β-Blockers Improve Survival of Patients With Chronic Obstructive Pulmonary Disease After Coronary Artery Bypass Grafting

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Background. **β-Blockers are known to improve survival of patients with cardiovascular disease, but their administration in patients with chronic obstructive pulmonary disease (COPD) remains controversial. The aim of the present study was to assess the effect of β-blocker administration in patients with COPD undergoing coronary artery bypass grafting.**

Methods. **A total of 388 consecutive patients with COPD who underwent isolated coronary artery bypass grafting were studied, and clinical follow-up was completed. Diagnosis of COPD was based on preoperative forced expiration volume; exacerbation episodes were defined as a pulsed-dose prescription of prednisolone or a hospital admission for an exacerbation. Two propensity-matched cohorts of 104 patients each either receiving or not receiving β-blockers were identified.**

Results. **At baseline, there was no significant difference among groups. After a median follow-up of 36 months, there were 8 deaths in 104 patients (7.7%) receiving β-blockers versus 19 deaths in 104 patients (18.3%) who did not receive β-blockers ($p = 0.03$). Kaplan-Meyer analysis showed a survival of 91.8% ± 2.8% for patients taking β-blockers versus 80.6% ± 4.0% for control subjects (χ^2, 29.4; $p = 0.003$; hazard ratio, 0.38). In addition, β-blocker administration did not increase rates of COPD exacerbation, which was experienced by 46 of 104 patients (44.2%) receiving β-blockers versus 45 of 104 patients (43.3%) not receiving β-blockers ($p = 0.99$).**

Conclusions. **This study showed that in patients with COPD undergoing coronary artery bypass grafting the administration of β-blockers is safe and significantly improves survival at mid-term follow-up. Further randomized studies are needed to confirm these findings.**

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Chronic obstructive pulmonary disease (COPD) is a common disease with a marked negative impact on quality of life, hospitalization, and mortality rates [1], and it is expected to become the third most common cause of death in the Western world by the year 2020 [2]. Cigarette smoking and increased age (in addition to occupational exposure to dust and chemicals) are the two main risk factors for developing COPD, and a strong linkage between this respiratory disease and coronary artery disease has clearly been established. Chronic obstructive pulmonary disease, indeed, is also characterized by systemic inflammation, which promotes atherosclerotic disease progression independent of age, smoking, or other cardiovascular risk factors [3]. Therefore, patients with COPD are at high risk for experiencing cardiovascular morbidity, which involves more than half of these patients and accounts for most deaths [3–5]. Chronic obstructive pulmonary disease in fact is a frequent comorbidity of patients undergoing coronary artery bypass grafting (CABG); its incidence ranges from 4% to 27% [6, 7], and it is conventionally associated with increased postoperative mortality [8, 9].

Therapy with cardiovascular drugs, notably β-blockers (BB), is known to improve survival of patients within a large spectrum of cardiovascular diseases, including ischemic heart disease and heart failure [10–12]. In fact, several randomized clinical trials and meta-analyses have reported the efficacy of BB administration in terms of mortality in several settings of heart disease [13–18], and their administration is recommended for patients undergoing CABG [19].

However, BB are traditionally contraindicated in COPD patients because of their presumed bronchoconstrictive properties and competition with β_2-agonists [20, 21]; therefore, many physicians avoid prescribing BB in those patients [22]. Conversely, there is increasing evidence that BB could theoretically exert beneficial effects in patients with COPD by tempering the sympathetic nervous system or by reducing the ischemic burden [23]. Recent meta-analyses have shown that cardioselective BB are well tolerated by patients with COPD [24] and that single-dose or long-term treatment with cardioselective BB do not cause an increase in exacerbations, reduction in airway func-

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tion, or worsening of quality of life in these patients [24–26].

The aim of the present study was to assess the effect of BB therapy in patients with COPD operated on for CABG, which, to date, has not been investigated yet.

Patients and Methods

This study was reviewed and approved by the Institutional Review Board of the University of Rome and a waiver of consent was granted. The authors have no conflict of interest to disclose.

Patients and Definitions

A consecutive series of patients diagnosed with COPD who underwent isolated first-time elective CABG at one institution between April 2004 and April 2009 was studied.

All the operations were performed through a full median sternotomy on cardiopulmonary bypass, and cardiac arrest was obtained by means of antegrade cold-blood cardioplegia, repeated every 15 minutes. The left internal mammary artery was always used to graft the left anterior descending artery, and revascularization was completed using saphenous vein grafts to the right coronary and left circumflex artery segments.

Postoperative intensive care was performed according to standardized protocols: mechanical ventilation was performed with a tidal volume of 8 to 10 mL/kg, positive end-expiratory pressures between 5 and 10 cm H_2O, and fraction of inspired oxygen to maintain the partial pressure of oxygen at greater than 90%; weaning from mechanical ventilation generally lasted 60% of the mechanical ventilation time [27]. In case of COPD exacerbations, medical and mechanical ventilator support (by means of noninvasive ventilation in bilevel positive airway pressure mode for hypercapnia or in continuous positive airway pressure for hypoxia) was provided [28].

Data were prospectively collected and recorded in an electronic database, and clinical follow-up was completed during routine outpatient clinics. Patients who did not present at the visit were contacted by telephone, and all symptoms, mortality, and any complications that occurred during follow-up were recorded.

Preoperative spirometry was performed in every patient with a history of smoking or bronchodilator usage and those with respiratory symptoms such as chronic cough and sputum production. The diagnosis of COPD was made according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) executive summary [1]: postbronchodilator FEV_1/FVC less than 0.70 (where FEV_1 is the forced expiratory volume in the first second and FVC the forced expiratory vital capacity); FEV_1 values were compared with predicted values to stage the severity degree into four classes, as recommended [1]. In addition, exacerbation of COPD was defined as stated in the GOLD executive summary [1], and to reduce bias and standardize the diagnosis, we only recorded episodes with a pulsed-dose prescription of prednisolone or a hospital admission for an exacerbation of respiratory symptoms.

Indication for BB administration depended on the referral cardiologist: patients preoperatively receiving BB were discharged with BB therapy, whereas patients who never received BB before surgery were discharged without BB therapy.

In addition, to avoid crossover bias, before propensity-score matching only patients receiving BB therapy both before and after surgery were considered for inclusion in the cohort of patients receiving BB therapy and only patients not receiving BB at all were considered for inclusion in the cohort of patients not receiving BB therapy. Thus, patients starting or discontinuing BB therapy during the study period were excluded.

Furthermore, patients who were on nonselective BB therapy were excluded from the analysis, therefore only patients receiving cardioselective (predominant β_1-antagonists) BB, including atenolol, bisoprolol, metoprolol, and nebivolol, were considered for this study.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 11.0 (SPSS, Chicago, IL). Variables were checked for normality by means of the Kolmogorov-Smirnov test for normal distribution, and normality was accepted when the probability value was equal to or less than 0.05. Differences in baseline characteristics were compared using the χ^2 test for categorical variables and Student's *t* test for continuous variables.

Because of comorbidities, patients on preoperative BB therapy showed a slightly higher operative risk (mainly because of functional status and heart rhythm disorders, the reasons they were taking BB). To eliminate covariate differences that might lead to biased estimates, a propensity score model was built, and two cohorts of 1:1 perfectly matched patients were obtained [29]. The propen-

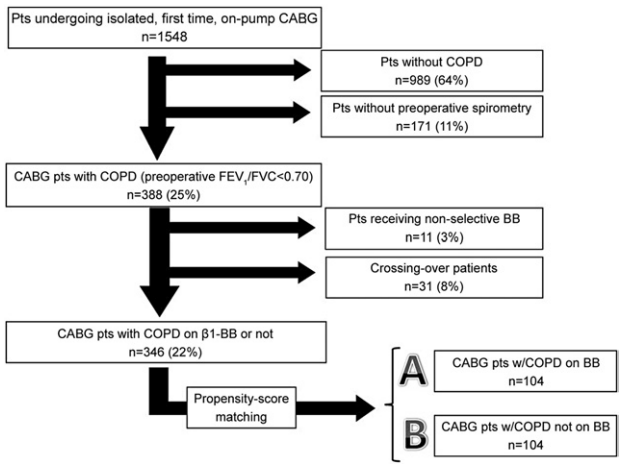

Fig 1. Flow-chart of the study. (BB = β-blocker therapy; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second; FVC = forced expiratory vital capacity; Pts = patients.)

Table 1. Baseline Characteristics Stratified After Propensity Matching[a]

Variable	Group A	Group B	*p* Value
Number of patients	104	104	N/A
Age (y)	70 ± 8	70 ± 9	0.84
Sex male, n (%)	89 (86)	91 (88)	0.62
Hypertension, n (%)	99 (95)	100 (96)	0.64
Diabetes, n (%)	46 (44)	47 (45)	0.81
Hyperlipemia, n (%)	77 (74)	75 (72)	0.59
History of smoking, n (%)	59 (57)	59 (57)	1
Current smoking, n (%)	9 (9)	8 (8)	0.72
Recent smoking history, n (%)	20 (19)	18 (17)	0.61
Past smoking history, n (%)	30 (29)	33 (32)	0.43
Preoperative LVEF	0.52 ± 0.10	0.51 ± 0.11	0.57
Preoperative GFR (mL/min)	68 ± 12	68 ± 14	0.77
Preoperative NYHA class >2, n (%)	32 (31)	33 (32)	0.84
Preoperative CCS class >2, n (%)	62 (60)	61 (59)	0.72
Recent MI, n (%)	33 (32)	32 (31)	0.86
Previous stroke, n (%)	5 (5)	6 (6)	0.83
Preoperative medications			
ACE inhibitors	71 (68)	70 (67)	0.58
ARBs	35 (34)	33 (32)	0.44
Statins	68 (65)	69 (66)	0.62
Diuretics	11 (11)	12 (12)	0.88
Inhaled β_2-sympathicomimetics, n (%)	74 (71)	75 (72)	0.63
Inhaled corticosteroids, n (%)	71 (68)	69 (66)	0.57
Inhaled anticholinergics, n (%)	67 (64)	66 (63)	0.66
Oral corticosteroids, n (%)	27 (26)	25 (24)	0.41
Degree of COPD ($FEV_1/FVC < 0.70$)			
Mild ($FEV_1 \geq 80\%$ predicted), n (%)	29 (28)	27 (26)	0.47
Moderate ($50\% \leq FEV_1 < 80\%$ predicted), n (%)	49 (47)	48 (46)	0.52
Severe ($30\% \leq FEV_1 < 50\%$ predicted), n (%)	22 (21)	23 (22)	0.39
Very severe ($FEV_1 < 30\%$ predicted), n (%)	4 (4)	6 (6)	0.58
Logistic EuroSCORE II, %	2.4 (0.6–8.2)[b]	2.3 (0.5–8.4)[b]	0.65
CPB time (min)	87 ± 29	88 ± 35	0.46
X-clamp time (min)	59 ± 22	60 ± 24	0.61
Distal anastomoses, mean	2.7 ± 0.8	2.8 ± 0.6	0.63

[a] Continuous variables are expressed as the mean ± standard deviation; categorical variables are expressed as percentages. [b] Values shown are medians and their 95% confidence intervals.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; EuroSCORE = European System for Cardiac Operative Risk Evaluation; FEV_1 = forced expiratory volume in the first second; FVC = forced expiratory vital capacity; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; X-clamp = aortic cross-clamp.

sity score was computed with logistic regression with the dependent variable being postoperative administration of BB and the independent variables (covariates) being age, sex, hypertension, diabetes, hyperlipemia, history of smoking, preoperative left ventricular ejection fraction, preoperative glomerular filtration rate, recent myocardial infarction, preoperative angina and dyspnea degrees, preoperative stroke, preoperative medications, cardiopulmonary bypass time, aortic cross-clamp time, and mean number of distal anastomoses. Mixing of continuous and binary variables was done to obtain a semisaturated model. Finally, the propensity score model showed acceptable goodness of fit (c-statistic, 0.76; $p < 0.0001$).

Patient-year rates were calculated using the time each participant contributed in the study until death or event. Event rates were used to calculate absolute risk reduction (control event rate divided by experimental event rate) and relative risk reduction (absolute risk reduction divided by control event rate).

Cumulative survival and freedom from exacerbations of COPD at follow-up were analyzed by means of the Kaplan-Meyer method and compared between groups using a log-rank test. Any cardiac-related, sudden, or unknown death was considered a cardiac-related death; in addition, stroke was considered as cardiac death. The survival or freedom from event time of a patient started at the time of surgery and ended at death or event or at last follow-up (censoring).

Results

A total of 1,548 consecutive patients undergoing isolated, elective, on-pump, first-time CABG were studied. Among these, we identified 388 (25%) patients with a spirometry-confirmed diagnosis of COPD. For the purpose of the study, two propensity-matched cohorts of patients were individuated: one of 104 individuals who received cardioselective BB therapy (group A) and one of 104 who did not (group B); a flow chart of the study is shown in Figure 1.

At baseline, propensity matching eliminated any potential selection bias; thus, there was no significant difference between groups with respect to age, sex, comorbidities, cardiac functional status, preoperative medical therapy, and operative variables (Table 1). The fair matching driven by propensity scoring was confirmed by the similar median logistic EuroSCORE II of the two cohorts: 2.4% (95% confidence interval, 0.6% to 8.2%) in group A versus 2.3% (95% confidence interval, 0.5% to 8.4%) in group B ($p = 0.65$).

Analysis of Survival

Postoperatively, overall 30-day mortality was 1.9% (4 of 208 patients) and total in-hospital mortality was 2.4% (5 of 208 patients), and no significant difference of outcomes was noted between groups (Table 2).

As anticipated, new onset of postoperative atrial fibrillation was more likely (although not statistically significant) to occur in patients not receiving BB (26 of 104 patients or 25% versus 20 of 104 patients or 19% from group A; $p = 0.09$). Furthermore, among those experiencing atrial fibrillation, patients receiving BB therapy showed a not statistically significant trend toward a higher rate of conversion to sinus rhythm (15 of 20 patients or 75% from group A versus 18 of 26 patients or 69% from group B; $p = 0.06$).

At a median follow-up of 36 months (mean, 30.8 ± 8.5 months), overall mortality was 12.3% (27 of 208 patients). There were 8 deaths in 104 patients (7.7%) receiving BB (group A) versus 19 deaths in 104 patients (18.3%) who did not (group B; $p = 0.03$). Overall, 534.8 patient-years of follow-up data were available, the cumulative incidence rate of deaths per 100 patient-years was 5.04, and patients from group A showed half the incidence of death compared with group B (3.02 deaths/100 patient-years versus 7.03 deaths/100 patient-years, respectively; 57% relative risk reduction; $p = 0.004$). Kaplan-Meyer analysis showed a significantly better survival in group A; 91.8% ± 2.8% versus 80.6% ± 4.0% in group B (hazard ratio, 0.38; χ^2, 29.4; $p = 0.003$ by log-rank test; Fig 2).

Table 2. Postoperative Morbidity and Mortality Stratified for β-Blocker Usage

Variable	Group A	Group B	*p* Value
MI, n (%)	2 (2)	1 (1)	0.47
AKI, n (%)	5 (5)	4 (4)	0.32
RRT, n (%)	3 (3)	3 (3)	1
MV >24 hours, n (%)	7 (7)	9 (9)	0.34
Pneumonia, n (%)	9 (9)	10 (10)	0.26
New-onset AF, n (%)	20 (19)	26 (25)	0.09
AF conversion, n (%)	15 of 20 (75)	18 of 26 (69)	0.06
RBC transfusions (units)	1.4 ± 2.5	1.4 ± 2.7	0.55
ICU stay (days)	3.6 ± 6.9	3.9 ± 7.8	0.62
30-day mortality, n (%)	2 (2)	2 (2)	1
Hospital mortality, n (%)	2 (2)	3 (3)	0.84

AF = atrial fibrillation; AKI = acute kidney injury; ICU = intensive care unit; MI = myocardial infarction; MV = mechanical ventilation; RBC = red blood cell; RRT = renal replacement therapy.

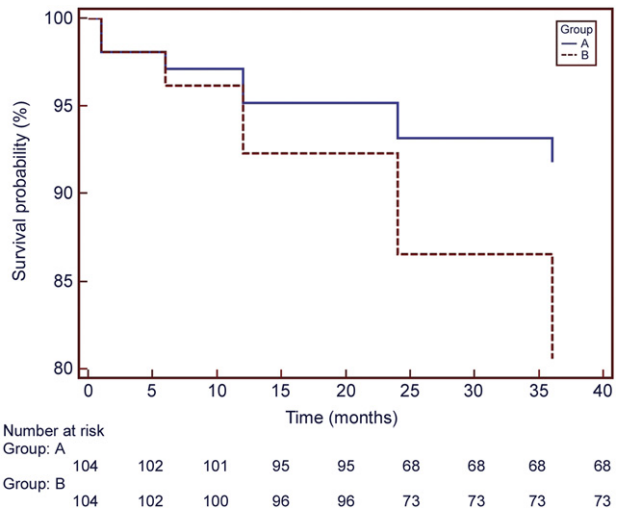

Fig 2. Kaplan-Meyer analysis of survival in patients with chronic obstructive pulmonary disease receiving (group A; solid line) or not receiving (group B; dashed line) β-blockers after coronary artery bypass graft surgery.

Cardiac-related mortality 3 years after the operation was 12 of 208 patients (5.8% or 2.24/100 patient-years); in the latter, cardiac-related deaths were 1.13/100 patient-years in group A and 3.33/100 patient-years in group B (66% relative risk reduction; $p < 0.0001$). Kaplan-Meyer analysis revealed a significant difference in cardiac-related survival between patients from group A (97.1% ± 1.7%) and those from group B (91.3% ± 2.8%; hazard ratio, 0.40; χ^2, 22.1; $p = 0.004$ by log-rank test; Fig 3).

Noncardiac-related death was also found to be significantly different between groups (1.89/100 patient-years in group A versus 3.70/100 patient-years in group B; 49% relative risk reduction; $p = 0.03$), and Kaplan-Meyer analysis showed a significant difference between groups: 94.6% ± 2.4% for group A versus 88.3% ± 3.5% for group B (hazard ratio, 0.41; χ^2, 19.6; $p = 0.02$ by log-rank test; Fig 3).

Analysis of Chronic Obstructive Pulmonary Disease Exacerbations

During follow-up, BB administration did not increase COPD exacerbation, which was recorded in 46 of 104 patients (44.2%) in group A versus 45 of 104 patients (43.3%) in group B ($p = 0.99$). Also, at person-time analysis, the incidence of COPD exacerbations was sim-

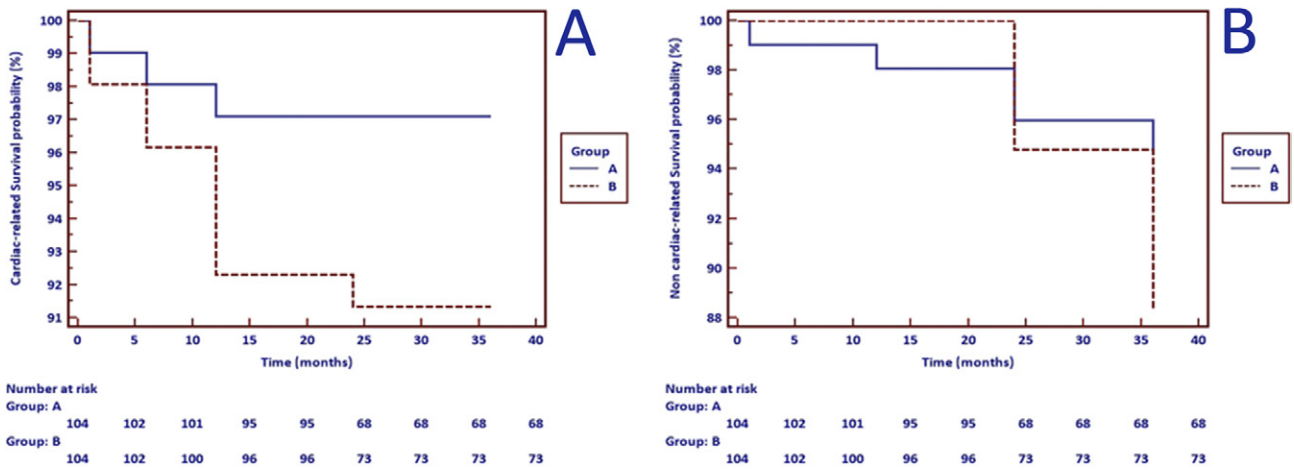

Fig 3. Kaplan-Meyer analysis of (A) cardiac-related and (B) noncardiac related survival in patients with chronic obstructive pulmonary disease (group A; solid line) receiving or (group B; dashed line) not receiving β-blockers after coronary artery bypass graft surgery.

ilar between groups: 17.4 events/100 patient-years for group A versus 16.7 events/100 patient-years for group B (4% relative risk increase; $p = 0.47$). Finally, Kaplan-Meyer analysis showed similar COPD exacerbation-free survival: 54.3% ± 4.9% in group A versus 55.8% ± 4.9% in group B (hazard ratio, 1.05; χ^2, 10.8; $p = 0.78$ by log-rank test; Fig 4).

Comment

This is an observational study to investigate the impact of BB therapy on mortality late after CABG in patients with COPD. The main finding was that BB therapy has a beneficial effect on survival after coronary surgery in patients with COPD.

At present, drugs found to reduce morbidity and mortality among COPD patients include statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers [30]. Beneficial effects of BB therapy in the field of cardiovascular disease are clearly established [10–19], but, on the other hand, BB administration in COPD patients is still debated, mainly because of the theoretical respiratory side effects. Interestingly, in a large observational study [5], the association of BB usage with all-cause mortality and risk of exacerbation of COPD did not change in patients taking two or more pulmonary drugs or inhaled β_2-sympathomimetics or anticholinergic agents; therefore, inhaled pulmonary medication seems not to interfere with the results of BB administration. Unfortunately, that large, population-based study [5] did not perform a subanalysis of patients who underwent cardiovascular surgery even if they accounted for something less than 20% of their cohort.

Other studies on animal models have previously shown that BB can upregulate β_2-receptors in the lung and thus even improve the bronchodilator responsiveness and effectiveness of inhaled β_2-sympathomimetics [31]. This effect, at first glance, seems a counterintuitive pathway by which BB could exhibit beneficial effects, but the possibility is that upregulation of β_2-adrenoceptors by chronic β-blockade may improve the effectiveness of β_2-agonists [20, 26]. This pathway is still valid independent of β-selectiveness because drugs such as atenolol and bisoprolol have been shown to exert significant β_2-adrenoceptor antagonism even at therapeutic doses, which may result in β_2-adrenoceptor upregulation [5, 20].

To date, direct effects of BB therapy on the natural history of COPD have not been clearly assessed, but recent animal experiments involving asthmatic mice receiving BB showed a significant reduction in the production of mucin from the airway epithelial cells and significantly lower values of inflammatory cytokines [32]. This resulted in a surprising, direct respiratory beneficial effect of β-blockade. From the latter, the idea that BB can exert an important effect on the airway epithelium itself is supported from the evidence of an increased number of β_2-adrenoceptors found in the airway epithelial cells, and from the fact that the overexpression of these receptors in the airway epithelium was found to reduce airway hyperresponsiveness [32, 33], which is characteristic of COPD.

In these settings, the beneficial effects of BB may extend beyond the classic, well-known cardiovascular field, directly influencing the clinical pattern of COPD, and resulting in lower rates of both cardiovascular and respiratory events, finally leading to improved all-cause mortality. Such a result is consistent with our finding of improved overall survival. Indeed, the incidence of all-cause mortality in COPD patients after CABG is reported as ranging between 4 and 9 per 100 patient-years [7]. Accordingly, in our study the incidence of mortality among COPD patients late after coronary surgery was 5 per 100 patient-years, but that rate was nearly halved (3 per 100 patient-years) in patients receiving BB compared with patients who did not (7 per 100 patient-years).

The well-known beneficial effects of BB on the cardiovascular system are connected to a modulation of the sympathetic nervous system, which mainly results in a reduction of the heart rate, which has been shown

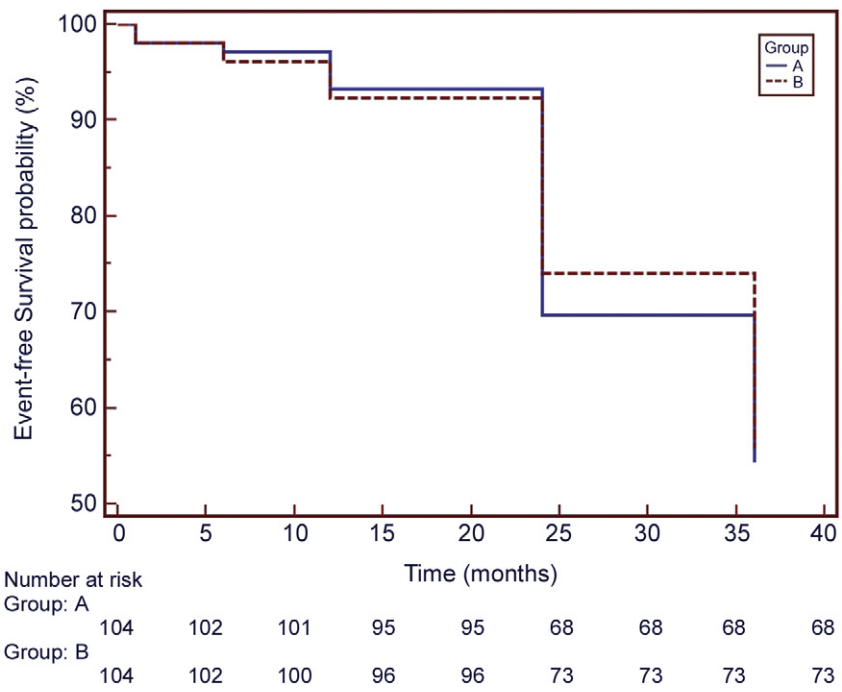

Fig 4. Kaplan-Meyer analysis of event-free survival in patients with chronic obstructive pulmonary disease receiving (group A; solid line) or not receiving (group B; dashed line) β-blockers after coronary artery bypass graft surgery.

to be an independent predictor of all-cause mortality [34]. Accordingly, cardioversion of perioperative atrial fibrillation (showed by 22% of patients) was more likely to occur among patients receiving BB. However, such an impressive result of BB in reducing mortality from any cause among COPD patients may reflect not only its prevalent cardiovascular effects (the heart rate control itself, indeed, has been shown to potentially diminish the negative systemic effects related to COPD [23]), but also the supposed effect of improved β_2-agonism; this issue, in fact, can account for a benefit in COPD-related survival, thus improving the overall survival of such patients. This was confirmed in our study in the statistically significant reduction of both cardiac-related and noncardiac-related mortality rates found in the group of patients receiving BB therapy.

A review and meta-analysis of 22 randomized controlled trials on the use of cardioselective BB in patients with COPD in fact showed no change in FEV_1 or respiratory symptoms compared with placebo, and did not affect the FEV_1 treatment response to β_2-agonists [26]. In addition, no significant change was found for those patients with severe chronic airways obstruction, for those with a reversible obstructive component, or for those with concomitant cardiovascular disease [26]. Therefore, accumulated evidence clearly indicates the safety of BB administration in COPD patients, and the experimental models, on the other hand, strongly suggest a novel pathway (β_2-receptor upregulation) through which BB can exert a beneficial effect on the respiratory function that can impact the well-established cardiovascular beneficial effects, thus improving overall survival.

Limitations

The main limitation of the present study is its retrospective nature. Despite the use of propensity score analysis to control for selection bias, eventually unidentified confounders may have influenced the results.

Furthermore, even if exclusion criteria and propensity matching led to balanced cohorts, the nonrandomized design exposed the present study to some selection bias because of the indications used to prescribe BB therapy.

Conclusions

Given the cornerstone relevance of BB administration after CABG [15–19], the absence of adverse respiratory effects of such therapy [24–26], and the demonstrated worse outcome of COPD patients after CABG [15–19], cardioselective BB should not be routinely withheld from patients with COPD. In addition, a direct beneficial effect of BB therapy on the respiratory system is plausibly supposed [5, 20, 30–32], and if confirmed can account for an amelioration of respiratory symptoms that could synergistically improve all-cause survival of such patients.

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INVITED COMMENTARY

The leading cause of death in the United States remains heart disease. Coronary artery bypass graft (CABG) surgery remains a mainstay therapy in the treatment of this condition. Patients who have coronary artery disease are often smokers and therefore frequently have a concurrent diagnosis of chronic obstructive pulmonary disease (COPD). Published incidence of patients undergoing CABG who also have COPD range from 4% to 27%. Because of the possible bronchoconstrictive effects of beta-blockers, the use of these agents in patients with COPD undergoing CABG has previously been contraindicated. It is well known that the use of beta-blockers in patients undergoing CABG provide both a survival benefit and a protective effect to the development of postoperative atrial fibrillation.

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