

## Supplementary Files

**Supplementary table S1. Therapeutic categories and ATC codes that were considered as proxies of comorbidities.**

<b>Drugs tracer of comorbidity</b>	<b>ATC Code</b>
Beta-blockers	C07
Antiarrhythmics	C01B
Other cardiovascular drugs	C01A; C01C-C01E; C02-03; C08-09
Antiplatelet/Anticoagulant agents	B01A
Antidiabetics	A10
Lipid-lowering agents	C10
Antipsychotics	N05A
Antiparkinsons	N04
Antidepressives	N06A
Antiepileptics	N03
Antiacids	A02

Systemic corticosteroid	H02
Antibiotics	J01
NSAIDs	M01A; N02B
Pain medications	N02A; N02BE
Antiglaucoma agents	S01E
Osteoporosis medications	M05; A12A

<b>Respiratory drugs</b>	<b>ATC Code</b>
Glicocorticoids (inhaled)	R03BA
Anticholinergics (ipratropium, oxitropium, tiotropium)	R03BB01, 02, 04
Long-Acting Beta-Agonists, LABA	R03AC12, 13, 18
Short-Acting Beta-Agonists, SABA	R03AC04, 02, 03
Antileukotriene medications	R03DC
Xanthines	R03DA

LABA, combinations	R03AK06, 07
SABA, combinations	R03AK03, 04
Antiallergics (e.g. Nedocromil)	R03BC
Other	R03DX

<b>Drugs used to evaluate severity of respiratory disease</b>	<b>ATC code</b>
(Oxítropium OR Ipratropium) OR all the other respiratory categories pertaining ATC=R OR Systemic corticosteroids (ATC=H02): 4 categories (0 respiratory drugs to $\geq 4$ classes)	R OR H02

**Supplementary table S2. Comparison of demographic characteristics and medical history between patients included in the Umbria study, the Dutch study<sup>1</sup> and the head-to-head RCT<sup>2</sup>.**

	Umbria: incident users of HandiHaler <sup>®</sup>	Umbria: incident users of Respimat <sup>®</sup>	Verhamme et al.: HandiHaler <sup>®</sup>	Verhamme et al.: Respimat <sup>®</sup>	Wise et al.: HandiHaler <sup>®</sup>	Wise et al.: Respimat <sup>®</sup> 2,5 µg	Wise et al.: Respimat <sup>®</sup> 5,0 µg
<b>Number of patients</b>	3,492	898	9,226	2,827	5,687	5,724	5,705
<b>Study type</b>	Observational, drug utilization		Observational, etiologic		Randomized controlled trial		
<b>Male(%)</b>	56.6	57.0	51.8	51.9	71.0	71.1	72.5
<b>Female (%)</b>	43.4	43.0	48.2	48.1	29.0	28.9	27.5
<b>Mean age (SD)</b>	74 (10)	73 (10)	68 (12)	68 (12)	65 (9)	65 (9)	65 (9)
<b>Criteria used to evaluate severity of the respiratory disease</b>	Number of respiratory drug classes in the 6 month period prior to starting tiotropium (from 0 to 4 or more classes)		<ul style="list-style-type: none"> <li>i. N. of antibiotics (1-year before);</li> <li>ii. N. of systemic corticosteroids (1-year before);</li> <li>iii. N. of GP visits (1-year before);</li> <li>iv. Hospitalizations for COPD exacerbation (1-year before);</li> <li>v. Specialist consulting (1-year before).</li> </ul>		Inclusion criteria: $FEV_1/FVC \leq 0.70$ and $FEV_1 \leq 70\%$  $FEV_1$ : forced expiratory volume in 1 second FVC: forced vital capacity		
<b>Previous use of respiratory drugs (%)</b>							
Short-Acting BetaAgonist (SABA)	22.9	26.8	17.3	21.2	53.3	54.4	53.1
Long-Acting BetaAgonist (LABA)	37.9	38.9	38.5	37.7	62.3	61.9	61.2
Tiotropium	NA	NA	NA	NA	47.3	46.5	46.8
Other anticholinergics (ipratropium, oxitropium)	6.8	7.5	6.3	11.3	17.1	17.3	17.5
Systemic corticosteroids	27.7	30.5	10.1	15.4	4.7	5.0	4.3
Glicocorticoids, inhaled	22.2	25.1	42.5	41.5	59.4	58.9	58.8
Antileukotriene agents	2.5	3.9	1.9	2.4	2.6	2.6	2.5
Xanthines	6.8	7.6	1.1	1.2	15.5	15.9	15.4
<b>Previous drug use as tracer of comorbidity (%)</b>							
antiarrhythmics	6.4	6.7	1.6	1.5			

Beta-blockers	22.7	26.5	21.8	22.5	14.6	14.5	14.1
Other cardiovascular drugs	75.1	74.4			50.8 §	51,7 §	50.9 §
Antiplatelet/anticoagulant agents	49.5	50.0	31.5*	34.7*	19.7 (ASA)	18.9 (ASA)	19.2 (ASA)
Antidiabetics	18.7	15.3	17.7**	19.3**	Exclusion criteria: Acute myocardial infarction in the previous six months; heart failure class III or IV; unstable or severe arrhythmia that required new treatments in the previous 12 months; severe respiratory conditions (active tuberculosis, asthma, cystic fibrosis, bronchiectasia clinically present, interstitial lung disease, surgical resection of the lung, pulmonary thromboembolism); COPD exacerbations in the previous 4 weeks; narrow-angle glaucoma; moderate or severe renal impairment; tumors that required therapy in the past 5 years. Participants were also excluded if they had significant diseases other than COPD that could be risky for patient participation in the study or that could interfere with study participation.		
Lipid-lowering agents	27.6	28.3	26.6	28.5			
Antipsychotics	2.5	3.5	1.5	1.2			
Antiparkinsons	2.4	3.6	0.6	0.9			
Antidepressives	19.2	17.6	4.7 (SSRI)	5.3 (SSRI)			
Antiepileptics	5.7	6.9	9.7	10.1			
Antacids	53.3	51.6					
Antibiotics	62.0	67.5	20.7	24.9			
Antiglaucoma agents	5.4	6.2					
NSAIDs	25.8	25.1	8.7	7.9			
Pain medications	8.8	8.8	5.4	6.9			
Osteoporosis medications	7.4	7.0					

\* Obtained as a sum of antiplatelets and anticoagulants.

\*\* Percentage related to the reported conditions, i.e. diabetes.

§ all types of cardiovascular drugs.

1) Verhamme KM, Afonso A, Romio S, et al. Use of tiotropium Respimat Soft Mist Inhaler versus HandiHaler and mortality in patients with COPD. *Eur Respir J* 2013;42:606-15.

2) Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med* 2013;369:1491-501.