European Heart Journal (2004) **25**, 1614–1619

Clinical research

Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure

The Rotterdam Study

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Received 8 March 2004; revised 14 June 2004; accepted 24 June 2004
Available online 21 August 2004

KEYWORDS
Heart failure;
Epidemiology;
Prevalence;
Incidence;
Lifetime risk;
Prognosis

Aims To determine the prevalence, incidence rate, lifetime risk and prognosis of heart failure.
Methods and Results The Rotterdam Study is a prospective population-based cohort study in 7983 participants aged ⩾55. Heart failure was defined according to criteria of the European Society of Cardiology. Prevalence was higher in men and increased with age from 0.9% in subjects aged 55–64 to 17.4% in those aged ⩾85. Incidence rate of heart failure was 14.4/1000 person-years (95% CI 13.4–15.5) and was higher in men (17.6/1000 man-years, 95% CI 15.8–19.5) than in women (12.5/1000 woman-years, 95% CI 11.3–13.8). Incidence rate increased with age from 1.4/1000 person-years in those aged 55–59 to 47.4/1000 person-years in those aged ⩾90. Lifetime risk was 33% for men and 29% for women at the age of 55. Survival after incident heart failure was 86% at 30 days, 63% at 1 year, 51% at 2 years and 35% at 5 years of follow-up.
Conclusion Prevalence and incidence rates of heart failure are high. In individuals aged 55, almost 1 in 3 will develop heart failure during their remaining lifespan. Heart failure continues to be a fatal disease, with only 35% surviving 5 years after the first diagnosis.

Introduction

Heart failure constitutes a major public health burden in the western world. Since incidence rates appear to remain stable over the years, at least in men,[1] prevalence estimates of heart failure are bound to increase as the

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0195-668X/$ - see front matter © 2004 Published by Elsevier Ltd on behalf of The European Society of Cardiology.
doi:10.1016/j.ehj.2004.06.038

population ages. Hospitalisation rates for heart failure have increased considerably.[2] The proportion of patients having multiple hospital admissions is rising. In addition, large observational studies have failed to show any substantial change in the prognosis of heart failure in the general population, despite evidence-based advances in treatment.[3] Hospitalisation rates do not necessarily reflect the true incidence and prevalence of heart failure in the general population, as only the more serious stages of this syndrome require in-hospital evaluation and treatment. Although data regarding heart failure incidence, prevalence and prognosis in the community are vital, few large prospective population-based studies have been published that provide recent estimates, especially in European populations. Furthermore, most recent population-based estimates originate from relatively short-term studies,[4–6] except for the Framingham Heart Study[1] and the Cardiovascular Health Study,[7] both of which were performed in the United States. The diagnosis of heart failure is complex. Signs and symptoms are not specific and a gold standard to assess the presence of this disease is lacking. Previously published studies have used various criteria to assess the presence of heart failure. The European Society of Cardiology has therefore provided guidelines for the diagnosis of heart failure, for use in clinical practice and epidemiological surveys.[8] According to these guidelines, objective evidence of cardiac dysfunction has to be present to establish the presence of heart failure, in addition to typical symptoms (e.g., breathlessness) suggestive of the diagnosis.

This study was designed to calculate the prevalence, incidence, and lifetime risk of heart failure in participants of the Rotterdam Study, a large prospective population-based cohort study with more than 10 years of follow-up. In addition, we studied the prognosis of cases of incident heart failure.

Methods

Setting and study population

The Rotterdam Study was a population-based prospective cohort study of cardiovascular, locomotor, neurologic and ophthalmologic diseases in the elderly.[9] All inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, who were 55 years of age or older were invited to participate. Of all 10 275 subjects in this age group, 7983 agreed to participate (78%). The Medical Ethics Committee of the Erasmus Medical Centre approved the study. The baseline examination was conducted between July 1989 and 1993. Participants were visited at home for a standardized questionnaire and were subsequently examined at the research centre. Since the start of the Rotterdam Study, cross-sectional surveys have been carried out periodically. In addition, participants are continuously monitored for major events that occur during follow-up, including heart failure, through automated linkage with files from general practitioners. Information on vital status is obtained regularly from municipal health authorities in Rotterdam and from the general practitioners working in the study district of Ommoord, and was complete for all participants until January 1, 2000. Furthermore, all drug prescriptions dispensed to participants by all pharmacies in the study area are routinely stored in the database.

To obtain recent estimates, the point prevalence of heart failure was determined at the 1st of January of 1997, 1998 and 1999. Calculations were performed in all participants of the Rotterdam Study who were alive and present at January 1 of each of these years. Four participants were excluded because of missing medical records. For estimation of incidence rates and lifetime risks, the study population comprised 7734 subjects who were free from heart failure at baseline. Subjects were followed from baseline until the first of one of the following: a diagnosis of incident heart failure, death, loss to follow-up (<1%), date of last collection of information for determination of heart failure, or January 1, 2000. The date of last information on heart failure status preceded January 1, 2000 for 14.4% of participants. For the calculation of survival estimates, incident heart failure patients were followed from the date of incident heart failure until the earliest of death, removal from the study area, or January 1, 2000.

Heart failure assessment

Assessment of prevalent heart failure at the baseline examination in the Rotterdam Study has been described in detail previously.[10] Briefly, a validated score was used, similar to the definition of heart failure of the European Society of Cardiology.[8] This score was based on the presence of at least two signs or symptoms suggestive of heart failure (shortness of breath, ankle swelling and pulmonary crepitations) or use of medication for the indication of heart failure, in combination with objective evidence of cardiovascular disease. Questions on indication of cardiovascular medication and breathlessness were lacking at the start of the Rotterdam Study, but were subsequently added. Consequently, this information was obtained in only 5540 participants. In addition, prevalent heart failure cases were obtained through a database containing hospital discharge diagnoses from all hospitals in the Rotterdam area as of January 1, 1991. Records from this database were linked to the Rotterdam Study database. For potential cases of heart failure identified in this way, copies of discharge letters were requested. Furthermore, all medical records were screened in retrospect for the occurrence of heart failure in the majority (97%) of participants of the Rotterdam Study. With these three methods, information on the presence of heart failure at baseline was available for all participants.

Cases of incident heart failure were obtained by continuously monitoring participants of the Rotterdam Study for the occurrence of heart failure during follow-up through automated linkage with files from general practitioners. All available data on these events, such as hospital discharge letters and notes from general practitioners, were copied from the medical records. Apart from this systematic follow-up procedure, we used verified hospital discharge diagnoses for case finding, gathered from all hospitals in the Rotterdam area as described above. The date of incident heart failure was defined as the day of the first occurrence of symptoms suggestive of heart failure, obtained from the medical records, or the day of receipt of a first prescription for a loop diuretic or an ACE-inhibitor, whichever came first.

The diagnosis of heart failure was classified as definite, probable, possible or unlikely. Definite heart failure was defined as a combination of the presence of at least one of the typical signs or symptoms of heart failure, such as breathlessness at rest or during exertion, ankle oedema and pulmonary crepitations, and confirmation by objective evidence of cardiac dysfunction (chest X-ray, echocardiography). This definition is in accordance with the criteria of the European Society of Cardiology.[8] Also, for definite heart failure, the diagnosis had to have been made by a medical specialist. Heart failure was classified as probable when

at least two typical symptoms suggestive of heart failure were present, and at least 1 of the following: history of cardiovascular disease (e.g., myocardial infarction, hypertension), response to treatment for heart failure, or objective evidence of cardiac dysfunction, while symptoms could not be attributed to another underlying disease, such as chronic obstructive pulmonary disease. Heart failure was classified as possible when one of the criteria for probable heart failure could not be met. For both probable and possible heart failure, a diagnosis of a general practitioner sufficed. Heart failure was considered unlikely if signs or symptoms were present, but when objective evidence failed to show cardiac dysfunction, and if signs or symptoms could be attributed to another underlying disease. Two research physicians independently classified all information on potential heart failure events. If there was disagreement, a consensus was reached in a separate session. Finally, a cardiologist verified all probable and possible cases, and all cases in which the two physicians could not reach consensus. If the cardiologist disagreed with the research physicians, the cardiologist's judgment was considered decisive. The research physicians and the cardiologist based their decisions on the same data. Only definite and probable cases were included in the analyses.

Statistical analysis

Prevalence of heart failure per calendar year was calculated by dividing the number of persons with prevalent heart failure by the number of subjects present in the study population at January 1 of each calendar year. 95% confidence intervals (CI) were calculated with Wilson's (score) method for a binomial proportion. Prevalence estimates were calculated for men and women separately and in 10-year age categories. The incidence rate of heart failure was determined by dividing the number of cases of incident heart failure by the total number of person-years accumulated in the study population without heart failure at baseline. The 95% CI around the estimates were calculated based on the Poisson distribution. Incidence rate estimates were calculated by gender and age (5-year categories).

To calculate the risk to develop heart failure over time, competing risk of death was taken into account. First, we calculated heart failure free survival at different ages with the Kaplan–Meier method, using incident heart failure and mortality data from the study cohort. Age at baseline was used as the entry time variable and age at the end of follow-up, incident heart failure, or death, as failure time variable. Both death and incident heart failure were classified as failures. Second, the cumulative absolute risk of heart failure over a period was calculated as the integrated product of the age-specific heart failure incidence rates and heart failure free survival.[11] The risks of heart failure over time were calculated for the total population and for men and women separately at the ages of 55, 65, 75, and 85 years.

The prognosis of heart failure was determined in 725 subjects with incident heart failure during follow-up. Survival after incident heart failure (30-day, 1-year, 2-year and 5-year) was calculated using the Kaplan–Meier method. Survival was also determined after exclusion of patients who died in the first 30 days, thereby excluding those with a first diagnosis of heart failure on the day of their death and the most severe cases of heart failure. We used Cox proportional hazards regression analysis to study gender differences in survival, adjusted for age.

Results

A total of 245 prevalent heart failure cases (88 men, 157 women) were identified at baseline in the Rotterdam Study. In the remaining study population ($n = 7734$), we identified 725 incident cases of heart failure (335 men, 390 women), of whom 673 were classified as definite, and 52 as probable cases. The median follow-up time in this population was 7.1 years (interquartile range: 5.7–8.0) and we had 50 268 person-years of observation in total. The majority of our study population was female (61%) and mean age at baseline was 70.4 years (standard deviation 9.7 years). Mean age at the onset of heart failure was significantly higher in women than in men (82.5 and 77.5 years, respectively).

Prevalence

Point prevalence of heart failure was determined at January 1 of 1997, 1998 and 1999 and was 6.4% (95% CI 5.8–7.0), 6.7% (95% CI 6.1–7.4) and 7.0% (95% CI 6.4–7.7), respectively. Mean age of the study population increased from 73.3 years in 1997 to 74.5 years in 1999. Prevalence was higher in men than in women (e.g., 1998: men 8.0%, women 6.0%). There was a sharp rise of prevalence estimates with age. For example, in 1998 point prevalence increased from 0.9% (95% CI 0.5–1.6) in subjects aged 55–64 years, 4.0% (95% CI 3.3–4.8) in subjects aged 65–74 years, 9.7% (95% CI 8.4–11.1) in those aged 75–84 years to 17.4% (95% CI 14.8–20.4) in those aged 85 years or over.

Incidence rate

The overall incidence rate of heart failure was 14.4/1000 person-years (95% CI 13.4–15.5) and was significantly higher in men (17.6/1000 man-years, 95% CI 15.8–19.5) than in women (12.5/1000 woman-years, 95% CI 11.3–13.8). The incidence rate increased with age from 1.4/1000 person-years in those aged 55–59 years to 47.4/1000 person-years in those aged 90 years or older (Table 1). This increase with age was evident for both genders (Figs. 1(a) and (b)). Incidence rates were on average approximately two times higher in men than in women in each age category, except for the youngest (55–59 years), in which no male cases occurred.

Period and lifetime risk

The period and lifetime risks for all subjects, and for men and women separately, at the ages of 55, 65, 75, and 85 years are shown in Table 2. All estimates account for the risk of competing causes of death. The lifetime risk of heart failure for a person aged 55 was 30.2%. For a man aged 55 years the lifetime risk was 33.0% and for a woman of the same age it was 28.5%. Lifetime risk of heart failure decreased with age in both sexes to approximately 23% in persons who reached 85 years of age without having heart failure. Stratification by gender showed that lifetime risks were higher in men than women at ages 55–75. In subjects aged 85 years, however, lifetime risks for developing heart failure were comparable and slightly higher in women (Table 2 and Fig. 2). Cumulative

Table 1 Incidence rates for heart failure per 5-year age category

Age category (years)	Number of incident cases	Person-years	Incidence rate[a] (95% CI)
55—59	4	2888.6	1.4 (0.5—3.3)
60—64	27	8713.6	3.1 (2.1—4.4)
65—69	56	10392.1	5.4 (4.1—6.9)
70—74	113	9665.6	11.7 (9.7—14.0)
75—79	136	8012.8	17.0 (14.3—20.0)
80—84	166	5513.5	30.1 (25.8—35.0)
85—89	137	3269.0	41.9 (35.3—49.4)
⩾ 90	86	1813.5	47.4 (38.6—58.2)

[a] Per 1000 person-years.

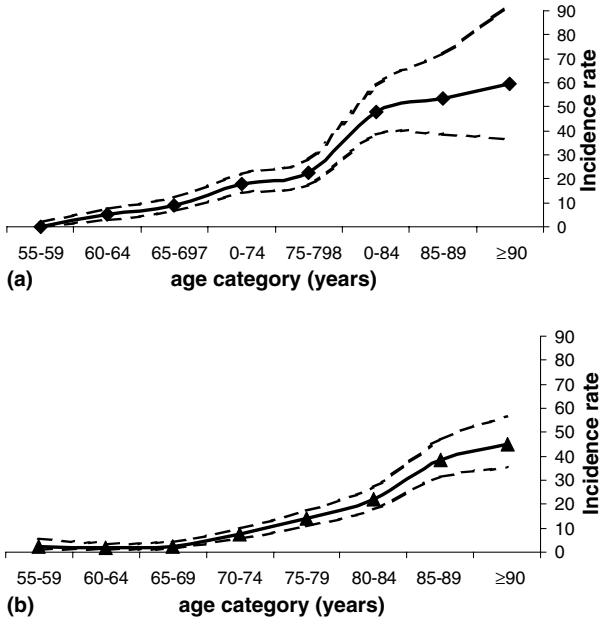

Fig. 1 (a) Age-specific male incidence rates (/1000 man years) and 95% confidence band. (b) Age-specific female incidence rates (/1000 woman-years) and 95% confidence band.

risks in shorter time intervals (5—25 years) increased with age and were higher in men at all ages, reflecting the higher incidence rates in men.

Prognosis

Of the 725 persons with incident heart failure, 445 subjects died following the diagnosis (198 men and 247 women). Median survival was 2.1 years (range: 1 day—9.0 years). Cumulative survival was 86% at 30 days after the onset of heart failure (95% CI 83—88%), 63% at 1 year (95% CI 59—66%), 51% at 2 years (95% CI 47—55%) and 35% at 5 years (95% CI 31—39%). There was no significant difference in cumulative survival after incident heart failure between men and women (Fig. 3, log rank test: $p = 0.15$). Age-adjusted survival in Cox proportional hazards analysis was similar in men and women (hazard ratio female gender: 0.88, 95% CI 0.72—1.07). After exclusion of patients who died in the first 30 days, 1-, 2- and 5-year survival were 73%, 59% and 41%, respectively. Age- and gender-adjusted survival was significantly lower in subjects with incident heart failure than in the remainder of our study cohort (hazard ratio 4.3, 95% CI 3.8—4.8).

Discussion

In this long-term prospective population-based cohort study, we found that heart failure prevalence, incidence and risk are high. The incidence rate was significantly higher in men than in women and increased with age from 1.4/1000 person-years in subjects aged 55—59 years to 47.4/1000 person-years in those aged 90 years or older. Our study showed that the probability for an individual aged 55 years to develop heart failure during his or her remaining lifetime is 30.2%. As expected, lifetime risk decreased at older ages, probably because of depletion of susceptibles and a shorter remaining lifespan. In our study, lifetime risk of heart failure was higher in young men than in young women. In the older individuals, however, lifetime risks were practically the same in men and women. Heart failure remains a deadly disease for both genders, with a 5-year survival of only 35%.

Our age-specific incidence rate estimates are similar to the results from an investigation in a general practitioner's database in the United Kingdom,[12] but differ somewhat from other recent population-based studies. Estimates in the Cardiovascular Health Study were higher in all age categories. Although this study also used clinical criteria for the assessment of heart failure, the investigators selected their participants through a Medicare eligibility list.[7] This may explain some of the differences with our study, which was performed in an unselected population. Besides differences in selection criteria and population characteristics, comparison between investigations is further complicated because studies have used different criteria to assess the presence of heart failure. For example, in the Framingham Heart Study, clinical criteria were used that do not include evidence of cardiac dysfunction on echocardiography, which is an important tool in heart failure diagnosis in clinical practice.[1] Therefore, in the Framingham Heart Study, the true incidence of heart failure may have been underestimated. In the Hillingdon heart failure study, potential cases were identified on the basis of referrals by general practitioners of patients with suspected heart failure.[6] Although similar

Table 2 Cumulative risk of heart failure in different time periods for participants aged 55, 65, 75, and 85 years old; total and stratified by gender

	Period risk[a] (years)							
Age	5	10	15	20	25	30	35	Lifetime
Total								
55	0.6	2.1	4.5	9.2	14.7	21.8	27.2	30.2
65	2.6	7.6	13.6	21.3	27.1			30.3
75	7.5	17.2	24.6					28.7
85	14.8							23.1
Men								
55	0	2.8	6.8	13.4	19.6	27.9	31.6	33.0
65	4.2	11.4	18.2	27.1	31.2			32.7
75	9.5	22.0	27.7					29.8
85	16.2							22.4
Women								
55	1.0	1.8	3.0	6.2	11.2	17.5	24.3	28.5
65	1.2	4.6	10.0	16.7	24.0			28.5
75	6.2	14.1	22.6					27.9
85	14.3							23.3

[a] Numbers are percentages. Competing risk of death is taken into account.

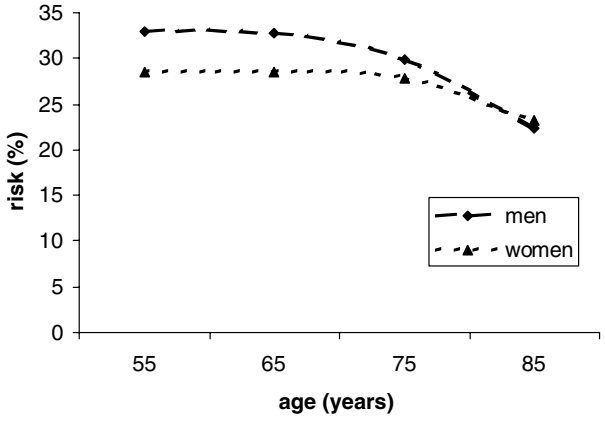

Fig. 2 Age-specific lifetime risk of heart failure startified by gender.

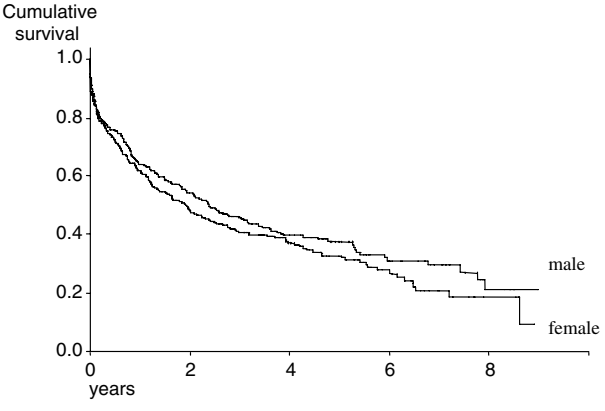

Fig. 3 Kaplan–Meier survival curve for incident heart failure cases stratified by gender.

criteria were used in this study, age-specific incidence was somewhat lower, possibly because not all potential cases were referred. Age-specific prevalence estimates of heart failure were also somewhat higher in the Cardiovascular Health Study, especially at younger ages.[13] Slightly lower prevalence estimates per age-category were found in a study in residents of Olmsted County, Minnesota and in the Framingham Heart Study.[4,14] Both used Framingham criteria for case ascertainment. The Echocardiographic Heart of England Screening study used criteria based on the guidelines of the European Society of Cardiology and found age-specific prevalence estimates of heart failure that were similar to ours.[5]

Only one other study, the Framingham Heart Study, calculated lifetime risks for heart failure.[15] Lifetime risk for the development of heart failure in this study was approximately 20% and was, in contrast to our findings, independent of age and gender. The investigators did not find a decrease in lifetime risk at older ages, which was attributed to an increasing incidence with advancing age, outpacing the increasing mortality from competing causes. However, no age-limit was set for the calculation of cumulative risks in the Rotterdam Study, while in the Framingham Heart Study cumulative risks were calculated until the age of 94 years. Furthermore, lifetime risks in the Framingham Study were calculated from 1971 to 1996, while in the Rotterdam Study they were calculated from 1989 to 2000. Therefore, changes in mortality from competing causes over calendar time may explain some of the differences between the two studies. Furthermore, although questioned by some,[16] improvements in myocardial infarction treatment over time might account for the higher incidence rates of heart failure that we found.

Heart failure is a fatal disease, despite advances in treatment over the past 15 years.[3] We found no

differences between men and women in heart failure prognosis. Our survival estimates are very similar to those found in three other recent population-based studies.[1,12,17] However, compared to heart failure mortality in hospital-based studies,[18–20] prognosis in our population-based study was better, probably as less severe cases of heart failure were also included. As the diagnosis of heart failure is difficult, some studies applied scores for the classification of heart failure, while other studies used clinical definitions or relied on hospital discharge codes. Therefore, a large part of the differences between studies may be explained by varying criteria. Besides a baseline screening in the majority of participants using a validated score, we applied clinical criteria for heart failure throughout the Rotterdam Study, based upon guidelines of the European Society of Cardiology. Apart from hospital discharge letters, medical records from general practitioners were available for assessment of cases. Consequently, less severe cases were also included in our study. However, some underestimation of the true prevalence and incidence may have been caused by the fact that old and diseased individuals were less likely to participate in the Rotterdam Study. Another limitation of our study is that we did not distinguish between underlying causes of heart failure. Among elderly patients, systolic hypertension and cardiac hypertrophy may be more important than ischaemic heart disease.[8]

In conclusion, heart failure prevalence and incidence are substantial. As age is an important risk factor for heart failure, the burden of this disease on health care systems in western societies increases as these populations age. In individuals aged 55 years, 30% will develop heart failure during their remaining lifespan; i.e., almost one out of three individuals. Heart failure continues to be a fatal disease, despite advances in treatment, with only 35% surviving 5 years after the first diagnosis. Prevention of the development of heart failure in high-risk patients is therefore fundamental.

References

1. Levy D, Kenchaiah S, Larson MG et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002;**347**:1397–402.
2. Stewart S, MacIntyre K, MacLeod MMC et al. Trends in hospitalisation for heart failure in Scotland, 1990–1996. *Eur Heart J* 2001;**22**:209–17.
3. Jessup M, Brozena S. Heart failure. *N Engl J Med* 2003;**348**:2007–18.
4. Redfield MM, Jacobsen SJ, Burnett Jr JC et al. Burden of systolic and diastolic ventricular dysfunction in the community. Appreciating the scope of the heart failure epidemic. *JAMA* 2003; **289**:194–202.
5. Davies MK, Hobbs FDR, Davis RC et al. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. *Lancet* 2001;**358**:439–44.
6. Cowie MR, Wood DA, Coats AJS et al. Incidence and aetiology of heart failure. A population-based study. *Eur Heart J* 1999;**20**:421–8.
7. Gottdiener JS, Arnold AM, Aurigemma GP et al. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2000;**35**:1628–37.
8. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Task Force for the diagnosis and treatment of chronic heart failure, European Society of Cardiology. *Eur Heart J* 2001;**22**:1527–60.
9. Hofman A, Grobbee DE, de Jong PTVM et al. Determinants of disease and disability in the elderly: the Rotterdam Study. *Eur J Epidemiol* 1991;**7**:403–22.
10. Mosterd A, Hoes AW, de Bruyne MC et al. Prevalence of heart failure and left ventricular dysfunction in the general population. *Eur Heart J* 1999;**20**:447–55.
11. Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. New York: Wiley; 1980.
12. Johansson S, Wallander M, Ruigómez A et al. Incidence of newly diagnosed heart failure in UK general practice. *Eur J Heart Fail* 2001;**3**:225–31.
13. Kitzman DW, Gardin JM, Gottdiener JS et al. Importance of heart failure with preserved systolic function in patients $\geqslant$ 65 years of age. *Am J Cardiol* 2001;**87**:413–9.
14. Ho KKL, Pinsky JL, Kannel WB et al. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993;**22**(Suppl. A): 6A–13A.
15. Lloyd-Jones DM, Larson MG, Leip EP et al. Lifetime risk for developing heart failure: the Framingham Heart Study. *Circulation* 2002;**106**:3068–72.
16. Hellermann JP, Goraya TY, Jacobsen SJ et al. Incidence of heart failure after myocardial infarction: is it changing over time?. *Am J Epidemiol* 2003;**157**:1101–7.
17. Cowie MR, Wood DA, Coats AJS et al. Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 2000;**83**:505–10.
18. MacIntyre K, Capewell S, Stewart S et al. Evidence of improving prognosis in heart failure. Trends in case fatality in 66,547 patients hospitalized between 1986 and 1995. *Circulation* 2000;**102**: 1126–31.
19. Croft JB, Giles WH, Pollard RA et al. Heart failure survival among older adults in the United States. *Arch Intern Med* 1999;**159**:505–10.
20. Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12,220 index admissions in Leicestershire 1993–2001. *Heart* 2003; **89**:615–20.