

Impact of Cardioselective β -Blockers on Mortality in Patients with Chronic Obstructive Pulmonary Disease and Atherosclerosis

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Rationale: β -Blocker use is associated with improved health outcomes in patients with cardiovascular disease. There is a general reluctance to prescribe β -blockers in patients with chronic obstructive pulmonary disease (COPD) because they may worsen symptoms.

Objectives: We investigated the relationship between cardioselective β -blockers and mortality in patients with COPD undergoing major vascular surgery.

Methods: We evaluated 3,371 consecutive patients who underwent major vascular surgery at one academic institution between 1990 and 2006. The patients were divided into those with and without COPD on the basis of symptoms and spirometry. The major endpoints were 30-day and long-term mortality after vascular surgery. Patients were defined as receiving low-dose therapy if the dosage was less than 25% of the maximum recommended therapeutic dose; dosages higher than this were defined as intensified dose.

Measurements and Main Results: There were 1,205 (39%) patients with COPD of whom 462 (37%) received cardioselective β -blocking agents. β -Blocker use was associated independently with lower 30-day (odds ratio, 0.37; 95% confidence interval, 0.19–0.72) and long-term mortality in patients with COPD (hazards ratio, 0.73; 95% confidence interval, 0.60–0.88). Intensified dose was associated with both reduced 30-day and long-term mortality in patients with COPD, whereas low dose was not.

Conclusions: Cardioselective β -blockers were associated with reduced mortality in patients with COPD undergoing vascular surgery. In carefully selected patients with COPD, the use of cardioselective β -blockers appears to be safe and associated with reduced mortality.

Keywords: chronic obstructive pulmonary disease; β -adrenergic blocking agents; peripheral arterial disease; vascular surgery

During the last decade, β -blocker therapy has become an increasingly important treatment in patients undergoing non-cardiac surgery. Several studies have shown that perioperative β -blocker therapy can reduce the incidence of peri- and post-operative cardiac complications, including sudden death, angina, and myocardial infarction in patients undergoing noncardiac vascular surgery (1–5). Accordingly, the American College of Cardiology and the American Heart Association recommend the

(Received in original form March 7, 2008; accepted in final form June 19, 2008)

Supported by an unrestricted research grant from "Lijf and Leven" Foundation, Rotterdam, The Netherlands (to Y.R.B.M.v.G. and S.E.H.); an unrestricted research grant from The Netherlands Organization of Health Research and Development, The Hague, The Netherlands (O.S.).

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Am J Respir Crit Care Med Vol 178, pp 695–700, 2008

Originally Published in Press as DOI: 10.1164/rccm.200803-3840C on June 19, 2008
Internet address: www.atsjournals.org

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

β -Blockers are often withheld from patients with chronic obstructive pulmonary disease (COPD) because of fear of pulmonary worsening. However, cardioselective β -blockers are demonstrated to be safe and beneficial in patients with COPD.

What This Study Adds to the Field

Cardioselective β -blockers are beneficial in the reduction of mortality in patients with COPD undergoing vascular surgery, with an intensified dosage being most effective.

use of β -blockers in patients undergoing major vascular surgery (6). Many patients with cardiovascular disease (CVD) have coexisting chronic obstructive pulmonary disease (COPD) and vice versa possibly because they share the same risk factor, cigarette smoking (7). In patients with COPD, approximately 30% of all deaths are from CVD (8). β -Blockers are, however, frequently withheld from patients with COPD with coexisting CVD because of the concern that they may induce bronchoconstriction from blockade of β_2 -adrenoreceptors. Although non-selective β -blockers act on the β_2 -adrenoreceptors to inhibit bronchodilation (9), there is substantial evidence that cardioselective β -blockade is likely safe and beneficial in patients with COPD and CVD (10–18). Additional concern regarding use of β -blockers in COPD is the potential for insensitivity. COPD is associated with systemic inflammation, which may accelerate metabolism of β -blockers, leading to reduced efficacy. Patients are particularly vulnerable to cardiac events during and after major vascular surgery (19). The primary aim of the present study was to investigate the association between cardioselective β -blockers and 30-day and long-term mortality in patients with COPD who undergo major vascular surgery. The secondary objective was to determine the relationship between low and intensified dosage and mortality. Some of the results of this study have been previously reported in the form of an abstract (20).

METHODS

Study Population

This observational retrospective study included 3,371 consecutive patients undergoing elective vascular surgery between 1990 and 2006 at the Erasmus Medical Center, Rotterdam, The Netherlands. The surgical procedures included abdominal aortic surgery (comprising

aortic-to-aortic or aortic-bifurcation prostheses procedures, removal of infected prostheses, and other operations of the abdominal aorta), carotid endarterectomy (including reconstruction or desobstruction of the carotid artery), and lower limb arterial reconstruction procedures (including iliac-femoral, femoral-popliteal, femoral-tibial artery bypass procedures, removal of infected prostheses, peripheral desobstruction and other elective peripheral arterial surgical reconstructions). Vascular reconstructions due to trauma and ruptured abdominal aortic aneurysms were excluded.

Abstracted variables included patient demographics (age and sex) and cardiac risk factors, including the following: hypertension (defined as a blood pressure $\geq 140/90$ mm Hg), hypercholesterolemia (total cholesterol of >5.2 mmol/L), diabetes mellitus (presence of fasting blood glucose of ≥ 140 mg/dl or treatment with insulin or oral hypoglycemic agents), serum creatinine renal dysfunction (baseline serum creatinine > 1.5 mg/dl), current smoking status, and body mass index (BMI) calculated as weight divided by height squared (kg/m^2). The patient's cardiovascular history was assessed and included the following: previous myocardial infarction, coronary revascularization (coronary artery bypass graft and/or percutaneous coronary intervention), heart failure (defined according to the New York Heart Association classification), angina pectoris, stroke, and/or transient ischemic attack. The use of bronchodilators and corticosteroids at baseline was captured. Cardiac medications at baseline were also evaluated. These included β -blockers, statins, angiotensin-converting enzyme inhibitors, diuretics, aspirin, anticoagulants, nitrates, and calcium channel blockers. Almost all (97%) of the prescribed β -blockers were cardioselective β -blocking agents: metoprolol, bisoprolol, and atenolol. To evaluate the association of low and intensified β -blocker dose with mortality, we converted the β -blocker dosage at initial hospitalization. Low dose was defined as patients using less than 25% of the maximum recommended therapeutic dose, whereas intensified dose was defined as an average dose exceeding or equal to 25% of the maximum recommended therapeutic dose. For metoprolol, a maximum recommended therapeutic dose of 400 mg was used, for bisoprolol 10 mg was used, and for atenolol 100 mg was used.

Pulmonary Function Testing

A diagnosis of COPD was based on post-bronchodilator spirometric values in conjunction with a history of cough, sputum production, and/or dyspnea. COPD was defined according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (FEV_1 to FVC ratio less than 70% [21]). Disease severity was classified into three groups: I = mild COPD ($\text{FEV}_1/\text{FVC} < 0.70$ and $\text{FEV}_1 \geq 80\%$ of the predicted FEV_1), II = moderate COPD ($\text{FEV}_1/\text{FVC} < 0.70$ and $\text{FEV}_1 50\% \leq \text{FEV}_1 < 80\%$ of the predicted FEV_1), and III = severe COPD ($\text{FEV}_1/\text{FVC} < 0.70$ and $\text{FEV}_1 30\% \leq \text{FEV}_1 < 50\%$ of the predicted FEV_1) (21). We used the equation of Quanjer and colleagues (22), adjusted for age, sex, and height, to calculate the predicted FEV_1 value, which has been demonstrated to make an accurate prediction (23). The equation for males is $4.30 \times \text{height (m)} - \text{age} \times 0.029 - 2.49$ and for women is $3.95 \times \text{height (m)} - \text{age} \times 0.025 - 2.60$ (22). In 82% of the patients with COPD, a preoperative spirometry was performed. The patients without a preoperative pulmonary function test were classified as having no COPD if they were free of pulmonary complaints (cough and dyspnea), and not currently receiving pulmonary medications (i.e., bronchodilators and corticosteroids) and demonstrated normal arterial blood gases on room air ($\text{Pco}_2 < 6.4$ kPa and $\text{Po}_2 > 10.0$ kPa).

Follow-up and Endpoints

Follow-up was completed in 96% of the study patients, with a median follow-up of 5 years. Survival status was obtained from the municipal civil registries. Clinical baseline characteristics were retrieved from the hospital medical records. Endpoints of the study were 30-day and long-term (10-yr) mortality regardless of the cause.

Statistical Analysis

Continuous data are presented as means \pm SD and compared using the Student's *t* test. Categorical variables among the patient groups are expressed as percentages and compared using χ^2 tests. Univariate and multivariate logistic regression analyses were used to determine the relationship of cardioselective β -blockers and their dose with 30-day

mortality. Cox proportional hazards models were used to analyze the impact of these drugs on long-term mortality, adjusted for salient covariates, including age, sex, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, BMI, type of surgery, year of surgery, and cardiovascular history. In addition, a composite variable of statins, aspirin, and angiotensin-converting enzyme inhibitors was included. Patients who received nonselective β -blockers ($n = 112$; 3%) were excluded from the analysis. In addition, using a multivariate logistic regression model, we developed a propensity score to adjust for the likelihood of receiving β -blockers in subjects with COPD and non-COPD subjects. The variables in this model included age, sex, COPD hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, BMI, type of surgery, year of surgery, all variables on cardiovascular history, and all cardiac and pulmonary medications (Table 1). The fit of the propensity score model was assessed using *c*-statistics and the Hosmer-Lemeshow goodness-of-fit test. In all comparative analysis of β -blockers, patients who were not on β -blocker therapy were used as the reference group. Odds ratios (ORs) and hazard ratios (HRs) were calculated from these models together with their 95% confidence intervals (CIs). For all tests, a two-sided *P* value of less than 0.05 was considered significant. All statistical analyses were performed using SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Baseline Characteristics

Of the 3,371 patients (mean age, 66 ± 12 yr; 73% male), 1,029 (31%) received cardioselective β -blockers at their initial hospitalization (Table 1). The commonly used β -blockers were bisoprolol at 50% ($n = 514$), atenolol at 15% ($n = 151$), and metoprolol at 32% ($n = 325$). Patients with β -blockers were more likely to have underlying history of cardiac disease, hypertension, and hypercholesterolemia (all $P < 0.001$). The percentage of β -blocker use was not significantly different among the COPD severity groups (mild COPD, 39%; moderate COPD, 35%; and severe COPD, 33%; $P = 0.20$).

Association between Cardioselective β -Blockers and Mortality

Overall, there were 1,265 (39%) patients with COPD. Of these patients, 462 (37%) used cardioselective β -blocking agents. In comparison, 567 (28%) of the patients who did not have COPD used β -blockers. Within 30 days of surgery, 16 (4%) patients with COPD who were receiving β -blockers died. In contrast, 66 (8%) patients who did not use β -blockers died during the same period of time ($P = 0.001$). Over the entire follow-up period, 184 (40%) patients with COPD who were and 532 (67%) who were not on β -blocker therapy died ($P < 0.001$). Cardioselective β -blockers were independently associated with reduced 30-day mortality in patients with (OR, 0.37; 95% CI, 0.19–0.72) and without COPD (OR, 0.34; 95% CI, 0.17–0.66) (Table 2). Over the entire follow-up period, cardioselective β -blocking agents reduced long-term mortality in patients with COPD (HR, 0.73; 95% CI, 0.60–0.88). In the long term, a trend was observed in patients without COPD, although it did not achieve statistical significance (HR, 0.84; 95% CI, 0.69–1.02).

A sensitivity analysis was performed using propensity score measurements for adjustment of various factors, including severity of disease to address the issue of confounding by indication. In this analysis, the relationship of cardioselective β -blockade with mortality in patients with COPD was similar to the main analysis (OR, 0.41; 95% CI, 0.20–0.81; and HR, 0.75; 95% CI, 0.61–0.91). In patients without COPD, a significant association was found between β -blocker use and 30-day mortality (OR, 0.36; 95% CI, 0.18–0.72). Similar to the main analysis, a trend was observed with long-term mortality, although the relationship was not significant (HR, 0.88; 95% CI, 0.72–1.07).

TABLE 1. BASELINE CHARACTERISTICS ACCORDING TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND β-BLOCKER USE

	COPD (n = 1,265)		P Value	No COPD (n = 1,994)		P Value
	β-Blocker (n = 462)	No β-Blocker (n = 803)		β-Blocker (n = 567)	No β-Blocker (n = 1,427)	
Demographics						
Mean age, yr (SD)	69 (9)	69 (10)	0.61	65 (11)	63 (13)	0.01
Male sex, %	82	78	0.07	70	68	0.30
Type of surgery, %			<0.001			<0.001
AAA	54	43		37	24	
CEA	15	13		31	31	
LLR	31	44		32	46	
Cardiovascular history, %						
Myocardial infarction	33	21	<0.001	31	14	<0.001
Coronary revascularization*	25	14	<0.001	22	11	<0.001
Heart failure	7	5	0.22	5	4	0.29
Angina pectoris	26	11	<0.001	23	9	<0.001
Stroke or TIA	24	20	0.14	35	35	0.76
Clinical characteristics, %						
Hypertension	49	36	<0.001	54	28	<0.05
Diabetes mellitus	17	12	<0.05	18	14	0.08
Hypercholesterolemia	26	11	<0.001	28	14	<0.001
Renal dysfunction	9	8	0.43	10	4	<0.001
Body mass index (SD)	26 (4)	25 (4)	<0.05	26 (4)	25 (4)	<0.05
Current smoking status	35	33	0.41	27	24	0.21
Cardiac medication, %						
Statins	49	11	<0.001	46	14	<0.001
ACE inhibitors	31	19	<0.001	34	18	<0.001
Calcium antagonists	28	22	<0.05	33	16	<0.001
Diuretics	28	19	<0.05	23	11	<0.001
Aspirin	47	30	<0.001	58	37	<0.001
Anticoagulants	32	38	<0.05	41	42	0.84
Nitrates	17	11	<0.05	18	7	<0.001
Pulmonary medication, %						
Bronchodilators	13	18	<0.05	0	0	0.85
Corticosteroids	23	11	<0.001	1	1	0.88

Definition of abbreviations: AAA = abdominal aortic surgery; ACE = angiotensin-converting enzyme; CEA = carotid endarterectomy; COPD = chronic obstructive pulmonary disease; LLR = lower limb arterial reconstruction; TIA = transient ischemic attack.

* Coronary artery bypass graft or percutaneous coronary intervention.

The relationship between β-blockers and mortality across different COPD severity groups is also summarized in Table 2. Even in moderate to severe group, β-blocker therapy was associated with reduced mortality in the short and long term.

Cardioselective β-Blocker Dose and Mortality

Of the patients using cardioselective β-blockers, 41% received low-dose β-blocker therapy at the time of surgery and 59% received an intensified dose. These percentages were similar

among patients with COPD, with 42% of the patients on a low-dose and 58% on an intensified dose. In patients with COPD, an intensified but not low dose was associated with reduced 30-day mortality (OR, 0.26; 95% CI, 0.10–0.66) (Figure 1). However, in the long term, both dosing regimens were associated with reduced mortality (low dose: HR, 0.70; 95% CI, 0.54–0.91; and intensified dose: HR, 0.76; 95% CI, 0.59–0.98). In patients without COPD, both low and intensified dosing regimens were associated with reduced 30-day mortality (OR, 0.30; 95% CI, 0.12–0.77, and OR, 0.36; 95% CI, 0.15–0.86, respectively). The relationships became insignificant for low-dose β-blockers when long-term mortality was considered, although a trend for reduced mortality was still observed in non-COPD patients who were treated with an intensified dose (HR, 0.80; 95% CI, 0.62–1.03).

TABLE 2. THE ASSOCIATION BETWEEN CARDIOSELECTIVE β-BLOCKERS AND MORTALITY

β-Blocker	30-Day Mortality		Long-Term Mortality	
	Univariate OR (95% CI)	Multivariate OR (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)
Total	0.45 (0.30–0.66)	0.35 (0.22–0.57)	0.84 (0.74–0.95)	0.78 (0.68–0.89)
No COPD	0.46 (0.26–0.81)	0.34 (0.17–0.66)	0.86 (0.73–1.02)	0.84 (0.69–1.02)
COPD	0.40 (0.23–0.70)	0.37 (0.19–0.72)	0.74 (0.63–0.88)	0.73 (0.60–0.88)
Mild COPD	0.45 (0.21–0.98)	0.46 (0.18–1.16)	0.70 (0.54–0.92)	0.68 (0.50–0.93)
Moderate/severe	0.34 (0.15–0.78)	0.32 (0.12–0.85)	0.79 (0.64–0.98)	0.82 (0.64–1.05)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; HR = hazard ratio; OR = odds ratio.

DISCUSSION

The present study demonstrated that cardioselective β-blockers were associated with reduced 30-day and long-term mortality in patients with COPD who underwent major vascular surgery. We also found that an intensified dosing regimen appeared to be superior to low-dose therapy in terms of its impact on 30-day mortality.

These findings are consistent with other studies that demonstrated the beneficial effects of β-blockers in patients with COPD who had recently experienced myocardial infarction (13, 15, 18). A major limitation of the previous studies was that there was no or little information on lung function and, as such,

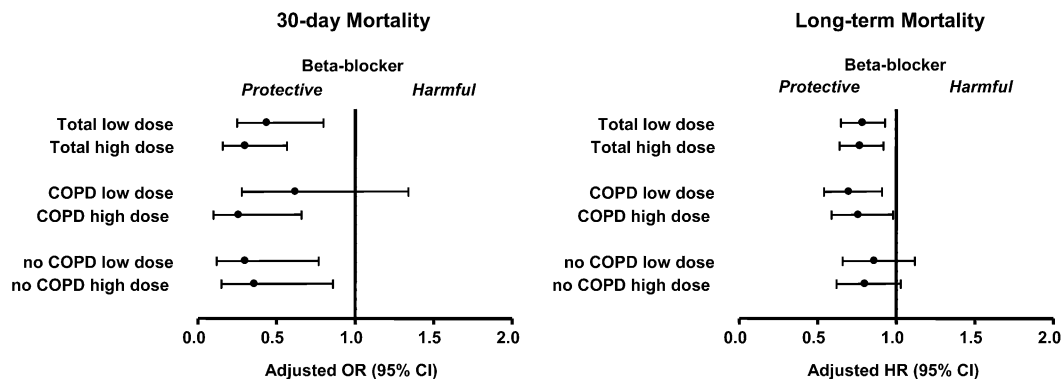


Figure 1. The association between low and intensified cardioselective β -blocker dose and mortality. Adjusted for age, sex, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, body mass index, type of surgery, year of surgery, and cardiovascular history. CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; OR = odds ratio.

the diagnosis of COPD could not be confirmed. We extend these findings by demonstrating among a large group of well-characterized patients with COPD, defined both clinically and spirometrically, that β -blockers were safe and beneficial in prolonging survival after major vascular surgery. There is evolving evidence showing that cardioselective β -blockade probably does not induce bronchospasm in patients with COPD (11, 12, 14, 16, 17). In addition, a meta-analysis of Salpeter and colleagues that evaluated the relationship between cardioselective β -blockers and COPD found no significant differences in FEV₁ or respiratory symptoms between those who were treated with cardioselective β -blockers or those treated with placebo, even in patients with severe COPD (24). In a study of patients with congestive heart failure, patients with and without COPD had similar rates of withdrawal from β -blockers because of intolerance (25). These data suggest that COPD does not increase the rate of adverse reactions to cardioselective β -blockers (leading to withdrawal). In view of the observed beneficial effect of cardioselective β -blockers in our study, we believe that cardioselective β -blocking agents may be used cautiously in patients with COPD with underlying ischemic vascular disease. Because cardioselective β -blocking agents may have some (although minor) effects on β_2 -adrenoreceptors, such patients should be monitored very closely for any adverse effects. Moreover, although we found that intensified dose was superior to low-dose therapy with regard to 30-day mortality, we believe that it may be prudent to initiate therapy at the lowest dose feasible and to gradually increase the dose to the target range over several weeks to ensure safety.

Why β -blockers would be effective in COPD is largely unknown; however, it is well established that CVD is an important comorbidity in COPD. In the Lung Health Study, for instance, which studied 5,887 smokers, aged 35 to 60 years, with GOLD stage 1 and 2 disease (FEV₁ \geq 50% predicted), CVDs were primarily responsible for 22% of all deaths (26) and cardiovascular events accounted for 42% of the first hospitalizations and 48% of the second hospitalizations (27). The increased CVD risk in COPD may, in part, be related to excess adrenergic activity. Using microneurography of the peroneal nerve, Heindl and colleagues showed that patients with COPD have a marked increase in peripheral sympathetic discharge compared with control subjects (28), which was inversely related to the patients' oxyhemoglobin saturation ($r = 0.54$) (29). Patients with COPD also demonstrate reduced cardiac accumulation of meta-iodobenzylguanidine, an analog of guanetidine, a higher washout rate from the heart, and increased plasma norepinephrine levels than control subjects, indicating excess activity of the sympathetic nervous system with increased norepinephrine turnover than do control subjects (30). In patients who demonstrate excess sympathetic nervous activity, such as those with chronic heart failure or previous myocardial

infarction, the use of β -adrenoreceptor blockers, which attenuate sympathetic nervous activity, improves cardiac function and reduces CVD morbidity and mortality (31). In addition, β -blockers may reduce peri- and postoperative cardiac complications by attenuating cardiac workload and myocardial ischemia through β_1 -blockade. β_1 -Blockade may also inhibit catecholamine-induced necrosis and apoptosis of the myocardium, which may confer additional benefits to the stressed heart (32).

Our finding that an intensified dosing regimen was superior to a low-dose regimen in reducing 30-day mortality is consistent with those from a previous study that examined the effect of low- and intensive-dose therapy in vascular surgery patients (19). It is also consistent from the findings of the MOCHA (Multicenter Oral Carvedilol Heart Failure Assessment), SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure), and the COMET (Carvedilol or Metoprolol European Trial) trials, which also demonstrated a dose-related reduction in mortality (33–35). Conversely, the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure) trial and the CIBIS (Cardiac Insufficiency Bisoprolol Study) II trial failed to demonstrate this dose-dependent effect (36, 37). However, all these trials were conducted in patients with heart failure and should therefore be carefully compared with our study. Unfortunately, in most of these trials, patients with COPD were excluded because of concerns about bronchoconstriction, which makes cross-comparisons difficult. To our knowledge, the present study is the first of its kind to investigate the dose-dependent association between β -blockers and mortality in vascular surgery patients with COPD.

There were limitations to the study. First, we could not fully rule out the possibility that some individuals with COPD also had asthma. However, although bronchial hyperresponsiveness is more common (and more severe) in asthma than in COPD, over 70% of patients with COPD also demonstrate bronchial hyperresponsiveness. Thus, in reality, a clear separation is not always possible in clinical practice (38). Second, this was an observational study and not a clinical trial, which raises the possibility of confounding. To mitigate this possibility, we carefully collected salient clinical and demographic information and used sophisticated statistical modeling and inclusion of lung function measurements. We calculated a propensity score for β -blocker use and included this propensity score in the multivariable analysis to correct for the conditional probability of receiving the medication. We found that this made no material difference to the overall results. Although we cannot entirely rule out confounding by reverse indication, the adjustments of these factors including spirometric data suggest that these findings are not spurious and unlikely due to treatment selection. Nevertheless, additional prospective studies are needed to validate these early findings. Third, the prescription of β -blockers increased during 10 years of follow-up. To minimize

the effect of this potential bias, we adjusted for the year of surgery in the analysis. Moreover, although we found that β -blocker therapy was associated with both short- and long-term survival, our measure of β -blocker exposure occurred at one time point. We did not have follow-up data on β -blocker use, which may have led to exposure misclassification. However, it is likely that patients who were prescribed β -blockers at baseline were more likely to have received similar therapy in subsequent periods of follow-up (39). Thus, the long-term benefits of β -blocker therapy are likely on the basis of ongoing use of these medications as an outpatient.

In summary, our results suggest that cardioselective β -blockers are beneficial in patients with COPD undergoing vascular surgery, with an intensive dose being most effective in the reduction of 30-day mortality. Therefore, cardioselective β -blocking agents should not be withheld from patients with COPD undergoing vascular surgery.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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