

EDITORIALS

Treatment with β blockers in people with COPD

May reduce respiratory symptoms and mortality independently of cardiovascular effects

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Treatment with β blockers reduces mortality associated with cardiovascular diseases. Unfortunately, doctors tend to avoid β blockers in patients who have concomitant obstructive lung disease. This stems from the fear of precipitating a catastrophic respiratory event—acute bronchospasm has been reported after administration of β blockers to patients with asthma and chronic obstructive pulmonary disease (COPD).¹⁻⁴ However, evidence suggests that β blockers reduce mortality in patients with COPD, which makes sense because patients often have concomitant cardiovascular disease.⁵ A study of 462 patients with COPD undergoing major vascular surgery found a 27% reduction in perioperative mortality in those who were receiving cardioselective β blockers compared with those who were not.⁶ Surprisingly, in addition to reducing overall mortality and death from cardiovascular disease in patients with COPD, long term use of β blockers may also reduce respiratory events and morbidity. One study reported a 30% reduction in mortality and risk of exacerbations in patients with COPD who were taking β blockers regardless of whether they had cardiovascular disease.⁷ The linked cohort study by Short and colleagues (doi:10.1136/bmj.d2549) adds to this evidence by further defining the respiratory effects of β blockers in COPD, in addition to their cardiovascular benefits.⁸

Short and colleagues assembled relevant data from robust Scottish databases. They selected more than 5000 patients by the presence or absence of concomitant β blocker treatment and reported outcomes systematically according to the stepwise tier of treatment for COPD. The death rate in the entire cohort was 34% a year. As expected, for each level of COPD severity (as judged by prescribed drugs) patients taking β blockers had significantly lower mortality from cardiac disease than those not taking β blockers. This mortality benefit persisted even after adjustment for known cardiovascular risk factors and events. Deaths classified as related to COPD were lower in those taking β blockers too. Respiratory related hospital admissions and emergency oral steroid prescription were also significantly lower in people taking β blockers (hazard ratios ranged from 0.23 to 0.88).

It is tempting to dismiss these results as being related to improvements in cardiovascular disease (such as chronic heart failure) resulting in reduced shortness of breath, which is then

interpreted as a reduction in COPD symptoms. However, these differences persisted after adjustment for cardiovascular disease, which suggests that β blockers have an independent effect on COPD itself. Is such a direct effect on COPD plausible?

Animal data suggest altered airway responsiveness and airway inflammation after chronic β blockade.^{9,10} A recent small pilot study in humans supports this observation. Despite initial acute bronchospasm, chronic escalating doses of β blockers in patients with asthma reduced airway responsiveness.¹¹ Thus, chronic β adrenoceptor blockade in COPD may exert positive effects through bronchoprotective, anti-inflammatory, and mucus resolving effects.

Short and colleagues' study suggests that COPD related events were reduced in patients taking β blockers, irrespective of disease severity. Should clinicians therefore prescribe these drugs to treat people with COPD? Not yet. Although the data on mortality from cardiovascular disease clearly show that β blockers should not be withheld for cardiovascular indications, using them directly for COPD is premature. The study was a retrospective analysis of healthcare databases, so confounding by indication and post hoc adjustment by doctors treating the patients cannot be eliminated. However, together with other data, these results indicate that the use of β blockers may help reduce the morbidity associated with COPD. Prospective studies are therefore needed to ascertain any beneficial effect of β blockers on COPD related outcomes.

How should clinicians start a patient with COPD on a β blocker for cardiac indications? It is advisable to use a cardioselective β blocker and to observe the patient during the administration of the first dose. In the rare case that bronchospasm does occur, anticholinergic agents should probably be used first. Of interest, the data from asthma suggest that β adrenoceptor agonists may still be effective in reversing bronchospasm in the presence of the low doses of β blockers used in asthma pilot studies.¹²

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Effect of β blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study

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ABSTRACT

Objective To examine the effect of β blockers in the management of chronic obstructive pulmonary disease (COPD), assessing their effect on mortality, hospital admissions, and exacerbations of COPD when added to established treatment for COPD.

Design Retrospective cohort study using a disease specific database of COPD patients (TARDIS) linked to the Scottish morbidity records of acute hospital admissions, the Tayside community pharmacy prescription records, and the General Register Office for Scotland death registry.

Setting Tayside, Scotland (2001–2010)

Population 5977 patients aged >50 years with a diagnosis of COPD.

Main outcome measures Hazard ratios for all cause mortality, emergency oral corticosteroid use, and respiratory related hospital admissions calculated through Cox proportional hazard regression after correction for influential covariates.

Results Mean follow-up was 4.35 years, mean age at diagnosis was 69.1 years, and 88% of β blockers used were cardioselective. There was a 22% overall reduction in all cause mortality with β blocker use. Furthermore, there were additive benefits of β blockers on all cause mortality at all treatment steps for COPD. Compared with controls (given only inhaled therapy with either short acting β agonists or short acting antimuscarinics), the adjusted hazard ratio for all cause mortality was 0.28 (95% CI 0.21 to 0.39) for treatment with inhaled corticosteroid, long acting β agonist, and long acting antimuscarinic plus β blocker versus 0.43 (0.38 to 0.48) without β blocker. There were similar trends showing additive benefits of β blockers in reducing oral corticosteroid use and hospital admissions due to respiratory disease. β blockers had no deleterious impact on lung function at all treatment steps when given in conjunction with either a long acting β agonist or antimuscarinic agent

Conclusions β blockers may reduce mortality and COPD exacerbations when added to established inhaled stepwise therapy for COPD, independently of overt cardiovascular disease and cardiac drugs, and without adverse effects on pulmonary function.

INTRODUCTION

The presence of cardiovascular disease and chronic obstructive pulmonary disease (COPD) are intertwined because of the risk of smoking induced atherosclerosis in patients with COPD.¹ Despite the proved benefits of β blockers in treating hypertension, ischaemic heart disease, and heart failure, many doctors are reluctant to prescribe β blockers for patients with concurrent COPD.²

Historically β blockers have been avoided in asthma because of the risk of acute bronchospasm.^{3–5} These concerns also apply to COPD, with evidence of a reduction in forced expiratory volume in one second (FEV₁), increased airway hyperresponsiveness, and inhibition of bronchodilator response to β agonists in patients receiving non-selective β blockers and high doses of cardioselective β blockers.^{6,7}

Despite these concerns, evidence suggests that cardioselective β blockers do not cause an increase in exacerbations, reduction in airway function, or worsening of quality of life in COPD patients.^{8–10} COPD is a highly heterogeneous condition, and the degree of comorbidities present seems to be independent of the degree of airway obstruction.¹¹ The treatment of comorbid cardiovascular disease in COPD is especially relevant since cardiac failure has been shown to be a leading cause of death in these patients.¹²

In this regard, the use of β blockers in patients with COPD and cardiovascular disease has been shown to reduce mortality.^{13,14} Whether the improved survival seen with β blockers in COPD is purely due to cardiovascular effects has been questioned. Recent evidence suggests that β blockers may improve survival and exacerbations even in COPD patients without cardiovascular disease.¹⁵

Although cardioselective β blockers have been designed to target β_1 adrenoceptors while avoiding β_2 adrenoceptors in the lung and elsewhere, so called cardioselective β blockers (such as atenolol and bisoprolol) are only relatively selective and exert significant β_2 antagonism at therapeutic doses, though to a lesser extent than non-selective β blockers such as propranolol.^{16–19} Thus, it might be considered counter-intuitive to prescribe both β blockers and β agonists in

the same patient, even when they are targeting different organs.

Current COPD management guidelines advocate a stepwise approach using long acting bronchodilators (including β agonists) and inhaled corticosteroids to reduce exacerbations and improve symptoms and lung function. With the exception of tiotropium, combination treatments involving long acting bronchodilators and inhaled corticosteroids have failed to show any significant improvement in mortality.^{20,21} We therefore wished to examine the use of β blockers in the management of COPD, assessing their interactions with β agonists and other COPD drug and assess whether they improve mortality, hospital admissions, and exacerbations when added to established treatment for COPD.

METHODS

We searched the NHS Tayside Respiratory Disease Information System (TARDIS) to identify patients from January 2001 to January 2010 with a diagnosis of COPD. TARDIS is a disease specific database developed in 2001 to support general practitioners and secondary care respiratory physicians in managing patients with COPD in Tayside, Scotland. Entry into TARDIS requires a diagnosis of COPD based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.²² Data within TARDIS include patient demographics, respiratory symptoms, lung function, and smoking history. Data stored in the TARDIS database (including spirometry data) are collected at annual visits by specialist respiratory nurses who have received structured training in order to standardise results.

We searched data provided by the Health Informatics Centre, at the University of Dundee on behalf of the Information Services Division of NHS Scotland, using Scottish morbidity records to identify patients

covered by the NHS Tayside Health Board who had had a hospital admission because of COPD. Discharge summaries with a diagnosis of COPD were used to identify respiratory related hospital admissions. Diagnoses were based on ICD-9 and ICD-10 codes (international classification of diseases, ninth and 10th revisions). The data held by the Health Informatics Centre undergo data quality checks before release.

We collected prescription data of respiratory and cardiovascular drugs from the Tayside Community Prescription database and records of deaths in our population from the General Register Office for Scotland. Each patient's deprivation index was based on their postcode and calculated with the Scottish Index of Multiple Deprivation (SIMD). A health board specific deprivation index (HBSIMD) was calculated in relation to the local population. A history of diabetes and admission to hospital for cardiovascular disease (including ischaemic heart disease, heart failure, and peripheral vascular disease) were identified from ICD-9 and ICD-10 codes.

Data analysis

Patients were initially divided into two groups dependent on β blocker use. We performed Kaplan-Meier analysis with log rank testing to compare all cause mortality dependent on β blocker use. Cox proportional hazard regression analysis was used to calculate crude and adjusted hazard ratios and their 95% confidence intervals for all cause mortality associated with β blocker use, and for cardioselective β blockers and non-selective β blockers. Adjusted hazard ratios were calculated after correction for the following covariates: cardiovascular and respiratory hospital admissions, diabetes, smoking, age, sex, and cardiac drug use (aspirin, statins, calcium channel blockers, and angiotensin converting enzyme inhibitors), FEV₁ (as percentage of predicted value), resting arterial oxygen

Table 1 Baseline characteristics of 5977 patients at diagnosis of COPD, grouped according to final treatment. Values are number (percentage) of patients unless otherwise stated

Treatment groups*	No of patients	Mean (SD) age (years)	Male	Mean (SD) FEV ₁ †	Mean (SD) SaO ₂ ‡	Mean (SD) smoking pack years	History of cardiovascular disease	History of diabetes	Mean (SD) deprivation index§
ICS	464	69.7 (9.8)	239 (51.5)	65.5 (19.5)	94.2 (10.9)	41 (16.5)	190 (40.9)	46 (9.9)	2.1 (1.4)
ICS+BB	71	71.7 (8.6)	36 (50.7)	64.2 (16.1)	93.3 (14.5)	39 (12.6)	51 (71.8)	18 (25.4)	2.2 (1.4)
ICS+LABA	996	68.9 (9.6)	547 (54.9)	62.7 (18.9)	92.5 (13.5)	41.2 (19.4)	429 (43.1)	148 (14.9)	2.3 (1.4)
ICS+LABA+BB	143	68.8 (9.7)	70 (49)	65.7 (16.7)	94.2 (9.8)	41.5 (18.4)	96 (67.1)	25 (17.5)	2.1 (1.4)
ICS+LABA+Tio	1857	68.3 (8.9)	972 (52.3)	50.8 (17.1)	91.3 (11.6)	44.8 (16)	874 (47.1)	259 (13.9)	2.2 (1.3)
ICS+LABA+Tio+BB	187	68.1 (8.4)	77 (41.2)	52.8 (16.4)	92.6 (9.5)	45.1 (18.6)	146 (78.1)	33 (17.6)	2.0 (1.2)
LABA or Tio (no ICS)	526	69.9 (9.2)	263 (50)	60 (17.4)	93.5 (7.9)	45.7 (19.9)	220 (41.8)	67 (12.7)	2.2 (1.4)
BB (no ICS)	276	70.8 (8.8)	109 (39.5)	73.7 (16.3)	95.5 (7.1)	44.7 (16.4)	181 (65.6)	57 (20.7)	2.2 (1.4)
ICS+Tio	158	69.1 (9.2)	70 (44.3)	55 (16.6)	93.2 (9.5)	44.1 (19.7)	73 (46.2)	25 (15.8)	2 (1.3)
(LABA or Tio)+BB	119	70.1 (8.1)	48 (40.3)	63.5 (14.2)	95 (2.1)	48.6 (22.3)	84 (70.6)	32 (26.9)	2.2 (1.4)
Control group¶	1180	70.5 (10.2)	617 (52.3)	69.1 (18.3)	94.7 (7.9)	43.5 (16.5)	534 (45.3)	145 (12.3)	2.1 (1.4)

*Treatments: ICS=inhaled corticosteroid, BB= β blocker, LABA=long acting β agonist, Tio=tiotropium.

†FEV₁=forced expiratory volume in one second, given as percentage predicted for age, sex, and race.

‡SaO₂=Resting arterial oxygen saturation.

§On a scale of 1–4 (1=most deprived, 4=least deprived).

¶Control treatment only with short acting β agonists or antimuscarinic agent.

Table 2 | Effect of different treatment regimens* on FEV₁† of patients with COPD during study period

Treatment groups*	Mean (SD) FEV ₁ †		Mean difference (95% CI)	P value
	First recording	Last recording		
ICS (n=204)	1.64 (0.61)	1.63 (0.62)	-0.01 (-0.04 to 0.03)	0.658
ICS+BB (n=43)	1.55 (0.57)	1.58 (0.55)	0.03 (-0.05 to 0.10)	0.459
ICS+LABA (n=459)	1.52 (0.60)	1.54 (0.62)	0.02 (-0.01 to 0.05)	0.123
ICS+LABA+BB (n=89)	1.55 (0.54)	1.57 (0.55)	0.03 (-0.03 to 0.08)	0.355
ICS+LABA+Tio (n=753)	1.22 (0.51)	1.19 (0.51)	-0.03 (-0.06 to -0.01)	<0.001
ICS+LABA+Tio+BB (n=88)	1.27 (0.50)	1.28 (0.53)	0.01 (-0.06 to 0.08)	0.749
LABA or Tio (no ICS) (n=197)	1.48 (0.58)	1.44 (0.57)	-0.04 (-0.08 to -0.01)	0.016
BB (no ICS) (n=276)	1.83 (0.53)	1.74 (0.55)	-0.09 (-0.11 to -0.06)	<0.001
ICS+Tio (n=81)	1.37 (0.53)	1.40 (0.49)	0.03 (-0.03 to 0.09)	0.257
(LABA or Tio)+BB (n=47)	1.67 (0.56)	1.65 (0.57)	-0.02 (-0.09 to 0.04)	0.435
Control‡ (n=475)	1.76 (0.62)	1.69 (0.59)	-0.07 (-0.09 to -0.05)	<0.001

*Treatments: ICS=inhaled corticosteroid, BB=β blocker, LABA=long acting β agonist, Tio=tiotropium.
†FEV₁=forced expiratory volume in one second (litres).

‡Control=treatment only with short acting β agonists with or without short acting antimuscarinic agent.

saturation (SaO₂), and deprivation index. We calculated a propensity score using covariates influencing β blocker use and repeated the Cox regression model in a subgroup of patients matched on propensity score.

Patients were then divided into subgroups based on their maximal stepwise inhaled therapy and β blocker use: inhaled corticosteroids (group 1); inhaled corticosteroids and long acting β agonists (salmeterol or formoterol) (group 2); inhaled corticosteroids, long acting β agonists, and β blockers (group 3); inhaled corticosteroids, long acting β agonists, and long acting antimuscarinic (tiotropium) (group 4); inhaled corticosteroids, long acting β agonists, tiotropium, and β blockers (group 5); long acting β agonists or tiotropium (no inhaled corticosteroids) (group 6); β blockers (no inhaled corticosteroids) (group 7); inhaled corticosteroids and β blockers (group 8); inhaled corticosteroids and tiotropium (group 9); and β blockers with either long acting β agonists or tiotropium (group 10). The control group comprised those who had received

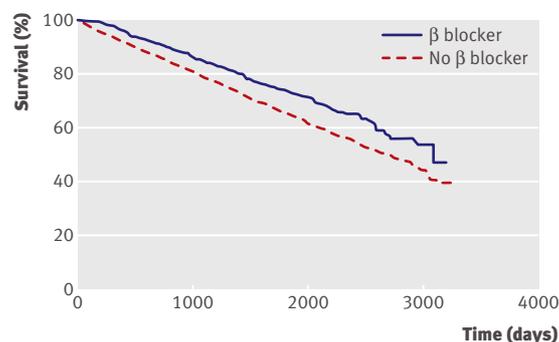
Table 3 | Effect of different treatment regimens* on FVC† of patients with COPD during study period

Treatment groups*	Mean (SD) FVC†		Mean difference (95% CI)	P value
	First recording	Last recording		
ICS (n=204)	2.75 (0.94)	2.78 (0.97)	0.03 (-0.03 to 0.09)	0.369
ICS+BB (n=43)	2.58 (0.82)	2.71 (0.87)	0.13 (-0.02 to 0.28)	0.086
ICS+LABA (n=459)	2.61 (0.94)	2.71 (0.97)	0.10 (0.05 to 0.14)	<0.001
ICS+LABA+BB (n=89)	2.63 (0.89)	2.69 (0.87)	0.06 (-0.05 to 0.15)	0.287
ICS+LABA+Tio (n=753)	2.46 (0.89)	2.48 (0.84)	0.02 (-0.01 to 0.06)	0.241
ICS+LABA+Tio+BB (n=88)	2.40 (0.88)	2.50 (0.89)	0.10 (-0.01 to 0.20)	0.08
LABA or Tio (no ICS) (n=197)	2.67 (0.93)	2.66 (0.93)	0.01 (-0.07 to 0.05)	0.767
BB (no ICS) (n=276)	2.91 (0.84)	2.80 (0.89)	0.11 (0.05 to 0.16)	<0.001
ICS+Tio (n=81)	2.48 (0.81)	2.59 (0.75)	0.11 (0.01 to 0.20)	0.043
(LABA or Tio)+BB (n=47)	2.77 (0.93)	2.82 (0.95)	0.05 (-0.05 to 0.17)	0.297
Control‡ (n=475)	2.90 (0.96)	2.86 (0.95)	-0.04 (-0.09 to -0.02)	0.041

*Treatments: ICS=inhaled corticosteroid, BB=β blocker, LABA=long acting β agonist, Tio=tiotropium.

†FVC=forced vital capacity (litres).

‡Control=treatment only with short acting β agonists with or without short acting antimuscarinic agent.

**Fig 1** | Kaplan-Meier estimate of probability of survival among patients with COPD by use of β blockers

only inhaled therapy with either short acting β agonists (salbutamol, terbutaline) or short acting antimuscarinic agent (ipratropium). Two or more sequential prescriptions were required for patients to be stratified into differing treatment groups.

Cox proportional hazard regression analysis was then used to calculate crude and adjusted hazard ratios for all cause mortality, hospital admissions due to respiratory disease, and emergency oral corticosteroid use dependent on treatment groups in reference to the control group. This was repeated for death from myocardial infarction and death from COPD as surrogate markers of cardiac and respiratory mortality.

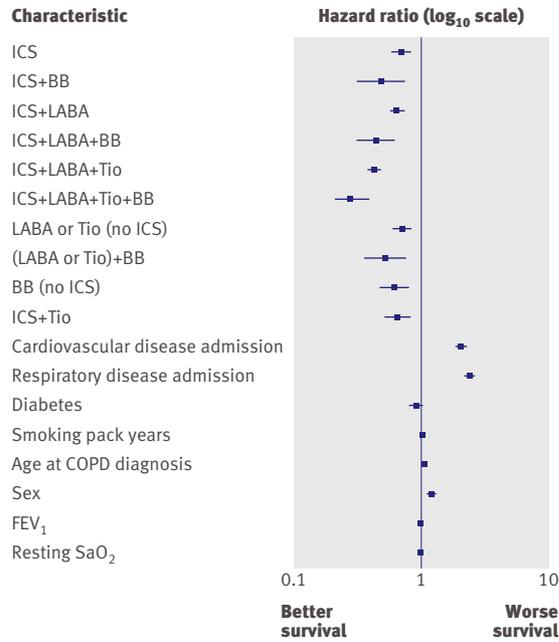
Subgroup analyses were also performed for hospital admissions related to respiratory disease, specifically due to COPD exacerbation. When calculating hazard ratios for all cause mortality, we censored patient data when they were lost to follow-up or reached the end of the study period (January 2010). For hospital admissions and oral corticosteroid use, we calculated treatment groups using prescription data before the respective event occurring, with censoring as described above.

Adjusted hazard ratios for mortality were calculated after correction with these covariates: cardiovascular and respiratory hospital admissions, diabetes, smoking, age at diagnosis, sex, cardiac drug use, FEV₁, resting SaO₂, and deprivation index. Additional models were developed to calculate adjusted hazard ratios, death from COPD or from myocardial infarction, hospital admissions due to respiratory disease, hospital admissions due to COPD, and oral corticosteroid use. All hazard ratios were calculated from Cox regression models after forced entry of all available covariates to reduce residual confounding.

For all tests, a two sided P value of <0.05 was considered significant. Analyses were performed using SPSS version 17.0.

RESULTS

A total of 6345 patients were identified through the TARDIS database. Within this cohort, 5977 were >50 years old and were included in our analysis. Patients were excluded from the analysis if they had a history of malignancy before entry into TARDIS.



ICS=inhaled corticosteroid, BB=β blocker, LABA=long acting β agonist, Tio=tiotropium, FEV₁=forced expiratory volume in one second, SaO₂=arterial oxygen saturation

Fig 2 | Adjusted hazard ratios for all cause mortality among patients with COPD in reference to the control group (who received only inhaled therapy with short acting β agonists or antimuscarinics)

Stratified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometry classification, 897 patients (15%) were stage 1 with mean FEV₁ 90.8% (SD 9.4), 3287 (55%) were stage 2 with FEV₁ 64.8% (8.3), 1494 (25%) were stage 3 with FEV₁ 40.9% (5.6), and 299 (5%) were stage 4 with FEV₁ 24.8% (4.6). Mean (SD) length of follow-up was 4.35 (2.28) years. The patients' mean (SD) age at diagnosis of COPD (time of entry into TARDIS database) was 69.1 (9.4) years, and 3048 (51%) were male. Of the β blockers used, 720 (88%) were cardioselective. All patients, including the control group, were receiving short acting β agonists with or without ipratropium. Table 1 shows the patients' characteristics at study entry.

Pulmonary function

We made a subgroup analysis of 2712 patients for whom 6639 serial measurements of FEV₁ and forced vital capacity (FVC) were available. Those patients being prescribed triple therapy with inhaled corticosteroids, long acting β agonists, and tiotropium had the lowest FEV₁, in keeping with increased disease severity. The addition of a β blocker had no deleterious impact when added to a regimen that included a long acting bronchodilator or inhaled corticosteroid (such as inhaled corticosteroids and long acting β agonists or inhaled corticosteroids, long acting β agonists, and tiotropium) (tables 2 and 3). Moreover, when FEV₁ values at the start of the study period were compared

Table 4 | Risk of all cause mortality among patients with COPD by treatment regimen* and covariates

Characteristic	Adjusted hazard ratios (95% CI)†
Treatment groups*	
ICS+LABA+Tio+BB	0.28 (0.21 to 0.39)
ICS+LABA+Tio	0.43 (0.38 to 0.48)
ICS+LABA+BB	0.44 (0.31 to 0.62)
ICS+LABA	0.64 (0.57 to 0.74)
ICS+BB	0.48 (0.31 to 0.74)
ICS	0.69 (0.58 to 0.83)
ICS +Tio	0.61 (0.47 to 0.80)
LABA or Tio (no ICS)+BB	0.52 (0.36 to 0.76)
LABA or Tio (no ICS)	0.71 (0.59 to 0.84)
BB (no ICS)	0.65 (0.51 to 0.83)
Covariates used in Cox regression model	
History of hospital admission:	
For cardiovascular disease	2.04 (1.84 to 2.27)
For respiratory disease	2.38 (2.16 to 2.62)
Age at study entry (years)	1.05 (1.05 to 1.06)
Sex (male)	1.19 (1.09 to 1.31)
Smoking (pack years)	1.01 (1.00 to 1.01)
History of diabetes	0.91 (0.80 to 1.03)
FEV ₁ ‡	0.98 (0.97 to 0.98)
Resting SaO ₂ §	0.99 (0.99 to 1.00)
Deprivation index¶:	
1	0.99 (0.89 to 1.11)
2	1.02 (0.88 to 1.19)
3	0.88 (0.76 to 1.02)
4	0.85 (0.73 to 1.00)
Cardiovascular drugs:	
Aspirin	0.80 (0.73 to 0.88)
Statins	0.89 (0.81 to 0.97)
ACE inhibitors	0.79 (0.72 to 0.88)
Calcium channel blockers	0.71 (0.64 to 0.78)

*Treatments: ICS=inhaled corticosteroid, BB=β blocker, LABA=long acting β agonist, Tio=tiotropium.
 †Adjusted hazard ratios relative to the control group, which received only treatment with short acting β agonists or antimuscarinic agent.
 ‡FEV₁=forced expiratory volume in one second, given as percentage predicted for age, sex, and race.
 §SaO₂=arterial oxygen saturation.
 ¶Health board specific Scottish Index of Multiple Deprivation (HBSIMD), rated on a scale of 1–4 (1=most deprived, 4=least deprived).

with those at the end, there was no clinically significant deterioration in any treatment group that included a β blocker (a clinically significant difference regarded as a 30 mL/year reduction in FEV₁²³).

All cause mortality

The Kaplan-Meier analysis and log rank testing to evaluate the impact of β blockers on survival showed a significant improvement in overall survival for the 819 patients who received β blockers compared with those who did not (χ² test 18.97, P<0.001) (fig 1). After matched propensity scoring analysis, to balance associated covariates between groups, we found that β blocker use was associated with a 22% reduction in mortality (hazard ratio 0.78 (95% confidence interval 0.67 to 0.92)).

Table 5 | Risk of death from myocardial infarction and from COPD among patients with COPD by treatment regimen*

Treatment group*	Adjusted hazard ratios (95% CI)†	
	Death from myocardial infarction (n=288)	Death from COPD (n=625)
ICS+LABA+Tio+BB	0.25 (0.11 to 0.58)	0.39 (0.20 to 0.78)
ICS+LABA+Tio	0.44 (0.31 to 0.62)	0.30 (0.24 to 0.38)
ICS+LABA+BB	0.49 (0.27 to 0.90)	0.23 (0.09 to 0.64)
ICS+LABA	0.53 (0.37 to 0.76)	0.52 (0.40 to 0.68)
ICS+BB	0.46 (0.19 to 1.13)	0.25 (0.06 to 0.99)
ICS	0.80 (0.51 to 1.27)	0.45 (0.32 to 0.65)
ICS +Tio	0.63 (0.29 to 1.37)	0.39 (0.25 to 0.61)
LABA or Tio (no ICS)+BB	0.54 (0.25 to 1.16)	0.38 (0.12 to 1.20)
LABA or Tio (no ICS)	1.09 (0.66 to 1.81)	0.42 (0.30 to 0.60)
BB (no ICS)	0.67 (0.41 to 1.10)	0.88 (0.32 to 2.38)

*Treatments: ICS=inhaled corticosteroid, BB=β blocker, LABA=long acting β agonist, Tio=tiotropium.

†Adjusted hazard ratios relative to the control group, which received only treatment with short acting β agonists or antimuscarinic agent. Covariates used in Cox regression model were history of cardiovascular and respiratory disease, age, sex, smoking, history of diabetes, and deprivation.

Comparing cardioselective β blockers with non-selective β blockers, we found no significant difference between groups (χ^2 test 0.77, $P=0.378$).

A total of 2005 patients died during the study period, equating to an annual mortality of 34%. We calculated Cox proportional hazards ratios for each treatment group based on stepwise management for COPD. At each comparison, the adjusted hazard ratio for treatment groups including a β blocker were lower than the respective treatment group without a β blocker. Thus the crude hazard ratios for those patients taking inhaled corticosteroids, long acting β agonists, and tiotropium with and without β blocker were 0.38 (95% confidence interval 0.28 to 0.52) and 0.54 (0.48 to 0.61), while their adjusted hazard ratios were 0.28 (0.21 to 0.39) and 0.43 (0.38 to 0.48), respectively. Similarly, the crude hazard ratios for the patients taking inhaled corticosteroids and long acting β agonists with and without β blocker were 0.43 (0.31 to 0.60) and 0.67 (0.59 to 0.78), and their adjusted hazard ratios were 0.44 (0.31 to 0.62) and 0.64 (0.57 to 0.74), respectively. Finally, the crude hazard ratios for patients taking inhaled corticosteroids with and without β blocker were 0.51 (0.33 to 0.79) and 0.66 (0.55 to 0.79), and their adjusted hazard ratios were 0.48 (0.31 to 0.74) and 0.69 (0.58 to 0.83). Adjusted hazard ratios for all treatment groups and covariates used in the Cox regression model are shown in figure 2 and table 4.

Cardiac and respiratory mortality

Of the 2005 patients who died during the study period, 288 (14%) had myocardial infarction recorded as their primary cause of death and 625 (32%) had COPD recorded as their primary cause. Similar benefits in reducing death from myocardial infarction and from COPD were seen when these patients were stratified by treatment group. For example, for those patients taking inhaled corticosteroids, long acting β agonists, tiotropium, and β blocker, the adjusted hazard ratios for death from myocardial infarction and from

COPD were 0.25 (0.11 to 0.58) and 0.39 (0.2 to 0.78), respectively (see table 5).

Emergency oral steroid prescription

Of the 5977 patients in the study, 3415 (57%) had at least one prescription of oral corticosteroids during the study period. The adjusted hazard ratios for oral corticosteroid prescription for those patients taking inhaled corticosteroids, long acting β agonists, and tiotropium with and without β blocker were 0.31 (0.22 to 0.43) and 0.68 (0.61 to 0.75). The adjusted hazard ratios for oral corticosteroids for patients taking inhaled corticosteroids and long acting β agonists with and without β blocker were 0.46 (0.34 to 0.63) and 0.93 (0.85 to 1.03). The adjusted hazard ratios for patients taking inhaled corticosteroids with and without β blocker were 0.51 (0.39 to 0.69) and 0.77 (0.69 to 0.87). The adjusted hazard ratios for covariates used in the Cox regression model are shown in figure 3 and listed in table 6.

Hospital admissions for respiratory disease

Of the study patients, 1608 (27%) had at least one hospital admission due to respiratory disease during the study period. The adjusted hazard ratios for such admission for those patients taking inhaled corticosteroids, long acting β agonists, and tiotropium with and without β blocker were 0.32 (0.22 to 0.44) and 0.70 (0.61 to 0.80). The adjusted hazard ratios for patients taking inhaled corticosteroids and long acting β agonists with and without β blocker were 0.39 (0.26 to 0.60) and 0.82 (0.70 to 0.96). The adjusted hazard ratios for inhaled corticosteroids with and without β blocker were 0.36 (0.22 to 0.58) and 0.79 (0.66 to 0.95). Adjusted hazard ratios for covariates used in the Cox regression model are shown in figure 4 and listed in table 7.

Hospital admissions for COPD

Of those who had a hospital admission due to respiratory disease, 1094 (68%) had a primary coded diagnosis of COPD exacerbation. Similar trends of improvement with β blockers were seen as with all hospital admissions due to respiratory disease. The adjusted hazard ratio for hospital admission due to COPD for patients taking inhaled corticosteroids, long acting β agonists, and tiotropium with and without β blocker were 0.25 (0.14 to 0.42) and 0.77 (0.65 to 0.91). The adjusted hazard ratios for patients taking inhaled corticosteroids and long acting β agonists with and without β blocker were 0.37 (0.22 to 0.64) and 0.81 (0.67 to 0.97). The adjusted hazard ratios for inhaled corticosteroids with and without β blocker were 0.24 (0.20 to 0.49) and 0.69 (0.54 to 0.87).

DISCUSSION

Through matched propensity scoring analysis, our data suggest a 22% overall reduction in all cause mortality for patients with COPD when their inhaled treatment regimen includes β blockers. Importantly, our data also suggest there may be benefits when β blockers

are added to established stepwise inhaled treatment regimens for COPD in reducing all cause mortality. Our Cox proportional hazard regression analyses have shown that the additive benefits of β blockers were independent of other cardiovascular drugs and history of overt cardiovascular disease (ischaemic heart disease, heart failure, peripheral vascular disease). These findings suggest that β blockers have effects on reducing mortality in COPD in addition to the benefits gained by reducing cardiovascular risk.

The baseline demographics of our treatment groups showed similar levels of social deprivation. Deprivation is known to influence mortality, and, with regard to use of β blockers to treat heart failure, patients with worse deprivation are less likely to be treated.²⁴ We used the Scottish Index of Multiple Deprivation to calculate the deprivation score in our study: 6.9% of the most deprived areas in Scotland are covered by Tayside Health Board.²⁵

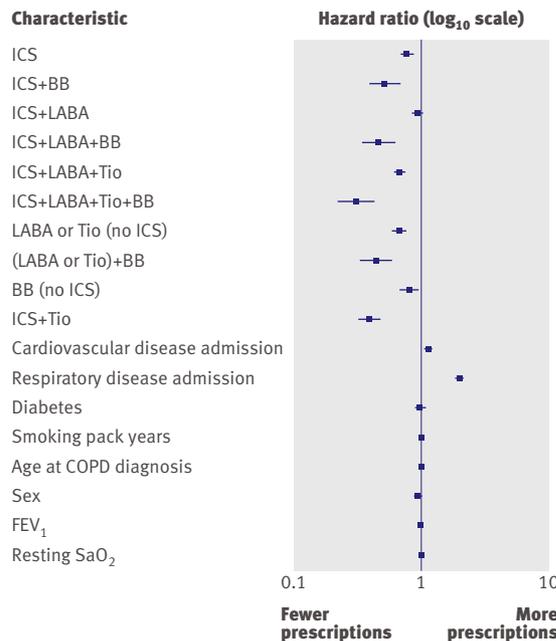
Comparison with other studies

Previous studies have focused on the presence or absence of β blockers and their influence on mortality.¹⁵ Rutten et al found that the benefit on mortality seen with β blockers was preserved in those individuals who were concurrently prescribed two or more pulmonary drugs or who were using inhaled β_2 agonists or antimuscarinics. However, their analysis did not stratify patients according to stepwise treatment regimens, in particular for long acting β agonists and long acting antimuscarinics. We believe this issue is

pertinent given the potential for co-prescription of drugs with agonist and antagonist properties with theoretical interactions.

FEV₁ has previously been shown to decline over time.²⁶ Using a 30 mL/year reduction (as observed in the placebo limb of the UPLIFT study²³) as our reference, we found no clinically significant decline in mean FEV₁ over time in each treatment group. Within treatment groups, decline in FEV₁ was observed in individual patients, but the percentage of patients showing a decline was consistent among the treatment groups.

In line with previous studies, we found a reduction in all cause mortality among patients with COPD who were taking statins and angiotensin converting enzyme inhibitors.^{27,28} As expected, our data showed significant mortality reductions with use of cardiovascular drugs (hazard ratios with aspirin 0.8 (95% confidence interval 0.73 to 0.88), statins 0.89 (0.81 to 0.97), angiotensin converting enzyme inhibitors 0.79 (0.72 to 0.88) and calcium channel blockers 0.71 (0.64 to 0.78)). These findings show the importance of recognising



ICS=inhaled corticosteroid, BB= β blocker, LABA=long acting β agonist, Tio=tiotropium, FEV₁=forced expiratory volume in one second, SaO₂=arterial oxygen saturation

Fig 3 | Adjusted hazard ratios for emergency oral corticosteroid prescription among patients with COPD in reference to the control group (who received only inhaled therapy with short acting β agonists or antimuscarinics)

Table 6 | Risk of emergency oral corticosteroid prescription among patients with COPD by treatment regimen* and covariates

Characteristic	Adjusted hazard ratios (95% CI)†
Treatment groups*	
ICS+LABA+Tio+BB	0.31 (0.22 to 0.43)
ICS+LABA+Tio	0.68 (0.61 to 0.75)
ICS+LABA+BB	0.46 (0.34 to 0.63)
ICS+LABA	0.93 (0.85 to 1.03)
ICS+BB	0.51 (0.39 to 0.69)
ICS	0.77 (0.69 to 0.87)
ICS +Tio	0.81 (0.68 to 0.96)
LABA or Tio (no ICS)+BB	0.44 (0.33 to 0.59)
LABA or Tio (no ICS)	0.67 (0.59 to 0.76)
BB (no ICS)	0.39 (0.32 to 0.48)
Covariates used in Cox regression model	
History of hospital admission:	
For cardiovascular disease	1.14 (1.06 to 1.22)
For respiratory disease	2.01 (1.87 to 2.16)
History of diabetes	0.99 (0.90 to 1.10)
Smoking (pack years)	1.00 (0.99 to 1.01)
Age at study entry (years)	1.01 (1.00 to 1.02)
Sex (male)	0.95 (0.89 to 1.02)
FEV ₁ ‡	1.00 (0.99 to 1.01)
Resting SaO ₂ §	1.01 (1.01 to 1.02)
Deprivation index¶:	
1	1.01 (0.93 to 1.10)
2	1.03 (0.91 to 1.15)
3	0.94 (0.84 to 1.06)
4	0.92 (0.82 to 1.04)

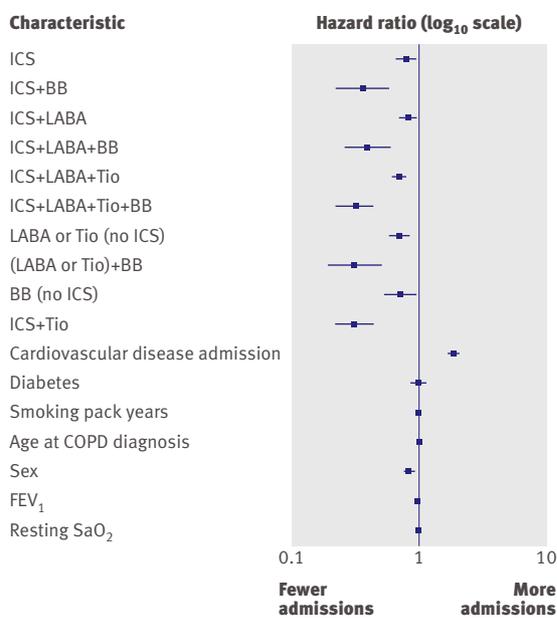
*Treatments: ICS=inhaled corticosteroid, BB= β blocker, LABA=long acting β agonist, Tio=tiotropium.

†Adjusted hazard ratios relative to the control group, which received only treatment with short acting β agonists or antimuscarinic agent.

‡FEV₁=forced expiratory volume in one second, given as percentage predicted for age, sex, and race.

§SaO₂=arterial oxygen saturation.

¶Health board specific Scottish Index of Multiple Deprivation (HBSIMD), rated on a scale of 1–4 (1=most deprived, 4=least deprived).



ICS=inhaled corticosteroid, BB=β blocker, LABA=long acting β agonist, Tio=tiotropium, FEV₁=forced expiratory volume in one second, SaO₂=arterial oxygen saturation

Fig 4 | Adjusted hazard ratios for hospital admissions due to respiratory disease among patients with COPD in reference to the control group (who received only inhaled therapy with short acting β agonists or antimuscarinics)

that patients with COPD have a high risk of developing cardiovascular disease.

Meaning of the study

In terms of the benefit of adding β blockers to stepwise inhaled therapy, our data showed the same trends for all cause mortality, oral corticosteroid prescriptions, and hospital admissions, which adds support to the value of using β blockers in COPD. Although it could be suggested that the reduction observed in all cause mortality with β blockers is attributable to their cardiovascular effects, similar benefits were seen in reducing deaths from COPD and deaths from myocardial infarction, although some hazard ratios within groups failed to reach statistical significance. These observations (together with the reductions in hospital admissions and emergency oral corticosteroid use) cannot easily be explained by simply improving cardiovascular risk.

This raises the question of whether β blockers confer independent beneficial effects in COPD, as has been suggested in asthma.²⁹ One possibility is that up-regulation of β₂ adrenoceptors by chronic β blockade may improve the effectiveness of β₂ agonists. Despite most of the β blockers in our study being relatively cardioselective, drugs such as atenolol and bisoprolol have been shown to exert significant β₂ adrenoceptor antagonism even at therapeutic doses, which may result in β₂ adrenoceptor up-regulation. Thus, up-regulation of β₂ adrenoceptors by cardioselective β blockers seems plausible. In this regard, we did not see any worsening of FEV₁ or FVC when analysing the effect of addition

of β blockers to treatment regimens that included long acting β agonists. Ind et al have shown that antimuscarinic drugs prevent β blocker induced bronchoconstriction in asthmatic patients.³⁰ This would suggest a rationale for using tiotropium when prescribing a β blocker for a patient with COPD, aside from the known benefits of tiotropium on exacerbations and symptoms.²³

Strength and limitations of study

TARDIS is a COPD database routinely used to guide COPD management in Tayside. The advantage of using this disease specific database is that all patients have a diagnosis of COPD made by a primary or secondary care physician on the basis of Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Since 2001, patients with COPD have been invited to be included in our database, and TARDIS has been used as the basis for previous published COPD research, thereby providing us with an unselected community population of COPD patients for analysis.³¹

Table 7 | Risk of hospital admissions due to respiratory disease among patients with COPD by treatment regimen* and covariates

Characteristic	Adjusted hazard ratios (95% CI)†
Treatment groups*	
ICS+LABA+Tio+BB	0.32 (0.22 to 0.44)
ICS+LABA+Tio	0.70 (0.61 to 0.80)
ICS+LABA+BB	0.39 (0.26 to 0.60)
ICS+LABA	0.82 (0.70 to 0.96)
ICS+BB	0.36 (0.22 to 0.58)
ICS	0.79 (0.66 to 0.95)
ICS +Tio	0.71 (0.53 to 0.96)
LABA or Tio (no ICS)+BB	0.31 (0.19 to 0.51)
LABA or Tio (no ICS)	0.70 (0.58 to 0.85)
BB (no ICS)	0.31 (0.22 to 0.44)
Covariates used in Cox regression model	
History of hospital admission for cardiovascular disease	1.87 (1.69 to 2.09)
History of diabetes	0.99 (0.87 to 1.14)
Smoking (pack years)	1.00 (0.99 to 1.01)
Age at study entry (years)	1.01 (1.01 to 1.02)
Sex (male)	0.84 (0.76 to 0.93)
FEV ₁ ‡	0.98 (0.97 to 0.99)
Resting SaO ₂ §	0.99 (0.98 to 1.01)
Deprivation index¶:	
1	1.07 (0.95 to 1.21)
2	1.26 (1.07 to 1.48)
3	1.04 (0.88 to 1.23)
4	0.92 (0.77 to 1.11)

*Treatments: ICS=inhaled corticosteroid, BB=β blocker, LABA=long acting β agonist, Tio=tiotropium.

†Adjusted hazard ratios relative to the control group, which received only treatment with short acting β agonists or antimuscarinic agent.

‡FEV₁=forced expiratory volume in one second, given as percentage predicted for age, sex, and race.

§SaO₂=arterial oxygen saturation.

¶Health board specific Scottish Index of Multiple Deprivation (HBSIMD), rated on a scale of 1–4 (1=most deprived, 4=least deprived).

WHAT IS ALREADY KNOWN ON THIS TOPIC

Despite the clear benefits of β blocker use in cardiovascular disease, their use is avoided in patients with concurrent chronic obstructive pulmonary disease (COPD) because of concerns about bronchospasm and the potential to block the bronchodilating effects of β agonist inhalers

Studies have suggested that β blockers may reduce mortality and exacerbations in COPD patients, but do not assess these benefits when stratified by concurrent established COPD drug treatments

WHAT THIS STUDY ADDS

β blockers (predominantly cardioselective) reduced mortality and COPD exacerbations when added to stepwise inhaled therapy for COPD (including long acting β agonists and antimuscarinics) in addition to the benefits attributable to addressing cardiovascular risk

The benefits observed occurred without adverse effects on pulmonary function

These data support the use of β blockers in patients with COPD

This is a retrospective and observational study, so our results should be interpreted with caution. Confounding by indication is a limitation when performing observational studies of this nature. As we used a disease specific database for patient identification, we do not know the specific indication for β blocker prescription. In order to address this, we used a Cox proportional hazard regression model that corrected for all available influential covariates. We evaluated the effects of β blockers on all cause mortality independently of cardiovascular outcomes, including cardiac drug prescription and overt cardiovascular disease as measured by hospital admissions due to ischaemic heart disease, heart failure, or peripheral vascular disease (although a history of hypertension was unavailable for analysis from our database). Furthermore, when assessing the impact of β blocker use on all cause mortality, we performed a matched propensity scoring analysis, which is designed to minimise the effects of confounding by indication.³²

We chose a minimum age of 50 years in order to alleviate any concerns that younger patients might be regarded as asthmatic. An age cut-off of 45 years and above has been used in previous COPD observational studies.¹⁵ Furthermore, when analysing all the patients in our dataset regardless of age ($n=6345$), we saw similar trends in survival as with our study cohort of 5977. For example, among patients taking inhaled corticosteroids, long acting β agonists, tiotropium, and β blockers, the adjusted hazard ratio for all cause mortality was 0.33 (0.24 to 0.44) in the full dataset compared with 0.28 (0.21 to 0.39) in our study population. From these data, we believe patient exclusion has not biased our study results.

Conclusions and policy implications

We have shown that β blockers (predominantly cardioselective) may confer reductions in mortality, exacerbations, and hospital admissions in patients with COPD, in addition to the benefits attributable to addressing cardiovascular risk. These additive benefits were seen across a spectrum of inhaled stepwise

therapy, including inhaled corticosteroids, long acting β agonists, and long acting antimuscarinics, and did not result in any worsening of pulmonary function in our study cohort. Our study supports the use of β blockers in COPD patients.

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/doi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the Tayside Medical Research Ethics Committee.

Data sharing: No additional data available.

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