International Journal of Cardiology 221 (2016) 198–204

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Addition of beta-blockers to digoxin is associated with improved 1- and 10-year survival of patients hospitalized due to decompensated heart failure

Ari Katz [a,*], Elad Maor [b], Jonathan Leor [b,c,d], Robert Klempfner [c,d]

[a] University of Illinois Hospital and Health Sciences System, Chicago, IL, United States
[b] Neufeld Cardiac Research Institute, Sheba Medical Center, Israel
[c] Leviev Heart Center, Sheba Medical Center, Israel
[d] Sackler School of Medicine, Tel Aviv University, Israel

ARTICLE INFO

Article history:
Received 21 January 2016
Received in revised form 12 May 2016
Accepted 25 June 2016
Available online 27 June 2016

Keywords:
Digoxin
Beta-blockers
Mortality
Heart failure

ABSTRACT

Background: Many of the studies associating digoxin use with increased mortality were conducted before beta-blockers became a standard therapy for heart failure (HF) patients. Our goal was to determine the effect of beta-blockers on the prognosis of patients hospitalized for decompensated HF who receive digoxin therapy at discharge.

Methods: We analyzed 2402 patients admitted with a primary diagnosis of decompensated HF during the prospective National Heart Failure Survey in Israel. Multivariate modeling was used to determine the effect of beta-blockers and digoxin on 1- and 10-year survival.

Results: Patients discharged on digoxin and beta-blockers (DIG+/BB+) had a lower 1-year mortality rate than those discharged on digoxin alone (DIG+/BB−), (31% vs. 44%; $p < 0.001$). Digoxin administration was associated with an increase in adjusted 1-year (Hazard ratio [HR] 1.28; 95% confidence interval (CI) 1.08–1.50) and 10-year mortality risk (HR 1.27; CI 1.16–1.42), whereas beta-blocker administration was associated with a decrease in adjusted 1-year (HR 0.76; CI 0.68–0.87) and 10-year mortality risk (HR 0.83; CI 0.77–0.89; all $p < 0.001$). In comparison to a DIG−/BB+ group serving as a reference, multivariate adjusted HR for DIG+/BB+ and DIG+/BB− groups were 1.36 (CI 1.03–1.91; $p < 0.001$) and 2.01 (CI 1.59–2.85; $p < 0.001$) at 1-year, and 1.04 (CI 0.84–1.28; $p > 0.1$) and 1.37 (CI 1.17–1.76; $p < 0.001$) at 10 years.

Conclusion: In patients hospitalized with decompensated HF, digoxin administration at discharge is associated with increased 1- and 10-year mortality risk. However, the simultaneous use of beta-blockers and digoxin is associated with lower 1- and 10-year mortality risk when compared to use of digoxin alone.

1. Introduction

Although digoxin has been used for decades in patients with heart failure (HF) [1], its safety and efficacy have recently been questioned. This notion is reflected in current guideline recommendations that have downgraded the use of digoxin therapy, and as a result the yearly prescription rate of digoxin has steadily decreased [2,3]. Multiple randomized clinical trials as well as post-hoc analyses have suggested that continuous use of digoxin is associated with an increase in mortality [4,5]. Moreover, digoxin therapy has also been associated with increased mortality in several specific subgroups including women [6], patients recovering from an acute myocardial infarction (MI) [7,8], patients with renal dysfunction [9], and patients with atrial fibrillation (AF) [10–12]. However, despite this mortality risk, a significant proportion of patients with HF continue to receive digoxin as they remain symptomatic and experience repeated HF hospitalizations despite optimal therapy [12]. Indeed, in the largest prospective randomized HF study to date, approximately 30% of patients with New York Heart Association class II/III (NYHA) were receiving digoxin [13].

The majority of data regarding the benefits and safety of digoxin is derived from clinical trials conducted before beta-blockers became a standard therapy for the management of patients with HF [14]. Multiple clinical trials have shown that beta-blockers improve the prognosis of HF patients with left ventricular dysfunction [14–18], and today the majority of these patients are receiving beta-blocker therapy. However, few studies have addressed the safety and side effects of digoxin in the setting of concomitant beta-blocker therapy. We thus aimed to determine the influence of beta-blockers on the short- and long-term

* Corresponding author at: University of Illinois Hospital and Health Sciences System, 1740 West Taylor Street, Chicago, IL 60612, United States.
E-mail address: arikatzmd@gmail.com (A. Katz).

http://dx.doi.org/10.1016/j.ijcard.2016.06.202
0167-5273/

prognosis of patients with decompensated heart failure discharged on digoxin therapy.

2. Methods

2.1. Study population

The data of this study was extracted from the national Heart Failure Survey in Israel (HFSIS) 2003 database that was previously published [20]. In brief, HFSIS was conducted in March and April 2003, and included 4515 patients with a diagnosis of either acute HF, acute exacerbation of chronic HF, or chronic HF, who were admitted to participating internal medicine and cardiology departments in all 25 public hospitals operating in Israel. The criteria used for the diagnosis of HF were described elsewhere [19,20]. Diagnosis of acute HF or exacerbation of chronic HF was determined by the attending physician based on history, clinical presentation (symptoms and physical examination), response to HF therapy, chest radiography, echocardiography, radionuclide studies, cardiac catheterization findings, and in-hospital course. Detailed data regarding patient characteristics, in-hospital course, management during hospitalization, pre-hospital and discharge medications, and diagnoses were collected and recorded by physicians on pre-specified structured forms. Mortality during the first year after index hospitalization, as well as 10-year vital status, were determined for 99% of patients by matching their identification numbers with the Israeli National Population Registry. The research protocol was approved by an ethics committee at each of the participating hospitals.

2.2. Endpoints

The endpoints of the present study were 1- and 10-year all-cause mortality. We included in our analysis patients admitted due to acute HF or an acute exacerbation of chronic HF. We excluded chronic HF patients admitted for non-cardiovascular causes, patients that died during the index hospitalization, and patients with missing admission or discharge medication information. Of 4515 patients in the HFSIS data set, 2402 met study criteria. Of these, 380 patients (16%) were discharged on digoxin therapy after their index admission (Fig. 1). Every effort was made to ensure the consistency and accuracy of the data. This included standardizing HF definitions and data validation at two time points: first, during data entry, by logical checks incorporated into the data entry interface which displayed error and warning signs to alert the data entry operator, and second, after data entry, by batch checks that were conducted for missing values, data conflicts, and out of range values. These data conflicts and inconsistencies were resolved, and missing data were completed appropriately.

2.3. Statistical analysis

Patients were categorized into four treatment groups according to their discharge medications: patients who were not given digoxin or beta-blockers (DIG −/BB −), patients who were not given digoxin but did receive beta-blockers (DIG −/BB +), patients who received both digoxin and beta-blockers (DIG +/BB +), and patients who were given digoxin but were not given beta-blockers (DIG +/BB −).

Demographic characteristics measured as continuous variables are expressed as mean values with standard deviations, while categorical data is displayed as counts and percentages. We used chi square tests to compare proportions, and unpaired t-test or Wilcox rank sum tests for comparison of continuous data. Predictors of digoxin administration were assessed using a binary logistic regression model which included the following covariates: age, gender, NYHA class III/IV, previous MI, digoxin administration prior to admission, LVEF < 30% (left ventricular ejection fraction), renal dysfunction (estimated glomerular filtration rate [eGFR] < 60 mL/Kg/1.73m^2), anemia (hemoglobin < 11 g/dL), admission heart rate, admission diagnosis of paroxysmal or chronic atrial fibrillation or flutter (AF), and exacerbation of chronic HF (vs. acute HF). Cumulative 1-year survival of the four treatment groups are presented as Kaplan–Meier curves and the difference between curves is compared by means of the Log-rank test. Similarly, we constructed 10-year survival curves for patients discharged on digoxin with and without beta-blockers.

In order to evaluate the independent association of digoxin and beta-blocker therapy with 1-year and 10-year all-cause mortality outcomes, we used a multivariate Cox proportional hazards model introducing pre-specified clinically important covariates according to the best subset method. In addition to digoxin and beta-blocker treatment, the covariates selected for the described models included: age, sex, Killip class > 1 on admission, NYHA class > 1 and LVEF < 30% on admission, past MI, renal function (creatinine), AF, anemia, systolic blood pressure, heart rate, glucose level, and use of furosemide, angiotensin II receptor blockers (ARB), and angiotensin converting enzyme inhibitors (ACE). Potential indications for withholding beta-blocker therapy were identified and compared between treatment groups. These indications included: asthma, significant conduction abnormalities (Mobitz type I/ II or marked 1st degree atrioventricular (AV) block), and low discharge heart rate (HR < 60 bpm) or systolic blood pressure (<100 mmHg). Additionally, a separate multivariate Cox proportional hazards model was constructed comparing the treatment groups (DIG −/BB −, DIG +/BB +, DIG +/BB −) to DIG −/BB +, which served as the reference group. The validity of the proportional hazards assumption was tested and no deviation was detected. Results of the model are presented as hazard ratios (HR) and 95% confidence intervals (CI) and a p-value of <0.05 was considered

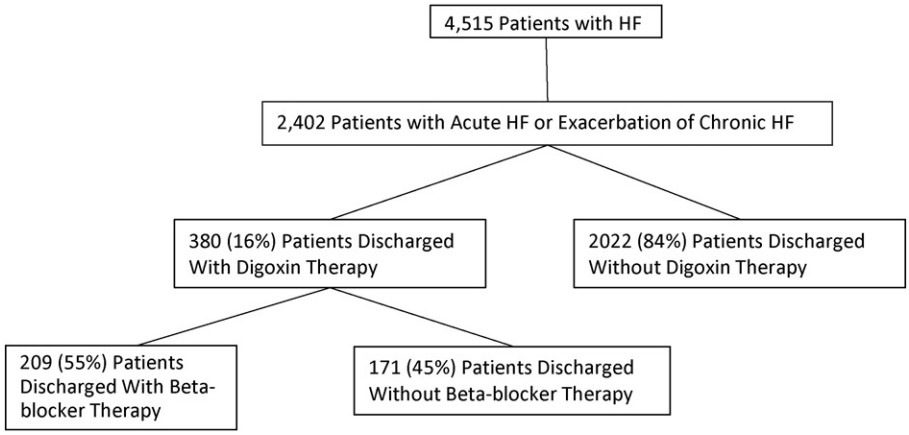

Fig. 1. Study population.