ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original Research Article

Acute effects of low dose bisoprolol on lung function and blood pressure in COPD patients

Thomas F Bradbury, Allison Martin, Robert J Hancox, Catherina L Chang, Richard Beasley, Jeremy P Wrobel, Vanessa M McDonald, Claudia C Dobler, Ian A Yang, Claude S Farah, Belinda Cochrane, Graham S Hillis, Caroline Polak Scowcroft, Ashutosh Aggarwal, Channa Ranasinha, Shane Galgey, Christine R Jenkins,

Please cite this article as: Bradbury TF, Martin A, Hancox RJ, *et al*. Acute effects of low dose bisoprolol on lung function and blood pressure in COPD patients. *ERJ Open Res* 2025; in press (https://doi.org/10.1183/23120541.00591-2025).

Acute effects of low dose bisoprolol on lung function and blood pressure in COPD patients

Thomas F Bradbury [1,2]; Allison Martin [1,2]; Robert J Hancox [3,4]; Catherina L Chang [4]; Richard Beasley [5]; Jeremy P Wrobel [6,7]; Vanessa M McDonald [8]; Claudia C Dobler [9]; Ian A Yang [10,11]; Claude S Farah [12]; Belinda Cochrane [13]; Graham S Hillis [14,15]; Caroline Polak Scowcroft [16]; Ashutosh Aggarwal [17]; Channa Ranasinha [18]; Shane Galgey [1]; Christine R Jenkins [1,2]; on behalf of the PACE in COPD Investigators*

[1] The George Institute for Global Health, Respiratory Group, Barangaroo, NSW, AU
[2] UNSW Sydney, Medicine & Health, Sydney, NSW, AU
[3] University of Otago, Preventive & Social Medicine, Dunedin, Otago, NZ
[4] Waikato Hospital, Respiratory Medicine, Hamilton, Waikato, NZ
[5] Medical Research Institute of New Zealand, Asthma Programme, Wellington, NZ
[6] Fiona Stanley Hospital, Respiratory Medicine, Murdoch, WA, AU
[7] The University of Notre Dame Australia - Fremantle Campus, School of Medicine, Fremantle, WA, AU
[8] The University of Newcastle, School of Nursing and Midwifery, Newcastle, NSW, AU
[9] Liverpool Hospital, Respiratory and Sleep Medicine, Liverpool, NSW, AU
[10] The Prince Charles Hospital, Department of Thoracic Medicine, Chermside, QLD, AU
[11] The University of Queensland, Faculty of Medicine, Brisbane, QLD, AU
[12] Concord Repatriation General Hospital, Respiratory / Thoracic Medicine, Concord, NSW, AU
[13] Campbelltown Hospital, Respiratory and Sleep Medicine, Campbelltown, NSW, AU
[14] Royal Perth Hospital, Department of Cardiology, Perth, WA, AU
[15] The University of Western Australia, UWA Medical School, Perth, WA, AU
[16] Consumer Representative, No Department, Canberra, ACT, AU
[17] Post Graduate Institute of Medical Education and Research, Department of Pulmonary Medicine, Chandigarh, CH, IN
[18] University of Kelaniya, Faculty of Medicine, Kelaniya, WP, LK
[*] listed in the acknowledgements section

Corresponding Author Information
Name: Dr Thomas Bradbury
Address: The George institute for Global Health
Level 18 / 300 Barangaroo Avenue
SYDNEY NSW 2000
Australia
Email: tfbradbury@gmail.com

Abstract word count: 238
Main text word count: 2843

Take-Home:4.5% of 292 COPD patients experienced an acute decrease in lung function a t2 hours following an oral 1.25mg dose of the cardioselective beta-blocker bisoprolol. A further 2.1% experienced systolic blood pressure decrease below 100mmHg.

Acute effects of low dose bisoprolol on lung function and blood pressure in COPD patients

Abstract

Background and Objective: Recent observational data suggests that cardioselective β-blockers like bisoprolol are safe and beneficial for patients with chronic obstructive pulmonary disease (COPD). However, the acute effects of bisoprolol on lung and cardiovascular function in these patients is unclear, a gap that this study aimed to address.

Methods: This was a sub-analysis of pre-randomisation screening visit data from the ongoing Preventing Adverse Cardiac Events (PACE) in COPD randomised controlled trial. If all other eligibility criteria were met, participants were orally administered an unblinded 1.25mg tablet of bisoprolol. Post-bronchodilator spirometry, heart rate and blood pressure were monitored at 0, 30 (cardiovascular parameters only), 60 and 120 minutes. For this sub-analysis, respiratory intolerance was defined as a decrease in forced expiratory volume in 1 minute (FEV1)(L) ≥200ml and ≥12% from the 0-minute FEV1(L) value; and cardiovascular intolerance was defined as systolic blood pressure (SBP) falling below 100mmHg at 1 or 2 hours.

Results: Of 359 consented participants, 292 conducted the test-dose procedure. Thirteen (4.5%) were respiratory intolerant and 6 (2.1%) were cardiovascular intolerant at 1 or 2 hours. No participant was intolerant for both. There was no significant difference in FEV1 (L) or SBP at baseline At 120 minutes the intolerant group's mean FEV1 (L) had significantly decreased to 1.05L (0.86–1.25; p<0.0001); the tolerant group experienced no change (1.10L (1.05–1.14); p=0.33).

Conclusion: The administration of 1.25mg bisoprolol was acutely well tolerated in over 95% of COPD patients.

Introduction

Chronic obstructive pulmonary disease (COPD) continues to be one of the most prevalent causes of global burden and mortality – ranking third in mortality behind cardiovascular diseases (CVD) [1,2]. Independent of tobacco smoking as a major shared risk factor [3], airflow limitation characteristic of COPD is also associated with development of CVD [4]. It is therefore unsurprising that these diseases are often comorbid [5], and that CVD-associated mortality is a significant cause of burden and mortality in COPD patients [6-8]. Despite advancements in the management of CVD and COPD, there is an ongoing need to further improve patient outcomes.

Beta blockers remain a cornerstone of pharmacotherapy for CVD, particularly in the management of heart failure with reduced ejection fraction, coronary heart disease and atrial fibrillation[9,10]. Their strong antagonism of beta-adrenergic receptors mediates clinically beneficial reductions in heart rate and stroke volume. However, in clinical practice the use of this class of drugs in patients with both COPD and CVD has historically been strongly cautioned, potentially discouraging use and leading to under-prescription [11,12]. This is due to the perceived risks in blocking the beta-agonist effects of inhaled bronchodilators on airway smooth muscle beta-2 (β_2)-receptors. Though a valid concern for the first generation of beta-blockers (e.g. propranolol) which non-specifically targeted all beta receptor subtypes, some of the beta blockers favoured in modern clinical practice such as bisoprolol and metoprolol, have a significantly higher affinity for beta-1 (β_1) receptors that are predominantly located on cardiomyocytes [13-15]. Most available literature evaluated the earlier, less selective beta blockers such as propranolol, often using superseded criteria and procedures for diagnosing COPD and assessing lung function [16-25]. As such there is a paucity of evidence describing if a single dose of a β_1 cardioselective beta blocker would deleteriously impact COPD patient respiratory and cardiovascular function.

Recently, there has been renewed interest in addressing the gap in literature regarding the long-term safety and efficacy profile of contemporary β_1 selective beta-blockers in people with COPD defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [2,26-30]. Using data from the ongoing Preventing Adverse Cardiac Events (PACE) in COPD trial, we investigated if a single low dose of bisoprolol, a cardioselective β_1 receptor blocker, would acutely impact the lung function and blood pressure in people with stable COPD.

Methods

The PACE in COPD trial (NCT03917914; CTRI/2020/08/027322.) protocol has been described previously [31]. It is an ongoing 1:1 randomised, double-blinded trial with a 24-month follow-up where eligible participants in Australia, India, New Zealand and Sri Lanka orally self-administer 1.25 – 5mg bisoprolol or a matched placebo once daily for two years.

The PACE in COPD study was approved by the Sydney Local Health District Human Research Ethics Committee at The Concord Repatriation General Hospital (2019/ETH08709). In New Zealand, the study was approved by the Health and Disability Ethics Committee at the Ministry of Health, Wellington (2022 AM 9124). In India, each clinical sites' Institutional Ethics committee individually approved the study. In Sri Lanka the study was approved by the ERC, Faculty of Medicine, University of Kelaniya (P/127/09/2021) and the National Medicines Regulatory Authority (NMRA/CTRD/P60/12-4/2022).

To be eligible for the PACE study, participants had a diagnosis of COPD, per the GOLD 2019 criteria [32] with a post-bronchodilator forced expiratory volume in 1 second (FEV_1) of ≥30% and ≤70% predicted and a 24-month history of at least one exacerbation that required treatment with antibiotics and/or oral corticosteroids.

If all other eligibility criteria were met, participants performed an unblinded test-dose procedure. This involved administration of a 1.25mg oral dose of bisoprolol (0-min) followed by regular spirometry (0, 60 and 120 minutes) and cardiovascular (0, 30, 60 and 120 minutes) measurements (systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR)) under study staff supervision. Participants withheld smoking tobacco for 1 hour prior to the test and were bronchodilated before the start of the test-dose procedure, either:

i. By 400mg of inhaled salbutamol for the pre-post spirometry, if all screening procedures were conducted in a single visit; or
ii. By taking their regular bronchodilator maintenance medication if the test dose procedure was conducted in a second, split screening visit.

This analysis defined respiratory intolerance as a decrease in a participant's 0 minute post-bronchodilator FEV1 values of ≥200mL and ≥12% of absolute FEV_1 at 1 or 2 hours. These thresholds were selected to align with the clinical definition of bronchodilator reversibility provided by the 2019 Global Initiative for Asthma (GINA) report [33]. A secondary definition which aligned with the PACE in COPD trial eligibility criteria for respiratory intolerance was also investigated, with the same thresholds but only applied to the 2-hour lung function measurements. Cardiovascular intolerance was defined as a reduction in SBP <100mmHg at the 1 or 2 hour time interval; this conservative threshold was selected to minimise the risk of a participant experiencing hypotension.

The primary outcome was the change in absolute FEV_1 (L), with a secondary outcome investigating the change in FEV_1 expressed as the percentage of predicted value after 120 minutes. Other secondary outcomes included the change in FVC (absolute), SBP, DBP and HR; as well as the change between successive measurements of FEV_1 and cardiovascular vital signs within each group. The authors and all study personnel of

this study remained blinded to subsequent participant randomisation and could access blinded data from the screening and baseline visits only.

Analysis was performed in STATA Basic Edition Version 18 (StataCorp LLC, Texas, USA). Participants were grouped by their tolerance status and differences between the groups for each outcome variable at each timepoint were analysed using generalised linear regression adjusted for age, sex and antihypertensive use (SBP and DBP analysis only). Least Square (adjusted) means were generated for each time point and compared to determine significant changes within, and between, tolerance groups. Univariable analysis of demographic and medical history (see table 1 for complete list of variables included) for predictors of respiratory intolerance was performed using binary logistic regression. For the analysis of difference in pre- and post-bronchodilator FEV_1 values, the pre-bronchodilator FEV1 was included as a covariate in a multivariable binary logistic analysis. A p-value of <0.05 was used to indicate statistical significance (hereafter referred to as "significant").

Results

From the 359 participants who consented to the study, 292 passed initial screening procedures and were administered the test-dose of bisoprolol (Figure 1). The baseline demographics and medical history are shown in Table 1. In brief, the mean age was 67.6 (7.6 SD) years, 242 (82.9%) were male and 91.8% had a history of tobacco smoking.

Two adverse events were reported as being associated with the test-dose procedure: a rapid decrease in SBP in a participant who self-administered oral opioids during the monitoring period without alerting investigators, and a participant reporting chest pain due to the number of spirometry manoeuvres performed. No acute emergence or worsening of respiratory symptoms were reported by participants.

Of the 292 participants, 13 (4.5%) were identified as respiratory intolerant at the 1- or 2-hour lung function measurements, with 9 participants (3.1%) intolerant at 2 hours only and deemed ineligible using the PACE in COPD eligibility criteria. A further 6 participants (2.1%) were identified as having cardiovascular intolerance. No participant was both respiratory and cardiovascular intolerant.

Respiratory Intolerant at 1 or 2 hours (n=13)

The change in FEV_1(L) during the monitoring interval is shown in Figure 2 for the respiratory intolerant group. At 0 minutes the adjusted mean FEV_1 (L) of the tolerant group was 1.10L (95%CI 1.06 – 1.14), and in the-intolerant group 1.24L (95%CI 1.05 – 1.44). The difference in these values was not significant (p=0.164). At 60 minutes the tolerant group's mean adjusted FEV_1 was 1.11L (95%CI 1.06 – 1.15), which was not a statistically significant change from the 0 minute value (p=0.460). The intolerant group's 60 minute value of 1.03L (95%CI 0.83 – 1.22) was a significant decrease from its 0 minute value ($p<0.0001$). The difference between the tolerant and intolerant group values was not significantly different (p=0.441). At 120 minutes the tolerant group mean adjusted FEV_1 (L) was 1.10L (95%CI 1.05 – 1.14), and 1.05L (95%CI 0.86 – 1.25) in the intolerant group. The tolerant group FEV1 (L) at 120 minutes was not significantly different from the 0 minute value (p=0.329), but the intolerant group mean FEV1 was significantly lower ($p<0.0001$) than baseline. Neither group's 120 minute values were significantly different from the 60 minute values. The difference between

the adjusted mean 120 minute FEV1 (L) values was not significant (p=0.674). There were no significant differences in FEV_1 (L) in the cardiovascular intolerant group (Table 2).

As shown in Figure 3, the FEV_1 expressed as % predicted was significantly different between the tolerant (45.25% [95%CI 43.82 – 46.69]) and intolerant (52.54% [95%CI 45.86 – 59.23]) respiratory groups at 0 minutes (p=0.037). At 60 minutes the tolerant group's mean adjusted value was 45.47% (95%CI 44.03 – 46.90), which was not significantly different from the 0 minute value. The intolerant group's decrease to 43.47% (95%CI 36.78 – 50.15) was significant (p<0.0001). At this time point the difference between the groups was not significant (p=0.567). At 120 minutes each group's adjusted mean percent predicted FEV_1 value had decreased; 45.00% (95%CI 43.56 – 46.44) for tolerant, and 43.93% (95%CI 37.24 – 50.62) for intolerant. The tolerant group FEV1 (%Pred) at 120 minutes was not significantly different from the 0 minute value (p=0.350), but the intolerant group mean FEV1 was significantly lower (p<0.0001) than baseline. Neither group's 120 minute values were significantly different from the 60 minute values. The difference between the two groups was not significant at 120 minutes (p=0.759). There were no significant differences in FEV1 % predicted in the cardiovascular intolerant group (Table 2).

The FVC was not significantly different between or within the tolerance groups in either the respiratory or cardiovascular outcomes (table 2).

Respiratory Intolerant at 2 hours (n=9)

Participants identified as respiratory intolerant using the PACE in COPD eligibility criteria definition had an adjusted 0 minute mean FEV_1(L) of 1.25L (95%CI 1.02 – 1.48); the tolerant group's was 1.10L (95%CI 1.06 – 1.14), with no statistically significant difference between the groups (p=0.219). At 120 minutes the intolerant, ineligible group's mean adjusted FEV1 had significantly decreased from the 0 minute value (p<0.0001) to 0.96L (95%CI 0.72 – 1.19). The tolerant, eligible group's had not changed (1.10L; p=0.219 [95%CI 1.06 – 1.14]). The difference between the adjusted mean 120 minute FEV1 (L) values was not significant (p=0.239).

Expressed as %predicted FEV, the PACE protocol-defined intolerant participants had a mean, adjusted 0 minute value of 51.97% (95%CI 43.96 – 59.98) that significantly (p<0.0001) decreased to 38.97% (95%CI 30.96 – 46.98) at 120 minutes. The tolerant, eligible participants had a 0 minute mean adjusted value of 45.38% (95%CI 43.95 – 46.80) and a 120 minute value of 45.14% (p=0.387; 95%CI 43.72 – 46.57). The difference between the two groups was not significant at 0 (p=0.112) or 120 minutes (p=0.137). Further analysis of cardiovascular values and FVC can be found in supplement 2.

Cardiovascular Intolerant at 1 or 2 hours (n=6)

The cardiovascular tolerant group (n=286) had a mean adjusted SBP of 131mmHg (95%CI 129 – 133) at 0 minutes, whilst the intolerant group (n=6) mean SBP was 111mmHg ([95%CI 100 – 123], which was significantly different (p=0.0013); Figure 4). By 120 minutes the tolerant group mean SBP had decreased to 125mmHg (95%CI 125 – 127), which was significantly different from baseline (p<0.0001). The intolerant group mean SBP at 120 minutes was 91mmHg (95%CI 80 – 103), which was a significant decrease from baseline (p<0.0001). The difference between the tolerant

and intolerant group SBP values at 120 minutes was significantly different (p<0.0001). There was no significant difference in SBP in the respiratory intolerant group (Table 2).

The mean adjusted DBP was similarly significantly different at 0 minutes between the cardiovascular tolerant (81mmHg [95%CI 80 – 82]) and intolerant groups (72mmHg [95%CI 64 – 79]; p<0.0001). At 120 minutes both the tolerant (77mmHg [95%CI 76 – 66]; <0.0001) and intolerant (59mmHg [95%CI 51 – 66]; p<0.0001) groups had DBP values significantly lower than their 0 minute values (Table 2).

Within each group for both cardiovascular and respiratory tolerance/intolerance, the adjusted mean heart rate values at 120 minutes were significantly decreased from the baseline 0 minute values (Table 2), but were not significantly different between tolerant/intolerant groups.

Analysis of predictors of respiratory intolerance

Respiratory intolerance at 1 or 2 hours was significantly associated with percentage difference between pre and post-bronchodilator FEV_1 (L) with an odds ratio (OR) of 1.07; p=0.015 (95%CI 1.01 – 1.105), followed by the participant residing in Sri Lanka with an odds ratio (OR) of 4.37 (p=0.019; 95%CI 1.27 – 15.03), and percentage-predicted post-bronchodilator FVC (OR=1.03; p=0.043 (1.00 – 1.06).

When using the PACE in COPD trial eligibility definition of respiratory intolerance (decrease in a participant's 0 minute post-bronchodilator FEV1 values of ≥200mL and ≥12% of absolute FEV_1 at 2 hours only), the percentage difference in pre and post-bronchodilator FEV_1 prior to test-dose administration was the strongest predictor of respiratory intolerance with an Odds Ratio of 1.10 (p=0.005; 95%CI 1.03 – 1.17), followed by the absolute difference (p=0.018). No other variables reached statistical significance.

Discussion

This analysis used data collected from the ongoing PACE in COPD trial and aimed to determine if oral administration of 1.25mg of the β_1 receptor selective drug bisoprolol would cause an acute decrease in lung function or blood pressure. The results suggest that while there was a potentially clinically significant decrease in FEV_1 in 4.5% of participants, lung function was preserved in the majority (>96.9%) over a two-hour period. When using the PACE in COPD protocol eligibility definition, this group decreased to 3.1%, with four participants from this analysis' intolerance criteria demonstrating an improvement in lung function between 60 minutes and 120 minutes that re-classified them as tolerant. For both groups the strongest predictor was the percentage difference between pre- and post-bronchodilator FEV_1 (L), even when adjusted for baseline pre-bronchodilator values. When investigating cardiovascular intolerance, only 2.1% experienced a decrease in SBP below 100mmHg. All participants regardless of respiratory intolerance experienced a pharmacologically predictable and statistically significant decrease in blood pressure and heart rate during the procedure. The results in this study suggest that low-dose bisoprolol does not have significant acute effects on lung function or blood pressure in a large majority of COPD patients, and should be safe to be prescribed for treatment of comorbid CVD.

Though there is some recent literature documenting the short-term impact of beta blockers on the lung function of COPD patients [34-36], there is scant literature describing the acute effects of a single dose of β_1 selective beta blockers such as bisoprolol. In addition, the studies with other beta-blockers that were conducted were reported between 1966 and 2002 [16-25]. As such, they lack the standardised definition and diagnostic criteria currently used to identify COPD, and their methodologies are no longer aligned with current clinical or respiratory research practice. Given the comorbidity of COPD and heart failure, such a gap in the literature is significant, particularly when the prevailing clinical sentiment was that this class of drugs should be avoided due to perceived safety risks despite their potential benefits in the management of CVD. The results of this analysis provide contemporary evidence indicating that the risk of experiencing acute effects of highly selective β_1 blockers may be marginal, whilst still providing cardiovascular benefit.

Bisoprolol, and other cardioselective beta blockers have been safely administered by clinicians for decades based on evidence in many observational studies conducted using different patient populations and designs [26, 37-48]. More recently, the BICS trial found no increased long-term risk of any kind in COPD patients administered bisoprolol versus placebo [2]. This contrasts with the results of the BLOCK COPD trial, which terminated early, due to an increased rate of severe exacerbations in the group that received metoprolol [27]. The reason for this disparity is unclear but could be due to metoprolol's inferior cardioselectivity [13, 15], potentially leading to off-target antagonism of the β_2 receptor in airway tissue. The results of the primary PACE analysis and the ongoing BRONCHIOLE trial investing metoprolol [49] may provide further evidence to inform future clinical decisions in this patient population.

This study has several strengths. Primarily it studied a large number of consented trial participants who underwent prior eligibility screening before the test dose procedure to ensure a representative sample of COPD patients. The study population was also drawn from diverse settings including Australasia and South Asia. Furthermore, it uses a robust statistical model to minimise the potential influence of confounding variables in the analysis. One limitation could be the use of multiple spirometry measurements in a single visit. As each time interval required at least 3 concordant manoeuvres to produce a reliable dataset, participants were required to perform a minimum of 9 manoeuvres over 2 hours in a single screening visit. This may have led to a decline in measured values in some patients due to fatigue, potentially leading to submaximal exhalation and thus overestimation of the deleterious effects of bisoprolol.

In conclusion these findings suggest that a low dose of a cardioselective beta-blocker such as bisoprolol may only adversely affect a small proportion of COPD patients, with most demonstrating the predictable clinical effect of safe reductions in heart rate and blood pressure.

Conflicts of Interest

Allison Martin, Claudia C Dobler, Ian A Yang, Claude S Farah, Graham S Hillis, Carol P Scoowcroft, Ashutosh Aggarwal and Shane Galgey have nothing to declare in relation to this work.

Thomas F Bradbury received a PhD top-up stipend funded by GSK for a portion of their candidature, during which time some work on this study was undertaken.

Robert Hancox declares that they are a staff member of the University of Otago, which received a grant from the Health Research Council of New Zealand; has received honoraria from GSK; received honoraria and travel funding from AstraZeneca.

Cat Chang declares that the Health Research Council of New Zealand provided a grant for study, which was paid to the University of Otago then subcontracted out to their employer, Waikato Hospital.

Richard Beasley declares that he has previously received project grant from the Health Research Council of New Zealand. They have received institutional research funding from AstraZeneca, Teva, and Fisher & Paykel Healthcare; received payment for personal fees from AstraZeneca and Cipla; received support from AstraZenca to attend meetings; has received medication and equipment from AstraZeneca to support clinical trials; was previously on the board of the Global Initiative for Obstructive Lung disease, and chaired the Asthma Guidelines group within the New Zealand Asthma and Respiratory Foundation

Jeremy Wrobel has received honoraria from Boehringer Ingelheim for lectures; has received support to attend the "Airways" conference in Sydney, Australia and the 2023 American Thoracic Society Annual Scientific Meeting in Washington, DC, USA.

Vanessa M McDonald declares that they have received a grant from the National Health and Medical Research Council of Australia.

Belinda Cochrane declares that they have received institutional grant funding from GSK for an investigator-sponsored study; has received personal consultancy fees from GSK and Sanofi; has received personal speaker's fees from AstraZeneca, Moderna and RX Global; are a member of the COPD coordinating committee and the COPDX Guidelines, which are both associated with the Lung Foundation of Australia. Channa Ranasinha declares that they have received payment from AstraZeneca for delivering lectures and received support for attending APSR 2024; received honorarium from The George Institute for Global Health via Remedium One.

Christine R Jenkins declares that she has received personal and institutional grants from GSK and AstraZeneca; institutional grants from Chiesi, Sanofi and Menarini; consulting fees and payments for other activities from GSK, AstraZeneca, Chiesi, Sanofi and Menar; payment for expert testimony from AstraZeneca and Chiesi; travel bookings and accomodation paid for by GSK and AstraZeneca; is a director of the Lung Foundation Australia and the Asbestos and Dust Disease Research Institute Board; was a member of the data safety monitoring board (DSMB) without payment for the LAMA by Night, COPERNICUS and VCAPS4 studies; was a member of the

CICERO - Catalina steering committee without payment; has received payment for participating on advisory boards for GSK, AstraZeneca, Chiesi, Sanofi and Menarini.

Acknowledgements

The authors would also like to thank The George Institute Australian research team: Ayesha Mallik, Brittany Aldridge, Chris Gianacas, Manuela Armenis and Junya Eguchi; the New Zealand Waikato coordinating centre team: Christine Tuffery and Anneke Marais; the George Institute Indian coordinating centre team: Shani Thankachen and Sachin Rana; the Sri Lankan RemediumOne coordinating centre team: Poornima Ellawalla, Anne Vithushi and Niran Perera; as well as all the study participants involved in the PACE in COPD trial. We would also like to acknowledge the principal investigators at each site below.

Name	Institution	Location
Prof John Wheatley	Westmead Hospital	Sydney, NSW Australia
Dr Christopher Kosky	Sir Charles Gairdner Hospital	Perth, WA Australia
A/Prof Siva Sivakumaran	Gold Coast University Hospital	Southport, QLD Australia
Prof John Upham	Princess Alexandra Hospital	Brisbane, QLD Australia
Dr Peter Bremner	TrialsWest Pty Ltd	Spearwood, WA, Australia
Dr Jack Drummer	Dunedin Hospital	Dunedin, New Zealand
Dr Conroy Wong	Middlemore Hospital	Auckland, New Zealand
Prof Lutz Beckert	University of Otago	Christchurch, New Zealand
Dr Christopher Lewis	Greenlane Clinical Centre	Auckland, New Zealand
Prof Uma Maheswari Krishnaswamy	St John's Medical College Hospital	Bangalore, India
Dr DJ Christopher	Christian Medical College	Vellore, India
Prof Anant Mohan	All India Institute of Medical Sciences	Ansari Nagar, New Delhi, India
Prof Dhruva Chaudhry	Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences	Rohtak, Haryana, India
A/Prof Alok Nath	Sanjay Gandhi Postgraduate Institute of Medical Sciences	Lucknow, India
Dr Amitha Fernando	Central Chest Clinic	Colombo, Sri Lanka
Dr Dushantha Madegedara	Kandy National Hospital	Kandy, Sri Lanka
Dr Eshanth Perera	National Institute of Respiratory Diseases	Wellisara, Sri Lanka
Dr Ravini Karunattilake	Central Chest Clinic - Borella	Colombo, Sri Lanka
Professor Vanessa McDonald	Hunter Medical Research Institute	Newcastle, NSW Australia
Dr Claudia Dobler	Liverpool Hospital	Sydney, NSW Australia

Name	Institution	Location
Dr Claude Farah	Concord & Repatriation Hospital	Sydney, NSW Australia
Dr Belinda Cochrane	Campbelltown Hospital	Sydney, NSW Australia
Adjunct Associate Professor Jeremy Wrobel	Fiona Stanley Hospital	Perth, WA Australia
Dr Ian Yang	The Prince Charles Hospital	Chermside, QLD Australia
Professor Robert Hancox	Dunedin Hospital	Dunedin, New Zealand
Adjunct Professor Richard Beasley	Medical Research Institute of New Zealand	Wellington, New Zealand
Dr Caterina Chang	Waikato Hospital	Hamilton, New Zealand
Professor Ashutosh Aggarwal	Postgraduate Institute of Medical Education and Research	Chandigarh, India
Dr Graham Hillis	Royal Perth Hospital	Perth, WA, Australia

Funding

This study was funded by the National Health and Medical Research Council (NHMRC) of Australia, Project Grant APP1163143 and the Health Research Council of New Zealand, Project Grant 19/487.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author and the PACE in COPD steering committee upon reasonable request.

Ethics Statement

Per the main text, this publication's data is derived from the PACE in COPD study, which is registered at clinicaltrials.gov (ID: NCT03917914) and the Clinical Trials Registry – India (ID: CTRI/2020/08/027322). The PACE in COPD study was approved by the Sydney Local Health District Human Research Ethics Committee at The Concord Repatriation General Hospital (2019/ETH08709). In New Zealand, the study was approved by the Health and Disability Ethics Committee at the Ministry of Health, Wellington (2022 AM 9124). In India, each clinical sites' Institutional Ethics committee individually approved the study. In Sri Lanka the study was approved by the ERC, Faculty of Medicine, University of Kelaniya (P/127/09/2021) and the National Medicines Regulatory Authority (NMRA/CTRD/P60/12-4/2022).

References

1. Safiri S, Carson-Chahhoud K, Noori M, Nejadghaderi SA, Sullman MJM, Ahmadian Heris J, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. *BMJ*. 2022;**378**:e069679.
2. Devereux G, Cotton S, Nath M, McMeekin N, Campbell K, Chaudhuri R, et al. Bisoprolol in Patients With Chronic Obstructive Pulmonary Disease at High Risk of Exacerbation: The BICS Randomized Clinical Trial. *JAMA*. 2024;**332**(6):462-70.
3. Banks E, Joshy G, Korda RJ, Stavreski B, Soga K, Egger S, et al. Tobacco smoking and risk of 36 cardiovascular disease subtypes: fatal and non-fatal outcomes in a large prospective Australian study. *BMC Med*. 2019;**17**(1):128.
4. Maclay JD, McAllister DA, MacNee W. Cardiovascular risk in chronic obstructive pulmonary disease. *Respirology*. 2007;**12**(5):634-41.
5. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail*. 2009;**11**(2):130-9.
6. Huiart L, Ernst P, Suissa S. Cardiovascular Morbidity and Mortality in COPD. *CHEST*. 2005;**128**(4):2640-6.
7. Mannino DM, Doherty DE, Sonia Buist A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. *Respir Med*. 2006;**100**(1):115-22.
8. Vestbo J, Anderson J, Brook R, Calverley P, Celli B, Crim C, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet*. 2016;**387**(10030):1817-26.
9. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;**140**(11):e596-e646.
10. Atherton JJ, Sindone A, De Pasquale CG, Driscoll A, MacDonald PS, Hopper I, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018. *Heart Lung Circ*. 2018;**27**(10):1123-208.
11. Lim KP, Loughrey S, Musk M, Lavender M, Wrobel JP. Beta-blocker under-use in COPD patients. *Int J Chron Obstruct Pulmon Dis*. 2017;**12**:3041-6.
12. Lipworth B, Skinner D, Devereux G, Thomas V, Ling Zhi Jie J, Martin J, et al. Underuse of β-blockers in heart failure and chronic obstructive pulmonary disease. *Heart*. 2016;**102**(23):1934.
13. Baker JG. The selectivity of beta-adrenoceptor antagonists at the human beta1, beta2 and beta3 adrenoceptors. *Br J Pharmacol*. 2005;**144**(3):317-22.
14. Schnabel P, Maack C, Mies F, Tyroller S, Scheer A, Böhm M. Binding Properties of β-Blockers at Recombinant β1-, β2-, and β3-Adrenoceptors. *J Cardiovasc Pharmacol*. 2000;**36**(4).
15. Smith C, Teitler M. Beta-Blocker Selectivity at Cloned Human Beta1- and Beta2-Adrenergic Receptors. *Cardiovasc Drugs Ther*. 1999;**13**(2):123-6.
16. McNeill RS, Ingram CG. Effect of propranolol on ventilatory function. *The Am J Cardiol.* 1966;**18**(3):473-5.
17. Tivenius L, Nyberg G. Effects of alprenolol and propranolol on ventilatory function. *Pharmacol. Clin*. 1969;**2**(1):51-7.

18. McGavin CR, Williams IP. The effects of oral propranolol and metoprolol on lung function and exercise performance in chronic airways obstruction. *Br J Dis Chest.* 1978;**72**(4):327-32.
19. Butland RJ, Pang JA, Geddes DM. Effect of beta-adrenergic blockade on hyperventilation and exercise tolerance in emphysema. *J Appl Physiol Respir Environ Exerc Physiol*. 1983;**54**(5):1368-73.
20. Quan SF, Fenster PE, Hanson CD, Coaker LA, Basista MP. Suppression of Atrial Ectopy with Intravenous Metoprolol in Chronic Obstructive Pulmonary Disease Patients. *J Clin Pharmacol*. 1983;**23**(8-9):341-7.
21. van Herwaarden CLA. β-Adrenoceptor Blockade and Pulmonary Function in Patients Suffering from Chronic Obstructive Lung Disease. *J Cardiovasc Pharmacol*. 1983;**5**.
22. Clague HW, Ahmad D, Carruthers SG. Influence of cardioselectivity and respiratory disease on pulmonary responsiveness to beta-blockade. *Eur J Clin Pharmacol*. 1984;**27**(5):517-23.
23. Fenster PE, Quan SF, Hanson CD, Coaker LA. Suppression of ventricular ectopy with intravenous metoprolol in patients with chronic obstructive pulmonary disease. *Crit Care Med*. 1984;**12**(1):29-32.
24. Dorow P. β1/ β2-Splitting of Bisoprolol. *J Cardiovasc Pharmacol*. 1986;**8**.
25. Kotlyar E, Keogh AM, Macdonald PS, Arnold RH, McCaffrey DJ, Glanville AR. Tolerability of carvedilol in patients with heart failure and concomitant chronic obstructive pulmonary disease or asthma. *J Heart Transplant*. 2002;**21**(12):1290-5.
26. Chung C-M, Lin M-S, Chang S-T, Wang P-C, Yang T-Y, Lin Y-S. Cardioselective Versus Nonselective β-Blockers After Myocardial Infarction in Adults With Chronic Obstructive Pulmonary Disease. *Mayo Clin Proc*. 2022;**97**(3):531-46.
27. Dransfield MT, McAllister DA, Anderson JA, Brook RD, Calverley PMA, Celli BR, et al. β-Blocker Therapy and Clinical Outcomes in Patients with Moderate Chronic Obstructive Pulmonary Disease and Heightened Cardiovascular Risk. An Observational Substudy of SUMMIT. *Ann Am Thorac Soc*. 2018;**15**(5):608-14.
28. Gulea C, Zakeri R, Alderman V, Morgan A, Ross J, Quint JK. Beta-blocker therapy in patients with COPD: a systematic literature review and meta-analysis with multiple treatment comparison. *Respir Res*. 2021;**22**(1):64.
29. Dransfield MT, Voelker H, Bhatt SP, Brenner K, Casaburi R, Come CE, et al. Metoprolol for the Prevention of Acute Exacerbations of COPD. *N Engl J Med*. 2019;**381**(24):2304-14.
30. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Prevention, Diagnosis and Management of COPD - 2024 Report. https://goldcopd.org: GOLD; 2024 (accessed 23 October 2024).
31. Martin A, Hancox RJ, Chang CL, Beasley R, Wrobel J, McDonald V, et al. Preventing adverse cardiac events (PACE) in chronic obstructive pulmonary disease (COPD): study protocol for a double-blind, placebo controlled, randomised controlled trial of bisoprolol in COPD. *BMJ open*. 2021;**11**(8):e053446.
32. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Prevention, Diagnosis and Management of COPD - 2019 Report. https://goldcopd.org: GOLD; 2019 (accessed 07 February 2022).
33. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention: 2019. https://ginasthma.org: GINA; 2019.
34. Jabbal S, Anderson W, Short P, Morrison A, Manoharan A, Lipworth BJ. Cardiopulmonary interactions with beta-blockers and inhaled therapy in COPD. *QJM.* 2017;**110**(12):785-92.

35. Jabbal S, Lipworth BJ. Tolerability of Bisoprolol on Domiciliary Spirometry in COPD. *Lung*. 2018;**196**(1):11-4.
36. Chang CL, Mills GD, McLachlan JD, Karalus NC, Hancox RJ. Cardio-selective and non-selective beta-blockers in chronic obstructive pulmonary disease: effects on bronchodilator response and exercise. *Intern Med Jl*. 2010;**40**(3):193-200.
37. Andersson C, Hansen PW, Steffensen IE, Andreasen C, Weeke PE, Køber L, et al. Mortality associated with cardiovascular drugs in patients with chronic obstructive pulmonary disease and right-sided heart failure - A danish nationwide registry-based study. *Eur J Intern Med*. 2019;**63**:56-61.
38. Bhatt SP, Wells JM, Kinney GL, Washko GR, Jr., Budoff M, Kim Y-I, et al. β-Blockers are associated with a reduction in COPD exacerbations. *Thorax*. 2016;**71**(1):8-14.
39. Coiro S, Girerd N, Rossignol P, Ferreira JP, Maggioni A, Pitt B, et al. Association of beta-blocker treatment with mortality following myocardial infarction in patients with chronic obstructive pulmonary disease and heart failure or left ventricular dysfunction: a propensity matched-cohort analysis from the High-Risk Myocardial Infarction Database Initiative. *Eur J Heart Fail*. 2017;**19**(2):271-9.
40. Karimi L, Lahousse L, De Nocker P, Stricker BH, Brusselle GG, Verhamme KMC. Effect of β-blockers on the risk of COPD exacerbations according to indication of use: the Rotterdam Study. *ERJ Open Res*. 2021;**7**(2):00624-2020.
41. Kubota Y, Tay WT, Teng TK, Asai K, Noda T, Kusano K, et al. Impact of beta-blocker use on the long-term outcomes of heart failure patients with chronic obstructive pulmonary disease. *ESC heart fail*. 2021;**8**(5):3791-9.
42. Liao KM, Lin TY, Huang YB, Kuo CC, Chen CY. The evaluation of β-adrenoceptor blocking agents in patients with COPD and congestive heart failure: a nationwide study. *Int J Chron Obstruct Pulmon Dis*. 2017;**12**:2573-81.
43. Oda N, Miyahara N, Ichikawa H, Tanimoto Y, Kajimoto K, Sakugawa M, et al. Long-term effects of beta-blocker use on lung function in Japanese patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2017;**12**:1119-24.
44. Rasmussen DB, Bodtger U, Lamberts M, Torp-Pedersen C, Gislason G, Lange P, et al. Beta-blocker use and acute exacerbations of COPD following myocardial infarction: a Danish nationwide cohort study. *Thorax*. 2020;**75**(11):928.
45. Rutten FH, Zuithoff NP, Hak E, Grobbee DE, Hoes AW. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. *Arch Intern Med*. 2010;**170**(10):880-7.
46. Short PM, Lipworth SI, Elder DH, Schembri S, Lipworth BJ. Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. *BMJ*. 2011;**342**:d2549.
47. Su TH, Chang SH, Kuo CF, Liu PH, Chan YL. β-blockers after acute myocardial infarction in patients with chronic obstructive pulmonary disease: A nationwide population-based observational study. *PLoS One*. 2019;**14**(3):e0213187.
48. van Gestel YRBM, Hoeks SE, Sin DD, Welten GMJM, Schouten O, Witteveen HJ, et al. Impact of Cardioselective β-Blockers on Mortality in Patients with Chronic Obstructive Pulmonary Disease and Atherosclerosis. *Am J Respir Crit Care Med*. 2008;**178**(7):695-700.
49. Sundh J, Magnuson A, Montgomery S, Andell P, Rindler G, Fröbert O. Beta-blockeRs tO patieNts with CHronIc Obstructive puLmonary diseasE (BRONCHIOLE) - Study protocol from a randomized controlled trial. *Trials*. 2020;**21**(1):123.

Table 1: Baseline demographics and medical history of consented participants who undertook the baseline bisoprolol test dose procedure (n=292); intolerance defined using this analysis' primary definition. All figures presented as mean (SD) unless specified otherwise.

	Respiratory		Cardiovascular		
	Tolerant (n = 279)	Intolerant (n = 13)	Tolerant (n = 286)	Intolerant (n = 6)	Total (n = 292)
Age	67.7 (7.5)	65.1 (8.5)	67.6 (7.6)	70.2 (5.4)	67.6 (7.6)
Sex, male; n(%)	230 (82.4)	12 (92.3)	237 (82.9)	5 (83.3)	242 (82.9)
BMI	22.7 (6.8)	22.2 (3.7)	22.8 (6.7)	19.9 (2.5)	22.7 (6.7)
Smoking Status, n(%)					
Never	21 (7.5)	3 (23.1)	24 (8.9)	0 (0.0)	24 (8.2)
Former	223 (79.9)	9 (69.2)	226 (79.0)	6 (100.0)	232 (79.5)
Current	35 (12.5)	1 (7.7)	36 (12.6)	0 (0.0)	36 (12.3)
Current Smoker Pack Years	33.0 (22.2)	40	32.2 (22.3)	0 (0.0)	32.2 (22.3)
LAMA, n(%)	106 (38.0)	7 (53.8)	112 (39.2)	1 (16.7)	113 (38.7)
LAMA/LABA, n(%)	22 (7.9)	2 (15.4)	24 (8.4)	0 (0.0)	24 (8.2)
Current LAMA/LABA/ICS, n(%)	30 (10.8)	0 (0.0)	29 (10.1)	1 (16.7)	30 (10.3)
Current antihypertensives n(%)	88 (31.5)	5 (38.5)	92 (32.2)	1 (16.7)	93 (31.8)
Spirometry [1]					
Pre-BD FEV1 (L)	1.02 (0.34)	1.15 (0.42)	1.03 (0.34)	0.83 (0.09)	1.03 (0.34)
Pre-BD FEV1 (%Pred)	42.1 (11.5)	46.2 (12.4)	42.3 (11.6)	38.7 (5.9)	42.3 (11.5)
Post-BD FEV1 (L)	1.10 (0.35)	1.28 (0.40)	1.11 (0.36)	0.89 (0.13)	1.11 (0.36)
Post-BD FEV1 (%Pred)	45.3 (11.9)	51.9 (10.4)	45.6 (12.0)	43.3 (8.0)	45.6 (11.9)
Pre-Post FEV change (%)	8.3 (10.0)	14.2 (10.8)	8.6 (10.2)	6.7 (5.7)	8.6 (10.1)
Post-BD FVC (L)	2.22 (0.71)	2.52 (1.01)	2.24 (0.7)	1.64 (0.43)	2.23 (0.73)

FEV1/FVC Ratio	0.51 (0.11)	0.53 (0.09)	0.51 (0.11)	0.57 (0.11)	0.51 (0.11)
Cardiovascular Parameters [2]					
Heart Rate (BPM)	82.2 (10.1)	84.8 (16.8)	82.3 (10.4)	80.7 (12.0)	80.7 (9.7)
SBP (mmHg)	131.0 (15.3)	127.6 (14.8)	131.3 (15.0)	111 (13.7)	130.9 (15.2)
DBP (mmHg)	80.7 (9.7)	84.8 (16.8)	80.9 (9.6)	71.5 (10.2)	82.3 (10.4)
Country of residence n(%)					
Australia	47 (16.8)	0 (0.00)	46 (16.1)	1 (16.7)	47 (16.1)
New Zealand	25 (9.0)	1 (7.7)	26 (9.1)	0 (0.0)	26 (8.9)
India	65 (23.3)	8 (61.5)	73 (25.5)	0 (0.0)	73 (25.0)
Sri Lanka	142 (50.9)	4 (30.8)	141 (49.3)	5 (83.3)	146 (50.0)

Abbreviations: LAMA: long-acting muscarinic antagonist; LABA: long acting beta agonist; ICS: inhaled corticosteroid; post-BD: post-bronchodilator; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; BPM: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; mmHg: millimetres of mercury.
[1]post-bronchodilator spirometry values set as time 0 for the test dose; [2]cardiovascular parameters set as time 0 for the test dose.

Table 2: Adjusted mean secondary cardiovascular and spirometry outcomes at 0, 30, 60 and 120 minutes following oral administration of 1.25mg bisoprolol in the respiratory tolerant and intolerant groups and the cardiovascular tolerant and intolerant groups. All figures presented as mean (95% CI).

		Respiratory Tolerance				Cardiovascular Tolerance				
Time (min)	**Group**	**SBP (mmHg)**	**DBP (mmHg)**	**HR (bpm)**	**FVC (L)**	**DBP (mmHg)**	**HR (bpm)**	**FEV_1 (L)**	**FEV_1 (%pred)**	**FVC (L)**
0	*Tolerant*	131 (129–133)	81 (80–82)	82 (81–83)	2.22 (2.14 – 2.30)	81 (80-82)	82 (81–83)	1.11 (1.07 – 1.15)	45.63 (44.21 – 47.05)	2.24 (2.16 – 2.32)
	Intolerant	127 (119–135)	81 (76–86)	84 (79–90)	2.46 (2.08 – 2.85)	72 (64–79)	81 (73–89)	0.92 (0.64 – 1.20)	43.07 (33.23 – 52.90)	1.67 (1.11 – 2.24)
30	*Tolerant*	128** (126–129)	79** (77–80)	79** (78–81)	*Not performed at 30 min*	79** (78–80)	80** (78–81)	*Not performed at 30 min*		
	Intolerant	124 (116–132)	81 (75–86)	79* (74–85)		62* (55–69)	77 (69–85)			
60	*Tolerant*	126* (124–127)	77* (76–78)	77** (76–78)	2.23 (2.15 – 2.32)	78* (77–79)	77** (76–78)	1.11 (1.07 – 1.15)	45.44 (44.01 – 46.86)	2.24 (2.16 – 2.32)
	Intolerant	122 (113–130)	79 (74–85)	76* (70–81)	2.15 (1.76 – 2.53)	62 (55–70)	72* (64–80)	0.91 (0.63 – 1.20)	42.57 (32.73 – 52.40)	1.75 (1.18 – 2.32)
120	*Tolerant*	125## (123–127)	77## (76–78)	75**, ## (73–76)	2.21* (2.12 – 2.29)	77## (76–79)	75**, ## (73–76)	1.10 (1.06 – 1.14)	43.66 (42.24 – 45.08)	2.21* (2.13 – 2.29)
	Intolerant	124 (115–132)	80 (75–86)	74## (69–80)	2.04 (1.66 – 2.43)	59## (51–66)	72* (64–80)	0.93 (0.64 – 1.22)	43.66 (33.72 – 53.60)	1.69 (1.12 – 2.26)

	Between group comparison	*p=0.771*	*p=0.192*	*p=0.979*	*p=0.423*	*p<0.0001*	*p=0.489*	*p=0.258*	*p=0.796*	*p=0.077*

Note: * and ** respectively indicates p<0.05 and p<0.0001 between the adjusted mean and previous adjusted mean within a tolerance group; # and ## respectively indicates p<0.05 and p<0.0001 between the 0 minute and 120 minute measurements.

Abbreviations: SBP: systolic blood pressure; mmHg: millimetres of mercury; DBP: diastolic blood pressure; HR: heart rate; BPM: beats per minute; FEV_1, forced expiratory volume in 1 second; FVC: forced vital capacity.

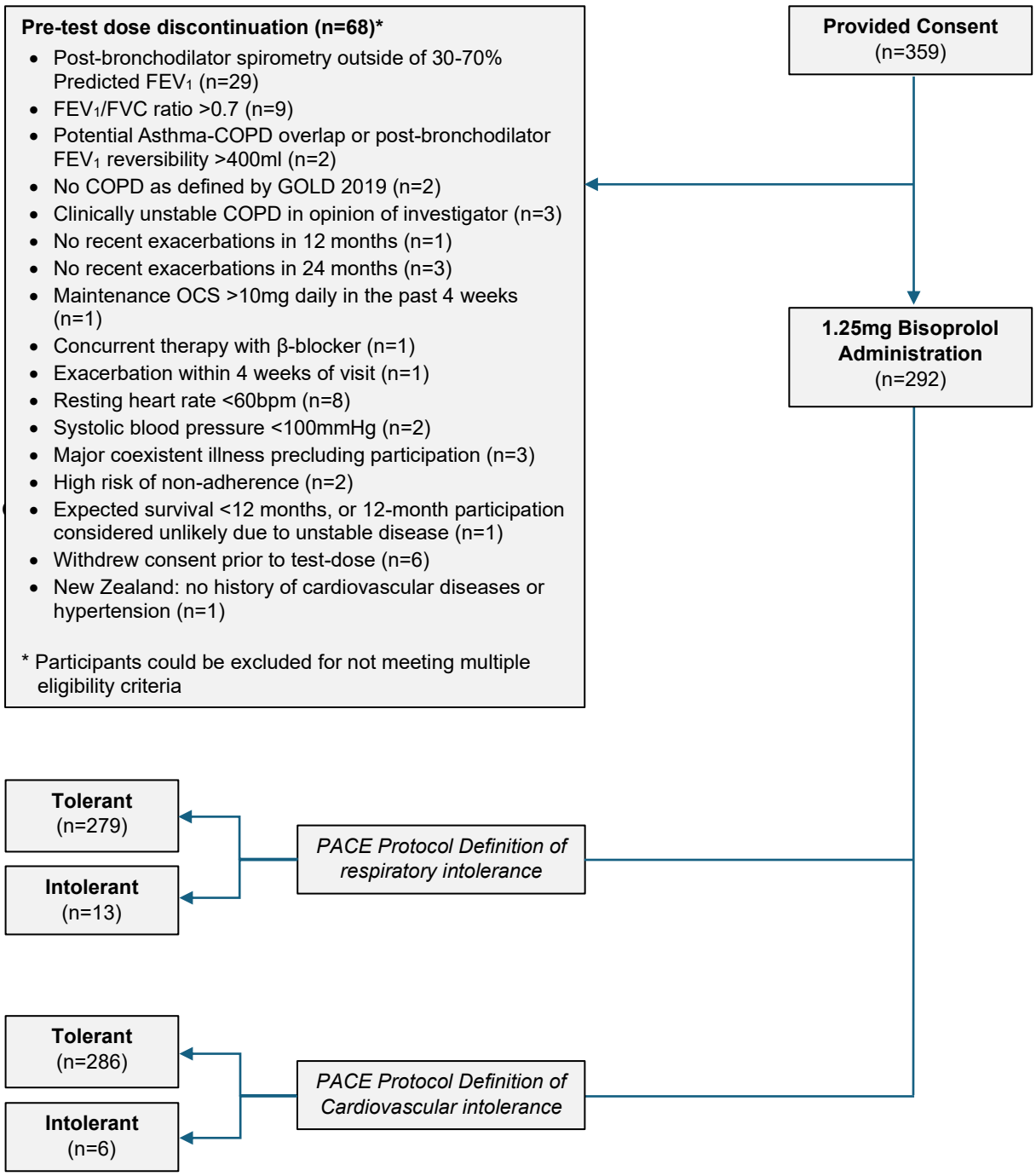

Figure 1: Assessment for eligibility of participants that consented to participate in the PACE in COPD trial, and bisoprolol test-dose outcome using the primary exploratory definition of respiratory intolerance

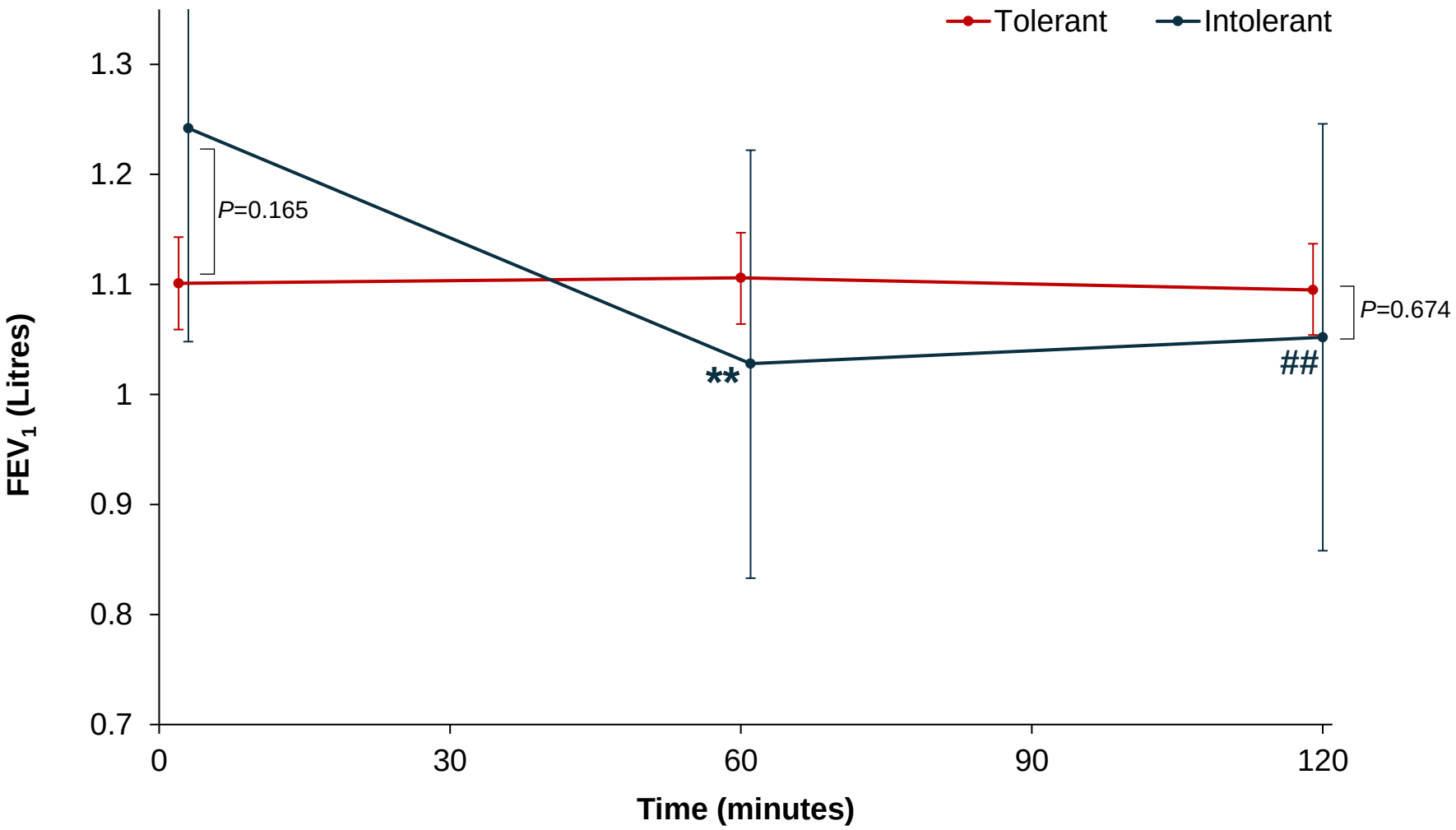

Figure 2: Adjusted mean post-bronchodilator FEV_1 (litre) values at 0, 60 and120 minutes following oral administration of 1.25mg bisoprolol, for the respiratory tolerant (n=279) and intolerant (n=13) groups. Note: ** indicates p<0.0001 between successive measurements within a tolerance group; ## indicates p<0.0001 between 0 minute and 120 minute measurements.

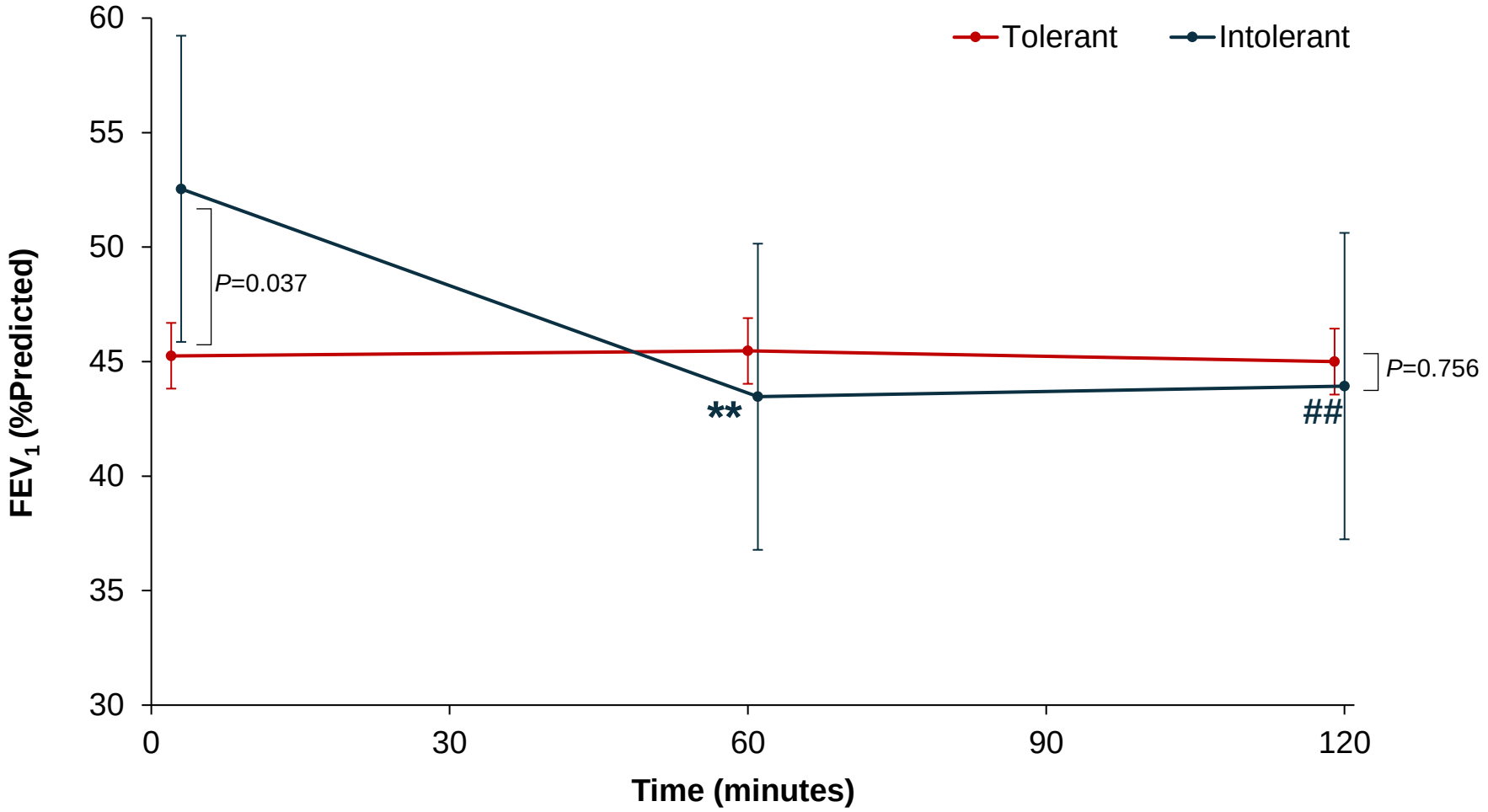

Figure 3: Adjusted mean post-bronchodilator FEV_1 (percentage predicted) values at 0, 60 and120 minutes following oral administration of 1.25mg bisoprolol for the respiratory tolerant (n=279) and intolerant (n=13) groups. Note: ** indicates p<0.0001 between successive measurements within a tolerance group; ## indicates p<0.0001 between 0 minute and 120 minute measurements.

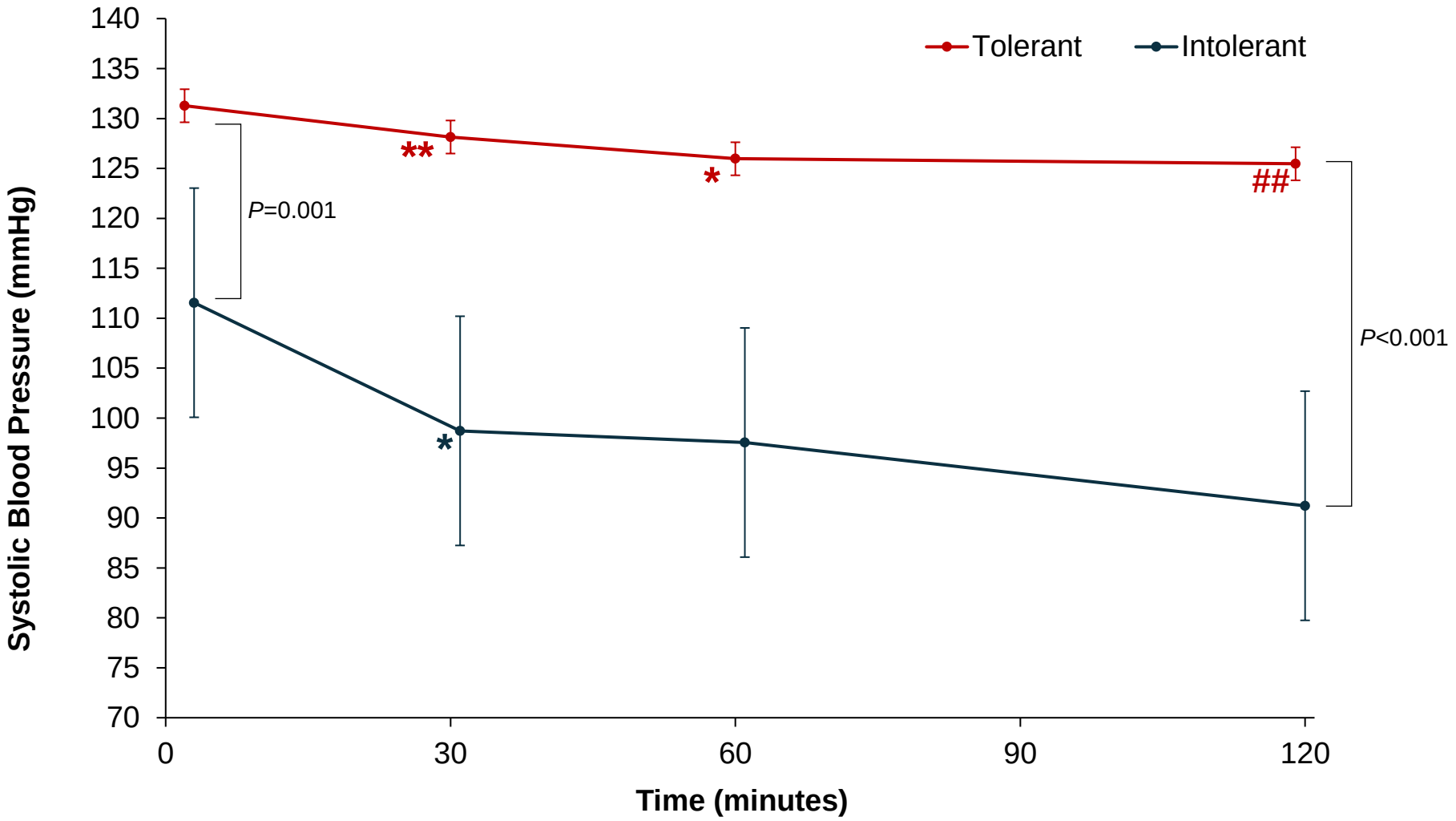

Figure 4: Adjusted mean systolic blood pressure values at 0, 30, 60 and 120 minutes following oral administration of 1.25mg bisoprolol for the cardiovascular tolerant (n=279) and intolerant (n=13) groups. Note: * and ** respectively indicates p<0.05 and p<0.0001 between successive measurements within a tolerance group; ## indicates p<0.0001 between 0 minute and 120 minute measurements.

Supplement 1: Baseline demographics and medical history of consented participants who undertook the baseline bisoprolol test dose procedure (n=292); intolerance defined using the PACE in COPD protocol definition for ineligibility. All figures presented as mean (SD) unless specified otherwise.

	PACE Eligibility Criteria		Total (n = 292)
	Tolerant (n = 283)	Intolerant (n = 9)	
Age	67.6 (7.6)	66.8 (6.9)	67.6 (7.6)
Sex, male; n(%)	234 (82.7)	8 (88.9)	242 (82.9)
BMI	22.7 (6.8)	22.9 (3.3)	22.7 (6.7)
Smoking Status, n(%)			
Never	22 (7.8)	2 (22.2)	24 (8.2)
Former	225 (79.5)	7 (77.8)	232 (79.5)
Current	36 (12.7)	0 (0.0)	36 (12.3)
Current Smoker Pack Years	32.2 (22.3)	-	32.2 (22.3)
LAMA, n(%)	109 (38.5)	4 (44.4)	113 (38.7)
LAMA/LABA, n(%)	22 (7.8)	2 (22.2)	24 (8.2)
LAMA/LABA/ICS, n(%)	30 (10.6)	0 (0.0)	30 (10.3)
Current antihypertensives n(%)	89 (31.4)	4 (44.4)	93 (31.8)
Spirometry [1]			
Pre-BD FEV1 (L)	1.02 (0.34)	1.11 (0.43)	1.03 (0.34)
Pre-BD FEV1 (%Pred)	42.17 (11.52)	44.78 (11.68)	42.3 (11.5)
Post-BD FEV1 (L)	1.10 (0.35)	1.27 (0.41)	1.11 (0.36)
Post-BD FEV1 (%Pred)	45.34 (11.94)	51.67 (9.57)	45.6 (11.9)
Pre-Post FEV change (%)	8.31 (9.95)	17.2 (11.22)	8.6 (10.1)
Post-BD FVC (L)	2.22 (0.71)	2.52 (1.15)	2.23 (0.73)
FEV1/FVC Ratio	0.51 (0.11)	0.53 (0.10)	0.51 (0.11)
Cardiovascular Parameters [2]			
Heart Rate (BPM)	82.3 (9.7)	82.9 (17.6)	80.7 (9.7)
SBP (mmHg)	131.0 (15.2)	126.6 (16.2)	130.9 (15.2)
DBP (mmHg)	80.7 (9.7)	80.7 (8.5)	82.3 (10.4)
Country of residence n(%)			
Australia	47 (16.6)	0 (0.0)	47 (16.1)
New Zealand	25 (8.8)	1 (11.1)	26 (8.9)
India	68 (24.0)	5 (55.6)	73 (25.0)
Sri Lanka	143 (50.5)	3 (33.3)	146 (50.0)

Abbreviations: LAMA: long-acting muscarinic antagonist; LABA: long acting beta agonist; ICS: inhaled corticosteroid; post-BD: post-bronchodilator; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; BPM: beats

per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; mmHg: millimetres of mercury.
[1]post-bronchodilator spirometry values set as time 0 for the test dose; [2]cardiovascular parameters set as time 0 for the test dose.

Supplement 2: Adjusted mean secondary cardiovascular and spirometry outcomes at 0, 30, 60 and 120 minutes following oral administration of 1.25mg bisoprolol in the PACE in COPD eligibility criteria for respiratory intolerance. All figures presented as mean (95% CI).

		Respiratory Tolerance			
Time (min)	**Group**	**SBP (mmHg)**	**DBP (mmHg)**	**HR (bpm)**	**FVC (L)**
0	*Tolerant*	131 (129–133)	81 (80–82)	82 (81–83)	2.22 (2.14 – 2.30)
	Intolerant	126 (116–136)	80 (74–87)	83 (76–89)	2.49 (2.03 – 2.96)
30	*Tolerant*	128** (126–129)	79** (77–80)	80** (78–81)	*Not performed at 30 min*
	Intolerant	122 (113–132)	80 (73–86)	78* (71–84)	
60	*Tolerant*	126* (124–127)	77* (76–78)	77** (76–78)	2.23 (2.15 – 2.31)
	Intolerant	119 (110–129)	79 (73–85)	74 (68–81)	2.16** (1.69 – 2.63)
120	*Tolerant*	125## (123–127)	77## (76–78)	75**, ## (73–76)	2.21 (2.12 – 2.29)
	Intolerant	122 (113–132)	80 (74–87)	73## (69–79)	2.00##, * (1.51 – 2.44)
	Between group comparison	*p=0.623*	*p=0.281*	*p=0.545*	*p=0.341*

Abbreviations: HR: Heart Rate; FVC: forced vital capacity; BPM: beats per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; mmHg: millimetres of mercury.