-blocker therapy. A clinical study of 142 HF patients found that left ventricular ejection fraction independently predicted survival among its study cohort.[10] It found that LVEF improved from 30% ± 11% to 40% ± 13% after β-blocker treatment. Even after accounting for β-blocker treatment, a positive change in LVEF independently improved survival. Negative change in EF and having lower EF at baseline predicted a lower survival rate. The MOCHA study also found a positive dose-response association between stratified levels of carvedilol and EF units ($p<.001$).[6]

ACEis are prescribed to heart failure patients because it improves haemodynamics by reducing the activity of the sympathetic nervous system and improving β receptor densities. They decrease the degradation of the vasodilator bradykinin, thereby increasing its concentrations. Studies have shown that ACEi improve exercise tolerance and overall prognosis, although some adverse effects include angio-edema, dry cough and hypotension.[11]

The Metoprolol CR/LX Randomized Intervention Trial in Heart Failure (MERIT-HF) study randomized men and women with symptomatic heart failure and depressed LVEF to take metoprolol CR/XL or placebo. The results showed that all-cause mortality was lower in the intervention group than in the placebo group (RR=0.66, 95% CI 0.52-0.81). A larger, international clinical trial similarly found that subjects on enalapril, an ACEi, experienced lowered all-cause mortality than those on placebo (HR=0.84, CI 95% 0.74-0.95).[12] The Studies of Left Ventricular Dysfunction (SOLVD) treatment was

another clinical trial in which systolic heart failure patients, with or without chronic kidney disease (CKD), were randomized into an enalapril intervention group or placebo group. After an average of 41.4 months, results showed that the overall mortality among those with CKD was lower for those on ACE inhibitors than those on placebo (HR=0.88, 95% CI 0.73-1.06). Participants without CKD and on enalapril had a significantly lower mortality than those on placebo (HR=0.82, 95% CI 0.69-0.98).[13]

Almost all of the clinical drug trials have been conducted on systolic heart failure cohorts. Unfortunately, the effects of drug therapies have largely been inconclusive in patients with preserved LVEF,[14-16] but there is some evidence that patients with diastolic heart failure may benefit from drug therapies. The CHARM-Preserved Trial has shown that, compared with placebo, being on ACEi or ARB lowers the risk of combined adverse effects, including cardiovascular-related deaths.[17] A study in the Netherlands, in which patients with preserved left ventricular EF made up 60% of the inpatient study cohort, found that all-cause mortality was lower among patients receiving β-blockers compared to those who did not use this medication (17.6% vs. 33.8%).[16]

Our study at Loma Linda Medical Center (LLUMC) explored the outcomes of the uptitration of β-blocker, ACEi and ARB dosages on an unselected population of heart failure patients. The study investigated the applications of drug therapy recommendations to see if results from the clinical trials were similar in an ordinary, clinical setting.

E. Epidemiology

1. Prevalence & Incidence

Over 5 million Americans live with heart failure today and the lifetime risk of heart failure in the US is 1 in 5 among men and women at age 40.[18] A 44-year

follow-up study found that yearly HF incidence is nearly 10 per 1000 persons after the age of 65.[19] According to the Heart, Lung, and Blood Institute, the yearly rate of new HF events per 1000 persons for white men between ages 65 and 74 is 15.2, 31.7 for those between 75 and 84 years of age and increases to 65.2 for ages 85 and older.[20] For black men in the same age categories, it is 16.9, 25.5 and 50.6, respectively. White women between ages 65 and 74 had an annual rate of new HF events of 8.2 per 1000 persons while black women had 14.2. Between 75 and 84 years, white women had an annual incidence of 19.8 per 1000 persons and black women had 25.5 per 1000 persons. The rate among white women in the oldest age category was 45.6 per 1000 compared to the rate of 44.0 per 1000 among black women.

A retrospective cohort study on elderly persons on Medicare estimated that the incidence of heart failure was 29 per 1000 person-years in 2003. Between the years 1994 and 2003, the incidence among beneficiaries 65 to 69 years of age increased from 17.5 per 1000 person-years to 19.3 per 1000 person-years while the incidence of beneficiaries 80 to 84 years of age decreased from 57.5 per 1000 person-years to 48.4 per 1000 person-years.[21] The Medicare enrollees had a risk-adjusted 1-year mortality rate of 27.5% (95% CI 27.1-27.9) and had more than three times higher mortality due to heart failure compared to the general population, with a standardized mortality ratio (SMR) of 3.3 in 2002.[21] Among the HF study cohort at LLUMC, the total mortality rate was 24.3% in the study's 4-year duration.

There is growing evidence that the incidence of diastolic heart failure is increasing. The Framingham Heart Study found that the average prevalence of heart failure with preserved EF increased from 38% to 47% to 54% during a 15-year span, in

which the average age among those with HF and preserved EF was 74.4 years and the HF diagnosis with preserved EF accounted for 49% among those 65 years and older.[22] A cross-sectional study of the asymptomatic population of Olmsted County in Minnesota found that 21% had mild diastolic dysfunction and 7% had moderate to severe diastolic dysfunction. A total of 6% had moderate to severe diastolic dysfunction with normal ejection fraction and a total of 6% had systolic dysfunction.[23] Diastolic heart failure patients accounted for nearly 44% of the HF population at LLUMC and 35.43% of the diastolic HF population were over 75 years of age. The study cohort was an unselected population in order to explore treatment opportunities in real-life, prevalent heart failure populations, including a substantial number of diastolic HF patients.

The biggest burden of heart failure lies with its associated hospitalizations. Heart failure as the primary reason for hospitalizations has tripled in recent years and the direct and indirect costs of HF are estimated to be over $33 billion per year.[18, 24] Because effective treatments of HF can be ambiguous due to complex etiologies of the disease, controlling the risk factors may be a good strategy to curtail the increasing incidence of HF.

2. *Important risk factors*

One of the leading risk factors of HF is hypertension. The lifetime risk for HF doubles for person with blood pressure greater than 160/90 mm Hg compared to those less than 140/90 mm Hg.[23] Among 5,143 Framingham Heart Study participants, aged 40 to 89 years, 392 developed heart failure during the 20.1 years of follow-up and 91% of the incidences were subsequent to hypertension.[25] Hypertensive men were twice as likely to develop heart failure compared to normotensive men and hypertensive

women had three times the risk as normotensive women, after adjusting for age and other heart failure risk factors. Hypertension accounted for 39% of heart failure in men and 59% in women. And the 5-year survival of HF with hypertension etiology was calculated to be a mere 24% for men and 31% for women.

Diabetes is also one of the strongest risk factors and comorbidities of HF. Heart failure patients with diabetes have higher prevalence of coronary artery disease, hypertension and obesity.[26] The increase in circulating free fatty acids may play a significant part in the myocardial dysfunction, among other biochemical events that characterize diabetes.

Many studies, including the Cardiovascular Health Study (CHS), have found that there is a significantly higher independent risk for incident heart failure with diabetes.[27] A collaborative study that combined multiple databases found that the incidence of HF was two times higher among subjects with baseline diabetes compared to those without.[28] Results showed that women without diabetes had an annual incidence rate of 0.4% compared to the annual incidence of 3% of diabetic women with no additional risk factors. The addition of any risk factor with diabetes greatly increased the incidence of HF. Diabetic women with elevated BMI had a rate of 7% and diabetic women with depressed creatinine clearance had a 13% annual incidence rate. Overall, the incidence increased to 8.2% for diabetic women with at least 3 additional risk factors.

Coronary artery disease (CAD) is a significant contributor of heart failure. It is a disease in which the plaque buildup in the coronary arteries restricts blood flow into the heart. A British study assessed the importance of the role that coronary artery disease played in heart failure etiology. CAD was identified as the primary etiology for 29% of

all cases of heart failure and 40% of incident cases under 75 years of age.[29] The Framingham study attributed CAD as the primary cause of heart failure in their participants in 59% of men and 48% of women.[19]

Renal disease is a common condition among patients with heart failure and is a major contributor to its poor prognosis. HF subjects with renal dysfunction are at significantly increased risk of HF hospitalization and mortality. Renal disease was a significant predictor of mortality among our systolic HF population at LLUMC. The development of renal failure may be mitigated by the use of diuretics by the up-regulation of the renin-angiotensin aldosterone system, further promoting basal sympathetic nerve discharge and increases in pro-inflammatory factors, which may eventually lead to impaired volume handling and pump failure.[30, 31] It is plausible that renal dysfunction is also a marker for worsening HF. There is also a high prevalence of renal dysfunction due to multiple unifying risk factors that associates heart failure with renal dysfunction such as advanced age, hypertension and diabetes.[32]

3. Modifiable risk factors

Recent studies have focused on the risk of heart failure and lifestyle factors. Healthy lifestyle habits such as normal body weight, not smoking, regular exercise, moderate alcohol intake, consumption of grains, fruits and vegetables may modify risk of HF incidence.[33]

Clinic trials have long since established the benefits of omega-3 polyunsaturated fatty acids (ω-3 PUFA), found in fish oil, for the prevention of coronary heart disease. Two major randomized controlled trials showed that participants on ω-3 PUFA supplementations experienced a 15% reduction in primary end points, which included

30% reductions of cardiovascular mortality, compared to usual care.[34] The Cardiovascular Health Study (CHS), a population-based study, found an inverse association between baked or broiled fish consumption and incident HF and also improved cardiac hemodynamics such as lower heart rate, lower systemic vascular resistance and greater stroke volume.[35] In another study, men who ate a moderate amount of fatty fish and omega-3 fatty acids, once per week, had an HR of 0.88 (95% CI 0.68-1.16) for incident heart failure compared to those with no fatty fish or omega-3-fatty acid consumption.[36]

The Physicians' Health Study found that there was a significant positive relationship between red meat consumption and incident heart failure among men. Those in the highest quintile of meat consumption experienced a 24% increase in risk compared to no consumption.[37] The study also found that healthy lifestyle habits, which included normal body weight, not smoking, regular exercise, moderate alcohol intake, eating breakfast cereals, fruits and vegetables, were individually and jointly associated with lower lifetime risk of heart failure. Several studies, including the Atherosclerosis Risk in Communities (ARIC) Study, found that greater consumption of high fat dairy, eggs and low intake of whole grains were associated with a higher incidence of HF.[38] Nut consumption has proven to be effective in decreasing risk of cardiovascular disease, but the benefits of nuts in preventing heart failure is not as clear. The Physicians' Health Study I, for example, failed to show a significant relationship between nut intake and incident heart failure.[33]

Studies have consistently shown that there is an association between moderate drinking and lower risk of cardiovascular disease, but there is limited data on its

relationship with heart failure. Multivariate models from the Physicians' Health Study found that alcohol consumption was significantly associated with a lower risk of HF with a dose response relationship among men with hypertension.[39]

Data on modifiable risk factors were not collected in the cardiomyopathy clinic at LLUMC, but it may be important to address these important risk factors in future research in order to fully describe the prognosis of its patients in regards to drug therapies.

F. Validity of self-reported heart failure

Large epidemiologic studies are essential in identifying risk factors of heart failure in order to work towards heart failure prevention. These studies rely on self-reported, but physician diagnosed, disease statuses. Validity of self-reported diseases likely depends on disease type, questionnaire design, population characteristics and other factors. It is therefore important to assess validity in the individual studies.

Few studies have measured the validity of self-reported heart failure. Among 51 self-reported cases of heart failure, the Olmsted Study found a sensitivity of 68.6%, specificity of 97.0%, accuracy of 96.3%, but heart failure was only validated through medical records in half of self-reports [3] giving a Positive Predictive Value (PPV) of about 50%. The Medicare Administrative and Health and Retirement Study (HRS) had a low sensitivity (25.2%) with a total agreement of 87.7%.[40] The study also found that Blacks and Hispanics were less likely to self-report CHF compared to whites (OR_{Blacks}=0.28, 95% CI 0.14–0.55, $OR_{Hispanics}$=0.30, 95% CI 0.11– 0.83).

Okura et al. found that advanced age (OR=0.22, 95% CI 0.13-0.37), a Charlson index greater than 1 (OR=0.10 95% CI 0.05-0.2), medical records archived older than 36

years (OR=0.60, 95% CI 0.37-0.97) predicted a lower agreement between self-reports of heart failure on questionnaires and medical records. The female gender (OR=3.14, 95% CI 1.87-5.27) and education level attained greater than 12 years (OR=2.60 95%, CI 1.61-4.19) predicted a higher agreement between questionnaire and medical record. The AHS-2 validation study also looked at the associations of demographic characteristics and the agreement between self-reports and medical records.

CHAPTER 3

FIRST PUBLISHABLE PAPER

Our Experience in the Effects of Reaching Target Dosages of β blockers, ACE Inhibitors and ARBs in an Unselected Population with Prevalent Heart Failure

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Abstract

Background

Heart failure (HF) is a disease with considerable burden on the US population due to its high hospitalization and mortality rates. Clinical trials have shown that drug therapies with β-adrenergic blockade (β blocker), angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) improve HF prognosis but there are few studies that show outcomes of such drug therapies in real-life populations with prevalent heart failure.

Methods and Results

This prospective study was conducted at the Loma Linda University Medical Center cardiomyopathy clinic to assess the effect of drug therapies on an unselected heart failure outpatient population.

A total of 292 subjects with prevalent CHF were followed for 4 years. At the end of the study, 71 (24.3%) were deceased. Those who survived tended to be younger, have lower NYHA class, were more likely to have been at target dosages of β-blockers and ACEi or ARBS, less likely to have used diuretics and less likely to have a history of renal disease. Results from multivariable analysis suggest that reaching target dosages of β-blocker, ACEi/ARB may improve survival among systolic HF patients ($HR_{\beta\text{-blocker}}$= 0.64, 95% CI 0.26-1.55 and $HR_{ACEi/ARB}$=0.50, 95% CI 0.22-1.14) and survival among diastolic HF may also be enhanced with β-blocker therapy (HR= 0.48, 95% CI 0.13-1.81) and ACEi/ARB therapy (HR =0.21, 95% CI 0.04-1.07).

Conclusions

This study showed that treatments with recommended target dosages of β-blockers, ACEi/ARB seemed to improve survival among both systolic and diastolic HF patients.

Key words

Heart failure, β blockers, ACEi, ARB, systolic heart failure, diastolic heart failure

Introduction

There are almost 6 million people living with heart failure (HF) in the US today.[20] The lifetime risk of HF at age 40 for both men and women is 1 in 5.[23] As heart failure-related hospitalizations have tripled in recent years, it is one of the most common reasons for hospitalizations and the direct and indirect costs of HF are estimated to be over $33 billion per year. [41] Efficient and comprehensive treatment of heart failure is necessary to stem its devastating impact on the health of the US population.

Clinical trials have shown that β-adrenergic blockade (β-blockers), angiotensin-converting-enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) in patients with severe systolic HF can reduce mortality and improve symptoms. The Heart Failure Society of America's (HFSA) recently published executive summary on heart failure practice guideline provides a standardization to HF treatment.[42] The summary recommends initial and target doses of β-blockers and angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARB) for the enhancement of HF survival and prognosis but its real-world applications have not yet been well studied.

This prospective study is based on a comprehensive review of all patients seen with a diagnosis of HF at Loma Linda University Medical Center (LLUMC) cardiomyopathy clinic with a 4-year follow-up. We assessed survival according to use and target dosages of β-blocker and ACEi/ARB treatment in this unselected patient population.

Methods

Study population

The study population included a total of 292 consecutive outpatients who were seen in the LLUMC cardiomyopathy clinic from January to July 2006 and followed up through the end of December 2010. Patients with congenital etiologies or without follow-up data were not included in the study. Systolic heart failure was defined as an ejection fraction (EF) below 40% at enrollment while patients with EF of 40% and above were classified as having diastolic heart failure, also known as heart failure with preserved EF.

Results of all echocardiograms (echos) and medical information, such as heart rate, weight, blood pressure, and medication list, from the first clinic visit and from visits approximate in time to when echos were performed were extracted from the medical records at LLUMC. B-blockers, ACEi and ARB dosages that were prescribed at least one month prior to the corresponding echos were recorded. Patients usually received a yearly echo but 92 patients had only one echo done at LLUMC during the time of the study. Patients' most current EFs were used as a predictor of their survival.

While patients were already on β-blocker, ACEi or ARB when they were referred to LLUMC, their dosages were uptitrated to the most tolerable levels in order to reach target dosages, as recommended by HFSA. Patients who were not able to tolerate ACEi were put on ARB.

Deaths were notified from LLUMC, skilled nursing facilities and families and were all confirmed through the Social Security Death Index (SSDI). The SSDI was checked annually for patients who were not seen by the clinic in over a year.
This study was approved by the Institutional Review Board of Loma Linda University.

Statistical analysis

Chi-square analysis compared the differences between potential covariates among participants who survived and those who did not.

Multivariable Cox regression was performed to assess survival in the study population, with attained age at study enrollment as the time variable. Regression models were developed separately for those with systolic heart failure and those with diastolic heart failure.

Demographic variables including gender, smoking history and race/ethnicity were considered as confounders in the model as were NYHA functional class, Body Mass Index (BMI) and heart failure etiology (ischemic and non-ischemic). Other candidate confounders were comorbidities such as history of hypertension, renal disease, diabetes and dyslipidemia, as well as heart rate and systolic and diastolic blood pressure around the time of the most recent EF.

Demographic confounders and comorbidities were assessed individually as predictors of survival and then considered in combinations with β-blocker and ACEi/ARB treatments. Variables that changed the effect of the medications (β-blockers, ACEi/ARB) more than 10% or more were significant predictors of survival were considered for the final model along with β-blockers and ACEi/ARBs. The proportional hazards assumption was satisfied through the evaluation of negative log-log plots, Schenfelds residual plots, and the absence of time interactions. Continuous covariates were assessed for linearity through Martingale residuals plots and by plots of residuals against individual covariates.

All statistical analyses were performed using SAS/STAT® software.

Results

Descriptive analysis

Of the 292 subjects, 71 (24.3%) were deceased as of the end of December 2010. The characteristics of the overall study population, comparing those who survived through 2010 to those who did not, are described in Table 3.1. Those who survived tended to be younger and have lower NYHA class. Subjects who survived were more likely to have been at target dosages of β-blockers and ACEi or ARBs, less likely to be using diuretics and less likely to have a history of renal disease.

Table 3.1 Descriptive characteristics of study population at baseline

	Total (%)	Non-survival (%)	Survival (%)	P value
Gender				
Men	154 (52.74)	120 (54.30)	34 (47.89)	0.36
Women	138 (47.26)	101 (45.70)	37 (52.11)	
Age				
<60	113 (38.70)	80 (36.20)	14 (19.72)	<0.01
60-75	98 (33.56)	76 (34.39)	21 (29.58)	
75+	81 (27.74)	65 (29.41)	36 (50.70)	
Race/ethnicity				
Black	48 (16.44)	36 (16.29)	12 (16.90)	0.67
Hispanic	52 (17.81)	37 (16.74)	15 (21.13)	
White, others	192 (65.75)	148 (66.97)	44 (61.97)	
Smoking history				
Never smoker	145 (49.83)	107 (48.42)	38 (54.29)	0.62
Past smoker	131 (45.02)	103 (46.61)	28 (40.00)	
Current smoker	15 (5.15)	11 (4.98)	4 (5.71)	
NYHA class				
1	43 (19.37)	42 (24.56)	1 (1.96)	<0.01
2	60 (27.03)	49 (28.65)	11 (21.57)	
3, 4	119 (53.60)	80 (46.78)	39 (76.47)	
BMI				
Slim-normal (≤24)	119 (40.89)	85 (38.46)	34 (48.57)	0.12
Overweight (25-29)	85 (29.21)	63 (28.51)	22 (31.43)	
Obese (≥30)	87 (29.90)	73 (75.95)	14 (20.00)	
Type				
Systolic				
Etiology				
Ischemic	69 (57.67)	53 (38.97)	20 (50.00)	0.21
Non-ischemic	94 (57.67)	83 (61.03)	20 (50.00)	
Diastolic (EF≥40)	127 (43.79)			
Etiology				
Ischemic	31 (25.20)	20 (24.69)	7 (23.33)	0.88
Non-ischemic	92 (74.80)	61 (75.31)	23 (76.67)	
Beta-blocker dose				
Target	92 (32.39)	60 (27.52)	11 (16.67)	0.02
Below target	169 (59.51)	145 (66.51)	45 (68.18)	
No use	23 (8.10)	13 (5.96)	10 (15.15)	
ACEi dose				
Target	98 (35.64)	83 (39.71)	15 (23.44)	0.03
Below target	96 (34.91)	71 (33.97)	23 (35.94)	
No use	81 (29.45)	55 (26.32)	26 (40.63)	

Table 3.1 (continued) Descriptive characteristics of study population at baseline

	Total (%)	Non-survival (%)	Survival (%)	P value
ARB dose				
Target	36 (13.53)	30 (14.85)	6 (9.38)	0.41
Below target	43 (16.17)	34 (16.83)	9 (14.06)	
No use	187 (70.30)	138 (68.32)	49 (76.56)	
Diuretics				
Use	87 (29.79)	55 (24.89)	32 (45.07)	<0.01
Nonuse	33 (11.30)	25 (11.31)	8 (11.27)	
Unknown	172 (58.90)	141 (63.80)	31 (43.66)	
Comorbidity history				
Hypertension	206 (70.55)	160 (72.40)	46 (64.79)	0.22
Type II Diabetes	98 (33.56)	68 (30.77)	30 (42.25)	0.08
Dyslipidemia	136 (46.58)	108 (48.87)	28 (39.44)	0.17
Renal disease	53 (18.15)	32 (14.48)	21 (29.58)	<0.01

Characteristics between systolic and diastolic HF population are described in Table 3.2. Patients with diastolic heart failure were more likely to be female and older than those with systolic HF. There were no current smokers in the diastolic HF population. Systolic HF patients had HF with ischemic etiology and were more likely to be at the target β-blocker dosage compared to the diastolic HF patients. A larger proportion of patients with diastolic HF had a history of hypertension and renal disease.

Table 3.2. Descriptive characteristics of study population at baseline between systolic and diastolic heart failure populations

	Systolic (%)	Diastolic (%)	P value
Gender			
Men	97 (59.51)	55 (43.31)	<0.01
Women	66 (40.49)	72 (56.69)	
Age			
<60	71 (43.56)	42 (33.07)	0.03
60-75	56 (34.36)	40 (31.50)	
75+	36 (22.09)	45 (35.43)	

Table 3.2 (continued) Descriptive characteristics of study population at baseline between systolic and diastolic heart failure populations

	Systolic (%)	Diastolic (%)	P value
Race/ethnicity			
Black	32 (19.63)	16 (12.60)	0.20
Hispanic	25 (15.34)	26 (20.47)	
White, others	106 (65.03)	85 (66.93)	
Smoking history			
Never smoker	72 (44.17)	72 (57.14)	<0.01
Past smoker	76 (46.63)	54 (42.86)	
Current smoker	15 (9.20)	0 (0.0)	
NYHA class			
1	65 (53.72)	53 (53.54)	0.28
2	29 (23.97)	31 (31.31)	
3, 4	27 (22.31)	15 (15.15)	
BMI			
Slim-normal (≤24)	73 (44.79)	46 (36.51)	0.35
Overweight (25-29)	46 (28.22)	39 (30.95)	
Obese (≥30)	44 (26.99)	41 (32.54)	
Type			
Ischemic	69 (42.33)	31 (25.20)	<0.01
Non-ischemic	94 (57.67)	92 (74.80)	
β-blocker dose			
Target	60 (37.27)	31 (25.62)	0.02
Below target	93 (57.76)	75 (61.98)	
No use	8 (4.97)	15 (12.40)	
ACEi dose			
Target	61 (38.85)	35 (30.17)	0.22
Below target	55 (35.03)	41 (35.34)	
No use	41 (26.11)	40 (34.48)	
ARB dose			
Target	17 (11.18)	19 (16.81)	0.35
Below target	23 (15.13)	19 (16.81)	
No use	112 (73.68)	75 (66.37)	
Diuretics			
Use	52 (31.90)	35 (27.56)	0.37
Nonuse	15 (9.20)	18 (14.17	
Unknown	96 (58.90)	74 (58.27)	
Comorbidity history			
Hypertension	105 (64.42)	99 (77.95)	0.01
Type II diabetes	57 (34.97)	40 (31.50)	0.53
Dyslipidemia	77 (47.24)	58 (45.67)	0.79
Renal disease	23 (14.11)	30 (23.62)	0.04

The causes of death in this population were largely unknown (Table 3.3).

Table 3.3 Causes of death

Total=71	Total (%)
Progressive Heart Failure	11 (15.49)
Non-cardiac	16 (22.54)
Unknown/other	44 (61.97)

Survival analysis

The comparison of the systolic and diastolic HF population survival curves in Figure 3.1 show that patients with diastolic HF had better survival than patients with systolic HF.

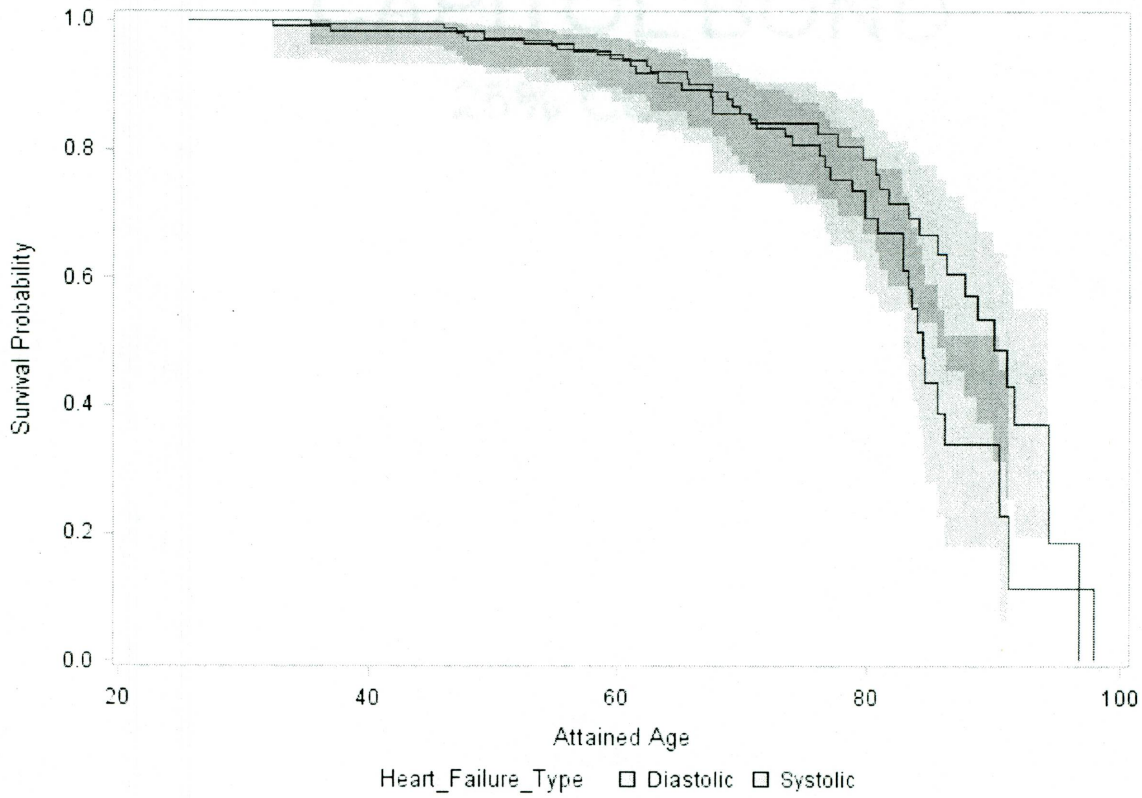

Figure 3.1 Survival curve comparison of systolic and diastolic heart failure populations

When assessed individually in univariate Cox regression models, NYHA stage 3 and heart rate were associated with higher hazard rate whereas EF and use of β-blockers were associated with better survival among patients with systolic heart failure and to a lesser degree in diastolic HF. Use of ACEi/ARB, on the other hand, was more strongly associated with lower hazard rate in diastolic HF (Table 3.4). Of the recorded comorbidities, prevalent kidney disease was associated with higher mortality among patients with diastolic HF.

The final model (Table 3.5) for the systolic HF population suggests that reaching target dosages of both β-blockers and ACEi/ARB may increase survival compared to not reaching target, although not significant ($HR_{\beta\ blocker}$= 0.64, 95% CI 0.26-1.55 and $HR_{ACEi/ARB}$=0.50, 95% CI 0.22-1.14). Ejection fraction and being of Hispanic race/ethnicity were both strong and independent predictors of survival. There was almost a 25% decrease in mortality with every 5% increase in EF (HR= 0.95, 95% CI 0.92-9.98). Hispanic ethnicity predicted almost a 4-fold increase in mortality compared to all other ethnicities with a hazard ratio of 3.90 (95% CI 1.41-10.78).

Table 3.4. Univariate models

	Systolic HF Population			*Diastolic HF Population*		
	Hazard Ratios	95% CI		Hazard Ratios	95% CI	
Hispanic	2.40	0.98	5.91	1.07	0.44	2.61
Female	1.38	0.70	2.73	0.88	0.41	1.92
Past/current smoker	0.87	0.44	1.72	0.75	0.34	1.67
NYHA Class 3+	3.17	1.19	8.46	4.97	1.33	18.5
BMI	0.95	0.91	1.00	1.01	0.96	1.06
Ischemic etiology	1.41	0.70	2.85	0.89	0.35	2.28
Comorbidity history						
Hypertension	0.43	0.22	0.85	0.88	0.33	2.34
Renal disease	1.23	0.52	2.90	3.06	1.31	7.14
Type II Diabetes	1.95	0.92	4.17	1.44	0.63	3.26
Dyslipidemia	0.55	0.27	1.13	0.88	0.40	1.92
Heart rate	1.03	1.00	1.05	1.04	1.00	1.08
Hypertensive						
Systolic Blood Pressure>140	1.13	0.49	2.59	1.01	0.40	2.53
Diastolic Blood Pressure>90	2.32	0.63	8.53	0.84	0.10	7.39
SBP>140 or DBP>90	1.26	0.56	2.82	1.01	0.40	2.53
Ejection fraction	0.96	0.93	0.99	1.00	0.97	1.03
β-blocker dose						
below target	0.51	0.27	0.96	0.59	0.27	1.28
at target	0.96	0.93	0.99	1.00	0.97	1.03
ACEi/ARB						
below target	0.62	0.25	1.58	0.12	0.03	0.54
at target	0.31	0.11	0.86	0.17	0.03	0.82

Table 3. 5. Final survival models

Systolic HF Population			
	Hazard Ratios	95% CI	
β-blocker target vs nontarget	0.64	0.26	1.55
ACEi/ARB target vs. nontarget	0.50	0.22	1.14
Hispanic	3.90	1.41	10.78
EF	0.95	0.92	0.98
Diastolic HF Population			
	Hazard Ratios	95% CI	
β-blocker any vs none	0.48	0.13	1.81
ACEi/ARB any vs none	0.21	0.04	1.07
Renal disease	3.68	1.39	9.74

Although not reaching statistical significance, use of β-blockers and ACEi/ARB treatments independently suggests a decrease in mortality in the final model among diastolic HF patients ($HR_{\beta\ blocker}$= 0.48, 95% CI 0.13-1.81 and $HR_{ACEi/ARB}$=0.21, 95% CI 0.04-1.07) (Table 5). History of renal disease among the diastolic HF patients strongly predicted mortality with a hazard ratio of 3.68 (95% CI 1.39-9.74).

Discussion

Our study has demonstrated that reaching target dosages of β-blockers and ACEi/ARB may independently enhance survival among systolic HF patients in this unselected, prevalent heart failure population. This is in agreement with clinical trials that have consistently shown that β-blockers, ACEi and ARBs significantly decrease all-cause mortality in patients with systolic heart failure with similar point estimates as in our study. Most recently, the HF-ACTION (Heart Failure: A controlled Trial Investigating Outcomes of Exercise Training) trial demonstrated that there was an inverse relationship between β-blockers and all-cause mortality among systolic HF patients receiving up to 50mg carvedilol or equivalent per day.[9] Due to random assignments of drug treatments, subjects in clinical trials are usually comparable in their exposure to other medications but the effect of one medication in the presence of another has not been explicitly described or tested as in our study.

The effects of drug treatments on the prognosis of subjects with preserved ejection fraction have mostly been inconclusive.[14, 15] The CHARM-Preserved Trial has shown that being on ACEi or ARB lowers the risk of combined adverse effects, including cardiovascular-related deaths, compared with placebo.[43] A study of an inpatient cohort in The Netherlands, in which 60% had preserved left ventricular EF, found that all-cause

mortality was lower among patients receiving β-blockers than those who were not (17.6% vs. 33.8%).[16] Diastolic HF patients in this study experienced considerably lower mortality with drug therapies. The increase in survival was seen with both β-blocker and ACEi/ ARB therapies. More research on the effects of drug treatments in diastolic heart failure is crucial due to the increased prevalence among the general population and the lack of improvement in survival.[22]

Increased ejection fraction during follow-up was a strong predictor of better survival in the systolic HF population of our study. Improvement in EF, referred to as cardiac reverse remodeling, was evident in the MOCHA (multicenter oral carvedilol heart failure assessment) study that reported a positive dose response relationship between higher doses of β-blockers and EF.[6] Increases in ejection fractions may be an approach to quantify possible reverse remodeling, which may in fact translate to better survival and prognosis in people living with heart failure. Studies have shown that positive change in EF are associated with increased survival rates[44] and furthermore that β-blockers and ACEi may aid in the reduction of ventricular mass and thus mitigate reverse modeling.[6, 45] Our data analysis suggests that improvements in EF may also be associated with survival, independent from drug treatments.

According to a 2005 study of Medicare enrollees, Hispanic Americans are one of the fastest growing segments of the US population[46] and thus it is important to note that mortality among Hispanics in our study population is much greater than the other race ethnicities.[47] The Hispanic population is at higher risk of known risk factors of heart failure than other race ethnic groups. The prevalence of diabetes among Hispanics is twice that of other racial ethnic groups, with poorer glycemic control.[48] More Mexican-

American men and women are overweight or obese than non-Hispanic whites and the prevalence of metabolic syndrome is higher than in non-Hispanic Whites (31.9% vs. 23.8%) or African Americans (21.6%).[49] Mexican Americans have high prevalence of hypertension, with poorer blood pressure control, and less medication treatment (35%) compared to African Americans (57%) and non-Hispanic whites (54%).[50] While these individual risk factors did not significantly predict survival in our study population, the poor survival seen in Hispanics may have been due to a combined effect of co-morbidities and less access to state of the art medical care. It is also possible that medication adherence may be poor in the Hispanic population.

Renal disease is an important non-cardiac comorbidity in HF and was a strong predictor of mortality among the diastolic HF patients in this study. HF subjects with renal dysfunction are at significantly higher risk for HF hospitalization and mortality.[32] It is plausible that renal dysfunction is a marker for worsening HF but there is also a high prevalence of renal dysfunction due to multiple unifying risk factors that associates heart failure with renal dysfunction like older age, hypertension and diabetes. Another factor implicated in the development of worsening renal failure is the use and overuse of diuretics among HF patients. This can be explained by the theory that the up-regulated renin-angiotensin aldosterone system promotes basal sympathetic nerve discharge, increasing pro-inflammatory factors and eventually leading to impaired volume handling and pump failure.[30, 31]

Limitations

Due to small numbers, many of our findings did not reach statistical significance. A longer follow-up time or larger number of HF patients is recommended in order to give

adequate power for more firm conclusions, especially with respect to the effect of these medications on the prognosis of the diastolic HF populations.

Conclusion

This study investigated the effectiveness of drug therapy in improving overall survival on an unselected patient population with HF at a hospital heart failure clinic. Results from data analysis showed that treatment at recommended target doses of β-blocker, ACEi and ARB may improve survival among both systolic and diastolic HF patients. Because there is little research data on the diastolic heart failure population, it is noteworthy that our study shows that drug therapy reduces mortality in patients with preserved EF. These findings can provide reassurance to clinicians that it is worthwhile to push to reach recommended target dosages in treating patients with heart failure from low to normal ejection fractions.

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CHAPTER 4

SECOND PUBLISHABLE PAPER FOR SUBMISSION

Validation of Self-Reported Congestive Heart Failure among the

Adventist Health Study-2 Cohort

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Abstract

Purpose

The purpose of this study was to validate self-reported, physician-diagnosed congestive heart failure (CHF) in the Adventist Health Study-2 (AHS-2) population.

Methods

Among 947 AHS-2 participants who reported that they were diagnosed with CHF on the baseline questionnaire, 200 were randomly selected as cases and 260 were selected as comparative non-cases among participants who said they did not have CHF. Medical records containing sufficient information of a physician diagnosis of CHF were requested for all cases. Phone surveys were conducted for non-cases and medical records were requested when necessary.

Results

Successful contact and validation was obtained from a total of 67 cases and XXX non-cases. Sensitivity was calculated to be 97.4%, specificity was 83.4%, negative predictive value (NPV) was 99.3%, positive predictive value (PPV) was 56.7% and the total agreement (accuracy) was 86.0 %.

Conclusions

Although sensitivity and NPV was excellent, the PPV was moderate. Self-reported congestive heart failure in the AHS-2 cohort needs further study with a larger number of cases and non-cases before reliable estimates of validity of self-reported physician diagnosed CHF can be determined.

Keywords

Congestive heart failure, self-report, validation study, Adventist Health Study

Background

As of 2010, approximately 5.8 million people in the United States are currently living with congestive heart failure (CHF) and 670,000 are diagnosed every year.[1] One of five people diagnosed with CHF die within a year of diagnosis and the cost of health care, medication and loss of productivity equates to a loss of $39.2 billion in the United States.[1]

Many epidemiologic studies use self-reported disease status to measure disease outcomes in subjects because of its cost-effectiveness. Validity will most likely depend on factors such as disease type, questionnaire design and study population. As a result, many prospective studies conduct validity studies to assess the accuracy of self-reported disease in their respective questionnaires. Establishing the accuracy of self-reported disease outcomes will greatly improve the quality of studies that use these disease statuses as their dependent variables.

The validity of self-reported CHF in the Adventist Health Study-2 (AHS-2) cohort has not yet been established. The purpose of this study was to validate self-reported, physician-diagnosed congestive heart failure in the AHS-2 population.

Methodology

Study population

The Adventist Health Study-2 is an ongoing, longitudinal cohort study investigating the association between lifestyle, diet, disease and mortality among more than 96,000 participants from the United States and Canada. Subjects who indicated that they have congestive heart failure by answering "yes" to "Have you been treated for congestive heart failure in the last 12 months?" and also replied to the "Years since first

diagnosis [of congestive heart failure]" question on the baseline questionnaire were considered cases. A total of 947 reported prevalent CHF at baseline.

Of these 947 self-reports, 200 were randomly selected as cases and 260 participants who stated they did not have CHF and who were older than 50 years of age were randomly selected as comparable non-cases using SAS® software.[2] The National Death Index (NDI) and Social Security Index (SSI) were checked for any deceased participants.

Methods

All selected subjects were initially contacted by phone (A1) to inquire as to willingness to release medical records pertaining to their potential CHF diagnosis. If phone numbers were not current, we contacted the person listed as a contact on the baseline questionnaire. If we were still not successful in contacting them, extensive searches in online phone registries were done to attempt to locate them. At least six phone call attempts were made if first contact was unsuccessful.

Follow-up of cases

Willing case participants were mailed a letter of correspondence containing an informed consent form (A2), information form for their current cardiologist and/or family physician, information form of their most recent hospitalization for heart failure and a short questionnaire on CHF symptoms, heart medication and past echocardiograms (echos).

Follow-up of non-cases

Non-cases were asked to answer a short survey over the phone (A3) with the following questions:

1. Have you ever been told by a physician that you have congestive heart failure or CHF?
2. Have you experienced regular swelling in your lower extremities within the last 5 years?
3. Have you experienced regular shortness of breath with exertion or when you're lying down within the last 5 years?
4. Are you currently taking any heart medicines such as beta blockers, diuretics, ARB, or ACE-inhibitor medications? Do you know why you are taking these?
5. Have you had an echo or a heart ultrasound?

Subjects who answered "yes" to question 1 or "yes" to combinations of either 2 or 3 with either 4 or 5 were asked if they were willing to sign a consent form for the release of their medical records. The same correspondence that was mailed to cases was mailed to willing non-cases whose medical records were required.

For the deceased population, the locations of medical records were sought through contacting next of kin and churches of affiliation. A minimum of 6 phone attempts were made for any unresponsive individuals, on different days of the week and different times of the day, leaving at least 3 voicemails.

When the consent forms were mailed back, a request of information (ROI) were faxed or mailed to their respective cardiology clinics or hospitals. The medical records department or the physicians of the consenting participants were contacted with a letter

from AHS-2 (A4) and a copy of their patients' consent forms. Informed consent was obtained from deceased participants at baseline. The ROI asked for a verification of a CHF diagnosis around the time of AHS-2 enrollment through a combination of clinic notes, echos, electrocardiograph (ECG), brain natriuretic peptide (BNP) levels, medication list and a date of diagnosis. A short questionnaire (A5) on the presence of dyspnea and edema in the patient was also included. If there was no evidence of CHF diagnosis, physicians were asked to mark a statement confirming that their patient had never been diagnosed with congestive heart failure.

Processing of medical records

Trained research personnel reviewed medical charts for CHF diagnosis validation and a board certified cardiologist was responsible for the final quality control of the medical records review. Explicit statements of CHF diagnosis in clinic notes qualified as a positive validation. Without clinic notes, test results such as echos and ECGs, along with the presence of dyspnea and edema qualified as validation of CHF diagnosis. Any CHF diagnosed after the date of baseline questionnaire completion were not included as confirmation of self-reported CHF.

Statistical methods

Chi-square frequency test was performed to evaluate representativeness of the sample population to the entire AHS-2 cohort. Sensitivity was calculated as (TP)/(TP+FN) and specificity was calculated as (TN)/(TN+FP). Accuracy was calculated as (TP+TN)/(TP+FN+TN+FP). Positive predictive value (PPV) was calculated as (TP)/(TP+FP) and negative predictive value (NPV) was calculated as (TN)/(TN+FN).

This study was reviewed by Loma Linda University Institutional Review Board (IRB). All research personnel completed the IRB certification and were trained in

conducting phone interviews and data entry. Statistical analysis was performed using SAS software, version 9.3.

Results

Table 4.1 shows the chi-square analysis between the entire CHF population and the validated cases. The validated cases tended to be younger compared to the entire CHF cohort (p value=0.02) and a lower proportion of the Black race/ethnicity was validated (p value<0.01). Other validated case characteristics were representative of the entire CHF cohort. Among the non-CHF population, there were no significant differences in distribution of age, gender, education levels and other characteristic variables between the validated sample population and the entire non-CHF cohort (Table 4.2).

Table 4.1. CHF population: Baseline characteristic comparison between entire cohort and validated cohort

	Entire CHF cohort (%)	Validated cohort (%)	P value
Gender			
Women	609 (64.31)	54 (68.35)	0.47
Men	338 (35.69)	25 (31.65)	
Age			
<70	393 (41.46)	33 (41.77)	0.02
70-80	277 (29.22)	33 (41.77)	
80+	278 (29.32)	13 (16.46)	
Race/ethnicity			
Black	216 (22.78)	7 (8.86)	<0.01
Non Black	732 (77.22)	72 (91.14)	
Smoking history			
Never smoker	635 (68.65)	58 (76.32)	0.16
Ever smoker	290 (31.35)	18 (23.68)	
Years since diagnosis			
<5 years ago	522 (55.06)	42 (53.16)	0.22
5-9 years ago	215 (22.68)	24 (30.38)	
10+ years ago	211 (22.26)	13 (16.46)	
BMI			
Slim-normal (≤24)	305 (32.55)	22 (28.57)	0.43
Overweight (25-29)	264 (28.18)	27 (35.06)	
Obese (≥30)	368 (39.27)	28 (36.36)	
Education			
High school or less	325 (34.87)	21 (26.92)	0.35
Some college	405 (43.45)	39 (50.00)	
College grad or more	202 (21.67)	18 (23.08)	
Comorbidity history			
Type II Diabetes	341 (35.97)	29 (36.71)	0.90
Angina	224 (23.63)	18 (22.78)	0.87
Myocardial infarction	290 (30.59)	24 (30.38)	0.97
Hypertension	707 (74.58)	51 (64.56)	0.05
Hypercholesterolemia	505 (53.27)	48 (60.76)	0.20
Stroke	95 (10.02)	6 (7.59)	0.49
TIA	156 (16.46)	7 (8.86)	0.08
Cancer	260 (27.46)	22 (27.85)	0.94

Table 4.1 (continued) CHF population: Baseline characteristic comparison between entire cohort and validated cohort

	Entire CHF cohort (%)	Validated cohort (%)	P value
Medication history			
Aspirin	530 (56.75)	44 (55.70)	0.86
Cholesterol reducing med.	402 (42.45)	42 (53.16)	0.06
Antihypertensives	688 (72.73)	51 (64.56)	0.12

Table 4.2. Non-CHF population: Baseline characteristic comparison between entire cohort and validated cohort

	Entire cohort (%)	Validated cohort (%)	P value
Gender			
Women	41106 (64.17)	98 (66.67)	0.53
Men	22954 (35.83)	49 (33.33)	
Age			
<70	41906 (65.38)	102 (69.69)	0.21
70-80	14893 (23.24)	35 (23.81)	
80+	7293 (11.38)	10 (6.80)	
Race/ethnicity			
Black	14123 (22.04)	36 (24.49)	0.47
Non Black	49969 (77.96)	111 (75.51)	
Smoking history			
Never smoker	49823 (78.64)	117 (80.69)	0.61
Ever smoker	13294 (21.06)	28 (19.31)	
BMI			
Slim-normal (≤24)	26731 (42.29)	50 (34.72)	0.18
Overweight (25-29)	21647 (34.15)	55 (38.19)	
Obese (≥30)	14830 (23.46)	39 (27.08)	
Eudcation			
High school or less	16276 (25.82)	41 (28.08)	0.52
Some college	24476 (38.84)	60 (41.10)	
College grad or more	22273 (35.34)	45 (30.82)	

Table 4.2 (continued) Non-CHF population: Baseline characteristic comparison between entire cohort and validated cohort

	Entire cohort (%)	Validated cohort (%)	P value
Type II Diabetes	6792 (10.60)	14 (9.52)	0.67
Angina	2048 (3.20)	4 (2.72)	0.74
Myocardial infarction	2322 (3.62)	5 (3.40)	0.89
Hypertension	22694 (35.41)	49 (33.33)	0.60
Hypercholesterolemia	20133 (31.41)	46 (31.29)	0.98
Stroke	894 (1.39)	2 (1.36)	0.97
TIA	2156 (3.36)	5 (3.40)	0.98
Cancer	11767 (18.38)	22 (14.97)	0.29
Medication history			
Aspirin	18851 (29.66)	53 (36.3)	0.08
Cholesterol	10375 (16.21)	23 (15.65)	0.85
High blood pressure	19746 (30.90)	47 (31.97)	0.78

The validity of self-reported CHF was assessed using sensitivity, specificity and predictive values. Sensitivity and NPV were excellent at 97.4% and 99.3%, respectively. Specificity was 83.4% and PPV was 56.7%, with a total agreement of 86.0 % (Table 4.3). Nine cases and one non-case were unable to be validated due to incomplete medical records.

Table 4.3 Validation Results

		Diagnosis confirmed	
		Yes	**No**
Self- reported CHF	**Yes**	38	29
	No	1	146

Discussion

The combination of the advanced age of the CHF population and the somewhat confusing terminology may make the validity of self-reported CHF challenging. There are few validation studies on self-reported congestive heart failure. Our findings were similar to other studies that involved CHF validation. The Olmsted Study validation study was the only epidemiological study that involved a large study cohort, similar to AHS-2. Among the total 2,037 self-reported cardiovascular diseases, the Olmsted Study found a sensitivity of 68.6%, specificity of 97.0% for CHF. It had a high NPV and low PPV at 36.8% and the accuracy was calculated at 96.3% for medical record-documented, self-reported heart failure.[3] The results indicated that self-reports of heart failure was almost three-fold higher than confirmed through medical records. The Medicare Administrative and Health and Retirement Study (HRS) found that validation of heart failure had lower sensitivity (25.2%) than the AHS-2 study, while the total agreement was similar at 87.7%.[4] The Cardiovascular Health Study (CHS), a cohort study of coronary disease and stroke risk factors, found that self-reported CHF was confirmed in 73.3% in men and 76.6% in women.[5]

Limitations

Difficulty in contacting subjects due to loss to follow-up or nonresponses could have potentially biased the results. Of the selected cohort, cases were more challenging to contact, possibly due to the older age distribution of the CHF population. Medical records were received for approximately 38% of the cases while the response rate for non-cases was almost 60%. Advanced ages of the cases is likely the primary reason for the lower response rate. Older study participants are more likely to have transitioned from an

independent living situation to assisted living facilities or nursing homes since the completion of the baseline questionnaires or have since died, making the acquisition of their medical records more difficult. The direction of the bias from non-responses is difficult to predict.

Conclusion

Our findings demonstrate that there was representativeness between the entire cohort and selected sample population among the cases and non-cases in age, gender, education level and deceased status. We found that self-report of CHF correctly classified in 85.6% of subjects as either cases or non-cases. Self-reported congestive heart failure among the AHS-2 population may not be a reliable measure for future outcome research.

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CHAPTER 5

ADDITIONAL STUDIES

Association between Exercise and Risk of Cardiovascular Disease-Specific Hospitalization among Heart Failure Patients in the Adventist Health Study 2

Of the 917 subjects who identified themselves as being diagnosed by a physician with heart failure at enrollment into the AHS-2, 637 subjects returned a questionnaire on hospitalizations two years later. Data on frequency, distance, duration and time spent walking and running was collected at baseline and was combined into indices signifying none, low and medium/high levels of exercise. Logistic regression was used to assess the risk of cardiovascular-specific hospitalization according to baseline exercise levels and other variables. Co-morbidities such as prevalent hypertension and type II diabetes were analyzed as potential confounders, but were not found to have significant effect on the outcome. Of several dietary factors tested, only meat intake made it into the final model.

In multivariate analysis, exercise was protective of cardiovascular-specific hospitalization when compared to no exercise (OR=0.52, 95% CI 0.32-0.96 and OR=0.71, 95% CI 0.42-1.81) for low and moderate/high levels, respectively.

Our findings suggest that exercise may be beneficial in preventing future heart failure-related hospitalizations among heart failure patients. Higher frequency of exercise may not be possible for many heart failure patients and may explain the point estimate we obtained. The possibility that exercise level is actually a marker for disease severity and

thus a better explanation of hospitalizations is a concern, but the variance in years living with heart failure among the subjects did not significantly contribute to the outcome in our analyses.

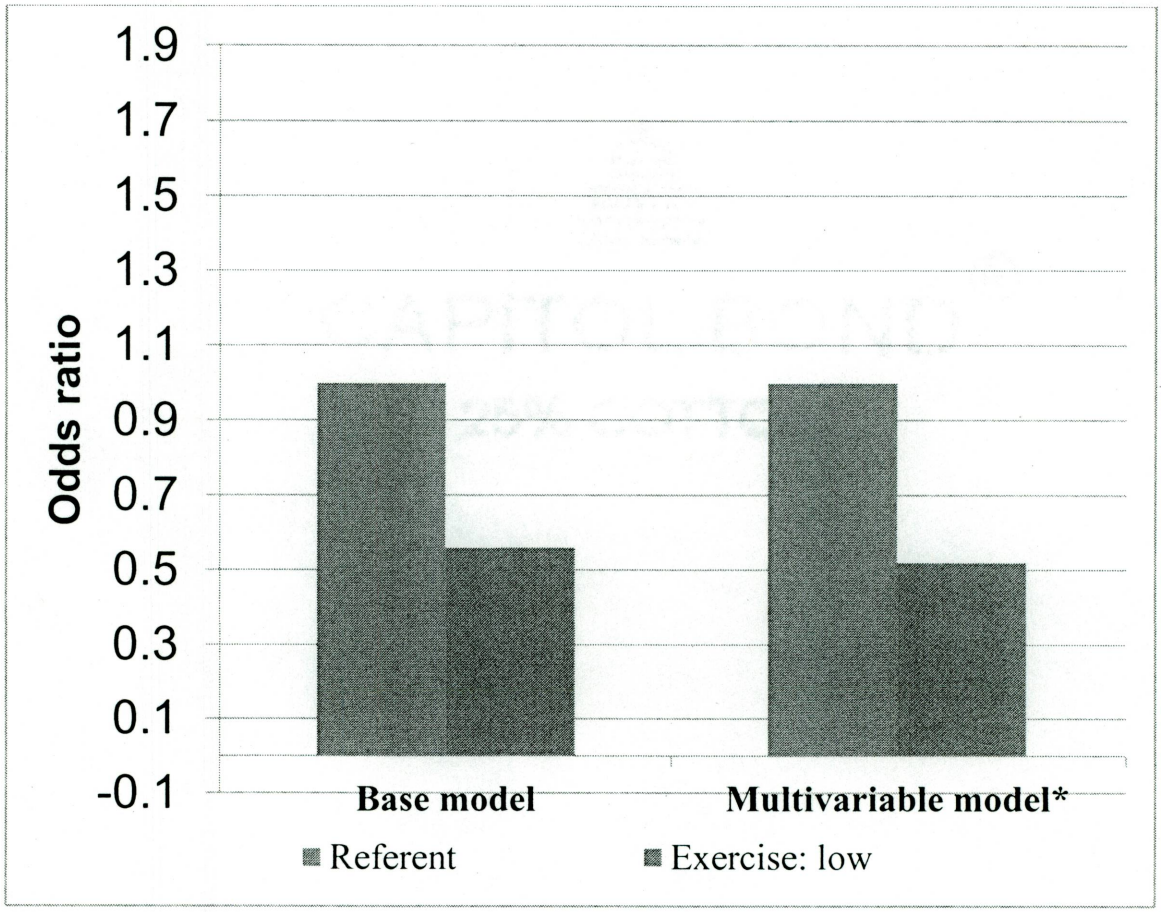

Figure 5.1 Risk of CVD-related hospitalization by exercise level

Table 5.1 Subject characteristics by hospitalization status

	CVD hospitalization (%)	Non-CVD or no hospitalization (%)	Total (%)
Gender			
Male	82 (12.9)	317 (49.8)	399 (62.7)
Female	59 (9.3)	178 (28.0)	237 (37.3)
Age			
Mean (in years)	72	73	
Body Mass Index (BMI)			
Normal & underweight	46 (7.3)	167 (26.4)	213 (33.7)
Overweight	33 (5.2)	152 (24.1)	185 (29.3)
Obese	60 (9.5)	174 (27.5)	234 (37.03)
Smoking status			
No history	91 (14.5)	356 (56.8)	447 (71.3)
Past or current use	47 (7.5)	133 (21.2)	180 (28.7)
Education level			
≤ High school degree	46 (7.3)	154 (24.5)	200 (31.9)
≤ Associate's degree	59 (9.4)	208 (33.1)	267 (42.5)
College degree & higher	34 (5.4)	127 (20.2)	161 (25.6)
Exercise level			
None	71 (12.0)	206 (34.7)	277 (46.7)
Low	22 (3.7)	114 (19.2)	136 (22.9)
Medium/high	35 (5.9)	145 (24.5)	180 (30.4)
Type II diabetes			
No history	96 (15.1)	344 (54.0)	440 (69.1)
History	45 (7.1)	152 (23.9)	197 (30.9)
Hypertension			
Not present	40 (6.3)	170 (26.7)	210 (40.0)
Present	101 (15.9)	326 (51.2)	427 (67.0)
Meat Consumption			
None	45 (7.3)	153 (24.9)	198 (32.3)
≤1x/week	11 (1.8)	29 (4.7)	40 (6.5)
≥2/week	78 (12.7)	298 (48.5)	376 (61.2)
Nut Consumption			
≤1x/week	34 (5.3)	102 (16.0)	136 (21.4)
≥2/week	107 (16.8)	394 (61.9)	501 (78.7)

CHAPTER 6

A. Summary

This dissertation explored multiple aspects of populations with prevalent heart failure. It consisted of investigating the relationship between drug therapy at recommended dosages and the survival of inpatients with both systolic and diastolic heart failure and it also evaluated the validity of self-reported congestive heart failure among the Adventist Health Study-2 cohort.

The clinic study demonstrated that β-blocker, ACEi and ARB therapy at the target dosages recommended by the Heart Failure Society of America improves survival among patients with systolic heart failure and seems to do the same among subjects with diastolic HF.

The validation study results show that the self-reported diagnosis of heart failure in the AHS-2 population has high negative predictive value, but lower positive predictive value. However, we were only able to contact a fraction of the subjects identified. The study needs more intensive work in being able to reach a larger proportion of the subjects in order to assess their status with respect to heart failure. Until a more complete follow-up has been done, it is unclear how useful self-report of CHF is as an outcome in the AHS-2.

B. Limitations

There are several limitations in the research work that must be addressed.

The major limitation with the study of the outpatient population at the cardiomyopathy clinic was number of subjects and thus power. The main risk estimates of survival did not reach statistical significance. The hazard ratios of β-blocker and ACEi/ARB dosages showed that survival of heart failure improved with recommended dosages of medication, but was not statistically significant for either systolic or diastolic hear failure.

The primary limitation of the Adventist Health Study-2 heart failure validation study was non-responsiveness due to loss-to-follow-up. Both cases and non-cases were attempted to be initially contacted by phone, but a significant portion of the phone numbers were disconnected. Up-to-date phone numbers of participants with disconnected numbers were sought by calling personal contacts and affiliate churches, and the information about these was obtained from the baseline questionnaire. Online people searches were done after these sources had been exhausted. Despite these efforts, many selected cases and non-cases were unable to be found. Tracking down the medical records of deceased participants was even less successful due to the difficulty tracing family members and close family friends who had knowledge of their former physicians. In addition, the records of the deceased were often in remote storage or were otherwise inaccessible.

C. Conclusions

Results from the study conducted at Loma Linda University Medical Center (LLUMC) cardiomyopathy clinic showed that recommended target dosages of B-adrenergic blockade (β-blockers) and angiotensin-converting-enzyme inhibitors ACE and/or angiotensin II receptor blockers (ARB) may reduce mortality among its systolic heart failure patients. It also showed that β-blockers and ACEi/ARB therapy may improve survival among diastolic heart failure patients. Improvements in heart failure prognosis due to drug therapies seen in clinical trials translate to actual heart failure prevalent populations such as the outpatients at LLUMC. These results may serve to give assurance to medical practitioners that pushing for recommended dosages will be worthwhile, whether their patients have systolic or diastolic heart failure.

The sensitivity, specificity and negative predictive values of self-reported congestive heart failure were high in the Adventist Health Study-2 (AHS-2) heart failure validation study. The total agreement between self-reported heart failure and medical records was also good. Nearly 57% of self-reports of heart failure were validated by medical records. Misperception of what heart failure is may have influenced the modest positive predictive value.

D. Recommendations

There is great potential, for both studies that make up this dissertation, for continuation in the future.

It would be beneficial to gain more power in the clinic study from the Loma Linda University Medical Center. Sufficient power can be achieved by an increase in person-years. This can be done by either extending the enrollment period to include more patients or by extending the length of the follow-up time of the study.

The Adventist Health Study-2 (AHS-2) self-reported heart failure study can be continued in order to improve the response rate. More extensive people searches, using online paid registries, can be done to minimize loss-to-follow-up. This will ensure that the results are a well-rounded representation of the entire AHS-2 cohort.

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APPENDICES

A. Telephone script for CHF subjects

Good morning, my name is [name] and I am calling from the Adventist Health Study at Loma Linda University. Is [name] available to answer some questions for the study?

If yes:

Hello, how are you doing today?

I am calling to confirm your responses to the questionnaire you completed when you enrolled in the study several years ago.

You said that you had been diagnosed with heart failure. And we'd like to confirm your diagnosis from your medical records. Would you give us permission to obtain a copy of your medical records to confirm your diagnosis?

If permission is given:

Thank you very much. Be assured that we will protect the confidentiality of your records just like any doctor's visit. We will need your signed permission so I am going to send you a standard consent form to sign and you should receive it in about a week. It just needs your signature and then on the back you can fill out the contact information of your cardiologist. Do you have a cardiologist that you see regularly, a family doctor?

Once you sign the consent form and fill out the information, you can send it right back to us in the stamped envelope that will be included.

Do you still live at [address]? Confirm address!

THANK YOU very much. We greatly appreciate your participation in AHS. We encourage you to sign and send back the consent form as soon as you receive it in your mail.

If no: Is there a better time to call back?

If deceased: I'm very sorry for your loss. When did he/she pass away?

The reason I'm calling is …

[Name] in indicated that he/she had been diagnosed with heart failure in the questionnaire when he/she first enrolled in the study. And we are trying to confirm his/her diagnosis from medical records. Do you still have the contact information of the family doctor or cardiologist that he/she saw regularly?

[Name of hospital/clinic, address, etc.] Again, THANK YOU very much. We greatly appreciated [name]'s participation in AHS-2.

B. Informed consent

The Adventist Health Study may be performed only by using personal information relating to your health. National and international data protection regulations give you the right to control the use of your medical information. Therefore, by signing this form, you specifically authorize your medical information to be used or shared as described below.

The following personal information, considered "Protected Health Information" (PHI) is needed to conduct this study and may include:

The date the congestive heart failure was diagnosed

Symptoms that prompted the diagnosis of the congestive heart failure

The ICD-10 code of the congestive heart failure

The level of disability after the event/ diagnosis and currently

The Imaging information and findings

The reporting hospital/ clinic

The primary physician

The individual(s) listed at the top of this page will use this protected health information (PHI) to conduct the Adventist Health Study. It may on occasion during the course of the study also be shared with the Institutional Review Board (IRB) and the Office of Research Affairs of Loma Linda University.

The main reason for sharing this information is to be able to conduct the study as described earlier in the consenting process. In addition, it is shared to ensure that the study meets legal, institutional and accreditation standards.

All reasonable efforts will be used to protect the confidentiality of your PHI, which may be shared with others to support this study, to carry out their responsibilities, to conduct public health reporting and to comply with the law as applicable. Those who receive the PHI may share with others if they are required by law.

Subject to any legal limitations, you have the right to access any protected health information created during this study. You may request this information from the Principal Investigators named above,, but it will only become available after the study analyses are complete. The authorization expires upon the conclusion of this research study.

You may change your mind about this authorization at any time. If this happens, you must withdraw your permission in writing. Beginning on the date you withdraw your permission, no new personal health information will be used for this study. However, study personnel may continue to use the health information that was provided before you withdrew your permission. If you sign this form and enter the study, but later change your mind and withdraw your permission, you will be removed from this part of the study

at that time. To withdraw your permission, please contact the Principal Investigator or study personnel at 1-800-247-1699.

You may refuse to sign this authorization. Refusing to sign will not affect the present or future care you receive at this institution and will not cause any penalty or loss of benefits to which you are entitled. However, if you do not sign this authorization form, you will not be able to take part in this portion of the Adventist Health Study. You will receive a copy of this signed and dated authorization.

I agree that my personal health information may be used for the study purposes described in this form.

C. Telephone script for non-CHF subjects

Good morning, my name is [name] and I am calling from the Adventist Health Study-2 at Loma Linda University. Can I speak to [name]?

If yes:

Hello, I am calling today to confirm your responses to the questionnaire you completed when you enrolled in the AHS in [date]. May I take a few moments of your time to clarify some things with you?

a. Have you ever been told by a physician that you have congestive heart failure or CHF? (If so, what date/year?)
b. Have you ever regularly experienced abnormal swelling in your lower extremities within the last 5 years (If yes, did the doctor tell you the cause of this?)?
c. Have you ever regularly experienced abnormal shortness of breath with exertion or when you're lying down within the last 5 years (If yes, did the doctor tell you the cause of this?)?
d. Are you currently taking any heart medicines such as beta blockers, diuretics, ARB, or ACE-inhibitor for (ankle) swelling or breathlessness? (Ask them to read list of their medicines from bottles or a list, not off the top of their heads, exclude vitamins or diet supplements)
e. Have you had an echo, or a heart ultrasound?

Will ask for medical records if:

1. subject answers yes to "a" OR
2. "b or "c" AND "d" or "e"

If their answers indicate that they have been diagnosed with CHF previous to enrollment date:

Would you give us permission to obtain a copy of your hospital records to confirm your diagnosis?

If permission is given: Thank you very much. Be assured that we will protect the confidentiality of your records just like any doctor's visit. We will need your signed permission so I will send you a standard consent form to sign. You should receive it in about a week. It will only need your signature and then you can send it right back to us in the stamped envelope that will be included.

Do you have a family doctor or cardiologist that you see regularly? Can we have his name and contact information?

[Name, name of hospital/clinic, address]

If their answers indicate that they have NOT been diagnosed with CHF: Go to end.

THANK YOU very much for your time. We greatly appreciate your participation in AHS-2. We expect that this work will lead to new understanding about lifestyle and heart disease and very much need you to continue on with the study.

If no: When would be a good time to call back? Thank you very much for your time.

If they cannot speak for themselves or confused with questions: Ask if there is someone there so can answer on their behalf (surrogate).

If they are next of kin: I am calling today to confirm Mr./Mrs. [name]'s responses to the AHS-2 enrollment questionnaire that was filled out in [date] May I take a few moments of your time to clarify some things with you? [Go to questions.]

If deceased: I'm very sorry for your loss.

Ask questions and ask for MD contact.

Conclusion

Again, THANK YOU very much. We greatly appreciate your participation in AHS-2. We expect that this work will lead to new understanding about lifestyle and heart disease and very much need you to continue on with the study.

D. Letter to cardiologist / medical records

Dear Dr. [name],

Your patient [name] ([date of birth]) is a member of a lifestyle-disease outcome research study called the Adventist Health Study (AHS-2), a longitudinal study of 96,000 subjects from all over the United States. The health experience of subjects like your patient is expected to be particularly informative in our research of how lifestyle factors may prevent and modify diseases like heart failure.

Mr./Ms. [name] reported that he/she was diagnosed with heart failure previous to the AHS-2 baseline questionnaire he/she completed in [date] and has signed the enclosed consent form allowing us to contact you so that we can validate his/her diagnosis status at study enrollment.

If your patient has **NEVER** been diagnosed with heart failure, we would appreciate it if you check the box for the statement on the back of this page and mail it back to us. If your patient has **EVER** been diagnosed with heart failure, we would appreciate if you could fill out the short questionnaire on the back of this page and provide us with the following information regarding the diagnosis and mail it back to us:

1. Date of HF diagnosis
2. HF clinic notes near time of HF diagnosis
3. echo near time of HF diagnosis
4. ECG near time of HF diagnosis
5. BNP near time of HF diagnosis
6. Medication list near time of HF diagnosis

Although some of this information may not be available and your patient may have been treated for HF prior to your first encounters, **ANY** details that you could supply would be most helpful. Please contact the study at (800) 247-1699 if you have any questions.

Thank you for your attention and assistance in this matter.

Yours sincerely,

Gary E. Fraser MD, PhD, FRACP, FACC

Professor of Medicine, School of Medicine

Professor of Epidemiology, School of Public Health, Loma Linda University

E. Short questionnaire

1. Did your patient ever experience **edema** due to heart failure?
2. Did your patient ever experience **dysnea** due to heart failure?