

Hymenoptera venom immunotherapy while maintaining cardiovascular medication: safe and effective

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ARTICLE INFO

Article history:

Received for publication January 11, 2015.

Received in revised form February 13, 2015.

Accepted for publication March 3, 2015.

ABSTRACT

Background: The hypothetical risks of cardiovascular medication during *Hymenoptera* venom immunotherapy (VIT) are still a matter of controversy.

Objective: To assess the potential influence of β -blockers (BBs) and/or angiotensin-converting enzyme inhibitors (ACEIs) on the long-term safety and outcome of VIT.

Methods: Data on the course of VIT maintenance phase, *Hymenoptera* re-stings, and concurrent medication were retrospectively derived from standardized questionnaires in a cohort of patients with significant cardiovascular comorbidity.

Results: Of 225 patients, 125 (55.6%) were taking cardiovascular medication at the time of data collection; 71 (31.6%) took an ACEI, and 40 (17.8%) took a BB. A total of 3,397 months of maintenance VIT during intake of an ACEI and 1,418 months during BB therapy were evaluated. Cumulative VIT-related reaction rates, including subjective symptoms, were 9.1% per treatment cycle and 0.31% per injection, with objective reaction rates of 1.7% and 0.06%, respectively. The incidence of adverse events was significantly higher in patients with a previous history of systemic reactions at VIT buildup ($P = .004$). Surprisingly, reaction rates were lower in patients taking any kind of cardiovascular medication ($P = .04$) or an ACEI ($P = .03$). The overall reexposure rate to *Hymenoptera* stings was 42.7%, and the field sting–induced objective reaction rate was 7.3%. There was no evidence of an increase of field sting–related relapse or hospitalization rates by concurrent cardiovascular medication.

Conclusion: Cardiovascular medication does not impair the safety and/or the efficacy of *Hymenoptera* VIT.

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Introduction

The hypothetical risks of concurrent cardiovascular medication in patients with a history of *Hymenoptera* venom–induced anaphylaxis have long been a matter of controversy. Extensive evidence supporting the use of angiotensin-converting enzyme inhibitors (ACEIs) and β -blockers (BBs) to reduce the morbidity and mortality in cardiac patients is founded on randomized clinical trials and meta-analyses and is represented in international treatment guidelines.^{1–7} Concerns regarding the safety of concurrent cardiovascular medication in patients with *Hymenoptera* venom allergy date back to the early 80s, when, on the basis of case reports, BBs were thought to aggravate sting-induced anaphylaxis^{8–10} and to possibly interfere with venom immunotherapy (VIT). Preliminary observational studies, however, failed to detect an increase or aggravation of sting-induced anaphylactic reactions^{11,12} or VIT-related anaphylactic adverse effects^{13–15} in patients taking BBs.

Currently, the general consensus is that BBs should ideally be replaced before initiation of VIT but may be maintained if no equivalent treatment options exist.^{16,17}

Recommendations on the use of ACEIs are less explicit. Two retrospective observational studies have recently revived the discussion by suggesting a substance-induced aggravation of field sting–induced anaphylaxis before the initiation of VIT¹² and an increased incidence of anaphylactic relapse reactions after in-hospital sting challenges.¹⁸ Clinical evidence supporting an ACEI-induced aggravation or accumulation of VIT-related anaphylactic reactions, however, is essentially anecdotal.^{19,20} In accordance with recent findings of other groups,^{14,21} we could not confirm an ACEI-induced increase of the incidence of systemic anaphylactic reactions during VIT buildup in a large cohort containing a representative proportion of patients receiving ACEI treatment ($n=90$ [11.6% of the total group]).¹⁵ While our preliminary study was restricted to the dose increase phase of VIT in a well-defined inpatient setting, our present study has been designed to extend our observations to VIT maintenance phase. Particular emphasis was put on the long-term follow-up of putative high-risk patients undergoing VIT maintenance while concurrently taking cardiovascular medication. Additional data were collected on re-sting and relapse rates.

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Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2015.03.001>

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Methods

Patients

Patients were eligible for evaluation of data if initiation of honey bee and/or *Vespula* VIT had been performed in our clinic between 2002 and 2013. Data on the buildup phase of VIT in an overlapping patient cohort was part of a previous study.¹⁵ All patient-related procedures were part of routine diagnostic practice; written informed consent was obtained for allergologic workup and initiation of VIT. The institutional review board of the University Hospital Würzburg consented to the retrospective review and publication of anonymized clinical data.

Collection of Data

Our routine follow-up schedule includes a minimum of 4 visits at our allergy center after inpatient initiation of VIT (1 day, 1 week, 4 weeks, 3 and/or 5 years after start of treatment). To ensure continuous surveillance, putative high-risk patients (concurrent cardiovascular disease or treatment with an ACEI or BB) choosing to continue VIT with their local family physician or allergist are additionally contacted by telephone every 12 to 18 months. A standardized questionnaire covering information on the course of VIT (venom doses and intervals between injections and adverse effects), *Hymenoptera* re-stings (stinging insect, symptoms, emergency self-treatment, and medical intervention), and clinical data (changes in comorbidities and concurrent medication) is completed on every control visit or telephone contact. In patients (n = 5) receiving VIT with both honey bee and *Vespula* venom, each treatment cycle was analyzed separately, whereas clinical baseline parameters and re-sting related data were recorded only once. Baseline serum tryptase concentrations (ImmunoCAP Tryptase, Thermo Fisher Scientific, Freiburg, Germany) were assessed in a subgroup of 155 patients with a history of moderate to severe index sting-induced anaphylaxis.

Venom Immunotherapy

Indications for VIT were made according to international guidelines (conclusive history of an anaphylactic reaction after a *Hymenoptera* sting and corresponding venom-specific IgE detected in intradermal and/or serologic tests).^{16,17,22} BBs were substituted before VIT initiation if judged appropriate by the treating cardiologist; treatment with ACEIs and any other cardiovascular drugs was routinely continued. VIT buildup with aqueous allergen products (ALK-lyophilisiert SQ, ALK-Abelló, Wedel, Germany) took place in an in-hospital setting using 3-day and 5-day rush protocols as described elsewhere.^{15,23} Once the maintenance dose of 100 µg was achieved, VIT was continued using aluminium hydroxide adsorbed depot preparations (ALK-depot SQ, ALK-Abelló), and the intervals between injections were gradually extended to 6 weeks. The first 3 depot injections after inpatient buildup were invariably administered in our allergy center. Subsequently, patients were permitted to consult their family physicians or local allergists for continuation of treatment.

Classification of VIT Related Systemic Reactions and Grading of Anaphylaxis

VIT-related reactions were categorized as objective if any one or more of the following symptoms were documented: mucocutaneous involvement (flushing, urticaria, or angioedema); respiratory compromise resulting from bronchospasm and/or laryngeal edema; arterial hypotension and/or collapse; or distinct gastrointestinal symptoms, such as diarrhea, abdominal cramps, and vomiting. Any other symptoms, such as sensations of warmth, itching, dizziness, headaches, or general anxiety, were categorized

Table 1

Patient cohort at time of data collection

Characteristic	No. (%) of the 225 Patients ^a
Age at time of data collection, mean (IQR), y	57 (18)
Sex	
Male	137 (60.9)
Female	88 (39.1)
Allergy diagnosis	
<i>Vespula</i> venom	189 (84.0)
Honey bee venom	31 (13.8)
<i>Vespula</i> and honey bee venom	5 (2.2)
Serum tryptase concentration, median (IQR), µg/L	4.4 (3.96)
Baseline serum tryptase concentration ^b	
>11.4 µg/L	27 (12.0)
>20.0 µg/L	9 (4.0)
Index sting-induced anaphylaxis	
Grade I (mild)	24 (10.7)
Grade II (moderate)	129 (57.3)
Grade III (severe)	72 (32.0)
Systemic adverse effects during VIT buildup	
None	206 (91.6)
Subjective symptoms	14 (6.2)
Objective anaphylaxis	5 (2.2)
Status of VIT at time of data collection	
Duration at time of data collection, median (IQR), mo	46 (35.5)
Discontinued	39 (17.3)
Maintenance VIT administered by	
University Hospital Würzburg (allergy center)	66 (29.3)
Local allergist	53 (23.6)
Family physician	106 (47.1)

Abbreviations: IQR, interquartile range; VIT, venom immunotherapy.

^aData are presented as number (percentage) of patients unless otherwise indicated.

^bTryptase concentrations available in 155 patients.

as subjective. The severity of objective anaphylactic reactions was graded as mild (grade I), moderate (grade II), or severe (grade III).²⁴

Field Sting-Induced Reactions

Patients were advised to avoid *Hymenoptera* field stings using standardized information material. All patients were provided with an emergency kit that contained dimethindene and betamethasone solutions and an epinephrine autoinjector. They were instructed to take antihistamines and corticosteroids to treat field sting-induced mucocutaneous reactions and to use the autoinjector in the case of any systemic reaction that involved other organs than the skin. Field sting-induced anaphylactic reactions were classified as described above.

Statistical Analysis

Metric variables are given as median and interquartile range (IQR), and categorically and ordinal scaled variables are presented as frequencies and relative frequencies. The Mann-Whitney test was performed to compare interval-scaled data. The χ^2 test or, if applicable, Fisher exact test was used to compare ordinal and categorical data. The McNemar test was used on paired nominal data with a dichotomous trait. All tests were 2-tailed, and $P < .05$ was considered statistically significant. Statistical analyses were performed with SPSS statistical software Windows, version 22.0 (SPSS Inc, Chicago, Illinois).

Results

Patient Cohort at Time of Data Collection

Follow-up questionnaires from 225 patients were available for evaluation. The median duration of VIT at the time of data collection was 46 months (IQR, 35.5 months). Detailed clinical information on the patient cohort is given in Table 1.

Table 2
Cardiovascular medication during VIT

Medication	No. (%) of the 225 Patients	
	Buildup	Maintenance Phase
Any cardiovascular drug	114 (50.7)	125 (55.6)
ACEI	84 (37.3)	71 (31.6)
Ramipril	50 (22.2)	42 (18.7)
Enalapril	15 (6.7)	12 (5.3)
Lisinopril	12 (5.3)	11 (4.9)
Captopril	5 (2.2)	4 (1.8)
Spirapril	1 (0.4)	1 (0.4)
Quinalapril	1 (0.4)	1 (0.4)
BB	22 (9.8)	40 (17.8)
Metoprolol	9 (4.0)	21 (9.3)
Bisoprolol	8 (3.6)	12 (5.3)
Carvedilol	4 (1.8)	5 (2.2)
Atenolol	1 (0.4)	1 (0.4)
Nebivololol	0	1 (0.4)
Combination of ACEI and BB	11 (4.9)	19 (8.4)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; BB, β -blocker; VIT, venom immunotherapy.

Cardiovascular Medication During VIT

A total of 114 patients (50.7%) were taking some kind of cardiovascular medication (eg, ACEIs, BBs, diuretics, calcium antagonists, and/or angiotensin II receptor blockers) during the inpatient buildup phase of VIT (Table 2): 84 (37.3%) took an ACEI, 22 (9.8%) a BB, and 11 (4.9%) took both an ACEI and a BB. By the time of data collection, the total number of patients taking cardiovascular medication had significantly increased to 125 (55.6%) ($P = .02$). The number of individuals undergoing BB treatment increased to 40 (17.8%) ($P < .001$), whereas the number of patients taking an ACEI had significantly decreased to 71 (31.6%) ($P = .01$). In total, 3,397 months of VIT (equaling approximately 2,265 single injections) were administered during the intake of ACEI, and 1,418 months (approximately 945 single injections) were given during treatment with BB. Patients taking any kind of cardiovascular medication at the time of data collection were significantly older than those who did not ($P < .001$), resulting in a median age difference of 15.5 years.

Course of VIT Maintenance Phase

In 5 patients receiving double VIT with both honey bee and *Vespa* venom, each treatment was evaluated separately, resulting in a total number of 230 cycles of VIT, including 95 treatment cycles given under the influence of ACEIs or BBs (Fig 1). Our study covers a total of 10,111 months of VIT maintenance with honey bee (1,644 months) or *Vespa* (8,467 months) venom, corresponding to 6,741 single injections. A total of 189 cycles (82.2%) of VIT maintenance were tolerated without any complications. Twenty patients (8.7%) had large local reactions. Seventeen patients (7.4%) reported subjective VIT-related adverse reactions on at least one occasion. Only 4 patients had a VIT-induced reaction that fulfilled the objective criteria of anaphylaxis (see the Methods section), resulting in an objective reaction rate of 1.7% per treatment cycle and 0.06% per injection. Cumulative reaction rates, including both objective and subjective symptoms, were 9.1% per treatment cycle and 0.31% per injection. Of 4 objective anaphylactic reactions, 1 was classified as mild (grade I), 2 as moderate (grade II), and 1 as severe (grade III). Only the patient with a mild (grade I) anaphylactic reaction during honey bee VIT was taking cardiovascular medication (ie, lisinopril, hydrochlorothiazide, verapamil, and nitrendipine).

The distribution of VIT-related subjective and objective adverse reactions ($n = 21$) with regard to potential risk factors is depicted in Figure 2. Systemic reaction rates during VIT maintenance phase were significantly higher in patients with a history of previous treatment-related adverse events during the inpatient buildup

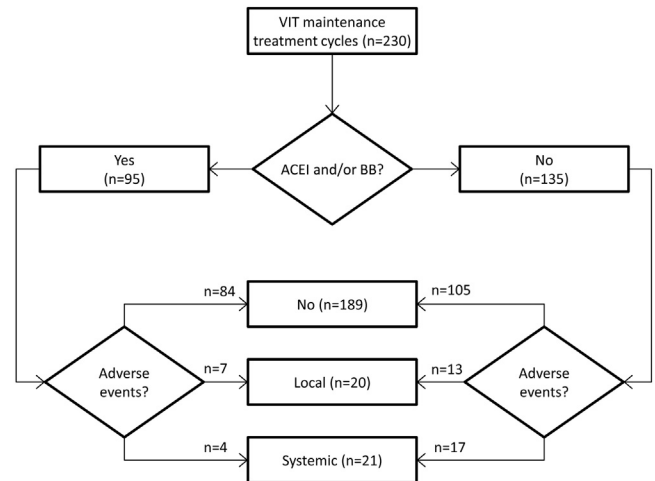


Figure 1. Adverse events during 230 cycles of maintenance venom immunotherapy (VIT) in patients taking and not taking angiotensin-converting enzyme inhibitors (ACEIs) and/or β -blockers (BBs).

phase of VIT ($P = .004$). Lower reaction rates were observed in patients taking any kind of cardiovascular medication ($P = .04$) or an ACEI ($P = .03$) during VIT maintenance. A tendency toward a higher rate of adverse events in bee venom allergic patients ($P = .11$) became statistically significant if only objective anaphylactic reactions were evaluated ($P = .01$). No significant association was detected between adverse reaction rates and baseline serum tryptase concentrations ($P > .99$; data are not included in Figure 2 because of the limited availability of tryptase concentrations in a subgroup of 159 treatment cycles).

Re-stings and Re-sting Reactions

A total of 140 *Hymenoptera* re-stings (90 *Vespa* stings, 29 honey bee stings, 1 hornet sting, 1 bumble bee sting, and 19 stings by unidentified *Hymenoptera* species) occurred in 96 of 225 patients, resulting in an overall re-sting rate of 42.7%. Twenty-four patients (10.7%) got re-stung on more than one occasion. Eighty-two patients (36.4%) were presumably reexposed to the venom they were treated with. Although 2 patients had an objective anaphylactic reaction on exposure to their hitherto nonrelevant insect, objective relapse rates were 7.3% (all *Hymenoptera* field stings) and 6.1% (re-stings by initially relevant insect only), respectively. Of 7 objective field sting reactions, 1 was graded as mild, 4 as moderate, and 2 as severe. To take into account all clinically relevant field sting reactions, the total number of 96 reexposed patients was included for statistical analysis (in patients with more than one *Hymenoptera* field sting, the latest or, if applicable, the most severe field sting reaction was evaluated). The median time elapsing between the initiation of VIT and reported re-stings was 30 months (IQR, 27.75 months).

Because of the relatively low number of re-stings and re-sting-related reactions, we were unable to identify any statistically relevant associations between relapse rates and potential risk factors. The distribution of field sting-induced objective anaphylactic relapse reactions with regard to baseline parameters is depicted in Figure 3. A total of 52 *Hymenoptera* re-stings occurred in patients undergoing antihypertensive treatment (including 25 patients taking ACEIs and 19 patients taking BBs). There was no evidence of higher or lower relapse rates in patients taking concurrent cardiovascular medication. Seven patients (7.3%) were hospitalized after a field sting. Hospitalization rates were higher in patients with objective field sting-induced anaphylaxis compared with non-reactors and patients with subjective symptoms only (57.1% vs

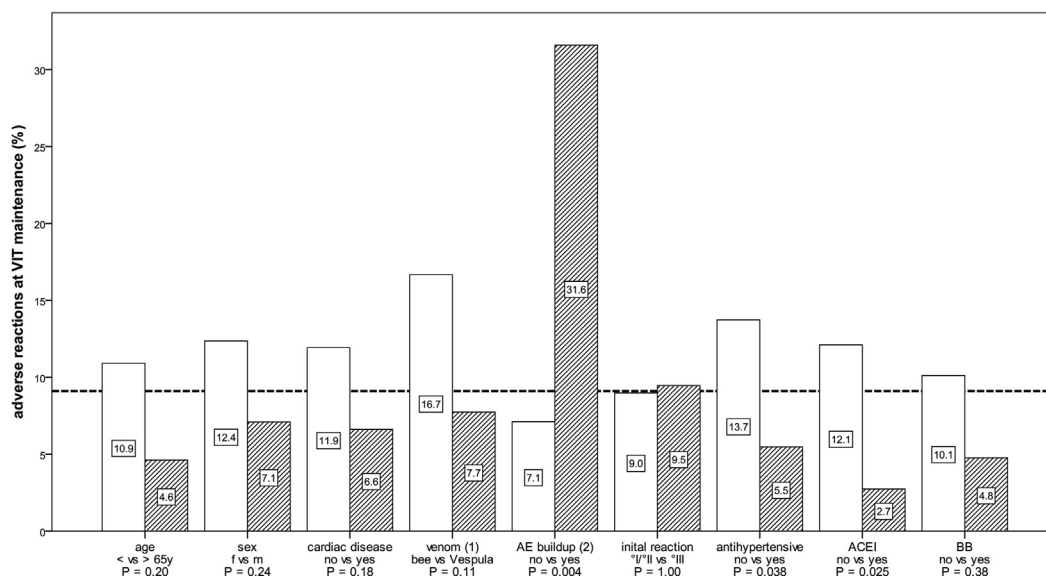


Figure 2. Cumulative rate of objective and subjective adverse reactions during 230 cycles of maintenance venom immunotherapy (VIT) with regard to potential risk factors. (1) This tendency toward a higher rate of adverse events in honey bee compared with *Vespula* VIT became statistically significant if only objective anaphylactic reactions were evaluated ($P = .01$). (2) Adverse events (AE) at VIT buildup included subjective and objective VIT-induced systemic reactions. Dotted line indicates the mean cumulative reaction rate (9.1%). ACEI indicates angiotensin-converting enzyme inhibitor; BB, β -blocker.

3.4%; $P < .001$). Hospitalizations rates in patients with any kind of cardiovascular medication (5.8%, $P = .70$), ACEI (8.0%, $P > .99$), or BB (0%, $P = .34$) did not significantly differ from hospitalization rates in the absence of respective medication.

Discussion

The present study was designed to assess potential influences of ACEIs and BBs on the long-term safety and outcome of *Hymenoptera* VIT. It includes the hitherto largest cohort of patients taking ACEIs and BBs during VIT maintenance phase^{13,18,21,25} and covers a total of 2,265 single injections administered during the intake of ACEIs and 945 injections with concurrent BB medication. Our study's limitations lie in its retrospective approach and in the

concentration on a relatively small group of patients with a high incidence of cardiovascular comorbidities (putative high-risk patients were contacted more often and are therefore over-represented). As a consequence, results may not be entirely generalizable to an average population of *Hymenoptera* venom allergic patients.

Safety of Maintenance VIT and Concurrent Cardiovascular Medication

Anaphylactic adverse effects have been reported to be more frequent at VIT buildup than during the maintenance phase of treatment.²⁶ Our present study confirms the rarity of objective anaphylactic reactions during VIT maintenance in a cohort of

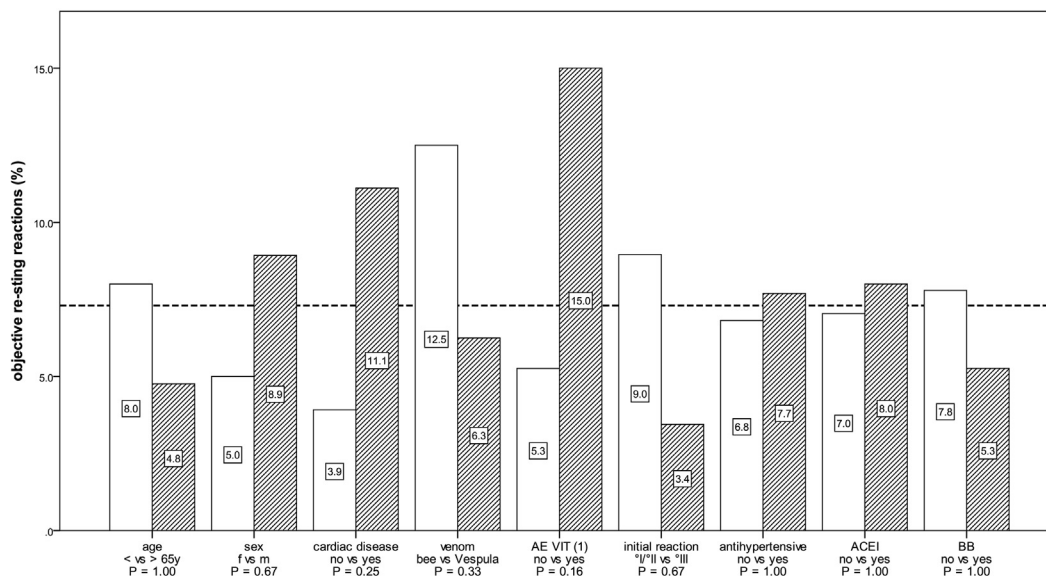


Figure 3. Distribution of objective anaphylactic sting reactions with regard to baseline parameters in 96 patients with *Hymenoptera* re-stings. (1) Adverse events (AE) at VIT buildup and/or maintenance included subjective and objective VIT-induced systemic reactions. Dotted line indicates mean objective re-sting reaction rate (7.3%). ACEI indicates angiotensin-converting enzyme inhibitor; BB, β -blocker.

patients at an increased cardiovascular risk, with objective reaction rates of 1.7% per treatment cycle and 0.06% per single injection. Cumulative adverse reaction rates, including subjective symptoms, such as isolated pruritus, sensations of heat, or dizziness, were considerably higher (9.1% per treatment cycle and 0.31% per injection) while still remaining within the range of previous studies.^{14,26,27} To comprehensively assess all VIT-related anaphylactic adverse effects comprising early stage symptoms, both objective and subjective adverse reactions were included for statistical evaluation (Fig 2). The following aspects require further discussion.

First, the observation that patients with systemic side effects at VIT buildup are at an increased risk for further anaphylactic reactions at VIT maintenance ($P = .004$) is hardly surprising but nonetheless clinically important. Once treatment-induced anaphylaxis has occurred, long-term intensive surveillance of the patient is warranted. Moreover, treatment-related anaphylaxis has been suggested to be indicative of insufficient protection and future sting-induced relapse reactions.^{18,28}

Second, a tendency toward an increased rate of adverse events during honey bee compared with *Vespula* VIT ($P = .11$) became statistically significant in our study cohort if only objective anaphylactic reactions were evaluated ($P = .01$), thereby once again confirming honey bee venom allergy as a risk factor for VIT-related adverse events.^{14,26,29,30}

Third, the rate of VIT-induced anaphylactic reactions was statistically lower in patients taking any kind of cardiovascular drug ($P = .04$) or an ACEI ($P = .03$) when compared with individuals who were not taking the respective medication. A similar trend in patients taking BBs did not prove to be statistically significant ($P = .38$). A tendency toward a decreased rate of VIT-related anaphylaxis in patients taking cardiovascular medication has likewise been observed by other groups and has also been described in our previous study assessing the dose-increase phase of VIT.^{13,15,21} As a matter of course, our observations do not imply a protective effect of antihypertensive medication during VIT. It is, however, tempting to speculate that VIT is tolerated best in patients continuing with their optimal cardiovascular treatment. The potentially deleterious effects of pretreatment withdrawal of an established cardiovascular medication have been documented on at least one occasion.¹³

Fourth, the proportion of patients taking BBs almost doubled from the start of VIT to the time of data collection ($P < .001$), whereas the use of ACEIs significantly decreased ($P = .01$). This observation is mainly attributed to the fact that only BBs were substituted before VIT initiation. With elapsing time, an increasing number of individuals were given their original BB by their treating physicians or family physicians. Reasons may be that substitute treatments were considered inferior to the initial BB treatment and/or that recommendations to avoid BBs during VIT were basically ignored. In any case, the general return to the initial medication is indicative of a fairly academic character of the BB discussion because it appears not to affect individual treatment concepts in the long term.

Field Sting–Related Reactions and Concurrent Cardiovascular Medication

Re-sting (42.7%) and field sting–related relapse rates (7.3%) in the present study are in line with published data,^{31,32} thereby confirming the efficiency of VIT in a cohort of patients at an increased cardiac risk. Previous studies have delineated a number of potential risk factors to be associated with an increased rate of VIT failure, namely, honey bee venom allergy,^{18,25,30} VIT-related anaphylactic reactions,^{18,28} elevation of baseline serum tryptase concentrations and/or mastocytosis,^{18,33–35} and severe index sting–induced anaphylaxis.^{32,36} Contradictory results regarding

potential influences of concurrent cardiovascular medication, particularly of ACEIs on the efficiency of VIT, have recently been reported by Ruëff et al.^{18,25} A prospective multicenter study evaluating the outcome of sting challenges and *Hymenoptera* field stings in 357 patients did not document any anaphylactic relapse reactions in 15 patients taking ACEIs and 9 patients taking BBs,²⁵ whereas a more recent evaluation retrospectively assessing the outcome of challenge stings in an overlapping patient cohort found concurrent treatment with ACEIs to be associated with an increased rate of VIT failure.¹⁸ Despite the impressive total number of 1,609 sting challenges in 1,532 patients, the validity of the latter study is clearly hampered by the selection of a small subgroup of predefined high-risk patients continuing to take ACEIs ($n = 30$). Despite the high proportion of patients taking ACEIs and BBs, but because of the relatively low rate of re-stings and field sting–induced systemic reactions, our present study is likewise underpowered to definitely exclude cardiovascular medication as a risk factor for VIT failure. Still, comparison of field sting–induced objective reaction rates did not provide any evidence of a detrimental influence of either ACEIs or BBs (Fig 3), and sting-related hospitalization rates did not statistically differ in patients with and without cardiovascular medication.

Potential Effects of Cardiovascular Medication on *Hymenoptera* Venom–Induced Anaphylaxis

In summary, our present study does not suggest an impairment of the safety and/or the efficacy of VIT by concurrent cardiovascular medication, thereby providing a piece of evidence in favor of continued use of ACEIs and BBs according to their indication in patients with coexisting *Hymenoptera* venom allergy. Consideration of the complexity of the issue, however, is imperative.

Potential effects of cardiovascular medication on *Hymenoptera* venom–induced anaphylaxis may differ, depending on specific situations. Information derived from the context of VIT may not necessarily be transferable to future field or challenge stings or vice versa.

In case of anaphylaxis, BBs are expected to inhibit the effects of both endogenously released and therapeutically administered epinephrine,³⁷ whereas ACEIs may interfere with compensatory physiologic responses by blocking conversion of angiotensin I to angiotensin II.²¹ As a consequence, both substance groups might aggravate the severity of VIT or sting-related anaphylactic reactions while not influencing their overall incidence. An association between the involvement of 3 or more organ systems or need for hospital admission and the use of ACEIs and BBs has been supported in a recent study retrospectively evaluating 302 emergency department visits due to anaphylactic reactions independent of the suspected trigger.³⁸ In an earlier multivariate logistic regression analysis examining 1,149 anaphylactic reactions, the use of ACEIs or BBs, however, was not significantly associated with hypotension, collapse, or hypoxia.³⁹ Previous studies assessing the severity of *Hymenoptera* sting–induced anaphylactic reactions did not confirm a detrimental effect of β -blockade but reported controversial results regarding the use of ACEIs.^{11,12} Clinical evidence in favor of an aggravation of VIT-induced anaphylaxis by ACEIs is exclusively anecdotal.^{19,20} Of note, none of the cited studies (including our own work) addressing the incidence of VIT- or field or challenge sting–induced anaphylactic reactions were designed to identify substance-specific effects on the severity of anaphylaxis.^{14,15,18,21,25} Large prospective studies that include a representative proportion of individuals taking ACEIs and/or BBs are required to enable a definite statement.

Clinical Impact

Severe or even fatal anaphylactic sting reactions commonly affect elderly patients who consequently represent the main

candidates not only for cardiovascular medication but also for VIT.^{11,12,40–42} For the time being, indications for both VIT and cardiovascular treatment should be made according to available evidence: (1) VIT is effective for preventing anaphylactic sting reactions⁴³; (2) ACEIs and BBs are first-line agents to treat a number of significant cardiovascular diseases^{1–7}; and (3) data supporting an interference between VIT and ACEIs or BBs are limited. A careful and individual risk assessment ought to precede any recommendation to substitute an established treatment with ACEIs or BBs or even to renounce VIT.

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