**Clinical research**

**Effect of age on short and long-term mortality in patients admitted to hospital with congestive heart failure**

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Received 2 January 2004; revised 24 June 2004; accepted 1 July 2004
Available online 19 August 2004

**Aims**

To describe the association between age and risk factors in patients hospitalised with congestive heart failure (CHF) and to determine the effect of age on mortality.

**Methods and results**

Consecutive patients admitted to 34 hospitals with CHF during a period of 2 years were registered. Mean age was 71.7 ± 10.2 years, 60% were male and 63% were in NYHA class III–IV. Moderate to severe left ventricular (LV) systolic dysfunction was present in 41%. Short and long-term survival status was obtained after 30 days and 5–8 years, respectively. Older patients less frequently had LV systolic dysfunction, were under treated with ACE-inhibitors and were more often female. The prevalence of hypertension, diabetes and ischaemic heart disease increased with age, until the oldest age group (>80 years). Age was an independent predictor of short-term mortality (risk ratio (RR) per 10-year increase was 1.23 (95% CI 1.04–1.47)). Advancing age significantly increased long-term mortality (RR 1.55 (1.50–1.61)). Age interacted with the LV ejection fraction ($P = 0.003$). In patients with LV systolic dysfunction, the RR per 10-year increase was 1.29 (1.19–1.39) whereas in patients with preserved systolic function the RR was 1.57 (1.43–1.72, multivariate analyses).

**Conclusion**

The clinical characteristics of CHF patients vary considerably with age. Elderly patients hospitalised with CHF face a very grave prognosis, particularly if their heart failure symptoms are caused by LV systolic dysfunction.

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**KEYWORDS**

Aged 80 and over; ACE-inhibition; Diabetes; Ejection fraction

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**Introduction**

The incidence and prevalence of congestive heart failure (CHF) increases dramatically with advancing age.\textsuperscript{1–5} Increasing age has been reported to increase mortality of heart failure patients,\textsuperscript{6–14} but in several studies, including some with large study populations such as the VHeFT study, no relation between age and mortality was found.\textsuperscript{15–18} A limited number of heart failure studies have been dedicated to examining age as a prognostic factor in detail. Most of these studies were of moderate...
size, included selected groups of patients enrolled in randomized clinical trials, or patients referred for cardiac transplantation. Other studies have exclusively examined the prognosis in the oldest age groups. Furthermore, it is far from clear how increasing age affects the relative importance of other potential prognostic factors, such as gender and left ventricular (LV) systolic function. The proportion of patients with CHF due to systolic dysfunction of the left ventricle clearly decreases with age. However, in most studies in which age was a primary object of analysis, LV systolic dysfunction was an inclusion criterion or no information about LV function was provided. Therefore, it is not clear whether age interacts with left ventricular systolic function with regard to short and long-term prognosis in more unselected CHF populations. Given these premises we decided to undertake a study of risk factor distribution, treatment pattern, and short and long-term mortality in different age groups in a consecutive cohort of patients admitted to hospital with CHF. Furthermore, we intended to analyse how age and a number of clinical variables including left ventricular systolic function interact with regard to mortality in CHF.

Methods

The study population consisted of the patients screened for entry into the DIAMOND-CHF (Danish Investigations of Arrhythmia and Mortality on Dofetilide) study. The study design has been described previously. The DIAMOND study was a multi-centre, randomized, double blind, placebo-controlled trial of the efficacy of the class III antiarrhythmic agent dofetilide on mortality in patients with acute myocardial infarction or CHF. The CHF arm of the drug trial included 27% of the screened population with CHF. The trial showed no significant effect of dofetilide when compared with placebo, and consequently the current study did not distinguish between patients randomized or only screened for entry into the study. The study was conducted at departments of cardiology or internal medicine in 34 hospitals in Denmark. A total of 5548 consecutive patients hospitalised with new or worsening CHF were screened for entry into the study between November 1993 and July 1996 and these patients comprise the DIAMOND-CHF screening registry. Patients were included in the DIAMOND-CHF registry if a clinical diagnosis of heart failure had been made by the local investigators and the patient had experienced at least one episode of shortness of breath, either upon minimal exertion or at rest (New York Heart Association [NYHA] functional class III or IV), or paroxysmal nocturnal dyspnoea within the preceding month. Patients with acute myocardial infarction within the last seven days were not included in the DIAMOND-CHF screening registry. At screening, a physical examination was performed and a clinical history and ECG were obtained. A history of hypertension was considered present if the patient currently or previously received medical therapy for high blood pressure. A diagnosis of diabetes or COPD was obtained from medical records or patient history. Furthermore, an echocardiogram was recorded on videotape and evaluated in a central laboratory. Left ventricular systolic function was assessed by calculation of wall motion index (WMI) as described previously, using a 16-segment model of the left ventricle. WMI multiplied by 0.3 gives an estimate of ejection fraction (LVEF), and significant left ventricular systolic dysfunction was defined as WMI = 1.2 (LVEF approximately below 0.35). Left ventricular geometry was characterised by measurements of left ventricular end-diastolic diameter obtained from 2-D recordings (apical 2-chamber view). Creatinine clearance was calculated from serum creatinine values using the formula by Cockcroft and Gault.

Survival status was obtained by means of the Danish Central Personal Registry in Autumn 2002 resulting in a follow-up time that ranged from 5 to 8 years. In Denmark, all deaths in the country are registered in this registry within two weeks. Survival status was available on 5419 patients. The remaining 57 patients were lost to follow-up due to emigration or due to incorrectly recorded central personal registry number. The study was conducted in accordance with the Declaration of Helsinki II and approved by the Central Danish Ethics Committee.

Statistical analysis

Baseline variables were compared using continuity-adjusted $\chi^2$ test for discrete variables and Wilcoxon rank sum tests for continuous variables. Differences in time to death between groups were analysed by a two-sided log-rank test. The Kaplan–Meier method was used to construct life-table plots. Relative risks (RR) and 95% confidence intervals were calculated as hazard ratios obtained from Cox proportional-hazard models. Initially, models were constructed using all available covariates considered of potential influence by the investigators. Models were created for both short (30 days) and long-term mortality. The final models fulfilled the criteria for proportional hazard. Subsequently, significant predictors of mortality in the multivariate model were identified using a backward selection procedure. Interaction analysis was performed using a likelihood ratio test in a multivariate Cox model. Given the high number of interaction tests performed, only interactions with a $P$-value <0.01 were considered significant. All calculations were made using the Statistical Analysis System software (SAS Institute, Cary, NC, USA).

Results

Clinical characteristics at screening

In the entire screened population of 5419 patients the mean age was 71.7 ± 10.2 years, 60% were male and 63% were in NYHA class III–IV. Moderate to severe left ventricular (LV) dysfunction was present in 41%. The age distribution was as follows: 13% were <61 years, 27% between 61 and 70 years, 40% between 71–80 years, and 20% aged 81 and older. Baseline characteristics of the patients according to age are presented in Table 1. Male gender was more common among the younger patients. The prevalence of ischaemic heart disease and previous MI increased with age until the age group of >80 years where the prevalence of ischaemia declined. A similar pattern was seen for several baseline risk factors (hypertension, diabetes and chronic obstructive pulmonary disease, Table 1). Restricting the population to those with significant LV dysfunction (WMI ≥ 1.2) did not alter the distribution across the age groups for these variables (data not shown). The prevalence of atrial
fibrillation increased with age in the younger patients but levelled off after the age of 70. Identical results with respect to atrial fibrillation were found in the subgroup of patients who had systolic dysfunction. LV systolic function was more severely depressed and the left ventricle was more dilated in the younger patients. Treatment with an ACE-inhibitor at the time of discharge from hospital was more frequent in the younger patients. Similarly, by looking only at those patients with significant LV dysfunction where ACE-inhibition was clearly indicated (WMI < 1.2) a significant difference between the age groups with regard to treatment with ACE-inhibitors was found. In patients younger than 60 years, 84% were receiving an ACE-inhibitor versus 60% of the patients > 80 years (P < 0.001). Compared with older patients a higher proportion of the younger patients were not requiring a diuretic at discharge. Overall, few patients were treated with β-blockers. The use of digoxin increased with advancing age.

**Mortality**

A total of 298 patients (5%) did not survive 30 days after the index hospitalisation. The proportion of patients who died ranged from 3% in the youngest patients to 10% in the oldest (Table 1). In a univariate analysis, increasing age by 10 years resulted in a highly significant increase in risk of death within the first 30 days (RR 1.55 (1.36–1.76)). A multivariate analysis was created containing age, sex, WMI, left ventricular end diastolic diameter (LVEDD), history of ischaemic heart disease or myocardial infarction, chronic obstructive pulmonary disease, diabetes, hypertension, valve disease, atrial fibrillation, smoking, creatinine clearance, and duration of heart failure. In this model, increasing age significantly af-

| Table 1 Baseline characteristics of 5491 patients admitted to hospital with congestive heart failure according to age |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable        | <61 years (n = 718) | 61–70 years (n = 1481) | 71–80 years (n = 2203) | >80 years (n = 1089) |
| Male gender (%) | 532 (74) | 990 (67) | 1294 (68) | 386 (45) |
| NYHA class III–IV (%) | 478 (62) | 907 (62) | 1406 (64) | 883 (63) |
| CHF duration (months) | 3.0 (1.0–96.0) | 8.0 (0.1–120.0) | 8.0 (0.1–120.0) | 12.0 (0.1–156.0) |
| History of IHD (%) | 363 (51) | 893 (60) | 1303 (59) | 560 (51) |
| Previous MI (%) | 254 (35) | 620 (42) | 850 (39) | 301 (28) |
| Hypertension (%) | 155 (22) | 385 (26) | 575 (26) | 218 (20) |
| Valvular disease (%) | 18 (3) | 57 (4) | 95 (4) | 38 (3) |
| COPD (%) | 142 (20) | 356 (24) | 540 (25) | 188 (17) |
| Diabetes (%) | 93 (13) | 278 (19) | 365 (17) | 164 (15) |
| Atrial fibrillation (%) | 115 (16) | 335 (23) | 593 (27) | 294 (27) |
| Current smoking (%) | 362 (52) | 598 (41) | 661 (31) | 196 (19) |
| VT/VF | 11 (2) | 32 (2) | 44 (2) | 11 (1) |
| WMI ≤ 1.2a | 361 (52) | 631 (45) | 809 (39) | 346 (33) |
| WMI | 1.1 (0.5–1.9) | 1.2 (0.9–2.0) | 1.4 (1.0–2.0) | 1.5 (1.0–2.0) |
| LVEDD (mm) | 52 (35–67) | 50 (35–66) | 47 (35–63) | 35 (32–60) |
| Creatinine clearance (ml/min) | 85 (45–147) | 63 (32–104) | 48 (24–80) | 36 (18–59) |

Values for continuous variables are medians (5–95% percentiles).

a Missing in 251 patients. IHD, ischaemic heart disease; MI, myocardial infarction; VT/VF, ventricular tachycardia/ventricular fibrillation; WMI, wall motion index; LVEDD, left ventricular end diastolic diameter.

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**Fig. 1** Mortality rate in 5491 CHF patients according to age.
fected 30 day mortality (RR per 10 years increase 1.23 (1.04–1.47, P = 0.02)).

During the entire follow-up period 3955 (72%) patients died. In a univariate analysis, the risk ratio for death during long-term follow-up associated with a 10-year increase in age was 1.55 (1.50–1.61, P < 0.001, Fig. 1). A multivariate analysis similar to the one described above was created. In this model, age interacted significantly with WMI (P = 0.003). Therefore separate multivariate models were generated for patients with left ventricular systolic dysfunction (WMI ≤ 1.2) and those with preserved or nearly preserved systolic function. In these models there was no significant interaction between age and WMI. Age was a significant predictor of death in both models. For patients with poor systolic function (WMI ≤ 1.2) the RR (10 year increase in age) was 1.29 (1.19–1.39) and for patients with normal or only slight depression of LV systolic function (WMI > 1.2) the RR was 1.57 (1.43–1.72, Fig. 2). Adding information about treatment with diuretics, β-blockers, ACE-inhibitors and digoxin at discharge to the multivariate model did not significantly alter the RR for the effect of age (data not shown).

The median survival time was calculated in order to give a more clinically useful impression of what to expect in terms of survival for hospitalised CHF patients (Table 2). The most striking result is the drop in survival in patients aged 61–70 with the greatest impairment of LV systolic function where the observed median time to death is less than half that of patients younger than 61 years.

**Discussion**

The study demonstrates in a large, consecutive population of hospitalised heart failure patients that increasing age is independently associated with increased short and long-term mortality. The influence of age on mortality was clearly greater in patients with non-systolic heart failure than in patients with systolic dysfunction, but the effect was significant in both groups.

**Baseline characteristics**

The study shows that older patients are more commonly female and less frequently have LV systolic dysfunction.

<table>
<thead>
<tr>
<th>WMI</th>
<th>&lt;61 years</th>
<th>61–70 years</th>
<th>71–80 years</th>
<th>&gt;80 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–0.8</td>
<td>5.8 (0.1–8.2)</td>
<td>2.0 (0.1–7.7)</td>
<td>1.3 (0.0–7.3)</td>
<td>1.2 (0.0–6.9)</td>
</tr>
<tr>
<td>0.9–1.2</td>
<td>6.6 (0.2–8.3)</td>
<td>3.4 (0.1–8.3)</td>
<td>2.4 (0.1–7.5)</td>
<td>1.4 (0.0–7.0)</td>
</tr>
<tr>
<td>1.3–1.6</td>
<td>6.8 (0.2–8.4)</td>
<td>6.1 (0.1–8.3)</td>
<td>3.0 (0.1–8.0)</td>
<td>2.0 (0.1–7.6)</td>
</tr>
<tr>
<td>&lt;1.6</td>
<td>6.9 (0.4–8.5)</td>
<td>6.7 (0.2–8.3)</td>
<td>4.5 (0.1–8.1)</td>
<td>2.4 (0.0–7.7)</td>
</tr>
</tbody>
</table>

WMI, wall motion index.
and dilatation. This is consistent with the results of previous studies. The presence of risk factors and co-morbidity was clearly dependent upon age. However, the frequency of several risk factors did not change linearly with the age groups, their prevalence at baseline increased instead with age until the age interval between 71 and 80 years and declined in the oldest patients. Very few studies have presented data on risk factors in heart failure patients according to several age groups. However, similar results regarding the distribution of hypertension, ischaemic heart disease and diabetes have been reported from a study in the DIG trial population. In the DIAMOND-CHF cohort we also found such a non-linear distribution for COPD, but to our knowledge this has not been investigated in other studies. The reason for the decline in hypertension, diabetes and ischaemic heart disease in the oldest patient group is not clear. It could be speculated that a higher frequency of CHF misdiagnosis was present in this age group, implying that the lower frequency of co-morbidity would simply reflect that the patients did not have heart failure. However, this seems unlikely as the pattern persisted when the analysis was restricted to the group of patients with documented LV systolic dysfunction. Another explanation may be that the presence of such co-morbidity in heart failure patients reduces the chance of surviving until the age of 80. Finally, it is possible that the elderly underwent less intensive diagnostic testing, which may have caused underreporting of risk factors or co-existing disease in this group of patients. In contrast to the results for diabetes, hypertension and ischaemic heart disease, atrial fibrillation increased more steadily with age, irrespective of systolic function. The finding that the risk of atrial fibrillation increases with age is consistent with previous studies. In our study advanced age was associated with a longer duration of heart failure and it could be speculated that the risk of developing atrial fibrillation among other things, particularly the severity of heart failure, results fairly similar to ours have been reported by MacIntyre et al., and McDermott (the two latter based on hazard ratios given per year rather than per decade). When comparing the results to those obtained in patients hospitalised with heart failure, results fairly similar to ours have been reported by Mosterd et al., and McDermott (two latter based on hazard ratios given per year rather than per decade). When in-hospital death, di Lenarda et al., recently published a study of hospitalised CHF patients comparable to the population of the present study. They reported an in-hospital death rate very similar to that found in our study and, in agreement with the present investigation, they found that age was an independent predictor of in-hospital death. In a number of studies, no effect of age on mortality has been found. In the VHeFT database the effect of age was complex. There was a small effect of age on mortality in VHeFT-I but no effect was found in VHeFT-II and overall there was no independent effect of advancing age. However, the study was limited by including only men and in particular by excluding those aged over 75 years, and this may to some extent explain why age did not emerge as an independent risk factor. Other previous studies in which an effect of ageing was not found may have been too small or included younger patients than seen in epidemiological CHF studies. In some studies a linear effect of age could not be demonstrated but increased mortality was seen in the oldest patients. In contrast, a log-linear effect of age on mortality was seen in our study. Taken together it seems reasonable to conclude that in studies that do not exclude elderly patients (either by age per se or by criteria correlating with advanced age) increasing age appears to have a clear negative impact on survival in patients with CHF. In the present study we found a solid interaction between age and systolic function. Advancing age was of greater importance in patients with preserved systolic function than in those with low ejection fraction. However, it should be emphasized that in patients with reduced systolic function, the effect of age was significant and of clinical relevance. Very few studies have previously addressed this issue. In the DIG trial population as well as in the VHeFT studies no interaction between age and systolic function was found. However, such an interaction does not seem unlikely. In CHF patients a normal ejection fraction is a potent independent predictor of mortality.
survival, and thus it could be speculated that advancing age and its associated risk of cardiac and non-cardiac morbidity could play a more prominent role in determining survival in these patients.

The mechanism behind the increased mortality in older heart failure patients is not clear. Ageing is associated with important structural and functional changes in the vascular system and the heart, but little is known about how ageing interacts with the pathophysiology underlying the process of developing heart failure. One study has demonstrated increased levels of noradrenaline in older patients with CHF, which is known to be associated with a poor prognosis. However, whether noradrenaline is merely a marker of risk or is truly a causal factor remains to be established. Another possibility is difference in treatment strategies; older patients are less frequently treated with drugs that have a documented effect on mortality, such as ACE-inhibitors and β-blockers. Obviously, as new and more invasive treatments emerge, such as cardiac resynchronization therapy, this gap is likely to increase even more. As we are facing increased longevity, it appears that more research is needed to clarify the interaction between ageing and the heart failure syndrome with regard to physiology as well as treatment strategies.

Limitations

Previous studies have suggested that advanced age increases the risk of clinical misdiagnosis of CHF and this could be a source of bias in our study. However, although age interacted with WMI, the effect of age on mortality was also present in the group of patients with reduced LV systolic function. Obviously, the risk of misdiagnosis in these patients is low. It cannot entirely be ruled out that misdiagnosis of older patients may have played a role in the analysis of the interaction between age and WMI. Given the magnitude of the interaction it seems unlikely, however, that this could have skewed the result significantly. Due to the potential limitations of the current study regarding the analysis of the interaction between age and LV systolic function, firm conclusions on this issue require confirmation in another study.

The results of the present study cannot readily be extrapolated to outpatients with CHF. In contrast, they are likely to apply to most hospitalised patients with CHF. Although being in NYHA III–IV at some time in the month preceding the admission was an inclusion criterion, this probably did not exclude many patients from entering the registry. In Denmark patients are rarely hospitalised for HF alone if they merely present with class I or II symptoms, but rather these patients are managed on an outpatient basis. The fact that a fair number of patients in the present study were classified as having class I–II symptoms most likely reflects that they improved from the time of admission to the time of screening (most likely from diuretic therapy). Therefore, we believe that the vast majority of patients who were hospitalised with CHF were in fact included in the registry.

Finally, for reasons already discussed few patients were treated with β-blockers and, among the elderly, ACE-inhibitor use was modest. Consequently, the mortality rates in the present study, in particular those of the elderly patients, may not accurately reflect prognosis of contemporary CHF patients, since the rate of utilization of these drugs has increased over the last decade.

Conclusions

In patients hospitalised with CHF the distribution of risk factors is highly age dependent. Older patients are likely to be undertreated with ACE-inhibitors. Advancing age is a potent risk factor for both short and long-term mortality in patients admitted to hospital with CHF. Although age may be less important in patients with LV systolic dysfunction than in those without, a clinically relevant effect of age is also detectable in patients with preserved ejection fraction. Hospitalisation of elderly patients for CHF is associated with a very grave prognosis, particularly if the heart failure symptoms are caused by LV systolic dysfunction.

References