SUPPLEMENTARY MATERIAL

Supplementary tables

Supplementary figures

Rasmussen DB, *et al. Thorax* 2020;0:1–6. doi: 10.1136/thoraxjnl-2019-214206

Table S1. Diagnoses and medicines used for definition of comorbidities and outcomes

Disease	Definition
Myocardial infarction	ICD10: I21; ICD8: 410
ST elevation myocardial infarction (STEMI)	ICD10: I210B, I211B, I213
Chronic obstructive pulmonary disease	ICD10: J42–J44; ICD8: 491–492
Hospital admission with exacerbation of chronic obstructive pulmonary disease	ICD10 J44 as primary diagnosis; or J44 as secondary diagnosis along with a primary diagnosis of DJ96 or DJ13–DJ18
Heart failure	ICD10: I110, I42, I50, J81
Atrial fibrillation	ICD10: I48
Angina pectoris	ICD10: I20
Hypertension	ICD10: I10–I15
Peripheral vascular disease	ICD10: I700, I702, I709, I739
Cerebrovascular disease	ICD10: I60–I64, G458, G459
Diabetes mellitus	ICD10: E10–14; or ATC: A10
Renal failure	ICD10: I120, I131, I132, E102, E112, E132, E142, N02–N08, N11, N14, N158, N159, N160, N162-N164, N168, N18, N19, N26, Z992
Depression	ICD10: F32–34; or ATC: N06A
Asthma	ICD10: J45
Cancer	ICD10: C00–C97

ICD10: 10th revision of the International Classification of Diseases system.

ICD8: 8th revision of the International Classification of Diseases system.

ATC: Anatomical Therapeutic Chemical Classification System.

Table S2. Definition of medications

Drugs	**ATC code**
Beta-blockers	C07
Oral corticosteroids	H02AB06
Long acting inhalation medication	Mono, dual, triple therapy corresponds to the usage of one, two or three of the medicines listed below.
Long-acting beta-2-agonists	R03AC1; R03AL03-R03AL06
Long-acting muscarinic antagonists	R03BB; R03AL03-R03AL06
Inhaled corticosteroids	R03BA; R03AK

ATC: Anatomical Therapeutic Chemical Classification System

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Table S3. Definition of beta-blocker dosage categorization.

Doses were categorized into thirds of the recommended maximum dosis for each type of beta-blocker, i.e. low dose (minimum dose to 33% of maximum dose), medium dose (>33% to 67%), and high dose (>67% to maximum dose). Uncommon beta-blocker types were not included in the analysis due to negligible low number of users.

Beta-blocker	Dosage category	Definition of daily dosage
Metoprolol	Low	12.5 - 67 mg
	Medium	68 - 133 mg
	High	134 - 200 mg
Carvedilol	Low	3.125 - 33 mg
	Medium	34 - 67 mg
	High	68 - 100 mg
Bisoprolol	Low	1.25 - 6.7 mg
	Medium	6.8 - 13.3 mg
	High	13.4 - 20 mg
Atenolol	Low	12.5 - 33 mg
	Medium	34 - 67 mg
	High	68 - 100 mg
Sotalol	Low	40 - 213 mg
	Medium	214 - 427 mg
	High	428 - 640 mg
Propranolol	Low	5 - 107 mg
	Medium	108 - 213 mg
	High	214 - 320 mg

Table S4. Usage of beta-blockers in patients with chronic obstructive pulmonary disease following first-time myocardial infarction.

Numbers represent the point prevalence of beta-blocker users among patients alive and free of exacerbations at the specified times during follow-up estimated by claimed prescriptions.

Time	Subjects alive (n)	Beta-blocker users	
Day 1	10,884	3,298	(30.3%)
Day 90	7,217	4,693	(65.0%)
6 months	6,159	3,752	(60.9%)
1 year	4,868	2,994	(61.5%)
5 years	1,263	734	(58.1%)
10 years	222	113	(50.9%)

Table S5. Baseline characteristics of patients according to type of myocardial infarction and presence of heart failure following first-time myocardial infarction (MI) from 2003 to 2015.

Characteristic	Type of myocardial infarction			Heart failure at baseline		
	STEMI	NSTEMI	*P* value	Yes	No	*P* value
N	1255	9633		3612	7276	
Age, median (IQR)	72 (64, 80)	75 (68, 82)	<0.0001	77 (70, 82)	74 (67, 81)	<0.0001
Sex						
Male	728 (58.0%)	4934 (51.2%)	<0.0001	1949 (54.0%)	3713 (51.0%)	0.0040
Frequent exacerbations	277 (22.1%)	2872 (29.8%)	<0.0001	1063 (29.4%)	2086 (28.7%)	0.41
Long-acting inhalation therapy						
None	518 (41.3%)	3517 (36.5%)	0.0018	1461 (40.4%)	2574 (35.4%)	<0.0001
Mono	167 (13.3%)	1202 (12.5%)		428 (11.8%)	941 (12.9%)	
Dual	316 (25.2%)	2628 (27.3%)		957 (26.5%)	1987 (27.3%)	
Triple	254 (20.2%)	2286 (23.7%)		766 (21.2%)	1774 (24.4%)	
Type of myocardial infarction						
ST-segment elevation MI (STEMI)	1255 (100.0%	0 (0.0%)	<0.0001	387 (10.7%)	868 (11.9%)	0.0615
Non-STEMI	0 (0.0%)	9633 (100.0%)		3225 (89.3%)	6408 (88.1%)	
Comorbidities						
Heart failure	387 (30.8%)	3225 (33.5%)	0.0615	3612 (100.0%	0 (0.0%)	<0.0001
Atrial fibrillation	188 (15.0%)	2261 (23.5%)	<0.0001	1156 (32.0%)	1293 (17.8%)	<0.0001
Angina pectoris	197 (15.7%)	2642 (27.4%)	<0.0001	1063 (29.4%)	1776 (24.4%)	<0.0001
Hypertension	491 (39.1%)	4339 (45.0%)	<0.0001	1839 (50.9%)	2991 (41.1%)	<0.0001
Diabetes mellitus	184 (14.7%)	2027 (21.0%)	<0.0001	950 (26.3%)	1261 (17.3%)	<0.0001
Peripheral vascular disease	123 (9.8%)	1399 (14.5%)	<0.0001	629 (17.4%)	893 (12.3%)	<0.0001
Cerebrovascular disease	126 (10.0%)	1314 (13.6%)	0.0004	577 (16.0%)	863 (11.9%)	<0.0001
Cancer	149 (11.9%)	1387 (14.4%)	0.0156	503 (13.9%)	1033 (14.2%)	0.70
Chronic kidney disease	62 (4.9%)	797 (8.3%)	<0.0001	433 (12.0%)	426 (5.9%)	<0.0001
Asthma	160 (12.7%)	1246 (12.9%)	0.85	459 (12.7%)	947 (13.0%)	0.65
Depression	235 (18.7%)	2353 (24.4%)	<0.0001	898 (24.9%)	1690 (23.2%)	0.0592

Table S6. Dosage of beta-blockers used in patients with chronic obstructive pulmonary disease (COPD) following first-time myocardial infarction.

Numbers represent the point prevalence of users of each beta-blocker dosage among patients alive and free of exacerbations of COPD at the specified times during follow-up. Numbers were estimated by claimed prescriptions. Uncommon beta-blockers were not included in the analysis due to negligible low number of users, and therefore the sum of users do not add up to the total number of beta-blocker users as shown in Table S5.

Time	Dosage	Beta-blocker users n(%)	
Day 1	Low	2190	(67.1%)
	Medium	800	(24.5%)
	High	274	(8.4%)
Day 90	Low	2816	(60.3%)
	Medium	1470	(31.5%)
	High	384	(8.2%)
6 months	Low	2218	(59.6%)
	Medium	1153	(31.0%)
	High	351	(9.4%)
1 year	Low	1702	(57.3%)
	Medium	972	(32.7%)
	High	296	(10.0%)
5 years	Low	363	(49.9%)
	Medium	278	(38.2%)
	High	87	(12.0%)
10 years	Low	57	(50.9%)
	Medium	40	(35.7%)
	High	15	(13.4%)

Table S7. Types of beta-blockers used in patients with COPD following first-time myocardial infarction.
Numbers represent the point prevalence of users of each beta-blocker type among patients alive and free of exacerbations of COPD at the specified times during follow-up. Numbers were estimated by claimed prescriptions.

Time	Beta-blocker category	Beta-blocker type	Number of users n(%)	
Day 1	Beta-1-selective	Metoprolol	2,300	(69.7%)
		Bisoprolol	383	(11.6%)
		Atenolol	97	(2.9%)
	Non-selective	Carvedilol	333	(10.1%)
		Propranolol	114	(3.5%)
		Sotalol	37	(1.1%)
		Other	34	(1.0%)
Day 90	Beta-1-selective	Metoprolol	3,562	(75.9%)
		Bisoprolol	522	(11.1%)
		Atenolol	49	(1.0%)
	Non-selective	Carvedilol	484	(10.3%)
		Propranolol	40	(0.9%)
		Sotalol	13	(0.3%)
		Other	23	(0.5%)
6 months	Beta-1-selective	Metoprolol	2,734	(72.9%)
		Bisoprolol	431	(11.5%)
		Atenolol	45	(1.2%)
	Non-selective	Carvedilol	464	(12.4%)
		Propranolol	36	(1.0%)
		Sotalol	12	(0.3%)
		Other	30	(0.8%)
1 year	Beta-1-selective	Metoprolol	2,174	(72.6%)
		Bisoprolol	329	(11.0%)
		Atenolol	37	(1.2%)
	Non-selective	Carvedilol	394	(13.2%)
		Propranolol	29	(1.0%)
		Sotalol	7	(0.2%)
		Other	24	(0.8%)
5 years	Beta-1-selective	Metoprolol	525	(71.5%)
		Bisoprolol	75	(10.2%)
		Atenolol	9	(1.2%)
	Non-selective	Carvedilol	112	(15.3%)
		Propranolol	5	(0.7%)
		Sotalol	2	(0.3%)
		Other	6	(0.8%)
10 years	Beta-1-selective	Metoprolol	79	(69.8%)
		Bisoprolol	14	(12.4%)
		Atenolol	3	(2.7%)
	Non-selective	Carvedilol	14	(12.4%)
		Propranolol	1	(0.9%)
		Sotalol	1	(0.9%)
		Other	1	(0.9%)

Table S8. Baseline characteristics of patients according to presence of complete clinical data from Danish Register of COPD, and a history of frequent exacerbations and triple inhalation therapy following first-time myocardial infarction (MI) from 2003 to 2015.

Characteristic	Complete clinical data from Danish Register of COPD			History of frequent exacerbations and triple therapy		
	Yes	No	*P* value	Yes	No	*P* value
N	1118	9766		1358	9526	
Age, median (IQR)	74 (67, 80)	75 (68, 82)	0.0006	75 (68, 81)	75 (67, 82)	0.46
Sex						
Male	537 (48.0%)	5122 (52.4%)	0.0051	590 (43.4%)	5069 (53.2%)	<0.0001
Frequent exacerbations	563 (50.4%)	2585 (26.5%)	<0.0001	1358 (100.0%	1790 (18.8%)	<0.0001
Long-acting inhalation therapy						
None	125 (11.2%)	3909 (40.0%)	<0.0001	0 (0.0%)	4034 (42.3%)	<0.0001
Mono	101 (9.0%)	1267 (13.0%)		0 (0.0%)	1368 (14.4%)	
Dual	236 (21.1%)	2707 (27.7%)		0 (0.0%)	2943 (30.9%)	
Triple	656 (58.7%)	1883 (19.3%)		1358 (100.0%	1181 (12.4%)	
Type of myocardial infarction						
ST-segment elevation MI (STEMI)	130 (11.6%)	1125 (11.5%)	0.91	120 (8.8%)	1135 (11.9%)	0.0009
Non-STEMI	988 (88.4%)	8641 (88.5%)		1238 (91.2%)	8391 (88.1%)	
Comorbidities						
Heart failure	369 (33.0%)	3241 (33.2%)	0.90	406 (29.9%)	3204 (33.6%)	0.0062
Atrial fibrillation	270 (24.2%)	2179 (22.3%)	0.16	279 (20.5%)	2170 (22.8%)	0.0650
Angina pectoris	328 (29.3%)	2509 (25.7%)	0.0085	319 (23.5%)	2518 (26.4%)	0.0208
Hypertension	580 (51.9%)	4248 (43.5%)	<0.0001	574 (42.3%)	4254 (44.7%)	0.0974
Diabetes mellitus	218 (19.5%)	1993 (20.4%)	0.47	226 (16.6%)	1985 (20.8%)	0.0003
Peripheral vascular disease	166 (14.8%)	1354 (13.9%)	0.37	173 (12.7%)	1347 (14.1%)	0.16
Cerebrovascular disease	134 (12.0%)	1305 (13.4%)	0.20	139 (10.2%)	1300 (13.6%)	0.0005
Cancer	172 (15.4%)	1362 (13.9%)	0.19	186 (13.7%)	1348 (14.2%)	0.65
Chronic kidney disease	82 (7.3%)	776 (7.9%)	0.47	69 (5.1%)	789 (8.3%)	<0.0001
Asthma	200 (17.9%)	1206 (12.3%)	<0.0001	254 (18.7%)	1152 (12.1%)	<0.0001
Depression	310 (27.7%)	2278 (23.3%)	0.0011	377 (27.8%)	2211 (23.2%)	0.0002

Table S9. Clinical characteristics of 1,118 patients with complete clinical data from Danish Register of Chronic obstructive Pulmonary Disease (COPD).

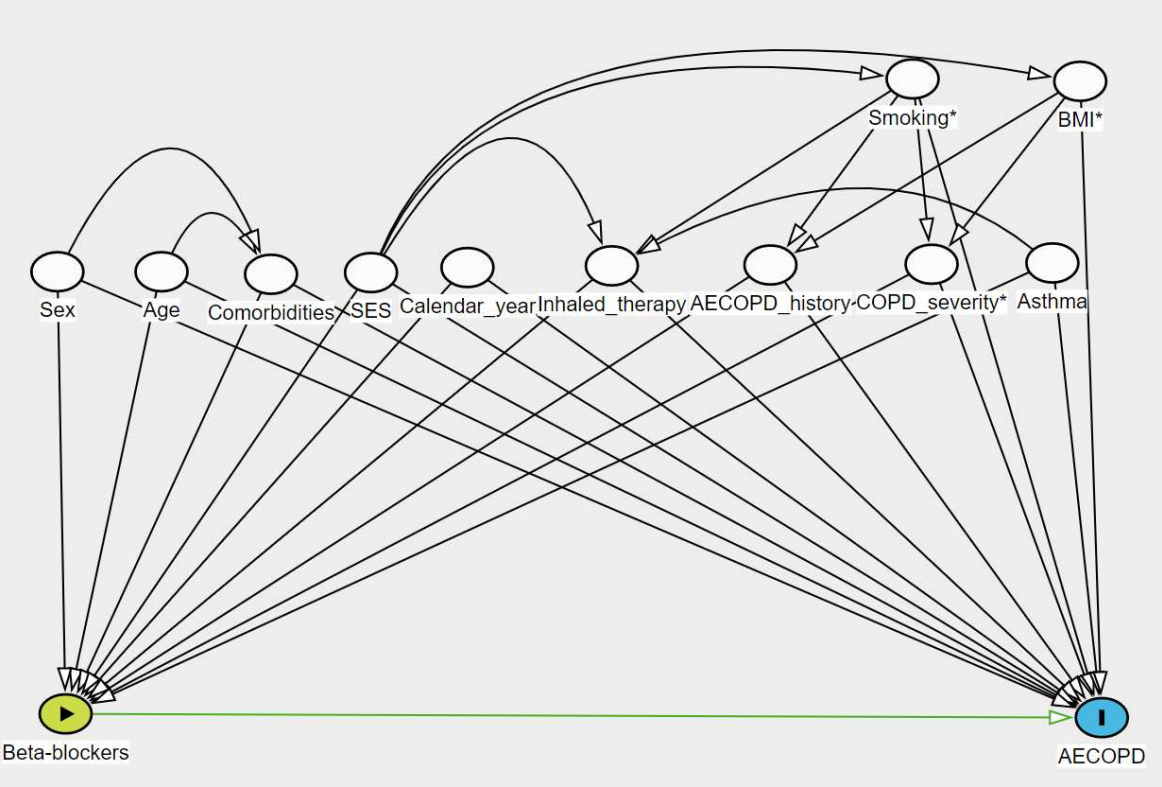
FEV1% = forced expiratory volume in 1 secund expressed as percentage of predicted; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council; BMI = body mass index.

Characteristic	Value
N	1,118
FEV_1%, median (IQR)	46 (33, 61)
GOLD class	
1	71 (6.4%)
2	417 (37.3%)
3	423 (37.8%)
4	207 (18.5%)
mMRC dyspnoea score	
0-1	327 (29.2%)
2	350 (31.3%)
3	256 (22.9%)
4	185 (16.5%)
BMI	
10 - 18.4	115 (10.3%)
18.5 - 24.9	456 (40.8%)
25+	547 (48.9%)
Smoking status	
Non smoker	754 (67.4%)
Smoker	364 (32.6%)

Table S10. Usage of secondary prevention medications within 90 days after first-time myocardial infarction in patients with COPD. Numbers represent the numbers and proportions of users among 7,217 patients alive and free of exacerbations at 90 days of follow-up. Medication use was defined as one or more claimed prescription.
AECi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

Medication	Number of users, n(%)	
Aspirin	5,104	(70.7%)
Statin	5,571	(77.2%)
Aspirin + statin	4,251	(58.9%)
Aspirin + statin + beta-blocker	3,079	(42.7%)
ACEi or ARB	3,776	(52.3%)
AECi or ARB + beta-blocker	2,637	(36.5%)

Figure S1. Directed acyclic graph (DAG) illustrating identification of potential confounders between beta-blocker use and exacerbations of chronic obstructive pulmonary disease (AECOPD).



SES = socio-economic status (income). BMI = body mass index.
*: COPD severity (lung function and dyspnoea score), smoking status, and BMI were only available in a subgroup of patients and was only included in subgroup analyses of patients with complete clinical data.