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**TRENDS OVER TIME IN COPD TREATMENT CHOICES BY RESPIRATORY
PHYSICIANS: AN ANALYSIS FROM THE COLIBRI-COPD FRENCH COHORT.**

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Running Head: Trends in COPD treatment choices

ABSTRACT (243/250)

Introduction: Over the last decade, new evidence and many guidelines have been published on COPD pharmacological treatments; prescriptions are often not in accordance with guidelines.

Materials and Methods: Trends in physician treatment choices from February 2012 to November 2018 (Feb.2012/Nov.2018) were analyzed using data from COPD patients (spirometry-confirmed diagnosis) included in the COLIBRI-COPD cohort. Inhaled drug treatments (short- or long-acting β 2-agonist [SABA or LABA], short- or long-acting anticholinergic [SAMA or LAMA], or corticosteroid [ICS]) were classified into 5 treatment categories: “No initial maintenance treatment (IMT)” (untreated, or only SAMA or SABA); “1 long-acting bronchodilator (LABD)” (LABA or LAMA); “2 LABDs” (LABA+LAMA); “1 LABD+ICS” (LABA or LAMA+ICS); “2 LABDs+ICS” (LABA+LAMA+ICS). For the purpose of the study, 4 periods were defined to achieve balanced samples (T1-T4).

Results: Data from 4537 patients were collected. Over time, 3 major changes were observed: (1) an increase in treatment category “No IMT”, mostly for GOLD 1 or GOLD A categories (GOLD A: from 19.1% at T1 to 41.2% at T4); (2) an increase in treatment category “2 LABDs” for GOLD 2 to 4 and GOLD A to D categories (GOLD B: from 15.4% to 29.7%); (3) a decrease in ICS use (“1 LABD+ICS” or “2 LABDs+ICS”), mostly for GOLD 1 to 3 and GOLD A categories (GOLD A, 2 LABDs+ICS: from 35.3% to 11.1%).

Conclusion: Changes over time in therapeutic profiles suggest that new evidence from scientific publications and recommendations may have had a rapid impact on clinical practice.

Keywords (6/6): COLIBRI, COPD, GOLD, real-world, treatment, trends

Abbreviations:

CAT: COPD Assessment Test; CEPRO: French Institutional Review Board (*Comité d'évaluation des protocoles de recherche observationnels*); CNIL: French acronym for the French national commission on personal data privacy (*Commission Nationale de l'Informatique et des Libertés*); COPD: Chronic Obstructive Pulmonary Disease; CPP: French Ethic Committee (*Comité de Protection des Personnes*); DIRECT: Disability Related to dyspnea COPD Tool; GOLD: Global Initiative for chronic obstructive lung disease; HAD: Hospital Anxiety and Depression scale; ICS: inhaled corticosteroid; IMT: initial maintenance treatment; LABA: long-acting B-2 agonist; LAMA: long-acting anticholinergic (muscarinic antagonist); LABD: long-acting bronchodilator; mMRC: modified Medical Research Council; SABA: short-acting β 2-agonist; SAMA: short-acting anticholinergic; T: Time period.

INTRODUCTION

Guidelines influence clinical decision making to some extent, but prescribing patterns in chronic obstructive pulmonary disease (COPD) are far from meeting available recommendations, as shown in several real-world studies [1][2]. For instance, physicians often tend to overprescribe inhaled corticosteroids (ICSs) in patients belonging to the GOLD A and B categories [2-5]. In addition, even if current guidelines are in principle evidence-based, there are grey zones in the evidence, e.g., in terms of diagnostic criteria or the definition of the asthma/COPD overlap [6,7]. The existence of these areas of uncertainty is further illustrated by differences between guidelines even when simultaneously released in countries with similar healthcare systems and gross income [8].

Guidelines can be informed by both clinical trials and observational studies, which sometimes do not converge. Even randomized controlled trials sometimes provide apparently contradictory results, likely explained by differences in recruited populations. Accordingly, cohort studies have clearly shown that COPD is a heterogeneous disease comprising several clinically important “phenotypes” [9]. In the last decade or so, the results of several large randomized controlled trials were published, showing beneficial effects of long-acting β 2-agonists (LABAs) +/- inhaled corticosteroids (ICSs) and long-acting anti-anticholinergics/muscarinic antagonists (LAMAs) on symptoms and exacerbation rates, as well as the additional effects obtained with various combinations of these treatment options [10-12]. In terms of possible harm, many studies addressed the issue of increased pneumonia risk associated with ICS use [13,14]. In 2016, LABA+LAMA became the preferred second-line treatment for patients belonging to GOLD B and C groups according to the Global Initiative for chronic obstructive lung disease (GOLD); it was the recommended first-line treatment for GOLD D patients [15].

To better understand the influence of new evidences from clinical trials and subsequent changes in guidelines, data from the COLIBRI-COPD cohort were analyzed to determine the trends in physician treatment choices between February 2012 (when the cohort was launched) and November 2018 (Feb.-2012/Nov.2018). Associations between these trends and GOLD classifications of airflow obstruction and clinical characteristics were also studied.

MATERIAL AND METHODS

The COLIBRI-COPD cohort

The COLIBRI program was designed in 2012 to provide specific standardized, structured, web-based medical consultations for COPD, Interstitial Lung Disease, and Pulmonary Rehabilitation. COLIBRI-COPD, which is part of the COLIBRI program, provides a unique unsupervised and unconstrained real-life database for extensive observational research [2, 16].

In November 2018, the COLIBRI-COPD database comprised 145 voluntary respiratory physicians working in hospitals (78%) or private practices (22%) on the French metropolitan territory. Among the hospital-based physicians, 83 (73%) worked in tertiary care university hospitals. All patients visiting a participating respiratory physician who had a spirometry-confirmed physician diagnosis of COPD could enter the database provided they gave oral consent after being informed by their physician. In accordance with French law, there was no requirement for written consent because the project was considered an observational cohort study.

The COLIBRI program received all legally required approvals in force at the time when the project was launched. The database was authorized by the French national commission on personal data privacy (*Commission Nationale de l'Informatique et des Libertés*, CNIL,

authorization number #2013-526). All entered data are stored in a secured central server certified for health data storage (OVH Healthcare, Claranet) [2]. The protocol was approved by the French Committee for Health Research Data Processing (*Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé*, CCTIRS, reference number #12.410.bis).

Collected data

Patients' data include demographic and anthropometric characteristics, risk factors (smoking history, professional exposure, occupation), comorbidities, respiratory symptoms, exacerbation history, findings at physical examination, self-estimated time spent walking outside the home, modified Medical Research Council (mMRC) scale, Epworth Sleepiness Scale, COPD assessment test (CAT), Hospital Anxiety and Depression (HAD) scale, Disability Related to dyspnea COPD Tool (DIRECT), lung function tests, arterial blood gases, and pharmacological and non-pharmacological treatments [2].

Definition of treatment schemes

Inhaled drug treatments (short- or long-acting β 2-agonist [SABA or LABA], short- and long-acting anticholinergic [SAMA or LAMA], and corticosteroid [ICS]) were classified into 5 categories: (1) "No IMT" (no initial maintenance treatment: untreated or treated with SAMA or SABA only); (2) 1 long-acting bronchodilator ("1 LABD": LABA or LAMA); (3) "2 LABDs" (LABA+LAMA); (4) "1 LABD+ICS" (LABA or LAMA+ICS); and (5) "2 LABDs+ICS" or triple therapy (LABA+LAMA+ICS).

Periods of interest

Four periods were defined to achieve balanced samples: (T1) Feb.-2012 to Sept.-2013; (T2) Oct.-2013 to May-2015; (T3) Jun.-2015 to Sept.-2016; (T4) Oct.-2016 to Nov.-2018. The third period (T3) ended at the same time that the FLAME study was published [12].

Statistical analysis

All analyses were performed using the R statistical software, version 3.2.4, and the SAS statistical software, version 9.2 (SAS Institute, Cary, NC, USA). Results were considered statistically significant when the probability of a type I error was below 5%.

Continuous data are presented as mean and standard deviations (SDs) while categorical data are presented as percentages. Patients were categorized in stages 1, 2, 3, or 4 using the GOLD spirometry-based classification of the severity of airflow obstruction and in the GOLD A-B-C-D groups with the mMRC stages to define symptoms (2017 GOLD groups).

RESULTS

Patients' characteristics

In November 2018, data from 4537 patients were recorded in the COLIBRI-COPD database. At baseline, minimal required information was known for 4061 patients. Exacerbation data were collected for 3518 of these and, among them, 1076 (31%) had at least 1 severe episode or 2 or more mild or moderate ones within the year. The mMRC dyspnea scale was completed for 3346 patients, and 3047 patients could be categorized in GOLD 1-2-3-4 stages and GOLD A-B-C-D groups. The breakdown of patients in these categories is shown in Table 1.

Finally, complete data (i.e., treatments prescribed and GOLD 2017 classification) were obtained for 2829 patients. Patients' characteristics (N=2829) are presented by period of interest in Table 2.

Overall treatment trends

As detailed in Table 3, COPD inhaled treatment prescriptions changed considerably from February 2012 to November 2018. The proportion of patients receiving ICS (i.e., with LABA, LAMA, and LABA+LAMA) decreased from 55.6% to 35.9%. In parallel, the proportion of patients who did not receive initial maintenance treatment ("No IMT" category) and who received LABA+LAMA ("2 LABDs" category) increased from 16.2% to 24.8% and from 11.1% to 23.1%, respectively. Finally, the proportion of patients who received LABA or LAMA ("1 LABD" category) remained stable (17.1% during the 1st treatment period [T1], Feb.-2012/Sept.-2013 versus 16.2% during T4, Oct.-2016/Nov.-2018).

Inhaled treatment schemes over time and by severity of airflow obstruction (GOLD classification)

From February 2012 to November 2018, treatment category "No IMT" significantly increased from 27.2% to 53.6% for GOLD 1 ($p < 0.001$), from 17.2% to 21.6% for GOLD 2, and decreased from 14.4% to 1.8% for GOLD 4. Treatment with only 1 LABD significantly decreased from 22.3% to 18.5% for GOLD 2 and from 3% to 0% for GOLD 4 ($p = 0.021$ and $p = 0.04$, respectively). The combination of 2 LABDs significantly increased in all spirometric categories except GOLD 1 ($p = 0.284$ for GOLD 1, $p < 0.001$ for GOLD 2 and 3, and $p = 0.015$ for GOLD 4). Triple therapy significantly decreased for all grades of airflow limitation except GOLD 4 ($p < 0.001$, $p = 0.001$, $p = 0.005$, and $p = 0.497$ for GOLD 1 to 4, respectively). Detailed results are graphically represented in Figure 1 and Table A.1.

Inhaled treatment loads over time by GOLD 2017 groups (A-B-C-D)

Treatment category “No IMT” significantly increased from 19.1% to 41.2% for GOLD A ($p < 0.001$) and decreased from 13.3% to 6.5 % for GOLD D ($p = 0.028$). The association of 2 LABDs significantly increased in each grade. Triple therapy (LABA+LAMA+ICS) significantly decreased only for GOLD A, from 35.3% at T1 to 11.1% at T4 (Figure 2 and Table A.2).

DISCUSSION

The present study identified 3 major changes in the prescription of inhaled treatments to COPD French patients over a 6-year period (February 2012 to November 2018). First, there was a clear increase in the percentage of patients without initial maintenance treatments or only with short-acting bronchodilators (“No IMT” category), which mostly concerned GOLD 1/GOLD A patients, i.e., those with less deteriorated lung function, symptoms and exacerbations. Then, there was also a significant increase in fixed or open combination of 2 long-acting bronchodilators (“2 LABDs” category) for GOLD 2 to GOLD 4 and for GOLD A to GOLD D. This trend was progressive since 2012 but increased at T3 and after. Finally, there was an important decrease of category “1 LABD+ICS” (mainly LABA+ICS) and an even more important decrease of category “2 LABDs+ICS” or triple therapy (LABA+LAMA+ICS), indicating reduced ICS use especially among the least severe patients (GOLD A) but also among GOLD C and D patients, although to a lesser extent.

Changes in prescription trends

The changes in prescription trends observed in the real-world COLIBRI-COPD cohort can be chronologically associated with the release of new data from large randomized controlled trials, and then with the evolution of guidelines. Following the results of the TORCH trial [10], more importance was given to the need to respect the indications of ICS in COPD, considering the associated risk of pneumonia among patients receiving these agents, as confirmed in several subsequent studies [17]. In parallel, several trials indicated that LAMAs improved lung function, quality of life, and also reduced exacerbations [11], with a greater effect than LABAs on this outcome [18]. Some data suggest that LAMAs could also alter disease progression especially in less severe patients [19,20], but this remains to be firmly established. Later, LABA+LAMA combinations were found to be more beneficial than monotherapy in terms of lung function [21], dyspnea, rescue medication use [22] and exacerbation rate [23]. Additionally, many observational studies indicated that a significant proportion of COPD patients is over-treated with ICS, which could expose them to significant risks. [3, 24]. Taken together, these results may contribute to explain the increase in the use of and recommendation for LABAs and LAMAs, while ICS use is decreasing across all GOLD categories.

Accordingly, a real-world study suggests that a LABA+LAMA fixed combination reduces exacerbations in symptomatic patients who receive a single bronchodilator or a LABA+ICS combination [25]. More recently, studies have shown that LABA+LAMA+ICS combinations are more effective than LAMAs alone, LABA+ICS, and LABA+LAMA combinations in terms of exacerbations [26-29]. In one of these studies, a LABA+LAMA combination has been less effective at preventing exacerbations than the ICS+LABA combination, which contradicts the findings of a previous study dedicated to this topic [12]. This discrepancy is likely the consequence of differences in populations, confirming the need

to identify biomarkers to help physicians individualize treatment choices more precisely [30]. Accordingly, the latest GOLD report [31] has introduced eosinophil counts among the biomarkers that should be used to determine the efficacy of corticosteroids in preventing exacerbations. How this will impact real-life treatment prescriptions is unknown.

Changes in patients' characteristics over time

Over time, the percentage of patients categorized as GOLD 1 significantly increased whereas the percentage of patients categorized as GOLD 2 remained stable and that of patients categorized as GOLD 3 or GOLD 4 significantly decreased. Similarly, the percentage of patients in GOLD A significantly rose, whereas the percentage of patients in GOLD B and C remained stable and the percentage of patients in GOLD D significantly decreased. The percentage of patients reporting frequent exacerbations (≥ 1 severe or ≥ 2 mild/moderate exacerbations) or mMRC scores ≥ 2 significantly diminished. In other words, the severity of disease decreased in the cohort as a whole, which could be partly due to improved adherence to diagnostic guidelines (earlier detection) and improved management (reduced burden).

Strengths and limitations

This study provided an analysis of data recorded during a daily consultation (COLIBRI-COPD software). It presents the advantage of being a real-world study drawing from a large population of physicians (N=145) and patients (N=4537) followed in various geographic areas and contexts in France.

These results give an original 6-year overview of respiratory physicians' treatment choices in a large cohort of patients. To the best of our knowledge, this has never been done before. The changes in therapeutic loads over time give also the opportunity to appreciate a potential influence of scientific publications and recommendations. A retrospective study to

describe changes in the management and outcomes of COPD patients in the UK was performed between 2000 and 2009, but results were not checked against guidelines and compliance requirements [32].

As a consequence of the unsupervised and unconstrained data recording process, only 62% of all patients could be analyzed. Importantly, we showed in a previous study that there were only marginal clinically significant differences in patients' characteristics between patients with and without missing data [2]. Another limitation is the voluntary nature of the participation in the project, which could bias the results of our analyses. Besides, the COLIBRI cohort is not designed to provide a population representative of the whole COPD population: indeed, it is based on patients' recruitment by clinicians during routine visits not dedicated to research, and these clinicians are not representative of all French respiratory physicians (73% of the respiratory physicians who participated in the COLIBRI project work in hospitals and therefore possibly see more patients with severe or complex diseases). Therefore, it is important to consider results by patients' category (GOLD classifications) rather than for the whole studied population.

Finally, several factors other than new evidence and changes in guidelines could influence prescription trends. These factors include, e.g., age, gender, comorbidities and co-treatments. Further analyses may help deciphering how all of these variables interact as determinants of treatment choices. This potential bias was largely accounted for by the analysis per GOLD group of airflow obstruction and clinical characteristics.

CONCLUSION

The results of this study suggest that new evidence from comparative studies and changes in recommendations may have contributed to the rapid impact on physicians' clinical

practice. This finding should trigger Guidelines Committees to update their recommendations quickly after the release of new evidence.

DECLARATION OF INTEREST - COMPETING INTEREST STATEMENT

Dr. Roche reports grants and personal fees from Boehringer Ingelheim, Novartis, Pfizer and personal fees from Teva, GSK, AstraZeneca, Chiesi, Mundipharma, Cipla, Sanofi, Sandoz, Trudell, 3M, Zambon.

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D. Hess and P. Z. Li declare that they have no conflicts of interest to declare.

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Figure 1: Graphical representation of the longitudinal evolution of inhaled treatment schemes for each GOLD 1-2-3-4 stage (GOLD 2011) from 2012 to 2018.

GOLD: Global Initiative for chronic obstructive lung disease; ICS: inhaled corticosteroid; LABD: long-acting bronchodilator, β 2 agonist (LABA) or anticholinergic (LAMA); T: time period.

Curves marked with an asterisk when p value significant (<0.001)

x-axis: period (T1: Feb.-2012/Sept.-2013; T2: Oct.-2013/May-2015; T3: Jun.-2015/Sept.-2016; T4: Oct.-2016/Nov.-2018); y-axis: % of treated patients

Figure 2. Graphical representation of the longitudinal evolution of inhaled treatment schemes for each GOLD A-B-C-D group (GOLD 2017) from 2012 to 2018.

GOLD: Global Initiative for chronic obstructive lung disease; ICS: inhaled corticosteroid; LABD: long-acting bronchodilator, β 2 agonist (LABA) or anticholinergic (LAMA); T: time period.

Curves marked with an asterisk when p value significant (<0.001)

x-axis: period (T1: Feb.-2012/Sept.-2013; T2: Oct.-2013/May-2015; T3: Jun.-2015/Sept.-2016; T4: Oct.-2016/Nov.-2018); y-axis: % of treated patients

Table 1. Baseline characteristics of all patients based on GOLD classifications (N=4061)

Variable	N	%	n
GOLD classification of airflow obstruction			
GOLD 1	4061	19.4	786
GOLD 2	4061	44.2	1794
GOLD 3	4061	23.6	960
GOLD 4	4061	12.8	521
GOLD 2017 clinical classification using mMRC			
GOLD A	3047	38.4	1170
GOLD B	3047	30.5	929
GOLD C	3047	8.9	272
GOLD D	3047	22.2	676
mMRC scale			
0	3346	14.2	474
1	3346	32.6	1091
2	3346	26.9	901
3	3346	18.3	611
4	3346	8.0	269
Exacerbation*	3518	30.6	1076

mMRC: modified Medical Research Council;

* ≥ 1 severe OR ≥ 2 light or moderate within the year.

Table 2: Patients characteristics per time period from 2012 to 2018 (N=2829)

	T1 (N=687)		T2 (N=698)		T3 (N=746)		T4 (N=698)		P-value
	Feb.-2012/Sept.-2013		Oct.-2013/May-2015		Jun.-2015/Sept.-2016		Oct.-2016/Nov.-2018		
	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	
Demographic, anthropomorphic, and behavioral characteristics									
Age (years), mean ± SD	687	66.5 ± 10.5	698	65.9 ± 9.9	746	64.8 ± 8.5	698	64.6 ± 9.7	<0.001
Gender, male, n (%)	687	503 (73.2)	698	488 (69.9)	746	531 (71.2)	698	482 (69.1)	0,349
BMI (kg/m ²), mean ± SD	686	25.9 ± 5.6	694	25.7 ± 5.9	744	25.6 ± 5.5	695	25.6 ± 5.3	0,539
Ever-smoker, n (%)	681	620 (91.0)	690	652 (94.5)	738	725 (98.2)	693	667 (96.2)	<0.001
Active smoker among smokers, Yes, n (%)	612	191 (31.2)	640	197 (30.8)	721	319 (44.2)	661	302 (45.7)	<0.001
Respiratory functional parameters									
mMRC Score ≥ 2/4, n (%)	687	394 (57.4)	698	419 (60.0)	746	370 (49.6)	698	332 (47.6)	<0.001
CAT score, mean ± SD	365	17.3 ± 7.6	335	16.5 ± 7.8	521	15.9 ± 7.9	419	15.8 ± 8.1	0,016
DIRECT, mean ± SD	382	12.2 ± 7.1	305	12.2 ± 7.7	515	10.5 ± 7.7	412	10.6 ± 8.0	<0.001
FEV ₁ (liters), mean ± SD	687	1.5 ± 0.6	698	1.4 ± 0.7	746	1.7 ± 0.7	698	1.8 ± 0.8	<0.001
FEV ₁ (% predicted), mean ± SD	687	57.3 ± 20.8	698	53.7 ± 22.3	746	61.6 ± 22.4	698	63.1 ± 21.4	<0.001
FVC (liters), mean ± SD	687	2.8 ± 0.9	698	2.7 ± 0.9	746	3.1 ± 1.1	698	3.1 ± 1.1	<0.001
FVC (% predicted), mean ± SD	687	83.9 ± 20.6	698	81.0 ± 22.1	746	89.2 ± 24.3	698	90.6 ± 21.8	<0.001
FEV ₁ /FVC (%), mean ± SD	687	52.9 ± 12.6	697	51.4 ± 14.0	742	54.0 ± 12.2	698	54.5 ± 12.4	<0.001
GOLD classification of airflow obstruction, n (%)									
GOLD 1	687	92 (13.4)	698	98 (14.0)	746	168 (22.5)	698	166 (23.8)	<0.001
GOLD 2	687	332 (48.3)	698	271 (38.8)	746	318 (42.6)	698	329 (47.1)	0,001
GOLD 3	687	173 (25.2)	698	185 (26.5)	746	182 (24.4)	698	146 (20.9)	0,09
GOLD 4	687	90 (13.1)	698	144 (20.6)	746	78 (10.5)	698	57 (8.2)	<0.001
GOLD clinical 2017-classification with mMRC, n (%)									
GOLD A	687	235 (34.2)	698	216 (30.9)	746	305 (40.9)	698	306 (43.8)	<0.001
GOLD B	687	228 (33.2)	698	205 (29.4)	746	226 (30.3)	698	209 (29.9)	0,419
GOLD C	687	58 (8.4)	698	63 (9.0)	746	71 (9.5)	698	60 (8.6)	0,892
GOLD D	687	166 (24.2)	698	214 (30.7)	746	144 (19.3)	698	123 (17.6)	<0.001
Anxiety and depression scores									
HAD Anxiety score ≥8, n (%)	151	42 (27.8)	293	105 (35.8)	501	166 (33.1)	388	111 (28.6)	0,136
HAD Depression score ≥8, n (%)	150	44 (29.3)	294	102 (34.7)	500	154 (30.8)	388	109 (28.1)	0,311
Comorbidities, n (%)									
Cardiovascular and/or diabetic comorbidity	676	372 (55.0)	679	409 (60.2)	729	393 (53.9)	676	398 (58.9)	0,051

Anxiety or depression declared or treated	676	137 (20.3)	679	197 (29.0)	729	173 (23.7)	676	152 (22.5)	0.001
Exacerbations within the year									
≥1 severe or ≥2 mild/moderate, n (%)	687	224 (32.6)	698	277 (39.7)	746	215 (28.8)	698	183 (26.2)	<0.001

BMI: Body Mass Index; CAT: COPD assessment test; DIRECT: Disability Related to dyspnea COPD Tool; FEV1: Forced expiratory volume in one second; FVC: Forced Vital Capacity; GOLD: Global Initiative for chronic obstructive lung disease; HAD: Hospital Anxiety and Depression scale; mMRC: modified Medical Research Council; T: time period

Statistical tests: Chi² analysis (categorical variables) or ANOVA test (continuous variables, normal distribution) or Kruskal-Wallis Test* (continuous variables, non-normal distribution).

Table 3: Distribution of inhaled treatment prescriptions per time period from 2012 to 2018 (N=2829)

Prescriptions	T1 (N=687)			T2 (N=698)			T3 (N=746)			T4 (N=698)			P-value
	Feb.-2012/Sept.-2013			Oct.-2013/May-2015			Jun.-2015/Sept.-2016			Oct.-2016/Nov.-2018			
	N	%	n	N	%	n	N	%	n	N	%	n	
No bronchodilator	687	12.7	87	698	9.5	66	746	20.4	152	698	20.2	141	<0.001
Short-acting bronchodilator	687	3.5	24	698	3.4	24	746	2.5	19	698	4.6	32	0,217
LABA	687	5.2	36	698	6.7	47	746	6.8	51	698	4.0	28	0.068
LAMA	687	11.9	82	698	12.9	90	746	12.1	90	698	12.2	85	0,949
2 LABDs: LABA+LAMA	687	11.1	76	698	13.8	96	746	20.4	152	698	23.1	161	<0.001
LABA+ICS	687	12.8	88	698	12.2	85	746	8.3	62	698	10.0	70	0.023
LAMA+ICS	687	0.4	3	698	0.6	4	746	0.3	2	698	0.1	1	0,541
TRIPLE (2 LABDs+ICS)	687	42.4	291	698	41.0	286	746	29.2	218	698	25.8	180	<0.001

ICS: inhaled corticosteroid; LABA: long-acting β 2-agonist; LABD: long-acting bronchodilator; LAMA: long-acting anticholinergic; T: time period

Statistical tests: Chi² analysis (categorical variables) or ANOVA test (continuous variables, normal distribution) or Kruskal-Wallis Test (continuous variables, non-normal distribution).