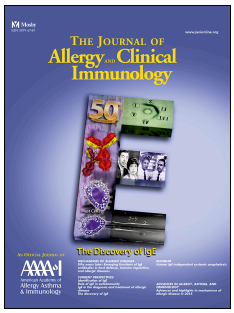
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Cardiovascular and cerebrovascular events among patients receiving omalizumab: Results from EXCELS, a prospective cohort study of moderate-to-severe asthma

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Conflict of interest

C. Iribarren is a member of the EXCELS Advisory Panel. A. A. Long is a member of the EXCELS Advisory Panel. A. Rahmaoui, M. S. Bradley, G. Carrigan, M. D. Eisner, H. Chen, and T. A. Omachi and are employees of Genentech, Inc. S. J. Szefler was a member of the EXCELS Advisory Panel, has consulted for and served on respiratory advisory panels for Aerocrine, AstraZeneca, Boehringer Ingelheim, Genentech, Inc., GlaxoSmithKline, Merck, Novartis, and Roche, and has received research grants from GlaxoSmithKline. M. E. Farkouh chaired the adjudication committee for cardiovascular and cerebrovascular events in EXCELS. K. J. Rothman is an employee of RTI Health Solutions, an independent nonprofit research organization that does work for government agencies and pharmaceutical companies.

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- Words: 3107
- Abstract word limit: 250
- Tables/figures: 3 tables/2 figures (maximum = 5)
- Supplemental material: 4 supplemental tables/1 supplemental figure

ABSTRACT

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

Objective: To examine a potential association between omalizumab and cardiovascular (CV)/cerebrovascular (CBV) events in EXCELS.

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

Results: At baseline, cohorts had similar demographic characteristics, but severe asthma was more common in the omalizumab versus non-omalizumab cohorts (50% vs 23%). Omalizumab-treated patients had a higher rate of CV/CBV serious adverse events (13.4 per 1000 person-years [PY]) than non-omalizumab–treated patients (8.1 per 1000 PY). ATE rate per 1000 PY was 6.66 (101 patients/15,160 PY) for the omalizumab cohort and 4.64 (46 patients/9904 PY) for the non-omalizumab cohort.

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After controlling for available confounding factors, the hazard ratio was 1.32 (95% CI, 0.91-1.91).

Conclusion: Results from this observational study demonstrated a higher incidence rate of CV/CBV events in the omalizumab versus non-omalizumab cohorts. Differences in asthma severity between cohorts likely contributed to this imbalance, but some increase in risk cannot be excluded (NCT00252135).

Clinical implications: Current asthma management guidelines should not be affected. However, health professionals should be aware of a possible association of omalizumab and serious cardiovascular/cerebrovascular events.

Capsule summary: Results from EXCELS data do not exclude a potential increased risk of serious cardiovascular/cerebrovascular events in patients treated with omalizumab. Controlling for confounding factors reduced this estimate of risk.

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

Abbreviations

ATE	Arterial thromboembolic event
CBV	Cerebrovascular
CV	Cardiovascular

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EXCELS	Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients With Moderate-to-Severe Asthma
FDA	Food and Drug Administration
ICS	Inhaled corticosteroid
IgE	Immunoglobulin class E
MI	Myocardial infarction
OCS	Oral corticosteroid
PY	Person-years
SAE	Serious adverse event
TIA	Transient ischemic attack

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INTRODUCTION

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

In the EXCELS (Epidemiologic Study of Xolair [omalizumab]: Evaluating Clinical Effectiveness and Long-term Safety in Patients With Moderate-to-Severe Asthma) study, a postmarketing observational cohort study, the primary objective was to compare the long-term (≤5 years) clinical safety profiles of patients, with a focus on malignancy. This observational study was designed to compare patients with asthma whom health care providers had treated with omalizumab with patients with asthma who had not treated with omalizumab. A numeric imbalance in rates of malignancy in allergic asthma pivotal trial data 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 patient baseline characteristics, are published.[11] In EXCELS, the incidence rates of primary malignancies (per 1000 person-years [PY]) were similar among omalizumab (Xolair®, Genentech, Inc., South San Francisco, Calif)-treated (12.3) and non-omalizumab–treated patients (13.0); however, study limitations preclude definitively ruling out a malignancy risk with omalizumab.[12] In an interim effectiveness analysis, patients who started omalizumab at enrollment showed clinically

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relevant improvements in asthma control that were maintained during 2 years of follow-up.[13]

This analysis focuses on cardiovascular (CV) and cerebrovascular (CBV) SAEs that occurred during EXCELS. EXCELS was not originally designed specifically to examine 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 below. In our companion article,[15] we present results from a pooled analysis of multiple omalizumab randomized, double-blind, placebo-controlled clinical trials that was planned after the results of the EXCELS interim analysis were evaluated.

METHODS

Overview of EXCELS

EXCELS (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 in a 2:1 ratio according to their use of omalizumab at or within 30 days of enrollment (omalizumab, n = 5007; non-omalizumab,

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n = 2829). Patients were excluded from EXCELS if they: 1) had a contraindication to omalizumab; 2) had an asthma exacerbation that required initiation or increased doses of systemic corticosteroids, doubling of inhaled corticosteroid dosing, 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; 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 US Food and Drug Administration regulations, the International Conference on Harmonisation E6 Guideline for Good Clinical Practice, and any other applicable country laws. Institutional review board approval 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 patient death, was life-threatening, required prolonged inpatient hospitalization, was disabling, was a congenital anomaly/birth defect, or was

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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 resulting in death and all potential CV/CBV SAEs identified using Standardized MedDRA Queries (Fig 1). This approach allowed for identification of cases that were highly likely to represent the condition of interest as well as 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 (TIA), hemorrhagic stroke, pulmonary embolism, venous thrombosis, pulmonary hypertension, arterial ischemic vascular disease, atrial fibrillation/flutter, and ventricular tachycardia/fibrillation.

An additional composite endpoint, 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 pathophysiological mechanism of arterial injury and/or inflammation and included CV death, MI, ischemic stroke, TIA, and unstable angina.

Descriptive analyses

Data were analyzed in terms of PY 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

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completed clinic visit for those who discontinued from the study, whichever came first. Overall incidence rates per 1000 PY of observation for adjudicated CV/CBV deaths and SAEs were calculated for each cohort and 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 to evaluate events with a common pathophysiology. As described for CV/CBV SAEs, overall incidence rates per 1000 PY were calculated with 95% CIs for both cohorts. Crude rate differences and rate ratios were calculated with 95% CIs. Similarly, the rate of patients experiencing ≥1 ATE event, expressed per 1000 PY of observation time, was computed by treatment cohort and reported with 95% CIs. A sensitivity analysis was conducted in which event rates per 1000 PY 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 for patients not experiencing an ATE were censored at the earliest of the following 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

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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, adjusting separately for each potential baseline CV/CBV risk factor. A final multivariable 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 $P \leq .20$ criteria for entry and $P > .20$ for removal. Model covariates are found in Table E1.

In addition, a *post hoc* exploratory analysis was conducted comparing ATE risk between the omalizumab and non-omalizumab cohorts while adjusting for the estimated probability of receiving omalizumab. For each patient, propensity scores[18] were 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 nonasthma-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 for omalizumab-treated patients, in addition to removal of 1% of observations from the lower tail of the propensity score distribution for non-omalizumab–treated patients. Patients were then stratified into deciles according to their

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propensity score. Standardized incidence rates per 1000 PY were calculated for each treatment cohort, as well as standardized rate differences and rate ratios (using the omalizumab cohort as the standard).

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

RESULTS

PY of follow-up

In the omalizumab cohort, the total cumulative PY were 18,426 (mean [SD] length of follow-up, 3.7 [1.8] years); in the non-omalizumab cohort, the total cumulative PY were 9963 (mean [SD], 3.5 [1.9] years).

Patient disposition

Baseline demographic and clinical characteristics have been previously reported.[12] On average, patients in the omalizumab cohort were slightly younger than those in the non-omalizumab cohort (44 vs 46 years, respectively). In both cohorts, ~65% were women 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%), lost to follow-up (16% and 15%), and physician decision (8% and 6%). In terms of person-time lost to follow-up, the proportion lost to

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follow-up was 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 (50% vs 23%, respectively). Among patients with moderate asthma in the omalizumab cohort, 78% had used an asthma controller and 16% had used a quick-relief medication in the 2 weeks before enrollment. In the non-omalizumab cohort, during the same time period, 70% of patients with moderate asthma had used an asthma controller and 12% 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 (Table E2).

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 can be attributed to the larger percentage of omalizumab- versus non-omalizumab–treated patients with moderate asthma taking OCS (28% vs 24%, respectively; Table E2). During the 5-year follow-up, more patients with severe asthma, regardless of treatment cohort, were taking OCS than were those with moderate asthma (Fig E1). The overall pattern of OCS use was similar; the lowest use rate was measured at month 6 (range, 17-33%), and the highest use rate was measured at month 18 (range, 20-52%). Overall, the use of OCS at baseline was higher among patients with severe versus moderate asthma (29% vs 26%, respectively).

Adjudicated study-emergent CV/CBV SAEs

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

Adjudicated study-emergent ATEs

The omalizumab cohort had a higher rate (per 1000 PY) of ATE SAEs, patients with ATE SAEs, and ATE SAEs (excluding non-ATE deaths) than the non-omalizumab cohort (Table E3).

The unadjusted (crude) rate of ATEs per 1000 PY was 6.66 (101 patients with an ATE event/15,160 PY) for the omalizumab cohort and 4.64 (46 patients with an ATE event/9904 PY) for the non-omalizumab cohort. The difference between the omalizumab and non-omalizumab cohorts in ATE rates per 1000 PY was 2.02 (95% CI, 0.15-3.89) and the unadjusted rate ratio was 1.43 (95% CI, 1.00-2.08; Table E4). The adjusted Cox proportional hazard 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 adjusting for the estimated probability of receiving omalizumab (propensity score), the difference between cohorts in ATE rates was 1.55 per 1000 PY (95% CI, −0.87 to 3.97) and the rate ratio was 1.32

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per 1000 PY (95% CI, 0.83-2.12). 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 post approval. Results of the primary analysis of overall SAEs and malignancy have been previously published.[12] The current analysis of the EXCELS data reveals a higher crude incidence rate of CV/CBV SAEs in omalizumab-treated patients compared with non-omalizumab–treated patients. However, in our companion article reporting the results of analyses of data pooled from 25 studies,[15] an association between omalizumab and CV/CBV SAEs or ATEs was not demonstrated.

In this nonrandomized study, confounding by indication for use of omalizumab is 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 omalizumab's indication such that the treated group included patients with more severe asthma. Analyses of CV/CBV SAE, unadjusted for potential confounders, demonstrated higher rates for patients in the omalizumab cohort. The findings were similar for the subset of CV/CBV SAEs meeting the definition of ATE. However, after taking confounding imbalances between the cohorts into account, using multivariable Cox regression analyses, stratification, and propensity score analyses, the crude associations were substantially reduced. We can expect that control of confounding was

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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.

Research indicates that asthma itself and the use of asthma medications may be independently associated with increased CV risk.[22-29] An analysis of 6792 patients in the Multi-Ethnic Study of Atherosclerosis (MESA) concluded that patients with asthma requiring controller medications, such as ICS, had higher rates of CV disease compared with those without asthma.[30] Additionally, as previously published, higher asthma severity predicted higher risk of ATEs within the non-omalizumab cohort of EXCELS.[28] Multiple hypotheses exist for the observed association between asthma and CV outcomes. Potential mechanisms include medications used to treat asthma,[31-33] most notably OCS, which are well known to increase CV risk factors such as diabetes,[34] and have been associated with increased risk of adverse CV/CBV outcomes.[35-38] In patients with severe asthma, medium to high exposure to chronic systemic corticosteroids appears to increase the risk for complications (eg, infections, CV, metabolic).[39] 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.[40-42] For example, patients with asthma requiring controller medications in MESA had higher levels of the inflammatory markers C-reactive protein and fibrinogen than both patients without asthma and patients with asthma not requiring controller medications.[30] 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

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comorbid diseases that increase CV risk, such as diabetes and chronic obstructive pulmonary disease.[34,43]

Elevated serum IgE levels have been described in some cardiovascular conditions and in patients with a positive history of cardiovascular disease[44,45] Moreover, IgE has been shown to be positively associated with cardiovascular risk.[46] None of these studies provides strong evidence that suggests that the anti-IgE properties of omalizumab would contribute to an increased risk of cardiovascular events. In summary, no definitive biological relationship has been identified.

In our multivariable analysis, we were able to control for the imbalance in prevalence of severe asthma (50% of patients in the omalizumab vs 23% in the non-omalizumab cohorts). Nonetheless, a dichotomous severity scale is unlikely to capture all 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, had the primary objective of EXCELS been to examine CV/CBV outcomes rather than malignancies, more careful details about the CV risk factor profile, such as low-density lipoprotein 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.

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Additionally, 44.1% of study participants discontinued before the full 5 years of follow-up was completed, although only slightly more than one-quarter 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 of serious CV/CBV events in patients treated with omalizumab. After controlling 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 the results from EXCELS and the pooled analysis of randomized controlled trials into account.

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550

551 **TABLE I.** Baseline clinical characteristics of the study cohorts

Body system and medical condition, no. (%)	**Non-omalizumab cohort (n = 2829)**	**Omalizumab cohort (n = 5007)**
Mean (SD) age (y)	46 (17) n=2827	44 (17) n=5006
Female	1880 (66.5) n=2827	3199 (63.9) n=5007
White	2322 (82.2) n=2826	3949 (78.9) n=5006
Mean (SD) BMI (kg/m^2)	31.0 (12.9) n=2824	31.1 (11.9) n=4996
Current smoker, no. (%)	159 (5.6) n=2827	245 (4.9) n=5005
Former smoker, no. (%)	826 (29.2)	1477 (29.5)
Median (range) IgE (IU/mL)	108 (0-23,237)	202 (2.0-33,200)

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	n=2728	n=4998
Physician-assessed asthma severity	n=2822	n=5001
Moderate	2185 (77.4)	2519 (50.4)
Severe	637 (22.6)	2482 (49.6)
Hypertension, no. (%)	658 (23.3)	1078 (21.5)
Hypercholesterolemia, no. (%)	306 (10.8)	516 (10.3)
Coronary artery disease, no. (%)	73 (2.6)	122 (2.4)
Congestive heart failure, no. (%)	26 (0.9)	64 (1.3)
Type 2 diabetes, no. (%)	189 (6.7)	430 (8.6)
Depression, no. (%)	417 (14.7)	864 (17.3)
Chronic obstructive pulmonary disease, no. (%)	161 (5.7)	407 (8.1)
OCS use, no. (%)†	724 (25.7)	1407 (28.1)
	n=2822	n=4997
Chronic	156 (5.5)	373 (7.5)
Periodic	568 (20.1)	1034 (20.7)

552 *BMI*, body mass index; *IgE*, immunoglobulin E; *OCS*, oral corticosteroid.

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

	Non-omalizumab cohort (n = 2829)			Omalizumab cohort (n = 5007)		
	No. of events	Crude incidence rate per 1000 PY	95% CI	No. of events	Crude incidence rate per 1000 PY	95% CI
CV/CBV event	80	8.1	6.5-10.1	201	13.4	11.6-15.4
Myocardial infarction	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	0	0	0.0-0.4	8	0.5	0.2-1.0

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hypertension						
Ischemic stroke	7	0.7	0.3-1.4	8	0.5	0.2-1.0
Cardiovascular 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 PY at risk for each individual event, not the overall PY at risk for any event during the study.

CBV, cerebrovascular; *CV*, cardiovascular; *PY*, person-years; *SAE*, serious adverse event.

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

	Non-omalizumab cohort* (n = 2829)	Omalizumab cohort† (n = 5007)
ATE SAEs, no.	46	101
PY§ at risk for ATE SAEs	9904	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).

‡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

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following comorbidities: chronic obstructive pulmonary disease, congestive heart failure, depression, hypercholesterolemia, hypertension, type 2 diabetes.

§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, PY at risk was 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.

ATE, arterial thromboembolic event; *PY*, person-years; *SAE*, serious adverse event.

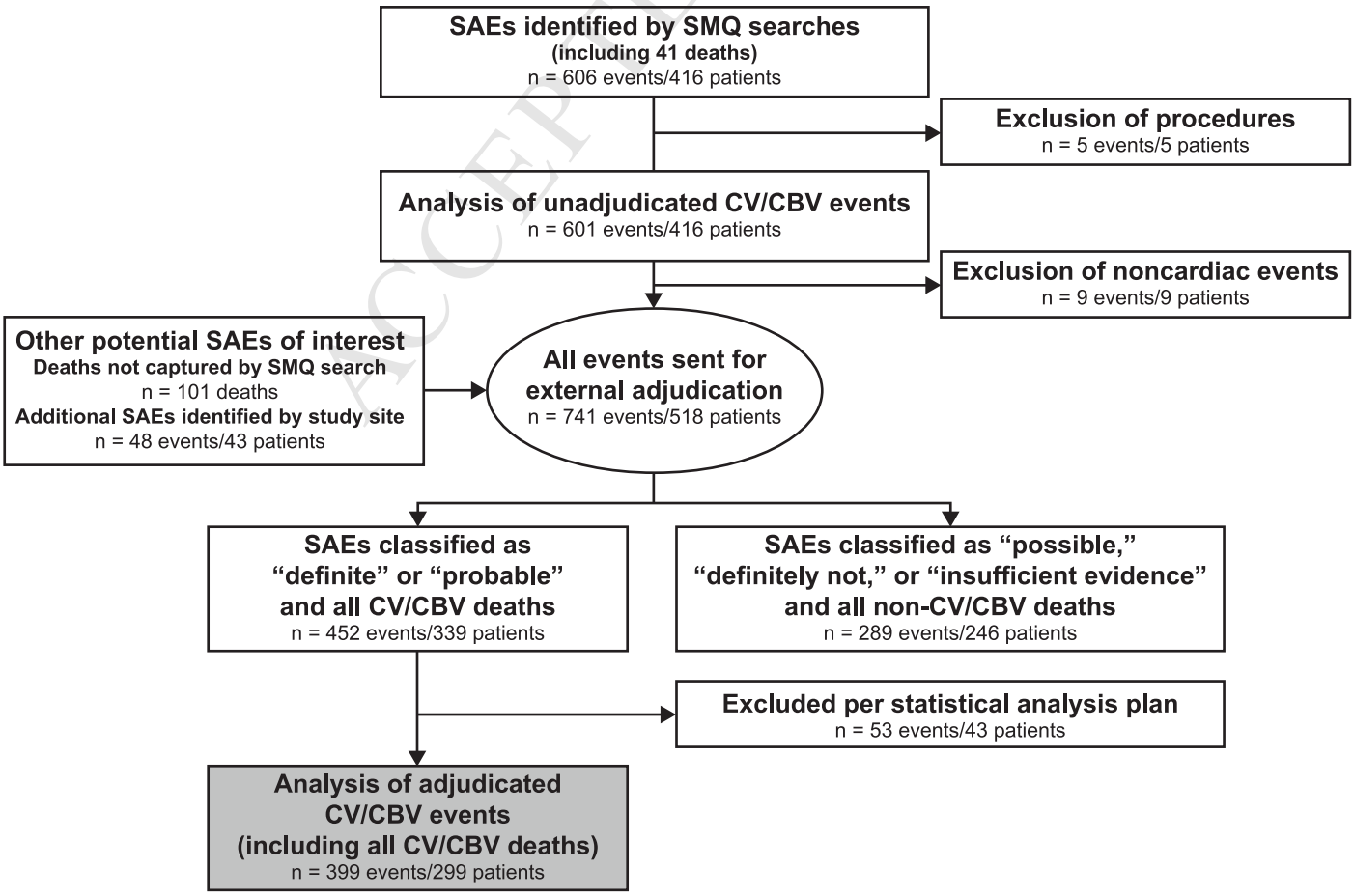
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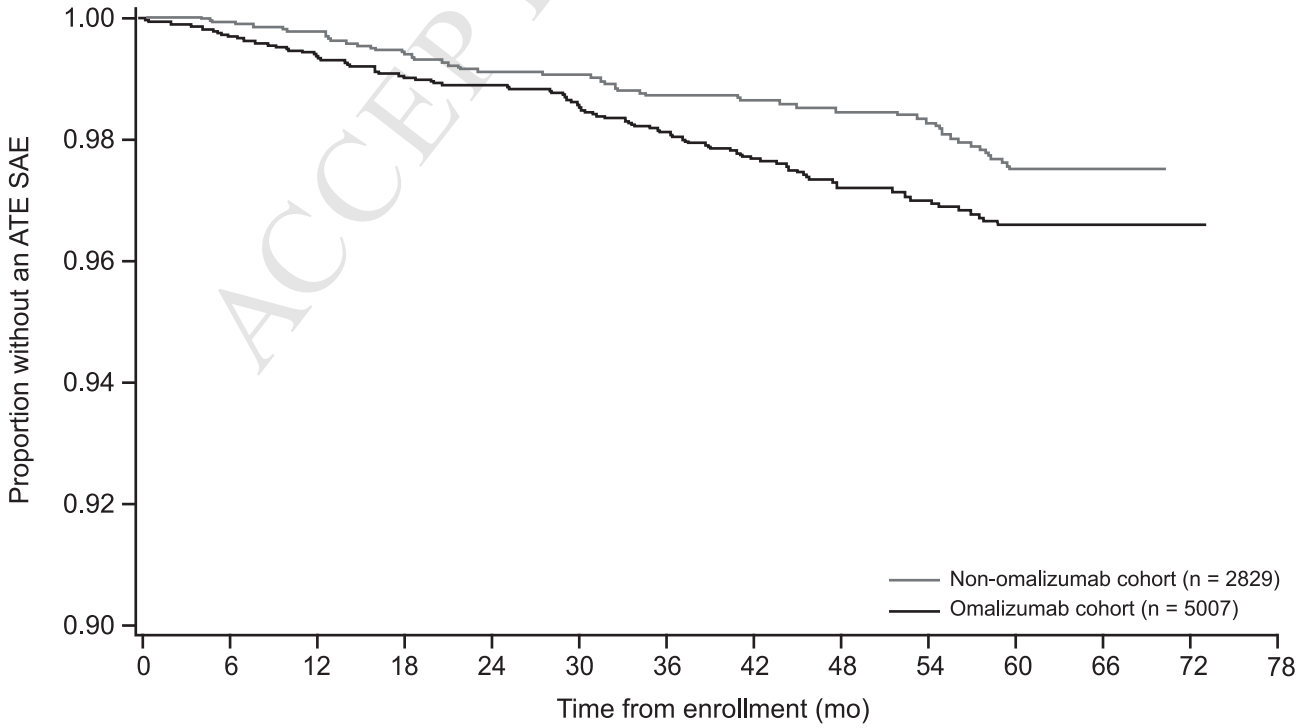
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573 **FIG 1.** Identification and adjudication of CV and CBV events. *CBV*,
574 cerebrovascular; *CV*, cardiovascular; *MedDRA*, Medical Dictionary for Regulatory
575 Activities; *SAE*, serious adverse event; *SMQ*, Standardized Medical Dictionary
576 for Regulatory Activities Query.
577
578
579 **FIG 2.** Kaplan-Meier plot of time to first adjudicated study-emergent ATE SAE.
580 *ATE*, arterial thromboembolic event; *SAE*, serious adverse event.
581

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No. at risk

Non-omalizmuab cohort	2829	2515	2328	2162	2015	1919	1823	1738	1656	1563	849	9	0	0
Omalizumab cohort	5007	4602	4056	3563	3167	2835	2546	2292	2087	1896	1016	16	1	0

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

	Parameter		HR
Main effect	**Estimate**	**SE**	**(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 (30-39 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)

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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)

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

†Patients, n = 4980; events, n = 101.

ATE, arterial thromboembolic event; *BMI*, body mass index; *HR*, hazard ratio; *SAE*, serious adverse event.

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

	Non-omalizumab cohort		Omalizumab cohort	
Asthma medication	**Moderate asthma* (n = 2185)**	**Severe asthma* (n = 637)**	**Moderate asthma* (n = 2519)**	**Severe asthma* (n = 2482)**
OCS use, no. (%)	533 (24.4)	191 (30.0)	695 (27.6)	712 (28.7)
Type of OCS, no. (%)†				
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, no. (%)‡	1524 (69.8)	542 (85.4)	1967 (78.1)	2205 (88.9)
Type of asthma controller, no. (%)				
Inhaled corticosteroid	1291 (59.1)	494 (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, no. (%)‡	259 (11.9)	161 (25.4)	392 (15.6)	728 (29.4)
Type of quick-relief agent, no. (%)				
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)

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*Physician-assessed asthma severity at baseline. †Omalizumab moderate asthma, n=2517; omalizumab severe asthma, n=2480. ‡Non-omalizumab moderate asthma, n=2183; non-omalizumab cohort severe asthma, n=635; Omalizumab cohort severe asthma, n=2480. *OCS*, oral corticosteroid.

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

	Non-omalizumab cohort* (n = 2829)	Omalizumab cohort† (n = 5007)	Crude rate difference (95% CI)	Crude rate ratio (95% CI)
ATE SAEs, no.	51	115	—	—
PY‡ at risk for ATE SAEs	9963	15,286	—	—
Rate per 1000 PY	5.12	7.52	2.40	1.47
(95% CI)	(3.81-6.73)	(6.21-9.03)	(0.16-4.62)	(1.02-2.18)
Patients with ATE SAEs, no.	46	101	—	—
PY at risk for ATE SAEs	9904	15,160	—	—
Rate per 1000 PY	4.64	6.66	2.02	1.43
(95% CI)	(3.40-6.19)	(5.43-8.10)	(0.15-3.89)	(1.00-2.08)

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ATE SAEs (excluding non-ATE deaths), no.	32	91	—	—
Rate per 1000 PY	3.21	5.95	2.74	1.85
(95% CI)	(2.20-4.53)	(4.79-7.31)	(0.74-4.68)	(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, PY at risk was 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.

ATE, arterial thromboembolic event; *PY*, person-years; *SAE*, serious adverse event.

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

		Rate per 1000 PY* (95% CI)			
	Propensity score† stratum	Non-omalizumab cohort‡ (n = 2829)	Omalizumab cohort (n = 5007)	Rate difference (95% CI)	Rate ratio (95% CI)
Unadjusted		4.64 (3.40-6.19)	6.66 (5.43-8.09)	2.02 (0.15-3.89)	1.43 (1.00-2.08)
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 (2.76-6.84)	6.35 (5.04-7.65)	1.55 (–0.87 to 3.97)	1.32 (0.83 to 2.12)

*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).

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†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).

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

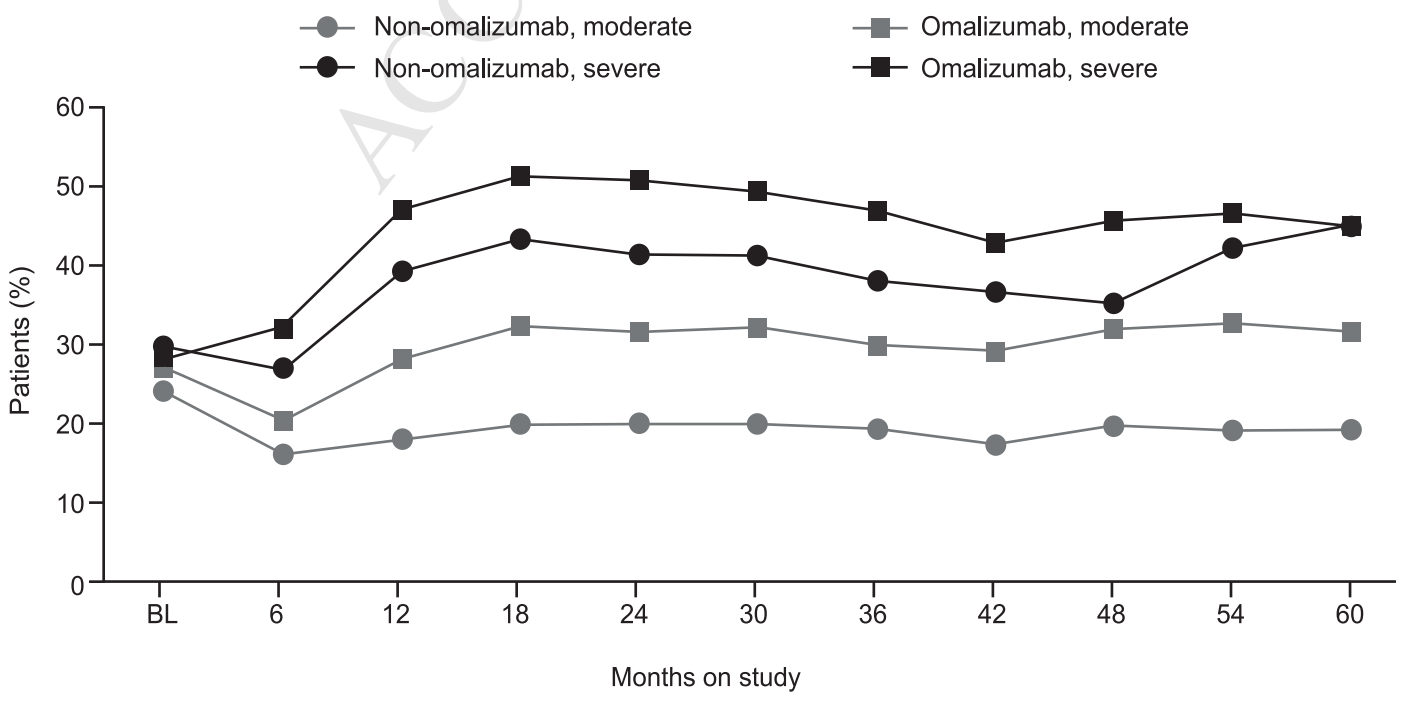
ATE, arterial thromboembolic event; *PY*, person-years; *SAE*, serious adverse event.

FIGURE LEGEND

FIG E1. Patient use of oral corticosteroids during EXCELS by treatment cohort and asthma severity. *BL*, baseline.

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