Replication of the POET-COPD Trial in Healthcare Claims Data

DUPLICATE POET-COPD

August 10, 2021

1. RCT Details

This section provides a high-level overview of an RCT that the described real-world evidence study is trying to replicate as closely as possible given the remaining limitations inherent in the healthcare databases.

1.1 Title

Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD (POET-COPD trial)

1.2 Intended aim(s)

The objective of the study is to assess the efficacy and safety of tiotropium, a long-acting anticholinergic (muscarinic antagonist) drug (LAMA) compared to salmeterol, a long-acting beta agonist (LABA) in patients with chronic obstructive pulmonary disease (COPD)

1.3 Primary endpoint for replication and RCT finding

Time to first COPD exacerbation

1.4 Required power for primary endpoint and noninferiority margin (if applicable)

With a sample size of approximately 6800 patients (3400 in each arm), the trial will have 80% power to detect a 10% reduction in the risk of first exacerbation with tiotropium as compared with salmeterol, with a two-sided test for the null hypothesis of a hazard ratio of 1 at a significance level of 0.05

1.5 Trial estimate

HR = 0.83 (95% CI 0.77–0.90) comparing tiotropium to salmeterol (Vogelmeier et al., 2011, NEJM)

2. Person responsible for implementation of replication in Aetion

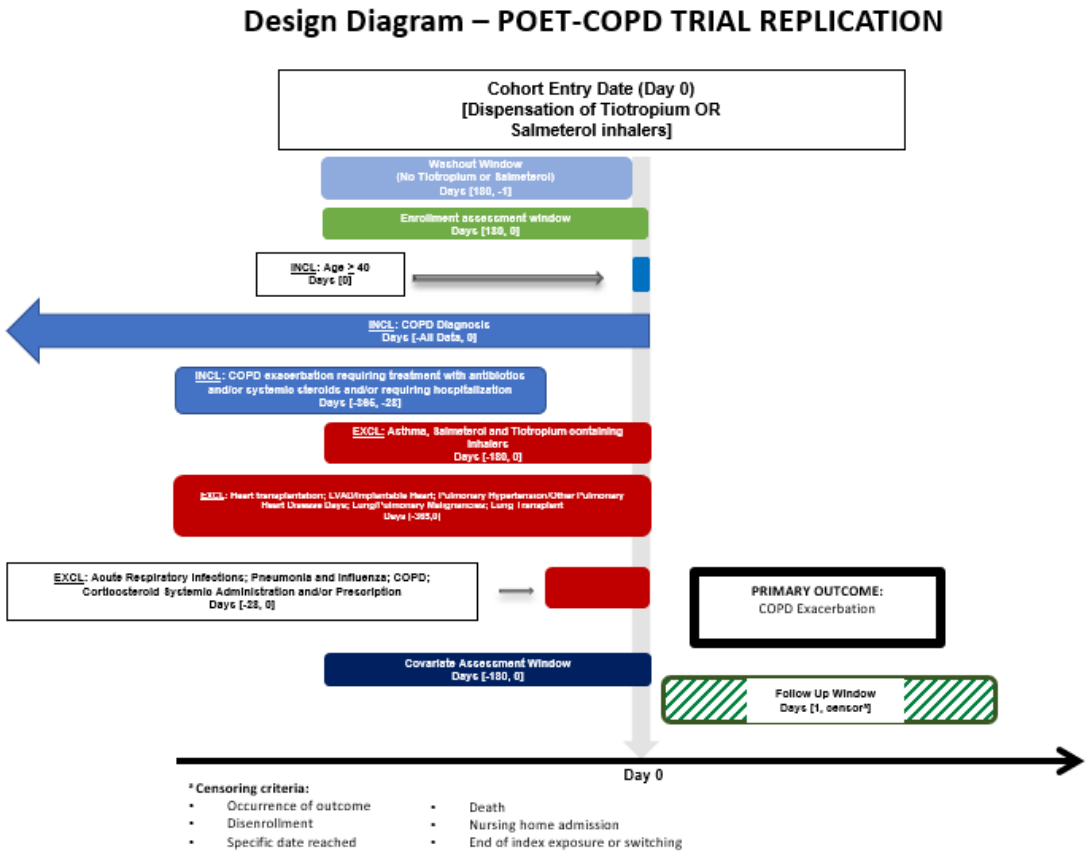
Helen Tesfaye, Pharm.D, ScM implemented the study design in the Aetion Evidence Platform. She is not responsible for the validity of design and analytic choices. All implementation steps are recorded, and implementation history is archived in the platform.

3. Data Source(s)

Optum Cliniformatics Data Mart, IBM MarketScan

4. Study Design Diagram

The study design diagram visualizes key aspects of the longitudinal study design for expediated review



5. Cohort Identification

5.1 Cohort Summary

This study will involve a new user, parallel group, propensity score matched retrospective cohort study design comparing tiotropium to salmeterol. The patients will be required to have continuous enrollment during baseline period of 180 days before initiation of tiotropium or salmeterol inhalers (cohort entry date).

5.2 Important steps for cohort formation

New users (defined as no use in 180 days prior to index date) of an exposure and a comparator drug will be identified.

5.2.1 Eligible cohort entry date

Tiotropium inhaler was first approved by FDA for market availability on January 30, 2004, and salmeterol on September 15, 1998

- Optum: January 30, 2004 – March 31, 2020 (end of data availability is December 31, 2020 but excluded data generated during COVID-19 pandemic)
- Marketscan: January 30, 2004 – December 31, 2018 (end of data availability)

5.2.2 Specify inclusion/exclusion criteria for cohort entry and define the index date

Inclusion and exclusion criteria were adapted from the trial as closely as possible. Definitions for all inclusion/exclusion are provided in **Appendix A** and are summarized in the flowcharts below.

5.3 Flowchart of the study cohort assembly

	OPTUM		MARKETSCAN	
	Less Excluded Patients	**Remaining Patients**	**Less Excluded Patients**	**Remaining Patients**
All patients		79,335,559		200,203,908
Did not meet cohort entry criteria	-78,723,324	612,235	-199,335,696	868,212
Excluded due to insufficient enrollment	-87,210	525,025	-98,266	769,946
Excluded due to prior use of referent	-22,073	502,952	-52,587	717,359
Excluded due to prior use of exposure	-298,940	204,012	-406,646	310,713
Excluded because patient qualified in >1 exposure category	-164	203,848	-292	310,421
Excluded based on Missing/Unknown Age	0	203,848	0	310,421
Excluded based on Missing/Unknown Gender	-37	203,811	0	310,421
Excluded based on Inclusion #1 - Age >=40 years old	-9,129	194,682	-19,097	291,324
Excluded based on Inclusion #2 - Diagnosis of COPD	-35,444	159,238	-78,651	212,673
Excluded based on Inclusion #4 - History of at least 1 COPD Exacerbation within the past year	-75,207	84,031	-105,442	107,231
Excluded based on Exclusion #2a - Asthma	-10,054	73,977	-8,159	99,072
Excluded based on Exclusion #2b - Severe cardiovascular or pulmonary disorders_V2	-8,122	65,855	-8,509	90,563
Excluded based on Exclusion #3 - Patients with any respiratory infection or COPD exacerbation in the 4 weeks prior to visit 1	-12,040	53,815	-14,085	76,478
Excluded based on Exclusion #5 - Salmeterol, Tiotropium containing inhaler use within 180 days*	-4,157	49,658	-7,817	68,661
Final cohort		**49,658**		**68,661**

* Additional exclusion criteria applied for replication

6 Variables

6.1 Exposure-related variables:

Study drug:

The study exposure of interest is initiation of tiotropium (LAMA). Initiation will be defined by no use of inhaled tiotropium during the prior 180 days before treatment initiation (washout period). Patients are required to be incident users with respect both exposure groups.

Comparator agents:

Initiators of salmeterol inhaler defined as no use of inhaled salmeterol during the 180 days prior to index date

6.2 Preliminary Covariates:

- Age
- Sex
- Combined Comorbidity Index (CCI), measured over the default baseline covariate assessment period of 180 days prior to and including the index prescription date

Covariates listed above are a small subset of covariates that will ultimately be controlled in the design and analysis phase of the study. They are included in the preliminary assessment to determine the presence of adequate overlap between the two population of patients to proceed to the next phase of the study. Remaining covariates are defined only after the study has passed the initial feasibility analysis and initial power assessment and are listed in Table 1 (**Appendix B**).

6.3 Outcome variables and study follow-up:

6.3.1 Outcome variables

Effectiveness outcome variables of interest (definitions provided in **Appendix A**):

- **Primary outcome:** Time to first COPD exacerbation
- Secondary outcome:
  - All-cause death

Control outcomes of interest (control outcomes only serve to assess aspects of study validity but are not further interpreted): Pneumonia

6.3.2 Study follow-up

Both as-treated (AT) and intention-to-treat (ITT) analysis will be conducted with treatment defined as the index drug on the day of cohort entry. Because adherence in the real-world databases is expected to be much worse than in the trial, the AT analysis is the **primary** analysis, as it targets the relative hazard of outcomes on treatment.

For the AT analysis, the follow-up will start the day after the initiation of tiotropium or salmeterol and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest,
- The date of end of continue registration in the database,
- End of the study period,
- Death,
- Nursing home admission
    - Nursing home admissions are considered a censoring event because the data sources utilized typically provide little to no data on a patient, particularly on drug utilization, after admission. We will utilize this as an exclusion reason for cohorts for the same reason.
- The date of drug discontinuation, defined as the date of the last continuous treatment episode of the index drug (tiotropium or salmeterol) + a 60-day grace period,
- The date of switching from an exposure to comparator and vice versa,
- The date of switching to or initiation of other LAMA (excluding tiotropium) and other LABA (excluding salmeterol), LAMA/LABA, LABA/ICS, and LAMA/LABA/ICS combination inhalers.

For the ITT analyses, the censoring based on the switching and treatment discontinuation will be replaced with a maximum allowed follow-up time of 365 days.

7 Initial Feasibility Analysis

Aetion report name:

Optum- https://bwh-dope.aetion.com/projects/details/1730/rwrs/71650

Marketscan- https://bwh-dope.aetion.com/projects/details/1732/rwrs/71648

Date conducted: 5/6/2021 (old version), 6/17/2021 (current) – In the current version, we removed the additional exclusion criteria "LABA, LAMA, or any combinations containing those (except study drugs) - 14 days washout period," which was applied in defining the cohort used in the old version.

Complete Aetion feasibility analysis using age, sex, and CCI as the only covariates and the primary endpoint (Section 6.3.1) as the outcome.

- Complete study flowchart from Section 5.3
- Report patient characteristics by treatment group

BEFORE MATCHING						
	Optum			Marketscan		
Variable	**Referent - Salmeterol**	**Exposure - Tiotropium**	**Difference**	**Referent - Salmeterol**	**Exposure - Tiotropium**	**Difference**
Number of patients	1,077	48,581	- (-, -)	3,397	65,264	- (-, -)
Age						
...mean (sd)	69.31 (10.79)	69.64 (9.85)	-0.34 (-0.99, 0.31)	70.81 (10.79)	68.26 (11.06)	2.55 (2.18, 2.92)
...median [IQR]	70.00 [62.00, 77.50]	70.00 [63.00, 77.00]	- (-, -)	72.00 [63.00, 79.00]	68.00 [60.00, 77.00]	- (-, -)
Gender						
...Male; n (%)	511 (47.4%)	21,601 (44.5%)	3.0% (-0.1%, 6.0%)	1,566 (46.1%)	31,139 (47.7%)	-1.6% (-3.3%, 0.1%)
...Female; n (%)	566 (52.6%)	26,980 (55.5%)	-3.0% (-6.0%, 0.1%)	1,831 (53.9%)	34,125 (52.3%)	1.6% (-0.1%, 3.3%)
Combined comorbidity score, 180 days						
...mean (sd)	2.37 (2.54)	2.59 (2.56)	-0.22 (-0.37, -0.06)	1.75 (1.88)	2.05 (2.14)	-0.31 (-0.37, -0.24)
...median [IQR]	2.00 [1.00, 3.00]	2.00 [1.00, 4.00]	- (-, -)	1.00 [1.00, 3.00]	1.00 [1.00, 3.00]	- (-, -)

- Report summary parameters of study population

FEASIBILITY FOR STUDY OUTCOME		
	Optum	Marketscan
Variable	Value	Value
Number of patients in full cohort	49,658	68,661
Number of patients dropped as incomplete cases	0	0
Number of patients that did not begin follow-up	57	72
Number of patients in analytic cohort	49,601	68,589
Number of events	11,400	15,086
Number of person-years	16,485.60	27,150.40
Number of patients in group: Referent - Salmeterol	1,073	3,389
Number of patients in group: Exposure - Tiotropium	48,528	65,200
Risk per 1,000 patients	229.83	219.95
Rate per 1,000 person-years	691.51	555.65

- Report median follow-up time by treatment group

FOLLOW-UP TIME FOR STUDY OUTCOME Median Follow-Up Time (Days) [IQR]		
	Optum	Marketscan
Patient Group	Median Follow-Up Time (Days) [IQR]	Median Follow-Up Time (Days) [IQR]
Overall Patient Population	88 [45, 140]	88 [57, 148]
Referent - Salmeterol	88 [56, 148]	88 [73, 148]
Exposure - Tiotropium	88 [45, 140]	88 [56, 148]

- Report reasons for censoring in the overall study population

CENSORING REASONS FOR STUDY OUTCOME		
	Optum	**Marketscan**
Overall	49,601	68,589
Death	911 (1.8%)	299 (0.4%)
Start of an additional exposure	137 (0.3%)	325 (0.5%)
End of index exposure	19,798 (39.9%)	29,908 (43.6%)
Specified date reached	1,539 (3.1%)	712 (1.0%)
End of patient data	0 (0.0%)	0 (0.0%)
End of patient enrollment	3,174 (6.4%)	7,894 (11.5%)
Switch to other LABA, LAMA + LABA/LAMA combo + LAMA/LABA/ICS combo + NH admissions Occurred	12,687 (25.6%)	14,442 (21.1%)

8 Initial Power Assessment

Aetion report name:

Optum- https://bwh-dope.aetion.com/projects/details/1730/rwrs/71651
Marketscan- https://bwh-dope.aetion.com/projects/details/1732/rwrs/71649

Date conducted: 5/4/2021 (old version), 6/17/2021 (current version) – In the current version, we removed the additional exclusion criteria "LABA, LAMA, or any combinations containing those (except study drugs) - 14 days washout period," which was applied in defining the cohort used in the old version.

In order to complete the initial power analysis, the dummy outcome of a 90-day gap in database enrollment will be used. Complete a 1:1 PS-matched comparative analysis using this outcome. PS should include only 3 covariates: age, sex, and combined comorbidity index.

	Optum	Marketscan	Pooled
Number of people matched			
Reference	1073.0	3389.0	4462.0
Exposure	1073.0	3389.0	4462.0
Risk per 1,000 patients	229.8	220.0	--
Rate per 1,000 person-years	691.5	555.7	
N of events	11,400	15,086	26,486
N of patients (both groups) at Step 1	49,658	68,661	118,319
Risk per 1,000 patients	229.57	219.72	223.85

Superiority Analysis (Pooled)	
Number of patients matched	
Reference	4,462
Exposed	4,462
Risk per 1,000 patients	223.85
Desired HR from RCT	0.83
Alpha (2-sided)	0.05
Number of events expected	1997.6374
Power	0.986238897

Superiority Analysis (Optum)	
Number of patients matched	
Reference	1,073
Exposed	1,073
Risk per 1,000 patients	229.57
Desired HR from RCT	0.83
Alpha (2-sided)	0.05
Number of events expected	492.65722
Power	0.542994909

Superiority Analysis (Marketscan)	
Number of patients matched	
Reference	3,389
Exposed	3,389
Risk per 1,000 patients	219.72
Desired HR from RCT	0.83
Alpha (2-sided)	0.05
Number of events expected	1489.26216
Power	0.949012649

- Stop analyses until feasibility and power are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Shirley Wang	Date reviewed:	
Reviewed by FDA:		Date reviewed:	
Reasons for stopping analysis (if required):			

9. Balance Assessment

Optum- https://bwh-dope.aetion.com/projects/details/1730/rwrs/72136
Marketscan- https://bwh-dope.aetion.com/projects/details/1732/rwrs/72137

Date conducted: 7/6/2021

After review of initial feasibility and power analyses, complete creation of the remaining covariates from Section 6.2. Again, using the dummy outcome of a 90-day gap in database enrollment, complete a 1:1 PS-matched analysis. The PS should include the complete list of covariates.

- Provide plot of PS distributions stratified by treatment group.

  Note- Please refer to **Appendix B**.

- Report covariate balance after matching.

  Note- For Table 1, please refer to **Appendix B**.

- Report reasons for censoring by treatment group.

	Overall	Referent	Exposure
Dummy outcome	0 (0%)	0 (0%)	0 (0%)
Death	104 (1.19%)	44 (1.01%)	60 (1.38%)
Start of an additional exposure	347 (3.98%)	317 (7.27%)	30 (0.69%)
End of Index Exposure	5,180 (59.43%)	2,735 (62.76%)	2,445 (56.1%)
Specified date reached	111 (1.27%)	56 (1.28%)	55 (1.26%)
End of patient enrollment	1,133 (13%)	485 (11.13%)	648 (14.87%)
Switch to other LABA, LAMA + LABA/LAMA combo + LAMA/LABA/ICS combo + NH admissions Occurred	1,841 (21.12%)	721 (16.54%)	1,120 (25.7%)

- Report follow-up time by treatment group.

Patient Group	Optum Median Follow-Up Time (Days) [IQR]	Marketscan Median Follow-Up Time (Days) [IQR]
Overall Patient Population	88 [83, 159]	123 [88, 214]
Referent - Salmeterol	88 [85, 154]	125 [88, 195]
Exposure - Tiotropium	88 [83, 169]	122 [88, 226]

- Report overall risk of the primary outcome.

	Optum	MarketScan	Pooled
Risk per 1,000 patients	229.57	219.72	223.85

10. Final Power Assessment

Date conducted: 7/9/2021

- Re-calculate power in the appropriate excel table, using the revised number of matched patients from the PS-match in Section 9. All other parameters in the table should be the same as in Section 8.

Superiority Analysis (Pooled)	
Number of patients matched	
Reference	4,358
Exposed	4,358
Risk per 1,000 patients	223.85
Desired HR from RCT	0.83
Alpha (2-sided)	0.05
Number of events expected	1951.0766
Power	0.984427581

Superiority Analysis (Optum)	
Number of patients matched	
Reference	1,073
Exposed	1,073
Risk per 1,000 patients	229.57
Desired HR from RCT	0.83
Alpha (2-sided)	0.05
Number of events expected	492.65722
Power	0.542994909

Superiority Analysis (Marketscan)	
Number of patients matched	
Reference	3,285
Exposed	3,285
Risk per 1,000 patients	219.72
Desired HR from RCT	0.83
Alpha (2-sided)	0.05
Number of events expected	1443.5604
Power	0.942918994

- Stop analyses until balance and final power assessment are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Shirley Wang	Date reviewed:	
Reviewed by FDA:		Date reviewed:	
Reasons for stopping analysis (if required):			

Appendix A: COPD Exacerbation (primary outcome), All-cause mortality (secondary outcome)

COPD Exacerbation

Measured 1 day after drug initiation in primary diagnosis position specified below and inpatient care setting -

COPD (Inpatient, Primary)
ICD-9 Diagnosis: 491.x, 492.x, 496
ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x

OR

Measured 1 day after drug initiation in any diagnosis position specified below and inpatient and outpatient care setting AND steroid use within 14 days -

COPD (Any care setting, Any position)
ICD-9 Diagnosis: 491.x, 492.x, 496
ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x

AND

Corticosteroid systemic administration and/or oral prescription of --
- Prednisone
- Prednisolone
- Methylprednisolone
- Dexamethasone
- Hydrocortisone

All-Cause Mortality

Identified using the discharge status codes-
Optum- Inpatient/Outpatient
• 20 = EXPIRED
• 21 = EXPIRED TO BE DEFINED AT STATE LEVEL
• 22 = EXPIRED TO BE DEFINED AT STATE LEVEL
• 23 = EXPIRED TO BE DEFINED AT STATE LEVEL
• 24 = EXPIRED TO BE DEFINED AT STATE LEVEL

- 25 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 26 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 27 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 28 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 29 = EXPIRED TO BE DEFINED AT STATE LEVEL
- 40 = EXPIRED AT HOME (HOSPICE)
- 41 = EXPIRED IN A MEDICAL FACILITY (HOSPICE)
- 42 = EXPIRED - PLACE UNKNOWN (HOSPICE)

Marketscan- Inpatient

- 20 - Died
- 22 - Died
- 23 - Died
- 24 - Died
- 25 - Died
- 26 - Died
- 27 - Died
- 28 - Died
- 29 - Died
- 40 - Other died status or Expired at home (Hospice claims only) (depends on year)
- 41 - Other died status or Expired in medical facility (Hospice claims only) (depends on year)
- 42 - Other died status or Expired - place unknown (Hospice claims only) (depends on year)
- 21 - Died or Disch./Transf. to court/law enforcement (depends on year)

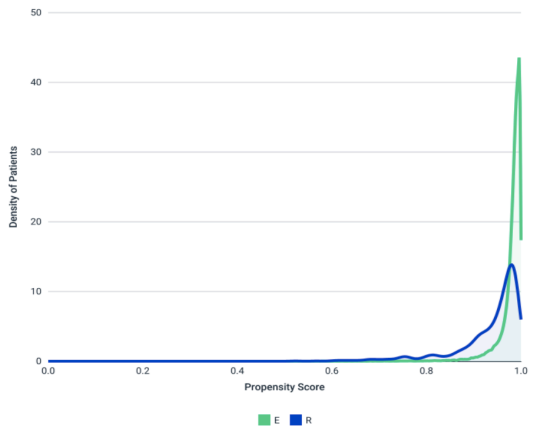
Appendix A

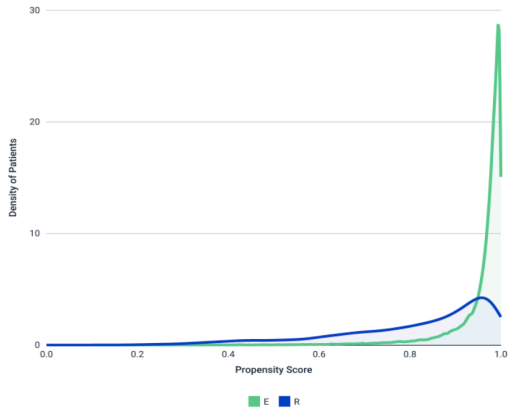
#	POET-COPD trial definitions	Implementation in routine care	References/Rationale	Color coding
	Trial details - Intended S with label change - 2 weeks run-in		**Please see the following Google drive for further details or any missing information** https://drive.google.com/drive/folders/1WD618wrywYjEaXzfLTcuK-VCcnb6b-gV	Criteria
	EXPOSURE vs. COMPARISON			Adequate mapping in claims
	Tiotropium 18 mcg once daily vs. Salmeterol hydrofluoroalkane 50 mcg twice daily Aim: To evaluate the effect of tiotropium compared to salmeterol on exacerbations of COPD	Tiotropium (Spiriva) vs. Salmeterol (Serevent) Exposure: Tiotropium Reference: Salmeterol		Intermediate mapping in claims
	PRIMARY OUTCOME			Poor mapping or cannot be measured in claims
	Primary endpoint: Time to first COPD exacerbation within 1 year	**Measured 1 day after drug initiation in primary diagnosis position and inpatient care setting:** COPD ICD-9 Diagnosis: 491.x, 492.x, 496 ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x **OR** **Measured 1 day after drug initiation in any diagnosis position and inpatient and outpatient care setting AND steriod use within 14 days:** COPD ICD-9 Diagnosis: 491.x, 492.x, 496 ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x **AND** Corticosteriod systemic administration and/or oral prescription of: - Prednisone - Prednisolone - Methylprednisolone - Dexamethasone - Hydrocortisone		Can't be measured in claims but not important for the analysis
	Tiotropium 18 mcg once daily vs. Salmeterol hydroflouroalkane 50 mcg twice daily			
1	40 years of age or older	**Measured on the day of drug initiation** Age >= 40		
2	Diagnosis of COPD	**Measured from the start of all available data to the day of drug initiation in any diagnosis position and in the inpatient and outpatient care setting:** COPD ICD-9 Diagnosis: 491.x, 492.x, 496 ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x		
3	Post-bronchodilator FEV1 ≤ 70% of predicted normal and FEV1 ≤ 70% of FVC and a smoking history of ≥ 10 pack years			
4	History of at least 1 COPD exacerbation within the past year requiring treatment with antibiotics and/or systemic steriods and/or requiring hospitalization	**Measured 365 days prior to 28 days prior to drug initiation in primary diagnosis position and inpatient care setting:** COPD ICD-9 Diagnosis: 491..x, 492.x, 496.0 ICD-10 Diagnosis: J41, J42.x, J43.x, J44.x **OR** **Measured 365 days prior to 28 days prior to drug initiation in any diagnosis position and inpatient and outpatient care setting AND steriod use within 14 days:** COPD ICD-9 Diagnosis: 491.x, 492.x, 496.0 ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x **AND** Corticosteriod systemic administration and/or prescription - Prednisone - Prednisolone - Methylprednisolone - Dexamethasone - Hydrocortisone		
	EXCLUSION CRITERIA			
1	Patients with significant diseases other than COPD that would preclude participation in the trial or interpretation of the results are excluded			
2	Patients with a current diagnosis of asthma, severe cardiovascular disorders and use of systemic corticosteroid medication at unstable doses	**Measured 180 days prior to and including the day of drug initiation in any diagnosis position and in the inpatient and outpatient care setting:** Asthma (3 Diagnosis within 180 days) ICD-9 Diagnosis: 493.x ICD-10 Diagnosis: J45.x **Measured 365 days prior to and including the day of drug initiation in any diagnosis position and in the inpatient and outpatient care setting:** Heart Transplantation ICD-9 Diagnosis: V42.1, V49.83, 996.83 ICD-10 Diagnosis: Z94.1, Z76.82, T86.20, T86.21, T86.22 ICD-9 Procedure: 33.6, 37.51 ICD-10 Procedure: 02YA0Z0, 02YA0Z1, 02YA0Z2 CPT-4 Code: 33935, 33945 LVAD/Implantable Heart ICD-9 Diagnosis: V43.2x ICD-10 Diagnosis: Z95.811, Z95.812 ICD-9 Procedure: 37.60, 37.66 ICD-10 Procedure: 02HA0RS, 02HA3RS, 02HA4RS, 5A02116, 5A02216, 02HA0QZ, 02HA3QZ, 02HA4QZ CPT-4 Code: 33975, 33976, 33979, 33981 - 33983, 33977, 33978, 33980		
3	Patients with any respiratory infection or COPD exacerbation* in the 4 weeks prior to the screening Visit (Visit 1) or during the run-in period * - Measurement included in Inclusion # 4	**Measured 28 days prior to and including the day of drug initiation in prescription claims:** Acute Resiratory Infections ICD-9 Diagnosis: 460 - 466.x ICD10 Diagnosis: J00 - J06.x, J20.x - J22.x Pneumonia and Influenza ICD-9 Diagnosis: 480.x - 488.x ICD-10 Diagnosis: J09.x - J18.x COPD (Inpatient, Primary) ICD-9 Diagnosis: 491.x, 492.x, 496.0 ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x **OR** COPD (Any care setting, Any position) ICD-9 Diagnosis: 491.x, 492.x, 496.0 ICD-10 Diagnosis: J41.x, J42, J43.x, J44.x **AND** **Corticosteroid systemic administration and/or prescription** - Prednisone - Prednisolone		
4	Exclude use of Salmeterol, tiotropium containing inhaler use within 180 days prior to CED	**Measured 180 days prior to and including the day of drug initiation in prescription claims:** Brand names STIOLTO RESPIMAT ADVAIR DISKUS ADVAIR HFA WIXELA INHUB **OR** Generic name TIOTROPIUM BROMIDE/OLODATEROL HCL FLUTICASONE PROPIONATE/SALMETEROL XINAFOATE		

Appendix B

Optum	MarketScan

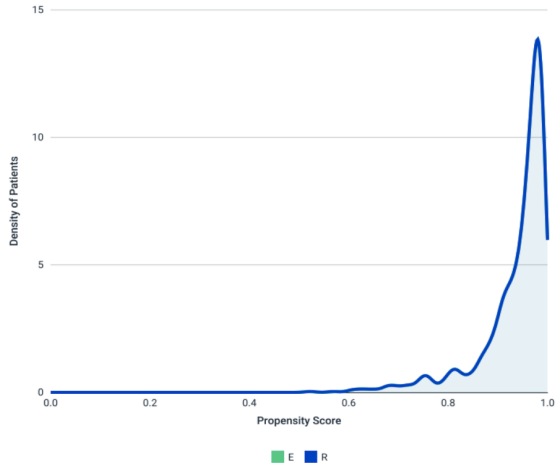
BEFORE PS MATCHING

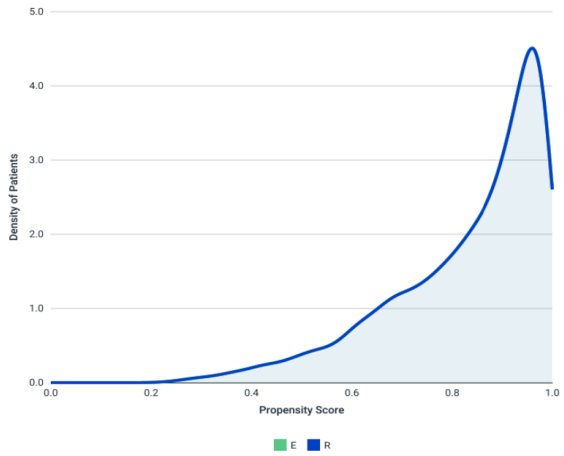




The c-statistics for the propensity score model, pre-matching was 0.783 The postmatching c-statistic was 0.581 .	The c-statistics for the propensity score model, pre-matching was 0.833. The postmatching c-statistic was 0.547.

AFTER PS MATCHING





Appendix B

UNMATCHED

	OPTUM			MARKETSCAN			POOLED		
	Referent - Salmeterol	Exposure - Tiotropium		Referent - Salmeterol	Exposure - Tiotropium		Referent - Salmeterol	Exposure - Tiotropium	
Number of patients	1,077	48,581		3,397	65,264		4,474	113,845	
Calendar Time - Year of Initiation (2004 - 2020)									
...2004-2006; n (%)	298 (27.7%)	2,777 (5.7%)	0.6173	1,955 (57.6%)	9,783 (15.0%)	0.9881	2,253 (50.4%)	12,560 (11.0%)	0.945
...2007-2008; n (%)	104 (9.7%)	3,944 (8.1%)	0.0562	404 (11.9%)	9,109 (14.0%)	-0.0626	508 (11.4%)	13,053 (11.5%)	-0.003
...2009-2011; n (%)	172 (16.0%)	8,025 (16.5%)	-0.0136	545 (16.0%)	17,106 (26.2%)	-0.2520	717 (16.0%)	25,131 (22.1%)	-0.156
...2012-2015; n (%)	157 (14.6%)	13,877 (28.6%)	-0.3452	316 (9.3%)	20,917 (32.0%)	-0.5842	473 (10.6%)	34,794 (30.6%)	-0.510
...2016-2018; n (%)	251 (23.3%)	13,687 (28.2%)	-0.1172	177 (5.2%)	8,349 (12.8%)	-0.2679	428 (9.6%)	22,036 (19.4%)	-0.281
...2019-Mar. 2020; n (%)	95 (8.8%)	6,271 (12.9%)	-0.1321				95 (8.8%)	6,271 (12.9%)	-0.132
DMG - Age									
...mean (sd)	69.31 (10.79)	69.64 (9.85)	-0.0319	70.81 (10.79)	68.26 (11.06)	0.2334	70.45 (10.79)	68.85 (10.56)	0.150
...median [IQR]	70.00 [62.00, 77.50]	70.00 [63.00, 77.00]	0.0000	72.00 [63.00, 79.00]	68.00 [60.00, 77.00]	0.3661	71.52 (10.79)	68.85 (10.56)	0.250
DMG - Gender									
...Male; n (%)	511 (47.4%)	21,601 (44.5%)	0.0582	1,566 (46.1%)	31,139 (47.7%)	-0.0321	2,077 (46.4%)	52,740 (46.3%)	0.002
...Female; n (%)	566 (52.6%)	26,980 (55.5%)	-0.0582	1,831 (53.9%)	34,125 (52.3%)	0.0321	2,397 (53.6%)	61,105 (53.7%)	-0.002
DMG - Geographic region									
...Northeast; n (%)	100 (9.3%)	5,118 (10.5%)	-0.0402	351 (10.3%)	10,691 (16.4%)	-0.1801	451 (10.1%)	15,809 (13.9%)	-0.117
...South; n (%)	385 (35.7%)	22,458 (46.2%)	-0.2148	845 (24.9%)	23,650 (36.2%)	-0.2472	1,230 (27.5%)	46,108 (40.5%)	-0.277
...North Central; n (%)	278 (25.8%)	10,162 (20.9%)	0.1160	1,108 (32.6%)	23,003 (35.2%)	-0.0549	1,386 (31.0%)	33,165 (29.1%)	0.041
...West; n (%)	314 (29.2%)	10,843 (22.3%)	0.1583	1,093 (32.2%)	7,920 (12.1%)	0.4989	1,407 (31.4%)	18,763 (16.5%)	0.355
DRS - Combined comorbidity score, 180 days									
...mean (sd)	2.37 (2.54)	2.59 (2.56)	-0.0863	1.75 (1.88)	2.05 (2.14)	-0.1489	1.90 (2.06)	2.28 (2.33)	-0.173
...median [IQR]	2.00 [1.00, 3.00]	2.00 [1.00, 4.00]	0.0000	1.00 [1.00, 3.00]	1.00 [1.00, 3.00]	0.0000	1.24 (2.06)	1.43 (2.33)	-0.086
DRS - Frailty Score: Empirical Version (mean)									
...mean (sd)	0.21 (0.07)	0.22 (0.07)	-0.1429	0.19 (0.06)	0.20 (0.07)	-0.1534	0.19 (0.06)	0.21 (0.07)	-0.307
...median [IQR]	0.19 [0.16, 0.24]	0.20 [0.16, 0.25]	-0.1429	0.18 [0.14, 0.22]	0.19 [0.15, 0.23]	-0.1534	0.18 (0.06)	0.19 (0.07)	-0.153
PLM - Smoking ; n (%)	304 (28.2%)	20,039 (41.2%)	-0.2757	328 (9.7%)	14,153 (21.7%)	-0.3344	632 (14.1%)	34,192 (30.0%)	-0.391
PLM - Pneumonia ; n (%)	121 (11.2%)	6,244 (12.9%)	-0.0522	361 (10.6%)	8,855 (13.6%)	-0.0921	482 (10.8%)	15,099 (13.3%)	-0.077
PLM - Alpha-1 antitrypsin def/Pneumoconioses & other lung disease/Pul fibrosis; n (%)	79 (7.3%)	3,040 (6.3%)	0.0397	153 (4.5%)	3,648 (5.6%)	-0.0503	232 (5.2%)	6,688 (5.9%)	-0.031
PLM - Oxygen usage; n (%)	155 (14.4%)	7,652 (15.8%)	-0.0391	588 (17.3%)	10,345 (15.9%)	0.0376	743 (16.6%)	17,997 (15.8%)	0.022
PLM - Respiratory arrest/dependence on oxygen ; n (%)	129 (12.0%)	7,778 (16.0%)	-0.1155	227 (6.7%)	7,027 (10.8%)	-0.1455	356 (8.0%)	14,805 (13.0%)	-0.164
PLM - CiPAP/BiPAP use; n (%)	63 (5.8%)	3,294 (6.8%)	-0.0412	132 (3.9%)	5,015 (7.7%)	-0.1631	195 (4.4%)	8,309 (7.3%)	-0.124
PLM - Pulmonary rehabilitation ; n (%)*	7 (0.6%)	341 (0.7%)	-0.0124	9 (0.3%)	470 (0.7%)	-0.0567	016 (0.4%)	811 (0.7%)	-0.041
PLM - Moderate COPD exacerbation - [Count with 365 to 181 days before CED]*									
...mean (sd)	1.67 (4.35)	2.72 (6.59)	-0.1881	1.53 (3.65)	1.65 (3.78)	-0.0323	1.56 (3.83)	2.11 (5.17)	-0.121
...median [IQR]	0.00 [0.00, 1.14]	0.42 [0.00, 2.57]	-0.0752	0.08 [0.00, 1.23]	0.15 [0.00, 1.62]	-0.0188	0.06 (3.83)	0.27 (5.17)	-0.046
PLM - Moderate COPD exacerbation - [Count 180 to 31 days before CED]*									
...mean (sd)	1.72 (3.96)	2.27 (4.41)	-0.1312	1.29 (2.41)	1.40 (2.48)	-0.0450	1.39 (2.86)	1.77 (3.44)	-0.120
...median [IQR]	0.64 [0.01, 1.82]	0.88 [0.13, 2.45]	-0.0573	0.53 [0.00, 1.35]	0.61 [0.00, 1.66]	-0.0327	0.56 (2.86)	0.73 (3.44)	-0.054
PLM - Moderate COPD exacerbation - [Count with 30 days to CED]*									
...mean (sd)	0.29 (1.12)	0.30 (1.11)	-0.0090	0.16 (0.53)	0.21 (0.65)	-0.0843	0.19 (0.72)	0.25 (0.88)	-0.075
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.72)	0.00 (0.88)	0.000
PLM - Moderate exacerbations >=1 in 365 days before CED; n (%)	864 (80.2%)	40,971 (84.3%)	-0.1075	2,520 (74.2%)	51,102 (78.3%)	-0.0965	3,384 (75.6%)	92,073 (80.9%)	-0.129
PLM - Moderate exacerbations >=2 in 365 days before CED ; n (%)	576 (53.5%)	31,738 (65.3%)	-0.2420	1,612 (47.5%)	35,919 (55.0%)	-0.1505	2,188 (48.9%)	67,657 (59.4%)	-0.212
PLM - Severe COPD exacerbation - [Count with 365 to 181 days before CED] *									
...mean (sd)	0.04 (0.20)	0.07 (0.29)	-0.1204	0.06 (0.25)	0.07 (0.26)	-0.0392	0.06 (0.24)	0.07 (0.27)	-0.039
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.24)	0.00 (0.27)	0.000
PLM - Severe COPD exacerbation - [Count with 180 to 31 days before CED] *									
...mean (sd)	0.06 (0.26)	0.06 (0.24)	0.0000	0.06 (0.22)	0.06 (0.21)	0.0000	0.06 (0.23)	0.06 (0.22)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.23)	0.00 (0.22)	0.000
PLM - Severe COPD exacerbation - [Count with 30 days lookback] *									
...mean (sd)	0.01 (0.09)	0.01 (0.10)	0.0000	0.01 (0.06)	0.01 (0.08)	0.0000	0.01 (0.07)	0.01 (0.09)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.07)	0.00 (0.09)	0.000
PLM - Severe exacerbations >=1 in 365 days before CED; n (%)	106 (9.8%)	6,395 (13.2%)	-0.1067	428 (12.6%)	9,050 (13.9%)	-0.0384	534 (11.9%)	15,445 (13.6%)	-0.051
PLM - Severe exacerbations >=2 in 365 days before CED ; n (%)	15 (1.4%)	1,226 (2.5%)	-0.0796	66 (1.9%)	1,138 (1.7%)	0.0150	081 (1.8%)	2,364 (2.1%)	-0.022
PLM - GOLD C/D Status ; n (%)	437 (40.6%)	26,005 (53.5%)	-0.2606	1,613 (47.5%)	35,581 (54.5%)	-0.1404	2,050 (45.8%)	61,586 (54.1%)	-0.167
PRX - LABA (except salmeterol) inhalers; n (%)	62 (5.8%)	847 (1.7%)	0.2171	195 (5.7%)	2,276 (3.5%)	0.1052	257 (5.7%)	3,123 (2.7%)	0.150
PRX - LAMA (except tiotropium) inhalers; n (%) *	14 (1.3%)	440 (0.9%)	0.0384	14 (0.4%)	520 (0.8%)	-0.0518	028 (0.6%)	960 (0.8%)	-0.024
PRX - ICS only inhalers; n (%)	416 (38.6%)	8,938 (18.4%)	0.4591	1,638 (48.2%)	14,424 (22.1%)	0.5683	2,054 (45.9%)	23,362 (20.5%)	0.560
PRX - LABA/LAMA inhaler use; n (%) *	17 (1.6%)	503 (1.0%)	0.0530	2 (0.1%)	206 (0.3%)	-0.0448	019 (0.4%)	709 (0.6%)	-0.028
PRX - LABA/ICS inhaler use; n (%)	45 (4.2%)	11,055 (22.8%)	0.5657	107 (3.1%)	14,588 (22.4%)	0.6045	152 (3.4%)	25,643 (22.5%)	0.593
PRX - COPD Maintenance therapy inhalers; n (%)	126 (11.7%)	12,434 (25.6%)	0.3627	236 (6.9%)	13,496 (20.7%)	0.4084	362 (8.1%)	25,930 (22.8%)	0.415
PRX - SAMA inhaler use; n (%)	108 (10.0%)	2,469 (5.1%)	0.1863	624 (18.4%)	3,835 (5.9%)	0.3898	732 (16.4%)	6,304 (5.5%)	0.355
PRX - SABA use; n (%)	523 (48.6%)	25,017 (51.5%)	-0.0580	1,562 (46.0%)	31,659 (48.5%)	-0.0501	2,085 (46.6%)	56,676 (49.8%)	-0.064
PRX - SABA/SAMA use; n (%)	243 (22.6%)	7,839 (16.1%)	0.1651	839 (24.7%)	10,570 (16.2%)	0.2119	1,082 (24.2%)	18,409 (16.2%)	0.200
PRX - Antibiotics treatment (180 days to 31 days before CED); n (%)	512 (47.5%)	24,200 (49.8%)	-0.0460	1,697 (50.0%)	34,160 (52.3%)	-0.0460	2,209 (49.4%)	58,360 (51.3%)	-0.038
PRX - Antibiotics treatment (30 days to CED); n (%)	152 (14.1%)	5,931 (12.2%)	0.0562	458 (13.5%)	9,458 (14.5%)	-0.0288	610 (13.6%)	15,389 (13.5%)	0.003
PRX - Systemic Corticosteroids (with CPT) use (180 to 31 days before CED); n (%)	539 (50.0%)	25,127 (51.7%)	-0.0340	1,638 (48.2%)	32,585 (49.9%)	-0.0340	2,177 (48.7%)	57,712 (50.7%)	-0.040
PRX - Systemic Corticosteroids (with CPT) use (30 days to CED); n (%)	102 (9.5%)	3,369 (6.9%)	0.0949	384 (11.3%)	5,550 (8.5%)	0.0939	486 (10.9%)	8,919 (7.8%)	0.107
PRX - Roflumilast; n (%) *	7 (0.6%)	378 (0.8%)	-0.0240	5 (0.1%)	487 (0.7%)	-0.0952	012 (0.3%)	865 (0.8%)	-0.068
CVD - Unstable angina/MI; n (%)	86 (8.0%)	4,729 (9.7%)	-0.0599	223 (6.6%)	4,791 (7.3%)	-0.0275	309 (6.9%)	9,520 (8.4%)	-0.056
CVD - Stable Angina ; n (%)	46 (4.3%)	2,338 (4.8%)	-0.0240	95 (2.8%)	2,405 (3.7%)	-0.0508	141 (3.2%)	4,743 (4.2%)	-0.053
CVD - Any Heart failure (HF) ; n (%)	183 (17.0%)	9,631 (19.8%)	-0.0723	518 (15.2%)	11,652 (17.9%)	-0.0727	701 (15.7%)	21,283 (18.7%)	-0.080
CVD - Atrial fibrillation; n (%)	144 (13.4%)	6,877 (14.2%)	-0.0232	393 (11.6%)	8,538 (13.1%)	-0.0456	537 (12.0%)	15,415 (13.5%)	-0.045
CVD - Other dysrythmias ; n (%)*	191 (17.7%)	8,444 (17.4%)	0.0079	352 (10.4%)	9,481 (14.5%)	-0.1244	543 (12.1%)	17,925 (15.7%)	-0.104
CVD - Valve disorder ; n (%)	34 (3.2%)	1,741 (3.6%)	-0.0221	74 (2.2%)	1,841 (2.8%)	-0.0384	108 (2.4%)	3,582 (3.1%)	-0.043
CVD - Implantable cardioverter defibrillator ; n (%)*	14 (1.3%)	951 (2.0%)	-0.0550	32 (0.9%)	961 (1.5%)	-0.0551	046 (1.0%)	1,912 (1.7%)	-0.061
CVD - CABG/PCI; n (%)	74 (6.9%)	4,336 (8.9%)	-0.0742	139 (4.1%)	3,428 (5.3%)	-0.0567	213 (4.8%)	7,764 (6.8%)	-0.086
CVD - Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	270 (25.1%)	13,906 (28.6%)	-0.0790	704 (20.7%)	17,219 (26.4%)	-0.1346	974 (21.8%)	31,125 (27.3%)	-0.128
CVD - Stroke/TIA ; n (%)	60 (5.6%)	2,727 (5.6%)	0.0000	169 (5.0%)	3,400 (5.2%)	-0.0091	229 (5.1%)	6,127 (5.4%)	-0.013
CVD - Peripheral Vascular Disease (PVD) or PVD Surgery; n (%)	112 (10.4%)	6,337 (13.0%)	-0.0810	218 (6.4%)	5,918 (9.1%)	-0.1011	330 (7.4%)	12,255 (10.8%)	-0.118
CVD - Hyperlipidemia ; n (%)	516 (47.9%)	26,282 (54.1%)	-0.1243	703 (20.7%)	22,385 (34.3%)	-0.3082	1,219 (27.2%)	48,667 (42.7%)	-0.329
CVD - Hypertension; n (%)	695 (64.5%)	33,432 (68.8%)	-0.0913	1,384 (40.7%)	33,730 (51.7%)	-0.2220	2,079 (46.5%)	67,162 (59.0%)	-0.252
CRX - ACEI or ARB; n (%)	457 (42.4%)	22,139 (45.6%)	-0.0645	1,444 (42.5%)	29,179 (44.7%)	-0.0444	1,901 (42.5%)	51,318 (45.1%)	-0.052
CRX - Mineralocorticoid receptor antagonist ; n (%)	44 (4.1%)	2,041 (4.2%)	-0.0050	161 (4.7%)	3,176 (4.9%)	-0.0094	205 (4.6%)	5,217 (4.6%)	0.000
CRX - Loop or Thiazide diuretics; n (%)	374 (34.7%)	16,506 (34.0%)	0.0147	1,379 (40.6%)	23,473 (36.0%)	0.0947	1,753 (39.2%)	39,979 (35.1%)	0.085
CRX - Statins and other lipid lowering agents; n (%)	487 (45.2%)	25,485 (52.5%)	-0.1464	1,511 (44.5%)	32,717 (50.1%)	-0.1123	1,998 (44.7%)	58,202 (51.1%)	-0.128
CRX - Beta blockers ; n (%)	342 (31.8%)	17,833 (36.7%)	-0.1034	957 (28.2%)	23,987 (36.8%)	-0.1844	1,299 (29.0%)	41,820 (36.7%)	-0.164
CRX - CCB and other antihypertensives; n (%)	336 (31.2%)	14,658 (30.2%)	0.0217	1,148 (33.8%)	19,244 (29.5%)	0.0926	1,484 (33.2%)	33,902 (29.8%)	0.073
CRX - Digoxin ; n (%)*	52 (4.8%)	1,689 (3.5%)	0.0652	307 (9.0%)	3,742 (5.7%)	0.1267	359 (8.0%)	5,431 (4.8%)	0.131
CRX - Nitrates; n (%)*	100 (9.3%)	4,486 (9.2%)	0.0035	431 (12.7%)	7,249 (11.1%)	0.0494	531 (11.9%)	11,735 (10.3%)	0.051
OCM - Type 1 or 2 DM; n (%)	290 (26.9%)	13,869 (28.5%)	-0.0358	681 (20.0%)	15,497 (23.7%)	-0.0896	971 (21.7%)	29,366 (25.8%)	-0.096
OCM - Occurrence of Diabetic retinopathy/nephropathy/neuropathy; n (%)*	91 (8.4%)	5,084 (10.5%)	-0.0718	127 (3.7%)	3,524 (5.4%)	-0.0816	218 (4.9%)	8,608 (7.6%)	-0.112
OCM - Hypertensive nephropathy; n (%)*	82 (7.6%)	4,127 (8.5%)	-0.0331	100 (2.9%)	2,758 (4.2%)	-0.0703	182 (4.1%)	6,885 (6.0%)	-0.087
OCM - Hypotension ; n (%)*	42 (3.9%)	2,601 (5.4%)	-0.0713	77 (2.3%)	2,518 (3.9%)	-0.0924	119 (2.7%)	5,119 (4.5%)	-0.097
OCM - Hyperkalemia ; n (%)*	29 (2.7%)	1,448 (3.0%)	-0.0180	59 (1.7%)	1,128 (1.7%)	0.0000	088 (2.0%)	2,576 (2.3%)	-0.021
OCM - CKD II, III, or IV; n (%)	94 (8.7%)	5,205 (10.7%)	-0.0676	80 (2.4%)	3,244 (5.0%)	-0.1381	174 (3.9%)	8,449 (7.4%)	-0.152
OCM - HD/PD/ESRD; n (%)*	16 (1.5%)	510 (1.0%)	0.0450	35 (1.0%)	849 (1.3%)	-0.0281	051 (1.1%)	1,359 (1.2%)	-0.009
OCM - Osteoporosis; n (%)	135 (12.5%)	6,026 (12.4%)	0.0030	473 (13.9%)	6,609 (10.1%)	0.1171	608 (13.6%)	12,635 (11.1%)	0.076
OCM - Sleep apnea ; n (%)	139 (12.9%)	7,636 (15.7%)	-0.0800	236 (6.9%)	8,922 (13.7%)	-0.2253	375 (8.4%)	16,558 (14.5%)	-0.192
OCM - Fractures ; n (%)	68 (6.3%)	3,465 (7.1%)	-0.0320	218 (6.4%)	4,379 (6.7%)	-0.0121	286 (6.4%)	7,844 (6.9%)	-0.020
OCM - Other Arthritis, Arthropathies and Musculoskeletal Pain ; n (%)	463 (43.0%)	22,638 (46.6%)	-0.0724	1,073 (31.6%)	25,228 (38.7%)	-0.1491	1,536 (34.3%)	47,866 (42.0%)	-0.159
OCM - Dorsopathies; n (%)	308 (28.6%)	16,451 (33.9%)	-0.1145	671 (19.8%)	16,991 (26.0%)	-0.1480	979 (21.9%)	33,442 (29.4%)	-0.172
OCM - Gout (acute/chronic) ; n (%)*	7 (0.6%)	562 (1.2%)	-0.0636	45 (1.3%)	799 (1.2%)	0.0090	052 (1.2%)	1,361 (1.2%)	0.000
OCM - Hyperthyroidism ; n (%)*	3 (0.3%)	420 (0.9%)	-0.0778	18 (0.5%)	417 (0.6%)	-0.0135	021 (0.5%)	837 (0.7%)	-0.026
OCM - Hypothyroidism ; n (%)*	99 (9.2%)	4,864 (10.0%)	-0.0272	217 (6.4%)	5,362 (8.2%)	-0.0692	316 (7.1%)	10,226 (9.0%)	-0.070
OCM - VTE; n (%)*	40 (3.7%)	1,870 (3.8%)	-0.0053	113 (3.3%)	2,558 (3.9%)	-0.0322	153 (3.4%)	4,428 (3.9%)	-0.027
OCM - GERD ; n (%)	203 (18.8%)	10,528 (21.7%)	-0.0722	244 (7.2%)	6,858 (10.5%)	-0.1164	447 (10.0%)	17,386 (15.3%)	-0.160
OCM - Cancer ; n (%)	150 (13.9%)	6,452 (13.3%)	0.0175	369 (10.9%)	7,334 (11.2%)	-0.0096	519 (11.6%)	13,786 (12.1%)	-0.015
OCM - Hypovolemia/volume depletion ; n (%)*	59 (5.5%)	2,625 (5.4%)	0.0044	106 (3.1%)	2,580 (4.0%)	-0.0487	165 (3.7%)	5,205 (4.6%)	-0.045
OCM - Anemia ; n (%)	190 (17.6%)	9,353 (19.3%)	-0.0438	387 (11.4%)	9,554 (14.6%)	-0.0953	577 (12.9%)	18,907 (16.6%)	-0.104
OCM - Dementia ; n (%)*	73 (6.8%)	3,560 (7.3%)	-0.0195	133 (3.9%)	3,059 (4.7%)	-0.0394	206 (4.6%)	6,619 (5.8%)	-0.054
OCM - Depression ; n (%)	204 (18.9%)	10,201 (21.0%)	-0.0526	301 (8.9%)	8,006 (12.3%)	-0.1106	505 (11.3%)	18,207 (16.0%)	-0.137
ORX - Metformin; n (%)*	129 (12.0%)	5,947 (12.2%)	-0.0061	312 (9.2%)	6,884 (10.5%)	-0.0436	441 (9.9%)	12,831 (11.3%)	-0.045
ORX - 1st and 2nd Generation SUs ; n (%)	96 (8.9%)	3,353 (6.9%)	0.0742	298 (8.8%)	4,753 (7.3%)	0.0552	394 (8.8%)	8,106 (7.1%)	0.063
ORX - Insulins ; n (%)	92 (8.5%)	3,588 (7.4%)	0.0407	198 (5.8%)	4,670 (7.2%)	-0.0568	290 (6.5%)	8,258 (7.3%)	-0.032
ORX - Other antidiabetic medications use; n (%)	49 (4.5%)	2,328 (4.8%)	-0.0142	169 (5.0%)	3,897 (6.0%)	-0.0439	218 (4.9%)	6,225 (5.5%)	-0.027
ORX - PPIs or H2RAs use; n (%)*	299 (27.8%)	15,836 (32.6%)	-0.1047	1,088 (32.0%)	18,374 (28.2%)	0.0829	1,387 (31.0%)	34,210 (30.0%)	0.022
ORX - NSAIDs ; n (%)*	151 (14.0%)	7,708 (15.9%)	-0.0533	640 (18.8%)	10,402 (15.9%)	0.0766	791 (17.7%)	18,110 (15.9%)	0.048
ORX - Use of opioids ; n (%)*	418 (38.8%)	20,336 (41.9%)	-0.0632	1,337 (39.4%)	28,226 (43.2%)	-0.0772	1,755 (39.2%)	48,562 (42.7%)	-0.071
ORX - Use of antipsychotics ; n (%)*	70 (6.5%)	2,908 (6.0%)	0.0207	139 (4.1%)	3,128 (4.8%)	-0.0340	209 (4.7%)	6,036 (5.3%)	-0.028
ORX - Use of antidepressants ; n (%)	409 (38.0%)	19,790 (40.7%)	-0.0553	1,183 (34.8%)	24,738 (37.9%)	-0.0645	1,592 (35.6%)	44,528 (39.1%)	-0.072
ORX - Use of anxiolytics/hypnotics ; n (%)	116 (10.8%)	5,649 (11.6%)	-0.0254	388 (11.4%)	8,447 (12.9%)	-0.0459	504 (11.3%)	14,096 (12.4%)	-0.034
ORX - Use of anticonvulsants ; n (%)*	207 (19.2%)	10,715 (22.1%)	-0.0717	474 (14.0%)	10,973 (16.8%)	-0.0776	681 (15.2%)	21,688 (19.1%)	-0.104
ORX - Use of Benzodiazepines ; n (%)*	215 (20.0%)	9,605 (19.8%)	0.0050	875 (25.8%)	16,742 (25.7%)	0.0023	1,090 (24.4%)	26,347 (23.1%)	0.031
ORX - Use of dementia meds ; n (%)*	37 (3.4%)	1,668 (3.4%)	0.0000	100 (2.9%)	2,021 (3.1%)	-0.0117	137 (3.1%)	3,689 (3.2%)	-0.006
ORX - Use of antiparkinsonian meds ; n (%)*	47 (4.4%)	2,335 (4.8%)	-0.0191	108 (3.2%)	2,814 (4.3%)	-0.0579	155 (3.5%)	5,149 (4.5%)	-0.051
ORX - Use of oral anticoagulants ; n (%)*	122 (11.3%)	5,383 (11.1%)	0.0063	423 (12.5%)	8,094 (12.4%)	0.0030	545 (12.2%)	13,477 (11.8%)	0.012
ORX - Use of antiplatelet agents ; n (%)*	123 (11.4%)	6,436 (13.2%)	-0.0548	515 (15.2%)	11,431 (17.5%)	-0.0622	638 (14.3%)	17,867 (15.7%)	-0.039
LFS - Obesity; n (%)	96 (8.9%)	5,778 (11.9%)	-0.0984	130 (3.8%)	4,329 (6.6%)	-0.1264	226 (5.1%)	10,107 (8.9%)	-0.149
LFS - Alcohol/Drug Abuse or Dependence ; n (%)	71 (6.6%)	3,750 (7.7%)	-0.0427	66 (1.9%)	2,540 (3.9%)	-0.1194	137 (3.1%)	6,290 (5.5%)	-0.119
PFT - Spirometry test only; n (%)	213 (19.8%)	12,956 (26.7%)	-0.1639	676 (19.9%)	20,587 (31.5%)	-0.2678	889 (19.9%)	33,543 (29.5%)	-0.224
PFT - Spirometry test only (Count - 180 days to 31 days before CED) *									
...mean (sd)	0.24 (0.71)	0.34 (0.92)	-0.1217	0.22 (0.67)	0.35 (0.87)	-0.1674	0.22 (0.68)	0.35 (0.89)	-0.164
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.68)	0.00 (0.89)	0.000
PFT - Spirometry test only (Count - 30 days to CED) *									
...mean (sd)	0.15 (0.63)	0.21 (0.70)	-0.0901	0.11 (0.44)	0.23 (0.66)	-0.2139	0.12 (0.49)	0.22 (0.68)	-0.169
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.49)	0.00 (0.68)	0.000
PFT - Lung volume, Diffuse capacity, pulmonary stress testing (any); n (%)	151 (14.0%)	9,997 (20.6%)	-0.1752	249 (7.3%)	10,616 (16.3%)	-0.2817	400 (8.9%)	20,613 (18.1%)	-0.272
HCU - Pulmonologist visit (180 to 1 day before CED); n (%)	30 (2.8%)	1,080 (2.2%)	0.0384	787 (23.2%)	20,540 (31.5%)	-0.1870	817 (18.3%)	21,620 (19.0%)	-0.018
HCU - Pulmonologist visit on CED; n (%)	2 (0.2%)	150 (0.3%)	-0.0200	84 (2.5%)	3,729 (5.7%)	-0.1619	086 (1.9%)	3,879 (3.4%)	-0.093
HCU - Pulmonologist visit (Number of during CAP) *									
...mean (sd)	0.25 (2.12)	0.17 (1.85)	0.0402	0.90 (2.40)	1.43 (3.17)	-0.1885	0.74 (2.34)	0.89 (2.69)	-0.059
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.0000	0.00 (2.34)	0.00 (2.69)	0.000
HCU - Number of Internal Medicine/Family Medicine Visits									
...mean (sd)	9.76 (13.79)	12.05 (16.93)	-0.1483	7.86 (13.60)	9.00 (13.56)	-0.0839	8.32 (13.65)	10.30 (15.09)	-0.138
...median [IQR]	5.00 [1.00, 12.00]	7.00 [3.00, 15.00]	-0.1295	4.00 [0.00, 9.00]	5.00 [2.00, 11.00]	-0.0736	4.24 (13.65)	5.85 (15.09)	-0.112
HCU - Number of Cardiologist visits									
...mean (sd)	2.40 (6.18)	2.46 (5.82)	-0.0100	1.27 (3.79)	1.74 (4.57)	-0.1120	1.54 (4.48)	2.05 (5.14)	-0.106
...median [IQR]	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.0000	0.00 (4.48)	0.00 (5.14)	0.000
HCU - Number of Emergency Department (ED) visits v3									
...mean (sd)	0.87 (1.95)	0.99 (2.07)	-0.0597	0.69 (3.14)	0.60 (2.44)	0.0320	0.73 (2.90)	0.77 (2.29)	-0.015
...median [IQR]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (2.90)	0.00 (2.29)	0.000

Appendix B

HCU - Old hospitalization (-180 days to -31 days before CED) ; n (%)	251 (23.3%)	11,887 (24.5%)	-0.0281	1,027 (30.2%)	20,572 (31.5%)	-0.0281	1,278 (28.6%)	32,459 (28.5%)	0.002
HCU - Recent hospitalization (-30 days to CED date) ; n (%)	28 (2.6%)	2,193 (4.5%)	-0.1028	152 (4.5%)	3,447 (5.3%)	-0.0371	180 (4.0%)	5,640 (5.0%)	-0.048
HCU - Number of hospitalizations during CAP									
...mean (sd)	0.35 (0.79)	0.38 (0.78)	-0.0382	0.42 (0.73)	0.44 (0.73)	-0.0274	0.40 (0.74)	0.41 (0.75)	-0.013
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.0000	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.0000	0.00 (0.74)	0.00 (0.75)	0.000
HCU - Blood eosinophilia or Serum IgE test order; n (%)*	10 (0.9%)	418 (0.9%)	0.0000	21 (0.6%)	461 (0.7%)	-0.0124	031 (0.7%)	879 (0.8%)	-0.012
HCU - Pneumococcal vaccine; n (%)	133 (12.3%)	7,651 (15.7%)	-0.0981	118 (3.5%)	4,286 (6.6%)	-0.1419	251 (5.6%)	11,937 (10.5%)	-0.181
HCU - Flu vaccine ; n (%)	192 (17.8%)	10,097 (20.8%)	-0.0761	368 (10.8%)	8,600 (13.2%)	-0.0739	560 (12.5%)	18,697 (16.4%)	-0.111
HCU - Bone mineral density ; n (%)	31 (2.9%)	2,136 (4.4%)	-0.0801	59 (1.7%)	1,728 (2.6%)	-0.0621	090 (2.0%)	3,864 (3.4%)	-0.086
HCU - Pap smear ; n (%)	40 (3.7%)	1,243 (2.6%)	0.0630	113 (3.3%)	2,079 (3.2%)	0.0056	153 (3.4%)	3,322 (2.9%)	0.029
HCU - Mammogram ; n (%)	120 (11.1%)	4,993 (10.3%)	0.0259	350 (10.3%)	5,340 (8.2%)	0.0725	470 (10.5%)	10,333 (9.1%)	0.047
HCU - Prostate exam for DRE ; n (%)	35 (3.2%)	1,790 (3.7%)	-0.0274	28 (0.8%)	1,170 (1.8%)	-0.0884	063 (1.4%)	2,960 (2.6%)	-0.086
HCU - Number of Echocardiogram *									
...mean (sd)	0.64 (3.49)	0.61 (2.97)	0.0093	0.43 (1.23)	0.47 (1.13)	-0.0339	0.48 (2.02)	0.53 (2.12)	-0.024
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (2.02)	0.00 (2.12)	0.000
HCU - Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy ; n (%)	60 (5.6%)	2,516 (5.2%)	0.0177	201 (5.9%)	4,071 (6.2%)	-0.0126	261 (5.8%)	6,587 (5.8%)	0.000
HCU - Number of Distinct Medication Prescriptions (not generalized to generics)									
...mean (sd)	29.01 (22.72)	28.46 (20.95)	0.0252	26.91 (17.53)	25.81 (17.21)	0.0633	27.42 (18.91)	26.94 (18.90)	0.025
...median [IQR]	23.00 [14.00, 37.00]	24.00 [14.00, 37.00]	-0.0458	23.00 [15.00, 34.50]	22.00 [14.00, 34.00]	0.0576	23.00 (18.91)	22.85 (18.90)	0.008
SES - Copay for pharmacy cost (charges in U.S. $)									
...mean (sd)	33.09 (30.71)	29.56 (35.50)	0.1064	26.74 (27.26)	24.27 (23.93)	0.0963	28.27 (28.13)	26.53 (29.43)	0.060
...median [IQR]	27.02 [12.96, 42.81]	21.96 [7.85, 38.52]	0.1524	21.25 [9.33, 35.86]	19.90 [9.93, 32.60]	0.0526	22.64 (28.13)	20.78 (29.43)	0.065
SES - Business type									
...Commercial; n (%)	394 (36.6%)	11,001 (22.6%)	0.3104				394 (36.6%)	11,001 (22.6%)	0.310
...Medicare; n (%)	683 (63.4%)	37,580 (77.4%)	-0.3104				683 (63.4%)	37,580 (77.4%)	-0.310
SES - Low income indicator ; n (%)	184 (17.1%)	12,414 (25.6%)	-0.2086				184 (17.1%)	12,414 (25.6%)	-0.209
SES - Insurance Plan type									
...Comprehensive; n (%)				1,232 (36.3%)	21,355 (32.7%)	0.0758	1,232 (36.3%)	21,355 (32.7%)	0.076
...HMO; n (%)				959 (28.2%)	7,748 (11.9%)	0.4158	959 (28.2%)	7,748 (11.9%)	0.416
...PPO; n (%)				961 (28.3%)	28,886 (44.3%)	-0.3374	961 (28.3%)	28,886 (44.3%)	-0.337
...Others; n (%)				245 (7.2%)	7,275 (11.1%)	-0.1356	245 (7.2%)	7,275 (11.1%)	-0.136

* Not included in PS model

Appendix B

MATCHED

	OPTUM			MARKETSCAN			POOLED		
	Referent - Salmeterol	Exposure - Tiotropium		Referent - Salmeterol	Exposure - Tiotropium		Referent - Salmeterol	Exposure - Tiotropium	
Number of patients	1,073	1,073		3,285	3,285		4,358	4,358	
Calendar Time - Year of Initiation (2004 - 2020)									
...2004-2006; n (%)	298 (27.8%)	303 (28.2%)	-0.0089	1,849 (56.3%)	1,872 (57.0%)	-0.0141	2,147 (49.3%)	2,175 (49.9%)	-0.012
...2007-2008; n (%)	103 (9.6%)	87 (8.1%)	0.0528	403 (12.3%)	376 (11.4%)	0.0278	506 (11.6%)	463 (10.6%)	0.032
...2009-2011; n (%)	171 (15.9%)	185 (17.2%)	-0.0350	543 (16.5%)	537 (16.3%)	0.0054	714 (16.4%)	722 (16.6%)	-0.005
...2012-2015; n (%)	157 (14.6%)	152 (14.2%)	0.0114	315 (9.6%)	348 (10.6%)	-0.0332	472 (10.8%)	500 (11.5%)	-0.022
...2016-2018; n (%)	250 (23.3%)	254 (23.7%)	-0.0094	175 (5.3%)	152 (4.6%)	0.0323	425 (9.8%)	406 (9.3%)	0.017
...2019-Mar. 2020; n (%)	94 (8.8%)	92 (8.6%)	0.0071				94 (8.8%)	92 (8.6%)	0.007
DMG - Age									
...mean (sd)	69.32 (10.77)	69.31 (10.55)	0.0009	70.76 (10.81)	70.58 (10.61)	0.0168	70.41 (10.80)	70.27 (10.60)	0.013
...median [IQR]	70.00 [62.00, 77.00]	70.00 [62.00, 78.00]	0.0000	72.00 [63.00, 79.00]	71.00 [63.00, 79.00]	0.0934	71.51 (10.80)	70.75 (10.60)	0.071
DMG - Gender									
...Male; n (%)	509 (47.4%)	496 (46.2%)	0.0241	1,517 (46.2%)	1,528 (46.5%)	-0.0060	2,026 (46.5%)	2,024 (46.4%)	0.002
...Female; n (%)	564 (52.6%)	577 (53.8%)	-0.0241	1,768 (53.8%)	1,757 (53.5%)	0.0060	2,332 (53.5%)	2,334 (53.6%)	-0.002
DMG - Geographic region									
...Northeast; n (%)	100 (9.3%)	99 (9.2%)	0.0035	348 (10.6%)	331 (10.1%)	0.0164	448 (10.3%)	430 (9.9%)	0.013
...South; n (%)	384 (35.8%)	379 (35.3%)	0.0104	845 (25.7%)	859 (26.1%)	-0.0091	1,229 (28.2%)	1,238 (28.4%)	-0.004
...North Central; n (%)	276 (25.7%)	265 (24.7%)	0.0230	1,107 (33.7%)	1,095 (33.3%)	0.0085	1,383 (31.7%)	1,360 (31.2%)	0.011
...West; n (%)	313 (29.2%)	330 (30.8%)	-0.0349	985 (30.0%)	1,000 (30.4%)	-0.0087	1,298 (29.8%)	1,330 (30.5%)	-0.015
DRS - Combined comorbidity score, 180 days									
...mean (sd)	2.37 (2.54)	2.30 (2.47)	0.0279	1.75 (1.88)	1.74 (1.84)	0.0054	1.90 (2.06)	1.88 (2.01)	0.010
...median [IQR]	2.00 [1.00, 3.00]	1.00 [1.00, 3.00]	0.3992	1.00 [1.00, 3.00]	1.00 [1.00, 2.00]	0.0000	1.25 (2.06)	1.00 (2.01)	0.123
DRS - Frailty Score: Empirical Version (mean)									
...mean (sd)	0.21 (0.07)	0.21 (0.07)	0.0000	0.19 (0.06)	0.19 (0.06)	0.0000	0.19 (0.06)	0.19 (0.06)	0.000
...median [IQR]	0.19 [0.16, 0.24]	0.19 [0.16, 0.24]	0.0000	0.18 [0.14, 0.22]	0.18 [0.14, 0.22]	0.0000	0.18 (0.06)	0.18 (0.06)	0.000
PLM - Smoking ; n (%)	302 (28.1%)	287 (26.7%)	0.0314	319 (9.7%)	329 (10.0%)	-0.0101	621 (14.2%)	616 (14.1%)	0.003
PLM - Pneumonia ; n (%)	120 (11.2%)	123 (11.5%)	-0.0095	350 (10.7%)	372 (11.3%)	-0.0192	470 (10.8%)	495 (11.4%)	-0.019
PLM - Alpha-1 antitrypsin def/Pneumoconioses & other lung disease/Pul fibrosis; n (%)	78 (7.3%)	93 (8.7%)	-0.0516	152 (4.6%)	144 (4.4%)	0.0096	230 (5.3%)	237 (5.4%)	-0.004
PLM - Oxygen usage; n (%)	155 (14.4%)	161 (15.0%)	-0.0169	575 (17.5%)	623 (19.0%)	-0.0388	730 (16.8%)	784 (18.0%)	-0.032
PLM - Respiratory arrest/dependence on oxygen ; n (%)	129 (12.0%)	123 (11.5%)	0.0155	223 (6.8%)	228 (6.9%)	-0.0040	352 (8.1%)	351 (8.1%)	0.000
PLM - CPAP/BiPAP use; n (%)	63 (5.9%)	57 (5.3%)	0.0261	129 (3.9%)	144 (4.4%)	-0.0251	192 (4.4%)	201 (4.6%)	-0.010
PLM - Pulmonary rehabilitation ; n (%)*	7 (0.7%)	2 (0.2%)	0.0748	8 (0.2%)	13 (0.4%)	-0.0366	015 (0.3%)	015 (0.3%)	0.000
PLM - Moderate COPD exacerbation - [Count with 365 to 181 days before CED]*									
...mean (sd)	1.67 (4.35)	2.13 (9.04)	-0.0648	1.55 (3.69)	1.48 (3.49)	0.0195	1.58 (3.86)	1.64 (5.41)	-0.013
...median [IQR]	0.00 [0.00, 1.11]	0.06 [0.00, 1.57]	-0.0085	0.10 [0.00, 1.28]	0.05 [0.00, 1.22]	0.0139	0.08 (3.86)	0.05 (5.41)	0.006
PLM - Moderate COPD exacerbation - [Count 180 to 31 days before CED]*									
...mean (sd)	1.73 (3.97)	1.77 (6.49)	-0.0074	1.29 (2.41)	1.31 (2.33)	-0.0084	1.40 (2.87)	1.42 (3.80)	-0.006
...median [IQR]	0.64 [0.01, 1.83]	0.62 [0.02, 1.60]	0.0037	0.54 [0.00, 1.36]	0.54 [0.00, 1.52]	0.0000	0.56 (2.87)	0.56 (3.80)	0.000
PLM - Moderate COPD exacerbation - [Count with 30 days to CED]*									
...mean (sd)	0.29 (1.12)	0.29 (1.32)	0.0000	0.16 (0.54)	0.18 (0.55)	-0.0367	0.19 (0.73)	0.21 (0.81)	-0.026
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.73)	0.00 (0.81)	0.000
PLM - Moderate exacerbations >=1 in 365 days before CED; n (%)	861 (80.2%)	872 (81.3%)	-0.0279	2,449 (74.6%)	2,496 (76.0%)	-0.0325	3,310 (76.0%)	3,368 (77.3%)	-0.031
PLM - Moderate exacerbations >=2 in 365 days before CED ; n (%)	574 (53.5%)	565 (52.7%)	0.0160	1,570 (47.8%)	1,617 (49.2%)	-0.0280	2,144 (49.2%)	2,182 (50.1%)	-0.018
PLM - Severe COPD exacerbation - [Count with 365 to 181 days before CED] *									
...mean (sd)	0.04 (0.20)	0.05 (0.25)	-0.0442	0.06 (0.25)	0.07 (0.27)	-0.0384	0.06 (0.24)	0.07 (0.27)	-0.039
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.24)	0.00 (0.27)	0.000
PLM - Severe COPD exacerbation - [Count with 180 to 31 days before CED] *									
...mean (sd)	0.06 (0.26)	0.04 (0.18)	0.0894	0.06 (0.22)	0.06 (0.23)	0.0000	0.06 (0.23)	0.06 (0.22)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.23)	0.00 (0.22)	0.000
PLM - Severe COPD exacerbation - [Count with 30 days lookback] *									
...mean (sd)	0.01 (0.09)	0.01 (0.09)	0.0000	0.01 (0.06)	0.01 (0.09)	0.0000	0.01 (0.07)	0.01 (0.09)	0.000
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.07)	0.00 (0.09)	0.000
PLM - Severe exacerbations >=1 in 365 days before CED; n (%)	106 (9.9%)	106 (9.9%)	0.0000	419 (12.8%)	431 (13.1%)	-0.0089	525 (12.0%)	537 (12.3%)	-0.009
PLM - Severe exacerbations >=2 in 365 days before CED ; n (%)	15 (1.4%)	14 (1.3%)	0.0087	63 (1.9%)	75 (2.3%)	-0.0279	078 (1.8%)	089 (2.0%)	-0.015
PLM - GOLD C/D Status ; n (%)	435 (40.5%)	424 (39.5%)	0.0204	1,569 (47.8%)	1,636 (49.8%)	-0.0400	2,004 (46.0%)	2,060 (47.3%)	-0.026
PRX - LABA (except salmeterol) inhalers; n (%)	62 (5.8%)	61 (5.7%)	0.0043	194 (5.9%)	221 (6.7%)	-0.0329	256 (5.9%)	282 (6.5%)	-0.025
PRX - LAMA (except tiotropium) inhalers; n (%) *	14 (1.3%)	9 (0.8%)	0.0491	14 (0.4%)	2 (0.1%)	0.0601	028 (0.6%)	011 (0.3%)	0.045
PRX - ICS only inhalers; n (%)	415 (38.7%)	401 (37.4%)	0.0268	1,534 (46.7%)	1,558 (47.4%)	-0.0140	1,949 (44.7%)	1,959 (45.0%)	-0.006
PRX - LABA/LAMA inhaler use; n (%) *	17 (1.6%)	8 (0.7%)	0.0845	2 (0.1%)	3 (0.1%)	0.0000	019 (0.4%)	011 (0.3%)	0.017
PRX - LABA/ICS inhaler use; n (%)	45 (4.2%)	51 (4.8%)	-0.0289	107 (3.3%)	110 (3.3%)	0.0000	152 (3.5%)	161 (3.7%)	-0.011
PRX - COPD Maintenance therapy inhalers; n (%)	126 (11.7%)	127 (11.8%)	-0.0031	235 (7.2%)	265 (8.1%)	-0.0339	361 (8.3%)	392 (9.0%)	-0.025
PRX - SAMA inhaler use; n (%)	108 (10.1%)	115 (10.7%)	-0.0197	565 (17.2%)	610 (18.6%)	-0.0365	673 (15.4%)	725 (16.6%)	-0.033
PRX - SABA use; n (%)	521 (48.6%)	510 (47.5%)	0.0220	1,486 (45.2%)	1,530 (46.6%)	-0.0281	2,007 (46.1%)	2,040 (46.8%)	-0.014
PRX - SABA/SAMA use; n (%)	242 (22.6%)	241 (22.5%)	0.0024	817 (24.9%)	880 (26.8%)	-0.0434	1,059 (24.3%)	1,121 (25.7%)	-0.032
PRX - Antibiotics treatment (180 days to 31 days before CED); n (%)	509 (47.4%)	517 (48.2%)	-0.0160	1,646 (50.1%)	1,659 (50.5%)	-0.0080	2,155 (49.4%)	2,176 (49.9%)	-0.010
PRX - Antibiotics treatment (30 days to CED); n (%)	150 (14.0%)	157 (14.6%)	-0.0171	450 (13.7%)	454 (13.8%)	-0.0029	600 (13.8%)	611 (14.0%)	-0.006
PRX - Systemic Corticosteroids (with CPT) use (180 to 31 days before CED); n (%)	537 (50.0%)	540 (50.3%)	-0.0060	1,582 (48.2%)	1,592 (48.5%)	-0.0060	2,119 (48.6%)	2,132 (48.9%)	-0.006
PRX - Systemic Corticosteroids (with CPT) use (30 days to CED); n (%)	100 (9.3%)	91 (8.5%)	0.0281	365 (11.1%)	352 (10.7%)	0.0128	465 (10.7%)	443 (10.2%)	0.016
PRX - Roflumilast; n (%) *	7 (0.7%)	1 (0.1%)	0.0952	5 (0.2%)	6 (0.2%)	0.0000	012 (0.3%)	007 (0.2%)	0.020
CVD - Unstable angina/MI; n (%)	86 (8.0%)	78 (7.3%)	0.0263	216 (6.6%)	205 (6.2%)	0.0163	302 (6.9%)	283 (6.5%)	0.016
CVD - Stable Angina ; n (%)	46 (4.3%)	45 (4.2%)	0.0050	92 (2.8%)	71 (2.2%)	0.0384	138 (3.2%)	116 (2.7%)	0.030
CVD - Any Heart failure (HF) ; n (%)	182 (17.0%)	180 (16.8%)	0.0053	501 (15.3%)	489 (14.9%)	0.0112	683 (15.7%)	669 (15.4%)	0.008
CVD - Atrial fibrillation; n (%)	143 (13.3%)	140 (13.0%)	0.0089	381 (11.6%)	361 (11.0%)	0.0190	524 (12.0%)	501 (11.5%)	0.016
CVD - Other dysrythmias ; n (%)*	189 (17.6%)	155 (14.4%)	0.0879	344 (10.5%)	368 (11.2%)	-0.0225	533 (12.2%)	523 (12.0%)	0.006
CVD - Valve disorder ; n (%)	34 (3.2%)	30 (2.8%)	0.0235	71 (2.2%)	76 (2.3%)	-0.0067	105 (2.4%)	106 (2.4%)	0.000
CVD - Implantable cardioverter defibrillator ; n (%)*	14 (1.3%)	22 (2.1%)	-0.0619	32 (1.0%)	36 (1.1%)	-0.0098	046 (1.1%)	058 (1.3%)	-0.018
CVD - CABG/PCI; n (%)	74 (6.9%)	59 (5.5%)	0.0581	136 (4.1%)	127 (3.9%)	0.0102	210 (4.8%)	186 (4.3%)	0.024
CVD - Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	268 (25.0%)	247 (23.0%)	0.0468	693 (21.1%)	657 (20.0%)	0.0272	961 (22.1%)	904 (20.7%)	0.034
CVD - Stroke/TIA ; n (%)	60 (5.6%)	66 (6.2%)	-0.0255	163 (5.0%)	159 (4.8%)	0.0093	223 (5.1%)	225 (5.2%)	-0.005
CVD - Peripheral Vascular Disease (PVD) or PVD Surgery; n (%)	112 (10.4%)	105 (9.8%)	0.0199	209 (6.4%)	218 (6.6%)	-0.0081	321 (7.4%)	323 (7.4%)	0.000
CVD - Hyperlipidemia ; n (%)	514 (47.9%)	511 (47.6%)	0.0060	690 (21.0%)	681 (20.7%)	0.0074	1,204 (27.6%)	1,192 (27.4%)	0.004
CVD - Hypertension; n (%)	692 (64.5%)	704 (65.6%)	-0.0231	1,347 (41.0%)	1,335 (40.6%)	0.0081	2,039 (46.8%)	2,039 (46.8%)	0.000
CRX - ACEI or ARB; n (%)	456 (42.5%)	471 (43.9%)	-0.0283	1,404 (42.7%)	1,370 (41.7%)	0.0202	1,860 (42.7%)	1,841 (42.2%)	0.010
CRX - Mineralocorticoid receptor antagonist ; n (%)	43 (4.0%)	39 (3.6%)	0.0209	156 (4.7%)	153 (4.7%)	0.0000	199 (4.6%)	192 (4.4%)	0.010
CRX - Loop or Thiazide diuretics; n (%)	373 (34.8%)	389 (36.3%)	-0.0313	1,326 (40.4%)	1,310 (39.9%)	0.0102	1,699 (39.0%)	1,699 (39.0%)	0.000
CRX - Statins and other lipid lowering agents; n (%)	486 (45.3%)	473 (44.1%)	0.0241	1,462 (44.5%)	1,412 (43.0%)	0.0302	1,948 (44.7%)	1,885 (43.3%)	0.028
CRX - Beta blockers ; n (%)	341 (31.8%)	324 (30.2%)	0.0346	937 (28.5%)	909 (27.7%)	0.0178	1,278 (29.3%)	1,233 (28.3%)	0.022
CRX - CCB and other antihypertensives; n (%)	334 (31.1%)	338 (31.5%)	-0.0086	1,107 (33.7%)	1,123 (34.2%)	-0.0106	1,441 (33.1%)	1,461 (33.5%)	-0.008
CRX - Digoxin ; n (%)*	52 (4.8%)	51 (4.8%)	0.0000	297 (9.0%)	283 (8.6%)	0.0141	349 (8.0%)	334 (7.7%)	0.011
CRX - Nitrates; n (%)*	100 (9.3%)	90 (8.4%)	0.0317	421 (12.8%)	386 (11.8%)	0.0305	521 (12.0%)	476 (10.9%)	0.035
OCM - Type 1 or 2 DM; n (%)	288 (26.8%)	277 (25.8%)	0.0227	660 (20.1%)	665 (20.2%)	-0.0025	948 (21.8%)	942 (21.6%)	0.005
OCM - Occurrence of Diabetic retinopathy/nephropathy/neuropathy; n (%)*	91 (8.5%)	104 (9.7%)	-0.0417	123 (3.7%)	115 (3.5%)	0.0107	214 (4.9%)	219 (5.0%)	-0.005
OCM - Hypertensive nephropathy; n (%)*	81 (7.5%)	79 (7.4%)	0.0038	100 (3.0%)	86 (2.6%)	0.0242	181 (4.2%)	165 (3.8%)	0.020
OCM - Hypotension ; n (%)*	42 (3.9%)	39 (3.6%)	0.0158	75 (2.3%)	88 (2.7%)	-0.0256	117 (2.7%)	127 (2.9%)	-0.012
OCM - Hyperkalemia ; n (%)*	29 (2.7%)	32 (3.0%)	-0.0180	56 (1.7%)	27 (0.8%)	0.0811	085 (2.0%)	059 (1.4%)	0.046
OCM - CKD II, III, or IV; n (%)	93 (8.7%)	99 (9.2%)	-0.0175	80 (2.4%)	92 (2.8%)	-0.0251	173 (4.0%)	191 (4.4%)	-0.020
OCM - HD/PD/ESRD; n (%)*	16 (1.5%)	7 (0.7%)	0.0768	35 (1.1%)	22 (0.7%)	0.0424	051 (1.2%)	029 (0.7%)	0.052
OCM - Osteoporosis; n (%)	134 (12.5%)	142 (13.2%)	-0.0209	457 (13.9%)	458 (13.9%)	0.0000	591 (13.6%)	600 (13.8%)	-0.006
OCM - Sleep apnea ; n (%)	139 (13.0%)	132 (12.3%)	0.0211	232 (7.1%)	258 (7.9%)	-0.0304	371 (8.5%)	390 (8.9%)	-0.014
OCM - Fractures ; n (%)	68 (6.3%)	67 (6.2%)	0.0041	212 (6.5%)	195 (5.9%)	0.0249	280 (6.4%)	262 (6.0%)	0.017
OCM - Other Arthritis, Arthropathies and Musculoskeletal Pain ; n (%)	461 (43.0%)	449 (41.8%)	0.0243	1,056 (32.1%)	1,004 (30.6%)	0.0323	1,517 (34.8%)	1,453 (33.3%)	0.032
OCM - Dorsopathies; n (%)	308 (28.7%)	300 (28.0%)	0.0155	662 (20.2%)	639 (19.5%)	0.0176	970 (22.3%)	939 (21.5%)	0.019
OCM - Gout (acute/chronic) ; n (%)*	7 (0.7%)	13 (1.2%)	-0.0516	45 (1.4%)	32 (1.0%)	0.0367	052 (1.2%)	045 (1.0%)	0.019
OCM - Hyperthyroidism ; n (%)*	3 (0.3%)	14 (1.3%)	-0.1124	18 (0.5%)	17 (0.5%)	0.0000	021 (0.5%)	031 (0.7%)	-0.026
OCM - Hypothyroidism ; n (%)*	98 (9.1%)	104 (9.7%)	-0.0206	208 (6.3%)	205 (6.2%)	0.0041	306 (7.0%)	309 (7.1%)	-0.004
OCM - VTE ; n (%)*	39 (3.6%)	46 (4.3%)	-0.0359	111 (3.4%)	99 (3.0%)	0.0227	150 (3.4%)	145 (3.3%)	0.006
OCM - GERD ; n (%)	202 (18.8%)	186 (17.3%)	0.0390	233 (7.1%)	255 (7.8%)	-0.0267	435 (10.0%)	441 (10.1%)	-0.003
OCM - Cancer ; n (%)	150 (14.0%)	166 (15.5%)	-0.0423	359 (10.9%)	349 (10.6%)	0.0097	509 (11.7%)	515 (11.8%)	-0.003
OCM - Hypovolemia/volume depletion ; n (%)*	59 (5.5%)	54 (5.0%)	0.0224	105 (3.2%)	115 (3.5%)	-0.0167	164 (3.8%)	169 (3.9%)	-0.005
OCM - Anemia ; n (%)	190 (17.7%)	161 (15.0%)	0.0731	376 (11.4%)	356 (10.8%)	0.0191	566 (13.0%)	517 (11.9%)	0.033
OCM - Dementia ; n (%)*	73 (6.8%)	93 (8.7%)	-0.0711	128 (3.9%)	148 (4.5%)	-0.0299	201 (4.6%)	241 (5.5%)	-0.041
OCM - Depression ; n (%)	204 (19.0%)	182 (17.0%)	0.0521	291 (8.9%)	280 (8.5%)	0.0142	495 (11.4%)	462 (10.6%)	0.026
ORX - Metformin; n (%)*	129 (12.0%)	117 (10.9%)	0.0346	300 (9.1%)	304 (9.3%)	-0.0069	429 (9.8%)	421 (9.7%)	0.003
ORX - 1st and 2nd Generation SUs ; n (%)	96 (8.9%)	88 (8.2%)	0.0250	284 (8.6%)	279 (8.5%)	0.0036	380 (8.7%)	367 (8.4%)	0.011
ORX - Insulins ; n (%)	92 (8.6%)	102 (9.5%)	-0.0314	190 (5.8%)	199 (6.1%)	-0.0127	282 (6.5%)	301 (6.9%)	-0.016
ORX - Other antidiabetic medications use; n (%)	49 (4.6%)	63 (5.9%)	-0.0583	164 (5.0%)	169 (5.1%)	-0.0046	213 (4.9%)	232 (5.3%)	-0.018
ORX - PPIs or H2RAs use; n (%)*	299 (27.9%)	286 (26.7%)	0.0269	1,054 (32.1%)	976 (29.7%)	0.0520	1,353 (31.0%)	1,262 (29.0%)	0.044
ORX - NSAIDs ; n (%)*	150 (14.0%)	172 (16.0%)	-0.0560	619 (18.8%)	557 (17.0%)	0.0470	769 (17.6%)	729 (16.7%)	0.024
ORX - Use of opioids ; n (%)*	418 (39.0%)	408 (38.0%)	0.0206	1,302 (39.6%)	1,273 (38.8%)	0.0164	1,720 (39.5%)	1,681 (38.6%)	0.018
ORX - Use of antipsychotics ; n (%)*	69 (6.4%)	60 (5.6%)	0.0337	137 (4.2%)	143 (4.4%)	-0.0099	206 (4.7%)	203 (4.7%)	0.000
ORX - Use of antidepressants ; n (%)	408 (38.0%)	393 (36.6%)	0.0290	1,150 (35.0%)	1,152 (35.1%)	-0.0021	1,558 (35.8%)	1,545 (35.5%)	0.006
ORX - Use of anxiolytics/hypnotics; n (%)	116 (10.8%)	106 (9.9%)	0.0295	383 (11.7%)	380 (11.6%)	0.0031	499 (11.5%)	486 (11.2%)	0.009
ORX - Use of anticonvulsants ; n (%)*	207 (19.3%)	215 (20.0%)	-0.0176	462 (14.1%)	422 (12.8%)	0.0381	669 (15.4%)	637 (14.6%)	0.022
ORX - Use of Benzodiazepines; n (%)*	214 (19.9%)	184 (17.1%)	0.0722	847 (25.8%)	863 (26.3%)	-0.0114	1,061 (24.3%)	1,047 (24.0%)	0.007
ORX - Use of dementia meds ; n (%)*	37 (3.4%)	45 (4.2%)	-0.0419	97 (3.0%)	125 (3.8%)	-0.0442	134 (3.1%)	170 (3.9%)	-0.044
ORX - Use of antiparkinsonian meds ; n (%)*	46 (4.3%)	43 (4.0%)	0.0150	104 (3.2%)	115 (3.5%)	-0.0167	150 (3.4%)	158 (3.6%)	-0.011
ORX - Use of oral anticoagulants ; n (%)*	121 (11.3%)	125 (11.6%)	-0.0094	416 (12.7%)	400 (12.2%)	0.0151	537 (12.3%)	525 (12.0%)	0.009
ORX - Use of antiplatelet agents ; n (%)*	123 (11.5%)	108 (10.1%)	0.0451	506 (15.4%)	482 (14.7%)	0.0196	629 (14.4%)	590 (13.5%)	0.026
LFS - Obesity; n (%)	95 (8.9%)	115 (10.7%)	-0.0606	126 (3.8%)	121 (3.7%)	0.0053	221 (5.1%)	236 (5.4%)	-0.013
LFS - Alcohol/Drug Abuse or Dependence ; n (%)	71 (6.6%)	62 (5.8%)	0.0332	64 (1.9%)	59 (1.8%)	0.0074	135 (3.1%)	121 (2.8%)	0.018
PFT - Spirometry test only; n (%)	213 (19.9%)	220 (20.5%)	-0.0149	672 (20.5%)	683 (20.8%)	-0.0074	885 (20.3%)	903 (20.7%)	-0.010
PFT - Spirometry test only (Count - 180 days to 31 days before CED) *									
...mean (sd)	0.24 (0.71)	0.28 (0.85)	-0.0511	0.23 (0.68)	0.20 (0.65)	0.0451	0.23 (0.69)	0.22 (0.70)	0.014
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.69)	0.00 (0.70)	0.000
PFT - Spirometry test only (Count - 30 days to CED) *									
...mean (sd)	0.15 (0.63)	0.13 (0.53)	0.0344	0.11 (0.45)	0.13 (0.47)	-0.0435	0.12 (0.50)	0.13 (0.49)	-0.020
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (0.50)	0.00 (0.49)	0.000
PFT - Lung volume, Diffuse capacity, pulmonary stress testing (any); n (%)	149 (13.9%)	155 (14.4%)	-0.0143	242 (7.4%)	260 (7.9%)	-0.0188	391 (9.0%)	415 (9.5%)	-0.017
HCU - Pulmonologist visit (180 to 1 day before CED); n (%)	30 (2.8%)	26 (2.4%)	0.0251	781 (23.8%)	794 (24.2%)	-0.0094	811 (18.6%)	820 (18.8%)	-0.005
HCU - Pulmonologist visit on CED; n (%)	2 (0.2%)	1 (0.1%)	0.0258	84 (2.6%)	87 (2.6%)	0.0000	086 (2.0%)	088 (2.0%)	0.000
HCU - Pulmonologist visit (Number of during CAP) *									
...mean (sd)	0.26 (2.12)	0.23 (2.09)	0.0143	0.92 (2.44)	0.95 (2.51)	-0.0121	0.76 (2.37)	0.77 (2.41)	-0.004
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.0000	0.00 (2.37)	0.00 (2.41)	0.000
HCU - Number of Internal Medicine/Family Medicine Visits									
...mean (sd)	9.78 (13.81)	10.82 (17.37)	-0.0663	7.74 (13.40)	7.87 (13.19)	-0.0098	8.24 (13.50)	8.60 (14.33)	-0.026
...median [IQR]	5.00 [1.00, 12.00]	6.00 [1.00, 13.00]	-0.0637	4.00 [0.00, 9.00]	4.00 [1.00, 9.00]	0.0000	4.25 (13.50)	4.49 (14.33)	-0.017
HCU - Number of Cardiologist visits									
...mean (sd)	2.39 (6.16)	2.06 (5.10)	0.0584	1.31 (3.84)	1.29 (4.06)	0.0051	1.58 (4.52)	1.48 (4.34)	0.023
...median [IQR]	0.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.0000	0.00 (4.52)	0.00 (4.34)	0.000
HCU - Number of Emergency Department (ED) visits v3									
...mean (sd)	0.87 (1.95)	0.82 (1.93)	0.0258	0.65 (2.71)	0.65 (3.32)	0.0000	0.70 (2.54)	0.69 (3.04)	0.004

Appendix B

...median [IQR]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (2.54)	0.00 (3.04)	0.000
HCU - Old hospitalization (-180 days to -31 days before CED) ; n (%)	251 (23.4%)	224 (20.9%)	0.0602	999 (30.4%)	969 (29.5%)	0.0196	1,250 (28.7%)	1,193 (27.4%)	0.029
HCU - Recent hospitalization (-30 days to CED date) ; n (%)	28 (2.6%)	23 (2.1%)	0.0330	147 (4.5%)	131 (4.0%)	0.0248	175 (4.0%)	154 (3.5%)	0.026
HCU - Number of hospitalizations during CAP									
...mean (sd)	0.35 (0.79)	0.32 (0.76)	0.0387	0.42 (0.72)	0.41 (0.72)	0.0139	0.40 (0.74)	0.39 (0.73)	0.014
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.0000	0.00 (0.74)	0.00 (0.73)	0.000
HCU - Blood eosinophilia or Serum IgE test order; n (%)*	10 (0.9%)	11 (1.0%)	-0.0103	20 (0.6%)	25 (0.8%)	-0.0240	030 (0.7%)	036 (0.8%)	-0.012
HCU - Pneumococcal vaccine; n (%)	133 (12.4%)	140 (13.0%)	-0.0180	115 (3.5%)	112 (3.4%)	0.0055	248 (5.7%)	252 (5.8%)	-0.004
HCU - Flu vaccine ; n (%)	192 (17.9%)	178 (16.6%)	0.0344	351 (10.7%)	334 (10.2%)	0.0163	543 (12.5%)	512 (11.7%)	0.025
HCU - Bone mineral density ; n (%)	31 (2.9%)	34 (3.2%)	-0.0174	58 (1.8%)	66 (2.0%)	-0.0146	089 (2.0%)	100 (2.3%)	-0.021
HCU - Pap smear ; n (%)	40 (3.7%)	49 (4.6%)	-0.0451	111 (3.4%)	124 (3.8%)	-0.0215	151 (3.5%)	173 (4.0%)	-0.026
HCU - Mammogram ; n (%)	120 (11.2%)	137 (12.8%)	-0.0493	334 (10.2%)	338 (10.3%)	-0.0033	454 (10.4%)	475 (10.9%)	-0.016
HCU - Prostate exam for DRE ; n (%)	35 (3.3%)	43 (4.0%)	-0.0373	27 (0.8%)	27 (0.8%)	0.0000	062 (1.4%)	070 (1.6%)	-0.016
HCU - Number of Echocardiogram .*									
...mean (sd)	0.64 (3.50)	0.46 (1.79)	0.0648	0.44 (1.24)	0.44 (1.13)	0.0000	0.49 (2.04)	0.44 (1.32)	0.029
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (2.04)	0.00 (1.32)	0.000
HCU - Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy ; n (%)	60 (5.6%)	62 (5.8%)	-0.0086	194 (5.9%)	190 (5.8%)	0.0043	254 (5.8%)	252 (5.8%)	0.000
HCU - Number of Distinct Medication Prescriptions (not generalized to generics)									
...mean (sd)	28.97 (22.63)	29.22 (22.55)	-0.0111	26.87 (17.54)	27.20 (17.32)	-0.0189	27.39 (18.92)	27.70 (18.74)	-0.016
...median [IQR]	23.00 [14.00, 37.00]	24.00 [14.00, 38.00]	-0.0443	23.00 [15.00, 35.00]	24.00 [15.00, 36.00]	-0.0574	23.00 (18.92)	24.00 (18.74)	-0.053
SES - Copay for pharmacy cost (charges in U.S. $)									
...mean (sd)	33.13 (30.75)	34.27 (37.75)	-0.0331	26.28 (26.21)	26.79 (30.17)	-0.0180	27.97 (27.40)	28.63 (32.20)	-0.022
...median [IQR]	27.07 [12.96, 42.81]	24.89 [11.22, 44.04]	0.0633	21.02 [9.00, 35.43]	21.11 [10.00, 36.00]	-0.0032	22.51 (27.40)	22.04 (32.20)	0.016
SES - Business type									
...Commercial; n (%)	392 (36.5%)	404 (37.7%)	-0.0248				392 (36.5%)	404 (37.7%)	-0.025
...Medicare; n (%)	681 (63.5%)	669 (62.3%)	0.0248				681 (63.5%)	669 (62.3%)	0.025
SES - Low income indicator ; n (%)	183 (17.1%)	201 (18.7%)	-0.0417				183 (17.1%)	201 (18.7%)	-0.042
SES - Insurance Plan type									
...Comprehensive; n (%)				1,230 (37.4%)	1,231 (37.5%)	-0.0021	1,230 (37.4%)	1,231 (37.5%)	-0.002
...HMO; n (%)				854 (26.0%)	819 (24.9%)	0.0253	854 (26.0%)	819 (24.9%)	0.025
...PPO; n (%)				956 (29.1%)	987 (30.0%)	-0.0197	956 (29.1%)	987 (30.0%)	-0.020
...Others; n (%)				245 (7.5%)	248 (7.5%)	0.0000	245 (7.5%)	248 (7.5%)	0.000

* Not included in PS model