

SUPPLEMENTARY MATERIALS

Prompt initiation of triple therapy following hospitalization for a chronic obstructive pulmonary disease exacerbation in the United States: An analysis of the PRIMUS study

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Supplementary Table #1. Diagnosis and procedure codes

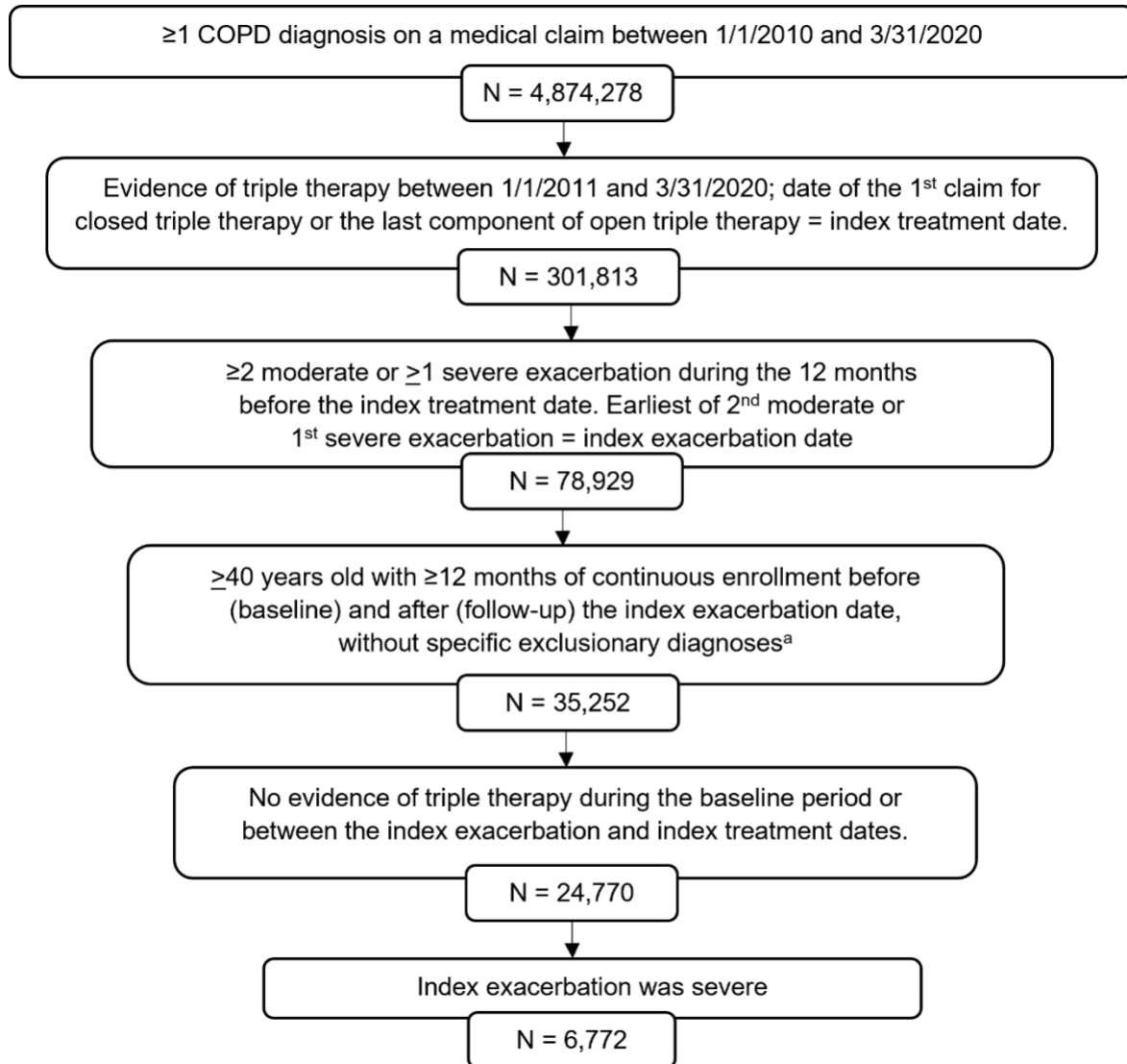
Diagnosis or procedure	Code type	Codes
COPD	ICD-9 diagnosis	491.xx, 492.xx, 494.xx, 496.xx
	ICD-10 diagnosis	J410, J411, J418, J42, J430-J432, J438-J441, J449, J470, J471, J479
Corticosteroid injection	HCPCS	J0702, J0704, J1020, J1030, J1040, J1094, J1100, J1700, J1710, J1720, J2920, J2930, J3300-J3303, J8540
Interstitial fibrosis	ICD-9 diagnosis	515, 516.30-516.37
	ICD-10 diagnosis	J8410, J84111-J84117
Sarcoidosis	ICD-9 diagnosis	135
	ICD-10 diagnosis	D860, D862, D869
Pulmonary embolism	ICD-9 diagnosis	415.11-415.13, 415.19, 416.2, 673.80-673.84, V12.55
	ICD-10 diagnosis	I2601, I2602, I2609, I2690, I2692, I2699, I2782, Z86711
Malignancy (other than basal/squamous cell skin cancer)	ICD-9 diagnosis	140.xx-172.xx, 173.x0, 173.x9, 174.xx-209.xx
	ICD-10 diagnosis	C00x-C43x, C4400, C4409, C4400, C4409, C4410x, C4419x, C4420x, C4429x, C4430x, C4439x, C4440, C4440, C4450x, C4459x, C4460x, C4469x, C4470x, C4479x, C4480, C4489, C4490, C4499, C4Ax, C45x-C96x

Supplementary Table #2. COPD maintenance medications

CLASS	GENERIC MEDICATIONS
Inhaled corticosteroids (ICS)	Beclomethasone
	Betamethasone
	Budesonide
	Ciclesonide
	Dexamethasone
	Flunisolide
	Fluticasone
	Mometasone
	Triamcinolone
Long-acting beta agonists (LABA)	Arformoterol
	Clenbuterol
	Formoterol
	Indacaterol
	Olodaterol
	Salmeterol
Long-acting muscarinic antagonist (LAMA)	Acclidinium
	Glycopyrrolate
	Tiotropium
	Umeclidinium
LAMA/LABA	Acclidinium/formoterol
	Glycopyrrolate/formoterol
	Glycopyrrolate/indacaterol
	Tiotropium/olodaterol
	Umeclidinium/vilanterol
ICS/LABA	Budesonide/formoterol
	Fluticasone/vilanterol
	Fluticasone/salmeterol

	Mometasone/formoterol
Short-acting beta agonist (SABA)	Albuterol
	Levalbuterol
	Metaproterenol
	Pirbuterol
	Terbutaline
Short-acting muscarinic antagonist (SAMA)	Ipratropium
SABA/SAMA	Albuterol ipratropium
Oral corticosteroids	Betamethasone
	Budesonide
	Dexamethasone
	Hydrocortisone
	Methylprednisolone
	Prednisolone
	Prednisone
	Triamcinolone

Supplementary Figure #1. Patient attrition



COPD: chronic obstructive pulmonary disease

Supplementary Table #3. Comorbidity diagnoses during the 12-month baseline period

	All Patients N=6,772	Prompt^a n=2,968	Delayed^b n=1,998	Very delayed^c n=1,806	P value
Cardiovascular disease	3,691 (54.5%)	1,495 (50.4%)	1,114 (55.8%)	1,082 (59.9%)	<0.001
Hypertension, uncomplicated	3,558 (52.5%)	1,508 (50.8%)	1,051 (52.6%)	999 (55.3%)	0.010
Asthma	1,669 (24.6%)	592 (19.9%)	501 (25.1%)	576 (31.9%)	<0.001
Acute bronchitis and bronchiolitis	1,599 (23.6%)	646 (21.8%)	477 (23.9%)	476 (26.4%)	0.001
Chronic cough	1,542 (22.8%)	613 (20.7%)	434 (21.7%)	495 (27.4%)	<0.001
Pneumonia	1,398 (20.6%)	536 (18.1%)	375 (18.8%)	487 (27.0%)	<0.001
Anxiety	1,192 (17.6%)	426 (14.4%)	348 (17.4%)	418 (23.1%)	<0.001
Depression	1,158 (17.1%)	424 (14.3%)	343 (17.2%)	391 (21.7%)	<0.001
Congestive heart failure	1,079 (15.9%)	382 (12.9%)	330 (16.5%)	367 (20.3%)	<0.001
Osteoarthritis	1,071 (15.8%)	443 (14.9%)	326 (16.3%)	302 (16.7%)	0.196
Fluid and electrolyte disorders	1,061 (15.7%)	371 (12.5%)	323 (16.2%)	367 (20.3%)	<0.001
Gastroesophageal reflux	1,008 (14.9%)	377 (12.7%)	296 (14.8%)	335 (18.5%)	<0.001
Other upper/lower respiratory infection	1,007 (14.9%)	421 (14.2%)	288 (14.4%)	298 (16.5%)	0.073
Diabetes, uncomplicated	970 (14.3%)	382 (12.9%)	281 (14.1%)	307 (17.0%)	<0.001
Obesity	934 (13.8%)	350 (11.8%)	282 (14.1%)	302 (16.7%)	<0.001
Peripheral vascular disease	889 (13.1%)	355 (12.0%)	262 (13.1%)	272 (15.1%)	0.009
Psychosis	841 (12.4%)	320 (10.8%)	245 (12.3%)	276 (15.3%)	<0.001
Sleep apnea	823 (12.2%)	293 (9.9%)	260 (13.0%)	270 (15.0%)	<0.001

Sinusitis	784 (11.6%)	316 (10.6%)	243 (12.2%)	225 (12.5%)	0.103
Diabetes, complicated	768 (11.3%)	316 (10.6%)	224 (11.2%)	228 (12.6%)	0.110
Valvular disease	744 (11.0%)	292 (9.8%)	225 (11.3%)	227 (12.6%)	0.012
Acute respiratory failure	742 (11.0%)	237 (8.0%)	215 (10.8%)	290 (16.1%)	<0.001
Hypothyroidism	691 (10.2%)	280 (9.4%)	211 (10.6%)	200 (11.1%)	0.158
Deficiency anemia	666 (9.8%)	245 (8.3%)	197 (9.9%)	224 (12.4%)	<0.001
Other (non-paralysis) neurological disorders	631 (9.3%)	218 (7.3%)	187 (9.4%)	226 (12.5%)	<0.001
Hypertension, complicated	568 (8.4%)	219 (7.4%)	169 (8.5%)	180 (10.0%)	0.007
Allergic rhinitis	503 (7.4%)	207 (7.0%)	145 (7.3%)	151 (8.4%)	0.196
Drug abuse	469 (6.9%)	163 (5.5%)	151 (7.6%)	155 (8.6%)	<0.001
Renal failure	423 (6.2%)	174 (5.9%)	117 (5.9%)	132 (7.3%)	0.093
Alcohol abuse	373 (5.5%)	128 (4.3%)	124 (6.2%)	121 (6.7%)	0.001
Rheumatoid arthritis/collagen vascular diseases	373 (5.5%)	139 (4.7%)	133 (6.7%)	101 (5.6%)	0.011
Weight loss	301 (4.4%)	117 (3.9%)	94 (4.7%)	90 (5.0%)	0.190
Osteoporosis	248 (3.7%)	100 (3.4%)	66 (3.3%)	82 (4.5%)	0.067
Liver disease	227 (3.4%)	92 (3.1%)	59 (3.0%)	76 (4.2%)	0.059
Pulmonary circulation disorders	197 (2.9%)	54 (1.8%)	67 (3.4%)	76 (4.2%)	<0.001
Coagulation deficiency	155 (2.3%)	61 (2.1%)	50 (2.5%)	44 (2.4%)	0.520
Paralysis	94 (1.4%)	33 (1.1%)	25 (1.3%)	36 (2.0%)	0.034
Peptic ulcer disease	67 (1.0%)	28 (0.9%)	13 (0.7%)	26 (1.4%)	0.046
Blood loss anemia	63 (0.9%)	22 (0.7%)	14 (0.7%)	27 (1.5%)	0.014

AIDS/HIV	53 (0.8%)	21 (0.7%)	14 (0.7%)	18 (1.0%)	0.483
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^a Triple therapy within 30 days after or on the index exacerbation date; ^b Triple therapy between 31 and 180 days after index exacerbation; ^c Triple therapy between 181 and 365 days after index exacerbation; AIDS/HIV: acquired immunodeficiency syndrome/human immunodeficiency virus

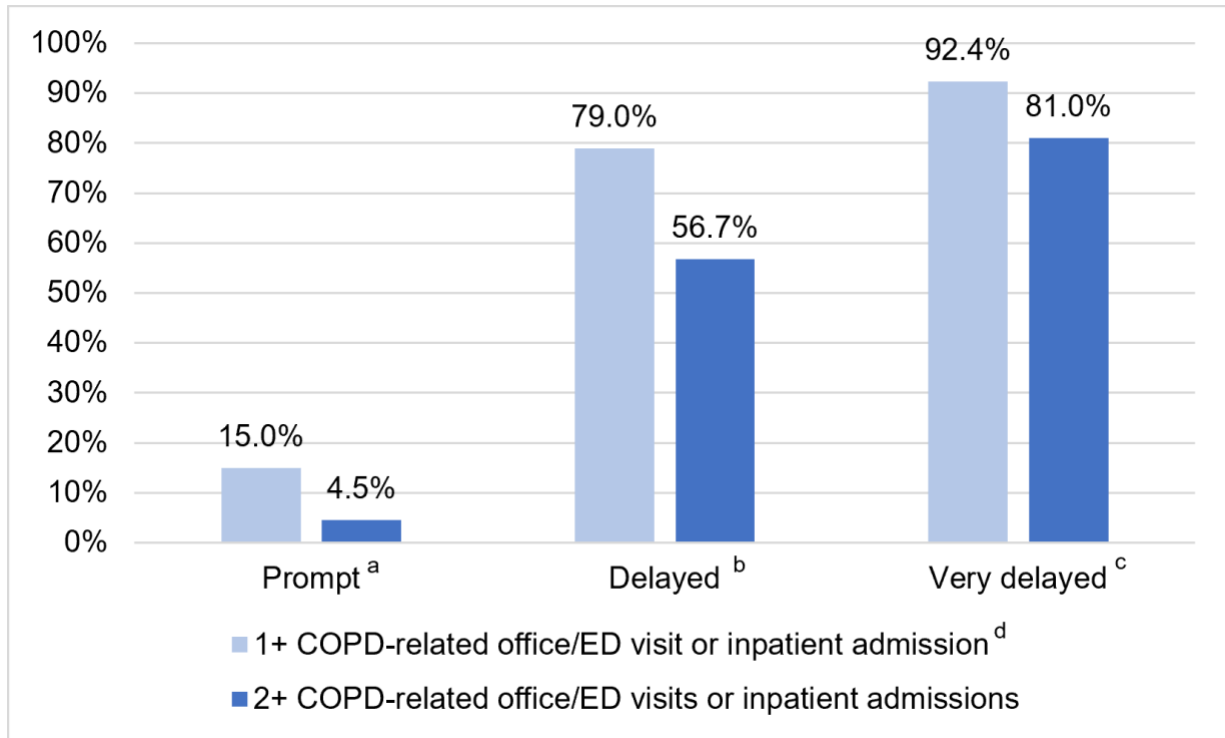
Supplementary Table #4. Patient characteristics, overall PRIMUS population vs patients with a severe exacerbation

	PRIMUS Population N=24,770	Severe Exacerbators n=6,772
Timing of triple therapy initiation, n (%)		
Prompt (≤ 30 days after exacerbation)	7,577 (30.6%)	2,968 (43.8%)
Delayed (31-180 days)	9,676 (39.1%)	1,998 (29.5%)
Very delayed (181-365 days)	7,517 (30.3%)	1,806 (26.7%)
Age, mean (SD)	62.0 (11.0)	63.7 (11.3)
Sex, n (%)		
Female	15,144 (61.1%)	4,077 (60.2%)
Male	9,626 (38.9%)	2,695 (39.8%)
Payer, n (%)		
Commercial	7,652 (30.9%)	2,161 (31.9%)
Medicare Supplemental	8,064 (32.6%)	2,573 (38.0%)
Medicaid	9,054 (36.6%)	2,038 (30.1%)
Race and ethnicity - Medicaid patients, n (%)		
American Indian or Alaska Native	39 (0.4%)	11 (0.5%)
Asian or Pacific Islander	65 (0.7%)	15 (0.7%)
Black	1,607 (17.8%)	543 (26.6%)
Hispanic	66 (0.7%)	14 (0.7%)
White	5,909 (65.3%)	1,146 (56.2%)
Other/unknown	1,368 (15.1%)	309 (15.2%)
U.S. region^a - Commercial/Medicare patients, n (%)		
Midwest	949 (6.0%)	247 (5.2%)
Northeast	4,018 (25.6%)	860 (18.2%)
South Atlantic	657 (4.2%)	139 (2.9%)
South Central	3,668 (23.3%)	954 (20.2%)

West	5,108 (32.5%)	1,264 (26.7%)
Unknown	1,316 (8.4%)	1,270 (26.8%)
Urban residence, n (%)	18,819 (76.0%)	5,401 (79.8%)
Insurance plan type, n (%)		
Comprehensive/indemnity	9,266 (37.4%)	2,676 (39.5%)
EPO/PPO	7,571 (30.6%)	2,133 (31.5%)
HMO	5,601 (22.6%)	1,268 (18.7%)
Other/unknown	2,332 (9.4%)	695 (10.3%)
Year of index exacerbation, N (%)		
2010-2014	14,107 (57.0%)	4,281 (63.2%)
2015-2019	10,663 (43.1%)	2,491 (36.8%)
Elixhauser Comorbidity Index, mean (SD)	3.9 (8.5)	4.1 (8.2)
Tobacco use, N (%)	10,351 (41.8%)	2,451 (36.2%)

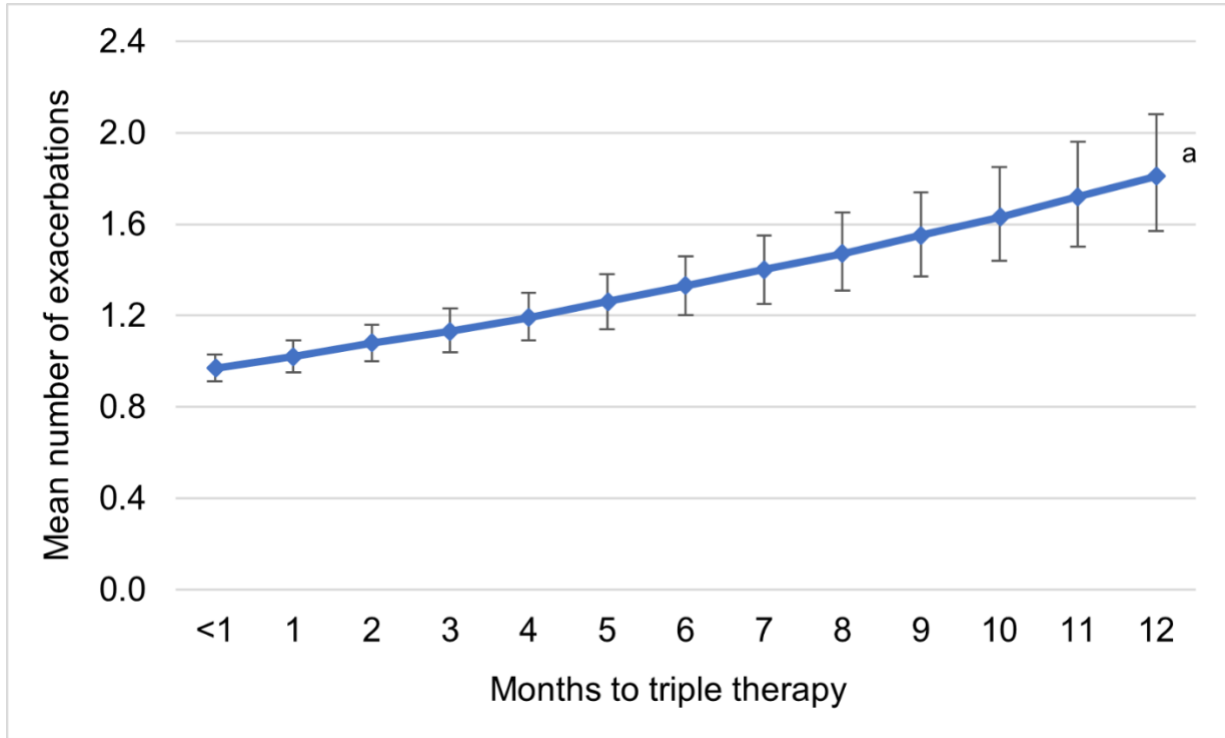
^a See https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf for states included in each region; EPO: exclusive provider organization; HMO: health maintenance organization; PPO: preferred provider organization

Supplementary Figure #2. Proportion of patients with 1+ or 2+ COPD-related office visits, ED visits, or inpatient admissions between their index severe exacerbation and triple therapy initiation



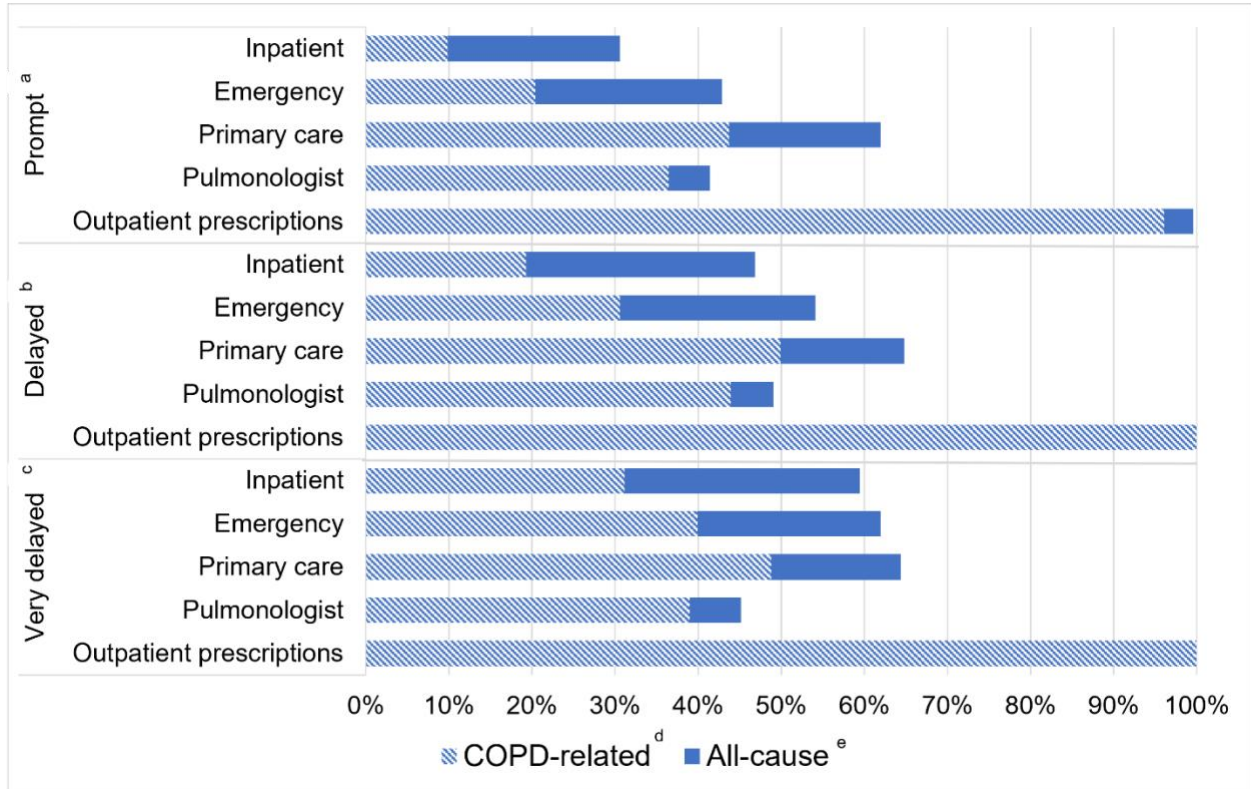
^a Triple therapy within 30 days after or on the index exacerbation date; ^b Triple therapy between 31 and 180 days after index exacerbation; ^c Triple therapy between 181 and 365 days after index exacerbation; ^d Office or ED visit claim with a COPD diagnosis code in any position, or an inpatient claim with a primary diagnosis of COPD; COPD: chronic obstructive pulmonary disease; ED: emergency department

Supplementary Figure #3. Adjusted mean (SD) number of COPD exacerbations during the 12-month follow-up period for patients with <1 to 12 months between index exacerbation and triple therapy initiation



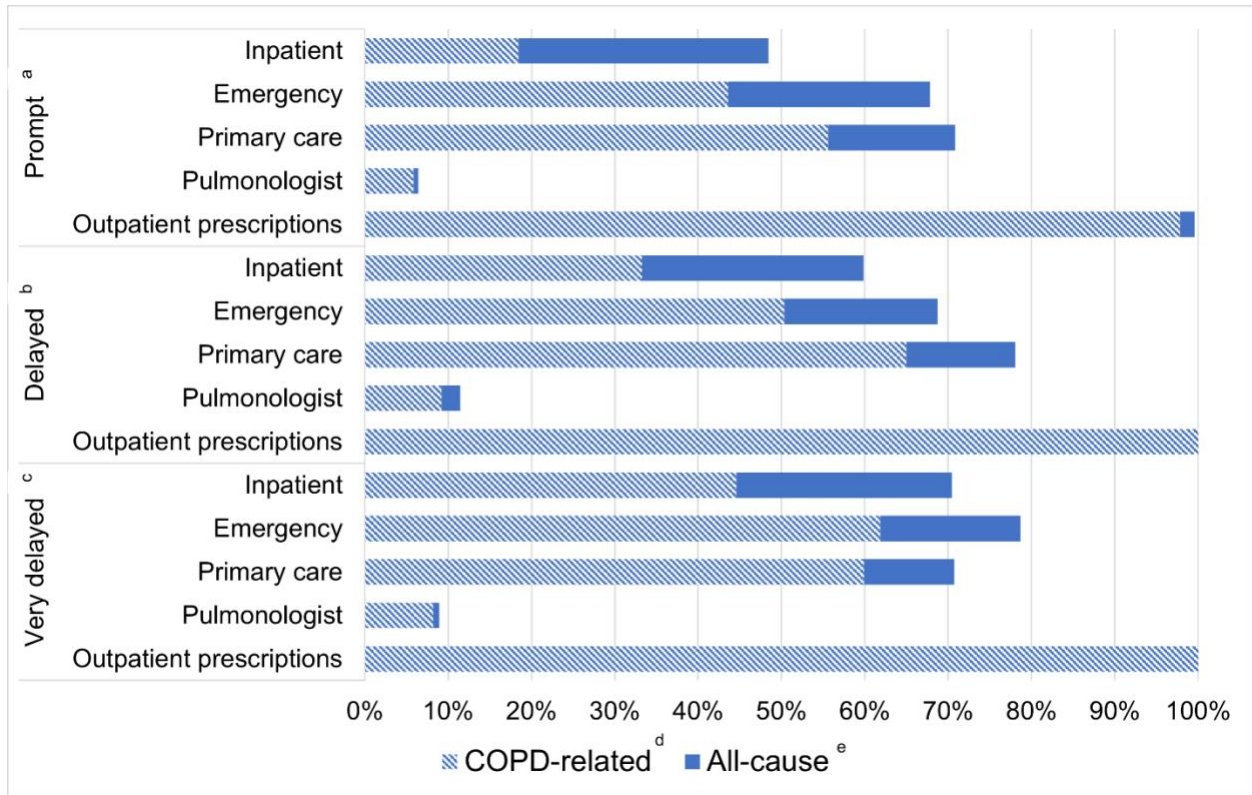
^a $P < 0.001$ for the change in the number of exacerbations per 30-day delay of triple therapy; COPD: chronic obstructive pulmonary disease; SD: standard deviation. Results from a negative binomial regression model controlling for age, sex, payer type, urban residence, index year, baseline comorbidities and tobacco use, baseline exacerbations, baseline short- and long-acting maintenance therapy use, nebulizer use, oxygen therapy, and number of COPD-related primary care provider and pulmonologist visits

Supplementary Figure #4. Unadjusted proportion of Commercial/Medicare patients with all-cause and COPD-related healthcare encounters during the 12-month follow-up period



^a Triple therapy within 30 days after or on the index exacerbation date; ^b Triple therapy between 31 and 180 days after index exacerbation; ^c Triple therapy between 181 and 365 days after index exacerbation; ^d $P < 0.001$ for all comparisons between prompt, delayed, and very delayed; ^e $P < 0.01$ for all comparisons except all-cause primary care visits ($P = 0.163$); COPD: chronic obstructive pulmonary disease

Supplementary Figure #5. Unadjusted proportion of Medicaid patients with all-cause and COPD-related healthcare encounters during the 12-month follow-up period



^a Triple therapy within 30 days after or on the index exacerbation date; ^b Triple therapy between 31 and 180 days after index exacerbation; ^c Triple therapy between 181 and 365 days after index exacerbation; ^d $P < 0.01$ for all comparisons between prompt, delayed, and very delayed except COPD-related pulmonologist visits ($P = 0.062$); ^e $P < 0.01$ for all comparisons except all-cause outpatient prescriptions ($P = 0.068$); COPD: chronic obstructive pulmonary disease

Supplementary Table #5. Unadjusted all-cause and COPD-related healthcare utilization during the 12-month follow-up period

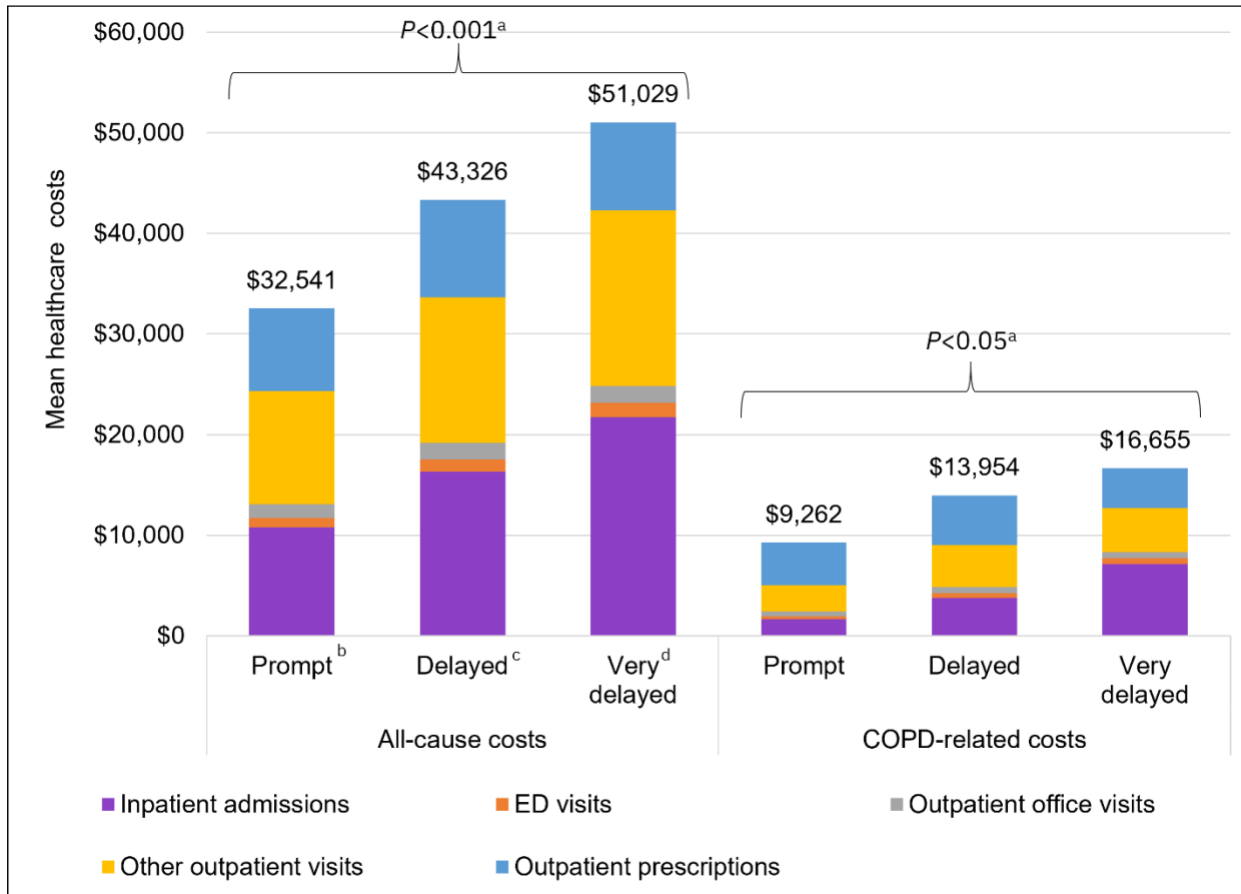
	Commercial & Medicare Patients				Medicaid Patients			
	Prompt ^a n = 2,268	Delayed ^b n = 1,378	Very delayed ^c n = 1,088	P value	Prompt ^a n = 700	Delayed ^b n = 620	Very delayed ^c n = 718	P value
All-Cause Utilization^d								
Number of inpatient admissions, mean (SD)	0.5 (0.9)	0.8 (1.2)	1.1 (1.5)	<0.001	1.1 (1.9)	1.7 (2.2)	2.5 (2.9)	<0.001
Length of stay (days) per admission, mean (SD)	4.7 (4.2)	5.2 (6.4)	5.0 (3.8)	0.140	5.1 (4.1)	4.6 (3.7)	4.6 (3.0)	0.180
Number of emergency department visits, mean (SD)	0.9 (1.7)	1.4 (2.3)	1.8 (2.7)	<0.001	2.7 (4.4)	2.9 (5.0)	4.4 (7.1)	<0.001
Number of total office visits, mean (SD)	11.9 (8.8)	13.7 (9.2)	14.1 (10.7)	<0.001	12.5 (10.2)	14.7 (10.6)	13.5 (10.7)	0.001
Number of primary care visits, mean (SD)	3.6 (4.9)	4.6 (5.9)	4.7 (7.7)	<0.001	6.1 (7.2)	7.1 (7.4)	6.6 (7.6)	0.051
Number of pulmonologist visits, mean (SD)	1.3 (2.0)	1.6 (2.3)	1.4 (2.1)	<0.001	0.2 (0.8)	0.4 (2.5)	0.2 (0.9)	0.055
Number of other outpatient visits, mean (SD)	30.3 (28.8)	40.6 (34.3)	42.1 (35.7)	<0.001	74.8 (115.2)	73.8 (101.1)	90.0 (121.5)	0.012
Number of prescriptions, mean (SD)	51.5 (33.8)	62.7 (36.6)	64.2 (37.1)	<0.001	110.3 (71.2)	119.0 (66.9)	122.1 (71.3)	0.005
COPD-Related Utilization^d								
Number of inpatient admissions, mean (SD)	0.1 (0.4)	0.3 (0.6)	0.5 (0.9)	<0.001	0.3 (0.8)	0.6 (1.0)	0.9 (1.5)	<0.001
Length of stay (days) per admission, mean (SD)	4.0 (3.4)	4.3 (3.4)	4.4 (3.0)	0.308	3.8 (3.6)	4.2 (3.4)	4.0 (2.8)	0.629

Patients with a 90-day COPD-related readmission ^e , N (%)	66 (2.9%)	89 (6.5%)	61 (5.6%)	< 0.001	48 (6.9%)	86 (13.9%)	109 (15.2%)	<0.001
Number of emergency department visits, mean (SD)	0.3 (0.8)	0.6 (1.3)	0.8 (1.6)	< 0.001	1.0 (1.7)	1.3 (2.3)	2.2 (3.9)	<0.001
Number of total office visits, mean (SD)	3.9 (3.5)	5.1 (4.0)	4.9 (4.0)	< 0.001	3.7 (3.6)	5.3 (4.9)	5.0 (4.2)	<0.001
Number of primary care visits, mean (SD)	1.3 (2.2)	1.8 (2.8)	1.9 (2.9)	< 0.001	2.0 (2.7)	2.7 (3.2)	2.6 (3.1)	<0.001
Number of pulmonologist visits, mean (SD)	1.0 (1.7)	1.3 (2.0)	1.0 (1.7)	< 0.001	0.1 (0.7)	0.3 (2.4)	0.2 (0.8)	0.298
Number of other outpatient visits, mean (SD)	9.8 (11.9)	14.3 (13.9)	14.5 (14.0)	< 0.001	14.5 (35.6)	16.7 (26.9)	23.0 (44.5)	<0.001
Number of prescriptions, mean (SD)	13.2 (9.7)	17.1 (10.0)	15.7 (10.2)	< 0.001	23.1 (15.0)	27.8 (14.0)	27.0 (15.5)	<0.001

^a Triple therapy within 30 days after or on the index exacerbation date; ^b Triple therapy between 31 and 180 days after index exacerbation; ^c Triple therapy between 181 and 365 days after index exacerbation; ^d Mean (SD) number of admissions, visits, and prescriptions reported among all patients, whether or not they had any utilization; ^e Inpatient admission with a primary COPD diagnosis within 90 days after discharge from a prior admission with a primary COPD diagnosis; COPD: chronic obstructive pulmonary disease; SD: standard deviation

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Supplementary Figure #6. Unadjusted all-cause and COPD-related healthcare costs among Commercial/Medicare patients

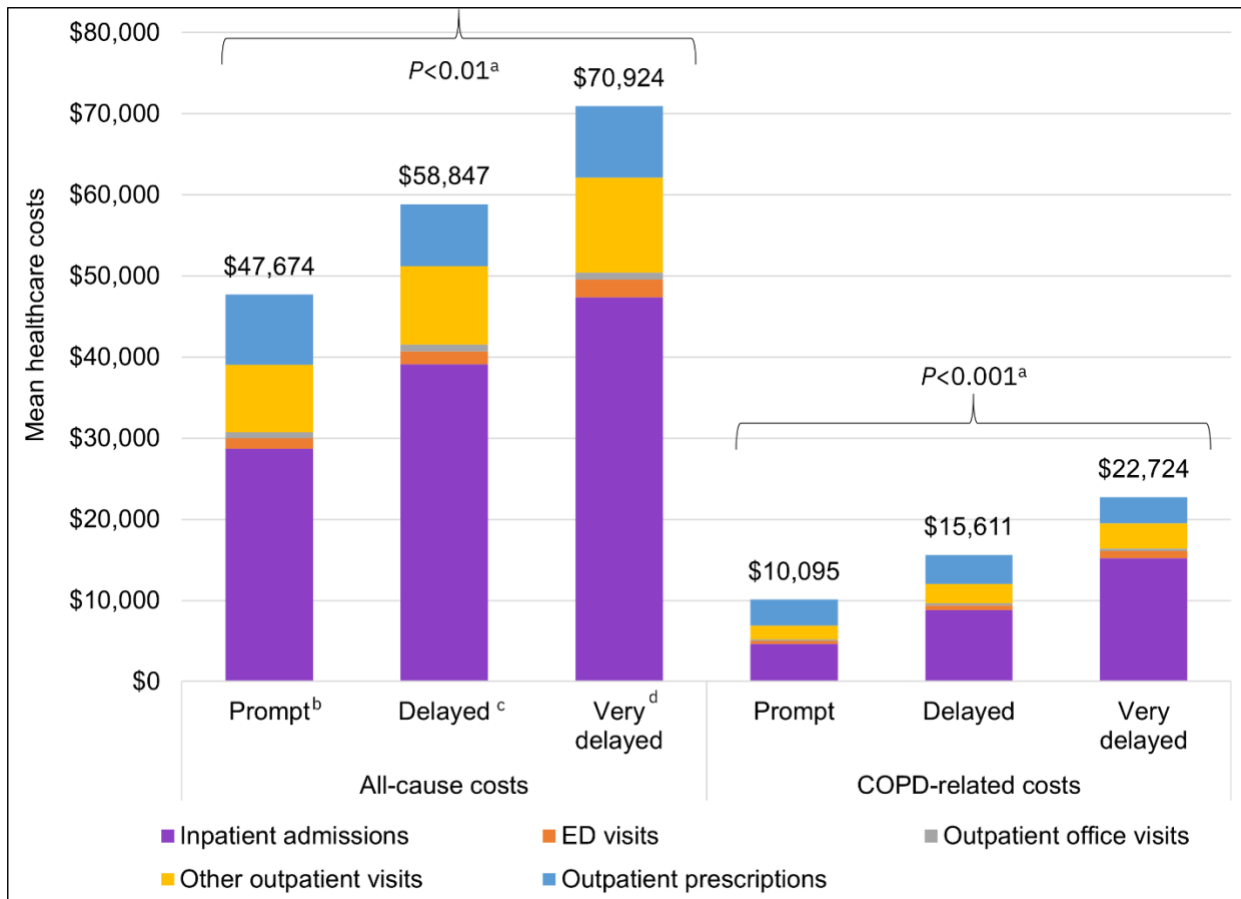


^a *P* values apply to all comparisons between groups, including total costs and costs within each service category;

^b Triple therapy within 30 days after or on the index exacerbation date; ^c Triple therapy between 31 and 180 days after index exacerbation; ^d Triple therapy between 181 and 365 days after index exacerbation; COPD: chronic obstructive pulmonary disease; ED: emergency department

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Supplementary Figure #7. Unadjusted all-cause and COPD-related healthcare costs among Medicaid patients



^a *P* values apply to all comparisons between groups, including total costs and costs within each service category, except COPD-related outpatient prescriptions (*P*=0.102); ^b Triple therapy within 30 days after or on the index exacerbation date; ^c Triple therapy between 31 and 180 days after index exacerbation; ^d Triple therapy between 181 and 365 days after index exacerbation; COPD: chronic obstructive pulmonary disease; ED: emergency department