Comorbidities and Physical and Cognitive Impairments in Elderly Heart Failure Patients: Impact on Total Mortality. The Cardiovascular Health Study

By

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I dedicate this work to the two most precious blessings in my life, my beloved wife Grace and our son Daniel.
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LIST OF ABBREVIATIONS

HF: Heart Failure

HFPEF: Heart Failure and Preserved left ventricular Ejection Fraction

HFREF: Heart Failure and Reduced left ventricular Ejection Fraction

WHI: the Women’s Health Initiative

CHS: the Cardiovascular Health Study

MMSE: Mini-Mental State Examination

3MSE: Modified Mini-Mental State Examination

NYHA: New York Heart Association

CKD: Chronic Kidney Disease

DIG: Digitalis Intervention Group

I-Preserve: the Irbesartan in Heart Failure with Preserved Ejection Fraction Study

RPM: Risk Prediction Model

LVEF: Left Ventricular Ejection Fraction

SHFM: Seattle Heart Failure Model

PRAISE1: the Prospective Randomized Amlodipine Survival Evaluation trial
ADL: Activities of Daily Living

IADL: Instrumental Activities of Daily Living

DM: Diabetes Mellitus

CHD: Coronary Heart Disease

PVD: Peripheral Vascular Disease

GFR: Glomerular Filtration Rate

AUC: Area Under the Curve
ABSTRACT

Heart failure (HF) in the elderly is increasing in incidence and prevalence, and its outcome has not changed in the past two decades. Elderly patients with HF have high burden of comorbidities and physical and cognitive impairments, which may contribute to their poor outcome. In this study, we aim to measure the prevalence of certain comorbid conditions and measures of physical and cognitive impairments, and their impact on total mortality among participants in the Cardiovascular Health Study (CHS) with incident HF. As a secondary aim, we will examine the utility of comorbidities and measures of physical and cognitive impairments in predicting mortality among CHS participants with incident HF.
Elderly Patients with Heart Failure: The Burden of Comorbidities and Physical and Cognitive Impairments
I. **Introduction:**

Heart failure (HF) has become a major public health problem. There are more than 5.7 million individuals who are afflicted with HF in the United States. HF is responsible for 1 million hospitalizations, 3.4 million outpatient visits, more than 60,000 deaths, and over 39 billion dollars in direct and indirect cost annually. Both incidence and prevalence of HF increase steeply with age. The annual incidence of HF in both men and women doubles with every decade increase in age after age 65, and the prevalence of HF increases from less than 0.5% in the age group of 20-39, to more than 10% in those 80 years and older (Figures 1 and 2). While age-adjusted incidence of HF has seen some decline in the past two decades, especially in women, the overall incidence and prevalence of HF in the elderly is rising. Because of these changes in its epidemiology, HF has become a disease of the elderly with more than 80% of affected individuals above age 65.

Mortality rates from HF in the elderly have not changed in the past 2 decades despite the remarkable innovations in diagnostic and therapeutic modalities for HF. According to the Framingham Heart Study, 59% of men and 45% of women age 65 to 74 die within 5 years of being diagnosed with HF, with an average one-year mortality rate of 20%. In Canada, hospitalized patients whose primary diagnosis was HF were found to have 3 fold greater risk of 30-day mortality than all other hospitalized patients. Although there has been some overall improvement in survival of patients with HF over the past two decades, this improvement has not impacted elderly patients with the more common type of HF, HF with preserved left ventricular ejection fraction (HFPEF).
HF in the elderly differs from HF in middle age adults in many aspects including its risk factors, pathophysiology, clinical course, and response to HF therapies. Elderly patients with HF are more likely to have hypertensive cardiomyopathy and diastolic dysfunction while middle age adults with HF are more likely to have ischemic cardiomyopathy and systolic dysfunction. Management of elderly patients with HF is challenging and often empirical due to insufficient evidence from randomized clinical trials. HF-specific therapies that are proven effective and beneficial in middle age adults with HF failed to show similar benefit when tried in older patients, especially in those with HFPEF.

In recent years, there has been a growing interest among researchers in understanding the differences between HF in the elderly and HF in younger persons, particularly in its clinical course, lack of response to therapies, and unchanging poor outcome. Perhaps the most striking feature that distinguishes elderly patients with HF is their high burden of comorbidities and physical and cognitive impairments. In a recent review, we discussed the complex relationship and potential interaction between HF and its associated frailty and multiple comorbidities in the elderly patient. This complex relationship imposes many challenges on the management of HF in the elderly and ultimately impacts its clinical course and outcome. For the remainder of this chapter, we will review available evidence about the prevalence of comorbidities and physical and cognitive impairments in elderly patients with HF, the impact of these conditions on outcome of HF, and their potential utility in survival prediction of this patient population. We will conclude this chapter by presenting our research aims and hypotheses.
II. The prevalence of comorbidities and physical and cognitive impairment in elderly patients with HF:

Comorbidities are common among the elderly and far more common in those with HF. Wolff reported that 82% of the 1999 US Medicare beneficiaries aged ≥ 65 had one or more chronic conditions and 65% had multiple chronic conditions. The burden of comorbidities in elderly patients with HF is much higher than in those without HF. Braunstein et al. studied the burden of non-cardiac comorbidities in 22,630 patients with HF, 65 years and older, identified in a 5% random sample of all US Medicare beneficiaries. They found that 40% of these patients had ≥ 5 comorbidities, 70% had ≥ 3 comorbidities, and only 4% had no (non-cardiac) comorbidities at all. This is in strong contrast to middle aged patients with HF who usually have a lesser burden of comorbidities. In a recent study by Ahluwalia et al. on similar population of US medicare beneficiaries with HF, the investigators reported an increase in the burden of comorbidities with age, and this increase was greatest for discordant comorbidities (comorbidities not directly related to HF) among the oldest old. Most recently, Dai et al. studied the burden of comorbidities among elderly patients admitted to acute care hospitals in Canada with a primary diagnosis of HF. He found that these patients have on average 3.9 comorbidities and the most commonly reported ones are ischemic heart disease, atrial fibrillation and flutter, diabetes mellitus, and renal failure. He also identified the most common primary admission diagnoses in patients who had HF reported as secondary diagnosis and those were acute myocardial infarction, exacerbation of chronic obstructive pulmonary disease, and pneumonia.

Physical impairment is common among the elderly, and especially those with HF. Frailty, an established objective measure of physical impairment, is recognized as a common
finding among the elderly. Based on the Fried criteria, it is estimated that 6.9% of older community dwelling adults are frail\textsuperscript{16}. Investigators found that the prevalence of frailty increased sharply with age, from 3.2% among persons 65-70 years old to 23.1% among persons 90 years and older\textsuperscript{16}. Frailty is even more common among the elderly with HF. Participants of the Womens Health Initiative (WHI) who had HF were 6 to 7 fold more likely to be frail than those without HF (Odds ratio (OR) = 6.16, 95% confidence interval (CI) = 4.97-7.64)\textsuperscript{17}. In the Cardiovascular Health Study (CHS), the prevalence of HF increased from 1.8% in the non-frail, 4.6% in the intermediate group, to 14.0% in the frail group, with an adjusted OR of 7.51 (95% CI: 4.66-12.12)\textsuperscript{18}.

Cognitive impairment is also common among elderly patients with HF. In a cross sectional study of 1075 individuals above the age of 65 in southern Italy, Cacciatore et al., reported that individuals with chronic HF were more likely to have cognitive impairment than those without HF (OR: 1.96, 95% CI: 1.07-3.58, $P < 0.028$)\textsuperscript{19}. They also found that individuals with cognitive impairment were 5 times more likely to have chronic HF. More recently, Debette et al. found higher prevalence of cognitive impairment in patients hospitalized with decompensated HF, and that the severity of cognitive impairment as measured by the mini-mental state examination scoring system (MMSE) was parallel to the severity of HF as measured by the New York Heart Association (NYHA) functional class\textsuperscript{20}. This finding remained significant even after adjusting for cerebrovascular disease (stroke and transient ischemic attacks).

III. **The impact of comorbidities and physical and cognitive impairment on outcome of elderly patients with HF:**
The comorbidities frequently seen in elderly patients with HF contribute greatly to their poor outcomes including rates of hospitalizations, rehospitalizations, and mortality. Braunstein et al. reported that risk of hospitalization, potentially preventable hospitalization, and death strongly increased with the increase in the number of chronic conditions among US Medicare Beneficiaries above the age of 65 who had HF\textsuperscript{11}. Interestingly, he found that the 40% of the elderly HF population who had ≥5 comorbidities were responsible for 81% of the total inpatient hospital days experienced by all HF patients. Among comorbidities that were found to be consistently associated with notably higher risks for CHF-preventable and all-cause preventable hospitalizations and mortality were chronic obstructive pulmonary disease and bronchiectasis, renal failure, diabetes mellitus, depression, and other lower respiratory disease\textsuperscript{11}.

Substantial variation exists in the reported impact of comorbidities on the outcome of elderly patients with HF. This variation may be driven in part by the complex relationships and possible interactions between these comorbidities and patient’s various characteristics including age, sex, type of HF, functional status, and cognition\textsuperscript{12}. The impact of certain comorbidities on outcome varies by the HF population being studied. For instance, while hypertension was found to increase risk of mortality among patients with stable HF\textsuperscript{11}, several studies have shown that higher blood pressure during acute decompensated HF, especially HF with Reduced left ventricular Ejection Fraction (HFREF) signifies better survival\textsuperscript{21,22}. The impact of certain comorbidities on outcomes also varies by the level of severity of the comorbidity. For instance, chronic kidney disease (CKD) was found to be associated with greater risk of all-cause mortality in a metanalysis of more than 80,000 hospitalized and non-hospitalized HF patients, and that risk was proportional to the degree of impairment in renal function (Hazard ratio (HR): 1.07 (1.04-1.10) for every 10 ml/min lower glomerular filtration rate)\textsuperscript{23}. Similar findings were reported by
Campbell et al. among participants in the digitalis intervention group (DIG) trial where CKD was associated with significantly greater risk of all-cause hospitalization, cardiovascular hospitalization, HF hospitalization, and all-cause mortality, and that the increased risk was proportional to the degree of renal impairment \(^24\). That

The relationship between the severity of comorbid conditions and outcomes in patients with HF is sometimes complex and non-linear. The obesity paradox in HF is an example of such a complex relationship. While several studies have reported a positive association of obesity with survival of patients with HF, they all indicated the complexity of the relationship \(^{25\text{-}27}\). Recently, Hass et al. reported that in patients with HFPEF who participated in the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-Preserve), higher BMI was associated with more favorable outcome, and the relationship between BMI and survival was non-linear and took a U shape \(^{28}\).

Physical impairment is associated with poor outcome in elderly patients with HF. Among 120 patients with HF (age 75.9±6.7), Cacciatore et al. found significantly higher risk of death in those with a Lachs frailty score of 2 or 3 than in those with a score of 0 or 1 (adjusted HR: 1.62, 95% CI: 1.08-2.45) \(^{29}\). After 9 years of follow-up, the probability of death in patients with HF and frailty score of 3 was 100% as compared with 55% in patients with HF and frailty score of 1. Another study by Pulignano showed significantly higher rate of 1-year mortality (16.9% vs. 4.8%; \(P < 0.001\)) and higher rate of hospitalization (20.5% vs. 13.3%; \(P = 0.01\)) in elderly patients with HF who had frailty than in those who did not \(^{30}\). Cognitive impairment is also associated with poor outcome in elderly patients with HF. Zuccala et al. reported almost 5 fold greater risk of in-hospital mortality among patients hospitalized with HF who had cognitive impairment \(^{31}\).
IV. Prediction of mortality risk and survival in elderly patients with HF; The role of comorbidities and physical and cognitive impairments:

In elderly patients with HF, where 5-year mortality exceeds 50%, accurate prediction of mortality risk and survival and the identification of its major determinants are of paramount clinical importance. Such knowledge facilitates the formulation of informed and responsible care plans that could improve patient and clinician satisfaction, patient outcomes, and efficiency of health care resource utilization. Several risk prediction models (RPM) for prediction of mortality risk and survival in HF have been developed in the past 2 decades. However, these models have been derived largely from participants of clinical trials targeting mostly middle age patients, mainly with HFREF and with little emphasis on comorbidities. None of the available RPMs has targeted specifically older patients with HF, or those with HFPEF. Below we will discuss 2 RPMs developed to predict mortality in 2 different populations of patients with HF.

The first model was developed by Brophy et al. for predicting survival among participants in the DIG trial who have primarily HFREF. They found that lower ejection fraction, worse renal function, cardiomegaly, worse NYHA functional class, signs or symptoms of heart failure, lower blood pressure, and lower body mass index were all associated with reduced 12-month survival. They also found that the same variables along with age and baseline use of nitrates were also predictive of 36-month mortality. When validating this model, Brophy found that the model performed better in predicting survival in those with the lowest mortality risk (correlation between predicted and observed survival rates were best in the lowest decile of mortality risk). This finding suggests that there are other determinants of death not included in this model that are responsible for death in those with higher rates of mortality. These
determinants are perhaps measures of comorbidities and physical and cognitive impairments. The population used to derive this model were relatively young (mean age: 63.3 ± 11.0 years), and had HFREF (mean left ventricular ejection fraction (LVEF): 28% ± 9%) who may not represent the majority of patients with HF who are elderly and have mostly HFPEF. Since these patients were participants in a randomized clinical trial, selection bias and exclusion of those who possibly had the highest burden of comorbidities and physical and cognitive impairment could not be avoided.

The second model, developed by Levy et al., is the Seattle Heart Failure Model (SHFM)\textsuperscript{33}. The model was designed to predict 1-, 2-, and 3-year survival of patients with HF using easy to obtain variables from patient’s history and basic laboratory tests. Like the model discussed earlier, patients used to derive this model were participants in a randomized clinical trial (the Prospective Randomized Amlodipine Survival Evaluation (PRAISE1) trial)\textsuperscript{37}, were relatively young (mean age of 65 ± 11), and had HFREF (mean LVEF of 21% ± 6%). The model was validated in 5 other cohorts of patients who were predominantly young (all but one cohort had mean age below 65 years), had mostly HFREF (only one cohort had about one third of its participants with LVEF>40%), and were mostly participants in RCTs with only one validation cohort taken from a population based study\textsuperscript{38-42}.

To our knowledge, there has been no RPM specifically developed in elderly patients with HF, and no RPM targeting patients with HF has comprehensively included measures of comorbidities and physical and cognitive impairments.

V. \textbf{Research Aims and Hypotheses:}
The majority of evidence we have discussed in this review about the prevalence of comorbidities and physical and cognitive impairments, and their impact on mortality in elderly patients with HF is derived from elderly populations with prevalent HF. Such knowledge may not be generalized to a growing elderly population with incident HF as a great deal of interaction may exist between HF and these conditions, precipitating their development and accelerating their progression. Determining the impact of comorbidities and physical and cognitive impairments on outcome at the time of HF diagnosis might empower clinicians to better estimate prognosis and formulate sound treatment plans. In addition, the evidence is scarce that addresses age and sex differences in the prevalence of these conditions and their association with mortality risk in HF.

In this study, we propose to examine the burden of comorbidities and physical and cognitive impairments among CHS participants with incident HF at the time of their diagnoses, and to determine the associations of these impairments with total mortality. In addition, we will examine the utility of measures of comorbidities and physical and cognitive impairments in predicting short-term and long-term mortality risk and survival in this patient population. Selection of comorbidities for this study was based on feasibility and data availability, clinical relevance, and available evidence. Selected comorbidities included hypertension, diabetes mellitus, CKD, coronary heart disease, peripheral vascular disease, atrial fibrillation, cerebrovascular disease, obstructive airway disease, and depression. Measures of physical impairment included activities of daily living, instrumental activities of daily living, and 15-minute walk time. Measures of cognitive impairment included the modified mini-mental status examination.
CHS is a population-based, longitudinal study of coronary heart disease and stroke in adults aged 65 years and older, funded by the National Heart, Lung, and Blood Institute [Fried 1991]. The main goal of the study was to identify factors related to the onset of coronary heart disease and stroke. HF is among 6 main outcomes with predetermined CHS ascertainment criteria, others being myocardial infarction, angina pectoris, transient ischemic attack, stroke, and death. Participants (n=5,888) were recruited between the years of 1989 and 1991 from 4 US counties (Forsyth county, NC; Sacramento county, CA; Washington county, MD; and Pittsburgh county, PA). Recruitment strategies and inclusion and exclusion criteria for the CHS were reported elsewhere [Tell 1993]. Participants were followed with clinic visits for the first 10 years and annual phone calls thereafter. During each clinic visit, participants had full history, physical examination, and certain tests performed and the development of any outcomes was ascertained. Phone calls were limited to ascertaining the development of any CHS main outcome.

Our study sample is an inception cohort of CHS participants with incident HF. The time of HF diagnosis is considered the baseline and the time of entry into the study. Cases of incident HF in CHS were included if their baseline characteristics at the time of diagnosis of HF could be determined. These baseline characteristics were determined by carrying forward measurements performed during the clinic visit preceding the diagnosis of HF. Missing values were replaced by values carried forward from prior clinic visits given that the carry forward time did not exceed a maximum of 3 years.

**Primary Aims and hypotheses:**
1) Identify the prevalence of specific comorbidities and measures of physical and cognitive impairments among elderly patients with incident HF in the CHS population, and examine whether this prevalence differs by sex and age group. 

_Hypothesis: Elderly patients with HF have a high burden of comorbidities and physical and cognitive impairment that may differ between men and women and between different age groups._

2) Determine the risk (hazard) of death associated with comorbidities and physical and cognitive impairments among elderly patients with incident HF in the CHS population, and examine whether this risk differs by sex and age group. 

_Hypothesis: Measures of comorbidities and physical and cognitive impairments are associated with greater risk of death among elderly patients with HF that increases in older age groups and may differ between men and women._

**Secondary Aim and hypothesis:**

Examine the utility of measures of comorbidities and physical and cognitive impairments in estimating mortality risk and predicting short-term and long-term survival in elderly patients with incident HF in the CHS population.

_Hypothesis: Inclusion of measures of comorbidities and physical and cognitive impairments in a risk prediction model for predicting survival among elderly patients with HF improves the performance of such model in predicting short-term and long-term survival._
Figure 1: Incidence of heart failure by age and sex (Framingham Heart study: 1980-2003). Source: National Heart, Lung, and Blood Institute.

**Figure 3:** An illustration of the complex relationships between frailty, comorbidities, and heart failure in the elderly (reproduced and modified with permission from Murad et al. 12):
CHAPTER 2

Comorbidities and Physical and Cognitive Impairments in Elderly Heart Failure Patients: Impact on Total Mortality. The Cardiovascular Health Study (CHS)
I. ABSTRACT

Background: Comorbidities and physical and cognitive impairments are common in the elderly and often associated with greater mortality risk. However, the prevalence of these conditions and their associated mortality risk in elderly patients with incident HF is unknown.

Methods: We examined the prevalence of 9 comorbidities, 3 measures of physical impairment, and 1 measure of cognitive impairment in 558 participants from the Cardiovascular Health Study (CHS) who developed incident HF between 1990 and 2002. Participants were followed prospectively until mid-2008 to determine their mortality risk.

Results: Mean age of participants was 79.2 ± 6.3 years with 52% being men. The burden of comorbidities was high; 60% of cases had ≥ 3 comorbidities, and only 2.5% had none. Twenty-two percent and 44% of cases had ≥ 1 activity of daily living (ADL) and ≥ 1 instrumental activity of daily living (IADL) impaired respectively. Cognitive impairment (modified mini-mental state exam (3MSE) score < 80) was present in 17% of cases. During follow up, 504 participants died, with 1-year and 5-year mortality rates of 19% and 56% respectively. In a multivariable-adjusted model, the following were significantly associated with greater total mortality risk (hazard ratio; 95% confidence interval): diabetes mellitus (1.64; 1.33-2.03), chronic kidney disease (1.32; 1.07-1.62 for moderate disease; 3.00; 1.82-4.95 for severe), cerebrovascular disease (1.53; 1.22-1.92), and depression (1.44; 1.09-1.90); physical impairment (1.30; 1.04-1.63 for 1 IADL impaired; 1.49; 1.07-2.04 for ≥ 2 IADL impaired); and cognitive impairment (1.33; 1.02-1.73 for 3MSE score < 80). Other comorbidities (hypertension, coronary heart disease, peripheral arterial disease, atrial fibrillation, and obstructive airway disease) and
measures of physical impairments (ADLs and 15-foot walk time) were not associated with mortality.

**Conclusion:** Elderly patients with incident HF have a high burden of comorbidities and physical and cognitive impairments, and some of these conditions are associated with greater mortality risk.
II. INTRODUCTION

Heart failure (HF) afflicts 5.7 million individuals in the United States with 80% of those afflicted above the age of 65. While age-adjusted incidence of HF has seen some decline in the past 2 decades, especially in women, the overall incidence and prevalence of HF in the elderly continue to rise. Mortality rates in elderly patients with HF remain high. According to the Framingham Heart Study, 59% of men and 45% of women age 65 to 74 die within 5 years of being diagnosed with HF, with an average one-year mortality rate of 20%. Although there has been some overall improvement in survival of patients with HF over the past two decades, this improvement has not impacted the elderly.

HF in the elderly differs markedly from HF in younger patients. Elderly patients with HF are more likely to have hypertension-associated diastolic dysfunction and often develop HF and preserved left ventricular ejection fraction (LVEF), (HFpEF), while younger patients with HF are more likely to have dilated cardiomyopathy and manifest with systolic dysfunction and reduced LVEF, (HFrEF). HFpEF, more commonly seen in the elderly, has shown no favorable response to HF therapies that were proven effective in those with HFrEF.

Perhaps the most striking feature that distinguishes elderly patients with HF from other HF populations is their high burden of comorbidities and physical and cognitive impairments, and these conditions could adversely impact their outcome. Several studies have consistently shown that these conditions are common in patients with prevalent HF and may be associated with higher rates of mortality and hospitalization. However, to our knowledge, the prevalence of these conditions among elderly patients with incident HF and their impact on mortality have not been assessed.
The two main objectives of this study were: to identify the prevalence of specific comorbidities and measures of physical and cognitive impairments in elderly patients with incident HF, and to determine the mortality risk associated with these conditions among participants in the Cardiovascular Health Study (CHS) with incident HF.

III. METHODS:

Study population and study design:

CHS is a population-based longitudinal study of cardiovascular disease in adults aged 65 years and older, funded by the National Heart, Lung, and Blood Institute. The total number of participants was 5,888; of these, 5201 were recruited between 1989 and 1990 and 687 were recruited between 1992 and 1993. Participants were recruited from 4 US counties (Forsyth county, NC; Sacramento county, CA; Washington county, MD; and Pittsburgh county, PA). Participants were followed with annual clinic visits through 1998-1999 and with phone calls every 6 months, which are ongoing. During each clinic visit, participants had a full medical history, a physical examination, and a panel of tests that varied each year. The development of CHS main outcomes (coronary disease, angina, HF, stroke, transient ischemic attack, claudication, and mortality) were assessed during each clinic visit and phone call and adjudicated according to study protocol.

Our study sample was an inception cohort of CHS participants with incident HF adjudicated according to pre-specified criteria. For a participant to be considered as having incident HF, he or she must report a new clinical diagnosis of HF made by a physician, and be actively on prescription medications for HF including both a diuretic and either a digitalis preparation or a vasodilator. All CHS participants with incident HF diagnosed between 1990
and 2002 were considered eligible for inclusion in our study if the values of associated characteristics could be determined within a maximum of 3 years prior to the date of the diagnosis of HF. Eligible participants entered our study at the time of their HF diagnosis and were followed until they died or were censored at the end of follow-up (June 30, 2008).

**Baseline characteristics:**

Two groups of baseline characteristics were considered in our study: patient-specific demographic and clinical characteristics, and measures of comorbidities and physical and cognitive impairments. Values of these characteristics for each participant were determined at the time of HF diagnosis by carrying forward measurements from the annual clinic visit immediately preceding that diagnosis. In cases when that clinic visit was missed or certain characteristics were not measured, values were carried forward from previous clinic visits provided that carrying forward time did not exceed a maximum of 3 years.

Patient-specific characteristics included age at the time of HF diagnosis, sex, race (white or non-white), smoking status (non-smoker, former smoker, or current smoker), body mass index (BMI) (kg/m²), and CHS clinic location. Measures of comorbidities included a general assessment of self-reported health status and the presence or absence of 9 specific comorbidities: hypertension (HTN), diabetes mellitus (DM), chronic kidney disease (CKD), coronary heart disease (CHD), peripheral arterial disease (PAD), atrial fibrillation (AF), cerebrovascular disease, obstructive airway disease, and depression. HTN was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or being treated with antihypertensive medications. DM was defined as fasting serum glucose ≥ 126 mg/dl, non-fasting serum glucose ≥ 200 mg/dl, or being treated with oral hypoglycemic medications or insulin. CKD was defined
according to estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease Study (MDRD) equation\textsuperscript{47}. CKD was considered moderate if eGFR < 60 and ≥ 30 ml/min/1.73 m\textsuperscript{2}, and severe if eGFR < 30 ml/min/1.73 m\textsuperscript{2}. CHD was defined as having a history of physician-diagnosed angina or myocardial infarction, or a history of coronary revascularization. PAD was defined based on the presence of CHS-adjudicated claudication (participant-reported exertional leg pain relieved by rest in addition to either physician diagnosis of claudication or an ankle-arm blood pressure ratio of less than or equal to 0.8). AF was defined as having a rhythm consistent with AF on electrocardiogram taken during clinic visit. Cerebrovascular disease was defined as having confirmed history of stroke or transient ischemic attack. Obstructive airway disease was defined as having a history of asthma, bronchitis, or emphysema. Depression was defined as having patient-reported depressive symptoms for 3 or more days within the past week preceding the clinic exam.

Measures of physical impairment included impairment in activities of daily living (ADLs), impairment in instrumental activities of daily living (IADLs), and 15-foot walking time. Impairment in ADLs and IADLs was determined based on participant’s response to whether or not the participant was having difficulty in each of 6 ADLs (walking around the home, getting out of bed, eating, dressing, bathing, and using the toilet) and 6 IADLs (heavy housework, light housework, shopping, preparing meals, paying bills, and using the phone). Fifteen-foot walking time was measured during clinic visits. The measure of cognitive impairment consisted of modified mini-mental state examination (3MSE) score, with a maximum score of 100. The 3MSE has been used reliably by Arnold et al. to screen for cognitive decline among CHS participants\textsuperscript{48}. Cognitive impairment was defined by a 3MSE score below 80 \textsuperscript{49}.

**Statistical analysis:**
Baseline (proximate to CHF onset) characteristics were reported using percentages for categorical variables, and means and standard deviations (SD) for continuous variables. Two sets of subgroup analyses were performed comparing baseline characteristics between men and women in the first set, and between 3 different age groups (age: 66-75, 76-85, and > 85) in the second set. These comparisons were carried out using table analysis with exact Fisher’s test for categorical variables, and 2-sample t-test or analysis of variance (ANOVA) for continuous variables. Normality was assessed and non-normally distributed continuous variables underwent logarithmic transformation.

Burden of comorbidities was measured as the total number of comorbidities, out of the 9 selected comorbidities. Burden was reported as a continuous variable, by reporting both mean and median, and as a categorical variable by dividing the study sample into 6 categories (0, 1, 2, 3, 4, and ≥ 5). Correlations between the burden of comorbidities and measures of physical and cognitive impairment were tested using Spearman correlation coefficients.

Cox proportional hazard regression analysis was used to calculate 2 estimates of the hazard (risk) ratio (HR) of death associated with each baseline characteristic. Estimate 1 was adjusted for patient-specific variables only (age, sex, race, BMI, smoking status, and CHS center). This estimate was calculated based on all available participants, as well as based on participants with complete data. The “all available participant estimate” was done to assess for selection bias. Estimate 2 was adjusted for patient-specific variables as well as all other measures of comorbidities and physical and cognitive impairments. A two-tailed alpha of 0.05 was used to determine significance of all statistical tests and parameter estimates. All HRs were reported with their 95% confidence intervals (CI). All analyses were performed using SAS 9.1 and SAS Enterprise Guide 4 (SAS Institute, Cary, NC, USA).
IV. RESULTS:

The prevalence of comorbidities and physical and cognitive impairments:

Among the 1193 CHS participants who were diagnosed with incident HF between 1990 and 2002, there were 558 participants who had all their baseline characteristics determined at the time of HF diagnosis and were included in our study. The remaining 635 participants were excluded because of having one or more baseline characteristics missing or not measured within a maximum of 3 years prior to HF diagnosis.

Baseline characteristics for the total study sample and for different sex and age group strata are shown in Table 1. The mean age of participants was 79.2 years with approximately 52% being men and 87% white. More than half of the participants reported being former or current smokers. The mean BMI was 27.1 kg/m$^2$, with 23.3% being obese (BMI $> 30$), 40.3% being overweight (BMI 25-30), and 3.2% being underweight (BMI $< 20$). Almost 40% of participants reported being in fair or poor health status. LVEF was measured in 53% of our sample (294 participants). 48% of participants with known LVEF had HFpEF (LVEF $> 45$%). HFpEF was significantly more common in women than in men, but did not differ among different age groups. Medication use (prior to, or at the time of HF diagnosis) was as follows: 68.4% used one or more anti-hypertensive medication; only 15.6% used a beta blocker and 19.0% used an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB); 20.1% used a digitalis medication; and 46.5% used one or more diuretic.

The burden of comorbidities was high. Only 2.5% of study participants had none of the 9 selected comorbidities while more than 60% had at least 3 comorbidities (Figure 1). The total number of comorbidities was significantly higher in those with worse self-reported health status.
(Spearman correlation coefficient: $\rho_S = 0.29$, $p < 0.0001$), and significantly correlated with the number of ADLs impaired ($\rho_S = 0.15$, $p = 0.0003$), the number of IADLs impaired ($\rho_S = 0.22$, $p < 0.0001$), and 15-foot walk time ($\rho_S = 0.13$, $p = 0.0027$). Among the selected comorbidities, HTN was by far the most common (82%) followed by CHD (60%). The prevalence of all selected comorbidities did not differ between men and women except for CHD and possibly PAD, which were more common in men than in women. Certain comorbidities, including CHD, cerebrovascular disease, obstructive lung disease, and possibly DM, were more common in the younger age groups (66-75 and 76-85 years old) than in the oldest age group (older than 85 years).

Physical impairment was common, with 10% of participants having $\geq 2$ ADLs impaired and 17% having $\geq 2$ IADLs impaired. More women than men had $\geq 2$ ADLs (22.3 vs 12.1, $P = 0.0016$), and women had significantly longer 15-foot walk time (8.1 vs 6.1 seconds, $P < 0.0001$). Physical impairment was most common in the oldest age group (85 years old) among whom 22.2% of participants had $\geq 2$ ADLs impaired and 31.1% had $\geq 2$ IADLs impaired. Most physical impairment measures, including 15-foot walk time, were significantly worse in the older age group, and some were worse in women. Cognitive impairment (3MSE score < 80) was also common, affecting almost 1 of every 5 participants. Cognitive impairment did not differ between men and women, but was significantly more common in the older age groups (table 1).

**Mortality risk associated with comorbidities and physical and cognitive impairments:**

During follow-up time that lasted up to 18.3 years, 504 participants died (90.3% of study sample). The median survival time was 4.3 years. Kaplan Meier estimates of 1-year and 5-year mortality were 0.19 (0.16-0.23) and 0.56 (0.52-0.61) respectively.
Among patient-specific variables, older age, male sex, former smoking, and current smoking were significantly associated with greater risk (hazard) of death in all estimates (Table 2). Non-white race was associated with greater risk of death, but this association was not significant after adjusting for measures of comorbidities and physical and cognitive impairments (Table 2). Participants who reported having fair-to-poor health status had 59% greater mortality risk compared to those who reported good-to-excellent health status in the demographic adjusted model, but this association was not significant after adjustment for other measures of comorbidities and physical and cognitive impairments. There was a trend toward greater mortality risk in participants with HFrEF as compared with those with HFpEF, which did not reach statistical significance.

Among the nine selected comorbidities, DM, CKD (both moderate and severe/ end-stage), PAD, cerebrovascular disease, and depression were associated with significantly greater mortality risk in all estimates, except for PAD, which lost significance when adjusted for other comorbidities and measures of physical and cognitive impairments. The remaining comorbidities including HTN, CHD, PVD, AF, and obstructive airway disease were not associated with mortality in our study population (Table 2).

Most measures of physical impairment were associated with greater mortality risk in the minimally adjusted estimate, but only impairments in IADLs remained significant after adjusting for other measures of comorbidities and physical and cognitive impairments. Cognitive impairment (3MSE score < 80) was strongly associated with greater mortality risk in all estimates.

V. DISCUSSION:
To our knowledge, this is the first study that used a large inception, population-based, cohort of elderly persons with HF in order to examine the combined burden of comorbidities and physical and cognitive impairments prior to the diagnosis of HF, and the impact of these conditions on total mortality after the diagnosis of HF. Our findings support two major conclusions. Elderly patients who develop HF have a high burden of comorbidities and physical and cognitive impairments at the time of HF diagnosis. Some of these comorbidities and impairments are strongly associated with increased mortality risk.

The demographic attributes of our study participants are similar to those of elderly patients with HF in the community\(^1\). Prevalence of most comorbidities and the burden of physical and cognitive impairments were generally similar to those reported in other studies among persons with prevalent HF\(^{11, 17, 19, 29, 30}\). Comorbidities were equally prevalent in men and women except for higher prevalence of CHD and PAD in men and a higher burden of physical impairment in women. Measures of both physical and cognitive impairments were worst in the oldest age group, consistent with previous reports \(^{16, 34}\).

Among patient-specific characteristics, older age, male sex, former smoking, and current smoking, were all associated with greater mortality risk, while higher BMI was associated with lower mortality risk. Obesity is a known risk factor for HF\(^{50}\), yet in this study and in others, we demonstrated the paradoxical effect of BMI on mortality in HF\(^{51-53}\). Similar paradoxical relationships have been described with blood pressure and serum cholesterol in their relationship with mortality in patients with HF and also in patients with end-stage renal disease and terminal cancers\(^{22, 54}\). Low BMI, cholesterol, and blood pressure in these patient populations could indicate a greater problem of frailty and cachexia, known to be associated with greater mortality risk\(^{12}\). The relationships observed between race and mortality and between self-reported health
status and mortality largely reflected the burden of comorbidities and physical and cognitive impairments, as these relationships became non-significant after adjusting for these conditions. The trend toward greater mortality risk in participants with HFrEF did not reach statistical significance, possibly due to insufficient power since these estimates were based on a much smaller sample size of participants with known LVEF. Previous studies from CHS have showed that participants with HFrEF have a higher mortality rate than those with HFpEF.85

Among the nine selected comorbidities, DM, CKD, cerebrovascular disease, and depression were associated with increased mortality risk, a finding consistent with evidence previously reported in elderly persons with prevalent HF.11, 24, 56, 57 The risk associated with CKD was several fold higher in those with severe and end-stage kidney disease (eGFR < 30 ml/min), than in those with moderate CKD (eGFR between 30-60 ml/min). The loss of association between PAD and increased mortality after adjusting for other comorbidities and impairments indicates the complex relationship these conditions. Most patients with PAD have other comorbidities (cerebrovascular disease, CKD, and DM) and physical impairment.

Contrary to the evidence reported in the general population, HTN and CHD were not associated with higher mortality risk in our elder participants with HF. This finding is consistent with evidence from other populations with HF. Blood pressure did not predict mortality in two large clinical trials, the Digitalis Investigation Group (DIG) Trial and the Irbesartan in heart failure with preserved ejection fraction (I-PRESEVE) trial.57, 58 In fact, Irbesartan had neutral effect on mortality in the I-PRESERVE trial despite reducing systolic and diastolic blood pressure by a mean of 3.8/2.1 mm Hg.9 Likewise, ischemic etiology of newly diagnosed HF was not associated with increased mortality in two separate studies.57, 59 This lack of association between major predictors of HF, namely HTN, CHD, and obesity,50, 60 with increased mortality.
in HF may represent an example of how etiological factors for certain conditions may have altered or negligible prognostic value once HF supervenes.

Conclusion regarding the lack of association between the remaining comorbidities (obstructive airway disease and AF) and mortality should be approached with caution. Unlike the preceding conditions, ascertainment of these comorbidities was either based on subjective measures, or potentially insufficient screening. Obstructive airway disease was determined based on participant’s reported history of asthma, emphysema, or bronchitis without having objective measures of pulmonary function testing. AF was based on the rhythm present on a 10-second electrocardiogram taken during clinic visit, which may have resulted in misclassification of a large number of participants with paroxysmal AF who were in sinus rhythm during their clinic visit. Further studies are necessary to identify the true relationship between these conditions and mortality among elderly patients with HF.

Most measures of physical impairment were associated with greater mortality risk among our study participants, a finding consistent with growing evidence that frailty is a major determinant of outcome in elderly patients with HF. Impairments in IADLs were associated with greater mortality risk than impairment in ADLs, and remained significant after adjusting for all other covariates. One plausible explanation of this paradox is that persons with impairment in ADLs are more likely to be institutionalized or fully dependent on others for the provision of their care, while those with impairment in IADLs can still maintain an independent living with various degrees of compromise to optimal management of their HF. Fifteen-foot walk time and gait speed are objective measures of physical function in the elderly and have been shown to be associated with mortality in the CHS population. However, it has not been shown if this relationship between 15-foot walk time and mortality is true in persons with HF. Our study
suggests that such a relationship may exist, and that the loss of significance in the estimates based on smaller sample size might be due to insufficient power.

The strong association between impaired cognition and mortality is of a great clinical importance and is consistent with the growing evidence that impaired cognition adversely impacts outcomes of persons with chronic diseases\textsuperscript{31}. Optimal management of HF requires active patient involvement that can easily be disrupted in persons with cognitive impairment, especially in the absence of assistance and support in the managing their illness.

Our study has several strengths. By using an inception cohort of participants with incident HF, we reduced the possibility of systematic errors that could result from enrolling participants with prevalent HF at various stages of their illness. HF was one of the primary outcomes of CHS; hence, its diagnosis was carefully ascertained and adjudicated according to pre-specified criteria. In contrast, HF is frequently identified based on its International Classification of Diseases (ICD) code in data from Medicare beneficiaries, a method prone to error. The values of our baseline characteristics were determined prior to, or at the time of, HF diagnosis, making our inferences clinically relevant for determining prognosis and guiding management of patients at the time of HF diagnosis. By using data from CHS we were able to include a wide range of frequent and clinically relevant comorbidities and measures of physical and cognitive impairments which may not be available in data collected from highly selected participants of randomized controlled trials. By including all these conditions together in the multivariable analysis, we reduced the risk of confounding as these conditions often coexist in persons with HF. Finally, one of the unique strengths of our study is the exceptionally long follow-up time during which more than 90\% of our study sample (504 of 558) reached the outcome.
Our study has limitations that may have potentially impacted some of our findings. Certain HF-specific variables and measures of comorbidities (i.e. NYHA functional class, brain natriuritic peptide, hemoglobin level, and thyroid disease) were not measured in all participants and, therefore, were not included in our analysis. Missing values of baseline characteristics were imputed by carrying forward values from measurements taken during prior clinic visits which may have resulted in some degree of misclassification. Failure to impute missing values would have resulted in a significant reduction in our sample size, and might have produced selection bias \(^{63}\). We believe that the amount of misclassification in our study was minimal since we carried forward variables with relatively stable values and we imposed a limitation on the carrying forward time. Furthermore, since most of our baseline characteristics were chronic and persistent, any misclassification of such variables would likely have been limited to falsely carrying forward negative values that would have resulted in shrinkage of parameter estimates and would have driven any associations toward the null \(^{64}\). By limiting carrying forward time to 3 years, a large number of cases of incident HF were excluded from the multi-variable analysis which could potentially have resulted in selection bias. While it is not possible to completely rule out selection bias, we carried out 2 types of sensitivity analysis and both did not show evidence that such bias existed in our data set. First, we compared those participants who were excluded because of missing baseline data within 3 years of HF diagnosis with study participants in respect to a wide range of baseline characteristics available in both groups (age, sex, race, smoking status, and CHS center), and no significant differences were found. Second, participants with missing values, who could not be included in multi-variable analysis, were used to calculate the “all-available subject” estimate of mortality risk (table 2). The more precise estimate based on all-available subject fell within the 95% CI of the estimate based on study
participants for all predictor variables, except for depression, which suggests that significant selection bias does not exist. Finally, since our data was collected before the institution of current guidelines for the management of HF, the usage rate of certain HF-specific medications, including ACEI/ARBs, and beta blockers, are noticeably low if compared with the current usage rate of these medications.

VI. CONCLUSION:

Elderly persons with incident HF have a substantial burden of comorbidities and physical and cognitive impairments. Specific comorbidities and physical and cognitive impairments are associated with greater mortality risk in this population. Given the high mortality rates observed in elderly persons with HF, research is needed to determine whether addressing and rigorously managing these conditions would improve their survival.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 558)</th>
<th>By Sex</th>
<th>By age group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women (n = 269)</td>
<td>Men (n = 289)</td>
<td>P value</td>
<td>66-75 yrs (n = 159)</td>
<td>76-85 yrs (n = 309)</td>
</tr>
<tr>
<td>Age, years</td>
<td>79.2 ± 6.3</td>
<td>79.0 ± 6.3</td>
<td>79.4 ± 6.3</td>
<td>0.46</td>
<td>71.8 ± 2.5</td>
</tr>
<tr>
<td>Sex (men), %</td>
<td>51.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>49.7</td>
</tr>
<tr>
<td>Race (White), %</td>
<td>87.3</td>
<td>84.8</td>
<td>89.6</td>
<td>0.099</td>
<td>83.7</td>
</tr>
<tr>
<td>HFPEF, %</td>
<td>48.3*</td>
<td>54.9*</td>
<td>42.9*</td>
<td>0.04</td>
<td>51.6*</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.1 ± 4.8</td>
<td>27.5 ± 5.7</td>
<td>26.7 ± 3.8</td>
<td>0.059</td>
<td>28.6 ± 5.6</td>
</tr>
<tr>
<td>Former smoker, %</td>
<td>45.9</td>
<td>33.1</td>
<td>57.8</td>
<td>&lt; 0.0001</td>
<td>49.1</td>
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<tr>
<td>Current smoker, %</td>
<td>8.1</td>
<td>8.2</td>
<td>8.0</td>
<td>0.99</td>
<td>12.6</td>
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<td>Fair-to-poor self-reported health status, %</td>
<td>39.1</td>
<td>39.4</td>
<td>38.8</td>
<td>0.93</td>
<td>37.1</td>
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<td>Hypertension, %</td>
<td>82.1</td>
<td>84.8</td>
<td>79.6</td>
<td>0.12</td>
<td>77.4</td>
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<tr>
<td>Diabetes mellitus, %</td>
<td>28.5</td>
<td>25.7</td>
<td>31.1</td>
<td>0.16</td>
<td>35.2</td>
</tr>
<tr>
<td>Moderate CKD, %</td>
<td>28.5</td>
<td>29.0</td>
<td>28.0</td>
<td>0.85</td>
<td>25.2</td>
</tr>
<tr>
<td>Severe CKD, %</td>
<td>3.8</td>
<td>3.0</td>
<td>4.5</td>
<td>0.38</td>
<td>2.5</td>
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<tr>
<td>Coronary heart disease, %</td>
<td>59.3</td>
<td>50.9</td>
<td>67.1</td>
<td>&lt; 0.0001</td>
<td>57.2</td>
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<tr>
<td>Peripheral vascular disease, %</td>
<td>9.1</td>
<td>6.7</td>
<td>11.4</td>
<td>0.057</td>
<td>10.1</td>
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<tr>
<td>Atrial fibrillation, %</td>
<td>8.1</td>
<td>8.6</td>
<td>7.6</td>
<td>0.76</td>
<td>6.3</td>
</tr>
<tr>
<td>Cerebrovascular disease, %</td>
<td>20.4</td>
<td>19.3</td>
<td>21.5</td>
<td>0.60</td>
<td>15.1</td>
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<tr>
<td>Obstructive airway disease, %</td>
<td>19.7</td>
<td>19.0</td>
<td>20.4</td>
<td>0.67</td>
<td>22.0</td>
</tr>
<tr>
<td>Depression, %</td>
<td>12.0</td>
<td>12.3</td>
<td>11.8</td>
<td>0.90</td>
<td>10.1</td>
</tr>
<tr>
<td>1 ADL impaired, %</td>
<td>12.5</td>
<td>14.9</td>
<td>10.4</td>
<td>0.13</td>
<td>8.8</td>
</tr>
<tr>
<td>≥ 2 ADL impaired, %</td>
<td>10.0</td>
<td>11.2</td>
<td>9.0</td>
<td>0.40</td>
<td>5.7</td>
</tr>
<tr>
<td>1 IADL impaired, %</td>
<td>26.7</td>
<td>27.9</td>
<td>25.6</td>
<td>0.57</td>
<td>27.0</td>
</tr>
<tr>
<td>≥ 2 IADL impaired, %</td>
<td>17.0</td>
<td>22.3</td>
<td>12.1</td>
<td>0.0016</td>
<td>10.1</td>
</tr>
<tr>
<td>15-foot walk time, sec</td>
<td>7.1 ± 5.7</td>
<td>8.1 ± 7.8</td>
<td>6.1 ± 2.2</td>
<td>&lt; 0.0001</td>
<td>6.6 ± 7.5</td>
</tr>
<tr>
<td>3MSE score ≤ 80, %</td>
<td>17.4</td>
<td>15.6</td>
<td>19.0</td>
<td>0.32</td>
<td>3.8</td>
</tr>
</tbody>
</table>

* These estimates were based on only 294 participants (53% of study sample) who had left ventricular ejection fraction available.

Abbreviations: HFPEF: Heart Failure and Preserved left ventricular Ejection Fraction; CKD: Chronic Kidney Disease; ADLs: Activities of Daily Living; IADLs: Instrumental Activities of Daily Living; 3MSE: Modified Mini-Mental State Examination.
Table 2: Adjusted death hazard associated with baseline characteristics including patient-specific variables, comorbidities, and measures of physical and cognitive impairments:

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Estimate 1*</th>
<th>Estimate 2**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All available Participants</td>
<td>Participants with Complete Data (N = 558)</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1088</td>
<td>1.07 (1.06-1.08)</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>1088</td>
<td>1.29 (1.17-1.47)</td>
</tr>
<tr>
<td>Race (non-white)</td>
<td>1088</td>
<td>1.14 (0.94-1.38)</td>
</tr>
<tr>
<td>HFREF</td>
<td>577</td>
<td>1.18 (0.99-1.42)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1088</td>
<td>0.97 (0.96-0.99)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1088</td>
<td>1.25 (1.09-1.44)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1088</td>
<td>1.38 (1.09-1.75)</td>
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<tr>
<td>Fair-to-poor self-reported health status</td>
<td>1081</td>
<td>1.55 (1.36-1.77)</td>
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<tr>
<td>Hypertension</td>
<td>1088</td>
<td>1.08 (0.91-1.27)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>1084</td>
<td>1.58 (1.36-1.82)</td>
</tr>
<tr>
<td>Moderate CKD</td>
<td>689</td>
<td>1.37 (1.15-1.64)</td>
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<tr>
<td>Severe and end-stage CKD</td>
<td>689</td>
<td>2.84 (1.80-4.47)</td>
</tr>
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<td>Coronary heart disease</td>
<td>1088</td>
<td>0.96 (0.84-1.09)</td>
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<tr>
<td>Peripheral arterial disease</td>
<td>1088</td>
<td>1.51 (1.23-1.84)</td>
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<tr>
<td>Atrial fibrillation</td>
<td>1087</td>
<td>0.99 (0.80-1.23)</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>1088</td>
<td>1.39 (1.20-1.62)</td>
</tr>
<tr>
<td>Obstructive airway disease</td>
<td>839</td>
<td>1.16 (0.97-1.38)</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>OR</td>
</tr>
<tr>
<td>-------------------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>Depression</td>
<td>1082</td>
<td>1.12</td>
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<tr>
<td>1 ADL impaired</td>
<td>1084</td>
<td>0.96</td>
</tr>
<tr>
<td>2 or more ADLs impaired</td>
<td>1084</td>
<td>1.40</td>
</tr>
<tr>
<td>1 IADL impaired</td>
<td>1087</td>
<td>1.07</td>
</tr>
<tr>
<td>2 or more IADLs impaired</td>
<td>1087</td>
<td>1.64</td>
</tr>
<tr>
<td>15-foot walk time (sec)</td>
<td>1059</td>
<td>1.02</td>
</tr>
<tr>
<td>3MSE score &lt; 80</td>
<td>1076</td>
<td>1.41</td>
</tr>
</tbody>
</table>

* Estimate 1 is adjusted for patient-specific characteristics including age, sex, race, smoking status, body mass index, and CHS center (estimates for CHS center are not reported here and were not statistically significant).

** Estimate 2 is adjusted for patient-specific characteristics in addition to all other comorbidities and measures of physical and cognitive functions.

*** These estimates are based on a sample size of 294 participants with complete data who also had their left ventricular ejection fraction available.

CKD: Chronic Kidney disease; ADLs: activities of daily living; IADLs: instrumental activities of daily living; 3MSE: modified mini-mental state examination; HFREF: Heart Failure and Reduced left ventricular Ejection Fraction.
Figure 1: Percentage of participants according to their number of comorbidities:
Chapter 3

Mortality Risk Prediction Models in Elderly Patients with Heart Failure are improved by Inclusion of Measures of Comorbidities and Physical and Cognitive Impairments: The Cardiovascular Health Study (CHS)
**Abstract:**

**Background:** Comorbidities and physical and cognitive impairments are important determinants of mortality in elderly patients with heart failure (HF), yet they have often been excluded from risk prediction models (RPMs) for prediction of mortality in HF. Many available RPMs were derived in younger HF patients who have lower burden of these conditions.

**Methods:** In 558 elderly patients with incident HF from CHS, we derived and calibrated 2 RPMs for mortality risk prediction, a combined model with and a base model without the inclusion of measures of comorbidities and physical and cognitive impairments. The 2 models were compared using generalized R² and likelihood ratio test; 1-year and 5-year survival predictions were compared by their respective areas under the curve (AUC).

**Results:** Both models performed well and passed goodness-of-fit tests. The combined model containing measures of comorbidities and physical and cognitive impairments was superior to the base model with larger generalized R² (0.331 versus 0.212) and significant likelihood ratio test (Chi-square: 224.4 versus 133.1; \( P < 0.0001 \)). The combined model also performed better in predicting 5-year survival (AUC: 0.775 versus 0.703; \( P = 0.001 \)) and possibly in predicting 1-year survival (AUC: 0.684 versus 0.638, \( P = 0.0556 \)).

**Conclusion:** The mortality risk of elderly patients with HF can be predicted using simple information readily available in the clinical setting. Measures of comorbidities and physical and cognitive impairments improve prediction of mortality risk and survival in this patient population.
I. **Introduction:**

Estimation of mortality risk and prediction of survival can be useful in clinical practice by enabling patients to make informed decisions regarding their health care and empowering clinicians to develop strategic care plans with their patients. The result could be more efficient utilization of health care resources that could positively impact patient outcomes. Such knowledge is especially important in elderly patients with HF where mortality rates are extremely high and the effectiveness of most therapies is uncertain. As we reported in the previous chapter, 20% of patients with HF die within 1 year and more than 50% die within 5 years of diagnosis with HF. Therefore, having a reliable tool that can accurately estimate mortality risk and predict survival among patients with incident HF could prove useful in individualizing care plans of these patients early in the course of their illness.

Several risk prediction models (RPM) have been developed in the past 2 decades for estimating mortality risk and survival in various populations with HF. However, the usefulness of these RPMs in elderly patients with HF who have high burden of comorbidities and physical and cognitive impairments is uncertain. Most of these models were derived from relatively younger populations who had predominantly HFREF. In addition, comorbidities and physical and cognitive impairment were not adequately represented in these models with few exceptions such as renal function, and New York Heart Association (NYHA) functional class. We saw in chapter 2 that elderly patients with HF have high burden of comorbidities and physical and cognitive impairments and that several measures of these conditions are associated with greater risk of death in this patient population. Therefore, the usefulness of these measures in mortality risk prediction should be evaluated.
We had 2 objectives of this study. The first objective was to identify a set of variables, readily available in the clinical setting, that best estimates mortality risk and predicts survival among elderly patients with incident HF. The second objective was to demonstrate the utility of adding to such a model measures of comorbidities and physical and cognitive impairments that are highly prevalent in this patient population.

II. Methods:

Study sample and study design:

Our study sample was an inception cohort of participants in the Cardiovascular Health Study (CHS) with incident HF. For detailed description of CHS and method of selection of our study sample, refer to chapters 1 and 2. Participants entered our study at the time of diagnosis of HF and were followed until they died or were censored. Several patient-specific characteristics and measures of comorbidities and physical and cognitive impairments were determined at the time of HF diagnosis. The approach used to determine these values was discussed in detail in chapter 2. Patient-specific characteristics included age, sex, race, smoking status, body mass index (BMI), and CHS clinic location. Measures of comorbidities included self-reported health status, systolic blood pressure, diastolic blood pressure, and glomerular filtration rate (GFR), and having history of diabetes mellitus, coronary heart disease (CHD), peripheral vascular disease, atrial fibrillation, cerebrovascular disease, and depression. Measures of physical and cognitive impairments included number of impaired activities of daily living (ADLs), number of impaired instrumental activities of daily living (IADL), 15-meter walk time, and modified mini-mental state examination (3MSE) score. These variables were described in detail in chapter 2. In order to improve precision of risk prediction, continuous variables, when available, were preferably
used instead of categorical variables as measures of comorbidities and physical and cognitive impairments\textsuperscript{66}. Such continuous variables included systolic and diastolic blood pressure, GFR, and 3MSE score.

**Statistical Analysis:**

In order to meet both study objectives we used 2 separate sets of variables to derive 2 risk prediction models. For the first model, the patient-specific or base model, we used patient specific characteristics only. For the second model, the combined model, we used measures of comorbidities and physical and cognitive impairments in addition to patient-specific characteristics. Both models were derived using Cox proportional hazard regression analysis. For each model, we used all possible subset selection procedure to identify the subset of variables that made the best model that minimized the AIC criteria. In order to facilitate comparison of the 2 models, we ensured that the base model was nested in the combined one by forcing variables that were in the base model into the combined model.

Each model was then calibrated by comparing 1-year (short term) and 5-year (long term) survival estimates of a random sample of participants with the respective observed 1-year and 5-year survival for each decile of estimated survival. Chi-square for goodness-of-fit test was then calculated for each model at 1 year and at 5 years. According to this test, a model’s goodness-of-fit is inversely related to the test value and considered significant when p value is > 0.05.

The explanatory powers of both models were compared using generalized $R^2$ and the likelihood ratio test. The performances of both models in predicting short-term and long-term survival were compared by their respective areas under the curve (AUC). The statistical test used to compare areas under the curves for the 2 models was that proposed by Hanley and
McNeil and used for comparing areas under the curves of nested models.\textsuperscript{67} SAS 9.1 statistical software (SAS Institute, Cary, NC, USA) was used for all analysis. All statistical tests were interpreted with a 2-way significance level of 0.05.

III. Results:

We included 558 participants from the CHS cohort with incident HF whose baseline characteristics were determined at the time of HF diagnosis (Table 1). Predictors that remained in the base and combined models with their regression coefficients, standard errors, p values, and hazard ratios (with 95% confidence intervals) are listed in Table 2 and Table 3. Predictor variables that were in both models were all significant with the exception of BMI that was forced into the patient-specific model in order to ensure that this model was nested in the combined model.

For calibration of these models, we created a different sample by randomly removing 25 participants from the original sample and replacing them with 25 participants who were not included in the original sample. These participants were originally excluded due to missing values of baseline variables that dropped out in the selection process of best model. Each model was calibrated separately by comparing predicted survival estimates with respective observed survival rates for each decile of predicted survival estimates for each model at 1 year and again at 5 years (Figures 2 and 3). Goodness-of-fit tests were significant at 1-year and at 5-year for both models, although Chi-square statistics were lower (indicating better goodness-of-fit) in the combined model than in the patient-specific model (Figures 2 and 3).

In comparing the 2 models we found the combined model to be superior to the patient-specific model with larger generalized $R^2$ (0.331 versus 0.212) and significant likelihood ratio
test (Chi-square: 224.4 versus 133.1; \(P < 0.0001\)) (Table 4). The performance of the combined model, as measured by the area under the curve (AUC), was significantly superior to the patient-specific model in predicting 5-year (long-term) survival (AUC: 0.775 versus 0.703; \(P = 0.001\)) and possibly superior in predicting 1-year (short-term) survival (AUC: 0.684 versus 0.638, \(P = 0.0556\)) (Table 5).

IV. Discussion:

In this study, we have shown that mortality risk and short-term and long-term survival can be accurately estimated at the time of diagnosis of HF based on a set of variables that are readily available in the clinical setting. Both models we developed (patient-specific model and the combined model) showed good explanatory power, calibration, and discrimination, with the combined model being superior in all of these 3 measures (table 4). The discriminatory benefit of adding measures of comorbidities and physical and cognitive impairments (as in the combined model) appeared greater and more significant in long-term (5-year) than in short-term (1-year) survival prediction. This finding suggests that comorbidities and physical and cognitive impairment have greater impact on long-term survival than on short-term survival of elderly patients with HF.

Our findings demonstrate the potential utility of adding measures of comorbidities and physical and cognitive impairments when estimating mortality risk and predicting long-term and possibly short-term survival in elderly patients with incident HF. With the high prevalence of comorbidities and physical and cognitive impairments in the elderly, such measures should be considered when developing risk prediction models for prediction of mortality in this patient population.
The following limitations that are related to the study sample and study design must be considered when interpreting the findings of this study. Certain HF specific variables that are clinically important and readily available in the clinical setting such as left ventricular ejection fraction, brain natriuretic peptide, and New York Heart Association functional class were not available in our dataset and, therefore, were not considered when deriving these risk prediction models. The mode of measurement of certain comorbidities might have affected our results. For instance, a participant was considered having CHD if there was a history of angina, myocardial infarction, or coronary revascularization. It is plausible to suspect that having stable angina may not have the same impact on mortality as having history of myocardial infarction or coronary artery bypass grafting. We used continuous variables whenever possible, yet several of the measures of comorbidities we used were categorical and that limitation might have caused some loss of precision 66.

V. **Conclusion:**

Mortality risk and survival in elderly patients with HF can be predicted with good accuracy using simple information readily available in the clinical setting. Measures of comorbidities and physical and cognitive impairments are useful in predicting mortality risk and survival in elderly patients with HF and should be included in risk prediction models developed for this purpose.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>79.2 ± 6.3</td>
</tr>
<tr>
<td>Sex (men) %</td>
<td>51.8</td>
</tr>
<tr>
<td>Race (White) %</td>
<td>87.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²) (mean ± SD)</td>
<td>27.1 ± 4.8</td>
</tr>
<tr>
<td>Former smoker %</td>
<td>45.9</td>
</tr>
<tr>
<td>Current smoker %</td>
<td>8.1</td>
</tr>
<tr>
<td>Fair-to-poor self-reported health status %</td>
<td>39.1</td>
</tr>
<tr>
<td>Systolic blood pressure (mean ± SD)</td>
<td>140.7 ± 22.8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mean ± SD)</td>
<td>69.1 ± 13.1</td>
</tr>
<tr>
<td>Diabetes mellitus %</td>
<td>28.5</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min) (mean ± SD)</td>
<td>72.5 ± 26.0</td>
</tr>
<tr>
<td>Coronary heart disease %</td>
<td>59.3</td>
</tr>
<tr>
<td>Peripheral vascular disease %</td>
<td>9.1</td>
</tr>
<tr>
<td>Atrial fibrillation %</td>
<td>8.1</td>
</tr>
<tr>
<td>Cerebrovascular disease %</td>
<td>20.4</td>
</tr>
<tr>
<td>Obstructive airway disease %</td>
<td>19.7</td>
</tr>
<tr>
<td>Depression %</td>
<td>12.0</td>
</tr>
<tr>
<td>1 ADL impaired</td>
<td>12.5</td>
</tr>
<tr>
<td>≥ 2 ADL impaired</td>
<td>10.0</td>
</tr>
<tr>
<td>1 IADL impaired</td>
<td>26.7</td>
</tr>
<tr>
<td>≥ 2 IADL impaired</td>
<td>17.0</td>
</tr>
<tr>
<td>15-meter walk time (sec) (mean ± SD)</td>
<td>7.1 ± 5.7</td>
</tr>
<tr>
<td>3 MSE score (mean ± SD)</td>
<td>87.4 ± 12.3</td>
</tr>
</tbody>
</table>
Table 2: Predictors of Patient-specific risk prediction model:

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Parameter estimate</th>
<th>P value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>0.07707 (0.00804)</td>
<td>&lt; 0.0001</td>
<td>1.08 (1.06-1.10)</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>0.33256 (0.09244)</td>
<td>0.0003</td>
<td>1.40 (1.16-1.67)</td>
</tr>
<tr>
<td>Former smoking</td>
<td>0.32209 (0.09679)</td>
<td>0.0009</td>
<td>1.38 (1.14-1.67)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.59430 (0.17721)</td>
<td>0.0008</td>
<td>1.81 (1.28-2.56)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>- 0.01774 (0.01061)</td>
<td>0.095</td>
<td>0.98 (0.96-1.00)</td>
</tr>
</tbody>
</table>

Table 3: Predictors of the combined risk prediction model:

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Parameter estimate</th>
<th>P value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>0.06941 (0.00869)</td>
<td>&lt; 0.0001</td>
<td>1.07 (1.05-1.09)</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>0.38414 (0.09816)</td>
<td>&lt; 0.0001</td>
<td>1.47 (1.21-1.78)</td>
</tr>
<tr>
<td>Former smoking</td>
<td>0.35147 (0.09805)</td>
<td>0.0003</td>
<td>1.42 (1.17-1.72)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.47450 (0.17846)</td>
<td>0.0078</td>
<td>1.61 (1.13-2.28)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>- 0.02784 (0.01097)</td>
<td>0.011</td>
<td>0.97 (0.95-0.99)</td>
</tr>
<tr>
<td>Fair-to-poor self-reported health status</td>
<td>0.25948 (0.10041)</td>
<td>0.0098</td>
<td>1.30 (1.07-1.58)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.47278 (0.10546)</td>
<td>&lt; 0.0001</td>
<td>1.60 (1.31-1.97)</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>- 0.00685 (0.00203)</td>
<td>0.0008</td>
<td>0.993 (0.989-0.997)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.36047 (0.11322)</td>
<td>0.0015</td>
<td>1.43 (1.15-1.79)</td>
</tr>
<tr>
<td>Frequent depressive symptoms (&gt; 3 days/week)</td>
<td>0.28998 (0.14042)</td>
<td>0.039</td>
<td>1.34 (1.02-1.76)</td>
</tr>
<tr>
<td>Number of IADL impaired</td>
<td>0.09911 (0.4406)</td>
<td>0.025</td>
<td>1.104 (1.013-1.204)</td>
</tr>
<tr>
<td>3MSE score</td>
<td>- 0.00725 (0.00340)</td>
<td>0.033</td>
<td>0.993 (0.986-0.999)</td>
</tr>
</tbody>
</table>

Abbreviations: GFR: glomerular filtration rate; IADL: instrumental activities of daily living; 3MSE: modified mini-mental examination score.
Table 4: Comparison between patient-specific model and the combined model:

<table>
<thead>
<tr>
<th>Model characteristic</th>
<th>Patient-specific model (M1)</th>
<th>Combined model (M2)</th>
<th>Significance of statistical test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likelihood Ratio</td>
<td>133.10</td>
<td>224.38</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Generalized R²</td>
<td>0.212</td>
<td>0.331</td>
<td></td>
</tr>
<tr>
<td>AUC for predicting 1-year survival</td>
<td>0.638</td>
<td>0.684</td>
<td>0.0556</td>
</tr>
<tr>
<td>AUC for predicting 5-year survival</td>
<td>0.703</td>
<td>0.775</td>
<td>0.0010</td>
</tr>
</tbody>
</table>
Figure 1: Comparing Short-term (left set of panels) and long-term (right set panels) predicted survival estimates, based on patient-specific model, with observed survival for each decile of predicted survival (Chi square and p value for goodness-of-fit test are reported for each set):
Figure 2: Comparing Short-term (left set of panels) and long-term (right set panels) predicted survival estimates, based on the combined model, with observed survival for each decile of predicted survival (Chi square and p value for goodness-of-fit test are reported for each set):
References:


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   Program Directors: Paul B. Iannini, MD and Winston Shih, MD
Clinical Rotation in Cardiology (August 2001):
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Mentors: David C Goff, Jr., MD, PhD; and Dalane W Kitzman, MD
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- Autonomic dysfunction in heart failure
- Quality of care and outcome in heart failure

Supervisor: Jeffery Ross, MD
Description: Studying the prognostic value of Her-2neu gene over-expression in advanced stage Breast and Lung Cancer

The Children Hospital, University of Damascus, Damascus, Syria (05/1995-04/1997):
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Description: A large Clinical Trial comparing different empirical antibiotics regimens for the treatment of serious infections in pediatric patients.

PUBLICATIONS AND PRESENTATIONS:

2) Khalil Murad; Elsayed Z Soliman; Timothy M Morgan; David M Fitzgerald; Joel D Eggebeen; David C Goff J; Dalane W Kitzman. Exercise Training Improves Heart Rate Variability in Older Patients with Heart Failure. A randomized, controlled, Single-Blinded Study. *Published on line Congestive Heart Failure, April 2012.*

3) Khalil Murad; Donald M. Lloyd-Jones; Elsayed Z Soliman; Mercedes Carnethon; Richard Sloan; Hongyan Ning; Sharina D Person; David C Goff J. Heart Rate Variability and Markers of Subclinical Cardiovascular Disease. The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Presented at the American College of Cardiology Annual meeting, 2011. Manuscript is in preparation.*

4) Khalil Murad; David C Goff J.; Timothy M Morgan; Gergory Burke; Dalane W Kitzman. Comorbidities and the Risk of Death in Elderly Patients with Heart Failure: The Cardiovascular Health Study. *A master’s thesis in preparation.*


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- Thomas Memorial Hospital, South Charleston, West Virginia (2003-2009)
- St. Francis Hospital, Charleston, West Virginia (2007-2009)
- Camden Clark Memorial Hospital, Parkersburg, West Virginia (2003-2006)

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- ACLS certified since July 2000

State Licenses:

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- Ohio (since 2006, currently inactive)