Cardiovascular and cerebrovascular events among patients receiving omalizumab: Results from EXCELS, a prospective cohort study in moderate to severe asthma

Carlos Iribarren, MD, MPH, PhD,[a] Abdelkader Rahmaoui, MD,[b] Aidan A. Long, MD,[c] Stanley J. Szefler, MD,[d] Mary S. Bradley, MS,[b] Gillis Carrigan, PhD, MSc,[b] Mark D. Eisner, MD, MPH,[b] Hubert Chen, MD, MPH,[b] Theodore A. Omachi, MD, MBA,[b] Michael E. Farkouh, MD, MSc,[e] and Kenneth J. Rothman, DrPH[f]   *Oakland and South San Francisco, Calif; Boston and Cambridge, Mass; Aurora, Colo; Toronto, Ontario, Canada; and Research Triangle Park, NC*

Background: EXCELS, a postmarketing observational cohort study, was a commitment to the US Food and Drug Administration to assess the long-term safety of omalizumab in an observational setting, focusing predominantly on malignancies.

Objective: The aim of this study was to examine a potential association between omalizumab and cardiovascular (CV)/ cerebrovascular (CBV) events in EXCELS.

Methods: Patients (≥12 years of age) with moderate to severe allergic asthma and who were being treated with omalizumab (n = 5007) or not (n = 2829) at baseline were followed up for ≤5 years. Analyses included overall CV/CBV events, but focused on the subset of arterial thromboembolic events (ATEs), comprising CV death, myocardial infarction, ischemic stroke, transient ischemic attack, and unstable angina. A prespecified analysis of the end point of ATE was conducted to control for available potential confounders. A blinded independent expert panel adjudicated all events.

Results: At baseline, the 2 cohorts had similar demographic characteristics, but severe asthma was more common in the omalizumab versus the non-omalizumab group (50% vs 23%). Omalizumab-treated patients had a higher rate of CV/CBV serious adverse events (13.4 per 1,000 person years [PYs]) than did non–omalizumab-treated patients (8.1 per 1,000 PYs). The ATE rates per 1,000 PYs were 6.66 (101 patients/15,160 PYs) in the omalizumab cohort and 4.64 (46 patients/9,904 PYs) in the non-omalizumab cohort. After control for available confounding factors, the hazard ratio was 1.32 (95% CI, 0.91-1.91).

Conclusion: This observational study demonstrated a higher incidence rate of CV/CBV events in the omalizumab versus the non-omalizumab cohort. Differences in asthma severity between cohorts likely contributed to this imbalance, but some increase in risk cannot be excluded. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: Adverse event, arterial thromboembolic event, clinical trials, moderate to severe asthma, omalizumab, safety, serious adverse event

Omalizumab (Xolair; Genentech, Inc, South San Francisco, Calif) is a recombinant humanized monoclonal antibody directed against IgE. In randomized, placebo-controlled trials and in open-label studies in patients on maintenance therapy with inhaled corticosteroids (ICSs) and/or long-acting β-agonists, the addition of omalizumab has been shown to reduce asthma exacerbations,[1-9] decrease the use of ICSs and rescue medications,[1,3,5,8,10] and improve symptom control and quality of life.[1,5,8,10]

In EXCELS (Epidemiologic Study of Xolair [Omalizumab]: Evaluating Clinical Effectiveness and Long-term Safety in Patients With Moderate to Severe Asthma), a postmarketing observational cohort study, the primary objective was to assess the long-term (≤5 years) clinical safety profile of omalizumab, with a focus on malignancy. This observational study was designed to compare adverse events in patients with asthma whom health care providers had treated with omalizumab to those in patients with asthma who had not been treated with omalizumab. A numeric imbalance in malignancy rates in patients with allergic asthma in pivotal trials was the motivation for EXCELS.[3,5] Accordingly, the primary outcome measures were primary malignancies, all malignancies excluding nonmelanoma skin cancer, and overall serious adverse events (SAEs). Details regarding the study design and methodology, including patients' baseline characteristics, have been published elsewhere.[11] In EXCELS, the incidence rates of primary malignancies (per 1000 person years [PYs]) were similar

```
Abbreviations used
      ATE:  Arterial thromboembolic event
      CBV:  Cerebrovascular
       CV:  Cardiovascular
   EXCELS:  Epidemiologic Study of Xolair (Omalizumab): Evaluating
            Clinical Effectiveness and Long-term Safety in Patients
            With Moderate to Severe Asthma
      FDA:  US Food and Drug Administration
      ICS:  Inhaled corticosteroid
       MI:  Myocardial infarction
      OCS:  Oral corticosteroid
       PY:  Person year
      SAE:  Serious adverse event
```

among patients treated with omalizumab and non–omalizumab-treated patients (12.3 vs 13.0); however, study limitations precluded definitively ruling out a malignancy risk with omalizumab.[12] In an interim effectiveness analysis, patients who started on treatment with omalizumab at enrollment showed clinically relevant improvements in asthma control that were maintained during 2 years of follow-up.[13]

This analysis focused on cardiovascular (CV) and cerebrovascular (CBV) SAEs that occurred during EXCELS. EXCELS was not originally designed specifically to assess CV/CBV events. A numeric imbalance in various CV/CBV events was first observed in an interim analysis presented to the US Food and Drug Administration (FDA), prompting a disclosure of such findings by the FDA in 2009.[14] The interim analysis also resulted in the development of a prespecified statistical analysis plan supporting methodology for the ascertainment of CV-related events, including external adjudication, as detailed subsequently. An analysis of data pooled from multiple randomized, double-blind, placebo-controlled clinical trials of omalizumab was also planned after the results from the EXCELS interim analysis were evaluated.[15]

METHODS
Overview of EXCELS

EXCELS (ClinicalTrials.gov identifier: NCT00252135) was conducted as part of a postmarketing commitment to the FDA to assess the long-term safety and effectiveness of omalizumab in the clinical practice setting. Patients (≥12 years of age; N = 7857) with moderate to severe asthma, willing to participate in a 5-year study, and with a history of either a positive response to allergy skin testing or *in vitro* serum–specific IgE reactivity to an aeroallergen were recruited from 445 US-based practice centers according to the use of omalizumab at or within 30 days of enrollment (2:1 ratio; omalizumab, n = 5007; non-omalizumab, n = 2829). Patients were excluded from EXCELS if they had: (1) a contraindication to omalizumab; (2) an asthma exacerbation that required initiation or increased doses of systemic corticosteroids, doubling of inhaled corticosteroid dosing, or an emergency department visit or hospitalization in the 2 weeks before screening; (3) acute flare of significant systemic disease or hospitalization for that disease in the 2 months prior to screening; and/or (4) use of an experimental drug within 30 days of screening, cystic fibrosis diagnosis, or participation in a blinded omalizumab study at screening or any time during the study. Patients in the non-omalizumab group could not have received any prior treatment with omalizumab. A small number of patients (n = 21) who had previously been treated with omalizumab but were not taking the drug at study enrollment were not included in the analyses. Assessments included the collection of detailed information regarding demographic and clinical characteristics,

physician-assessed asthma severity, spirometry, and patient-reported outcome measures. Study assessments were conducted every 6 months for the 5-year study duration.

This study was conducted in accordance with FDA regulations, the International Conference on Harmonisation E6 Guideline for Good Clinical Practice, and any other applicable country laws. Institutional review board approval was obtained at each study site, and informed consent was obtained from all research subjects.

Identification and adjudication of CV and CBV SAEs

In EXCELS, the definition of an SAE was any untoward medical occurrence that, after enrollment, resulted in a patient's death, was life-threatening, required prolonged inpatient hospitalization, was disabling, was a congenital anomaly/birth defect, or was medically significant or required medical or surgical intervention to prevent one of these outcomes, and was based on the definition of an SAE as outlined by the FDA.[16]

During EXCELS, verbatim terms for all study-emergent SAEs were coded and analyzed using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes, High-Level Terms, and Preferred Terms. An independent panel of experts performed a blinded review of patient narratives and supporting documents for all SAEs that resulted in death and all potential CV/CBV SAEs identified using Standardized MedDRA Queries (Medical Dictionary for Regulatory Activities; http://www.meddra.org/standardised-meddra-queries) (Fig 1). This approach allowed for the identification of cases that were highly likely to have represented the condition of interest as well as the identification of all possible cases. The panel also classified the CV/CBV SAEs into standardized categories: myocardial infarction (MI), unstable angina, congestive heart failure, ischemic stroke, transient ischemic attack, hemorrhagic stroke, pulmonary embolism, venous thrombosis, pulmonary hypertension, arterial ischemic vascular disease, atrial fibrillation/flutter, and ventricular tachycardia/fibrillation.

An additional composite end point, arterial thromboembolic event (ATE), was defined using an approach adapted from the 2002 Antiplatelet Trialists' Collaboration.[17] The ATE category comprised CV/CBV events sharing a common pathophysiologic mechanism of arterial injury and/or inflammation and included CV death, MI, ischemic stroke, transient ischemic attack, and unstable angina.

Descriptive analyses

Data were analyzed in terms of *PYs of observation*, defined as the time from study day 0 to the date of death, date of event of interest, study completion, or the last completed clinic visit in those who discontinued from the study, whichever came first. Overall incidence rates per 1000 PYs of observation of adjudicated CV/CBV-related deaths and SAEs were calculated in each cohort and are reported with 95% CIs. Crude rate differences were calculated with 95% CIs. The same analyses were performed for each of the adjudicated event categories and for all event categories combined (CV or CBV SAEs).

The prespecified analysis of ATEs was applied to the cumulative adjudicated data for the evaluation of events with a common pathophysiology. As described for CV/CBV SAEs, overall incidence rates per 1000 PYs were calculated with 95% CIs for both cohorts. Crude rate differences and rate ratios were calculated with 95% CIs. Similarly, the rates of patients experiencing ≥1 ATE event, expressed per 1000 PYs of observation time, were calculated by treatment cohort and reported with 95% CIs. A sensitivity analysis was conducted in which event rates per 1000 PYs were computed by treatment cohort for the set of ATEs that excluded deaths not associated with any of the following SAEs: MI, ischemic stroke, ventricular tachycardia, or ventricular fibrillation.

To adjust for potential confounders, we used a Cox proportional hazards regression model. The *time to a patient's first ATE* was defined as the number of months from study day 0 to the date of onset of symptoms of the first SAE experienced by the patient that met the ATE definition. Data from patients not experiencing an ATE were censored at the earliest of the following
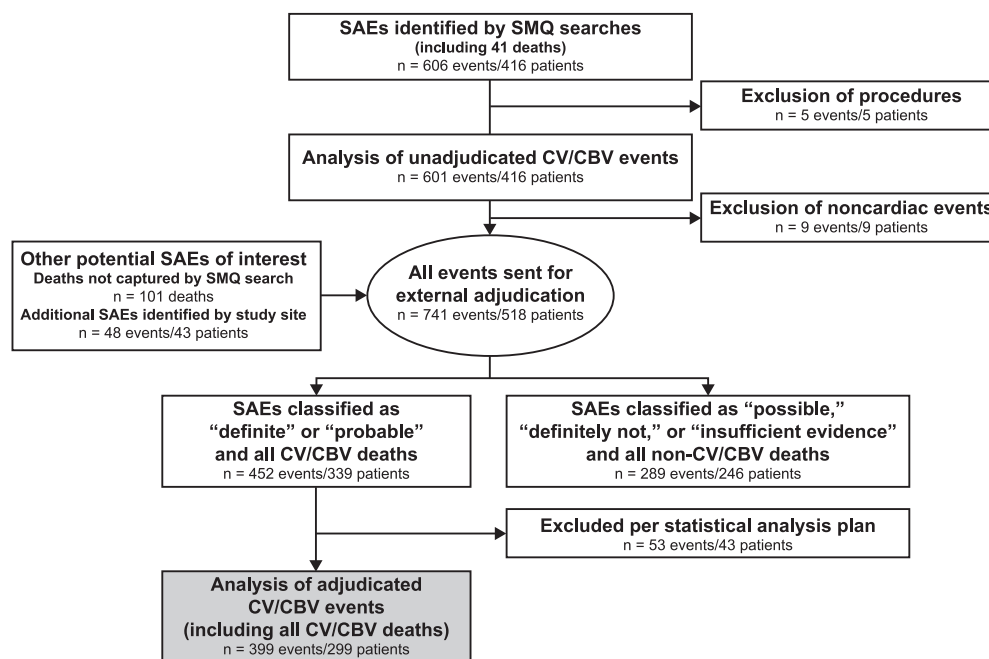
FIG 1. Identification and adjudication of CV and CBV events. *MedDRA*, Medical Dictionary for Regulatory Activities; *SMQ*, Standardized Medical Dictionary for Regulatory Activities Query.

dates: death from a documented non-CV cause, loss to follow-up, discontinuation from the study, initiation of omalizumab treatment (non-omalizumab cohort only), >6 months after the omalizumab stop date (omalizumab cohort only), or study completion. A Cox proportional hazards model was fit for time to first study-emergent ATE to estimate the unadjusted hazard ratio between treatment cohorts and corresponding 95% CIs. Models were subsequently fit for time to first study-emergent ATE to estimate the hazard ratio between cohorts, with adjustments separately for each potential baseline CV/CBV risk factor. A final multivariate Cox proportional hazards model was developed to adjust fully for all available baseline CV/CBV risk factors, according to the prespecified analysis plan, with covariates for age (<65 vs ≥65 years), sex, and asthma severity (severe vs moderate). Stepwise variable selection was then used to select a final model from potential baseline risk factors based on P ≤.20 criteria for entry and P >.20 for removal. Model covariates can be found in Table E1 in this article's Online Repository at www.jacionline.org.

In addition, a *post hoc* exploratory analysis was conducted to compare ATE risk between the omalizumab and non-omalizumab cohorts, with adjustment for the estimated probability of receiving omalizumab. In each patient, a propensity score[18] was calculated using logistic regression to model the probability of receiving omalizumab as a function of potentially confounding baseline variables, including, but not limited to, age, race, ethnicity, sex, investigator-assessed asthma severity, IgE level, selected asthma and allergy history, and non–asthma-related medical history, as well as selected socioeconomic characteristics and variables specific to CV risk factors. Subsequent to trimming all nonoverlapping propensity score values between treatment cohorts, an additional 1% of observations were removed from the upper tail of the propensity score distribution in the omalizumab-treated group, in addition to removal of 1% of observations from the lower tail of the propensity score distribution in the non–omalizumab-treated group. Patients were then stratified into deciles according to each patient's propensity score. A standardized incidence rate per 1000 PYs was calculated for each treatment cohort, as well as a standardized rate difference and a rate ratio (using the omalizumab cohort as the standard).

Kaplan-Meier estimates were used for summarizing the distribution of time to first adjudicated study-emergent ATE SAE. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC).

RESULTS
PYs of follow-up

In the omalizumab cohort, the total cumulative PYs were 18,426 (mean ± SD duration of follow-up, 3.7 ± 1.8 years); in the non-omalizumab cohort, the total cumulative PYs were 9,963 (duration of follow-up, 3.5 ± 1.9 years).

Patient disposition

Baseline demographic and clinical characteristics have been previously reported.[12] On average, the omalizumab cohort was slightly younger than the non-omalizumab cohort (44 vs 46 years, respectively). In both cohorts, ~65% were female and 80% were white. Clinical characteristics and CV risk factors are shown in Table I. Fifty-six percent of all patients remained in the study for 5 years and completed a clinic visit at month 60. The most frequently reported reasons for early discontinuation in the omalizumab and non-omalizumab groups, respectively, were patient decision (18% and 15%), loss to follow-up (16% and 15%), and physician decision (8% and 6%). In terms of person-time lost to follow-up, the proportions lost to follow-up were 26.4% in the omalizumab cohort and 29.6% in the non-omalizumab cohort.

The percentage of patients with severe asthma in the omalizumab cohort was more than twice that in the non-omalizumab cohort (49.6% vs 22.6%, respectively). Among patients with moderate asthma in the omalizumab cohort, 78.1% had used an asthma controller and 15.6% had used a quick-relief medication, in the 2 weeks before enrollment. In the non-omalizumab cohort, during the same time period, 69.8% of patients with moderate asthma had used an asthma controller and 11.9% had used a quick-relief medication. In both groups, the majority of patients with severe asthma were taking an ICS or long-acting ß-agonist to control their symptoms (see Table E2 in this article's Online Repository).

TABLE I. Baseline clinical characteristics of the study cohorts

Characteristic	Non-omalizumab cohort (n = 2,829)	Omalizumab cohort (n = 5,007)
Age, means ± SDs (y)	46 ± 17 (n = 2,827)	44 ± 17 (n = 5,006)
Female, no. (%)	1,880* (66.5)	3,199 (63.9)
White, no. (%)	2,322* (82.2)	3,949* (78.9)
BMI, means ± SDs (kg/m^2)	31.0 ± 12.9 (n = 2,824)	31.1 ± 11.9 (n = 4,996)
Smoking habit, no. (%)	n = 2,827	n = 5,005
Current	159 (5.6)	245 (4.9)
Former	826 (29.2)	1477 (29.5)
IgE, median (range) (IU/mL)	108 (0-23,237) (n = 2,728)	202 (2.0-33,200) (n = 4,998)
Physician-assessed asthma severity, no. (%)	n = 2,822	n = 5,001
Moderate	2,185 (77.4)	2,519 (50.4)
Severe	637 (22.6)	2,482 (49.6)
Comorbidities, no. (%)		
Hypertension	658 (23.3)	1,078 (21.5)
Hypercholesterolemia	306 (10.8)	516 (10.3)
Coronary artery disease	73 (2.6)	122 (2.4)
Congestive heart failure	26 (0.9)	64 (1.3)
Type 2 diabetes	189 (6.7)	430 (8.6)
Depression	417 (14.7)	864 (17.3)
Chronic obstructive pulmonary disease	161 (5.7)	407 (8.1)
OCS use, no. (%)†	n = 2,822	n = 4,997
Any	724 (25.7)	1,407 (28.1)
Chronic	156 (5.5)	373 (7.5)
Periodic	568 (20.1)	1,034 (20.7)

BMI, Body mass index.

*Non-omalizumab cohort, female, n = 2,827, white, n = 2,826; omalizumab cohort, white, n = 5,006.

†Reported oral corticosteroid use in the past 12 months at the baseline visit.

By treatment cohort, a larger percentage of omalizumab-versus non–omalizumab-treated patients reported chronic oral corticosteroid (OCS) use (7.5% vs 5.5%, respectively), which might be attributable to the larger percentage of omalizumab-versus non–omalizumab-treated patients with moderate asthma taking OCSs (27.6% vs 24.4%, respectively; see Table E2 in this article's Online Repository). During the 5-year follow-up, more patients with severe asthma, regardless of treatment cohort, were taking an OCS than were those with moderate asthma (see Fig E1 in this article's Online Repository). The overall pattern of OCS use was similar; the lowest use rate was measured at month 6 (range, 17% to 33%), and the highest use rate was measured at month 18 (range, 20% to 52%). Overall, the use of OCSs at baseline was higher among patients with severe versus moderate asthma (29% vs 26%, respectively).

Adjudicated study-emergent CV/CBV SAEs

A higher incidence rate of CV/CBV SAEs was observed in the omalizumab-treated group (13.4 per 1000 PYs; 95% CI, 11.6-15.4) compared with the non–omalizumab-treated group (8.1 per 1000 PYs; 95% CI, 6.5-10.1) (Table II). Higher rates were observed, respectively, for transient ischemic attack (0.7 vs 0.1 per 1000 PYs), MI (2.1 vs 0.8 per 1000 PYs), pulmonary hypertension (0.5 vs 0.0 per 1000 PYs), pulmonary embolism/venous thrombosis (3.2 vs 1.5 per 1000 PYs), and unstable angina (2.2 vs 1.4 per 1000 PYs), while the rates observed for ischemic stroke and CV death were similar among both study cohorts.

Adjudicated study-emergent ATEs

The omalizumab cohort had higher rates (per 1000 PYs) of ATE SAEs, patients with ATE SAEs, and ATE SAEs (excluding non-ATE deaths) than did the non-omalizumab cohort (see Table E3 in this article's Online Repository).

The unadjusted (crude) rates of ATEs per 1,000 PYs were 6.66 (101 patients with an ATE event per 15,160 PYs) in the omalizumab cohort and 4.64 (46 patients with an ATE event per 9,904 PYs) in the non-omalizumab cohort. The difference between the omalizumab and non-omalizumab cohorts in ATE rates per 1000 PYs was 2.02 (95% CI, 0.15-3.89), and the unadjusted rate ratio was 1.43 (95% CI, 1.00-2.08) (see Table E4 in this article's Online Repository). The adjusted Cox proportional hazards analysis indicated a hazard ratio of ATE events among those treated with omalizumab, compared with those who did not take omalizumab, of 1.32 (95% CI, 0.91-1.91; Table III). After adjustment for the estimated probability of receiving omalizumab (propensity score), the difference between cohorts in ATE rates was 1.55 per 1000 PYs (95% CI, −0.87 to 3.97), and the rate ratio was 1.32 per 1000 PYs (95% CI, 0.83 to 2.12). The Kaplan-Meier estimates of time to first adjudicated study-emergent ATE are shown in Fig 2.

DISCUSSION

Omalizumab has proven efficacy as adjunctive therapy in the management of moderate to severe allergic asthma.[1-9] EXCELS was conducted to collect longer-term safety data on omalizumab after approval. The results from the primary analysis of overall SAEs and malignancy have been previously published.[12] The current analysis of the EXCELS data revealed a higher crude incidence rate of CV/CBV SAEs in omalizumab-treated patients compared with non–omalizumab-treated patients. However, in the results from analyses of data pooled from 25 studies,[15] an association between omalizumab and CV/CBV SAEs or ATEs was not demonstrated.

TABLE II. Crude incidence rate (per 1000 PYs) of study-emergent CV/CBV SAEs*

Parameter	Non-omalizumab cohort (n = 2829)			Omalizumab cohort (n = 5007)		
	No. of events	Crude incidence rate per 1000 PYs	95% CI	No. of events	Crude incidence rate per 1000 PYs	95% CI
Any CV/CBV event	80	8.1	6.5-10.1	201	13.4	11.6-15.4
MI	8	0.8	0.3-1.6	32	2.1	1.4-3.0
Unstable angina	14	1.4	0.8-2.4	33	2.2	1.5-3.0
Transient ischemic attack	1	0.1	0.0-0.6	11	0.7	0.4-1.3
Pulmonary embolism/venous thrombosis	15	1.5	0.8-2.5	49	3.2	2.4-4.3
Pulmonary hypertension	0	0	0.0-0.4	8	0.5	0.2-1.0
Ischemic stroke	7	0.7	0.3-1.4	8	0.5	0.2-1.0
CV-related death	20	2.0	1.2-3.1	36	2.4	1.6-3.3

*Estimates are reflective of the number of patients and not the number of occurrences of each event, and on the PYs at risk for each individual event, not the overall PYs at risk for any event during the study.

TABLE III. Hazard ratio (HR) for adjudicated study-emergent ATE SAEs

Parameter	Non-omalizumab cohort* (n = 2,829)	Omalizumab cohort† (n = 5,007)
No. of ATE SAEs	46	101
PYs‡ at risk for ATE SAEs	9,904	15,160
Unadjusted HR (95% CI)	1.47 (1.04-2.08)	
Adjusted HR§ (95% CI)	1.32 (0.91-1.91)	

*All non–omalizumab- or omalizumab-treated patients before any change in baseline treatment status.

†After initiation of omalizumab treatment (non-omalizumab cohort) or >6 months after last omalizumab dose (omalizumab cohort).

‡Defined as the time from day 0 to the earliest of the following events: study completion, death, first ATE SAE, start of omalizumab treatment (non-omalizumab cohort), >6 months after discontinuation of omalizumab (omalizumab cohort), or the last completed study visit date (discontinued patients). For patients who changed omalizumab treatment status, PYs at risk were calculated from omalizumab start date (non-omalizumab cohort) or >6 months after the end date (omalizumab cohort) to the earliest of the previously mentioned events.

§Cox proportional hazard model including adjustments for baseline age, sex, steroid use, body mass index, smoking history, physician-assessed asthma severity (moderate vs severe), and the presence or absence of the following comorbidities: chronic obstructive pulmonary disease, congestive heart failure, depression, hypercholesterolemia, hypertension, type 2 diabetes.

In this nonrandomized study, confounding by indication for use of omalizumab was a possibility.[19,20] While EXCELS was reasonably well-balanced for malignancy risk factors and showed similar rates of malignancy in the omalizumab and non-omalizumab cohorts, CV risk was greater at baseline in the omalizumab cohort,[21] possibly the result of the indication for omalizumab, such that the treated group included patients with more severe asthma. Higher rates of CV/CBV SAEs in the omalizumab cohort were noted when analyses were not adjusted for potential confounders. The findings were similar in the subset of CV/CBV SAEs meeting the definition of ATE. However, after taking confounding imbalances between the cohorts into account, using multivariate Cox regression analyses, stratification, and propensity score analyses, the crude associations were substantially reduced. We can expect that control of confounding was imperfect, and that the adjusted differences that we reported were affected by some further residual confounding, very likely in the same direction as the confounding that was controlled for.

Research indicates that asthma itself and the use of asthma medications may be independently associated with increased CV risk.[22-29] An analysis of data from 6792 patients in the Multi-Ethnic Study of Atherosclerosis concluded that a subgroup of patients with asthma requiring controller medications, such as ICSs, had a higher rate of CV disease compared with the subgroup without asthma.[30] Additionally, as previously published, greater asthma severity predicted a higher risk for ATEs in the non-omalizumab cohort of EXCELS.[28] Multiple hypotheses exist for the observed association between asthma and CV outcomes. Potential mechanisms include medications used for treating asthma,[31-33] most notably OCSs, which are well known to increase the risk for CV risk factors such as diabetes,[34] and have been associated with an increased risk for adverse CV/CBV outcomes.[35-37] In patients with severe asthma, moderate to high exposure to chronic systemic corticosteroids appears to increase the risk for complications (eg, infections, CV events, metabolic events).[38] Additionally, a more direct link between asthma and CV disease has been suggested, by virtue of systemic inflammation associated with asthma as well as specific cytokine upregulation.[39-41] For example, the subgroup of patients with asthma requiring controller medications in the Multi-Ethnic Study of Atherosclerosis[30] had higher levels of the inflammatory markers C-reactive protein and fibrinogen than did the subgroups of patients without asthma and patients with asthma not requiring controller medications. Clinically, studies have confirmed that asthma severity measures, such as lung function impairment, are an independent risk factor for CV disease, and epidemiologic studies also have confirmed an association between asthma and comorbid diseases that increase CV risk, such as diabetes and chronic obstructive pulmonary disease.[34,42]

Elevated serum IgE levels have been described in some CV conditions and in patients with a positive history of CV disease.[43,44] Moreover, IgE has been shown to be positively associated with CV risk.[45] None of these studies provides strong evidence that suggests that the anti-IgE properties of omalizumab contribute to an increased risk for CV events. In summary, no definitive biological relationship has been identified.

In our multivariate analysis, we were able to control for the imbalance in prevalence of severe asthma (49.6% in the omalizumab cohort vs 22.6% in the non-omalizumab cohort). Nonetheless, the dichotomous severity scale is unlikely to have captured all of the confounding by severity in data, leading to residual confounding. Additionally, there are likely to be unmeasured risk factors, including comorbid disease severity, further confounding the estimates.

Our findings also must be interpreted in the context of these and other limitations. For example, if the primary objective of EXCELS had been to examine CV/CBV outcomes rather than malignancies, more careful details about the CV risk factor
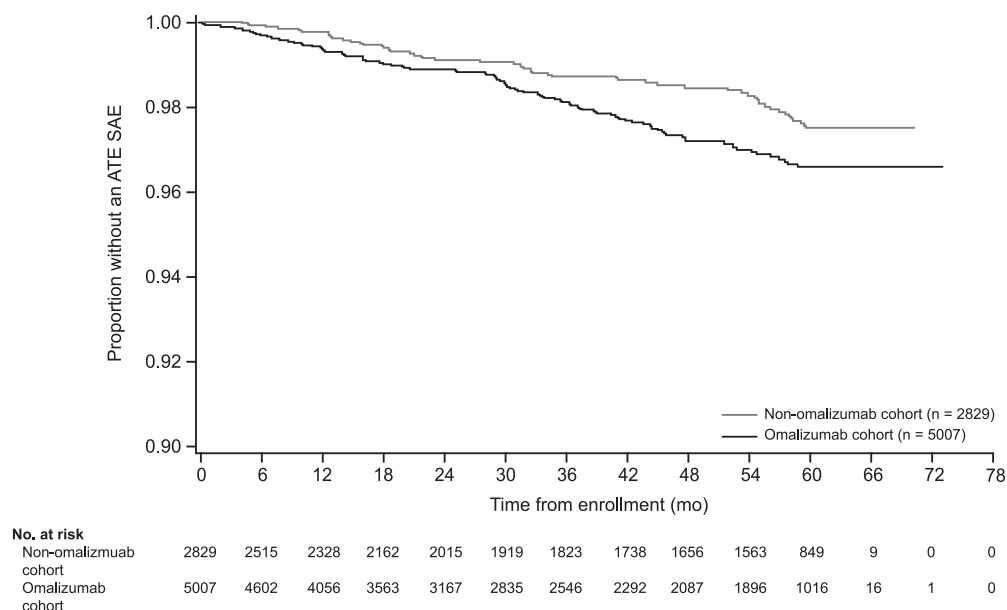
FIG 2. Kaplan-Meier plot of time to first adjudicated study-emergent ATE SAE.

profile, such as low- and high-density lipoprotein cholesterol levels or glycosylated hemoglobin levels to measure diabetes control, may have been collected. Second, ~90% of the patients in the omalizumab cohort were being treated with omalizumab before study enrollment. Consequently, only a minority of patients in the omalizumab cohort were new users. The experience of new users may well differ from that of prevalent users, who constituted the majority of exposed patients in our study. Additionally, 44.1% of study participants discontinued before the full 5 years of follow-up was completed, although only slightly more than one fourth of person-time was lost to follow-up.[12] Finally, the reported estimates are imprecise owing to the relatively low numbers of CV/CBV events adjudicated to the individual categories.

The results from EXCELS do not exclude a potential increased risk for CV/CBV SAEs in patients treated with omalizumab. After control for measured confounders, however, the magnitude of the estimated increase in risk was reduced considerably from the crude estimates. The assessment of CV/CBV risk should take into account the results from EXCELS and the pooled analysis of randomized controlled trials.

Clinical implications: Current asthma-management guidelines should not be affected by the findings from this study of CV/CBV SAEs in patients receiving omalizumab. However, health care professionals should be aware of a possible association of omalizumab with CV/CBV SAEs.

REFERENCES

1. Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. Allergy 2004;59: 701-8.
2. Bousquet J, Cabrera P, Berkman N, Buhl R, Holgate S, Wenzel S, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy 2005; 60:302-8.
3. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001; 108:184-90.
4. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann Intern Med 2011;154:573-82.
5. Holgate ST, Chuchalin AG, Hébert J, Lötvall J, Persson GB, Chung KF, et al, Omalizumab 011 International Study Group. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. Clin Exp Allergy 2004;34:632-8.
6. Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005;60:309-16.
7. Niven R, Chung KF, Panahloo Z, Blogg M, Ayre G. Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: an open-label study. Respir Med 2008;102:1371-8.
8. Solèr M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J 2001;18:254-61.
9. Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedgecock S, Blogg M, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy 2004;59:709-17.
10. Humbert M, Berger W, Rapatz G, Turk F. Add-on omalizumab improves day-to-day symptoms in inadequately controlled severe persistent allergic asthma. Allergy 2008;63:592-6.
11. Long AA, Fish JE, Rahmaoui A, Miller MK, Bradley MS, Taki HN, et al. Baseline characteristics of patients enrolled in EXCELS: a cohort study. Ann Allergy Asthma Immunol 2009;103:212-9.
12. Long A, Rahmaoui A, Rothman KJ, Guinan E, Eisner M, Bradley MS, et al. Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. J Allergy Clin Immunol 2014;134:560-7.e4.
13. Eisner MD, Zazzali JL, Miller MK, Bradley MS, Schatz M. Longitudinal changes in asthma control with omalizumab: 2-year interim data from the EXCELS study. J Asthma 2012;49:642-8.

14. Early communication about an ongoing safety review of omalizumab (marketed as Xolair). Silver Spring, MD: US Food and Drug Administration; 2009. Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationfor PatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm 172218.htm. Accessed December 8, 2015.

15. Iribarren C, Rothman KJ, Bradley MS, Carrigan G, Eisner M, Chen H. Cardiovascular and cerebrovascular events among patients receiving omalizumab: pooled analysis of patient-level data from 25 randomized, double-blind, placebo-controlled clinical trials. J Allergy Clin Immunol 2016; in press.

16. CFR-Code of Federal Regulations Title 21. Silver Spring, MD: US Food and Drug Administration; 2011. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32. Accessed December 8, 2015.

17. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.

18. Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clin Pharmacol Toxicol 2006;98: 253-9.

19. Grobbee DE, Hoes AW. Confounding and indication for treatment in evaluation of drug treatment for hypertension. BMJ 1997;315:1151-4.

20. Psaty BM, Koepsell TD, Lin D, Weiss NS, Siscovick DS, Rosendaal FR, et al. Assessment and control for confounding by indication in observational studies. J Am Geriatr Soc 1999;47:749-54.

21. FDA Drug Safety Communication: FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events. Silver Spring, MD: US Food and Drug Administration; 2014. Available at http://www.fda.gov/Drugs/DrugSafety/ucm414911.htm. Accessed December 8, 2015.

22. Onufrak SJ, Abramson JL, Austin HD, Holguin F, McClellan WM, Vaccarino LV. Relation of adult-onset asthma to coronary heart disease and stroke. Am J Cardiol 2008;101:1247-52.

23. Appleton SL, Ruffin RE, Wilson DH, Taylor AW, Adams RJ. North West Adelaide Cohort Health Study Team. Cardiovascular disease risk associated with asthma and respiratory morbidity might be mediated by short-acting beta-2-agonists. J Allergy Clin Immunol 2009;123:124-30.e1.

24. Iribarren C, Tolstykh IV, Miller MK, Sobel E, Eisner MD. Adult asthma and risk of coronary heart disease, cerebrovascular disease, and heart failure: a prospective study of 2 matched cohorts. Am J Epidemiol 2012;176:1014-24.

25. Lee HM, Truong ST, Wong ND. Association of adult-onset asthma with specific cardiovascular conditions. Respir Med 2012;106:948-53.

26. Schanen JG, Iribarren C, Shahar E, Punjabi NM, Rich SS, Sorlie PD, et al. Asthma and incident cardiovascular disease: the Atherosclerosis Risk in Communities Study. Thorax 2005;60:633-8.

27. Salpeter SR. Cardiovascular safety of beta-$_2$-adrenoceptor agonist use in patients with obstructive airway disease: a systematic review. Drugs Aging 2004; 21:405-14.

28. Omachi TA, Haselkorn T, Miller DP, Shah M, Eisner MD, Chen H, et al. Asthma severity and increased risk of cardiovascular and cerebrovascular outcomes in patients with moderate-to-severe persistent asthma. Ann Allergy Asthma Immunol 2014;113(suppl 5):A37.

29. Cazzola M, Calzetta L, Bettoncelli G, Cricelli C, Romeo F, Matera MG, et al. Cardiovascular disease in asthma and COPD: a population-based retrospective cross-sectional study. Respir Med 2012;106:249-56.

30. Tattersall M, Guo M, Korcarz C, Gepner A, Barr R, Donohue K, et al. Chronic asthma predicts cardiovascular disease events: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2014;130(suppl 2):A15991.

31. Fardet L, Petersen I, Nazareth I. Risk of cardiovascular events in people prescribed glucocorticoids with iatrogenic Cushing's syndrome: cohort study. BMJ 2012;345: e4928.

32. Nussinovitch U, de Carvalho JF, Pereira RM, Shoenfeld Y. Glucocorticoids and the cardiovascular system: state of the art. Curr Pharm Des 2010;16:3574-85.

33. Varas-Lorenzo C, Rodriguez LA, Maguire A, Castellsague J, Perez-Gutthann S. Use of oral corticosteroids and the risk of acute myocardial infarction. Atherosclerosis 2007;192:376-83.

34. Song Y, Klevak A, Manson JE, Buring JE, Liu S. Asthma, chronic obstructive pulmonary disease, and type 2 diabetes in the Women's Health Study. Diabetes Res Clin Pract 2010;90:365-71.

35. Aviña-Zubieta JA, Abrahamowicz M, De Vera MA, Choi HK, Sayre EC, Rahman MM, et al. Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study. Rheumatology (Oxford) 2013;52:68-75.

36. Maradit Kremers H, Reinalda MS, Crowson CS, Davis JM 3rd, Hunder GG, Gabriel SE. Glucocorticoids and cardiovascular and cerebrovascular events in polymyalgia rheumatica. Arthritis Rheum 2007;57:279-86.

37. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med 2004;141:764-70.

38. Lefebvre P, Duh MS, Lafeuille MH, Gozalo L, Desai U, Robitaille MN, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. J Allergy Clin Immunol 2015;136:1488-95.

39. Halász A, Cserháti E, Magyar R, Kovács M, Cseh K. Role of TNF-α and its 55 and 75 kDa receptors in bronchial hyperreactivity. Respir Med 2002;96:262-7.

40. Zietkowski Z, Skiepko R, Tomasiak-Lozowska MM, Bodzenta-Lukaszyk A. Anti-IgE therapy with omalizumab decreases endothelin-1 in exhaled breath condensate of patients with severe persistent allergic asthma. Respiration 2010; 80:534-42.

41. Zietkowski Z, Tomasiak-Lozowska MM, Skiepko R, Mroczko B, Szmitkowski M, Bodzenta-Lukaszyk A. High-sensitivity C-reactive protein in the exhaled breath condensate and serum in stable and unstable asthma. Respir Med 2009;103:379-85.

42. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet 2007;370:765-73.

43. Korkmaz ME, Oto A, Saraclar Y, Oram E, Oram A, Ugurlu S, et al. Levels of IgE in the serum of patients with coronary arterial disease. Int J Cardiol 1991;31:199-204.

44. Sinkiewicz W, Blazejewski J, Bujak R, Kubica J, Dudziak J. Immunoglobulin E in patients with ischemic heart disease. Cardiol J 2008;15:122-8.

45. Criqui MH, Lee ER, Hamburger RN, Klauber MR, Coughlin SS. IgE and cardiovascular disease. Results from a population-based study. Am J Med 1987;82:964-8.
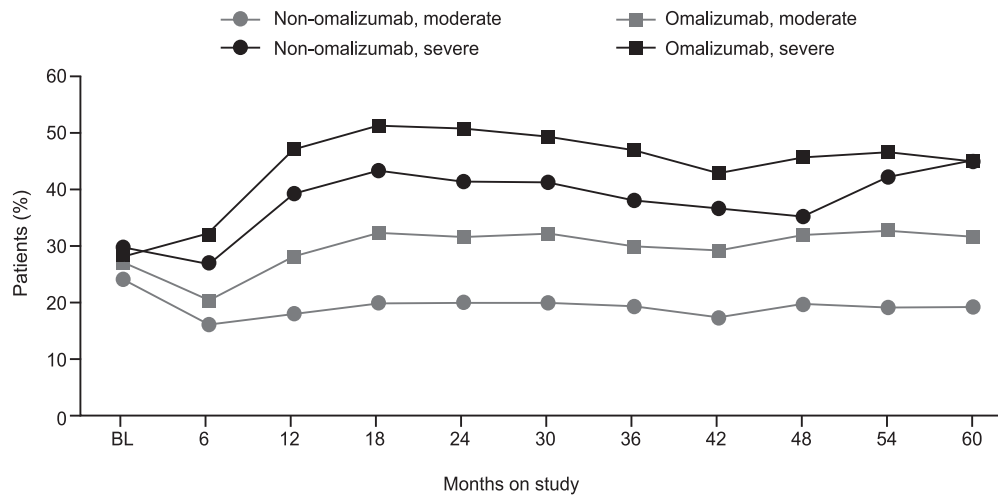
FIG E1. Patient use of OCSs during EXCELS, by treatment cohort and asthma severity. *BL*, Baseline.

TABLE E1. Cox proportional hazards model of time to first adjudicated study-emergent ATE SAEs (adjusted)

Main effect	Estimate	SE	HR (95% CI)
Treatment (omalizumab* vs non-omalizumab†)	0.278	0.188	1.321 (0.913-1.910)
Covariate			
Age (≥65 vs <65 y)	1.003	0.187	2.725 (1.891-3.928)
Asthma severity (severe vs moderate)	0.088	0.176	1.091 (0.773-1.540)
Sex (female vs male)	−0.326	0.178	0.722 (0.509-1.023)
Steroid use (periodic vs none)	−0.014	0.216	0.986 (0.646-1.505)
Steroid use (chronic vs none)	0.480	0.250	1.616 (0.990-2.637)
BMI (30-<40 vs <30 kg/m^2)	0.682	0.190	1.978 (1.364-2.869)
BMI (≥40 vs <30 kg/m^2)	0.276	0.287	1.318 (0.751-2.313)
Smoking history (ever vs never)	0.441	0.174	1.555 (1.106-2.184)
History of type 2 diabetes (yes vs no)	0.623	0.204	1.864 (1.250-2.781)
History of chronic obstructive pulmonary disease (yes vs no)	0.450	0.217	1.568 (1.024-2.400)
History of coronary artery disease (yes vs no)	1.139	0.240	3.125 (1.954-4.997)
History of hypercholesterolemia (yes vs no)	0.310	0.201	1.363 (0.920-2.021)
History of congestive heart failure (yes vs no)	0.775	0.296	2.172 (1.215-3.880)
History of hypertension (yes vs no)	0.778	0.189	2.176 (1.502-3.153)
History of depression (yes vs no)	0.424	0.194	1.528 (1.044-2.235)

BMI, Body mass index; *HR*, hazard ratio.

*Patients, n = 2818; events, n = 46.

†Patients, n = 4980; events, n = 101.

TABLE E2. Daily use of asthma and allergy medications at baseline

Asthma medication	Non-omalizumab cohort		Omalizumab cohort	
	Moderate asthma* (n = 2185)	Severe asthma* (n = 637)	Moderate asthma* (n = 2519)	Severe asthma* (n = 2482)
OCS use	533 (24.4)	191 (30.0)	695 (27.6)	712 (28.7)
Type of OCS†				
Chronic	100 (4.6)	56 (8.8)	133 (5.3)	240 (9.7)
Periodic	433 (19.8)	135 (21.2)	562 (22.3)	472 (19.0)
Asthma controller use‡	1524 (69.8)	542 (85.4)	1967 (78.1)	2205 (88.9)
Type of asthma controller§				
ICS	1291 (59.1)	494/637 (77.8)	1673 (66.4)	1968 (79.4)
Long-acting β-agonist	1190 (54.5)	463 (72.9)	1602 (63.6)	1880 (75.8)
Leukotriene receptor antagonist	459 (21.0)	213 (33.5)	817 (32.4)	1073 (43.3)
Theophylline	44 (2.0)	47 (7.4)	96 (3.8)	237 (9.6)
Asthma quick-relief use‡	259 (11.9)	161 (25.4)	392 (15.6)	728 (29.4)
Type of quick-relief agent‡				
Anticholinergic	59 (2.7)	57 (9.0)	126 (5.0)	263 (10.6)
Short-acting ß-agonist	247 (11.3)	161 (25.4)	386 (15.3)	711 (28.7)

Data are expressed as no. (%) of patients.

*Physician-assessed asthma severity at baseline.

†Omalizumab, moderate asthma: n = 2517; omalizumab, severe asthma: n = 2480.

‡Non-omalizumab, moderate asthma: n = 2183; non-omalizumab, severe asthma: n = 635; omalizumab, severe asthma: n = 2480.

§Non-omalizumab cohort (moderate asthma, n = 2183, severe asthma, n = 635); omalizumab cohort (moderate asthma, n = 2519, severe asthma, n = 2480).

TABLE E3. Crude rates of adjudicated study-emergent ATE SAEs

Parameter	Non-omalizumab cohort* (n = 2,829)	Omalizumab cohort† (n = 5,007)	Crude rate difference (95% CI)	Crude rate ratio (95% CI)
No. of ATE SAEs	51	115	—	—
PYs‡ at risk for ATE SAEs	9,963	15,286	—	—
Rate per 1000 PYs (95% CI)	5.12 (3.81-6.73)	7.52 (6.21-9.03)	2.40 (0.16-4.62)	1.47 (1.02-2.18)
No. of patients with ATE SAEs	46	101	—	—
PYs at risk for ATE SAEs	9,904	15,160	—	—
Rate per 1000 PYs (95% CI)	4.64 (3.40-6.19)	6.66 (5.43-8.10)	2.02 (0.15-3.89)	1.43 (1.00-2.08)
No. of ATE SAEs (excluding non-ATE deaths)	32	91	—	—
Rate per 1000 PYs (95% CI)	3.21 (2.20-4.53)	5.95 (4.79-7.31)	2.74 (0.74-4.68)	1.85 (1.16-3.09)

*All non–omalizumab- or omalizumab-treated patients before any change in baseline treatment status.

†After initiation of omalizumab treatment (non-omalizumab cohort) or >6 months after last omalizumab dose (omalizumab cohort).

‡Defined as the time from day 0 to the earliest of the following events: study completion, death, start of omalizumab treatment (non-omalizumab cohort), >6 months after discontinuation of omalizumab (omalizumab cohort), or the last completed study visit date (discontinued patients). For patients who changed omalizumab treatment status, PYs at risk were calculated from omalizumab start date (non-omalizumab cohort) or >6 months after the end date (omalizumab cohort) to the earliest of the previously mentioned events.

TABLE E4. Rates of adjudicated study-emergent ATE SAEs, by propensity score stratum

Propensity score* stratum	Rate per 1000 PYs† (95% CI)		Rate difference (95% CI)	Rate ratio (95% CI)
	Non-omalizumab cohort‡ (n = 2829)	Omalizumab cohort (n = 5007)		
Unadjusted	4.64 (3.40 to 6.19)	6.66 (5.43 to 8.09)	2.02 (0.15 to 3.89)	1.43 (1.00 to 2.08)
Stratified				
1	3.91	8.95	—	—
2	2.58	8.37	—	—
3	4.46	8.42	—	—
4	6.34	6.81	—	—
5	3.40	5.37	—	—
6	3.58	5.22	—	—
7	12.97	5.37	—	—
8	2.22	7.76	—	—
9	2.69	4.25	—	—
10	4.58	6.32	—	—
Adjusted	4.80 (2.76 to 6.84)	6.35 (5.04 to 7.65)	1.55 (–0.87 to 3.97)	1.32 (0.83 to 2.12)

*Predictive probability of a patient receiving omalizumab as a function of baseline characteristics; patients were stratified into deciles according to their propensity score (higher scores/strata reflect a higher probability of receiving omalizumab).

†Defined as the time from day 0 to the earliest of the following events: study completion, death, start of omalizumab treatment (non-omalizumab cohort), 6 months after discontinuation of omalizumab (omalizumab cohort), first ATE SAE, or study visit date (discontinued patients).

‡All non–omalizumab- or omalizumab-treated patients before any change in baseline treatment status.