

## Appendix

### Data requirements and data extracted from OPCRD

To estimate the patient characteristics in each cohort, and to prevent user bias in the study of patients in cohort 2, every patient had to be registered with a general practitioner (GP) for at least one year before the ID. Patients had to have had continuous medical record data between January 1, 2014 and December 31, 2016, to have had at least one record of a modified MRC (mMRC) dyspnoea score per year between January 1, 2014 and December 31, 2016, and to have had at least one record of exacerbation frequency (including none) per year between January 1, 2013 and December 31, 2015. Patients were excluded if they had a previous diagnosis of other lower respiratory disease other than COPD, asthma, or bronchitis at any time.

For eligible patients the following data were extracted from the OPCRD: age at ID; sex; body mass index (BMI, kg/m<sup>2</sup>) within 5 years prior to ID; smoking status (categorised as never smokers, current smokers, former smokers); FEV<sub>1</sub>% predicted (categorised by GOLD stage: GOLD 1: ≥80, GOLD 2: 50-79, GOLD 3: 30-49, GOLD 4: <30); mMRC dyspnoea score (categorised as: 0-1 and ≥2); blood eosinophil count (categorised as ≥0.30 x 10<sup>9</sup>/L (high) and <0.30 x 10<sup>9</sup>/L (low)); prescription of respiratory drugs; the presence of comorbidities recorded as active problems in the year prior to the ID; and whether or not patients had a diagnosis of pneumonia in the year prior to the ID. Based on their mMRC score and history of exacerbations in the previous year, patients within each cohort were then classified by the GOLD 2017 classification scheme as GOLD group A, B, C or D in the year 2014 and 2016

COPD exacerbations were defined as the occurrence of the following events:

- a. Unscheduled hospital admission with acute COPD exacerbation as the primary diagnosis AND/OR,
- b. Unscheduled COPD-related accident & emergency (A&E) attendance AND/OR,
- c. An acute course of oral corticosteroid AND/OR
- d. Antibiotics prescribed with evidence of a lower respiratory consultation.

When oral corticosteroids and antibiotics were prescribed during a routine respiratory review (mMRC and a prescription of oral corticosteroids and/or antibiotics at the same day) the prescription of both of these drugs was not be included in the algorithm for estimating the number of exacerbations. An exacerbation within 14 days from a previous one was considered to belong to the same event.

### **Complementary analysis on comorbidities**

We compared the comorbidities of the patients in cohort 2 with the ones from cohort 1 by conducting a logistic regression to derive odds ratios (ORs) and 95% CIs. We also examined the prevalence of comorbid conditions in a general population to determine whether the overall prevalence of comorbidities was higher in patients with established COPD. For each patient with COPD we randomly selected up to four controls matched by age ( $\pm 2$  years), sex and smoking status (never/ever/ex-smoker), and randomly selected from the population of patients at risk for COPD at the index date of the patient with COPD. We then assessed the association between the prevalence of comorbid conditions and having COPD using conditional logistic regression.

Treatment according to Gold 2019 Report	mMRC <2		mMRC ≥ 2	
	< 2 exacerbations	≥ 2 exacerbations	< 2 exacerbations	≥ 2 exacerbations
Eos < 100				
Under-treatment	N/A	NONE, LABA, LAMA	NONE, LABA, LAMA	NONE, LABA, LAMA
Appropriate treatment	NONE, LABA, LAMA	LAMA/LABA	LAMA/LABA	LAMA/LABA
Over-treatment	LAMA/LABA, ICS, LABA/ICS, LAMA/ICS, LAMA/LABA/ICS	ICS, LABA/ICS, LAMA/ICS, LAMA/LABA/ICS	ICS, LABA/ICS, LAMA/ICS, LAMA/LABA/ICS	ICS, LABA/ICS, LAMA/ICS, LAMA/LABA/ICS
Eos 100-300				
Under-treatment	N/A	NONE, LABA, LAMA, ICS, LAMA/ICS, LABA/ICS	NONE, LABA, LAMA, ICS, LAMA/ICS,	NONE, LABA, LAMA, ICS, LAMA/ICS, LAMA/LABA, LABA/ICS,
Appropriate treatment	NONE, LABA, LAMA	LAMA/LABA, LAMA/LABA/ICS	LAMA/LABA, LABA/ICS, LAMA/LABA/ICS	LAMA/LABA/ICS
Over-treatment	LAMA/LABA, ICS, LABA/ICS, LAMA/ICS, LAMA/LABA/ICS	N/A	N/A	N/A
Eos > 300				
Under-treatment	N/A	NONE, LABA, LAMA, ICS, LAMA/ICS,	NONE, LABA, LAMA, ICS, LAMA/ICS,	NONE, LABA, LAMA, ICS, LAMA/ICS, LAMA/LABA, LABA/ICS,
Appropriate treatment	NONE, LABA, LAMA	LAMA/LABA, LABA/ICS, LAMA/LABA/ICS	LAMA/LABA, LABA/ICS, LAMA/LABA/ICS	LAMA/LABA/ICS
Over-treatment	LAMA/LABA, ICS, LABA/ICS, LAMA/ICS, LAMA/LABA/ICS	N/A	N/A	N/A

*Supplemental Table S1. Criteria used to classify appropriateness of maintenance therapy in established patients (cohort 1)*

GOLD group A		
	under-treatment	not applicable (N/A)
	appropriate treatment	None, LABA, LAMA
	over-treatment	LAMA/LABA, ICS, LABA/ICS, LAMA/ICS, LAMA/LABA/ICS
GOLD group B		
	under-treatment	None
	appropriate treatment	LABA, LAMA
	over-treatment	LAMA/LABA, ICS, LABA/ICS, LAMA/ICS, LAMA/LABA/ICS
GOLD group C		
	under-treatment	None, LABA, ICS
	appropriate treatment	LAMA
	over-treatment	LAMA/LABA, LABA/ICS, LAMA/ICS, LAMA/LABA/ICS
GOLD group D		
	under-treatment	None, LABA, ICS
	appropriate treatment	LAMA, LAMA/LABA, LABA/ICS, LAMA/ICS,
	over-treatment	LAMA/LABA/ICS

*Supplemental table S2. Criteria used to assess appropriateness of initial maintenance therapy in cohort 2.*

Maintenance therapy 2014	Maintenance therapy 2016	Classification of change in therapy
ICS	LAMA	Escalation
LAMA	ICS	De-escalation
ICS	ICS/LABA	Escalation
ICS/LABA/LAMA	ICS/LABA	De-escalation
LAMA	LABA	Switching
ICS/LAMA	ICS/LABA	Switching
LABA	ICS/LABA	Escalation
ICS	ICS	No change
LABA	LABA	No change
LAMA	LAMA	No change
LABA	LAMA	Switching
ICS/LABA	ICS/LABA	No change
ICS/LABA/LAMA	ICS/LABA/LAMA	No change
LABA/LAMA	LABA/LAMA	No change
ICS/LAMA	ICS/LAMA	No change
LAMA	LABA/LAMA	Escalation
LAMA	ICS/LABA	Switching
ICS/LABA	LABA	De-escalation
ICS/LAMA	ICS/LABA/LAMA	Escalation
ICS	LABA/LAMA	Escalation
ICS/LABA	LAMA	Switching
ICS/LABA	ICS	De-escalation
LABA	LABA/LAMA	Escalation
LAMA	ICS/LABA/LAMA	Escalation
ICS/LABA	ICS/LABA/LAMA	Escalation
ICS/LABA	LABA/LAMA	Switching

*Supplemental Table S3. Criteria used to classify changes in therapy between 2014 and 2016*

Over-treatment according to Gold 2019 Report	Baseline Characteristics			
	mMRC <2		mMRC ≥ 2	
	< 2 exacerbations	≥ 2 exacerbations	< 2 exacerbations	≥ 2 exacerbations
Eos < 100	N=131	N=57	N=115	N=69
ICS (%)	24 (18.3)	<5	16 (13.9)	<5
ICS/LABA (%)	62 (47.3)	26 (45.6)	53 (46.1)	24 (34.8)
ICS/LABA/LAMA (%)	37 (28.3)	28 (49.1)	43 (37.4)	43 (62.3)
LABA/LAMA (%)	6 (4.6)	0	0	0
ICS/LAMA (%)	<5	0	<5	<5
Eos 100-300	N=1383	N=0	N=0	N=0
ICS (%)	213 (15.4)	0 (0)	0 (0)	0 (0)
ICS/LABA (%)	718 (51.9)	0 (0)	0 (0)	0 (0)
ICS/LABA/LAMA (%)	386 (27.9)	0 (0)	0 (0)	0 (0)
LABA/LAMA (%)	40 (2.9)	0 (0)	0 (0)	0 (0)
ICS/LAMA (%)	26 (1.9)	0 (0)	0 (0)	0 (0)
Eos > 300	N=832	N=0	N=0	N=0
ICS (%)	105 (12.6)	0 (0)	0 (0)	0 (0)
ICS/LABA (%)	475 (57.1)	0 (0)	0 (0)	0 (0)
ICS/LABA/LAMA (%)	215 (25.9)	0 (0)	0 (0)	0 (0)
LABA/LAMA (%)	22 (2.6)	0 (0)	0 (0)	0 (0)
ICS/LAMA (%)	15 (1.8)	0 (0)	0 (0)	0 (0)

*Supplemental Table S4. Medication prescribed to established COPD patients (cohort 1) assessed as over-treated by GOLD group.*

Co-morbidity ever before or at the index date, n (%)	<b>Group A</b>	<b>Group B</b>	<b>Group C</b>	<b>Group D</b>
	N=5053	N=2938	N=1574	N=1844
Diabetes mellitus	695 (13.8)	571 (19.4)	226 (14.4)	309 (16.8)
Osteoporosis	313 (6.2)	224 (7.6)	127 (8.1)	210 (11.4)
Cardiovascular disease*	448 (8.9)	358 (12.2)	173 (11.0)	237 (12.9)
Heart failure*	36 (0.7)	58 (2.0)	17 (1.1)	51 (2.8)
Anxiety/Depression*	842 (16.7)	636 (21.7)	309 (19.6)	539 (29.2)
Hypertension	2289 (45.3)	1501 (51.1)	671 (42.6)	898 (48.7)
Ischaemic heart disease	750 (14.8)	715 (24.3)	288 (18.3)	401 (21.8)
Gastroesophageal reflux disease*	667 (13.2)	453 (15.4)	271 (17.2)	372 (20.2)
Pneumonia*	25 (0.5)	14 (0.5)	40 (2.5)	45 (2.4)

*Supplemental Table S5. Prevalence of comorbidities in established COPD patients (cohort 1) by GOLD group. \*Active at the index date.*

Co-morbidity at the index date n (%)	Group A	Group B	Group C	Group D
	N=316	N=199	N=110	N=74
Diabetes mellitus	42 (13.3)	37 (18.6)	14 (12.7)	10 (13.5)
Osteoporosis	8 (2.5)	14 (7.0)	2 (1.8)	6 (8.1)
Cardiovascular disease*	26 (8.2)	22 (11.1)	14 (12.7)	9 (12.2)
Heart failure*	3 (0.9)	5 (2.5)	2 (1.8)	2 (2.7)
Anxiety/Depression*	54 (17.1)	40 (20.1)	28 (25.4)	14 (18.9)
Hypertension	126 (39.9)	94 (47.2)	48 (43.6)	35 (47.3)
Ischaemic heart disease	49 (15.5)	47 (23.6)	21 (19.1)	11 (14.9)
Gastroesophageal reflux disease*	34 (10.8)	32 (16.1)	17 (15.5)	9 (12.2)
Pneumonia*	2 (0.6)	1 (0.5)	1 (0.9)	5 (6.8)

*Supplemental Table S6. Prevalence of comorbidities in COPD patients initiating maintenance therapy (cohort 2) by GOLD group. \*Active at the index date.*



Co-morbidity ever or in the year before the index date, n (%)	<b>COPD patients</b> N=11360	<b>Controls</b> N=45437	OR 95% CI	P-value
Diabetes mellitus	1795 (15.8)	6680 (14.7)	1.09 (1.03 – 1.15)	0.003
Hypertension	5338 (47.0)	19736 (43.4)	1.17 (1.12 – 1.22)	<0.0001
Cardiovascular disease*	1212 (10.7)	3419 (7.5)	1.48 (1.38 – 1.59)	<0.0001
Heart failure*	162 (1.4)	412 (0.9)	1.58 (1.32 – 1.90)	<0.0001
Ischaemic heart disease	2141 (18.9)	6968 (15.3)	1.31 (1.23 – 1.38)	<0.0001
Sleep apnoea	43 (0.4)	95 (0.2)	1.81 (1.27 – 2.60)	0.001
Nasal polyps	24 (0.2)	62 (0.1)	1.55 (0.97 – 2.49)	0.07
Osteoporosis	870 (7.7)	2207 (4.9)	1.68 (1.54 – 1.83)	<0.0001
Chronic Kidney Disease Stage IV-V	246 (2.2)	895 (2.0)	1.10 (0.96 – 1.28)	0.18
Anxiety/Depression*	2319 (20.4)	6477 (14.3)	1.57 (1.49 – 1.65)	<0.0001
Eczema*	385 (3.4)	1393 (3.1)	1.11 (0.99 – 1.25)	0.08
Rhinitis*	901 (7.9)	2439 (5.4)	1.52 (1.41 – 1.65)	<0.0001
Gastroesophageal reflux disease*	1758 (15.5)	4749 (10.5)	1.57 (1.48 – 1.67)	<0.0001

*Supplemental table S7. Baseline characteristics of established COPD patients (cohort 1), and age, sex and smoking-matched controls. OR=Odds ratio; CI=confidence intervals; SD=standard deviation. \*in the year before index date*

Co-morbidity ever or in the year before the index date, n (%)	COPD patients N=698	Controls N=2792	OR 95% CI	P-value
Diabetes mellitus	103 (14.8)	422 (15.1)	0.97 (0.77 – 1.23)	0.81
Hypertension	303 (43.4)	1210 (43.3)	1.00 (0.84 – 1.20)	0.97
Cardiovascular disease*	71 (10.2)	216 (7.7)	1.37 (1.03 – 1.83)	0.03
Heart failure*	12 (1.7)	24 (0.9)	2.08 (1.02 – 4.26)	0.05
Ischaemic heart disease	128 (18.3)	400 (14.3)	1.37 (1.09 – 1.72)	0.007
Sleep apnoea	<5**	<5	0.80 (0.09 – 6.85)	0.84
Nasal polyps	<5	<5	2.67 (0.45 – 15.96)	0.28
Osteoporosis	30 (4.3)	125 (4.5)	0.96 (0.63 – 1.46)	0.83
Chronic Kidney Disease Stage IV-V	14 (2.0)	61 (2.2)	0.92 (0.51 – 1.65)	0.77
Anxiety/Depression*	136 (19.5)	410 (14.7)	1.42 (1.14 – 1.77)	0.002
Eczema*	22 (3.2)	78 (2.8)	1.14 (0.70 – 1.84)	0.61
Rhinitis*	48 (6.9)	131 (4.7)	1.52 (1.07 – 2.14)	0.02
Gastroesophageal reflux disease*	92 (13.2)	265 (9.5)	1.44 (1.12 – 1.85)	0.004

*Supplemental table S8. Baseline characteristics of COPD patients initiating maintenance therapy (cohort 2), and age, sex and smoking-matched controls OR=Odds ratio; CI=confidence intervals; SD=standard deviation. \*in the year before index date, \*\*To avoid unintentional disclosure and to preserve confidentiality, cell counts <5 are reported as <5.*

GOLD Group	n	Mean Exacerbation rate/year (SD) for group	Treatment according to 2019 GOLD Report	n	% of group	Mean Exacerbation rate/year (SD)	RR <sub>adjusted</sub> (95% CI)*
A	316	0.6 (0.8)	Under-treated	-	-	-	reference 1.41 (1.07 – 1.86)
			Appropriate	174	55.1	0.5 (0.7)	
			Over-treated	142	44.9	0.7 (0.8)	
B	199	1.0 (1.2)	Under-treated	-	-	-	reference 1.05 (0.74 – 1.48)
			Appropriate	107	53.8	0.9 (1.1)	
			Over-treated	92	46.2	1.0 (1.1)	
C	110	1.5 (1.6)	Under-treated	22	20.0	1.5 (1.3)	1.17 (0.71 – 1.94) reference 1.52 (1.02 – 2.29)
			Appropriate	44	40.0	1.3 (1.3)	
			Over-treated	44	40.0	1.9 (1.8)	
D	74	1.8 (1.9)	Under-treated	7	9.5	2.0 (1.6)	1.14 (0.56 – 2.32) reference 0.75 (0.38 – 1.48)
			Appropriate	57	77.0	1.7 (1.5)	
			Over-treated	10	13.5	1.6 (2.7)	

*Supplemental Table S9. Mean annual exacerbation rates over 2 years in patients initiating maintenance therapy in each GOLD group in 2014 by appropriateness of initial therapy according to GOLD 2019. \*age and sex adjusted rate ratio (RR) for under- and over treated patients versus appropriately treated patients.*

GOLD Group	N	Change in maintenance treatment during 2 years	N (%)	RRR <sub>crude</sub> 95% CI	RRR <sub>age- and sex-adjusted</sub> 95% CI	p-value
A	316	No change	169 (53.5)	1.00 (reference)	1.00	-
		De-escalated	56 (17.7)	1.00	1.00	-
		Switched	25 (7.9)	1.00	1.00	-
		Escalated	66 (20.9)	1.00	1.00	-
B	199	No change	84 (42.2)	1.00	1.00	-
		De-escalated	32 (16.1)	1.15 (0.69 – 1.91)	1.15 (0.69 – 1.92)	0.58
		Switched	29 (14.6)	2.33 (1.29 – 4.23)	2.26 (1.24 – 4.11)	0.008
		Escalated	54 (27.1)	1.65 (1.06 – 2.57)	1.71 (1.09 – 2.67)	0.02
C	110	No change	60 (54.6)	1.00	1.00	-
		De-escalated	12 (10.9)	0.60 (0.30 – 1.20)	0.61 (0.30 – 1.21)	0.15
		Switched	13 (11.8)	1.47 (0.70 – 3.05)	1.45 (0.69 – 3.01)	0.32
		Escalated	25 (22.7)	1.07 (0.62 – 1.84)	1.09 (0.63 – 1.88)	0.77
D	74	No change	35 (47.3)	1.00	1.00	-
		De-escalated	13 (17.6)	1.12 (0.55 – 2.27)	1.13 (0.56 – 2.28)	0.74
		Switched	8 (10.8)	1.55 (0.64 – 3.71)	1.49 (0.62 – 3.58)	0.38
		Escalated	18 (24.3)	1.32 (0.70 – 2.49)	1.38 (0.73 – 2.62)	0.32

*Supplemental Table S10. Changes in therapy over 2 years after patients initiated maintenance therapy in 2014 by initial GOLD compared with GOLD group A and no change in maintenance therapy, with crude and age and sex adjusted relative risk ratio (RRR) for change.*

	Assessment of treatment at initiation in 2014		Assessment of treatment at follow-up in 2016 (based on characteristics in 2014)		
		N (%)	Under-treated N (%)	Appropriate treated N (%)	Over-treated N (%)
Group A					
	Under-treated N (%)	0 (0)	0 (0)	0 (0)	0 (0)
	Appropriate treatment N (%)	174 (55.1)	0 (0)	127 (73.0)	47 (27.0)
	Over-treated N (%)	142 (44.9)	0 (0)	40 (28.2)	102 (71.8)
Group B					
	Under-treated N (%)	0 (0)	0 (0)	0 (0)	0 (0)
	Appropriate treatment N (%)	107 (53.8)	9 (8.4)	63 (58.9)	35 (32.7)
	Over-treated N (%)	92 (46.2)	10 (10.9)	19 (20.6)	63 (68.5)
Group C					
	Under-treated N (%)	22 (20.0)	11 (50.0)	8 (36.4)	<5*
	Appropriate treatment N (%)	44 (40.0)	7 (15.9)	30 (68.2)	7 (15.9)
	Over-treated N (%)	44 (40.0)	<5	35 (79.6)	7 (15.9)
Group D					
	Under-treated N (%)	7 (9.5)	<5	<5	0 (0)
	Appropriate treatment N (%)	57 (77.0)	5 (8.8)	52 (91.2)	0 (0)
	Over-treated N (%)	10 (13.5)	<5	9 (90.0)	0 (0)

*Supplemental Table S11. Changes in appropriateness of therapy (categorised as under-, appropriate or over-treated based on the recommendations of the GOLD 2019 report and on baseline characteristics) between 2014 and 2016 among patients with COPD initiating treatment in 2014 per GOLD group. CI=confidence interval. \*To avoid unintentional disclosure and to preserve confidentiality, cell counts <5 are reported as <5.*