Long-term macrolide therapy for chronic obstructive pulmonary disease: a population-based time series analysis

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Abstract

Background: Macrolides are recommended as an adjunctive treatment for patients with moderate to severe chronic obstructive pulmonary disease (COPD) who experience recurrent exacerbations. The objective of this study was to examine temporal trends in the provision of long-term macrolide therapy, specifically before and after publication of the landmark MACRO trial in August 2011 showing efficacy of macrolides for this indication.

Methods: We performed an interrupted time series analysis using population-level health administrative data. The study cohort consisted of all Ontario residents who had COPD, were using at least 1 long-acting inhaler, and were aged 65 years and older between Apr. 1, 2004, and Mar. 31, 2018. We compared the baseline characteristics of eligible patients before and after publication of the MACRO trial. Our primary outcome was overall prevalence of long-term macrolide therapy; secondary outcomes were incidence of COPD-related hospitalizations, emergency department visits and outpatient exacerbations requiring high-dose steroids in each quarter. We performed an interrupted time series analysis to assess for changes in the incidence of macrolide prophylaxis by quarter-year over the study period.

Results: The rate of long-term macrolide use increased from 0.8 per 1000 people in 2004 to 13.8 per 1000 people in 2018 (in the severe COPD group, the rate increased from 1.3 to 32.3 per 1000 people). The interrupted time series analysis showed that, before 2011, the prevalence of macrolide prophylaxis increased at a rate of 0.44 (95% confidence interval [CI] 0.39–0.50) per 1000 people per year; after 2011, the rate of increase grew by 1.18 (95% CI 1.07–1.29) per 1000 people to 1.63 (95% CI 1.56–1.69) per 1000 people per year. The seasonal pattern of COPD-related health care visits remained stable over the study period, and there was no detectable reduction in hospitalizations or emergency department visits at the population level.

Interpretation: In the past decade, there has been a significant rise in the use of long-term macrolide therapy for patients with COPD. As this practice becomes increasingly common, it will be important to monitor its potential benefits on COPD exacerbations but also its potential effects on adverse events and antimicrobial resistance patterns.

Chronic obstructive pulmonary disease (COPD) is one of the most common respiratory conditions worldwide.[1–3] One of the priorities of COPD management is preventing acute exacerbations, which are associated with increased mortality, accelerated disease progression and reduced quality of life. In addition, COPD exacerbations contribute substantially to the economic burden associated with the disease.[4,5]

Although inhaled therapies are the mainstay of COPD treatment, many patients continue to experience exacerbations despite intensive inhaler regimens, and adjunctive therapies are required. In 2011, a seminal randomized controlled trial (RCT) by Albert and colleagues reported a decrease in the frequency of exacerbations when oral azithromycin (v. placebo) was added to usual care (MACRO trial).[6] The benefits of macrolide prophylaxis for prevention

of exacerbations have subsequently been corroborated by other studies and systematic reviews.[7–10] The mechanism is thought to be related to the anti-inflammatory and immunomodulatory properties of macrolides, in addition to their antibacterial action.[6,11,12]

Current guidelines suggest that long-term macrolide use should be considered for patients with moderate to severe COPD and recurrent exacerbations.[13,14] However, the

prevalence of patients who receive prophylaxis is not known, and data are also lacking on the impact of this practice on exacerbation rates and potential adverse events in the real-world setting. In this study, we examined the trends in the provision of macrolide prophylaxis for patients with COPD over time to determine whether publication of the landmark RCT was associated with increased use of this intervention across the spectrum of COPD severity, and whether this coincided with changes in clinical outcomes at the population level.

Methods

Study design and data sources

This population-based time series analysis was performed at ICES using health administrative data from the province of Ontario, Canada.[15–17] The Ontario Health Insurance Plan (OHIP) is publicly funded and covers all medically necessary services for residents of the province. The Ontario Drug Benefit program covers prescription medications (including respiratory inhalers) for patients aged 65 years and older, and its database has an accuracy exceeding 99% for drugs dispensed by Ontario pharmacies.[15] Four other administrative databases were used for information on demographic characteristics, supplemental oxygen use, and health care encounters including hospitalizations and emergency department visits, and further details can be found in Appendix 1, available at www.cmajopen.ca/content/9/2/E576/suppl/DC1. All data sets were linked at the individual level using unique encoded identifiers and analyzed at ICES.

Residents of the province with COPD were identified using the ICES-derived COPD database, which has a sensitivity of 85% and a specificity of 78% for identifying patients with COPD (in our study, the specificity is presumed to be augmented since all included patients were required to be using at least 1 long-acting inhaler).[18] ICES-derived chronic disease cohorts that have been previously developed and validated using administrative databases were used to identify baseline comorbid conditions, such as asthma and congestive heart failure.[19,20]

Participants

Our study cohort consisted of Ontario residents with COPD who were aged 65 years and older between Apr. 1, 2004, and Mar. 31, 2018. Patients were eligible for the study if they were receiving at least 1 long-acting inhaler available through the Ontario Drug Benefit program, such as a long-acting muscarinic antagonist, a long-acting β agonist, an inhaled corticosteroid or a combination thereof. The study period was divided into quarter-years (3-mo intervals). A patient could be included in multiple quarters, as long as they met eligibility criteria on or before the first day of the quarter.

We excluded patients with a history of bronchiectasis or nontuberculous mycobacterial infection, given that these are also indications for prolonged macrolide treatment. These patients were identified using the *International Classification of Diseases, 10th Revision* (ICD-10) and OHIP diagnostic codes, as well as previous prescriptions for rifampin or ethambutol.

Baseline characteristics

Baseline variables of interest included demographic characteristics, comorbidities, medication use and health care utilization. We compared the baseline characteristics of eligible patients with COPD before and after the MACRO trial was published in August 2011 (designated as pre-Q3 2011 and post-Q3 2011);[6] for the purposes of this comparison, we randomly selected 1 eligible quarter per person from each period.

Outcomes

Our primary outcome was the overall prevalence of long-term macrolide therapy among all patients with COPD in Ontario. This was calculated as the number (per 1000) of patients with COPD who were receiving long-term macrolide prophylaxis overlapping the quarter, which was defined as having an active prescription for azithromycin, clarithromycin or erythromycin for 90 or more consecutive days. To account for possible delays in dispensing refills, we allowed any number of gaps between prescriptions, provided that each gap was no longer than 14 days.

For secondary outcomes, we measured the potential benefits of macrolide prophylaxis via the incidence of COPD-related hospitalizations, emergency department visits and outpatient exacerbations requiring high-dose steroids (receipt of an oral corticosteroid within 7 days of an outpatient visit for COPD) in each quarter. We captured the potential harms of macrolide prophylaxis via the incidence of hospitalization or emergency department visits for any 1 of the following: arrhythmias potentially related to macrolide-induced QT prolongation including cardiac death, hearing impairment, general adverse medication events and drug allergy, antibiotic-resistant organisms, *Clostridioides difficile* colitis and noninfectious diarrhea, or candidiasis (ICD-10 codes listed in Appendix 1, Supplemental Table 1). For all outcomes, the denominator of at-risk individuals included all patients with COPD meeting eligibility criteria at the start of the quarter.

We examined for potential indication creep by stratifying by COPD severity and comparing the proportion of patients with mild, moderate and severe COPD who received macrolide prophylaxis. We did not have individual spirometry data; therefore, COPD severity was defined using 2 surrogates: baseline inhaler therapy and exacerbation rate. We defined therapy-based severity by the number of classes of long-acting inhaler treatments in the preceding 2 years: 1 inhaler class (mild), 2 inhaler classes (moderate), or 3 inhaler classes and/or supplemental oxygen (severe). Exacerbation-based severity was defined using COPD-related hospital encounters in the preceding 2 years: an inpatient hospitalization (severe), an emergency department visit (moderate) or neither (mild). After assigning patients to responsible physicians (based on who prescribed their chronic inhaler therapy), we examined physician variability in the percentage of their patients with COPD for whom they prescribed macrolides in the most recent study year (fiscal year 2017).

Table 1: Baseline characteristics of patients with chronic obstructive pulmonary disease pre- and post-Q3 2011		
	No. (%) of patients*	
Characteristic	Pre-Q3 2011 n = 254 457†	Post-Q3 2011 n = 312 370†
Demographic		
Sex		
Female	132 279 (52.0)	162 602 (52.1)
Male	122 178 (48.0)	149 768 (47.9)
Age at index, yr		
Mean ± SD	76.42 ± 7.64	76.37 ± 8.13
Median (IQR)	76 (70–82)	75 (69–82)
Age at COPD diagnosis, yr		
Mean ± SD	68.73 ± 9.34	66.53 ± 10.73
Median (IQR)	68 (62–75)	66 (59–74)
Income quintile		
Missing	1232 (0.5)	967 (0.3)
1 (lowest)	61 399 (24.1)	78 962 (25.3)
2	55 665 (21.9)	69 872 (22.4)
3	49 324 (19.4)	61 227 (19.6)
4	45 992 (18.1)	53 434 (17.1)
5 (highest)	40 845 (16.1)	47 908 (15.3)
Rural‡		
Missing	287 (0.1)	374 (0.1)
No	211 047 (82.9)	261 532 (83.7)
Yes	43 123 (16.9)	50 464 (16.2)
Comorbidities		
Asthma	96 907 (38.1)	107 543 (34.4)
Congestive heart failure	70 177 (27.6)	78 542 (25.1)
Ischemic heart disease (preceding 2 yr)	35 404 (13.9)	34 650 (11.1)
Pneumonia (preceding 2 yr)	69 587 (27.3)	78 700 (25.2)
Health care utilization		
Hospitalizations per year§		
Mean ± SD	0.42 ± 0.69	0.37 ± 0.67
ED visits per year§		
Mean ± SD	0.77 ± 1.54	0.83 ± 1.56
Medication use		
Corticosteroid, days per year§		
Mean ± SD	12.92 ± 51.62	11.12 ± 47.22
High-dose corticosteroid, days per year§		
Mean ± SD	1.01 ± 4.95	1.26 ± 5.15
Any oral steroid in previous 2 years	70 570 (27.7)	96 733 (31.0)
No. of long-acting inhaled agents at baseline		
1	140 977 (55.4)	140 905 (45.1)
2	76 832 (30.2)	111 904 (35.8)
3	36 648 (14.4)	59 561 (19.1)
Inhaled therapy types		
LAMA only	73 406 (28.8)	90 693 (29.0)
ICS only	64 056 (25.2)	48 270 (15.5)
LABA only	3515 (1.4)	1942 (0.6)
LABA + ICS	66 114 (26.0)	94 058 (30.1)
LAMA + LABA	2157 (0.8)	11 697 (3.7)
LAMA + ICS	8561 (3.4)	6149 (2.0)
LAMA + LABA + ICS	36 648 (14.4)	59 561 (19.1)
Supplemental oxygen	17 841 (7.0)	27 679 (8.9)

Note: COPD = chronic obstructive pulmonary disease, ED = emergency department, ICS = inhaled corticosteroid, IQR = interquartile range, LABA = long-acting β-agonist, LAMA = long-acting muscarinic antagonist, SD = standard deviation.
*Unless stated otherwise.
†132 701 individuals were eligible in both eras.
‡Rurality had 0.1% missing data for each era.
§Based on the preceding 2 years.

Statistical analysis

We examined temporal trends in the incidence of macrolide prophylaxis over time (per 1000 people) between Apr. 1, 2004, and Mar. 31, 2018 (14 yr, 56 quarters). The unit of analysis was the quarter. To test the specificity of our findings, we also examined temporal trends in other common antimicrobial agents that have not been endorsed for chronic prophylaxis in this population, namely cephalexin and nitrofurantoin. We performed an interrupted time series analysis to assess for changes in the incidence of macrolide prophylaxis, using a linear model with 2 parameters in addition to the intercept: the preperiod slope and the postperiod slope change.[21] In a sensitivity analysis, we repeated the interrupted time series using a first-order autoregressive model. Statistical analyses were performed using SAS version 9.4M5 (2017, SAS Institute).

Ethics approval

The use of data in this project was authorized under section 45 of Ontario's *Personal Health Information Protection Act*; thus, review by a research ethics board was not required.

Results

We found a total of 919 008 Ontarians aged 65 years or older with COPD between Apr. 1, 2004, and Mar. 31, 2018. We excluded 472 480 individuals who were not receiving a long-acting inhaler and 12 402 with a history of bronchiectasis or mycobacterial infection, resulting in 434 126 eligible participants for our study (Appendix 1, Supplemental Figure 1). A total of 254 457 patients were eligible pre-Q3 2011, and 312 370 patients were eligible post-Q3 2011. Characteristics of patients with COPD were similar in the periods pre-Q3 2011 and post-Q3 2011 (Table 1).

Prevalence of macrolide prophylaxis

The prevalence of macrolide prophylaxis increased during the study period from 0.8 per 1000 people in Q2 2004 to a high of 13.8 per 1000 people by the end of the follow-up period. In contrast, the prevalence of long-term prophylaxis with cephalexin and nitrofurantoin was generally stable throughout the study period (Figure 1).

When stratified by therapy-based COPD severity, patients in the severe group exhibited a steep increase in the prevalence of macrolide prophylaxis over time (from 1.3 to 32.3 per 1000). Those with mild and moderate severity exhibited less pronounced increases in prevalence over the study period (Figure 2A). With stratification by exacerbation-based severity, the prevalence in all groups increased substantially, but the prevalence in the moderate and severe groups increased by about twice as much as that of the mild group (Figure 2B).

The interrupted time series model showed that initially macrolide prophylaxis increased at a rate of 0.44 (95% confidence interval [CI] 0.39–0.50) per 1000 people each year
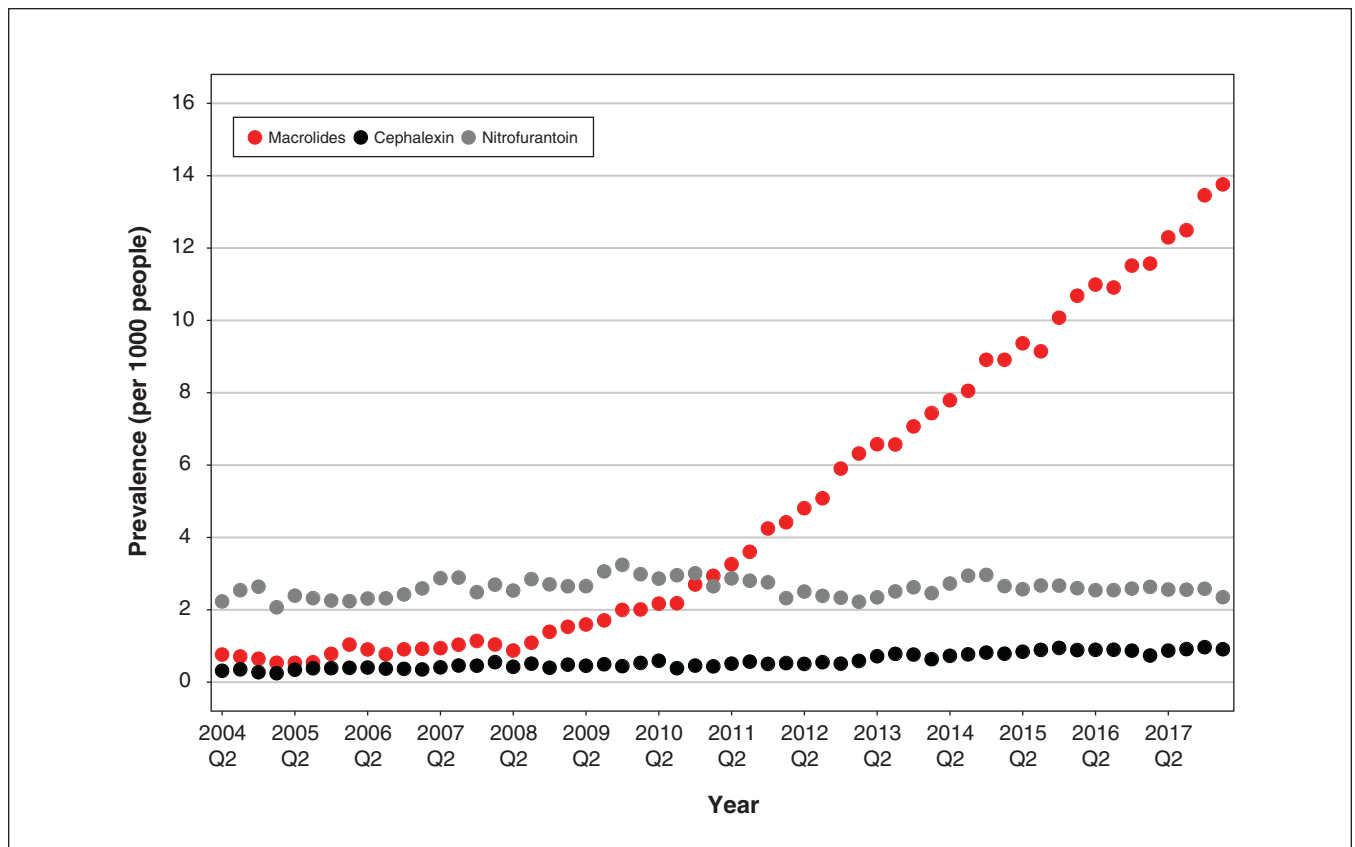
Figure 1: Increase in the prevalence of long-term macrolide therapy over time among patients with chronic obstructive pulmonary disease, as compared with trends in chronic prophylaxis with other common antimicrobial agents.
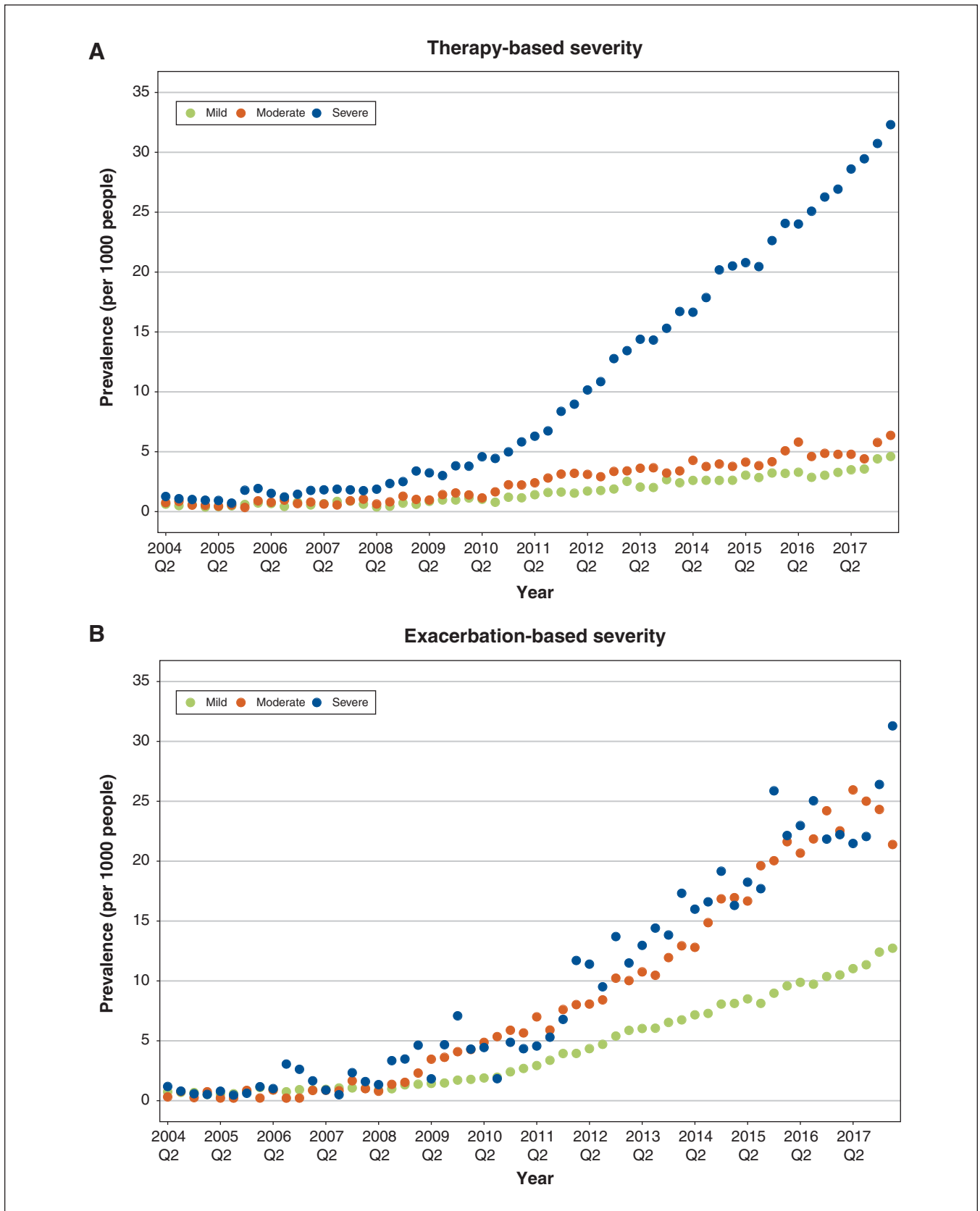
Figure 2: Prevalence of long-term macrolide therapy over time among patients with chronic obstructive pulmonary disease, stratified by therapy-based severity (A) and exacerbation-based severity (B).

before the publication of the MACRO RCT in August 2011; thereafter, the rate increased by 1.18 (95% CI 1.07–1.29) per 1000 people to 1.63 (95% CI 1.56–1.69) per 1000 people per year (Figure 3). In a sensitivity analysis incorporating a first-order autoregressive model, there was a slightly shallower slope in the pre-RCT period (0.40/yr instead of 0.44/yr) and no change in post-RCT slope, thus suggesting a slightly greater influence of the RCT on macrolide prescribing trends.

A total of 84.1% of macrolide prophylaxis regimens used azithromycin. The most common regimens were equivalent to a daily dose of less than 150 mg of azithromycin (35.7% of regimens), followed by 250–499 mg of azithromycin (30.8%) and 150–249 mg of azithromycin (13.7%). Physicians who prescribed chronic macrolides had a median of 6.3% of their patients with COPD taking prophylaxis, with wide variability across prescribers (interquartile range [IQR] 3.6%–12.5%). Median use and variability across prescribers were higher among patients with severe COPD (by therapy-based criterion, median 9.9%, IQR 5.0%–20.0%).

Temporal trends in clinical outcomes

There was a strong seasonality in COPD-related outcomes but no observable change in frequency or slope after Q3 2011 (Figure 4). Among the patients with severe COPD by the therapy-based definition, for whom macrolide prophylaxis was more common, there was also no detectable change in outcomes after Q3 2011 (Figure 5). Similar results were seen for those with severe COPD defined by exacerbations (data not shown).

Interpretation

In this population-level study involving patients with COPD aged 65 years and older in Ontario, Canada, we found that there has been a significant increase in the use of macrolide prophylaxis in the past decade, from 0.8 per 1000 people in 2004 to 13.8 per 1000 people in 2018.

The rise in macrolide use we observed is presumed to be related to the landmark MACRO trial — published in 2011 — that demonstrated the efficacy of macrolides in reducing exacerbations, and the subsequent inclusion of this practice into major clinical guidelines.[6] The slight upward trend in macrolide use we observed several years earlier may be due to the 2008 publication of another influential RCT, in which erythromycin was used, or to early information from the MACRO trial before its final publication.[22]

Our study contributes to the understanding of the prevalence of macrolide prophylaxis at a population level. Previously, one study using the United Kingdom primary care database between 2000 and 2009 had reported that only
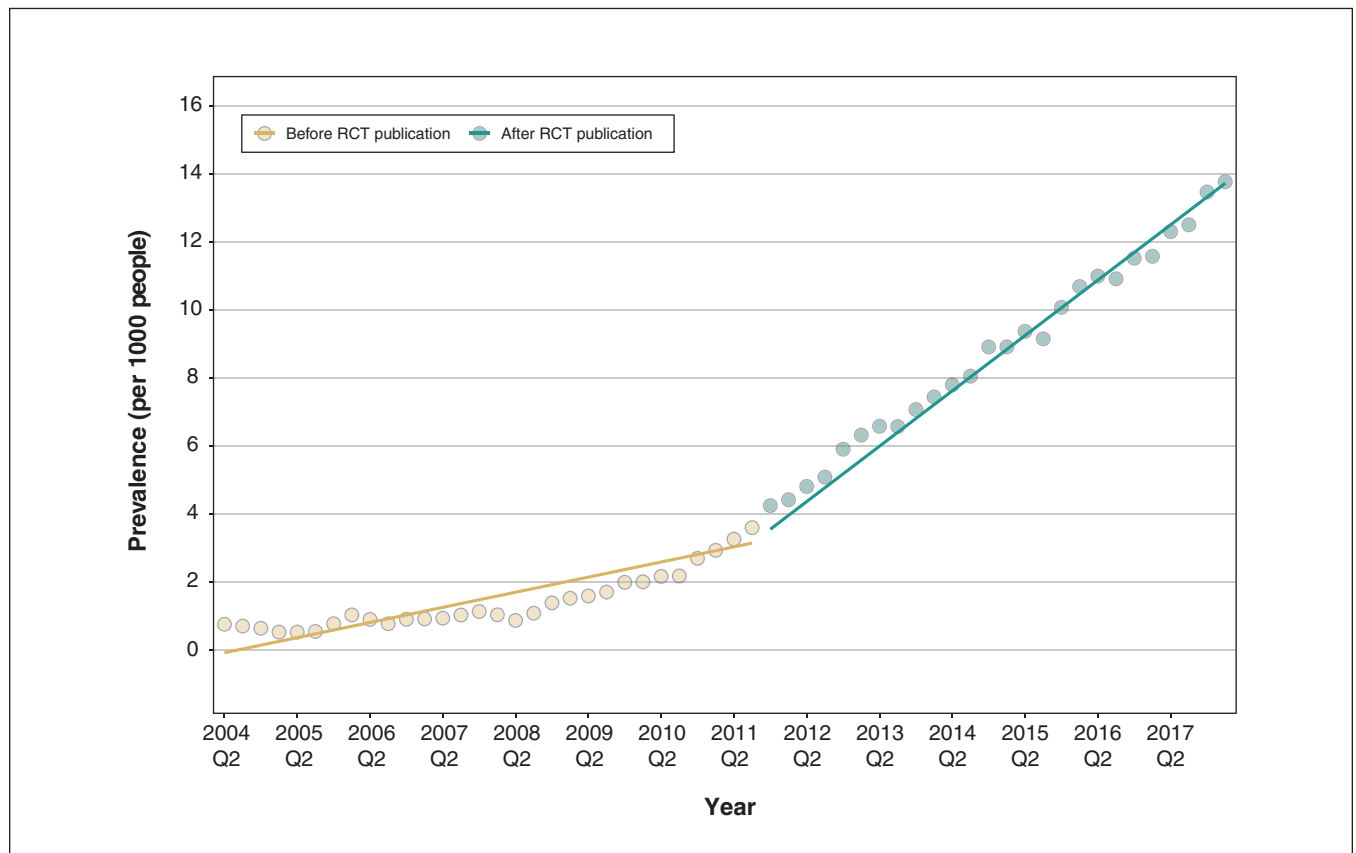
Figure 3: Interrupted time series analysis showing an increase in long-term macrolide therapy associated with the publication of a seminal randomized controlled trial (RCT) in 2011 demonstrating the efficacy of azithromycin for prevention of exacerbations of chronic obstructive pulmonary disease.[6]
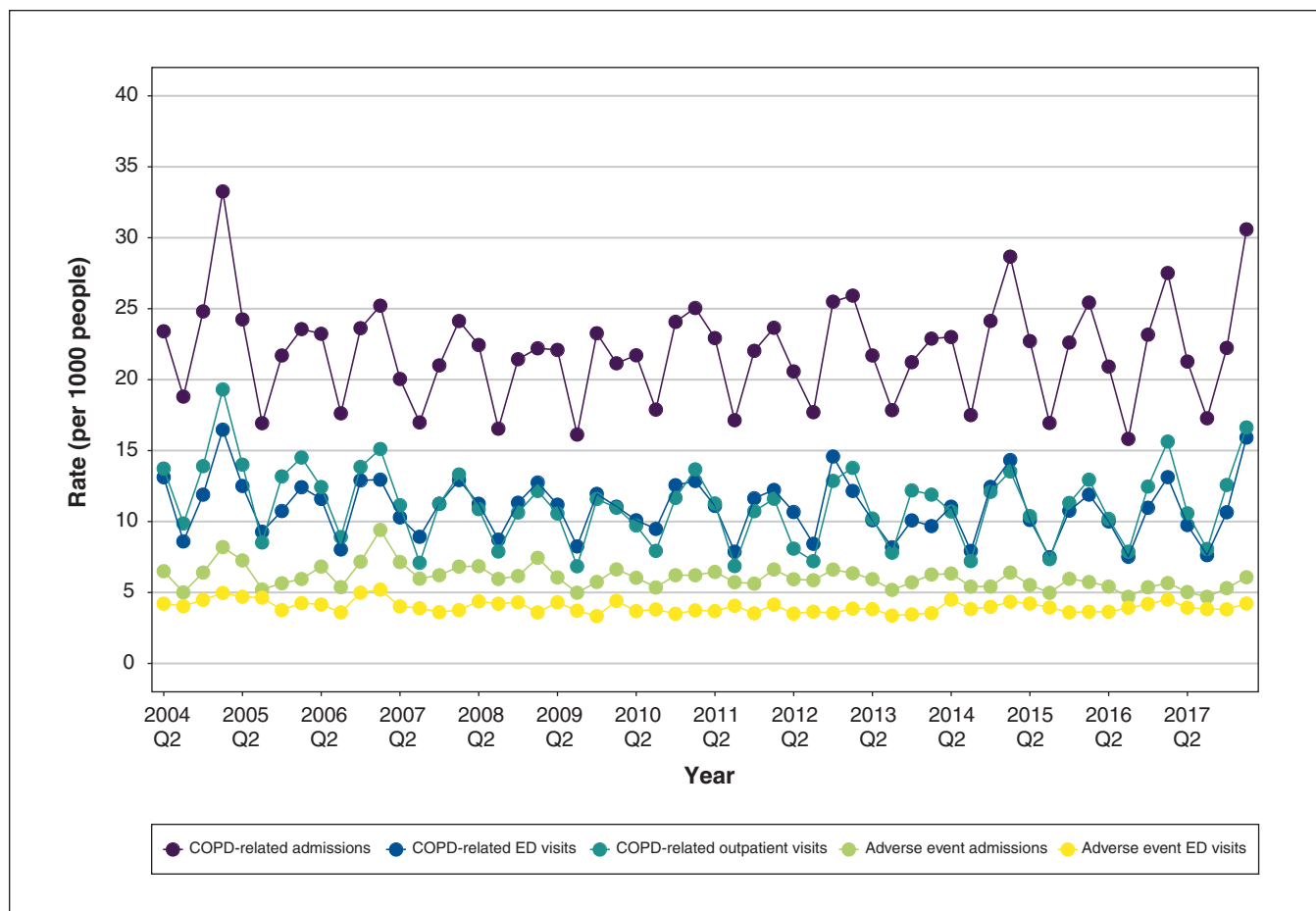
Figure 4: Overall temporal trends in clinical outcomes related to chronic obstructive pulmonary disease (COPD) among all patients. Note: ED = emergency department.

0.61% of patients with COPD received antibiotic prophylaxis (most frequently with nonmacrolide antibiotics); however, this study was conducted before the 2011 MACRO trial publication and before the practice was widely incorporated into clinical guidelines.[23]

Most of the trials involving macrolide prophylaxis focused on patients with moderate to severe COPD, and this is reflected in all the major clinical guidelines. Specifically, the latest joint statement from the American Thoracic Society and the European Respiratory Society in 2017 suggests macrolides for patients with "moderate to very severe airflow obstruction and exacerbations despite optimal inhaled therapy."[14] Similar recommendations have been published by the Canadian Thoracic Society and American College of Chest Physicians.[13,24] To examine for indication creep, we stratified the patients by severity based on their long-acting inhaler medications and exacerbation rates in the preceding 2 years. Our results showed that, in general, physicians are prescribing in accordance with these guidelines. Patients who received macrolides are overwhelmingly those who were already taking triple inhaled agents and presumably continued to have exacerbations despite this. When COPD severity was stratified by exacerbation rates, there was also a notable upward trend in the use of macrolide prophylaxis in the group with mild severity. Although this may reflect indi-

cation creep, these patients may have also had outpatient exacerbations that were not captured in the study.

There was heterogeneity in the antibiotic regimens that patients received. The most common one — accounting for 35.7% of all regimens — was equivalent to a daily dose of less than 150 mg of azithromycin. This likely corresponds to the regimen of azithromycin 250 mg 3 times weekly. Of note, this is a smaller dosage than the 250 mg daily regimen tested in the MACRO trial.[6] This may be a deliberate choice by clinicians, possibly owing to concerns regarding adverse effects or patient inconvenience. Certain commentators have argued that given the long half-life of azithromycin, daily dosing may be too aggressive.[25,26] Respirologists may also have more familiarity with 3-times-weekly regimens since this approach is also routinely applied to patients with cystic fibrosis and other causes of bronchiectasis.[27,28]

In terms of patient outcomes, the seasonal pattern of COPD-related health care visits remained stable over the years, and there was no appreciable reduction in COPD hospitalizations or emergency department visits associated with the increase in macrolide use. These results should be interpreted cautiously and do not imply a lack of effectiveness with macrolide usage, as overall use of prophylaxis remained low at the end of the study period (maximum 13.8/1000 patients with
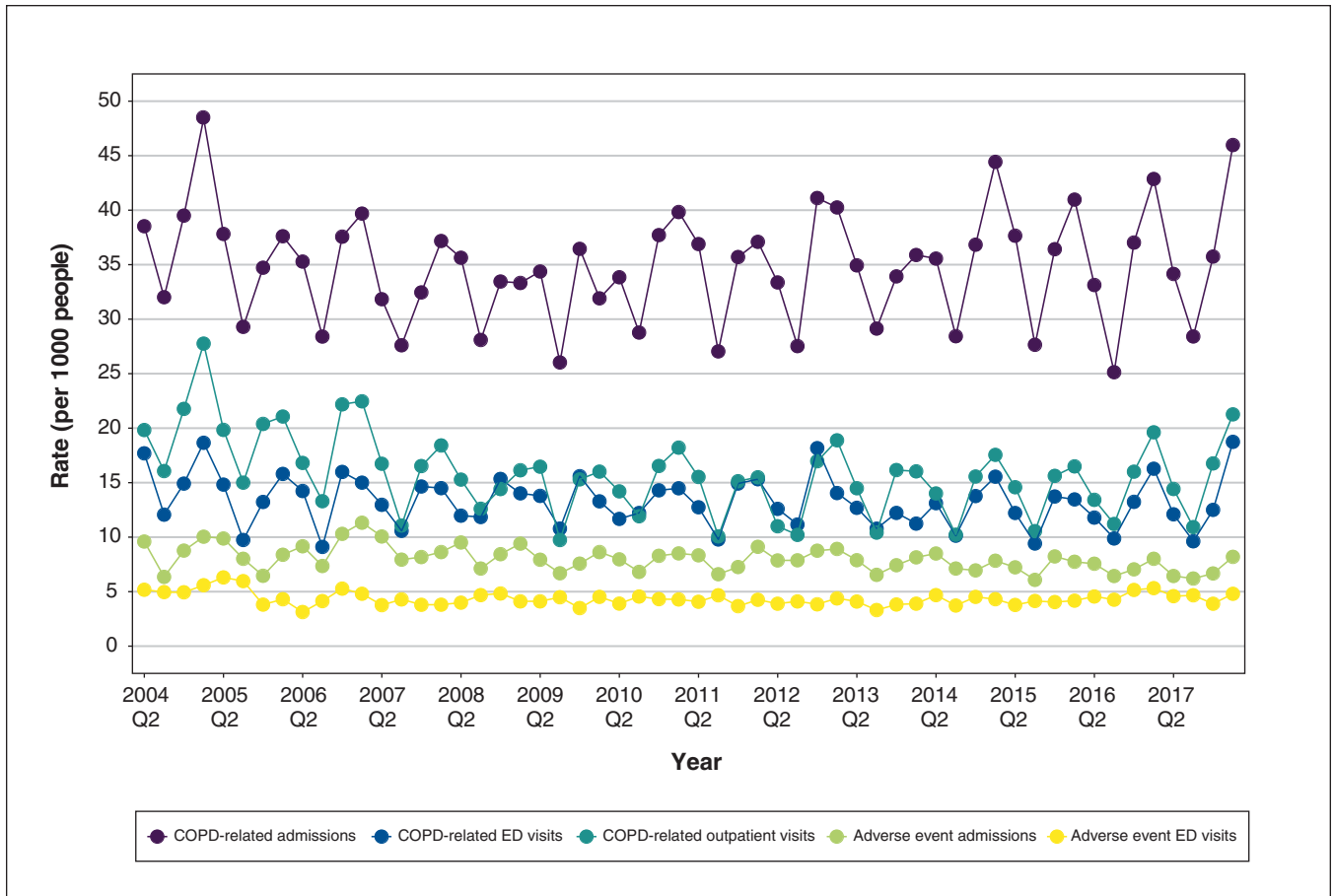
Figure 5: Temporal trends in clinical outcomes related to chronic obstructive pulmonary disease (COPD) among patients with severe COPD (intensity of inhaled therapy used as surrogate for severity). Note: ED = emergency department.

COPD and 32.3/1000 patients with severe COPD). Therefore, any benefits at the individual level would not necessarily translate to measurable changes at the population level. Furthermore, patient adherence was inferred from drug-dispensing data, but true adherence is not known.

There were also no apparent changes in the overall pattern of possible macrolide-related adverse events over time. In the MACRO trial,[6] there were no differences in the rate of serious adverse events between the 2 arms of the study, but hearing decrements on audiometry testing were more common in the azithromycin group. Our composite outcome also included other risks associated with macrolides, such as cardiac arrhythmias, allergic reactions, and diarrhea or *C. difficile* colitis. However, there are limitations with how these events were captured in this study. Because administrative databases were used, it is difficult to determine the proportion of events that should be attributed to macrolide use. Additionally, some of the minor or more subtle adverse effects (e.g., hearing loss) may not be recognized by patients or may not lead to health care encounters that would be captured in this study. Furthermore, the absence of population-wide microbiology data during this study interval meant that we were unable to examine for one of the most important potential patient- and societal-level harms of widespread macrolide use, namely the selection of increased macrolide resistance in key human pathogens, such as *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus aureus*.

Limitations

In addition to our inability to determine adherence to treatment regimens and to precisely capture all adverse effects of macrolide treatment, there were several other notable study limitations. The COPD cohort was identified using an ICES-derived definition. Although it has been previously validated, its sensitivity and specificity are imperfect.[18] We were unable to include younger patients in the cohort for pragmatic reasons since the Ontario Drug Benefit provided coverage only to residents aged 65 and older. Because we used health administrative data, we also did not have individual spirometry data to help classify patients by COPD severity (other relevant variables such as smoking status were also not available). However, our method of stratifying by baseline inhaler medications and exacerbation rates appears to be valid given the clear delineation in trends in treatment and outcomes between the different groups. Although we found that patient selection for prophylaxis generally conformed to clinical guidelines, we do not have specific data to determine whether patients were also appropriately screened for contraindications such as prolonged QT intervals and baseline hearing impairment.

Conclusion

Since the publication of the landmark MACRO trial in August 2011, there has been a significant rise in the use of macrolides as prophylaxis for patients with moderate to severe COPD and recurrent exacerbations. As this practice becomes increasingly common, it will be important to monitor its potential benefits on COPD exacerbations but also its potential impact on adverse events and antimicrobial resistance patterns.

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Data sharing: The data set from this study is held securely in coded form at ICES. Although data-sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at https://www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors on request, with the understanding that the computer programs may rely on coding templates or macros that are unique to ICES and, therefore, are inaccessible or may need modification. Please send inquiries to the corresponding author.

Supplemental information: For reviewer comments and the original submission of this manuscript, please see www.cmajopen.ca/content/9/2/E576/suppl/DC1.