PREDICTIVE MODELING OF INCIDENT HEART FAILURE

IN SUBJECTS WITH NEWLY DIAGNOSED ATRIAL FIBRILLATION.

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ABSTRACT OF THE DISSERTATION

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Heart failure (HF) and atrial fibrillation (AF) are chronic diseases with high costs, both in human and monetary terms in the US and the world. While the cost of each disease is high, the cost of the two as comorbid conditions is exceedingly high. To be able to predict, early on, which patients with newly diagnosed AF will go on to develop HF will allow clinicians the opportunity to address the problem and prevent or delay the onset of HF. The goal of this research was to develop predictive models for incident HF in subjects with newly diagnosed AF.

HF is a clinical syndrome wherein the heart is unable to supply sufficient blood flow for the body's needs. HF can be due to a deficit on either the left or the right side of the heart. Left side HF is the focus of this research. The prevalence of HF is nearly 6 million in the US and over 23 million people worldwide, with yearly costs over $20B in the US and over $100B worldwide. There are 2 types of HF based on the proportion of blood

ejected from the left ventricle during systole. Normally, 50-70% of the blood in the left ventricle is ejected during systole. In HF with reduced ejection fraction (HFrEF), the heart ejects less than 40% of the blood volume in the left ventricle during the contractile phase of the cardiac cycle. In HF with preserved ejection fraction (HFpEF), a normal proportion of the ventricular volume is ejected during systole. In this form of HF, the total volume of blood ejected is insufficient for the body's needs due to lower ventricular filling during diastole, the relaxation phase of the heart cycle.

AF is the most common form of cardiac arrythmia. It is an abnormal atrial rhythm initiated by ectopic foci in the atria and pulmonary veins and manifested by circular, uncoordinated depolarization of the atrial muscle, ineffective atrial contraction, and rapid irregular conduction of depolarizations through the atrioventricular node to the ventricles. Worldwide, it is estimated that AF occurs in about 0.5% or 33.5M people. The rates are higher in the US and western Europe with estimates of 3.3% in men and 2.6% in women.

AF by itself tends to reduce cardiac output and is a risk factor for HF. The function of the atria, which normally aid ventricular filling by contracting just before ventricular systole, is lost; and filling time may be shortened by too rapid a pulse. Over time, tachycardia from the abnormal rhythm may lead to cardiomyopathy which may progress into HF. Outcomes for patients who develop HF after AF are poor. In a study involving the Framingham cohort, the mortality rate in patients with AF who developed HF was 3 times that of subjects who did not develop HF. The ability to predict, early on, those who will develop HF after AF may reduce the health burden from these diseases.

There are many examples of predictive model use in health care. For example, the Charlson index is used to predict mortality using 19 indicators. These models provide additional information for the clinician and the patient on risk assessment and help to determine the most appropriate treatment. Predictive models are designed to answer the patient's question, "What is going to happen to me?"

The objective of the research in this dissertation was to develop models to predict incident heart failure in those with newly diagnosed atrial fibrillation. We had two specific aims: one, to develop predictive models for those under age 65 years old; and two, to develop models for those over 65. Age differences in the frequency and predictors of heart failure led us to separate the models for these two broad age groups.

We used three data sources for developing the models. OptumInsight's de-identified Clinformatics™ Datamart (Optum) provides information on about 81 million lives insured for periods of time between May 1, 2000 and December 31, 2017. Under age 65 it mainly consists of US commercial claims patients while over age 65 it is based on Medicare. We also used the IBM MarketScan Commercial Claims and Encounters (CCAE) with information on about 138 million lives between January 1, 2000 and December 31, 2017. It includes health insurance claims from large employers and health plans that provide coverage to employees, their spouses, and dependents. Finally, we used the IBM MarketScan Medicare (MDCR) with information on about 10 million lives insured at times between January 1, 2000 and December 31, 2017. This dataset represents health services of retirees in the United States with primary or Medicare supplemental coverage through privately insured health plans. Each dataset

was converted to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). These datasets were reviewed by the New England Institutional Review Board (IRB) and were determined to be exempt from broad IRB approval.

We developed models on cohorts of subjects using, as an index date, the first diagnosis code of AF followed by a second AF code within one year. We also required that each included subject had at least a 365-day observation period prior to AF diagnosis and no prior evidence of HF. To develop the model, we used patient demographic information including the age at index date, sex, and race/ethnicity. We also used all medical conditions, based on diagnosis codes; drug exposures, based on prescriptions filled; clinical procedures; and health scores including CHADS2 and the Charlson Index. We modeled 3 outcomes, based on the first diagnosis of any HF, HFpEF, and HFrEF. Each subject was determined to have the outcome if the first diagnosis was followed by a second HF, HFpEF, or HFrEF code, respectively, within one year after the initial diagnosis. We examined 2 times-at-risk: 3 months to 1 year and 1 year to 3 years following the index date. For the 1-3y time-at-risk, the index date was adjusted to one year following initial diagnosis of AF.

The machine learning algorithm used to develop the models was regularized logistic regression. We used the Least Absolute Shrinkage and Selection Operator (LASSO) extension of this algorithm. The code used for developing these models were from R language packages which were open-source and freely available on the Observational Health Data Sciences and Informatics (OHDSI) library (ohdsi.org) website. We trained the models on 75% of the data in a dataset based on a random selection by subject. In

the under 65year cohort, we trained on the CCAE dataset and for the over 65 year cohort, we trained on the Optum dataset. We performed internal validation of the models on the remaining 25% of the data. We also performed external validation of the models on an external dataset. For the under 65 cohort, we validated on the Optum dataset and on the over 65 cohort we validated on the MDCR dataset. We evaluated model performance through 3 measures. We examined the capability of the model to discriminate between those with and without the outcome by measuring the area under the Receiver Operator Characteristic curve (AUC). We also determined model calibration which compares estimated probabilities from the model to the observed frequency across the full range of predicted probabilities. For some models, we also examined the Likelihood Ratio Positive (LR+) which is calculated as the sensitivity divided by (1 – the specificity) of the model at any prediction threshold.

In the cohort of subjects under age 65, we found that, for those who developed HF during either time at risk, the rates of many prior conditions were higher than for those who did not develop HF. In those who developed HFrEF, the prior rates of acute myocardial infarction (AMI) and coronary artery disease (CAD) were higher than in those who did not develop HF and in those who developed HFpEF. Those who developed HFpEF had higher prior rates of hypertension, diabetes, and obesity compared to those who did not develop HF and those who developed HFrEF. In our prediction models, the AUCs were between 0.70 and 0.75 for all 3 outcomes at both times-at-risk indicating good model discrimination. The calibration curves had y-intercepts near 0 and slopes near the ideal value of 1 indicating the prediction models were well-calibrated across

the full range of predicted probabilities. We found similar discrimination and calibration results on external validation of the models which indicates that these models had good generalizability. In the models where the outcome was HFpEF, we found that diabetes was a strong predictor with many features of diabetes included in the final model. Other predictors included the use of diuretics and the presence of hypertension. The models where the outcome was HFrEF included predictors in the model for cardiomyopathy and chronic ischemic heart disease.

We found similar differences between subjects who developed HF compared to those who did not in the cohorts over age 65. We found, in those who developed HFrEF, higher prior levels of AMI and CAD compared to those who did not develop HF and those who developed HFpEF. In those who developed HFpEF, there were prior higher levels of hypertension and obesity compared to those who did not develop HF and in those who developed HFrEF. We did not find higher levels of diabetes compared to those who developed HFrEF. In those who developed HFrEF, we found higher prior levels of AMI and with and without the outcome as well in those over age 65 compared to those under age 65. The AUCs ranged from 0.65 to 0.70 in this group. The models were well calibrated with y-intercepts near 0 and calibration curve slopes near unity. The models showed fair generalizability with AUCs on external validation similar to those found on internal validation.

The results from this research show that it is possible to develop good models for predicting any HF, as well as HFrEF and HFpEF, in those with newly diagnosed AF. The models demonstrated reasonable discrimination in both internal and external

validation. These models may provide the basis for starting the conversation between clinician and subject in the design of personalized treatment regimens. When patients know their personal risk of developing a poor outcome it may help to convince them of the importance of adhering to their treatment plan. As treatment becomes more specific based on personal risk and patient adherence to treatment increases, the human and financial cost of HF following AF will hopefully be significantly reduced.

Dedication

This dissertation is dedicated to my wife, Audrey Snyder, whose love, support, and patience made this work possible.

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Chapter 1: Understanding the Need for the Development of Predictive Models for Incident Heart Failure in Subjects with Newly Diagnosed Atrial Fibrillation.

Epidemiology of heart failure

Heart failure (HF) is a chronic condition in which the heart does not supply enough blood, and thereby oxygen, to meet the demands of the body. The American Heart Association and the American College of Cardiology define HF as "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood".[1] It is estimated that the prevalence of HF is nearly 6 million in the US and over 23 million worldwide.[2] The syndrome imposes a huge economic burden. In the US the estimated annual cost of HF is over $20B and the worldwide annual cost is well over $100B.[3] It is projected that by 2030 the prevalence of HF in the US will be over 8M or 1 in 33 people with a yearly economic burden of over $53B.[4]

The Multi-Ethnic Study of Atherosclerosis (MESA) study examined the racial/ethnic differences in HF in a cohort in the US.[5] These researchers found that African-Americans had the highest rate of new-onset HF during the follow-up period, followed by Hispanic, White, and Chinese-Americans. The Atherosclerosis Risk in Communities (ARIC) study found that the rate of HF was lowest in White females where the rate of incident HF was 3.0 per 1000 person-years.[6] It was highest in Black males where the rate was found to be 9.1 per 1000 person-years. Overall, the incidence of HF doubles each decade after age 65 in males and triples each decade after 65 in females.[7]

Pathophysiology of HF

HF can be divided into left and right ventricular dysfunction. The focus of this research will be on left ventricular dysfunction. Left ventricular dysfunction can be further divided into two categories: systolic and diastolic dysfunction. In those with HF, systolic dysfunction accounts for about 50-70% of all HF.[8, 9] In systolic dysfunction, the left ventricle fills adequately but does not eject sufficient blood for the body's needs. This type of HF is now also referred to as HF with reduced ejection fraction (HFrEF), that is, the fraction of blood ejected from the ventricle during systole is decreased. Diastolic dysfunction accounts for about 30-50% of those with HF. In this type of HF, the left ventricle does not fill sufficiently during diastole and, while the left ventricular output is insufficient to meet the needs of the body, the ejection fraction is normal. This type of HF is also referred to as HF with preserved ejection fraction (HFpEF). The prevalence of HFpEF has been increasing and in some western countries surpasses the prevalence of HFrEF.[10]

HF with Reduced EF

In HFrEF, the ejection fraction falls below what is considered "normal". A normal ejection fraction (EF) is considered to be between 55 and 65%.[11] Most studies on subjects with HFrEF use <40% EF as a guide to determine those with this form of HF. HFrEF is usually due to a loss of functional cardiac muscle, often due to either ischemic heart disease or myocardial infarction.[12] Reduced ejection fraction leads to a decrease in cardiac output resulting in a hypoperfusion of the body. HFrEF will often lead to increased end systolic pressure in the left ventricle. This sets off a cascade of effects

resulting in increased pressure in the left atrium followed by increased pressure in the pulmonary capillary bed. This leads to increased fluid in the lungs and usually dyspnea.

In response to the cascade of effects that take place during the process of developing HFrEF the body attempts to compensate for the hypoperfusion. The compensation takes many forms and is often seen as early symptoms of the HF syndrome. The reduction in EF leads to a decrease in cardiac output (CO). CO is one of the parameters in determining mean arterial pressure (MAP) with the other parameter being total peripheral resistance (TPR). As CO decreases the body uses several mechanisms to increase TPR to maintain perfusion pressure. TPR may be increased through both neural and humeral mechanisms. Neural mechanisms involve increased sympathetic nerve activity stimulating the β_1, β_2, and α_1 adrenergic receptors.[13] Immediate effects of this stimulation is an increase in heart rate. Sympathetic stimulation in the peripheral vasculature through the β_1 and α_1 receptors leads to an activation of the renin-angiotensin-aldosterone system (RAAS). The effects of RAAS are peripheral vasoconstriction, salt and water retention by the kidneys, and increased thirst ultimately driving MAP up.[14, 15]

Ventricular remodeling is another important compensatory mechanism that is often observed in those with HFrEF.[16] Remodeling alters the shape of the ventricles making the heart less elongated and more spherical. The spherical shape allows for an increase in ventricular volume and an increase in CO. At the same time, myocardial mass increases leading to increased contractility of the heart. This form of compensation eventually exacerbates the condition as ventricular wall tension increases with the

development of fibrous tissue in the ventricular walls. These longer-term changes in the ventricles lead to less effective pumping over time.

HF with Preserved EF

In contrast to those with HFrEF, patients with HFpEF have lower CO due to dysfunction during diastole. The European Society of Cardiology defines HFpEF as having near normal left ventricular function but with abnormal left ventricular relaxation, filling, diastolic distensibility, and stiffness.[17] The stiffness and delayed recoil during relaxation may be due to either increased fibrosis or changes to the myocyte structure. The likely cause of the increase in fibrosis is an increase in the volume or the structure of collagen fibers in the heart walls.[18] The cause of the increase in fibrosis in HFpEF may be similar to HFrEF through activation of the RAAS in response to lower MAP over time causing increased fibrosis.[19]

The compensatory response by the body to HFpEF is also similar to HFrEF. The RAAS is activated due to decreases in MAP. Many of the compensatory mechanisms are made less effective by comorbid conditions frequently occurring in those with HFpEF such as diabetes and obesity.

Diagnosing HF

While the pathophysiology of HFrEF and HFpEF differ, those with either condition are observed with many of the same symptoms. Determining which of the patients with these symptoms has which of the diseases becomes the challenge for the clinician.[20] Patients with HF will often present with some form of dyspnea such as orthopnea,

difficulty breathing while lying down.[21] The patient's history may include renal insufficiency or chronic renal failure, prior myocardial infarction, cardiac arrhythmias, coronary artery disease, hyperlipidemia, diabetes, and hypertension.[22] Jugular vein distension and leg edema are often found in these patients.[21] Chest radiography is used to determine pulmonary edema and heart enlargement.[23] High levels of B-type natriuretic peptide (BNP) or N-terminal proB-type natriuretic peptide (NT-proBNP) are also used as part of the diagnosis.[21, 23] Lung ultrasound is used to diagnose pulmonary edema especially in patients with dyspnea. Echocardiography is used to determine ventricular ejection fraction.[24]

Predictors of HF

Ho and colleagues examined risk factors for incident HF in a cohort of over 6000 subjects, 512 of whom developed HF during the study.[25] They found that the risk of developing HF was increased in those who were older, male, with hypertension, a high body-mass index, a high resting heart rate, coronary heart disease, a prior myocardial infarction (MI), diabetes, a history of smoking, valvular heart disease, low HDL cholesterol, atrial fibrillation, and the presence of LV hypertrophy or left bundle branch block. Of these factors, the strongest associations were with valvular disease and prior MI, both with hazard ratios of 2.5 or higher. This study also attempted to differentiate risk factors in subjects with HFrEF and HFpEF. Using a multivariable analysis, they found the following characteristics associated with a higher risk of HFrEF: male sex, hypertension, higher heart rate, prior cardiovascular disease, higher cholesterol level, left ventricular hypertrophy, and left bundle branch block. The characteristics

associated with a higher risk of HFpEF were: high BMI, smoking, and a history of atrial fibrillation. In addition to the factors shown by Ho et al, other studies have shown that renal dysfunction is a greater risk factor for new onset HFpEF than HFrEF.[26, 27]

Treatment of HF with Reduced EF

Currently, the treatment for HFrEF is more well established than for HFpEF. The principle pharmacological treatment for patients with HFrEF is inhibition of the RAAS.[28] Initially, diuretics are given to relieve peripheral edema but caution is advised as these will activate the RAAS. Furosemide and other loop diuretics are commonly given. For control of the RAAS, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are indicated. Aldosterone antagonists have been shown to be effective to reduce mortality.[29] Beta-blockers have also been shown to reduce mortality if given early in the course of HFrEF.[30]

Treatment of HF with Preserved EF

Treatment for HFpEF is less well defined. The TOPCAT trial provided evidence for the use of the mineralocorticoid-receptor antagonist (MRA) spironolactone in patients with this form of the syndrome.[31] In a meta-analysis, it was shown that there was a reduction in biomarkers for ventricular fibrosis following MRA administration.[32] Diuretics are indicated for symptom relief although caution is advised as those with HFpEF are sensitive to reductions in cardiac pre-load (end diastolic volume).[33] Clinical studies have shown little to no beneficial effect of ACE inhibitors or ARBs for those with HFpEF.[34, 35] While heart rate reduction has been proposed as a possible beneficial

mechanism for HFpEF, studies have not shown this to be effective in improving outcomes.[36]

While few treatments have been shown to improve outcomes directly associated with HFpEF, managing common comorbid conditions is important. Obesity is more common in HFpEF than HFrEF patients and weight loss has been shown to improve left ventricular systolic and diastolic function.[37] Atrial ablation for those patients with AF has been shown to improve outcomes for those with HFpEF.[38] The results of treating pulmonary hypertension, a downstream effect of HFpEF, has shown mixed results. Phosphodiesterase type 5A (PDE5A) inhibition with sildenafil was shown to be effective in reducing cardiac remodeling.[39] However, a double-blind clinical trial comparing sildenafil against placebo did not show improved exercise capacity or clinical status in patients with HFpEF.[40]

Outcomes of HF

Mortality estimates after initial diagnosis of HF are high and have improved only slightly in recent decades. Survival was 57% at 18 months following HF diagnosis in a London general practitioner cohort.[41] In a Scottish cohort, the 5-year survival rate was just above 25%.[42] In the US, median survival was about 4 years after diagnosis which did not appear to improve over time.[43] In this study, the risk of death was more than 3 times higher in HF patients compared to age and sex matched controls. The increasing proportion of HFpEF, where treatment options are limited, underscores the need to understand risk factors that may prevent HF onset.

Primarily due to the aging population, hospitalization rates for HF continue to rise. The American Heart Association, in their 2012 heart disease statistics, estimated that there are nearly 1 million hospitalizations for HF in the US annually.[44] Immediate prognosis after discharge is also poor as 25% of the patients are re-hospitalized within 30 days, 35% of which primarily due to HF.[45] There have been changes in the rates of HF as primary vs. secondary causes of admission over time. The number of primary hospitalizations for HF in the US declined slightly from 1.13M in 2001 to 1.08M in 2009 whereas secondary admissions for HF increased during this time from 2.75M to 3.16M.[46] This finding further emphasizes the need to understand the relationship between HF and other cardiac and non-cardiac conditions.

Epidemiology of Atrial Fibrillation

AF is the most common cardiac arrhythmia with an estimated worldwide burden of 0.5% or about 33.5M people.[47] Chugh et al found rates of AF for both men and women are over twice as high in developed countries compared to developing countries.[47] The authors cautioned that the lack of community-based reporting for AF in developing countries must be taken into consideration when comparing these rates. The rates in the US and Western Europe were found to be 3.3% in men and 2.6% in women.[48] Chugh et al developed models for assessing mortality rates due to AF.[49] They found that the mortality rate has been growing steadily during the period examined (1990-2010) in developed countries from about 1 death per 100K in 1990 to about 2.5 deaths per 100K in 2010. Increases in AF risk factors including population aging, hypertension, obesity,

and diabetes are likely contributors to the increases in both AF morbidity and mortality.[50-52]

In the US and Western Europe, racial differences in AF prevalence have also been shown. The Atherosclerosis Risk in Communities (ARIC) study found that the rate of AF in African-Americans was 41% lower than in whites.[53] Other studies examining AF and race found that South Asians and Black Caribbians had lower rates of AF than whites in the UK.[54] It is important to note that there is evidence that Blacks are less likely to be aware of AF than whites, possibly leading to significant under-ascertainment of rates.[55] It is also critical to understand that these authors found that the lack of awareness of AF in Blacks leads to underutilization of effective treatment for secondary prevention of stroke such as warfarin.

Pathophysiology of AF

In normal cardiac rhythm, the initiation of a contraction occurs with the depolarization of the tissue in the sino-atrial (SA) node. The depolarization spreads through the atria causing a synchronized contraction. When the wave of depolarization reaches the atrio-ventricular (AV) node, the signal is delayed for a fraction of a second before spreading to the ventricles where it initiates ventricular contraction. The delay allows the atria to empty into the ventricles prior to ventricular contraction. About 70% of ventricular filling is passive, i.e., the ventricles fill from the flow of blood from either the vena cava or the pulmonary veins. The other 30% of filling is from atrial contraction. When the atria fail to effectively contract, e.g., during AF, sufficient cardiac output can still be maintained except in periods of high need such as during exercise. This excess capacity

during normal physiological conditions allows those with AF to function normally with only mild, and often unrecognized, symptoms.

The development of cardiac arrhythmias is complex. It is thought that a non-sinus rhythm, i.e., a rhythm not initiated by the SA node, is caused by ectopic foci in other areas of the atria.[56] The cause of these foci are thought to be due to the development of irritable tissues from some underlying cause. For example, mitral valve stenosis, poor functioning of the valve connecting the left atrial chamber to the left ventricle, can cause leakage from the ventricle to the atria during systole. The increased pressure in the atria from the increased volume causes stretch of the relatively thin atrial walls. Over time, the walls of the atria become more fibrotic and increase the chance of developing ischemia in the atrial muscle leading to irritability.[57] Atrial ischemia due to compromised blood flow from atherosclerosis may also contribute to atrial tissue irritability.[58] HF may also contribute as diastolic pressure increases cascade from the ventricles to the atria, stretching the atrial walls similar to valvular disorders.

Atrial remodeling, changes to the electrical, contractile, and structural components of the atria, is a critical element in the development of AF.[59] Early AF is usually episodic, i.e., fibrillation occurs for a short period of time, e.g., hours or days, and then the heart returns to a normal sinus rhythm. If untreated, the number and duration of the AF episodes may increase causing the atrial structure to change to accommodate the resultant increase in atrial pressure. It has been shown in animal models that these changes can be induced through experimental stimuli and can resolve to normal following removal of the stimuli.[60] However, over longer periods of time the reversal

takes longer and in some instances reversal does not occur and leads to permanent atrial arrhythmia.

Diagnosing AF

Patients with AF may present to the clinician in several ways.[61] Many patients are asymptomatic, and the initial diagnosis is through an examination with an electrocardiogram (ECG). Others will be determined to have AF after a diagnosis from an outcome of AF such as stroke or HF. Most patients will have some symptoms of AF such as heart palpitations, fatigue, and chest pain.

Following diagnosis, the cause of AF may sometimes be determined and allow for specific treatment options. Many cases of AF are due to valvular dysfunction.[61] Other causes may be from prior heart disease including myocardial damage from infarction. Other non-cardiac causes may be from a prior history of alcohol or other drug abuse, pneumonia, and pulmonary embolism.

Predictors of AF

Age and sex are likely the strongest predictors of AF.[62] The rate of AF in the population doubles with each 10-year increase of age. In addition, after adjusting for age, it has been shown that males have a 50% higher risk of developing AF.

As discussed previously, a history of valvular disease is a strong predictor of AF. While AF has been associated with any valvular disorder, left side valve stenosis has been shown to be most prevalent in AF patients.[63] The more severe the stenosis, the more likely that AF will occur.[64] The risk varies with gender; women with a valvular disorder

have an 80% higher risk of developing AF while the risk in men with valvular disorders is 3.4 times that of men without valve disorders.[64]

Several common chronic diseases are also common predictors of AF. While the increased risk of AF in those with hypertension is relatively small, a 10-15% increased risk, it is estimated that hypertension accounts for about 15% of all AF due to its high prevalence especially in the older population.[63] Obesity may double the risk of AF.[65] Each unit increase in BMI increases the risk of AF by 3-7%. Chronic kidney disease is another important risk factor. Severe cases of renal disease may lead to a 3-fold increased risk of AF.[66] Diabetes may increase the risk by 40-60%.[67] The diabetes duration and poor glycemic control increases the overall risk of developing AF.

Treatment of AF

Treatment for AF is usually through medical or surgical treatment or a combination of both. The most effective medical treatment is through ventricular rate control.[68] Ventricular rates are controlled to 80 to 110 beats per minute. Beta blockers are the first line of treatment for rate control.[61] Rhythm control is also used but has been shown to be less effective as measured by factors such as rate of hospitalization.[69] Rhythm control can be achieved through cardioversion, the restoration of normal rhythm, either electrically or pharmacologically.

The use of surgical treatments has increased in the last decade. The maze procedure is used to prevent conduction of the depolarizations from ectopic foci.[70] Occlusion of the left atrial appendage is another technique used.[71] The left atrial appendage is the site of

more than 90% of the thrombi that form in the atria during AF. This technique decreases the risk of emboli formation. It also decreases the need for anti-coagulants which may be important in those who may not be able to tolerate these drugs due to risk of intestinal bleeding.

Cather ablation in another technique that has increased in use over the past decade.[72] In this technique, radiofrequency or cryothermic energy is applied to the area where the pulmonary veins enter the atria. Ablation in this area has been found to significantly reduce ectopic foci responsible for AF. However, studies on the long-term efficacy of ablation have shown that recurrence of AF may be as high as 90% 2 years following the procedure.[73]

Outcomes of AF

Many people live relatively symptom-free with AF for years. However, the long-term implications of the disease are significant. Ischemic stroke is the most serious adverse event that occurs with AF.[74] Thrombi forming in the left atria may break off and the resulting emboli may enter the cerebral arteries causing occlusion and infarction. AF accounts for a 3-5-fold increased risk of stroke and likely accounts for about 20% of all ischemic stroke.[75]

Cognitive impairment is another serious outcome of AF that may occur independent of stroke. The risk of dementia is 2.3 times higher in AF patients.[76] The relationship is not fully understood. It is hypothesized that it may involve long-term hypoperfusion due to micro-emboli occurring over time.[77] This hypothesis was challenged following clinical

studies showing similar increase in risk for dementia in those with and without anti-thrombotic therapy.[78]

Rationale for HF over AF

There are many factors that may be involved in the development of HF in patients with AF. Many of the changes stem from ventricular tachycardia induced by AF. Ventricular tachycardia can lead to cardiomyopathy which often precedes HF development.[79] Myocytes may become elongated or may hypertrophy leading to ventricular dilation or increases in ventricular wall thickness. The extracellular matrix may also change with increases in fibrotic tissue in the endocardium and myocardium.[80] Changes may also occur at the atrioventricular annulus surrounding the atrioventricular valves.[81] These may dilate over time causing an increase in regurgitation. Valvular regurgitation will cause a cascade of diastolic pressure increases worsening the already disturbed heart muscle with resultant decreased cardiac capacity.

Intracellular changes also occur in the ventricles following AF that increase the likelihood of developing HF.[82] Downregulation of Ca+ channels in myocytes has been demonstrated in animal models during cardiac pacing studies.[83] This downregulation decreases the strength of the contraction reducing cardiac capacity. Downregulation has also been shown in beta-adrenergic receptors reducing central level of control of heart rate.[84] It has also been shown that AF increases the rate of myocardial apoptosis. Each of these changes decrease cardiac capacity leading to a mismatch between blood flow supply and demand.

Outcomes for HF over AF

The combination of HF over AF produces higher rates of downstream comorbid conditions than either syndrome alone. In the SOLVD trials, which enrolled subjects with left ventricular diastolic dysfunction, the presence of AF was associated in an increased risk of all-cause mortality and death from HF.[85] AF was also associated with an increased risk of re-hospitalization. Subjects in the Framingham study with AF followed by HF were found to have about 3 times the risk of all-cause mortality compared to subjects who did not develop HF.[86] The risk of mortality was approximately doubled in those with existing HF following by AF compared to those who did not develop AF. Chamberlain and colleagues showed similar increases in mortality risk whether AF was developed before or after HF.[87] In a meta-analysis of 7 clinical trials and 9 observational studies, the presence of AF was associated with an increased risk of death compared to those without AF in subjects with either HFrEF or HFpEF.[88] Khazanie et al found in Medicare enrollees that hospital readmissions for heart failure and stroke were increased in HF patients with AF compared to those without AF.[89] Understanding the risk factors associated with developing either AF or HF in the presence of the other is critical to reducing the cost, both in human and health care terms, of these syndromes.

Predictive modeling in Health Care

History

In their seminal paper, Charlson and colleagues described a method for assessing the mortality risk of patients through the use of 19 indicators.[90] They described their

methodology and rationale for their indicators as well as their validation criteria. Many consider this the start of using clinical data to inform decision making on behalf of the clinicians. Over time many other predictive indicators have been developed to assess a wide variety of conditions and outcomes such as the $CHADS_2$ score for stroke risk in AF patients and the DCSI score for diabetes severity and mortality.[91, 92] These measures and similar ones that followed have led to improvements in clinical care as well as reductions in health care costs.

Use of Electronic Health Records

The ability to use predictive modeling for health care is dependent on the availability of electronic health records (EHR). EHR have been available for the past several decades. State and federal governments as well as private agencies, principally health insurance companies, have provided records of high quality to health researchers. Provisions of the Patient Protection and Affordable Care Act (ACA) increased both the quantity and quality of EHR. The Medicare Electronic Health Records Incentive Program, an off-shoot of the ACA, began in 2011 to encourage the use of electronic health care data for improving health care in the US while reducing costs to the Medicare system.[93] Included in the agreement between The Centers for Medicare & Medicaid Services (CMS) and participating clinical organizations was that the data would produce results demonstrating “meaningful use”, that is improving health care and reducing costs.

Research using PM in HF and AF

Much of the PM research in HF and AF have been using small-scale applications, i.e., 30 covariates or less, on small cohorts. In a 2008 review, Ross and colleagues found little

evidence of effective models to predict hospital readmission in HF patients.[94] The discrimination capabilities of the models in their review was modest with c-statistics around 0.6. The studies reviewed were all small-scale models of small cohorts.

Since the Ross 2008 review, several studies have been conducted to predict incident HF. Butler and colleagues developed the Health ABC score based on about 3000 older (average age 73.6 years) subjects.[95] They found that age, history of coronary disease and smoking, baseline systolic blood pressure and heart rate, serum glucose, creatinine, and albumin levels, and left ventricular hypertrophy were predictive of incident HF and included these factors in their 5-year risk score. The c-statistic in this model was 0.73. In a large insurance claims dataset, Goyal et al used 5 predictive factors (coronary heart disease, hypertension, diabetes mellitus, atrial fibrillation, and valvular heart disease) to develop their risk model.[96] The choice of variables was based on what the group considered factors that were relatively modifiable. Their large dataset, more than 1M person-years of follow-up, was capable of good discrimination (> 0.8) in predicting incident HF in both men and women. The Framingham cohort was used to develop a model with many known biomarkers for HF.[97] The use of biomarkers, including B-type natriuretic peptide (BNP) and urinary albumin-to-creatinine ratio, modestly improved their predictive model which showed very good discrimination (> 0.84). B-type natriuretic peptide (hazard ratio 1.52 per 1 standard deviation increase in log biomarker) and urinary albumin-to-creatinine ratio (hazard ratio 1.35 per 1 standard deviation increase in log biomarker) were the factors associated with the greatest increased risk of incident HF. deFilippi et al found that baseline troponin and changes in troponin were

predictive of new HF in older subjects.[98] A >50% increase in troponin levels from baseline was associated with a 61% increased risk of developing HF. Smith and colleagues found that the additions of midregional pro-atrial natriuretic peptide (MR-proANP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) significantly improved their discriminating ability for both the development of HF and AF.[99] The c-statistic for HF was 0.84 and that for AF 0.73. The addition of N-terminal pro-brain natriuretic peptide also improved the discrimination capability in a model using the subjects in the Atherosclerosis Risk in Communities (ARIC) Study.[100]

Schnabel et al examined the risk of new onset HF in AF patients.[101] Their study, using the Framingham cohort, had modest discrimination (c-statistic 0.71). They found that advancing age, LV hypertrophy, body mass index, diabetes, significant heart murmur, and history of myocardial infarction were important clinical predictors of HF in AF patients. Their study was based on 725 individuals with AF and 161 incident cases of HF.

Recently research has been undertaken to use large-scale predictive models to understand the risk of developing HF and its outcomes. Panahiazar and colleagues compared a model using EHR to a small-feature model, the Seattle Heart Failure Model.[102] Their large-scale model modestly improved the predicted survival risk in HF patients compared to the small-scale model.

Research Objectives

The broad aim of this research is to develop models to predict incident heart failure in those with newly diagnosed atrial fibrillation. The specific aims are as follows:

Specific Aim 1 (Chapter 2):

Development and Validation of a Predictive Model for Incident Heart Failure in subjects under 65 Years Old with Newly Diagnosed Atrial Fibrillation.

Specific Aim 2 (Chapter 3):

Development and Validation of a Predictive Model for Incident Heart Failure in subjects over 65 Years Old with Newly Diagnosed Atrial Fibrillation.

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Chapter 2: Development and Validation of a Predictive Model for Incident Heart Failure in subjects under 65 Years Old with Newly Diagnosed Atrial Fibrillation.

Introduction

As discussed in Chapter 1, while the health burden due either to atrial fibrillation (AF) or to heart failure (HF) is high, the burden is significantly greater in patients with both conditions. The problem could be substantially reduced if we could decrease the likelihood of developing HF in the those with existing AF. An early step in achieving this goal is to identify which AF patients are at high risk of HF. This chapter will discuss the development of such a prediction model in patients under age 65 with newly diagnosed AF.

While HF is commonly considered a condition of older adults, there is a significant epidemiological burden in younger persons as well. It was estimated that the prevalence of HF is 1.9% in males and 1.4% in females in those 40-59 years old.[1] Results from the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) program indicated that, in those with HF, heart failure with reduced ejection fraction (HFrEF) was more predominant in the young and decreased in prevalence relative to heart failure with preserved ejection fraction with age.[2] Perhaps most important, the youngest patients reported the lowest quality-of-life scores emphasizing the need to develop predictive models for HF development in this age group.

Models predicting the likelihood of developing HF following a diagnosis of AF would be useful clinical tools for patients and clinicians discussing possible treatment options. The objective of this study was to develop a large-scale predictive model examining the predictors for developing any HF, HFrEF, and HFpEF in patients under age 65 years old with newly diagnosed AF.

Methods

The data management and statistical software packages used in this study were developed in R by the Observational Health Data Sciences and Informatics (OHDSI) interdisciplinary collaborative[3]. The software packages and database specifications are open source and freely available.

Data for this study was from data collected from 2 data sets: IBM® MarketScan® Commercial Claims and Encounters Database (CCAE) (data from January 1, 2000 to December 31, ~~2017)~~2017) and Optum© De-Identified Clinformatics® Data Mart Database – Date of Death (Optum) (data from May 1, 2000 to December 31, 2017). The CCAE database contains health insurance administrative claims from large employers and health plans who provide private healthcare coverage to employees, their spouses, and dependents. As the clear majority of those in the database were 65 years and younger, we restricted our analysis to those in this age group. Each dataset was converted to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), version 5.01. The Optum and IBM® MarketScan® databases used in this study were reviewed by the New England Institutional Review Board (IRB) and were determined to be exempt from broad IRB approval, as this research project did not involve human subject research.

For this analysis a diagnosis of AF required two AF codes within one year of each other. A minimum 365-day look-back period from the first of these was used to qualify it as a first diagnosis. AF Subjects were included if they are 62 years of age or younger at the index date (date of first AF diagnosis). AF subjects were excluded if there existed a code

for any evidence of AF or atrial flutter, a condition similar to AF, during the look-back period. The Systematized Nomenclature of Medicine (SNOMED) condition codes used and the full specification of this cohort are in Appendix 1.

The outcome conditions of HF (all), HFpEF, and HFrEF were determined by initial diagnosis codes for any HF, HFpEF, or HFrEF, respectively. Each required a follow-up second HF, HFpEF, or HFrEF code within one year after the initial diagnosis. A minimum 365-day look-back period was used to ensure first diagnosis. Two times-at-risk for development of HF following initial AF diagnosis were examined: 3 to 12 months and 12 to 36 months. We limited the age at AF diagnosis to 62 or younger to ensure that these subjects would be under age 65 at the end of the 3-year time-at-risk. The full specification for this cohort is in Appendix 1.

We used all available data in each data set for development of the prediction model. The covariates used were: age as a continuous variable; sex; presence/absence of in-patient or out-patient diagnosed condition classes based on SNOMED hierarchy of conditions in the 365 or 30 day window prior to or on index date; presence/absence of drug exposures based on filled drug prescriptions and using the RxNorm naming system for generic and branded drugs in the 365 or 30 day window prior to or on index date; presence/absence of a clinical procedure based on the Current Procedural Terminology, 4th Edition (CPT-4) in the 365 or 30 day window prior to or on index date; the presence/absence of laboratory measurements in the 365 or 30 day window prior to or on index date.

Statistical Analysis

The predictive modeling algorithm in this study was logistic regression using Least Absolute Shrinkage and Selection Operator (LASSO) L1-regularization.[4] This method was chosen based on its use in a prior study involving HF.[5] The logistic regression algorithm used in this study was developed using the R statistical software environment and is available as open-source software in the OHDSI Patient Level Prediction R package.[6-8]

The models were first developed using the CCAE dataset. This was the larger of the 2 datasets and contained the larger number of outcomes. We followed the predictive modeling framework as proposed by Reps et al.[6] We validated the 6 models (2 times-at-risk for 3 outcomes) through both internal and external validation. Internal validation was performed by applying the model learned from 75% of the data, the "training" set, to the remaining 25% of the data, the "testing" set. Internal validation estimated the discrimination of the model through examination of the area under the Receiver Operator Characteristic curve (ROC AUC) and model over/under fitting through calibration curves. The ROC was developed by plotting sensitivity vs. 1-specificity throughout the range of prediction thresholds. External validation of the model was performed by applying the model to Optum. External validation also estimated the precision of the model by examining AUC and model over/under fitting through calibration curves. Qualitative evaluation of model performance (i.e., poor, good, excellent) was based on generally accepted standards.[9] For model comparison, we also calculated the positive predictive value (PPV) and the Likelihood Ratio Positive (LR+) at defined prediction threshold cut-points.[10] To compare the effect of using all available

data vs. a limited set of data to inform the predictive model, we also developed models for predicting any HF at both times-at-risk. using the 7 clinical variables described by Yang et al.[11] The covariates included in this model were coronary artery disease, diabetes mellitus, age, hypertension, smoking status, sex, and body mass index (BMI). Our data did not include values for BMI. We used the presence of diagnostic condition codes for obesity and morbid obesity as proxies for BMI.

Results

The demographic, comorbid conditions, and medication history for the subjects included in this study are displayed in Tables 1a and 1b. Those subjects who developed HF of any type tended to be older than those who did not in both datasets and at both times-at-risk. The differences in ages between the groups seemed to be somewhat attenuated at 1-3Y v. 3M-1Y. The majority of the subjects in the study were male and the gap grew larger in the subset of subjects who developed HF. The gap between males and females was more pronounced in those who developed HFrEF where the proportion of males ranged from 73-82%. Those who developed HF also tended to have higher rates of comorbid conditions as seen by higher Charlson Indices as well as in specific comorbid conditions. The mean Charlson Index for those who developed HF was about 1 point higher than those who did not develop the outcome. There were pronounced differences in several important comorbid conditions. For example, those who developed HF were about twice as likely to have had a prior acute myocardial infarction (AMI) with larger proportional differences among those who developed HFrEF. Following the higher rates of comorbid conditions in those developing HF, higher rates of medication use including antihypertensive and diabetes medications were found in this group.

The internal validation of the predictive model showed good performance (Table 2). In the primary analysis of subjects in CCAE, the AUCs ranged from 70% (1Y-3Y, HFrEF) to 76% (3M-1Y and 1Y-3Y, HFpEF). Calibration of the model also showed good performance characteristics with intercepts at or near 0 along with most of the

calibration slopes near 1.0. Model performance tended to be better for predicting HFpEF compared to HFrEF. As an example, the AUC for the 3M-1Y time-at-risk in CCAE for HFpEF was 76% compared to 72% for HFrEF. Graphical representations of the AUC and calibration curves for the CCAE and Optum models for the outcome of any HF during the 3M to 1 Y time-at-risk are displayed in Figure 1.

The models demonstrated good generalizability as shown by the external validation results (Table 3). Testing the model developed from the CCAE database on the Optum dataset produced AUCs ranging from 72% (3M-1Y, HFrEF) to 76% (3M-1Y, HFpEF). The AUC values were similar between internal and external validation providing evidence for good model generalization. Calibration intercepts and slopes also showed good performance characteristics. The slopes of the calibration curves for the HFpEF model for both times-at-risk were closer to unity, indicating better model fit across the full range of predicted probabilities, compared to the model predicting HFrEF.

A more detailed examination of the performance characteristics for several models for the outcome of any HF at the 3M-1Y time-at-risk is shown in Table 4. In the upper portion of the table, the performance characteristics based on deciles of prediction threshold cut-points are shown. For example, for the CCAE model using all available data, at a cut-point of 2.08%, the sensitivity is 76.4%, the specificity is 60.9%, and the PPV is 4.82%. The LR+ is 2 indicating an increased probability of disease of about 15% based on this test.[10] The middle portion of the table displays the characteristics and deciles of sensitivity; the lower portion at deciles of specificity. The PPVs from the external validation of the CCAE model on the Optum dataset are generally higher at

each corresponding cut-point, likely due to the higher prevalence of any HF in this population. Graphical representations of these data in the CCAE population for the outcome of any HF during the 3M-1Y time-at-risk are shown in Figures 2 (for 3 sensitivity cut-points) and 3 (for 3 specificity cut-points).

Due to the nature of the LASSO regression algorithm, it is not valid to use the final model coefficients for determining the degree of association for predictors of HF in those with AF. Coefficients in the model have undergone shrinkage toward 0 by the algorithm for optimization as per the constraint imposed by the LASSO (L1) penalty. In addition, covariate collinearity is highly likely, and the choice of covariate included in the model between highly colinear covariates often involves selecting one but not both of two colinear factors. Thus, the examination of covariate differences included in the model should be considered only for hypothesis generation for future, properly designed studies. Covariates included in the model (i.e., with non-zero beta coefficients) where there were large relative differences between subjects who developed any HF compared to those subjects who did not develop any HF are shown in Table 5. Some of the covariates included as predictors of HF were cardiomyopathy, chronic obstructive pulmonary disease, renal impairment, use of type 2 diabetes drugs, and use of high ceiling diuretics. The full specification for each of the models is in Appendix 2.

The results of our comparison between our large scale model using all available data and a limited model using the 7 covariates described by Yang and colleagues are shown in Table 6.[12] The mean of the AUC for internal validation for the 3M-1Y model on the

limited data set in CCAE and Optum was about 66% compared to 74% in our large scale model. At the 1Y-3Y time-at-risk, the limited data set model AUC again averaged 66% while our large-scale model averaged 75%. The comparison of other performance characteristics of the small model to the large model is shown in Table 4. As an example, at a sensitivity of 50%, the large model has a PPV of 7.6% compared to 4.3% in the small model. The LR+ in the large model at this sensitivity is 3.2 compared to 1.7 in the small model.

Discussion

The results this study indicate that it is possible to develop good prognostic predictive models for determining the likelihood of developing HF in those age 65 years and younger with recently diagnosed AF. The models have good performance characteristics when tested through internal and external validation. We were also able to show that we could build good performance models for predicting any HF as well as for predicting the two subtypes of HF, HFpEF and HFrEF. To the best of our knowledge this is the first model to show this level of performance for the 3 outcomes.

The models developed in this study may become an important tool for clinicians to help their patients understand the risks of HF. As many other researchers have found, the combination of HF and AF has particularly poor outcomes for both morbidity and mortality.[13, 14] It is possible that once patients know their personal risk of poor future outcomes, they will be more motivated to reduce their risk for these outcomes. Becker et al, in proposing the “Health Belief Model”, conceptualized that a person’s health behavior is predicted by "the threat posed by illness, comprised of the likelihood of its

occurrence ('perceived susceptibility') and its potential for causing physical harm and interfering with social functioning ('perceived severity')".[15] Researchers have found that patient non-adherence to cardiovascular treatment is highly prevalent.[16-18] Models, such as those developed in this study, may help patients better understand his or her individual risk of illness and improve therapeutic compliance.

By examining two periods of follow-up, the models developed provide an estimate of the probability of developing HF within one year following initial AF diagnosis as well as in the period after one year of potential treatment following the diagnosis. This is important as treatment varies between individuals and the effects of the treatments may confer different risks of outcomes. These models offer both the patient and the clinician the opportunity to evaluate individual risk of HF over the course of early treatment for AF.

Our comparison of the models using all available data vs. a limited set of data from prior studies showed an increase in performance using all data. The small-scale model demonstrated a fair performance in predicting any HF (an AUC of about 66%) as compared to our performance (AUC ~74%). This 12% improvement in AUC underscores the value of using all available data to improve the predictive capabilities of these models particularly for complex diseases such as HF. The importance of the increase in AUC in the large model is further illustrated by the larger PPVs and LR+s across the range of prediction thresholds, sensitivities, and specificities in this model indicating a greater level of discrimination capability compared to the small model (Table 4).

Improvements in PPV and LR+ with increases in AUC similar to those we found in this study have been previously reported.[19]

The primary goal for developing a predictive model is to provide clinicians with a tool to better understand their patient's risk of an outcome. This allows clinicians to use their judgment to balance the risks and benefits of any treatment. It also provides clinicians with a tool to better educate their patients on their personal risk of disease and in this way, as previously discussed, increases the likelihood of patient compliance. An ancillary benefit of the model is that it may provide insight into previously unknown predictors of disease. Due to the nature of the modeling process, these predictors must not be conflated with independent risk factors for disease. Outside of their use within the model, predictors should only be used in hypothesis generation and to motivate properly designed future studies. Studies specifically designed for analyzing causal inference should follow to truly assess possible associations. Many of the predictors found in our models were well known to researchers prior to this study such as cardiomyopathy, diabetes, and edema.[20] The appearance of these predictors in our model provides a measure of face validity. Others, such as the anti-seizure medication gabapentin and anti-psychotics, have not been previously considered and may be examined in future studies.

The high prevalence of hypertension and diabetes in the base population as well as higher levels in those with the outcome, while previously understood as predictors for the outcome, requires further examination. Many features from the datasets indicative of these disease states were included in the models. It is interesting to note that, while

the prevalence of hypertension is much higher than that of diabetes, diabetes appears to be more frequently incorporated into the models predicting both HFpEF as well as HFrEF. Hypertension is generally limited to models predicting HFpEF. Recently, the anti-diabetic drug class Sodium/Glucose co-transporter 2 inhibitors (SGLT2i) have shown efficacy in reducing morbidity and mortality from HF.[21, 22] While the full mechanism of action is unknown, there is evidence that reducing afferent renal nerve activity leading to overall reduction in sympathetic activity may play a role.[23] This may be critical in reducing poor outcomes in HF especially in those with HFpEF. SGLT2i administration was also shown to increase the blood level of erythropoietin (EPO), increasing the production of red blood cells and thereby increasing the hematocrit.[24] The increase in hematocrit may act to reduce poor outcomes from the weakened heart found in HFrEF. Each of the 12 models in this study included diabetes as an important predictor for the outcome of HF. This provides strong evidence of the importance of diabetes in the development of HF in those with newly diagnosed AF.

As previously noted, many of the predictors in the model were well known from prior studies. Some, such as cardiomyopathy and myocardial disease, may even be considered precursors for heart failure. It is interesting to note that, while these may be considered precursors for HF, their presence does not make HF inevitable. As shown in Table 7, a wide majority of patients with these prior conditions did not go on to develop HF at either time-at-risk. For example, in those with cardiomyopathy, in either the year prior to AF diagnosis or the year following AF diagnosis, only about 10% of the patients went on to develop HF. This emphasizes the importance of predictive models as a key

element in the move toward personalized medicine. In these models, the full complement of predictors is evaluated to understand the true risk of an outcome for the individual.

There are several limitations to this study. Most of the subjects in this study were diagnosed with the general diagnostic code for HF and only a small proportion met the criteria we used for HFrEF or HFpEF. The predictive models for the subtypes of HF may reflect those subjects where specific diagnostic tests, e.g., cardiac ejection fraction, were performed. Another limitation of this work derives from the uncertain accuracy of the administrative claims on which it is based. Including all possible covariates with the use of regularization provides more confidence in the results as does the generalizability of a model developed on one large dataset on a second large dataset. In this study, while we used multiple datasets covering millions of lives, each dataset only includes a sample of the US population and may not be representative of the whole US population. It is also possible for predictors such as conditions or drugs to be missing from the databases (e.g., over the counter medication) and missing data will result in no record for the condition or drug and therefore be treated as an absence of the condition or drug. Therefore, the datasets are likely to contain noise, and this could potentially lead to misclassification. Observational datasets often lack certain variables such as genetic factors or lifestyle factors that may be highly predictive of the outcome being investigated. This may result in models that do not perform as well as models developed on datasets that contain variables on genetics or lifestyle. However,

observational datasets often contain thousands of variables that may be used as proxies for genetic or lifestyle factors and observational data is often more readily available.

In conclusion, the models developed in this study showed good performance characteristics, including external generalizability and can likely be used by clinicians as another tool in their arsenal to combat HF and its sequelae. These models may help to reduce the cost of HF, both financially and in human terms.

Tables and Figures

Table 1a: Patient Demographic, Prior Comorbid Condition, and Prior Prescription Drug Data for Subjects with an Initial Diagnosis of Atrial Fibrillation and a Time at Risk of Developing Heart Failure of 3 Months to 1 Year After Diagnosis Derived from the IBM® MarketScan® Commercial Claims and Encounters Database (CCAE) and Optum© De-Identified Clinformatics® Data Mart Database between January 1, 2000 and December 31, 2017.

Database	CCAE				DOD			
Outcome:	No HF	Any HF	HFrEF	HFpEF	No HF	Any HF	HFrEF	HFpEF
N (%)	119572	3095	482	414	52198	1658	206	221
Age at DIagnosis (yrs.) Mean (SD)	54.9 (8.7)	57.5 (6.3)	57.1 (6.8)	58.4 (5.3)	54.5 (9.2)	57.7 (6.9)	57.5 (6.6)	58.3 (7.4)
Female N (%)	45538 (38.1)	1044 (33.7)	130 (27.0)	155 (37.4)	19483 (37.3)	557 (33.6)	54 (26.2)	84 (38.0)
Charlson Index Mean (SD)	1.7 (2.1)	2.8 (2.8)	2.7 (2.7)	3.1 (2.9)	2.0 (2.4)	3.4 (3.1)	2.9 (2.9)	4.0 (3.3)
Prior Comorbid Conditions N (%)								
AMI	6602 (5.5)	377 (12.2)	70 (14.5)	39 (9.4)	3815 (7.3)	267 (16.1)	31 (15.0)	24 (10.9)
Angina	11823 (9.9)	446 (14.4)	78 (16.2)	62 (15.0)	6191 (11.9)	289 (17.4)	32 (15.5)	36 (16.3)
CAD	22036 (18.4)	959 (31.0)	162 (33.6)	109 (26.3)	11212 (21.5)	612 (36.9)	81 (39.3)	74 (33.5)
Cerebral Infarction	4395 (3.7)	181 (5.8)	32 (6.6)	22 (5.3)	2294 (4.4)	136 (8.2)	18 (8.7)	23 (10.4)
Hypertension	75529 (63.2)	2401 (77.6)	362 (75.1)	360 (87.0)	34975 (67.0)	1377 (83.1)	161 (78.2)	199 (90.0)
Obesity	8289 (6.9)	396 (12.8)	46 (9.5)	78 (18.8)	4940 (9.5)	273 (16.5)	27 (13.1)	56 (25.3)
Tobacco Dependence Syndrome	10043 (8.4)	368 (11.9)	66 (13.7)	61 (14.7)	8033 (15.4)	387 (23.3)	54 (26.2)	61 (27.6)
Transient Cerebral Ischemia	4828 (4.0)	177 (5.7)	30 (6.2)	21 (5.1)	2412 (4.6)	108 (6.5)	12 (5.8)	13 (5.9)
Type 2 Diabetes	27401 (22.9)	1193 (38.5)	164 (34.0)	202 (48.8)	12888 (24.7)	712 (42.9)	70 (34.0)	112 (50.7)
Medications N (%)								
ACE Inhibitors	37573 (31.4)	1479 (47.8)	248 (51.5)	209 (50.5)	15947 (30.6)	709 (42.8)	98 (47.6)	101 (45.7)
Aldosterone Antagonists	2338 (2.0)	160 (5.2)	22 (4.6)	21 (5.1)	931 (1.8)	84 (5.1)	14 (6.8)	11 (5.0)
Anti-arrhythmics	5697 (4.8)	170 (5.5)	27 (5.6)	20 (4.8)	1708 (3.3)	71 (4.3)	8 (3.9)	12 (5.4)
Antiepileptics	19214 (16.1)	722 (23.3)	94 (19.5)	121 (29.2)	8739 (16.7)	425 (25.6)	38 (18.4)	74 (33.5)
Anti-thrombotic Agents	37919 (31.7)	1349 (43.6)	230 (47.7)	187 (45.2)	13981 (26.8)	646 (39.0)	82 (39.8)	83 (37.6)
Beta Blockers	52557 (44.0)	1744 (56.3)	268 (55.6)	254 (61.4)	20946 (40.1)	893 (53.9)	112 (54.4)	123 (55.7)
Beta-lactam antibiotics	56444 (47.2)	1495 (48.3)	226 (46.9)	227 (54.8)	23678 (45.4)	803 (48.4)	94 (45.6)	114 (51.6)
Calcium Channel Blockers	30057 (25.1)	1153 (37.3)	154 (32.0)	168 (40.6)	12292 (23.5)	591 (35.6)	71 (34.5)	91 (41.2)
Cardiac Glycosides	4614 (3.9)	204 (6.6)	38 (7.9)	14 (3.4)	1763 (3.4)	95 (5.7)	14 (6.8)	5 (2.3)
Factor Xa Inhibitors	3180 (2.7)	116 (3.7)	20 (4.1)	29 (7.0)	1027 (2.0)	40 (2.4)	4 (1.9)	9 (4.1)
Glucose Lowering Drugs	18780 (15.7)	868 (28.0)	128 (26.6)	138 (33.3)	7795 (14.9)	456 (27.5)	48 (23.3)	74 (33.5)
Insulin	5078 (4.2)	345 (11.1)	46 (9.5)	52 (12.6)	2451 (4.7)	211 (12.7)	26 (12.6)	35 (15.8)
Lipid Lowering Agents	52422 (43.8)	1645 (53.2)	258 (53.5)	231 (55.8)	21757 (41.7)	876 (52.8)	113 (54.9)	123 (55.7)
Loop Diuretics	10567 (8.8)	759 (24.5)	103 (21.4)	119 (28.7)	4227 (8.1)	386 (23.3)	42 (20.4)	67 (30.3)
Nitrates	7870 (6.6)	335 (10.8)	43 (8.9)	44 (10.6)	2852 (5.5)	187 (11.3)	23 (11.2)	25 (11.3)
Platelet Aggregation Inhibitors	10026 (8.4)	466 (15.1)	87 (18.0)	67 (16.2)	4161 (8.0)	227 (13.7)	29 (14.1)	27 (12.2)
Sulfonamides	20906 (17.5)	630 (20.4)	92 (19.1)	109 (26.3)	7622 (14.6)	302 (18.2)	33 (16.0)	51 (23.1)
Thiazide Diuretics	33843 (28.3)	1170 (37.8)	164 (34.0)	186 (44.9)	13715 (26.3)	524 (31.6)	62 (30.1)	93 (42.1)
Vitamin K Antagonists	19561 (16.4)	688 (22.2)	115 (23.9)	71 (17.1)	8094 (15.5)	339 (20.4)	44 (21.4)	38 (17.2)

* CCAE – Commercial Claims and Encounters; HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction; SD – Standard Deviation; AMI – Acute Myocardial Infarction; CAD – Coronary Artery Disease; ACE – Angiotensin Converting Enzyme

Table 1b: Patient Demographic, Prior Comorbid Condition, and Prior Prescription Drug Data for Subjects with an Initial Diagnosis of Atrial Fibrillation and a Time at Risk of Developing Heart Failure of I Year to 3 Years After Diagnosis Derived from the IBM® MarketScan® Commercial Claims and Encounters Database (CCAE) and Optum© De-Identified Clinformatics® Data Mart Database between January 1, 2000 and December 31, 2017.

Database	CCAE				DOD			
Outcome:	No HF	Any HF	HFrEF	HFpEF	No HF	Any HF	HFrEF	HFpEF
N (%)	65646	2324	315	337	28315	1351	148	184
Age at DIagnosis (yrs.) Mean (SD)	56.3 (7.9)	58.0 (6.0)	57.6 (7.0)	58.7 (4.9)	56.3 (8.4)	58.9 (6.7)	59.5 (5.7)	59.9 (5.8)
Female N (%)	25427 (38.7)	821 (35.3)	83 (26.3)	144 (42.7)	10869 (38.4)	487 (36.0)	27 (18.2)	85 (46.2)
Charlson Index Mean (SD)	2.2 (2.3)	3.4 (2.9)	3.2 (2.8)	3.8 (2.9)	2.6 (2.6)	4.1 (3.2)	3.9 (2.8)	4.1 (3.4)
Prior Comorbid Conditions N (%)								
AMI	4690 (7.1)	321 (13.8)	47 (14.9)	38 (11.3)	2647 (9.3)	261 (19.3)	35 (23.6)	28 (15.2)
Angina	9207 (14.0)	511 (22.0)	64 (20.3)	72 (21.4)	4545 (16.1)	337 (24.9)	29 (19.6)	51 (27.7)
CAD	17915 (27.3)	978 (42.1)	141 (44.8)	119 (35.3)	8687 (30.7)	657 (48.6)	77 (52.0)	85 (46.2)
Cerebral Infarction	3335 (5.1)	156 (6.7)	20 (6.3)	26 (7.7)	1647 (5.8)	126 (9.3)	12 (8.1)	16 (8.7)
Hypertension	48375 (73.7)	1953 (84.0)	266 (84.4)	300 (89.0)	21989 (77.7)	1229 (91.0)	137 (92.6)	175 (95.1)
Obesity	6406 (9.8)	334 (14.4)	41 (13.0)	74 (22.0)	3594 (12.7)	262 (19.4)	22 (14.9)	47 (25.5)
Tobacco Dependence Syndrome	6246 (9.5)	297 (12.8)	62 (19.7)	45 (13.4)	4930 (17.4)	344 (25.5)	44 (29.7)	52 (28.3)
Transient Cerebral Ischemia	3852 (5.9)	157 (6.8)	27 (8.6)	20 (5.9)	1926 (6.8)	111 (8.2)	9 (6.1)	20 (10.9)
Type 2 Diabetes	17820 (27.1)	1055 (45.4)	144 (45.7)	179 (53.1)	8249 (29.1)	671 (49.7)	73 (49.3)	95 (51.6)
Medications N (%)								
ACE Inhibitors	25059 (38.2)	1213 (52.2)	174 (55.2)	181 (53.7)	10591 (37.4)	690 (51.1)	80 (54.1)	93 (50.5)
Aldosterone Antagonists	2019 (3.1)	161 (6.9)	21 (6.7)	26 (7.7)	774 (2.7)	83 (6.1)	5 (3.4)	12 (6.5)
Anti-arrhythmics	19833 (30.2)	750 (32.3)	101 (32.1)	120 (35.6)	7543 (26.6)	366 (27.1)	40 (27.0)	55 (29.9)
Antiepileptics	13827 (21.1)	644 (27.7)	89 (28.3)	107 (31.8)	6091 (21.5)	404 (29.9)	46 (31.1)	63 (34.2)
Anti-thrombotic Agents	43481 (66.2)	1878 (80.8)	263 (83.5)	280 (83.1)	17262 (61.0)	1011 (74.8)	115 (77.7)	138 (75.0)
Beta Blockers	47037 (71.7)	1838 (79.1)	250 (79.4)	266 (78.9)	19267 (68.0)	1013 (75.0)	120 (81.1)	133 (72.3)
Beta-lactam antibiotics	37141 (56.6)	1448 (62.3)	191 (60.6)	212 (62.9)	15532 (54.9)	724 (53.6)	79 (53.4)	94 (51.1)
Calcium Channel Blockers	27064 (41.2)	1183 (50.9)	145 (46.0)	212 (62.9)	11084 (39.1)	674 (49.9)	68 (45.9)	106 (57.6)
Cardiac Glycosides	7706 (11.7)	446 (19.2)	46 (14.6)	45 (13.4)	3144 (11.1)	218 (16.1)	25 (16.9)	22 (12.0)
Factor Xa Inhibitors	9480 (14.4)	368 (15.8)	65 (20.6)	76 (22.6)	3195 (11.3)	147 (10.9)	22 (14.9)	27 (14.7)
Glucose Lowering Drugs	12060 (18.4)	741 (31.9)	109 (34.6)	136 (40.4)	4945 (17.5)	427 (31.6)	51 (34.5)	61 (33.2)
Insulin	3538 (5.4)	337 (14.5)	48 (15.2)	66 (19.6)	1602 (5.7)	216 (16.0)	20 (13.5)	36 (19.6)
Lipid Lowering Agents	35038 (53.4)	1473 (63.4)	209 (66.3)	230 (68.2)	14772 (52.2)	855 (63.3)	102 (68.9)	125 (67.9)
Loop Diuretics	9778 (14.9)	875 (37.7)	105 (33.3)	143 (42.4)	3824 (13.5)	461 (34.1)	44 (29.7)	69 (37.5)
Nitrates	6211 (9.5)	411 (17.7)	51 (16.2)	44 (13.1)	2325 (8.2)	218 (16.1)	25 (16.9)	34 (18.5)
Platelet Aggregation Inhibitors	8314 (12.7)	476 (20.5)	71 (22.5)	68 (20.2)	3463 (12.2)	267 (19.8)	29 (19.6)	39 (21.2)
Sulfonamides	14854 (22.6)	574 (24.7)	82 (26.0)	84 (24.9)	5367 (19.0)	317 (23.5)	39 (26.4)	47 (25.5)
Thiazide Diuretics	21814 (33.2)	926 (39.8)	115 (36.5)	176 (52.2)	8901 (31.4)	524 (38.8)	47 (31.8)	88 (47.8)
Vitamin K Antagonists	25991 (39.6)	1241 (53.4)	161 (51.1)	164 (48.7)	11243 (39.7)	699 (51.7)	64 (43.2)	91 (49.5)

* CCAE – Commercial Claims and Encounters; HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction; SD – Standard Deviation; AMI – Acute Myocardial Infarction; CAD – Coronary Artery Disease; ACE – Angiotensin Converting Enzyme

Table 2: Internal Validation of the Prediction Models Derived from the IBM® MarketScan® Commercial Claims and Encounters Database (CCAE) and Optum© De-Identified Clinformatics® Data Mart Database between January 1, 2000 and December 31, 2017.

Database	Analysis	Outcome	Train AUC (95% CI)	Test AUC (95% CI)	Test Cal. Intercept	Test Cal. Slope
CCAE	3M-1Y	Any HF	0.767 (0.764, 0.770)	0.732 (0.727, 0.737)	0.000	1.018
CCAE	3M-1Y	HFrEF	0.780 (0.778, 0.782)	0.719 (0.714, 0.724)	-0.001	1.242
CCAE	3M-1Y	HFpEF	0.815 (0.813, 0.817)	0.760 (0.755, 0.765)	0.000	1.046
CCAE	1Y-3Y	Any HF	0.771 (0.768, 0.774)	0.735 (0.728, 0.742)	-0.001	1.026
CCAE	1Y-3Y	HFrEF	0.809 (0.806, 0.812)	0.702 (0.695, 0.709)	0.000	0.962
CCAE	1Y-3Y	HFpEF	0.808 (0.805, 0.811)	0.759 (0.753, 0.765)	0.000	1.028
Optum	3M-1Y	Any HF	0.773 (0.769, 0.777)	0.752 (0.745, 0.759)	-0.004	1.129
Optum	3M-1Y	HFrEF	0.791 (0.788, 0.794)	0.678 (0.670, 0.686)	0.000	0.976
Optum	3M-1Y	HFpEF	0.859 (0.856, 0.862)	0.740 (0.733, 0.747)	0.001	0.733
Optum	1Y-3Y	Any HF	0.794 (0.789, 0.799)	0.758 (0.748, 0.768)	-0.004	1.075
Optum	1Y-3Y	HFrEF	0.837 (0.833, 0.841)	0.778 (0.769, 0.787)	-0.002	1.299
Optum	1Y-3Y	HFpEF	0.826 (0.822, 0.830)	0.747 (0.737, 0.757)	0.000	1.043

* AUC – Area Under the Receiver Operator Characteristics Curve; CI – Confidence Interval; Cal. – Calibration; CCAE – Commercial Claims and Encounters; 3M-1Y – 3 Month to 1Year Time-at-Risk; 1Y-3Y – 1 Year to 3 Year Time-at-Risk; HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction

Table 3: External Validation of the Prediction Models Derived from the IBM® MarketScan® Commercial Claims and Encounters Database (CCAE) and Optum© De-Identified Clinformatics® Data Mart Database between January 1, 2000 and December 31, 2017.

Model Database	External Validation Database	Analysis	Outcome	Test AUC (95% CI)	Test Cal. Intercept	Test Cal. Slope
CCAE	Optum	3M-1Y	Any HF	0.746 (0.742, 0.750)	0.001	1.044
CCAE	Optum	3M-1Y	HFrEF	0.717 (0.713, 0.721)	0.000	0.838
CCAE	Optum	3M-1Y	HFpEF	0.757 (0.753, 0.761)	0.000	0.948
CCAE	Optum	1Y-3Y	Any HF	0.733 (0.728, 0.738)	0.000	1.328
CCAE	Optum	1Y-3Y	HFrEF	0.750 (0.745, 0.755)	-0.001	1.167
CCAE	Optum	1Y-3Y	HFpEF	0.727 (0.722, 0.732)	0.001	1.057

* AUC – Area Under the Receiver Operator Characteristics Curve; CI – Confidence Interval; Cal. – Calibration; CCAE – Commercial Claims and Encounters; 3M-1Y – 3 Month to 1Year Time-at-Risk; 1Y-3Y – 1 Year to 3 Year Time-at-Risk; HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction

Table 4: Model performance characteristics for the 3 Month to 1 Year Time-at-Risk Models across the range of prediction thresholds, sensitivities, and specificities for the CCAE large model, the external validation of the CCAE model on Optum, and the CCAE small model.

CCAE - Large Model					External Validation CCAE on Optum - Large Model					CCAE - Small Model				
Prediction Threshold Cut-point	Sensitivity	Specificity	PPV	LR+	Prediction Threshold Cut-point	Sensitivity	Specificity	PPV	LR+	Prediction Threshold Cut-point	Sensitivity	Specificity	PPV	LR+
0.79%	98.9%	10.2%	2.77%	1.1	0.80%	98.9%	10.3%	3.38%	1.1	1.15%	97.5%	10.2%	2.73%	1.1
1.03%	96.1%	20.4%	3.03%	1.2	1.05%	96.9%	20.5%	3.73%	1.2	1.42%	92.5%	20.5%	2.92%	1.2
1.25%	93.0%	30.6%	3.35%	1.3	1.28%	92.9%	30.7%	4.08%	1.3	1.66%	86.4%	30.5%	3.11%	1.2
1.48%	89.0%	40.7%	3.74%	1.5	1.53%	87.5%	40.9%	4.49%	1.5	1.90%	79.7%	40.5%	3.35%	1.3
1.75%	83.5%	50.9%	4.21%	1.7	1.83%	81.7%	51.0%	5.03%	1.7	2.17%	71.8%	50.7%	3.64%	1.5
2.08%	76.4%	60.9%	4.82%	2.0	2.21%	74.5%	61.1%	5.74%	1.9	2.42%	61.8%	60.6%	3.90%	1.6
2.55%	67.1%	71.0%	5.65%	2.3	2.78%	65.6%	71.1%	6.73%	2.3	2.81%	50.6%	70.5%	4.26%	1.7
3.28%	55.5%	80.9%	7.00%	2.9	3.67%	51.9%	81.0%	7.99%	2.7	3.48%	36.6%	80.4%	4.62%	1.9
4.88%	37.1%	90.7%	9.36%	4.0	5.69%	33.8%	90.8%	10.41%	3.7	4.29%	21.0%	90.3%	5.29%	2.2
11.75%	10.0%	98.7%	16.54%	7.7	13.13%	10.0%	98.4%	16.63%	6.3	5.68%	10.0%	96.1%	6.21%	2.6
7.88%	20.0%	96.6%	13.06%	5.8	8.63%	20.0%	95.8%	13.21%	4.8	4.42%	20.0%	90.9%	5.41%	2.2
5.82%	30.0%	93.4%	10.56%	4.6	6.32%	30.0%	92.3%	10.99%	3.9	3.78%	30.0%	84.8%	4.86%	2.0
4.62%	40.0%	89.6%	9.07%	3.9	4.77%	40.0%	87.4%	9.15%	3.2	3.35%	40.0%	78.3%	4.55%	1.8
3.68%	50.0%	84.3%	7.62%	3.2	3.88%	50.0%	82.5%	8.35%	2.9	2.84%	50.0%	71.0%	4.28%	1.7
2.99%	60.0%	77.7%	6.52%	2.7	3.10%	60.0%	75.4%	7.19%	2.4	2.49%	60.0%	62.3%	3.95%	1.6
2.38%	70.0%	67.6%	5.29%	2.2	2.49%	70.0%	66.5%	6.23%	2.1	2.23%	70.0%	52.3%	3.66%	1.5
1.90%	80.0%	55.6%	4.46%	1.8	1.91%	80.0%	53.4%	5.18%	1.7	1.89%	80.0%	40.0%	3.34%	1.3
1.42%	90.0%	38.3%	3.64%	1.5	1.41%	90.0%	36.1%	4.28%	1.4	1.53%	90.0%	25.0%	3.01%	1.2
0.79%	98.9%	10.0%	2.77%	1.1	0.80%	99.0%	10.0%	3.38%	1.1	1.15%	97.5%	10.0%	2.73%	1.1
1.02%	96.3%	20.0%	3.02%	1.2	1.04%	97.0%	20.0%	3.71%	1.2	1.41%	92.8%	20.0%	2.91%	1.2
1.23%	93.3%	30.0%	3.33%	1.3	1.26%	93.3%	30.0%	4.06%	1.3	1.64%	86.7%	30.0%	3.10%	1.2
1.46%	89.4%	40.0%	3.71%	1.5	1.51%	88.0%	40.0%	4.45%	1.5	1.89%	80.0%	40.0%	3.34%	1.3
1.72%	84.0%	50.0%	4.17%	1.7	1.79%	82.0%	50.0%	4.95%	1.6	2.17%	72.4%	50.0%	3.62%	1.4
2.05%	77.0%	60.0%	4.74%	1.9	2.16%	75.4%	60.0%	5.65%	1.9	2.42%	62.6%	60.0%	3.89%	1.6
2.49%	68.0%	70.0%	5.54%	2.3	2.70%	66.7%	70.0%	6.59%	2.2	2.77%	51.4%	70.0%	4.24%	1.7
3.19%	57.1%	80.0%	6.89%	2.9	3.55%	53.5%	80.0%	7.83%	2.7	3.45%	37.3%	80.0%	4.61%	1.9
4.71%	39.1%	90.0%	9.18%	3.9	5.43%	35.6%	90.0%	10.16%	3.6	4.25%	21.4%	90.0%	5.26%	2.1

* CCAE – Commercial Claims and Encounters; PPV- Positive Predictive Value; LR+ - Likelihood Ratio Positive

Table 5: Univariate comparisons of prior comorbid conditions and drugs included in one or more predictive models.

Database	Analysis	Outcome	Covariate Name	Covariate Mean Proportion in Subjects With Outcome	Covariate Mean Proportion in Subjects With No Outcome	Rel. Ratio
Optum	3M-1Y	HFpEF	Renal disorder due to type 2 diabetes mellitus	0.10	0.02	6.52
Optum	3M-1Y	HFpEF	Diabetic on insulin	0.08	0.01	5.89
CCAE	3M-1Y	HFrEF	Cardiomyopathy	0.15	0.03	5.87
Optum	1Y-3Y	HFpEF	ANTIHYPERTENSIVES	0.13	0.03	4.78
CCAE	1Y-3Y	HFpEF	Ulcer of lower extremity	0.07	0.02	4.77
Optum	1Y-3Y	HFpEF	Furosemide	0.19	0.04	4.62
Optum	1Y-3Y	HFpEF	Type 1 diabetes mellitus	0.13	0.03	4.29
CCAE	1Y-3Y	HFpEF	Insulins and analogues for injection, long-acting	0.16	0.04	4.24
Optum	3M-1Y	HFrEF	Chronic ischemic heart disease	0.14	0.03	4.19
Optum	3M-1Y	HFpEF	HIGH-CEILING DIURETICS	0.25	0.06	4.15
Optum	1Y-3Y	HFpEF	Hypoxemia	0.10	0.03	4.11
CCAE	3M-1Y	HFpEF	Edema	0.09	0.02	3.93
Optum	1Y-3Y	Any HF	Renal impairment	0.07	0.02	3.84
Optum	1Y-3Y	HFpEF	Polyneuropathy	0.11	0.03	3.84
CCAE	3M-1Y	HFrEF	carvedilol	0.12	0.03	3.63
Optum	3M-1Y	Any HF	Acute exacerbation of chronic obstructive airways disease	0.07	0.02	3.62
Optum	1Y-3Y	HFrEF	Alpha and beta blocking agents	0.14	0.04	3.56
Optum	3M-1Y	HFpEF	ANTIPSYCHOTICS	0.11	0.03	3.35
Optum	3M-1Y	HFpEF	gabapentin	0.19	0.06	3.33
CCAE	3M-1Y	HFpEF	Morbid obesity	0.09	0.03	3.32
CCAE	3M-1Y	HFpEF	Chronic kidney disease	0.09	0.03	3.21
CCAE	3M-1Y	HFpEF	Pneumonitis	0.16	0.05	3.16
CCAE	3M-1Y	HFpEF	Tracheobronchial disorder	0.17	0.06	3.16
Optum	1Y-3Y	HFrEF	Myocardial disease	0.39	0.13	3.14
Optum	3M-1Y	Any HF	Polyneuropathy	0.07	0.02	3.11
Optum	3M-1Y	HFpEF	Type II diabetes mellitus uncontrolled	0.20	0.06	3.11
CCAE	3M-1Y	HFpEF	Chronic obstructive lung disease	0.16	0.05	3.01
CCAE	3M-1Y	HFpEF	Direct factor Xa inhibitors	0.07	0.02	2.94
CCAE	3M-1Y	HFpEF	Thiazolidinediones	0.07	0.02	2.91
CCAE	3M-1Y	HFpEF	Major depressive disorder	0.08	0.03	2.88

* Rel. Ratio – Relative Ratio; CCAE – Commercial Claims and Encounters; 3M-1Y – 3 Month to 1Year Time-at-Risk; 1Y-3Y – 1 Year to 3 Year Time-at-Risk; HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction

Table 6: Comparison of the performance characteristics from the internal validation of the prediction models using the small v. large set of covariates developed on the Commercial Claims and Encounters and Optum datasets.

Database	Analysis	Model	Outcome	Train AUC (95% CI)	Test AUC (95% CI)	Test Cal. Intercept	Test Cal. Slope
CCAE	3M-1Y	Small	Any HF	0.657 (0.654, 0.660)	0.645 (0.640, 0.650)	0.003	0.888
CCAE	3M-1Y	Large	Any HF	0.767 (0.764, 0.770)	0.732 (0.727, 0.737)	0.000	1.018
CCAE	1Y-3Y	Small	Any HF	0.654 (0.650, 0.658)	0.622 (0.615, 0.629)	0.005	0.846
CCAE	1Y-3Y	Large	Any HF	0.771 (0.768, 0.774)	0.735 (0.728, 0.742)	-0.001	1.026
Optum	3M-1Y	Small	Any HF	0.675 (0.671, 0.679)	0.678 (0.670, 0.686)	-0.003	1.057
Optum	3M-1Y	Large	Any HF	0.773 (0.769, 0.777)	0.752 (0.745, 0.759)	-0.004	1.129
Optum	1Y-3Y	Small	Any HF	0.678 (0.673, 0.683)	0.702 (0.692, 0.712)	-0.011	1.243
Optum	1Y-3Y	Large	Any HF	0.794 (0.789, 0.799)	0.758 (0.748, 0.768)	-0.004	1.075

* AUC – Area Under the Receiver Operator Characteristics Curve; CI – Confidence Interval; Cal. – Calibration; CCAE - Commercial Claims and Encounters; 3M-1Y – 3 Month to 1Year Time-at-Risk; 1Y-3Y – 1 Year to 3 Year Time-at-Risk; HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction

Table 7: Comparison of proportions of subjects with and without the outcome of any heart failure with prior conditions and drugs highly prevalent in those with heart failure.

	CCAE 3M-1Y TAR		Optum 3M-1Y TAR		CCAE 1Y-3Y TAR		Optum 1Y-3Y TAR	
Characteristic	No HF	Any HF	No HF	Any HF	No HF	Any HF	No HF	Any HF
High Ceiling Diuretics	0.92	0.08	0.90	0.10	0.91	0.09	0.88	0.12
Cardiomyopathy	0.92	0.08	0.90	0.10	0.92	0.08	0.89	0.11
Myocardial Disease	0.94	0.06	0.93	0.07	0.93	0.07	0.93	0.07
Edema	0.95	0.05	NIM		NIM		0.91	0.09
Cardiomegaly	0.95	0.05	NIM		0.93	0.07	NIM	
Carvedilol	NIM		0.92	0.08	NIM		NIM	

* CCAE – Commercial Claims and Encounters; 3M-1Y TAR – 3 Month to 1Year Time-at-Risk; 1Y-3Y TAR – 1 Year to 3 Year Time-at-Risk; NIM – Not in Model

Figure 1: Area Under the Receiver Operator Characteristic Curves and the Calibration Curves of the Commercial Claims and Encounters (CCAE) and Optum models for the Outcome of Any Heart Failure at the 3 Month to 1 Year Time at Risk.

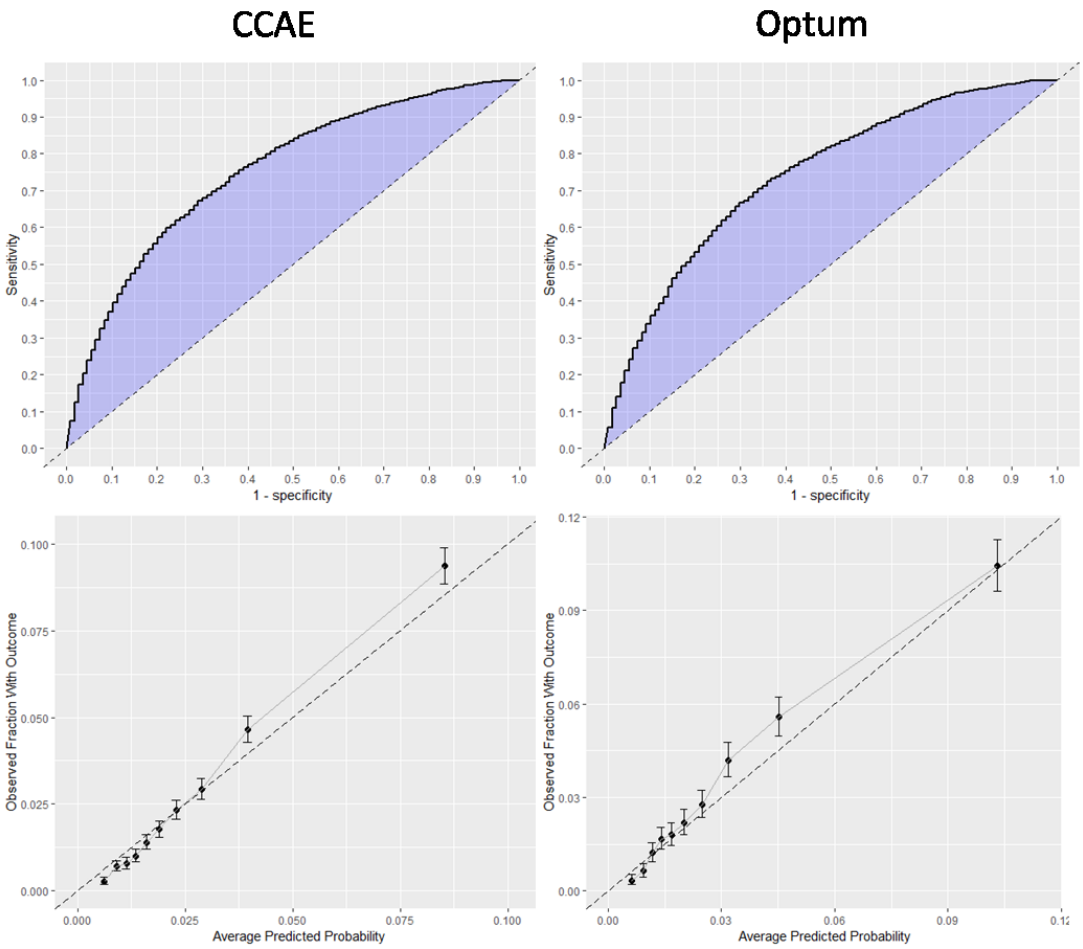
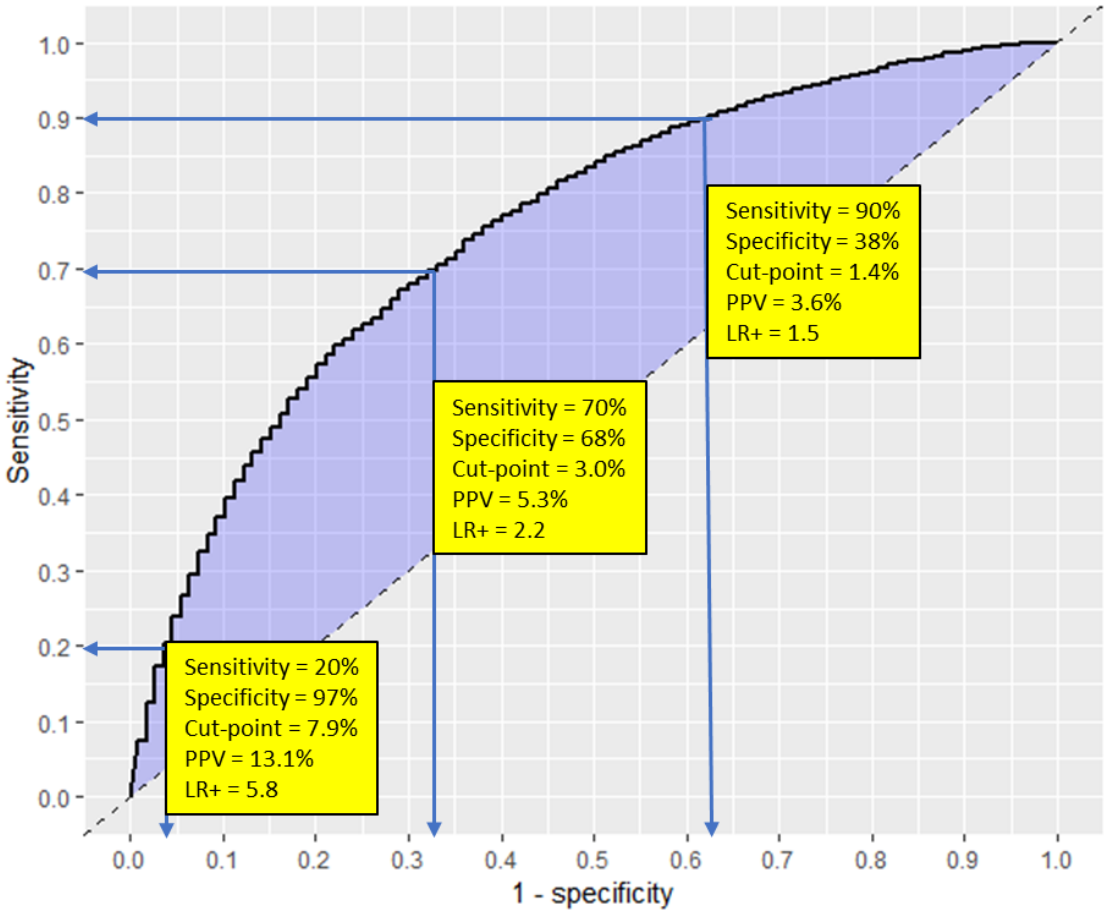
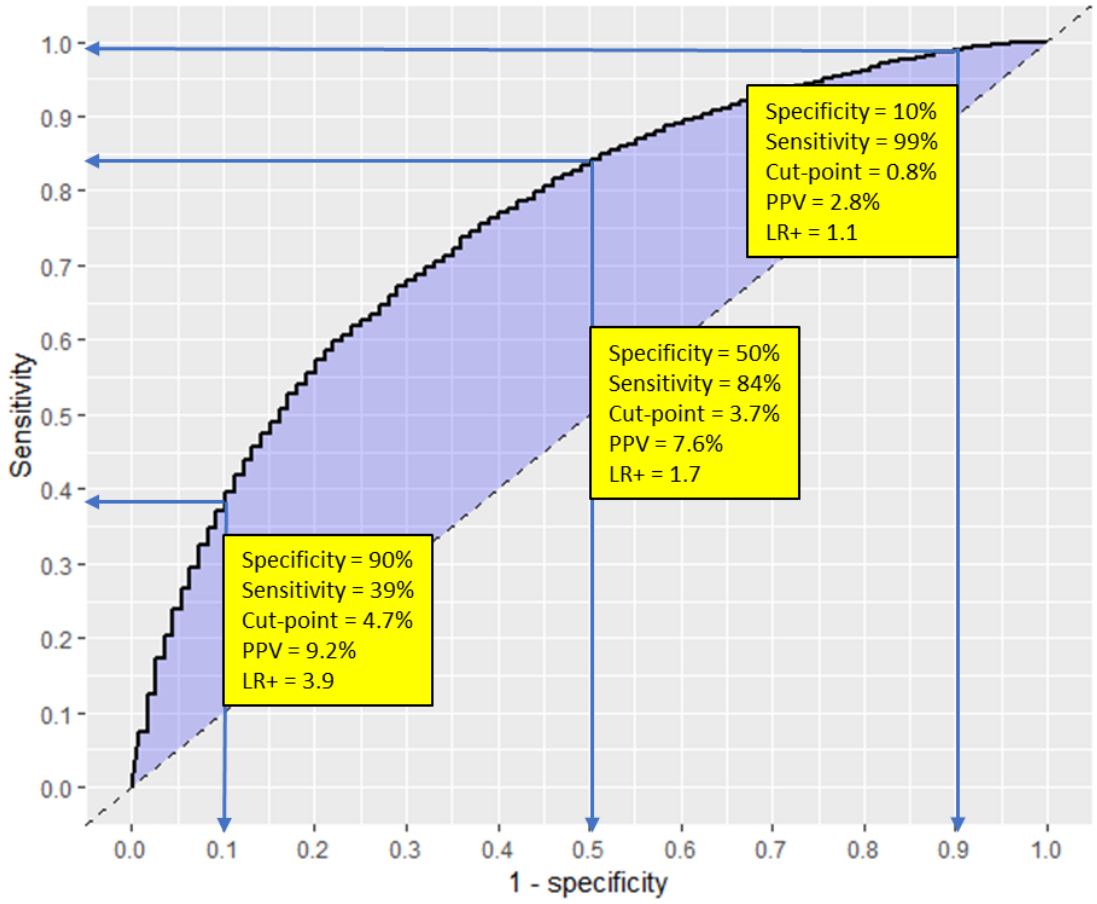


Figure 2: Performance Characteristics of the Commercial Claims and Encounters (CCAE) Model for the Outcome of Any Heart Failure at the 3 Month to 1 Year Time at Risk for Selected Levels of Sensitivity.



* Cut-point – Prediction Threshold Cut-point; PPV – Positive Predictive Value; LR+ - Likelihood Ratio Positive

Figure 3: Performance Characteristics of the Commercial Claims and Encounters (CCAE) Model for the Outcome of Any Heart Failure at the 3 Month to 1 Year Time at Risk for Selected Levels of Specificity.



* PPV – Positive Predictive Value; LR+ - Likelihood Ratio Positive

Appendices

Appendix 1: Full Specifications used in Cohort development

Cohort 1: Subjects Newly Diagnosed with Atrial Fibrillation <= age 62 for Time-at-Risk window 91-365 Days

Initial Event Cohort

People having any of the following:

- a condition occurrence of Atrial Fibrillation
    - for the first time in the person's history
    - with age <= 62

with continuous observation of at least 365 days prior and 91 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:

Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of Atrial Fibrillation/Flutter starting between all days Before and 1 days Before event index date
- and at least 1 occurrence of a condition occurrence of Atrial Fibrillation starting between 1 days After and 90 days After event index date
- and exactly 0 occurrences of a condition occurrence of Heart Failure - All starting between all days Before and 90 days After event index date
- and at least 1 occurrence of a visit occurrence of Any Visit starting between 179 days Before and 1 days Before event index date

- and at least 1 occurrence of a visit occurrence of Any Visit

  starting between 365 days Before and 180 days Before event index date

- and at least 1 occurrence of a visit occurrence of Any Visit

  starting between 1 days After and 90 days After event index date

Limit cohort of initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

Cohort 2: Subjects Newly Diagnosed with Atrial Fibrillation <= age 62 for Time-at-Risk window 366-1095 Days

Initial Event Cohort

People having any of the following:

- a visit occurrence of Any Visit

with continuous observation of at least 730 days prior and 1 days after event index date, and limit initial events to: all events per person.

For people matching the Primary Events, include:

Having all of the following criteria:

- at least 1 occurrence of a condition occurrence of Atrial Fibrillation
  - for the first time in the person's history
  - with age <= 62

    Having all of the following criteria:

        - exactly 0 occurrences of a condition occurrence of Atrial Fibrillation/Flutter

          starting between all days Before and 1 days Before event index date
        - and at least 1 occurrence of a condition occurrence of Atrial Fibrillation

          starting between 1 days After and 90 days After event index date
        - and at least 1 occurrence of a visit occurrence of Any Visit

          starting between 179 days Before and 1 days Before event index date
        - and at least 1 occurrence of a visit occurrence of Any Visit

          starting between 365 days Before and 180 days Before event index date
        - and at least 2 occurrences of a visit occurrence of Any Visit

          starting between 1 days After and 180 days After event index date
        - and at least 1 occurrence of a visit occurrence of Any Visit

          starting between 181 days After and 365 days After event index date

      starting between 425 days Before and 365 days Before event index date

- and exactly 0 occurrences of a condition occurrence of Heart Failure – All starting between all days Before and 0 days After event index date

Limit cohort of initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

Cohort 3: Subjects with First Occurrence of Heart Failure – All Left Side

Initial Event Cohort

People having any of the following:

- a condition occurrence of Heart Failure - All Left Side

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:

Having all of the following criteria:

- Having any of the following criteria:
    - at least 1 occurrence of a condition occurrence of Heart Failure - All Left Side
        - visit occurrence is any of: Emergency Room Visit, Inpatient Visit

      starting between 0 days Before and 60 days After event index date
    - or at least 2 occurrences of a condition occurrence of Heart Failure - All Left Side
        - visit occurrence is any of: Outpatient Visit

      starting between 0 days Before and 60 days After event index date

Limit cohort of initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

Cohort 4: Subjects with First Occurrence of Heart Failure with Reduced Ejection Fraction (Systolic Heart Failure)

Initial Event Cohort

People having any of the following:

- a condition occurrence of Heart Failure - All Left Side
    - for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:

Having all of the following criteria:

- at least 1 occurrence of a condition occurrence of Heart Failure - All Left Side starting between 1 days After and 60 days After event index date
- and at least 1 occurrence of a condition occurrence of Systolic Heart Failure starting between 0 days Before and 365 days After event index date
- and exactly 0 occurrences of a condition occurrence of Diastolic Heart Failure starting between 0 days Before and 365 days After event index date

Limit cohort of initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

Cohort 5: Subjects with First Occurrence of Heart Failure with Preserved Ejection Fraction (Diastolic Heart Failure)

Initial Event Cohort

People having any of the following:

- a condition occurrence of Heart Failure - All Left Side
    - for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:

Having all of the following criteria:

- at least 1 occurrence of a condition occurrence of Heart Failure - All Left Side

  starting between 1 days After and 365 days After event index date
- and at least 1 occurrence of a condition occurrence of Diastolic Heart Failure

  starting between 0 days Before and 365 days After event index date
- And having all of the following criteria:
    - exactly 0 occurrences of an observation of Evidence of Reduced Left Ventricular Ejection Fraction

      starting between all days Before and all days After event index date
    - and exactly 0 occurrences of a measurement of Evidence of Reduced Left Ventricular Ejection Fraction

      starting between all days Before and all days After event index date

- and exactly 0 occurrences of a condition occurrence of Evidence of Reduced Left Ventricular Ejection Fraction
  starting between all days Before and all days After event index date

- and exactly 0 occurrences of a condition occurrence of Systolic Heart Failure starting between all days Before and 365 days After event index date

Limit cohort of initial events to: all events per person.

Limit qualifying cohort to: earliest event per person.

Appendix 2: Concept Set Definitions used in cohort development and Full Model Specifications

All files may be found at https://1drv.ms/f/s!AjcitS8A0AtDgaY0c1p0vlGfa-Cwaw

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Chapter 3: Development and Validation of a Predictive Model for Incident Heart Failure in subjects over 65 Years Old with Newly Diagnosed Atrial Fibrillation.

Introduction

The health burdens of atrial fibrillation (AF) and heart failure (HF), both as individual and comorbid conditions, has been discussed in prior chapters. This chapter will discuss the development of a prognostic prediction model for developing HF in patients over age 65 years old with newly diagnosed AF.

The burden of HF is much higher in those over 65 years old , in which up to 80% of all HF occurs, compared to younger individuals.[1] In this population, the proportion of those with heart failure with preserved ejection fraction (HFpEF) is higher than heart failure with reduced ejection fraction (HFrEF).[2] The clinical characteristics of those with HF in this age group differ significantly from those under age 65. In the VERITAS study, which enrolled subjects with acute HF, those over 65 were found to have lower heart rate, higher blood pressure, and lower body mass index at the start of the study compared to those under 65.[3] Prognostic models have shown that in those with either acute or chronic HF advanced age predicts an increased risk of all-cause mortality, cardiovascular mortality, and hospitalization for HF.[4] Psaty and colleagues found that predictors of cardiovascular disease in elderly populations differed from those in younger populations.[5] They found weaker associations between factors such as lipid measures and the risk of cardiovascular events in elderly compared to younger populations. This has lead researchers to question the usefulness of current risk scoring systems, such as the Framingham Risk Score, for predicting the risk of cardiovascular disease in older

populations.[6] As the population ages, understanding the predictors of HF in those over 65 becomes particularly important.

In this chapter, we recognize the importance of developing predictive models for HF in those with newly diagnosed AF in older populations. The objective of this study was to develop a large-scale predictive model examining the predictors for developing any HF, HFrEF, and HFpEF in patients over age 65 years old with newly diagnosed AF.

Methods

The data management and statistical software packages used in this study were developed by the Observational Health Data Sciences and Informatics (OHDSI) interdisciplinary collaborative[7]. The software packages and database specifications are open source and freely available.

Data for this study was from data collected from two data sets: IBM® MarketScan® Medicare (MDCR) (data from January 1, 2000 to December 31, 2017) and Optum© De-Identified Clinformatics® Data Mart Database – Date of Death (Optum) (data from May 1, 2000 to December 31, 2017). The MDCR database represents health services of retirees in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. As the clear majority of those in the database were 65 years and older, we restricted our analysis to those in this age group. Each dataset was converted to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), version 5.01. The Optum and IBM® MarketScan® databases used in this study were reviewed by the New England Institutional Review Board (IRB) and were determined to be exempt from broad IRB approval, as this research project did not involve human subject research.

The condition of AF was determined by an initial diagnosis code for AF followed by a second AF code within one year after the initial diagnosis. A minimum 365-day look-back period was used to ensure first diagnosis. AF Subjects were included if they were 66 years of age or older at the index date (date of first AF diagnosis). Age 66 was used to provide the full 365 days look-back in each dataset for those entering the dataset at

age 65. AF subjects were excluded if there existed a code for any evidence of AF or atrial flutter, a condition similar to AF, during the look-back period. The Systematized Nomenclature of Medicine (SNOMED) condition codes used and the full specification of this cohort are in Appendix 1.

As described in Chapter 2, the outcome conditions of HF (all), HFpEF, and HFrEF was determined by initial diagnosis codes for any HF, HFpEF, or HFrEF, respectively. Each required a follow-up second HF, HFpEF, or HFrEF code within one year after the initial diagnosis. A minimum 365-day look-back period was used to ensure first diagnosis. Two times-at-risk for development of HF following initial AF diagnosis were examined: 3 to 12 months and 12 to 36 months. The full specification for this cohort is in Appendix 1.

Also, as described in Chapter 2, we used all available data in each data set for development of the prediction model. The covariates used were: age as a continuous variable; sex; presence/absence of in-patient or out-patient diagnosed condition classes based on SNOMED hierarchy of conditions in the 365 or 30 day window prior to or on index date; presence/absence of drug exposures based on filled drug prescriptions and using the RxNorm naming system for generic and branded drugs in the 365 or 30 day window prior to or on index date; presence/absence of a clinical procedure based on the Current Procedural Terminology, 4th Edition (CPT-4) in the 365 or 30 day window prior to or on index date; the presence/absence of laboratory measurements in the 365 or 30 day window prior to or on index date.

The predictive modeling algorithm in this study was logistic regression using Least Absolute Shrinkage and Selection Operator (LASSO) L1-regularization.[8] This method was chosen based on its use in a prior study involving HF.[9] The logistic regression algorithm used in this study was developed using the R statistical software environment and is available as open-source software in the OHDSI Patient Level Prediction R package.[10-12]

The models were first developed using the Optum dataset. This is the larger of the 2 datasets and will contain the larger number of outcomes. We followed the predictive modeling framework as proposed by Reps et al.[10] We validated the 6 models, 2 times-at-risk for 3 outcomes, through both internal and external validation. Internal validation was performed by applying the model developed with 75% of the data, the "training" set, to the remaining 25% of the data, the "testing" set. Internal validation estimated the discrimination of the model through examination of the area under the Receiver Operator Characteristic curve (AUC) and model over/under fitting through calibration curves. The ROC was developed by plotting sensitivity vs. 1-specificity throughout the range of prediction thresholds. External validation of the model was performed by applying the model to MDCR. External validation also estimated the precision of the model by examining AUC and model over/under fitting through calibration curves. Qualitative evaluation of model performance (i.e., poor, fair, good, excellent) was based on generally accepted standards.[13] For model comparison, we also calculated the positive predictive value (PPV) and the Likelihood Ratio Positive (LR+) at defined prediction threshold cut-points.[14] To compare the effect of using all available data vs. a limited set of data to inform the predictive model, we also developed models for

predicting any HF at both times-at-risk using the 7 clinical variables described by Yang et al.[15] The covariates included in this model were coronary artery disease, diabetes mellitus, age, hypertension, smoking status, sex, and body mass index (BMI). Our data did not include values for BMI. We used the presence of diagnostic condition codes for obesity and morbid obesity as proxies for BMI.

Results

The demographic, comorbid conditions, and medication history for the subjects included in this study are displayed in Tables 1a and 1b. Those subjects who developed HF of any type tended to be older than those who did not in both datasets and at both times-at-risk. There was little difference in the proportions of males and females in those without the outcome as well as those with any HF. The differences were more distinct in those with either HFrEF or HFpEF. For those developing HFrEF there was a larger proportion of males (~60%) than females (~40%). However, in HFpEF the reverse was true: the proportion of females (~60%) was larger than the proportion of males (~40%). These proportions were similar at both times-at-risk. There was little difference in the Charlson indices between those developing the outcome and those that did not develop either any HF, HFrEF, or HFpEF. There were several large differences in individual prior comorbid conditions between those who developed HFrEF and HFpEF. Those who developed HFrEF in the first year had higher rates of comorbid acute myocardial infarction (AMI), coronary artery disease (CAD), and tobacco dependence syndrome compared to those who developed HFpEF during the first year following AF diagnosis. Those who developed HFpEF during the first year following AF

diagnosis had higher rates of prior cerebral infarction and obesity compared to those who developed HFrEF. In general, those who developed any HF had higher rates of most examined comorbid conditions compared to those who did not develop any HF.

The internal validation of the predictive model showed fair performance as displayed in Table 2. In the primary analysis of subjects in Optum, the AUCs ranged from 66% (1Y-3Y, HFrEF) to 70% (3M-1Y, HFpEF and 1Y-3Y, Any HF). Internal validation was slightly better in the MDCR subjects where the AUCs ranged from 67% (3M-1Y, HFrEF) to 72% (3M-1Y, HFpEF). Calibration of the model showed good performance characteristics with intercepts at or near 0 along with most of the calibration slopes near 1.0. Model performance was similar for predicting HFpEF and HFrEF.

The models demonstrated fair generalizability as shown by the external validation results (Table 3). Testing the model developed from the Optum database on the MDCR dataset produced AUCs ranging from 66% (3M-1Y, HFrEF) to 70% (3M-1Y, HFpEF). The AUC values were similar between internal and external validation providing evidence for good model generalization. Calibration intercepts and slopes showed good performance characteristics.

The performance characteristics from both internal and external validation were lower in this study compared to our previous study where we performed a completely analogous study in subjects under age 65. The average AUC for internal validation across all outcomes and times-at-risk was about 74% in those under age 65 and about

69% for those in this study with similar results from external validation. Poorer discriminatory capability existed in the older cohort despite much larger sample size.

A more detailed examination of the performance characteristics for several models for the outcome of any HF at the 3M-1Y time-at-risk is shown in Table 4. In the upper portion of the table, the performance characteristics based on deciles of prediction threshold cut-points are shown. For example, for the Optum model using all available data, at a cut-point of 9.1%, the sensitivity is 55.5%, the specificity is 72.2%, and the positive predictive value (PPV) is 14.9%. The Likelihood Ratio Positive (LR+) is 2 indicating an increased probability of disease of about 15% based on this test.[14] The middle portion of the table displays the characteristics and deciles of sensitivity; the lower portion at deciles of specificity. The PPVs from the external validation of the Optum model on the MDCR dataset are generally lower at each corresponding cut-point, likely due to the lower prevalence of any HF in this population. Graphical representations of these data in the Optum population for the outcome of any HF during the 3M-1Y time-at-risk are shown in Figures 2 (for 3 sensitivity cut-points) and 3 (for 3 specificity cut-points).

Covariates included in the model (i.e., with non-zero beta coefficients) where there were large relative differences between subjects who developed any HF compared to those subjects who did not develop any HF are shown in Table 5. Some of those included as predictors of HF were cardiomyopathy, non-atrial cardiac arrythmias, cardiac valvular disease, chronic obstructive pulmonary disease, renal impairment, use

of type 2 diabetes drugs, and use of high ceiling diuretics. The full specification for each of the models is in Appendix 2.

We compared the results from our large scale model using all available data to a limited model using the 7 covariates as described by Yang and colleagues (Table 6).[16] The mean of the AUC for internal validation for the 3M-1Y model on the limited data set in CCAE and Optum was about 61% compared to 68% in our large scale model. At the 1Y-3Y time-at-risk, the limited data set model AUC again averaged 61% while our large-scale model averaged 70%. The comparison of other performance characteristics of the small model to the large model is shown in Table 4. As an example, at a sensitivity of 50%, the large model has a PPV of 15.8% compared to 11.6% in the small model. The LR+ in the large model at this sensitivity is 2.1 compared to 1.5 in the small model.

Discussion

The results this study indicate that it is possible to develop a prognostic predictive model for determining the likelihood of developing HF in those with recently diagnosed AF in cohorts of subject older than age 66. The model appears to have fair performance characteristics when tested through internal and external validation.

The principal goal of this study was to develop models to inform both clinicians and their patients with newly diagnosed AF on the risk of developing HF in both the near term and longer term. Prior studies examined the risk of developing any HF following initial AF diagnosis and were unable to differentiate between the major forms of HF due to small sample size.[17-19] Owing to the use of large administrative datasets, we were able to develop models that separated the major types of left-side HF. In addition, the model where the time-at-risk was 1-3 years allowed for the prediction of HF following the first year of treatment for AF. To the best of our knowledge, this is the first study to incorporate early treatment for AF in a prognostic prediction model.

The features included in the prediction models included all clinical characteristics from the administrative datasets, such as conditions, drugs, and clinical procedures. The model developed using these characteristics, while detailed, is complex and may be difficult to use in practice for clinicians without access to the full electronic health record of their patients. The average model from this study contained about 175 features with non-zero beta coefficients as predictors. Future enhancements to these models may aim to develop methods to simplify the model features. However, it should be noted that due to the complexity of the disease especially in older individuals,

reducing the complexity of the model may not be possible without compromising predictive ability. This is evident in comparing the results from our models using all available covariates compared to the models where only 7 covariates described in prior studies were used.[15] The models using the full set of available covariates demonstrated higher AUCs as well as higher levels of PPV and LR+ compared to the simpler model. Thus, the cost of simplifying the models may be reducing the precision of discriminating between those who will eventually develop HF and those who will not.

The decline in performance characteristics between this study and our previous study where we predicted HF in newly diagnosed AF patients under age 65 is likely due to multiple reasons. Kusumastuti and colleagues also found lower discrimination capability in their models examining mortality risk in older subjects compared to younger subjects.[20] They cited the complexity of the ageing process. As comorbid conditions increase with ageing, the interactions between the effect of the disease itself along with the variability of treatment make prediction difficult. In addition, as the rates of comorbid conditions increase due to ageing, errors due to inherent misclassification increase as misclassification is a known issue in administrative datasets.[21] These errors reduce the effectiveness of the modeling process.[22] Our comparison of the models where the AUC increased about 13% using all available data vs. a limited set of data from prior studies showed how using all available data helps to mitigate the decrease in performance seen in older subjects.

There are several limitations to this study. Most of the subjects in this study were diagnosed with the general diagnostic code for HF and only a small proportion met the

criteria we used for HFrEF or HFpEF. The predictive models for the subtypes of HF may reflect those subjects where specific diagnostic tests, e.g., cardiac ejection fraction, were performed. Another limitation of this work is the use of administrative claims data which are known to contain errors and to miss diagnoses that are not coded or are miscoded. The data also do not contain information on important biological attributes that bear on patients' risk profiles. Nevertheless, the fact that these data predict future outcomes not only in the data set used to develop the prediction regression, but also in other similar datasets, provides evidence of their value. The accuracy of the predictions achieved is limited to a level comparable to published disease risk factors. The predictions presented may provide useful stratification of risk that can be used in health education, in patients' personal planning, for allocating preventive interventions and for planning the resources needed for future disease occurrence. The improvements associated with use of the large datasets provides a welcome increment in our ability to serve these purposes. The performance of these methods falls short of the specificity and sensitivity of good diagnostic tests and should be used with caution to make predictions of HF for individual patients. Finally, it should be remembered that these results have been achieved in insured populations that are not fully representative of the US population.

In conclusion, the models developed in this study demonstrate that stratifying risk of HF in patients over age 65 and older with newly diagnosed AF is possible, and that it is enhanced by using a large number of predictors available in existing claims datasets. The results of these models may be helpful in encouraging patients to be more adherent to

clinician advice. In the near future these models may be improved through the use of richer datasets informed by electronic medical records which may include variables distilled from clinician notes, laboratory results, and measurements from clinical procedures such as cardiac ultrasound and catheterization studies.

Tables and Figures

Table 1a: Patient Demographic, Prior Comorbid Condition, and Prior Prescription Drug Data for Subjects with an Initial Diagnosis of Atrial Fibrillation and a Time at Risk of Developing Heart Failure of 3 Months to 1 Year After Diagnosis Derived from the IBM® MarketScan® Medicare (MDCR) and Optum© De-Identified Clinformatics® Data Mart Database between January 1, 2000 and December 31, 2017.

Database	Optum				MDCR			
Outcome:	No HF	Any HF	HFrEF	HFpEF	No HF	Any HF	HFrEF	HFpEF
N (%)	119181 (91.9)	10475 (8.1)	1445 (1.1)	1892 (1.5)	151796 (92.3)	12602 (7.7)	1550 (0.95)	642 (1.3)
Age at Dlagnosis (yrs.) Mean (SD)	76.4 (6.1)	78.2 (6.1)	78.0 (6.2)	78.8 (6.2)	77.6 (7.1)	80.0 (7.3)	79.3 (7.1)	79.1 (6.2)
Female N (%)	61288 (51.4)	5370 (51.3)	583 (40.3)	1151 (60.8)	76249 (50.2)	6478 (51.4)	634 (40.9)	379 (59.0)
Charlson Index Mean (SD)	3.5 (2.8)	4.1 (3.0)	4.1 (2.9)	4.4 (3.1)	2.9 (2.6)	3.6 (2.8)	3.8 (2.9)	4.8 (3.0)
Prior Comorbid Conditions N (%)								
AMI	13609 (11.4)	1670 (15.9)	275 (19.0)	256 (13.5)	12932 (8.5)	1529 (12.1)	266 (17.2)	112 (17.4)
Angina	16073 (13.5)	1659 (15.8)	219 (15.2)	283 (15.0)	21867 (14.4)	2195 (17.4)	291 (18.8)	114 (17.8)
CAD	40150 (33.7)	4465 (42.6)	676 (46.8)	744 (39.3)	52423 (34.5)	5390 (42.8)	776 (50.1)	275 (42.8)
Cerebral Infarction	12444 (10.4)	1225 (11.7)	164 (11.3)	254 (13.4)	13823 (9.1)	1403 (11.1)	195 (12.6)	92 (14.3)
Hypertension	102774 (86.2)	9413 (89.9)	1294 (89.6)	1749 (92.4)	119041 (78.4)	10245 (81.3)	1326 (85.5)	617 (96.1)
Obesity	5447 (4.6)	648 (6.2)	86 (6.0)	163 (8.6)	2720 (1.8)	335 (2.7)	44 (2.8)	67 (10.4)
Tobacco Dependence Syndrome	10627 (8.9)	1095 (10.5)	172 (11.9)	200 (10.6)	5537 (3.6)	516 (4.1)	91 (5.9)	66 (10.3)
Transient Cerebral Ischemia	12072 (10.1)	1102 (10.5)	129 (8.9)	200 (10.6)	15890 (10.5)	1459 (11.6)	201 (13.0)	102 (15.9)
Type 2 Diabetes	39575 (33.2)	4165 (39.8)	607 (42.0)	773 (40.9)	39861 (26.3)	4190 (33.2)	580 (37.4)	279 (43.5)
Medications N (%)								
ACE Inhibitors	44754 (37.6)	4381 (41.8)	655 (45.3)	828 (43.8)	59703 (39.3)	5627 (44.7)	810 (52.3)	292 (45.5)
Aldosterone Antagonists	2324 (1.9)	332 (3.2)	49 (3.4)	68 (3.6)	3985 (2.6)	515 (4.1)	58 (3.7)	26 (4.0)
Anti-arrhythmics	3401 (2.9)	322 (3.1)	56 (3.9)	52 (2.7)	6941 (4.6)	651 (5.2)	100 (6.5)	111 (17.3)
Antiepileptics	18639 (15.6)	1926 (18.4)	261 (18.1)	444 (23.5)	26708 (17.6)	2622 (20.8)	326 (21.0)	159 (24.8)
Anti-thrombotic Agents	38764 (32.5)	3707 (35.4)	534 (37.0)	654 (34.6)	63204 (41.6)	5880 (46.7)	776 (50.1)	467 (72.7)
Beta Blockers	53707 (45.1)	5252 (50.1)	756 (52.3)	1008 (53.3)	82852 (54.6)	7440 (59.0)	987 (63.7)	414 (64.5)
Beta-lactam antibiotics	42523 (35.7)	3598 (34.3)	514 (35.6)	700 (37.0)	63810 (42.0)	5273 (41.8)	713 (46.0)	285 (44.4)
Calcium Channel Blockers	38476 (32.3)	3883 (37.1)	550 (38.1)	796 (42.1)	58483 (38.5)	5773 (45.8)	747 (48.2)	337 (52.5)
Cardiac Glycosides	4268 (3.6)	538 (5.1)	79 (5.5)	57 (3.0)	12082 (8.0)	1294 (10.3)	130 (8.4)	55 (8.6)
Factor Xa Inhibitors	2144 (1.8)	162 (1.5)	29 (2.0)	44 (2.3)	4616 (3.0)	375 (3.0)	76 (4.9)	121 (18.8)
Glucose Lowering Drugs	20111 (16.9)	2202 (21.0)	331 (22.9)	445 (23.5)	26757 (17.6)	2957 (23.5)	401 (25.9)	145 (22.6)
Insulin	4882 (4.1)	710 (6.8)	108 (7.5)	146 (7.7)	6131 (4.0)	845 (6.7)	125 (8.1)	47 (7.3)
Lipid Lowering Agents	61056 (51.2)	5416 (51.7)	797 (55.2)	1048 (55.4)	90102 (59.4)	7626 (60.5)	1058 (68.3)	376 (58.6)
Loop Diuretics	14128 (11.9)	2355 (22.5)	299 (20.7)	475 (25.1)	25449 (16.8)	3944 (31.3)	457 (29.5)	209 (32.6)
Nitrates	10246 (8.6)	1240 (11.8)	193 (13.4)	230 (12.2)	21015 (13.8)	2363 (18.8)	317 (20.5)	86 (13.4)
Platelet Aggregation Inhibitors	13402 (11.2)	1456 (13.9)	209 (14.5)	243 (12.8)	24428 (16.1)	2695 (21.4)	375 (24.2)	103 (16.0)
Sulfonamides	18232 (15.3)	1758 (16.8)	241 (16.7)	357 (18.9)	29690 (19.6)	2709 (21.5)	348 (22.5)	136 (21.2)
Thiazide Diuretics	40245 (33.8)	3800 (36.3)	502 (34.7)	764 (40.4)	60203 (39.7)	5309 (42.1)	665 (42.9)	275 (42.8)
Vitamin K Antagonists	17524 (14.7)	1643 (15.7)	228 (15.8)	259 (13.7)	33844 (22.3)	3006 (23.9)	364 (23.5)	280 (43.6)

* MDCR - Medicare; HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction; SD – Standard Deviation; AMI – Acute Myocardial Infarction; CAD – Coronary Artery Disease; ACE – Angiotensin Converting Enzyme

Table 1b: Patient Demographic, Prior Comorbid Condition, and Prior Prescription Drug Data for Subjects with an Initial Diagnosis of Atrial Fibrillation and a Time at Risk of Developing Heart Failure of 1 Year to 3 Years After Diagnosis Derived from the IBM® MarketScan® Medicare (MDCR) and Optum© De-Identified Clinformatics® Data Mart Database between January 1, 2000 and December 31, 2017.

Database	Optum				MDCR			
Outcome:	No HF	Any HF	HFrEF	HFpEF	No HF	Any HF	HFrEF	HFpEF
N (%)	51238 (87.4)	7394 (12.6)	1002 (1.7)	1463 (2.5)	62590 (87.8)	8708 (12.2)	1045 (1.5)	1635 (2.3)
Age at DIagnosis (yrs.) Mean (SD)	76.8 (6.1)	78.6 (5.9)	78.3 (5.9)	79.1 (6.0)	78.0 (6.8)	80.4 (7.0)	80.1 (6.9)	80.8 (7.2)
Female N (%)	26098 (50.9)	3884 (52.5)	415 (41.4)	902 (61.7)	31034 (49.6)	4455 (51.2)	409 (39.1)	985 (60.2)
Charlson Index Mean (SD)	4.0 (2.9)	4.6 (3.0)	4.8 (3.0)	4.6 (2.9)	3.4 (2.7)	4.1 (2.8)	4.4 (2.8)	4.3 (2.8)
Prior Comorbid Conditions N (%)								
AMI	6663 (13.0)	1314 (17.8)	212 (21.2)	240 (16.4)	6198 (9.9)	1166 (13.4)	160 (15.3)	217 (13.3)
Angina	8494 (16.6)	1446 (19.6)	213 (21.3)	284 (19.4)	11201 (17.9)	1926 (22.1)	245 (23.4)	339 (20.7)
CAD	21022 (41.0)	3694 (50.0)	555 (55.4)	652 (44.6)	26448 (42.3)	4665 (53.6)	652 (62.4)	794 (48.6)
Cerebral Infarction	6747 (13.2)	1099 (14.9)	154 (15.4)	199 (13.6)	7267 (11.6)	1245 (14.3)	137 (13.1)	252 (15.4)
Hypertension	47044 (91.8)	7001 (94.7)	948 (94.6)	1398 (95.6)	53942 (86.2)	7796 (89.5)	945 (90.4)	1529 (93.5)
Obesity	3036 (5.9)	514 (7.0)	64 (6.4)	128 (8.7)	1625 (2.6)	276 (3.2)	28 (2.7)	67 (4.1)
Tobacco Dependence Syndrome	4775 (9.3)	815 (11.0)	117 (11.7)	157 (10.7)	2432 (3.9)	427 (4.9)	56 (5.4)	87 (5.3)
Transient Cerebral Ischemia	6766 (13.2)	1145 (15.5)	148 (14.8)	229 (15.7)	8420 (13.5)	1405 (16.1)	164 (15.7)	288 (17.6)
Type 2 Diabetes	18097 (35.3)	3069 (41.5)	459 (45.8)	603 (41.2)	17700 (28.3)	3088 (35.5)	416 (39.8)	615 (37.6)
Medications N (%)								
ACE Inhibitors	21755 (42.5)	3495 (47.3)	509 (50.8)	673 (46.0)	28093 (44.9)	4449 (51.1)	589 (56.4)	822 (50.3)
Aldosterone Antagonists	1470 (2.9)	276 (3.7)	36 (3.6)	51 (3.5)	2318 (3.7)	514 (5.9)	61 (5.8)	104 (6.4)
Anti-arrhythmics	10254 (20.0)	1409 (19.1)	194 (19.4)	262 (17.9)	15868 (25.4)	2168 (24.9)	266 (25.5)	403 (24.6)
Antiepileptics	9360 (18.3)	1528 (20.7)	205 (20.5)	344 (23.5)	13025 (20.8)	2139 (24.6)	257 (24.6)	446 (27.3)
Anti-thrombotic Agents	35869 (70.0)	5386 (72.8)	735 (73.4)	1058 (72.3)	51492 (82.3)	7432 (85.3)	896 (85.7)	1397 (85.4)
Beta Blockers	33062 (64.5)	4972 (67.2)	687 (68.6)	982 (67.1)	47244 (75.5)	6900 (79.2)	864 (82.7)	1343 (82.1)
Beta-lactam antibiotics	21942 (42.8)	3181 (43.0)	459 (45.8)	637 (43.5)	31559 (50.4)	4559 (52.4)	548 (52.4)	907 (55.5)
Calcium Channel Blockers	22529 (44.0)	3665 (49.6)	484 (48.3)	769 (52.6)	32566 (52.0)	5117 (58.8)	599 (57.3)	1047 (64.0)
Cardiac Glycosides	5695 (11.1)	1034 (14.0)	133 (13.3)	149 (10.2)	11946 (19.1)	2042 (23.4)	224 (21.4)	299 (18.3)
Factor Xa Inhibitors	9440 (18.4)	1019 (13.8)	163 (16.3)	258 (17.6)	11085 (17.7)	1310 (15.0)	190 (18.2)	334 (20.4)
Glucose Lowering Drugs	8938 (17.4)	1626 (22.0)	252 (25.1)	312 (21.3)	11370 (18.2)	2137 (24.5)	295 (28.2)	411 (25.1)
Insulin	2279 (4.4)	497 (6.7)	67 (6.7)	97 (6.6)	2733 (4.4)	640 (7.3)	81 (7.8)	124 (7.6)
Lipid Lowering Agents	29639 (57.8)	4328 (58.5)	613 (61.2)	866 (59.2)	41292 (66.0)	5875 (67.5)	763 (73.0)	1151 (70.4)
Loop Diuretics	8856 (17.3)	2169 (29.3)	309 (30.8)	440 (30.1)	14428 (23.1)	3703 (42.5)	413 (39.5)	702 (42.9)
Nitrates	5487 (10.7)	1101 (14.9)	165 (16.5)	210 (14.4)	10106 (16.1)	2063 (23.7)	260 (24.9)	371 (22.7)
Platelet Aggregation Inhibitors	7096 (13.8)	1322 (17.9)	207 (20.7)	242 (16.5)	11825 (18.9)	2147 (24.7)	301 (28.8)	374 (22.9)
Sulfonamides	9507 (18.6)	1482 (20.0)	200 (20.0)	310 (21.2)	15132 (24.2)	2373 (27.3)	279 (26.7)	483 (29.5)
Thiazide Diuretics	19311 (37.7)	3065 (41.5)	392 (39.1)	652 (44.6)	27772 (44.4)	4199 (48.2)	490 (46.9)	841 (51.4)
Vitamin K Antagonists	21409 (41.8)	3598 (48.7)	476 (47.5)	647 (44.2)	35200 (56.2)	5390 (61.9)	616 (58.9)	936 (57.2)

* MDCR - Medicare; HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction; SD – Standard Deviation; AMI – Acute Myocardial Infarction; CAD – Coronary Artery Disease; ACE – Angiotensin Converting Enzyme

Table 2: Internal Validation of the Prediction Models Derived from Two Comparison Cohorts Derived from the IBM® MarketScan® Medicare (MDCR) and Optum© De-Identified Clinformatics® Data Mart Database between January 1, 2000 and December 31, 2017.

Database	Analysis	Outcome	Train AUC (95% CI)	Test AUC (95% CI)	Test Cal. Intercept	Test Cal.
Optum	3M-1Y	Any HF	0.704 (0.701, 0.707)	0.678 (0.673, 0.683)	0.001	0.996
Optum	3M-1Y	HFrEF	0.719 (0.717, 0.721)	0.671 (0.666, 0.676)	-0.001	1.087
Optum	3M-1Y	HFpEF	0.740 (0.738, 0.742)	0.697 (0.692, 0.702)	0.000	0.994
Optum	1Y-3Y	Any HF	0.726 (0.722, 0.730)	0.697 (0.690, 0.704)	0.005	0.962
Optum	1Y-3Y	HFrEF	0.735 (0.731, 0.739)	0.657 (0.649, 0.665)	-0.001	1.032
Optum	1Y-3Y	HFpEF	0.723 (0.719, 0.727)	0.680 (0.672, 0.688)	-0.002	1.095
MDCR	3M-1Y	Any HF	0.704 (0.702, 0.706)	0.682 (0.677, 0.687)	0.000	0.998
MDCR	3M-1Y	HFrEF	0.708 (0.706, 0.710)	0.670 (0.665, 0.675)	-0.001	1.149
MDCR	3M-1Y	HFpEF	0.757 (0.755, 0.759)	0.717 (0.713, 0.721)	0.000	0.992
MDCR	1Y-3Y	Any HF	0.726 (0.723, 0.729)	0.704 (0.697, 0.711)	0.002	0.977
MDCR	1Y-3Y	HFrEF	0.745 (0.742, 0.748)	0.711 (0.704, 0.718)	-0.005	1.311
MDCR	1Y-3Y	HFpEF	0.754 (0.751, 0.757)	0.685 (0.678, 0.692)	0.003	0.864

* AUC – Area Under the Receiver Operator Characteristics Curve; CI – Confidence Interval; Cal. – Calibration; MDCR - Medicare; HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction

Table 3: External Validation of the Prediction Models Derived from Two Comparison Cohorts Derived from the IBM® MarketScan® Medicare (MDCR) and Optum© De-Identified Clinformatics® Data Mart Database between January 1, 2000 and December 31, 2017.

Model Database	External Validation Database	Analysis	Outcome	Test AUC (95% CI)	Test Cal. Intercept	Test Cal. Slope
Optum	MDCR	3M-1Y	Any HF	0.669 (0.667, 0.671)	-0.003	0.942
Optum	MDCR	3M-1Y	HFrEF	0.655 (0.653, 0.657)	-0.001	0.947
Optum	MDCR	3M-1Y	HFpEF	0.694 (0.692, 0.696)	-0.001	1.015
Optum	MDCR	1Y-3Y	Any HF	0.691 (0.688, 0.694)	-0.009	0.990
Optum	MDCR	1Y-3Y	HFrEF	0.687 (0.684, 0.690)	-0.002	0.991
Optum	MDCR	1Y-3Y	HFpEF	0.688 (0.685, 0.691)	-0.005	1.173

* AUC – Area Under the Receiver Operator Characteristics Curve; CI – Confidence Interval; Cal. – Calibration; MDCR – Medicare; HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction

Table 4: Model performance characteristics for the 3 Month to 1 Year Time-at-Risk Models across the range of prediction thresholds, sensitivities, and specificities for the Optum large model, the external validation of the Optum model on Medicare, and the Optum small model.

Optum - Large Model					External Validation Optum on MDCR - Large Model					Optum - Small Model				
Prediction Threshold Cut-point	Sensitivity	Specificity	PPV	LR+	Prediction Threshold Cut-point	Sensitivity	Specificity	PPV	LR+	Prediction Threshold Cut-point	Sensitivity	Specificity	PPV	LR+
3.42%	97.8%	10.7%	8.78%	1.1	3.94%	97.1%	10.6%	8.27%	1.1	5.10%	95.6%	10.7%	8.60%	1.1
4.29%	94.2%	21.2%	9.51%	1.2	4.83%	92.7%	21.1%	8.88%	1.2	5.81%	89.2%	21.4%	9.07%	1.1
5.07%	89.3%	31.7%	10.31%	1.3	5.63%	87.1%	31.4%	9.53%	1.3	6.49%	81.9%	31.3%	9.49%	1.2
5.87%	83.2%	42.0%	11.21%	1.4	6.43%	80.2%	41.7%	10.25%	1.4	7.08%	73.9%	41.2%	9.95%	1.3
6.76%	75.4%	52.2%	12.18%	1.6	7.28%	71.9%	51.8%	11.02%	1.5	7.71%	64.8%	51.3%	10.47%	1.3
7.80%	66.5%	62.3%	13.43%	1.8	8.27%	62.5%	61.9%	11.97%	1.6	8.40%	54.4%	61.3%	10.99%	1.4
9.08%	55.5%	72.2%	14.94%	2.0	9.51%	51.2%	71.8%	13.08%	1.8	9.20%	43.7%	71.2%	11.77%	1.5
10.95%	41.8%	81.9%	16.89%	2.3	11.27%	38.2%	81.5%	14.63%	2.1	10.11%	30.7%	80.9%	12.41%	1.6
14.32%	25.1%	91.3%	20.31%	2.9	14.47%	22.5%	91.0%	17.27%	2.5	11.68%	16.6%	90.6%	13.43%	1.8
20.43%	10.0%	97.5%	25.95%	4.0	19.31%	10.0%	96.8%	20.67%	3.1	12.68%	10.0%	94.5%	13.71%	1.8
15.80%	20.0%	93.7%	21.71%	3.2	15.16%	20.0%	92.3%	17.73%	2.6	11.29%	20.0%	88.6%	13.35%	1.8
13.14%	30.0%	88.9%	19.18%	2.7	12.76%	30.0%	86.9%	15.98%	2.3	10.18%	30.0%	81.5%	12.48%	1.6
11.27%	40.0%	83.2%	17.28%	2.4	10.96%	40.0%	80.1%	14.28%	2.0	9.43%	40.0%	74.1%	11.96%	1.5
9.81%	50.0%	76.5%	15.75%	2.1	9.65%	50.0%	72.7%	13.21%	1.8	8.73%	50.0%	65.6%	11.33%	1.5
8.53%	60.0%	68.4%	14.28%	1.9	8.53%	60.0%	64.2%	12.21%	1.7	8.02%	60.0%	55.9%	10.68%	1.4
7.36%	70.0%	58.3%	12.85%	1.7	7.46%	70.0%	53.8%	11.18%	1.5	7.37%	70.0%	45.8%	10.19%	1.3
6.25%	80.0%	46.6%	11.63%	1.5	6.44%	80.0%	41.9%	10.26%	1.4	6.67%	80.0%	34.0%	9.63%	1.2
4.97%	90.0%	30.3%	10.20%	1.3	5.24%	90.0%	26.3%	9.21%	1.2	5.78%	90.0%	20.3%	9.03%	1.1
3.35%	98.0%	10.0%	8.73%	1.1	3.88%	97.2%	10.0%	8.23%	1.1	5.02%	96.0%	10.0%	8.57%	1.1
4.19%	94.7%	20.0%	9.42%	1.2	4.75%	93.2%	20.0%	8.82%	1.2	5.77%	90.2%	20.0%	9.02%	1.1
4.95%	90.2%	30.0%	10.17%	1.3	5.52%	87.9%	30.0%	9.44%	1.3	6.42%	83.0%	30.0%	9.44%	1.2
5.71%	84.6%	40.0%	11.03%	1.4	6.29%	81.4%	40.0%	10.12%	1.4	7.03%	75.1%	40.0%	9.91%	1.3
6.56%	77.2%	50.0%	11.95%	1.5	7.12%	73.6%	50.0%	10.89%	1.5	7.65%	66.2%	50.0%	10.42%	1.3
7.54%	68.4%	60.0%	13.07%	1.7	8.07%	64.2%	60.0%	11.77%	1.6	8.30%	55.8%	60.0%	10.92%	1.4
8.75%	58.1%	70.0%	14.56%	1.9	9.27%	53.4%	70.0%	12.88%	1.8	9.08%	45.1%	70.0%	11.68%	1.5
10.51%	45.0%	80.0%	16.50%	2.2	10.95%	40.1%	80.0%	14.27%	2.0	10.03%	32.1%	80.0%	12.35%	1.6
13.64%	27.9%	90.0%	19.71%	2.8	13.98%	24.6%	90.0%	16.97%	2.5	11.58%	17.6%	90.0%	13.43%	1.8

* MDCR – Medicare; PPV- Positive Predictive Value; LR+ - Likelihood Ratio Positive

Table 5: Univariate comparisons of prior comorbid conditions and drugs included in one or more predictive models.

Database	Analysis	Outcome	Covariate Name	Covariate Mean Proportion in Subjects With Outcome	Covariate Mean Proportion in Subjects With No Outcome	Rel. Ratio
Optum	3M-1Y	HFrEF	Cardiomyopathy	0.10	0.03	4.09
Optum	1Y-3Y	HFrEF	Myocardial disease	0.08	0.03	2.94
MDCR	1Y-3Y	HFrEF	carvedilol	0.10	0.04	2.61
Optum	3M-1Y	HFpEF	HIGH-CEILING DIURETICS	0.13	0.05	2.49
MDCR	1Y-3Y	HFrEF	Renal impairment	0.08	0.03	2.43
MDCR	1Y-3Y	HFrEF	Paroxysmal ventricular tachycardia	0.05	0.02	2.42
MDCR	3M-1Y	HFrEF	Chronic kidney disease stage 3	0.09	0.04	2.32
MDCR	1Y-3Y	HFpEF	Respiratory insufficiency	0.05	0.02	2.31
Optum	1Y-3Y	HFrEF	Ischemic heart disease	0.07	0.03	2.28
MDCR	3M-1Y	HFrEF	Alpha and beta blocking agents	0.09	0.04	2.26
MDCR	1Y-3Y	HFrEF	Ventricular tachycardia	0.06	0.03	2.26
Optum	1Y-3Y	HFrEF	Left bundle branch block	0.05	0.02	2.2
MDCR	1Y-3Y	HFpEF	Renal failure syndrome	0.14	0.06	2.15
Optum	3M-1Y	Any HF	Furosemide	0.17	0.08	2.11
Optum	3M-1Y	HFpEF	Acute exacerbation of chronic obstructive airways disease	0.08	0.04	2.09
Optum	3M-1Y	HFpEF	Glipizide	0.06	0.03	2.09
Optum	3M-1Y	HFpEF	Albuterol	0.08	0.04	2.04
Optum	1Y-3Y	HFpEF	Hypertensive renal disease with renal failure	0.08	0.04	2.02
MDCR	1Y-3Y	HFpEF	tiotropium	0.06	0.03	1.99
MDCR	1Y-3Y	Any HF	Organic nitrates	0.07	0.04	1.98
Optum	3M-1Y	HFpEF	Polyneuropathy	0.09	0.05	1.98
MDCR	3M-1Y	HFpEF	Neurologic disorder associated with diabetes mellitus	0.07	0.04	1.95
Optum	1Y-3Y	HFpEF	Difficulty breathing	0.07	0.04	1.94
MDCR	3M-1Y	HFpEF	Prednisone	0.09	0.05	1.93
MDCR	3M-1Y	HFrEF	Cardiac pacemaker in situ	0.05	0.02	1.91
Optum	1Y-3Y	Any HF	Chronic obstructive lung disease	0.10	0.05	1.91
Optum	3M-1Y	HFpEF	Heart valve stenosis	0.05	0.03	1.91
Optum	3M-1Y	HFpEF	INSULINS AND ANALOGUES	0.07	0.04	1.91
MDCR	3M-1Y	HFrEF	HIGH-CEILING DIURETICS	0.15	0.08	1.89
MDCR	3M-1Y	HFrEF	Nicotine dependence	0.05	0.02	1.89

* Rel. Ratio – Relative Ratio; MDCR – Medicare; 3M-1Y – 3 Month to 1Year Time-at-Risk; 1Y-3Y – 1 Year to 3 Year Time-at-Risk; HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction

Table 6: Internal validation of the prediction models using either the small or large set of covariates developed on the Commercial Claims and Encounters and Optum datasets.

Database	Analysis	Model	Outcome	Train AUC (95% CI)	Test AUC (95% CI)	Test Cal. Intercept	Test Cal.
Optum	3M-1Y	Small	Any HF	0.613 (0.610, 0.616)	0.611 (0.606, 0.616)	-0.008	1.094
Optum	3M-1Y	Large	Any HF	0.704 (0.701, 0.707)	0.678 (0.673, 0.683)	0.001	0.996
Optum	1Y-3Y	Small	Any HF	0.624 (0.620, 0.628)	0.618 (0.610, 0.626)	-0.006	1.043
Optum	1Y-3Y	Large	Any HF	0.726 (0.722, 0.730)	0.697 (0.690, 0.704)	0.005	0.962
MDCR	3M-1Y	Small	Any HF	0.620 (0.618, 0.622)	0.612 (0.607, 0.617)	-0.006	1.073
MDCR	3M-1Y	Large	Any HF	0.704 (0.702, 0.706)	0.682 (0.677, 0.687)	0.000	0.998
MDCR	1Y-3Y	Small	Any HF	0.634 (0.630, 0.638)	0.636 (0.629, 0.643)	-0.012	1.09
MDCR	1Y-3Y	Large	Any HF	0.726 (0.723, 0.729)	0.704 (0.697, 0.711)	0.002	0.977

* AUC – Area Under the Receiver Operator Characteristics Curve; CI – Confidence Interval; Cal. – Calibration; MDCR – Medicare; 3M-1Y – 3 Month to 1Year Time-at-Risk; 1Y-3Y – 1 Year to 3 Year Time-at-Risk; HF – Heart Failure; HFrEF – Heart Failure with Reduced Ejection Fraction; HFpEF – Heart Failure with Preserved Ejection Fraction

Figure 1: Area Under the Receiver Operator Characteristic Curves and the Calibration Curves of the Optum and Medicare models for the Outcome of Any Heart Failure at the 3 Month to 1 Year Time at Risk.

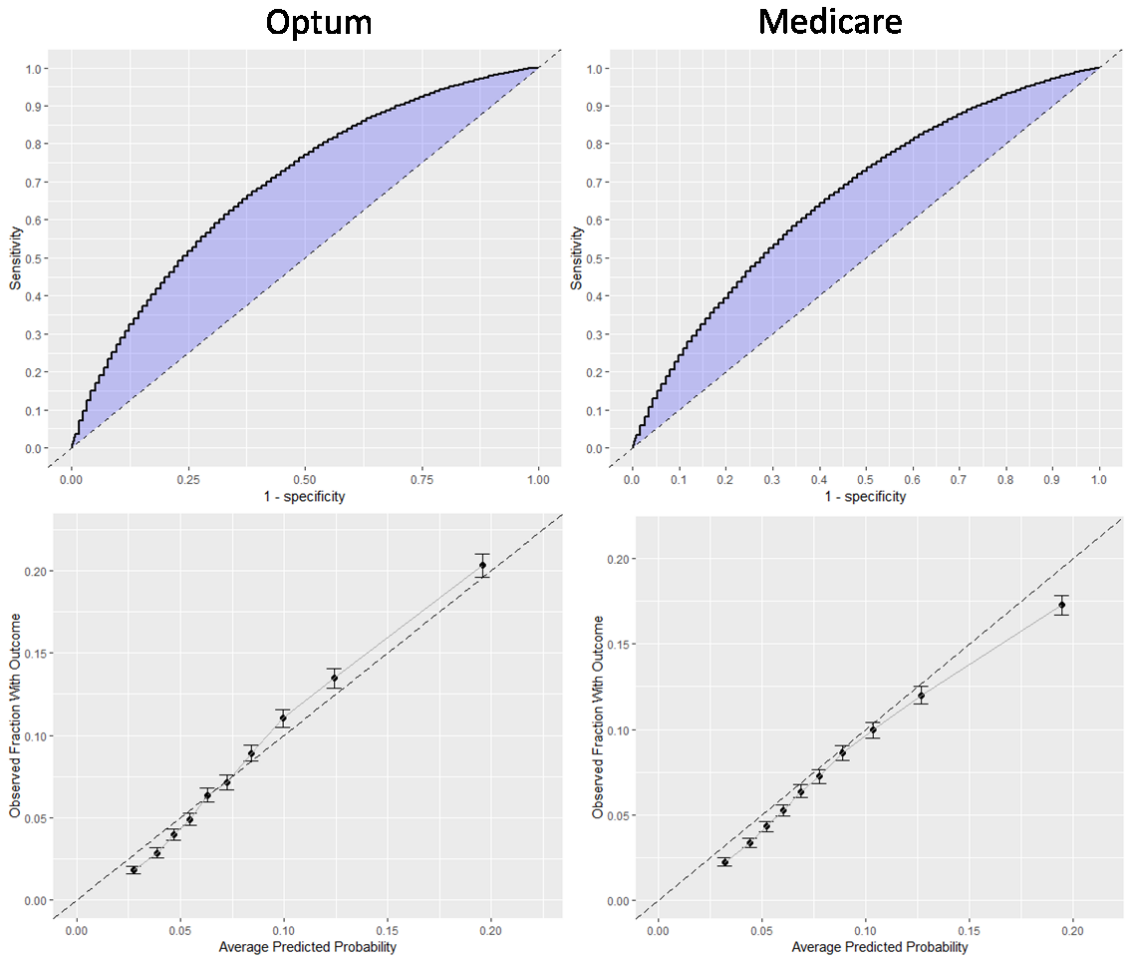
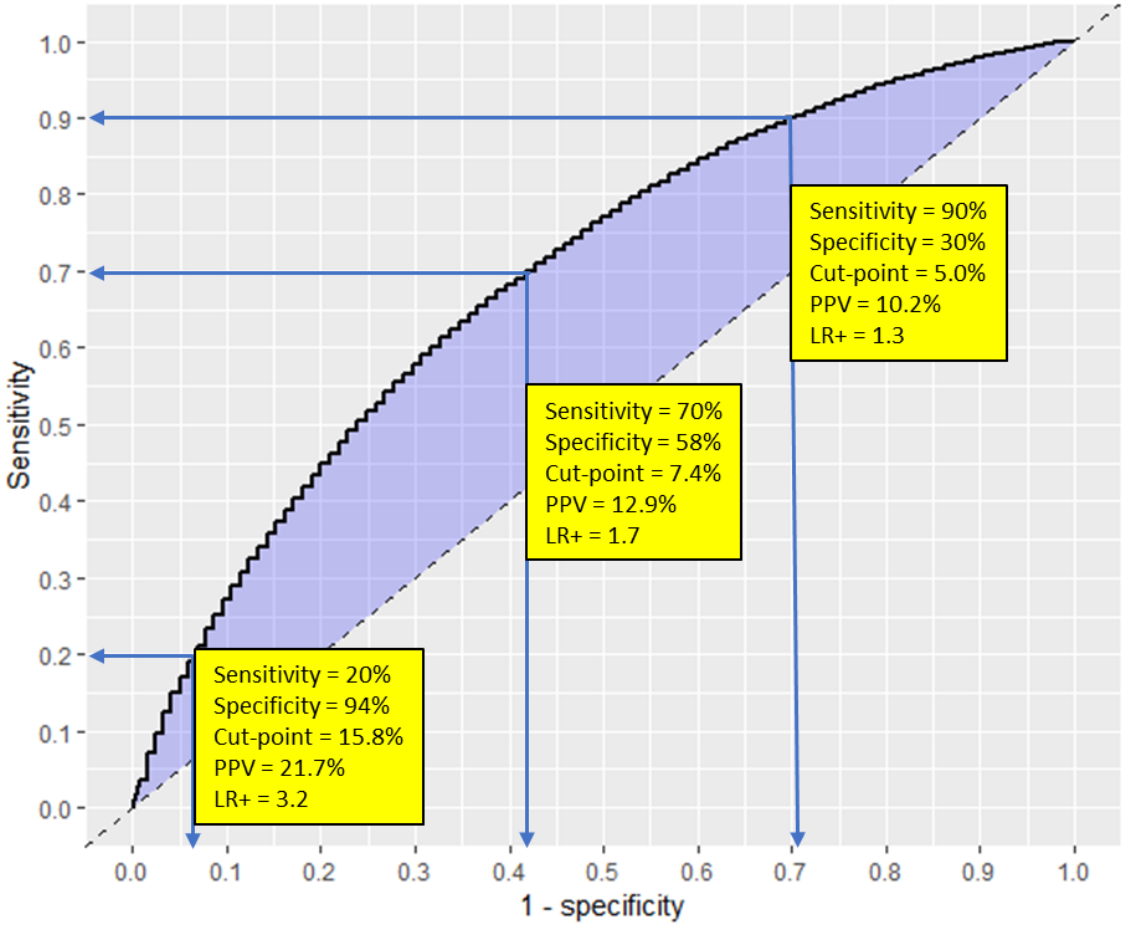
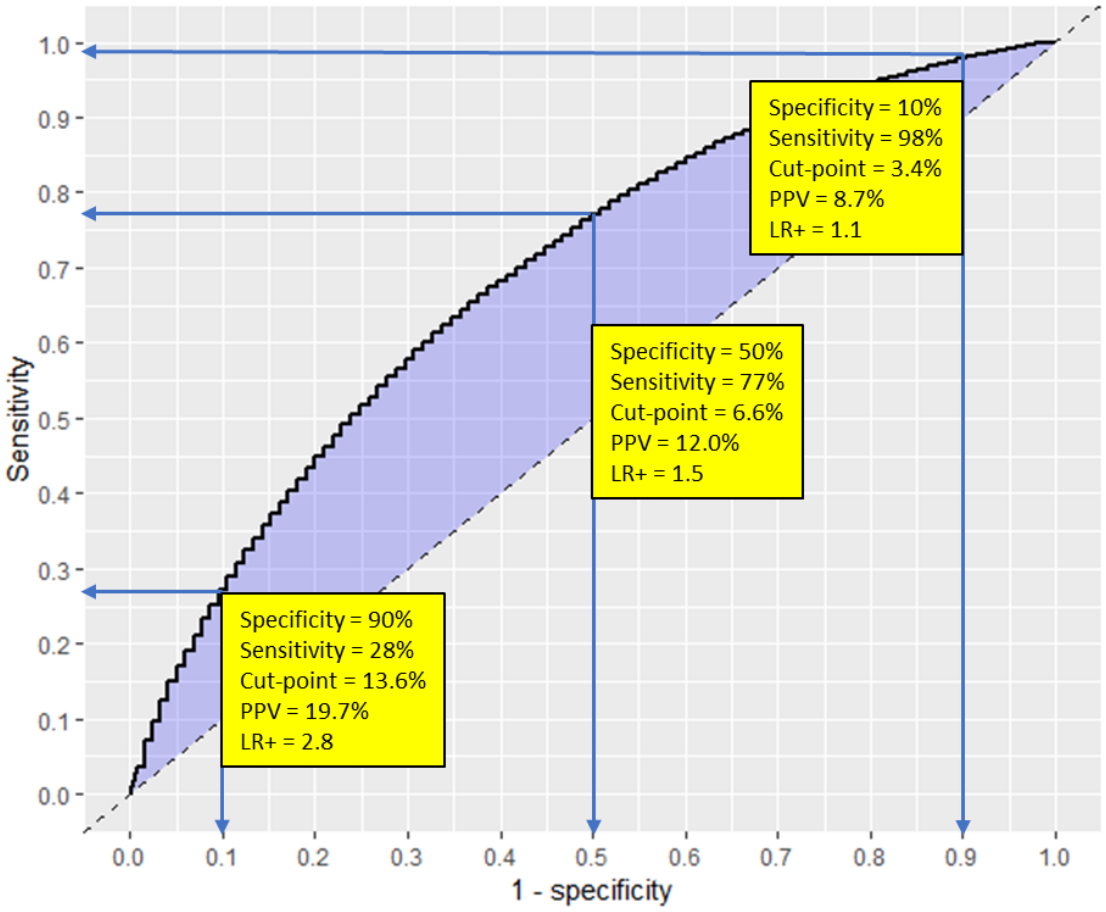


Figure 2: Performance Characteristics of the Optum Model for the Outcome of Any Heart Failure at the 3 Month to 1 Year Time at Risk for Selected Levels of Sensitivity.



* Cut-point – Prediction Threshold Cut-point; PPV – Positive Predictive Value; LR+ - Likelihood Ratio Positive

Figure 3: Performance Characteristics of the Optum Model for the Outcome of Any Heart Failure at the 3 Month to 1 Year Time at Risk for Selected Levels of Specificity.



* PPV – Positive Predictive Value; LR+ - Likelihood Ratio Positive

Appendices

Appendix 1: Full Specifications used in Cohort development

Cohort 1: Subjects Newly Diagnosed with Atrial Fibrillation >= age 66 for Time-at-Risk window 91-365 Days

Initial Event Cohort

People having any of the following:

- a condition occurrence of Atrial Fibrillation
    - for the first time in the person's history
    - with age >= 66

with continuous observation of at least 365 days prior and 91 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:

Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of Atrial Fibrillation/Flutter starting between all days Before and 1 days Before event index date
- and at least 1 occurrence of a condition occurrence of Atrial Fibrillation starting between 1 days After and 90 days After event index date
- and exactly 0 occurrences of a condition occurrence of Heart Failure - All starting between all days Before and 90 days After event index date
- and at least 1 occurrence of a visit occurrence of Any Visit starting between 179 days Before and 1 days Before event index date

- and at least 1 occurrence of a visit occurrence of Any Visit

  starting between 365 days Before and 180 days Before event index date

- and at least 1 occurrence of a visit occurrence of Any Visit

  starting between 1 days After and 90 days After event index date

Limit cohort of initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

Cohort 2: Subjects Newly Diagnosed with Atrial Fibrillation >= age 66 for Time-at-Risk window 366-1095 Days

Initial Event Cohort

People having any of the following:

- a visit occurrence of Any Visit

with continuous observation of at least 730 days prior and 1 days after event index date, and limit initial events to: all events per person.

For people matching the Primary Events, include:

Having all of the following criteria:

- at least 1 occurrence of a condition occurrence of Atrial Fibrillation
  - for the first time in the person's history
  - with age >= 66

    Having all of the following criteria:

        - exactly 0 occurrences of a condition occurrence of Atrial Fibrillation/Flutter

          starting between all days Before and 1 days Before event index date
        - and at least 1 occurrence of a condition occurrence of Atrial Fibrillation

          starting between 1 days After and 90 days After event index date
        - and at least 1 occurrence of a visit occurrence of Any Visit

          starting between 179 days Before and 1 days Before event index date
        - and at least 1 occurrence of a visit occurrence of Any Visit

          starting between 365 days Before and 180 days Before event index date
        - and at least 2 occurrences of a visit occurrence of Any Visit

          starting between 1 days After and 180 days After event index date
        - and at least 1 occurrence of a visit occurrence of Any Visit

          starting between 181 days After and 365 days After event index date

      starting between 425 days Before and 365 days Before event index date
    - and exactly 0 occurrences of a condition occurrence of Heart Failure - All

      starting between all days Before and 0 days After event index date

Limit cohort of initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

Cohort 3: Subjects with First Occurrence of Heart Failure – All Left Side

Initial Event Cohort

People having any of the following:

- a condition occurrence of Heart Failure - All Left Side

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:

Having all of the following criteria:

- Having any of the following criteria:
    - at least 1 occurrence of a condition occurrence of Heart Failure - All Left Side
        - visit occurrence is any of: Emergency Room Visit, Inpatient Visit

      starting between 0 days Before and 60 days After event index date
    - or at least 2 occurrences of a condition occurrence of Heart Failure - All Left Side
        - visit occurrence is any of: Outpatient Visit

      starting between 0 days Before and 60 days After event index date

Limit cohort of initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

Cohort 4: Subjects with First Occurrence of Heart Failure with Reduced Ejection Fraction (Systolic Heart Failure)

Initial Event Cohort

People having any of the following:

- a condition occurrence of Heart Failure - All Left Side
    - for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:

Having all of the following criteria:

- at least 1 occurrence of a condition occurrence of Heart Failure - All Left Side starting between 1 days After and 60 days After event index date
- and at least 1 occurrence of a condition occurrence of Systolic Heart Failure starting between 0 days Before and 365 days After event index date
- and exactly 0 occurrences of a condition occurrence of Diastolic Heart Failure starting between 0 days Before and 365 days After event index date

Limit cohort of initial events to: earliest event per person.

Limit qualifying cohort to: earliest event per person.

Cohort 5: Subjects with First Occurrence of Heart Failure with Preserved Ejection Fraction (Diastolic Heart Failure)

Initial Event Cohort

People having any of the following:

- a condition occurrence of Heart Failure - All Left Side
    - for the first time in the person's history

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:

Having all of the following criteria:

- at least 1 occurrence of a condition occurrence of Heart Failure - All Left Side

  starting between 1 days After and 365 days After event index date
- and at least 1 occurrence of a condition occurrence of Diastolic Heart Failure

  starting between 0 days Before and 365 days After event index date
- And having all of the following criteria:
    - exactly 0 occurrences of an observation of Evidence of Reduced Left Ventricular Ejection Fraction

      starting between all days Before and all days After event index date
    - and exactly 0 occurrences of a measurement of Evidence of Reduced Left Ventricular Ejection Fraction

      starting between all days Before and all days After event index date

- and exactly 0 occurrences of a condition occurrence of Evidence of Reduced Left Ventricular Ejection Fraction
  starting between all days Before and all days After event index date
- and exactly 0 occurrences of a condition occurrence of Systolic Heart Failure starting between all days Before and 365 days After event index date

Limit cohort of initial events to: all events per person.

Limit qualifying cohort to: earliest event per person.

Appendix 2: Concept Set Definitions used in cohort development and Full Model Specifications

All files may be found at https://1drv.ms/f/s!AjcitS8A0AtDgaY0c1p0vlGfa-Cwaw

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Chapter 4: Summary of the Development of Predictive Models for Incident Heart Failure in Subjects with Newly Diagnosed Atrial Fibrillation.

The results described in Chapters 2 and 3 demonstrate that it is possible to develop models for predicting heart failure (HF) in subjects with newly diagnosed atrial fibrillation (AF). These models can provide clinicians and patients additional knowledge needed to make critical health decisions. The models developed in this study can be improved in the future as more health data, such as electronic health records (EHR), becomes available.

We attempted to create models that would be useful for a wide range of clinical applications. Overall, we developed 24 models. These included 2 times-at risk for HF after AF diagnosis, 3 months to 1 year and 1 year to 3 years. This allows clinicians and their patients to consider both short- and longer-term outcomes. The longer-term model additionally incorporates early treatment of AF in the prediction of HF. We developed separate models for patients under and over age 65. We did this based on prior studies indicating that age plays a critical factor in determining patient outcomes for cardiovascular events.[1] We developed models for 3 different outcomes, any HF and both sub-types of HF, heart failure with preserved ejection fraction, and heart failure with reduced ejection fraction. As the etiologies for the two sub-types of HF are very different, these models allow for more accurate predictions based on the patient's health history at the time of diagnosis.[2] Finally, we developed models using 4 different datasets, two for each age group. This important in order to validate the models both internally, within a held-back sample of subjects, as well as externally, on a set of

patients outside the patient population on which the model was learned. This external validation is vital for gaining an understanding of model generalizability.

The first model, as discussed in Chapter 2 where the model was developed for subjects who were diagnosed with AF at age 62 or younger, showed particular promise. We found with these subjects that the measures of model performance were higher than previously developed smaller models.[3] Our primary performance measures, area under the receiver operator characteristics curve (AUC), were generally around 0.75 for both internal and external validation for the 12 models developed in this age group. These results indicate that the models are externally generalizable and may be used for applying the model to individual patients. The model was well calibrated with calibration slopes near unity meaning that the model works well across the full range of patient predicted values.

Chapter 3 describes the results of the model developed for subjects who were initially diagnosed with AF after age 65. Developing models for this age group proved to be more challenging. These models did not perform as well as the models developed for younger subjects. The AUCs for these models were generally between 0.65 and 0.70, which is borderline acceptable. The results were not unexpected. Prior research indicated that predictors of cardiovascular events with strong associations in younger patients have much weaker associations in older patients. As discussed in Chapter 3, the reasons for these weaker associations are thought to be related to the high number of comorbid conditions in older patients.[4] These comorbid conditions may interact with one another thereby reducing the effect of any one of the conditions. This model does

showed promise and will likely be improved when more detailed observational data, e.g., data with laboratory measurements, becomes available. Laboratory measurements, for example, will provide information to the models on levels of severity of comorbid conditions. These measurements will also inform the model as to temporal changes, how the comorbid condition changed over time as well as the effectiveness of prior therapeutic treatment.

Prognostic predictive models may be used by patients to gain a better understanding of their individual risk of developing an outcome. The Health Belief Model proposes that a person's health behavior is predicted by "the threat posed by illness, comprised of the likelihood of its occurrence ('perceived susceptibility') and its potential for causing physical harm and interfering with social functioning ('perceived severity')".[5] These models provide personalized evidence of the likelihood of an outcome, clearly demonstrating the "threat" to the patient. This may encourage increased compliance with the recommendations of health care professionals such as improved adherence to medication and, as often is the case of cardiovascular disease, increased exercise, weight loss, or better control of dietary habits.

Future work in this field may consider adjusting the model to use covariates that are more easily understood by patients, allowing the models to be used directly by patients to understand their risk of HF and, eventually, other outcomes. Other outcomes may include developing models for the situation where HF is developed initially and understanding the likelihood of later developing AF is needed. These models could be developed to be used by patients from applications on their computer or their phone,

possibly automatically incorporating laboratory data received from their clinician. Eventually, patients with cardiovascular disease could receive individualized feedback on how their current health behaviors are affecting their future health state. The patient could, for example, receive immediate feedback on how their personal risk of disease is altered by losing weight or maintaining their hemoglobin A1C levels below some threshold. Feedback such as this may play an important role in motivating patients to improve their health behaviors.

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