Gender and drug treatment as determinants of mortality in a cohort of heart failure patients

Ana Ruigómez1, Saga Johansson2,3, Mari-Ann Wallander2,4 & Luis Alberto García Rodriguez1
1Centro Español de Investigación Farmacoepidemiológica (CEIFE), Madrid, Spain; 2AstraZeneca R&D Mölndal; 3Section of Preventive Cardiology, Göteborg University; 4Department of Public Health and Caring Science, Uppsala University, Sweden

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Abstract. Aim: We assessed gender differences in the risk of mortality in heart failure (HF) patients and evaluated the association between HF drug treatment and mortality. Methods and Results: We identified a cohort of 820 patients with newly diagnosed HF in 1996 in UK general practices. The diagnosis of HF was confirmed by the general practitioner. Fifty per cent were females and 27% were less than 70 years old. During a mean follow-up of 2 years, 172 patients died. We used computerized records to assess risk factors and drugs prescribed as treatment. The information on severity was assessed through a questionnaire. We performed a nested case-control analysis, and observed that men had twice the risk of dying than females, however the effect of age on mortality was stronger in females than males. We found a similar interaction between HF severity and sex. Data on use of some cardiovascular drugs such as diuretics, β-blockers ACE-inhibitors and calcium channel blockers were suggestive of a reduced mortality risk. Current use of nitrates and glycosides carried an increased risk. Conclusion: Older age, male sex and severity of HF were the main predictors of mortality among HF patients. Long-term use of β-blockers was associated with a significantly reduced risk of mortality.

Key words: Automated database, Cardiovascular drugs, Gender differences, Heart failure, Mortality, Odds ratio

Introduction

Heart failure (HF) is a serious health problem that is becoming increasingly common both in men and women and particularly in the elderly [1, 2]. Gender-related differences have been reported in incidence, management and prognosis of HF [3, 4]. The incidence rate is higher in men than in women but this difference in incidence decreases with advancing age [2, 5].

Early population based studies on HF, as the Framingham study, have shown a better survival of women than men with HF [2, 6]. Other studies however, have shown a worse prognosis of women after a myocardial infarction [7–9]. Whether these gender differences can be explained by differences in referral or treatment, or whether biological differences play a major role, remains unclear [3, 10, 11].

Treatment management has been evolving in recent years. The beneficial effects of β-blockers [12–14] and angiotensin-converting enzyme inhibitors (ACE-inhibitors) [15–18] have been documented in numerous studies, yet their use is still not so widely extended as recommended [19].

We assessed gender difference in the risk of mortality in patients newly diagnosed with HF in general practice. We also evaluated the association between HF drug treatment and mortality.

Subjects and methods

Data resource

The General Practice Research Database (GPRD) in the UK is a database including medical information of approximately three million individuals who are registered with general practitioners (GPs) participating in this scheme. They have agreed to provide information anonymously to the Medicines Control Agency in order to be used in research projects. The information recorded includes demographics, medical diagnoses, referrals to consultants and hospital. Also, medical prescriptions are automatically produced from the computer and recorded on the patient’s computerized file. A modification of the OXMIS classification is used to code specific diagnoses, and a drug dictionary based on the Prescription Pricing Authority drug dictionary is used to record drugs. There are multiple epidemiologic studies published using the GPRD as the primary data resource that have confirmed its validity [20].
Study cohort

In a previous study we identified a cohort of 938 patients with newly diagnosed HF in 1996 [5]. Briefly, to validate incident cases of HF, we sent a questionnaire to the GPs to confirm the diagnosis and assess the severity of the initial episode, as well as information on symptoms at presentation and investigations performed. We adapted the operational definition of HF used in previous studies performed in UK general practice [21]; dyspnea along with other clinical signs, and objective evidence of heart disease. From this original cohort, we identified all HF patients alive 1 month after the initial diagnosis (start date). These patients constituted our study cohort (n = 820). The cohort was followed-up until the earliest of death or end of the study period (September 98). One hundred and seventy-two patients died during follow-up. Information on cause of death was extracted from computerized files, and was grouped in three broad categories; those related to cardiovascular disease, non-cardiovascular causes and unknown cause.

Nested case–control analysis

We used the 172 HF patients deceased during follow-up as cases and the remaining HF patients alive at end of follow-up as controls (n = 648). The date of death was used as index date among the cases. A date during the period of follow-up was randomly generated for each control and used as index date. Information on factors related to mortality was obtained from computerized files and included age, sex, smoking status, body mass index (BMI), and units of alcohol consumed per week, for both cases and controls.

We requested the GP to categorize the severity of HF according to the grades of the New York Heart Association (NYHA) classification of functional status [22]. Definition of NYHA categories were provided in the questionnaire.

Drug exposure definition

We ascertained the exposure history of drug therapy between HF diagnosis date and index date (diuretics, β-blockers, ACE-inhibitors, calcium channel blockers, other antihypertensive drugs, nitrates, glycosides, lipid-lowering drugs, warfarin and aspirin). We also assessed the use of NSAIDs. A person was defined as a current drug user when the supply of the most recent prescription lasted until the index date or ended in the previous month. A person was defined as a past user when the end of the most recent prescription was more than 30 days before the index date. Non-users were persons who did not receive drug treatment between the start date and index date. Among current users, two mutually exclusive categories were created: current short-term users with less than 3 months duration, and current long-term users who received treatment for longer than 3 months.

We recorded the dose of all drugs received by the patient and categorize them in medium–low dose, when it was equal or below maintenance dose proposed by the British National Formulary (BNF) and all doses above that level were considered high dose.

We estimated the odds ratios (OR) and 95% confidence intervals (CI) of mortality associated with different risk factors using unconditional logistic regression. We calculated estimates of mortality risk associated with drug use compared to non-use. In addition, we compared the risk among users of combined cardiovascular drugs vs. users of diuretics only. All estimates were adjusted for age, sex and severity of HF. We also performed all these analyses stratified by sex.

Results

The study cohort included 820 patients, mean age at diagnosis in males was 71 years (SD 9.0) and 74 years (SD 7.4) in females. One hundred and seventy-two patients (21%) died during the follow-up period of close to 2 years (range 1–37 months). The major cause of death was cardiovascular disease (59%). Non-cardiovascular cause accounted for 26% of the deaths, and in the remaining 15% of patients the cause could not be clearly assessed. Cumulative survival at 1 year follow-up was not significantly different for men and women, but at the end of 2 years follow-up 87% of women survived vs. 78% of men. This gender difference continued to increase over time and at the end of follow-up, only 68% of men survived compared to 82% of women.

The mortality risk was higher in men, elderly patients and smokers (Table 1). High alcohol consumption and low BMI were associated with a small increased risk of mortality (data not shown). Furthermore, an excess risk of dying was found among patients with chronic renal disease (OR: 4.1; 95% CI: 2.2–7.9).

Severity of HF was the most important predictor of death independently of age and sex. Patients with a HF NYHA – class III or IV, which implies a marked functional limitation or inability, carried a twofold increased risk of death compared to those patients with HF NYHA – class I/II.

The effect of age on mortality was stronger among females with a risk of mortality of 3.6 comparing females 80–84 years old vs. 40–69 years old. The corresponding estimate was 1.9 among males (Figure 1(a)). We found a similar interaction between HF severity and sex, where females presented an OR of 3.0 whereas males had an OR of 1.9 when comparing patients with NYHA III/IV vs. NYHA I/II (Figure 1(b)).