International Journal of Cardiology 250 (2018) 164–170

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Trends and predictors of non-cardiovascular death in patients hospitalized for acute heart failure

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ARTICLE INFO

Article history:
Received 16 April 2017
Received in revised form 17 July 2017
Accepted 6 September 2017

Keywords:
Non-cardiovascular death
Trends and predictors
Acute heart failure

ABSTRACT

Background: Little information is available on non-cardiovascular (CV) death in acute heart failure (AHF) patients. The present study determined the incidence, time course, and factors associated with long-term non-CV death in AHF patients in a real-world setting.
Methods: The ATTEND registry, a nationwide, prospective observational multicenter cohort study, included 4842 consecutive patients hospitalized for AHF. The primary endpoint of the present study was non-CV death.
Results: Median follow-up duration from admission was 513 (range, 385–778) days. Over the study period, 1183 patients died; 356 deaths (30.1%) were non-CV related. The proportion of non-CV deaths increased in the later follow-up phase (0–180 days, 26.7%; 181–360 days, 38.4%; >360 days, 36.6%, $p < 0.001$). After adjustment for all variables at baseline, age (hazard ratio [HR] 1.6 per decade, $p < 0.001$) and non-cardiac comorbidities including chronic obstructive pulmonary disease (HR 1.58, $p = 0.003$), history of stroke (HR 1.44, $p = 0.011$), renal insufficiency (HR 1.07, per 10 ml/min/1.73 m^2 decrease in estimated glomerular filtration, $p = 0.015$), and hemoglobin (HR 1.15 per 1.0 g/dl decrease, $p < 0.001$) were strongly associated with non-CV death. Other predictors included ischemic etiology (HR 1.33, $p = 0.023$), prior hospitalization for heart failure (HR 1.34, $p = 0.017$), C-reactive protein (HR 1.04, $p < 0.001$), and statin use (HR 0.70, $p = 0.016$).
Conclusions: The incidence of non-CV death was high in patients with AHF, accounting for 30% of long-term mortality. Furthermore, the proportion of non-CV death increased in the later follow-up phase. Better understanding of non-CV death and more comprehensive treatment of non-CV comorbidities are vital to further improving prognosis in AHF patients.

1. Introduction

Morbidity and mortality associated with acute heart failure (AHF) are major public health concerns in advanced countries [1–2]. Projections show that the prevalence of heart failure will increase from 2012 to 2030. Recent large registries of hospitalized AHF populations have provided ample information regarding risk factors for cardiovascular (CV) complications and death [3–8]. Further, evidence-based approaches to treat heart failure risk factors and the implementation of angiotensin-converting enzyme inhibitors, β-blockers, coronary revascularization, implantable cardioverter-defibrillators, and cardiac resynchronization therapies have led to a decline in long-term mortality [9]. However, the Atherosclerosis Risk in Communities study sponsored by the United States National Heart, Lung, and Blood Institute demonstrated high fatality rates after hospitalization for AHF at 30-day, 1-year, and 5-year follow-up (10.4%, 22%, and 42.3%, respectively) [1]. One major reason for this finding may be the frequency of non-CV death after hospitalization for AHF. Based on recent data from Olmsted County, MN, 5-year mortality was 52.6% in heart failure patients overall, and 54.3% of deaths were ascribed to non-CV causes

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http://dx.doi.org/10.1016/j.ijcard.2017.09.004
0167-5273/

[10]. These results underscore the importance of non-CV death and the need for more information on this issue. Trends and predictors of non-CV death have not been reported in AHF patients. The present study, therefore, investigated the time course and factors associated with long-term non-CV death in patients hospitalized for AHF enrolled in the Acute Decompensated Heart Failure Syndromes (ATTEND) Registry.

2. Methods

2.1. Study design

The ATTEND registry is a nationwide, prospective observational multicenter cohort study including 53 participating hospitals across Japan, established to elucidate the features of AHF patients such as clinical characteristics, current treatments, and in-hospital and post-discharge long-term outcomes. Detailed descriptions of the objectives, social significance, and study design of the ATTEND registry were submitted for clinical trial registration with the University Hospital Medical Information Network (UMIN 000000736), and its rationale, design, and patient characteristics have been published [11]. Briefly, the ATTEND registry enrolled AHF patients who met the modified Framingham criteria [12], which only includes variables estimated at admission. Patients hospitalized for newly diagnosed or aggravated heart failure were eligible for the study. Patients aged <20 years, with acute coronary syndrome, or considered otherwise unsuitable for study enrollment by their physicians were excluded. Patients are enrolled at admission and then followed for at least 12 months. Data collection is patient based and not event based. The registry was conducted in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the institutional review boards of the participating centers. Written informed consent was obtained from each patient, or a relative or legal representative.

2.2. Data collection

Patients were enrolled in the ATTEND registry between April 2007 and December 2011. Data were collected from ATTEND case reports and included full details on the following: baseline characteristics, vital status, physical examination, medical history, complications, biochemistry tests, echocardiography, medications at admission, medications at discharge, in-hospital treatment, procedure, and clinical outcomes. Each case report was completed by the attending physicians and sent to an independent biostatistics and data center (STATZ Institute, Inc., Tokyo, Japan).

2.3. Clinical endpoints and definitions

The primary outcome of the present study was non-CV death. The criteria for the modes of mortality were defined in a prospective manner according to the central study protocol. The causes of death were divided broadly into CV-related, non-CV related, and unknown. CV death included heart failure death; sudden death; cardiac death by another cause, namely, myocardial infarction, lethal arrhythmia, or fatal valve disease; and death from cerebral or vascular causes such as pulmonary embolism, aortic dissection, aortic aneurism rupture, or arterial embolism. Deaths from non-CV causes such as malignancy or respiratory, infectious, renal, or gastrointestinal disease were registered as non-CV deaths. The attending physician determined the mode of death according to the central study protocol and recorded data in the case report as presented above. The endpoint classification committee consisted of two experienced cardiologists who were not study investigators and were independent from the team providing patient care. The committee reviewed clinical endpoints and consulted with the attending physician as necessary to confirm the mode of death.

Standardized definitions and the clinical data standards of the American College of Cardiology/American Heart Association were used for all patient-related variables and clinical diagnoses [13]. eGFR was calculated using revised modification of diet in renal disease (MDRD) equations for Japanese. According to previously validated calculations [14], eGFR (ml/min/1.73 m^2) = 194 × Serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female).

2.4. Statistical analysis

Normally distributed, continuous variables are expressed as mean ± standard deviation. For variables that are not normally distributed, median and interquartile ranges are reported. Student's *t*-test or the Mann Whitney *U* test was used for 2-group comparisons, and one-way ANOVA or the Kruskal Wallis test was used for 3-group comparisons, as appropriate. For categorical variables, proportions and percentages were calculated, and the differences were tested using the chi-squared test or Fisher's exact probability test, as appropriate. The chi-squared test (2 by 3) was used to assess differences in the proportion of non-CV deaths depending on the period of follow-up (0–180 days vs. 181–360 days vs. after 360 days). The cumulative probability of events was estimated using Kaplan–Meier analysis. Univariable and multivariable Cox's proportional hazards regression models were used to identify significant predictors of the end point of non-CV death. All variables at baseline shown in Table 1 were assessed for associations with non-CV death. In-hospital treatments and medications at discharge were not included in the analysis, because non-CV death was predicted on admission. Multivariable analysis was performed with stepwise selection methods. The proportional hazards assumption was confirmed by the log (–log survival function), and the influence of profile, interaction, and multicollinearity in these models was examined by regression diagnostic analysis. Statistical analysis was performed using SAS 9.3 software (SAS Institute, Cary, North Carolina). A p value of <0.05 was considered to indicate statistical significance. All analyses were performed at an independent biostatistics and data center, STATZ Institute, Inc.

3. Results

The ATTEND registry includes 4842 consecutive patients enrolled from April 2007 to December 2011. The median follow-up duration from admission was 513 (385–778) days in the overall cohort of 4842 AHF patients. Thirty-three patients (0.9%) withdrew their consent or were lost to follow-up within 1 year. There was no missing data on the mode of death during follow-up.

The incidence of all-cause 1-year mortality was 17.1% ($n = 827$). All-cause mortality over the entire study period was 24.4% ($n = 1183$): 15.7% of patients ($n = 760$) died from CV causes, 7.4% ($n = 356$) died from non-CV causes, 1.3% of patients ($n = 67$) died from unknown cause, and 76.5% ($n = 3659$) of patients survived. The mean age of the total cohort was 73.0 years, and 2812 of the patients (58.1%) were men. Clinical baseline characteristics of the survivor, CV death, and non-CV death groups are shown in Table 1 (p value in Supplemental Table 1). The information on the therapeutic strategy during index hospitalization and medications at discharge are shown in Supplemental Table 2 (p value in Supplemental Table 1).

Newly diagnosed or acutely decompensated chronic heart failure may be associated with different pathophysiological backgrounds, comorbidities, and prognoses. We therefore performed an additional comparison between subgroups of newly diagnosed and acutely decompensated chronic heart failure patients. The baseline characteristics are shown in Supplemental Table 3. The information on newly diagnosed or acutely decompensated chronic heart failure was missing in 110 patients. The patients with acutely decompensated chronic heart failure seem sicker in vital sign, co-morbidities and medications. The incidence of non-CV death differed between the newly diagnosed and acutely decompensated chronic heart failure patients [197 (6.6%) vs. 155 (8.9%), $p = 0.003$]. The baseline characteristics were therefore compared between the subgroups of newly diagnosed and acutely