



Usage of Long-Acting Muscarinic Antagonists and Biologics as Add-on Therapy for Patients in the United States with Moderate-to-Severe Asthma

C. Victor Spain, Parul Dayal, Yingjie Ding, Carlos Iribarren, Theodore A. Omachi & Hubert Chen

To cite this article: C. Victor Spain, Parul Dayal, Yingjie Ding, Carlos Iribarren, Theodore A. Omachi & Hubert Chen (2021): Usage of Long-Acting Muscarinic Antagonists and Biologics as Add-on Therapy for Patients in the United States with Moderate-to-Severe Asthma, Journal of Asthma, DOI: [10.1080/02770903.2021.1922915](https://doi.org/10.1080/02770903.2021.1922915)

To link to this article: <https://doi.org/10.1080/02770903.2021.1922915>



Accepted author version posted online: 10 May 2021.



Submit your article to this journal [↗](#)



Article views: 28



View related articles [↗](#)



View Crossmark data [↗](#)



Running head: LAMA and biologic treatment patterns in asthma

Usage of Long-Acting Muscarinic Antagonists and Biologics as Add-on Therapy for Patients in the United States with Moderate-to-Severe Asthma

C. Victor Spain, DVM, PhD^a, Parul Dayal, MS, PhD^a, Yingjie Ding, MS^b, Carlos Iribarren, MD, MPH, PhD^c, Theodore A. Omachi, MD^a, and Hubert Chen MD, MPH^a

^aGenentech, Inc, South San Francisco, CA

^bGenesis Research, Hoboken, NJ

^cDivision of Research, Kaiser Permanente Northern California, Oakland, CA

Corresponding author: C. Victor Spain Genentech, Inc., 1 DNA Way, South San Francisco, CA

94080. Email: spain.vic@gene.com Tel: (215) 870-7218

Abstract

Objective: Many asthma patients remain uncontrolled on inhaled corticosteroids (ICS) and long-acting beta agonists (LABAs), but guidance for selecting add-on therapies, including long-acting muscarinic antagonists (LAMAs) or biologics, is limited. We describe how prescribing practices for add-on LAMA and biologic therapy have changed with increased treatment options and revised treatment guidelines. We further identify differences in treatment initiation and discontinuation rates by patient characteristics, including concomitant COPD.

Methods: This retrospective cohort study analyzed insurance claims in the IBM MarketScan database for adult US asthma patients treated with medium- or high-dose ICS/LABA between 2012 and 2019 ($n = 277,373$). We used negative binomial regression models to evaluate LAMA and biologic initiation rates and their association with patient characteristics, and survival analysis methods for assessing discontinuation rates.

Results: Between 2012 and 2019, LAMA and biologic uptake increased approximately 5-fold and 20-fold, respectively. LAMA initiation was significantly higher among patients with concomitant COPD, a group typically unstudied in clinical trials, versus those with asthma only (rate ratio of 5.90, 95% CI: 5.76-6.04). High-dose ICS/LABA treatment and the need for oral corticosteroid (OCS) bursts had stronger associations with biologic initiation. Probability of discontinuation (i.e. non-persistence) in the first year was 40.5% and 22.7% for those initiating LAMAs and biologics, respectively, with higher LAMA discontinuation rates among patients with asthma only versus those with concomitant COPD.

Conclusions: Our results provide insights into how clinicians apply treatment guidelines for initiating add-on LAMA and biologic therapies in moderate-to-severe asthma patients and highlight patients who have an unmet treatment need after discontinuation.

Keywords COPD, treatment patterns, treatment guidelines, discontinuation, persistence

Introduction

Despite the common use of inhaled corticosteroids (ICSs) combined with long-acting beta-agonists (LABAs), the standard-of-care asthma treatments, many patients experience uncontrolled symptoms. Historically, treatment options for patients who remain uncontrolled on ICS/LABA were limited mainly to leukotriene modifiers and methylxanthines (e.g. theophylline), of which neither proved greatly effective (1–5). Over the past decade, global asthma treatment guidelines have evolved, and now include additional options for add-on therapy, specifically LAMAs (long-acting muscarinic antagonists) and several biologics (6). Clinical guidance for selecting the appropriate add-on therapy remains limited, however, and to date, our understanding of patient and provider characteristics associated with add-on therapy usage in general US clinical practice is incomplete.

LAMAs, such as tiotropium, have been available as maintenance therapy for chronic obstructive pulmonary disease (COPD) in the United States since 2004, but were approved for use in asthma only in 2015. Add-on LAMA treatment has generally been associated with improved FEV₁ (forced expiratory volume in 1 s), but only modestly improved quality of life (7). A recent meta-analysis showed an association of LAMAs with a lower risk of exacerbations when added to ICS, but not when added to ICS/LABA (8). Despite their limited efficacy as add-on therapy, LAMAs are convenient to administer and have a relatively low cost.

Biologics, which include omalizumab (anti-immunoglobulin (Ig) E), mepolizumab (anti-interleukin (IL)-5), reslizumab (anti-IL-5), benralizumab (anti-IL-5 receptor alpha (R α)) and dupilumab (anti-IL-4R α), are the newest category of asthma therapies. Biologic clinical trials have shown significant and meaningful reductions in asthma exacerbations, but generally in more narrowly defined populations, including those with more severe disease (9, 10). Potential barriers for implementing therapy include the need for injections every 2-4 weeks and the added administrative burden associated with obtaining insurance coverage.

Little research has been published describing how availability of new asthma medications and evolving treatment guidelines influence treatment selection. Establishing how often these treatments are used, the typical duration of therapy, and the patient and health care provider (HCP) characteristics associated with their use may provide insights into how HCPs are applying current guidelines and thus provide insights for future revisions. Using US insurance claims data, we sought to describe the real-world utilization of LAMAs and biologics as add-on therapy for moderate-to-severe asthma. Given increasing awareness that many patients with asthma also present with clinical features of COPD, and because these patients are understudied, are typically excluded from clinical trials, and are difficult to diagnose and treat, we also considered how treatment patterns vary in patients who may have both conditions.

Methods

Study Design and Data Source

This retrospective cohort study used data from the IBM MarketScan Commercial and Medicare Supplemental insurance claims databases. These databases include longitudinal medical and pharmacy claims for US patients covered by employer-sponsored insurance, including Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans and represents roughly one-fifth of the commercially insured US population (11, 12). The study period included medical encounters from January 1, 2012 to December 31, 2019.

Patient Inclusion Criteria

We sought to identify adult patients with moderate-to-severe asthma who were treated with medium- to high-dose ICS/LABA and would be candidates for add-on therapy. To operationalize this, we defined patients as eligible if they i) were at least 18 years old at time of earliest insurance enrollment, ii) had an asthma diagnosis (billing diagnoses of 493.x (ICD-9) or J45.x (ICD-10)) recorded at ≥ 2 medical encounters at least 13 days apart, iii) had an identifiable 180-day period during which they continued to fill an ICS-containing product (Table S1), but had no evidence of LAMA or biologic treatment, and iv) had ≥ 2 pharmacy claims for medium- or high-dose ICS/LABA (6) before any treatment with a LAMA or biologic. We also required evidence of ongoing treatment with ICS/LABA until the end of insurance enrollment, until the end of the study period, or until treatment escalation, whichever came first. Therefore, patients were excluded if they exhausted their supply of ICS/LABA >90 days before the end of enrollment or >90 days before LAMA or biologic initiation (Figure 1).

Two disease cohorts were identified: patients with i) asthma only and ii) asthma and concomitant COPD. A COPD diagnosis was defined as having ≥ 2 medical encounters during the study period at age 40 or older with a diagnosis of chronic bronchitis, emphysema, or bronchiectasis, following diagnostic billing codes commonly used in healthcare quality measures (ICD-9-CM: 491x, 492x, 494x, 496, 506.4; ICD-10-CM: J41x, J42, J43x, J44x, J47x) (13, 14).

Study Variables

LAMA medications were those containing acclidinium bromide, tiotropium bromide, umeclidinium or glycopyrrolate, either as monotherapy or as combination products (Table S1). LAMA initiation was defined as obtaining ≥ 1 pharmacy fills for any LAMA after receiving ≥ 2 fills for medium- or high-dose ICS/LABA and before, or without, treatment with a biologic. Biologic treatment was defined by having ≥ 1 pharmacy claims for omalizumab, mepolizumab, benralizumab, reslizumab, or dupilumab, the biologics marketed during the study period, or a medical claim with an administration procedure for any medication. Biologic initiation was defined as receiving ≥ 1 biologic treatments after receiving ≥ 2 fills for medium- or high-dose ICS/LABA and before, or without, treatment with a LAMA. The definition of medium and high dose was determined by the total daily dose of the ICS component following the classification in the Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention (6). Patients were classified as receiving high-dose ICS/LABA if they had ≥ 2 fills for high-dose ICS/LABA, irrespective of whether medium-dose ICS/LABA was also filled.

To better characterize baseline asthma severity, we determined if patients had an exacerbation requiring an oral corticosteroid (OCS) burst in the 180 days before LAMA or biologic initiation, with a burst defined as a pharmacy claim for a short supply (≤ 29 days) of OCS (Table S2). For patients without LAMA or biologic initiation, we assessed a randomly selected 180-day period for OCS bursts. For each patient, we identified the HCP specialty (allergist or pulmonologist) most commonly associated with their medical encounters for asthma treatment at any time during the observation period. If a patient did not have relevant medical encounters associated with an allergist or pulmonologist, they were assigned to the primary care or “other” categories based on the providers associated with encounters for asthma treatment.

Outcomes, Statistical Methods, and Analyses

To assess temporal trends in LAMA and biologic add-on therapy uptake, we calculated for each calendar year the proportion of patients filling a medium- or high-dose ICS/LABA who also received treatment with a LAMA or biologic. For purposes of calculating treatment initiation rates, the *observation period* for each patient was the time from their earliest medium- or high-dose

ICS/LABA fill until the end of insurance enrollment or the end of the study period, whichever occurred first, and the *ICS/LABA-only treatment period* was the time from their earliest fill for medium- or high-dose ICS/LABA until either initiation of add-on treatment or until the end of their observation period, whichever occurred first. A schematic of the time periods assessed is presented in Figure 2. The denominator of the initiation rate was the sum of patient-years for the ICS/LABA-only treatment period for all patients in the relevant cohort, and; the numerator was the number of these patients who initiated LAMA or biologic add-on treatment. We used negative binomial regression models, with follow-up time as an offset variable, to determine rate ratios (RRs) comparing initiation rates across patient subgroups and to estimate 95% confidence intervals (CIs) for both the rates and RRs.

Survival analysis was used to compare LAMA and biologic treatment discontinuation rates between the two disease cohorts, accounting for differential observation periods and censoring. Patients were considered to have persistent LAMA treatment (i.e. did not discontinue treatment) if there was evidence of ongoing treatment until 90 days before the end of the observation period (i.e. the exhaustion of their last pharmacy fill occurred <90 days before, or any time after, the end of their observation period). Otherwise, patients were considered to have discontinued LAMA treatment (i.e. were non-persistent) after the exhaustion of their last fill. Persistence and discontinuation were defined similarly for biologics, assuming each administration lasted for 28 days (i.e. supply of 28 days). For persistent patients, any gap between successive pharmacy fills or administration procedures was allowed, and follow-up time was censored at the end of their observation period.

To investigate how often biologic treatment was used among patients who discontinued LAMAs, we identified patients who initiated a biologic within 90 days after the exhaustion of the last LAMA fill, or who initiated a biologic prior to LAMA exhaustion and the treatment period continued past their last LAMA fill. Patients were included in these calculations only if their observation period extended at least 90 days past the LAMA discontinuation date (i.e. there was sufficient follow-up time to identify potential biologic treatment initiation).

This study used de-identified data and was therefore exempt from the requirement of institutional review board approval.

Results

Of the 2 298 737 adult patients with an asthma diagnosis recorded between January 2012 and December 2019 in the databases, 277 373 patients met our inclusion criteria (Figure 1). The median observation period for all patients was 3.0 years (interquartile range: 1.9–4.9 years). Patients were most commonly female (61.6%), 45–64 years old (54.7%), treated with only medium-dose ICS/LABA (68.5%), and obtained asthma care from primary care physicians (PCPs) (47.1%) (Table 1). A total of 27 997 (10.1%) asthma patients on medium- or high-dose ICS/LABA added a LAMA, and 4 553 (1.6%) added a biologic at any point during their observation period. The remaining 244 817 (88.1%) did not add either a LAMA or biologic. 60 204 patients (21.7%) had a concomitant COPD diagnosis (Table 1, Table S3).

Temporal Trends in LAMA and Biologic Uptake

Among patients with concomitant COPD, LAMA treatment increased almost 5-fold during the study period for both ICS/LABA doses (from 4.1% in 2012 to 17.4% in 2019, medium-dose ICS/LABA; 3.8% to 17.8%, high-dose ICS/LABA; Figure 3a). For patients with asthma only, the absolute LAMA uptake was lower than those with concomitant COPD, but the relative uptake increased 6- to 7-fold, with differential trends by ICS/LABA dose (from 0.4% in 2012 to 2.8% in

2019, medium-dose ICS/LABA; 0.9% to 5.5%, high-dose ICS/LABA; Figure 3a). More than half of the increase occurred after the first LAMA approval for an asthma indication.

Biologic treatment increased 13- to 32-fold from 2012 to 2019 for all patient subgroups (Figure 3b), although as expected, the absolute proportion of patients using biologics was substantially less than that for LAMAs overall. In contrast to LAMA uptake, biologic uptake was highest among those taking high-dose ICS/LABA in both disease cohorts (from 0.2% to 5.7%, concomitant COPD; from 0.3% to 4.2%, asthma only; Figure 3b). Biologic uptake increased the most from 2016 to 2019, all years in which new biologics entered the US market.

Treatment Patterns by Patient and HCP characteristics

LAMA initiation was generally highest among those with concomitant COPD and those with evidence of more severe disease and poor control. In particular, the rate of LAMA initiation was 6-fold higher for patients with concomitant COPD (10.10 per 100 patient-years) compared to patients with asthma only (1.71 per 100 patient-years; Figure 4(a); see Table S4 for absolute rates), yielding an RR of 5.90 (95% CI: 5.76–6.04). Among those with asthma only, the LAMA initiation rate was 2-fold higher among those treated with high-dose versus medium-dose ICS/LABA (RR = 2.13; Table 2). LAMA initiation was also 2- to 3-fold higher for patients with an OCS burst (RR = 3.68, asthma only; RR = 2.02, concomitant COPD). The LAMA initiation rate was also lower among patients aged 18–44 years compared to those 45–64 years old (RR = 0.75, asthma only; RR = 0.83, concomitant COPD) (Table 2; Table S4). Among patients with asthma only, those primarily treated by a pulmonologist were more likely to initiate LAMA treatment compared with those primarily treated by an allergist (RR = 1.44) (Figure 4a; Table 2; Table S4). Table S4 contains further data on initiation rates stratified by COPD status, patient characteristics, and provider type.

In contrast to LAMA initiation, the biologic initiation rate was comparable between patients with concomitant COPD and those with asthma only (0.58 per 100 patient-years for both groups; Figure 4(b); Table S4). The biologic initiation rate was more strongly associated, however, with indicators of disease severity and control. Biologic initiation rates were 3-fold higher among those treated with high-dose versus medium-dose ICS/LABA (RR = 2.83, asthma only; RR = 3.06, concomitant COPD; Table 2) and 5- to 6-fold higher for patients with versus without a prior OCS burst (RR = 6.17, asthma only; RR = 5.00, concomitant COPD). In contrast to LAMA initiation, the biologic initiation rate was highest among patients aged 18–44 years old (RR = 1.26, asthma only; RR = 1.84, concomitant COPD) and notably lower among those aged 65 or older (RR = 0.41, asthma only; RR = 0.28, concomitant COPD) as compared to those aged 45–64 years (Table 2). In contrast to the pattern for LAMAs, patients who were primarily treated by a pulmonologist were half as likely or less to initiate biologic treatment as those primarily treated by an allergist (RR = 0.53, asthma only; RR = 0.32, concomitant COPD) (Table 2).

Treatment Persistence

Among those who initiated LAMA treatment, the probability of discontinuation (i.e. non-persistence) in the first year was approximately 40.5% (95% CI, 39.9%–41.2%). LAMA discontinuation at 1 year was higher among those with asthma only (50.4%) than among those with concomitant COPD (35.1%; Figure 5a). The estimated median time to LAMA discontinuation was shorter for those with asthma only (360 days) than for those with concomitant COPD (869 days) (Figure S1; Table S5). Inflections in the Kaplan-Meier curves at 30 days and 90 days represent patients who had a single LAMA fill with a 30-day or 90-day supply and no subsequent fills in the observation period. Among those who discontinued LAMA treatment, only 3.5% of the patients

received biologic treatment near the time of discontinuation (5.2%, asthma only; 2.3%, concomitant COPD).

Among those initiating biologic treatment, the probability of discontinuation at the end of 1 year was 22.7% (95% CI, 21.3%-24.1%)—lower than that for the LAMA add-on cohort—with little difference between those with asthma only and those with concomitant COPD (21.7% and 25.8%, respectively; Figure 5b). In contrast to LAMA treatment, the estimated median time to biologic discontinuation was higher for those with asthma only (1 871 days) than for those with concomitant COPD (1 604 days) (Figure S2; Table S6).

Discussion

This study evaluated the utilization of LAMA and biologic therapy as add-on treatments for asthma in a large, nationally representative sample of almost 300 000 patients with moderate-to-severe asthma, with and without concomitant COPD. We found that over a relatively short time span of 8 years (2012–2019) the proportion of patients using add-on LAMAs or biologics increased by several fold, but uptake patterns differed substantially between these two classes. The absolute LAMA initiation rate far exceeded that of biologics, and was particularly high among asthma patients with concomitant COPD. This subpopulation, which has garnered increasing attention over the past several years, was more likely to be treated by pulmonologists than by allergists. Despite the lower utilization, biologic-treated patients appeared to demonstrate greater persistence of treatment compared with LAMA-treated patients, who discontinued at a higher rate in the first year.

Our findings highlight the point that, unlike ICS/LABA therapy, which underlies standard of care in all moderate-to-severe asthma patients, add-on treatments such as LAMAs and biologics may be more specifically tailored to individual patients based on asthma severity and control, COPD status, biologic phenotype, and demographics. As might be expected, our study showed that initiation of biologics and LAMAs was greater among patients with more severe disease, as indicated by high-dose ICS/LABA. More interesting, however, was the increasing use of add-on treatment even among patients prescribed only medium-dose ICS/LABA. One explanation could be the earlier initiation of add-on treatments in step-based therapy as HCPs gain more familiarity with these newer medications. For asthma patients with concomitant COPD, HCPs may not feel compelled to maximize ICS/LABA dose before initiating a LAMA therapy. This approach is consistent with our findings that usage of add-on LAMA in this disease cohort appeared to be independent of ICS/LABA dose. Higher initiation of biologics among those who need OCS bursts is consistent with a perception among patients and HCPs that increased efficacy outweighs the potential burden of initiating treatment. The trend towards lower uptake of biologics among patients ≥ 65 years old highlights differences in the care of older individuals with asthma, which is often influenced by several complex factors, including patient preferences (e.g. route of administration), the patient's ability to cover out of pocket expenses (such as copays), or physician behavior.

Our study also showed that while the rate of LAMA treatment has grown over time, approximately 21% of patients discontinue treatment within 3 months, with this rate increasing to over 40% by the end of the first year. Notably, discontinuation rates are higher among asthma patients without concomitant COPD. Given that LAMAs are relatively safe and easy to prescribe, our finding may reflect the clinical practice of utilizing a “trial period” of LAMA therapy for asthma patients who remained uncontrolled on ICS/LABA to determine if they will respond. Other possible reasons for discontinuation may include lower adherence associated with addition of a second inhaler (15) or poor tolerance, as 5–10% of patients reported dry mouth in LAMA clinical trials (16–18). Only 3.5% of patients who discontinued LAMA therapy received biologic therapy within 90 days.

Therefore, LAMAs are apparently not being used as an intermediate step before treatment escalation with a biologic.

While our data indicate that use of biologic therapies have increased by several fold in recent years, their use remains substantially less than that of LAMAs. Limited uptake of biologic therapies relative to LAMAs likely reflects the limited pool of eligible patients, the need for regular injections, and the higher burden of initiating therapy. The notable increase in utilization from 2016 to 2019 may be related to increasing familiarity with the class and recent availability of multiple biologics with various mechanisms of action. Despite the lower uptake of biologics relative to LAMAs, treatment persistence appears to be higher. Our findings show that while approximately 40% of patients discontinued LAMA treatment within one year, only 23% of patients discontinued biologic treatments, and the estimated median time to discontinuation was almost 3 times longer than that of LAMAs.

A major strength of this analysis is the large population studied, with findings generalizable to adults having employer-sponsored commercial insurance or supplemental Medicare insurance. Patients who are self-insured or have public insurance are not included, however, and may have different treatment utilization patterns. As with any analysis of claims data, there may be some misclassification of patients based on billing diagnoses. In particular, we did not have data on lung function measures or other clinical data that was used to determine a diagnosis of chronic bronchitis or emphysema (i.e. COPD). For patients who had both diagnoses, we were unable to determine whether features of asthma or COPD were predominant and which of the diagnoses was the focus for treatment selection. For our analysis, we assumed that patients with LAMA pharmacy fills took their medication for the number of days listed, but we could not determine actual patient utilization from the database. We assumed that if medications were prescribed to a patient already treated with ICS/LABA, then the prescription was intended as add-on, not replacement, therapy. Because clinical measures such as FEV₁ and detailed information on exacerbations are not available in the database, we relied on ICS dose level and prescribed OCS bursts as proxies for asthma severity and control, respectively. Despite these limitations, our use of actual prescription data and administration procedures provides valuable insights into how treatment patterns in the real world have changed over the last several years. Our findings may also provide useful context for future studies that would inform treatment guidelines.

Conclusions/Key Findings

Our results show that practice patterns in asthma are evolving as newer treatment options become increasingly available and as our understanding of their use in specific patient populations is incorporated into treatment guidelines and clinical practice. LAMAs are increasingly prescribed as add-on treatment for patients with moderate to severe asthma, but the bulk of initiating patients are those with concomitant COPD. Biologic treatment is less common and tends to be reserved for patients with more severe disease. The higher uptake, but relatively short treatment period for LAMAs suggests there is an unmet need for highly effective therapies that provide the convenience and ease of administration of inhaled therapies.

Acknowledgements

The authors thank Deborah Solymar, PhD (Genentech, Inc.), for providing editing and writing assistance, which was funded by Genentech, Inc.

Author contributions

C. V. Spain and H. Chen were responsible for the study concept and design. C. V. Spain, P. Dayal, and Y. Ding performed the statistical analysis. P. Dayal and Y. Ding provided administrative, technical, or material support. All authors were responsible for the acquisition, analysis, or interpretation of data. C. V. Spain, P. Dayal, H. Chen, and Y. Ding drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

Declaration of interest

C. V. Spain, P. Dayal, T. Omachi, and H. Chen are employees of Genentech, Inc., a member of the Roche group, and own Roche stock and/or options. Y. Ding is an employee of Genesis Research. C. Iribarren is a consultant to Genentech, Inc.

Funding

This work was supported by Genentech, Inc.

Data availability statement

The data that support the findings of this study are available from the IBM MarketScan Commercial Database and Medicare Supplemental Database (<https://www.ibm.com/products/marketscan-research-databases/databases>). Restrictions apply to the availability of these data, which were used under license for this study.

References

1. Tee AK, Koh MS, Gibson PG, Lasserson TJ, Wilson AJ, Irving LB. Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma. *Cochrane Database Syst Rev*. 2007;(3):CD001281. doi: 10.1002/14651858.CD001281.pub2.
2. American Lung Association Asthma Clinical Research Centers. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. *Am J Respir Crit Care Med*. 2007;175(3):235–242. doi: 10.1164/rccm.200603-416oc.
3. Kaplan A, FitzGerald JM, Buhl R, Vogelberg C, Hamelmann E. Comparing LAMA with LABA and LTRA as add-on therapies in primary care asthma management. *NPJ Prim Care Respir Med*. 2020;30(1):50. doi: 10.1038/s41533-020-00205-9.
4. Ducharme FM, Lasserson TJ, Cates CJ. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. *Cochrane Database Syst Rev*. 2011;(5):CD003137. doi: 10.1002/14651858.cd003137.pub4.
5. Weir NA, Levine SJ. Achieving symptom control in patients with moderate asthma. *Clin Med*

Insights Circ Respir Pulm Med. 2012;6:1–11. doi: 10.4137/ccrpm.s5100.

6. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2020 [accessed 2020 Jun 20]. <http://www.ginasthma.org>.
7. Lipworth BJ. Emerging role of long acting muscarinic antagonists for asthma. *Br J Clin Pharmacol*. 2014;77(1):55–62. doi: 10.1111/bcp.12123.
8. Sobieraj DM, Baker WL, Nguyen E, Weeda ER, Coleman CI, White CM, Lazarus SC, Blake KV, Lang JE. Association of inhaled corticosteroids and long-acting muscarinic antagonists with asthma control in patients with uncontrolled, persistent asthma: a systematic review and meta-analysis. *JAMA*. 2018;319(14):1473–1484. doi: 10.1001/jama.2018.2757.
9. Hanania NA, Alpan O, Hamilos DL. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med*. 2011;154(9):573–582. doi: 10.7326/0003-4819-154-9-201105030-00002.
10. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371(13):1198–1207. doi: 10.1056/nejmoa1403290.
11. Kulaylat AS, Schaefer EW, Messaris E, Hollenbeak CS. Truven Health Analytics MarketScan databases for clinical research in colon and rectal surgery. *Clin Colon Rectal Surg*. 2019;32(1):54–60. doi: 10.1055/s-0038-1673354.
12. Zuvekas SH. Comparing MEPS use and expenditure estimates for the privately insured to Truven MarketScan® and OptumLabs™ claims data, 2008–2013. Agency for Healthcare Research and Quality (AHRQ); US Department of Health and Human Services. 2017 [accessed 19 Feb 2021]. https://www.meps.ahrq.gov/data_files/publications/workingpapers/wp_17001.pdf.
13. Agency for Healthcare Research and Quality (AHRQ); US Department of Health and Human Services. Prevention Quality Indicator 05 (PQI 05) Chronic Obstructive Pulmonary Disease (COPD) or Asthma in Older Adults. AHRQ Quality Indicators™ (AHRQ QI™) ICD-9-CM Specification Version 6.0. Admission Rate. Area-Level Indicator. Type of Score: Rate. 2016

[accessed 2019 Nov 19]. [https://www.qualityindicators.ahrq.gov/Downloads/Modules/PQI/V60-ICD09/TechSpecs/PQI_05_Chronic_Obstructive_Pulmonary_Disease_\(COPD\)_or_Asthma_in_Older_Adults_Admission_Rate.pdf](https://www.qualityindicators.ahrq.gov/Downloads/Modules/PQI/V60-ICD09/TechSpecs/PQI_05_Chronic_Obstructive_Pulmonary_Disease_(COPD)_or_Asthma_in_Older_Adults_Admission_Rate.pdf).

14. Agency for Healthcare Research and Quality; US Department of Health and Human Services. Prevention Quality Indicator 05 (PQI 05) Chronic Obstructive Pulmonary Disease (COPD) or Asthma in Older Adults. AHRQ Quality IndicatorsTM (AHRQ QITM) ICD-10-CM/PCS Specification v2019 [accessed 2019 Nov 19].
[https://www.qualityindicators.ahrq.gov/Downloads/Modules/PQI/V2019/TechSpecs/PQI_05_Chronic_Obstructive_Pulmonary_Disease_\(COPD\)_or_Asthma_in_Older_Adults_Admission_Rate.pdf](https://www.qualityindicators.ahrq.gov/Downloads/Modules/PQI/V2019/TechSpecs/PQI_05_Chronic_Obstructive_Pulmonary_Disease_(COPD)_or_Asthma_in_Older_Adults_Admission_Rate.pdf).
15. van der Palen J, Moeskops-Van Beurden W, Dawson CM, James WY, Preece A, Midwinter D, Barnes N, Sharma R. A randomized, open-label, single-visit, crossover study simulating triple-drug delivery with Ellipta compared with dual inhaler combinations in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2018;13:2515–2523. doi: 10.2147/copd.s169060.
16. Donohue JF, Van Noord JA, Bateman ED, Langley SJ, Lee A, Witek TJ Jr, Kesten S, Towse L. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest*. 2002;122(1):47–55.
doi: 10.1378/chest.122.1.47.
17. Voshaar T, Lapidus R, Maleki-Yazdi R, Timmer W, Rubin E, Lowe L, Bateman E. A randomized study of tiotropium Respimat[®] Soft MistTM Inhaler vs. ipratropium pMDI in COPD. *Respir Med*. 2008;102(1):32–41. doi: 10.1016/j.rmed.2007.08.009.
18. Hodder R, Kesten S, Menjoge S, Viel K. Outcomes in COPD patients receiving tiotropium or salmeterol plus treatment with inhaled corticosteroids. *Int J COPD*. 2007;2(2):157–167.

Table 1. Baseline characteristics of the study population.

Patient Characteristics	Total, No. (%)
	277,373 (100%)
Age at first ICS/LABA, y	
18–44	79,720 (28.7%)
45–64	151,676 (54.7%)
65+	45,977 (16.6%)
Sex	
Male	106,648 (38.5%)
Female	170,725 (61.6%)
Maximum ICS/LABA dose	
Medium	189,911 (68.5%)
High	87,462 (31.5%)
OCS bursts ^a	
0	191,694 (69.1%)
1–2	72,267 (26.1%)
≥3	13,412 (4.8%)
Concomitant COPD	
Yes	60,204 (21.7%)
No	217,169 (78.3%)
HCP specialty	
Allergists	51,658 (18.6%)
Pulmonologists	62,780 (22.6%)
PCPs	130,617 (47.1%)
Other ^b	32,318 (11.7%)

ICS/LABA: inhaled corticosteroid/long-acting beta agonist; OCS: oral corticosteroid; COPD: chronic obstructive pulmonary disease; HCP: health care provider; PCPs: primary care physicians.

^aOCS burst is defined as:.

LAMA add-on cohort: OCS fill <30 days' supply within 180 days prior to first LAMA.

Biologic add-on cohort: OCS fill <30 days' supply within 180 days prior to first biologic.

^bIncludes multi-specialty physician groups, acute care facilities, and other specialties.

Table 2. Associations between LAMA and biologic treatment initiation rates and patient characteristics.

	Asthma only (<i>n</i> = 217,169)		Asthma with COPD (<i>n</i> = 60,204)	
	LAMA initiation	Biologic initiation	LAMA initiation	Biologic initiation
No. of patients initiating add-on therapy	10,425	3,549	17,572	1,004
Patient Characteristics, RR (95% CI) ^a				
Age at first ICS/LABA (y)				
18–44	0.75 (0.72-0.79)	1.26 (1.18-1.35)	0.83 (0.76-0.90)	1.84 (1.49-2.26)
45-64	REF	REF	REF	REF
65+	1.07 (1.01-1.14)	0.41 (0.34-0.49)	0.95 (0.92-0.98)	0.28 (0.23-0.33)
Sex				
Male	REF	REF	REF	REF
Female	1.23 (1.18-1.28)	1.03 (0.97-1.11)	0.98 (0.95-1.01)	0.95 (0.83-1.07)
Maximum ICS/LABA dose				
Medium	REF	REF	REF	REF
High	2.13 (2.05-2.22)	2.83 (2.65-3.03)	1.09 (1.06-1.12)	3.06 (2.71-3.47)
OCS bursts				
No	REF	REF	REF	REF
Yes	3.68 (3.54-3.82)	6.17 (5.75-6.62)	2.02 (1.96-2.08)	5.00 (4.34-5.76)
HCP Specialty				
Allergists	REF	REF	REF	REF
Pulmonologists	1.44 (1.37-1.50)	0.53 (0.49-0.57)	1.06 (1.00-1.12)	0.32 (0.28-0.36)
PCPs	0.33 (0.31-0.35)	0.08 (0.07-0.08)	0.85 (0.81-0.90)	0.04 (0.03-0.05)
Other ^b	0.43 (0.39-0.48)	0.14 (0.12-0.17)	1.09 (1.02-1.16)	0.04 (0.03-0.06)

CI: confidence interval; COPD: chronic obstructive pulmonary disease; HCP: health care provider; ICS/LABA: inhaled corticosteroid/long-acting beta agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroid; PCPs: primary care physicians; REF: referent; RR: rate ratio.

^aRate ratio (RR) represents the ratio between the initiation rate of a LAMA or biologic for that patient category as compared to the referent (REF) category for the variable. Rates and rate ratios account for each patient's follow-up time.

^bIncludes multi-specialty physician groups, acute care facilities, and other specialties.

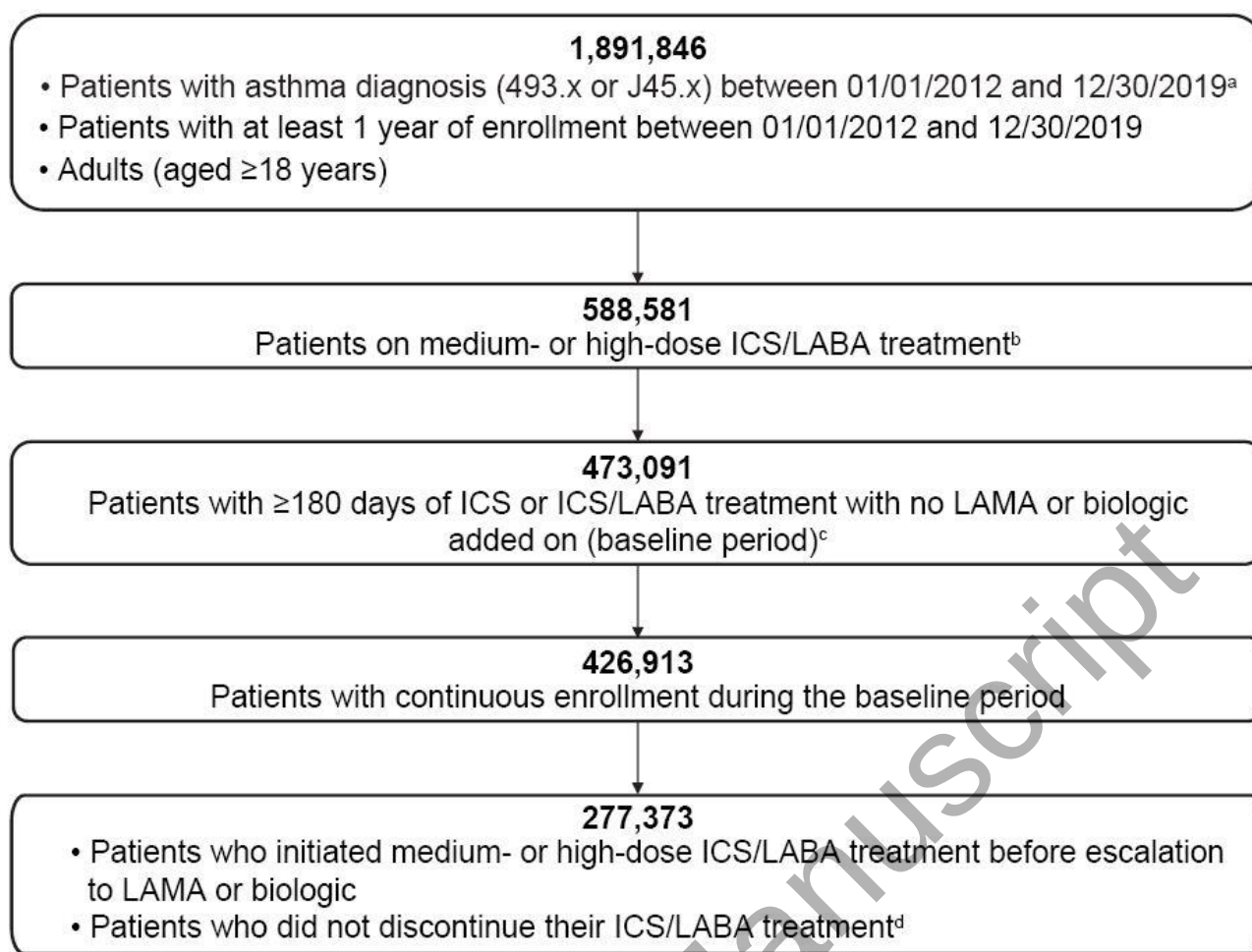


Figure 1. Patient flow.

^a≥2 medical encounters for asthma.

^b≥2 medical or pharmacy claims for medium- or high-dose ICS/LABA, ≥13 days apart.

^cBaseline period was defined as 180 days from the patient's first ICS or ICS/LABA fill.

^dPatients who added a LAMA or biologic had ≥2 claims for medium- or high-dose ICS/LABA prior to LAMA or biologic initiation, and added LAMA or biologic during an ICS/LABA treatment period or within 90 days of exhaustion of their last ICS/LABA fill. Patients who remained enrolled for 90 days or more after the exhaustion of their last ICS/LABA were excluded.

ICS: inhaled corticosteroid; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist.

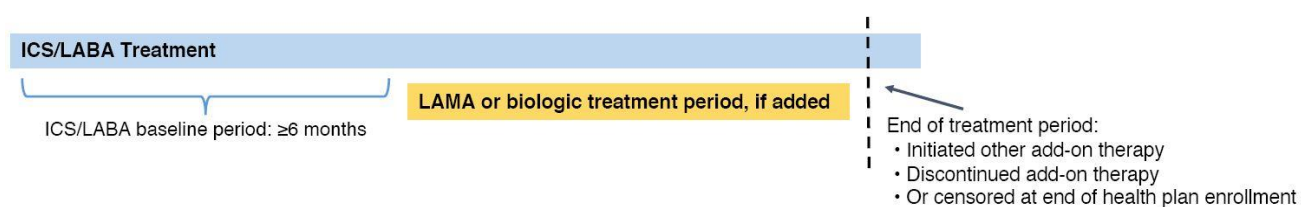


Figure 2. Schematic representation of observation period for each patient.

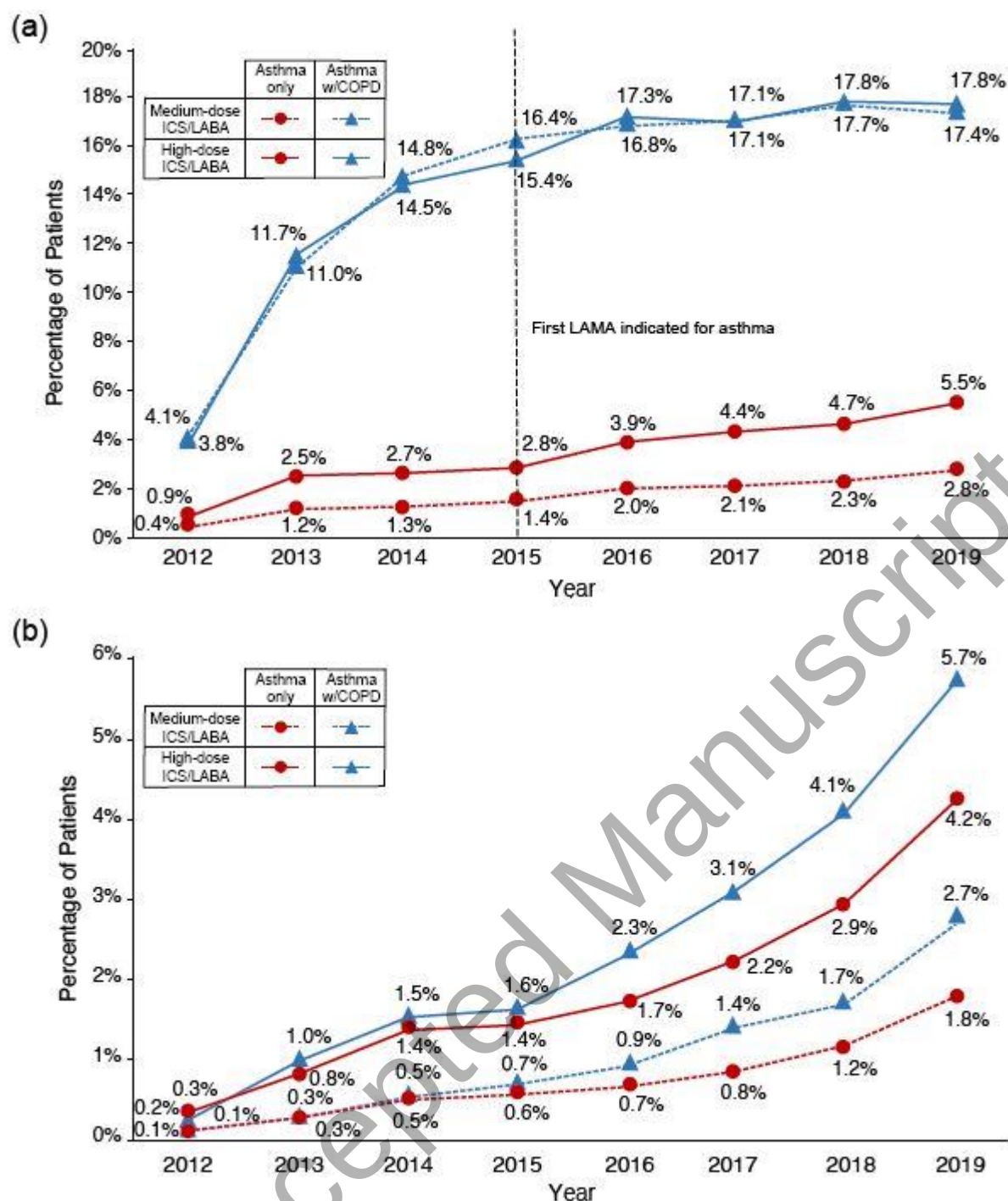


Figure 3. Percentage of patients initiating either a (a) LAMA or a (b) biologic by year, ICS/LABA dose, and concomitant COPD status. In (a), the dashed vertical line indicates year of FDA approval (2015) for tiotropium bromide. COPD, chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist.

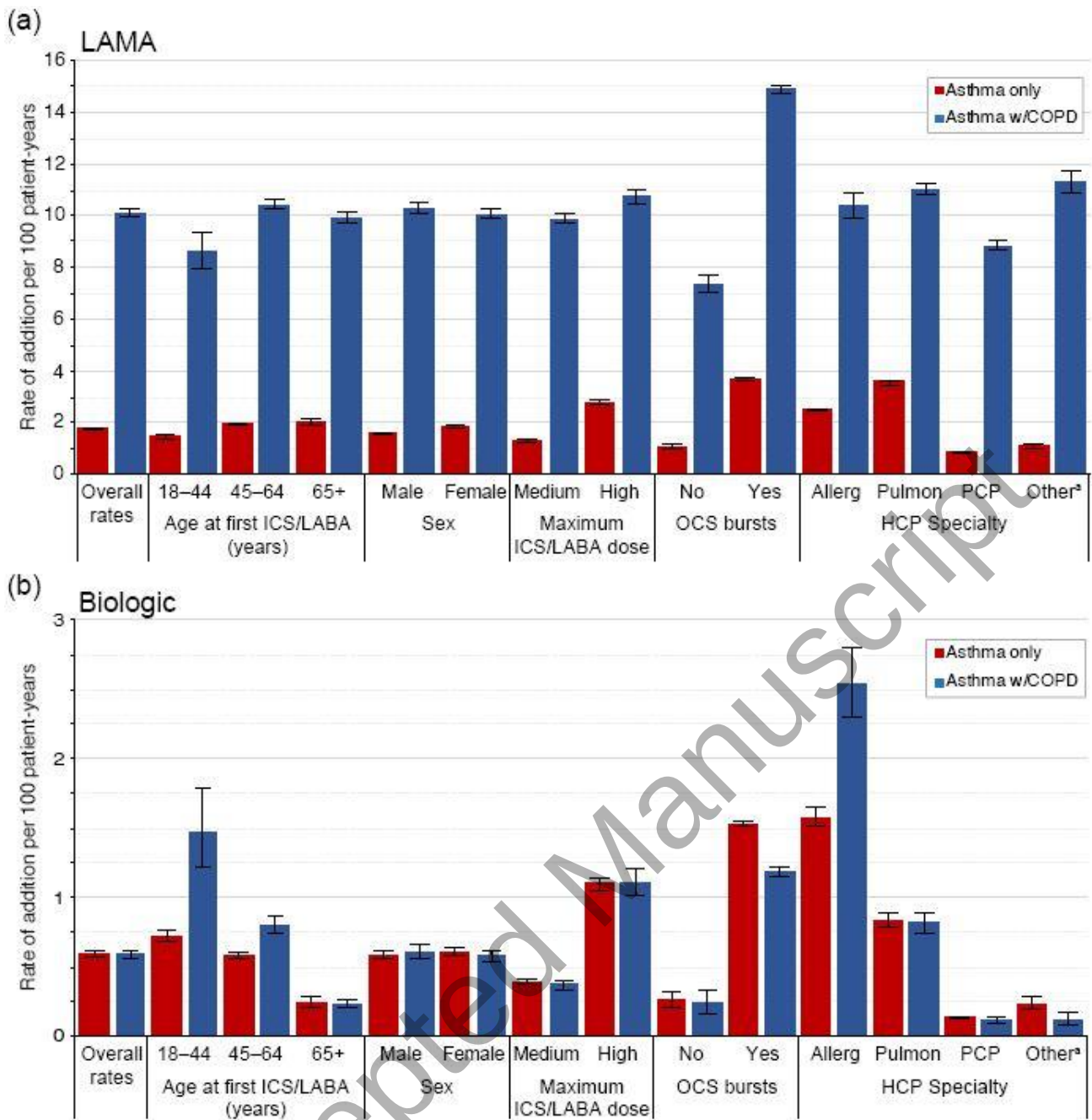


Figure 4. Rates of add-on (a) LAMA and (b) biologic treatment initiation per 100 patient-years. Error bars, 95% confidence intervals.

^aIncludes multi-specialty physician groups, acute care facilities, and other specialties. Allerg: allergist; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta agonist; HCP: health care provider; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroid; PCP: primary care physician; Pulmon: pulmonologist.

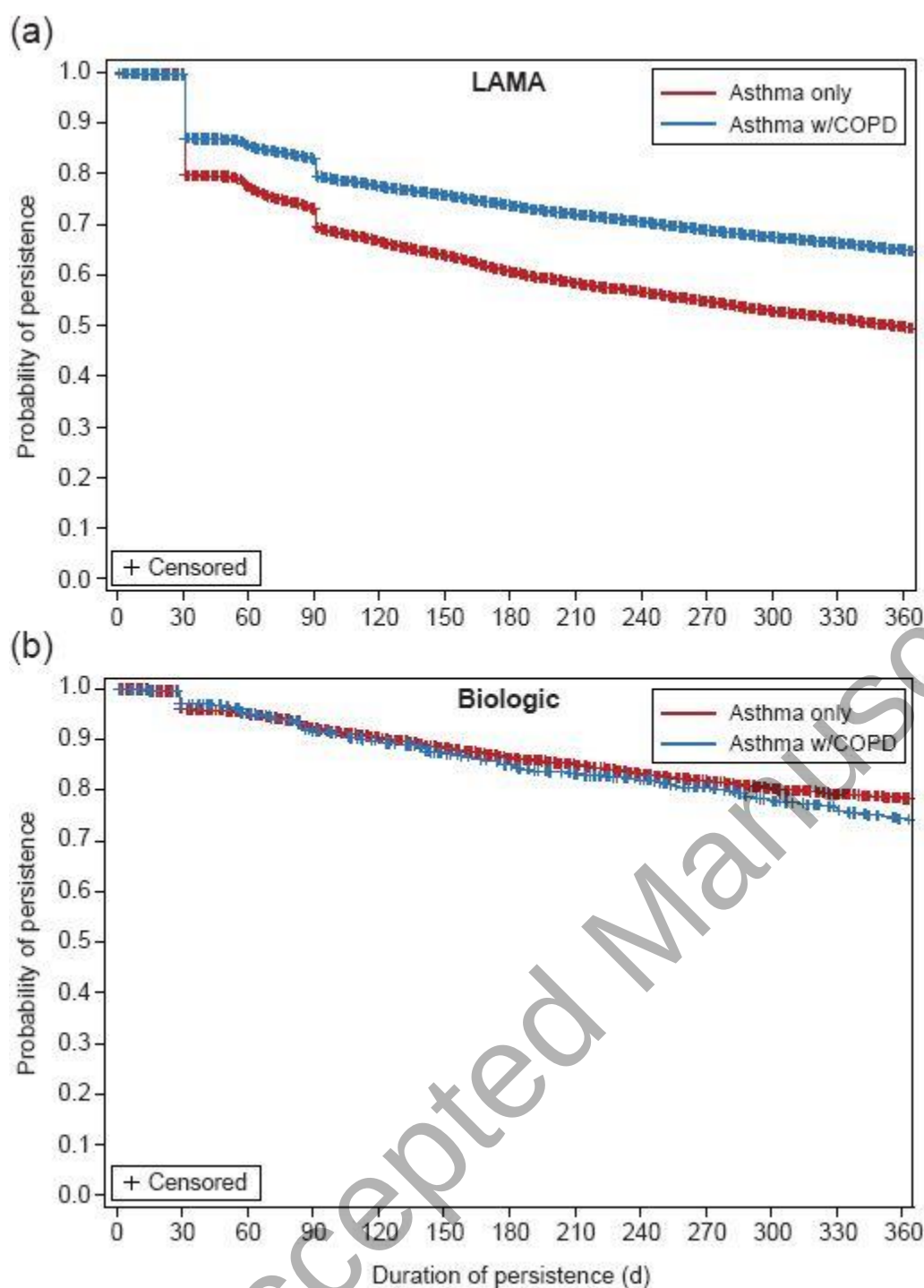


Figure 5. Persistence of (a) LAMA or (b) biologic treatment for one year after initiation. COPD: chronic obstructive pulmonary disease; LAMA: long-acting muscarinic antagonist.