APPENDIX A

Table A1: Baseline characteristics of the cohort of 31,123 patients who added tiotropium to a LABA or vice-versa (combination) and their propensity score and prior ICS-matched 31,123 users of a LABA or tiotropium who did not add (monotherapy), used for the analysis of the stroke outcome (primary objective)

	Combination	Monotherapy
Number of patients	31,123	31,123
Age at cohort entry, mean (sd)	71.9 (8.5)	72.2 (8.6)
Female sex, n (%)	14347 (46.1)	14596 (46.9)
Year of cohort entry, n (%)		
Before 2007	7285 (23.4)	7249 (23.3)
2007-2009	11063 (35.5)	11046 (35.5)
2010-2013	12775 (41)	12828 (41.2)
Time since monotherapy initiation, years, mean(sd)	2.2 (2.0)	2.2 (2.1)
Smoker, n (%)	28856 (92.7)	27876 (89.6)
Obesity Status, n (%)		
Obese	8032 (25.8)	8362 (26.9)
Non-Obese	21960 (70.6)	21749 (69.9)
Missing data	1131 (3.6)	1012 (3.3)
Alcohol Abuse, n (%)	393 (1.3)	423 (1.4)
COPD exacerbation in 30 days prior to cohort entry, n (%)	3072 (9.9)	3077 (9.9)
Comorbidity in year prior to cohort entry, n (%)		
Myocardial infarction	401 (1.3)	403 (1.3)
Arrhythmia	982 (3.2)	1006 (3.2)
Atherosclerosis/PVD	414 (1.3)	458 (1.5)
Stroke	214 (0.7)	207 (0.7)
Heart Failure	973 (3.1)	946 (3.0)
Hypertension	2817 (9.1)	2871 (9.2)
Hyperlipidemia	494 (1.6)	484 (1.6)
Congenital CV abnormalities	4 (0.0)	10 (0.0)
Diabetes	3861 (12.4)	4087 (13.1)
Pneumonia	828 (2.7)	717 (2.3)
Renal disease	2024 (6.5)	2062 (6.6)
Thyroid disease	2840 (9.1)	2907 (9.3)

	Combination	Monotherapy
Medications in year prior to cohort entry, n (%)		
Cardiovascular drugs		
ACE inhibitors	9236 (29.7)	9050 (29.1)
Angiotensin receptor blockers	3706 (11.9)	3978 (12.8)
Beta-blockers	4000 (12.9)	4045 (13.0)
Thiazide diuretics	5705 (18.3)	5737 (18.4)
Loop diuretics	8113 (26.1)	7827 (25.1)
Antiarrhythmics	1790 (5.8)	1825 (5.9)
Digoxin (digitalis)	1687 (5.4)	1610 (5.2)
Nitrates	3088 (9.9)	3140(10.1)
Non-aspirin antiplatelets	2434 (7.8)	2432 (7.8)
Statins	13398 (43.0)	13466 (43.3)
Respiratory drugs		
Short-acting beta-agonists	28648(92.0)	28192 (90.6)
Ipratropium bromide	9862 (31.7)	12897 (41.4)
Inhaled corticosteroids	26832 (86.2)	26832 (86.2)
Oral corticosteroids	15170 (48.7)	14623 (47.0)
Methylxanthines	1724 (5.5)	1482 (4.8)
Drugs prolonging QT interval		
Macrolides	8560 (27.5)	8403 (27.0)
Antidepressants	6928 (22.3)	6843 (22.0)
Antipsychotics	416 (1.3)	424 (1.4)
Others	29792 (95.7)	29481 (94.7)
Other medications		
Insulin	790 (2.5)	857 (2.8)
Aspirin	10627 (34.1)	10749 (34.5)
NSAIDs	5427 (17.4)	5515 (17.7)
Acetaminophen	15478 (49.7)	15514 (49.8)
Opioids	13613 (43.7)	13639 (43.8)

Table A2: Baseline characteristics of the cohort of 31,174 patients who added tiotropium to a LABA or vice-versa (combination) and their propensity score and prior ICS-matched 31,174 users of a LABA or tiotropium who did not add (monotherapy), used for the analysis of the heart failure outcome (primary objective)

	Combination	Monotherapy
Number of patients	31,174	31,174
Age at cohort entry, mean (sd)	72.0 (8.5)	72.3 (8.6)
Female sex, n (%)	14367 (46.1)	14583 (46.8)
Year of cohort entry, n (%)		
Before 2007	7286 (23.4)	7258 (23.3)
2007-2009	11085 (35.6)	11050 (35.4)
2010-2013	12803 (41.1)	12866 (41.3)
Time since monotherapy initiation, years, mean(sd)	2.3 (2.0)	2.2 (2.1)
Smoker, n (%)	28907 (92.7)	27959 (89.7)
Obesity Status, n (%)		
Obese	8049 (25.8)	8438 (27.1)
Non-Obese	21994 (70.6)	21737 (69.7)
Missing data	1131 (3.6)	999 (3.2)
Alcohol Abuse, n (%)	393 (1.3)	404 (1.3)
COPD exacerbation in 30 days prior to cohort entry, n (%)	3080 (9.9)	3048 (9.8)
Comorbidity in year prior to cohort entry, n (%)		
Myocardial infarction	396 (1.3)	398 (1.3)
Arrhythmia	983 (3.2)	1063 (3.4)
Atherosclerosis/PVD	413 (1.3)	450 (1.4)
Stroke	212 (0.7)	207 (0.7)
Heart Failure	977 (3.1)	952 (3.1)
Hypertension	2815 (9.0)	2797 (9.0)
Hyperlipidemia	495 (1.6)	505 (1.6)
Congenital CV abnormalities	4 (0.0)	10 (0.0)
Diabetes	3864 (12.4)	4087 (13.1)
Pneumonia	829 (2.7)	685 (2.2)
Renal disease	2031 (6.5)	2078 (6.7)
Thyroid disease	2849 (9.1)	2866 (9.2)

	Combination	Monotherapy
Medications in year prior to cohort entry, n (%)		
Cardiovascular drugs		
ACE inhibitors	9250 (29.7)	9222 (29.6)
Angiotensin receptor blockers	3714 (11.9)	3943 (12.6)
Beta-blockers	3999 (12.8)	4021 (12.9)
Thiazide diuretics	5713 (18.3)	5813 (18.6)
Loop diuretics	8129 (26.1)	7894 (25.3)
Antiarrhythmics	1790 (5.7)	1820 (5.8)
Digoxin (digitalis)	1695 (5.4)	1694 (5.4)
Nitrates	3098 (9.9)	3156 (10.1)
Non-aspirin antiplatelets	2442 (7.8)	2378 (7.6)
Statins	13415 (43.0)	13542 (43.4)
Respiratory drugs		
Short-acting beta-agonists	28702 (92.1)	28183 (90.4)
Ipratropium bromide	9879 (31.7)	12902 (41.4)
Inhaled corticosteroids	26883 (86.2)	26883 (86.2)
Oral corticosteroids	15212 (48.8)	14450 (46.4)
Methylxanthines	1730 (5.5)	1483 (4.8)
Drugs prolonging QT interval		
Macrolides	8577 (27.5)	8352 (26.8)
Antidepressants	6950 (22.3)	6837 (21.9)
Antipsychotics	416 (1.3)	431 (1.4)
Others	29844 (95.7)	29469 (94.5)
Other medications		
Insulin	788 (2.5)	847 (2.7)
Aspirin	10642 (34.1)	10797 (34.6)
NSAIDs	5442 (17.5)	5628 (18.1)
Acetaminophen	15508 (49.7)	15714 (50.4)
Opioids	13645 (43.8)	13788 (44.2)