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A post hoc pooled analysis of exacerbations among US participants in randomized controlled trials of tiotropium

Antonio Anzueto [a,*], Dennis E. Niewoehner [b], Inge Leimer [c], Fee Rühmkorf [d], Bartolome R. Celli [e], Marc Decramer [f], Donald P. Tashkin [g]

[a] *Pulmonary/Critical Care, University of Texas Health Science Center, 111E, 7400 Merton Minter Blvd, San Antonio, TX 78229, USA*
[b] *Veterans Affairs Medical Center, Pulmonary Section (111N), One Veterans Drive, Minneapolis, MN 55417, USA*
[c] *Global BCA, Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Strasse 173, D-55216 Ingelheim am Rhein, Germany*
[d] *Medical Affairs, Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Strasse 173, D-55216 Ingelheim am Rhein, Germany*
[e] *Pulmonary Division, Brigham and Women's Hospital, 75 Francis Street, PBB Clinics 3, Boston, MA 02115, USA*
[f] *Respiratory Division, Katholieke Universiteit Leuven, University Hospital, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium*
[g] *Department of Medicine, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Los Angeles, CA 90095-1690, USA*

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Summary
Background: Exacerbations are a defining outcome of chronic obstructive pulmonary disease (COPD). We evaluated the effect of tiotropium on COPD exacerbations and related hospitalizations among patients from the USA enrolled in clinical trials.
Methods: Data were pooled from six randomized, double-blind, placebo-controlled trials (6 to ≥12 months' duration) of tiotropium in patients with COPD. Exacerbations were defined retrospectively as an increase in or new onset of >1 respiratory symptom lasting for ≥3 days and

* Corresponding author. Tel.: +1 210 617 5256; fax: +1 210 949 3006.
E-mail address: anzueto@uthscsa.edu (A. Anzueto).

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requiring treatment with systemic corticosteroids and/or antibiotics. Time to first exacerbation or hospitalization and exacerbation rates were analyzed at 6 months, and at 1 year for studies ≥1 year.

Results: In total, 4355 patients (tiotropium, 2268, placebo, 2087; mean age 66.5 years; forced expiratory volume in 1 s [FEV_1] 1.03 L [35.5% predicted]) were analyzed at 6 months and 2455 at 1 year (tiotropium 1317, placebo 1138; mean age 65.5 years; FEV_1 1.03 L [37.0% predicted]). Tiotropium delayed time to first exacerbation or first hospitalized exacerbation at 6 months (hazard ratios [HRs], 0.80, 0.65, respectively; $p < 0.001$ vs placebo) and 1 year (HRs, 0.73 and 0.55; $p < 0.001$ vs placebo) and reduced exacerbation rates and hospitalization rates (6 months: HRs, 0.79, 0.64; 1 year: HRs, 0.78, 0.56, respectively; all $p < 0.01$ vs placebo). Tiotropium significantly reduced exacerbations, irrespective of inhaled corticosteroid use at baseline. Tiotropium was not associated with an increased risk of cardiac-related events.

Conclusions: Tiotropium significantly reduced the risk and rates of exacerbations and hospitalizations among US patients with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of disability and death worldwide [1—3] and is characterized by a progressive decline in lung function and periodic exacerbations of respiratory symptoms [4]. As COPD progresses, the exacerbation incidence increases [5,6]; however, patients with any Global Initiative for Chronic Obstructive Lung Disease stage may experience exacerbations that impact on their life, health status, and prognosis [7]. Frequent exacerbations are associated with a more rapid decline in lung function (forced expiratory volume in 1 s [FEV_1]) [5,8], diminished patient quality of life [9], and increased mortality [10]. Death rates for patients hospitalized for a COPD exacerbation reportedly range from 4 to 30% [11]. COPD exacerbations also incur a substantial health economic burden [12—14]. Hospitalization due to an exacerbation is particularly costly [15], and has been estimated to consume 68% of medical expenses for patients with COPD [16]. Consequently, preventing a COPD exacerbation is an important management goal [17].

Tiotropium reduced COPD exacerbations in several clinical trials when compared with placebo [18—20] and salmeterol [21]. However, the actual treatment received by patients with a COPD exacerbation (particularly in hospital or emergency room [ER] settings) frequently deviates from best practice recommendations, creating variation between countries and treatment centers [22—25]. The likelihood of hospitalization for a COPD exacerbation may also show regional discrepancies [26—28].

Country-specific data on the risk and rates of exacerbations in COPD patients receiving long-term maintenance therapy will help to guide healthcare decisions relating to additional COPD treatment and resource utilization. Exacerbation rates for patients receiving the same maintenance treatment may vary between countries due to differences in healthcare systems. By analyzing the data for one country only, this helps to remove some of this potential bias.

We conducted a pooled analysis to evaluate the effect of tiotropium on COPD exacerbations and hospitalizations in patients resident in the United States based on collated data from previously published trials.

Methods

Study design

This retrospective, non-prespecified pooled analysis included all Boehringer Ingelheim/Pfizer-sponsored placebo-controlled trials of ≥6 months' duration that enrolled patients from the United States, assessed tiotropium (SPIRIVA®, Boehringer Ingelheim International GmbH, Ingelheim, Germany, and Pfizer Inc, New York, USA) in patients with COPD, and included exacerbations as an outcome. Completed trials with full reports available from December 31, 2010, were included. Six trials met these criteria (e-Table 1) [18—20,29—31].

Concomitant medication was permitted in all studies (e-Table 1), including all respiratory medications except other inhaled anticholinergics in two studies [19,20]. In three studies, other inhaled anticholinergics or long-acting β_2-agonist (LABA) medication use was not permitted [18,29,31]. Patients could use a salbutamol metered-dose inhaler as needed for symptom relief; theophylline, inhaled corticosteroid (ICS) monotherapy, or oral steroids (up to the equivalent of prednisolone, 10 mg/day).

For this pooled analysis, the following exacerbation definition was applied: an increase in, or new onset of >1 respiratory symptom (cough, sputum, wheezing, dyspnea), lasting for ≥3 days, and requiring treatment with systemic corticosteroids and/or antibiotics. Exacerbations requiring hospitalization were collated separately.

Analyses were performed at 6 months (all trials) and at 1 year for trials of ≥1-year duration.

Patients

Inclusion criteria were a clinical diagnosis of COPD, age ≥40 years, smoking history of ≥10 pack-years, postbronchodilator FEV_1 of ≤65—70% predicted, and FEV_1/forced vital capacity of ≤70%.

Key exclusion criteria are listed online in e-Table 2. All studies excluded patients with a history/diagnosis of asthma.

Assessments

Patient baseline demographics, lung function, pulmonary medication use, and concomitant disease prevalence were recorded. COPD exacerbations and hospitalized exacerbations were characterized by time to first event and number.

Safety evaluations included collating of adverse events (AEs), serious AEs, and all-cause mortality.

Statistical analyses

Exacerbations with onset during treatment (or until day of last contact for the Veterans' Affairs Medical Center study) [19] and ≤6 months or 1 year since treatment start were included in the pooled analysis. Follow-up of dropout patients was only performed in study number 205.266.

Time to first exacerbation/first hospitalized exacerbation and associated hazard ratios (HRs) and 95% confidence intervals (CIs) for tiotropium/placebo for the risk of an event were calculated using Cox regression with trial as the stratification variable. The analyses were rerun adding the interaction term *trial * treatment*.

Exacerbation rate ratios (RRs) were generated by comparing the number of exacerbations between study groups using Poisson regression analysis and correcting for treatment exposure and overdispersion. Trial was included as a stratification variable. The analyses were rerun adding the interaction term *trial * treatment*.

Subgroup analyses were performed for both time to event and number of event, with use of "ICS either alone or with a LABA" and "LABA either alone or with an ICS" at baseline as subgroup variables. The analyses were rerun adding the interaction term *subgroup * treatment*. The LABA subgroup

Table 1 Patient baseline characteristics.

Analysis	Tiotropium		Placebo		Total	
	≥6 months	≥1 year	≥6 months	≥1 year	≥6 months	≥1 year
Patients, *n*	2268	1317	2087	1138	4355	2455
Age (SD), y	66.3 (8.5)	65.5 (8.2)	66.7 (8.5)	65.6 (8.3)	66.5 (8.5)	65.5 (8.2)
Male sex, %	78.7	65.3	78.9	63.4	78.8	64.4
Smoking status						
Current smoker, %	31.0	32.1	30.5	30.5	30.7	31.4
Smoking history (SD), pack-years	63.9 (33.0)	61.6 (31.0)	64.2 (34.5)	60.3 (32.3)	64.1 (33.7)	61.0 (31.7)
COPD duration (SD), y	10.4 (8.8)	9.2 (7.4)	10.4 (9.0)	9.2 (7.3)	10.4 (8.9)	9.2 (7.3)
BMI (kg/m^2), %						
<20	7.5	7.4	9.3	9.7	8.4	8.4
≥20—25	31.4	33.3	29.7	31.6	30.6	32.5
≥25—30	33.9	33.3	34.6	34.6	34.2	33.9
≥30	27.2	26.0	26.4	24.0	26.8	25.1
FEV_1 (SD), L	1.04 (0.41)	1.04 (0.41)	1.02 (0.41)	1.02 (0.42)	1.03 (0.41)	1.03 (0.42)
FEV_1 (SD), % predicted	35.8 (12.6)	37.3 (13.0)	35.2 (12.5)	36.6 (12.8)	35.5 (12.6)	37.0 (12.9)
FVC (SD), L	2.31 (0.77)	2.41 (0.82)	2.30 (0.78)	2.41 (0.85)	2.31 (0.77)	2.41 (0.84)
FVC (SD), % predicted	62.7 (18.5)	68.4 (18.4)	62.1 (18.4)	68.7 (18.6)	62.4 (18.4)	68.6 (18.5)
FEV_1/FVC (SD)	0.45 (0.12)	0.44 (0.11)	0.45 (0.11)	0.43 (0.11)	0.45 (0.11)	0.43 (0.11)
GOLD stage, %						
I + II	15.6	19.4	14.5	17.6	15.1	18.5
III	47.5	47.5	46.6	46.6	47.0	47.1
IV	36.2	32.0	37.9	33.9	37.0	32.9
Pulmonary medicine use, %	91.5	88.3	92.4	89.6	91.9	88.9
SAAC	64.2	53.3	65.9	55.3	65.0	54.2
SABA	82.1	76.7	84.4	78.9	83.2	77.7
LABA	35.6	34.2	38.1	38.7	36.8	36.3
ICS	54.6	49.4	53.9	50.4	54.2	49.9
LABA use alone	7.4	7.2	9.2	7.9	8.3	8.0
ICS use alone	26.4	22.4	25.0	20.6	25.7	21.5
LABA + ICS use: free or fixed dose	28.2	27.0	28.8	29.8	28.5	28.3
LABA + ICS use: fixed dose	9.7	15.4	10.1	17.3	9.9	16.3
Xanthines	15.3	15.3	13.2	13.7	14.3	14.6

No patients were using long-acting anticholinergics at baseline.
BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; SAAC: short-acting anticholinergic; SABA: short-acting β_2-agonist; SD: standard deviation.

analysis was restricted to trials allowing LABAs as concomitant medication and included patients receiving combined LABA/ICS.

Adverse event incidence rates were computed as the number of patients experiencing an event (during treatment + 30 days, censored at day 182 [6 months] or 365 [1 year]), divided by the person-years at risk. Time at risk was defined as minimum (182 or 365, time till death, time of exposure + 30 days) for subjects not experiencing an event, and time from start of treatment to onset for subjects who experienced an event at day 182/365, whichever came earlier. To measure the effect strength, incidence ratios for tiotropium vs placebo were calculated using the Cochran–Mantel–Haenszel test, stratified by study. Rate ratios <1 indicated a decreased risk with tiotropium; an RR > 1 indicates a decreased risk with placebo.

Results

Baseline characteristics

A total of 4355 patients (tiotropium, 2268/placebo, 2087) were included in the analysis of data from studies ≥6 months' duration; 2455 patients (tiotropium, 1317/placebo 1138) were also included in analysis of data from studies ≥1-year duration. Baseline characteristics (Table 1) and baseline comorbidities (e-Table 3) were balanced between the tiotropium and placebo groups in both analyses. e-Table 4 shows the number of patients in each study.

Time to first exacerbation and hospitalized exacerbation

Tiotropium delayed the time to first exacerbation and time to first hospitalized exacerbation, corresponding to reduced risks of both events by 6 months (HR, 0.80; 95% CI, 0.71–0.89 and HR, 0.65; 95% CI, 0.51–0.83, respectively; both $p < 0.001$) (Fig. 1A and B). There was no *trial* * *treatment* interaction ($p > 0.58$ and $p > 0.86$, respectively).

A similar pattern was seen with events occurring by 1 year, with tiotropium delaying time to first exacerbation (HR, 0.73; 95% CI, 0.65–0.83; $p < 0.001$) (Fig. 1C) and hospitalized exacerbations (HR, 0.55; 95% CI, 0.42–0.73; $p < 0.001$) (Fig. 1D). There was no *trial* * *treatment* interaction ($p > 0.62$ and $p > 0.83$, respectively).

Table 2 shows the analysis of time to first COPD exacerbation/exacerbation leading to hospitalization (events occurring until 6 months and 1 year) according to treatment group and LABA or ICS use at baseline. There were no *subgroup* * *treatment* interactions ($p > 0.1$). At both time points, tiotropium significantly reduced the number of exacerbations and hospitalized exacerbations vs placebo, irrespective of whether patients were receiving ICS at baseline. Tiotropium also reduced exacerbations and hospitalized exacerbations vs placebo by 6 months and 1 year in the LABA use or no LABA use subgroups, although some subgroup comparisons did not reach statistical significance.

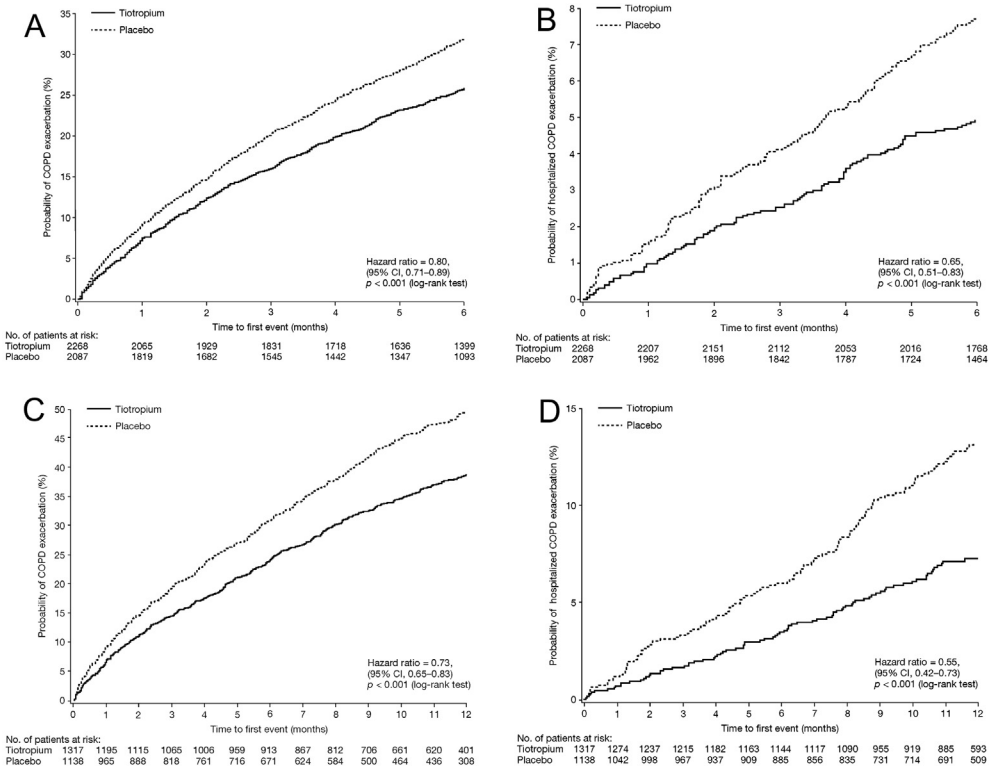

Figure 1 Cumulative incidence for A) Time to first exacerbation until 6 months for studies of ≥6 months' duration; B) Time to first hospitalized exacerbation until 6 months for studies of ≥6 months' duration; C) Time to first exacerbation until 1 year for studies of ≥1-year duration; D) Time to first hospitalized exacerbation until 1 year for studies of ≥1-year duration. CI: confidence interval; COPD, chronic obstructive pulmonary disease.

Table 2 Analysis of time to first exacerbation and first hospitalized exacerbation (Cox regression) for patients using ICS or LABA at baseline.

	Subgroup	Tiotropium		Placebo		Subgroup by treatment interaction *p*-value	Tiotropium/placebo	
		Number of patients treated	Number of patients with event	Number of patients treated	Number of patients with event		HR (95% CI)	*p*-Value
By 6 months (cut-off day 182)[a]								
Time to first exacerbation analysis	ICS use	1238	363	1124	398	0.6312	0.76 (0.66—0.88)	0.0002
	No ICS use	1030	210	963	230		0.81 (0.67—0.98)	0.0268
	LABA use	768	227	763	279	0.3451	0.74 (0.62—0.88)	0.0008
	No LABA use	913	214	919	247		0.84 (0.70—1.01)	0.0572
Time to first hospitalized exacerbation analysis	ICS use	1238	71	1124	98	0.9992	0.62 (0.46—0.84)	0.0022
	No ICS use	1030	36	963	52		0.62 (0.41—0.95)	0.0296
	LABA use	768	50	763	66	0.8127	0.71 (0.49—1.03)	0.0694
	No LABA use	913	43	919	63		0.67 (0.45—0.98)	0.0409
By 1 year (cut-off day 365)								
Time to first exacerbation analysis	ICS use	651	261	573	288	0.1214	0.67 (0.56—0.79)	<0.0001
	No ICS use	666	204	565	198		0.82 (0.67—0.99)	0.0409
	LABA use	422	173	412	211	0.2898	0.67 (0.54—0.81)	<0.0001
	No LABA use	345	110	355	131		0.79 (0.62—1.02)	0.0755
Time to first hospitalized exacerbation analysis	ICS use	651	49	573	75	0.5593	0.51 (0.35—0.73)	0.0002
	No ICS use	666	36	565	48		0.60 (0.39—0.93)	0.0211
	LABA use	422	42	412	56	0.1314	0.66 (0.44—0.99)	0.0431
	No LABA use	345	13	355	33		0.37 (0.19—0.70)	0.0024

HR and *p*-value based on subgroup restricted Cox regression with treatment as covariate. Subgroup by treatment interaction *p*-value based on Cox regression adjusted for treatment, subgroup and subgroup-by-treatment interaction.
CI: confidence interval; HR: hazard ratio; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist.
[a] In trial 205.266, exacerbations until the date of last contact are also included. The LABA as well as the ICS subgroup also included patients on LABA/ICS combination.

Rates of exacerbations and hospitalized exacerbations

Tiotropium significantly reduced the rate of exacerbations and hospitalized exacerbations by the 6-month and 1-year time points (Tables 3 and 4).

Table 5 shows the rates of exacerbations and hospitalized exacerbations (events occurring until 6 months and 1 year) according to treatment group and LABA or ICS use at baseline. There were no *subgroup * treatment* interactions ($p > 0.05$). At both time points, tiotropium reduced exacerbations and exacerbations requiring hospitalization compared with placebo, irrespective of whether patients were receiving LABA or ICS at baseline (although some subgroup comparisons did not reach statistical significance).

Table 3 Annual exacerbation rates and RRs at 6 months in studies ≥6 months' duration.[a]

	Tiotropium ($n = 2268$)		Placebo ($n = 2087$)		Tiotropium/placebo	
	Number of events	Rate per patient-year (95% CI)	Number of events	Rate per patient-year (95% CI)	RR (95% CI)	*p*-Value
Exacerbations	786	0.73 (0.60—0.90)	890	0.93 (0.76—1.13)	0.79 (0.70—0.89)	0.0001
Hospitalized exacerbations	124	0.10 (0.05—0.17)	178	0.15 (0.08—0.27)	0.64 (0.46—0.89)	0.0079

RRs were calculated with the use of Poisson regression corrected for treatment exposure and overdispersion with trial as a stratification variable. *p*-Value for *trial * treatment* interaction: 0.3467/0.5782.
CI: confidence interval; RR: rate ratio.
[a] In trial 205.266, exacerbations until the date of last contact are also included.

Table 4 Annual exacerbation rates and RRs at 1 year in studies of ≥1-year duration.

	Tiotropium (n = 1317)		Placebo (n = 1138)		Tiotropium/placebo	
	Number of events	Rate per patient-year (95% CI)	Number of events	Rate per patient-year (95% CI)	RR (95% CI)	p-Value
Exacerbations	750	0.67 (0.60—0.75)	775	0.86 (0.77—0.96)	0.78 (0.68—0.90)	<0.001
Hospitalized exacerbations	98	0.09 (0.06—0.12)	141	0.15 (0.11—0.21)	0.56 (0.38—0.84)	0.005

RRs were calculated with the use of Poisson regression corrected for treatment exposure and overdispersion with trial as a stratification variable. p Value for *trial* * *treatment* interaction: 0.5619/0.9642.
CI: confidence interval; RR: rate ratio.

Adverse events

Table 6 shows the most common AEs reported in this pooled analysis. The total incidence of AEs was 58.7% in the tiotropium group compared with 56.3% in the placebo group (RR, 0.88; 95% CI, 0.81—0.95). The most frequently specified AEs were "COPD" (21.6% vs 25.3%; RR, 0.72; 95% CI, 0.63—0.81) and "upper respiratory tract infection" (12.7% vs 10.1%; RR, 0.98; 95% CI, 0.82—1.17).

The incidence of serious AEs was 19.1% with tiotropium group and 20.6% with placebo (RR, 0.86; 95% CI, 0.75—0.98) (Table 7). The most frequent serious AE was COPD (114 [5.0%] for tiotropium and 173 [8.3%] for placebo; RR, 0.55; 95% CI, 0.44—0.70). The risk of serious cardiac events was

Table 5 Exacerbation rates and RRs for patients using ICS or LABA at baseline.

		Tiotropium		Placebo		Subgroup by treatment interaction p-value	Tiotropium/placebo	
		Number of events	Adjusted rate of events per patient-year	Number of events	Adjusted rate of events per patient-year		RR (95% CI)	p-Value
By 6 months (cut-off day 182)[a]								
Exacerbations	ICS use	1238	0.86 (0.77—0.96)	1124	1.14 (1.03—1.27)	0.4967	0.75 (0.65—0.88)	0.0002
	No ICS use	1030	0.58 (0.50—0.67)	963	0.70 (0.61—0.81)		0.82 (0.67—1.01)	0.0602
	LABA use	768	0.88 (0.77—1.00)	763	1.15 (1.02—1.30)	0.5285	0.76 (0.64—0.91)	0.0034
	No LABA use	913	0.66 (0.58—0.77)	919	0.80 (0.70—0.91)		0.83 (0.68—1.01)	0.0606
Exacerbations leading to hospitalization	ICS use	1238	0.14 (0.10—0.19)	1124	0.23 (0.18—0.30)	0.9278	0.61 (0.41—0.89)	0.0109
	No ICS use	1030	0.09 (0.06—0.13)	963	0.14 (0.10—0.20)		0.62 (0.37—1.07)	0.0861
	LABA use	768	0.15 (0.11—0.21)	763	0.23 (0.17—0.30)	0.8358	0.65 (0.42—1.00)	0.0519
	No LABA use	913	0.12 (0.09—0.17)	919	0.18 (0.13—0.23)		0.69 (0.45—1.08)	0.1079
By 1 year (cut-off day 365)								
Exacerbations	ICS use	651	0.77 (0.68—0.88)	573	1.10 (0.98—1.25)	0.0586	0.70 (0.59—0.84)	<0.0001
	No ICS use	666	0.57 (0.49—0.66)	565	0.62 (0.53—0.72)		0.92 (0.74—1.15)	0.4609
	LABA use	422	0.76 (0.65—0.89)	412	1.04 (0.90—1.20)	0.3581	0.74 (0.60—0.91)	0.0043
	No LABA use	345	0.54 (0.44—0.67)	355	0.63 (0.52—0.76)		0.87 (0.65—1.15)	0.3248
Exacerbations leading to hospitalization	ICS use	651	0.10 (0.07—0.15)	573	0.20 (0.14—0.27)	0.6453	0.52 (0.31—0.87)	0.0131
	No ICS use	666	0.07 (0.05—0.12)	565	0.12 (0.08—0.18)		0.63 (0.33—1.19)	0.1518
	LABA use	422	0.12 (0.08—0.19)	412	0.19 (0.13—0.26)	0.2194	0.67 (0.39—1.14)	0.1380
	No LABA use	345	0.05 (0.02—0.10)	355	0.13 (0.08—0.20)		0.36 (0.15—0.85)	0.0200

RRs were calculated with the use of Poisson regression corrected for treatment exposure and overdispersion with subgroup as a stratification variable. Subgroup by treatment interaction p-value is based on the same Poisson regression including subgroup-by-treatment interaction in addition.
CI: confidence interval; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; RR: rate ratio.
[a] In trial 205.266, exacerbations until the date of last contact are also included. The LABA subgroup also included patients on LABA/ICS combination.

Table 6 AEs: incidence and rate (≥5% in any group) by MedDRA SOC and PT.

SOC/PT	Tiotropium (n = 2268)		Placebo (n = 2087)		RR (95% CI)
	Incidence (%)	Rate per 100 patient-years	Incidence (%)	Rate per 100 patient-years	
Total AEs	58.7	152.60	56.3	156.75	0.88 (0.81—0.95)[a]
Cardiac	6.0	8.31	7.0	10.76	0.78 (0.61—0.98)[a]
Gastrointestinal disorders	16.5	25.72	11.7	19.02	1.25 (1.06—1.47)[a]
General disorders and administration-site conditions	10.1	14.56	8.1	12.63	1.00 (0.82—1.22)
Infections and infestations	31.3	54.67	29.5	55.43	0.91 (0.81—1.01)
Sinusitis	5.1	7.13	4.1	6.27	1.04 (0.78—1.37)
Upper respiratory tract infection	12.7	18.88	10.1	16.07	0.98 (0.82—1.17)
Injury, poisoning, and procedural complications	6.9	9.75	5.4	8.29	1.09 (0.85—1.39)
Musculoskeletal and connective tissue disorders	10.5	15.47	7.8	12.25	1.17 (0.96—1.43)
Nervous system disorders	8.6	12.38	8.4	13.31	0.82 (0.67—1.00)[a]
Respiratory, thoracic, and mediastinal disorders	30.5	52.42	33.8	65.20	0.76 (0.69—0.85)[a]
COPD	21.6	34.20	25.3	45.03	0.72 (0.63—0.81)[a]

Rate per 100 patient-years is derived as 100 * (number of patients with event)/sum of time at risk. For each type of AE, time at risk is time till onset of AE for patients with AE or time on treatment + 30 days for patients without AE. RRs were calculated based on a Cochran—Mantel—Haenszel test stratified by trial.

AE: adverse event; CI: confidence interval; COPD: chronic obstructive pulmonary disease; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RR: rate ratio; SOC: system organ class.

[a] Ratio significantly different from 1.

lower with tiotropium than with placebo (3.5% vs 4.9%; RR, 0.67; 95% CI, 0.50—0.90). The fatality incidence was the same (73 [3.2%] for tiotropium and 67 [3.2%] for placebo, RR, 0.98; 95% CI, 0.70—1.36). The most frequent cause of deaths was COPD (8 [0.4%] for tiotropium and 14 [0.7%] for placebo; RR, 0.53; 95% CI, 0.22—1.24).

Discussion

We conducted a pooled analysis of exacerbations from randomized, double-blind, placebo-controlled trials at both ≥6 months and ≥1 year, in the United States. Tiotropium significantly delayed the time to an exacerbation and time to a hospitalized exacerbation at both time points, indicating a reduced risk of both events ($p < 0.001$). Tiotropium also significantly reduced the rate of exacerbations and hospitalized exacerbations at both ≥6 months ($p = 0.0001$ and $p = 0.0079$, respectively) and ≥1 year ($p < 0.001$ and $p = 0.005$, respectively). Supporting these data, a meta-analysis of several trials previously showed that tiotropium reduces the risk of COPD exacerbations, including those leading to hospital admission [32].

For patients with moderate to very severe COPD, current guidelines recommend regular maintenance treatment with a long-acting bronchodilator [33]. Aside from the reported benefits of tiotropium (for up to 4 years of treatment) [20], a reduction in COPD exacerbations vs placebo has also been shown with salmeterol over 3 years (alone or combined with fluticasone propionate) [34] and indacaterol over 12—52 weeks of treatment [35—39]. No significant benefit on moderate to severe exacerbations has been demonstrated for formoterol, although a trial has yet to be designed to examine this outcome specifically [40,41]. While no single long-acting bronchodilator is recommended over another in current guidelines [33,42,43], the Prevention Of Exacerbations with Tiotropium in COPD (POET-COPD®) trial (N = 7376) demonstrated that tiotropium is significantly more effective than salmeterol in reducing risk and annual exacerbation rates in moderate to very severe disease, irrespective of concomitant ICS use [21]. Current guidelines support adding ICS to bronchodilator treatment in patients with severe COPD and a history of repeated exacerbations [33,42], although when to select combination therapy over monotherapy is not clearly established [43]. The long-acting phosphodiesterase type 4 inhibitor, roflumilast, has been shown to reduce exacerbations significantly in patients with severe COPD and a history of chronic bronchitis and at least one exacerbation in the previous year, regardless of whether they were receiving a LABA or a short-acting anticholinergic [44].

Our analysis of time to first event by treatment group showed that tiotropium reduced COPD exacerbations and hospitalized exacerbations at 6 months and 1 year in both the ICS use and no ICS use subgroups. However, the rates of exacerbations and hospitalized exacerbations were not significantly different to placebo in the no ICS subgroup. In patients receiving long-acting bronchodilators at baseline,

Table 7 Serious and fatal AEs incidence and rate (≥1% in any group) by MedDRA SOC and PT.

SOC/PT	Tiotropium (n = 2268)		Placebo (n = 2087)		RR (95% CI)
	Incidence (%)	Incidence per 100 patient-years	Incidence (%)	Incidence per 100 patient-years	
Total serious AEs	19.1	28.63	20.6	34.05	0.86 (0.75–0.98)[a]
Cardiac disorders	3.5	4.86	4.9	7.44	0.67 (0.50–0.90)[a]
Cardiac failure congestive	0.7	0.90	1.3	1.99	0.50 (0.27–0.93)[a]
Gastrointestinal disorders	1.8	2.41	1.7	2.57	0.95 (0.60–1.48)
General disorders and administration site conditions	1.6	2.16	1.1	1.71	1.26 (0.76–2.11)
Infections and infestations	4.5	6.21	5.9	9.01	0.72 (0.55–0.93)[a]
Pneumonia	2.4	3.26	3.4	5.17	0.64 (0.45–0.91)[a]
Metabolism and nutrition disorders	1.0	1.32	0.9	1.35	1.00 (0.53–1.88)
Neoplasms benign, malignant, and unspecified	3.0	4.12	2.6	3.94	1.06 (0.74–1.51)
Nervous system disorders	1.5	2.11	1.5	2.21	0.97 (0.60–1.59)
Respiratory, thoracic, and mediastinal disorders	6.9	9.63	9.2	14.20	0.69 (0.56–0.86)[a]
COPD	5.0	6.97	8.3	12.71	0.55 (0.44–0.70)[a]
Vascular disorders	1.1	1.56	0.9	1.35	1.18 (0.66–2.11)
Total with fatal AEs[b]	3.2	4.42	3.2	4.80	0.98 (0.70–1.36)
Respiratory, thoracic, and mediastinal disorders[b]	0.8	1.14	1.1	1.71	0.73 (0.40–1.33)

Rate per 100 patient-years is derived as 100 * (number of patients with event)/sum of time at risk. For each type of AE, time at risk is time till onset of AE for patients with AE or time on treatment + 30 days for patients without AE. RRs were calculated based on a Cochran–Mantel–Haenszel test stratified by trial.

AE: adverse event; CI: confidence interval; COPD: chronic obstructive pulmonary disease; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RR: rate ratio; SOC: system organ class.

[a] Ratio significantly different from 1.

[b] Incidence of fatal AEs.

tiotropium reduced time to first exacerbation and hospitalized exacerbations at 6 months and 1 year (with p-values < 0.05, except for hospitalized exacerbations, $p = 0.0694$); this subgroup had a relatively small sample size (patients from the Understanding Potential Long-term Impacts on Function with Tiotropium [UPLIFT®] and 205.266 studies only). Our results suggest that the reduction in exacerbations with tiotropium vs placebo was not consistently related to the use of LABA and/or ICS therapy at baseline.

The data reported here are specific to patients in the United States and are important for health professionals and insurers based in this country. This is because they provide an insight into the proportion of patients likely to experience exacerbations (including severe events that require inpatient treatment), while receiving guideline-recommended, long-term maintenance therapy for COPD. Reducing the impact of COPD exacerbations is of major concern in the United States; in 2009 alone, there were 698,836 hospitalizations for COPD in non-Federal hospitals, with the average length of stay being 4.7 days [45]. A retrospective, cross-sectional analysis of managed-care administrative claims data in the United States (N = 42,565 for patients with COPD in the commercial claims dataset) found that 13.9% of patients experiencing at least one COPD exacerbation were managed as an inpatient and, within that group, 4.5% of patients had an ER visit. Exacerbation frequency and healthcare service use has also been shown to increase with disease complexity [46]. The huge burden of COPD exacerbations is similarly observed in other countries: in the United Kingdom, for example, up to 10% of all hospital admissions have been attributed to COPD, totaling 100,000 per year, with an average length of stay of 1 week [47]. An economic analysis of data from a large-scale international survey found that the majority (52–84%) of direct costs were attributable to hospitalization in five of the seven nations studied, including the United States. Regional differences in healthcare practices will affect hospitalization rates for exacerbations; for example, ER therapy may be more aggressive in Canada than in the United States, which may reduce subsequent admissions [24,25]; in the United Kingdom, early discharge rates have increased through the provision of "hospital-at-home" care services [42], a concept initiated in France in the 1960s [48].

In general, a previous COPD exacerbation (especially a hospitalized exacerbation) is a strong predictor of the likelihood of a subsequent exacerbation [7], while age, male gender, and certain comorbid conditions are also associated with an increased risk of death and rehospitalization in

patients discharged after a severe COPD exacerbation [49]. In the United States, the 30-day readmission rate for COPD has been estimated at around 7% (20% for all causes) [45], with a 1-year readmission rate of approximately 25% and 1-year mortality at approximately 21% [45].

Evaluating the likelihood of rehospitalization following a COPD exacerbation (and other risk factors for subsequent events) was beyond the scope of our pooled analysis. Further limitations were that our analysis did not examine how COPD exacerbations were managed during the trials, or whether adjustments to concomitant medications influenced the timing or rate of events in the tiotropium or placebo arms. Further research is warranted into the interventions employed in the outpatient and inpatient setting for COPD exacerbations and their correspondence with US-specific and global guideline recommendations. This information would help inform interventions to avoid subsequent exacerbations or to minimize their impact.

Particular strengths from this pooled analysis include the large body of data from several trials using similar entry criteria, a uniform definition of exacerbations, and uniform assessment tools across a broad range of COPD severity. Confining the data to those obtained in the United States also reduces the heterogeneity of healthcare practice patterns and systems that may influence the use of resources by which exacerbations are often defined (e.g., systemic corticosteroid or antibiotic use).

Our assessments of AEs and mortality showed tiotropium to be well tolerated, in accordance with previous analyses [50]. Tiotropium was not associated with an increased risk of cardiac disorders or fatal AEs.

Conclusions

Tiotropium significantly reduced the risk and rate of COPD exacerbations and hospitalized exacerbations in patients with COPD in the United States, supporting current COPD management guidelines, which recommend long-acting bronchodilator therapy for the prevention and management of COPD exacerbations.

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Antonio Anzueto, MD has participated as a speaker in scientific meetings or courses organized and financed by various pharmaceutical companies, including AstraZeneca, Boehringer Ingelheim, Bayer-Schering Pharma, Pfizer, and GlaxoSmithKline (GSK). He has been a consultant for AstraZeneca, Boehringer Ingelheim, Pfizer, GSK, and Bayer-Schering Pharma. Professor Anzueto has been the principal investigator in receipt of research grants, and the University of Texas Health Science Center at San Antonio was paid for participating in multicenter clinical trials sponsored by GSK, Lilly, and the National Institutes of Health.

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Marc Decramer, MD has been part of an Advisory Board for Boehringer Ingelheim, Pfizer, GSK, Novartis, Nycomed, Vectura, and Altana. He has performed consulting work for Boehringer Ingelheim, Pfizer, GSK, AstraZeneca, and Dompé. Professor Decramer has also received lecture fees from these companies (all amounting to $<$10,000 Euros/year). He receives a research grant of 45,000 Euros/year from AstraZeneca.

Inge Leimer, PhD and **Fee Rühmkorf, MD** are employees of Boehringer Ingelheim.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.rmed.2013.07.020.

References

[1] Buist AS, Vollmer WM, McBurnie MA. Worldwide burden of COPD in high- and low-income countries. Part I. The burden of obstructive lung disease (BOLD) initiative. Int J Tuberc Lung Dis 2008;12(7):703—8.

[2] Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006;27(2):397—412.

[3] Menezes AM, Perez-Padilla R, Hallal PC, Jardim JR, Muino A, Lopez MV, et al. Worldwide burden of COPD in high- and low-income countries. Part II. Burden of chronic obstructive lung disease in Latin America: the PLATINO study. Int J Tuberc Lung Dis 2008;12(7):709—12.

[4] Decramer M, Rennard S, Troosters T, Mapel DW, Giardino N, Mannino D, et al. COPD as a lung disease with systemic

consequences — clinical impact, mechanisms, and potential for early intervention. COPD 2008;5(4):235—56.
[5] Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002;57(10):847—52.
[6] Gompertz S, Bayley DL, Hill SL, Stockley RA. Relationship between airway inflammation and the frequency of exacerbations in patients with smoking related COPD. Thorax 2001; 56(1):36—41.
[7] Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363(12): 1128—38.
[8] Kesten S, Celli B, Decramer M, Liu D, Tashkin D. Adverse health consequences in COPD patients with rapid decline in FEV1 — evidence from the UPLIFT trial. Respir Res 2011;12:129.
[9] Spencer S, Jones PW. Time course of recovery of health status following an infective exacerbation of chronic bronchitis. Thorax 2003;58(7):589—93.
[10] Soler-Cataluna JJ, Martinez-Garcia MA, Roman SP, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005;60(11):925—31.
[11] Patil SP, Krishnan JA, Lechtzin N, Diette GB. In-hospital mortality following acute exacerbations of chronic obstructive pulmonary disease. Arch Intern Med 2003;163(10):1180—6.
[12] National Heart LaBI. Morbidity and mortality: 2009 chart book on cardiovascular, lung and blood diseases. Bethesda, MD: National Heart LaBI; 2009.
[13] Ramsey SD, Sullivan SD. The burden of illness and economic evaluation for COPD. Eur Respir J Suppl 2003;41:29s—35s.
[14] Wouters EF. Economic analysis of the confronting COPD survey: an overview of results. Respir Med 2003;97(Suppl. C): S3—14.
[15] Toy EL, Gallagher KF, Stanley EL, Swensen AR, Duh MS. The economic impact of exacerbations of chronic obstructive pulmonary disease and exacerbation definition: a review. COPD 2010;7(3):214—28.
[16] Strassels SA, Smith DH, Sullivan SD, Mahajan PS. The costs of treating COPD in the United States. Chest 2001;119(2): 344—52.
[17] Miravitlles M, Anzueto A, Legnani D, Forstmeier L, Fargel M. Patient's perception of exacerbations of COPD — the PERCEIVE study. Respir Med 2007;101(3):453—60.
[18] Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J 2002;19(2):217—24.
[19] Niewoehner DE, Rice K, Cote C, Paulson D, Cooper Jr JA, Korducki L, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med 2005;143(5):317—26.
[20] Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008;359(15):1543—54.
[21] Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Molken MP, Beeh KM, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med 2011; 364(12):1093—103.
[22] Cydulka RK, Rowe BH, Clark S, Emerman CL, Camargo Jr CA. Emergency department management of acute exacerbations of chronic obstructive pulmonary disease in the elderly: the Multicenter Airway Research Collaboration. J Am Geriatr Soc 2003;51(7):908—16.
[23] Lodewijckx C, Sermeus W, Vanhaecht K, Panella M, Deneckere S, Leigheb F, et al. Inhospital management of COPD exacerbations: a systematic review of the literature with regard to adherence to international guidelines. J Eval Clin Pract 2009;15(6):1101—10.
[24] Rowe BH, Cydulka RK, Tsai CL, Clark S, Sinclair D, Camargo Jr CA. Comparison of Canadian versus United States emergency department visits for chronic obstructive pulmonary disease exacerbation. Can Respir J 2008;15(6):295—301.
[25] Rowe BH, Villa-Roel C, Guttman A, Ross S, Mackey D, Sivilotti ML, et al. Predictors of hospital admission for chronic obstructive pulmonary disease exacerbations in Canadian emergency departments. Acad Emerg Med 2009;16(4):316—24.
[26] Brown DW, Croft JB, Greenlund KJ, Giles WH. Trends in hospitalization with chronic obstructive pulmonary disease — United States, 1990—2005. COPD 2010;7(1):59—62.
[27] Holt JB, Zhang X, Presley-Cantrell L, Croft JB. Geographic disparities in chronic obstructive pulmonary disease (COPD) hospitalization among Medicare beneficiaries in the United States. Int J Chron Obstruct Pulmon Dis 2011;6:321—8.
[28] Lash TL, Johansen MB, Christensen S, Baron JA, Rothman KJ, Hansen JG, et al. Hospitalization rates and survival associated with COPD: a nationwide Danish cohort study. Lung 2011;189(1):27—35.
[29] Briggs Jr DD, Covelli H, Lapidus R, Bhattycharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. Pulm Pharmacol Ther 2005;18(6):397—404.
[30] Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 2003;58(5):399—404.
[31] Donohue JF, van Noord JA, Bateman ED, Langley SJ, Lee A, Witek Jr TJ, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest 2002; 122(1):47—55.
[32] Halpin DM, Miravitlles M. Chronic obstructive pulmonary disease: the disease and its burden to society. Proc Am Thorac Soc 2006;3(7):619—23.
[33] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global initiative for chronic obstructive lung disease website. Available at: http://www.goldcopd.com [accessed 23.01.12].
[34] Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356(8):775—89.
[35] Buhl R, Dunn LJ, Disdier C, Lassen C, Amos C, Henley M, et al. Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. Eur Respir J 2011;38(4):797—803.
[36] Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B. Long-term safety and efficacy of indacaterol, a long-acting beta-agonist, in subjects with COPD: a randomized, placebo-controlled study. Chest 2011;140(1):68—75.
[37] Dahl R, Chung KF, Buhl R, Magnussen H, Nonikov V, Jack D, et al. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. Thorax 2010;65(6):473—9.
[38] Korn S, Kerwin E, Atis S, Amos C, Owen R, Lassen C. Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: a 12-week study. Respir Med 2011; 105(5):719—26.
[39] Kornmann O, Dahl R, Centanni S, Dogra A, Owen R, Lassen C, et al. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J 2011;37(2):273—9.
[40] Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, et al. Efficacy and safety of

budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003;21(1):74—81.
[41] Vogelmeier C, Kardos P, Harari S, Gans SJ, Stenglein S, Thirlwell J. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. Respir Med 2008;102(11):1511—20.
[42] National Institute for Health and Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. National clinical guideline centre website. Available at: http://guidance.nice.org.uk/CG101/Guidance/pdf/English [accessed 07.12.11].
[43] Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner G, van der Molen T, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 2011;155(3):179—91.
[44] Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 2009;374(9691):685—94.
[45] HCUPnet. Healthcare, cost and utilization project. HCUPnet com website. Available at: http://www.hcup.ahrg.gov [accessed 20.11.11].
[46] Mapel DW, Dutro MP, Marton JP, Woodruff K, Make B. Identifying and characterizing COPD patients in US managed care. A retrospective, cross-sectional analysis of administrative claims data. BMC Health Serv Res 2011;11:43.
[47] Currie GP, Wedzicha JA. ABC of chronic obstructive pulmonary disease. Acute exacerbations. BMJ 2006;333(7558):87—9.
[48] Shepperd S, Doll H, Broad J, Gladman J, Iliffe S, Langhorne P, et al. Early discharge hospital at home. Cochrane Database Syst Rev 2009;1:CD000356.
[49] McGhan R, Radcliff T, Fish R, Sutherland ER, Welsh C, Make B. Predictors of rehospitalization and death after a severe exacerbation of COPD. Chest 2007;132(6):1748—55.
[50] Tashkin DP. Long-acting anticholinergic use in chronic obstructive pulmonary disease: efficacy and safety. Curr Opin Pulm Med 2010;16(2):97—105.