β-Blockers Are Safe in Patients with Chronic Obstructive Pulmonary Disease, But Only with Caution

Despite clear evidence of the effectiveness of β-blockers in the management of patients with cardiac disease (heart failure and coronary artery disease) or arterial hypertension, use of these agents has traditionally been contraindicated in chronic obstructive pulmonary disease (COPD) mainly because of anecdotal evidence and case reports citing acute bronchospasm after their administration (1). In particular, it has been reported that selective or nonselective β-blockers increase airway hyperresponsiveness (AHR) (2), a real problem considering that AHR is associated with augmented mortality in patients suffering from COPD (3). The concern of inducing bronchospasm is a likely explanation of the fact that physicians appear to underprescribe β-blockers when patients with cardiac disease are also suffering from COPD (4).

The diminished use of β-blockers in patients with COPD is of concern considering that many patients with COPD ultimately die of cardiovascular causes, and from ischemic heart disease in particular (5). Impaired lung function seems to be an independent risk factor for arrhythmias, coronary events, and all-cause mortality and a specific predictor of mortality resulting from cardiac causes (6).

The cumulative evidence from trials and meta-analyses indicates that "cardioselective" β_1-blockers (exemplified by metoprolol and atenolol) should not be routinely withheld from patients with COPD because the benefits of selective β_1-blockers in patients with COPD who also have cardiac disease far outweigh the risks (7). In this issue of the *Journal* (pp. 695–700), van Gestel and coworkers (8) reinforce this view by providing solid proof that, in carefully selected patients with COPD undergoing vascular surgery, cardioselective β-blockers are safe and indeed beneficial in prolonging survival. This finding indicates that at least β_1-blockers are well tolerated in patients with COPD.

Although the information from van Gestel and colleagues' study is reassuring, we cannot forget recent analyses that examined the affinity of a wide range of cardioselective β-blockers to a homogenous population of human β-adrenoceptor (AR) subtypes expressed in cell lines, which showed a more limited preference for β_1-AR than previously thought, suggesting that many cardioselective β-blockers are blocking β_2-ARs in bronchi in addition to blocking β_1-ARs in the heart (8). This finding could explain why the effects of the cardioselective β-blocker metoprolol on AHR are the same as those of the nonselective β-blocker propranolol in patients with COPD (2).

In a murine model of antigen-induced airway inflammation and AHR, duration of therapy was the determinant of response to β-AR ligands (9). That is, acute treatment with β-blockers increased AHR, whereas chronic treatment (28 d) significantly decreased AHR (10). The mechanism of this phenomenon has not been established but has been suggested to be associated with an increase in β-AR density (10). This intriguing experimental finding was also confirmed in humans. In fact, a small open-label pilot study documented that dose-escalating administration of nadolol, a nonselective β-blocker (with β_2-AR inverse agonist properties) that is currently contraindicated in patients with asthma, may be well tolerated and may have a beneficial effect for most subjects with mild asthma when administered chronically (11).

Traditionally, the treatment of COPD is based on the use of long-acting bronchodilators, in particular β_2-agonists, but there is accumulating evidence showing that β_2-agonist use leads to an increased risk for adverse cardiovascular events in patients with COPD (12). It is possible that the antagonist effects of β-blockers may neutralize the actions of β-agonists, so that the risk of adverse cardiovascular events associated with β-agonists may be different in subjects already using β-blockers than among nonusers of β-blockers. However, if it is true that the use of β-blockers leads to an increase in the density of β-ARs, this effect might suggest an increased risk associated with the concomitant use of β-agonists and β-blockers in COPD. Apparently, cardioselective β-blockers not only do not produce increased respiratory symptoms in patients with COPD but they are also associated with an augmented bronchodilator response to subsequent β-agonists (13). This is a clear indication of facilitated β-AR stimulation. However, facilitated β-AR stimulation would also increase heart rate and myocardial oxygen demand (14). Case-control studies have demonstrated an association between β_2-agonist use and an increased risk for myocardial infarction, congestive heart failure, cardiac arrest, and acute cardiac death. Intriguingly, the absence of a concurrent possible protective effect of β-blockers has been reported in this situation (15).

If the above considerations lead to fear of the unconditional use of β-blockers in COPD, one should also consider a pharmacologic phenomenon that is opposite of what we have just described. In effect, exposure to β-agonists may alter β-ARs such that the affinity for ligands is reduced 10-fold (16). Consequently, prior exposure to β-agonists may reduce binding of antagonists to β_2-ARs. This relationship may explain the high tolerance for β-blockers in patients with COPD, who routinely inhale β_2-agonists, reported not only by van Gestel and coworkers (8) but also observed in trials and meta-analyses (7).

The data therefore are reassuring and indicate that it is possible to use β-blockers in all patients with COPD who need them for concurrent diseases. However, the pharmacologic relationships that we have described come from studies that generally included few patients. In addition, there are currently no prospective long-term data on the safety of β-blockers in COPD. Therefore, although β-blockers can be introduced in any medical setting, it still seems appropriate to use cardioselective β-blockers in patients with COPD at the lowest dose and to titrate slowly with attention to lung function and symptoms (1).

Conflict of Interest Statement: M.C. has participated as a speaker in scientific meetings or courses organized and financed by various pharmaceutical companies (Boehringer Ingelheim, GlaxoSmithKline, Sigma-Tau, Recordati); served on an advisory board for Dey (2006, $3,000; 2007, $3,000), Novartis (2007, €2,000 + $2,000), GlaxoSmithKline (2007, €4,500; 2008, €1,700), and Istituto Pirri (2007, €2,000); served as a consultant to Almirall (2005, €450; 2007, €1,000), Altana (2006, €12,500), Boehringer Ingelheim (2008, €5,000), and AstraZeneca (2008, €3,000); received in 2005 €30,000 from Altana, and €1,500 from Valeas, in 2007 €3,300 from GlaxoSmithKline and €5,000 from Istituto Pirri, in 2008 €8,000 from Keryos for serving as an expert witness; has been reimbursed by Novartis, Encysive, Altana, and Menarini Farmaceutici for attending several conferences. M.G.M. has been reimbursed by Novartis, Encysive, and Altana for attending several conferences.

Am J Respir Crit Care Med Vol 178. pp 661–666, 2008
Internet address: www.atsjournals.org

MARIO CAZZOLA, M.D.
University of Rome "Tor Vergata"
Rome, Italy

MARIA GABRIELLA MATERA, M.D., PH.D.
Second University of Naples
Naples, Italy

References

1. Cazzola M, Noschese P, D'Amato G, Matera MG. The pharmacologic treatment of uncomplicated arterial hypertension in patients with airway dysfunction. *Chest* 2002;121:230–241.
2. van der Woude HJ, Zaagsma J, Postma DS, Winter TH, van Hulst M, Aalbers R. Detrimental effects of beta-blockers in COPD: a concern for nonselective β-blockers. *Chest* 2005;127:818–824.
3. Hospers JJ, Postma DS, Rijcken B, Weiss ST, Schouten JP. Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. *Lancet* 2000;356:1313–1317.
4. Egred M, Shaw S, Mohammad B, Waitt P, Rodrigues E. Under-use of beta-blockers in patients with ischaemic heart disease and concomitant chronic obstructive pulmonary disease. *QJM* 2005;98:493–497.
5. Huiart L, Erns P, Suissa S. Cardiovascular morbidity and mortality in COPD. *Chest* 2005;128:2640–2646.
6. Sin DD, Man SF. Chronic obstructive pulmonary disease: a novel risk factor for cardiovascular disease. *Can J Physiol Pharmacol* 2005;83:8–13.
7. Albouaini K, Andron M, Alahmar A, Egred M. Beta-blockers use in patients with chronic obstructive pulmonary disease and concomitant cardiovascular conditions. *Int J Chron Obstruct Pulmon Dis* 2007; 2:535–540.
8. van Gestel YRBM, Hoeks SE, Sin DD, Welten GMJM, Schouten O, Witteveen HJ, Simsek C, Stam H, Mertens FW, Bax JJ, *et al.* Impact of cardioselective β-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis. *Am J Respir Crit Care Med* 2008;178:695–700.
9. Bond RA, Spina D, Parra S, Page CP. Getting to the heart of asthma: can "β blockers" be useful to treat asthma? *Pharmacol Ther* 2007;115:360–374.
10. Callaerts-Vegh Z, Evans KL, Dudekula N, Cuba D, Knoll BJ, Callaerts PF, Giles H, Shardonofsky FR, Bond RA. Effects of acute and chronic administration of beta-adrenoceptor ligands on airway function in a murine model of asthma. *Proc Natl Acad Sci U S A* 2004;101: 4948–4953.
11. Hanania NA, Singh S, El-Wali R, Flashner M, Franklin AE, Garner WJ, Dickey BF, Parra S, Ruoss S, Shardonofsky F, *et al.* The safety and effects of the beta-blocker, nadolol, in mild asthma: an open-label pilot study. *Pulm Pharmacol Ther* 2008;21:134–141.
12. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of β-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004;125:2309–2321.
13. Salpeter SR, Buckley NS. Use of β-blockers and β-agonists in COPD: a review of clinical outcomes. *Respiratory Medicine: COPD Update* 2007; 2:133–139.
14. Cazzola M, Matera MG, Donner CF. Cardiovascular safety of inhaled β_2-adrenoceptor agonists in obstructive lung disease. *Drugs* 2005;65: 1595–1610.
15. Au DH, Lemaitre RN, Curtis JR, Smith NL, Psaty BM. The risk of myocardial infarction associated with inhaled β-adrenoceptor agonists. *Am J Respir Crit Care Med* 2000;161:827–830.
16. Baker JG, Hall IP, Hill SJ. Influence of agonist efficacy and receptor phosphorylation on antagonist affinity measurements: differences between second messenger and reporter gene responses. *Mol Pharmacol* 2003;64:679–688.

DOI: 10.1164/rccm.200806-963ED

Translating the Genome

The Toll-like receptors (TLRs) are the primary receptors that recognize molecules released by microorganisms. This fundamental responsibility in immunosurveillance may explain why this family of receptors has proven to play such a critical role in a broad array of immune and autoimmune diseases. The findings of Wurfel and colleagues (1), reported in this issue of the *AJRCCM* (pp. 710–720), demonstrate the vital role that *TLR1* plays in sepsis and septic shock. Moreover, these results illustrate the potential clinical utility of specific sequence changes in *TLR1* that can identify individuals at increased risk of gram-positive sepsis and its ensuing complications. Their findings add to the growing list of polymorphisms in innate immune genes ($TLR2_{\text{Arg753Gln}}$, $TLR4_{\text{Asp299Gly}}$, $TLR5_{\text{Arg392STOP}}$, $TIRAP_{\text{Ser180Leu}}$, and $IRAK4_{\text{Glu293STOP}}$) that have been found to alter the risk of developing a number of different diseases and conditions (2–6). On the basis of this body of research, one could develop a personalized innate single-nucleotide polymorphism (SNP) profile that would prove useful in risk-stratifying patients, especially those more prone to infections and their complications (e.g., the elderly, diabetics, and alcoholics). Because the scientific and clinical consequences of Wurfel and colleagues' findings have been comprehensively considered in their DISCUSSION (1), I will focus this editorial on a few more general questions.

Why were these investigators successful? Bill Clinton's response to this question would probably be "It's the phenotype, stupid." And he'd probably be right. While 275 healthy subjects seem like a large group of individuals to screen for innate immune phenotypes, these numbers are small compared with most genetic studies. Despite these small numbers, the investigators were able to confirm the phenotypes of other innate immune polymorphisms ($TLR4_{\text{Asp299Gly}}$, $TLR5_{\text{Arg392Ter}}$, and $TIRAP_{\text{Ser180Leu}}$) and discover a highly significant ($P < 10^{-20}$) relationship between $TLR1_{-720\ g}$ and an enhanced response to pam_3CSK_4. I believe that this was only possible because the investigators were exploiting an exposure–response relationship by probing specific biological pathways with unique stimuli. In fact, one could argue that, if they evaluated more proximal indices of TLR activation (rather than the downstream cytokines), additional significant polymorphisms would have been identified. The point here is that the more narrowly a phenotype can be defined (especially in terms of basic biology), the more likely one will be able to identify the genetic etiology. Moreover, specific exposures (in this case, microbial peptides) can (and should) be used to narrow the pathophysiologic phenotype to enhance the discovery of genes and gene variants that drive these basic biological responses. After all, such basic biological processes cause disease, so let's exploit them to understand genetic susceptibility.

Why are these detrimental polymorphisms preserved in the genome? The answer to this is in part related to the multifunctional nature of TLRs. These receptors have evolved in response to the unique challenges presented by the diversity of microorganisms and their negative consequences. However, to ensure their own future (7), these receptors have assumed additional responsibilities and, in a polygamous fashion, now serve as the critical link between the cell and a broad range of endogenous and exogenous ligands, including fibronectin, oxidized low-density lipoprotein, and hyaluronin. While many of these innate immune polymorphisms were discovered because of their adverse effects on host defense, one could reasonably hypothesize that their preservation in human evolution was based on survival advantages that were realized through other receptor–ligand interactions. These trade-offs and evolutionary pressures are best illustrated for *TLR4*, in which the prevalence of the

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

Yvette R. B. M. van Gestel[1], Sanne E. Hoeks[1], Don D. Sin[2], Gijs M. J. M. Welten[3], Olaf Schouten[3], Han J. Witteveen[4], Cihan Simsek[4], Henk Stam[5], Frans W. Mertens[5], Jeroen J. Bax[6], Ron T. van Domburg[4], and Don Poldermans[1]

[1]Department of Anesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands; [2]Department of Medicine, University of British Columbia and the James Hogg iCAPTURE Center, St. Paul's Hospital, Vancouver, Canada; [3]Department of Vascular Surgery, [4]Department of Cardiology, and [5]Department of Pulmonology, Erasmus Medical Center, Rotterdam, The Netherlands; and [6]Department of Cardiology, Leiden Medical Center, Leiden, The Netherlands

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 noncardiac surgery. Several studies have shown that perioperative β-blocker therapy can reduce the incidence of peri- and postoperative 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 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 nonselective 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).

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.

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

(*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.).

Correspondence and requests for reprints should be addressed to Don Poldermans, M.D., Ph.D., Erasmus Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. E-mail: d.poldermans@erasmusmc.nl

Am J Respir Crit Care Med Vol 178. pp 695–700, 2008
Originally Published in Press as DOI: 10.1164/rccm.200803-384OC on June 19, 2008
Internet address: www.atsjournals.org

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-tibila 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 $\geq$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 ($FEV_1/FVC < 0.70$ and $FEV_1 \geq$ 80% of the predicted FEV_1), II = moderate COPD ($FEV_1/FVC < 0.70$ and FEV_1 50% $\leq FEV_1 <$ 80% of the predicted FEV_1), and III = severe COPD ($FEV_1/FVC < 0.70$ and FEV_1 30% $\leq FEV_1 <$ 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 × height (m) − age × 0.029 − 2.49 and for women is 3.95 × height (m) − age × 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 ($P_{CO_2} < 6.4$ kPa and $P_{O_2} > 10.0$ 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 ± 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*)			No COPD (*n = 1,994*)		
	β-Blocker (*n = 462*)	No β-Blocker (*n = 803*)	*P* Value	β-Blocker (*n = 567*)	No β-Blocker (*n = 1,427*)	*P* Value
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

	30-Day Mortality		Long-Term Mortality	
β-Blocker	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,

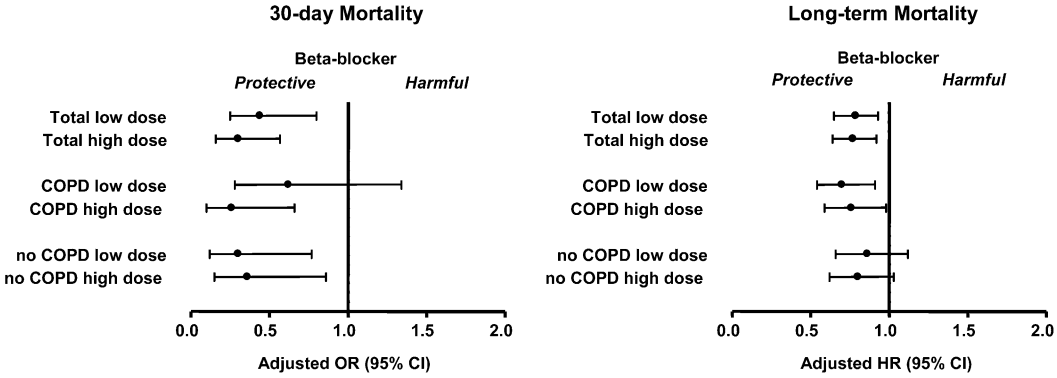

Figure 1. The association between low and intensified cardioselective β-blocker dose and mortality. Adjusted for age, sex, hypertension, hypercholesterolemia, diabetes mellitus, renal dysfunction, current smoking status, body mass index, type of surgery, year of surgery, and cardiovascular history. CI = 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 FEV_1 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-adreneroreceptors, 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 ($FEV_1 \geq 50\%$ 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-adrenoceptor 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.

References

1. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. *N Engl J Med* 1996;335:1713–1720.
2. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, *et al*. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999;341:1789–1794.
3. Poldermans D, Boersma E, Bax JJ, Thomson IR, Paelinck B, van de Ven LL, Scheffer MG, Trocino G, Vigna C, Baars HF, *et al*. Bisoprolol reduces cardiac death and myocardial infarction in high-risk patients as long as 2 years after successful major vascular surgery. *Eur Heart J* 2001;22:1353–1358.
4. Schouten O, Shaw LJ, Boersma E, Bax JJ, Kertai MD, Feringa HH, Biagini E, Kok NF, Urk H, Elhendy A, *et al*. A meta-analysis of safety and effectiveness of perioperative beta-blocker use for the prevention of cardiac events in different types of noncardiac surgery. *Coron Artery Dis* 2006;17:173–179.
5. Auerbach AD, Goldman L. Beta-blockers and reduction of cardiac events in noncardiac surgery: scientific review. *JAMA* 2002;287:1435–1444.
6. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, *et al*. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2007;116:e418–e499.
7. Centers for Disease Control. The Surgeon General's 1989 report on reducing the health consequences of smoking: 25 years of progress. *MMWR Morb Mortal Wkly Rep* 1989;38:1–32.
8. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007;62:411–415.
9. Wellstein A, Palm D, Belz GG, Butzer R, Polsak R, Pett B. Reduction of exercise tachycardia in man after propranolol, atenolol and bisoprolol in comparison to beta-adrenoceptor occupancy. *Eur Heart J* 1987;8(Suppl M):3–8.
10. Ashrafian H, Violaris AG. Beta-blocker therapy of cardiovascular diseases in patients with bronchial asthma or COPD: The pro viewpoint. *Prim Care Respir J* 2005;14:236–241.
11. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;CD003566.
12. Camsari A, Arikan S, Avan C, Kaya D, Pekdemir H, Cicek D, Kiykim A, Sezer K, Akkus N, Alkan M, *et al*. Metoprolol, a beta-1 selective blocker, can be used safely in coronary artery disease patients with chronic obstructive pulmonary disease. *Heart Vessels* 2003;18:188–192.
13. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998;339:489–497.
14. Kieran SM, Cahill RA, Browne I, Sheehan SJ, Mehigan D, Barry MC. The effect of perioperative beta-blockade on the pulmonary function of patients undergoing major arterial surgery. *Eur J Vasc Endovasc Surg* 2006;32:305–308.
15. Chen J, Radford MJ, Wang Y, Marciniak TA, Krumholz HM. Effectiveness of beta-blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma. *J Am Coll Cardiol* 2001;37:1950–1956.
16. Sirak TE, Jelic S, Le Jemtel TH. Therapeutic update: non-selective beta- and alpha-adrenergic blockade in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2004;44:497–502.
17. Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med* 2002;137:715–725.
18. Dransfield MT, Rowe SM, Johnson JE, Bailey WC, Gerald LB. Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax* 2008;63:301–305.
19. Feringa HH, Bax JJ, Boersma E, Kertai MD, Meij SH, Galal W, Schouten O, Thomson IR, Klootwijk P, van Sambeek MR, *et al*. High-dose beta-blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. *Circulation* 2006;114:I344–I349.
20. van Gestel YRBM, Hoeks SE, Welten GMJM, Schouten O, Stam H, Mertens FW, van Domburg RT, van Sambeek MRHM, Goei D, Poldermans D. Beta-blockers in patients with chronic obstructive pulmonary disease and atherosclerosis: from contraindication to indication? *Eur Heart J* 2007;28(Abstract Suppl):214.
21. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532–555.
22. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:5–40.
23. Subbarao P, Lebecque P, Corey M, Coates AL. Comparison of spirometric reference values. *Pediatr Pulmonol* 2004;37:515–522.
24. Salpeter SR, Ormiston TM, Salpeter EE, Poole PJ, Cates CJ. Cardioselective beta-blockers for chronic obstructive pulmonary disease: a meta-analysis. *Respir Med* 2003;97:1094–1101.
25. Mascarenhas J, Lourenco P, Lopes R, Azevedo A, Bettencourt P. Chronic obstructive pulmonary disease in heart failure: prevalence, therapeutic and prognostic implications. *Am Heart J* 2008;155:521–525.
26. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005;142:233–239.
27. Anthonisen NR, Connett JE, Enright PL, Manfreda J. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med* 2002;166:333–339.
28. Heindl S, Lehnert M, Criee CP, Hasenfuss G, Andreas S. Marked sympathetic activation in patients with chronic respiratory failure. *Am J Respir Crit Care Med* 2001;164:597–601.
29. Wieland DM, Wu J, Brown LE, Mangner TJ, Swanson DP, Beierwaltes WH. Radiolabeled adrenergi neuron-blocking agents: adrenomedullary imaging with [^{131}I]iodobenzylguanidine. *J Nucl Med* 1980;21:349–353.
30. Sakamaki F, Oya H, Nagaya N, Kyotani S, Satoh T, Nakanishi N. Higher prevalence of obstructive airway disease in patients with thoracic or abdominal aortic aneurysm. *J Vasc Surg* 2002;36:35–40.
31. McMurray JJ, Pfeffer MA. Heart failure. *Lancet* 2005;365:1877–1889.
32. Cruickshank JM. Are we misunderstanding beta-blockers. *Int J Cardiol* 2007;120:10–27.
33. Metra M, Torp-Pedersen C, Swedberg K, Cleland JG, Di Lenarda A, Komajda M, Remme WJ, Lutiger B, Scherhag A, Lukas MA, *et al*. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial. *Eur Heart J* 2005;26:2259–2268.
34. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, *et al*. Carvedilol produces dose-related improvements in left ventricular

function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation* 1996;94:2807–2816.
35. Dobre D, van Veldhuisen DJ, Mordenti G, Vintila M, Haaijer-Ruskamp FM, Coats AJ, Poole-Wilson PA, Flather MD. Tolerability and dose-related effects of nebivolol in elderly patients with heart failure: data from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial. *Am Heart J* 2007;154:109–115.
36. Simon T, Mary-Krause M, Funck-Brentano C, Lechat P, Jaillon P. Bisoprolol dose–response relationship in patients with congestive heart failure: a subgroup analysis in the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Eur Heart J* 2003;24:552–559.
37. Wikstrand J, Hjalmarson A, Waagstein F, Fagerberg B, Goldstein S, Kjekshus J, Wedel H. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol* 2002;40:491–498.
38. Woolcock AJ, Anderson SD, Peat JK, Du Toit JI, Zhang YG, Smith CM, Salome CM. Characteristics of bronchial hyperresponsiveness in chronic obstructive pulmonary disease and in asthma. *Am Rev Respir Dis* 1991;143:1438–1443.
39. Sin DD, Tu JV. Inhaled corticosteroid therapy reduces the risk of rehospitalization and all-cause mortality in elderly asthmatics. *Eur Respir J* 2001;17:380–385.