Effect of β-Blockers on Cardiac and Pulmonary Events and Death in Older Adults With Cardiovascular Disease and Chronic Obstructive Pulmonary Disease

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Title:

Effect of Beta Blockers on Cardiac and Pulmonary Events and Death in Older Adults with Cardiovascular Disease and Chronic Obstructive Pulmonary Disease

Short title:

β-blocker: older adults with CVD & COPD

ABSTRACT

Context In older adults with multiple conditions, medications may not impart the same benefits seen in patients who are younger, or without multi-morbidity. Furthermore, medications given for one condition may adversely affect other outcomes. Beta-blocker (β-Blocker) use with coexisting cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD) is such a situation.

Objective To determine the effect of β-Blocker use on cardiac and pulmonary outcomes and mortality in older adults with coexisting COPD and CVD.

Design, Setting, Participants The 1062 participants were members of the 2004-2007 Medicare Current Beneficiary Survey cohorts, a nationally representative sample of Medicare beneficiaries. Study criteria included age 65+ years plus coexisting CVD and COPD/asthma. Follow-up occurred through 2009. We determined the association between β-Blocker use and the outcomes with propensity score-adjusted and covariate-adjusted Cox proportional hazards.

Main Outcome Measures The three outcomes were major cardiac and pulmonary events, and all-cause mortality.

Results Half of the participants used β-Blockers. During follow-up 179 participants experienced a major cardiac event; 389 participants experienced a major pulmonary event; and 255

participants died. Each participant could have experienced any one or more of these events. The hazard ratio for β-blocker use was 1.18 (95% CI, 0.85-1.62) for cardiac events; 0.91 (95% CI, 0.73-1.12) for pulmonary events; and, 0.87 (95% CI, 0.67-1.13) for death.

Conclusion In this population of older adults, β-Blockers did not seem to affect occurrence of cardiac or pulmonary events or death in those with CVD and COPD.

Keywords: multiple chronic conditions;multimorbidity;chronic obstructive pulmonary disease;cardiovascular disease;beta-blocker;cardiac events;pulmonary events;COPD;CVD;Coronary artery disease;CAD

INTRODUCTION

As older adults accumulate diseases and conditions, they meet criteria for an increasing number of disease guidelines with resultant accumulation of multiple medications.[1] It is unclear whether over time, and in the face of multiple diseases and medications, each medication conveys benefits that outweigh harms.[1,2] This is a particular concern in situations when a drug may impart harm to a coexisting condition. Beta blocker (β-Blocker) use in individuals with coexisting coronary or vascular disease (CVD) and chronic obstructive pulmonary disease (COPD) is such a situation.

Current American Heart Association/American College of Cardiology (AHA/ACC) guidelines note that β-Blockers should be used for three years after the initial event in all patients who have had a myocardial infarction (MI) or acute coronary syndrome (ACS).[3] Guidelines further recommend continuing β-Blockers indefinitely in patients with left ventricular dysfunction while noting it is also deemed reasonable to continue them in those with normal left ventricular function. These recommendations are based on results from randomized clinical trials (RCTs) from which older individuals with multiple conditions, particularly COPD or asthma, were largely excluded.[4,5] The noncommittal statement that β-Blockers "may be considered as chronic therapy for all other patients with other CVD" was due to the lack of RCT evidence in any population.[3] No specific mention was made of patients who have both CVD and COPD.

Two recent observational studies have suggested no benefits to long-term β-Blocker use. In the REACH study of 21,860 propensity matched adults with CVD (mean age±SD, 68.5±10.0) followed for up to four years (median follow-up = 44 months), no difference in the composite outcome (fatal and nonfatal MI, and nonfatal stroke) was observed for β-Blockers users and nonusers.[6] In an observational study from 25 hospitals in the Osaka region of Japan, 5,628 adults (age, 64.7±11.8) with MI were treated with primary percutaneous coronary intervention. With a median follow-up of nearly 4 years, no difference was observed in all-cause

death, fatal MI, or non-MI death.[7] Unfortunately, these trials make no specific mention of patients with both CVD and COPD.

β-Blockers, particularly non-selective ones, may increase airway hyperresponsiveness and compete with β2-agonists, thus theoretically increasing risk of adverse pulmonary outcomes, such as exacerbations.[8,9] Observational studies suggest a survival benefit with β-Blocker use in individuals with COPD and CVD, but these studies included few older participants.[10-14] One study involving individuals with a mean age of 75 years found a survival benefit with β-Blocker in the year following an MI but not in the subgroup receiving β2-agonists or with severe COPD.[10] The benefits and harms of β-Blockers in older adults with coexisting CVD and COPD remains relatively unexplored.

Among persons 65 years and older, almost 60% take at least five medications; almost 20% take at least ten.[15] Risk of adverse effects increases 10% with each medication.[16] Evidence of benefit and absence of harm should guide decision-making in older adults with multiple conditions to reduce medication burden and risk of adverse medication effects. Only if benefits outweigh harms is the use of β-Blockers in older adults with CVD and COPD warranted. Given the impracticality of employing RCTs to determine the benefits and harms of every treatment in older adults with multiple coexisting conditions, **we have** to rely on observational data to inform medication decision-making. Inclusion of well-characterized nationally representative cohorts, control of confounding factors, attenuation of indication and contraindication biases, and determination of benefits and harms among key clinical subgroups are important to evaluating medication effects in observational studies.[17-23] We determined the effect of β-Blocker use on CVD and COPD outcomes in a nationally representative cohort of older adults with coexisting COPD and CVD.

METHODS

Study Sample

The study population included Medicare Current Beneficiary Survey (MCBS) participants who were enrolled during 2004 through 2007.[24] MCBS is a nationally representative sample of Medicare beneficiaries obtained using stratified multi-stage sampling from the Centers for Medicare and Medicaid Services (CMS) enrollment file. MCBS **employs** a rolling cohort design where each fall a new cohort of participants are enrolled and followed for up to four years (follow-up data until 2011). MCBS participants eligible for this study sample were aged 65 years and over and had CVD as well as either COPD or asthma. Because of the lack of health claims in the MCBS data files, Medicare Advantage beneficiaries (Medicare Part C), including those enrolled in HMOs and PPOs, were excluded from the current study.

A combination of self-report, medication data, and Medicare hospital, outpatient, physician, or skilled nursing facility claims data were used to identify eligible participants and was agreed upon by consensus of four coauthors (DSHL, CPG, JAD, and MET). CVD included any history of MI, angina, other acute/subacute/or chronic ischemic heart disease, or peripheral vascular disease (PVD). COPD criteria included any of chronic bronchitis, emphysema, COPD, asthma, or use of any of beta-adrenergic bronchodilators, anticholinergic bronchodilators, combination bronchodilators, or inhaled corticosteroids. Upon enrollment, claims data was retrospectively gathered for the preceding 9 months. Pre-enrollment information and the first year of follow-up were used to define eligibility.

A total of 20,236 beneficiaries were enrolled in MCBS during 2004 through 2007 and of these participants, a total of 16,542 were aged 65 and over. Of these, we excluded: 3,425 participants who were either lacking health claims at baseline due to Medicare Advantage use, 974 who did not have medication data available, and 2,049 who were non-respondents at baseline. Of the remaining 10,094 participants, a total of 3,385 met the criteria for CVD and

1,062 met the criteria for both CVD and COPD. Thus, 1,062 MCBS participants constituted this study subset.

Descriptive Data

Baseline socio-demographic, medical, behavioral, and functional data were obtained from the Cost and Use annual in-person interviews, and from Medicare hospital, outpatient, physician, and skilled nursing home claims data. Medical, behavioral, and functional data included several self-reported health conditions; medication insurance coverage; self-perceived health; smoking status; body mass index; falls in the past year; depression, defined by a claim for depression[25] or self-reported depression plus loss of interest; cognition; activities of daily living (ADLs); and physical function. Cognitive impairment or dementia was considered present if there was a claim for dementia or cognitive disorder[25] or self-reported memory loss plus either trouble concentrating or difficulty making decisions that interfered with ADL. Basic ADL (BADL) dependency was defined as not performing independently one or more of: walking, transferring, dressing, bathing, eating, and toileting. Instrumental ADLs (IADLs) dependency was defined as not performing independently one or more of: using the telephone, light housework, heavy housework, preparing meals, shopping, and paying bills. Physical function was defined by the amount of difficulty (1=No difficulty to 5=Unable to do) with stooping, lifting, extending arms, handling objects, and walking ¼ mile; physical function scores ranged from 5 to 25. The Elixhauser comorbidity scale was computed based on the ICD-9 codes from claims data excluding cardiac and pulmonary conditions.[25]

Medication Use Data

Prescription medication data were obtained by direct observation during in-person interviews. Interviews occurred every four months and participants were asked to record their drug purchases and save their medicine containers to aid their recall. Medications were identified by therapeutic name and class codes. Starting in 2006, Medicare Part D was

implemented; however, to keep medication use consistent in all enrolled cohorts, Part D information was not used.

β-blocker medications were classified as selective (acebutolol, atenolol, betaxolol, bisoprolol, esmolol, nebivolol, metoprolol), nonselective (levabunolol, metipranolol, nadolol, propranolol, sotalol, timolol), and nonselective β-Blocker agent with alpha-blocking properties (carvedilol and labetalol). Classification of β-blocker users and nonusers was based on interviews during the first year of follow-up.

Outcomes

The three outcomes were major cardiac events major pulmonary events, and all-cause mortality. The outcomes were ascertained for three years, during years two through four; the criteria to identify these outcomes were agreed upon by four coauthors (DSHL, CPG, JAD, and MET).[24] Major cardiac events were ascertained from hospital claims data during follow-up and included diagnosis codes for ACS (acute MI or unstable angina) or procedure codes relating to cardiac revascularization procedures including coronary artery bypass graft, cardiac angioplasty, cardiac stent, or insertion of intraaortic balloon assist. Major pulmonary events, also ascertained from hospital claims data during follow-up, included diagnosis codes related to exacerbations or complications of COPD or asthma (i.e. bronchitis, emphysema, asthma, bronciectasis, and respiratory failure) or procedure codes for endotracheal intubation, plication of emphysematous bleb, or lung volume reduction surgery. Death was ascertained from three years of Medicare vital status data.

Statistical Analysis

Baseline characteristics of the study population and distributions of β-blocker use during follow-up were summarized using means and standard deviations, or frequency and percentages, as appropriate.

To control for confounding by indication, we estimated a propensity score (PS) using a logistic regression model with β-Blocker use as the dependent variable. A propensity score is the conditional probability of treatment based on a set of participant characteristics at baseline. Baseline for both β-Blocker users and nonusers is considered the 9 months of pre-enrollment and first year of follow-up (up to the end of year 1). Of the demographic and health variables selected to characterize our study population, those variables associated with **any** of the outcomes or β-Blocker use and **any** of the outcomes were included in the PS model (listed in **Table 1**, n=32 variables).[26-30] To assess proper PS model specification, and its subsequent utility in controlling for the differences between β-Blocker use and nonuse, we regressed each covariate on β-Blocker use, adjusting for the PS (**Table 1**). [26,29,30,31]

For each outcome, the association between β-Blocker use and time to first outcome event was examined using a Cox proportional hazards model controlling for fixed-in-time confounding.[31,32] Events were determined during the three years of follow-up (years 2-4) for both β-Blocker users and nonusers. Participants who did not experience an outcome event were censored at the time of loss to follow-up, the end of follow-up, or death for the cardiac and pulmonary event analyses. We first fit a bivariate model that included β-Blocker use as the sole predictor (unadjusted model). To account for potential indication or selection bias, we then constructed a PS-adjusted model in which we added the PS as a continuous variable to the unadjusted model, along with the year of enrollment and additional confounding variables. In order to assess the independent effect of β-Blockers, as well as check the robustness of the PS model results, we then created a covariate-adjusted model in which we added the year of enrollment and additional confounding covariates to the unadjusted model. Covariates were considered confounders if they changed the magnitude of the estimate hazard ratio (HR) by more than ten percent. Model diagnostics were performed and the proportional hazard assumptions were not violated in any model.

Because death was a relatively common outcome (24.3% of β-Blocker nonusers died versus 23.7% of users), we used proportional hazard competing risk analyses as described by Fine and Gray[34] to determine the association between β-Blocker use and cardiac or pulmonary events, accounting for the death rate. Competing risk models were unadjusted, covariate-adjusted, and PS-adjusted.

Statistical tests were conducted at the 0.05 (two-tailed) level of significance. Analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC). The association between β-blocker use vs. nonuse on outcomes are presented as HRs with corresponding 95% confidence intervals (CIs). Cumulative hazard plots are also provided for the purpose of graphically displaying the relationship between β-blocker use and time to first event for each outcome.

RESULTS

The mean age of our 1,062 participants was 77.4 (±7.1) years, 512 (48.2%) were male. Among this cohort with coexisting CVD and COPD, 400 (37.7%) had a prior MI. By happenstance, exactly 50% of the participants used a β-Blocker. Among the 531 β-Blocker users, 385 (72.5%) used a cardioselective β-Blocker, 23 (4.3%) a nonselective β-Blocker, 98 (18.5%) a β-Blocker with α-blocking properties, and 25 (4.7%) multiple β-Blocker agents. Non-users differed from β-Blocker users in several characteristics as shown in **Table 1**. Using the PS as a continuous variable we were able to balance the differences between β-Blocker users and nonusers, as shown by the PS-adjusted p-values. The mean and PS range for β-Blocker users was 0.58 (± 0.19) and 0.14 - 0.94, and was 0.42 (± 0.18) and 0.05 - 0.93 for nonusers; the propensity score range indicates good overlap and comparability between users and nonusers.

The cumulative hazard plots for cardiac and pulmonary events and death are shown in **Figure 1;** these display the total amount of risk (hazard) for each event accumulated put to each time point. Over three years of follow-up, 179 participants experienced a major cardiac event; 102 were among β-Blocker users and 77 were among nonusers. The PS-adjusted HR for β-blocker use was 1.18 (95% CI, 0.85-1.62) for cardiac events (**Table 2**). Among the 389 participants that experienced a major pulmonary event, 199 were β-Blocker users. The PS-adjusted HR for β-blocker use was 0.91 (95% CI, 0.73-1.12) for pulmonary events. Of the 255 participants who died over the three years, 126 were β-Blocker users. The PS-adjusted HR for β-blocker use was 0.87 (0.67, 1.13) for death. In each of these outcomes, the covariate-adjusted HR produced similar results. After accounting for rates of death in the competing risk analysis, the PS-adjusted HR for β-blocker use was nearly unchanged, 1.22 (95% CI, 0.87-1.71) for cardiac events and 0.91 (95% CI, 0.73-1.13) for pulmonary events.

DISCUSSION

The likelihood of both benefit and harm is important in determining the appropriateness of medication use in older adults with multiple chronic conditions. In this nationally representative cohort of older adults with coexisting CVD and COPD, β-Blockers did not adversely affect pulmonary outcomes, but there was also no observed beneficial effect on cardiac outcomes or mortality. Cohort members may represent survivors who have lower risk of the outcomes compared with individuals who died earlier. Also, the use of other cardio-protective drugs, such as statins, diuretics, and ACEI, was greater among β-Blocker users than nonusers, perhaps lessening any protective cardiac effect of β-Blockers.

Similar results showing no significant cardiac or mortality benefit for β-Blocker users were seen recently in two observational studies, the REACH and STEMI studies. The REACH

study included 21,860 propensity score-matched participants 45 years or older with CVD.[6] The STEMI study included 3,846 propensity score-matched percutaneous coronary intervention patients followed for nearly 4 years (age, 64.7±11.8).[7] Neither study showed β-blockers improved cardiac outcomes nor mortality, and the results appear to extend to this older cohort with coexisting COPD. This current study also provides the additional information -- that there is no overall β-Blocker effect for pulmonary events, either.

Previous studies suggesting a benefit of β-Blockers in individuals with coexisting CVD and COPD involved a younger population.[11-14] In the current study of older adults, factors such as functional and cognitive status were determinants of receiving β-blockers and of experiencing the outcomes. Previous studies did not account for the fact that more functional and cognitively intact individuals may be more likely to receive β-blockers and to experience better outcomes.

While we accounted for many factors that affect the risk of major cardiac events, we lacked prognostic factors such as measures of left ventricular ejection fraction (LVEF).[4] The possibility that β-blocker users were at higher risk for subsequent cardiac events compared to nonusers cannot be excluded. Studies following older adults beyond one year post MI, that account for LVEF and other prognostic factors, are needed to confirm or refute the current findings.

The lack of pulmonary harm may be a result of nearly two-thirds of the participants using a cardioselective β-Blocker; the theoretical harms are associated with nonselective β-Blockers causing airway hyperreactivity.[8,9] While we were not able to test for the association of nonselective β-Blockers due to the small number of participants using a nonselective β-Blocker, caution should still be used for nonselective β-Blocker use in patients with COPD. In a study by Düngen et al., older adults randomized to carvedilol (a nonselective β-Blocker agent with alpha-blocking properties) showed more adverse pulmonary events compared to bisoprolol (a cardioselective β-Blocker).[36]

This study has strengths, as well as limitations. This nationally representative cohort enhances the generalizability of prior results observing a lack of benefit of β-Blockers for CVD and mortality. These results can be extended to the older adult population with concomitant CVD and COPD.[22] The well-characterized cohort allowed us to account for a wide range of factors, including function and cognition, which affected both the propensity to receive β-blockers and to experience the outcomes. This finding confirms earlier reports that cognition and function are potent determinants of outcomes in older adults with cardiac disease.[33] We used propensity score adjustment and covariate adjustment to account for biases and confounding inherent in observation studies.[30] Findings were similar with each method, suggesting robust results regardless of adjustment method. However, we cannot exclude the possibility of additional unmeasured confounders. While not detected in the current study, we cannot exclude the possibility of an increased risk of pulmonary outcomes with β-blockers in the subset with severe COPD. The results of this current study match other observations studies, but there is the possibility of a lack of power due to low sample size or variability. β-blocker use was defined as prevalent use, therefore prior use information was not known. Outcomes in prevalent user may be different than users starting a β-Blocker for the first time (as in what happens in RCTs). For example, those with increased pulmonary outcomes may have already stopped using a β-Blocker prior to initiation of this study. While this cohort is nationally representative, there are several factors that may have contributed to selection bias. First, individuals with severe disease or functional disability may have declined participation in MCBS. Secondly, because of the lack of health claims data for participants in Medicare Advantage plans, including HMO and PPO, these were excluded from this analysis. As for any observational study, we cannot infer a causal relationship for these findings.

The main study implication is that β-Blockers may not confer the same cardiac and survival benefits in older adults with CVD and COPD as seen in younger adults. Also taking into

account the recent results in the REACH study, consideration should be given to whether β-Blockers are warranted in older adults with COPD and CVD beyond the first year post MI. This recommendation does not conflict with AHA/ACC guidelines.[3] The long-term effects of β-Blockers after MI in older adults with COPD should be determined before recommending indefinite use of β-blockers post MI. The inherent difficulty in disentangling risk from treatment effect may necessitate an RCT in this subgroup. In the meantime, we cannot assume the same benefit as seen in younger adults, with or without COPD, in whom most current evidence was obtained. It is important to point out that this current study does not address other conditions for which a β-Blocker may be indicated, such as heart failure.

Determining whether benefits outweigh harms provides an evidence-based approach to polypharmacy in older adults with multiple health conditions. Medications causing greater harm than benefit should be stopped, as should medications without evidence of benefit. We studied the effect of one medication in older adults with one common combination of coexisting conditions. There are many similar situations which will require investigation to inform clinical decision-making for the growing population of older adults with multiple conditions who currently receive multiple medications.

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Table and figure legend.

Table 1. Baseline characteristics of Beta-Blocker Users and Non-Beta-Blocker Users

Table 2. Major cardiac and pulmonary events and all-cause mortality according to beta-blocker use among MCBS cohort members with CVD and COPD (N=1,062)

Figure 1 Cumulative Hazard Plots for Cardiac and Pulmonary Events and All-Cause Mortality by β-Blocker Use.

Figure Legend: Cumulative hazard plots display the total amount of risk (hazard) for each event accumulated up to each time point. The hazard ratios provided were estimated using Cox proportional hazard models adjusted by propensity score and year of entry for all models, with the addition of the total number of Elixhauser Comorbities to the COPD model and heart failure to the cardiac and all-cause mortality models. Follow-up was three years. Variables included in the propensity score are noted in Table 1. Abbreviations: CI, confidence intervals; COPD, Chronic Obstructive Pulmonary Disease; HR, Hazard Ratio.