

Online Data Supplement

Axson EL, Bottle A, Cowie MC, and Quint JK. The relationship between heart failure and the risk of acute exacerbation of COPD.

Read codes used to identify HF in CPRD GOLD

G580.00	G5yyA00	G583.12
G581.00	G581000	G583.11
G58..00	662p.00	G580400
G580.11	G580100	8CMW800
9N0k.00	8CL3.00	G21z100
G5yy900	585g.00	G232.00
G58z.00	8B29.00	G211100
8HBE.00	G580200	G234.00
662T.00	G5yyD00	8CeC.00
662W.00	8CMK.00	G210100
G58..11	G58z.12	SP11111
1O1..00	G580000	G1yz100
662g.00	G582.00	G580.14
585f.00	Zrad.00	G580.12
G581.13	662i.00	G580.13
33BA.00	G583.00	G584.00
662f.00	8H2S.00	G41z.11
662h.00	G580300	G400.00

Results of Sensitivity Analyses

Keeping patients with chronic kidney and liver disease, COPD patients with a diagnosis of HF experienced greater risk for moderate-to-severe AECOPD (aHR = 1.47, 95%CI: 1.32, 1.63) compared to COPD patients without a diagnosis of HF.

COPD patients with possible HF who had no evidence of ever being investigated for HF experienced greater risk for moderate-to-severe AECOPD (aHR = 1.27, 95%CI: 1.18, 1.38) compared to COPD patients with possible HF with evidence of ever being investigated for HF. COPD patients with possible HF with evidence of ever being investigated for HF still experienced greater risk for moderate-to-severe AECOPD (aHR = 1.54, 95%CI: 1.43, 1.65) than COPD patients with no evidence of HF.

Classifying COPD patients with a HF hospitalisation during follow-up, but no HF diagnosis recorded in primary, as having a HF diagnosis made 449 possible HF patients become prevalent HF patients prior to the start of follow-up and made 532 possible HF patients become newly diagnosed HF patients during follow-up. Patients were then matched according to their new status and regression performed per the methods.

Compared to COPD patients without evidence of HF, COPD patients with newly diagnosed HF (including patients with HF hospitalisation during follow-up, but no primary care HF diagnosis) experienced greater risk for moderate-to-severe AECOPD (aHR = 1.63, 95%CI: 1.49, 1.79). This estimate is larger than that seen in the main analysis. The new definition by its nature shifted more symptomatic and sicker individuals into the newly diagnosed HF category and that would increase AECOPD risk.

Compared to COPD patients without evidence of HF, COPD patients with possible HF (excluding patients with history of HF hospitalisation or HF hospitalisation during follow-up, but no primary care diagnosis) experienced a greater risk for moderate-to-severe AECOPD (aHR = 1.69, 95%CI: 1.61, 1.76). The risk for moderate-to-severe AECOPD was not affected by the new categories compared to the main analysis.

	Possible HF N = 8,476	Newly Diagnosed HF N = 2,066
Median length of time on LDs before end of follow-up or HF diagnosis	1.85 years (IQR: 0.90, 3.81)	0.50 years (IQR: 0.11, 2.12)
History of HF hospitalisation (n, %) HF as primary or secondary diagnostic code	981 (11.6)	692 (33.5)
Median time between most recent HF hospitalisation and end of follow-up or HF diagnosis	1.68 years (IQR: 0.42, 4.13)	1.00 year (IQR: 0.72, 1.04)
History of echocardiography (n, %)	3,569 (42.1)	1,854 (89.7)
Median time between most recent echocardiography and end of follow-up or HF diagnosis	2.76 years (IQR: 1.18, 5.28)	1.00 year (IQR: 0.83, 1.15)
History of BNP test (n, %)	1,480 (17.5)	425 (20.6)
Median time between most recent BNP test and end of follow-up or HF diagnosis	1.78 (IQR: 0.81, 3.18)	1.08 years (IQR: 1.00, 1.31)
History of an outpatient cardiology visit (n, %)	1,249 (14.7)	435 (21.1)
Median time between most recent outpatient cardiology visit and end of follow-up or HF diagnosis	1.93 years (IQR: 0.67, 4.63)	2.98 years (IQR: 1.54, 4.99)
History of HF investigation: echocardiography, BNP test, and/or outpatient cardiology visit	4,545 (53.6)	1,898 (91.9)

Table E1. Proportion of chronic obstructive pulmonary disease (COPD) patients with possible heart failure (HF) and newly diagnosed HF with a history of hospitalisation due to HF, a history of echocardiography, a history of brain natriuretic peptide (BNP) measures, and/or a history of an outpatient cardiology visit and the median (interquartile range, IQR) time between the most recent of these and the end of follow-up or HF diagnosis.

	COPD patients without evidence of HF	COPD patients with diagnosed HF		COPD patients without evidence of HF	COPD patients with diagnosed HF
Number of Patients (N)	4,132	2,066	Exacerbation History*	1 (0, 2)	2 (1, 4)
Female	1,486 (36.0)	743 (36.0)	COPD medications[†]		
Age, years (IQR)	71 (64, 78)	74 (67, 81)	SABA/SAMA	2,600 (62.9)	1,489 (72.1)
Smoking Status			LABA alone	106 (2.57)	31 (1.50)
Current Smoker	1,411 (34.2)	497 (24.1)	LAMA alone	256 (6.20)	163 (7.89)
Former Smoker	2,721 (65.9)	1,569 (75.9)	ICS alone	532 (12.9)	92 (4.45)
Body Mass Index			LABA+LAMA	35 (0.85)	29 (1.40)
Underweight (< 18.5)	200 (4.84)	113 (5.47)	LABA+ICS	1,077 (26.1)	476 (23.0)
Healthy Weight (18.5-24.9)	1,521 (36.8)	640 (31.0)	LAMA+ICS	78 (1.89)	27 (1.31)
Overweight (25.0-29.9)	1,415 (34.2)	595 (28.8)	Triple	578 (14.0)	823 (39.8)
Obese (>= 30)	910 (22.0)	667 (32.3)	No long-acting inhaler	1,470 (35.6)	425 (20.6)
Missing Data	86 (2.08)	51 (2.47)	History of Cardiovascular Disease[‡]	2,288 (55.4)	1,687 (81.7)
Index of Multiple Deprivation			Atrial fibrillation	172 (4.16)	671 (32.5)
1 – Most deprived	695 (16.8)	268 (13.0)	Hypertension	1,935 (46.8)	1,033 (50.0)
2	856 (20.7)	403 (19.5)	Ischaemic heart disease	610 (14.8)	838 (40.6)
3	826 (20.0)	406 (19.7)	Peripheral artery disease	210 (5.08)	222 (10.8)
4	909 (22.0)	473 (22.9)	Stroke	229 (5.54)	231 (11.2)
5 – Least deprived	846 (20.5)	516 (25.0)	Diabetes mellitus	341 (8.25)	459 (22.2)
GOLD Stage			CVD medications[†]		
1: Mild	1,577 (38.2)	703 (34.0)	ACEi	697 (16.9)	1,230 (59.5)
2: Moderate	1,122 (27.2)	486 (23.5)	ARB	262 (6.34)	332 (16.1)
3: Severe	605 (14.6)	426 (20.6)	Beta-blockers	293 (7.09)	737 (35.7)
4: Very Severe	112 (2.71)	166 (8.03)	Calcium channel blockers	397 (9.61)	329 (15.9)
Missing	716 (17.3)	285 (13.8)	MRA	10 (0.24)	479 (23.2)
			Statins	1,215 (29.4)	1,152 (55.8)
			Vasodilators	254 (6.15)	320 (15.5)

Table E2. Descriptive statistics for the matched cohort of chronic obstructive pulmonary disease (COPD) patients without evidence of heart failure (HF) and COPD patients with diagnosed HF. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). *Average number of exacerbations per patient (range) in the year prior to the start of follow-up. †At least two prescriptions >15 days apart in the year prior to the start of follow-up. ‡Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	COPD patients without evidence of HF	COPD patients with possible HF		COPD patients without evidence of HF	COPD patients with possible HF
Number of Patients (N)	16,792	8,423	Exacerbation History*	1 (0, 2)	2 (0, 3)
Female	8,365 (49.8)	4,206 (49.9)	COPD medications[†]		
Age, years (IQR)	73 (65, 80)	73 (66, 80)	SABA/SAMA	10,834 (64.5)	6,194 (73.5)
Smoking Status			LABA alone	454 (2.70)	250 (2.97)
Current Smoker	5,872 (35.0)	2,561 (30.4)	LAMA alone	1,068 (6.36)	535 (6.35)
Former Smoker	10,920 (65.0)	5,862 (69.6)	ICS alone	2,115 (12.6)	939 (11.2)
Body Mass Index			LABA+LAMA	129 (0.77)	80 (0.95)
Underweight (< 18.5)	1,005 (5.98)	351 (4.17)	LABA+ICS	4,421 (26.3)	2,423 (28.8)
Healthy Weight (18.5-24.9)	6,448 (38.4)	2,231 (26.5)	LAMA+ICS	373 (2.22)	205 (2.43)
Overweight (25.0-29.9)	5,458 (32.5)	2,323 (27.6)	Triple	2,414 (14.4)	1,915 (22.7)
Obese (>= 30)	3,353 (20.0)	3,180 (37.8)	No long-acting inhaler	5,818 (34.7)	2,076 (24.7)
Missing Data	528 (3.14)	338 (4.01)	History of Cardiovascular Disease[‡]	9,353 (55.7)	6,485 (77.0)
Index of Multiple Deprivation			Atrial fibrillation	716 (4.26)	987 (11.7)
1 – Most deprived	2,699 (16.1)	1,123 (13.4)	Hypertension	7,818 (46.6)	5,444 (64.6)
2	3,491 (20.8)	1,707 (20.3)	Ischaemic heart disease	2,381 (14.2)	2,218 (26.3)
3	3,310 (19.7)	1,602 (19.0)	Peripheral artery disease	1,004 (5.98)	652 (7.74)
4	3,759 (22.4)	1,964 (23.3)	Stroke	1,018 (6.06)	786 (9.33)
5 – Least deprived	3,533 (21.0)	2,021 (24.0)	Diabetes mellitus	1,388 (8.27)	1,354 (16.1)
GOLD Stage			CVD medications[†]		
1: Mild	6,208 (37.0)	2,985 (35.4)	ACEi	2,721 (16.2)	2,436 (28.9)
2: Moderate	4,347 (25.9)	1,753 (20.8)	ARB	1,053 (6.27)	896 (10.6)
3: Severe	2,383 (14.2)	1,447 (17.2)	Beta-blockers	1,062 (6.32)	1,002 (11.9)
4: Very Severe	503 (3.00)	401 (4.76)	Calcium channel blockers	1,770 (10.5)	1,462 (17.4)
Missing	3,351 (20.0)	1,837 (21.8)	MRA	62 (0.37)	276 (3.28)
			Statins	4,611 (27.5)	3,490 (41.4)
			Vasodilators	1,142 (6.80)	1,250 (14.8)

Table E3. Descriptive statistics for the matched cohort of chronic obstructive pulmonary disease (COPD) patients without evidence of heart failure (HF) and COPD patients with possible HF. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). *Average number of exacerbations per patient (range) in the year prior to the start of follow-up. †At least two prescriptions >15 days apart in the year prior to the start of follow-up. ‡Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	COPD-HF Patients		COPD-HF Patients
Number of Patients (N)	8,901	Exacerbation History (IQR)	2 (0, 3)
Female	3,278 (36.8)	COPD medications[†]	
Age, years (IQR)	77.5 (70.5, 83.3)	SABA/SAMA	8,901 (100)
Smoking Status		LABA alone	194 (2.18)
Current Smoker	1,848 (20.8)	LAMA alone	703 (7.90)
Former Smoker	7,053 (79.2)	ICS alone	775 (8.71)
Body Mass Index		LABA+LAMA	109 (1.22)
Underweight (< 18.5)	303 (3.40)	LABA+ICS	2,203 (24.8)
Healthy Weight (18.5-24.9)	2,470 (27.8)	LAMA+ICS	150 (1.69)
Overweight (25.0-29.9)	2,769 (31.1)	Triple	2,174 (24.4)
Obese (>= 30)	3,014 (33.9)	No long-acting inhaler	0
Missing Data	345 (3.88)	History of Cardiovascular Disease[‡]	7,926 (89.1)
Index of Multiple Deprivation		Atrial fibrillation	3,142 (35.3)
1 – Most deprived	1,236 (13.9)	Hypertension	5,037 (56.6)
2	1,770 (19.9)	Ischaemic heart disease	4,878 (54.8)
3	1,760 (19.8)	Peripheral artery disease	1,202 (13.5)
4	2,041 (22.9)	Stroke	1,271 (14.3)
5 – Least deprived	2,094 (23.5)	Diabetes mellitus	2,366 (26.6)
GOLD Stage			
1: Mild	3,220 (36.2)		
2: Moderate	1,923 (21.6)		
3: Severe	1,345 (15.1)		
4: Very Severe	353 (3.97)		
Missing	2,060 (23.1)		

Table E4. Descriptive statistics of chronic obstructive pulmonary disease (COPD) patients with heart failure (HF) comorbidity at baseline. Interquartile range (IQR). Global Initiative for Chronic Obstructive Lung Diseases (GOLD) staging of COPD severity [1]. †Recorded at baseline; patients could have multiple risk factors.

	Non-Users of ACEi	Incident Users of ACEi (<6 months)	Prevalent Users of ACEi (≥6 months)		Non-Users of ACEi	Incident Users of ACEi (<6 months)	Prevalent Users of ACEi (≥6 months)
Number of Patients (N)	4,136	1,237	5,055	Exacerbation History (IQR)	2 (1, 4)	3 (1, 4)	2 (1, 4)
Female	1,707 (41.3)	455 (36.8)	1,698 (33.6)	COPD medications[†]			
Age, years (IQR)	78.5 (72.0, 84.2)	77.2 (70.4, 83.0)	76.5 (69.5, 82.5)	SABA/SAMA	4,136 (100)	1,237 (100)	5,055 (100)
Smoking Status				LABA alone	81 (1.96)	30 (2.43)	111 (2.20)
Current Smoker	776 (18.8)	281 (22.7)	1,131 (22.4)	LAMA alone	331 (8.00)	92 (7.44)	395 (7.81)
Former Smoker	3,360 (81.2)	956 (77.3)	3,924 (77.6)	ICS alone	356 (8.61)	97 (7.84)	422 (8.35)
Body Mass Index				LABA+LAMA	45 (1.09)	16 (1.29)	73 (1.44)
Underweight (< 18.5)	158 (3.82)	41 (3.31)	156 (3.09)	LABA+ICS	1,055 (25.5)	321 (26.0)	1,221 (24.2)
Healthy Weight (18.5-24.9)	1,167 (28.2)	386 (31.2)	1,403 (27.8)	LAMA+ICS	58 (1.40)	19 (2.34)	94 (1.86)
Overweight (25.0-29.9)	1,260 (30.5)	367 (29.7)	1,592 (31.5)	Triple	1,016 (24.6)	313 (25.3)	1,253 (24.8)
Obese (≥ 30)	1,340 (32.4)	414 (33.5)	1,766 (34.9)	No long-acting inhaler	0	0	0
Missing Data	211 (5.10)	29 (2.34)	138 (2.73)	History of Cardiovascular Disease[‡]	3,604 (87.1)	1,119 (90.5)	4,583 (90.7)
Index of Multiple Deprivation				Atrial fibrillation	1,461 (35.3)	450 (36.4)	1,803 (35.7)
1 – Most deprived	572 (13.8)	155 (12.5)	696 (13.8)	Hypertension	2,265 (54.8)	707 (57.2)	2,940 (58.2)
2	823 (19.9)	242 (19.6)	1,006 (19.9)	Ischaemic heart disease	2,105 (50.9)	699 (56.5)	2,916 (57.7)
3	840 (20.3)	233 (18.8)	978 (19.4)	Peripheral artery disease	548 (13.3)	140 (11.3)	693 (13.7)
4	961 (23.2)	306 (24.7)	1,156 (22.9)	Stroke	603 (14.6)	181 (14.6)	719 (14.2)
5 – Least deprived	940 (22.7)	301 (24.3)	1,219 (24.1)	Diabetes mellitus	1,038 (25.1)	353 (28.5)	1,420 (28.1)
GOLD Stage				CVD medications[†]			
1: Mild	1,511 (36.5)	429 (34.7)	1,826 (36.1)	ARB	1,648 (39.9)	106 (8.57)	147 (2.91)
2: Moderate	850 (20.6)	279 (22.6)	1,156 (22.9)	Beta-blockers	1,140 (27.6)	331 (26.8)	1,780 (35.2)
3: Severe	569 (13.8)	213 (17.2)	819 (16.2)	Calcium channel blockers	687 (16.6)	221 (17.9)	775 (15.3)
4: Very Severe	149 (3.60)	72 (5.82)	223 (4.41)	Loop diuretics	2,760 (66.7)	801 (64.8)	3,523 (69.7)
Missing	1,057 (25.6)	244 (19.7)	1,031 (20.4)	MRA	858 (20.7)	226 (18.3)	1,130 (22.4)
				Statins	2,180 (52.7)	713 (57.6)	3,294 (65.2)
				Vasodilators	907 (21.9)	287 (23.2)	1,162 (23.0)

Table E5. Descriptive statistics for non-users, incident users, and prevalent users of angiotensin converting enzyme inhibitors (ACEi) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin receptor blockers (ARB). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). [†]At least two prescriptions >15 days apart in the year prior to the start of follow-up. [‡]Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	Non-Users of ARB	Incident Users of ARB (<6 months)	Prevalent Users of ARB (≥6 months)		Non-Users of ARB	Incident Users of ARB (<6 months)	Prevalent Users of ARB (≥6 months)
Number of Patients (N)	7,253	668	1,914	Exacerbation History (IQR)	2 (0, 3)	2 (1, 4)	2 (1, 4)
Female	2,645 (36.5)	257 (38.5)	723 (37.8)	COPD medications[†]			
Age, years (IQR)	77.5 (70.5, 83.5)	76.9 (69.6, 82.4)	76.6 (70.1, 82.2)	SABA/SAMA	7,253 (100)	668 (100)	1,914 (100)
Smoking Status				LABA alone	156 (2.15)	10 (1.50)	45 (2.35)
Current Smoker	1,606 (22.1)	110 (16.5)	277 (14.5)	LAMA alone	554 (7.64)	60 (8.98)	166 (8.67)
Former Smoker	5,647 (77.9)	558 (83.5)	1,637 (85.5)	ICS alone	648 (8.93)	54 (8.08)	143 (7.47)
Body Mass Index				LABA+LAMA	90 (8.93)	6 (0.90)	21 (1.10)
Underweight (< 18.5)	280 (3.86)	14 (2.10)	29 (1.52)	LABA+ICS	1,776 (24.5)	162 (24.3)	494 (25.8)
Healthy Weight (18.5-24.9)	2,092 (28.8)	177 (26.5)	445 (23.3)	LAMA+ICS	121 (1.67)	15 (2.25)	33 (1.72)
Overweight (25.0-29.9)	2,242 (30.9)	205 (30.7)	611 (31.9)	Triple	1,759 (24.3)	206 (30.8)	519 (27.1)
Obese (≥ 30)	2,328 (32.1)	263 (39.4)	796 (41.6)	No long-acting inhaler	0	0	0
Missing Data	311 (4.29)	9 (1.35)	33 (1.72)	History of Cardiovascular Disease[‡]	6,369 (87.8)	616 (92.2)	1,803 (94.2)
Index of Multiple Deprivation				Atrial fibrillation	2,548 (35.1)	242 (36.2)	697 (36.4)
1 – Most deprived	988 (13.6)	108 (16.2)	287 (15.0)	Hypertension	3,927 (54.1)	435 (65.1)	1,269 (66.3)
2	1,428 (19.7)	136 (20.4)	403 (21.1)	Ischaemic heart disease	3,886 (53.6)	394 (59.0)	1,149 (60.0)
3	1,383 (19.1)	144 (21.6)	430 (22.5)	Peripheral artery disease	968 (13.4)	102 (15.3)	283 (14.8)
4	1,690 (23.3)	143 (21.4)	408 (21.3)	Stroke	1,055 (14.6)	66 (9.88)	246 (12.9)
5 – Least deprived	1,764 (24.3)	137 (20.5)	386 (20.2)	Diabetes mellitus	1,883 (26.0)	223 (33.4)	581 (30.4)
GOLD Stage				CVD medications[†]			
1: Mild	2,545 (35.1)	284 (42.5)	798 (41.7)	ACEi	4,918 (67.8)	380 (56.9)	425 (22.2)
2: Moderate	1,528 (21.1)	169 (25.3)	463 (24.2)	Beta-blockers	2,234 (30.8)	233 (34.9)	669 (35.0)
3: Severe	1,114 (15.4)	101 (15.1)	271 (14.2)	Calcium channel blockers	1,117 (15.4)	127 (19.0)	330 (17.2)
4: Very Severe	305 (4.21)	26 (3.89)	60 (3.13)	Loop diuretics	4,967 (68.5)	449 (67.2)	1,288 (67.3)
Missing	1,761 (24.3)	88 (13.2)	322 (16.8)	MRA	1,536 (21.2)	163 (24.4)	453 (23.7)
				Statins	4,205 (58.0)	434 (65.0)	1,298 (67.8)
				Vasodilators	1,592 (22.0)	179 (26.8)	498 (26.0)

Table E6. Descriptive statistics for non-users, incident users, and prevalent users of angiotensin receptor blockers (ARB) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). [†]At least two prescriptions >15 days apart in the year prior to the start of follow-up. [‡]Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	Non-Users of BB	Incident Users of BB (<6 months)	Prevalent Users of BB (≥6 months)		Non-Users of BB	Incident Users of BB (<6 months)	Prevalent Users of BB (≥6 months)
Number of Patients (N)	6,161	1,163	3,259	Exacerbation History (IQR)	2 (1, 3)	2 (1, 4)	2 (1, 4)
Female	2,457 (40.0)	356 (30.6)	985 (30.2)	COPD medications[†]			
Age, years (IQR)	78.4 (71.5, 83.8)	76.9 (70.1, 82.7)	75.7 (68.5, 81.8)	SABA/SAMA	6,161 (100)	1,163 (100)	3,259 (100)
Smoking Status				LABA alone	139 (2.26)	25 (2.15)	62 (1.90)
Current Smoker	1,199 (19.5)	202 (17.4)	723 (22.2)	LAMA alone	389 (6.31)	77 (6.62)	345 (10.6)
Former Smoker	4,962 (80.5)	961 (82.6)	2,536 (77.8)	ICS alone	620 (10.1)	50 (4.30)	189 (5.80)
Body Mass Index				LABA+LAMA	75 (1.22)	9 (0.77)	40 (1.23)
Underweight (< 18.5)	239 (3.88)	31 (2.67)	77 (2.36)	LABA+ICS	1,706 (27.7)	268 (23.0)	627 (19.2)
Healthy Weight (18.5-24.9)	1,783 (28.9)	335 (28.8)	849 (26.1)	LAMA+ICS	106 (1.72)	20 (1.72)	56 (1.72)
Overweight (25.0-29.9)	1,849 (30.0)	351 (30.2)	1,052 (32.3)	Triple	1,519 (24.7)	345 (29.7)	826 (25.4)
Obese (≥ 30)	1,991 (32.3)	432 (37.2)	1,230 (37.7)	No long-acting inhaler	0	0	0
Missing Data	299 (4.85)	14 (1.20)	51 (1.56)	History of Cardiovascular Disease[‡]	5,367 (87.1)	1,095 (94.2)	3,048 (93.5)
Index of Multiple Deprivation				Atrial fibrillation	2,029 (32.9)	535 (46.0)	1,355 (41.6)
1 – Most deprived	831 (13.5)	173 (14.9)	480 (14.7)	Hypertension	3,371 (54.7)	705 (60.6)	1,978 (60.7)
2	1,240 (20.1)	220 (18.9)	637 (19.6)	Ischaemic heart disease	3,115 (50.6)	760 (65.4)	2,090 (64.1)
3	1,228 (19.9)	216 (18.6)	619 (19.0)	Peripheral artery disease	803 (13.0)	183 (15.7)	490 (15.0)
4	1,397 (22.7)	272 (23.4)	768 (23.6)	Stroke	891 (14.5)	186 (16.0)	473 (14.5)
5 – Least deprived	1,465 (23.8)	282 (24.3)	755 (23.2)	Diabetes mellitus	1,517 (24.6)	380 (32.7)	1,017 (31.2)
GOLD Stage				CVD medications[†]			
1: Mild	2,108 (34.2)	462 (39.7)	1,341 (41.2)	ACEi	3,406 (55.3)	700 (60.2)	2,100 (64.4)
2: Moderate	1,263 (20.5)	314 (27.0)	806 (24.7)	ARB	1,144 (18.6)	249 (21.4)	721 (22.1)
3: Severe	970 (15.7)	179 (15.4)	460 (14.1)	Calcium channel blockers	1,155 (18.8)	201 (17.3)	320 (9.82)
4: Very Severe	288 (4.67)	36 (3.10)	79 (2.42)	Loop diuretics	4,178 (67.8)	811 (69.7)	2,295 (70.4)
Missing	1,532 (24.9)	172 (14.8)	573 (17.6)	MRA	1,095 (17.8)	282 (24.3)	994 (30.5)
				Statins	3,322 (53.9)	785 (67.5)	2,346 (72.0)
				Vasodilators	1,378 (22.4)	319 (27.4)	803 (24.6)

Table E7. Descriptive statistics for non-users, incident users, and prevalent users of beta-blockers (BB) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). [†]At least two prescriptions >15 days apart in the year prior to the start of follow-up. [‡]Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	Non-Users of LD	Incident Users of LD (<6 months)	Prevalent Users of LD (≥6 months)		Non-Users of LD	Incident Users of LD (<6 months)	Prevalent Users of LD (≥6 months)
Number of Patients (N)	3,037	2,105	6,334	Exacerbation History (IQR)	1 (0, 3)	2 (1, 4)	2 (1, 4)
Female	1,025 (33.8)	746 (35.4)	2,428 (38.3)	COPD medications[†]			
Age, years (IQR)	76.2 (69.1, 82.3)	78.1 (71.4, 83.6)	78.2 (71.4, 83.7)	SABA/SAMA	3,037 (100)	2,105 (100)	6,334 (100)
Smoking Status				LABA alone	67 (2.21)	34 (1.63)	136 (2.15)
Current Smoker	747 (24.6)	402 (19.1)	1,186 (18.7)	LAMA alone	262 (8.63)	153 (7.27)	474 (7.48)
Former Smoker	2,290 (75.4)	1,703 (80.9)	5,148 (81.3)	ICS alone	248 (8.17)	166 (7.89)	544 (8.59)
Body Mass Index				LABA+LAMA	35 (1.15)	30 (1.43)	76 (1.20)
Underweight (< 18.5)	135 (4.45)	83 (3.94)	186 (2.94)	LABA+ICS	695 (22.9)	525 (24.9)	1,606 (25.4)
Healthy Weight (18.5-24.9)	935 (30.8)	592 (28.1)	1,703 (26.9)	LAMA+ICS	52 (1.71)	45 (2.14)	105 (1.66)
Overweight (25.0-29.9)	964 (31.7)	647 (30.7)	1,935 (30.6)	Triple	688 (22.7)	579 (27.5)	1,678 (26.5)
Obese (≥ 30)	891 (29.3)	717 (34.1)	2,271 (35.9)	No long-acting inhaler	0	0	0
Missing Data	112 (3.69)	66 (3.14)	239 (3.77)	History of Cardiovascular Disease[‡]	2,649 (87.2)	1,908 (90.6)	5,702 (90.0)
Index of Multiple Deprivation				Atrial fibrillation	875 (28.8)	827 (39.3)	2,468 (39.0)
1 – Most deprived	450 (14.8)	308 (14.6)	842 (13.3)	Hypertension	1,624 (53.5)	1,225 (58.2)	3,696 (58.4)
2	576 (19.0)	430 (20.4)	1,283 (20.3)	Ischaemic heart disease	1,625 (53.5)	1,167 (55.4)	3,524 (55.6)
3	610 (20.1)	424 (20.1)	1,256 (19.8)	Peripheral artery disease	413 (13.6)	292 (13.9)	873 (13.8)
4	709 (23.4)	286 (23.1)	1,444 (22.8)	Stroke	414 (13.6)	322 (15.3)	938 (14.8)
5 – Least deprived	692 (22.8)	457 (21.7)	1,509 (23.8)	Diabetes mellitus	667 (22.0)	554 (26.3)	1,817 (28.7)
GOLD Stage				CVD medications[†]			
1: Mild	1,146 (37.7)	785 (37.3)	2,272 (35.9)	ACEi	1,684 (55.5)	1,159 (55.1)	3,728 (58.9)
2: Moderate	664 (21.9)	481 (22.9)	1,397 (22.1)	ARB	566 (18.6)	466 (22.1)	1,295 (20.5)
3: Severe	439 (14.5)	341 (16.2)	1,005 (15.9)	Beta-blockers	941 (31.0)	616 (29.3)	2,054 (32.4)
4: Very Severe	110 (3.62)	92 (4.37)	260 (4.10)	Calcium channel blockers	501 (16.5)	353 (16.8)	983 (15.5)
Missing	678 (22.3)	406 (19.3)	1,400 (22.1)	MRA	367 (12.1)	402 (19.1)	1,643 (25.9)
				Statins	1,781 (58.6)	1,227 (58.3)	3,810 (60.2)
				Vasodilators	591 (19.5)	507 (24.1)	1,553 (24.5)

Table E8. Descriptive statistics for non-users, incident users, and prevalent users of loop diuretics (LD) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Mineralocorticoid receptor antagonists (MRA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). [†]At least two prescriptions >15 days apart in the year prior to the start of follow-up. [‡]Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

	Non-Users of MRA	Incident Users of MRA (<6 months)	Prevalent Users of MRA (≥6 months)		Non-Users of MRA	Incident Users of MRA (<6 months)	Prevalent Users of MRA (≥6 months)
Number of Patients (N)	7,146	1,335	2,244	Exacerbation History (IQR)	2 (0, 3)	3 (1, 5)	2 (1, 4)
Female	2,674 (37.4)	428 (32.1)	731 (32.6)	COPD medications[†]			
Age, years (IQR)	77.6 (71.1, 83.5)	77.3 (70.8, 83.4)	75.9 (68.6, 81.9)	SABA/SAMA	7,146 (100)	1,335 (100)	2,244 (100)
Smoking Status				LABA alone	155 (2.17)	27 (2.02)	46 (2.05)
Current Smoker	1,468 (20.5)	239 (17.9)	460 (20.5)	LAMA alone	561 (7.85)	80 (5.99)	169 (7.53)
Former Smoker	5,678 (79.5)	1,096 (82.1)	1,784 (79.5)	ICS alone	629 (8.80)	78 (5.84)	158 (7.04)
Body Mass Index				LABA+LAMA	89 (1.25)	17 (1.27)	24 (1.07)
Underweight (< 18.5)	265 (3.71)	32 (2.40)	53 (2.36)	LABA+ICS	1,764 (24.7)	325 (24.3)	558 (24.9)
Healthy Weight (18.5-24.9)	2,048 (28.7)	354 (26.5)	554 (24.7)	LAMA+ICS	119 (1.67)	26 (1.95)	39 (1.74)
Overweight (25.0-29.9)	2,234 (31.3)	409 (30.6)	702 (31.3)	Triple	1,698 (23.8)	458 (34.3)	683 (30.4)
Obese (≥ 30)	2,316 (32.4)	491 (36.8)	863 (38.5)	No long-acting inhaler	0	0	0
Missing Data	283 (3.96)	49 (3.67)	71 (3.21)	History of Cardiovascular Disease[‡]	6,355 (88.9)	1,230 (92.1)	2,028 (90.4)
Index of Multiple Deprivation				Atrial fibrillation	2,458 (34.4)	615 (46.1)	942 (42.0)
1 – Most deprived	998 (14.0)	179 (13.4)	301 (13.4)	Hypertension	4,064 (56.9)	780 (58.4)	1,275 (56.8)
2	1,425 (19.9)	285 (21.4)	436 (19.4)	Ischaemic heart disease	3,861 (54.0)	813 (60.9)	1,333 (59.4)
3	1,416 (19.8)	278 (20.8)	453 (20.2)	Peripheral artery disease	983 (13.8)	196 (14.7)	298 (13.3)
4	1,635 (22.9)	319 (23.9)	531 (23.7)	Stroke	1,052 (14.7)	200 (15.0)	302 (13.5)
5 – Least deprived	1,672 (23.4)	274 (20.5)	523 (23.3)	Diabetes mellitus	1,827 (25.6)	418 (31.3)	701 (31.2)
GOLD Stage				CVD medications[†]			
1: Mild	2,591 (36.3)	469 (35.1)	820 (36.5)	ACEi	4,104 (57.4)	773 (57.9)	1,354 (60.3)
2: Moderate	1,531 (21.4)	321 (24.0)	524 (23.4)	ARB	1,349 (18.9)	342 (25.6)	537 (23.9)
3: Severe	1,061 (14.9)	261 (19.6)	385 (17.2)	Beta-blockers	2,030 (28.4)	475 (35.6)	989 (44.1)
4: Very Severe	276 (3.86)	64 (4.79)	103 (4.59)	Calcium channel blockers	1,217 (17.0)	200 (15.0)	263 (11.7)
Missing	1,687 (23.6)	220 (16.5)	412 (18.4)	Loop diuretics	4,657 (65.2)	1,076 (80.6)	1,818 (81.0)
				Statins	4,186 (58.6)	833 (62.4)	1,433 (63.9)
				Vasodilators	1,589 (22.2)	369 (27.6)	584 (26.0)

Table E9. Descriptive statistics for non-users, incident users, and prevalent users of mineralocorticoid receptor antagonists (MRA) at start of follow-up. Proportions may not sum to 100% due to rounding. Severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Calcium channel blockers (CCB). Interquartile range (IQR). Long-acting beta agonists (LABA). Inhaled corticosteroids (ICS). Long-acting muscarinic antagonist (LAMA). Short-acting beta agonists (SABA). Short-acting muscarinic antagonist (SAMA). [†]At least two prescriptions >15 days apart in the year prior to the start of follow-up. [‡]Prior diagnosis of ischaemic heart disease, peripheral artery disease, atrial fibrillation, hypertension, and/or stroke.

Exposure	Adjusted Hazard Ratio (95% confidence interval)
ACEi	5.38 (4.79, 6.05)
ARB	5.99 (5.08, 7.07)
BB	5.65 (4.92, 6.49)
LD	4.76 (4.31, 5.25)
MRA	6.01 (5.31, 6.80)

Table E10. Adjusted hazard ratios comparing incident-use to non-use of heart failure medications. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Loop diuretics (LD). Mineralocorticoid receptor antagonists (MRA).

Exposure	Adjusted Hazard Ratio (95% confidence interval)
ACEi	1.11 (1.03, 1.19)
ARB	1.22 (1.12, 1.32)
BB	1.41 (1.32, 1.51)
LD	1.12 (1.05, 1.20)
MRA	1.61 (1.48, 1.74)

Table E11. Adjusted hazard ratios comparing prevalent-use to non-use of heart failure medications. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Loop diuretics (LD). Mineralocorticoid receptor antagonists (MRA).

Exposure	Adjusted Hazard Ratio (95% confidence interval)
ACEi	0.24 (0.22, 0.27)
ARB	0.23 (0.20, 0.26)
BB	0.27 (0.25, 0.30)
LD	0.25 (0.23, 0.27)
MRA	0.32 (0.28, 0.35)

Table E12. Adjusted hazard ratios comparing prevalent-use to incident-use of heart failure medications. Angiotensin converting enzyme inhibitors (ACEi). Angiotensin receptor blockers (ARB). Beta-blockers (BB). Loop diuretics (LD). Mineralocorticoid receptor antagonists (MRA).

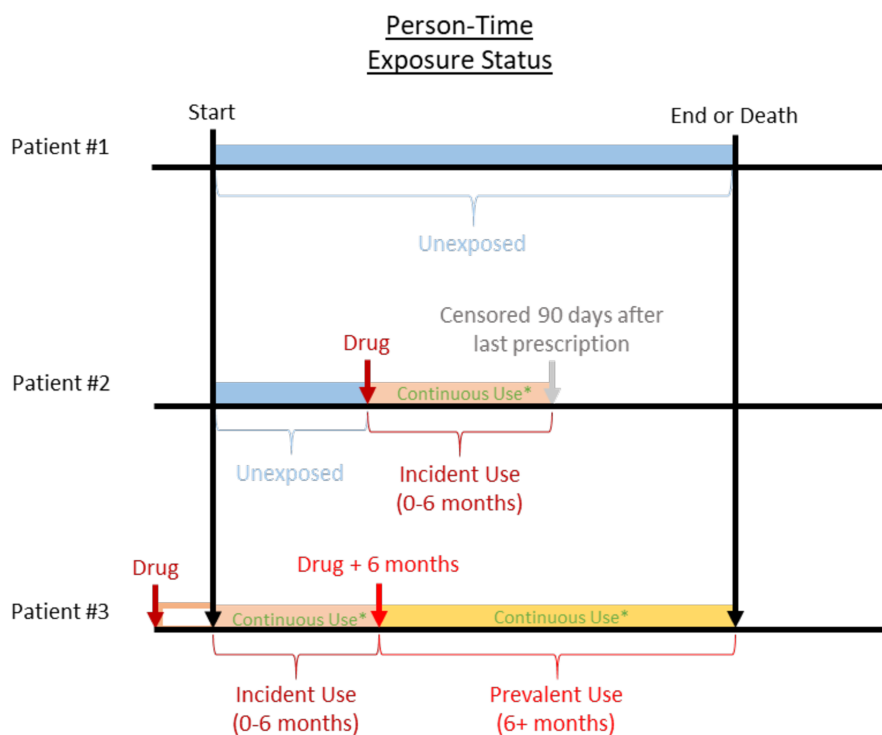


Figure E1. Example of person-time based follow-up.

Patient #1 enters the study at their start of follow-up unexposed, they remain unexposed until their end of follow-up. **Patient #2** enters the study at their start of follow-up unexposed. They become exposed to incident drug use upon first prescription of the drug of interest and remain exposed throughout continuous use of the drug. They are censored 90 days after their last prescription within continuous use, which occurs within 6 months of their first prescription. **Patient #3** enters the study at their start of follow-up exposed to incident continuous drug use, whereby their first prescription of the drug of interest was within 6 months of their start of follow-up. They remain exposed to incident continuous drug use until 6 months after their first prescription, thereafter they are exposed to prevalent continuous drug use until their end of follow-up. *Continuous drug use was defined as at least two prescriptions of the drug of interest and gaps between prescriptions were no more than 90 days. Patients were censored 90 days after their last prescription in a continuous run.

A) ACEi				B) ARB				C) BB						
		End of Follow-up					End of Follow-up					End of Follow-up		
		Non-User	Incident User	Prevalent User			Non-User	Incident User	Prevalent User			Non-User	Incident User	Prevalent User
Start of Follow-up	Non-User	3,497 (39.3)	213 (2.39)	426 (4.79)	Start of Follow-up	Non-User	6,851 (77.0)	99 (1.11)	303 (3.40)	Start of Follow-up	Non-User	5,364 (60.3)	212 (2.38)	585 (6.57)
	Incident User		136 (1.53)	462 (5.19)		Incident User		37 (0.42)	229 (2.57)		Incident User		66 (0.74)	300 (3.37)
	Prevalent User			4,167 (46.8)		Prevalent User			1,382 (15.5)		Prevalent User			2,374 (26.7)
D) LD				E) MRA										
		End of Follow-up					End of Follow-up							
		Non-User	Incident User	Prevalent User			Non-User	Incident User	Prevalent User					
Start of Follow-up	Non-User	1,884 (21.2)	430 (4.83)	723 (8.12)	Start of Follow-up	Non-User	6,231 (70.0)	325 (3.65)	590 (6.63)					
	Incident User		253 (2.84)	699 (7.85)		Incident User		101 (1.13)	319 (3.58)					
	Prevalent User			4,912 (55.2)		Prevalent User			1,335 (15.0)					

Figure E2. Cardiovascular medication exposure status for chronic obstructive pulmonary disease (COPD) patients with heart failure (HF) at start and end of follow-up for A) angiotensin converting enzyme inhibitors (ACEi), (B) angiotensin receptor blockers (ARB), (C) beta-blockers (BB), (D) LDs (LD), and (E) mineralocorticoid receptor antagonists (MRA). Population size: N = 8,901. Count (%).

References

1. GOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. [Webpage] 2017 [cited 10 Jan 2018]; Available from: <http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/>