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One-year mortality among unselected outpatients with heart failure

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Objective To estimate 1-year mortality and prognostic factors in unselected outpatients with heart failure, and to compare the observed mortality with the estimates of the primary care physicians.

Methods and Results Four hundred and eleven consecutive patients with heart failure New York Heart Association (NYHA) class II–IV (mean population age 75 years, 56% males) were enrolled in 71 primary care offices throughout Switzerland. During a mean follow-up period of 1.4 years, 68 patients had died. One-year total mortality was 12.6% compared to 4.3% in the underlying Swiss population (standardized mortality ratio 3.0). Among patients with heart failure NYHA II, III and IV, mortality was 7.1%, 15.0% and 28.0%, respectively. In multivariate Cox regression, statistically significant ($P < 0.05$) predictors of mortality were NYHA class (NYHA III: risk ratio [RR]=1.6; NYHA IV: RR=2.2), recent hospital stay for heart disease (RR=2.3), creatinine $> 120 \mu\text{mol} \cdot \text{l}^{-1}$ (RR=1.8) systolic blood pressure $< 100 \text{ mmHg}$ (RR=2.4), heart rate $> 100 \text{ min}^{-1}$ (RR=2.7), age (per 10 years, RR=1.6) and female gender (RR=0.49). Among patients

with reduced left ventricular ejection fraction, 1-year mortality was 14.3%, and predictors were similar except that female gender was no longer associated with reduced mortality. Primary care physicians significantly overestimated 1-year mortality (estimated mortality 25.9% vs observed mortality 12.6%, $P = 0.001$).

Conclusions Unselected outpatients with heart failure have a poor prognosis, particularly those with advanced heart failure and a recent hospital stay for heart disease. Primary care physicians are aware of the high mortality of this growing patient population.
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Introduction

With the ageing of the general population, improved survival of patients with acute coronary artery disease and advances in management of heart failure, the prevalence of heart failure has increased^[1,2]. Current estimates of the prevalence vary widely, but it may be 5% or higher in the general population over 65 years of age^[3,4]. Despite the growing number of patients with chronic heart failure, most studies on prognosis and prognostic factors have been performed in high-risk populations of hospitalized patient^[5–11] or among select outpatients attending heart failure clinics^[12,13] including heart

transplant units^[14,15]. Additional information regarding outcome comes from clinical trials^[16–18] which, however, have generally been performed among younger patients with stable heart failure and fewer co-morbidities compared to the general heart failure population. In contrast, there are only a few studies on mortality^[19–21] and prognostic factors^[21] in unselected patients with prevalent heart failure. In addition, little is known about primary care physicians' perception of mortality. As risk stratification as well as the perception of risk may affect medical care of these patients, we addressed these issues in a prospective study.

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Methods

Study population and data collection

The baseline for this follow-up study formed the Swiss component of the European IMPROVEMENT of HF

survey^[22]. It assesses diagnosis, therapy and perception in the management of heart failure in Europe^[23]. After random selection from a complete list of Swiss primary care physicians, in Spring 1999, 250 office-based physicians throughout Switzerland were invited to participate in this survey. Seventy-nine primary care physicians agreed to provide data regarding care of patients with heart failure. During a 6-week period, they prospectively listed all office visits of patients whom they considered had heart failure. A trained study person (medical student or research fellow) reviewed and abstracted the charts in collaboration with the physician. For uniformity of functional classification, a list of the New York Heart Association (NYHA) classes was provided. For each patient, physicians also estimated the 1-year mortality risk. In the fall of 2000, we asked the physicians to provide a survival follow-up including date and cause of death or date of last contact with the patient. Seventy-one primary care physicians with 484 patients were willing to contribute to the follow-up study. We excluded 62 patients who at enrolment were in NYHA functional class I. Among the remaining 422 patients NYHA II–IV, 11 could not be identified from the initials and date of birth, leaving 411 people for the follow-up analysis. Of these patients, 90% fulfilled either the current European Society of Cardiology (ESC) criteria for chronic heart failure (heart failure symptoms with objective impairment of left ventricular function^[24]) or the Framingham criteria^[25] (48% ESC criteria with or without Framingham criteria and 42% Framingham criteria only). Among the remaining 41 patients who did not meet these criteria, in 15, a cardiologist initially established the diagnosis or was currently involved in follow-up management of the patient.

Statistical analysis

We calculated means \pm SD and proportions for the overall sample and subgroups. Survival estimates for all cause and cardiovascular mortality were calculated with the method of Kaplan and Meier. To compare the mortality in the cohort with the general population we calculated age- and sex-standardized mortality rates from the Swiss life table statistics^[26]. To assess predictors of all-cause mortality within the heart failure cohort, Cox regression was used. We calculated age- and sex-adjusted as well as multivariate adjusted hazard ratios. Multivariate predictors were included into the model with a forward stepwise procedure. To compare the observed mortality with the estimates of the physicians, the Wilcoxon signed-rank test was used. All analyses were done with SAS 6.12, and *P*-values <0.05 were taken as significant.

Results

Baseline characteristics are given in Table 1. Age and the frequency distribution of important variables

Table 1 Baseline characteristics

Number of subjects	411
Sex (male)	56%
Age all (years)	75 \pm 12
Cause of heart failure	
Coronary heart disease	39%
Hypertension	20%
Valvular heart disease	9%
Other causes/unknown	32%
Personal history of heart failure	
Dyspnea	100%
Fatigue	83%
Signs of congestion*	87%
Recent hospital stay for heart disease†	26%
Involvement of cardiologist in diagnosis/management of heart failure	67%
Current NYHA class	
II/III/IV	49%/39%/12%
Blood pressure and heart rate	
Systolic blood pressure (mmHg)	134 \pm 22
Diastolic blood pressure (mmHg)	78 \pm 11
Heart rate (min ⁻¹)	76 \pm 13
Left ventricular ejection fraction	
Reduced (<50%/normal/not assessed)	42%/18%/41%
Additional characteristics	
Diabetes	18%
Creatinine >120 $\mu\text{mol} \cdot \text{l}^{-1}$	29%
Atrial fibrillation	31%
Drug therapy	
Renin-angiotensin system blockers‡	65%
Beta-blockers	26%
Diuretics	76%
Digitalis	31%

*Rales, neck vein distension, or peripheral oedema.

†Hospital stay within 12 months prior to enrolment.

‡Includes ACE inhibitors and angiotensin receptor blockers.

was similar to other population-based heart failure studies^[21,27,28]. Fifty-six percent were male, and mean age was 75 \pm 12 years (male: 73 \pm 12; female: 78 \pm 11 years). The distribution of NYHA classes II–IV was 49%, 39% and 12%, respectively. Twenty-six percent of the patients had a hospital stay for heart disease within 12 months prior to enrolment. In 67% of the study population, cardiologists were involved in establishing the diagnosis and/or the subsequent management of heart failure, and in 30% in routine follow-up management together with the primary care physicians. ACE-inhibitors/angiotensin receptor blockers, beta-blockers and diuretics were prescribed to 65%, 26% and 76% of the study population, respectively.

During a mean follow-up period of 1.4 years, 68 patients died, 54 (79% of deaths) from cardiovascular causes. One-year all-cause mortality was 12.6% (95% confidence interval [CI] 9.3–15.8%) as opposed to an age- and sex-standardized 1-year mortality risk of 4.3% among the Swiss population (standardized mortality ratio = 3.0; 95% CI 2.3–3.9). The standardized mortality ratios for men and women were 3.6 (95% CI 2.6–5.1) and 2.2 (95% CI 1.4–3.4), respectively. One-year cardiovascular mortality was 10.0% (95% CI 7.0–12.9%). Among patients with heart failure NYHA II, III and IV, total mortality was 7.1%, 15.0% and 28.0%, respectively

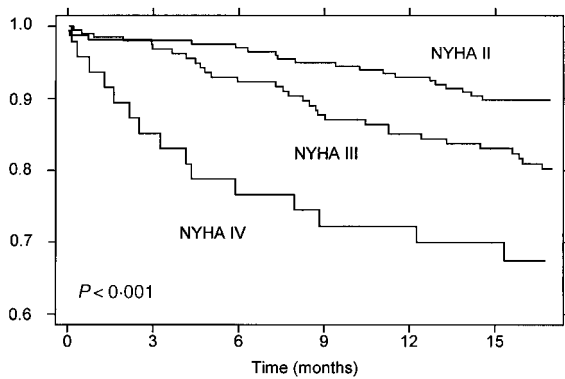


Figure 1 Survival probability according to NYHA class among outpatients with heart failure.

(Fig. 1). In patients with a recent hospital stay for heart disease, mortality was 25.4% compared to 8.1% in those without a recent admission. The two variables NYHA class and recent hospital stay for heart disease discriminated quite well between high-risk and lower-risk subsets (Table 2). In Table 3, predictors of survival are

presented. In multivariate analysis, age, sex, NYHA class, recent hospital stay for heart disease, systolic blood pressure <100 mmHg, heart rate >100 min^{-1} , and creatinine >120 $\mu\text{mol} \cdot \text{l}^{-1}$ were significant predictors of mortality. In the age- and sex-adjusted analysis, compared to those with reduced ($<50\%$) left ventricular ejection fraction (LVEF), patients with normal LVEF and those without assessment of LVEF had a non-significant reduction in risk. When LVEF was added to the final multivariate model, the risk ratio for those with normal LVEF was 1.0 (0.49–2.1) and 0.96 (95% CI 0.53–1.8) for those without assessed LVEF as compared to those with reduced LVEF. In an additional model, we tested whether involvement of a cardiologist in the routine follow-up management was associated with the prognosis. There was no significant association with mortality ($P=0.35$), although the estimated risk ratio was compatible with a reduced mortality in those followed-up together with a cardiologist (RR=0.75, 95% CI 0.41–1.4). However, there were several differences in patient characteristics among these groups (results not shown) possibly limiting the validity of the risk estimate.

Table 2 Observed 1-year mortality according to NYHA class and recent hospital stay, and estimates of the primary care physicians

NYHA class	Recent hospital stay for heart disease	n	Cardiovascular mortality	Total mortality	Physicians' estimated total mortality
NYHA II	No	167	3.1 (0.0–5.8)*	5.5 (2.0–9.0)	17.9 (15.0–20.8)
	Yes	35	12.3 (1.0–23.7)	15.1 (2.9–27.3)	19.5 (14.3–24.8)
NYHA III	No	112	7.8 (2.6–13.0)	12.2 (6.4–18.4)	29.5 (25.1–33.7)
	Yes	49	19.5 (8.0–31.0)	21.5 (9.7–33.4)	29.9 (23.2–36.7)
NYHA IV	No	24	8.3 (0.0–20.4)	12.7 (0.0–26.2)	38.2 (25.7–50.6)
	Yes	24	48.2 (27.6–68.8)	48.2 (27.6–68.8)	56.4 (41.1–71.8)
All		411	10.0 (7.0–12.9)	12.6 (9.3–15.8)	25.9 (23.5–27.7)

*Values given as percent with 95% confidence intervals.

Table 3 Predictors of total mortality in outpatients with heart failure

Variable	Age- and sex adjusted RR (95% CI)	Multivariate RR (95% CI)
Age (10 years)	1.4 (1.1–1.8)	1.6 (1.2–2.1)
Female sex	0.50 (0.30–0.84)	0.49 (0.28–0.85)
NYHA class II (reference)	1.0	1.0
NYHA class III	2.2 (1.3–3.8)	1.6 (0.9–2.8)
NYHA class IV	4.1 (2.1–7.9)	2.2 (1.1–4.6)
Recent hospital stay for heart disease	3.5 (2.2–5.7)	2.3 (1.4–3.9)
Heart rate >100 min^{-1}	4.3 (2.2–8.3)	2.7 (1.3–5.4)
Systolic blood pressure <100 mmHg	4.5 (2.2–9.1)	2.4 (1.1–5.1)
Diastolic blood pressure <60 mmHg	2.6 (1.5–4.7)	—
Reduced LVEF (reference)	1.0	—
Normal LVEF	0.77 (0.38–1.5)	—
LVEF not assessed	0.75 (0.75–1.3)	—
Creatinine >120 $\mu\text{mol} \cdot \text{l}^{-1}$	2.4 (1.5–3.9)	1.8 (1.1–3.0)
Diabetes mellitus	1.8 (1.1–3.1)	—
Atrial fibrillation	1.5 (0.9–2.5)	—

To exclude a potential dilution of true heart failure cases with patients with false diagnosis of CHD, resulting in the possibility of underestimating mortality and to bias risk estimates, we performed secondary analyses among those with reduced LVEF. In this selected population of 163 patients with established systolic heart failure, 1-year mortality was 14.3% (NYHA class II–IV, 4.1%, 15.4% and 37.2%, respectively). In the restricted multivariate model, the risk estimates were not materially different from the primary model, with the exception that there was no longer a significant association between the predictor female gender and outcome (RR=0.86; 95% CI 0.35–2.1).

Physicians significantly overestimated 1-year mortality ($P<0.001$). Table 2 shows that the difference between the physicians' estimates and the observed mortality was most pronounced among groups at lower risk without a recent hospital stay.

Discussion

In this cohort of outpatients with heart failure 1-year prognosis was poor. All-cause mortality was increased three-fold compared to the general population. However, there were large differences in prognosis according to NYHA functional class, recent hospital stay and additional predictors of mortality. Primary care physicians were aware of the poor prognosis, and even overestimated the mortality in strata of lower risk.

The standardized mortality ratios of 3.6 among men and 2.2 among women with heart failure in our study compared to the underlying Swiss population agrees well with the risk estimates from the Rotterdam Study^[21] (3.4 and 2.2, respectively). One-year mortality in the current cohort was also similar (12.6% vs 11%), and moreover agreed well with a sample of heart failure clinic outpatients (14%)^[12].

Although the observed overall mortality appears to be relatively favourable compared to samples of patients with acute heart failure, there were subgroups with strongly increased mortality. Patients with advanced heart failure, in particular when they had had a recent hospital stay for heart disease, had a very high 1-year mortality. For example, patients with recent hospital stay who were in NYHA class IV at enrolment had a 48% 1-year mortality. The importance of these predictors agrees with results from previous studies indicating that NYHA class is a powerful predictor of prognosis^[7,12,29], and the observation from hospital admission cohorts demonstrating a high mortality in the first months after hospital discharge^[5,7,9]. There is still room to improve prognosis of high-risk outpatients with heart failure. Although ACE inhibitors and angiotensin receptor blockers were used more frequently in our cohort than in previous years, one third of the patients did not receive drugs of this class. Moreover, use of beta-blockers was low. Increased use of these drugs, together with case management systems^[30,31] should further improve the prognosis of this high-risk population.

In contrast to the high-risk groups, subjects in NYHA class II who were not recently hospitalized for heart disease had only a moderate mortality risk. This was also true for those with reduced LVEF. There is only limited data available regarding prognosis of patients with mild stable heart failure. In a heart failure clinic study^[12], 1-year mortality risk in NYHA class II was in a comparable range. Advances in medical care may account for these favourable results, such as better control of blood pressure, advances in treatment of coronary artery disease including coronary revascularization and increased use of ACE-inhibitors and angiotensin receptor blockers^[32].

Apart from NYHA class and recent hospital stay, there were additional simple clinical variables that predicted mortality. An increased heart rate and low systolic blood pressure as well as increased creatinine levels were independently associated with an about two-fold increased mortality risk. These variables were associated with poor prognosis in studies of acute heart failure^[33,34] as well as in cohorts of incident^[29,35] and prevalent cases^[21,36]. In several studies, there was also an association between gender and mortality^[21,37], but not in others^[29]. In the current cohort female gender was associated with a substantially lower mortality. Our sample size was not large enough to explore this issue in detail. The finding that the gender difference was diminished when the analysis was restricted to those with established systolic heart failure could indicate that among women with normal or not assessed LVEF an increased proportion had a false positive diagnosis of heart failure. However, in two recent studies among patients with strongly reduced LVEF women had also a lower risk than men^[36,38] (RR 0.64 and 0.46, respectively) indicating that the apparently better prognosis among women with chronic heart failure may be real.

Because many patients, particularly elderly people, are mainly cared for by primary care physicians, their perception regarding outcome and mortality risk is of interest. In our study, physicians did not underestimate the mortality risk. On the contrary, there was an overestimation of 1-year mortality, particularly among patients with mild heart failure and in those who had not undergone a recent hospital stay. The overestimation of mortality may prompt physicians to apply the best possible therapy for heart failure. However, it might also bear the risk of withholding important diagnostic steps and therapies for concomitant health conditions and risk factors. For example, a recent study showed that among patients with coronary heart disease, those with heart failure had a markedly reduced likelihood of receiving lipid-lowering drugs^[39].

Our study has several potential limitations. It is important to recognise that our cohort represents a sample of patients with prevalent heart failure, providing lower risk estimates for mortality than incident case studies. In about two thirds^[28] or more^[29] of the cases diagnosis of heart failure is established during a hospital stay, and 10–15% of inpatients with heart failure die^[7,40]. Subjects who die early after the initial diagnosis of heart

failure are therefore not included in outpatient cohorts, and patients with a stable disease course are over-represented. For example, in the Olmsted county cohort^[28] of incident cases, 1-year mortality after diagnosis of heart failure was 24%, but only 12% in the subsequent year among those who survived the first 3 months. Conversely, unselected prevalence case cohorts represent samples of patients as seen in daily practice by office based physicians. For this reason, estimation of mortality and risk prediction in this setting is of importance to daily patient care. A second potential limitation is that inclusion was based on the working diagnosis of the primary care physicians. However, in this study in patients with chronic heart failure, 90% fulfilled either the ESC or Framingham criteria for diagnosis of heart failure, and in two thirds, a cardiologist was involved in the diagnosis and/or subsequent therapy. Despite this, we cannot rule out that a number of patients without true heart failure were included. Nevertheless, among patients with reduced LVEF estimates of mortality and risk predictors were close to the results from the overall cohort. Third, NYHA classification has a high interrater variability, indicating that misclassification among NYHA classes can occur. Despite this, NYHA class was a strong predictor of risk. Fourth, because our sample size was limited, confidence intervals for the mortality and risk estimates were wide. For more reliable prediction of risk in clinical practice larger studies will be required to provide more precise risk estimates. Finally, the proportion of participating physicians was limited. This should not affect the composition of the cohort with respect to patient characteristics but it would be possible that the management of heart failure differed between the participating physicians and general medical practice. Our cohort, however, is similar in age and other characteristics^[21,29] including current drug therapy^[41,42] as compared to other European heart failure populations. Therefore our findings should be applicable to outpatients in most European countries.

In conclusion 1-year prognosis of unselected outpatients with heart failure is poor. With a set of simple characteristics, including NYHA class and recent hospital stay for heart disease, those at very high risk for death can be identified. With vigorous drug therapy and close follow-up programmes the prognosis of these high-risk outpatients may be further improved.

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