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SHORT REPORT

Patients with Higher Exacerbation Burden and Eosinophil Counts are More Likely to Require Multiple Biologics for Asthma Control

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Background: Multiple biologics are now available for severe asthma, creating opportunities to switch between therapies.

Purpose: To identify characteristics of patients with asthma who switch biologics.

Methods: We examined biologic switching in 1611 patients with moderate-to-severe asthma on maintenance therapy who initiated a biologic between 2014 and 2023 within a large health system and had no alternate indication. Chart reviews were performed to determine reasons for switching. We compared the characteristics of patients who: 1) did not switch therapy versus switched due to suboptimal response, and 2) switched once versus switched multiple times using descriptive statistics. Exacerbation incidence rates were assessed using Poisson regression. Inverse-probability-weighted-logistic regression accounting for demographic and clinical variables was conducted to evaluate factors associated with switching.

Results: Fourteen percent (230/1611) switched: 81% once, 19% ≥2 times. Suboptimal response accounted for >70% of switches. Higher pre-initiation exacerbation rates were associated with a stepwise increase in likelihood of switching (1.4 in non-switchers vs 2.3 in patients who switched twice; 2.8 switched twice; and 3.4 in patients switching ≥3 times). Patients using ≥3 biologics had more baseline exacerbations (2.9 vs 2.3 in one-time switchers, p=0.01) and higher maximum blood eosinophil counts (BEC) in the year prior to treatment (662 vs 334 cells/μL, p=0.02), though median baseline BEC did not differ (229 vs 244 cells/μL, p=0.60). In weighted analyses, exacerbations (odds ratio, OR: 1.03; 95% Confidence Intervals, CI: 1.01–1.04, p<0.001) and baseline BEC (OR, 2.0 for each 50 cells/mcl increase; 95% CI: 1.2–3.4, p=0.002) were significantly different between switchers and non-switchers. However, only higher baseline exacerbations differentiated those who switched once to those who switched two or more times (1.02, 1.00–1.05, p=0.04). Exacerbations declined significantly in non-switchers during the first treatment year (1.42 to 0.99, p<0.001) but not among switchers.

Conclusion: Patients with more severe asthma and higher maximum eosinophil counts at biologic initiation were more likely to switch therapies, predominantly due to suboptimal response. These findings emphasize the importance of selecting the first biologic carefully and optimizing timing of initiation.

Keywords: asthma, biologics, monoclonal antibodies, switch, eosinophil, exacerbations

Introduction

With six biologic therapies currently approved for the treatment of moderate-to-severe asthma, there are ample opportunities for patients to switch between biologics to achieve asthma control.[1,2] While suboptimal response is the leading reason for switching respiratory biologics,[3–5] little is known about the characteristics of patients who switch. Identifying these features could help anticipate poor responders. We sought to evaluate switching patterns and patient characteristics associated with switching events between biologics. We hypothesized that patients with higher exacerbation rates at baseline and eosinophil count would be more likely to switch between biologics due to suboptimal response over follow-up.

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Methods

Study Population

We analyzed data from adult patients with asthma (International Classification of Diseases (ICD)- 9th revision: 493.x or 10th revision: J45) from the Mass General Brigham health system who were on maintenance therapy with inhaled steroids and a long-acting beta agonist and initiated a respiratory biologic between January 2014, shortly before the first anti-IL5 was approved, and June 2023 and evaluated if they switched to another biologic on or before our study end date of June 2024. All patients were seen by an allergist and/or pulmonologist in the MGB Severe Asthma Clinics. We included omalizumab, mepolizumab, benralizumab, and dupilumab. Only one patient initiated reslizumab and so it was not included. We did not include tezepelumab due to its relatively newer introduction into the market and its approval for type-2-low asthma which would both limit switching opportunities. We also excluded patients with other chronic lung diseases, except chronic obstructive pulmonary disease (COPD). To focus on asthma-related use, given that a comorbidity could influence preference for a biologic and switching, we excluded patients with alternate indications for these biologics. These included chronic spontaneous urticaria, atopic dermatitis as well as anyone whose dupilumab was initiated by a dermatologist given the likelihood that this was initiated for the treatment of atopic dermatitis, another leading indication for dupilumab, chronic rhinosinusitis with nasal polyps (CRSwNP) since three of these biologics, but not all, are approved for CRSwNP treatment, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, eosinophilic esophagitis, and prurigo nodularis. The resulting cohort of patients represent a group of patients with moderate-to-severe asthma who had initiated the respiratory biologic specifically for their asthma and with potentially similar opportunities of being switched to another biologic due to an asthma-related factor. We followed every patient from the date of initiation of their first biologic to the end of the follow up period (June 2024) and evaluated if they switched to an alternate biologic during follow-up.

Chart Reviews/Data Collection

Two authors (AB and AA) reviewed the charts of patients who switched to identify the reasons for switching. For each switching event, we categorized the reason for switch as: 1) for effectiveness (eg suboptimal improvement in asthma symptoms, exacerbations, or lung function), or 2) not for effectiveness (eg due to insurance for payment-related reasons or for patient-specific reasons such as a woman stopping therapy because she found out she was pregnant). In the event that the reason for switching was: 1) not singular- multiple reasons were recorded, 2) unclear- the chart was re-reviewed and the final reason for switching was resolved by consensus, or 3) unreported- the switch was categorized as "not for effectiveness". We focused on the switches for effectiveness in our analyses.

Statistical Analyses

We presented continuous variables as mean with standard deviation (SD) or median with interquartile range (IQR) and categorical variables as proportions. Using the Wilcoxon rank-sum test for continuous variables and the Chi-square test for categorical variables, we compared the baseline characteristics of switchers at the initiation of their first biologic to the characteristics of non-switchers, and among switchers, those who switched once were compared to those who switched multiple times. Given the preliminary evidence that most patients switched due to effectiveness,[3,4] we evaluated the difference in the reduction in exacerbation rates (incidence rates) using Poisson regression in the one year following the initiation of the first biologic for patients who switched and those who did not switch, adjusting for baseline exacerbations. An asthma exacerbation was defined as an emergency room visit or hospitalization for asthma, wheezing, or bronchospasm, or a new prescription for ≥3 days of oral corticosteroids.[6] Given that patients who switched over follow up might have differed in systematic ways at baseline from patients who did not switch, we conducted inverse probability weighted analyses (IPTW) which sought to balance switchers and non-switchers on the first biologic initiated and their baseline covariates which included age, sex, race, BMI, smoking status, insurance type, presence of COPD, and LAMA use. These weights were then applied to a model predicting switching with predictors (baseline exacerbations, baseline (most recent) BEC, and maximum BEC in the 3 years prior to therapy initiation). This final model also included the follow-up length from biologic initiation given that the longer the follow-up, the higher the opportunities for switching. A similar model was constructed to compare those who switched once to those who switched two or more times. This retrospective study was approved by the Mass General Brigham IRB (#2021P003227) with a waiver of patient

consent. All procedures adhered to the Declaration of Helsinki and data were deidentified and reported in aggregate to assure confidentiality. All analyses were performed using R version 4.1.0 (2021, The R Foundation for Statistical Computing).

Results

We identified 2502 eligible patients. We excluded 835 patients with alternate biologic indications and 56 patients who initiated tezepelumab or reslizumab. Our final study population included 1611 individuals (Figure E1). Omalizumab made up 47% (N=752) of these initiations, dupilumab, 33% (526), mepolizumab, 16% (254), and benralizumab, 5% (79). Baseline characteristics varied by biologic. Patients initiating omalizumab were younger (mean age: 43.6 years). Those on mepolizumab and benralizumab had the highest median blood eosinophil counts (BEC) of 370 and 271 cells/μL respectively. Eighteen percent of mepolizumab users and 11% of dupilumab users had COPD (Table E1).

Fourteen percent (230 patients; 300 switches; Figure E2) switched: 81% switched once; 19% switched ≥2 times. Suboptimal effectiveness accounted for the majority (70%; 162) of these switches. We were unable to identify the reason for one patient who switched from omalizumab. Among those switching due to suboptimal response: multiple demographic factors were associated with switching including higher BMI (30.5 vs 29.3 kg/m^2, p=0.008), race (p=0.03), and concomitant COPD (18.9% vs 8.6%, p<0.001) (Table 1). Patients who switched had worse asthma control at baseline (2.4 vs 1.5 in year pre-biologic, p<0.001). Higher exacerbation rates at initiation of the *first* biologic were associated with lower 12-month exacerbation reduction and a higher likelihood of switching (Figure 1a and Table E2). There was a stepwise trend: the worse the baseline exacerbation rate before starting the first biologic, the higher the likelihood of switching multiple times over follow-up. In the year prior to initiation of their first biologic, single biologic users

Table 1 Baseline Characteristic Comparing Patients Who Did Not Switch to Patients Who Switched (Used Two or More Biologics)

	Switched Once or More	Did not Switch	p-value
Number of patients	230	1381	
Age in years, mean (SD)	51.3 (16.46)	48.97 (18.74)	0.13
Female, n (%)	166 (72.2)	1014 (68.3%)	0.69
Body mass index, kg/m^2; mean (SD)	30.5 (7.9)	29.3 (7.5)	0.008
Race, n (%)			0.03
Asian	3 (1.3)	55 (3.7%)	
Black	27 (11.7)	124 (8.4%)	
White	162 (70.4)	1115 (75.1%)	
Other	38 (16.5)	191 (12.9%)	
Hispanic, n (%)	10 (4.3)	56 (3.8%)	0.86
Smoking status, n (%)			0.03
Current smoker	12 (5.2)	48 (3.2%)	
Former smoker	43 (18.7)	204 (13.7%)	
Never smoker	175 (76.1)	1233 (83.0%)	
Allergic rhinitis, n (%)	190 (82.6)	1127 (75.9%)	0.78
Chronic obstructive pulmonary disease, n (%)	40 (17.4)	128 (8.6%)	<0.001
Long-acting muscarinic antagonist use, n (%)	76 (33.0)	238 (16.0%)	<0.001
Leukotriene receptor antagonist use, n (%)	107 (46.5)	545 (36.7%)	0.05
On oral corticosteroids for ≥6 months/year, n (%)	27 (11.7)	72 (4.8%)	<0.001
Insurance, n (%)			0.04
Private	151 (65.7)	1076 (72.5%)	
Public	79 (34.3)	409 (27.5%)	
Baseline exacerbation rate, mean (SD)	2.4 (1.6)	1.5 (1.3)	<0.001
Blood eosinophil counts, cells/μL; median [IQR]			
Baseline	233 [79–532]	189 [85–388]	0.52
Maximum within 1 year	353 [180–721]	185 [83–412]	<0.001
Maximum within 3 years	370 [192–722]	256 [133–510]	<0.001

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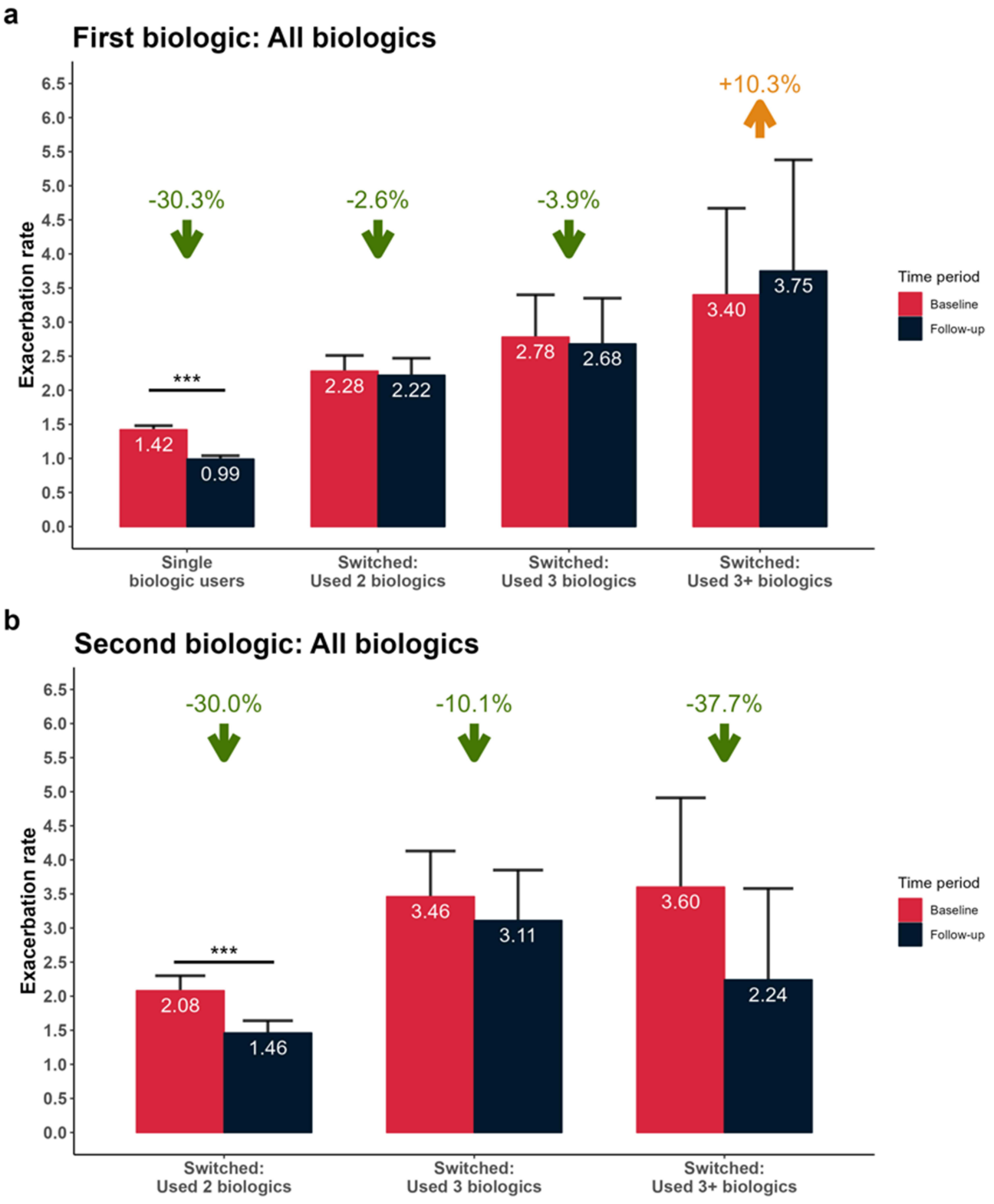

Figure 1 (**a**) Exacerbation rates at baseline and in the year following the first biologic stratified by switch status. (**b**) Exacerbation rates at initiation of second biologic and in the year following the second biologic stratified by switch status. ***p<0.001.

(N=1381) had about 1.4 exacerbations on average compared to 2.3 in those who switched once (N=186), 2.8 in those who switched twice (N=34), and 3.4 in those who switched three times or more (N=10). In weighted analyses, baseline exacerbations (odds ratio, OR: 1.03; 95% Confidence Intervals, CI: 1.01–1.04, p<0.001) and baseline BEC (OR, 2.03 for

Table 2 Inverse Probability Treatment-Weighted Analyses Evaluating the Impact of Baseline Exacerbations and Eosinophil Counts on Switching

	OR	95% CI Low	95% CI High	p-value
Switched vs Did not switch				
Exacerbations in the year before biologic initiation	1.03	1.01	1.04	<0.001
Baseline (most recent) BEC (per +50 cells/mcl)	2.03	1.20	3.43	0.005
Maximum BEC in the 3-year period before baseline (per +50 cells/mcl)	0.91	0.80	1.01	0.71
Switched once vs ≥2 times				
Exacerbations in the year before biologic initiation	1.02	1.00	1.05	0.04
Baseline (most recent) BEC (per +50 cells/mcl)	1.00	0.66	1.53	0.93
Maximum BEC in the 3-year period before baseline (per +50 cells/mcl)	0.90	0.60	1.34	0.68

Notes: The model was weighted by the first biologic used, baseline age, sex, race, BMI, smoking status, insurance, COPD, and LAMA use. These weights were applied to a model predicting switching with covariates (baseline exacerbations, baseline BEC, and maximum BEC. This final model also included the follow-up length from biologic initiation).
Abbreviation: BEC, blood eosinophil count.

each 50 cells/mcl increase; 95% CI: 1.20–3.43, p=0.002) remained significant, while the maximum BEC in 3 years was not (OR, 0.91 per 50 cells/mcl increase; 95% CI: 0.80–1.01, p=0.71) (Table 2).

Among switchers, those who used three or more biologics (switched ≥2 times) were similar on multiple clinical characteristics to those who switched only once (Table E3). However, they had more exacerbations at first-biologic start (2.9 vs 2.3 in one-time switchers, p=0.01) and had a higher historical maximum BEC (662 vs 334 cells/μL, p=0.02), though baseline BEC was similar (229 vs 244 cells/μL, p=0.60). When evaluating the improvement after initiation of the second biologic, patients who used only two biologics experienced a 30% reduction in exacerbations in the year following initiation of the second biologic which was statistically significant (rate ratio, RR, 0.70 [0.65–0.75]; Figure 1b and Table E2). In weighted analyses comparing those who switched once to those who switched two or more times, baseline exacerbations remained a significant predictor of switching (OR: 1.02; 95% CI: 1.00–1.05, p=0.04). Neither baseline BEC or maximum BEC in 3 years were significantly different between those who switched once or two or more times (Table 2).

Only 12 of the 526 patients who initiated dupilumab switched due to suboptimal response. For mepolizumab, switchers had lower baseline BEC (235 vs 410 cells/mcL, p= 0.01) and lower maximum BEC in the 3 years prior (441 vs 740 cells/mcL, p= 0.03). This relationship was reversed for omalizumab with switchers having higher BEC (315 vs 143 cells/mcL, p<0.001) (Table E4).

Discussion

We evaluated the switching events in about 1600 patients with moderate-to-severe asthma and no alternate indication for biologic therapy. Fourteen percent of patients switched over the course of follow up and most of these switches were due to suboptimal effectiveness of the initial biologic. About 20% of patients who switched initially switched again a second time. Less than 2% of patients who switched used five biologics over the course of follow up. Patients who switched had higher exacerbation rates in the year prior to initiation of the first biologic. Patients who switched multiple times had higher maximum eosinophil counts in the year and three years prior to initiation of the first biologic compared to those who switched once though recent eosinophil count was similar between both groups. In weighted analyses, the burden of baseline exacerbations remained the top predictor of switching (3% higher risk of switching for each additional exacerbation) and was associated with the frequency of switching (2%). However, while every 50 cell/mcl increase in the most recent eosinophil count at biologic initiation doubled the likelihood that the patient would switch over follow-up, neither the most recent eosinophil count nor the maximum BEC in 3 years differentiated those who switched once vs those who switched two or more times.

Consistent with prior evidence, this study showed that most biologic switches were due to suboptimal effectiveness.[4,5] Switching patterns may serve as proxies for biologic effectiveness. Patients who switched had a higher exacerbation burden and had higher eosinophil counts at baseline. Prior studies have shown that greater

asthma severity correlates with higher switching rates.[5,7] Indeed, these patient characteristics might suggest eligibility for alternate biologics. For instance, five of the six currently approved biologics are effective in eosinophilic asthma. Thus, patients with higher eosinophil counts might benefit from these. However, our observing that even at initiation of the first biologic, patients who went on to receive multiple biologics had more baseline exacerbations than their counterparts with fewer exacerbations might suggest we are starting these therapies too late in some patients. In a recent study by Pérez-de-Llano et al, lower baseline exacerbation rates was associated with achieving asthma remission, defined as 0 exacerbations per year, no long-term oral corticosteroid, and percent predicted forced expiratory volume in one second ⩾ 80%, suggesting biologics have a window of opportunity when initiation is likely to yield the best benefits.[6,8] Based on our findings, we propose that patients with at-risk features, such as current smoking, concomitant COPD, or BMI ≥30 kg/m^2 and experiencing ≥1 asthma exacerbation within a 12-month period despite maximal medication therapy should be *considered* for initiation of biologic therapy. All patients with ≥2 exacerbations within a 12-month period or ≥1 exacerbation within any 6-month rolling window, should be *strongly* considered for biologic therapy. However, the need to initiate therapy promptly needs to be balanced with the costs of these therapies. Patients who switched twice had significant improvements in their exacerbation rates in the year following initiation of the second biologic suggesting indeed that switching therapy led to improvements in exacerbations.

This study in a large cohort adds to prior evidence that we might be missing an important window of opportunity if we start therapy only after patients have had a higher burden of exacerbations, but our results should be interpreted with caution. While we reviewed the charts of all patients who switched and were able to confirm they initiated the prior biologic and switched to another, we did not review the charts of those who did not switch and some of these patients may not have initiated the first biologic. However, given that we limited to patients seen in the severe asthma clinics staffed by allergists and pulmonologists, this is likely to be infrequent. Secondly, although we tried to limit to latter years when two or more biologics were on the market, patients whose biologics were later in the study period would have a higher likelihood of switching given the availability of more biologics on the market. However, our finding that patients with higher exacerbation rates are likely to switch between multiple biologics corroborates prior studies and is less likely to change. Thirdly, this is a single health system study and most of our patients were privately insured. Given that patients with public insurance are less likely to initiate biologics, our findings may not be directly translatable to other populations.[9] Lastly, the numbers of those who switched three or more times was minimal limiting our evaluation of this group. Likewise, we did not have sufficient numbers to appropriately evaluate switching rates across biologics. Thus, we have made within-biologic comparisons.

In summary, we found that patients with higher exacerbation burden and eosinophil counts at initiation of their first biologic were more likely to switch between multiple biologics due to suboptimal control of their asthma. These findings highlight the importance of carefully selecting the first biologic and starting at the most opportune time.

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Disclosure

The authors have no conflicts of interest relevant to this article.

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