Familial Mortality Risks in Patients With Heart Failure—A Swedish Sibling Study

Magnus P. Lindgren, MD; J. Gustav Smith, MD, PhD; Xinjun Li, PhD; Jan Sundquist, MD, PhD; Kristina Sundquist, MD, PhD; Bengt Zöller, MD, PhD

Background—The influence of familial factors on the prognosis of heart failure (HF) is unknown. This nationwide follow-up study aimed to determine familial mortality risks of HF among Swedish siblings hospitalized for HF.

Methods and Results—We linked several Swedish nationwide registers for individuals aged 0 to 80 years. The study population consisted of 373 people hospitalized for HF for the first time between 2000 and 2012 with 1 proband sibling previously hospitalized for HF for the first time between 2000 and 2007. Families with congenital heart disease were excluded. Familial hazard ratios (HRs) for mortality after first HF hospitalization were determined with Cox regression. The influence of proband survival was categorized as short survival (<5 years) or long survival (≥5 years) and determined continuously for the initial 5 years of proband survival. Adjustments were made for age, sex, time period, and common HF comorbidities. Short proband survival was associated with a HR of 2.02 (95% confidence interval, 1.32–3.09) for overall mortality. This HR was 2.35 (95% confidence interval, 1.18–4.67) in patients without preceding coronary heart disease, whereas patients with ischemic HF had an HR of 1.84 (95% confidence interval, 1.05–3.23). For each year of proband survival, the risk of death decreased, with a HR of 0.86 (95% confidence interval, 0.77–0.98).

Conclusions—Our results suggest that family history of poor survival in specific relation to HF is an important risk factor for death in HF patients. Additional studies are needed to characterize the molecular underpinnings and detailed phenotypic characteristics of such patients. (***J Am Heart Assoc***. 2018;7:e010181. DOI: 10.1161/JAHA.118.010181.)

Key Words: family study • heart failure • mortality • prognosis

Family history of heart failure (HF), independent of common comorbidities, has been associated with an increased risk of HF.[1,2,3] It is largely unknown to what extent familial and possibly genetic factors influence the prognosis of HF. Several candidate genetic polymorphisms have been proposed to influence HF progression or prognosis.[4–8] More recently, genome-wide association studies have explored genetic determinants of survival in HF patients with the finding of a single nucleotide polymorphism (rs9885413) on chromosome 5q22 associated with a 36% increased mortality risk.[9] However, as with the incidence of HF,[10] the prognosis of HF likely depends on the cumulative effect of several contributing factors including shared environment and epigenetic and genetic factors; all of these factors may be reflected by family studies, providing important tools for determining clinical risk as well as direction for future genetic studies.[11,12] To the best of our knowledge, no population study has assessed familial prognosis of HF. In this sibling study, we aimed to determine the effect of poor HF survival in family members on the prognosis of HF patients.

From the Center for Primary Health Care Research, Lund University and Region Skåne, Malmö, Sweden (M.P.L., X.L., J.S. K.S. B.Z.); Department of Cardiology, Clinical Sciences, Lund University and Skåne University Hospital, Lund, Sweden (J.G.S.); Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA (J.G.S.).

Correspondence to: Magnus P. Lindgren, MD, Center for Primary Health Care Research, CRC, Building 28, Floor 11, Jan Waldenströms gata 35, Skåne University Hospital, S-20502 Malmö, Sweden. E-mail: magnus.lindgren@med.lu.se

Methods

Registers

The data, analytic methods, and study materials will not be made available to researchers for purposes of reproducing the results or replicating the procedure. The cohort data used were compiled from several national registers maintained by Statistics Sweden and the Swedish National Board of Health and Welfare. The registers used included the Hospital Discharge Register (HDR), which contains nationwide coverage

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Clinical Perspective

What Is New?

- Few genetic polymorphisms have been confirmed to influence the progression or prognosis of heart failure, and the net effect of familial factors relating to survival in heart failure is unknown.
- This study determined the risk of death due to familial factors in heart failure.
- Measured from time of first hospitalization for heart failure, having an affected sibling with short survival was associated with an increased risk of death, also after adjusting for other important covariates.

What Are the Clinical Implications?

- The results of this study identify heart failure patients with an increased risk of death.
- Further studies are warranted on genetic polymorphisms important for the prognosis of heart failure.

of hospital discharge diagnoses since 1987 with a missing main discharge diagnosis for <1% of patients. The positive predictive values for many diagnoses in the HDR vary between 85% and 95%, although the validity of many cardiovascular diseases tends to be higher (90–95%).[13] HF registered as a main diagnosis, as used in this study, has been found to carry a positive predictive value of >95%.[13–15] The Multigeneration Register contains information on maternal parentage (97% coverage) and paternal parentage (95% coverage) of all individuals born in Sweden since 1932 who did not emigrate or die between 1932 and 1960.[16] The Cause of Death Register, which is considered to be valid for use in epidemiological studies for several diagnoses, including ischemic heart disease, contains data from 1964 and onward.[17,18]

This study was conducted in compliance with the Helsinki Declaration and was approved by the ethics committee of Lund University, Sweden, which waived the requirement of informed consent because of the use of anonymized register data.

Study Sample

The cohort consisted of patients (referred to as *subjects*) hospitalized for HF for the first time (HF registered as a main diagnosis in the HDR) between calendar years 2000 and 2012, all of whom also had 1 proband sibling (referred to as a *proband*) who was previously hospitalized for HF for the first time between 2000 and 2007. With survival data available until 2012 for both subject and proband, to obtain 5 year records of proband survival, only subjects with a proband first hospitalized for HF no later than 2007 were included.

Only a main diagnosis of HF was used to ensure that primary and not secondary HF cases were included and to increase the validity of HF diagnosis. *International Classification of Diseases (ICD)* code 428 (*ICD, Ninth Revision* [*ICD-9*]; 1987–1996) and code I50 (*ICD, 10th Revisions* [*ICD-10*]; 1997–2012) were used to define HF.

To reduce the risk of registering a recurrent HF hospitalization event as the first hospitalization for HF, all families recorded with a main HF diagnosis in HDR between calendar years 1987 and 1999 were excluded.

We excluded all families with a member recorded as having emigrated or immigrated to Sweden during the period 1987–2012. Half siblings (ie, individuals born of either the same mother or father only) were not counted as eligible sibling relatives. We also excluded patients diagnosed with malignant (in situ excluded) cancer, main and secondary diagnoses 140 to 208 (*ICD-9*) or C00-C97 (*ICD-10*) during the period of 5 years before and 2 years after the event of HF hospitalization.

Families with a member recorded with main or secondary diagnoses of congenital heart disease 745 to 747 (*ICD-9*) or Q20-Q28 (*ICD-10*) in 1987–2012 were excluded throughout the study. Families with any member with a main or secondary diagnosis of cardiomyopathy 428 (*ICD-9*) or I42 (*ICD-10*) in 1987–2012 were included in the analyses if not explicitly stated otherwise. For descriptive purposes, the first recorded diagnosis of cardiomyopathy in 1987–2012 was further stratified: alcoholic cardiomyopathy 425F (*ICD-9*) or I426 (*ICD-10*); dilated cardiomyopathy (not a standalone diagnosis in *ICD-9*) or I420 (*ICD-10*); hypertrophic cardiomyopathy, including hypertrophic obstructive cardiomyopathy 425B (*ICD-9*) or I421–I422 (*ICD-10*); restrictive cardiomyopathy 425D (*ICD-9*) or I423–I425 (*ICD-10*). The category *other causes* or unspecified phenotypes were defined as cardiomyopathies recorded with other 428 (*ICD-9*) or I42 (*ICD-10*) diagnoses.

Predictor Variable

The predictor variable was survival time of the proband after first hospitalization for HF in 2000–2007, which allowed for a minimum range of measure of 5 years at the end of follow-up on December 31, 2012. Proband survival was used as both a continuous predictor and a categorized predictor with survival dichotomized as <5 years or longer (≥5 years).

Outcome Variable and Subjects Studied

Subject mortality was calculated from the date of hospital admission for HF and measured as both overall mortality (main outcome) and death from cardiovascular causes

(secondary outcome), as registered in the Swedish Cause of Death Register.

Other Covariates

Additional variables used in all analyses were subject sex, age, and calendar year at onset (time of first recorded main diagnosis) of HF. The following comorbidities (main and secondary diagnoses), recorded previous to (earliest January 1, 1987) or at the time of HF admission, were also used: coronary heart disease (CHD), code 410 to 414 (*ICD-9*) or I20 to I25 (*ICD-10*); diabetes mellitus, code 250 (*ICD-9*) or E10 to E14 (ICD-10); hypertension, code 401 to 405 (*ICD-9*) or I10 to I15 (*ICD-10*); nonrheumatic valvular disease, code 424 (*ICD-9*)

or I34 to I37 (*ICD-10*); stroke (430, 431, 434–436, 438 (*ICD-9*) or I60 to I64, I69 (ICD-10).

Statistical Analysis

Subject mortality was analyzed using survival analysis with Cox regression and relative risks expressed as hazard ratios (HRs). The smaller models were adjusted for subject sex, age at onset, and year of onset of HF. The variables age at onset and year of onset were calculated as the number of years deviated from the subject mean. The full models also included adjustments made for subject comorbidities, as specified earlier.

All covariates were tested for interaction, and assumptions of proportional hazards were tested with Schoenfeld tests.

Table 1. Baseline Characteristics of Subjects* at First Hospitalization for HF

Characteristic	Proband Survival After Proband First Hospitalization for HF		P Value[†]
	≥5 y	<5 y	
Total, n	283	90	
Female sex, n (%)	102 (36.0)	33 (36.7)	1.00
Age interval at diagnosis, y, n (%)			
<50	12 (4.2)	1 (1.1)	0.016
50–59	45 (15.9)	8 (8.9)	
60–69	98 (34.6)	47 (52.2)	
≥70	128 (45.2)	34 (37.8)	
Mean	66.4	67.1	0.47
Median	68.6	68.1	0.78
Time period of first hospitalization, n (%)			
2000–2007	100 (35.3)	38 (42.2)	0.26
2008–2012	183 (64.7)	52 (57.8)	
Hospital record of comorbidities, n (%)			
CHD	136 (48.1)	53 (58.9)	0.090
Diabetes mellitus	84 (29.7)	31 (34.4)	0.43
Hypertension	149 (52.7)	50 (55.6)	0.72
Nonrheumatic valvular disease	43 (15.2)	10 (11.1)	0.39
Stroke	52 (18.4)	17 (18.9)	0.88
Cardiomyopathy, n (%)			
Alcoholic	1 (0.4)	0	0.98
Dilated	34 (12.0)	11 (12.2)	
Hypertrophic	4 (1.4)	1 (1.1)	
Restrictive	1 (0.4)	0	
Other causes or unspecified phenotype	11 (3.9)	2 (2.2)	

CHD indicates coronary heart disease; HF, heart failure.
*Only families with 2 cases of HF and no case of congenital heart disease included.
[†]Two independent-samples *t* test, Wilcoxon rank sum test, and Fisher exact test were performed for calculations of mean, median, and expected frequencies of categorical variables, respectively.

Table 2. Baseline Characteristics of Subjects at First Hospitalization for HF, Cardiomyopathies Excluded*

Characteristic	Proband Survival After First Hospitalization for HF		P Value[†]
	>5 y	<5 y	
Total, n	175	66	
Female sex, n (%)	65 (37.1)	24 (36.4)	1.00
Age interval at diagnosis, y, n (%)			
<50	3 (1.7)	0	0.074
50–59	20 (11.4)	6 (9.1)	
60–69	56 (32.0)	33 (50.0)	
≥70	96 (54.9)	27 (40.9)	
Mean	68.5	67.6	0.34
Median	70.3	68.2	0.080
Time period of first hospitalization, n (%)			
2000–2007	49 (28.0)	28 (42.4)	0.044
2008–2012	126 (72.0)	38 (57.6)	
Hospital record of comorbidities, n (%)			
CHD	88 (50.3)	41 (62.1)	0.11
Diabetes mellitus	54 (30.9)	22 (33.3)	0.76
Hypertension	97 (55.4)	40 (60.6)	0.56
Nonrheumatic valvular disease	31 (17.7)	9 (13.6)	0.56
Stroke	37 (21.1)	12 (18.2)	0.72

CHD indicates coronary heart disease; HF, heart failure.

*Only families with 2 cases of HF and no case of cardiomyopathy or congenital heart disease included.

[†]Two independent-samples *t* test, Wilcoxon rank sum test, and Fisher exact test were performed for calculations of mean, median, and expected frequencies of categorical variables, respectively.

Log linearity was also tested graphically using log–log survival plots. In addition, overall mortality was also calculated as incidence ratios.[2]

The results included 95% confidence intervals (CIs), which were applied with 2-decimal accuracy. All analyses were made using STATA v14.1 (StataCorp).

Results

A total of 96 deaths occurred among 373 eligible subjects found in 372 families. Total follow-up time was 1195.97 years with an overall mortality incidence ratio of 80.27 (95% CI, 65.71–98.06) per 1000 person-years. In one family, both affected siblings were hospitalized on the same day, and these patients were regarded as both subjects and probands. Limited by the event of death or regression right censoring, subject mean and median follow-up time was 3.21 and 2.59 years, respectively.

Table 1 shows the baseline characteristics of subjects at the time of first hospitalization for HF based on whether survival time of the proband was <5 years or ≥5 years. A total of 59 (20.8%) deaths occurred among 283 subjects with a proband surviving ≥5 years, whereas 37 (41.1%) of 90 subjects died among those with a proband surviving <5 years. The majority of patients with cardiomyopathy had a dilated phenotype. Table 2 shows the same baseline characteristics for the 241 subjects in families with no registered case of cardiomyopathy.

HF Mortality Risk According to Sibling HF Survival Time Status

Figures 1 and 2 depict unadjusted Kaplan–Meier survival functions of overall mortality and cardiovascular mortality, respectively, from the time of subject first hospitalization for HF in 2000–2012, as determined by proband survival time after first HF hospitalization in 2000–2007. Proband survival time was categorized as <5 years and ≥5 years.

The overall mortality incidence rate (137.15 cases per 1000 person-years) among subjects having a proband that survived <5 years was >2 times the incidence rate (63.70 per 1000 person years) of subjects with longer proband survival, conferring an incidence ratio of 2.15 (95% CI, 1.39–3.30). Stratified by subject sex, this incidence ratio was 2.08 (95% CI, 1.29–3.54) for male subjects and 2.32 (95% CI, 1.06–4.90) for female subjects.

With the same basis, Table 3 analogously describes small and full multivariable Cox regression models, with covariates as specified earlier, of subject overall mortality after the first admission for HF. With reference to proband HF survival ≥5 years, shorter proband HF survival was associated with an increased risk of death, both in the small model (HR: 1.98; 95% CI, 1.31–3.00) and in the fully adjusted model (HR: 2.02; 95% CI, 1.32–3.09). Similar results were obtained when we restricted the outcome to registered cardiovascular death only (Table 4).

After excluding families with any cardiomyopathy, short proband survival <5 years was still similarly associated with an increased relative risk of subject overall mortality (Table 5), with a fully adjusted HR of 2.22 (95% CI, 1.33–3.71). Likewise, the risk of cardiovascular death also remained significantly increased in this cohort (Table 6).

HF Overall Mortality Risk in Stratified Models

Table 7 shows the results of analogous analyses, with the inclusion of cardiomyopathies, for overall mortality stratified by subject median age at first HF hospitalization, by sex, and by occurrence of previous diagnosis of CHD. Fewer deaths occurred among younger subjects, and among this half at or below the median age (68.3 years) of first hospitalization for HF, the increased risk associated with short proband HF
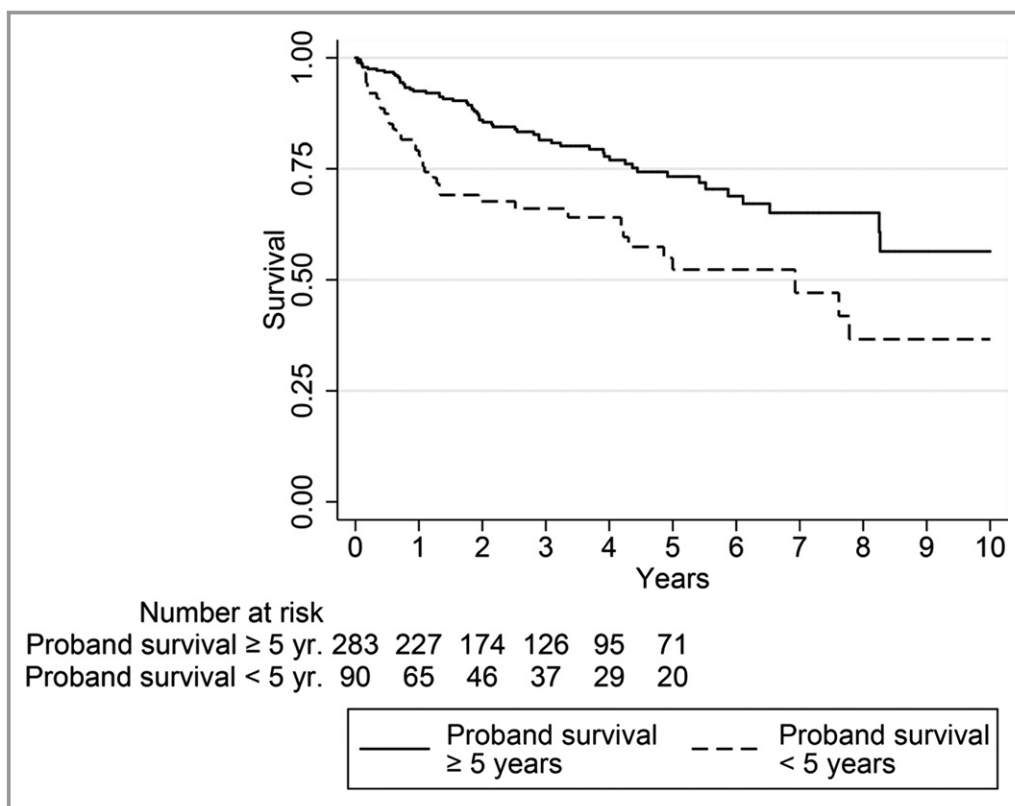
Figure 1. Unadjusted Kaplan–Meier survival functions for overall mortality from first hospitalization for heart failure 2000–2012, as determined by proband heart failure survival.

survival <5 years was not significant, with a fully adjusted HR of 1.76 (95% CI, 0.88–3.54). However, short proband survival was significantly associated with an increased risk of death among older subjects as well as among male and female subjects.

Subjects were also stratified by nonischemic and ischemic HF, the latter defined as the presence of a recorded diagnosis (main or secondary) of CHD from 1987 to the day of first hospitalization for HF. Occurrence of a CHD diagnosis only after first hospitalization for HF would consequently be classified as nonischemic HF. Among subjects with nonischemic HF, proband survival <5 years was associated with a full-model HR of 2.35 (95% CI, 1.18–4.67). As for subjects with ischemic HF, this association was slightly lower, with a fully adjusted HR of 1.84 (1.05–3.23, 95% CI).

HF Overall Mortality as Determined by Proband Per-Year Survival

The per-year prognostic effect of proband survival on subject overall mortality was calculated during the first 5 years after initial proband hospitalization (Table 8). Proband survival time was thus viewed as a continuous predictor during this minimum of 5 years of proband follow-up. The fully adjusted

model rendered an annual HR of 0.86 (95% CI, 0.77–0.98). Thus for every year of proband survival, there was an associated ≈14% reduction in subject mortality risk.

Secondary Analyses

To consider differences in time of hospitalization between the study subject and the proband, which could suggest differences in HF therapeutics and management, the cohort was stratified at the median sibling pair hospitalization time difference (1726 days, ≈ 4.72 years; Table 9). For both strata, the relative risk of death associated with proband survival <5 years remained significant and was approximately 2 times that of longer proband survival.

To recognize the effect of family survival on subject overall mortality not specifically related to HF per se, the incidence ratio[19] of the death of siblings without HF (non-HF siblings) was calculated and used to adjust the model. All families with no non-HF sibling alive on January 1, 1987, were excluded, leaving 69 deaths associated with 276 subjects with HF at risk, all of whom had at least 1 non-HF sibling. The non-HF sibling cohort was categorized by birth year (starting in 1932) into 5-year strata, for which incidence of death was calculated as number of deaths occurring in the period 1987–2012
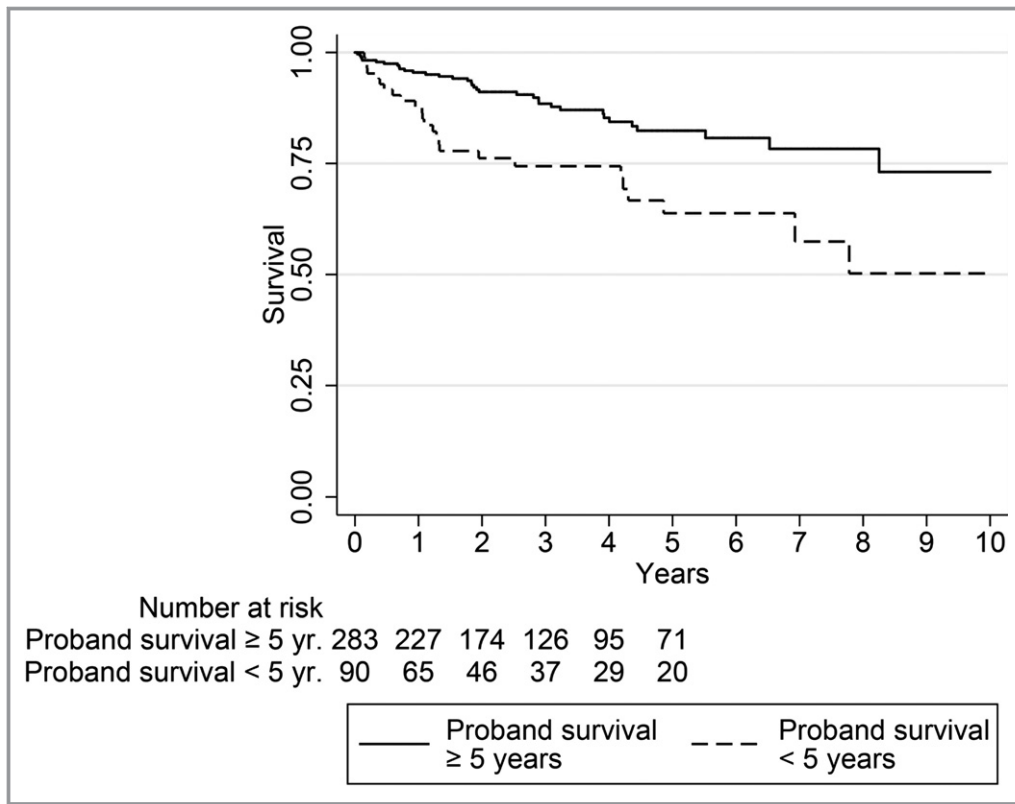
Figure 2. Unadjusted Kaplan–Meier survival functions for cardiovascular mortality from first hospitalization for heart failure 2000–2012, as determined by proband heart failure survival.

divided by the total number of years each non-HF sibling contributed until time of death or end of follow-up on December 31, 2012. The mean incidence for non-HF siblings

in each family was divided by the corresponding incidence by age stratum of the cohort, creating a family incidence ratio as a measure of family survival not pertaining to HF. In addition,

Table 3. Overall Mortality of Subjects* First Hospitalized for HF, as Determined by Survival of Previously Affected Sibling (Proband)

	Small Model, HR (95% CI)[†]	P Value	Fully Adjusted Model, HR (95% CI)[†]	P Value
Proband HF survival <5 y (yes/no)[‡]	1.98 (1.31–3.00)	0.001	2.02 (1.32–3.09)	0.001
Subject characteristics				
Sex (female/male)	0.92 (0.60–1.41)	0.69	0.98 (0.63–1.51)	0.91
Age at onset[§]	2.14 (1.52–3.02)	<0.001	2.11 (1.44–3.08)	<0.001
Year of onset[§]			0.97 (0.88–1.06)	0.46
CHD (yes/no)			0.90 (0.58–1.42)	0.66
Diabetes mellitus (yes/no)			2.68 (1.73–4.16)	<0.001
Hypertension (yes/no)			0.80 (0.53–1.20)	0.30
Stroke (yes/no)			2.18 (1.40–3.39)	0.001
VHD (yes/no)			1.75 (1.01–3.00)	0.044

CHD indicates coronary heart disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; VHD, valvular heart disease.

*Only families with 2 cases of HF and no case of congenital heart disease included.

[†]Cox regression HRs, adjustments as specified below.

[‡]37 deaths among 90 subjects with proband survival <5 y, from a total of 96 deaths among 373 subjects at risk.

[§]Age at onset and year of onset presented as per 10- and 1-y deviations from mean, respectively.

Table 4. Cardiovascular Mortality of Subjects* First Hospitalized for HF, as Determined by Survival of Previously Affected Sibling (Proband)

	Small Model, HR (95% CI)[†]	P Value	Fully Adjusted Model, HR (95% CI)[†]	P Value
Proband HF survival <5 y (yes/no)[‡]	2.24 (1.34–3.76)	0.002	2.35 (1.38–4.03)	0.002
Subject characteristics				
Sex (female/male)	0.92 (0.54–1.58)	0.76	1.16 (0.66–2.03)	0.61
Age at onset[§]	2.45 (1.56–3.85)	<0.001	2.16 (1.30–3.59)	0.003
Year of onset[§]			0.99 (0.88–1.11)	0.89
CHD (yes/no)			1.42 (0.79–2.56)	0.24
Diabetes mellitus (yes/no)			1.70 (0.97–2.97)	0.065
Hypertension (yes/no)			0.48 (0.28–0.81)	0.007
Stroke (yes/no)			2.94 (1.70–5.08)	<0.001
VHD (yes/no)			1.62 (0.83–3.18)	0.16

CHD indicates coronary heart disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; VHD, valvular heart disease.
*Only families with 2 cases of HF and no case of congenital heart disease included.
[†]Cox regression HRs, adjustments as specified below.
[‡]25 cardiovascular deaths among 90 subjects with proband survival <5 y, from a total of 60 cardiovascular deaths among 373 subjects at risk.
[§]Age at onset and year of onset presented as per 10- and 1-y deviations from mean, respectively.

besides the adjustment made for subject CHD in the main analysis, adjustments were also made for familial risk of CHD by introducing a covariate calculated as the number of siblings recorded with CHD during the specified period 1987–2012 or until time of death, divided by number of siblings alive on January 1, 1987. Overall mortality of subjects with HF proband survival time <5 years was approximately 2 times that of subjects with longer proband HF survival time and remained significant when these 2 covariates were added to the models (Table 10).

Discussion

In subjects first hospitalized for HF, poor proband (ie, sibling) HF survival <5 years was associated with overall mortality and risk of cardiovascular death >2 times those of subjects with longer proband survival. These associations remained significant after excluding families with any recorded cardiomyopathy. Overall mortality decreased with every year of proband survival during the 5-year observation period; this finding is congruent with an underlying familial association

Table 5. Overall Mortality of Subjects First Hospitalized for HF, as Determined by Survival of Previously Affected Sibling (Proband)—Cardiomyopathies Excluded*

	Small Model, HR (95% CI)[†]	P Value	Fully Adjusted Model, HR (95% CI)[†]	P Value
Proband HF survival <5 y (yes/no)[‡]	2.04 (1.24–3.36)	0.005	2.22 (1.33–3.71)	0.002
Subject characteristics				
Sex (female/male)	1.03 (0.61–1.74)	0.90	1.19 (0.69–2.07)	0.53
Age at onset[§]	1.68 (1.07–2.64)	0.025	1.65 (1.01–2.70)	0.046
Year of onset[§]			1.01 (0.90–1.13)	0.88
CHD (yes/no)			0.93 (0.54–1.59)	0.78
Diabetes mellitus (yes/no)			1.96 (1.14–3.36)	0.014
Hypertension (yes/no)			0.86 (0.52–1.42)	0.55
Stroke (yes/no)			2.44 (1.42–4.21)	0.001
VHD (yes/no)			1.34 (0.70–2.60)	0.38

CHD indicates coronary heart disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; VHD, valvular heart disease.
*Only families with 2 cases of HF and no case of cardiomyopathy or congenital heart disease included.
[†]Cox regression HRs, adjustments as specified below.
[‡]28 deaths among 66 subjects with proband survival <5 y, from a total of 64 deaths among 241 subjects at risk.
[§]Age at onset and year of onset presented as per 10- and 1-y deviations from mean, respectively.

Table 6. Cardiovascular Mortality of Subjects First Hospitalized for HF, as Determined by Survival of Previously Affected Sibling (Proband)—Cardiomyopathies Excluded*

	Small Model, HR (95% CI)[†]	P Value	Fully Adjusted Model, HR (95% CI)[†]	P Value
Proband HF survival <5 y (yes/no)[‡]	1.98 (1.05–3.73)	0.034	2.30 (1.19–4.45)	0.013
Subject characteristics				
Sex (female/male)	0.85 (0.43–1.68)	0.65	1.26 (0.61–2.62)	0.54
Age at onset[§]	2.16 (1.18–3.97)	0.013	1.81 (0.94–3.47)	0.076
Year of onset[§]			1.06 (0.91–1.24)	0.42
CHD (yes/no)			1.55 (0.76–3.16)	0.23
Diabetes mellitus (yes/no)			1.25 (0.62–2.50)	0.54
Hypertension (yes/no)			0.53 (0.28–1.01)	0.054
Stroke (yes/no)			3.18 (1.61–6.26)	0.001
VHD (yes/no)			1.15 (0.51–2.60)	0.74

CHD indicates coronary heart disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; VHD, valvular heart disease.
*Only families with 2 cases of HF and no case of cardiomyopathy or congenital heart disease included.
[†]Cox regression HRs, adjustments as specified below.
[‡]17 deaths among 66 subjects with proband survival <5 y, from a total of 40 deaths among 241 subjects at risk.
[§]Age at onset and year of onset presented as per 10- and 1-y deviations from mean, respectively.

with HF survival. The HF overall mortality risk remained significantly associated with short proband HF survival when considering survival of non-HF siblings, which suggests a familial association of HF survival per se. Such a familial, and perhaps hereditary, association may be related to either the severity of the condition triggering HF or, in turn, long-term maladaptive factors influencing the progression of HF, in conjunction with the neurohormonal hypothesis.[20,21] The

hypothesis of severity of comorbidities, however, is not suggested by the results of increased familial risk with both ischemic and nonischemic HF and with adjustment for potential etiologies such as diabetes mellitus and hypertension. In addition, the observed mortality risks were not ameliorated when we adjusted for familial aggregation of CHD. Risks were not predominantly elevated among younger subjects, possibly reflecting factors affecting progression and

Table 7. Overall Mortality of Subjects* First Hospitalized for HF, as Determined by Survival of Previously Affected Sibling (Proband), Stratified Analyses

	Small Model, HR (95% CI)[†]	P Value	Fully Adjusted Model, HR (95% CI)[‡]	P Value
Subjects with median age of onset ≤68.3 y (total at risk, n=187; deaths, n=39)				
Proband HF survival <5 y (yes/no)	1.87 (0.97–3.61)	0.061	1.76 (0.88–3.54)	0.11
Subjects with median age of onset ≥68.3 y (total at risk, n=186; deaths, n=57)				
Proband HF survival <5 y (yes/no)	1.99 (1.16–3.43)	0.013	2.41 (1.35–4.29)	0.003
Male subjects (total at risk, n=238; deaths, n=63)				
Proband HF survival <5 y (yes/no)	1.81 (1.09–3.01)	0.023	1.74 (1.03–2.97)	0.040
Female subjects. (total at risk, n=135; deaths, n=33)				
Proband HF survival <5 y (yes/no)	2.27 (1.12–4.59)	0.022	2.53 (1.21–5.29)	0.014
Subjects without CHD (total at risk, n=184; deaths, n=38)[§]				
Proband HF survival <5 y (yes/no)	2.19 (1.12–4.25)	0.021	2.35 (1.18–4.67)	0.015
Subjects with CHD (Total at risk, n=189; deaths, n=58)[§]				
Proband HF survival <5 y (yes/no)	1.87 (1.10–3.18)	0.021	1.84 (1.05–3.23)	0.033

CHD indicates coronary heart disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; VHD, valvular heart disease.
*Only families with 2 cases of HF and no case of congenital heart disease included.
[†]Cox regression HRs, adjusted for subject age at onset and sex within appropriate strata.
[‡]Cox regression HRs, adjusted for subject age at onset, sex, coronary heart disease, diabetes mellitus, hypertension, nonrheumatic valvular heart disease, and stroke, within appropriate strata.
[§]Status at time of first hospitalization for HF.

Table 8. Overall Mortality of Subjects* First Hospitalized for HF, as Determined by Yearly Survival of Previously Affected Sibling (Proband), Calculated for First 5 Years of Proband Survival

	Small Model, HR (95% CI)[†]	P Value	Fully Adjusted Model, HR (95% CI)[†]	P Value
Effect on subject mortality conferred by proband per-year survival[‡]	0.88 (0.78–0.99)	0.031	0.86 (0.77–0.98)	0.018
Subject characteristics				
Sex (female/male)	0.90 (0.58–1.38)	0.62	0.94 (0.61–1.46)	0.79
Age at onset[§]	2.16 (1.54–3.02)	<0.001	2.14 (1.47–3.12)	<0.001
Year of onset[§]			0.96 (0.87–1.05)	0.34
CHD (yes/no)			0.90 (0.57–1.41)	0.64
Diabetes mellitus (yes/no)			2.69 (1.74–4.17)	<0.001
Hypertension (yes/no)			0.79 (0.53–1.20)	0.27
Stroke (yes/no)			2.26 (1.46–3.51)	<0.001
VHD (yes/no)			1.61 (0.94–2.76)	0.082

CHD indicates coronary heart disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; VHD, valvular heart disease.
*Only families with 2 cases of HF and no case of congenital heart disease included.
[†]Cox regression HRs, adjustments as specified below.
[‡]37 deaths among 90 subjects with proband survival <5 y, from a total of 96 deaths among 373 subjects at risk.
[§]Age at onset and year of onset presented as per 10- and 1-y deviations from mean, respectively.

prognosis first when the processes of HF are triggered. However, fewer deaths occurred among younger subjects in general and may account for the results not reaching significant levels in this group. The overall results could also, at least in part, be reflected by a familial susceptibility to malignant arrhythmias triggered by HF progression.[22]

The nondichotomized phenotype with a continuous pattern of decreasing subject mortality risk with the length of proband survival is suggestive of a complex trait caused by multifactorial determinants, as in a polygenic model, potentially with environmental interactions.[23]

Strengths and Limitations

As a nationwide register study with almost complete coverage of hospital records,[13] there was an inherently reduced risk of recall and selection bias that was further ameliorated by the

structure of the Swedish healthcare system, a low-cost all-embracing system readily available to the entire population. Consequently, this study also represents the morbidity and mortality of female HF patients, who are often disproportionally studied in relation to prevalence.[24] Furthermore, the diagnoses studied have been found to have validity of 90% to 95%.[13–15] This study concerns prognostic effects of familial survival in HF—a strength from a clinical perspective, taking into account genetic, epigenetic, and environmental factors.

Limitations of this study design include the lack of genetic data and information about other variable parameters with the potential to influence the risk of HF and death, including left ventricular ejection fraction and precise reading of blood pressure. No comorbidities diagnosed only after first hospitalization for HF were recorded, allowing, for example, the presence of insidious CHD not yet diagnosed at first HF hospitalization to still contribute to the etiology of HF and

Table 9. Overall Mortality of Subjects* First Hospitalized for HF, as Determined by Survival of Previously Affected Sibling (Proband), Stratified by Median Difference in Time Between Subject and Proband Time of Hospitalization

	Small Model, HR (95% CI)[†]	P Value	Fully Adjusted Model, HR (95% CI)[‡]	P Value
Occurrence of subject hospitalization within median 1726 d after that of proband				
Proband HF survival <5 y (yes/no)[§]	1.93 (1.16–3.20)	0.012	2.17 (1.25–3.78)	0.006
Occurrence of subject hospitalization median >1726 d after that of proband (total at risk, n=186; deaths, n=33)				
Proband HF survival <5 y (yes/no)[‖]	2.07 (1.02–4.22)	0.044	2.98 (1.34–6.62)	0.008

CHD indicates coronary heart disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; VHD, valvular heart disease.
*Only families with 2 cases of HF and no case of congenital heart disease included.
[†]Cox regression HRs, adjusted for subject age at onset and sex, within appropriate strata.
[‡]Cox regression HRs, adjusted for subject age at onset, sex, CHD, diabetes mellitus, hypertension, nonrheumatic VHD, and stroke, within appropriate strata.
[§]25 deaths among 47 subjects with proband survival <5 y, from a total of 63 deaths among 187 subjects at risk.
[‖]12 deaths among 43 subjects with proband survival <5 y, from a total of 33 deaths among 186 subjects at risk.

Table 10. Overall Mortality After First Hospitalization for HF, as Determined by Survival Time of the First Affected Sibling (Proband), Related to CHD in Family and to Mortality of Siblings Without HF*

	Small Model, HR (95% CI)[†]	*P* Value	Fully Adjusted Model, HR (95% CI)[‡]	*P* Value
Regular Cox regression calculation				
Proband HF survival <5 y (yes/no)[§]	1.78 (1.09–2.89)	0.021	1.79 (1.08–2.96)	0.024
Cox regression calculation with added adjustment in both models for the relative number of siblings with CHD and for the effect of mortality incidence ratio of non-HF siblings				
Proband HF survival <5 y (yes/no)[§]	1.80 (1.08–3.02)	0.025	1.91 (1.12–3.25)	0.017

CHD indicates coronary heart disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; VHD, valvular heart disease.
*Only families with 2 cases of HF and with at least 1 sibling free of HF included. Families with a recorded case of congenital heart disease excluded.
[†]Cox regression HRs, adjusted for subject age at onset and sex.
[‡]Cox regression HRs, adjusted for subject age at onset, sex, CHD, diabetes mellitus, hypertension, nonrheumatic VHD, and stroke.
[§]27 deaths among 70 subjects with proband survival <5 y, from a total of 69 deaths among 276 subjects at risk.

mortality of HF. However, when adjusting for CHD in a family, as an additional proxy of familial risk of CHD, the results remained essentially unchanged. Patients may have been diagnosed with but not hospitalized for HF before being included in this study. However, with relatively evenly distributed prerequisites for health care and with HF being underdiagnosed in its earlier stages[25] and being a progressive condition,[21] survival measured from the first event requiring hospitalization for HF would be an important point of reference. Although follow-up time was limited, there were no signs of risk decreasing with time elapsed from the date of hospitalization. The numbers of participants and failures were relatively few, thus limiting the number of adjusting variables.

Conclusions

In conclusion, these results suggest that family history of poor survival in specific relation to HF is an important risk factor for death in HF patients. Further genetic analyses of individuals in families with poor HF survival are needed to explore the molecular underpinnings of our findings. Careful monitoring may be considered for HF patients with a history of poor familial HF survival. Additional studies are needed to identify whether a specific phenotypic presentation is characterized by increased progression or susceptibility to arrhythmias to be able to offer optimized treatment.

Acknowledgments

The authors wish to thank science editor Patrick Reilly for his useful comments on the text.

Sources of Funding

Disclosures

None.

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