Published in final edited form as:

Am Heart J. 2007 November ; 154(5): 855–860.

Secular Trends of Heart Failure among US Male Physicians

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Abstract

Background—Heart failure remains a major public health issue. Data on long-term trends in the incidence of heart failure and survival after its onset are limited.

Methods—A prospective cohort study conducted between 1985 and 2004 in 21,831 participants of the Physicians' Health Study I who were alive and free of heart failure on January 1, 1985.

Results—After an average follow up of 16.8 years, a total of 909 incident cases of heart failure occurred in this cohort. There was no evidence for a substantial change in the incidence rate of heart failure across the four periods (p for trend 0.29). From 1985 through 2004, there were 457 deaths among 909 subjects with heart failure. Compared with the period of 1985 to 1989, the age-adjusted hazard ratio of all-cause mortality after onset of heart failure was 0.61 (0.46–0.81), 0.37 (0.28–0.48), and 0.10 (0.07–0.15) in the second, third, and fourth period, respectively (p for trend <0.0001). Additional adjustment for treatment arm, diabetes, myocardial infarction, hypertension, atrial fibrillation, coronary angioplasty or bypass, valvular heart disease, and left ventricular hypertrophy did not alter these results. Similar findings were seen in subjects with heart failure with and without antecedent myocardial infarction (p for trend <0.0001 each).

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Drs. Djoussé and Gaziano have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Djoussé

Acquisition of data: Gaziano

Analysis and interpretation of data: Djoussé, Kochar, and Gaziano

Drafting of the manuscript: Djoussé

Critical revision of the manuscript for important intellectual content: Djoussé, Kochar, and Gaziano

Statistical analysis: Djoussé

Obtaining funding: Gaziano and Djoussé

Administrative, technical, or material support: Djoussé, Kochar, and Gaziano

Study supervision: Gaziano

Role of the Sponsor: The sponsors of the study had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Financial disclosures: Dr. Gaziano has received investigator-initiated research grants from BASF, DSM Pharmaceuticals, Wyeth Pharmaceuticals, McNeil Consumer Products, and Pliva; has received honoraria from Bayer and Pfizer for speaking engagements; and is a consultant for Bayer, McNeil Consumer Products, Wyeth Pharmaceuticals, Merck, Nutraquest, and GlaxoSmithKline. Drs. Djoussé and Kochar: None to disclose.

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Conclusions—Over the past 20 years, we observed a lower risk of all-cause mortality after onset of heart failure whereas no major change in the incidence of heart failure was seen among US male physicians.

Keywords

Heart failure; epidemiology; and mortality

The lifetime risk of heart failure (HF) is estimated at 20% (1 in 5) for both men and women aged 40 years¹. Heart failure is the leading cause of hospitalization among elderly people in the United States². About 4.9 million Americans are affected with this condition and HF costs were estimated at 27.9 billion dollars for 2005 in the US³. Once diagnosed, mortality after onset of HF is very high⁴⁻⁶, ranging from 20% to 50%⁷⁻¹⁰. Data on the incidence rate of HF and survival after its onset in community settings are sparse. Previous studies have suggested a constant rate of HF in men but an increase of incident HF in women¹¹⁻¹³. In contrast, several studies have reported an improvement in survival over time after the onset of any HF^{11,12} or HF with reduced ejection fraction only¹⁴. Nearly half of the people with HF in the community have normal left ventricular function¹⁵⁻²⁰. It is not known whether HF patients with antecedent myocardial infarction – more likely to have a poorer left ventricular function – have a poorer survival than those without antecedent myocardial infarction.

In the current project, we sought to prospectively assess temporal trends in incidence of and survival after onset of HF from 1985 through 2004 in the Physicians' Health Study I. In addition, we assessed the influence of antecedent myocardial infarction on temporal trends in survival after onset of HF in the same time period.

Methods

Study population

The current study analyzed data from the Physicians' Health Study (PHS) I, which was a randomized trial among US male physicians. A detailed description of the PHS I has been published previously²¹. For the current project, after the exclusion of 165 subjects (33 prevalent HF and 132 individuals who were deceased before January 1, 1985 or had missing data), the final sample consisted of 21,906 participants. Each participant gave written informed consent and the study protocol was approved by the Institutional review Board at Brigham and Women's Hospital.

Ascertainment of incident HF and death

A questionnaire was mailed to each participant every 6 months during the first year and has been mailed annually thereafter to gather information on compliance with the intervention and the occurrence of new medical diagnoses including HF and death. For participants who do not return the follow-up questionnaire within 5 to 6 weeks of the initial mailing, a second follow-up questionnaire is sent to them. If necessary, a third and a fourth questionnaire are sent to non-respondents followed by a telephone call to obtain follow-up information if the mail is not answered. If the follow-up information is not obtained by questionnaires or telephone call, vital status of the corresponding participants is ascertained. A letter and return postcard are also mailed to the participants at the 6-month interval between annual mailings. Participants are asked to return the postcard if they have experienced any major problem affecting their participation in the study. For all reported cases of death, medical records, death certificates, and search of national death index were used by the Endpoint Committee of the PHS for confirmation.

Details on validation of heart failure in the PHS have been published²². Briefly, in a previous pilot study, a total of 100 participants who reported a HF diagnosis on a follow-up questionnaire were contacted by mail. The mailing included a HF questionnaire with detailed questions about time and place of HF diagnosis, clinical signs and symptoms, medical treatment, and diagnostic methods (echocardiography, angiogram, and radionuclide imaging). Of the 100 physicians, 4 had died and 8 participants had a routine follow-up method that deviates from the normal mailing procedure (example: some participants have requested to be contacted by telephone only). After 2 mailings, we obtained a completed questionnaire from 73 out of 88 (83%) participants. Among respondents, 90% of the HF cases were confirmed using the Framingham criteria²³. Of note is that these estimates are very conservative because our experience in the PHS is that after 4-5 mailings, non-respondents are contacted via telephone calls. With this approach, the response rate has been well above 90-95%.

Other variables

Demographic data were collected at baseline. Information on incident atrial fibrillation, hypertension, coronary angioplasty or bypass surgery, myocardial infarction, valvular heart disease, left ventricular hypertrophy, and diabetes mellitus has been collected through annual follow-up questionnaires as described above.

Statistical analyses

We created 4 periods of 5 years each: January 1, 1985 through December 31, 1989; January 1, 1990 through December 31, 1994; January 1, 1995 through December 31, 1999; and January 1, 2000 through December 31, 2004. Within each period, we calculated age-adjusted incidence rate of HF using direct standardization. Specifically we calculated weighted average of age-specific incidence rates using the person-time distribution across 5-year age categories (<55, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and 85+ years) in the total cohort as weights. We calculated age-adjusted incidence rate ratios of HF using Poisson regression model (*Proc Genmod* procedure in SAS). Goodness-of-fit was evaluated by the model deviance. We used the period from 1985-1989 as reference and created 3 indicators variables.

Actuarial survival analyses after onset of HF were performed using the Kaplan-Meier method and we used log-rank test for statistical significance. We used Cox proportional hazards regression to compute age-adjusted and multivariable adjusted hazard ratios with corresponding 95% confidence intervals using subjects in period of 1985 through 1989 as the reference. The full model included age, treatment arm (aspirin, beta-carotene, both drugs, or placebo), and prevalence of hypertension, myocardial infarction, atrial fibrillation, diabetes mellitus, coronary bypass surgery or angioplasty, valvular heart disease, and left ventricular hypertrophy at the beginning of each period. We obtained p value for linear trend by modeling period effect as a continuous variable.

We conducted stratified analyses to examine survival among people with HF with and without antecedent myocardial infarction. In addition, we examined the incidence of coronary revascularization or angioplasty over time as well as the incidence of and mortality after onset of myocardial infarction over time. Analyses were completed using SAS, version 9.1 (SAS Institute, NC). Significance level was set at 0.05.

Results

Table 1 presents characteristics of the study population by time period. A total number of 909 cases of HF occurred in this cohort between 1985 and 2004. The mean ($\pm$ SD) age at diagnosis of HF was 67.1 ± 9.2 years in the period from 1985 through 1989 and 78.6 ± 8.3 years in the

period from 2000 through 2004. Subjects in the most recent period had a higher prevalence of comorbidity and were older on average compared with subjects in the first period.

Trends in the incidence rate of HF

Standardized incidence rates of HF and adjusted rate ratios are presented in Table 2. Compared with the period from 1985 through 1989, the age-adjusted incidence rate of HF increased slightly over time. However, in a multivariable model controlling for age, treatment group, atrial fibrillation, hypertension, diabetes mellitus, left ventricular hypertrophy, valvular heart disease, and coronary angioplasty or bypass surgery, there was no evidence for an increase in the incidence rate of HF over time (p for trend 0.29, Table 2). There was no evidence of interaction between treatment group and time period on the risk of HF (p=0.99).

Trends in mortality after onset of HF

From 1985 through 2004, 457 cases of death occurred among 909 participants with HF. The mean ($\pm$ SD) age at the time of death was 77.5 ± 8.6 years in the period from 1985 through 1989 and 85.7 ± 7.6 years in the period from 2000 through 2004. There was evidence for a lower risk of death after onset of HF from 1985 to 2004 (log rank p <0.0001). Compared with the period from 1985 through 1989, the risk of total mortality after onset of HF was 39%, 63%, and 90% lower in the second, third, and fourth period, respectively, after adjustment for age (p for trend <0.0001, Table 3). Additional adjustment for treatment arm (aspirin, beta-carotene, both drugs, or placebo), and prevalence of hypertension, myocardial infarction, atrial fibrillation, diabetes mellitus, coronary bypass surgery or angioplasty, valvular heart disease, and left ventricular hypertrophy did not alter the results (Table 3). This inverse association was observed across all four treatment groups (p for trend <0.0001 for each group) and there was no evidence of interaction between treatment group and time period on the risk of death after onset of HF (p for interaction 0.30). Furthermore, we observed similar trends in survival among participants with HF with and without antecedent myocardial infarction. Compared with the period from 1985 through 1989, the multivariable adjusted risk of all-cause mortality was 46%, 67%, and 90% lower in the second, third, and fourth period, respectively, among participants with HF without antecedent myocardial infarction (p for trend <0.0001, Table 4). Corresponding values for participants with antecedent myocardial infarction were 13%, 56%, and 88%, respectively (p for trend <0.0001, Table 4).

Secular trends for coronary intervention, myocardial infarction, and survival after myocardial infarction

There was evidence for an increase in incidence rate of coronary intervention (coronary angioplasty or bypass surgery). Age-adjusted incidence rate ratio (95% CI) were 1.0 (reference), 1.22 (1.09-1.36), 1.53 (1.37-1.71), and 1.32 (1.16-1.50) for periods between 1985-1989; 1990-1994; 1995-1999, and 2000-2004; respectively (p for trend <0.0001). After additional adjustment for baseline prevalence of myocardial infarction, atrial fibrillation, diabetes mellitus, left ventricular hypertrophy, hypertension, valvular heart disease, and treatment arm (aspirin, beta-carotene, both drugs, or placebo), corresponding values were 1.0 (reference), 1.18 (1.05-1.32), 1.46 (1.30-1.63), and 1.24 (1.09-1.41), respectively (p for trend <0.0001). In this cohort, there was evidence for a decrease in incident myocardial infarction over time (p for trend <0.0001) and improved survival after the diagnosis of myocardial infarction (p for trend <0.0001).

Discussion

In this prospective cohort, we demonstrated that there were no major changes in incidence rates of HF from 1985 through 2004 among US male physicians. In contrast, we found that the risk of all-cause mortality after onset of HF decreased over time during the same 20-year period in

the PHS I. The lower risk of all-cause mortality after onset of HF was seen among participants with and without antecedent myocardial infarction and was lowest in the period of 2000 through 2004 compared with the period of 1985 through 1989 in either group.

While HF remains a major public health issue, data on secular trends in incidence of and mortality after onset of HF in community settings have been inconsistent. Senni and colleagues²⁴ reported no difference in incidence of or survival after onset of HF between 1981 and 1991. In addition, Framingham investigators found no statistically significant temporal change in survival after the diagnosis of HF between 1948 through 1988²⁵. Furthermore, Bhatia et al.²⁶ reported no difference in 1-year mortality between HF subjects with and without preserved ejection fraction. In contrast, other investigators reported temporal decline in mortality after hospitalization for HF^{13,27}. Data from the Worcester Heart Attack Study reported a temporal decrease in mortality among individuals with HF over 20 years, with a 54% lower odds of death in the period from 1993 to 1995 compared with the period between 1975 and 1978²⁸. Subsequent findings from the Framingham Heart Study¹¹ showed a decline in the incidence rate of HF in women but not in men and an improved survival in both sexes after onset of HF during the period of 1950 through 1999. Data from the Olmsted County, MN, showed no change in HF rate but an improved survival after onset of HF between 1979 and 2000¹². Another report from the same cohort found that the improved survival was restricted to HF with reduced ejection fraction¹⁴. Our data are consistent with findings from other community-based populations^{11,12} supporting a decrease in mortality after onset of HF over time and no change in rates of HF over time in men. What could possibly explain the large effect observed in our study compared with the Framingham and Olmsted County data?

Although there was no statistically significant increase in the incidence rate over time and we used the same method to ascertain HF from 1985 through 2004, it is possible that that lead-time bias played a major role in our study in that physicians in the most recent period were more likely to report mild cases of HF detected through novel diagnostic methods (including BNP and imaging studies). It is reasonable to argue that improved medical treatment of HF may partially account for the improved survival. Data from the Worcester Heart Attack Study showed an increased use of angiotensin-converting enzyme inhibitors and digoxin among patients with HF^{11,12}, suggesting that pharmacotherapy could partially explained these findings. In addition, aggressive treatment of myocardial infarction and other risk factors for HF (including blood pressure, weight control, and lipid management) may have averted severe forms of HF with a higher case fatality. If physicians in our cohort were more likely to receive these treatment compared to the general population, this might partially explain the large effect observed in our data. Unfortunately, we did not have data on medications to assess the effects of treatment on the observed temporal decline in mortality after onset of HF. The fact that we observed a significant increase in the incidence rate of coronary angioplasty and bypass surgery over time; a decrease in the incidence rate of myocardial infarction; and decreased mortality after diagnosis of myocardial infarction over time is consistent with such hypothesis. An aggressive detection and treatment of hypertension, coronary heart disease, and other conditions might confer a lower baseline rate of death in the reference category and thus favor large relative effect measures in other categories. In addition, physicians may be more likely to initiate and adhere to an effective treatment for the management of HF and thereby decrease the risk of death from the disease.

We were not able to determine the severity of HF at the time of diagnosis (i.e. NYHA classification). It is likely that with a wider use of novel diagnostic tools, the likelihood of reporting mild cases of HF increased over time. Such differential reporting could have led to an overestimation of all-cause mortality and might also help explain the large difference in the magnitude of effect between our study and other large cohorts. On the other hand, age at diagnosis of HF increased over time and one would expect older age at HF diagnosis to be

associated with a higher mortality. Since we observed the opposite in our data, it is possible that subjects with late onset of HF had favorable genetic factors that protected them from chronic diseases in general and/or contributed to their longevity (irrespective of chronic conditions) compared with those who died earlier during the follow up. This scenario will bias our results towards improved survival irrespective of HF onset. The lack of genetic data at this point precludes the testing of such hypothesis.

We did not collect data on the type of HF to evaluate secular trends in survival after onset of HF with and without preserved left ventricular function. Although less likely, it is possible that we may have missed some cases of HF in this population. However, we did not anticipate that such loss would be differential over time periods since study participants were physicians. The generalizability of our findings is limited by the fact that our cohort consists of men with a higher socioeconomic status and the majority of participants are whites. Given the observational nature of our findings, we cannot completely exclude chance as possible explanation for our findings. Another limitation of our study is the relatively small number of deaths in some of the strata, especially in the most recent period. Thus, our effect measure should be interpreted with caution. Lastly, except for aspirin use, we did not have data on first line cardioprotective drugs (i.e. angiotensin converting enzyme inhibitors, statins, beta-blockers, angiotensinogen receptor blockers, etc) and length of treatment to evaluate their impact on the observed effects. On the other hand, the large sample size, the longer duration of follow up, the use of standardized ascertainment methods for endpoints are strengths of the present study.

Our data provide evidence for a lower risk of all-cause mortality over time after onset of HF among US male physicians in the period of 1985 through 2004. Given the public health impact of HF in the community, factors contributing to such lower mortality should be evaluated in future studies. In addition, given a higher prevalence of HF with preserved left ventricular function^{16,19,20}, additional studies examining temporal trends in incidence of and survival after onset of HF with and without preserved left ventricular function are warranted. Since most cases of HF are accounted for by antecedent coronary artery disease and hypertension²⁹⁻³³, primary prevention of hypertension and coronary heart disease should remain the highest priority in curbing the HF epidemic.

Acknowledgements

We are indebted to the participants in the PHS for their outstanding commitment and cooperation and to the entire PHS staff for their expert and unfailing assistance.

Funding/Support: The Physicians' Health Study is supported by grants CA-34944 and CA-40360 from the National Cancer Institute and grants HL-26490 and HL-34595 from the National Heart, Lung, and Blood Institute, Bethesda, MD. Dr. Djoussé is Principal Investigator on a K01 HL-70444 from the National Heart, Lung, and Blood Institute, Bethesda, MD.

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Table 1
Baseline characteristics of the study participants in the Physicians' Health Study

Characteristics	Period			
	1985-1989 (n=21,906)	1990-1994 (n=21,192)	1995-1999 (n=19,985)	2000-2004 (n=18,241)
Age (y)	55.7±9.5	60.3±9.3	64.7±8.9	68.8±8.3
Age at heart failure diagnosis (y)	67.1±9.2	72.7±8.2	75.1±8.6	78.6±8.3
Heart failure cases (%)	0.6	0.9	1.9	1.3
Aspirin arm (%)	50.0	50.1	50.0	49.9
Myocardial infarction (%)	0.7	1.9	3.1	4.1
Hypertension (%)	4.2	10.4	15.4	19.7
Atrial fibrillation (%)	1.9	3.5	5.7	9.0
Left ventricular hypertrophy (%)	0.3	0.5	1.1	2.0
Diabetes mellitus (%)	2.6	4.1	5.6	7.6
Valvular heart disease (%)	0.4	1.0	1.5	2.0
Coronary angioplasty or bypass (%)	1.4	3.7	6.8	10.6

Table 2
Age-adjusted incidence rates and ratios of heart failure from 1985 to 2004 in the PHS I *

Period	Age-standardized rates of failure per 100,000 person-years (95% CI)	Rate ratio (95% CI) ‡
1985-1989 †		
1990-1994	175 (142-209)	1.0
1995-1999	212 (181-243)	0.92 (0.58-1.47)
2000-2004	327 (293-361)	1.25 (0.97-1.93)
P for trend	196 (170-222)	0.74 (0.46-1.19)

* Adjusted for age (<55, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and 85+ years).

† This period served as the reference period.

‡ Using Poisson regression model adjusted for age (categories as above), treatment arm (aspirin, beta-carotene, both drugs, or placebo), and prevalence of hypertension, myocardial infarction, atrial fibrillation, diabetes mellitus, coronary bypass surgery or angioplasty, valvular heart disease, and left ventricular hypertrophy.

Table 3
Long-term trends in the adjusted risk of death after the onset of heart failure, 1985 through 2004 in the PHS I

Period	Deaths/N	Hazard ratio (95% CI)	
		Age-adjusted*	Model 1†
1985-1989	84/123	1.0	1.0
1990-1994	133/185	0.61 (0.46-0.81)	0.59 (0.45-0.79)
1995-1999	182/370	0.37 (0.28-0.48)	0.36 (0.27-0.47)
2000-2004	58/231	0.10 (0.07-0.15)	0.10 (0.07-0.14)
P value for linear trend		<0.0001	<0.0001

* Adjusted for age as continuous variable.

† Model 1 adjusted for age, treatment arm (aspirin, beta-carotene, both drugs, or placebo), and prevalence of myocardial infarction, diabetes mellitus, atrial fibrillation, hypertension, coronary angioplasty or revascularization, valvular heart disease, and left ventricular hypertrophy at the beginning of each interval.

Influence of myocardial infarction on long-term trends in the risk of death after the onset of heart failure in the PHS I

Period	Heart failure without antecedent myocardial infarction			Heart failure with antecedent myocardial infarction		
	Deaths/N	Age-adjusted*	Model 1*	Deaths/N	Age-adjusted	Model 1*
1985-1989 [†]	69/100	1.0	1.0	15/23	1.0	1.0
1990-1994	110/157	0.56 (0.41-0.77)	0.54 (0.39-0.74)	23/28	0.93 (0.47-1.86)	0.87 (0.42-1.78)
1995-1999	152/308	0.34 (0.25-0.46)	0.33 (0.24-0.46)	30/62	0.50 (0.26-0.95)	0.44 (0.21-0.93)
2000-2004	49/193	0.10 (0.07-0.14)	0.10 (0.06-0.15)	9/38	0.12 (0.05-0.30)	0.12 (0.05-0.31)
P for trend		<0.0001	<0.0001		<0.0001	<0.0001

* Adjusted for age, treatment arm (aspirin, beta-carotene, both drugs, or placebo), and prevalence of diabetes mellitus, atrial fibrillation, hypertension, coronary angioplasty or revascularization, valvular heart disease, and left ventricular hypertrophy at the beginning of each interval.

[†]This period served as reference category.