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Beta-blocker Therapy and Clinical Outcomes in Patients with Moderate COPD and Heightened Cardiovascular Risk: An Observational Sub-study of SUMMIT

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Running Head: Beta-blocker Therapy in the SUMMIT trial

Abstract

Rationale: Cardiovascular disease is a common comorbidity in patients with chronic obstructive pulmonary disease (COPD). Although beta-blockers can be used safely in COPD, concerns remain regarding safety and efficacy interactions in patients using concomitant inhaled long-acting beta-agonists.

Objectives: To compare the differential effects of long-acting beta agonist or inhaled corticosteroid use on clinical outcomes in patients with heightened cardiovascular risk treated and not treated with beta-blockers.

Methods: We examined data from 16,485 participants in the Study to Understand Mortality and MorbidITy in COPD (SUMMIT) who were randomized to once daily inhaled fluticasone furoate (FF), vilanterol (VI), their combination (FF/VI), or placebo and examined the associations between treatment allocation and lung function, COPD exacerbations, cardiovascular events, and all-cause mortality stratified by baseline beta-blocker therapy.

Results: Baseline beta-blocker therapy was used by 31% (n=5,159) of SUMMIT participants. There was no evidence of an interaction between baseline beta-blocker therapy and the association between inhaled treatments and FEV_1 at 3 months (p=0.27), 6 months (p=0.14), or 12 months (p=0.33). The placebo-adjusted mean difference in post-bronchodilator FEV_1 at 3 months in the VI alone group was 58 mL [95% confidence interval (CI) 38, 78] in those taking baseline beta-blocker therapy, and 51 mL [95%CI 38, 65], in those not taking baseline beta-blocker therapy. The placebo-adjusted mean difference in post-bronchodilator FEV1 at 3 months in the FF/VI group was 85 mL [95%CI 65, 105] in those taking baseline beta-blocker therapy, and 68 mL [95%CI 54, 82] in those not taking baseline beta-blocker therapy. Overall,

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there was no evidence of interactions by randomized treatment, including VI alone or in combination with FF, for COPD exacerbations (p=0.18), cardiovascular composite events (p=0.33), and all-cause mortality (p=0.41).

Conclusions: There is no evidence to suggest that baseline beta-blocker therapy reduces the respiratory benefits or increases the cardiovascular risk of inhaled long-acting beta-agonists in patients with COPD and heightened cardiovascular risk.

Clinical trial registered with ClinicalTrials.gov (NCT01313676)

Inhaled type 2 beta-adrenoreceptor agonists are bronchodilators with proven efficacy in patients with chronic obstructive pulmonary disease (COPD).[1] Beta-1 selective-adrenoreceptor antagonists (beta-blocker therapy) are effective anti-anginal[2] and anti-hypertensive[3] therapies, and are also associated with secondary preventative and mortality benefits in patients with a prior myocardial infarction (MI)[4] or left ventricular systolic dysfunction.[5] Whilst modern inhaled beta-2 agonists and oral beta-1 antagonists are designed to be highly selective for their respective receptors, there remains concern about cross reactivity between receptors and the potential for pharmacological interactions that might adversely affect their safety and efficacy, particularly at high doses often required in clinical practice.[6-8]

Despite concerns that beta-blockers may adversely affect lung function, particularly those that are not cardioselective[9], numerous studies have suggested that cardioselective drugs are safe and well tolerated in patients with COPD[10,11]. Indeed, they do not affect the change in lung function over time[12], and may in fact reduce the risk of exacerbations and all-cause mortality[13-15]; a question being tested in a large placebo-controlled clinical trial[16]. However, no studies have adequately examined the impact of beta-blocker use on the short and long term responses to inhaled long-acting beta-agonist treatment, although reviews have highlighted the need for these data.[7,17]

The Study to Understand Mortality and MorbidITy (SUMMIT) assessed the effects of an inhaled corticosteroid (fluticasone furoate) and a long-acting beta-agonist (vilanterol), alone or in combination, in patients with moderate COPD and either pre-existing or at heightened risk of cardiovascular disease.[18] While there was no effect on all-cause mortality, all active treatments reduced the risk of COPD exacerbations compared with placebo and both of the corticosteroid-

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containing arms reduced the rate of decline of the forced expiratory volume in one second (FEV1).[18] There was also no evidence that vilanterol was associated with adverse cardiovascular events.[19] However, given the high prevalence of cardiovascular disease and the frequent use of beta-blockers among participants, the study provides a unique opportunity to examine whether the drugs impacted the therapeutic effects of vilanterol and fluticasone.

We hypothesized that beta-blocker use at baseline would not impact the associations between vilanterol, fluticasone, or their combination and lung function, exacerbations, cardiovascular events, or mortality.

Methods

The study design, analysis approach and primary results have been published previously.[18,20] In brief, we recruited 16,485 participants who were diagnosed with moderate COPD and had a history, or were at increased risk, of cardiovascular disease. Participants were allocated equally to one of four treatments (placebo, fluticasone furoate (100 µg; GlaxoSmithKline), vilanterol (25 µg; GlaxoSmithKline) or the combination of fluticasone furoate and vilanterol (100/25 µg; Relvar®/Breo®, GlaxoSmithKline)) administered once daily as a dry powder with the use of an inhaler (Ellipta®, GlaxoSmithKline).

Participants were categorised according to beta-blocker usage at baseline, irrespective of subsequent changes to therapy during the course of the trial. Those receiving beta-blockers were further sub-classified according to whether they used beta-1 selective or beta non-selective adrenoreceptor antagonist.

Outcomes reported here are on-treatment and post-treatment all-cause mortality, on-treatment change from baseline in FEV_1 at 3 (primary analysis), 6 and 12 months, on-treatment time to first adjudicated cardiovascular composite event, on-treatment revascularization or adjudicated cardiovascular composite event, and on-treatment time to first exacerbation of COPD. The 3 month time point for FEV_1 was chosen given that any potential association between baseline beta-blocker use and lung function would have been apparent by that time. The time to event endpoints were analysed using data up to and including the Common End Date (CED) as per the overall analysis of these endpoints reported in the primary publication.[18]

Statistical Analysis

All analyses in this report were pre-specified and based on the Intent-To-Treat-Efficacy population. Baseline characteristics were summarised using mean and standard deviation for continuous covariates or percentages for categorical covariates for participants receiving beta-blocker therapy at study entry (baseline), those not receiving the therapy, and overall.

Post-bronchodilator FEV_1 was analyzed using a Mixed Effects Repeated Measures Model (MMRM) adjusted for age, gender and baseline post-bronchodilator FEV_1 (mL). This analysis included the covariates of treatment, visit, beta-blocker use at study entry and their two and three-way interactions as well as gender and the continuous covariates of age, baseline FEV_1 and baseline FEV_1-by-visit interaction. The differences in adjusted mean change between placebo and treatment arms at 3, 6 and 12 months were assessed overall and within each beta-blocker usage group.

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Cox Proportional Hazards (PH) analyses of time to first moderate or severe COPD exacerbation were performed. First an unadjusted analysis was conducted, fitting a beta-blocker usage covariate in the placebo arm only, to compare participants taking beta-blockers with those who were not. This analysis was then adjusted for potential confounders of age, gender, ischemic heart disease indicator (if participants had a previous MI or coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)), vascular disease indicator (if participants had a previous cerebrovascular accident or transient ischemic attack or had previous surgery for or were taking medication for carotid or aorto-femoral vascular disease), prior medication for ventricular arrhythmia, congestive heart failure history, hypertension history, smoking status, cardiovascular entry criteria (aged 40-<60 with CV disease or 60-80 with CV risk or 60-80 with CV disease), region, body-mass index (BMI) and the number of COPD exacerbations in the year prior to the study (0,1, ≥2). To assess the associations with treatment, an unadjusted Cox PH model was fitted including treatment, beta-blocker use at study entry and beta-blocker-use-by-treatment interaction.

These survival analyses were repeated for cardiovascular composite event, revascularization or cardiovascular composite event, and all-cause mortality. Kaplan-Meier plots of time to first moderate or severe COPD exacerbation and cardiovascular composite event were produced to illustrate the differences between treatments within beta-blocker usage subgroup. Kaplan-Meier plots for these endpoints were also made within beta-blocker usage subgroup subdivided by beta-1 selectivity (i.e. participants not receiving baseline beta-blocker therapy vs. receiving baseline selective beta-1-blocker therapy vs. receiving baseline non-selective beta-blocker therapy).

Results

Of the 16,485 participants of SUMMIT, just under one third (n=5,159) were receiving oral beta-blocker therapy at baseline. Of those subjects taking beta blockers at baseline, 82% were taking cardioselective beta blockers. Compared with participants not receiving beta-blocker therapy, they had a higher BMI, increased prevalence of cardiovascular risk factors, and were more likely to have cardiovascular disease, especially ischemic heart disease (Table 1). Overall follow up and treatment exposure were similar irrespective of beta-blocker therapy usage at baseline (mean treatment exposure 1.6 years up to the CED).

Lung Function and Exacerbations of Chronic Obstructive Pulmonary Disease

Baseline lung function was similar for those receiving beta-blocker therapy and those who were not (Mean FEV_1 60% of predicted, Table 1). Presence or absence of beta-blocker therapy at baseline was not associated with differences in the association between inhaled treatments compared with placebo and post-bronchodilator FEV_1 at 3 months (interaction p=0.27), 6 months (interaction p=0.14), or 12 months (interaction p=0.33). The placebo-adjusted mean difference in post-bronchodilator FEV_1 at 3 months in the VI alone group was 58 mL [95% confidence interval (CI) 38, 78] in those taking baseline beta-blocker therapy, and 51 mL [95%CI 38, 65], in those not taking baseline beta-blocker therapy. The placebo-adjusted mean difference in post-bronchodilator FEV_1 at 3 months in the FF/VI group was 85 mL [95%CI 65, 105] in those taking baseline beta-blocker therapy, and 68 mL [95%CI 54, 82] in those not taking baseline beta-blocker therapy. (Table 2). Similarly, there were no differences in the

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association between vilanterol alone or of FF/VI compared with placebo and post-bronchodilator FEV_1 at 6 months or 12 months between the two beta-blocker groups.

There were similar percentages of participants with a history of previous COPD exacerbations in the year prior to the study in the beta-blocker and no beta-blocker groups (Table 1). After randomization, in those receiving placebo moderate or severe exacerbations were equally likely to have occurred in participants receiving beta-blocker therapy (30.9%) as those not receiving beta-blocker therapy (29.2%) (unadjusted analysis HR 1.06; 95% CI 0.94, 1.19; p=0.35). There were also no significant interactions with study treatment, i.e. the association between study treatment and exacerbation risk was similar regardless of beta-blocker therapy (p=0.18; Table 3A, Figure 1).

Cardiovascular Events and All-cause Mortality

The time to first cardiovascular event was similar irrespective of beta-blocker therapy and was not associated with study treatment (Figure 2 and Table 3B). In the placebo group, the proportion of participants experiencing cardiovascular events appeared to be higher among participants receiving beta-blocker therapy (4.8%) than those not receiving beta-blocker therapy (4.0%), although this difference was not statistically significant (HR=1.21; 95% CI 0.89, 1.66 p=0.23). The association was further attenuated towards the null after adjusting for potential confounders (HR=0.96; 95% CI 0.68, 1.36; p=0.82). There were also no interactions between study treatment and beta-blocker therapy (p=0.33; Table 3B). In the placebo arm, there was a somewhat higher risk of cardiovascular events in those taking beta-blockers when

revascularization was added to the primary composite cardiovascular event endpoint (6.9% versus 4.7%) (unadjusted HR 1.50; 95% CI 1.14, 1.96; p<0.01).

All-cause mortality was similar irrespective of beta-blocker therapy. In the placebo group, there were no differences in the percentage of participants who died (6.3% with beta-blocker therapy and 6.9% without beta-blocker therapy (HR=0.92; 95% CI 0.71,1.19; p=0.52). This was unchanged after adjusting for all potential confounders (HR=0.94; 95% CI 0.71, 1.25; p=0.67). Again there were no interactions between study treatment and beta-blocker therapy (p=0.41; Table 3C).

Sensitivity analyses restricted to beta-1 selective agents yielded similar results for the risk of exacerbations, cardiovascular events and mortality.

Discussion

We have investigated the influence of baseline beta-blocker therapy on the potential benefits and hazards of inhaled therapy in patients with moderate COPD and heightened cardiovascular risk. We have demonstrated that despite the increased cardiovascular risk profile of SUMMIT participants, study efficacy and safety outcomes were similar irrespective of baseline beta-blocker therapy. Specifically, beta-blocker therapy was not associated with a detrimental effect on lung function or COPD exacerbations, and did not appear to attenuate the treatment benefits associated with inhaled therapies including the beta-2 agonist vilanterol. Similarly, vilanterol was not associated with an excess of adverse cardiovascular events and this was apparently unaffected by the presence or absence of baseline beta-blocker therapy.

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SUMMIT was a major prospective trial of inhaled corticosteroid and long-acting beta-agonist therapy.[20] It was distinguished by its large size and inclusion of patients with mild to moderate COPD who also had or were at risk for cardiovascular disease. As such, it provided an ideal platform to explore the potential mitigating effects of beta-blocker therapy on the benefits and hazards of inhaled beta-2 agonist therapy.

We demonstrated that vilanterol improved lung function irrespective of baseline beta-blocker therapy. Indeed, in contrast to the Rotterdam study,[21] patients receiving beta-blockers appeared to have similar lung function at enrolment and comparable increases in FEV1 with vilanterol (alone and in combination with FF) versus placebo at 3, 6, and 12 months when compared with those not taking beta-blockers. These findings were consistent irrespective of whether beta-blocker therapy was beta-1 selective or non-selective. Our observations are also consistent with previous studies suggesting cardioselective beta-blockers do not affect lung function or the response to beta-agonists in the short term.[10,11] These results extend those of Duffy *et al* who found no association between beta-blocker use and the change in lung function over time in the NIH-sponsored MACRO and STATCOPE trials, by showing that the long term FEV_1 response to inhaled beta-agonists was similarly unaffected.[12]

Though our primary objective was not to examine the association between beta-blockers and exacerbations, we found no difference between patients taking and not taking beta-blockers at baseline in this population with heightened cardiovascular risk. This contrasts with a number of prior observational studies suggesting protective effects[13,15] but is again consistent with the data from Duffy *et al* who found no association between beta-blocker use and exacerbation risk, regardless of the presence of cardiac comorbidities,[12] and emphasizes

the importance of ongoing randomized trials.[16] Similar to the trend for lung function, the benefit of vilanterol alone or in combination with fluticasone was numerically better in patients taking baseline beta-blockers than in those not taking beta-blockers, although there were no statistically significant interactions between treatment and use of baseline beta-blocker therapy.

Previous studies have suggested an increased cardiovascular risk associated with inhaled beta-agonist therapies.[6] If this association were mediated through beta-1 cross reactivity and resultant cardiac toxicity, it would be hypothesized that patients in SUMMIT would have increased risk especially in the absence of the protective effects of beta-blocker therapy. We observed no such excess cardiovascular hazard in patients not receiving beta-blocker therapy with risk of an event being similar irrespective of baseline therapy. This suggests there is no major cardiovascular hazard of beta-2 agonist therapy in patients with COPD and heightened cardiovascular risk who are not receiving baseline beta-blocker therapy. Again, this is borne out by previous meta-analyses of observational cohort studies.[13,22]

The present analysis incorporates observational data within a randomized controlled trial. The use of baseline beta-blocker therapy at study entry was not randomized and changes in beta-blocker use during the trial were not captured precisely. As such, it remains possible that our results could be affected by residual bias, including confounding by indication, and causal interactions between beta-blocker use and the response to inhaled treatments cannot be determined. In addition, although compliance with the inhaled treatments was excellent (96-97% across treatment groups regardless of whether the patient was taking beta-blockers at study entry), we do not know whether beta-blockers were continued after enrolment or if

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patients were compliant. Patients in SUMMIT who were receiving beta-blocker therapy had a higher cardiovascular risk profile with 2-3 fold higher percentages of previous ischemic heart disease, heart failure and arrhythmia than those not taking the drugs. As such, it is biologically quite plausible that they would be particularly sensitive to the potential hazards of beta-agonists. However, we observed no differences in the risk of adverse cardiovascular events irrespective of baseline beta-blocker therapy.

In conclusion, patients with COPD and heightened cardiovascular risk continue to receive respiratory benefit without an excess of cardiovascular risk from long-acting beta-agonist therapy irrespective of baseline beta-blocker therapy. We suggest that treatment decisions regarding the use of inhaled beta-agonist therapy should not be influenced by the presence or absence of beta-blocker therapy. Moreover, beta-blocker therapy should be initiated in patients with COPD when there is a clear indication for therapy to prevent or treat cardiovascular disease.

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Table 1. Baseline characteristics of patients in the Study to Understand Mortality and MorbidITy (SUMMIT) according to use of beta-blocker therapy at baseline

	All	No Beta-Blocker Therapy	Beta-Blocker Therapy
Number of patients	16,485	11,326	5,159
Age (years)	65.2±7.9	65.1±8.0	65.4±7.7
Sex (female)	4,196 (25%)	2,915 (26%)	1,281 (25%)
Body-mass Index (kg/m^2)	28±6	27.4±5.9	29.2±5.9
Smoking Habit (current smokers)	7,678 (47%)	5,293 (47%)	2,385 (46%)
Smoking pack years	40.8±24.3	40.0±24.2	42.5±24.5
FEV_1 (L)	1.70±0.40	1.67±0.40	1.76±0.40
FVC (L)	2.95±0.74	2.93±0.74	3.01±0.72
FEV_1/FVC	58.38±8.32	58.03±8.50	59.14±7.84
FEV1 % predicted	59.7±6.1	59.6±6.1	59.8±6.1
≥1 COPD Exacerbation in 12 months prior to study entry	6,464 (39%)	4,637 (41%)	1,827 (35%)
≥1 Hospitalized COPD Exacerbation in 12 months prior to study entry	2205 (13%)	1,606 (14%)	599 (12%)
Hypertension	14,851(90%)	9,967 (88%)	4,884 (95%)
Diabetes Mellitus	4,997 (30%)	3,289 (29%)	1,708 (33%)
Hypercholesterolemia	11,518 (70%)	7,468 (66%)	4,050 (79%)
Family History of MI or Stroke	3,429 (21%)	2,132 (19%)	1,297 (25%)
Ischemic Heart Disease	3,436 (21%)	1,401 (12%)	2,035 (39%)
Prior Myocardial Infarction	2,486 (15%)	987 (9%)	1,499 (29%)
Coronary Revascularization	2,273 (14%)	837 (7%)	1,436 (28%)
Congestive Heart Failure	3,456 (21%)	2,104 (19%)	1,352 (26%)
Ventricular Arrhythmia	804 (5%)	423 (4%)	381 (7%)
Stroke	1,164 (7%)	774 (7%)	390 (8%)
Peripheral Arterial Disease	2,645 (16%)	1,803 (16%)	842 (16%)

n (%), mean±SD.

FEV_1 – forced expiratory volume in one second; FVC – forced vital capacity; COPD – chronic obstructive pulmonary disease; MI – Myocardial Infarction.

Note: All reported lung function measurements are post-bronchodilator and were assessed at the screening visit.

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Table 2. Forced expiratory volume in one second at 3 months according to treatment allocation and use of beta-blocker therapy at baseline

	Placebo **N=4,111**	**Fluticasone Furoate** **N=4,135**	**Vilanterol** **N=4,118**	**Fluticasone Furoate/ Vilanterol** **N=4,121**
No Beta-blockers at Baseline				
No Beta-blocker Therapy, n	2,831	2,805	2,872	2,818
Adjusted change in FEV_1 from Baseline at 3 months; mL (SE)	-7 (5)	29 (5)	44 (5)	61 (5)
Treatment difference from placebo (Baseline to 3 Months; mL) (95% CI)		36 (23, 50)	51 (38, 65)	68 (54, 82)
Beta-blockers at Baseline				
Beta-blocker Therapy, n	1,280	1,330	1,246	1,303
Adjusted change in FEV_1 from Baseline at 3 months; mL (SE)	1 (7)	31 (7)	59 (7)	85 (7)
Treatment difference from placebo (Baseline to 3 Months; mL) (95% CI)		30 (10, 50)	58 (38, 78)	85 (65, 105)
Treatment by Beta-blocker Interaction p-value	0.27			

Mean (standard error)

FEV1 – forced expiratory volume in one second

Table 3. Time to first outcome event according to treatment allocation and use of beta-blocker therapy at Baseline

	Placebo **N=4,111**	**Fluticasone Furoate** **N=4,135**	**Vilanterol** **N=4,118**	**Fluticasone Furoate/ Vilanterol** **N=4,121**
(A) Time to first exacerbation of chronic obstructive pulmonary disease				
No Beta-blockers at Baseline				
Hazard Ratio vs. Placebo (95% CI)		0.95 (0.86, 1.04)	0.94 (0.85, 1.03)	0.83 (0.75, 0.91)
Beta-blockers at Baseline				
Hazard Ratio vs. Placebo (95% CI)		1.00 (0.87, 1.15)	0.86 (0.75, 1.00)	0.73 (0.63, 0.85)
Treatment by Beta-blocker Interaction p-value	0.18			
(B) Time to first cardiovascular event				
No Beta-blockers at Baseline				
Hazard Ratio vs. Placebo (95% CI)		0.82 (0.62, 1.07)	0.87 (0.66, 1.13)	0.94 (0.72, 1.22)
Beta-blockers at Baseline				
Hazard Ratio vs. Placebo (95% CI)		1.02 (0.72, 1.45)	1.23 (0.88, 1.72)	0.97 (0.68, 1.37)
Treatment by Beta-blocker Interaction p-value	0.33			
(C) Time to death				
No Beta-blockers at Baseline				
Hazard Ratio vs. Placebo (95% CI)		0.86 (0.70, 1.05)	0.90 (0.73, 1.10)	0.80 (0.65, 0.99)
Beta-blockers at Baseline				
Hazard Ratio vs. Placebo (95% CI)		1.01 (0.75, 1.37)	1.11 (0.82, 1.50)	1.09 (0.81, 1.48)
Treatment by Beta-blocker Interaction p-value	0.41			

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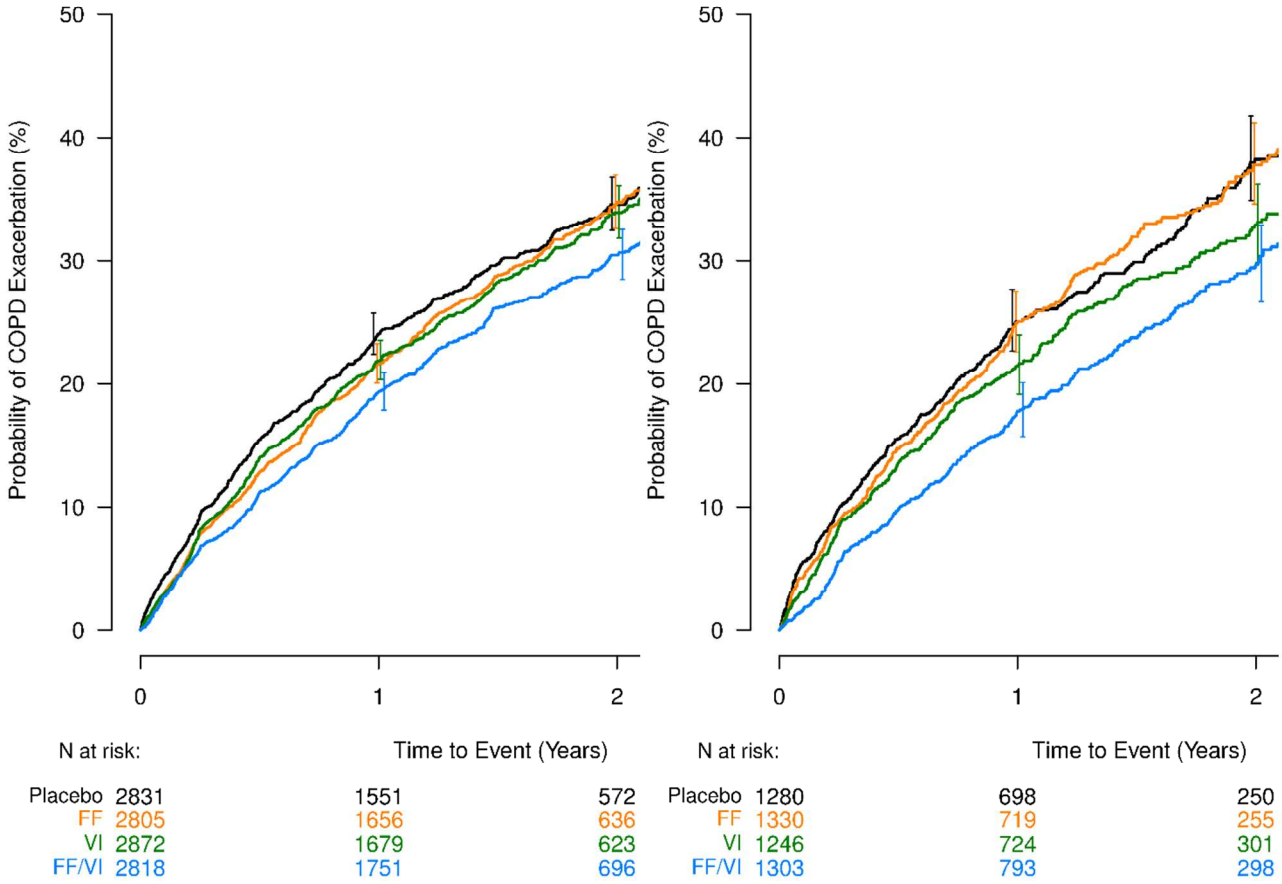
Figure Legends

Figure 1. Time to first exacerbation of chronic obstructive pulmonary disease (COPD) in the absence (A) or presence (B) of beta-blocker therapy at Baseline

Figure 2. Time to first cardiovascular event in the absence (A) or presence (B) of beta-blocker therapy at study entry

Figure 1



(A) No Beta-blockers at study entry (B) Beta-blockers at study entry

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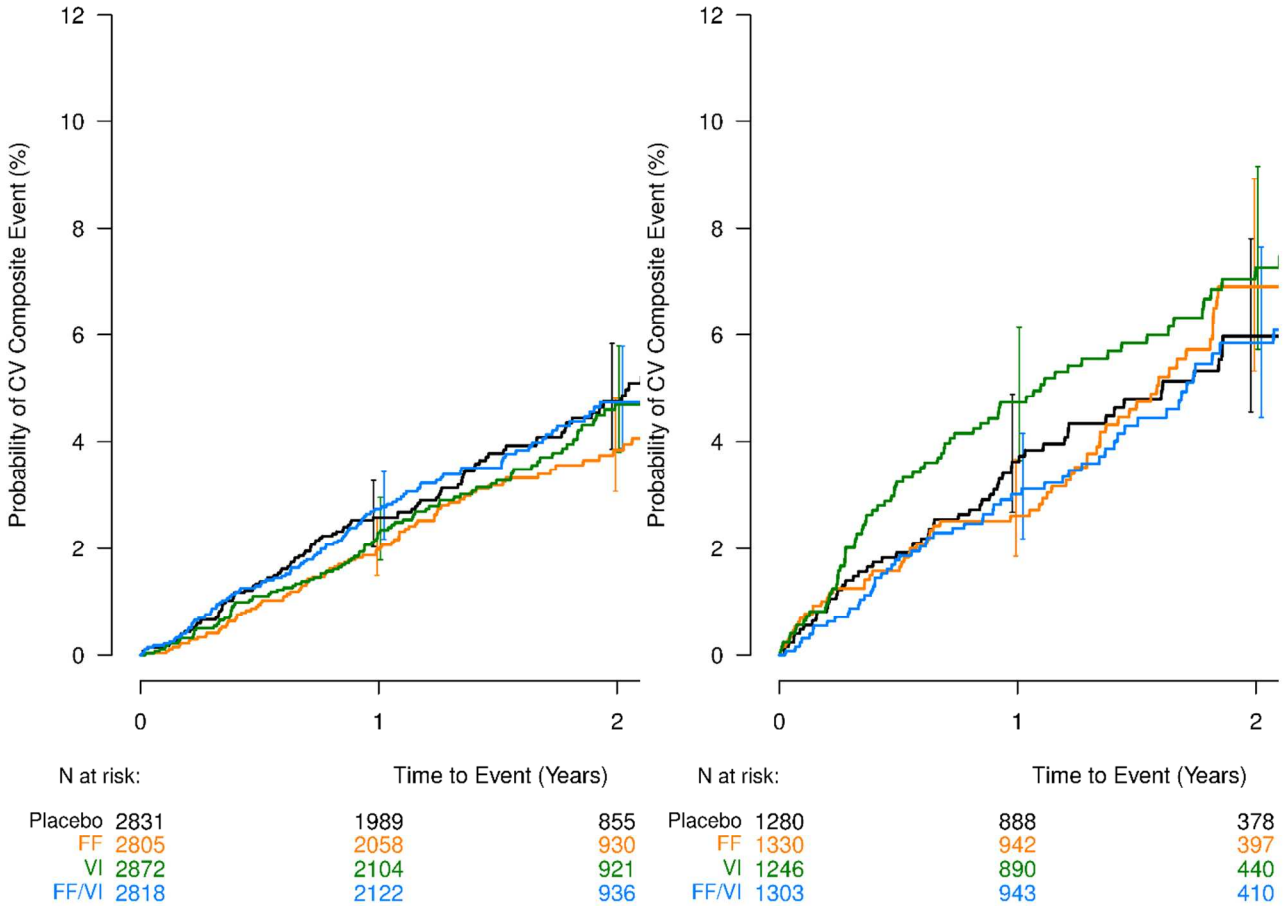
Figure 2



(A) No Beta-blockers at study entry (B) Beta-blockers at study entry