

Angiotensin-converting enzyme inhibitors do not impair the safety of Hymenoptera venom immunotherapy build-up phase

J. Stoevesandt¹, J. Hain², I. Stolze¹, A. Kerstan¹ and A. Trautmann¹

¹Department of Dermatology and Allergy, University Hospital Würzburg, Würzburg, Germany and ²Institute of Mathematics, Department of Statistics, University of Würzburg, Würzburg, Germany

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Summary

Background There is an ongoing debate on whether angiotensin-converting enzyme inhibitors (ACEI) should be substituted prior to initiation of venom immunotherapy (VIT) for safety reasons.

Objective We aimed to assess the influence of ACEI medication on the incidence of systemic reactions (SR) during the build-up phase of VIT in a large and homogeneous cohort of patients. **Methods** The frequency of SR during 775 consecutive cycles of VIT initiation was analyzed in relation to cardiovascular medication, age, sex, venom, reactivity in diagnostic tests, severity of preceding sting-induced anaphylaxis, comorbidities, latency before the initiation of VIT, and treatment protocols. ACEI were routinely maintained throughout VIT, beta-blockers replaced if appropriate.

Results During VIT-initiation, 190 (24.5%) patients were on some kind of cardiovascular treatment, 90 (11.6%) on ACEI, 23 (3.0%) on beta-blockers. VIT-related SR rates were 11.7% (any documented reactions including subjective symptoms) and 3.0% (reactions fulfilling objective diagnostic criteria of anaphylaxis). Medication with ACEI ($P = 0.097$) or beta-blockers ($P = 1.0$) was not significantly related to the incidence of SR. A reduced rate of SR in patients taking cardiovascular drugs was not statistically significant in the final multivariate regression model. A prolonged latency before the initiation of VIT ($P = 0.018$, odds ratio = 1.010), and use of 5-day compared to 3-day rush protocols ($P = 0.008$, odds ratio = 3.522) increased the frequency of SR.

Conclusions and Clinical Relevance Study data do not provide evidence of an ACEI-mediated increase of VIT-related SR, supporting the continued use of these valuable and hard-to-replace substances throughout VIT.

Keywords ACE inhibitor, anaphylaxis, beta-blocker, build-up phase, cardiovascular medication, Hymenoptera venom, immunotherapy, risk factor, rush protocol, safety

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Correspondence:

Dr Johanna Stoevesandt, Department of Dermatology and Allergy, University Hospital Würzburg, Josef-Schneider-Straße 2, 97080 Würzburg, Germany.

E-mail: Stoevesandt_J@klinik.uni-wuerzburg.de

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Introduction

Venom immunotherapy (VIT) effectively protects Hymenoptera venom allergic patients from recurring sting-induced anaphylaxis [1]. VIT itself, however, is a potential elicitor of systemic anaphylactic side effects [1–4] which are most likely to occur during the dose-increase phase [3] and may occasionally be severe [5–7] even though hardly ever fatal [8, 9]. Previous studies have identified a limited number of risk factors for VIT-induced systemic reactions (SR) including the type of dose-increase protocol [2, 3, 10], an elevation of the baseline serum tryptase concentration

[2, 11, 12], and honey bee compared to vespid VIT [2, 3, 10, 13]. Putative influences of cardiovascular medication with beta-blockers or angiotensin-converting enzyme inhibitors (ACEI) on the incidence or the severity of VIT-related SR, however, remain a matter of controversial discussion [5, 6, 14, 15]. The use of anti-hypertensive medication has currently been associated with an increased risk of severe anaphylaxis in emergency department patients [16] and a recent observational cohort study has refocused the debate on ACEI by supporting a substance-related aggravation of field sting-induced anaphylaxis prior to the initiation of VIT [17].

The widespread use of ACEI in the treatment of cardiovascular diseases causing significant morbidity and mortality is founded on a large number of randomized controlled trials and meta-analyses [18–25]. Depending on the underlying indication, international treatment guidelines advise to prefer ACEI over angiotensin receptor blockers as the first line agents because of the greater evidence of their efficacy [19]. Theoretical considerations in support of a detrimental effect of ACEI on the course of anaphylaxis include an impaired degradation of the vasodilator bradykinin [15] and imbalances in the renin-angiotensin system [26]. Clinical evidence of an ACEI-induced aggravation or accumulation of VIT-related SR, however, is essentially anecdotal [5, 6] and has not been confirmed in preliminary studies including limited numbers of patients on ACEI [2, 15]. Given the strength of evidence supporting an adequate use of ACEI, it is remarkable that considerations to discontinue or substitute an established treatment prior to initiation of VIT have been incorporated not only in prescribing information of both, ACEI and venom extracts for VIT, but also in international guidelines on the treatment of Hymenoptera venom allergy [27, 28].

We aimed to investigate the influence of cardiovascular medication and other relevant parameters on the incidence of VIT-related SR in a large and homogeneous cohort of patients including a high proportion of individuals on ACEI.

Methods

Patients

Patients were eligible for evaluation, if VIT was indicated according to the international guidelines [27–29] (conclusive history of a systemic reaction following a Hymenoptera sting and evidence of corresponding venom-specific IgE as detected in skin and/or serologic tests) and initiation of treatment had been performed between 2004 and 2012, using rush protocols in an inpatient setting. Large local reactors and patients following an outpatient conventional protocol for VIT-initiation were not included. All patient-related procedures were part of routine diagnostic practice; written informed consent was obtained for allergologic work-up and initiation of VIT.

Collection of data

Data on patient-specific details (age, sex, comorbidities, detailed cardiovascular medication, causative insect, date and severity of the most severe sting reaction prior to initiation of VIT) and the results of diagnostic tests (serum-specific IgE, intradermal testing, baseline serum tryptase concentration) were retrieved from patient files.

Information on SR during VIT build-up (venom dose at presentation, symptoms and severity of anaphylaxis, treatment and outcome) was gathered from standardized treatment protocols. In patients undergoing VIT build-up several times because of double allergy to both honey bee and *Vespula* venom or following discontinuation of VIT for various reasons, each treatment cycle was evaluated separately. All medical records were monitored by the institutional head allergist (A.T.) to ensure consistent quality of data. The ethics committee of the University Hospital Würzburg consented to the retrospective review and publication of anonymized clinical data.

Diagnostic procedures

Intradermal skin testing with honey bee and *Vespula* venom (ALK-Abelló, Wedel, Germany) was performed according to the international guidelines [30]. Venom-specific serum IgE was determined using the ImmunoCAP™ method (Thermo Fisher Scientific, Freiburg, Germany); baseline serum tryptase levels were measured using ImmunoCAP Tryptase™ (Thermo Fisher Scientific) according to the manufacturer's instructions. Determination of tryptase concentrations was confined to a subgroup of 465 patients with a history of moderate-to-severe index sting-related anaphylaxis.

Venom immunotherapy

Venom immunotherapy was administered using standardized aqueous allergen products containing *Vespula* or honey bee venom (ALK-lyophilisiert SQ™, ALK-Abelló, Wedel, Germany) according to the manufacturer's instructions. The maintenance dose of 100 µg was achieved using a 5-day dose increase schedule consisting of 14 injections and a cumulative dose of 311.5 µg before 2007 which was subsequently replaced by a 3-day rush protocol involving nine injections and a total dose of 301.1 µg. Preventive medication with antihistamines was not routinely given. Depending on the clinical context, cardiovascular disease was not considered as a contraindication against VIT, but as a reason to recommend treatment with high priority. Beta-blockers were substituted prior to initiation of VIT if judged appropriate by the patient's cardiologist. If no adequate alternative was available, beta-blockers were maintained. In our allergy clinic, medication with ACEI or any other cardiovascular drug is routinely continued throughout VIT.

Classification of VIT-related SR and grading of anaphylaxis

Venom immunotherapy-related SR were classified as 'objective' if any one or more of the following anaphylactic signs [31] occurred after VIT injections:

mucocutaneous symptoms (urticaria, angioedema, and/or flushing), respiratory compromise due to bronchospasm and/or laryngeal oedema, arterial hypotension and/or collapse, distinct gastrointestinal symptoms such as abdominal cramps, diarrhoea or vomiting. Any other symptoms including sensation of heat, pruritus, lightheadedness, throat tightness, headache, anxiety, or perception of an 'impending doom' were categorized as 'subjective'. The severity of VIT-induced SR and pre-VIT Hymenoptera sting-induced anaphylaxis was graded as mild (grade I), moderate (grade II), or severe (grade III) according to a modified version of the system proposed by Muraro as has been described previously [32, 33].

Statistical analysis

Interval-scaled data are given as median and interquartile range (IQR). Ordinally and categorically scaled data are presented as frequencies and relative frequencies. To evaluate the relation of cardiovascular medication to patient-specific clinical data including a potential influence on the course of VIT, a univariate analysis was performed first. To this end, the Mann–Whitney test was performed to compare the two groups for interval-scaled data. The Chi-square or, if applicable, Fisher's exact test were conducted in case of ordinal and categorical data. For a multivariate analysis of the data, a logistic regression model was used to assess the influence of the individual variables on the incidence of VIT-related SR. All tests were 2-tailed, and P values < 0.05 were considered statistically significant. Statistical analyses were done by using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient cohort

Seven hundred and seventy five consecutive cycles of VIT build-up administered to 743 patients were evaluated. Thirty patients underwent VIT-initiation more than once, either because of double allergy to honey bee and *Vespula* venom ($n = 15$) or following discontinuation of VIT for various reasons ($n = 15$). Clinical information on the patient cohort is depicted in detail in Table 1.

Clinical characteristics of patients on cardiovascular medication

During VIT build-up, 190 (24.5%) patients took some kind of cardiovascular medication (including ACEI, beta-blockers, and other drug classes such as diuretics, calcium antagonists, and/or angiotensin II receptor blockers). Ninety (11.6%) were on ACEI, mainly on

Table 1. Patient cohort

	<i>n</i>	%
No. of patients*	775	
Age (years) at time of VIT-initiation, median (IQR)	46 (21)	
Male/female	436/339	
Diagnosis: IgE-mediated allergy to		
<i>Vespula</i> venom	630	81.3
Honey bee venom	145	18.7
Severity of anaphylaxis at the index field sting		
Grade I (mild)	110	14.2
Grade II (moderate)	459	59.2
Grade III (severe)	206	26.6
Elevation of baseline serum tryptase		
$> 11.4 \mu\text{g/l}$	61	7.9
$> 20.0 \mu\text{g/l}$	26	3.4
History of cardiovascular disease	195	25.2
Cardiovascular medication		
Any cardiovascular drug	190	24.5
ACEI	90	11.6
Ramipril	54	
Enalapril	22	
Lisinopril	10	
Captopril	3	
Quinalapril	1	
Beta-blocker	23	3.0
Metoprolol	10	
Bisoprolol	8	
Carvedilol	4	
Atenolol	1	
Combination of beta-blocker and ACEI	12	1.5
Latency (mo) from index sting to initiation of VIT, median (IQR)	7 (8)	
Treatment protocol		
3-day rush	566	73.0
5-day rush	203	26.2
Modified	6	0.8

*Percentages refer to the total number of 775 evaluated treatment cycles. In 30 patients receiving more than one cycle of VIT build-up, each treatment was evaluated separately.

ramipril ($n = 54$) and enalapril ($n = 22$). Twenty three (3.0%) remained on beta-blockers, and 12 (1.5%) took both ACEI and beta-blockers (Table 1). Figs 1 and 2 depict the clinical characteristics of patients taking cardiovascular medication compared to those who were not under the respective treatment. Patients taking cardiovascular drugs did not significantly differ from other patients with regard to their sex (any cardiovascular drug: $P = 0.13$; ACEI: $P = 0.26$; beta-blockers: $P = 0.68$) while being significantly older (any: $P < 0.001$; ACEI: $P < 0.001$; beta-blockers: $P < 0.001$). Cardiovascular medication was positively related to a history of cardiovascular disease (any: $P < 0.001$; ACEI: $P < 0.001$; beta-blockers: $P < 0.001$). Cardiovascular treatment was not significantly related to a history of severe (grade III)

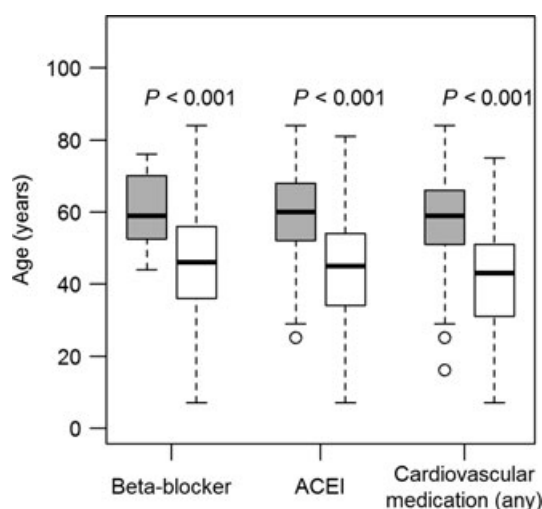


Fig. 1. Box plots displaying the patients' age. Shaded boxes: patients on beta-blockers (left), ACEI (middle), or any cardiovascular medication (right). White boxes: no respective medication. Horizontal lines correspond to the median, the top and the bottom of the boxes to the IQR. The ends of the whiskers indicate data within the 1.5 IQR of the lower and upper quartile, outliers are plotted with small circles.

anaphylaxis following pre-VIT index stings compared to mild or moderate (grade I-II) anaphylactic reactions (any: $P = 0.22$; ACEI: $P = 0.31$; beta-blockers: $P = 0.47$).

VIT-related SR

Our study covers a total of 775 cycles of VIT build-up with honey bee ($n = 145$) or *Vespula* ($n = 630$) venom, using 3-day ($n = 566$) and 5-day ($n = 203$) rush protocols, modifications of which were documented in 6 (0.8%) patients (Table 1). Ninety-one patients complained of some type of adverse reaction during initiation of VIT (including subjective and objective symptoms, but excluding large local reactions), resulting in an overall reaction rate of 11.7%. 23 reactions fulfilled the criteria of an objective anaphylactic SR (see Methods section), corresponding to an objective reaction rate of 3.0% (Fig. 3). Of 23 objective SR, 20 were classified as mild (grade I), 2 as moderate (grade II), and 1 as severe (grade III). Of all documented reactions (objective reactions: 100%; subjective reactions: 45.6%), 59.3% were found to necessitate specific treatment by the physician in charge of VIT. All reactions responded promptly to the administration of antihistamines and/or corticosteroids and/or inhaled beta2-adrenergic agonists. Administration of epinephrine was not performed during the study inclusion period.

Cardiovascular medication and VIT-related SR

The relation between VIT-induced reactions and cardiovascular medication as assessed by the preliminary

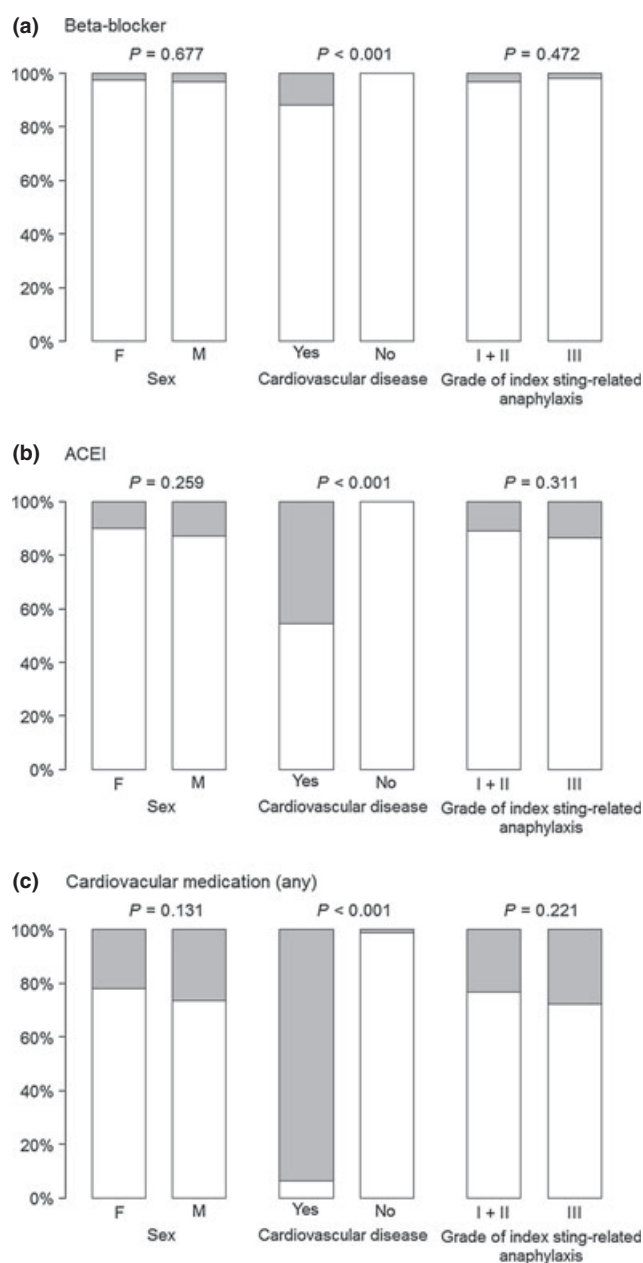


Fig. 2. Relation between cardiovascular medication and clinical parameters. Bar heights indicate relative frequencies of patients with (shaded bars), and without (white bars) respective medication.

univariate analysis is depicted in Fig. 4. No VIT-related objective SR occurred in patients taking beta-blockers or ACEI. However, neither medication did significantly influence the frequency of objective anaphylactic SR (ACEI: $P = 0.097$; beta-blocker: $P = 1.0$), and a tendency towards a lower incidence of undefined SR including subjective symptoms did likewise fail to reach statistical significance (ACEI: $P = 0.055$; beta-blocker: $P = 0.51$). The total group of 190 patients taking any type of cardiovascular medication during the course of VIT build-up was found to have a significantly reduced

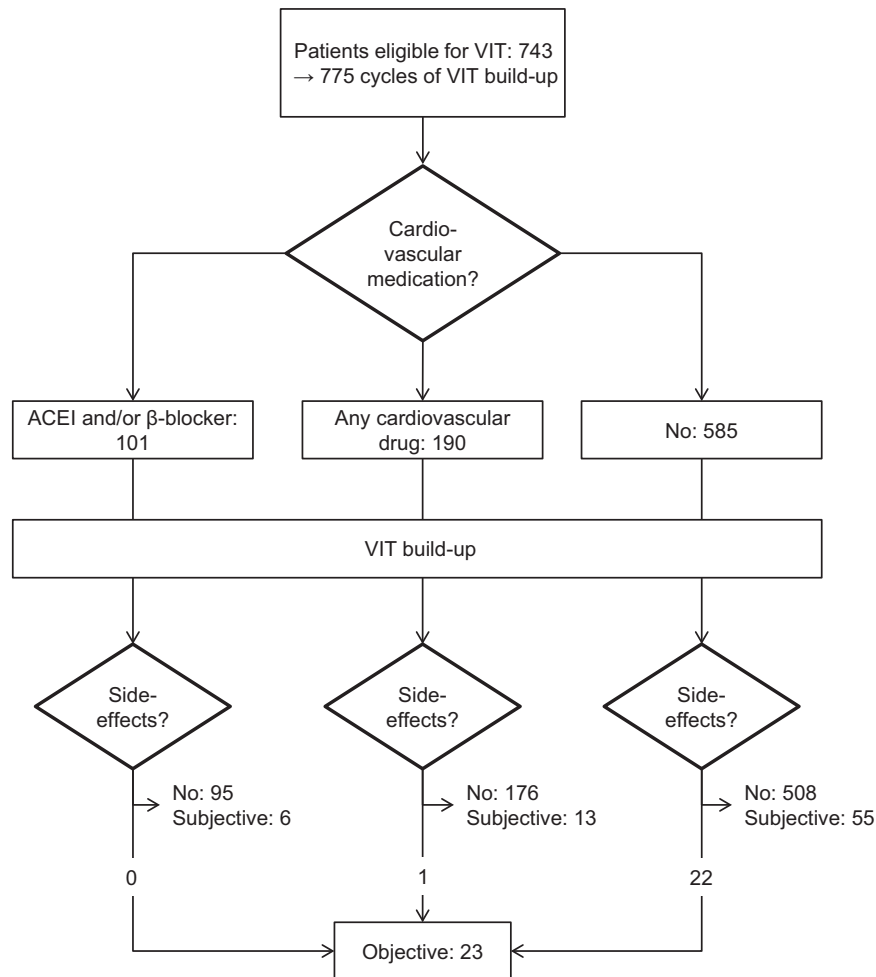


Fig. 3. Algorithmic summary of data on objective and subjective side effects during VIT build-up in patients with or without cardiovascular medication.

risk of both objective ($P = 0.024$) and any undefined ($P = 0.037$) treatment-related SR when assessed by univariate analysis. This statistical significance, however, was not maintained in the final logistic regression model (Table 2).

Risk factors for VIT-related SR

Results of the multivariate logistic regression model examining objective anaphylactic SR and 'any documented' SR as the binary outcome variables are depicted in Table 2. A prolonged latency time between the index sting and initiation of VIT was positively related to a higher incidence of objective SR ($P = 0.018$, odds ratio = 1.010), and objective anaphylactic SR were more common if the 5-day rush protocol was used instead of the shorter protocol ($P = 0.008$, odds ratio = 3.522): objective reaction rates per injection were 0.22% in the 3-day protocol and 0.39% in the 5-day protocol. This difference was statistically significant ($P = 0.023$, one-sided binominal test). A

tendency towards a higher risk of objective anaphylactic SR was observed during honey bee VIT, but did not reach statistical significance ($P = 0.115$). All other variables including cardiovascular medication (ACEI: $P = 0.997$; beta-blockers: $P = 0.998$; any: $P = 0.949$) were not significantly related to the occurrence of treatment-induced objective SR. No parameters were identified to predict an increased incidence of VIT-related reactions if subjective reactions were included for evaluation: tendencies indicating a higher frequency of any documented SR in women ($P = 0.059$) and patients with a history of mild-to-moderate (grade I or II) compared to severe (grade III) pre-VIT index sting reactions ($P = 0.058$) did not reach statistical significance. The baseline serum tryptase concentration was not selected for the final statistical model because of its limited availability. Univariate analysis, however, did not yield a significant influence of tryptase levels on the incidence of VIT-induced adverse reactions (objective SR: $P = 0.16$; any reactions: $P = 0.24$).

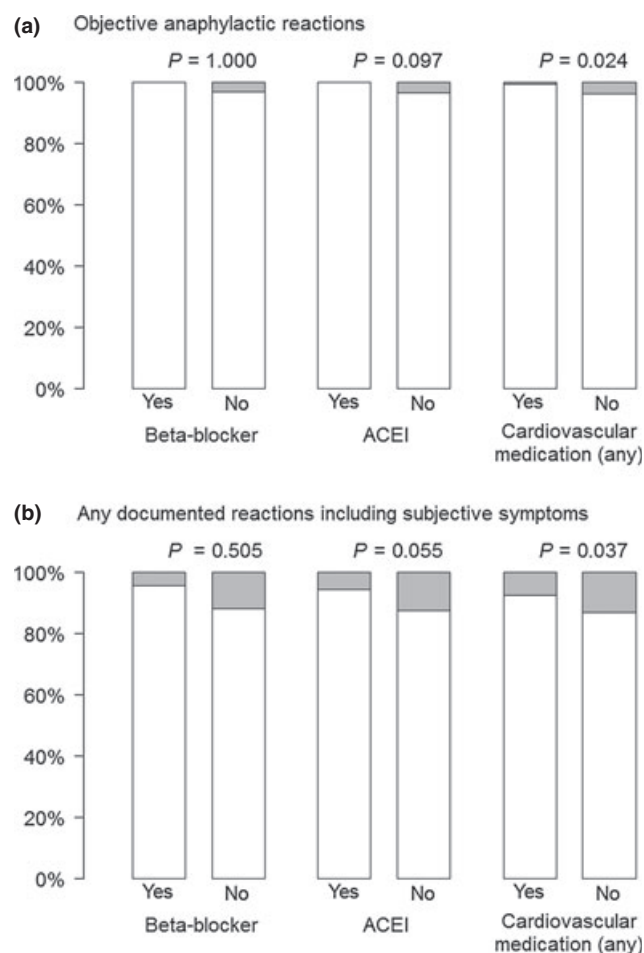


Fig. 4. Relation between VIT-induced SR and cardiovascular medication with beta-blockers (left), ACEI (middle), or any antihypertensives (right). Bar heights indicate relative frequencies of patients with (shaded bars), and without (white bars) respective reactions.

Discussion

We herein present a large single-centre observational cohort study examining the incidence of SR during the build-up phase of VIT in an inpatient setting. Compared to the recent multi-centre studies of a comparable size [2, 3] and to the much larger questionnaire-based historical study by Lockey et al. [4], it has the advantage of a homogeneous patient cohort and consistent treatment conditions including adherence to only two standardized treatment protocols, persistent use of the same venom extracts and minimal variations in the perception, documentation, and treatment of SR.

As it has always been our policy to maintain ACEI throughout VIT, our study cohort includes a representative proportion of patients on ACEI ($n = 90$, 11.6% of the study group) which has not been altered by recommendations to discontinue or substitute an established treatment. In contrast, beta-blockers were replaced whenever judged appropriate. The highly significant association of

Table 2. Results of multivariate logistic regression analyses examining potential risk factors of any documented and objective SR

Variable	Any reactions (<i>P</i>)	Objective SR (<i>P</i>)*
Age (years) at time of VIT-initiation	0.340	0.138
Sex		
Male (reference category)		
Female	0.059	0.767
Diagnostic tests		
Venom-specific IgE (kU/L)	0.318	0.389
Intradermal reactivity	0.436	0.998
Immunotherapy with		
<i>Vespula</i> venom (reference category)		
Honey bee venom	0.740	0.115
Severity of anaphylaxis to index field sting		
Grade I/II (reference category)		
Grade III	0.058	0.310
Cardiovascular disease	0.303	0.716
Cardiovascular medication		
Any cardiovascular drug	0.251	0.949
ACEI	0.411	0.997
Beta-blocker	0.566	0.998
Latency (mo) from index sting to initiation of VIT	0.971	0.018
		OR: 1.010
		CI: 1.002–1.018
Treatment protocol		
3-day rush (reference category)		
5-day rush	0.373	0.008
		OR: 3.522
		CI: 1.395–8.894
Modified	0.288	0.079

*Odds ratios (OR) and 95% confidence intervals (CI) are displayed in the case of significance.

cardiovascular medication and concurrent cardiovascular disease ($P < 0.001$, Fig. 2), although hardly surprising, is indicative of an adequate medical treatment of patients at the time of VIT-initiation, meaning that those requiring antihypertensive drugs were actually treated while others were not. The higher age of patients taking cardiovascular medication ($P < 0.001$), while not unexpected either, constitutes a well-defined risk factor for severe anaphylactic sting reactions [17, 33–35]. Of note, cardiovascular medication (any: $P = 0.22$; ACEI: $P = 0.31$; beta-blockers: $P = 0.47$) was not significantly related to a higher incidence of severe (grade III) anaphylaxis following pre-VIT index stings which is in accordance with our previous observations [33] while other groups have reported conflicting results [17].

VIT build-up is rarely complicated by objective anaphylaxis

Our 3.0% rate of SR (that is 23 of 775 VIT build-up cycles) is well below that of previous studies which did not require documentation of objective symptoms to

define a SR [2–4, 10]. Subjective VIT-related symptoms such as sensation of heat, pruritus, throat tightness, or lightheadedness, although often related to anxiety, may also precede an objective anaphylactic reaction in the sense of an 'impending doom'. In our study, 31 (45.6%) of 68 patients reporting subjective symptoms were treated with oral or intravenous antihistamines. While H1-antihistamines alone do not relieve or prevent high grade anaphylaxis involving severe respiratory or cardiovascular compromise [36], this early intervention may have inhibited the development of mucocutaneous symptoms in some cases. To avoid underdiagnosis of early stage anaphylaxis, we additionally evaluated patients reporting *any* kind of treatment-related reactions (objective as well as subjective), resulting in an overall reaction rate of 11.7%. The observed rarity of severe VIT-related SR is likewise reflected in the medical literature [3, 4, 10]. Of two documented VIT-related fatalities, one occurred following pre-treatment withdrawal of a beta-blocker [9, 14]. Of note, there are no reports describing fatal SR during VIT in patients on either beta-blockers or ACEI.

The incidence of VIT-related SR is influenced by a limited number of risk factors

Using multiple logistic regression models, we identified only two variables to be significantly related to the incidence of objective SR (Table 2). (i) VIT-induced anaphylaxis was more common if the interval between the most recent index sting reaction and initiation of VIT was long ($P = 0.018$, odds ratio = 1.010). This phenomenon which has likewise been observed by Rüeff et al. [2] appears at least paradoxical, considering that clinical and immunological reactivity to Hymenoptera venom diminishes with elapsing time [37, 38]. It may possibly be explained by the presence of protective venom-specific IgG4 antibodies in the direct aftermath of the index sting [2]. (ii) The use of the 5-day dose increase schedule instead of the shorter protocol augmented the risk of objective treatment-related anaphylactic events by the factor 2.5 ($P = 0.008$, odds ratio = 3.522). This observation is in line with previous studies providing evidence of a superior safety of rush protocols including a limited number of injections [10] and/or lower cumulative doses [39]. Given the solid evidence of an increased risk of treatment-related anaphylaxis in honey bee VIT compared to vespid VIT [1–3, 10, 13], we consider our inability to confirm its statistical significance ($P = 0.115$) to result from the comparatively small number of patients receiving honey bee VIT and the overall low incidence of objective reactions. The same may hold true for a potential influence of the baseline serum tryptase concentration on the course of VIT [2, 11, 12].

ACEI do not increase the incidence of SR during VIT build-up

No significant relation was observed between concurrent treatment with ACEI or beta-blockers and the incidence of SR in our study group – no matter if only objective SR (ACEI: $P = 0.097$; beta-blocker: $P = 1.0$), or any reactions including subjective symptoms (ACEI: $P = 0.055$; beta-blocker: $P = 0.51$) were assessed (Fig. 4). No objective anaphylactic SR occurred in patients on ACEI or beta-blockers, and treatment-related reactions in patients taking any kind of cardiovascular medication were actually less frequent than expected when compared to the overall reaction rates of 3.0% (objective SR) and 11.7% (subjective reactions included). This tendency—which has likewise been observed by other groups examining VIT-induced SR and their relation to cardiovascular medication [14, 15], but failed to reach significance in the final logistic regression model (Table 2)—should by no means be overinterpreted as a 'protective' effect of cardiovascular medication. An underlying detection bias, however, can be excluded as the physicians in charge of the administration of VIT and documentation of SR were not involved in the study. It is tempting to speculate that the low rate of VIT-related adverse events in patients on cardiovascular medication might reflect the optimal medical preconditions in individuals receiving an appropriate cardiovascular treatment.

In conclusion, our study provides convincing evidence that ACEI do not increase the incidence of VIT-related SR as has been suggested by previous studies including a smaller number of patients taking ACEI during VIT dose increase [2, 15] and/or maintenance phase [15]. While our data may not exclude a substance-specific influence on the severity of treatment-related SR, the rarity of severe or even life-threatening SR on the one hand [3, 4, 10] and the importance of ACEI as first line agents to treat a number of wide spread and significant cardiovascular diseases on the other [18–25], imply that it is reasonable to primarily maintain ACEI throughout VIT. If ever severe VIT-induced SR are thought to be related to treatment with an ACEI in an individual case, a subsequent change of medication or temporary discontinuation prior to VIT injections remain an option [5, 6].

Available data allow no definite statement with regard to beta-blockers

Our data regarding beta-blockers corroborate the results of previous studies on VIT or immunotherapy with inhalant allergens, failing to detect a detrimental influence of beta-blockers on the course of treatment [2, 14, 40]. These studies, however, did likewise include a relatively

small number of patients on beta-blockers which has been biased by recommendations to discontinue or substitute the pre-existing treatment. The only way to assess a potential influence of beta-blockade on the course of VIT and possibly to work out different safety profiles of selective and non-selective beta-blockers would be to deliberately expose a much larger number of patients to beta-blockers while receiving VIT within a prospective study design. This approach, however, would undoubtedly raise ethical concerns. We conclude that, to date, no definite statement can be made on the use of beta-blockers during VIT except that a careful risk-benefit analysis ought to precede any individual recommendation to discontinue these hard-to-replace substances, keeping in mind that the heart disease benefit of beta-blockers [41, 42] may outweigh the likelihood of severe anaphylaxis as has been convincingly described in the case of peanut allergy [43].

Conclusions and clinical implications

Our study data confirm the relative infrequency of VIT-induced objective anaphylactic reactions. Due to the

rarity of high grade anaphylaxis, no definite conclusions can be made on parameters influencing the severity of SR during VIT build-up. The incidence of VIT-related objective SR is increased by a limited number of risk factors including a prolonged latency time before initiation of VIT and variations of treatment protocols. ACEI do not increase the likelihood of treatment-induced anaphylaxis and may therefore be maintained during VIT. While no definite statement can be made regarding a potential influence of beta-blockers on the course of VIT, any recommendations to withhold these valuable substances should be the result of a careful risk-benefit assessment.

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Conflict of interest

The authors declare no conflict of interest.

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