JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2014 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 3, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.04.042

Beta-Blocker Therapy and Cardiac Events Among Patients With Newly Diagnosed Coronary Heart Disease

Charlotte Andersson, MD, PhD,* David Shilane, PhD,† Alan S. Go, MD,‡ Tara I. Chang, MD, MS,§ Dhruv Kazi, MD, MS,‖ Matthew D. Solomon, MD, PhD,‡ Derek B. Boothroyd, PhD,† Mark A. Hlatky, MD†§

ABSTRACT

BACKGROUND The effectiveness of beta-blockers for preventing cardiac events has been questioned for patients who have coronary heart disease (CHD) without a prior myocardial infarction (MI).

OBJECTIVES The purpose of this study was to assess the association of beta-blockers with outcomes among patients with new-onset CHD.

METHODS We studied consecutive patients discharged after the first CHD event (acute coronary syndrome or coronary revascularization) between 2000 and 2008 in an integrated healthcare delivery system who did not use beta-blockers in the year before entry. We used time-varying Cox regression models to determine the hazard ratio (HR) associated with beta-blocker treatment and used treatment-by-covariate interaction tests (p_{int}) to determine whether the association differed for patients with or without a recent MI.

RESULTS A total of 26,793 patients were included, 19,843 of whom initiated beta-blocker treatment within 7 days of discharge from their initial CHD event. Over an average of 3.7 years of follow-up, 6,968 patients had an MI or died. Use of beta-blockers was associated with an adjusted HR for mortality of 0.90 (95% confidence limits [CL]: 0.84 to 0.96), and an adjusted HR for death or MI of 0.92 (CL: 0.87 to 0.97). The association between beta-blockers and outcomes differed significantly between patients with and without a recent MI (HR for death: 0.85 vs. 1.02, $p_{int} = 0.007$; and HR for death or MI: 0.87 vs. 1.03, $p_{int} = 0.005$).

CONCLUSIONS Use of beta-blockers among patients with new-onset CHD was associated with a lower risk of cardiac events only among patients with a recent MI. (J Am Coll Cardiol 2014;64:247-52) © 2014 by the American College of Cardiology Foundation.

The clinical effectiveness of beta-blockers in reducing death and major adverse cardiac events among patients with coronary heart disease (CHD) has recently been questioned. Randomized clinical trials have shown that beta-blockers are effective in reducing cardiac events and mortality among patients who have had a recent myocardial infarction (MI) or who have heart failure with systolic dysfunction (1-5). In contrast, among patients with stable ischemic heart disease, only small, short-term randomized trials have tested whether beta-blockers reduce anginal symptoms compared with placebo, and no large trials have been performed to assess their effectiveness in reducing major cardiac events (6,7). Thus, the general belief that beta-blockers are cardioprotective for all patients with CHD is largely on the basis of extrapolating

From the *Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark; †Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California; ‡Division of Research, Kaiser Permanente, Oakland, California; §Department of Medicine, Stanford University School of Medicine, Stanford, California; and the ‖Department of Medicine, University of California, San Francisco, California. This research was funded in part by a grant (0875162) from the American Heart Association, Dallas, Texas, with additional support by a grant (FSS - 11-120873) from the Danish Agency for Science, Technology and Innovation, Copenhagen, Denmark. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.
You can also listen to this issue's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received February 21, 2014; revised manuscript received April 23, 2014, accepted April 25, 2014.

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

CABG = coronary artery bypass graft surgery

CHD = coronary heart disease

CL = 95% confidence limits

HR = hazard ratio

MI = myocardial infarction

NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

the results of clinical trials in patients with MI or heart failure to all patients with CHD.

A recent analysis of the observational data from the REACH (REduction of Atherothrombosis for Continued Health) registry found no significant association of beta-blocker therapy with major adverse cardiovascular events among patients with stable CHD (8). This finding initiated a vigorous debate about whether beta-blockers improve prognosis among patients with CHD. The effectiveness of beta-blockers as first-line therapy for hypertension in reducing cardiovascular events (9,10) and as cardioprotective agents for noncardiac surgery (11) also has been called into question. In light of these recent concerns, we sought to assess the association of beta-blocker therapy with major adverse cardiac outcomes among patients with incident CHD.

SEE PAGE 253

METHODS

SOURCE OF DATA. We used electronic health records from Kaiser Permanente Northern California, a large, integrated healthcare delivery system that provides care to 3.2 million subjects. The membership is broadly representative of the local population, apart from slightly lower representation of the extremes of age and income. The electronic health records collect comprehensive data on hospitalizations, outpatient encounters, laboratory test results, and prescription medications. Diagnoses are coded according to the International Classification of Diseases (ICD)-9th version, and procedures are coded using ICD-9CM codes and Current Procedural Terminology codes, 4th edition.

STUDY POPULATION. We included all patients age 30 years and older who had an initial diagnosis of CHD between January 1, 2000, and December 31, 2008, which we defined as hospitalization for acute MI (non-ST-segment elevation myocardial infarction [NSTEMI] ICD-9CM codes 410.7 and 410.9 or ST-segment elevation myocardial infarction [STEMI] codes 410.0 to 410.6 and 410.8), unstable angina (ICD-9CM 411.1), or having undergone coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). We excluded patients with any prior diagnoses of MI, unstable angina, or coronary revascularization. We also excluded patients with a history of chronic lung disease (ICD-9CM 491.x, 492.x, 493.x, 496, 518.1, 518.2), which is a relative contraindication to beta-blocker therapy. We adopted a new user design by excluding patients who received a prescription for a beta-blocker within the year before study entry. Patients were classified according to their initial presentation as having had a recent MI, defined as an index hospitalization for either STEMI or NSTEMI.

DEFINITION OF COMORBIDITY, PHARMACOLOGICAL TREATMENT, AND PATIENT-RELATED CHARACTERISTICS. We defined comorbid conditions on the basis of in-hospital and outpatient diagnosis codes in the year before the incident CHD event. Unless otherwise described, comorbidities were considered present if at least 1 prior diagnosis was available in the electronic health records. A diagnosis of heart failure required at least 2 outpatient visits with an ICD-9CM code for heart failure or an inpatient admission with a primary diagnosis of heart failure (12). Full codes for classification of the different diseases are available elsewhere (13).

We identified drug use (beta-blockers, statins, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARB], and clopidogrel) on the basis of filled prescriptions from a Kaiser pharmacy in the year before the index hospitalization (for baseline exposure) and during subsequent follow-up. To account for partial adherence, dose reductions, and possible persistence of any drug effects after discontinuation, we considered patients to be on treatment with a given drug from the date they filled the prescription until 30 days after the date when the prescription would need to be refilled (i.e., allowing a 30-day "grace period"), on the basis of the dosage and the number of pills dispensed. The grace period is a conservative assumption in the analysis, as events that occur within the grace period are then counted as occurring on-treatment rather than off-treatment.

STUDY START, END, AND DEFINITION OF OUTCOMES. We followed patients from the index date (7 days after hospital discharge for their qualifying event) until December 31, 2008, or disenrollment from the health plan. We assessed 2 study endpoints: 1) all-cause mortality, identified from health plan administrative databases, Social Security Administration vital status files, and the California state death certificate registry; and 2) the composite of death from any cause or hospitalization for an acute MI (primary discharge diagnosis code of 410.x1).

This study was approved by the institutional review boards of the Kaiser Foundation Research Institute and Stanford University.

STATISTICS. We used time-varying multivariable Cox proportional hazard regression models to assess the association of beta-blocker use with outcomes, which allows patients to have on-treatment and off-treatment periods during follow-up. We used a series of Cox regression analyses to adjust for