

Relationship Between Anaphylaxis and Use of Beta-Blockers and Angiotensin-Converting Enzyme Inhibitors: A Systematic Review and Meta-Analysis of Observational Studies



Miguel A. Tejedor-Alonso, MD, PhD^{a,b}, Enrique Farias-Aquino, MD^a, Elia Pérez-Fernández, PhD^a, Eulalia Grifol-Clar, BA^a, Mar Moro-Moro, MD, PhD^a, and Ana Rosado-Ingelmo, MD^a *Madrid, Spain*

What is already known about this topic? Beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) have been associated with an increased risk of anaphylaxis and with increased severity of anaphylaxis. However, evidence supporting these findings is contradictory.

What does this article add to our knowledge? Evidence of an increased risk of more severe anaphylaxis in patients who take BBs and ACEIs is low owing to the heterogeneous control of confounding variables arising from the concomitant presence of cardiovascular disease.

How does this study impact current management guidelines? It is necessary to perform observational studies on the severity of anaphylaxis that control for confounders arising from the presence of cardiovascular disease in patients receiving BBs and ACEIs.

BACKGROUND: Beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) have been associated with an increased risk and severity of anaphylaxis. However, the evidence supporting these findings is contradictory.

OBJECTIVE: We carried out a systematic review and meta-analysis of studies that assess the influence of BBs and ACEIs on anaphylaxis.

METHODS: We searched PubMed/MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, and the Web of Science for relevant observational studies. We searched for studies where the presence and severity of anaphylaxis were compared between patients taking BBs, ACEIs, both types of drug, or neither type of drug. We performed a meta-analysis using a random-effects model.

RESULTS: A total of 21 studies met the study criteria. Of these, 15 assessed the severity and 9 the incidence of anaphylaxis. The studies brought together 22,313 anaphylaxis episodes for the

severity studies and 18,101 anaphylaxis episodes for the studies of new cases of anaphylaxis. BBs and ACEIs increased the severity of anaphylaxis (BBs, odds ratio [OR] 2.19, 95% confidence interval [CI] 1.25-3.84; ACEIs, OR 1.56, 95% CI 1.12-2.16), but not the presence of new cases of anaphylaxis (BBs, OR 1.40, 95% CI 0.91-2.14; ACEIs, OR 1.38, 95% CI 0.39-4.86). It was not possible to perform an analysis adjusted for cardiovascular diseases, because only 1 study each for BBs and ACEIs, respectively, had adjusted data.

CONCLUSIONS: The quality of evidence showing that the use of BBs and ACEI increases the severity of anaphylaxis is low owing to differences in the control of confounders arising from the concomitant presence of cardiovascular diseases. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:879-97)

Key words: Anaphylaxis; New cases; Severity; Beta-blockers; ACEI; Systematic review; Meta-analysis

^aAllergy Unit, Hospital Universitario Fundación Alcorcón, Madrid, Spain

^bFacultad Ciencias de la Salud, Universidad Rey Juan Carlos, Madrid, Spain

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Corresponding author: Miguel A. Tejedor-Alonso, MD, PhD, Allergy Unit, Hospital Universitario Fundación Alcorcón, Avda Budapest 1, 28922 Alcorcón, Madrid, Spain. E-mail: m914674227@telefonica.net, matejedor@fhacorcon.es.

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Beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) are key components of the pharmacologic treatment of ischemic heart disease. BBs can reduce mortality and reinfarction rates in patients after myocardial infarction.¹⁻³ ACEIs are widely used in patients with hypertension and chronic ischemic heart disease^{1,2} and reduce the mortality rate and rate of recurrent infarction after acute myocardial infarction with ST-segment elevation.³

BBs and ACEIs have been associated with an increased risk of anaphylaxis and increased severity of anaphylaxis.⁴⁻¹² However, evidence supporting these observations is controversial. In the international medical literature, both confirmatory and

Abbreviations used

ACEI- Angiotensin-converting enzyme inhibitors

BB- Beta-blockers

CI- Confidence interval

OR- Odds ratio

nonconfirmatory data are available in the form of case reports and case series,^{13,14} cross-sectional studies,^{9-11,15-17} case-control studies,^{5,6,18} experimental animal studies,¹⁹ *in vivo* studies with skin tests,^{20,21} and studies with murine mast cells.¹⁷ However, discontinuation of these drugs in patients at risk of recurrence of anaphylaxis (eg, patients receiving allergen immunotherapy, patients undergoing challenge tests with drugs or insect venom) is common practice among allergists.^{22,23}

The influence of BBs and ACEIs on anaphylaxis and their biases and weaknesses have not been examined in a systematic review and meta-analysis. In the present article, we focus on a key confounding factor, namely, the presence of cardiovascular disease. A systematic review and a meta-analysis that establishes whether there are solid reasons for withdrawing these drugs or at least to determine the grade of evidence for this practice will help allergists to make reasoned decisions.

METHODS

The study was designed according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology²⁴ checklist and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for systematic reviews.²⁵

Search strategy

We searched PubMed/MEDLINE, EMBASE, Web of Science, and Cochrane Database of Systematic Reviews for relevant publications. The electronic search included titles and abstracts of studies in humans and published in English, Spanish, French, and German. In addition, the grey literature was investigated in Web of Science and Google Scholar. The last search was run on May 31, 2017, by 2 investigators (EF-A and EG-C). Articles cited in the articles and review papers selected were reviewed by the investigators to find articles not included in the original search. The types of studies reviewed were multicenter studies, comparative studies, and observational studies. Our search strategy consisted in the identification of publications based on the key words "BBs or ACEI and severe and anaphylaxis." We then examined the abstract and title of the articles, which were screened to choose those that met the study criteria. Two investigators (EF-A and MAT-A) performed the search independently. Disagreements between reviewers were resolved by consensus and discussion.

Selection criteria

We searched for studies where the severity and presence of anaphylaxis episodes were compared between patients receiving BBs, ACEIs, both types of drug, or neither type of drug. There were no restrictions with respect to age or sex. The series included studies with all the major causes of anaphylaxis (ie, food, drugs, hymenoptera, and latex) or series involving the specific cause of anaphylaxis (eg, insect venom and radiographic contrast media).

We excluded the following studies: studies with duplicate dates, systematic reviews and/or meta-analyses, reviews, letters, editorials, case reports, guidelines, book chapters, and animal studies. We also

excluded cases of anaphylaxis where kinins were the main trigger (eg, anaphylaxis in patients undergoing hemodialysis with AN69 dialyzers with or without concomitant ACEIs^{26,27}), because ACEIs are not an associated aggravating factor, as is the case in the classic causes of anaphylaxis, namely, food, drugs, and hymenoptera venom.

Data collection and extraction

We designed an electronic data extraction form that contained information on the following: (1) study data (first author, year of publication, country, type of anaphylaxis studied), (2) characteristics of studies (design [cohort, cross-sectional, case-control studies], origin of patients [eg, field stings, anaphylaxis registries]), (3) confounding or exposure variables (use of antihypertensive drugs, comorbidities [cardiovascular, respiratory diseases], sex, age), and (4) outcomes of severity (previously published scores, admissions to hospital wards or critical care areas, hypotension, use of mechanical ventilation). One author obtained all the information and the other checked its accuracy. Disagreement was resolved by consensus (MAT-A and MM-M).

Given the observational nature of almost all the studies included in the systematic review, our priority was to find adjusted statistics (odds ratios [ORs]) (Table 1).

In order not to include the same patients several times, we chose only the most severe outcome in each study. When the same group published several reports about the same exposure in different years (for instance, anaphylaxis due to hymenoptera venom), duplication was ruled out if the exposure was in different circumstances (eg, hymenoptera anaphylaxis in the field or after the build-up or maintenance phase of venom immunotherapy).

Risk of bias in individual studies

The quality of the studies and the presence of bias were assessed using the Newcastle-Ottawa scale.³⁸ The maximum score is 8 for cross-sectional and case-control studies. In addition, the quality of evidence was assessed again using the recommendations of the GRADE guidelines,³⁹ which classify quality from very low to high based on 4 grades.

Ethical approval

Given that our study was a systematic review of the published literature, it was not necessary to request approval from our local ethics committee.

Summary measures and meta-analyses

Severity and new cases of anaphylaxis were modeled as a binary variable independently of the criterion used to establish severity in each study. ORs with a 95% confidence interval (CI) were calculated as a summary measure.

The heterogeneity of the studies was measured using the I^2 statistic (inconsistency), as recommended elsewhere.^{25,40} Given the probable heterogeneity of the studies, we performed the meta-analysis using a random-effects model, following the approach of DerSimonian and Laird.⁴¹ In the case of cells with zero in the contingency table, 0.5 was added to enable the analysis. Likewise, to explain the heterogeneity of the studies, we used meta-regression models where we checked whether design, type of anaphylaxis, outcome, and the presence of adjustment played a key role in determining heterogeneity. Publication bias or bias due to small studies was determined by graphical analysis of the symmetry of the funnel plot and using Egger's test, which is more reliable than other tests published in the literature and tries to overcome the subjectivity of funnel plots.⁴² When the weight of a specific study in the

TABLE I. Characteristics of studies included in the meta-analysis of the severity and incidence of anaphylaxis and the use of beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs)

Author, country, year	Design	Type of Records	Type of anaphylaxis	Antihypertensive drug	Outcome	Outcome of severity	Adjustment of variables	Quality of study	N
Aggarwal, USA, 2015 ¹⁸	Case-control study	Structured questionnaire before computed coronary angiography	Drug	BB	Severity and incidence	Ring grade 3-4	Matched by likelihood of receiving BBs, ie, the differences in heart disease were not significant. Adjusted for demographics, heart rate, previous reactions to RCM, volume of contrast. Stratified univariate analysis	7	8/11,200
Alam, USA, 2005 ²⁸	Cross-sectional study	Chart review of patients with anaphylaxis and hypotension	All subtypes	BB	Severity	Requiring cardiopulmonary resuscitation	Not adjusted	5	80
Benitah, France, 1986 ⁴	Cross-sectional study	Clinical database of patients with venom immunotherapy at outpatient allergy clinic	Hymenoptera	BB	Severity	Müller grade 4	Not adjusted	5	249
Bernkopf, Germany, 2016 ¹²	Cross-sectional study	Clinical database of patients with venom immunotherapy at outpatient allergy clinic	Hymenoptera	BB, ACEI	Incidence	Not applicable	Age, sex, basal serum tryptase, honey-bee immunotherapy, ACEI, acetylsalicylic acid	7	173
Brown, Australia, 2013 ²⁹	Cross-sectional study	Data of research protocol questionnaire, emergency department	All subtypes	BB, ACEI	Severity	Hypotension	Lists several adjusted covariates (age, gender, lung diseases, drug anaphylaxis, cardiovascular [CV] diseases, CV medication). Use of binomial logistic regression	7	315
Clark, USA, 2014 ¹¹	Cross-sectional study	No state health system record, several HMOs including Medicare	All subtypes	BB, ACEI	Severity	Admission to critical care area	Lists several adjusted covariates (age, gender, Charlson-Deyo score, autoinjectors, previous visit to allergist, ACEIs, previous laboratory tests, previous visit to emergency department, previous hospitalization, CV disease)	7	11,972

(continued)

TABLE I. (Continued)

Author, country, year	Design	Type of Records	Type of anaphylaxis	Antihypertensive drug	Outcome	Outcome of severity	Adjustment of variables	Quality of study	N
Lang, USA, 1993 ⁶	Case-control study	Structured questionnaire of anaphylaxis in patients with the use of RCM	Drug	BB	Severity and incidence	Hypotension or stridor	Confounders (same iodinated radiologic contrast, age, date of study) and in the multivariate analysis (asthma, CV diseases, and BBs). Use of binomial logistic regression	7	278
Lantner, USA, 1989 ³⁰	Cross-sectional study	Clinical database of patients with venom at immunotherapy outpatient allergy clinic	Hymenoptera	BB	Severity	Loss of consciousness	Not adjusted	5	158
Lee, USA, 2013 ³¹	Cross-sectional study	Data of research protocol questionnaire, emergency department	All subtypes	BB, ACEI	Severity	Syncope or hypotension or hypoxia	List of several adjusted covariates (age, gender, cause of anaphylaxis, lung disease, BBs, ACEIs, calcium channel blockers, diuretics). Use of binomial logistic regression	7	302
Muller, Switzerland, 2005 ³²	Cross-sectional study	Clinical database of patients with venom at immunotherapy, outpatient allergy clinic	Hymenoptera	BB	Severity and incidence	Müller grade 3-4	Analysis stratified by BB in sample with heart disease	6	17/142
Nassiri, Germany, 2015 ¹⁷	Cross-sectional study	Data of research protocol questionnaire, registry of anaphylaxis	All subtypes	BB, ACEI	Severity	Ring grade 3-4	Age and sex, any antihypertensive (BB, ACEI, both). Use of binomial logistic regression	7	4783
Rueff, Germany, 2014 ⁹	Cross-sectional study	Clinical database of patients with venom at immunotherapy outpatient allergy clinic	Hymenoptera	BB, ACEI	Severity	Ring grade 3-4	Basal tryptase, type of insect, number of preceding minor systemic reactions to field sting, BB, ACEI, and any antihypertensive drug, use of binomial logistic regression	7	962
Moneret-Vautrin, France, 2009 ⁸	Cross-sectional study	Clinical database of patients with food anaphylaxis, outpatient allergy clinic of a university hospital	Food	BB, ACEI	Severity	Anaphylactic shock	Males, <45 y without drugs, acetylsalicylic acid, NSAID, ACEI, BB, other drugs, alcohol, exercise, hidden allergens, isolated drugs, drugs and alcohol, drugs and exercise, more than 1 factor	7	1040
Stoevesandt, Germany, 2012 ³³	Cross-sectional study	Clinical database of patients with venom immunotherapy, outpatient allergy clinic	Hymenoptera	BB, ACEI	Severity	Muraro grade 3	Not matched, not adjusted	5	657

Stoevesandt, Germany, 2015 ¹⁶	Cross-sectional study	Clinical database of patients with venom immunotherapy at outpatient allergy clinic	Hymenoptera	BB, ACEI	Severity	Muraro grade 3	Not matched, not adjusted	5	225
Summers, UK, 2008 ¹⁴	Cross-sectional study	Data of Manchester Allergic Research Database, outpatient allergy clinic	Peanut and true nuts	BB, ACEI	Severity	Loss of consciousness	Upper airways disease, lower airways disease, eczema, age. Use of binomial logistic regression	7	1094
Greenberger, USA, 1987 ³⁵	Cross-sectional study	Consecutive patients undergoing cardiac angiography at Northwestern Memorial Hospital between 1984 and 1985	Drug Anaphylaxis	BB	Incidence		Not adjusted	5	663
Hepner, USA, 1990 ³⁶	Cross-sectional study	Consecutive injections of immunotherapy with aeroallergens, during 1 y	Hymenoptera and aeroallergen immunotherapy	BB	Incidence		Not adjusted	5	3178
Rueff, Germany, 2014 ¹⁰	Cross-sectional study	Patients with venom immunotherapy who underwent an in-hospital sting challenge	Hymenoptera	BB, ACEI	Incidence		ACEI, honey bee venom, tryptase >20, time build-up and challenge, double VIT, >200 µg VIT	7	1609
Stoevesandt, Germany, 2014 ³⁷	Cross-sectional study	Clinical database of patients with venom immunotherapy, outpatient allergy clinic	Hymenoptera	BB, ACEI	Incidence		Age, sex, venom IgE, intradermal test, severity anaphylaxis in the field, CV disease, ACEI, BB, latency time, treatment protocol	7	779
White, USA, 2008 ¹⁵	Cross-sectional study	Consecutive injections of venom immunotherapy, for 5 y	Hymenoptera	ACEI	Incidence		Not adjusted	5	79
Total 21			Type of anaphylaxis						Severity 22,313 Incidence 18,101

HMO, Health maintenance organization; NSAID, nonsteroidal anti-inflammatory drug; RCM, radiographic contrast media; VIT, venom immunotherapy.

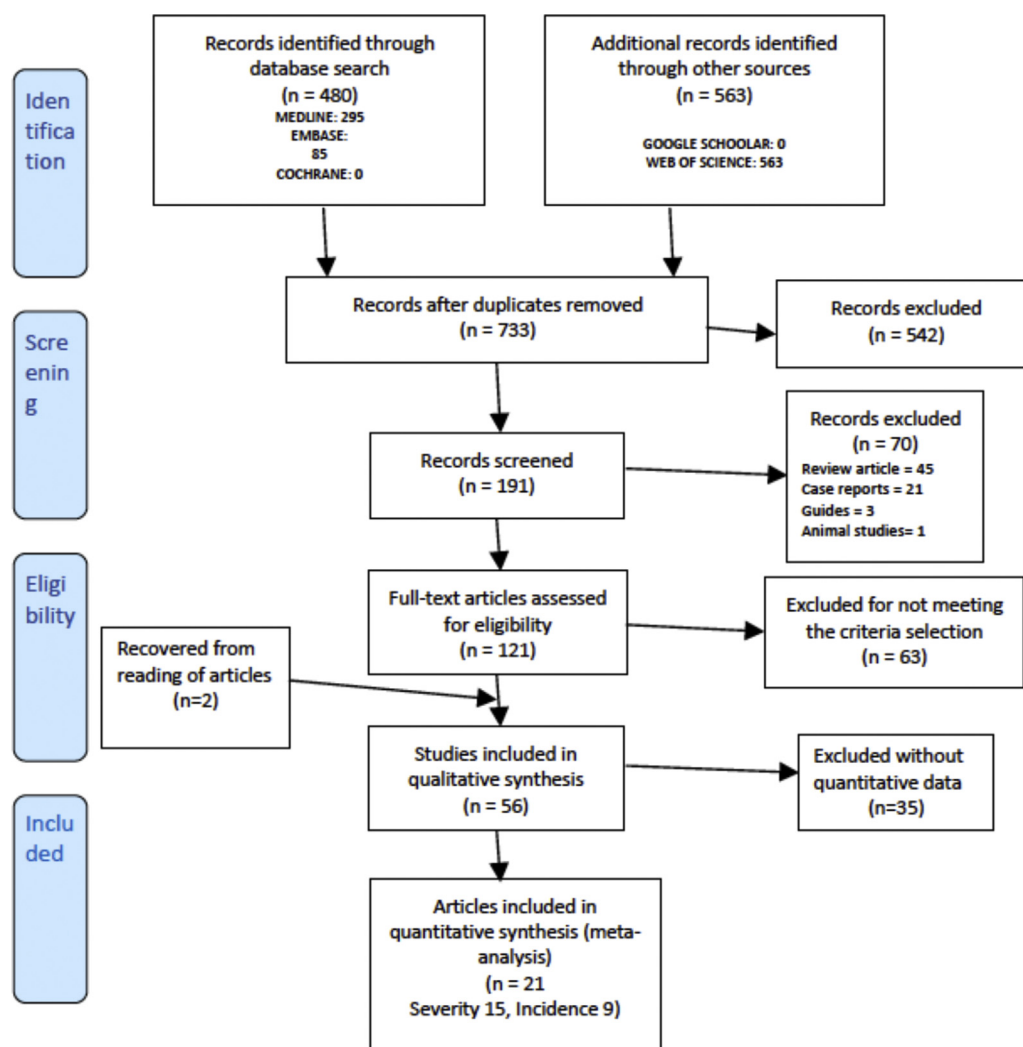


FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram summarizing the study selection process.

individual meta-analysis was more than 50%, it was excluded from the subsequent sensitivity analysis. All statistical analyses were carried out using STATA (version 15.1; College Station, Tex).

RESULTS

Selection of studies

Our literature search revealed 1043 publications (Figure 1). After excluding duplicate studies, the number of publications decreased to 733. A further 542 articles were excluded during the screening phase. Of the remaining 191 studies, 70 were excluded because they were reviews, case reports, guidelines, or animal studies. Of the remaining 121 studies, 63 were excluded because they did not meet the inclusion criteria. Three articles^{29,34,36} were found by checking the references of the excluded articles. Of the remaining 56 articles, 21 met our criteria for inclusion in the review^{4,6,9-11,12,15-18,30,34,36,43} and had sufficient data for the quantitative analysis. Fifteen of the 21 studies assessed the severity of anaphylaxis, 9 the incidence of anaphylaxis, and 3 both (Table I). Two studies that met our inclusion criteria could not be included, because not all of the data were available in all the cells of the table and the authors did not or could not answer

the queries sent by e-mail.^{44,45} Almost all of the studies were cross-sectional observational studies (19), and only 2 were case-control studies.^{6,18} The studies were published from 1987 to May 2017. All studies were published in English except 1, which was in French.⁸

Characteristics of the studies

The severity studies brought together 22,313 anaphylaxis episodes; the studies of new episodes of anaphylaxis brought together 18,101 episodes (Table I). With respect to severity, the most frequent analysis was carried out between hymenoptera anaphylaxis (5 for BBs and 4 for ACEIs) and studies with all major causes of anaphylaxis (6 for BBs and 3 for ACEIs), whereas in new cases, hymenoptera was the only cause of anaphylaxis (4 for BBs and 3 for ACEIs), followed by drug anaphylaxis (3).

The number of different outcomes in the severity studies was 9 for BBs and 6 for ACEIs. Almost half of the outcomes had a different severity score (Table I).

In the case of severity, the authors followed various strategies to control for confounders. Nine confounders were frequently identified, with age, sex, type of anaphylaxis, and lung disease

being the most common (6, 8, 5, and 4 studies, respectively). [Table E1](#) (available in this article's Online Repository at www.jaci-inpractice.org) shows how each variable was adjusted for the remaining variables.

Analysis of bias using the Newcastle-Ottawa scale³⁸ showed that more than half of the cross-sectional studies and both case-control studies yielded high scores (12 with scores >6 and 7, respectively), with nonresponse rate being the only condition not met in the 21 studies.

[Table II](#) shows individual studies with their contingency tables.

Effects of BBs on the severity of anaphylaxis

When we studied the effects of BBs on the severity of anaphylaxis without stratifying according to the study design (cross-sectional and case-control studies), we observed that the risk was significant (OR, 2.19; 95% CI, 1.25-3.84), yet heterogeneous ($I^2 = 52.6\%$, $P = .011$). The OR for cross-sectional studies was similar in terms of both size and statistical significance. The pooled and individual ORs of 2 case-control studies were not significant ([Figure 2](#)), although if we had used a less severe variable such as that used in the study of Lang et al⁶ (bronchospasm) than we used (life-threatening reactions), the pooled OR would have been significant (OR, 3.45; 95% CI, 1.13-10.59).

An additional analysis revealed that the pooled ORs were not significant in the nonadjusted studies, although they were significant in the adjusted studies (OR, 2.07; 95% CI, 1.14-3.75). We performed an additional analysis of adjusted studies excluding the study of Lee et al³¹ (weight, 61%), with no loss of the strength of the OR (OR, 3.09; 95% CI, 1.20-7.96). Heterogeneity was only noted in the nonadjusted studies ($I^2 = 70.8\%$, $P = .001$) ([Table III](#)).

In the studies that reported the presence of cardiovascular disease, we also analyzed the strength of the association between cardiovascular disease and severity of anaphylaxis. Only 3 studies were available.^{6,8,11} The OR for cardiovascular disease was higher than the pooled OR for BBs (more than 3-fold). An analysis of the effect of the risk of therapy with BBs on the severity of anaphylaxis adjusted for cardiovascular disease was not possible, given that therapy with BBs was adjusted for cardiovascular disease in only 1 study.⁶

The meta-regression analysis did not reveal any variables that could explain this heterogeneity.

The funnel plot revealed the presence of small studies with a protective effect for anaphylaxis and the absence of small studies with a facilitating effect ([Figure E1](#), available in this article's Online Repository at www.jaci-inpractice.org). The Egger test for the objective measurement of bias of small studies with large effects did not show evidence of bias ($P = .91$).

Effects of BBs favoring new episodes of anaphylaxis

BBs did not increase the risk for new episodes of anaphylaxis in the pooled meta-analysis, the meta-analysis of cross-sectional studies and case-control studies, or the analysis with adjusted or nonadjusted ORs. We did not note heterogeneity between studies in any of the meta-analyses ([Figure 3](#)). With the adjusted studies, we performed an additional analysis excluding the study by Lang et al⁶ (weight 53.9%). Once again, the difference was not statistically significant (OR, 1.9; 95% CI, 0.41-3.42).

The funnel plot shows the presence of small studies with protective effects for anaphylaxis and the absence of small studies with facilitating effects (high ORs with broad dispersions), whereas the results of the Egger test for small effect bias were significant ($P = .033$).

Effects of ACEIs on the severity of anaphylaxis

In this meta-analysis, ACEIs increased the severity of anaphylaxis (OR, 1.56). The general analysis of the studies did not reveal heterogeneity ($I^2 = 21.1\%$, $P < .28$). The separate analysis of adjusted studies also showed the presence of significant ORs (OR, 1.70; $P < .001$); however, when the study of Clark et al¹¹ (weight 89.9%) was excluded, the 95% CI included 1 (OR, 1.91; 95% CI, 0.95-3.83). In the 2 nonadjusted studies,^{16,33} whose authors belonged to the same research group, the ORs were not significant ([Figure 4](#)). The examination of the meta-analyses did not reveal heterogeneity.

The study by Clark et al¹¹ was the only study where cardiovascular disease was used to adjust for the effect of ACEIs. In this study, the OR of the severity of anaphylaxis was 5 times higher than the global OR of the severity of anaphylaxis for ACEIs.

The funnel plot was similar to that of the 2 previous assessments, and findings were confirmed with the Egger test ($P = .782$).

Effects of ACEIs on episodes of anaphylaxis

Overall, ACEIs did not favor new anaphylaxis episodes. The OR of 2 adjusted analyses^{10,12} was higher and significant (OR, 5.34; 95% CI, 2.37-12.00) in both cases, although the weight in the study of Rueff et al¹⁰ was 71.2%. Heterogeneity was only observed in the global meta-analysis ($I^2 = 75.5\%$, $P = .003$) ([Figure E2](#), available in this article's Online Repository at www.jaci-inpractice.org).

It was not possible to perform meta-regression owing to the insufficient number of studies. The funnel plot did not show the presence of bias in favor of the effects of small studies. The results of the Egger test for this bias were not significant ($P = .646$).

[Table IV](#) summarizes the quality of evidence in the meta-analysis according to the GRADE guidelines.⁴⁶ Except for the incidence of new cases of anaphylaxis taking ACEIs and severity of anaphylaxis in patients taking BB (both with individual studies with adjusted ORs), where the quality of evidence was moderate and low, respectively, all the grades were very low.

DISCUSSION

Severity and new episodes of anaphylaxis

Our meta-analysis showed that BBs and ACEIs increased the severity of anaphylaxis in studies that were adjusted or not adjusted for individual studies. In the case of studies performed with adjusted individual studies, ACEIs also increased the risk of new anaphylaxis episodes. However, using the recommendations of the GRADE guidelines,⁴⁶ the quality of evidence was only low for adjusted meta-analyses examining severity and BBs and moderate for adjusted meta-analyses examining incidence of anaphylaxis and ACEIs. In the remaining meta-analyses, the quality was very low. Therefore, these observations must be interpreted very cautiously because of the presence of cardiovascular disease, for which BBs and ACEIs are prescribed in a large percentage of patients (69%). Cardiovascular disease also increased the severity of anaphylaxis, with ORs higher than the pooled effect of both drugs. Therefore, this increased severity in

TABLE II. Contingency table for studies included in the meta-analysis of the severity and incidence of anaphylaxis and use of beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs)

Author	Type of patients	Exposure	Outcome	Exposed, cases	Not exposed, cases	Exposed, not cases	Not exposed, not cases	Odds ratio (OR)	Lower limit, 95% confidence interval (CI)	Upper limit, 95% CI	Adjusted OR
Aggarwal, 2015 ¹⁸	Iodinated contrast administration	BB	Severity	1	0	6	1	0.69	0.02	26.91	No
Alam, 2005 ²⁸	Admitted patients	BB	Severity	1	4	32	43	0.34	0.01	3.65	No
Benitah, 1986 ⁴	Field hymenoptera stings	BB	Severity	14	107	0	128	34.67	2.04	587.92	No
Clark, 2014 ¹¹	Emergency department and admissions	BB	Severity	21	2601	11	9339	6.85	3.30	14.24	No
Clark, 2014 ¹¹	Emergency department and admissions	ACEI	Severity	29	2593	13	9337	1.68	1.40	2.02	Yes
Lang, 1993 ⁶	Iodinated contrast administration	BB	Severity	5	8	14	87	1.64	0.38	8.10	Yes
Lantner, 1989 ³⁰	Hymenoptera immunotherapy	BB	Severity	3	42	2	111	3.96	0.43	48.52	No
Lee, 2013 ³¹	Emergency department	BB	Severity	13	42	36	211	1.60	0.68	3.43	Yes
Lee, 2013 ³¹	Emergency department	ACEI	Severity	8	47	26	221	1.20	0.44	3.00	Yes
Moneret-Vautrin, 2009 ⁸	Food anaphylaxis	BB	Severity	8	68	4	231	6.79	1.78	27.78	Yes
Moneret-Vautrin, 2009 ⁸	Food anaphylaxis	ACEI	Severity	4	72	1	234	13	1.34	310.38	Yes
Muller, 2005 ³²	Stable doses of immunotherapy with cardiovascular disease	BB	Severity	0	1	2	9	1.27	0.04	41.56	Yes
Muller, 2005 ³²	Increasing doses of immunotherapy with cardiovascular disease	BB	Severity	0	3	1	13	1.29	0.04	38.90	Yes
Muller, 2005 ³²	Resting in ICU or field with cardiovascular disease	BB	Severity	0	0	1	4	3.00	0.04	228.68	Yes
Rueff, 2009 ⁹	Field hymenoptera stings	BB	Severity	18	188	34	722	2.03	1.12	3.68	No
Rueff, 2009 ⁹	Field stings	ACEI	Severity	18	188	24	732	2.27	1.30	4.56	Yes

Stoevesandt, 2012 ³³	Field hymenoptera stings	BB	Severity	15	157	44	441	0.96	0.52	1.77	No
Stoevesandt, 2015 ¹⁶	Stable doses of immunotherapy	BB	Severity	0	4	40	181	0.50	0.03	9.43	Yes
Stoevesandt, 2012 ³³	Field stings	ACEI	Severity	7	165	25	460	0.78	0.33	1.84	No
Stoevesandt, 2015 ¹⁶	Stable doses of immunotherapy	ACEI	Severity	1	3	70	151	0.72	0.07	7.04	No
White, 2008 ¹⁵	Immunotherapy	ACEI	New cases	0	13	17	49	0.10	0.01	1.86	No
Rueff, 2014 ¹⁰	Resting in ICU	ACEI	New cases	6	98	24	1481	5.24	1.83	13.60	Yes
Stoevesandt, 2014 ³⁷	Increasing doses of immunotherapy	ACEI	New cases	11	78	77	581	1.06	0.54	2.09	No
Aggarwal, 2015 ¹⁸	Iodinated contrast administration	BB	New cases	1	1	5099	5099	1.00	0.06	15.99	Yes
Bernkopf, 2016 ¹²	Increasing doses of immunotherapy	BB	New cases	0	19	9	147	0.59	0.03	10.95	No
Bernkopf, 2016 ¹²	Increasing doses of immunotherapy	ACEI	New cases	3	16	27	129	5.51	1.23	24.67	Yes
Greenberger, 1987 ³⁵	Iodinated contrast administration	BB	New cases	16	20	200	427	1.71	0.87	3.37	No
Hepner, 1990 ⁴³	Increasing doses of immunotherapy and stable doses of immunotherapy	BB	New cases	1	143	60	2978	0.35	0.05	2.52	No
Lang, 1993 ⁶	Iodinated contrast administration	BB	New cases	19	103	18	138	1.62	0.61	4.30	Yes
Muller, 2005 ³²	Stable doses of immunotherapy with cardiovascular disease	BB	New cases	2	10	23	107	0.93	0.19	4.53	Yes
Muller, 2005 ³²	Resting in ICU or field with cardiovascular disease	BB	New cases	1	4	6	25	1.04	0.10	11.09	Yes
Muller, 2005 ³²	Increasing doses of immunotherapy with cardiovascular disease	BB	New cases	1	16	3	122	2.54	0.25	25.93	Yes

(continued)

TABLE II. (Continued)

Author	Type of patients	Exposure	Outcome	Exposed, cases	Not exposed, cases	Exposed, not cases	Not exposed, not cases	Odds ratio (OR)	Lower limit, 95% confidence interval (CI)	Upper limit, 95% CI	Adjusted OR
Rueff, 2014 ¹⁰	Resting in ICU	BB	New cases	0	104	18	1487	0.38	0.02	6.43	No
Stoevesandt, 2014 ³⁷	Increasing doses of immunotherapy	BB	New cases	5	90	22	662	1.67	0.62	4.52	No
White, 2008 ¹⁵	Field hymenoptera stings	ACEI	New cases	0	5	12	17	0.13	0.01	2.52	No

Note: Bold indicates statistical significance of studies. In the publication of Summers et al,³⁴ the frequencies were obtained from the ORs of each outcome and their 95% CIs. ICU, Intensive care unit.

patients taking BBs or ACEIs can also be explained by concomitant cardiovascular disease, which warranted the use of these drugs.

Observational studies, such as those included in this systematic review, are at risk of bias because of differences in prognosis in exposed and unexposed populations,^{39,47} because they cannot control for the confounders arising from the fact that the different groups are not chosen randomly.⁴⁸

The GRADE framework classifies evidence from observational studies as low.⁴⁶ However, the risk of bias is diminished if methodologically rigorous observational studies (those that comprehensively and accurately measure prognostic factors associated with the outcome of interest and the outcome) minimize loss to follow-up (the worst reported variable/item in the studies in our systematic review), the 2 groups are similar (in terms of time, place, and population, as in our study), and the analysis is an adjusted analysis that controls for differences in the distribution of prognostic factors between exposure and control groups (as in 14 of 21 studies in the present review). In addition, if the studies show a sufficiently large effect (risk ratio greater than 2 and strength higher than 5), one can reasonably deduce that this effect is real.^{39,46} These conclusions can translate to ORs if the baseline risk is 20% or lower.⁴⁷ If the studies meet these conditions, evidence can be upgraded to moderate.

The assessment of confusion bias was very important in our review for several closely related variables, such as old age, use of BBs or ACEIs, and cardiovascular disease, because it enabled us to determine the variable that best accounted for the severity of anaphylaxis. The authors of the studies reviewed followed various strategies to control for confounders. ACEIs, BBs, demographic variables, lung and heart diseases, and type of anaphylaxis frequently tended to have crossed adjustments. Studies using the OR of adjusted and nonadjusted studies for BBs and ACEIs showed positive ORs, thus increasing severity, although only 1 study¹¹ adjusted for cardiovascular diseases and use of ACEIs with high ORs (>8). The association was low for the relationship between BBs and the severity of anaphylaxis using the GRADE guidelines and individual adjusted studies, whereas for ACEIs, the quality of evidence was very low. Therefore, our study cannot categorically prove whether BBs and ACEIs independently increase the severity of anaphylaxis (this is even truer for ACEIs) or whether cardiovascular disease is the only explanation for the severity of anaphylaxis or whether there is an interaction between both. Likewise, age was very heterogeneous in the individual studies (2 values under or over a cutoff, age-group variables), thus preventing us from carrying out the meta-analysis of age and severity of anaphylaxis.

The variable gender is also involved in the presence of new anaphylaxis episodes or in their severity.⁴⁹ It was controlled for in 6 of 15 severity studies and in 3 of 9 incidence studies.

Application of the same GRADE scale for the influence of BBs on new anaphylaxis episodes revealed the quality of evidence to be very low, whereas the same scale showed that the quality of evidence for the association between ACEIs and new episodes of anaphylaxis was moderate when the adjusted OR was used. However, this meta-analysis included only 2 studies.

In our review, we found 2 case-control studies^{6,18} that assessed the relationship between anaphylaxis and use of BBs and therefore provided stronger evidence than cross-sectional studies. However, these 2 case-control studies do not help to resolve the confusion. In the study by Lang et al,⁶ therapy with BBs was an

Severity of anaphylaxis if intake of beta-blocker cross-sectional studies

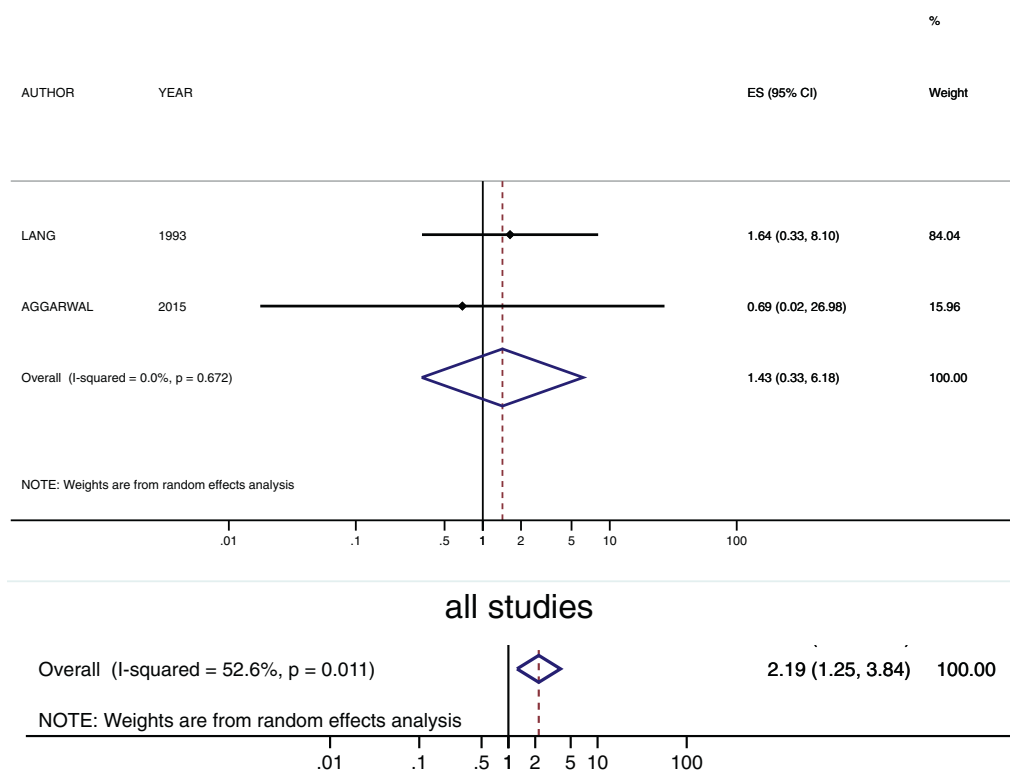
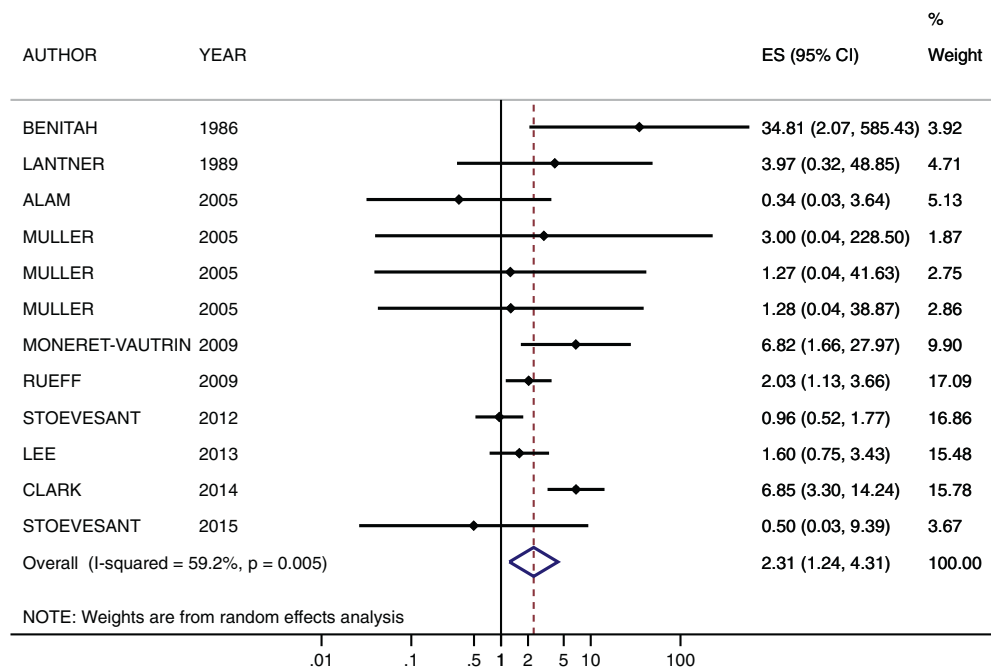


FIGURE 2. Meta-analysis of beta-blockers and severity of anaphylaxis. *CI*, Confidence interval; *ES*, effect size.

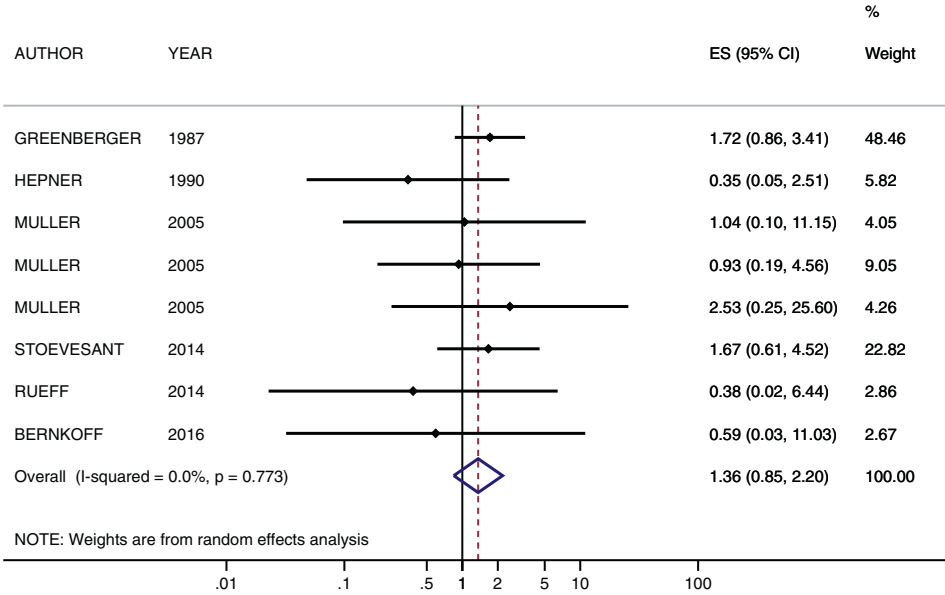
TABLE III. Synthesis and heterogeneity statistics in the meta-analysis of the severity and incidence of anaphylaxis and use of beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs)

Compared groups	Outcome	Type of studies	Overall OR, meta-analysis random effects	Lower limit, 95% CI	Upper limit, 95% CI	Heterogeneity, I ²	Heterogeneity, P value
Patients taking or not taking BBs	Severity	All studies	2.19	1.25	3.84	52.6%	.011
Patients taking or not taking BBs	Severity	Cross-sectional studies	2.31	1.124	4.31	59.2%	.005
Patients taking or not taking BBs	Severity	Case-control studies	1.43	0.33	6.18	0%	.672
Patients taking or not taking BBs	Severity	Adjusted OR	2.07	1.14	3.75	0%	.632
Patients taking or not taking BBs	Severity	Nonadjusted OR	2.12	0.90	5.02	70.8%	.001
Patients with cardiovascular diseases taking or not taking BBs	Severity (only 3 studies)	Cross-sectional studies	7.03	4.06	12.16	0%	.475
Patients taking or not taking BBs	New cases	All studies	1.40	0.91	2.14	0%	.897
Patients taking or not taking BBs	New cases	Cross-sectional studies	1.36	0.85	2.20	0%	.773
Patients taking or not taking BBs	New cases	Case-control studies	1.53	0.61	3.86	0%	.748
Patients taking or not taking BBs	New cases	Adjusted OR	1.40	0.68	2.88	0%	.952
Patients taking or not taking BBs	New cases	Nonadjusted OR	1.39	0.82	2.36	0%	.477
Patients taking or not taking ACEI	Severity	All studies	1.56	1.12	2.16	21.1%	.275
Patients taking or not taking BBs and ACEI	Severity	Adjusted OR	1.70	1.43	2.03	0%	.426
Patients taking or not taking ACEI	Severity	Nonadjusted OR	0.77	0.35	1.72	0%	.947
Patients with cardiovascular diseases taking or not taking ACEI	Severity (only 1 study)	Cross-sectional study	8.24	4.39	15.46		
Patients taking or not taking ACEI	New cases	Cross-sectional studies	1.38	0.39	4.86	75.1%	.003
Patients taking or not taking ACEI	New cases	Adjusted OR	5.34	2.37	12.00	0%	.956
Patients taking or not taking ACEI	New cases	Nonadjusted OR	0.40	0.07	2.20	50.3%	.134
Patients taking or not taking together BB and ACEI	Severity	Cross-sectional studies	2.21	0.75	6.52	20.4	.262
Patients taking or not taking together BB and ACEI	New cases	Cross-sectional studies	0.33	0.04	2.51	Only 1 study	

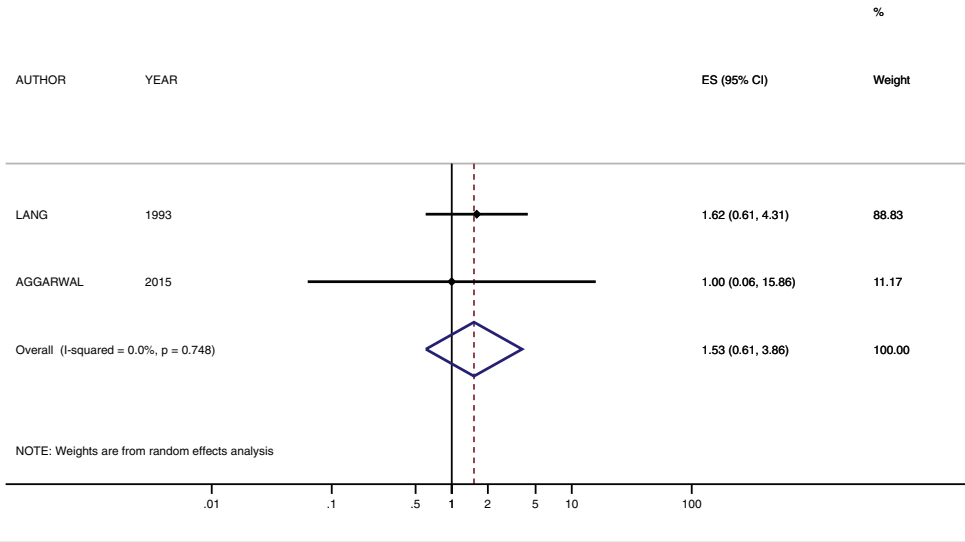
Bold indicates a new group of analyses.

OR, Odds ratio; CI, confidence interval.

Incidence of anaphylaxis if intake of beta-blocker
cross-sectional studies



case-control studies



all studies

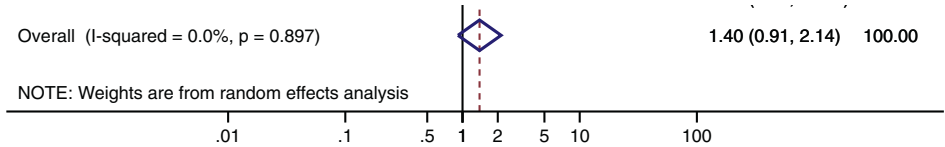


FIGURE 3. Meta-analysis of beta-blockers and presence of new episodes of anaphylaxis. *CI*, Confidence interval; *ES*, effect size.

Severity of anaphylaxis if intake of ACEI

all adjusted studies

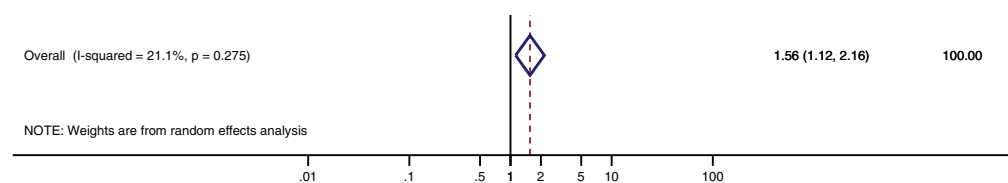
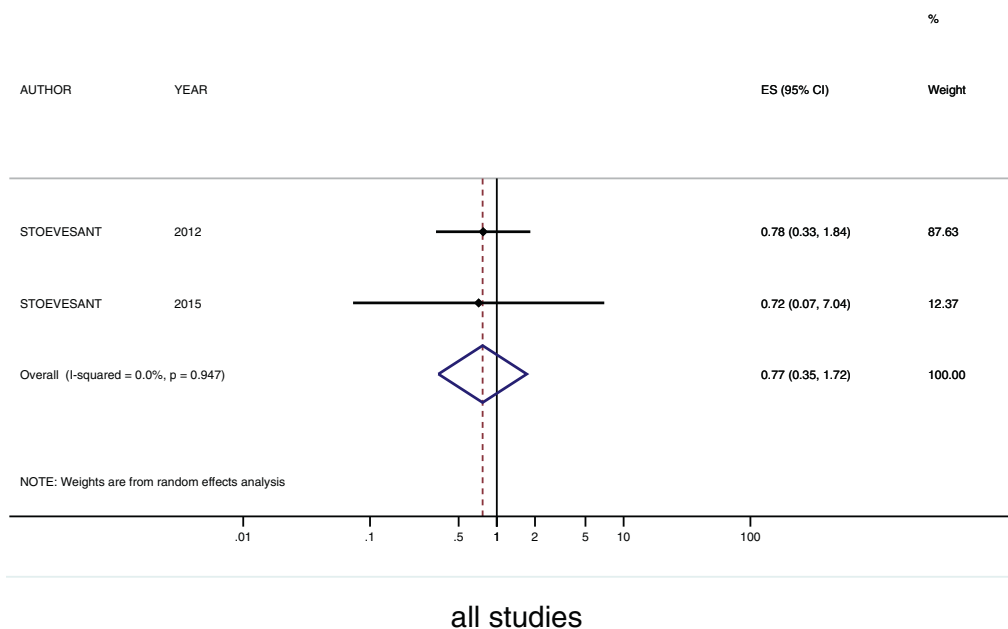
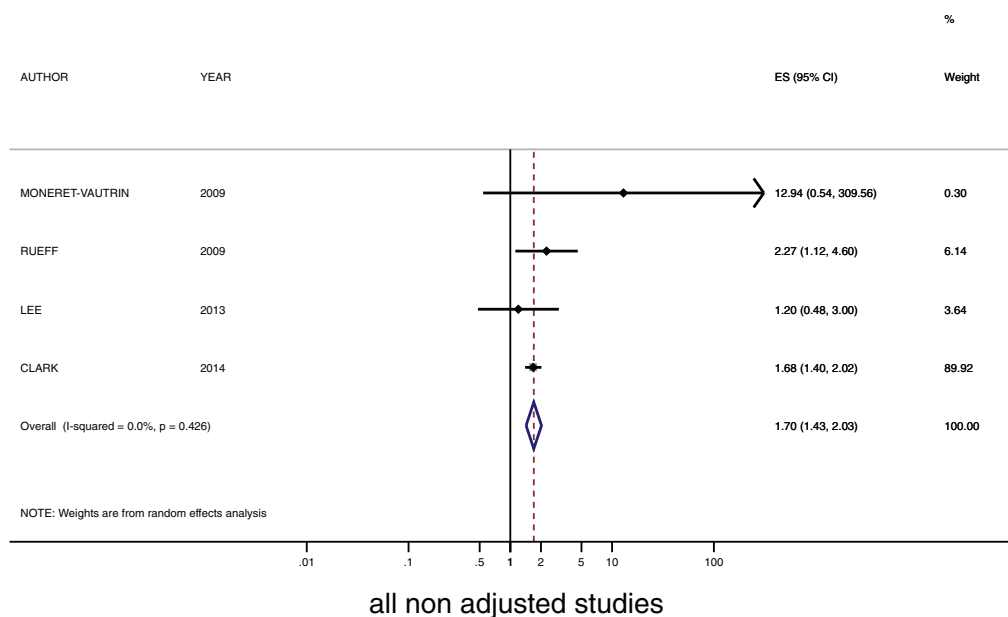


FIGURE 4. Meta-analysis of angiotensin-converting enzyme inhibitors (ACEIs) and the severity of anaphylaxis. *CI*, Confidence interval; *ES*, effect size.

TABLE IV. Analysis of the quality of evidence of the different meta-analyses using the GRADE guidelines

Antihypertensive medication compared with nonantihypertensive medication for severity of anaphylaxis											
Certainty assessment							Summary of findings				
No. of participants (studies), follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With nonantihypertensive medication	With antihypertensive medication		Risk with non-antihypertensive medication	Risk difference with antihypertensive medication
Severe anaphylaxis with BB, all studies (assessed with: adjusted OR meta-analysis)											
15,072 (14 observational studies)	Serious*	Serious†	Not serious	Not serious	Strong association, all plausible residual confounding would reduce the demonstrated effect	⊕⊕○○ Low	3,225/14,746 (21.9%)	99/326 (30.4%)	OR 2.19 (1.25-3.84)	219 per 1,000	161 more per 1,000 (41 more to 299 more)
New cases of anaphylaxis with BB, all studies (assessed with: adjusted OR meta-analysis)											
12,261 (10 observational studies)	Serious*	Serious†	Not serious	Serious‡	All plausible residual confounding would reduce the demonstrated effect	⊕○○○ Very low	510/11,705 (4.4%)	46/556 (8.3%)	OR 1.40 (0.91-2.14)	44 per 1,000	16 more per 1,000 (4 fewer to 45 more)
Severe anaphylaxis with ACEI, all studies (assessed with: adjusted OR meta-analysis)											
2457 (6 observational studies)	Serious*	Serious†	Not serious	Serious§	All plausible residual confounding would reduce the demonstrated effect	⊕○○○ Very low	475/2,273 (20.9%)	38/184 (20.7%)	OR 1.56 (1.12-2.16)	209 per 1,000	83 more per 1,000 (19 more to 154 more)
New cases of anaphylaxis with ACEI, all studies (assessed with: adjusted OR meta-analysis)											
2644 (5 observational studies)	Serious*	Serious†	Not serious	Serious‡,§	All plausible residual confounding would reduce the demonstrated effect	⊕○○○ Very low	209/2,484 (8.4%)	21/160 (13.1%)	OR 1.38 (0.39-4.86)	84 per 1,000	28 more per 1,000 (50 fewer to 225 more)
Severe anaphylaxis with BB, only adjusted studies (assessed with: adjusted OR meta-analysis)											
661 (6 observational studies)	Serious*	Not serious	Not serious	Serious§	Strong association, all plausible residual confounding would reduce the demonstrated effect†	⊕⊕○○ Low	122/577 (21.1%)	26/84 (31.0%)	OR 2.07 (1.14-3.75)	211 per 1,000	145 more per 1,000 (23 more to 290 more)

(continued)

TABLE IV. (Continued)

Antihypertensive medication compared with nonantihypertensive medication for severity of anaphylaxis											
Certainty assessment							Summary of findings				
No. of participants (studies), follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With nonantihypertensive medication	With antihypertensive medication		Risk with non-antihypertensive medication	Risk difference with antihypertensive medication
New cases of anaphylaxis with BB, only adjusted studies (assessed with: adjusted OR meta-analysis)											
10,774 (5 observational studies)	Serious*	Not serious	Not serious	Serious†	All plausible residual confounding would reduce the demonstrated effect	⊕○○○ Very low	134/5,625 (2.4%)	24/5,149 (0.5%)	OR 1.40 (0.68-2.88)	24 per 1,000	9 more per 1,000 (7 fewer to 42 more)
Severe anaphylaxis with ACEI, only adjusted studies (assessed with: Adjusted OR meta-analysis)											
1,575 (4 observational studies)	Serious*	Not serious	Not serious	Serious§	All plausible residual confounding would reduce the demonstrated effect¶	⊕○○○ Very low	307/1,494 (20.5%)	30/81 (37.0%)	OR 1.70 (1.43-2.03)	205 per 1,000	100 more per 1,000 (65 more to 139 more)
New cases of anaphylaxis with ACEI, only adjusted studies (assessed with: adjusted OR meta-analysis)											
1,671 (2 observational studies)	Serious*	Not serious	Not serious	Serious§	Very strong association, all plausible residual confounding would reduce the demonstrated effect#	⊕⊕⊕○ Moderate	113/1,628 (6.9%)	10/43 (23.3%)	OR 5.34 (2.37-12.00)	69 per 1,000	215 more per 1,000 (81 more to 403 more)

Bold indicates statistical significance of studies.

ACEI, Angiotensin-converting enzyme inhibitor; BB, beta-blocker; CI, confidence interval; OR, odds ratio.

*Not control of all confusion factors.

†Different results among studies.

‡Wide range between 95% CI.

§Size of sample low (under 4000) or number of events low.

¶Only 3 studies.

#Only 2 studies.

independent risk factor in only 1 of 3 outcomes of severity; in that of Aggarwal et al,¹⁸ BBs did not increase the severity of anaphylaxis, although severity was only adjusted for the single dose of BB before coronary computed tomography angiography and not for long-term use of the BB, which is more likely to be the case in patients undergoing this diagnostic technique.

An issue not resolved by our meta-analysis was that, although BBs and ACEIs can aggravate an anaphylaxis episode, the huge benefits of BBs in chronic heart failure or ischemic coronary heart disease may be more important than the risk of anaphylaxis. In a computerized sensitivity model, TenBrook et al⁵⁰ found that patients taking BBs for heart diseases and at risk of severe anaphylaxis benefit from BBs, because their average life expectancy increases from 9.4 to 17 months, with greater benefits for patients with chronic heart failure. Thus, the lack of positive effects of these drugs in patients with severe cardiovascular disease would strengthen the recommendation not to discontinue these drugs in patients at risk of recurrence of anaphylaxis.

Limitations of the study

We added 0.5 in the cells of tables with zero values in some cells. This practice is controversial and can induce bias.⁵¹ To assess the possible bias introduced, we removed studies with 0 in some cells from the meta-analysis. For all meta-analyses, the values of summary statistics (pooled ORs) and statistical significance remained similar when these studies were excluded (data not shown).

In studies assessing small study bias or publication bias, the Egger test did not reveal bias in many meta-analyses, although the result of the test was significant for the meta-analysis of new cases of anaphylaxis in patients taking BBs. The Egger test “is conservative and frequently suggests that caution is needed when interpreting the results of the meta-analysis.”⁴⁰ Using the qualitative funnel plot, most studies did not seem to show the absence of small studies with negative results (no association between BBs and ACEIs and severity of anaphylaxis).

Our findings were also limited by the heterogeneity of the studies. The populations were very varied: several studies were carried out in different clinical settings, anaphylaxis occurred during different diagnostic or therapeutic protocols, the agents used may have had a greater or lesser capacity to induce more anaphylaxis episodes or higher severity (old high⁶ or modern low osmolar¹⁸ iodinated radiocontrast media), the types of anaphylaxis were different, or the use of BBs could be different (single dose vs long-term therapy in some groups of patients^{6,18}) (Table I). These findings could explain the heterogeneity of some meta-analyses.

Nevertheless, as up to 13 different outcomes were used as proxies for the severity of anaphylaxis, it seems that the heterogeneity of the meta-analyses cannot be explained by the heterogeneity of the outcomes. Authors use the highest grade(s) of severity, which are similar in each organ or system evaluated. Therefore, there may be a high degree of correlation between the different scores for severity of anaphylaxis, although, to our knowledge, this possibility has not been investigated. On the other hand, when authors do not use these scores, individual proxies of severity belong to the last or 2 highest grades of severity.

Since completing our review, applying the algorithm used in our meta-analysis to find articles, we found 3 additional articles

that met the inclusion criteria of our review. These 3 new articles are subject to the same problems commented on in the present article: differences in the control of or lack of control of confusion between BBs and ACEIs and cardiovascular diseases. Harper et al⁵² reported the effects of BBs and ACEIs on the severity of anaphylaxis during anesthesia, although these effects were not adjusted for cardiovascular diseases. Worm et al⁵³ reported data from a logistic regression model where BBs and ACEIs were risk factors for increasing the severity of anaphylaxis. Once again, these factors were not adjusted for cardiovascular diseases due to the correlations present between BB and ACEI, thus precluding the incorporation of these drugs and cardiovascular disease in the same logistic regression model. The authors did not explain why they chose these drugs instead of cardiovascular diseases as covariables. In the study of White et al,⁵⁴ the effect of BBs was adjusted for cardiovascular diseases and chronic obstructive pulmonary disease. The use of BBs did not increase the use of 2 or more doses of epinephrine.

Summary

The authors of the GRADE guidelines recommend not rating up for a large effect size if there are major concerns about the risk of bias (a confounding factor for cardiovascular disease and use of BBs in the present review), accuracy, and publication bias.³⁹ Therefore, in a conservative assessment, evidence obtained according to the GRADE guidelines will generally be low for the influence of BBs and ACEIs on anaphylaxis, without decreasing the GRADE score. However, if we used the 4 grades for quality of evidence according to the GRADE score as a continuous scale, then the quality of evidence would generally be low to moderate.

Furthermore, the authors of the guidelines emphasize the transparency of the process and the ways in which decisions are made.⁵⁵ Therefore, a different assessment of an item used in this methodology could increase the quality of evidence by 1 grade in our study (for instance, from low to moderate). However, performing a different assessment does not alleviate concern with respect to the unresolved confusion between ACEIs or BBs and cardiovascular diseases.

A series of studies should be carried out to determine whether BBs or ACEIs act as confounders for cardiovascular disease or whether they truly increase the severity of anaphylaxis. These should include all main cofounders reported in the literature (age, ACEIs, BBs, heart and lung diseases, comorbidity score, type of anaphylaxis, and basal serum tryptase), a validated severity outcome (as based on validated grades such as Brown's score), confounding variables with uniform grades of severity (eg, same grade of severity for heart disease and lung disease), and use of age or tryptase as continuous variables. Another possible strategy could be to use patients who take BBs for reasons other than cardiovascular diseases (eg, migraine, tremor). However, to our knowledge, studies of this type have not been published, because, in our opinion, it is difficult to find such patients. Lang et al^{5,6} identify these patients in 2 case-control studies: in the more recent of the two,⁶ only 1 case (1.8% of patients with severe anaphylaxis) and 2 controls (1.3%) who took BBs without cardiovascular disease were collected. Neither of the 2 studies made a separate analysis of these patients, although the small sample may have prevented such an analysis.

In summary, evidence that the use of antihypertensive medication increases the severity of anaphylaxis and the presence of new cases of anaphylaxis is low to moderate owing to the

different ways of controlling for confounders in the different studies. However, these studies yield a profile of patients at high risk of experiencing severe anaphylaxis. Such a patient would be older, with cardiovascular disease, for which he or she takes BBs or ACEIs, irrespective of whether these drugs independently increase the severity of anaphylaxis.

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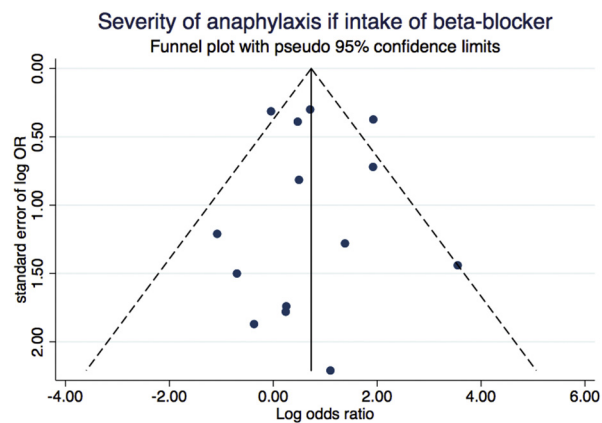


FIGURE E1. Funnel plot of studies with beta-blockers showing the lack of marked facilitating effects of small studies. *OR*, Odds ratio.

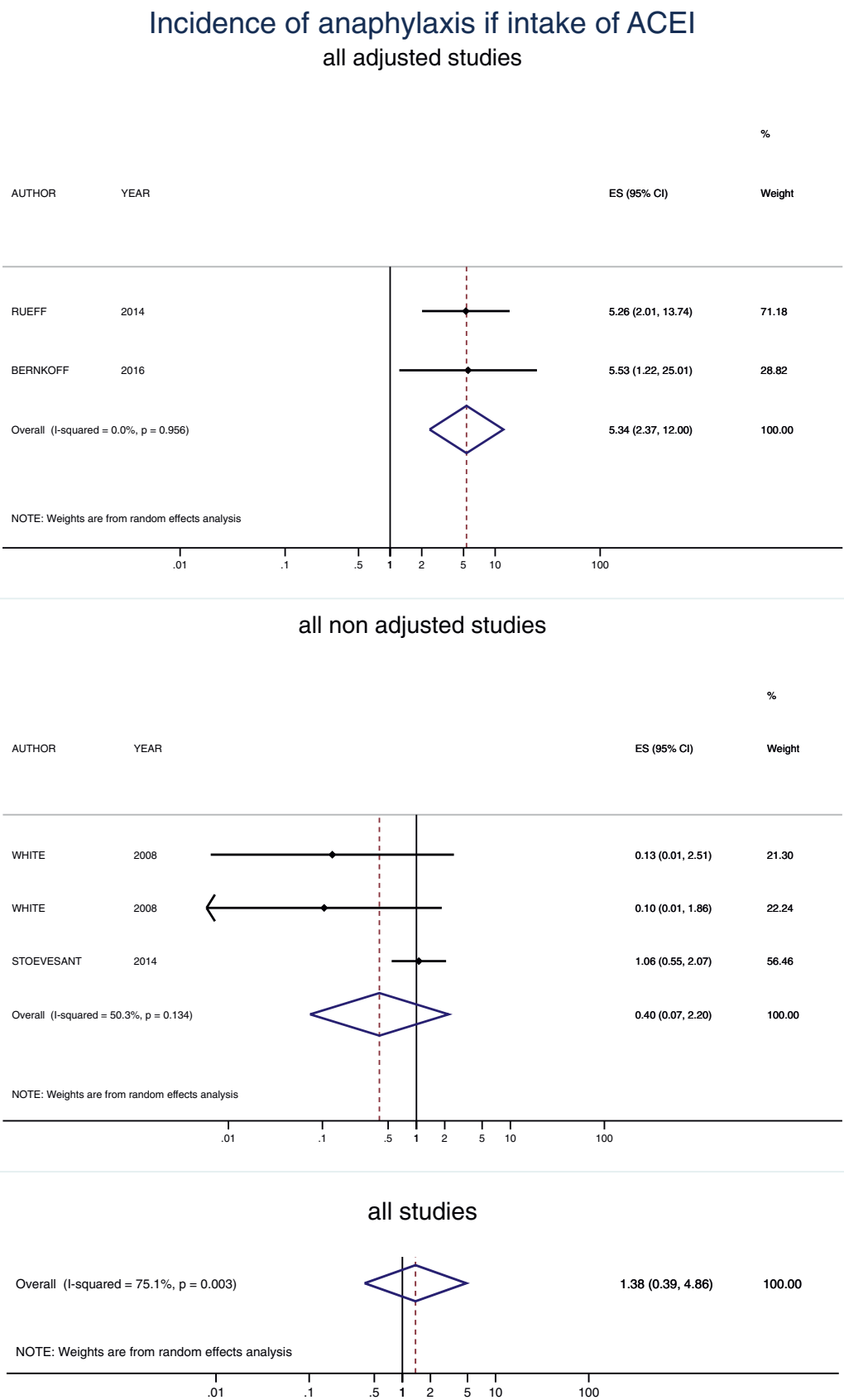


FIGURE E2. Meta-analysis of angiotensin-converting enzyme inhibitors (ACEIs) and the presence of new episodes of anaphylaxis. *CI*, Confidence interval; *ES*, effect size.

TABLE E1. Adjustment of variables in the studies included in the meta-analysis of severity and incidence of anaphylaxis and use of beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs)

Author, year	Outcome	Age	Sex	Ethnicity	ACEI	BB	Heart diseases	Lung Diseases	Visit to health care centers	Other comorbidities	Type of anaphylaxis	Basal tryptase
Aggarwal, 2015 ^{E1}	Severity and incidence	Yes	Yes			Yes					Previous reaction to RCM	
Alam, 2005 ^{E2}	Severity											
Benitah, 1986 ^{E3}	Severity											
Brown, 2013 ^{E4}	Severity	Yes	Yes		Yes	Yes		Yes			Yes	
Clark, 2014 ^{E5}	Severity	Yes	Yes		Yes	Yes	Yes		Allergist, any health care resource	Charlson-Deyo score		
Lang, 1993 ^{E6}	Severity and incidence	Yes				Yes	Yes	Asthma			The same iodinated radiologic contrast medium	
Lantner, 1989 ^{E7}	Severity											
Lee, 2013 ^{E8}	Severity	Yes	Yes		Yes	Yes		Yes			Yes	
Moneret-Vautrin, 2009 ^{E9}	Severity	Yes	Yes		Yes	Yes				Other drugs, including NSAIDs Cofactors: alcohol, exercise		
Muller, 2005 ^{E10}	Severity and incidence					Yes	Yes					
Nassiri, 2015 ^{E11}	Severity	Yes	Yes		Yes	Yes						
Rueff, 2009 ^{E12}	Severity				Yes	Yes					Yes	Yes
Stoevesandt, 2012 ^{E13}	Severity											
Stoevesandt, 2015 ^{E14}	Severity											
Summers, 2008 ^{E15}	Severity	Yes						Lower and upper airways diseases		Eczema		
Total severity		8/15	6/15	0/15	6/15	9/15	3/15	4/15	1/15	3/15	5/15	1/15
Bernkopf, 2016 ^{E16}	Incidence	Yes	Yes		Yes						Yes	Tryptase >11.2
Greenberger, 1987 ^{E17}	Incidence											
Hepner, 1990 ^{E18}	Incidence				Yes					Honey bee venom, time build-up, and challenge, double VIT, >200 µg VIT		

Rueff, 2014 ^{E19}	Incidence												
Stoevesandt, 2014 ^{E20}	Incidence	Yes	Yes		Yes	Yes					Venom IgE, intradermal test, anaphylaxis in the field, latency time, treatment protocol		Tryptase >20
White, 2008 ^{E21}	Incidence												
Total incidence		4/9	2/9	0/9	3/9	4/9	2/9	1/9		0/9	2/9	3/9	2/9

NSAID, Nonsteroidal anti-inflammatory drug; *RCM*, radiographic contrast media; *VIT*, venom immunotherapy.

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