The Epidemiology of Congestive Heart Failure: Contributions from the Framingham Heart Study

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SUMMARY

In 1971, McKee et al. at the Framingham Heart Study published a seminal paper on the epidemiology of congestive heart failure. The authors proposed a set of standardized criteria for heart failure for use in research studies and described the risk factors for developing heart failure. Their data demonstrated the strong association between advanced age and increased incidence of heart failure and underscored the importance of hypertension as a precursor of heart failure in the community. The authors were also among the first to demonstrate the poor long-term outcomes of heart failure in the community, with 1 in 2 affected individuals dying within 5 years of the diagnosis. Subsequent Framingham studies have documented other predictors of new onset heart failure, including elevated plasma natriuretic peptide levels, asymptomatic left ventricular systolic dysfunction, and increased left ventricular diastolic dimension. These findings have highlighted potential opportunities for prevention based on the modification of risk factors such as hypertension, and they continue to provide a foundation for future investigations aimed at reducing the burden of heart failure.

The Framingham Heart Study was established in 1948, setting into motion over 6 decades of dedicated study of cardiovascular disease, including congestive heart failure (CHF). Indeed, one of the seminal papers describing the epidemiology of CHF arose out of Framingham. The 1971 paper by McKee et al. [1] described criteria for CHF that continued to be used to this day in clinical and epidemiologic studies, demonstrated that hypertension was an important precursor of CHF, and characterized the poor prognosis of individuals with CHF in the community. This paper briefly reviews the key findings from that paper and summarizes several contemporary Framingham publications on the topic.

CONGESTIVE HEART FAILURE: THE FRAMINGHAM CRITERIA

Until the 1960s, there were no standardized criteria for adjudicating CHF in clinical studies. McKee and colleagues recognized the need for such criteria to facilitate efforts to document the risk factors and natural history of CHF. As they wrote, "if preventive and prophylactic programs are to be developed, the identification of factors that predispose and influence the course of the disease become important" [1].

The criteria they proposed are shown in Table 1. Included in the list were physician's assessment of neck-vein distension, rales, S^3 gallop, venous pressure >16 cm of water, and hepatojugular reflux (major criteria). Weight loss of 4.5 kg in 5 days due to diuretic therapy was a major criterion only if it could not be attributed to a condition other than CHF, otherwise it was considered a minor criterion. Other minor criteria were ankle edema, night cough, dyspnea on exertion, hepatomegaly, tachycardia, and weight loss. "Definite CHF" was defined as having at least 2 major criteria, or 1 major criterion and 2 minor criteria, as long as the minor criteria could not be attributed to any other condition.

The emphasis in the criteria on symptoms and physical examination findings, rather than antecedent comorbidities or cardiac function assessment, underscored the fact that CHF is a clinical syndrome with many etiologies [2]. Today, the approach to detecting the clinical manifestations of CHF is largely unchanged, despite important advances in knowledge about the biology of cardiac remodeling since the early 1970s. Consequently, the Framingham criteria remain relevant in the 21st century and continue to be used in epidemiologic research.

The reliance on overt symptoms and signs of CHF in the Framingham criteria has occasionally led to the criticism that the criteria lack sensitivity, particularly for milder presentations of CHF. Sometimes, individuals will fail to fulfill an adequate number of major or minor criteria and will be regarded as having "probable" or "questionable" CHF. It is important to recognize the value in research of using diagnostic criteria that are highly specific, even at the expense of sensitivity. The number of CHF cases in any epidemiologic cohort will be far lower than the number of control cases. Consequently, misclassification of cases (as might occur with criteria lacking specificity) will cause greater problems than misclassification of control cases (as might occur with criteria lacking sensitivity).

EPIDEMIOLOGY AND NATURAL HISTORY OF CHF

Applying these new criteria, McKee and colleagues characterized the epidemiology of CHF in the Framingham cohort. They followed 5,209 men and women from the

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TABLE 1. Framingham criterion for congestive heart failure introduced in 1971

Major criteria
Paroxysmal nocturnal dyspnea or orthopnea
Neck-vein distension
Rales
Cardiomegaly
Acute pulmonary edema
S_3 gallop
Increased venous pressure >16 cm of water
Circulation time ≥25 s
Hepatojugular reflux
Minor criteria
Ankle edema
Night cough
Dyspnea on exertion
Hepatomegaly
Pleural effusion
Vital capacity ↓ 1/3 from maximum
Tachycardia (rate of ≥120/min)
Major or minor criterion
Weight loss ≥4.5 kg in 5 days in response to treatment

Adapted, with permission, from McKee et al. [1].

Framingham cohort for up to 16 years. Eliminated from the analysis were 17 subjects who had a diagnosis of CHF at the time of Framingham recruitment. Subjects were assessed every 2 years with vital signs, electrocardiogram (ECG), chest x-ray, urinalysis, vital capacity on pulmonary function testing, and blood work. Only 2% of subjects were completely lost to follow-up [3]. A total of 142 individuals developed "definite" CHF according to the Framingham criteria. The rate of CHF per person-year rose more than 10-fold between the age of 29 to 39 years (0.6 to 0.8 cases/1,000 years) and 70 to 74 years (8.7 cases/1,000 years).

The longitudinal design of the cohort facilitated the characterization of antecedent comorbidities in the 142 individuals with CHF (Fig. 1). Definite hypertension, defined using criteria employed at the time (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥95 mm Hg), was present in 75% of cases. This was typically accompanied by evidence of cardiomegaly on chest x-ray or ECG. Coronary heart disease was present in approximately one-half of the individuals with hypertension. Conversely, coronary heart disease without hypertension was present in only 10% of individuals with CHF.

Prior to the advent of modern therapies, treatment of CHF primarily involved diuresis and digoxin. Clinical perceptions of survival were based on relatively limited experiences in the hospital setting. Thus, a key contribution of McKee and colleagues was to document the poor prognosis of individuals with CHF in the community. They examined the outcomes of individuals meeting criteria for definite, probable, or questionable CHF. As seen in Figure 2, approximately 1 in 2 subjects with CHF died within 5 years of the initial diagnosis. Among men, the mortality rate was substantially higher than that observed in Framingham individuals with myocardial infarction (approximately 30% at 5 years). This difference was even more pronounced a decade after the index event: roughly 4

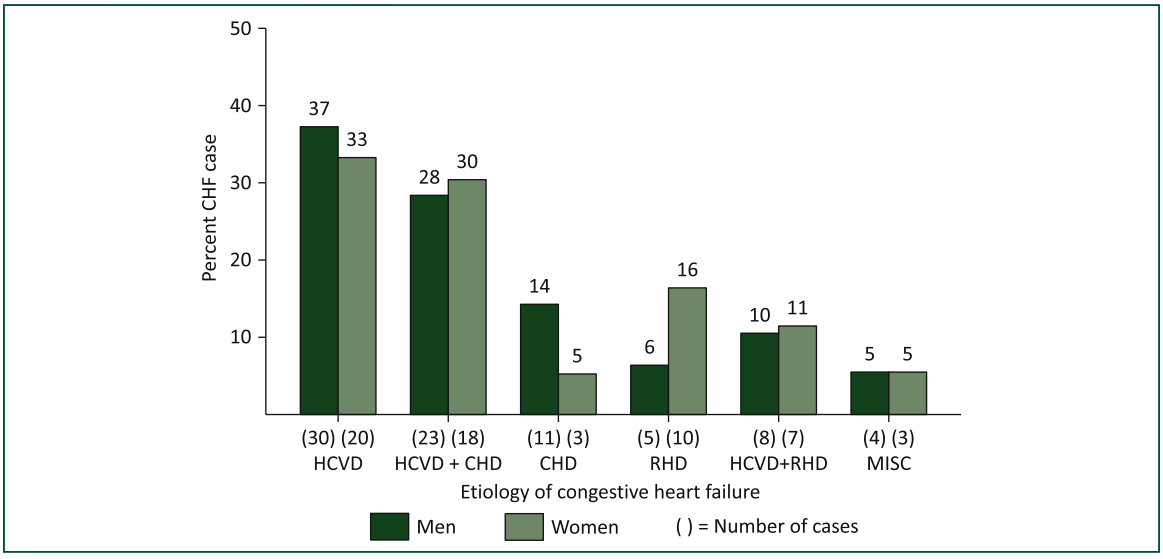

FIGURE 1. Risk factors seen in patients who developed congestive heart failure during 16 years of follow-up. CHD, coronary heart disease; HCVD, hypertensive cardiovascular disease; RHD, rheumatic heart disease. Adapted, with permission, from McKee et al. [1].

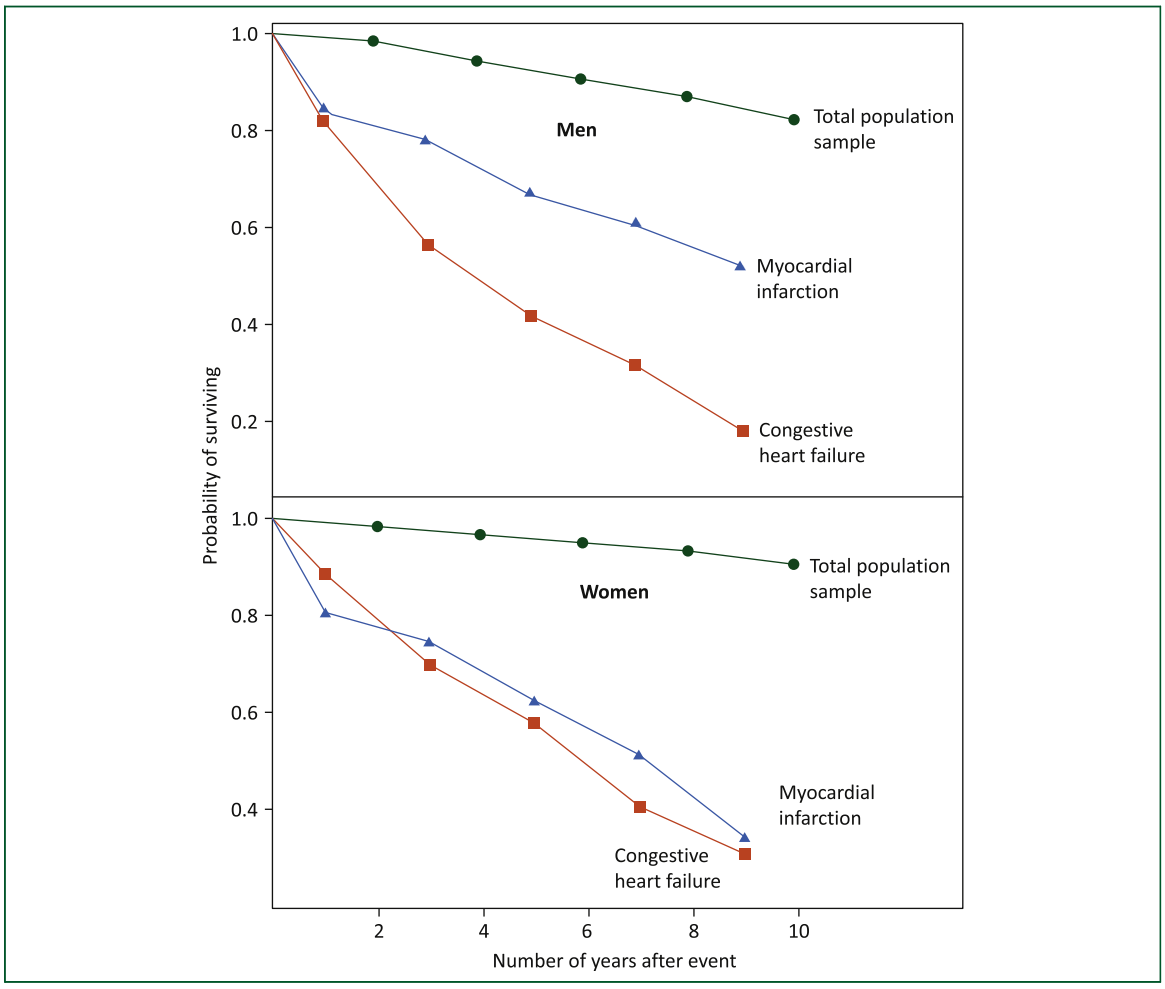

FIGURE 2. Survival probability among subjects who developed congestive heart failure to those who had myocardial infarctions, or neither cardiac event. Adapted, with permission, from McKee et al. [1].

of every 5 men with CHF had died, compared with 1 of every 2 with myocardial infarction.

The highest rate of death was observed in the first year after diagnosis. Unexpectedly, women who were diagnosed with heart failure had a slightly higher relative risk of death than did men, compared with age and sex-matched control subjects. This elevated relative risk persisted even 9 years after diagnosis.

CONTEMPORARY STUDIES OF CHF MORTALITY IN FRAMINGHAM

Several studies updating the observations of McKee and colleagues have been published in the past several decades. In 1993, Ho et al. [4] studied 652 individuals from the Framingham original and offspring cohorts with new, definite CHF. The investigators demonstrated that there had been no reduction in mortality after CHF since the McKee report. CHF continued to be a lethal condition with short median survival. The median survival after the onset of congestive heart failure was only 1.7 years in men and 3.2 years in women. They did note, however, an 11% reduction in CHF incidence in men, and 17% reduction in women ($p < 0.05$) [5].

In 2002, Levy et al. [6] assessed a half century of Framingham data between 1950 and 1999, encompassing 1,075 individuals who developed heart failure. The overall trend for CHF mortality, from 1950 to 1999, revealed a 10%–11% reduction in the risk of death in both sexes, after adjusting for age ($p < 0.03$). Individuals with CHF diagnosed in the 1990 to 1999 period had a one-third lower mortality after CHF than those diagnosed in the 1950 to 1969 period, after adjusting for cardiovascular risk factors (hazard ratio [HR]: 0.69, 95% confidence interval [CI]: 0.50 to 0.95 in men, and HR: 0.68, 95% CI: 0.48 to 0.98 in women). Nonetheless, in spite of this favorable trend, the investigators noted that CHF in the community continued to carry a poor prognosis, with 3 of 5 men and 2 of 5 women dying within 5 years of diagnosis.

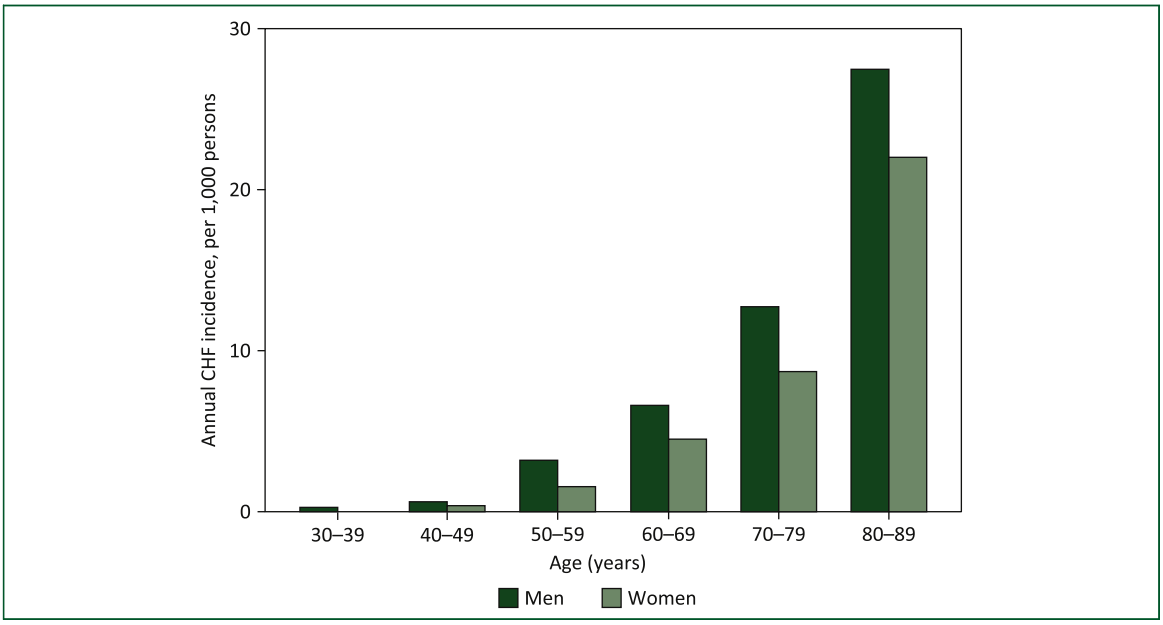

FIGURE 3. Comparison of congestive heart failure annual incidence per decade between men and women. CHF, congestive heart failure. Adapted, with permission, from Ho et al. [5].

RISK FACTORS FOR CHF

The comprehensive characterization of Framingham participants over the course of decades provides a unique opportunity to study conditions that may predispose people to CHF. As noted, McKee and colleagues provided one of the first systematic descriptions of the potential contribution of hypertension to CHF incidence. A follow-up study by Kannel et al. [3] demonstrated that hypertensive men, compared with normotensive men, had a nearly 8-fold risk of developing CHF. Similarly, hypertensive women, compared with normotensive women, had a 4-fold risk. A later study by Levy et al. [7] used an updated definition of hypertension and found that more than 90% of Framingham participants who developed CHF had antecedent hypertension. Using multivariable models, they estimated the population-attributable risk for CHF from hypertension to be nearly 40% in men and 60% in women.

The study by McKee and colleagues was also among the first to document the age- and sex-related variation in CHF incidence. This observation was updated in the study by Ho et al. [5] 20 years later. As shown in Figure 3, incidence rates of CHF rose markedly with age and were higher in men than in women at all ages.

More recent studies from Framingham have looked comprehensively at predictors of new onset CHF. The goal of these studies is to provide general practitioners with a cost-effective method to identify patients at high 4-year risk of developing heart failure, to enable better targeting of preventive measures. In 1999, Kannel et al. [8] used 38 years of Framingham follow-up data to describe a clinical risk score for predicting CHF. Incorporated in the score were the following variables, all of which can be assessed in the outpatient clinic: age, sex, ECG left ventricular hypertrophy, heart rate, systolic blood pressure, diabetes mellitus, prior myocardial infarction, valvular disease by examination, and hypertension (Table 2) [8]. They found that 60% of new CHF events in men and 73% in women occurred in individuals in the top quintile of multivariable risk according to the risk score.

Framingham investigators have also examined newer predictors of CHF, including circulating biomarkers. For instance, in 2004, Wang et al. [9] published the first large, longitudinal study showing that levels of plasma natriuretic peptides predicted future CHF in ambulatory individuals. Individuals with B-type natriuretic peptide concentrations in the top quintile (>20 pg/ml in men, and >23.3 pg/ml in women) had a 3-fold increased risk of developing CHF over 5 years.

Studies from Framingham have also defined echocardiographic predictors of future heart failure. For instance, Vasan et al. [10] demonstrated the higher left ventricular diastolic dimensions in individuals free of myocardial infarction predicted future heart failure (adjusted HR: 1.5, 95% CI: 1.25 to 1.73, per SD increment in end-diastolic dimension). More recently, Wang et al. [11] showed that individuals with asymptomatic left ventricular systolic dysfunction (ejection fraction ≤50%) had a nearly 5-fold increased risk for developing heart failure (adjusted HR: 4.7, 95% CI: 2.7 to 8.1). Recent guidelines have embraced the concept that subclinical abnormalities of cardiac structure and function ("stage B heart failure") are important precursors of overt heart failure [12]. Ongoing studies in other cohorts are investigating the cost-effectiveness of targeted echocardiographic screening programs [13].

TABLE 2. Four-year probability for developing congestive heart failure among men 45 to 94 years of age

	Points									
	0	+1	+2	+3	+4	+5	+6	+7	+8	+9
Variables										
Age, yrs	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89	90–94
Systolic blood pressure, mm Hg	<120	120–139	140–169	170–189	190–219	>219				
Heart rate, beats/min	<55	55–64	65–79	80–89	90–104	>104				
LVH on ECG	No				Yes					
Coronary heart disease	No							Yes		
Valve disease	No					Yes				
Diabetes	No	Yes								

Points	4-Year Probability of Congestive Heart Failure	Points	4-Year Probability of Congestive Heart Failure
5	1	24	30
10	2	25	34
12	3	26	39
14	5	27	44
16	8	28	49
18	11	29	54
20	16	30	59
22	22		

ECG, electrocardiogram; LVH, left ventricular hypertrophy.
Adapted, with permission, from Kannel et al. [8].

RELEVANCE TO LOWER- AND MIDDLE-INCOME COUNTRIES

Over the past decades, global socioeconomic development has resulted in an "epidemiological transition," with shifts in the leading causes and death. As of 2008, 4 of every 5 deaths globally from cardiovascular disease occurred in developing nations [14]. A paucity of data exists on the global prevalence of heart failure, although some estimate that more than 23 million people worldwide are living with the condition [15]. A limitation of the original Framingham cohort is that the volunteers were almost entirely Caucasian, although the new Omni cohorts of the Framingham study reflect a more diverse U.S. population.

Nevertheless, multiple observations from the study of McKee and colleagues are relevant to the global problem of heart failure. As in the United States, hypertension has been identified as a key risk factor for heart failure in the other countries; for instance, it accounts for an estimated 45% of all acute heart failure cases in sub-Saharan Africa [16]. Similarly, the powerful association between age and heart failure risk has important implications in the developing world, where life expectancy has risen from 52 to 57 years in lower income nations, and from 63 to 68 years in middle-income nations, between 1990 and 2009 [17]. In India, it is estimated that the number of individuals over the age of 60 years will have risen to 113 million by 2016, nearly twice the number for this age group in 1996 [18].

CONCLUSIONS

The landmark publication by McKee and colleagues defined the epidemiology and natural history of CHF using a set of standardized criteria for the first time in a community-based study. The study underscored the high mortality associated with CHF, but it also highlighted potential opportunities for prevention based on the modification of risk factors such as hypertension. Subsequently, their observations have been validated in numerous studies from both Framingham and other epidemiologic cohorts and continue to provide a foundation for future investigations aimed at reducing the burden of CHF.

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