International Journal of Cardiology 173 (2014) 393–401

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Beta-blockers in older patients with heart failure and preserved ejection fraction: Class, dosage, and outcomes

Kanan Patel [a], Gregg C. Fonarow [b], O. James Ekundayo [c], Inmaculada B. Aban [d], Meredith L. Kilgore [d], Thomas E. Love [e], Dalane W. Kitzman [f], Mihai Gheorghiade [g], Richard M. Allman [h], Ali Ahmed [d,i,*]

[a] University of California, San Francisco, CA, United States
[b] University of California, Los Angeles, CA, United States
[c] Meharry Medical College, Nashville, TN, United States
[d] University of Alabama at Birmingham, Birmingham, AL, United States
[e] Case Western Reserve University, Cleveland, OH, United States
[f] Wake Forest School of Medicine, Winston-Salem, NC, United States
[g] Northwestern University, Chicago, IL, United States
[h] Department of Veterans Affairs, Geriatrics and Extended Care Services, Washington, DC, United States
[i] Veterans Affairs Medical Center, Birmingham, AL, United States

ARTICLE INFO

Article history:
Received 27 November 2013
Received in revised form 24 February 2014
Accepted 3 March 2014
Available online 11 March 2014

Keywords:
Beta-blockers
Heart failure
Preserved ejection fraction

ABSTRACT

Background: We examined the clinical effectiveness of beta-blockers considered evidenced-based to heart failure and reduced ejection fraction (HFrEF) and their recommended target doses in older adults with HF and preserved ejection fraction (HFpEF).
Methods: In OPTIMIZE-HF (2003–2004) linked to Medicare (2003–2008), of the 10,570 older (age ≥ 65 years, mean, 81 years) adults with HFpEF (EF ≥ 40%, mean 55%), 8373 had no contraindications to beta-blocker therapy. After excluding 4614 patients receiving pre-admission beta-blockers, the remaining 3759 patients were potentially eligible for new discharge prescriptions for beta-blockers and 1454 received them. We assembled a propensity-matched cohort of 1099 pairs of patients receiving beta-blockers and no beta-blockers, balanced on 115 baseline characteristics. Evidence-based beta-blockers for HFrEF, namely, carvedilol, metoprolol succinate, and bisoprolol and their respective guideline-recommended target doses were 50, 200, and 10 mg/day.
Results: During 6 years of follow-up, new discharge prescriptions for beta-blockers had no association with the primary composite endpoint of all-cause mortality or HF rehospitalization (hazard ratio, 1.03; 95% confidence interval {CI}, 0.94–1.13; p = 0.569). This association did not vary by beta-blocker evidence class or daily dose. Hazard ratios for all-cause mortality and HF rehospitalization were 0.99 (95% CI, 0.90–1.10; p = 0.897) and 1.17 (95% CI, 1.03–1.34; p = 0.014), respectively. The latter association lost significance when higher EF cutoffs of ≥45%, ≥50% and ≥55% were used.
Conclusions: Initiation of therapy with beta-blockers considered evidence-based for HFrEF and in target doses recommended for HFrEF had no association with the composite or individual endpoints of all-cause mortality or HF rehospitalization in HFpEF.

1. Introduction

Beta-blockers constitute one of the mainstays of evidence-based therapy for patients with heart failure and reduced ejection fraction (HFrEF) [1]. Nearly half of the estimated 6 million HF patients have HF with preserved ejection fraction (HFpEF) [2]. Findings from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry suggest that despite some differences in baseline characteristics, patients with HFpEF are prognostically similar to those with HFrEF [3,4]. The vast majority of HF patients are ≥65 years, and most of the older HF patients have HFpEF [5]. Yet, they were often excluded from major randomized controlled trials (RCTs) [6]. In the OPTIMIZE-HF, the initiation of beta-blocker therapy had no association with all-cause mortality or all-cause hospital readmission during the first year of follow-up in older HFpEF patients [6]. However, their associations with hospital readmission due to HF, long-term mortality beyond one year, and whether these outcomes varied between beta-blockers considered evidence-based for HFrEF (versus other beta-blockers) and between target doses recommended for HFrEF (versus below-target doses) remain unknown and these important questions are unlikely to be answered by

* Corresponding author at: University of Alabama at Birmingham, 1720 2nd Ave South, CH-19, Ste-219, Birmingham, AL 35294-2041, United States. Tel.: +1 205 934 9632; fax: +1 205 975 7099.
E-mail address: aahmed@uab.edu (A. Ahmed).

http://dx.doi.org/10.1016/j.ijcard.2014.03.005
0167-5273/

new RCTs. When RCTs are unavailable, impractical, or unethical, propensity score-matched non-RCT studies, which allow outcome-blinded retrospective assembly of balanced cohorts, may provide timely and cost-effective [7–10]. Therefore, in the current study, we examined the association of beta-blocker therapy with long-term outcomes in propensity-matched cohorts of real-world older HFpEF patients, overall, and by their HFrEF evidence class and target doses.

2. Materials and methods

2.1. Source of data and study patients

The OPTIMIZE-HF is a United States national registry of hospitalized HF patients and has been well described in the literature [11–13]. Briefly, patients with a primary discharge diagnosis of HF based on International Classification of Diseases, 9th Revision codes were eligible for inclusion in OPTIMIZE-HF [14]. Extensive data on baseline demographics, medical history including admission and discharge medications, hospital course, and discharge disposition were abstracted and collected by trained staff from 48,612 charts from 259 hospitals from 48 states between March 2003 and December 2004 [11]. To prevent out-of-range entry or duplicate patients, electronic data checks were done automatically. A random 5% sample of the first 10,000 patients was verified against source documents [13]. Considering that HF patients with EF 40% to 50% are characteristically and prognostically similar to those with EF > 50% [4], we used EF ≥ 40% to define HFpEF. Of the 48,612 hospitalizations, 20,839 were due to HFpEF (EF ≥ 40%). Because of unavailability of long-term outcomes data in OPTIMIZE-HF, we linked OPTIMIZE-HF to Medicare outcomes data up to December 31, 2008, obtained from the Centers for Medicare and Medicaid Services [15]. Of the 20,839 HF hospitalizations due to HFpEF, we were able to link 13,270 to the Medicare data that occurred in 11,997 unique patients, of whom 10,889 were 65 years or older and 10,570 of them were discharged alive (Fig. 1) [15].

2.2. Data on beta-blocker use

Names, doses and frequency of beta-blockers and for those not receiving these drugs, data on reason for non-use or contraindications were collected. From the 10,570 patients, we excluded 101 patients with missing data on discharge beta-blocker use, 1740 patients with contraindications, and 356 patients whose pre-admission beta-blocker therapy was discontinued prior to hospital discharge. Contraindications included prior allergy, second or third-degree heart block without a pacemaker, symptomatic bradycardia, symptomatic hypotension, cardiogenic shock, or reactive airway disease [16]. The final working sample consisted of 8373 patients who were considered potentially eligible for beta-blocker therapy, of which 2305 (28%) were not prescribed one (Fig. 1). Of the 6068 who received a discharge prescription for beta-blockers, 3234 (58%) received beta-blockers considered evidence-based for HFrEF: carvedilol (n = 1401), metoprolol succinate (n = 1799), and bisoprolol (n = 34). Of the non-evidence-based beta-blockers, 1105 received atenolol, 1330 received metoprolol tartrate, and 399 received other beta-blockers. Based on guideline recommended target doses for HFrEF, target doses for evidence-based beta-blockers

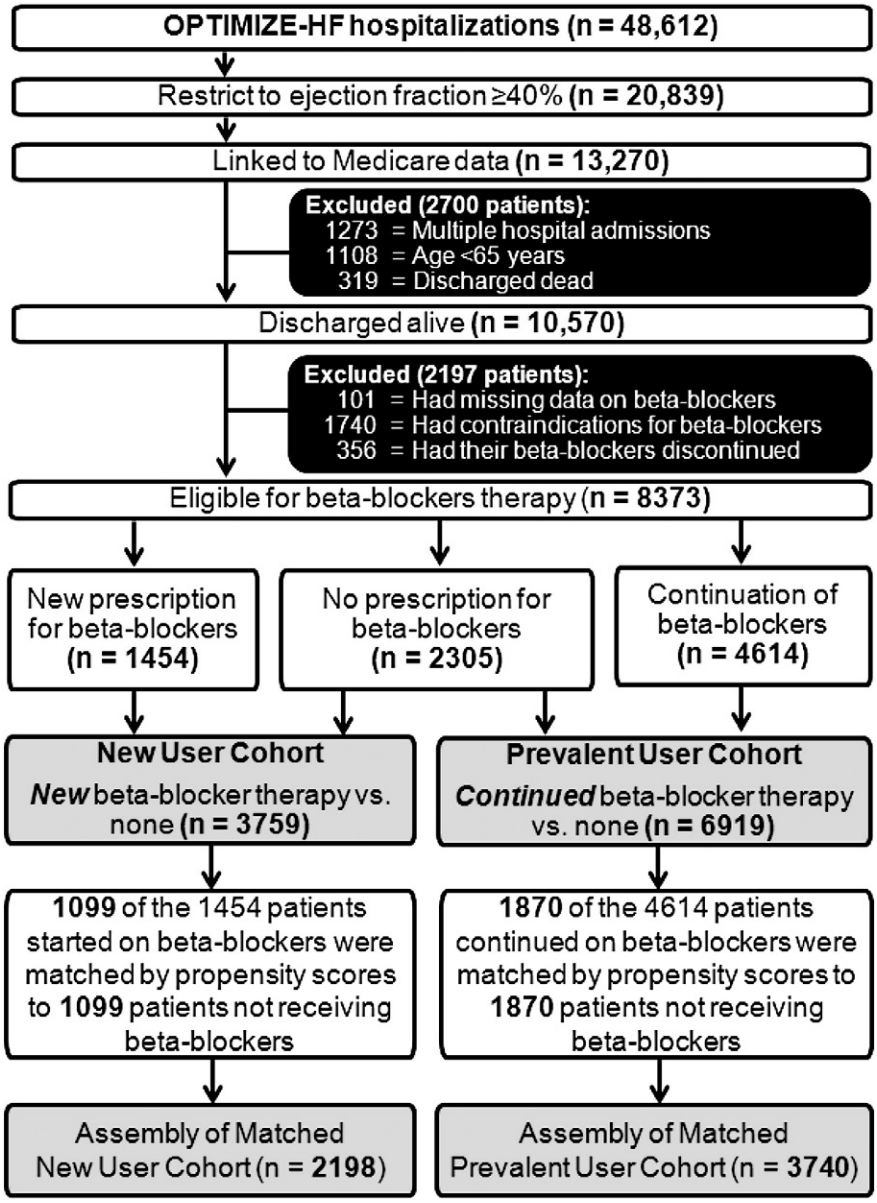

Fig. 1. Flow chart displaying assembly of matched new user and prevalent user cohorts of patients with heart failure and preserved ejection fraction.