INVESTIGATING INFECTION-RELATED HOSPITALIZATION AS A RISK FACTOR FOR INCIDENT HEART AND MORTALITY AMONG HEART FAILURE PATIENTS

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Dedication

For my parents and grandparents, without whom I would not be the person that I am today.

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Abstract

HF is a growing epidemic with an estimated prevalence of 6.5 million individuals in the U.S., and poor outcomes persist despite recent therapeutic advancements. Studies have shown that an inflammatory response to infections may become dysregulated, thereby promoting collateral myocardial damage that may result in HF. Infection is also a common cause of hospitalization among HF patients and may lead to poor prognosis and high mortality. Limited data exist examining the relationship between infection-related hospitalization (IRH) and HF along with HF subtypes, HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF). Further, few studies have explored mortality rates following an IRH in HF patients or whether certain types of IRH are stronger predictors of mortality. This dissertation leveraged the strengths of large claims data (MarketScan) and a community-based study (ARIC) to address these limitations and parse out the dynamic relationship between infection-related hospitalization and HF with several manuscripts.

The first manuscript, a case-crossover study of beneficiaries in the MarketScan databases, assessed the association between IRH and incident HF. IRH was associated with incident HF after both 1- and 3-months. The second manuscript investigated the association between IRH and long-term incident HF in the Atherosclerosis Risk in Communities study (ARIC). IRH was associated with a two-fold greater risk of incident HF, HFrEF, and HFpEF. Findings were stronger among those with HFpEF, for which treatment options are limited. Results from the first manuscript aligned with those of the second manuscript

and both found respiratory, pneumonia, and blood/circulatory infections to have the strongest associations with incident HF. The third manuscript explored the relationship between IRH and mortality among HF patients in ARIC. IRH was associated with a two-fold greater risk of mortality among those with HFpEF, HFrEF, or unclassified HF. Respiratory, pneumonia, and other infections had the strongest associations with mortality.

Our findings support prior literature linking IRH to HF risk and increased mortality among HF patients. These findings may have significant population-level implications given the high prevalence of IRH and the burden of HF on our aging society.

<u>Aim 1</u>: Investigate the association between infection-related hospitalization and incident HF using U.S.-based claims data from MarketScan.

<u>Aim 2</u>: Investigate the association between infection-related hospitalization and incident HF and HF subtypes (HFrEF or HFpEF) using a longitudinal community-based cohort study, ARIC.

<u>Aim 3</u>: Among HF (HFrEF and HFpEF) patients, investigate the association between infection-related hospitalization and mortality using a longitudinal community-based cohort study, ARIC.

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Chapter 1. Pathophysiology of Heart Failure

Natural History of Heart Failure

The heart normally accepts blood at low filling pressures during diastole and then propels it forward at higher pressures in systole. Heart failure (HF) is present when the heart is unable to pump blood forward at a sufficient rate to meet the metabolic demands of the body. HF is caused by any condition that reduces the efficiency of the heart muscle, through damage or overloading. Volume overload occurs when too large a volume of blood exists within a chamber of the heart for it to function efficiently. Over time, these increases in workload are exacerbated by long-term activation of neurohormonal systems including the sympathetic nervous system, the renin-angiotensin system, and the antidiuretic hormone system. In turn, these initially helpful and eventually maladaptive responses lead to fibrosis, dilation, and structural changes in the shape of the left ventricle (LV) from elliptical to spherical[3].

In a normal heart, increased filling of the ventricle results in increased contraction force, and thus a rise in cardiac output. However, a person with HF may have a reduced force of contraction when the heart muscle is over-stretched due to volume overload. In this instance, the ventricle is loaded with blood to the point where heart muscle contraction becomes less efficient. This phenomenon is due to reduced ability to cross-link actin and myosin myofilaments in over-stretched muscle[4]. Accordingly, HF results is a clinical syndrome characterized by signs and symptoms of volume overload, including fatigue, shortness of breath, and edema. It may be the final common pathway and the most severe

manifestation of nearly every form of cardiac disease, including coronary atherosclerosis, myocardial infraction, valvular disease, hypertension, congenital heart disease, and the cardiomyopathies[4].

Many patients with HF remain asymptomatic for extended periods either because the impairment is mild or because cardiac dysfunction is balanced by initially compensatory mechanisms, such as the neurohormonal mechanisms described earlier. Often, clinical manifestations are precipitated by activities that increase the cardiac workload and tip the precariously balanced state into one of decompensation. Factors that may precipitate symptoms in patients with chronic compensated HF include increased metabolic demands (fever, infection, anemia, tachycardia, hyperthyroidism, pregnancy), increased circulating volume (excessive sodium content in diet, excessive fluid administration, renal failure), conditions that increase afterload (uncontrolled hypertension, pulmonary embolism, increased right ventricle afterload), conditions that impair contractility (negative inotropic medications, myocardial ischemia or infraction, excessive alcohol consumption), and failure to take prescribed HF medications and presence of tachy- or bradyarrhythmias.

Heart Failure and HF Subtypes

Heart failure is a complex clinical syndrome resulting from structural and functional impairment of ventricular filling or ejection of blood[2,5,6]. The clinical syndrome of HF may arise due to abnormalities or disorders involving any aspect of cardiac structure or function[2]. Clinical manifestations include pulmonary and

systemic venous congestion that leads to inadequate peripheral oxygen delivery, which manifests as edema, dyspnea, and fatigue. Among HF patients, ejection fraction (EF) is often calculated to diagnose the type of HF. EF is the percentage of blood volume ejected in each cardiac cycle and is a representation of LV systolic performance. Using echocardiography, it is calculated as the difference between end-diastolic blood volume (i.e., blood in the LV before the heart contracts), and end-systolic blood volume (i.e., blood in the LV at the end of contraction)[7].

HF diagnoses are classified into three categories based on left ventricle performance: HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), and midrange HF(HFmEF). From the standpoint of pharmacotherapy, the HFmEF and HFrEF are usually grouped together. HFrEF occurs when the heart muscle is not able to contract adequately, leading to reduced cardiac output and insufficient delivery of oxygen-rich blood to body tissues. Those with HFrEF have an EF of ≤40%, representing a state of systolic dysfunction. The affected ventricle has a diminished capacity to eject blood because of impaired myocardial contractility or pressure overload. Loss of contractility may result from destruction of myocytes, abnormal myocyte function, or fibrosis[4]. Pressure overload impairs ventricular ejection by significantly increasing resistance to flow. During diastole, the persistently elevated LV pressure is transmitted to the left atrium and to the pulmonary veins and capillaries. An elevated pulmonary capillary hydrostatic pressure, when

sufficiently high (usually greater than 20 mm Hg), results in the transudation of fluid into the pulmonary interstitium and symptoms of pulmonary congestion[4].

In contrast, HFpEF occurs when the LV is not able to properly fill with blood during the diastolic phase, again leading to a decrease in cardiac output. Those with HFpEF have an EF of ≥50%[7]. Patients who exhibit HFpEF frequently demonstrate abnormal ventricular diastolic function: impaired early diastolic relaxation, increased stiffness of the ventricle wall, or both[4]. Acute myocardial ischemia is an example of a condition that transiently inhibits energy delivery and diastolic relaxation. Conversely, left ventricle hypertrophy, fibrosis, or restrictive cardiomyopathy causes the LV walls to become chronically stiffened. Patients with diastolic dysfunction often manifest signs of vascular congestion because the elevated diastolic pressure is transmitted retrograde to the pulmonary and systemic veins[4].

The prevalence of HF increases with age for both sexes with women more likely than men to have HFpEF, while HFrEF has roughly the same prevalence in both men and women.[8]. Despite the rising prevalence of HF, recent successful therapeutic advances have primarily targeted HFrEF, [28] while no therapy has been shown to extend life among patients with HFpEF[40].

Heart Failure Etiology

In the United States, approximately 115 million people have hypertension, 100 million have obesity, 92 million have prediabetes, 26 million have diabetes, and 125 million have atherosclerotic cardiovascular disease (CVD)[9]. These are

known risk factors with high relative risk and population attributable risk for development of HF. Therefore, a large proportion of the U.S. population can be categorized as being at-risk for HF. The common causes of HF include ischemic heart disease and myocardial infarction (MI), hypertension, and valvular heart disease (VHD). Other causes can include familial or genetic cardiomyopathies, such as dilated, hypertrophic and amyloidosis; cardiotoxic side effects of medications, such as doxorubicin; heavy substance use of alcohol, cocaine, or methamphetamine; tachycardia, right ventricular (RV) pacing, or stress-induced cardiomyopathies; peripartum cardiomyopathy; myocarditis; autoimmune causes, sarcoidosis; iron overload, including hemochromatosis; and endocrine diseases, such as disorders of the thyroid; and nutritional causes[10].

Given the complexity of HF and the multiple potential causes, it can be difficult to decipher the primary etiology of HF in a patient. HF has an estimated 17 primary etiologies[11]. More than two-thirds of all cases of HF can be attributed to four underlying conditions: ischemic heart disease, chronic obstructive pulmonary disease, hypertensive heart disease, and rheumatic heart disease[12]. In Western developed countries, coronary artery disease, either alone or in combination with hypertension, seems to be the most common cause of HF. It is important to note that the absence of overt or previously diagnosed hypertension in a patient presenting with new HF does not rule out a hypertensive etiology, as normalization of once high blood pressure can occur as the patient develops HF[13]. Common precursors of chronic HF have been associated with infection and include coronary artery disease (consequent upon acute myocardial infarction)[14-

[21], chronic hypertension[22-25], cardiomyopathy (dilated, hypertrophic, alcoholic, and idiopathic)[26-28], valve dysfunction (diseases of the aortic and mitral valve)[29-31], cardiac arrhythmias/conduction disturbance (heart block and atrial fibrillation)[32-35] and pericardial disease and infection (rheumatic fever, Chagas disease, viral myocarditis, and HIV).

Diagnosis & Treatment

Diagnosis

HF diagnosis can be straightforward if a patient presents with classic signs and symptoms in the appropriate clinical setting (**Table 1**). Physical findings of HF are imprecise, often requiring further diagnostic workup to characterize a patient's HF as depicted in **Figure 1**. It is also important to note that there are no symptoms specific to HFrEF vs. HFpEF. However, cardinal signs of HF, such as worsening dyspnea and lower extremity edema, are typically related to increases in cardiac filling pressures, volume overload, and decreased cardiac output. Thus, clinical assessment of HF most often depends on information that is gathered from a variety of sources including medical history, physical examination, laboratory tests, cardiac imaging, and functional studies. Patients with HF may be in a state of "compensated" or "decompensated" HF, with decompensated HF patients having the most pronounced signs and symptoms of disease and requiring urgent treatment and often hospitalization.

Table 1: Signs and symptoms of heart failure[2].

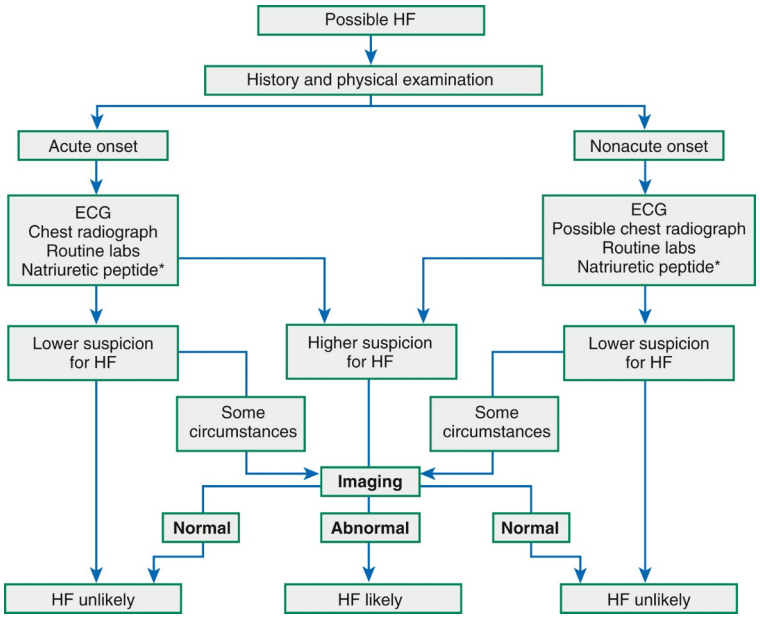
Physical Findings:	**Symptoms:**	**Medical Historical:**

Tachycardia	Fatigue	A history of heart failure
Extra beats or irregular rhythm	Shortness of breath at rest or during exercise	Cardiac disease (e.g., coronary artery, valvular or congenital disease, previous myocardial infarction)
Narrow pulse pressure or thready pulse*	Dyspnea	Risk factors for heart failure (e.g., diabetes, hypertension, obesity)
Pulses alternans*	Tachypnea	Systemic illnesses that can involve the heart (e.g., amyloidosis, sarcoidosis, inherited neuromuscular diseases)
Tachypnea	Cough	Recent viral illness or history of HIV or Chagas disease
Cool and/or mottled extremities*	Diminished exercise capacity	Family history of heart failure or sudden cardiac death
Elevated jugular venous pressure	Orthopnea	Environmental and/or medical exposure to cardiotoxic substances
Dullness and diminished breath sounds at one or both lung bases	Paroxysmal nocturnal dyspnea	Substance abuse

Rales, rhonchi, and/or wheezes	Nocturia	Noncardiac illnesses that could affect the heart indirectly (including high output states such as anemia, hyperthyroidism, arteriovenous fistulae)
Apical impulse displaced leftward and/or inferiorly	Weight gain/Weight loss	
Sustained apical impulse	Edema (of the extremities, scrotum, or elsewhere)	
Parasternal lift	Increasing abdominal girth or bloating	
S3 and/or S4 (either palpable and/or audible)	Abdominal pain (particularly if confined to the right upper quadrant)	
Tricuspid or mitral regurgitant murmur	Loss of appetite or early satiety	
Hepatomegaly (often accompanied by right upper quadrant discomfort)	Cheyne-Stokes respirations (often reported by the family rather than the patient)	
Ascites	Somnolence or diminished mental acuity	
Pre-sacral edema		
Anasarca*		
Pedal edema		

Chronic venous stasis changes		
*Indicative of more severe disease		

Figure 1: Flow chart for the evaluation of patients with heart failure[2].



Once a patient is diagnosed with HF, they can then be further categorized into 4 different stages of HF. The American College of Cardiology (ACC) and the American Heart Association (AHA) created these stages to classify HF severity[36]. These 4 stages include: (1) Stage A, at-risk for HF, (2) Stage B, pre-HF, (3) Stage C, symptomatic HF and (4) Stage D, advanced HF (**Table 2**). The New York Heart Association also offers a prominent classification system from Class 1-4 organized by functional status (**Table 3**)[10].

Table 2: Stages of Chronic Heart Failure	
Stage	**Description**

A	The patient is at risk for developing heart failure but has not yet developed structural cardiac dysfunction (e.g., patient with coronary artery disease, hypertension, or family history of cardiomyopathy).
B	The patient with structural heart disease associated with heart failure but has not yet developed symptoms
C	The patient with current or prior symptoms of heart failure associated with structural heart disease
D	The patient with structural heart disease and refractory heart failure symptoms despite maximal medical therapy who requires advanced interventions (e.g., cardiac transplantation)

Table 3: New York Heart Association Classification of Chronic Heart Failure

Class	**Definition**
I	No limitations of physical activity
II	Slight limitation of activity. Dyspnea and fatigue with moderate exertion (e.g., walking up stairs quickly)
III	Marked limitations of activity. Dyspnea with minimal exertion (e.g., slowly walking up stairs)
IV	Severe limitation of activity. Symptoms are present even at rest.

Defining HF in epidemiological studies

Several criteria have been proposed to diagnose HF, such as the Framingham criteria[37], the Boston criteria[38], the Gothenburg criteria[39], and the European Society of Cardiology criteria[40] (**Table 4**). These criteria include similar

symptoms and physiologic markers such as elevated filling pressures, and they combine data from medical history, physical examination, and chest radiograph to diagnose HF[41]. Specifically, the Framingham Heart Study provides clinical criteria for HF diagnosis based on physical examination and physician adjudication[42]. It utilized major and minor criteria to establish definite, probable, or questionable diagnoses for congestive HF[37]. The Framingham and Boston criteria have been compared against the masked assessment of a cardiologist and resulted in a sensitivity of 100%[43]. The specificity and positive predictive value of the Framingham criteria are lower than those of the Boston score for definite HF, but provided greater sensitivity to diagnose possible HF.

The European Society of Cardiology criteria require objective evidence of cardiac dysfunction[40]. To apply this criteria, cardiac function must be uniformly evaluated by appropriate tests for population sciences studies. The latest guidelines on the echocardiographic assessment of left ventricular function from the American Society of Echocardiography, published in 2015, recommend that an ejection fraction of ≤52% for men and ≤54% for women should be considered abnormal[44]. In the Cardiovascular Health Study, HF was diagnosed on the basis of a physician panel review of all pertinent medical records, including chest x-rays and echocardiograms[45]. The comparison of the Framingham criteria to the Cardiovascular Health Study criteria yielded similar results[45]. The Framingham Heart Study criteria is the most common and is referred to as the “gold standard” for HF validation[46].

Table 4: Heart Failure Diagnostic Criteria[8]

Framingham	Boston	European Society of Cardiology	Gothenburg Score Item and Method of Assessment	
Major criteria	**Category I: History**	1. Symptoms of heart failure (at rest or during exercise)	**Cardiac score**	
Paroxysmal nocturnal dyspnea or orthopnea	Rest dyspnea (4 pts) Orthopnea (4 pts)		History of heart disease (1–2 pts)	Self-report
Neck vein distension	Paroxysmal nocturnal dyspnea (3 pts)	and	Angina (1–2 pts)	Self-report
		2. Objective evidence of cardiac dysfunction (at rest)	Edema (1 pt)	Self-report
Rales	Dyspnea on walking on level (2 pts)		Nocturnal dyspnea (1 pt)	Self-report
		and	Rales (1 pt)	Physical examination
Cardiomegaly	Dyspnea on climbing (1 pt)	3. Response to treatment directed toward heart failure (in cases where diagnosis is in doubt)	Atrial fibrillation (1 pt)	ECG
			Pulmonary score	
Acute pulmonary edema	**Category II: Physical examination**		History of chronic bronchitis/ asthma(1–2 pts)	Self-report
S3 gallop	Heart rate abnormality (1–2 pts)	Criteria 1 and 2 should be fulfilled in all cases	Cough, phlegm, or wheezing (1 pt)	Self-report
Increased venous pressure ≥16 cm water	Jugular venous pressure elevation (1–2 pts)		Rhonchi (2 pts)	Physical examination
Circ. time ≥25 s	Lung crackles (1–2 pts)			
Hepatojugular reflux	Wheezing (3 pts)		Cardiac and pulmonary score are calculated and used to differentiate cardiac from pulmonary dyspnea	
Minor criteria				
Ankle edema	Third heart sound (3 pts)			
Night cough	**Category III: Chest radiography**			
Dyspnea on exertion				
Hepatomegaly	Alveolar pulmonary edema (4 pts)			
Pleural effusion	Interstitial pulmonary edema (3 pts)			
Vital capacity decreased 1/3 from maximum	Bilateral pleural effusions (3 pts)			
Tachycardia rate of ≥120/min	Cardiothoracic ratio ≥0.50 (3 pts)			
Major or minor criterion	Upper zone flow redistribution (2 pts)			
Weight loss ≥4.5 kg in 5 d in response to treatment	Definite heart failure 8–12 pts, possible 5–7 pts, unlikely ≤4 pts			
Heart failure present with 2 major or 1 major and 2 minor criteria				

Circ. indicates circulation; and pts, points.

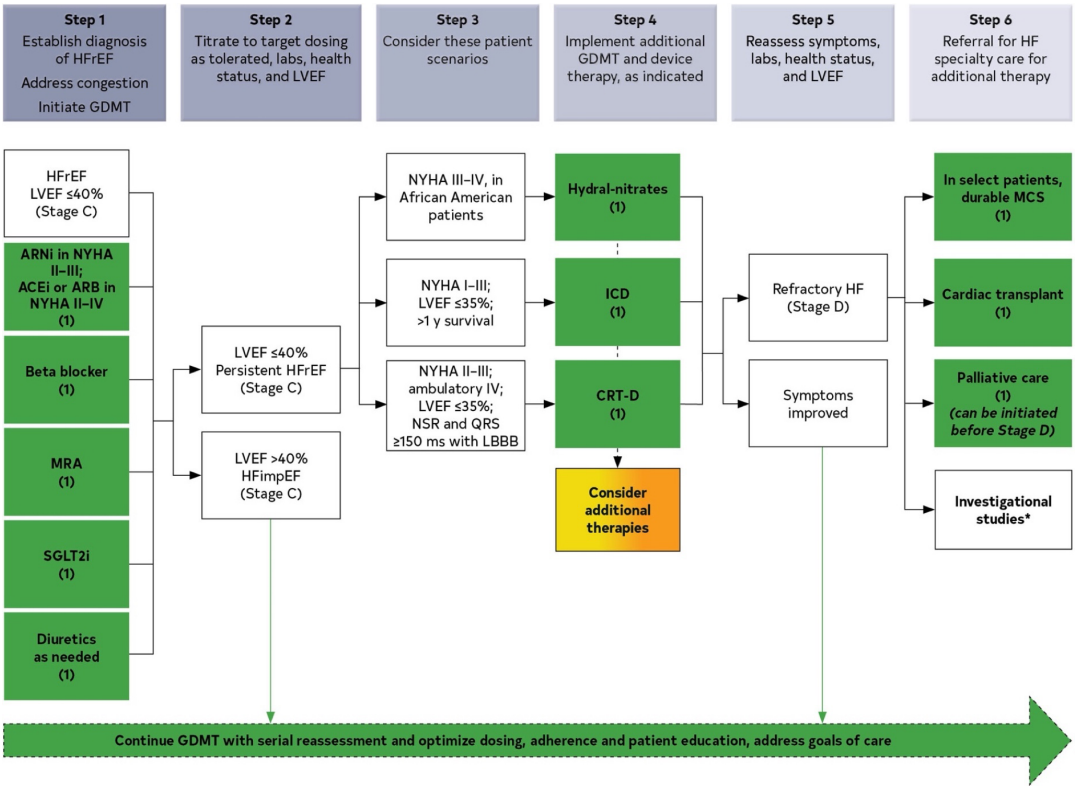
Treatment

Treatment for HF varies depending on the stage or severity of HF and type of HF. Different treatments set forth by AHA/ACC for patients with HF Stage A (those at risk for HF) and Stage B (those with pre-HF) include treating or controlling current risk factors. As some examples, among those in Stage A, (1) patients with hypertension should try and achieve optimal control of their blood pressure, (2) patients with type 2 diabetes and CVD or high risk for CVD should take an SGLT2 inhibitor (SGLT2i), and (3) patients at risk for HF should undergo natriuretic peptide biomarker screening. Among patients in Stage B, patients with

LVEF <=40% should start on an ACE inhibitor (ACEi) or beta blocker, while patients with a LVEF <= 30%, >1y survival and >40 days post MI should have an implantable cardioverter-defibrillator (ICD) placed[10]. Management strategies implemented in patients at risk for HF Stage A should be continued though Stage B. Heart failure treatment strategies are often holistic and multidisciplinary; that is, not limited to solely medications. Implementing healthy lifestyle habits is important. Lifestyle changes such as maintaining regular physical activity, normal weight, blood pressure, blood glucose levels, healthy diet, and smoking cessation reduce primordial risk and have been associated with a lower lifetime risk of developing HF[47-53].

Treatment recommendations for patients with HFrEF Stage C (symptomatic HF) and D (advanced HF) can be found outlined in **Figure 2**[10]. Multiple medications can be started simultaneously at initial doses recommended for HFrEF. Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating the next medication. Medication doses should be titrated to physiologic targets as tolerated.

Figure 2: Treatment recommendations for patients with HFrEF Stage C and D[10]



When it comes to those with HFpEF (LVEF ≥50%), treatment recommendations are different. HFpEF is a heterogenous disorder, contributed to by comorbidities that include hypertension, diabetes, obesity, CAD, CKD, and specific causes such as cardiac amyloidosis[54-56]. Unlike HFrEF, clinical trials have shown no benefit from HF treatments on mortality and marginal benefits on HFpEF hospitalizations until recently[57-60]. Thus, recommended management for HFpEF is that used for HF in general with use of diuretics to reduce congestion

and improve symptoms. These include diuretics as needed, SFLT2i, ARNi, MRA and ARB[10].

Some patients with chronic HF will continue to progress and develop persistently severe symptoms despite guideline-directed medical therapy. The European Society of Cardiology has defined advanced HF, which now includes four distinct criteria[61]. Overall, in patients with advanced HF, timely referral for HF specialty care is recommended to review HF management and assess suitability for advanced therapies which include LVAD, cardiac transplantation, palliative care, or palliative inotropes[61-63].

Chapter 2. Burden of Heart Failure

Incidence and Prevalence

The global incidence and prevalence rates of heart failure (HF) have continued to rise, marked by the increase in the number of HF hospitalizations, the growing number of HF deaths, and the growing costs associated with HF care. Specifically, HF affects more than 64 million individuals globally[64]. In the US, 6.2 million adults ≥20 years of age had HF between 2013 and 2016, compared with 5.7 million between 2009 and 2012.The prevalence of HF is projected to increase 46% between 2012 and 2030 in the U.S.,[64] and mortality rates among patients with HF remain high despite medical improvements. In the U.S., the mortality rate after diagnosis of HF was 10% after 30 days, 20-30% after 1 year and 45-60% after 5 years[43]. Patient survival rate after five years of their first HF hospital admission is less then 50%[8].

Economic Burden

In 2012, HF costs were estimated to be $30.7 billion[29]. Given the aging population in the U.S. and the increased risk of HF with age, HF costs are expected to escalate to $69.8 billion by 2030. Hospital admissions account for the majority of direct medical costs. There has been increased focus on decreasing HF-related hospital readmission rates in the US for the past decade; however, few interventions have affected hospital readmission rates.

A systematic review across the HF literature in the U.S. between 2014 and 2020 was conducted in order to compute the cost of HF[65]. The review found the

median cost for HF-specific hospitalizations to be $13,418 per patient. Patients with comorbidities had a slightly higher cost at $14,015. A 30-day post-discharge cost of outpatient care following a decompensated HF admission was estimated at $6,283 per patient, while a patient readmitted within 30 days of HF hospitalization showed an estimated cost of $15,732 per patient in the same hospital. Based on median data, HF hospitalizations contributed to 65% of all medical HF costs over a 1-year treatment period post hospitalization[65]. Patients with HF often have multiple comorbidities that contribute to treatment complexity. Even with a focus on readmissions and implementation of programs to incentivize hospitals to meet 30-day readmission benchmarks, hospitals are still face challenges developing effective solutions to target hospital readmissions and improve clinical outcomes.

Chapter 3. Heart Failure Risk Factors

Demographics

It has been well established that the incidence and prevalence of HF increases with age[66,67]. Over 10% of those ≥85 years of age have HF[68]. The overall lifetime risk of HF is similar between men and women, however, there are sex differences in HF subtypes. While the prevalence of HFrEF is similar among men and women, women are approximately two time more likely to develop HFpEF compared to men[69,70].

There are also differences in HF with regards to race and ethnicity. Disparities in the incidence of HF have been reported within large multi-racial cohorts supported by the National Heart Lung and Blood Institute of the National Institutes of Health[71-74]. There is a disproportionate burden of HF among Black compared to White persons. In addition, the incidence of HF among Hispanics is 3.5 per 1000 person-years, higher than that observed among non-Hispanic Whites (2.4 per 1000 person-years), and lower than that observed among non-Hispanic Blacks (4.6 per 1000 person-years)[72,75].

Clinical and Behavioral

Certain medical conditions, such as coronary artery disease (CAD)[76,77], diabetes (DM)[78-80], high blood pressure[81,82], obesity[83-85] and myocarditis[86,87], are well-established HF risk factors. For diabetes in particular, observational studies have consistently demonstrated a 2- to 4-fold increased risk of HF in individuals with diabetes compared to those without[78]. Specifically, the Framingham Heart

Study found diabetes to be associated with a nearly 2-fold increase in the risk of incident HF in men and a 4-fold increase in women, even after adjustment for cardiovascular risk factors[80]. The risk of incident HF among patients with DM increases with older age, CAD, peripheral arterial disease, nephropathy, retinopathy, longer duration of DM, obesity, hypertension, and higher NT-proBNP (N-terminal pro-B-type natriuretic peptide)[88-91]. Blood pressure is also an important risk factor for HF. A treatment goal of <130/80 mm Hg is recommended for those with a CVD risk of ≥10%[92,93].

Behaviors can also increase the risk of HF. Healthy lifestyle habits such as maintaining regular physical activity, normal weight, healthy dietary patterns, and not smoking has been associated with a lower lifetime risk of developing HF[50-52,94-96]. The AHA/ACC primary prevention guidelines provide recommendations for diet, physical activity, and weight control in order to decrease HF risk[97]. Guidelines include at least 150 minutes per week of accumulated moderate-intensity to 75 minutes per week of vigorous-intensity aerobic physical activity and a diet emphasizing intake of vegetables, fruits, legumes, nuts, grains, and fish.

Infection

An infection is the invasion of pathogens, also referred to as microorganisms, their multiplication, and the reaction of host tissues to the infectious agent and the toxins they produce[98]. Infections can be caused by a wide range of pathogens, such as parasites and fungi, though human infections

are predominantly caused by bacteria and viruses. Human hosts react to infections with an innate response, often involving inflammation, followed by an adaptive response. The main functions of the human innate immune system are: (1) recruiting immune cells to infection sites, (2) identifying bacteria, and promoting clearance of antibody complexes or dead cells, (3) identifying and removing foreign substances present in organs, tissues, blood, and lymph by specialized white blood cells, (4) activating the adaptive immune system, and (5) acting as a physical and chemical barrier to infectious agents[99]. The adaptive immune response subsequently activates and provides a more targeted response to infection, as it is composed of specialized, systemic cells that eliminate pathogens or prevent their growth[99].

Inflammation

Inflammation is a biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants[100]. It is a protective response involving immune cells, blood vessels, and molecular mediators. The function of inflammation is to eliminate the initial cause of cell injury, remove injurious stimuli and tissues damaged from the original insult, and initiate tissue repair[101,102]. Inflammation is therefore a defense mechanism vital to health[103]. Often, during acute inflammatory responses, cellular and molecular events and interactions efficiently minimize impending injury or infection. This mitigation contributes to the restoration of tissue homeostasis and resolves acute inflammation. However,

uncontrolled acute inflammation may become chronic, contributing to a variety of chronic inflammatory diseases[104].

Acute Infection and Chronic Disease

Several studies have reported an increased risk of cardiovascular disease (CVD) during or shortly after hospital admission for acute infection[105-108]. Infections can result in local and systemic inflammation, coagulation disturbances, endothelial dysfunction, inflammatory changes in atherosclerotic plaques, and downstream ischemia, including ischemic cardiomyopathy[109-111]. Inflammation has been found to play a central role in the atherosclerotic process, from initiation of atherosclerosis to progression and rupture of plaques[112]. Alone, or in combination, these effects may increase the short-term risk of cardiovascular events[113]. A large register-based cohort study with long-term follow-up found that the risk of experiencing a CVD event is the highest within the first year following an acute infection and subsequently declines over the years, though remains elevated five years after the acute infection[102]. In addition, a case-crossover study conducted in a population-based cohort study (ARIC) found that in- and outpatient infections are a trigger for CVD[114].

Chronic Infection and Chronic Disease

Heightened systemic inflammatory and pro-coagulant activity can persist long after infections resolve[115]; therefore, the effect of infections on CVD risk could also extend for several years after infection. However, only a few studies

have reported associations between severe infections and subsequent long-term risk of CVD[116-118]. Chronic low-grade inflammation accompanies all stages of atherosclerotic disease, from onset to overt disease and ischemia, thereby potentially offering a new and important therapeutic option[119]. Several inflammatory markers have been identified; however, clinical trials have provided inconclusive results[120-122]. One recent success in The Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) showed promising results, as they were able to significantly reduced high-sensitivity C-reactive protein levels, a measure of inflammation,[123] making it an active and important area of research.

Infection and Adverse Events in HF Cohorts

Only a small number of studies have explored the effect of infection on those with HF. Alon et al. found that 38% of people with HF had at least one sepsis hospitalization and an increased 30-day mortality after infection as compared to those hospitalized for reasons other than infection[124]. Ueda et al. similarly reported a high short-term mortality rate in people with HF after hospitalization with infection[125]. Lastly, a prospective observational cohort study assessing infection-related hospitalization among those with HFrEF found that short- and long-term survival after infection-related hospitalization is as poor as those after admission with decompensated HF, a high-risk event[126,127]. In addition, the study found that after an infection requiring hospitalization, the predominant cause of rehospitalization is infection[128].

A relationship between infection, inflammation, and chronic diseases has been established and lays the foundation for our study question. We will focus on the relationship between infection requiring hospitalization and HF and look at infection in the context of a HF population. In addition, most of these studies look at specific infections, such as pneumonia and sepsis. We will expand on this literature by looking at a more comprehensive range of infections, including respiratory, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other infections.

Biomarkers

NT-proBNP

Natriuretic peptides are useful biomarkers for HF diagnosis and estimation of HF severity and prognosis[2]. The most commonly measured natriuretic peptides are B-type natriuretic peptide (BNP) and its amino-terminal cleavage pro-peptide equivalent, NT-proBNP. These two biomarkers are released from cardiomyocytes in response to stretch and can be detected in blood[129]. Given the prevalence of myocardium in the ventricles, BNP and NT-proBNP mainly reflect ventricular stretch and are synthesized in response to wall stress. In addition, beyond left ventricular systolic and diastolic dysfunction, concentrations of both peptides are higher in patients with valvular heart disease, pulmonary hypertension, ischemic heart disease, atrial arrhythmias, and even pericardial processes, such as constriction[130].

Troponin

Cardiac troponin (cTn) is the primary biomarker for the diagnosis of myocardial necrosis in acute coronary syndrome (ACS). cTn levels can also be elevated in many other conditions, including heart failure[131]. In acute or chronic HF with reduced or preserved ejection fraction, increased cTn levels carry prognostic value for adverse outcomes[132]. Specifically, in acute decompensated heart failure (AHF), an elevated cTn level has been repeatedly shown to correlate with increased short- and long-term mortality and, to a lesser extent, readmission rates[131]. cTn is also independently predictive of increased mortality risk across the HF spectrum. These associations have been demonstrated with both the I and T isoforms of cTn. Among HF patients, cTn may be elevated even in the absence of an acute coronary syndrome or significant CAD[2]. Therefore, cTn is an important biomarker for prognosis in acute and chronic HF.

CRP

C-reactive protein (CRP) is produced by the liver and circulates through the bloodstream in response to inflammation. Activation of the immune system may also play a role in the pathogenesis of heart failure (HF)[133,134]. Small studies have shown that plasma CRP is elevated in patients with HF[135,136]. In several community studies, plasma CRP predicted the development of HF and other adverse events[137,138]. In a large randomized trial, Val-HeFT (Valsartan Heart Failure Trial), higher CRP levels were found to be associated with features of

more severe heart failure and were independently associated with mortality and morbidity[139].

A variety of key inflammatory markers have been identified that have been subsequently tested as potential targets for the treatment of HF. Even though clinical trials have provided inconclusive results, modulation of inflammation remains a promising target for the treatment of HF[140]. However, it is important to note that treatments to reduce CRP levels and the prognostic importance of reducing CRP require further study. In particular, The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), found that Canakinumab significantly reduced high-sensitivity C-reactive protein levels from baseline, as compared with placebo, without reducing LDL cholesterol levels, and the 150-mg dose resulted in a significantly lower incidence of recurrent cardiovascular events than placebo[123]. The CANTOS study specifically focused on anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months, which led to a significantly lower rate of recurrent cardiovascular events than the placebo. Such therapies remain an active area of research.

Chapter 4. Adverse Outcomes Associated with Heart Failure

Hospitalization

Heart failure (HF) is one of the leading causes for hospital admission in the US, accounting for almost 6.5 million hospital days annually[141]. HF hospitalization rates differ between ethnic groups. HF hospitalizations are 50% higher for Black individuals, 20% higher for Hispanic individuals, and 50% lower for Asian individuals compared to White individuals[142]. HF hospitalizations are at high risk of readmission, and such cumulative events are a strong predictor of mortality[143]. Given the high morbidity, efforts have been made to reduce the number of hospitalizations related to HF. A number of therapies have been developed over the last two decades that have been shown to reduce HF hospitalizations[144]. Although primary HF hospitalizations declined, rates of hospitalizations with a secondary diagnosis of HF have been stable over the past decade[144]. Thus, strategies to reduce the high burden of hospitalizations of HF patients should include consideration of both cardiac disease and noncardiac conditions.

Mortality

HF is a condition with an adverse prognosis; one-year mortality rates in population-based studies have been reported to be 35% to 40%[145]. The incidence and prevalence of HF have continued to increase with the aging of the U.S. population. Despite improvements in medical therapy, the prognosis of patients with HF remains poor, with almost 20% of patients dying within one year

of initial diagnosis and >80% 8-year mortality. Of the deaths in patients with HF, up to 50% are sudden and unexpected. Patients with HF have 6- to 9-times the rate of sudden cardiac death of the general population[146]. Epidemiological studies have shown that despite increased total number of HF hospitalizations and readmissions rates in recent decades, the mean length of hospital stay, as well as the in-hospital mortality, have significantly decreased[147,148].

Chapter 5. Study Populations

Manuscript 1 uses MarketScan data to examine the association between infection-related hospitalization as a trigger of incident heart failure (HF). Manuscripts 2 and 3 uses data from the Atherosclerosis Risk in Communities (ARIC) study to assess (1) the long-term association between infection-related hospitalization and incident HF and (2) the association between infection-related hospitalization and mortality among HF patients.

MarketScan Databases

Database Population

MarketScan Commercial Claims and Encounters and MarketScan Medicare Supplemental databases (IBM Corporation) are one of the largest claims databases in the U.S. MarketScan's Commercial Claims and Encounters database includes data from employers and health plans, while its Medicare Supplemental database includes beneficiaries with Medicare supplemental insurance paid by employers[149]. These databases contain deidentified individual-level healthcare data, including demographics, medical services, and prescriptions. For manuscript 1 of this dissertation, we conducted a study using MarketScan data from 2013 to 2019.

HF Ascertainment

This analysis includes patients diagnosed with HF. HF is defined based on at least one inpatient or outpatient HF code using International Classification of

Disease, Ninth or Tenth Revision, Clinical Modification (**Table 4**)[46]. The positive predictive value, sensitivity, and specificity of the ICD-9-CM codes for HF are approximately 90%, 77% and 99%, respectively[46,150-153]. This definition was previously validated using medical records and applied the Framingham heart study criteria[154].

Table 5. International Classification of Diseases (ICD) Codes Utilized for the Ascertainment of Heart Failure

Description	**ICD-9-CM Code**	**ICD-10-CM Code**
Heart failure	428.XX	I50
Congestive heart failure, unspecified	428.0	I50.814, I50.9
Left heart failure	428.1	I50.1
Systolic heart failure	428.2	
Systolic heart failure, unspecified	428.20	I50.20
Acute systolic heart failure	428.21	I50.21
Chronic systolic heart failure	428.22	I50.22
Acute on chronic systolic heat failure	428.23	I50.23
Diastolic heart failure	428.3	
Diastolic heart failure, unspecified	428.30	I50.30
Acute diastolic heart failure	428.31	I50.31
Chronic diastolic heart failure	428.32	50.32
Acute on chronic diastolic heart failure	428.33	I50.33
Combined systolic and diastolic heart failure	428.4	

Combined systolic and diastolic heart failure, unspecified	428.40	I50.40
Acute combined systolic and diastolic heart failure	428.41	I50.41
Chronic combined systolic and diastolic heart failure	428.42	I50.42
Acute on chronic combined systolic and diastolic heart failure	428.43	I50.43
Heart failure, unspecified	428.9	I50.810, I50.811, I50.812, I50.813, I50.82, I50.83, I50.84, I50.89, I50.9
Rheumatic heart failure (congestive)	398.91	I09.81
Malignant hypertensive heart disease with heart failure	402.01	I11.0
Benign hypertensive heart disease with heart failure	402.11	
Unspecified hypertensive heart disease with heart failure	402.91	
Malignant hypertensive heart and renal disease with heart failure	404.01	I13.0
Benign hypertensive heart and renal disease with heart failure	404.11	
Unspecified hypertensive heart and renal disease with heart failure	404.91	

Malignant hypertensive heart and renal disease with heart failure and renal failure	404.03	I13.2
Benign hypertensive heart and renal disease with heart failure and renal failure	404.13	
Unspecified hypertensive heart and renal disease with heart failure and renal failure	404.93	
ICD-9- [10]-CM = International Classification of Diseases, Ninth [Tenth] Revision, Clinical Modification		

The Atherosclerosis Risk in Communities (ARIC) Study

The ARIC study is a prospective, community-based study that was developed to evaluate the etiology and natural history of atherosclerosis, as well as conduct community surveillance of cardiovascular disease[155,156]. Since inception in 1987, the ARIC study has expanded its research beyond cardiovascular disease to include several other chronic conditions, such as chronic kidney disease, diabetes, cancer, cognitive decline/dementia, and others.

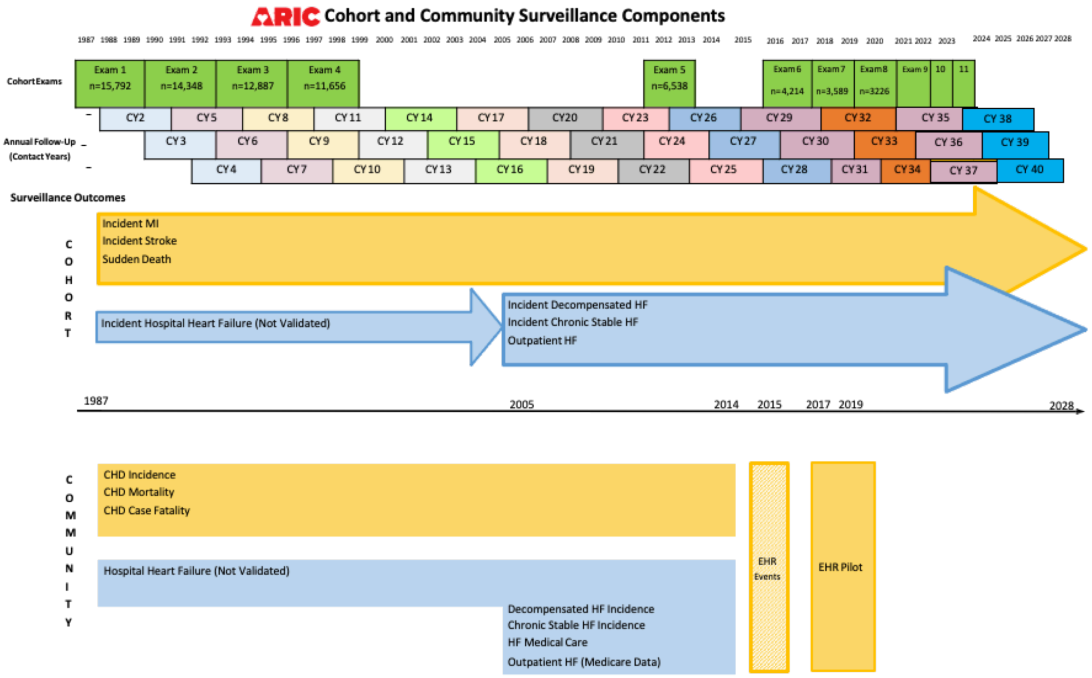
Study Design and Population

The ARIC study is a multi-center prospective cohort that enrolled 15,792 adults aged 45-64 years in 1987-1989 from four U.S. communities (Forsyth County, North Carolina; Jackson, Mississippi; northwest suburbs of Minneapolis, Minnesota, and Washington County, Maryland). Participants were selected by

probability sampling in each community. In Forsyth County, households were identified by area sampling, while other communities sampled age-eligible lists to identify their households. Age-eligible lists included the use of the following: driver's license or state identification cards in Jackson; jury duty eligibility with driver's license, identification cards, or voter registration cards in Minneapolis; and driver's license or listed in a 1975 private county health census in Washington County. The Jackson center only recruited Black participants, while the other three centers recruited participants representative of the local population's demographics. In the Minneapolis and Washington County centers, most participants were White, while in the Forsyth County center approximately 15% of participants were Black and 85% of participants were White.

Eight clinic visits have been completed (visit 1 [1987-98], visit 2 [1990-92], visit 3 [1993-95], visit 4 [1996-98], visit 5 [2011-13], visit 6 [2016-17], visit 7 [2018-19]), with visit 8 conducted by telephone (2020). Visit 9 is currently ongoing (**Figure 1**). In addition to clinic visits, the clinic made regular telephone calls (conducted annually prior to 2012 and twice-yearly thereafter) to continue contact with participants and obtain medical events that may have occurred[155]. For manuscript 2, baseline was set at visit 1 (1987-1998). In contrast, for manuscript 3, the study period began in 2005 and covariates measures at visit 4 (1996-1998) were used.

Figure 3. ARIC study visits and annual follow-up, 1987-present.



HF Ascertainment

ARIC defined HF using the following criteria: (1) reported use of HF medication, (2) the presence of HF according the Gothenburg criteria at ARIC v1, or (3) having developed incident HF since v1 based on the presence of ICD-9-CM code 428 in any hospitalization during follow-up[74]. Participants with prevalent HF at v1 were removed from the analysis in manuscript 1.

Beginning in 2005, ARIC implemented committee adjudication of HF hospitalizations based on chart abstraction as previously described[157]. To summarize, hospitalizations or deaths with potentially HF-related ICD codes were identified, with hospitalization records abstracted and adjudicated by the ARIC HF Committee. Abstraction included results of imaging studies and left ventricular ejection fraction (LVEF), when available. Reviewers determined if

evidence of an LVEF<50% at the time of hospitalization was present and recorded a numerical LVEF if available. Participants with quantifiable LVEF were categorized as HFpEF (LVEF ≥ 50%) or HFrEF (LVEF < 50%). If adjudication of the HF type was not possible, participants were defined as having “unknown” HF in all analyses.

Mortality Ascertainment

Participants were contacted annually to ascertain vital status after baseline. If a participant was reported deceased by the next of kin or other designated contact person, then the date of death and hospitalizations before death (if applicable) were ascertained. If the participant was not located during annual follow-up, an attempt was made to determine vital status via search of obituaries, funeral and hospital records, and the National Death Index. All participant deaths occurring in or before 1998 were classified with the use of International Classification of Diseases, 9th Revision (ICD-9) codes as neoplasms (ICD-9 140 to 239), diseases of the circulatory system (ICD-9 390 to 459), and all other causes of death. Deaths occurring in or after 1999 were converted from analogous codes assigned with the use of the International Statistical Classification of Diseases, 10th Revision (ICD-10) codes.

Chapter 6. Manuscript 1: Infection-related hospitalization and incident heart failure in MarketScan: a case-crossover study

Abstract

Introduction: Heart failure (HF) is a growing public health burden with high mortality rates. Chronic elevated levels of systemic inflammation are commonly observed in HF patients and are believed to be directly related to disease pathogenesis. Infection is a potential acute trigger of prolonged unresolving inflammation. Limited data exist examining the relationship between infection-related hospitalization (IRH) and HF.

Methods: We studied 152,008 beneficiaries in the U.S.-based MarketScan® databases from 2013-2019 who had at least 15 months of continuous enrollment. IRH was identified using select ICD-9 and -10 codes in the first five positions. Incident HF was defined using a single in- or outpatient ICD-9 or -10 code in the primary position and the absence of previous HF claims during the study period. A case-crossover study design was implemented with case periods of 3 months and 1 month, with equivalent control periods (3 months, and 1 month) that began 12 months prior to the start of the case period. We used logistic regression to calculate odds ratios (ORs) to assess the association between IRH and incident HF.

Results: Among 152,008 beneficiaries, 53% were male with a mean age of 56±11 at the start of the study period. IRH in the case period was associated with an increased risk of HF for both the 3-month case period (OR, 4.39; 95% CI,

4.18-4.60), and 1-month case period (OR, 7.39; 95% CI, 6.88-7.94), compared with IRH in the equivalent control periods after adjusting for the total number of hospitalizations. This relationship persisted across different types of infections (respiratory, pneumonia, influenza, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other).

Conclusion: IRH was associated with incident HF after both 1- and 3-months. IRH might represent a modifiable risk factor for inflammation-induced heart failure pathophysiology.

Introduction

Heart failure (HF) is a growing public health burden. In the US alone, it is estimated that >8 million people will be living with HF by the year 2030, and projected direct medical costs of HF will be doubling in the next several decades[64]. Despite development of novel therapeutics, HF mortality rates are high: up to half of HF patients die within 5 years of initial diagnosis[158,159].

To better prevent HF, upstream mechanisms that lead to HF have been the subject of substantial research in recent years. Chronic elevated levels of systemic inflammation are commonly observed in HF patients, and these findings are believed to be directly related to the disease pathogenesis[160]. Inflammation is multifactorial and can differ between patients though, severe infection is a potential acute trigger of prolonged chronic unresolving inflammation. Specifically, community-acquired bacteremia (CAB) is a well-defined clinical entity that encapsulates a wide range of mechanisms whereby infection may trigger cardiovascular events[161-164].

Previous research has provided evidence that acute infections trigger cardiovascular disease (CVD) events, including myocardial infarction (MI), stroke, and coronary artery disease (CAD)[114,161,165]. However, few studies have assessed HF as an outcome. Among this limited literature, only specific infections, such as pneumonia and periodontal disease, were considered[163,166-168]. In this manuscript, we investigate whether infection-related hospitalization (IRH) is a trigger for HF using a case-crossover design in the context of MarketScan, a large administrative claims dataset. We hypothesized that infections — including

respiratory, pneumonia, influenza, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other infections — are associated with a higher risk of incident HF within 1- and 3-months following infection.

Methods

Study population

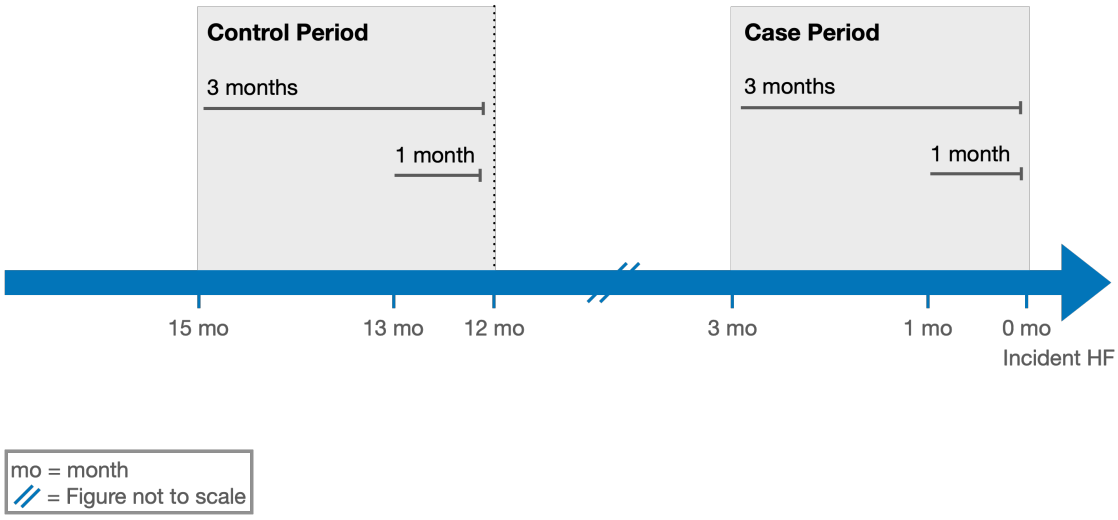
This study was conducted using the U.S.-based MarketScan® databases (Merative Corporation) from 2013-2019. Two databases were used. The Commercial Claims and Encounters database includes data from employers and health plans, while the Medicare Supplemental database includes beneficiaries with Medicare supplemental insurance paid by employers[149]. The databases contain linked deidentified individual-level health care data, including enrollment, demographics, medical services, and prescriptions.

We used a case-crossover study design, in which each HF patient served as their own control. The case-crossover design mitigates time-invariant confounding that might otherwise occur in designs that use between-group comparisons[169]. All enrollees with incident HF during follow-up and aged 18-100 were included. In addition, only incident HF cases will be included (i.e., recurrent events will not be considered), making each case independent.

In addition, enrollees with less than 15 months of continuous enrollment in their insurance before their incident HF event will be excluded. This is necessary to define incident HF, and to allow for case and control periods to

have identical seasonality, which is important given the seasonality of infections. Case periods are designated at 3 months, and 1 month before the HF event is defined, with equivalent control periods (3 months, and 1 month) and begins 12 months prior to the start of the case period (**Figure 1**). Two case period lengths were selected to evaluate the time frame in which HF events could be triggered after an infection-related hospitalization (IRH).

Figure 1: Case-crossover study design



HF Ascertainment

Outcomes were defined using a single in- or outpatient ICD-9-CM or ICD-10-CM code in the primary position (**Supplementary Table 1**). Prior studies evaluating the validity of identifying patients with HF have found high positive predictive values (PPVs), most being >90%[46]. Studies that included patients with a primary hospital discharge diagnosis of *ICD-9*, code 428.X had the highest PPV and specificity for HF[46]. Diagnostic accuracy measures of the primary discharge diagnosis were as follows: sensitivity 96% (95% CI: 91% - 99%),

specificity 90% (95% CI: 81% - 96%), PPV 94% (95% CI: 88% - 97%), and NPV 93% (95% CI: 85% - 98%)[170]. This algorithm, however, may compromise sensitivity because many HF patients are managed on an outpatient basis. Thus, we also included outpatient ICD codes to increase sensitively, although it may slightly decrease our PPV[170]. The most common forms of validation used were the Framingham Heart Study criteria, Carlson, and European Society of Cardiology.

We defined incident HF based on the absence of previous HF claims during the 15 months prior to the defining HF event, in which beneficiaries are continuously insured (**Figure 1**). As noted above, we chose a longer lookback period to account for the seasonality of infections.

Infection-Related Hospitalization Ascertainment

The occurrence of an IRH was identified by select ICD-9 or -10 codes (**Supplementary Table 2**) in the first five ICD positions. For our primary analysis, the occurrence of any IRH is considered. In our secondary analysis, we consider specific types of infection including respiratory, pneumonia, influenza, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other infections. A sensitivity analysis was conducted defining IRH as the primary discharge diagnosis (ICD position 1).

Risk Factor Measurements

Population characteristics are measured prior to their HF event. These measures include age, sex, and clinical characteristics such as the total number of hospitalizations, medications (i.e., lipid-lowering, and diabetes medications, cardiac calcium channel blockers), and prevalent conditions (i.e., hypertension, diabetes, kidney disease, myocardial infraction (MI), peripheral artery disease (PAD), chronic pulmonary disease (CPD) and stroke). Total number of hospitalizations was defined as the sum of any inpatient encounters that occurred during the case period and the sum of any inpatient encounters that occurred during the control periods, excluding any hospitalizations due to our main exposure (IRHs) or outcome (HF hospitalizations).

Statistical Analysis

Baseline characteristics are described using mean ± SD for continuous variables and count (%) for categorical variables. A case-crossover study design was used, in which everyone with HF serves as their own control. We defined exposure case periods of 3 months or 1 month before the incident HF event. Exposure control periods (3 months and 1 month) started and stopped 12 months prior to the beginning and end of the case period (**Figure 1**). Control periods started 1 year prior to case periods to control for seasonality (15 months and 13 months prior to the incident HF event). One- and 3-month case and control period lengths were selected to evaluate different time frames during which HF events could be triggered after an IRH.

Logistic models regressed the odds of IRH on case vs. control period; odds ratios (OR) and 95% confidence intervals (CI) were reported. A secondary analysis considered specific types of infections (respiratory, pneumonia, influenza, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other infections), reporting ORs (95%CI) for each infection type.

Sensitivity Analysis

A sensitivity analysis was conducted with IRH being defined as a primary diagnosis (ICD position 1). This was carried out to examine the effects of a more rigorous exposure definition. In addition, a secondary sensitivity analysis was conducted among a subgroup of beneficiaries who did not have any hospitalizations (aside from IRH) during their case or control period.

Results

Among 152,008 beneficiaries who met our definition of incident HF, 53% were male, and the mean age of 56±11 (range: 18-100 years) at the start of the 15-month follow-up period. Characteristics of beneficiaries are presented in **Table 1.** Overall, prior to their HF event, 92% of beneficiaries had at least 1 prescription, 57% were prescribed a beta blocker, 42% were prescribed an ACE inhibitor, 85% had hypertension, and 44% had diabetes. During the 3-month study period, 15.7% had at least 1 non-IRH during the case period vs. 4.1% during the control period. Similar results were found during the 1-month study period, 9.7% vs. 1.6%, respectively (**Table 2**). Among beneficiaries who had at

least 1 non-IRH during the 3-study period, 22.7% had an IRH while 9.3% did not have an IRH. Similar results were found during the 1-month study period, 10.9% vs. 5.5%, respectively (**Table 3**).

Infection-Related Hospitalization and Incident Heart Failure

In the 3-month case and control period, the prevalence of IRH was 21% during the control period and 79% during the case period. In the 1-month case and control period, the prevalence of IRH was 13% during the control period and 87% during the case period. IRH in the case period was associated with an increased odds of HF for both the 3-month case period (OR, 4.39; 95% CI, 4.18-4.60), and 1-month case period (OR, 7.39; 95% CI, 6.88-7.94), compared with IRH in the equivalent control periods after adjusting for the total number of hospitalizations (**Table 4**). This relationship persisted across different types of infections (**Table 5**). Respiratory, pneumonia, and blood-circulatory infections had the highest associations with HF during both the 3- and 1-month study periods.

Sensitivity Analyses

Results remained statically significant, though slightly attenuated when restricting our IRH definition to ICD-9/10 codes in the first position of diagnosis discharge compared to the first five positions for both the 3-month (OR, 4.08; 95% CI, 3.85-4.32) and 1-month (OR, 7.12; 95% CI, 6.51-7.80) study periods (**Table 4**). When we restricted our sample to those without any hospitalizations

(aside from our exposure of interest, IRH in the first 5 positions, and our outcome of interest, incident HF), IRH in the case period remained to be associated with an increased risk of HF for both the 3-month case period (OR, 4.88; 95% CI, 4.62-5.16), and 1-month case period (OR, 7.69; 95% CI, 7.11-8.30), compared with IRH in the equivalent control periods (**Table 4**).

Discussion

Infection-related hospitalization was strongly associated with incident HF in the 1- and 3-month periods following infection, in this case-crossover study of >150,000 insured Americans. Findings were consistent when considering different types of infections and remained after adjustment for the total number of hospitalizations in the case and control periods. Even after restricting to those without any hospitalizations aside from our exposure and outcome of interest, the odds of HF was significantly higher among those with an IRH hospitalization. These findings suggest that severe infections are a trigger for incident HF. IRH might represent an easy and cost-effective modifiable risk factor for inflammation-induced heart failure pathophysiology. Given the high prevalence of HF, this could have a large impact on public health.

Earlier evidence about specific infections supports our findings. For example, several ecological studies have found parallel seasonal trends in influenza and cardiovascular deaths[171-173]. Individual-level studies have also reported short-term associations between various infections including influenza, COVID-19, pneumonia, urinary tract infections, and bacteremia and myocardial

infarction (MI) or major cardiovascular events. The relative risk of MI or major cardiovascular events among those with versus without infection have ranged from 2.4-21.7 for respiratory tract infections, 2.2-35.2 for bacteremia, and 1.7-2.7 for urinary tract infections[105,107,116,174-176].

A study using data from the UK Biobank and 3 prospective cohort studies comprised of community-dwelling participants in Finland found that infections that are severe enough to require hospital treatment were associated with increased risks for major cardiovascular disease events specifically, MI, cardiac death, or fatal or nonfatal stroke immediately after hospitalization[177]. In the UK Biobank, the strongest association was seen the first month after infection (HR, 7.87 [95% CI, 6.36–9.73]), but remained elevated during the entire follow-up (HR, 1.47 [95% CI, 1.40–1.54] during mean follow-up, 11.6 years). Findings were similar in the Finland cohort studies (HR, 7.64 [95% CI, 5.82–10.03] during the first month; HR, 1.41 [95% CI, 1.34–1.48] during mean follow-up of 19.2 years)[177]. Our results, specific to incident HF, are strikingly similar with an OR of 7.39(6.88-7.94) during the first month following an IRH.

A case-crossover study using data from the Atherosclerosis Risk in Communities study compared in- and outpatient infection as a trigger for coronary artery disease (CAD) and ischemic stroke cases (14, 30, 42, and 90 days before the event) with corresponding control periods 1 and 2 years previously also found similar results[114]. Inpatient infections (14-day odds ratio [OR]=12.83 [5.74, 28.68], 30-day OR=8.39 [4.92, 14.31], 42-day OR=6.24 [4.02, 9.67], and 90-day OR=4.48 [3.18, 6.33]) and outpatient infections (14-

day OR=3.29 [2.50, 4.32], 30-day OR=2.69 [2.14, 3.37], 42-day OR=2.45 [1.97, 3.05], and 90-day OR=1.99 [1.64, 2.42]) were more common in all CHD case periods compared with control periods[114]. In addition, inpatient infection was a stronger predictor than outpatient infection of CHD at all time periods. Findings were generally similar for stroke, though slightly attenuated[114]. Our results are consistent with previous studies that used different study designs, time frames and large datasets. Even with these differences, the measure of association continues to be large and significant even in fully adjustment models.

There are several mechanisms that may explain why infections could trigger acute cardiovascular events. One such mechanism includes inflammatory and immune responses which are associated with dramatic shifts in tissue metabolism[178]. Changes include local depletion of nutrients, increased oxygen consumption and the generation of large quantities of reactive nitrogen and oxygen intermediates[178]. This increases the oxygen need of myocardial cells and decreases oxygen supply to the heart by shortening the filling time of coronary arteries during diastole, a combination of changes that predisposes to demand ischemia[179]. In addition, increased levels of catecholamines and inflammatory cytokines may contribute to arrhythmias, and infections might also cause direct myocardial damage[179]. Moreover, infections may increase inflammation in atheromatous plaques, making them less stable, and creating a prothrombotic state, increasing the risk of arterial occlusion subsequent to thrombosis[179-181].

There is also evidence that inflammatory changes could persist after resolution of the acute phase of a severe infection[115,182]. Adaptive immune cells

play critical roles in the host response to infection, resolution of inflammation and in tissue repair[183,184]. Their accumulation defines the post resolution phase of the inflammatory response and assures a more rapid response to subsequent exposure to the same antigens[183]. Interruption of this process at any point such as prolonged leukocyte recruitment and survival, impairments in apoptotic cell removal, and alterations in macrophage phenotype switching could potentially lead to chronic inflammation with resultant tissue damage, excessive fibrosis, and loss of function, as is seen in many cardiovascular diseases such as atherosclerosis and heart failure[185-188]. In fact, the cardiovascular disease most closely linked with chronic unresolved inflammation is atherosclerosis [189,190].

Strengths and Limitations

This study has several strengths, including the use of large administrative claims data, a case-crossover study design, and controlled for seasonality. MarketScan allowed us to capture a large sample of people with broad coverage across the U.S. enhancing the generalizability of our results. The implementation of a case-crossover design helps attenuate measured and unmeasured confounding of variables that are static (e.g., genetics, race/ethnicity) relatively static, or slowly varying factors (e.g., SES, smoking status, diet) which are not captured in MarketScan. However, confounding by time-varying variables remains a possibility such as the onset of comorbidities during our study period. Other changes in life events and health behaviors could similarly be important although most established HF risk factors (diet, activity, lipids, blood pressure)

are generally stable over a 1-year period[191,192]. To help address time-variant confounding, we are adjusting for the total number of hospitalizations that occurred during the study period, not including hospitalizations for our exposure or outcome. In addition, we controlled for seasonality by starting our case period 1 year after our control period.

This study also has some limitations. MarketScan only includes people who are commercially or publicly insured; therefore, our results may not be generalizable to the uninsured population. MarketScan also lacks well-validated HFrEF or HFpEF adjudication and mortality information. In addition, and with any case-crossover study, our analysis may suffer from survival bias given that we did not consider infections in beneficiaries who did not have a HF event. Our study only considers the relationship between infection-related hospitalization and HF among those who survived a diagnosed infection-related hospitalization and later had a HF event. However, this would likely bias our results towards the null. Lastly, the use of ICD codes can lead to misclassification, though we are leveraging a HF definition with a high PPV, sensitivity, and specificity[46,150-152], with diagnostic accuracy measures for HF being: sensitivity 96% (95% CI: 91% - 99%), specificity 90% (95% CI: 81% - 96%), PPV 94% (95% CI: 88% - 97%)[170]. For infection-related hospitalization, the occurrence of an ICD code in the first five positions was used. Although this definition is not validated, it has been previously used in ARIC.[13]

Conclusion

Our results support the role of infection as a short-term risk factor for HF. We hypothesize that infection-related hospitalizations contribute to the development of an acute inflammatory state that in many situations can persist indefinitely, possibly leading to increased HF risk both during the infection-related hospitalization and beyond. These findings may also have large public health implications given the high prevalence of infection-related hospitalization and HF, suggesting that greater efforts are required to prevent infection in those susceptible to HF. Future studies are necessary to examine the role of inflammation as a mediator linking infections to incident HF.

Tables/ Figures:

Table 1. Characteristics (% or mean±SD) of beneficiaries who met the incident heart failure inclusion criteria, MarketScan 2013-2019 (N = 152,008 individuals and N=304,016 case/control periods)

	Overall
Demographics	
Age (years)	56.5±11.3
Male (%)	53.1
Clinical Characteristics	
Any prescription (%)	92.1
Prescriptions	
ACE Inhibitors (%)	41.6
ARB (%)	27.0
Beta Blocker (%)	56.7
Statin (%)	50.6
Antihyperlipidemic Drugs, NEC (%)	5.9
Cardiac calcium channel blocker (%)	32.9
Diabetes Medications (%)	13.2
Prevalent conditions	
Hypertension (%)	84.8
Diabetes (%)	43.5
Ischemic Stroke (%)	18.8
Myocardial Infarction (%)	17.4
PAD (%)	22.1
CPD (%)	37.9
Kidney disease (%)	18.8

Sample size represents individuals who were in the MarketScan for at least 15 months prior to meeting our criteria for incident HF.
NEC = not elsewhere classified
PAD = Peripheral arterial disease
CPD = chronic pulmonary disease
Number of hospitalizations = total number of non-IRH and non-HF-related hospitalizations during case or control periods. IRH in the first 5 positions (our exposure of interest) and HF (our outcome of interest) are excluded from the total hospitalization count that is being adjusted for.

Table 2. Total number of hospitalizations among beneficiaries during the case and control period for the 3-month and 1-month study periods, MarketScan 2013-2019 (N = 152,008 individuals)

	Total	Case Period N (%) *	Control Period N (%) *
Number of Hospitalizations During the 3 Month Case/Control Periods			
0	273,953 (91.1)	128,303 (84.4)	145,650 (95.8)
1	25,368 (8.3)	19,836 (13.1)	5,532 (3.6)
≥2	4,695 (1.5)	3,869 (2.6)	826 (0.5)
Number of Hospitalizations During the 1 Month Case/Control Periods			
0	286,980 (94.4)	137,328 (90.3)	149,652 (98.5)
1	15,563 (5.1)	13,364 (8.8)	2,199 (1.5)
≥2	1,473 (0.5)	1,316 (0.9)	157 (0.1)

*Column % are presented and can be interpreted as the % of individuals with 0, 1 or >=2 hospitalizations among all individuals during their respective case or control periods.

Number of hospitalizations = total number of non-IRH and non-HF-related hospitalizations during case or control periods. IRH in the first 5 positions (our exposure of interest) and HF (our outcome of interest) are excluded from the total hospitalization count that is being adjusted for.

Table 3. Total number of hospitalizations among beneficiaries with and without an infection-related hospitalization during the 3-month and 1-month study periods, MarketScan 2013-2019 (N = 152,008 individuals)

	Total Hospitalizations	**With IRH N (%)**	**Without IRH N (%)**
Number of Hospitalizations During the 3 Month Case/Control Periods			
0	273,953 (91.1)	10,486 (77.3)	263,467 (90.7)
1	25,368 (8.3)	2,329 (17.2)	23,039 (7.9)
≥2	4,695 (1.5)	749 (5.5)	3,946 (1.4)
Number of Hospitalizations During the 1 Month Case/Control Periods			
0	286,980 (94.4)	6,770 (89.1)	280,210 (94.5)
1	15,563 (5.1)	747 (9.8)	14,816 (5.0)
≥2	1,473 (0.5)	81 (1.1)	1,392 (0.5)

*Column % are presented and can be interpreted as the % of individuals with 0, 1 or ≥2 hospitalizations among individuals who had an IRH and those who did not have an IRH.

Number of hospitalizations = total number of non-IRHs and non-HF-related hospitalizations during case or control periods. IRH in the first 5 positions (our exposure of interest) and HF (our outcome of interest) are excluded from the total hospitalization count that is being adjusted for.

Table 4. Odds ratios summarizing the association between infection-related hospitalization and incident heart failure in MarketScan, 2013-2019 (N = 152,008 individuals)

	Infection-Related Hospitalization N (%)		**Odds Ratio (95% CI)**	
Models	Case Period	Control Period	Crude	Adjusted*
IRH in the first five positions				
3 months	10,746 (79)	2,818 (21)	4.56 (4.36, 4.78)	4.39 (4.18, 4.60)
1 month	6,582 (87)	1,016 (13)	7.28 (6.79, 7.81)	7.39 (6.88, 7.94)
IRH in the first position				
3 months	6,679 (79)	1,819 (21)	4.12 (3.90, 4.36)	4.08 (3.85, 4.32)
1 month	3,947 (86)	622 (14)	6.88 (6.29, 7.51)	7.12 (6.51, 7.80)

IRH hospitalization include claims in the first five positions.
*Adjusted for total number of non-IRHs and non-HF-related hospitalizations during case or control periods. IRH in the first 5 positions (our exposure of interest) and HF (our outcome of interest) are excluded from the total hospitalization count that is being adjusted for.

Table 5. Odds ratios summarizing the association between infection-related hospitalization in the first five positions and incident heart failure in MarketScan, 2013-2019 (N = 152,008 individuals)

	Infection-Related Hospitalization N (%)		**Odds Ratio (95% CI)**	
Models	Case Period	Control Period	Crude	Adjusted*
3 months				
Respiratory	4,101 (88)	878 (18)	5.21 (4.82, 5.63)	5.08 (4.69, 5.50)
Influenza	75 (69)	33 (31)	2.27 (1.51, 3.42)	2.07 (1.36, 3.15)
Pneumonia	2,959 (83)	622 (17)	5.24 (4.79, 5.74)	5.25 (4.78, 5.78)
Urinary tract	766 (73)	282 (27)	2.85 (2.47, 3.28)	2.67 (2.30, 3.10)
Digestive tract	364 (69)	161 (31)	2.32 (1.92, 2.80)	2.17 (1.78, 2.65)
Skin	1,006 (70)	430 (30)	2.44 (2.17, 2.74)	2.42 (2.15, 2.74)
Blood/circulatory	302 (86)	49 (14)	6.62 (4.84, 9.06)	6.64 (4.80, 9.17)
Hospital-acquired	656 (74)	234 (26)	2.90 (2.49, 3.38)	2.47 (2.10, 2.91)
Other	6,533 (80)	1,611 (20)	4.64 (4.38, 4.92)	4.48 (4.22, 4.77)
1 month				
Respiratory	2,444 (89)	305 (11)	8.51 (7.52, 9.62)	8.67 (7.64, 9.83)
Influenza	40 (77)	12 (23)	3.33 (1.75, 6.35)	3.27 (1.71, 6.23)
Pneumonia	1,747 (89)	214 (11)	8.55 (7.40, 9.89)	8.85 (7.63, 10.28)

Urinary tract	410 (80)	103 (20)	4.07 (3.27, 5.07)	3.97 (3.16, 4.98)
Digestive tract	198 (81)	45 (19)	4.40 (3.18, 6.08)	4.69 (3.35, 6.55)
Skin	537 (79)	145 (21)	3.84 (3.19, 4.63)	4.01 (3.31, 4.86)
Blood/circulatory	179 (90)	21 (11)	8.52 (5.42, 13.4)	8.03 (5.08, 12.68)
Hospital-acquired	338 (79)	89 (21)	3.83 (3.03, 4.84)	3.68 (2.89, 4.70)
Other	3,985 (87)	578 (13)	7.63 (6.96, 8.36)	7.78 (7.08, 8.55)

*Adjusted for total number of non-IRHs and non-HR-related hospitalizations. IRH in the first 5 positions (our exposure of interest) and HF (our outcome of interest) are excluded from the total hospitalization count that is being adjusted for.

IRH are not mutually exclusive

Table 6. Odds ratios summarizing the association between infection-related hospitalization in the first five positions and incident heart failure among beneficiaries without any hospitalizations in the case or control periods. MarketScan, 2013-2019

	Infection-Related Hospitalization N(%)		**Odds Ratio (95% CI)**
Models	Case Period	Control Period	Crude
3 months	7,601 (6.2)	1,857 (1.5)	4.88 (4.62, 5.16)
1 month	5,680 (4.2)	833 (0.6)	7.69 (7.11, 8.30)

(3 months: N = 246,946, 1 month: N = 270,606)

*Analysis done among those without any hospitalizations in their case or control period.

Supplementary Tables

Supplementary Table 1: International Classification of Diseases (ICD) Codes Utilized for the Ascertainment of Heart Failure

Description	**ICD-9-CM Code**	**ICD-10-CM Code**
Heart failure	428.XX	I50
Congestive heart failure, unspecified	428.0	I50.814, I50.9
Left heart failure	428.1	I50.1
Systolic heart failure	428.2	
Systolic heart failure, unspecified	428.20	I50.20
Acute systolic heart failure	428.21	I50.21
Chronic systolic heart failure	428.22	I50.22
Acute on chronic systolic heat failure	428.23	I50.23
Diastolic heart failure	428.3	
Diastolic heart failure, unspecified	428.30	I50.30
Acute diastolic heart failure	428.31	I50.31
Chronic diastolic heart failure	428.32	50.32
Acute on chronic diastolic heart failure	428.33	I50.33
Combined systolic and diastolic heart failure	428.4	
Combined systolic and diastolic heart failure, unspecified	428.40	I50.40
Acute combined systolic and diastolic heart failure	428.41	I50.41
Chronic combined systolic and diastolic heart failure	428.42	I50.42

Acute on chronic combined systolic and diastolic heart failure	428.43	I50.43
Heart failure, unspecified	428.9	I50.810, I50.811, I50.812, I50.813, I50.82, I50.83, I50.84, I50.89, I50.9
Rheumatic heart failure (congestive)	398.91	I09.81
Malignant hypertensive heart disease with heart failure	402.01	I11.0
Benign hypertensive heart disease with heart failure	402.11	
Unspecified hypertensive heart disease with heart failure	402.91	
Malignant hypertensive heart and renal disease with heart failure	404.01	I13.0
Benign hypertensive heart and renal disease with heart failure	404.11	
Unspecified hypertensive heart and renal disease with heart failure	404.91	
Malignant hypertensive heart and renal disease with heart failure and renal failure	404.03	I13.2
Benign hypertensive heart and renal disease with heart failure and renal failure	404.13	

Unspecified hypertensive heart and renal disease with heart failure and renal failure	404.93	
ICD-9- [10]-CM = International Classification of Diseases, Ninth [Tenth] Revision, Clinical Modification		

Supplementary Table 2: International Classification of Diseases (ICD) Codes Utilized for the Ascertainment of Hospitalization with Infection.

Type	ICD-9-CM Code	ICD-10-CM Code
Respiratory Infection	460, 461, 462, 463, 464, 465, 466, 472, 473, 474.0, 475, 476.0, 476.1, 478.21, 478.22, 478.24, 478.29, 480, 481, 482, 483, 484, 485, 486, 487, 488, 490, 491.1, 494, 510, 511, 513.0, 518.6, 519.01	J00, J01, J02, J03, J04, J05, J06, J07, J08, J09, J11, J12, J13, J14, J15, J16, J17, J18, J20, J21, J31, J32, J36, J37, J35.1, J35.2, J35.3, J39.0, J39.1, J39.2, J40, J41.1, J47, J85.0, J85.1, J85.2, J86, J90, J91, J95.02, R09.1
Pneumonia	480, 481, 482, 483, 484, 485, 486	J12, J13, J14, J15, J16, J17, J18
Influenza	487, 488	J09, J11
Urinary Tract Infection	590, 595.0, 595.1, 595.2, 595.3, 595.4, 597, 598.0, 599.0	N10, N11, N12, N15.1, N15.9, N16, N28.84, N28.85, N28.86, N30.0, N30.1, N30.2, N30.3, N30.8, N34, N37, N39.0
Digestive Tract Infection	522.5, 522.7, 527.3, 528.3, 540, 541, 542, 566, 567, 569.5, 572.0, 572.1, 573.1, 573.2, 573.3, 575.0, 575.1	K04.0, K04.1, K04.4, K04.5, K04.6, K04.7, K11.3, K12.2, K35, K36, K37, K61, K63.0, K65, K67, K68.12, K68.19, K68.9, K71, K75.0, K75.1,

		K75.2, K75.3, K75.81, K75.89, K75.9, K77, K81
Skin Infection	680, 681, 682, 683, 684, 685, 686, 706.0	E82.2, K12.2, L01, L02, L03, L04, L05, L08, L70.2, L88, L98.0
Blood/Circulatory System Infection	390, 391, 392, 393, 421.0, 421.1, 422.0, 422.91, 422.92, 422.93, 790.7, 790.8	I00, I01, I02, I09.2, I33.0, I39, I40.0, I40.1, I40.8, I41, R78.81
Hospital-Acquired Infection	996.6, 997.62, 998.5, 999.3	K68.11, T80.211, T80.212, T80.218, T80.219, T80.22, T80.29, T81.4, T82.6, T82.7, T83.5, T83.6, T84.5, T84.6, T84.7, T85.7, T87.4, T88.0

Other Infections	001-139, 254.1, 320, 321, 322, 323, 324, 325, 326, 331.81, 372.0, 372.1, 372.2, 372.3, 373.0, 373.1, 373.2, 382.0, 382.1, 382.2, 382.3, 382.4, 383, 386.33, 386.35, 388.60, 601, 604, 607.1, 607.2, 608.0, 608.4, 611.0, 614, 615, 616.0, 616.1, 616.3, 616.4, 616.8, 670, 711, 730.0, 730.1, 730.2, 730.3, 730.8, 730.9	A01-A99, B01-B99, D86, E32.1, G00, G01, G02, G03, G04.00, G04.01, G04.02, G04.2, G04.30, G04.31, G04.32, G04.39, G04.81, G04.82, G04.83, G04.84, G04.85, G04.86, G04.87, G04.88, G04.89, G04.90, G04.91, G05, G06, G07, G08, G09, G92, G14, G93.7, H00, H01.0, H10, H32, H66.0, H66.1, H66.2, H66.3, H66.4, H67, H70, H83.0, H92.1, H95.0, H95.1, I32, K90.81, L44.4, L94.6, M60.009, M00, M01, M02.1, M35.2, M46.2, M46.3, N41, N45, N47.6, N48.1, N48.2, N49, N51, N61, N70, N71, N72, N73, N74, N75.1, N75.9, N76.0, N76.1, N76.2, N76.3, N76.4, N76.5, N76.81, N76.89, N77.1, O85, O86.12, O86.8,
ICD-9- [10]-CM = International Classification of Diseases, Ninth [Tenth] Revision, Clinical Modification		

Chapter 7. Manuscript 2: Infection-related hospitalization and incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study

Abstract

Introduction: Heart failure (HF) affects more than 37.7 million individuals globally and poor outcomes persist despite recent therapeutic advancements. Studies have shown that the inflammatory response to infections may become dysregulated (i.e., pathophysiologic), thereby promoting collateral myocardial damage that may result in HF. Limited data exist examining the relationship between infection-related hospitalization (IRH) and HF in large population-based settings; there are no data investigating whether infection is differentially associated with HF subtypes, HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF).

Methods: We studied 14,468 participants enrolled in the Atherosclerosis Risk in Communities Study who were HF free at visit 1(1987-1989). IRH was identified using select international classification of disease codes in the first five positions and was treated as a time-varying exposure. All IRH and HF events that occurred in the same hospital visit were excluded. The same exclusions were applied to our HF subtype analysis that began in 2005, when HF adjudication began. Covariates measured at visit 4 (1996-1998) were used and participants were HF free in 2005. We used multivariable-adjusted Cox proportional hazards models to assess the association between IRH and incident HF, HFrEF, and HFpEF.

Results: Among participants, 46% had an IRH, and 3,565 had incident HF (382 HFpEF, 360 HFrEF). Hazard ratio (HR) for incident HF events among participants who had an IRH compared to those who did not was 2.35 (95% CI: 2.19-2.52). This relationship was generally consistent across different types of infections (e.g., respiratory, influenza, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other infections). In addition, after multivariable adjustment, IRH was associated with both HFrEF and HFpEF: 1.77(1.35, 2.32) and 2.97(2.36, 3.75), respectively.

Conclusion: IRH was associated with both incident HF, HFrEF and HFpEF. IRH might represent a modifiable risk factor for inflammation-induced HF pathophysiology.

Introduction

An estimated >37 million individuals have heart failure (HF) globally,[64] and prognosis after HF diagnosis is poor, with a <50% survival rate at five years[8,193,194]. The total number of HF patients continues to rise due to the growing aging population. The prognosis among HF patients remains poor, and quality of life remains severely reduced. A recent American Heart Association (AHA) Presidential Advisory emphasized that the current pipeline for development of novel therapies is flat, necessitating innovative solutions to counteract increasing rates of cardiovascular death[195,196].

Left ventricular ejection fraction (LVEF) is generally viewed as a clinically useful phenotypic marker, commonly dichotomizing HF patients into HF with

reduced ejection fraction (HFrEF; LVEF<50%) or preserved ejection fraction (HFpEF; LVEF≥50%). Although HFrEF and HFpEF represent distinct clinical entities with respect to the etiologies and response to therapies, they share common pathophysiologic pathways[197,198]. Despite significant progress in pharmacologic armamentarium to treat HFrEF, most of these therapeutics have neutral effect against HFpEF. However, promising results from a recent double-blind trail of Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have shown effectiveness to reduce composite of HF admission and cardiovascular death, among those with HFpEF[199].

Inflammation plays a key role in the development of HFrEF and HFpEF[200-203]. Elevated concentrations of pro-inflammatory biomarkers are common in both HFpEF and HFrEF[140,204,205]. Identifying potential upstream triggers of the pro-inflammatory phenotype commonly characterizing HF could yield new prevention opportunities. One such trigger of pro-inflammatory phenotype could be infection-related hospitalizations. However, few studies have evaluated infections as a risk factor for incident HF and HF subtypes, and no study had explored this relationship in a large prospective cohort study with long-term follow up[166,206].

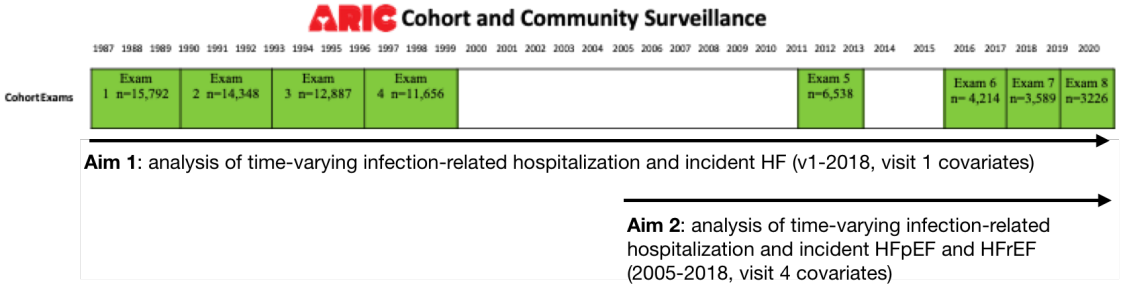
The aim of our study was to investigate the association between infection-related hospitalization and incident HF during 31-years of longitudinal follow-up in the Atherosclerosis Risk in Communities (ARIC) Study. We hypothesize that infection-related hospitalization will be associated with increased risk of incident HFrEF and HFpEF after accounting for a robust set of cardiometabolic risk factors.

Methods

Study population

The ARIC study is a prospective population-based study of cardiovascular disease incidence in adults aged 45-64 year who were recruited from 4 U.S. communities between 1987 and 1989 (visit 1)[156]. Participants have attended additional follow-up clinic visits and received phone calls (annually until 2012; twice yearly thereafter). The study protocol was approved by the institutional review boards (IRB) of all participating centers, and all participants provided written informed consent at each clinic visit. In addition, the study has had continual IRB oversight. For the present primary analyses, we used longitudinal data from the visit 1 baseline until the end of 2018. For our secondary analysis looking at HF subtypes, we used longitudinal data from 2005 until the end of 2018, using covariates measures at visit 4 (1996-1998) (**Figure 1**).

Figure 1: Analysis timelines.



Of the 15,792 participants who attended visit 1, we excluded those with missing covariables information, race other than Black or White, non-White participants in the Minneapolis and Washington County center, and those that

had prevalent HF. The same exclusions were applied to the HF subtype analysis, in which those with prevalent HF prior to 2005 were excluded (**Figure 2**).

Heart Failure Definitions

Prevalent HF at baseline was defined as: *1)* an affirmative response to "Were any of the medications you took during the last 2 weeks for heart failure?" or *2)* stage 3 or "manifest heart failure" by Gothenburg criteria[207,208]. All current medications (taken within the last 2 weeks) were brought into the clinic and documented. Incident HF events through December 31, 2018, were identified through 1) annual telephone calls to ARIC cohort participants to identify all hospitalizations, 2) review of local hospital discharge indexes, and 3) retrieval of death certificates. HF incidence was defined as the first occurrence of either a hospitalization that included an *International Classification of Diseases, 9th Revision* (*ICD-9*) discharge code of 428 (428.0–428.9) among the primary or secondary diagnoses or else a death certificate with an *ICD-9* code of 428 or an *International Classification of Diseases, 10th Revision* (*ICD-10*) code of I50 among any of the listed diagnoses or underlying causes of death[74].

Starting in 2005, ARIC implemented an adjudication committee of HF hospitalizations based on chart abstraction as previously described[157]. Briefly, hospitalizations or deaths with potentially HF-related ICD codes were identified, and hospitalization records were abstracted and adjudicated by the ARIC HF Committee. Abstraction included results of imaging studies and LVEF when available. Participants with quantifiable LVEF were categorized as HFpEF (LVEF

≥ 50%) or HFrEF (LVEF< 50%). If adjudication of the HF type was not possible, participants were defined as having “unknown” HF in all analyses.

Infection-Related Hospitalization Definitions

In ARIC, all hospitalization events were identified through phone calls, surveillance of local hospitals, and death interviews with proxies. The primary exposure variable is defined as the first occurrence of infection-related hospitalization, identified by selected ICD-9 or 10 codes (**Supplemental Table 1**) in the first five diagnostic positions, as previously done in ARIC[13]. For the primary analysis, infection-related hospitalization was treated as a time-varying exposure, with participants considered unexposed until their first infection-related hospitalization, after which they were considered exposed. A depiction of our study design with examples of the four different possible exposure-disease combinations are represented in **Figure 3**. A secondary analysis considered specific types of infection-related hospitalization (e.g., respiratory, influenza, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other infections).

Risk Factors

Covariates were measured at baseline (visit 1) via questionnaires, clinical exam, and laboratory analysis of blood samples. These measures included age, sex, race (Black or White and included as a proxy for social, not biological, risk factors[209]), and education level (less than a high school degree, high school,

general education diploma (GED), or vocational school and college, graduate, or professional school). Participants brought bottles for medications and supplements taken in the prior 2 weeks to the clinic visit; medication names were recorded. In addition, physical activity was assessed at visit 1 via a modified Baecke questionnaire. A physical activity index score (1: lowest activity and 5: highest activity) was calculated based on intensity and time dedicated to sport and exercise. Smoking status (never, former, or current), and access to healthcare variables were collected, including insurance status (private insurance, Medicare/Medicaid only, none).

During the visit 1 clinical examination, fasting blood was collected for the assessment of lipid profile (total cholesterol, high density lipoprotein (HDL) and low-density lipoprotein (LDL)). Diabetes mellitus was defined as a self-reported physician diagnosis of diabetes, fasting glucose ≥126 mg/dL, ≥200 mg/dL if non-fasting, or reported pharmacological treatment for diabetes. In addition, body mass index (BMI) was collected and defined as measured weight in kilograms divided by height in meters squared. Blood pressure was measured three times after a five-minute rest. The average of the last two blood pressure measurements was used for analysis. Use of anti-hypertensive medication was assessed by medications that participants brought to the clinic. Baseline prevalence of chronic kidney disease (CKD) was identified by estimated glomerular filtration rate (eGFR), atrial fibrillation (AF) was identified by past electrocardiograms (ECGs), while coronary artery disease (CAD) and stroke were defined via self-report.

Statistical Analysis

Baseline characteristics by exposure status were described using mean ± standard deviation (SD) for continuous variables and count (%) for categorical variables. Cox proportional hazards models were used to assess the relationship between infection-related hospitalization and incident HF. For our primary analysis, infection-related hospitalization was treated as time-varying and defined using pre-specified ICD-9 or 10 codes (**Supplemental Table 1**) in the first five positions of discharge diagnosis. Follow-up time began at visit 1 (1987-1989) and accrued until date of HF diagnosis, loss to follow-up, death, or December 31, 2018, whichever occurred first. Hazard ratios (HR) and 95% confidence intervals (CI) were reported. Multivariable models adjusted for the following variables: *Model 1:* age, sex, race/center education, health insurance; *Model 2***:** model 1 + physical activity, smoking status, BMI; *Model 3*: model 2 + diabetes, systolic blood pressure (SBP), antihypertensive medication use, LDL cholesterol, and prevalent CAD. Our secondary analyses explored specific infections (respiratory, influenza, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other infections).

We replicated these analyses with incident HFrEF and HFpEF as outcomes. Follow-up time started in 2005 for these analyses, when HF adjudication began, to the occurrence of incident HFrEF or HFpEF, loss to follow-up, death, or December 31, 2018, whichever occurred first. Participants who developed HF or were censored before 2005 were excluded from this analysis.

A sensitivity analysis defining IRH as a primary diagnosis (ICD diagnostic position 1) was conducted to examine the effects of a more rigorous exposure definition. To minimize potential confounding, we performed 1:1 matching using the greedy method[210]. Participants were 1:1 matched on baseline age, sex, race/center, and diabetes status. In our matching method, an infected participant (index) is matched at the time of infection to an uninfected participant. The uninfected matched participant's person-time begins on the same date as the index infection and contributes uninfected person-time until incident HF, death, or December 31, 2018, or until they become infected; if they become infected, they then start contributing infected person-time until censoring as described above. Thus, they contribute both infected and uninfected person-years to the analysis (emulating an as-treated approach) (**Figure 4**). A multivariable Cox regression was carried out with the following models: model 1: crude (matched sample); model 2: model 1 + adjusted for covariates measured in 1987-89: education, insurance, BMI, smoking status, LDL cholesterol, physical activity, hypertension medication, prevalent CAD, and SBP. Other matched analyses performed along with their results can be found in the supplemental (**Supplement Table 2**).

Results

Among 14,468 participants, median follow-up time was 27 years, 55% were women, 26% were Black, and the mean age at baseline was 54±6 years (range: 44-66 years). Overall, 6,673 participants (46%) had at least one IRH throughout the entire study duration, not limited to those who had an infection

after an HF event. Baseline characteristics of patients stratified by the IRH status at the end of follow-up are presented in **Table 1.** When compared to patients with no IRH, patients with at least one IRH had higher mean BMI, SBP, total cholesterol, and greater prevalence of DM.

Infection-Related Hospitalization and Incident Heart Failure

Between visit 1 (1987-1989) and 2018, 3,565 (25%) had incident HF, with an incidence rate of 107.6 events per 10,000 person-years. Infection-related hospitalization was associated with any incident HF after multivariable adjustment (**Table 2**). Results from the Cox model indicate that the rate of HF among those with an infection-related hospitalization was 2.35 (95% CI: 2.19-2.52) compared to those who did not have an infection-related hospitalization in the fully adjusted model (model 3). This relationship was generally consistent across different types of infections (**Table 2**).

In our HF subtype analysis beginning in 2005, we had 7,669 participants with a median follow-up time was 13 years. The cumulative incidence of the HF subtypes between 2005 and 2018 was 4.7% (HFrEF, 360/7,669) and 5.0% (HFpEF, 382/7,669), respectively. The incidence rate of HFrEF and HFpEF were 42.2 per 10,000 person-years and 44.8 per 10,000-person years, respectively. After multivariable adjustment, IRH was associated with both HFrEF and HFpEF [HR (95% CI)]: 1.77 (1.35, 2.32) and 2.97 (2.36, 3.75), respectively (**Table 3**).

Sensitivity Analyses

Results remained statically significant, though slightly attenuated when restricting our exposure definition, infection-related hospitalization, to ICD-9/10 codes in the first position of diagnosis discharge compared to anywhere in the first five positions (**Table 4**). This relationship persisted across different infection types (respiratory, influenza, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other infections) (**Table 4**). In the fully adjusted model, model 3, blood/circulatory and respiratory infections had the strongest associations with HF, [HR (95% CI)]: 2.57 (1.62, 4.09) and 2.25 (2.05, 2.48), respectively. In contrast, digestive tract infections were only marginally associated with HF 1.25 (1.01, 1.54). Results for the matched analysis were slightly attenuated compared to our main results, with a HR of 1.62 (95% CI: 1.45, 1.82) in the fully adjusted model, model 3 (**Table 5**).

Discussion

We found infection-related hospitalization to be associated with incident HF during a maximum of 31 years of follow-up. Findings were consistent when considering both HFrEF and HFpEF, with results being empirically stronger for incident HFpEF. The observed associations remained consistent after extensive adjustment for sociodemographic, behavioral, and HF risk biomarkers along with other comorbidities.

Few studies have evaluated infection as a risk factor for new onset HF[166,206], though some prior studies have assessed infection and incident

cardiovascular events[114,165,211,212]. A previous report from ARIC observed that in- and outpatient infections increased the risk of CAD and ischemic stroke[114,116]. Studies investigating HF outcomes following infection are less common, and most have focused specifically on pneumonia. Eurich et al. evaluated the risk of HF after community-acquired pneumonia during 10 years of follow-up[167] and reported that community-acquired pneumonia increased the risk of HF. Similarly, three additional studies have reported elevated incidence of HF within 30-days of community-acquired pneumonia, with reported rates ranging from 1.4% in outpatient populations[33] to as high as 24% among inpatients[166,213]. In ARIC, pneumonia was included within the respiratory infection category and therefore not assessed as a separate outcome. In addition, studies have found COVID-19 hospitalization to be associated with increased risk of incident HF[182,214]. After adjustments, COVID-19 hospitalization was associated with a 45% higher hazard of incident HF[214].

To our knowledge, there are no data investigating whether different types of infections are associated with HFrEF versus HFpEF. Only HIV, a chronic infection, has been found to be associated with an increased risk of HFpEF, borderline HFpEF, and HFrEF compared with individuals not infected with HIV[215]. Another study looking at inflammatory biomarkers found interleukin 6 (IL-6) and c-reactive protein (CRP) to be associated with incident HFpEF but not HFrEF or HF midrange (HFmrEF)[205]. Thus, our study is the first large longitudinal cohort study to assess various types of acute infections in relation to HFrEF and HFpEF.

Our findings that infection-related hospitalizations are associated with incident HF have a plausible biological rationale. A normal inflammatory response prompted by an infection is characterized by the temporally restricted upregulation of inflammatory activity that occurs when an infection is present, which then resolves once the threat has passed[216,217]. However, biological, psychological, environmental and social factors may delay or prevent resolution of this acute phase and result in chronic inflammation and immune activation[218]. Shifts in the inflammatory response from short- to long-lived can cause a breakdown of immune tolerance[183,216], leading to major alterations in end-organ structure and function[183,216,219-222]. Notable examples of low-grade asymptomatic inflammation causing end organ damage include obesity[223] and aging, as evidenced by an increase in circulating levels of tumor necrosis factor alpha (TNF-α) and IL-6[224].

Inflammation can contribute to the pathogenesis and progression of HF. Inflammatory cytokines, such as IL-6 and TNF-α, exert direct effects on myocardial and vascular cells that predispose individuals to HF[225,226]. TNF-α promotes cardiac apoptosis, hypertrophy, and fibrosis, and also alters calcium handling in the myocytes leading to a direct negative inotropic (systolic)[227] and lusinotropic (diastolic) effect[226]. IL-6 promotes myocyte hypertrophy and increases myocardial stiffness by reducing the phosphorylation of titin[228-231]. Interleukin-6 and TNF-α are elevated in HFrEF and HFpEF patients, although a stronger association may exist in the context of HFpEF. This was demonstrated in two recent analyses of biomarker profiles from the Counseling in Heart Failure

(COACH) and Biology Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) trials, which found a stronger relationship between biomarkers of inflammation and HFpEF compared to HFrEF[232,233]. The increased burden of pro-inflammatory comorbidities in HFpEF, such as diabetes, hypertension, COPD, obesity, and CKD, may account for these findings[234].

Infection and HF also have shared risk factors, such as diabetes[235-237], stroke[238,239] and older age[240,241]. One of the most frequent causes of HF is ischemic heart disease (IHD), which leads to the loss of myocardial tissue and contractile force[242]. Patients with IHD who develop HF have a clinical history of myocardial infarction with atherosclerotic disease of epicardial arteries[243,244]. Similarly, acute infections are known to be associated with an increased risk of myocardial infarction (MI); in particular, respiratory tract infections, including pneumonia, bronchitis, and influenza, in addition to digestive and urinary tract infections[245]. Our results suggest that IRH may contribute and ultimately lead to HF. Future studies are necessary to validate causal association between infections and HF development.

Strengths and Limitations

Some important limitations to this study should be noted. We used covariates that were measured once at baseline (visit 1 for our analysis examining any HF and visit 4 for our analysis examining HF subtypes) to estimate remote associations for the outcomes that occurred over the next 31 years. Differential loss to follow-up related to risk for infection (or incident HF)

could have contributed to selection bias. For example, very sick participants could die prior to developing HF (or clinically apparent HF) since HF can progress slowly. There is also some potential for reverse causality. It is possible that asymptomatic or undiagnosed HF was present at baseline and could have contributed to future infection-related hospitalization, giving the spurious appearance of increased HF incidence among people with infection-related hospitalization.

In addition, the use of ICD codes can lead to misclassification, though a prior validation of heart failure hospitalizations indicated that the positive predictive value of 428.x was 93% for acute decompensated heart failure and 97% for chronic heart failure[246]. ARIC implemented a rigorous approach to adjudicate HFrEF and HFpEF, and prior studies also used the first five ICD positions when assessing infection in ARIC[13]. Our analysis did not consider less severe acute or chronic outpatient infections (i.e., those infections that did not require inpatient hospitalization), which are also hypothesized to be a risk factor for incident HF. For example, our prior work reported a relationship between periodontal infections and incident HFpEF and HFrEF[168]. The lack of information on complete infectious history is likely to be non-differential and would bias results toward the null in expectation.

There were also many strengths to this study, including the study population composed of a large, multi-racial, community-based cohort of participants followed for up to 31 years (from 1987-1989 to 2018). In addition, the rigorous approach used to adjudicate HFrEF and HFpEF in ARIC enabled

focused analyses for HF subtypes in the same study, which has not been previously performed. Our exposure assessment was time-varying, allowing for risk to begin accruing immediately following IRH as opposed to using a participant self-report of historical IRH without knowledge of IRH timing. We were further able to assess specific categories of infections in relation to our outcome as opposed to any (i.e., uncategorized) infection.

Conclusion

We have observed infection-related hospitalization to be associated with incident HF among a diverse, community-based sample of adults. Findings were notably stronger among those with HFpEF, for which treatment options are limited. Our findings support prior literature linking infection to HF risk as well as the need for more research exploring the potential for infection-prevention strategies, such as vaccination, to minimize HF burden. Moreover, history of infection could potentially become an important tool for risk assessment and patient management. If future studies were to provide evidence of causal association, there could be significant population-level implications given the high prevalence of infections and the burden of HF on our aging society.

Tables/ Figures:

Figure 2: Study Population

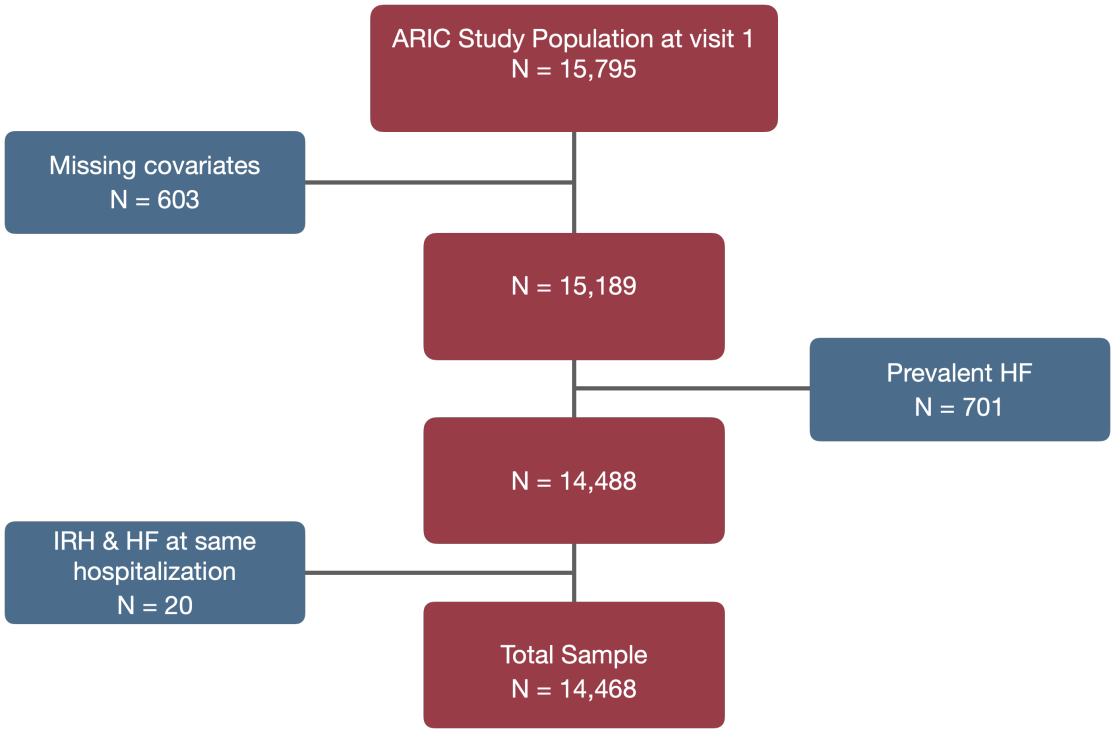


Figure 3: Study design with examples of the four different possible exposure-disease combinations.

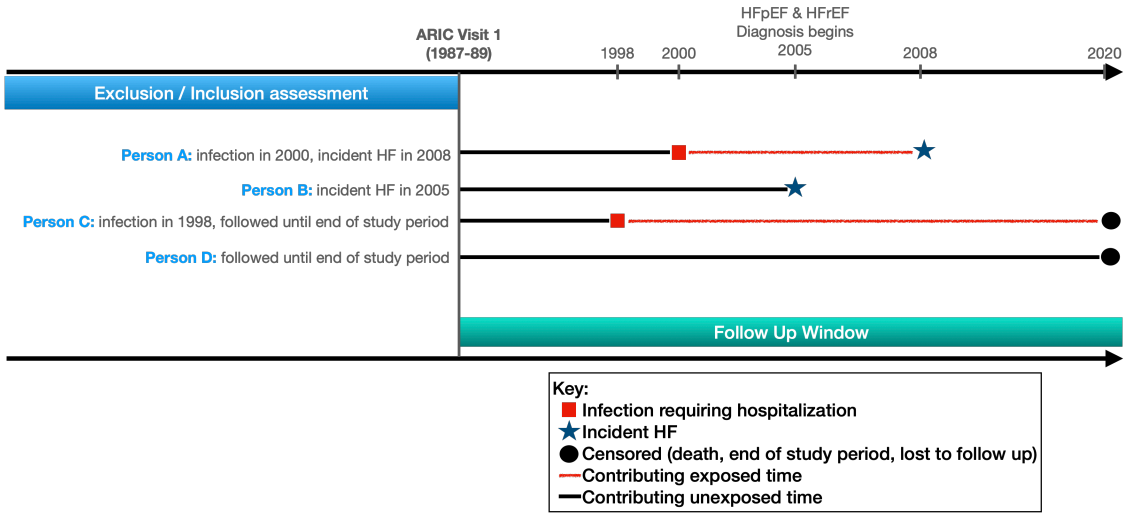


Figure 4: Diagram depicting an example of how person-time in accrued according to infection status in the matched analysis.
Infected participant (index) is matched at the time of their infection to an uninfected participant with person-time beginning at the same time for both participants in the matched pair. If the uninfected matched comparator becomes infected, they begin contributing infected person-time. Thus, they contribute both infected and uninfected person-time to the analysis.

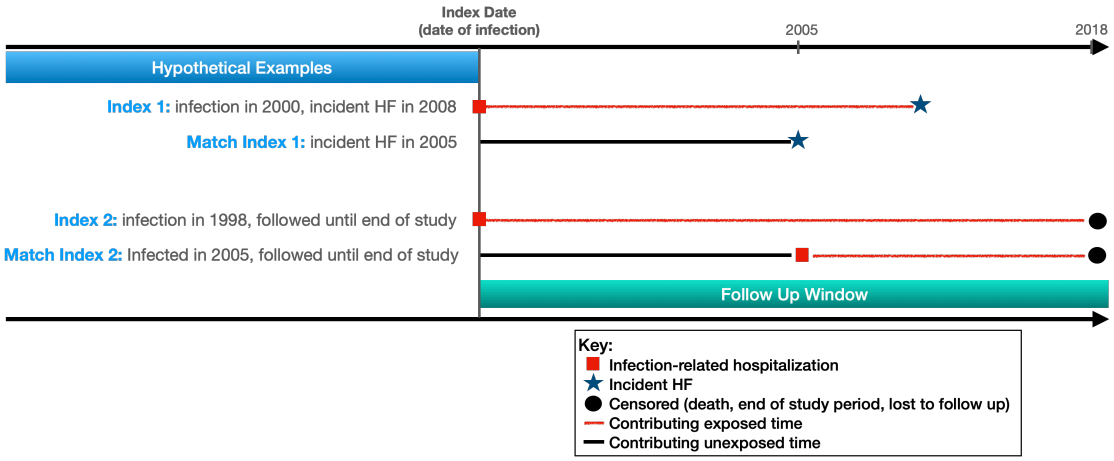


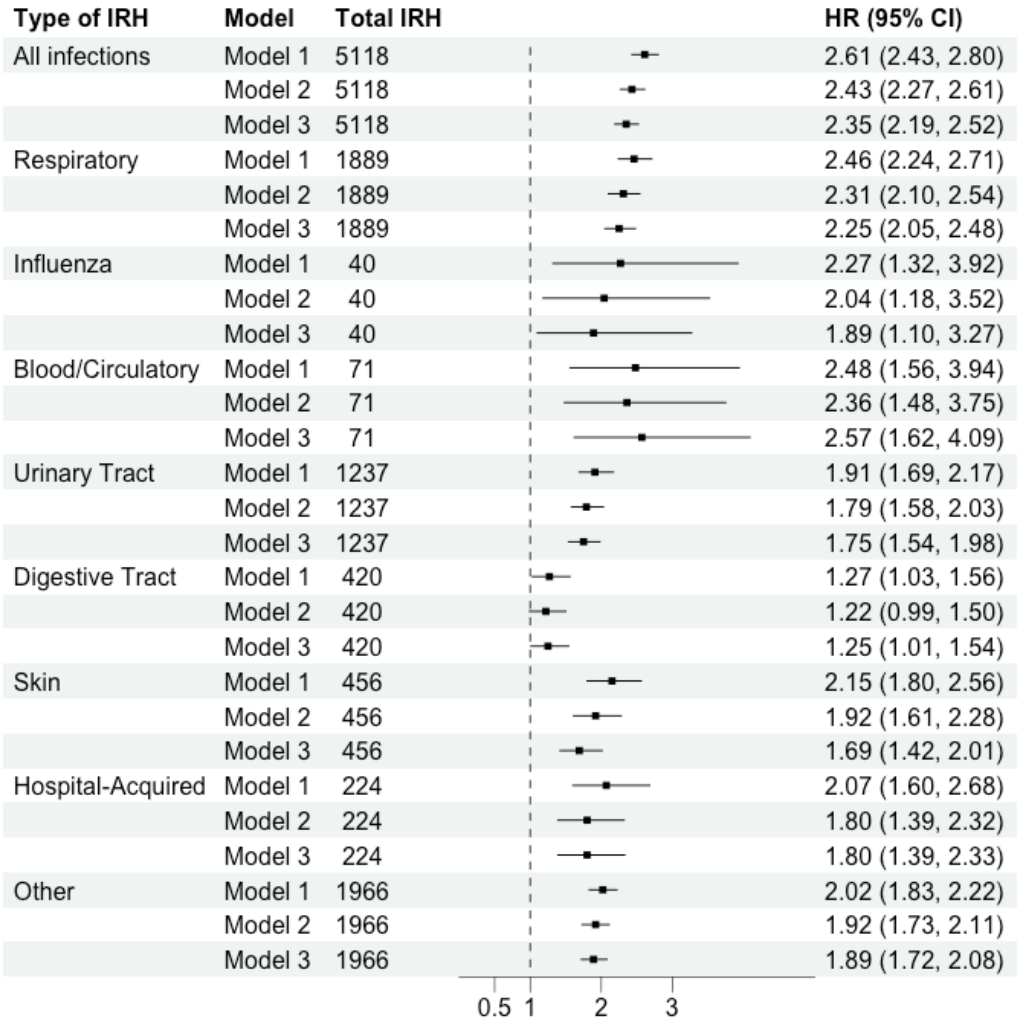
Table 1. Baseline participant characteristics by infection-related hospitalization status, Mean±SD or %(N) among N = 14,468 ARIC participants, 1987-89		
	No Infection-Related Hospitalization (N= 7,795)	Infection-Related Hospitalization (N= 6,673)
Demographics		
Age	53.4±5.7	54.9±5.8
Male	45.7% (3562)	45.3% (3021)
Race/Center		
White Minneapolis	28.4% (2217)	22.9% (1528)
White Washington	23.6% (1840)	27.8% (1855)
White Forsyth	22.0% (1714)	24.1% (1606)
Black Forsyth	2.7% (208)	3.2% (215)
Black Mississippi	23.3% (1816)	22.0% (1469)
Education		
Basic	19.6% (1531)	26.5% (1769)
Intermediate	41.1% (3203)	41.2% (2747)
Advanced	39.3% (3061)	32.3% (2157)
Insurance status (Yes)	91.1% (7104)	89.9% (6002)
Behavioral Characteristics		
Physical Activity	2.5±0.81	2.4±0.78
Smoking status		
Never	44.6% (3480)	38.7% (2581)
Former	32.2% (2511)	32.2% (2149)
Current	23.1% (1804)	29.1% (1943)
Clinical Characteristics		

Body mass index, kg/m^2	27.1±5.0	28.0±5.5
Systolic blood pressure, mmHg	119.9±18.5	122.0±18.9
Diastolic blood pressure, mmHg	73.5±11.1	73.6±11.4
Using blood pressure medication	24.1% (1878)	30.2% (2013)
Total cholesterol, mg/dL	213.8±40.6	215.3±42.1
HDL cholesterol, mg/dL	52.9±17.1	51.0±16.8
LDL cholesterol, mg/dL	136.9±38.7	138.6±39.8
Prevalent diabetes	8.3% (647)	13.0% (865)
Prevalent CHD	3.6% (283)	4.5% (298)
Prevalent AF	0.1% (7)	0.2% (15)
Prevalent stroke	1.4% (111)	1.6% (106)

Means±SD for continuous variables and N (%) for categorical variables.
Coronary heart disease (CHD), atrial fibrillation (AF)

Figure 5. Forest plot of the association between infection-related hospitalization and incident heart failure.

Multivariable adjusted hazard ratios (95% confidence interval) for the association between infection-related hospitalization in the first five positions and incident heart failure among N=14,468 ARIC participants 1987-2018.



Total of 3,565 incident HF events

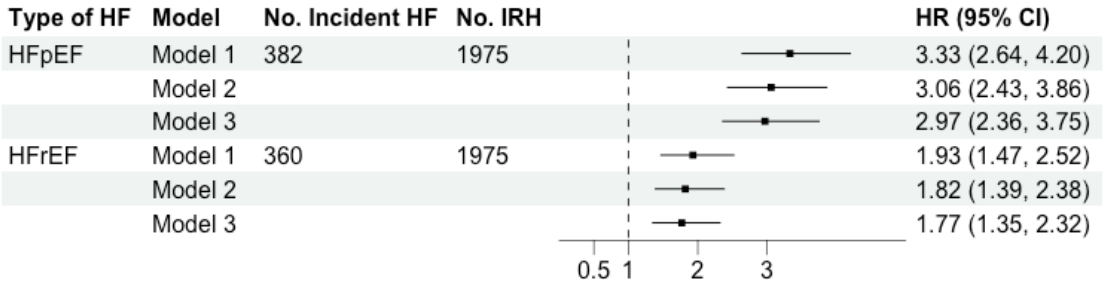
Model 1: adjusted for covariates measured in 1987-89: age, sex, race/center education, health insurance

Model 2: model 1 + physical activity, smoking status, BMI

Model 3: model 2 + diabetes, systolic blood pressure, antihypertensive medication use, LDL cholesterol, prevalent CHD.

Figure 6. Forest plot of the association between infection-related hospitalization and HF subtypes.

Multivariable adjusted hazard ratios (95% confidence interval) for the association between all infection-related hospitalizations in the first five positions and incident HFrEF and HFpEF among N=7,669 ARIC participants 1996-2018



Total of 1,975 infections

Model 1: adjusted for covariates measured in 1996-98: age, sex, race/center education, health insurance

Model 2: model 1 + physical activity, smoking status, BMI

Model 3: model 2 + diabetes, systolic blood pressure, antihypertensive medication use, LDL cholesterol, prevalent CHD

Table 2. Multivariable adjusted hazard ratios (95% confidence interval) of the association between infection related hospitalization in the first position and incident heart failure among N=14,468 ARIC participants 1987-2018

	No. Infections	HR (95%CI)	p-value
All Infections			
Model 1	3,092	2.52 (2.33, 2.74)	<.0001
Model 2	3,092	2.34 (2.16, 2.54)	<.0001
Model 3	3,092	2.28 (2.10, 2.47)	<.0001
Influenza			
Model 1	35	2.40 (1.33, 4.34)	0.004
Model 2	35	1.90 (1.05, 3.44)	0.03
Model 3	35	1.82 (1.01, 3.30)	0.05
Respiratory Infections			
Model 1	1,096	2.62 (2.34, 2.94)	<.0001
Model 2	1,096	2.44 (2.17, 2.74)	<.0001
Model 3	1,096	2.40 (2.14, 2.69)	<.0001
Blood/Circulatory System Infection			
Model 1	26	4.73 (2.36, 9.46)	<.0001
Model 2	26	4.80 (2.40, 9.61)	<.0001
Model 3	26	3.83 (1.91, 7.68)	0.0002
Urinary Tract Infection			
Model 1	333	1.45 (1.13, 1.87)	0.003
Model 2	333	1.42 (1.10, 1.82)	0.01
Model 3	333	1.34 (1.04, 1.72)	0.02
Digestive Tract Infection			
Model 1	269	1.16 (0.89, 1.50)	0.27

Model 2	269	1.12 (0.87, 1.45)	0.39
Model 3	269	1.11 (0.85, 1.43)	0.45
Skin Infection			
Model 1	271	2.52 (2.04, 3.11)	<.0001
Model 2	271	2.22 (1.80, 2.75)	<.0001
Model 3	271	2.04 (1.65, 2.52)	<.0001
Hospital-Acquired Infection			
Model 1	193	2.63 (2.03, 3.42)	<.0001
Model 2	193	2.28 (1.75, 2.96)	<.0001
Model 3	193	2.14 (1.65, 2.78)	<.0001
Other Infections			
Model 1	905	2.34 (2.02, 2.70)	<.0001
Model 2	905	2.21 (1.91, 2.56)	<.0001
Model 3	905	2.26 (1.95, 2.61)	<.0001

Total of 3,560 incident HF events

Model 1: adjusted for covariates measured in 1987-89: age, sex, race/center education, health insurance

Model 2: model 1 + physical activity, smoking status, BMI

Model 3: model 2 + diabetes, systolic blood pressure, antihypertensive medication use, LDL cholesterol, prevalent CHD

Table 3. Matched analyses with multivariable adjusted hazard ratios (95% confidence interval) of the association between infection related hospitalization in the first five positions and incident heart failure among ARIC participants 1987-2018

	Matched uninfected that get infected	**No. Infections**	**No. HF**	**HR (95%CI)**	**p-value**
Matched Analysis: emulating an as treated approach					
Model 1	1,481	4,735	1,556	1.68 (1.50, 1.88)	<.0001
Model 2	1,481	4,735	1,556	1.62 (1.45, 1.82)	<.0001

Total sample n=6,508

Model 1: Unadjusted (but matched for age, sex, race/center, and diabetes status at baseline)

Model 2: model 1+ adjusted for covariates measured in 1987-89: education, insurance, BMI, smoking status, LDL cholesterol, physical activity, hypertension medication, prevalent CHD, and SBP

Supplemental Tables/ Figures:

Supplemental Table 1: International Classification of Diseases (ICD) Codes Utilized for the Ascertainment of Hospitalization with Infection.

Type	ICD 9 Codes	ICD 10 Codes
Respiratory Infection	460, 461, 462, 463, 464, 465, 466, 472, 473, 474.0, 475, 476.0, 476.1, 478.21, 478.22, 478.24, 478.29, 480, 481, 482, 483, 484, 485, 486, 487, 488, 490, 491.1, 494, 510, 511, 513.0, 518.6, 519.01	J00, J01, J02, J03, J04, J05, J06, J07, J08, J09, J11, J12, J13, J14, J15, J16, J17, J18, J20, J21, J31, J32, J36, J37, J35.1, J35.2, J35.3, J39.0, J39.1, J39.2, J40, J41.1, J47, J85.0, J85.1, J85.2, J86, J90, J91, J95.02, R09.1
Influenza	487, 488	J09, J11
Urinary Tract Infection	590, 595.0, 595.1, 595.2, 595.3, 595.4, 597, 598.0, 599.0	N10, N11, N12, N15.1, N15.9, N16, N28.84, N28.85, N28.86, N30.0, N30.1, N30.2, N30.3, N30.8, N34, N37, N39.0
Digestive Tract Infection	522.5, 522.7, 527.3, 528.3, 540, 541, 542, 566, 567, 569.5, 572.0, 572.1, 573.1, 573.2, 573.3, 575.0, 575.1	K04.0, K04.1, K04.4, K04.5, K04.6, K04.7, K11.3, K12.2, K35, K36, K37, K61, K63.0, K65, K67, K68.12, K68.19, K68.9, K71, K75.0, K75.1, K75.2, K75.3, K75.81, K75.89, K75.9, K77, K81

Skin Infection	680, 681, 682, 683, 684, 685, 686, 706.0	E82.2, K12.2, L01, L02, L03, L04, L05, L08, L70.2, L88, L98.0
Blood/Circulatory System Infection	390, 391, 392, 393, 421.0, 421.1, 422.0, 422.91, 422.92, 422.93, 790.7, 790.8	I00, I01, I02, I09.2, I33.0, I39, I40.0, I40.1, I40.8, I41, R78.81
Hospital-Acquired Infection	996.6, 997.62, 998.5, 999.3	K68.11, T80.211, T80.212, T80.218, T80.219, T80.22, T80.29, T81.4, T82.6, T82.7, T83.5, T83.6, T84.5, T84.6, T84.7, T85.7, T87.4, T88.0
Other Infections	001-139, 254.1, 320, 321, 322, 323, 324, 325, 326, 331.81, 372.0, 372.1, 372.2, 372.3, 373.0, 373.1, 373.2, 382.0, 382.1, 382.2, 382.3, 382.4, 383, 386.33, 386.35, 388.60, 601, 604, 607.1, 607.2, 608.0, 608.4, 611.0, 614, 615, 616.0, 616.1, 616.3, 616.4, 616.8, 670, 711, 730.0, 730.1, 730.2, 730.3, 730.8, 730.9	A01-A99, B01-B99, D86, E32.1, G00, G01, G02, G03, G04.00, G04.01, G04.02, G04.2, G04.30, G04.31, G04.32, G04.39, G04.81, G04.82, G04.83, G04.84, G04.85, G04.86, G04.87, G04.88, G04.89, G04.90, G04.91, G05, G06, G07, G08, G09, G92, G14, G93.7, H00, H01.0, H10, H32, H66.0, H66.1, H66.2, H66.3, H66.4, H67, H70, H83.0, H92.1, H95.0, H95.1, I32, K90.81, L44.4, L94.6, M60.009, M00,

		M01, M02.1, M35.2, M46.2, M46.3, N41, N45, N47.6, N48.1, N48.2, N49, N51, N61, N70, N71, N72, N73, N74, N75.1, N75.9, N76.0, N76.1, N76.2, N76.3, N76.4, N76.5, N76.81, N76.89, N77.1, O85, O86.12, O86.8,

Supplemental Matched Analyses:

Additional sensitivity analyses were performed to better understand the potential influence of confounding on our findings. In order to better control for potential measured and unmeasured confounding, we performed 1:1 matching at the time of infection using a greedy method[210]. Participants were 1:1 matched on baseline age, sex, race/center, and diabetes status.

Five matching scenarios were considered: In our first matching scenario, an infected participant (index) is matched at the time of their infection to an uninfected participant at that point in time. The uninfected matched participant is analyzed as uninfected until censored even if they subsequently become infected (emulating an intent-to-treat approach).

In our second matching scenario, an infected participant (index) is matched at the time of their infection to an uninfected participant at that point in time. If the uninfected matched comparator becomes infected, they continue to be treated as uninfected and are only censored if loss to follow-up, death, HF, or end of study. They are however re-matched to a new uninfected participant at the time of their infection. Thus, they contribute multiple observations (emulating aspects of both an intention to treat approach and an as treated approach).

In our third matching scenario, an infected participant (index) is matched at the time of their infection to an uninfected participant at that point in time. If the uninfected matched comparator becomes infected, they then start contributing infected person time and are re-matched at the time of their infection to a new

uninfected participant. Thus, they contribute both infected and uninfected person-years to the analysis (emulating an as-treated approach).

In our fourth matching scenario, an infected participant (index) is matched at the time of their infection to an uninfected participant at that point in time. If the uninfected matched comparator becomes infected, they then start contributing infected person time Thus, they contribute both infected and uninfected person-years to the analysis (emulating an as-treated approach).

Lastly, in our fifth matching scenario, only those who had an infection throughout the duration of the study period could be matched with only those who did not get infected throughout the duration of the study period. Those who had an infection were matched at the time of their infection with a participant who never had an infection (emulating an observational approach where we know future exposure).

Hazard ratios (HR) and 95% confidence intervals (CI) were reported for each matching scenario. A multivariable cox regression was carried out with the following models: model 1: crude (matched sample); model 2: model 1 + adjusted for covariates measured in 1987-89: education, insurance, BMI, smoking status, LDL cholesterol, physical activity, hypertension medication, prevalent CHD, and SBP.

Results for the matched analysis were similar to the main analysis. As expected, scenario 5 had the strongest HR (2.43 (2.10, 2.80)) while scenarios 3 and 4, which mimic an as treated approach have slightly lower HRs (1.66 (1.50, 1.84), 1.62 (1.45, 1.82)) respectively, with scenario 1 and 2, which mimic an

intention to treat approach having the weakest HRs [1.30 (1.18, 1.44) and 1.29 (1.21, 1.38)], respectively (**Supplemental Table 2**).

Supplemental Table 2. Matched analyses with multivariable adjusted hazard ratios (95% confidence interval) of the association between infection-related hospitalization in the first five positions and incident heart failure among ARIC participants 1987-2018

	Total	No. matched uninfected that get infected	No. Infections	No. HF	HR (95%CI)	p-value
Scenario 1						
Model 1:	6,508	1,481	4,735	1,556	1.29 (1.17, 1.42)	<.0001
Model 2:	6,508	1,481	4,735	1,556	1.30 (1.18, 1.44)	<.0001
Scenario 2*						
Model 1:	9,676	2,166	7,004	2,284	1.30 (1.22, 1.39)	<.0001
Model 2:	9,676	2,166	7,004	2,284	1.29 (1.21, 1.38)	<.0001
Scenario 3*						
Model 1:	9,676	1,710	6,548	2,284	1.72 (1.56, 1.91)	<.0001
Model 2:	9,676	1,710	6,548	2,284	1.66 (1.50, 1.84)	<.0001
Scenario 4						
Model 1:	6,508	1,481	4,735	1,556	1.68 (1.50, 1.88)	<.0001
Model 2:	6,508	1,481	4,735	1,556	1.62 (1.45, 1.82)	<.0001
Scenario 5						
Model 1:	5,074	2,537	2,537	892	2.58 (2.24, 2.98)	<.0001

Model 2:	5,074	2,537	2,537	892	2.43 (2.10, 2.80)	<.0001

*Analytical samples with repeated measures (scenarios 2&3) use sandwich variance estimates.
Model 1: Unadjusted (but matched)
Model 2: model 1+ adjusted for covariates measured in 1987-89: education, insurance, BMI, smoking status, LDL cholesterol, physical activity, hypertension medication, prevalent CHD, and SBP

Chapter 8. Manuscript 3: Infection-related hospitalization and mortality among heart failure patients: the Atherosclerosis Risk in Communities (ARIC) study

Abstract

Introduction: Five-year survival rate among heart failure (HF) patients, following an initial HF hospital admission, is less then 50%. Infection is a common cause of hospitalization in HF patients and may be associated with poor prognosis and high mortality. We hypothesize that infection-related hospitalization (IRH) is associated with increased mortality among those with HF, HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF).

Methods: We studied 1,998 participants of the Atherosclerosis Risk in Communities Study who had an incident HF event after 2005. Infection-related hospitalization was identified using select ICD-9 and -10 codes in the first five positions. IRH was treated as a time-varying exposure and the co-occurrence of IRH and HF in the same hospital visit were excluded. We used multivariable-adjusted Cox proportional hazards models to assess the association between IRH and mortality among incident HF, HFrEF, and HFpEF patients.

Results: Of the 1,998 participants with HF, 606 had HFpEF, 543 had HFrEF, and 849 had HF with unknown type. During an average follow-up of 3.29 years, 48% had an infection-related hospitalization and 69% died. Among those with an IRH (N=678), the average number of years(range) from IRH to death was 2.3(0.003-14.2) while those without an IRH (N = 706), average number of years(range) to

death was 1.7(0-12.3). After multivariable adjustment, infection-related hospitalization was associated with mortality among those with any HF, HFpEF, HFrEF, and HFunknown with hazard rations (HR) and 95% confidence intervals (CI) of 1.99 (1.77, 2.23), 2.08 (1.69, 2.56), 1.96 (1.57, 2.45), and 1.98 (1.65, 2.39), respectively.

Conclusion: Infection-related hospitalization was associated with mortality among people with HF, regardless of HF type. Infection-related hospitalization might represent a modifiable risk factor to decrease mortality. Targeted infection prevention strategies or more aggressive infection management should be considered.

Introduction

Heart failure (HF) is a rising epidemic with an estimated prevalence of 6.5 million individuals in the U.S.,[1] and has a high morbidity. The five-year survival rate following an initial HF hospital admission is less than 50%[8] and in the context of HFpEF, there are limited treatment options that have been proven to reduce mortality.

Infection is a common cause of hospitalization in HF patients and is associated with poor prognosis and high mortality[125,128,197,247]. A prior study found that 38% of HF patients experienced at least one infection-related hospital admission and patients admitted for infectious causes had significantly higher 30-day (13% vs. 8%)[124]. A similar study reported a high short-term mortality rate in people with HF after hospitalization with infection[125]. However, few studies among HF patients have explored (i) long-term[124,128,248] mortality following an infection-related hospitalization in a large population-based setting (ii) whether certain types of infection (e.g., respiratory infection, urinary tract infection, etc.) are stronger predictors of mortality, or (iii) whether infections have different prognostic implications in patients with HF with preserved ejection fraction (HFpEF)[249,250] versus those with HF with reduced ejection fraction (HFrEF)[128,250]. A better understanding of infection-related predictors of long-term outcomes among HF patients could reduce mortality through more targeted infection prevention strategies or more aggressive infection management.

Using data from the Atherosclerosis Risk in Communities (ARIC) study we examined the association between infection-related hospitalization and mortality

among participants with HF, HFpEF, or HFrEF during up-to 15 years (2005-2019) of longitudinal follow-up. We hypothesize that among ARIC participants with HF: (i) participants with infection-related hospitalization will experience higher mortality rates; and (ii) the association between infection-related hospitalization and mortality will be present and consistent among participants with either HFrEF or HFpEF.

Methods

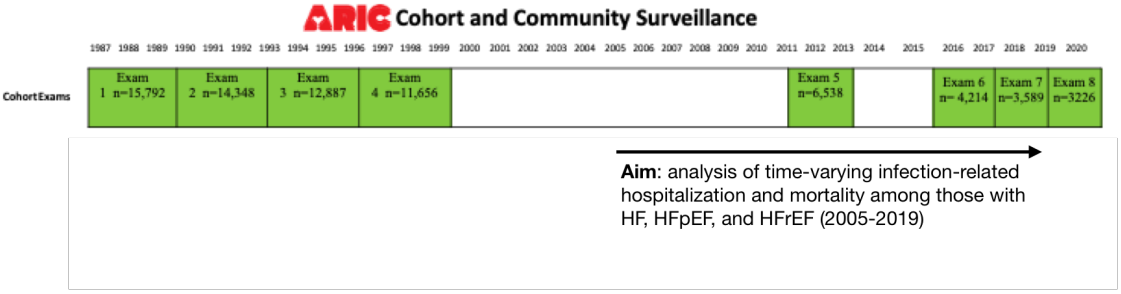
Study population

The ARIC study is a prospective, community-based cohort that began in 1987-89. At baseline, 15,792 Black and White adults aged 45-64 years were recruited for four US communities: northwest suburbs of Minneapolis, MN; Forsyth County, NC; Jackson, MS; Washington County, MD; [156]. Participants have attended additional follow-up clinic visits, participated in regular phone interviews (annually before 2012, twice-yearly thereafter), and have been continuously surveilled for hospitalizations and mortality. In addition, adjudication for cardiovascular disease endpoints is independent of visits.

Our study period begins in 2005, when HF adjudication was initiated, and continues until 2019 (**Figure 1**). Participants with incident HF after 2005 with non-missing demographic information are included in this analysis. We excluded races other than Black, White, or non-White participants in the Minneapolis and Washington County center (due to small sample sizes), and participants missing

data on important covariables. Additionally, participants with prevalent HF prior to 2005 have been excluded (**Figure 2**).

Figure 1: Study timeline.



A detailed graphic of our study design is depicted in **Figure 3** and includes an example of the four different possible exposure-disease combinations. HF diagnosis acts as the index date (person-time = 0) for this analysis. All participants with HF were considered unexposed to infection-related hospitalization at baseline and contribute unexposed person-time. At the first incidence of infection-related hospitalization, a participant begins contributing exposed person-time until death, lost to follow-up, or the end of the study period. In the event of multiple infections, the first infection was used as exposure date in the analyses regardless of other infections thereafter.

HF Ascertainment

Starting in 2005, ARIC implemented committee adjudication of HF hospitalizations based on chart abstraction as previously described[157]. To summarize, hospitalizations or deaths with potentially HF-related ICD codes were identified, and hospitalization records were abstracted and adjudicated by the

ARIC HF Committee. Abstraction included results of imaging studies and left ventricular ejection fraction (LVEF) when available. Reviewers determined whether evidence of an LVEF<50% at the time of hospitalization was present and recorded a numerical LVEF when available. Participants with quantifiable LVEF were categorized as HFpEF (LVEF ≥ 50%) or HFrEF (LVEF < 50%). If adjudication of the HF type was not possible, participants were defined as having HF of "unknown" type, which we referred to as HFunknown. Only participants with an HF diagnosis after 2005 was included in this analysis.

Infection-Related Hospitalization Ascertainment

Our main exposure is the first occurrence of infection requiring hospitalization, identified by selected International Classification of Diseases (ICD) 9 or 10 codes (**Supplemental Table 1**) in the first five ICD positions, as previously performed in ARIC[13]. Hospitalizations were identified through phone calls, surveillance of local hospitals, and death interviews with proxies. Infection-related hospitalization is treated as a time-varying exposure, with participants considered unexposed until their first infection-related hospitalization and will remain exposed thereafter. For our second analysis, we classify participants as having one of the following types of infection: respiratory, pneumonia, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other infections to determine whether specific types of infection are more strongly associated with mortality.

Mortality Ascertainment

The primary outcome is all-cause mortality. Participants were contacted by phone regularly (annually before 2012, twice-yearly thereafter) to ascertain vital status after baseline. If a participant was reported deceased by the next of kin or other designated contact person, then the date of death and circumstances of the death, as well as hospitalizations before death, were ascertained via informant interview. If the participant was not located during annual follow-up, an attempt was made to determine vital status via search of obituaries, funeral and hospital records, and the National Death Index.

Risk Factor Measurements

Covariables were measured at visit 4 (1996-1998) via questionnaires, clinical exam, and laboratory analysis of blood samples. These measures included age, sex, race (Black or White and included as a proxy for social, not biological, risk factors[209]), and education level (1: less than a high school degree, 2: high school, GED, or vocational school and 3: college, graduate, or professional school), and medication use. In addition, physical activity was assessed at visit 3 (and if missing, was taken from visit 1) via a modified Baecke questionnaire. A physical activity index score (1: lowest activity and 5: highest activity) was calculated based on intensity and time dedicated to sport and exercise. Smoking status (never, former, or current).

Participants fasted for eight hours before the visit 4 clinical examination and blood was collected for the assessment of lipids (including total cholesterol,

HDL cholesterol, and LDL cholesterol [estimated via the Friedewald equation]). If LDL cholesterol was missing at visit 4, values from visit 3 and visit 2 were used, respectively. Diabetes mellitus was defined as a self-reported physician diagnosis of diabetes, fasting glucose ≥126 mg/dL, ≥200 mg/dL if non-fasting, or reported pharmacological treatment for diabetes. In addition, body mass index (BMI) was collected and defined as measured weight in kilograms divided by height in meters squared. If BMI measures were missing at visit 4 than visit 3 values were used. Blood pressure was measured twice after a five-minute rest and the average was used for analysis. Use of anti-hypertensive medication was self-reported. Prevalence of heart failure (HF), coronary heart disease (CHD), atrial fibrillation (AF), and stroke were defined via self-report.

Statistical Analysis

Characteristics captured at visit 4 were described across exposure status (infection-related hospitalization versus no infection-related hospitalization) using mean ± SD for continuous variables and count (%) for categorical variables. Incident mortality rates along with incident mortality rate differences were reported to assess the probability of mortality among HF patients during our study period. Cox proportional hazards models were used to assess whether time to death (outcome) is associated with infection-related hospitalization status (exposure). For our primary analysis, infection-related hospitalization is the primary exposure and is treated as time-varying, while incident all-cause mortality is our primary outcome. Follow-up time began at the time of an incident

HF event and accrued until mortality date, loss to follow-up, or December 31, 2019, whichever occurred first.

Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using multivariable Cox proportional hazards models. Multivariable models adjusted for the following variables: model 1: age, sex, race/center education, health insurance; model 2: model 1 + physical activity, smoking status, BMI; model 3: model 2 + diabetes, systolic blood pressure, antihypertensive medication use, LDL cholesterol, prevalent CHD, and prior infection-related hospitalization in the first five positions. This analysis was replicated among those with HFrEF, HFpEF, and HFunknown. For all analyses, we identified and removed instances where HF and infection occurred in the same hospitalization. We also considered specific types of infections (respiratory, pneumonia, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other infections), reporting HRs and 95%CI for each infection type to see if a particular type of infection is more strongly associated with mortality.

Lastly, a sensitivity analysis was conducted defining infection-related hospitalization using ICD-9 or ICD-10 codes in the first position of diagnostic discharge. This is intended to represent a more stringent exposure ascertainment, as it increases the likelihood that hospitalization was due to the infection.

Results

Among the 1,998 participants with incident HF, 54% were women, 24% were Black, and the mean age at HF was 80±6.5 years (range: 62-96 years). Overall, 606 participants were classified as having HFpEF, 543 had HFrEF, and 849 had HFunknown. On average (mean±SD) participants contributed 3.3±3.5 years of follow-up to the analysis, 48% of participates had at least one infection-related hospitalization which occurred an average of 1.4 (range=0.003-13.3) years after HF development. Visit 4 took place on average(±SD) 15.0±4.3 years prior to incident HF diagnosis when participants entered this analysis. Characteristics of participants at visit 4 are presented by post-HF infection-related hospitalization status in **Table 1.** When compared to patients without an infection-related hospitalization, patients with at least one infection-related hospitalization were slightly younger at HF diagnosis, had fewer prior infection-related hospitalizations, lower DBP, but higher BMI.

Infection-Related Hospitalization and Mortality among HF Patients

Among ARIC participants with HF, the cumulative incidence of mortality between 2005 and 2019 was 69% (1,384 cases), and the incidence density was 210.3 events per 1,000 person-years. Mortality incident rates among those with HFpEF, HFrEF and HFunknown were 202.4, 223.2, and 207.9, respectively. The average time to death was 2.6 (range 0-14.3). After multivariable adjustment, infection-related hospitalization was associated with mortality among those with any HF, HFpEF, HFrEF, and HFunknown HR(95% CI): 1.99 (1.77, 2.23), 2.08

(1.69, 2.56), 1.96 (1.57, 2.45), and 1.98 (1.65, 2.39), respectively (**Table 2**). Results were strongest among those with HFpEF.

Although we set out to look at the following types of infections: respiratory, pneumonia, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other, due to the small sample size for influenza (N=16), digestive tract (N=18) and blood/circulatory system (N=15) infections, results were not reported. In addition, we signified any low cell counts (<5) in analyses we performed since it can lead to unreliable and inflated standard errors. In our fully adjusted models respiratory, pneumonia, and other infections had the strongest relationship with mortality among our HF population with HRs and 95%CI of 1.82 (1.60, 2.07), 1.83 (1.59, 2.12), 1.98 (1.72, 2.27), respectively (**Table 3**). In contrast, urinary tract infections were found to only be slightly associated with HFunknown 1.48 (1.10, 1.99). Lastly, skin infections were not associated with HFpEF while hospital-acquired infections were not associated with HFrEF (**Table 3**).

When we restricted our infection-related hospitalization definition to ICD-10 codes in the first position of diagnosis discharge, our HRs increased compared to our primary analysis. The association between infection-related hospitalization and mortality strengthen with a more stringent definition for infection-related hospitalization with HRs and 95% CI of 2.40 (2.13, 2.70), 2.44 (1.97, 3.03), 2.59 (2.03, 3.30) and 2.37 (1.96, 2.86) in our fully adjusted models for any HF, HFpEF, HFrEF and HFunknown, respectively (**Table 4**).

Discussion

Among HF patients, we found infection-related hospitalization to be associated with a 2-fold greater risk of mortality. Associations were similar whether the patient had HFpEF, HFrEF, or if type of HF was not classified. The observed associations remained after extensive adjustment for sociodemographic, behavioral, and HF risk factors along with other comorbidities. Different types of infection-related hospitalizations, specifically respiratory infections, had the strongest association with mortality. Cumulatively, our results suggest that infection is a common, serious, and a cause of hospitalization in people with HF and HF subtypes, which may benefit from improved prevention, early identification, and intensive management.

Few studies have evaluated the relationship between infection and outcomes in patients with HF and HF subtypes. Alon et al[124] observed an overall 30-day mortality rate of 10% among HF patients. Admissions due to infections were associated with a 60% increase in short-term mortality, predominately related to respiratory and systemic infections [124]. Ueda et al[125] similarly reported a high short-term mortality rate in people with HF after hospitalization with infection. In addition, Drozd et. al[128] found infection to be a common driver of hospitalization in HFrEF patients and is associated with high mortality rates. Similarly, Cheng et al[251] found infection-related re-hospitalizations in patients discharged for acute decompensated HF independently predicted worse long-term survival. The increased risk of death associated with infection-related re-

hospitalizations was predominantly for lower respiratory tract infections, urogenital tract infections, and sepsis[251].

The higher mortality rates seen among HF patients who experienced an infection-related hospitalization may reflect the complex and harmful interaction between HF and infection-related hospitalization. Respiratory infections, have been demonstrated as a major trigger for cardiac complications, affecting more than a quarter of those hospitalized with community acquired pneumonia[252]. The acute systemic inflammation associated with an infection response can directly depress myocardial function as well as alter the balance of oxygen demand and supply[211,212]. This interplay is well known in sepsis and bacteremia and involves mechanistic pathways, which are also common in acute decompensated HF[253,254]. In addition, an increase in pneumonia and related pathogens such as streptococcal pneumonia, Haemophilus influenza, and Mycomplasma pneumoniae, has been found to increase pulmonary pressure and direct myocardial depressant effect[124,255]. It is thus biologically plausible that infection-related hospitalization could be driving worse outcomes among HF patients.

The improving survival rates of people with HF have been accompanied by notable changes in the mode of death, with noncardiovascular causes becoming increasingly important.[197,247,256] Our research and others have shown that infection-related hospitalization accounts for a substantial proportion of mortality. It is also established that infection is a common primary cause of hospitalization in people with heart failure.[124,125] Our data advance the literature

by showing high mortality rates after infection-related hospitalization among those with HFrEF, HFpEF, and HFunknown.

Our findings have implications for patients, clinicians, and healthcare systems. The high infection-related hospitalization rates among HF populations suggests that greater efforts are required to prevent infection in this vulnerable population. Such efforts include increasing the uptake of vaccinations. Influenza vaccinations remain suboptimal in many healthcare systems, including the US[257], and there may be scope to improve the efficacy of vaccination. In addition, the high mortality rate associated with infection poses the question of whether more intensive monitoring, supportive care, and post-discharge care could improve survival and long-term functioning. Moreover, prior research has found recurrent infection hospitalization to be common[124,128], highlighting a need for secondary prevention strategies.

Strengths and Limitations

Some important limitations to this study should be noted. Asymptomatic or undiagnosed HF may be present among ARIC participants. Since these participants do not meet our study inclusion criteria, we may be capturing a sicker HF population. This phenomenon should minimally bias our results, as it will equally affect our exposed and unexposed populations, but it could make our study less generalizable to the broader HF population. In addition, most of our covariates were measures at visit 4 (1996-1998) which occurred on average 15

years prior to HF diagnosis. Lastly, given that this is an observational study, causal inference is limited and uncontrolled confounding may be present.

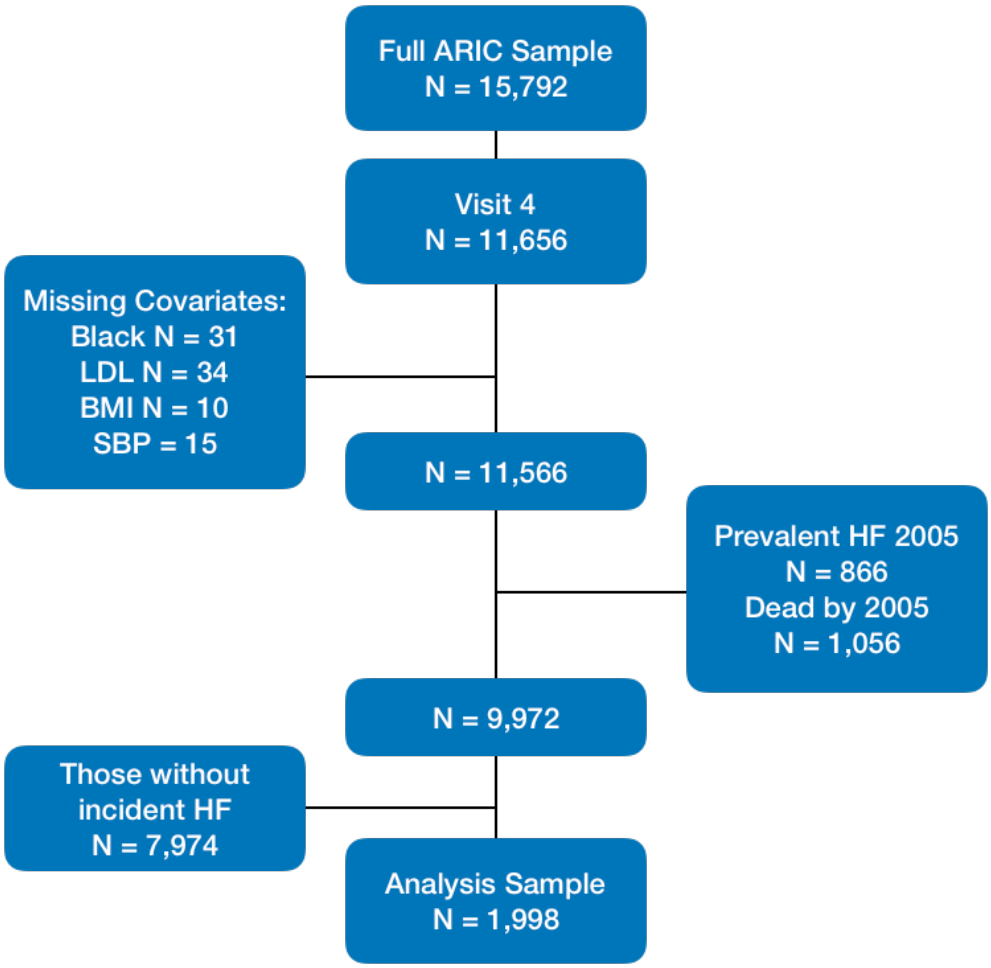
There are also many strengths to this study, most notably the ability to specify HF subtype in a subgroup of participants, along with the rigorous approach used to adjudicate HFrEF and HFpEF in ARIC. The robust data collection and surveillance implemented in ARIC enabled us to follow participants over a long period of time and collect incident events of interest.

Conclusion:

Infection-related hospitalization is common among people with HF. Infection-related infection was found to be associated with a 2-fold greater risk of mortality among those with HFpEF, HFrEF, or unclassified HF. Different types of infection, specifically respiratory, pneumonia, and other infections, were all individually associated with mortality. Future research is necessary to better understand causality, the underlying biology, and whether new approaches to either prevent infection or monitor patients following infection-related hospitalization discharge could reduce mortality among HF patients.

Tables/ Figures:

Figure 2: Study population.



PA = Physical activity

LDL = LDL cholesterol

BMI = body mass index

SBP = systolic blood pressure

*PA was measured at visit 3 and if not available, visit 1 was used

*LDL was measured at visit 4 and if not available, visit 3 and visit 2 was used, respectively

*BMI was measured at visit 4 and if not available, visit 3 was used

Figure 3: Study design with examples of the four different possible exposure-disease combinations.

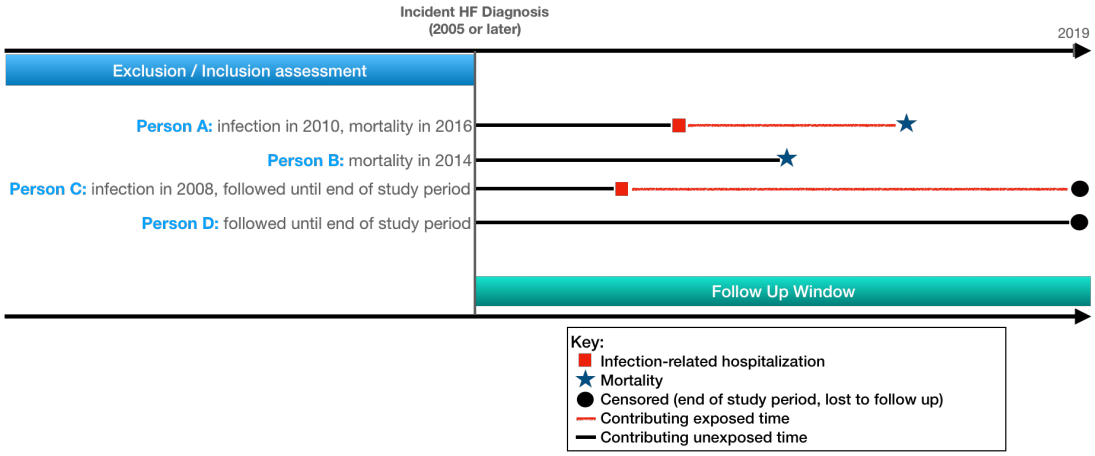


Table 1. Study population characteristics by infection-related hospitalization status among patients with HF in the Atherosclerosis Risk in Communities study, 2005-2019 (N=1,998)

	Infection-related hospitalization (n=956)	No Infection-related hospitalization (n=1,042)	P-value
Demographics			
Age at HF diagnosis	79.4±6.5	80.0±6.4	0.04
Age	64.2±5.5	64.3±5.4	0.71
Male	435 (45.5)	487 (46.7)	0.58
Race/Center			0.001
White Minneapolis	238 (24.9)	280 (26.9)	
White Washington	285 (29.8)	292 (28.0)	
White Forsyth	232 (24.3)	191 (18.3)	
Black Forsyth	24 (2.5)	21 (2.0)	
Black Mississippi	177 (18.5)	258 (24.8)	
Education			0.45
Basic	244 (25.5)	241 (23.1)	
Intermediate	393 (41.1)	446 (42.8)	
Advanced	319 (33.4)	355 (34.1)	
Behavioral Characteristics			
Smoking status			0.40
Never	361 (37.8)	390 (37.4)	
Former	431 (45.1)	494 (47.4)	
Current	164 (17.2)	158 (15.2)	
Physical Activity*	2.5±0.8	2.5±0.8	0.94

Clinical Characteristics			
Prior IRH	191 (20.0)	249 (23.9)	0.03
Body mass index, kg/m^2*	30.2±6.0	29.6±5.9	0.04
Systolic blood pressure, mmHg	123.6±17.6	123.5±17.9	0.89
Diastolic blood pressure, mmHg	73.4±10.5	74.5±11.0	0.03
Blood pressure medication	545 (57.0)	571 (54.8)	0.32
Diabetes	209 (21.9)	229 (22.0)	0.95
Total cholesterol, mg/dL	199.5±37.2	202.0±38.1	0.15
HDL cholesterol, mg/dL	47.6±15.6	48.7±15.5	0.11
LDL cholesterol, mg/dL*	122.4±33.6	123.7±35.5	0.38
Lipid lowering medications	171 (17.9)	195 (18.7)	0.63
Prevalent CHD	116 (12.1)	123 (11.8)	0.82
Prevalent AF	2 (0.2)	2 (0.2)	0.93
Prevalent stroke	28 (2.9)	36 (3.5)	0.50

Means±SD for continuous variables and N (%) for categorical variables
All measures were taken at visit 4 (1996-1998)
*Physical activity was measured at visit 3 and if not available, visit 1 was used
*LDL cholesterol was measured at visit 4 and if not available, visit 3 and visit 2 was used, respectively

*Body mass index (BMI) was measured at visit 4 and if not available, visit 3 was used

P-values: type 3 sum of squares for continuous variables and chi-square for categorical variables

Infection-related hospitalization (IHR), coronary heart disease (CHD), atrial fibrillation (AF)

Table 2. Multivariable adjusted hazard ratios (95% confidence interval) of the association between infection-related hospitalization in the first five positions and mortality among participants with heart failure, the Atherosclerosis Risk in Communities study 2005-20019 N = 1,998

Type of HF	No. IRH / Total N	Incident Rate per 10,000 person-years*	Incident Rate Difference (95% CI) per 10,000 person-years*	Hazard Ratio (95% CI)		
				Model 1	Model 2	Model 3
Any HF	956 / 1,998	210.3	73.5	2.00 (1.78, 2.24)	1.98 (1.77, 2.22)	1.99 (1.77, 2.23)
HFpEF	328 / 606	202.4	115.6	2.13 (1.74, 2.61)	2.07 (1.69, 2.54)	2.08 (1.69, 2.56)
HFrEF	244 / 543	223.2	66.3	1.83 (1.48, 2.27)	1.85 (1.49, 2.30)	1.96 (1.57, 2.45)
HFunknown	384 / 849	207.9	46.5	2.01 (1.67, 2.42)	1.99 (1.66, 2.40)	1.98 (1.65, 2.39)

IRH = infections in the first five positions of diagnostic discharge

Model 1: adjusted for covariates measured in 1996-98: age, sex, race/center, education

Model 2: model 1 + physical activity, smoking status, BMI

Model 3: model 2 + prior IRH in the first five positions, diabetes, systolic blood pressure, antihypertensive medication use, LDL cholesterol, prevalent CHD

*All incident rates are crude mortality rates

Table 3. Multivariable adjusted hazard ratios (95% confidence interval) of the association between infection-related hospitalization and mortality, among participants with heart failure in the Atherosclerosis Risk in Communities Study, 2005-2019 (N = 1,998)

Type of Infection	No. of IRH	HF any N =1,998	No. of IRH	HFpEF N = 606	No. of IRH	HFrEF N=543	No. of IRH	HFunknown N = 849
Respiratory	512		196		144		172	
Model 1		1.85 (1.62, 2.11)		2.04 (1.63, 2.55)		1.94 (1.52, 2.47)		1.68 (1.34, 2.10)
Model 2		1.82 (1.60, 2.07)		2.00 (1.59, 2.51)		1.93 (1.51, 2.46)		1.70 (1.35, 2.13)
Model 3		1.82 (1.60, 2.07)		2.03 (1.62, 2.56)		1.95 (1.53, 2.50)		1.69 (1.35, 2.13)
Pneumonia	369		142		101		126	
Model 1		1.88 (1.63, 2.16)		2.16 (1.71, 2.73)		2.03 (1.55, 2.65)		1.57 (1.22, 2.03)
Model 2		1.83 (1.59, 2.12)		2.09 (1.64, 2.65)		2.03 (1.55, 2.66)		1.58 (1.22, 2.04)
Model 3		1.83 (1.59, 2.12)		2.08 (1.64, 2.65)		2.01 (1.53, 2.64)		1.59 (1.23, 2.06)
Urinary tract	189		59		39		91	
Model 1		1.19 (0.98, 1.45)		1.05 (0.73, 1.51)		0.88 (0.59, 1.32)		1.49 (1.12, 1.98)
Model 2		1.19 (0.98, 1.45)		1.04 (0.72, 1.51)		0.91 (0.60, 1.36)		1.47 (1.10, 1.96)
Model 3		1.20 (0.99, 1.46)		1.09 (0.75, 1.58)		0.93 (0.62, 1.40)		1.48 (1.10, 1.99)
Skin	78		24		19*		35	

Model 1		1.50 (1.15, 1.96)		1.08 (0.65, 1.77)		2.18 (1.32, 3.60)		1.63 (1.09, 2.46)
Model 2		1.58 (1.21, 2.06)		1.08 (0.64, 1.83)		2.18 (1.32, 3.61)		1.74 (1.14, 2.64)
Model 3		1.50 (1.15, 1.97)		0.91 (0.53, 1.55)		2.28 (1.38, 3.77)		1.70 (1.12, 2.60)
Hospital-acquired	33		14*		8*		11*	
Model 1		1.54 (1.04, 2.28)		2.01 (1.14, 3.55)		0.83 (0.34, 2.04)		1.71 (0.85, 3.47)
Model 2		1.59 (1.07, 2.35)		2.13 (1.19, 3.79)		0.84 (0.34, 2.07)		1.68 (0.83, 3.42)
Model 3		1.58 (1.07, 2.35)		2.01 (1.11, 3.62)		0.86 (0.35, 2.13)		1.71 (0.82, 3.58)
Other	424		134		109		181	
Model 1		1.99 (1.73, 2.28)		2.55 (2.00, 3.25)		1.82 (1.40, 2.37)		1.75 (1.39, 2.19)
Model 2		2.00 (1.74, 2.30)		2.53 (1.98, 3.23)		1.83 (1.40, 2.39)		1.76 (1.40, 2.21)
Model 3		1.98 (1.72, 2.27)		2.41 (1.87, 3.11)		1.95 (1.49, 2.56)		1.76 (1.40, 2.21)

Hazard Ratios (95% CI)

Model 1: adjusted for covariates measured in 1996-98: age, sex, race/center, education

Model 2: model 1 + physical activity, smoking status, BMI

Model 3: model 2 + prior IRH, diabetes, systolic blood pressure, antihypertensive medication use, LDL cholesterol, prevalent CHD

* Unreliable inflated standard errors due to small number of infections (cell counts < 5)

Table 4. Multivariable adjusted hazard ratios (95% confidence interval) of the association between infection-related hospitalization in the first position and mortality among participants with heart failure, the Atherosclerosis Risk in Communities study 2005-20019 N = 1,998

Type of HF	No. IRH / Total No.	Hazard Ratio (95% CI)		
		Model 1	Model 2	Model 3
Any HF	657 / 1,998	2.34 (2.08, 2.64)	2.38 (2.11, 2.68)	2.40 (2.13, 2.70)
HFpEF	218 / 606	2.53 (2.05, 3.12)	2.47 (2.00, 3.05)	2.44 (1.97, 3.03)
HFrEF	154 / 543	2.36 (1.87, 2.99)	2.48 (1.96, 3.14)	2.59 (2.03, 3.30)
HFunknown	285 / 849	2.30 (1.91, 2.77)	2.33 (1.93, 2.81)	2.37 (1.96, 2.86)

IRH = infections in the first position of diagnostic discharge

Model 1: adjusted for covariates measured in 1996-98: age, sex, race/center, education

Model 2: model 1 + physical activity, smoking status, BMI

Model 3: model 2 + prior IRH in the first five positions, diabetes, systolic blood pressure, antihypertensive medication use, LDL cholesterol, prevalent CHD

Supplemental Tables/ Figures:

Supplemental Table 1: International Classification of Diseases (ICD) Codes Utilized for the Ascertainment of Infection-Related Hospitalization.

Type	ICD 9 Codes	ICD 10 Codes
Respiratory Infection	460, 461, 462, 463, 464, 465, 466, 472, 473, 474.0, 475, 476.0, 476.1, 478.21, 478.22, 478.24, 478.29, 480, 481, 482, 483, 484, 485, 486, 487, 488, 490, 491.1, 494, 510, 511, 513.0, 518.6, 519.01	J00, J01, J02, J03, J04, J05, J06, J07, J08, J09, J11, J12, J13, J14, J15, J16, J17, J18, J20, J21, J31, J32, J36, J37, J35.1, J35.2, J35.3, J39.0, J39.1, J39.2, J40, J41.1, J47, J85.0, J85.1, J85.2, J86, J90, J91, J95.02, R09.1
Pneumonia	480, 481, 482, 483, 484, 485, 486	J12, J13, J14, J15, J16, J17, J18
Urinary Tract Infection	590, 595.0, 595.1, 595.2, 595.3, 595.4, 597, 598.0, 599.0	N10, N11, N12, N15.1, N15.9, N16, N28.84, N28.85, N28.86, N30.0, N30.1, N30.2, N30.3, N30.8, N34, N37, N39.0
Digestive Tract Infection	522.5, 522.7, 527.3, 528.3, 540, 541, 542, 566, 567, 569.5, 572.0, 572.1, 573.1, 573.2, 573.3, 575.0, 575.1	K04.0, K04.1, K04.4, K04.5, K04.6, K04.7, K11.3, K12.2, K35, K36, K37, K61, K63.0, K65, K67, K68.12, K68.19, K68.9, K71, K75.0, K75.1, K75.2, K75.3,

		K75.81, K75.89, K75.9, K77, K81
Skin Infection	680, 681, 682, 683, 684, 685, 686, 706.0	E82.2, K12.2, L01, L02, L03, L04, L05, L08, L70.2, L88, L98.0
Blood/Circulatory System Infection	390, 391, 392, 393, 421.0, 421.1, 422.0, 422.91, 422.92, 422.93, 790.7, 790.8	I00, I01, I02, I09.2, I33.0, I39, I40.0, I40.1, I40.8, I41, R78.81
Hospital-Acquired Infection	996.6, 997.62, 998.5, 999.3	K68.11, T80.211, T80.212, T80.218, T80.219, T80.22, T80.29, T81.4, T82.6, T82.7, T83.5, T83.6, T84.5, T84.6, T84.7, T85.7, T87.4, T88.0
Other Infections	001-139, 254.1, 320, 321, 322, 323, 324, 325, 326, 331.81, 372.0, 372.1, 372.2, 372.3, 373.0, 373.1, 373.2, 382.0, 382.1, 382.2, 382.3, 382.4, 383, 386.33, 386.35, 388.60, 601, 604, 607.1, 607.2, 608.0, 608.4, 611.0, 614, 615, 616.0, 616.1, 616.3, 616.4, 616.8, 670, 711,	A01-A99, B01-B99, D86, E32.1, G00, G01, G02, G03, G04.00, G04.01, G04.02, G04.2, G04.30, G04.31, G04.32, G04.39, G04.81, G04.82, G04.83, G04.84, G04.85, G04.86, G04.87, G04.88, G04.89, G04.90, G04.91, G05, G06, G07, G08, G09, G92, G14, G93.7, H00, H01.0, H10, H32, H66.0,

	730.0, 730.1, 730.2, 730.3, 730.8, 730.9	H66.1, H66.2, H66.3, H66.4, H67, H70, H83.0, H92.1, H95.0, H95.1, I32, K90.81, L44.4, L94.6, M60.009, M00, M01, M02.1, M35.2, M46.2, M46.3, N41, N45, N47.6, N48.1, N48.2, N49, N51, N61, N70, N71, N72, N73, N74, N75.1, N75.9, N76.0, N76.1, N76.2, N76.3, N76.4, N76.5, N76.81, N76.89, N77.1, O85, O86.12, O86.8,

Chapter 9. Summary

The aims of this dissertation were to 1) investigate infection-related hospitalization as a trigger for incident HF, 2) assess the association between infection-related hospitalization and long-term incident HF, HFrEF, and HFpEF, and 3) explore the relationship between infection-related hospitalization and mortality among HF, HFrEF, and HFpEF patients.

In the first manuscript, a case-crossover study of beneficiaries in the U.S.-based MarketScan databases was implemented. We found IRH in the case period to be associated with an increased risk of HF for both the 3-month case period and 1-month case period, compared with IRH in the equivalent control periods. Results were notably stronger during the 1-month study period. This relationship persisted across different types of infections (respiratory, pneumonia, influenza, urinary tract, digestive tract, skin, blood/circulatory system, hospital-acquired, and other). We hypothesize that IRHs contribute to the development of an acute inflammatory state that in many situations can persist indefinitely, possibly leading to increased HF risk both during the IRH and beyond. Thus, IRH might represent a modifiable risk factor for inflammation-induced heart failure pathophysiology.

In the second manuscript, data from a longitudinal cohort study, ARIC, was used to assess the association between infection-related hospitalization and future, long-term, incident HF and HF subtypes (HFrEF or HFpEF). We observed infection-related hospitalization to be associated with long-term incident HF, HFrEF and HFpEF among a diverse sample of adults. Findings were notably

stronger among those with HFpEF, for which treatment options are limited. Results from the first manuscript aligned with those of the second manuscript; both found respiratory, pneumonia, and blood/circulatory infections to have the strongest associations with incident HF. Our findings support prior literature linking infection to HF risk, as well as the need for more research exploring the potential for infection-prevention strategies, such as vaccination, to minimize HF burden.

Lastly, the third manuscript, is a longitudinal study that investigated the relationship between infection-related hospitalization and mortality among HF, HFrEF, HFpEF and HFunknown patients in ARIC. After multivariable adjustment, infection-related hospitalization was associated with mortality among those with any HF, HFpEF, HFrEF, and HFunknown. Different types of infection, specifically respiratory, pneumonia, and other infections, had the strongest associations with mortality. Infection-related hospitalization might represent a modifiable risk factor to decrease mortality. Targeted infection prevention strategies or more aggressive infection management should be considered.

Our findings support prior literature linking infection-related hospitalization to HF risk and increased mortality among HF patients. These findings can have significant population-level implications given the high prevalence of infections and the burden of HF on our aging society. In addition, our findings point to the need for more research exploring the potential for infection-prevention strategies, such as vaccination, to reduce HF burden. Future research is also necessary to

better understand causality, investigate the underlying biology and physiology, and examine the role of inflammation as a mediator that links infections to HF.

This dissertation leveraged the strengths of large claims data (MarketScan) and a community-based cohort study (ARIC) to parse out the dynamic relationship between infection-related hospitalization and HF. Overall, these three manuscripts extend our knowledge of the impact of IRH on HF and mortality among HF patients and help to address research gaps in HF and preventative strategies. Results from this dissertation could potentially contribute to identifying new approaches to either prevent infection or monitor and intervene on patients following IRH discharge.

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