Beta-blockers in Chronic Obstructive Pulmonary Disease: a Cohort Study from the TONADO Research Programme

Maltais, F., Buhl, R., Koch, A., Amatto, V., Reid, J., Grönke, L., ... Ferguson, G. T. (2018). Beta-blockers in Chronic Obstructive Pulmonary Disease: a Cohort Study from the TONADO Research Programme. Chest, 153(6), 1315-1325. DOI: 10.1016/j.chest.2018.01.008

Published in:
Chest

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

CHEST

β-Blockers in COPD

A Cohort Study From the TONADO Research Program

François Maltais, MD; Roland Buhl, MD; Andrea Koch, MD; Valeria C. Amatto, MD; Jim Reid, MBChB DipObs, FCCP, MPS; Lars Grönke, MD; Ulrich Bothner, MD; Florian Voß, PhD; Lorcan McGarvey, MD; and Gary T. Ferguson, MD

BACKGROUND: Cardiovascular disease is a frequent comorbidity in patients with COPD. Many physicians, particularly pulmonologists, are reluctant to use β-adrenoceptor blocking agents (β-blockers) in patients with COPD, despite their proven effectiveness in preventing cardiovascular events.

METHODS: The large (5,162 patients) phase III TONADO 1 and 2 studies assessed lung function and patient-reported outcomes in patients with moderate to very severe COPD receiving long-acting bronchodilator treatment across 1 year. This post hoc analysis characterized lung-function changes, patient-reported outcomes, and safety in the subgroup of patients receiving β-blockers in the studies.

RESULTS: In total, 557 of 5,162 patients (11%) received β-blockers at baseline. Post-bronchodilator FEV_1 at baseline was higher in the β-blocker group (1.470 L) compared with that in the no β-blocker group (1.362 L). As expected, patients receiving β-blockers had a more frequent history of cardiovascular comorbidities and medications. Lung function improved from baseline in patients with or those without β-blocker treatment, and no relevant between-group differences were observed in trough FEV_1 or trough FVC at 24 or 52 weeks. No relevant differences were observed for St. George's Respiratory Questionnaire results and Transition Dyspnea Index in patients with β-blockers compared with those in patients without. Safety findings were comparable between groups.

CONCLUSIONS: Lung function, overall respiratory status, and safety of tiotropium/olodaterol were not influenced by baseline β-blocker treatment in patients with moderate to very severe COPD. Results from this large patient cohort support the cautious and appropriate use of β-blockers in patients with COPD and cardiovascular comorbidity.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT01431274 and No. NCT01431287; URL: www.clinicaltrials.gov

CHEST 2018; 153(6):1315-1325

KEY WORDS: β-blockers; COPD; lung function; safety

FOR EDITORIAL COMMENT, SEE PAGE 1289

ABBREVIATIONS: AE = adverse event; GOLD = Global Initiative for Chronic Obstructive Lung Disease; SGRQ = St. George's Respiratory Questionnaire

AFFILIATIONS: From the Centre de Recherche (Dr Maltais), Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec City, QC, Canada; Pulmonary Department (Dr Buhl), Mainz University Hospital, Mainz, Germany; the Medizinische Klinik und Poliklinik V (Dr Koch), Klinikum der Ludwig-Maximilians-Universität, and the German Center for Lung Research (DZL), Klinikum der Ludwig-Maximilians-Universität, Munich, Germany; Boehringer Ingelheim International GmbH (Drs Amatto, Grönke, Bothner), and Boehringer Ingelheim Pharma GmbH & Co. KG (Dr Voß), Ingelheim, Germany; the Dunedin School of Medicine (Dr Reid), University of Otago, Dunedin, New Zealand; the Centre for Infection and Immunity (Dr McGarvey), School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, Northern Ireland; and the Pulmonary Research Institute of Southeast Michigan (Dr Ferguson), Farmington Hills, MI.

Part of this article has been presented at the 20th Congress of the Asian Pacific Society of Respirology, December 3-6, 2015, Kuala Lumpur, Malaysia, and the California Association of Nurse Practitioners Annual Educational Conference, March 16-19, 2016, San Francisco, CA.

Cardiovascular disease is linked closely with COPD, mainly because of, but not limited to, the shared risk of smoking.[1,2] Cardiac failure is a leading cause of death in patients with COPD.[3] Physicians often are reluctant to use β-blockers in patients with COPD because of a fear that their use leads to deterioration in lung function[2] or that the effectiveness of COPD medications—specifically, inhaled β-agonists—may be reduced. This concern is reflected by their underuse, with limited prescription of β-blockers[2,4] and low daily dosage in patients with COPD.

As a drug class, β-agonists have the potential to be associated with cardiovascular adverse events (AEs) in obstructive lung disease.[5-7] Even though the risk-benefit profiles of β-agonists, including olodaterol,[8] are well established,[6,9] there is no strict guidance for their use in patients with very severe cardiovascular disorders who may benefit from β-blocker treatment. Consequently, it has been advised that β-agonists are to be used with caution in patients with pulmonary disease or severe cardiovascular disease and who are taking β-blockers.[6,10]

Both cardioselective and noncardioselective β-blockers have been reported to worsen pulmonary function in patients with concomitant heart failure and COPD,[11,12] and cardioselective β-blockers worsen dynamic hyperinflation during cycling exercise in patients with stable COPD.[13] There may be some reluctance among physicians to continue β-blockers during an episode of acute COPD exacerbation, perceiving the patients' respiratory condition as more delicate.[14] In contrast, administrative database studies suggest that β-blocker use is associated with a 30% reduction in COPD exacerbation rate and even may reduce mortality in patients with COPD.[15-17] A large prospective follow-up study in the COPDGene cohort provided evidence that β-blockers have an acceptable safety profile in patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) II through IV COPD, including those with severe COPD using home oxygen, and are associated with fewer exacerbations in this population.[18] This issue is important because a large number of patients with COPD theoretically could benefit from β-blocker use, including patients with cardiac comorbidities such as heart failure, coronary artery disease, and hypertension.[19]

The TONADO studies established the efficacy and safety of once-daily maintenance treatment with the combination of tiotropium/olodaterol in patients with moderate to very severe COPD (GOLD II-IV).[20] Overall, approximately 10% of the 5,162 patients in the TONADO studies were receiving β-blockers, providing a unique opportunity to study their impact on lung function, quality of life, and AEs in a large cohort of patients across 1 year. This post hoc analysis was designed to compare lung function, quality of life, dyspnea, and frequency of COPD exacerbations in patients with COPD according to baseline β-blocker use in the TONADO studies.

Materials and Methods

Study Design

The study design of the TONADO research program, which comprised multinational, replicate, phase III, multicenter, randomized, double-blind, active-controlled, five-arm, parallel-group studies (study 1237.5, NCT01431274; study 1237.6, NCT01431287) has been published previously.[20] Randomization details are summarized in e-Appendix 1. Data combined from all treatment arms were used for this cohort study. Baseline β-blocker use was a surrogate for use throughout the study duration; patients who received β-blockers at baseline were allowed, and expected, to continue with this treatment for the duration of the 1-year study.

Patients

Inclusion and exclusion criteria of the TONADO studies have been published previously[20] and are summarized in e-Appendix 1. Both studies were performed in accordance with the Declaration of Helsinki, the International Conference on Harmonisation's Harmonised Tripartite Guideline for Good Clinical Practice, and local regulations. Details of institutional review board approval are provided in e-Appendix 1.

End Points and Assessments

The end points for lung function were trough FEV_1 response (change from baseline) and FVC response at 24 and 52 weeks. Patient-reported outcomes evaluated were St. George's Respiratory Questionnaire (SGRQ) total score and Transition Dyspnea Index score at 24 and 52 weeks.

Further safety end points were investigator-reported AEs (AEs, serious AEs, fatal AEs, AEs leading to discontinuation, and most frequent AEs according to system organ class) and frequency of COPD exacerbations. Moderate exacerbations were those requiring antibiotics or systemic steroids without hospitalization, and severe exacerbations were those requiring hospitalization.

FUNDING/SUPPORT: This work was supported by Boehringer Ingelheim Pharma GmbH & Co. KG. Medical writing assistance was contracted and compensated by Boehringer Ingelheim Pharma GmbH & Co. KG.

CORRESPONDENCE TO: François Maltais, MD, Centre de Recherche, Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725 Chemin Sainte Foy, Quebec City, QC, G1V 4G5, Canada; e-mail: Francois.Maltais@fmed.ulaval.ca

DOI: https://doi.org/10.1016/j.chest.2018.01.008

Statistical Analysis

To compare patients with and those without β-blockers and to take into account potential confounding variables, we adapted the model used for treatment comparisons in the TONADO studies and adjusted it for additional variables. The adjusted means (SEs) for the efficacy comparisons were obtained from fitting a mixed-effects model for repeated measures, with further information provided in e-Appendix 1. Time to first exacerbation is presented for the first quartile (ie, the time at which 25% of patients reached this end point) using Kaplan-Meier estimates of probability of COPD exacerbation across the 1-year study. Hazard ratios between patients with and those without β-blockers were estimated using a Cox proportional hazards model adjusting for the same additional variables as the mixed-effects model for repeated measures. Analyses of AEs were descriptive and not adjusted for potential confounding variables. All *P* values and comparisons presented are nominal because this is a post hoc analysis, and no adjustment for multiplicity has been performed.

Results

In total, 5,163 patients (2,624 from study 1237.5 and 2,539 from study 1237.6) were randomly assigned to receive treatment; all patients were treated, except one in study 1237.6 (Fig 1). At study entry, 557 patients were treated with β-blockers, and 4,605 were not, with 468 (84.0%) and 3,900 (84.7%) patients, respectively, completing the studies. Cardioselective β-blockers were used by at least 80% of β-blocker users (e-Table 1).

Baseline patient characteristics between groups were generally well balanced (Table 1). Patients in the β-blocker group had less severe COPD and higher mean baseline postbronchodilator FEV_1, which also was reflected in a higher number of patients with GOLD II COPD and fewer patients with GOLD III or IV COPD than in the no β-blocker group. Change in prebronchodilator to postbronchodilator FEV_1 was consistent in patients with and those without β-blockers at 162 and 172 mL, indicating no influence of β-blockers on short-term bronchodilator reversibility. A similar proportion of patients in each group had received pulmonary medications before the study. More patients took lipid-modifying drugs and angiotensin-converting enzyme inhibitors in the β-blocker group than in the no β-blocker group. Most patients (99%) also took β-blockers during the study. More patients in the β-blocker group had a history of myocardial infarction, cerebrovascular accidents, and cardiac arrhythmia than did those in the no β-blocker group (Table 2).

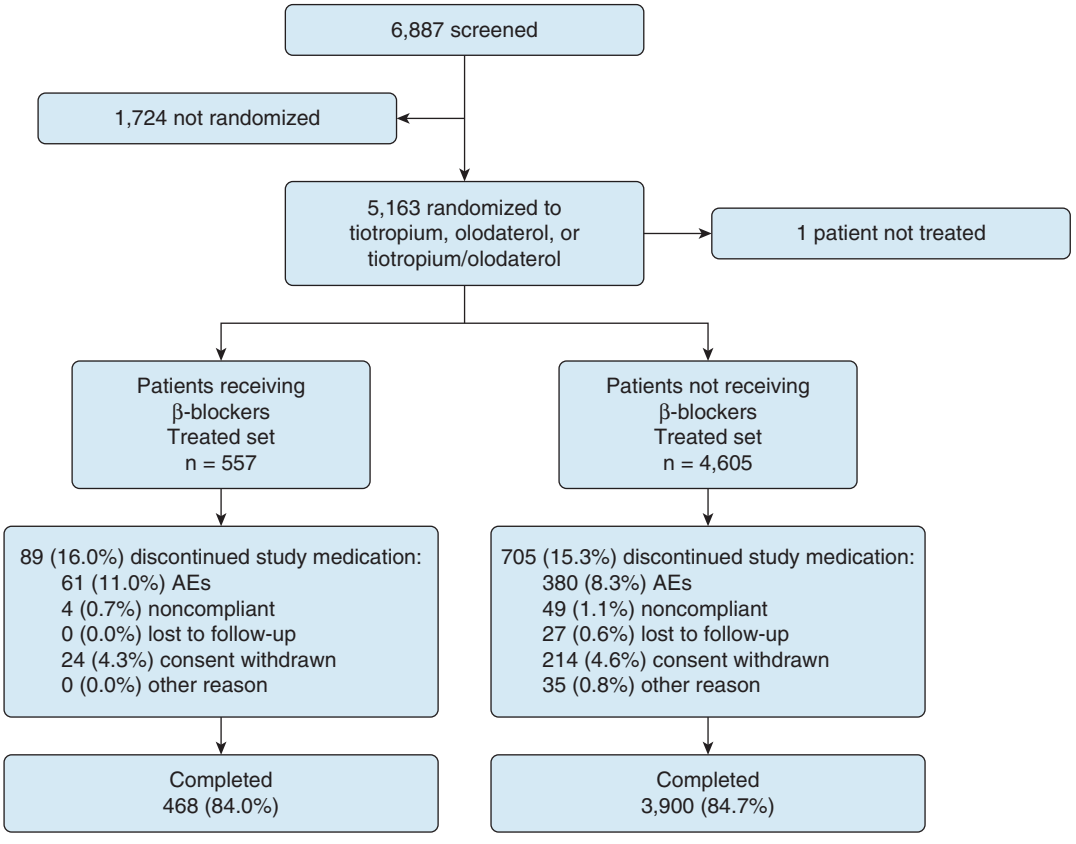


Figure 1 – *Consolidated Standards of Reporting Trials diagram by baseline β-blocker, including discontinuations and causes, for combined studies. AE = adverse event.*

TABLE 1] Demographic and Baseline Patient Characteristics (Treated Population): Combined Data (N = 5,162)

Characteristic	β-Blocker (n = 557)	No β-Blocker (n = 4,605)
Male, No. (%)	393 (70.6)	3,369 (73.2)
Age, mean (SD), y	65.0 (7.7)	63.9 (8.4)
Smoking status, No. (%)		
Exsmoker	359 (64.5)	2,895 (62.9)
Current smoker	198 (35.5)	1,710 (37.1)
BMI, mean (SD), kg/m^2	28.5 (5.6)	25.5 (5.4)
Exacerbations in the y before study entry, No. (%)	220 (39.5)	1,976 (42.9)[a]
No. of exacerbations, mean	0.7	0.8
Prebronchodilator screening FEV_1, mean (SD), L	1.308 (0.502)	1.190 (0.491)
Postbronchodilator screening FEV_1, mean (SD), L	1.470 (0.504)	1.362 (0.510)
Change from prebronchodilator to postbronchodilator FEV_1, mean (SD), L	0.162 (0.143)	0.172 (0.145)
FEV_1/FVC, mean (SD), %	49 (11)	45 (12)
% predicted normal FEV_1, mean (SD)	53 (14)	50 (15)
GOLD, No. (%)[b]		
I (≥ 80%)	0 (0.0)	3 (0.1)
II (50% to < 80%)	330 (59.2)	2,258 (49.0)
III (30% to < 50%)	191 (34.3)	1,798 (39.0)
IV (< 30%)	36 (6.5)	545 (11.8)
Baseline pulmonary medication, No. (%)		
SAMA[c]	89 (16.0)	576 (12.5)
LAMA[d]	217 (39.0)	1,623 (35.2)
SABA[e]	230 (41.3)	1,849 (40.2)
LABA[f]	276 (49.6)	2,117 (46.0)
ICS[g]	241 (43.3)	2,205 (47.9)
Xanthines[h]	52 (9.3)	464 (10.1)
Baseline cardiovascular medication, No. (%)[i]		
Lipid-modifying drugs	276 (49.6)	771 (16.7)
ACE inhibitors	163 (29.3)	556 (12.1)
ACE inhibitor combinations	39 (7.0)	125 (2.7)
Angiotensin II antagonist combinations	40 (7.2)	155 (3.4)
Angiotensin II antagonists	84 (15.1)	369 (8.0)
Cardiac glycosides	14 (2.5)	25 (0.5)
Cardiac stimulants excluding cardiac glycosides	3 (0.5)	22 (0.5)

ACE = angiotensin-converting enzyme; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β-agonist; SAMA = short-acting muscarinic antagonist.
[a]Three patients had missing values.
[b]Based on postbronchodilator FEV_1 % predicted (in study 1237.6, one patient receiving tiotropium 2.5 μg was not categorized).
[c]Ipratropium, ipratropium with fenoterol or ipratropium with salbutamol, and oxitropium.
[d]Tiotropium.
[e]Salbutamol, fenoterol, ipratropium with fenoterol, and ipratropium with salbutamol.
[f]Including salmeterol, formoterol, indacaterol, salmeterol with fluticasone, formoterol with budesonide, and formoterol with beclomethasone.
[g]Including beclomethasone, budesonide, ciclesonide, fluticasone, mometasone, salmeterol with fluticasone, formoterol with budesonide, formoterol with beclomethasone, and formoterol with mometasone.
[h]Including aminophylline and theophylline. Total number of patients includes only those with values for β-blocker use at baseline.
[i]Combination therapies are listed under each monotherapy drug class.

Lung Function

Adjusted mean trough FEV_1 responses at 24 weeks were similar in both the β-blocker and no β-blocker groups, with a between-group difference of 0.010 L (95% CI, −0.009 to 0.028) (Table 3). Similarly, the adjusted mean trough FVC responses were not modified

TABLE 2] Preexisting Disease Diagnoses by β-Blocker Use

Diagnosis, No. (%)	β-Blocker (n = 557)	No β-Blocker (n = 4,605)
Cardiac disorders	289 (51.9)	818 (17.8)
Coronary artery disease	99 (17.8)	190 (4.1)
Myocardial infarction	55 (9.9)	78 (1.7)
Angina pectoris	40 (7.2)	66 (1.4)
Myocardial ischemia	39 (7.0)	88 (1.9)
Cardiac arrhythmia	84 (15.1)	211 (4.6)
Vascular disorders	487 (87.4)	1,994 (43.3)
Hypertension	468 (84.0)	1,789 (38.8)
Cerebrovascular accidents	41 (7.4)	126 (2.7)
Transient ischemic attack	22 (3.9)	68 (1.5)
Stroke	22 (3.9)	66 (1.4)
Heart failure NYHA class III or IV	12 (2.2)	20 (0.4)
Prostatic hyperplasia or bladder neck obstruction	56 (10.1)	409 (8.9)
Renal or urinary tract diseases	43 (7.7)	225 (4.9)
Narrow-angle glaucoma	7 (1.3)	16 (0.3)
Cancer	43 (7.7)	190 (4.1)

NYHA = New York Heart Association.

significantly by β-blocker use, with a between-group difference of −0.010 L (95% CI, −0.048 to 0.028). At 52 weeks, the differences between the β-blocker and no β-blocker groups for trough FEV_1 and FVC responses were also similar (−0.005 L and −0.008 L, respectively).

Symptom Benefit

There was no difference in baseline mean SGRQ total score between the β-blocker and no β-blocker groups. After 24 weeks, there was a greater, significant reduction (improvement) in adjusted mean SGRQ total score in the β-blocker group compared with that in the no β-blocker group (treatment difference, −1.39; 95% CI, −2.581 to −0.207) (Table 4). This treatment difference decreased to −0.60 (95% CI, −1.810 to 0.602) at 52 weeks. Dyspnea improved from baseline after 24 and 52 weeks in both groups (Table 4). Only small, nonsignificant differences in improvement in Transition Dyspnea Index were observed in the β-blocker group compared with those in the no β-blocker group (−0.18; 95% CI, −0.469 to 0.115 and −0.13; 95% CI, −0.424 to 0.170 at 24 and 52 weeks, respectively).

Safety

After 52 weeks of treatment, the proportion of patients with an AE was similar in both groups (Table 5), as was the proportion with specific AEs with an incidence > 2%. Respiratory AEs, specifically COPD, occurred at a slightly higher frequency in the no β-blocker group. In the β-blocker group, 19.4% experienced a serious AE compared with 16.0% in the no β-blocker group. The most frequent class of serious AEs in the β-blocker group was respiratory, thoracic, and mediastinal disorders (5.4% compared with 7.2% in the no β-blocker group), followed by infections and infestations (3.6% compared with 2.8%), cardiac disorders (3.2% compared with 1.6%), and neoplasms (2.9% compared with 2.1%) (Table 5).

Incidence of fatal AEs was low across both groups: 2.0% in the β-blocker group and 1.4% in the no β-blocker group (Table 5). The most frequent class of fatal AEs in both groups was cardiac disorders (1.1% compared with 0.3% in the no β-blocker group). Incidence of major adverse cardiovascular events was low, with 2.7% in the β-blocker group and 2.0% in the no β-blocker group (data not shown).

TABLE 3] Adjusted Mean (SE) Trough FEV_1 and Trough FVC Responses (Change From Baseline) After 24 and 52 Weeks of Treatment by β-Blocker Use at Baseline (Full Analysis Set): Combined Data

Response	β-Blocker (n = 557)	No β-Blocker (n = 4,605)	Treatment Difference (95% CI), L
24 wk			
Trough FEV_1 response, adjusted mean (SE), L	0.080 (0.009)	0.070 (0.003)	0.010 (−0.009 to 0.028)
Trough FVC response, adjusted mean (SE), L	0.140 (0.018)	0.150 (0.006)	−0.010 (−0.048 to 0.028)
52 wk			
Trough FEV_1 response, adjusted mean (SE), L	0.044 (0.009)	0.049 (0.003)	−0.005 (−0.024 to 0.014)
Trough FVC response, adjusted mean (SE), L	0.111 (0.018)	0.119 (0.006)	−0.008 (−0.047 to 0.030)

Data obtained from fitting a mixed-effects model for repeated measures, including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors; and Kenward-Roger approximation of denominator degrees of freedom.

TABLE 4] Adjusted Mean (SE) SGRQ Total Score and TDI Focal Score After 24 and 52 Weeks of Treatment by β-Blocker Use at Baseline (Full Analysis Set): Combined Data

Score	β-Blocker (n = 557)	No β-Blocker (n = 4,605)	Difference (95% CI), L
Baseline			
SGRQ total score, mean (SE)	43.58 (0.76)	43.60 (0.28)	…
BDI focal score, mean (SE)	6.40 (0.09)	6.55 (0.03)	…
24 wk			
SGRQ total score, adjusted mean (SE)	36.36 (0.57)	37.75 (0.19)	−1.39 (−2.581 to −0.207)
TDI focal score, adjusted mean (SE)	1.61 (0.14)	1.79 (0.05)	−0.18 (−0.469 to 0.115)
52 wk			
SGRQ total score, adjusted mean (SE)	37.29 (0.58)	37.90 (0.19)	−0.60 (−1.810 to 0.602)
TDI focal score, adjusted mean (SE)	1.57 (0.14)	1.70 (0.05)	−0.13 (−0.424 to 0.170)

BDI = Baseline Dyspnea Index; SGRQ = St. George's Respiratory Questionnaire; TDI = Transition Dyspnea Index.

Patients using β-blockers at study entry experienced fewer COPD exacerbations during the study than did patients not using β-blockers (150 [26.9%] and 1,420 [30.8%], respectively). Time to first COPD exacerbation was not significantly different between groups (271 vs 236 days for patients with and those without β-blocker use, respectively; adjusted hazard ratio, 0.878; 95% CI, 0.732-1.053; $P = .1604$) (Fig 2). Moderate or severe exacerbations were experienced by 145 (26.0%) and 1,339 (29.1%) patients with and those without β-blocker use at study entry, respectively. There was no difference in time to first moderate or severe exacerbation between groups: 304 vs 261 days for patients with and those without β-blocker use at baseline, respectively (adjusted hazard ratio, 0.896; 95% CI, 0.745-1.079; $P = .2471$).

Analysis of Safety by Indication for β-Blockers

Approximately one-half of all patients in TONADO had an indication for β-blocker treatment according to their recorded cardiovascular disease at baseline: tachyarrhythmias, including supraventricular and ventricular tachyarrhythmias; ischemic heart disease, including myocardial infarction and noninfarction; any diagnosis of cardiac failure or heart failure New York Heart Association class III or IV; or hypertension. Within the β-blocker indication subgroup, the demographic characteristics relating to preexisting disease and concomitant medications of patients with and those without β-blocker treatment were more similar than in the total cohort. Age, sex, and smoking history were similar in the β-blocker and no β-blocker groups, and, as in the entire cohort, baseline FEV_1 was higher in patients receiving β-blockers than in those not receiving them (e-Table 2).

Within the β-blocker indication subgroup, cardiovascular events (e-Table 3) and major adverse cardiovascular events incidences were similar for patients who were receiving β-blocker treatment (2.7%) and those who were not (2.7%). The incidence of fatal AEs was low across both groups: 1.9% in the β-blocker group and 1.8% in the no β-blocker group. As in the total cohort, in the β-blocker indication subgroup the incidence of the majority of respiratory events was numerically lower in patients receiving β-blockers than in patients not receiving β-blockers (e-Table 3).

Discussion

The TONADO studies offered a unique opportunity to investigate the influence of β-blocker use on the safety and efficacy of long-acting bronchodilator treatment with tiotropium/olodaterol. To our knowledge, this study is also the first to investigate whether β-blocker use modifies clinical responses to long-acting bronchodilators by assessing well-defined and relevant patient-orientated end points such as dyspnea, quality of life, and exacerbation frequency. In the TONADO studies, in which lung function was improved significantly by use of long-acting bronchodilator treatment, lung-function measures were similar between patients receiving β-blocker treatment and those without. In the β-blocker group, however, mean postbronchodilator FEV_1 at baseline was higher, and there were more patients with GOLD II COPD and fewer patients with GOLD III or IV compared with those in the no β-blocker group. This result is consistent with that observed in the COPDGene cohort and may reflect a reluctance among physicians to use β-blockers in patients with more severe COPD.[18] Results of the

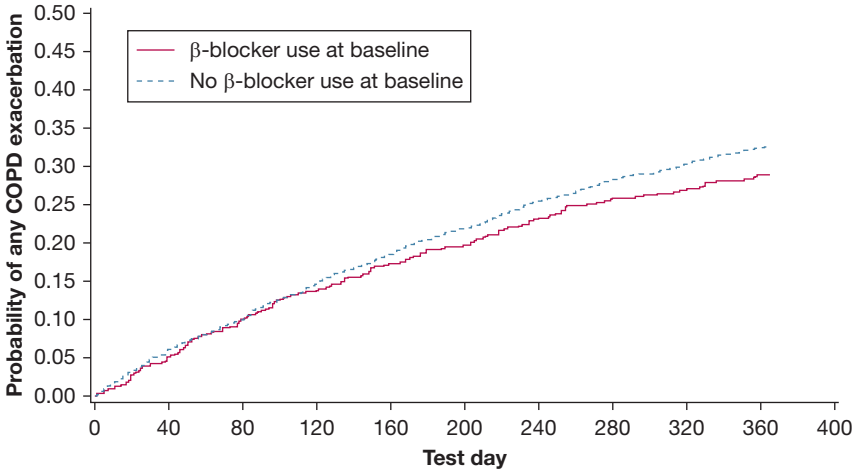
TABLE 5] Frequency of AEs, Serious AEs, and Fatal AEs After 52 Weeks of Treatment Occurring in > 2% of Patients by β-Blocker Use at Baseline (Treated Set): Combined Data

Variable, No. (%)	β-Blocker	No β-Blocker
Total No. of patients	557 (100)	4,605 (100)
All AEs	412 (74.0)	3,428 (74.4)
Serious AEs	108 (19.4)	738 (16.0)
Respiratory, thoracic, and mediastinal disorders	30 (5.4)	331 (7.2)
COPD	24 (4.3)	282 (6.1)
Cardiac disorders	18 (3.2)	75 (1.6)
Infections and infestations	20 (3.6)	131 (2.8)
Neoplasms benign, malignant, and unspecified	16 (2.9)	99 (2.1)
Vascular disorders	13 (2.3)	22 (0.5)
Fatal AEs	11 (2.0)	64 (1.4)
Specific AEs with an incidence > 2%		
Respiratory, thoracic, and mediastinal disorders	208 (37.3)	1,954 (42.4)
COPD exacerbation or worsening	158 (28.4)	1,537 (33.4)
Cough	21 (3.8)	184 (4.0)
Dyspnea	26 (4.7)	183 (4.0)
Infections and infestations	207 (37.2)	1,665 (36.2)
Nasopharyngitis	72 (12.9)	565 (12.3)
Urinary tract infection	23 (4.1)	83 (1.8)
Upper respiratory tract infection	24 (4.3)	273 (5.9)
Pneumonia	14 (2.5)	137 (3.0)
Bronchitis	16 (2.9)	122 (2.6)
Influenza	12 (2.2)	119 (2.6)
GI disorders	86 (15.4)	674 (14.6)
Diarrhea	16 (2.9)	120 (2.6)
Musculoskeletal and connective tissue disorders	91 (16.3)	580 (12.6)
Back pain	23 (4.1)	131 (2.8)
Arthralgia	13 (2.3)	59 (1.3)
Nervous system disorders	52 (9.3)	413 (9.0)
Headache	11 (2.0)	143 (3.1)
General disorders and administration site conditions	55 (9.9)	349 (7.6)
Chest pain	15 (2.7)	70 (1.5)
Edema peripheral	11 (2.0)	53 (1.2)
Vascular disorders	48 (8.6)	248 (5.4)
Hypertension	16 (2.9)	155 (3.4)
Cardiac disorders	48 (8.6)	232 (5.0)
Neoplasms benign, malignant, and unspecified	21 (3.8)	142 (3.1)

Percentages were calculated using the total number of patients in the β-blocker use groups at baseline divided by the treatment class as the denominator. AE = adverse event.

present analysis did not show any negative effects of β-blocker treatment, even in patients with severe COPD.

Our study adds to the current knowledge regarding the use of β-blockers in patients with COPD by showing that patient quality of life and dyspnea were not impacted negatively by β-blocker use. At 24 weeks, SGRQ total score was also improved in both groups, with similar findings for dyspnea, measured by using the Transition Dyspnea Index. Overall, the AE profile was similar in both groups. Fewer patients in the β-blocker group had respiratory AEs, including fewer COPD events, than did those in the no β-blocker group. Patients receiving β-blockers with less severe



No. at risk										
β-blocker use at baseline	557	514	480	450	425	405	385	369	357	340
No β-blocker use at baseline	4,605	4,251	3,980	3,722	3,499	3,304	3,115	2,970	2,857	2,710

	Hazard ratio	95% CI	*P* value
β-blocker use at baseline vs no β-blocker use at baseline	0.878	0.732-1.053	.1604

Figure 2 – *Kaplan-Meier estimates of probability of COPD exacerbation across the 1-year study by β-blocker use at baseline (treated set), for combined data. Hazard ratio of time to first COPD exacerbation was calculated by using a Cox proportional hazards model adjusting for COPD treatment, sex, age, BMI, race (Asian vs non-Asian), Global Initiative for Chronic Obstructive Lung Disease stage, cardiac disorders, hypertension, angiotensin-converting enzyme inhibitors, angiotensin II antagonists, and lipid-modifying agents.*

COPD at baseline may have contributed to this observation. As expected, cardiac disorder AEs had a higher frequency in the β-blocker group, likely because of more preexisting cardiac disease at baseline. Similarly, the overall number of patients with serious AEs was slightly higher in the β-blocker group, which may reflect the higher proportion of patients with general comorbidities in this group.

To explore this issue further, we performed a secondary analysis that was restricted to patients who had a clinical indication for the use of a β-blocker. Approximately one-half of patients in the TONADO studies had an existing indication for β-blockers, but only 20% of them received a β-blocker, another possible reflection of the tendency to avoid the use of β-blockers in patients with COPD. We found that the differences in cardiac disorder AEs and serious AEs between patients with β-blockers and those without became smaller compared with what was seen in the overall cohort. This finding would support the contention that the differences in AEs and serious AEs that were seen between those receiving β-blockers and those who were not were likely driven by individuals with better cardiovascular health in the no β-blocker group. In the subgroup of patients with a β-blocker indication, cardiovascular events and major adverse cardiovascular events incidences between patients who were receiving β-blocker treatment and those who were not were similar. In this analysis, β-blockers were not protective against cardiovascular events in the indication subgroup. However, it is not known from the available data whether the severity of cardiovascular conditions between the patients receiving β-blockers and those not receiving β-blockers was the same. Also, we would not expect that hypertension, a relatively mild cardiovascular disease and the most frequent condition of the β-blocker indications in the present study would have led to cardiovascular events in the 1-year study follow-up.

Within the β-blocker indication subgroup, there was a numerical advantage for patients in the β-blocker treatment group in terms of respiratory events compared with patients not receiving β-blockers. This finding suggests that treatment with β-blockers does not increase respiratory events in patients with COPD, although this finding could be influenced by the better lung function at baseline in the group of patients receiving β-blockers.

The most frequent system organ class of serious AEs—respiratory, thoracic, and mediastinal disorders—was observed more frequently in the no β-blocker group (7.2% compared with 5.4%). Correcting for differences in baseline characteristics, the tendency to prolonged time to first COPD exacerbation in the β-blocker group

did not reach statistical significance. However, this trend is consistent with the results of a prospective follow-up of the COPDGene cohort, which included 3,464 individuals with COPD GOLD II through IV, although that analysis had a median follow-up of 2 years compared with 1 year in our study and reported delayed time to first exacerbation in patients treated with a β-blocker.[18]

Mortality was low and not substantially different between groups. We did not see a negative pulmonary consequence with respect to AEs for patients taking a β-blocker in this vulnerable population of patients with COPD.

A 2005 systematic review provided reassurance that the use of selective β-blockers is generally safe in stable COPD[21] and that their use should not be withheld routinely from patients with COPD. However, exposure to β-blockers in the included studies was short (2 days to 16 weeks), and diagnosing COPD via administrative databases is poorly validated and potentially unreliable.[22,23] A 2011 study suggested that β-blockers reduce mortality in patients admitted to the hospital with acute COPD exacerbations.[24] Another retrospective study of patients with ischemic heart disease, congestive heart failure, or hypertension who were hospitalized for an acute COPD exacerbation found no association between β-blocker use, in-hospital mortality, 30-day readmission, or initiation of mechanical ventilation.[25]

Similarly to patients in this study, the COPDGene cohort led to the conclusion that β-blockers were safe and associated with significantly reduced total and severe exacerbations, including in patients with severe oxygen-dependent disease.[18] This finding is in contrast to those of a 2013 study involving patients with COPD requiring oxygen, which concluded that β-blocker use may increase mortality in these individuals.[26] Nevertheless, most available evidence indicates that β-blockers are generally safe in patients with COPD,[27] with the possible exception of patients with GOLD IV receiving oxygen therapy. There are compelling reasons to use cardioselective β-blockers in patients with COPD who also have heart failure or have had myocardial infarction.[2] Guidance from the GOLD strategy document, which is based on many of these studies, suggests that the benefits of selective β-blocker use for ischemic heart disease, heart failure, atrial fibrillation, and hypertension are larger than the potential risks associated with treatment, even in patients with severe COPD.[28] Our data appear to support the recommendation to continue the concomitant use of β-blockers in these patients.

Although counterintuitive at first glance, there is a strong pharmacologic rationale to support the safety and/or potential pulmonary benefits of β-blocker therapy in patients with COPD, particularly in the presence of a concomitant chronic heart disease.[29] Long-term adrenergic stimulation, related either to the presence of a chronic disease or to long-term use of β-agonists, is seen in COPD and eventually may down-regulate the expression of β-adrenergic receptors and attenuate the airway relaxation effects of β-agonists.[29] These adverse consequences of long-term adrenergic stimulation could be mitigated by the long-term use of β-blockers[30] through the reduction in sympathetic tone and the upregulation of β-adrenoceptors in the lungs.[29,31] Irrespective of the exact underlying pharmacologic mechanisms, a meta-analysis of 15 pooled cohort studies on the use of β-blockers in patients with COPD suggested that β-blockers may reduce the risk of overall mortality and exacerbation in those patients.[32]

This analysis was across 12 months, compared with previously reported, shorter-term data,[21] and was performed in patients who were well characterized with thorough clinical monitoring of relevant outcomes. β-Blocker use at baseline was a surrogate for use throughout the study; however, adherence to β-blockers was not monitored during the study. The analysis does not have the strength of a prospective randomized clinical trial, and the trial was not designed and randomized to test for the effect of β-blocker use on outcome measures. Therefore, baseline characteristics showed some differences (eg, in COPD severity and comorbidities), though analyses were controlled for these differences in patient characteristics. However, the large data set for this post hoc analysis from the TONADO studies with a close follow-up provides confidence regarding the surveillance of COPD exacerbations and AEs.

One limitation of these analyses is that patients with myocardial infarction, hospitalization for heart failure in the 12 months prior to screening, or unstable or life-threatening cardiac arrhythmias were excluded from the TONADO studies. However, the study included patients with clinically significant cardiac disease, including those with cerebrovascular accidents, heart failure, and a history of cardiac disorders according to the Medical Dictionary for Regulatory Activities system organ class

definition available at www.meddra.org/. Furthermore, the multicenter and international nature of the trial led to a broad study population, adding further confidence to the application of these findings to clinical practice. Some limitations could be circumvented by the ongoing clinical trial evaluating the efficacy of β-blockers to prevent COPD exacerbation; however, all patients with an indication for β-blocker treatment are excluded from participation in this trial.[33] Therefore, data about the safety of β-blockers in this population are unlikely to emerge from randomized studies. Although confounding by indication is a potential caveat to the validity of our results, all analyses (except safety analyses) were performed after adjusting for important baseline variables, including comorbid conditions. Therefore, we are confident that this analysis provides important insights concerning the safety of β-blockers in patients with COPD and adds to the evidence base for their use in patients with COPD.

Conclusions

Overall, there was no relevant effect of β-blocker use on lung function, SGRQ score, or dyspnea in patients with moderate to very severe COPD treated with tiotropium/olodaterol in the TONADO studies. No increase in respiratory AEs or exacerbations was observed in patients receiving tiotropium/olodaterol and β-blockers. Our findings are consistent with the guidance supporting the continuation of usual maintenance therapy in patients with COPD with β-blocker use when clinically indicated.

Acknowledgments

Author contributions: F. M. contributed to the design and conduct of the study and is the guarantor of the content of the manuscript, including the data and analysis. R. B. was the coordinating investigator and contributed to the design and conduct of the study. A. K., J. R., L. M., and G. T. F. contributed to the design and conduct of the study. V. C. A., L. G., and U. B. are employees of Boehringer Ingelheim and were involved in all aspects of the design, conduct, and data analysis of the study. F. V. is an employee of Boehringer Ingelheim and provided statistical support and was involved in the data analysis of this post hoc study. The authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors. They take full responsibility for the scope, direction, content of, and editorial decisions relating to the manuscript; were involved at all stages of development; and have approved the submitted manuscript. The authors received no compensation related to the development of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: F. M. reports research support from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, and Novartis; advisory board participation for Boehringer Ingelheim and GlaxoSmithKline; and speaking engagements for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, and Novartis. R. B. reports personal fees from AstraZeneca, Chiesi, Cipla, and Teva and grants and personal fees from Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Roche. A. K. has received a grant from Actelion Pharmaceuticals and has taken part in congresses for Actelion, Almirall, Bayer, Boehringer Ingelheim, Novartis, Roche, and Teva. J. R. reports contract research for AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline and advisory committee participation for Asthma and Respiratory Foundation NZ and GlaxoSmithKline New Zealand. L. M. reports personal fees from Applied Clinical Intelligence during the conduct of the study; grants from Asthma UK, British Heart Foundation, Chiesi, NC3Rs, and Northern Ireland Chest Heart and Stroke; travel and subsistence for attendance at scientific meetings from Boehringer Ingelheim, Chiesi, and GlaxoSmithKline; and advisory board and consultancy fees from Almirall, Boehringer Ingelheim, GlaxoSmithKline, and Napp Pharmaceuticals outside the submitted work. G. T. F. reports consulting and advisory board participation for AstraZeneca, Boehringer Ingelheim, Forest Laboratories, Novartis, Pearl Therapeutics, Sunovion, and Verona Pharma; consulting fees from Receptos; speaking engagements for AstraZeneca, Boehringer Ingelheim, Forest Laboratories, GlaxoSmithKline, Pearl Therapeutics, and Sunovion; and research grants from AstraZeneca, Boehringer Ingelheim, Forest Laboratories, GlaxoSmithKline, Novartis, Pearl Therapeutics, Sanofi, Sunovion, and Theravance Biopharma. V. C. A., L. G., U. B., and F. V. are employees of Boehringer Ingelheim.

Role of sponsors: The sponsor was involved in the design and conduct of the study, the collection, management, analysis and interpretation of the data, and the preparation, review and approval of the manuscript.

Other contributions: Medical writing assistance was provided by Kathryn Whitfield, PhD, of Complete HealthVizion, which was contracted and compensated by Boehringer Ingelheim Pharma GmbH & Co. KG.

Additional information: The e-Appendix and e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation*. 2003;107(11):1514-1519.
2. Lipworth B, Wedzicha J, Devereux G, Vestbo J, Dransfield MT. Beta-blockers in COPD: time for reappraisal. *Eur Respir J*. 2016;48(3):880-888.
3. Zvezdin B, Milutinov S, Kojicic M, et al. A postmortem analysis of major causes of early death in patients hospitalized with COPD exacerbation. *Chest*. 2009;136(2):376-380.
4. Komajda M, Follath F, Swedberg K, et al. The EuroHeart Failure Survey programme—a survey on the quality of care among patients with heart failure in Europe: Part 2: treatment. *Eur Heart J*. 2003;24(5):464-474.
5. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of β-agonists in patients with asthma and COPD: a meta-analysis. *Chest*. 2004;125(6):2309-2321.
6. Ormiston TM, Salpeter SR. Beta-blocker use in patients with congestive heart failure and concomitant obstructive airway disease: moving from myth to evidence-based practice. *Heart Fail Monit*. 2003;4(2):45-54.
7. Salpeter SR, Buckley NS. Systematic review of clinical outcomes in chronic obstructive pulmonary disease: beta-agonist use compared with anticholinergics and inhaled corticosteroids. *Clin Rev Allergy Immunol*. 2006;31(2-3):219-230.
8. Buhl R, Magder S, Bothner U, et al. Long-term general and cardiovascular safety of tiotropium/olodaterol in patients with moderate to very severe chronic

obstructive pulmonary disease. *Respir Med*. 2017;122:58-66.

9. Calverley PM, Anderson JA, Celli B, et al. Cardiovascular events in patients with COPD: TORCH study results. *Thorax*. 2010;65(8):719-725.
10. Hawkins NM, Petrie MC, MacDonald MR, et al. Heart failure and chronic obstructive pulmonary disease: the quandary of beta-blockers and beta-agonists. *J Am Coll Cardiol*. 2011;57(21):2127-2138.
11. Light RW, Chetty KG, Stansbury DW. Comparison of the effects of labetalol and hydrochlorothiazide on the ventilatory function of hypertensive patients with mild chronic obstructive pulmonary disease. *Am J Med*. 1983;75(4A):109-114.
12. Hawkins NM, MacDonald MR, Petrie MC, et al. Bisoprolol in patients with heart failure and moderate to severe chronic obstructive pulmonary disease: a randomized controlled trial. *Eur J Heart Fail*. 2009;11(7):684-690.
13. Mainguy V, Girard D, Maltais F, et al. Effect of bisoprolol on respiratory function and exercise capacity in chronic obstructive pulmonary disease. *Am J Cardiol*. 2012;110(2):258-263.
14. de Miguel Diez J, Chancafe Morgan J, Jimenez Garcia R. The association between COPD and heart failure risk: a review. *Int J Chron Obstruct Pulmon Dis*. 2013;8:305-312.
15. 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):880-887.
16. Dransfield MT, Rowe SM, Johnson JE, Bailey WC, Gerald LB. Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax*. 2008;63(4):301-305.
17. Etminan M, Jafari S, Carleton B, FitzGerald JM. Beta-blocker use and COPD mortality: a systematic review and meta-analysis. *BMC Pulm Med*. 2012;12:48.
18. Bhatt SP, Wells JM, Kinney GL, et al. Beta-blockers are associated with a reduction in COPD exacerbations. *Thorax*. 2016;71(1):8-14.
19. Mascarenhas J, Lourenco P, Lopes R, Azevedo A, Bettencourt P. Chronic obstructive pulmonary disease in heart failure: prevalence, therapeutic and prognostic implications. *Am Heart J*. 2008;155(3):521-525.
20. Buhl R, Maltais F, Abrahams R, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). *Eur Respir J*. 2015;45(4):969-979.
21. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2005;(4)CD003566.
22. Lacasse Y, Daigle JM, Martin S, Maltais F. Validity of chronic obstructive pulmonary disease diagnoses in a large administrative database. *Can Respir J*. 2012;19(2):e5-e9.
23. Roberts CM, Lopez-Campos JL, Pozo-Rodriguez F, Hartl S; on behalf of the European COPD Audit Team. European hospital adherence to GOLD recommendations for chronic obstructive pulmonary disease (COPD) exacerbation admissions. *Thorax*. 2013;68(12):1169-1171.
24. 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.
25. Stefan MS, Rothberg MB, Priya A, Pekow PS, Au DH, Lindenauer PK. Association between beta-blocker therapy and outcomes in patients hospitalised with acute exacerbations of chronic obstructive lung disease with underlying ischaemic heart disease, heart failure or hypertension. *Thorax*. 2012;67(11):977-984.
26. Ekstrom MP, Hermansson AB, Strom KE. Effects of cardiovascular drugs on mortality in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;187(7):715-720.
27. Lopez-Campos JL, Márquez-Martín E, Casanova C. Beta-blockers and COPD: the show must go on. *Eur Respir J*. 2016;48(3):600-603.
28. Global Initiative for Chronic Obstructive Lung Disease. GOLD 2017 global strategy for the diagnosis, management and prevention of COPD. http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/. Accessed January 29, 2018.
29. Cazzola M, Calzetta L, Rinaldi B, et al. Management of chronic obstructive pulmonary disease in patients with cardiovascular diseases. *Drugs*. 2017;77(7):721-732.
30. Rinaldi B, Capuano A, Gritti G, et al. Effects of chronic administration of beta-blockers on airway responsiveness in a murine model of heart failure. *Pulm Pharmacol Ther*. 2014;28(2):109-113.
31. Rutten FH, Hoes AW. Chronic obstructive pulmonary disease: a slowly progressive cardiovascular disease masked by its pulmonary effects? *Eur J Heart Fail*. 2012;14(4):348-350.
32. Du Q, Sun Y, Ding N, Lu L, Chen Y. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies. *PLoS One*. 2014;9(11):e113048.
33. Bhatt SP, Connett JE, Voelker H, et al. β-Blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease (βLOCK COPD): a randomised controlled study protocol. *BMJ Open*. 2016;6(6):e012292.