β-blockers and ACE inhibitors are not a risk factor for severe systemic sting reactions and adverse events during venom immunotherapy

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Abstract

Background: There is controversy whether taking β-blockers or ACE inhibitors (ACEI) is a risk factor for more severe systemic insect sting reactions (SSR) and whether it increases the number or severity of adverse events (AE) during venom immunotherapy (VIT). Methods: In this open, prospective, observational, multicenter trial, we recruited patients with a history of a SSR and indication for VIT. The primary objective of this study was to evaluate whether patients taking β-blockers or ACEI show more systemic AE during VIT compared to patients without such treatment. Results: In total, 1,425 patients were enrolled and VIT was performed in 1,342 patients. Of all patients included, 388 (27.2%) took antihypertensive (AHT) drugs (10.4% took β-blockers, 11.9% ACEI, 5.0% β-blockers and ACEI). Only 5.6% of patients under AHT treatment experienced systemic AE during VIT as compared with 7.4% of patients without these drugs (OR: 0.74, 95% CI: 0.43–1.22, p=0.25). The severity of the initial sting reaction was not affected by the intake of β-blockers or ACEI (OR: 1.14, 95% CI: 0.89–1.46, p=0.29). In total, 210 (17.7%) patients were re-stung during VIT and 191 (91.0%) tolerated the sting without systemic symptoms. Of the 19 patients with VIT treatment failure, 4 took β-blockers, none an ACEI. Conclusions: This trial provides robust evidence that taking β-blockers or ACEI does neither increase the frequency of systemic AE during VIT nor aggravate SSR. Moreover, results suggest that these drugs do not impair effectiveness of VIT. (Funded by Medical University of Graz, Austria; Clinicaltrials.gov number, NCT04269629)

Introduction

Insect stings by Hymenoptera species are very common with data indicating that 56.6–94.5% of the general population has been stung at least once in their lifetime.[1] Systemic sting reactions (SSR) have been reported in 2.3–5.4% of adults in European and US epidemiological studies.[2-4] Hymenoptera venom allergy is a potentially life-threatening disease, and venom immunotherapy (VIT) is the only treatment that can potentially prevent further SSR.[5] It is effective in 77–84% of patients treated with honeybee venom[6,7], and in 91–96% of patients receiving vespid venom.[6,7] There are two well-established risk factors for severe SSR: higher age[8-10] and elevated tryptase levels >11.4 mg/L indicating clonal mast cell disorders.[8,9,11] The major risk factor for systemic adverse events (AE) during VIT is treatment with bee venom.[12,13] There has been an ongoing debate over decades whether antihypertensive (AHT) treatment with β-blockers and/or ACE-inhibitors (ACEI) is a risk factor for the development of more severe SSR and whether it increases the number of (more severe) AE during VIT. The global prevalence of arterial hypertension in the adult population ranges from 26.4–27.7%, and 40.7% of patients older than 35 years suffer from hypertension.[14,15] Overall, ACEI or angiotensin receptor blockers are the most commonly used blood pressure-lowering agents followed by diuretics and β-blockers in high-income countries.[14] Given that higher age is a major risk factor for severe SSR, it is very likely that these patients also take antihypertensive medication. Replacing or discontinuing antihypertensive medication is cumbersome, time-consuming, and may even be harmful. This could prevent patients from receiving potentially life-saving VIT. Available data are controversial and invariably originate from case reports or studies with underpowered designs to evaluate the effect of antihypertensive drugs.[8,16,17] We hypothesized that the risk of β-blockers and/or ACEI for AE during VIT could have been overestimated, and the alleged higher risk for more severe sting reactions could have been biased by patients' age. We therefore initiated an open, prospective, observational, multicenter study, recruiting 1,425 patients in 26 centers from eight European countries.

Methods

Study design and oversight

The study was conducted as an open, prospective, observational, multicenter study (Clinicaltrials.gov number

NCT04269629). Patients were recruited in 26 centers in eight European countries. The study was approved by the ethics committee of the sponsor of the study (Medical University of Graz; approval no. 26-442 ex 13/14) as well as local ethics committees in each country, and patients gave their written, informed consent.

Legally competent male and female patients aged 35 to 85 years with a history of an SSR ([?] grade I according to the classification by Ring and Messmer[18]) were eligible for the study. Absolute contraindications to VIT and pretreatment with Omalizumab were exclusion criteria.

After giving their written informed consent, patients were included after carefully reviewing all inclusion and exclusion criteria at Visit 1. All data concerning the index sting reaction, laboratory parameters like specific immunoglobulin E (sIgE) and tryptase levels and skin test results were recorded as well as concomitant diseases and medication. If patients agreed to receive VIT, data concerning the up-dosing phase (premedication, venom preparation, up-dosing protocol, systemic AE (classification by Ring and Messmer[18]), changes in concomitant diseases, and medication) were recorded at Visit 2. There was no standard up-dosing protocol used for VIT. All centers used their own in-house protocols including conventional, cluster, ultrarush- and rush-protocols.[5] One year after reaching the maintenance dose, Visit 3 was performed. At this visit, changes in premedication, venom preparation, concomitant diseases and medication were recorded as well as systemic AE during the maintenance phase and, if applicable, the outcome of field stings and/or sting challenges. No additional study-related visits were required. All procedures (diagnosis and treatment of Hymenoptera venom allergy) had to be in concordance with current EAACI guidelines[5,19,20] and were conducted individually by each study center.

Objectives

The primary objective of this study was to evaluate whether patients under antihypertensive treatment with β-blockers or ACEI show more systemic AE during VIT compared with patients without antihypertensive therapy.

Secondary objectives included the evaluation of whether patients under antihypertensive treatment (β-blockers or ACEI) have more severe SSR and whether prevalence of cardiovascular diseases or hypertension is associated with the risk of more severe SSR and more frequent systemic AE during VIT. Furthermore, we evaluated whether bee venom, high sIgE levels, high tryptase levels, or quicker up-dosing protocols are correlated with a higher frequency of systemic AE. In addition, the effectiveness of VIT was monitored by the outcome of sting challenges or field stings, and these results were compared between patients with and without antihypertensive treatment.

Statistics

Sample size calculation

It was assumed that 24% of the patients would be on β-blockers and/or ACEI. A $\chi 2$ test with a two-sided 5% significance level has an 80% power to detect the difference between the group without antihypertensive medication with 6% systemic AE during VIT and the group on β-blockers and/or ACEI with 12.3% systemic AE during VIT (OR = 2.2) when the sample sizes are 631 and 200 (a total sample size of 831), respectively. The drop-out rate included study drop-outs (30%) who did not start VIT and study drop-outs (10%) who did not finish VIT. This resulted in a drop-out rate of 37% and a required number of 1,319 patients.

Statistical analysis

All patients participating in this study belong to one of the following two groups for analysis: the group with antihypertensive treatment (β-blockers or ACEI) and the group without such treatment. The analyses concerning the outcome "systemic adverse event" are based on the patients who completed the up-dosing phase of immunotherapy, while analyses concerning the outcome "systemic sting reaction" are based on all patients included in the study.

The primary outcome and secondary outcomes were analyzed using logistic linear mixed models with a random intercept. This model type takes into account the clustered structure of the data, i.e., observations

clustered in the different participating centers. Parameters, having a p-value <0.15 in the univariable model analysis were kept for further analysis with multivariable models. For further parameter reduction, the Bayesian information criterion (BIC) was calculated as a measure of the relative quality of the models. However, age and taking antihypertensive treatment were always kept in the multivariable models for the outcome "systemic adverse event" as well as for the outcome "systemic sting reaction." For these outcomes, complete case model analyses were performed, if missing data in parameters of interest were rare (<1%). Otherwise, missing at random was assumed, and multiple imputations were conducted with 50 imputations taking into account the cluster design. The level of significance was set at 0.05.

All analyses were performed using the statistical software R (version 3.6.3) with the lme4 package (version 1.1-23) to carry out multilevel modeling and the MICE package for the multiple imputation analysis (version 3.8.0).[21,22]

Results

Patients

From August 2014 until January 2018, a total of 1,425 patients were included in the study. The demographic data of the patients are shown in Table 1. Seventy-five patients refused VIT, eight patients were lost to follow-up, and therefore Visit 2 was performed with 1,342 patients. The majority of patients returned to the clinics for the first annual check-up; Visit 3 was performed with 1,186 patients.

Of all patients included, 388 (27.2%) took antihypertensive drugs: 10.4% took β-blockers, 11.9% ACEI, and 5.0% β-blockers and ACEI, respectively. Ninety-three (7.0%) patients who underwent VIT had a systemic adverse event, and these reactions were predominantly mild (Table 2). Only one patient suffered from a Grade III reaction with flush and bronchospasm. Large local reactions (LLR) were observed in 348 (26.3%) patients undergoing VIT.

Primary Outcome

Of all patients who underwent VIT, 338 (25.2%) took β-blockers and/or ACEI. Only 19 (5.6%) of patients, who were taking β-blockers or ACEI, experienced a systemic AE compared to 74 (7.4%) of patients not taking such drugs resulting in an odds ratio (OR) of 0.74 (95% confidence interval (CI): 0.43–1.22, p=0.25; Table 3). In detail, 4 of 123 (3.3%) had systemic AE taking β-blockers, 13 of 157 (8.3%) experienced systemic AE under ACEI treatment, and 2 of 58 (3.5%) had systemic AE taking β-blockers and ACEI (p=0.15). All systemic AE in patients with antihypertensive treatment were mild to moderate reactions. The most severe reaction occurred in a patient not taking AHT drugs (Table 2).

Secondary outcomes

Adverse events (Table 3)

The prevalence of cardiovascular diseases or hypertension was no risk factor for systemic AE during VIT (p=0.11). Bee venom caused more systemic AE during VIT: 13.0% of patients treated with bee venom had systemic reactions, but only 4.3% of patients treated with vespid venom (p<0.001). We did not detect a statistically significant effect of elevated basal tryptase levels on the frequency of systemic AE during VIT: 6.8% of patients with normal tryptase levels compared with 10.8% of patients with elevated tryptase levels had systemic AE (p=0.16). Verified mastocytosis was also not a risk factor: Only 12.1% of patients with verified mastocytosis had a systemic reaction compared with 6.9% without mastocytosis (p=0.41). Neither high sIgE levels to bee venom nor high sIgE levels to vespid venom correlated with a higher frequency of systemic AE during VIT (p=0.99 and p=0.15, respectively).

The severity of the initial sting reaction had no influence on the frequency of systemic AE during VIT: systemic AE occurred in 51 (6.7%) patients with a previous Grade I or II reaction and in 42 (7.4%) patients with a severe (Grade III or IV) initial sting reaction (p=0.66). Premedication with oral non-sedative antihistamines was taken by half of the patients during the up-dosing phase, but this had no effect on the frequency

of systemic AE (p=0.07); however, the frequency of LLR was lower in patients taking premedication as compared with those not taking antihistamines (23.5% vs. 29.3%; p<0.001).

Quicker up-dosing protocols (conventional vs. rush, cluster, and ultrarush) did not cause more frequent systemic AE during VIT (p=0.50). Nevertheless, large local reactions were seen more frequently when quicker up-dosing protocols were used (OR: 8.72; 95% CI: 3.59–24.37; p<0.001).

The parameters age, antihypertensive treatment, and bee venom were kept for further analysis in a multivariable model: The risk of a systemic adverse event during VIT was still 3.4 times (OR 3.35; 95% CI: 2.17–5.16) higher for patients treated with bee venom, compared with patients treated with vespid venom (p<0.001).

During the first year of the maintenance phase, systemic AE occurred in only 20 (1.7%) patients. Systemic adverse reactions were mild or moderate in 17 patients; three bee-venom-allergic patients had a Grade III reaction with loss of consciousness or bronchospasm. None of them took β-blockers or ACEI, but one patient with loss of consciousness suffered from systemic mastocytosis. Taking AHT drugs did not increase the frequency of systemic AE (p=0.99). The intake of antihistamine premedication decreased from about 50.0% during the up-dosing phase to about 20.0% during the maintenance phase.

Systemic sting reactions (Table 4)

Taking β-blockers or ACEI had no influence on the severity of the initial sting reaction: 41.7% of patients not taking AHT drugs and 44.1% of patients under antihypertensive treatment had a severe SSR (Grade III or IV; p=0.29). The proportions of severe SSR did not differ significantly between patients taking β-blockers, ACEI, and β-blockers and ACEI with 43.9, 47.9, and 35.2% respectively (p=0.14). The prevalence of cardiovascular diseases or hypertension appeared to be a risk factor (p=0.04). However, this result was biased by patients' age; when patients' age was taken into consideration, the effect of cardiovascular disease on the severity of SSR vanished (p=0.91).

We additionally investigated whether bee venom or elevated basal tryptase levels or verified mastocytosis are associated with more severe SSR. Severe sting reactions occurred in 43.4% of patients stung by bees and 41.8% of patients reacting to vespid stings (p=0.50). Elevated basal tryptase levels were associated with more severe sting reactions: 42.0% of patients with normal tryptase levels but 63.8% with elevated tryptase levels had a systemic reaction Grade III or IV (OR: 2.37; 95% CI: 1.61–3.50; p<0.001). The risk for a severe reaction was even 3.7-fold higher for patients with verified mastocytosis compared to patients without mastocytosis (p<0.001).

The parameters age, treatment with β-blockers or ACEI, and tryptase levels were further analyzed in a multivariable model: Antihypertensive treatment still had no influence on the severity of the initial sting reaction (OR: 0.95; 95% CI: 0.72–1.24; p=0.70), and patients with elevated basal tryptase levels still had a 2.4-times higher risk of developing a severe SSR compared with patients with normal tryptase levels (p<0.001).

Effectiveness of VIT

The effectiveness of VIT can solely be monitored by the outcome of sting challenges or field stings. Sting challenges were performed in 18 patients; 192 patients experienced field stings within the first year of the maintenance phase. In total, 210 (17.7%) patients were stung, and 91.0% of patients tolerated the sting without systemic symptoms. Thirty-four (16.2%) patients suffered from a LLR. Of the patients with SSR, 12 experienced a grade I reaction, and among these, two took β-blockers. Five patients had a grade II reaction, and one of them took a β-blocker, while two had a Grade III reaction, and one patient took a β-blocker. None of the patients with therapy failure took an ACEI. 191 patients tolerated the sting; among these, 20 (10.5%) took a β-blocker, 23 (12.0%) an ACEI, and 10 (5.2%) both drugs. Taking antihypertensive drugs did not increase the risk for therapy failure (p=0.72).

Discussion

This open, prospective, observational, multicenter study is the first multicenter study primarily focusing on the potential effect of β-blockers and ACEI on systemic AE during VIT and the severity of SSR. It is by far the largest study, with 388 insect-venom-allergic patients under antihypertensive drugs, and the first study with appropriate sample size estimation to calculate the patients' risk. It therefore provides robust evidence that taking β-blockers or ACEI does not increase the risk of systemic AE or aggravate sting reactions in patients with insect venom allergy. Previously published reports evaluating the influence of β-blockers on AE have already shown that β-blocker medication was not associated with a higher prevalence of (more severe) systemic AE;[12,23-25] however, although usually hundreds of patients were included, the low number of patients under β-blocker therapy provided only statistically fragile evidence. We could now show that in 181 patients, taking β-blockers did not increase the risk for systemic AE, and if AE occurred, they were not more severe.

ACEI also appeared to be safe with VIT[25], and although one small study reported more severe AE in patients taking ACEI, no significant difference in the number of treatment doses of epinephrine was observed.[26]

Another study reported an even lower frequency of AE in patients taking antihypertensive treatment, although not statistically significant.[27] This is in agreement with our results; VIT was safe in patients taking ACEI.

Whether β-blockers and ACEI are able to aggravate anaphylaxis is still a controversial issue. A systematic review and meta-analysis revealed that evidence of an increased risk of more severe anaphylaxis in patients who take β-blockers and ACEI was tenuous owing to the heterogeneous control of confounding variables.[28] Importantly, higher age is an established risk factor for more severe sting reactions.[8-10] Previous data had already suggested that older patients are more likely to take β-blockers and ACEI and that older age was the relevant predictor for severe anaphylaxis[16,17] or SSR.[9] We were able to demonstrate in 219 patients taking β-blockers and in 240 patients taking ACEI that higher age, but not taking antihypertensive drugs, was a major risk factor for severe anaphylaxis.

It was also hypothesized that AE could be refractory to emergency treatment and that epinephrine may cause paradoxical treatment effects due to concomitant β-blocker therapy.[29] Recent data suggest that patients with β-blockers do not require increased doses of epinephrine.[30] In our study, epinephrine was rarely used to treat AE, indicating that VIT was very safe. In detail, in 19 patients, epinephrine was administered to treat low to moderate adverse reactions. It is, however, important to note that only two patients taking β-blockers required epinephrine: One had a Grade I reaction and was taking β-blockers and ACEI, the other had a Grade II reaction and was only taking a β-blocker. Importantly, these patients tolerated emergency treatment well and responded quickly. Therefore, the beneficial effects of β-blockers by far outweigh the hypothetical negative effects.

Treatment with ACE-inhibitors or β-blockers during VIT was considered as contraindicated for years; therefore, ACEI and β-blocker therapy was usually stopped and only maintained in patients with severe cardiovascular diseases. These highly selective samples of patients may have biased previous study results. Over recent years, guidelines have become less restrictive, resulting in more patients taking antihypertensive drugs with VIT. This may explain why older studies sometimes reported a higher risk for AE[12], while more recent data suggested that taking ACEI and β-blockers is safe.[25] The situation is similar in terms of the effectiveness of VIT: While one study reported a higher risk of VIT failure in a small number of highly selected patients[7], others did not detect such a risk.[27,31] In our study, the effectiveness of VIT was comparable in patients with or without antihypertensive drugs. Interestingly, none of the patients who relapsed took ACEI.

Limitations of the study: The number of patients who experienced more severe AE during VIT requiring epinephrine treatment was very low. Only two patients taking β-blockers received epinephrine and no conclusion can be drawn as to whether epinephrine was less effective or caused paradoxical effects in patients taking β-blockers.

The effect of age on the severity of SSR may have been underestimated in our study. Only patients aged 35 to 85 years were included because it was assumed that 24% of this age group would take β-blockers or

ACEI. We still observed an age effect. However, we could not compare severity of SSR between our age group and younger patients. Monitoring VIT effectiveness by sting challenge was optional for study centers and the evaluation was primarily based on the reported outcome of field stings. Therefore, results should be interpreted with caution, as patients may not have correctly identified the stinging insect.

This study provides robust evidence that β-blockers and ACEI do not increase the frequency of systemic AE during VIT. The number of AE was even lower compared with patients not taking antihypertensive treatment (5.6% and 7.4%, respectively; OR: 0.74; CI: 0.43–1.22); moreover, β-blockers and ACEI did not aggravate the severity of insect sting reactions.

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Statement of contribution

Conceptualization: GJS and CS; Supervision: GJS; Project administration: LAG; Investigation: GJS, TAA, DAA, PB, EB, AB, MC, BE, NF, RG, AG, TH, WH, AJB, KK, RK, MK, KL, RL, FM, MM, MNM, IPG, VP, DP, OQ, NR, MRB, BRL, CS, PS, AS, BAS, JS, AT, MV, LAG; Formal analysis: SAH; Methodology: SAH, KL; Writing-original draft: GJS, SAH and LAG; Writing-review & editing: WA, TAA, DAA, PB, EB, AB, MC, BE, NF, RG, AG, TH, WH, AJB, KK, RK, MK, RL, FM, MM, MNM, IPG, VP, DP, OQ, NR, MRB, BRL, CS, PS, AS, BAS, JS, AT, MV; Funding acquisition: GJS. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Tables

Table 1: Demographic data. The percentages refer to the total number of observations. Missing data are not explicitly stated in the table. Age at Visit 1 was the age at index sting, age at Visit 2 was the age when venom immunotherapy was started.

	Visit 1 (n=1,425) pre-treatment	Visit 2 (n=1,342) up-dosing phase	Visit 3 (n=
Age range (mean age) [years]	35–80 (52)	35–84 (54)	36–85 (55)
Sex, n (%)			
male	810 (56.8)	774 (57.7)	679 (57.3)
female	615 (43.2)	568 (42.3)	507 (42.7)
Grade of SSR (index sting), n (%)			
Grade I	122 (8.6)	..	..
Grade II	700 (49.1)	..	..
Grade III	589 (41.3)	..	..
Grade IV	14 (1.0)	..	..
Antihypertensive treatment, n (%)			
no medication	1,035 (72.6)	1,001 (74.6)	886 (74.7)
β-blockers	148 (10.4)	123 (9.2)	105 (8.9)
ACEI	169 (11.9)	159 (11.9)	136 (11.5)
β-blockers and ACEI	71 (5.0)	58 (4.3)	55 (4.6)
Cardiovascular disease, n (%)			
no disease	845 (59.3)	801 (59.7)	715 (60.3)
coronary heart disease or hypertension	571 (40.1)	533 (39.7)	463 (39.0)
Causal venom, n (%)			
Bee	320 (22.5)	351 (26.2)	297 (25.0)
Vespid	838 (58.8)	923 (68.8)	829 (69.9)
Bee & vespid	206 (14.5)	67 (5.0)	57 (4.8)
Basal tryptase level, n (%)			?¿?

	Visit 1 (n=1,425) pre-treatment	Visit 2 (n=1,342) up-dosing phase	Visit 3 (n=
11.4µg/L	1,159 (81.3)	1,092 (81.4)	972 (82.0)
> 11.4µg/L	127 (8.9)	121 (9.0)	108 (9.1)

Table 2: Details of adverse events during VIT. The percentages refer to the total number of adverse events (n=93). Classification according to Ring and Messmer.[18]

	Grade I	Grade II	Grade III	total
Adverse events, n (%)	54 (58.1)	38 (40.9)	1 (1.1)	93 (100.0)
Up-dosing protocol, n (%)				
Conventional	2 (2.2)	3 (3.2)	0 (0.0)	5 (5.4)
cluster, ultrarush	27 (29.0)	17 (18.3)	1 (1.1)	45 (48.4)
rush	23 (24.7)	16 (17.2)	0 (0.0)	39 (41.9)
Premedication, n (%)				
no	21 (22.6)	15 (16.1)	0 (0.0)	36 (38.7)
yes	33 (35.5)	23 (24.7)	1 (1.1)	57 (61.3)
Tryptase level, n (%)				
>11.4 µg/l	7 (7.5)	5 (5.4)	1 (1.1)	13 (14.0)
Τρєατμєντ ωιτη β-βλοςκєρς ανδ/ορ ACEI, ν (%)				
no	43 (46.2)	30 (32.3)	1 (1.1)	74 (79.6)
β-blockers	1 (1.1)	3 (3.2)	0 (0.0)	4 (4.3)
ACEI	8 (8.6)	5 (5.4)	0 (0.0)	13 (14.0)
β-blockers and ACEI	2 (2.2)	0 (0.0)	0 (0.0)	2 (2.2)

Table 3: Impact of decisive parameters on the frequency of systemic adverse events during VIT.

parameter	**categories**	**no systemic reaction**	**systemic reacti**
age		1240 (93.0)	93 (7.0)
antihypertensive treatment with β-blockers or ACEI	no	920 (92.6)	74 (7.4)
	yes	319 (94.4)	19 (5.6)
cardiovascular disease	no	734 (92.1)	63 (7.9)
	yes	498 (94.3)	30 (5.7)
bee venom	no	879 (95.8)	39 (4.3)
	yes	360 (87.0)	54 (13.0)
tryptase*	[?] 11.4µg/L	1010 (93.2)	74 (6.8)
	> 11.4µg/L	107 (89.2)	13 (10.8)
verified mastocytosis*	no	1,144 (93.1)	85 (6.9)
	yes	29 (87.9)	4 (12.1)
sIgE levels (bee venom)	>0.35–3.5 kU/l	96 (85.0)	17 (15.0)
	>3.5–17.5 kU/l	97 (85.1)	17 (14.9)
	>17.5 kU/l	45 (84.9)	8 (15.1)
sIgE levels (vespid venom)	>0.35–3.5 kU/l	270 (94.1)	17 (5.9)
	>3.5–17.5 kU/l	281 (96.9)	9 (3.1)
	>17.5 kU/l	148 (97.4)	4 (2.6)
Grading Ring-Messmer (initial sting reaction)	1&2	714 (93.3)	51 (6.7)
	3&4	526 (92.6)	42 (7.4)
Premedication with H_1-antihistamine	no	606 (94.3)	37 (5.8)
	yes	634 (91.9)	56 (8.1)

parameter	categories	no systemic reaction	systemic reacti
up-dosing protocol	conventional	104 (95.4)	5 (4.6)
	rush, cluster, ultrarush	1128 (93.1)	84 (6.9)

[a]no adjustments

[b]multivariable model

*data imputation for univariable model

Table 4: Impact of decisive parameters on the severity of the systemic (index) sting reactions.

parameter	categories	Grade 1&2	Grade 3&4	OR (95% CI)[a]
age		822 (57.7)	603 (44.3)	1.02 (1.01–1.04)
antihypertensive treatment with β-blockers and/or ACEI	no	603 (58.3)	432 (41.7)	1.00
	yes	217 (55.9)	171 (44.1)	1.14 (0.89–1.46)
cardiovascular disease	no	502 (59.4)	343 (40.6)	1.00
	yes	313 (54.8)	258 (45.2)	1.27 (1.01–1.60)
bee venom*	no	488 (58.2)	350 (41.8)	1.00
	yes	298 (56.7)	228 (43.4)	0.92 (0.72–1.17)
tryptase*+	[?] 11.4µg/L	672 (58.0)	487 (42.0)	1.00
	> 11.4µg/L	46 (36.2)	81 (63.8)	2.37 (1.61–3.50)
verified mastocytosis*	no	765 (58.3)	548 (41.7)	1.99
	yes	11 (29.7)	26 (70.3)	3.73 (1.74–7.98)

[a]no adjustments

[b]multivariable model

*data imputation for univariable model

[+]data imputation for multivariable model