

Diagnosis and treatment of Hymenoptera venom allergy

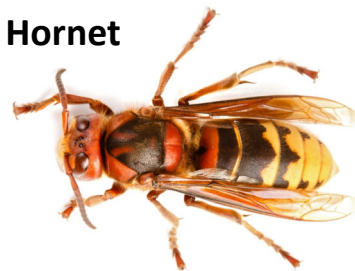


Relevant insects

Vespula



Hornet



Honey bee



Bumble bee



Cross-reactivity: *Vespa crabro* & *Vespula vulgaris*

Vespa crabro Vesp c 1 **Phospholipase A1** *Vespula vulgaris* Ves v 1



Vespa crabro Vesp c 5 **Allergen 5** *Vespula vulgaris* Ves v 5



Sturm GJ, Boni E et al. Allergy 2023

Hornets: rare causes of systemic sting reactions

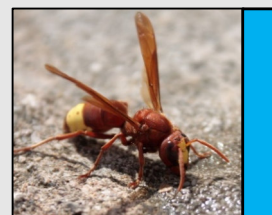
Vespa crabro



Vespa velutina



Vespa orientalis



- Usually not aggressive
- Stings are rare

Sturm GJ, Boni E et al. Allergy 2023

Cross-reactivity: *Vespa velutina* & *Vespa crabro*

Vespa velutina Vesp v 1 **Phospholipase A1** *Vespa crabro* Vesp c 1

69%

Vespa velutina Vesp v 5 **Allergen 5** *Vespa crabro* Vesp c 5

90%

Sturm GJ, Boni E et al. Allergy 2023

Hornets: rare causes of systemic sting reactions

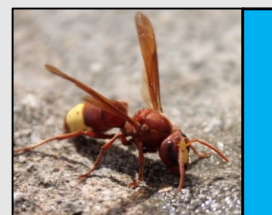
Vespa crabro



Vespa velutina



Vespa orientalis



- Cross-reactivity between *V. crabro* and *Vespa* is well-documented
- Antigen 5 of *V. velutina* & *orientalis* is nearly identical to *Vespa crabro*

Diagnosis and treatment with vespid venom sufficient

Sturm GJ, Boni E et al. Allergy 2023

Cross-reactivity: honeybee & bumble bee



Api m 1 **Phospholipase A2** Bom t 1

54%

Api m 7 **CUB serine protease** Bom t 4

25%

Serine protease: major allergen in BB venom and structurally different

Sturm GJ, Boni E et al. Allergy 2023; 78:2089-2108

Summary - insects

- The venom of different hornet species is allergologically very similar
- Hornet venoms: similar to vespid venom
- Bumble bee venom: major allergen is structurally different
- Diagnosis & treatment primarily with bee and vespid venom
- Primary bumblebee venom allergy: diagnose and treat with bumblebee venom



Diagnosis

Skin testing

Prick

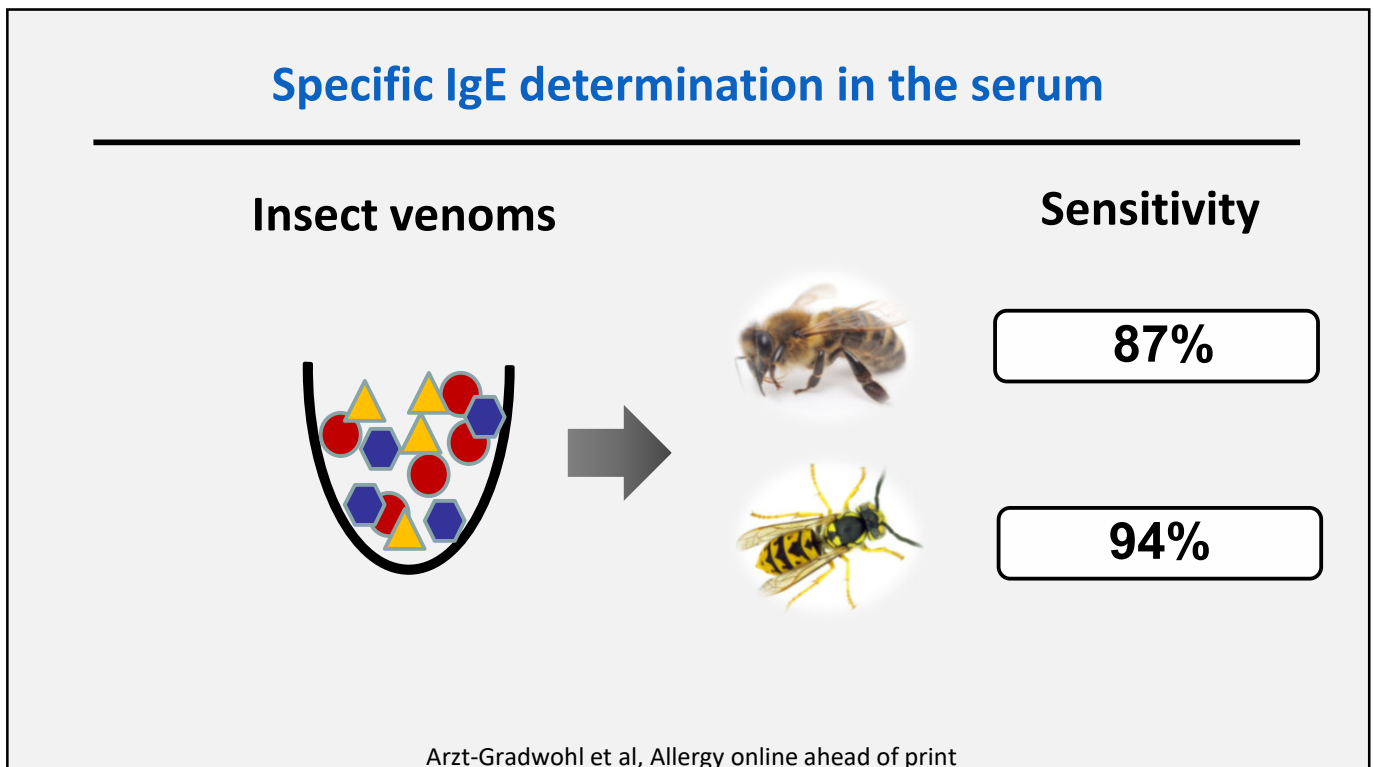
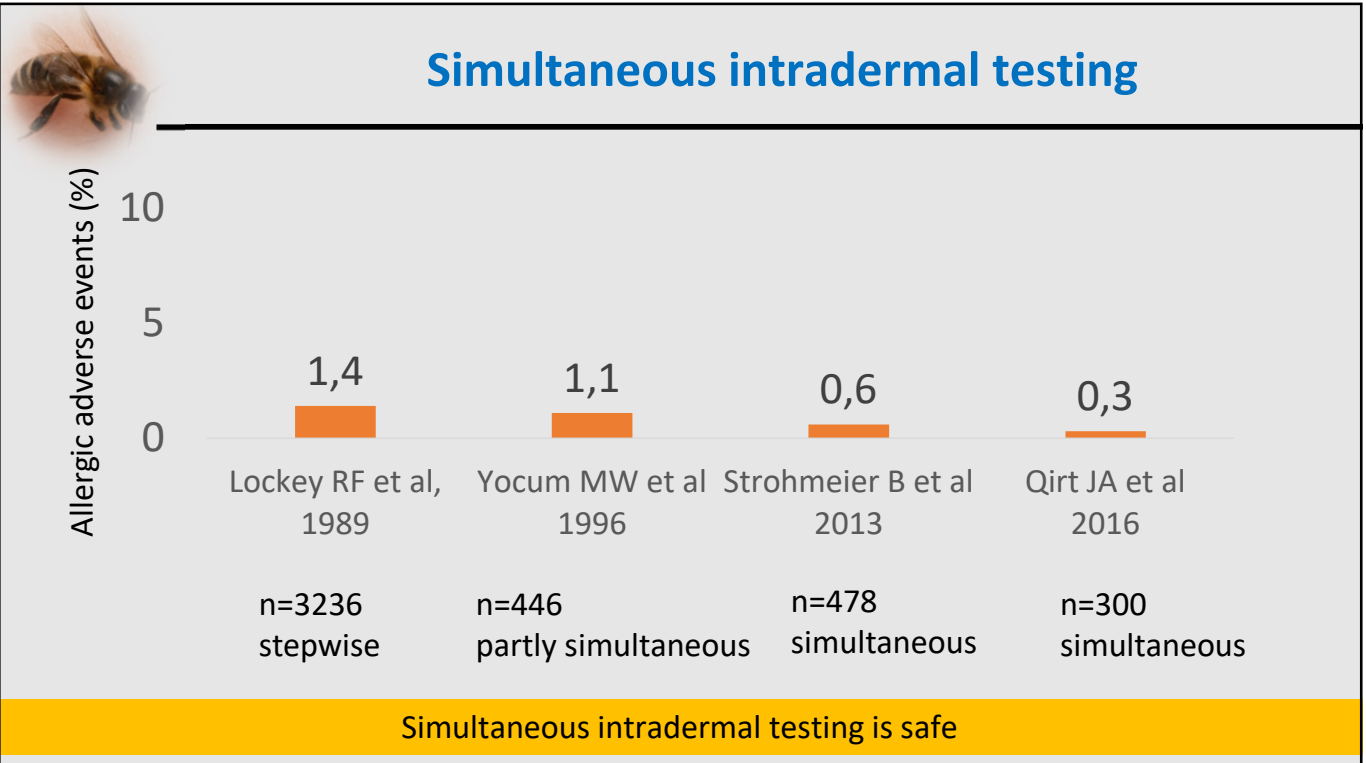


Intradermal test



Simultaneous testing should be feasible (20ng vs 22.22ng!)





Using lower the cut-off in patients with low tIgE



190 bee

86.8%

94.2%

98.9%

slgE >0.35 kU/L

slgE >0.1 if tIgE <30

Intradermal test



809 wasp

94.2%

97.9%

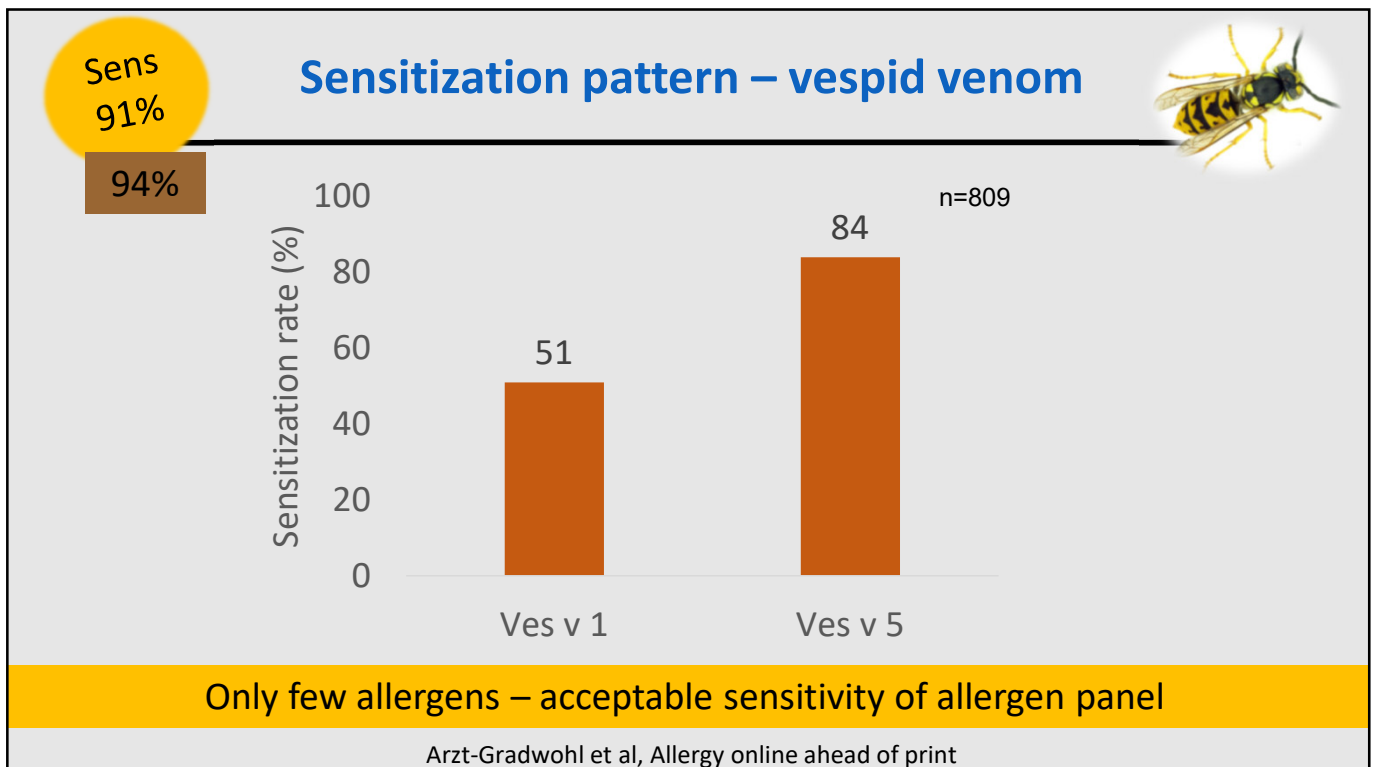
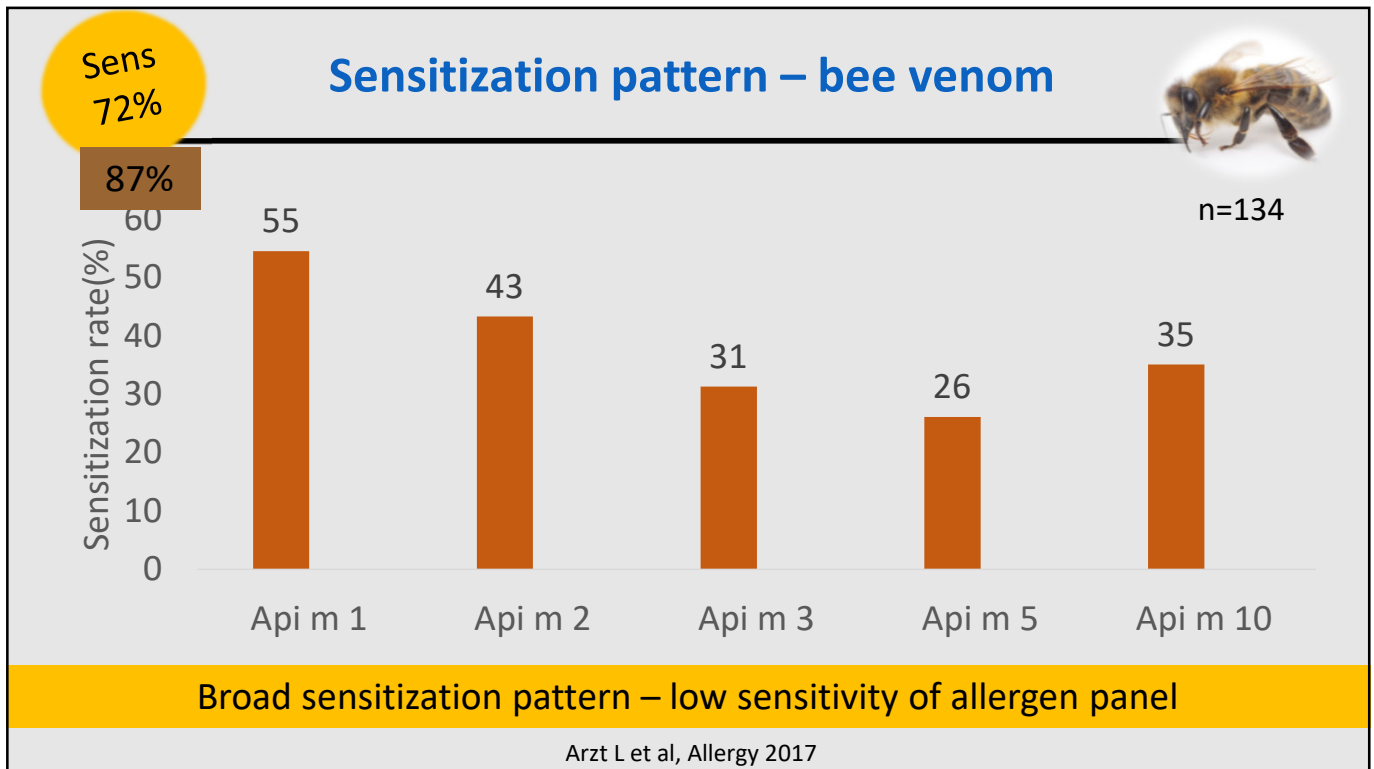
99.1%

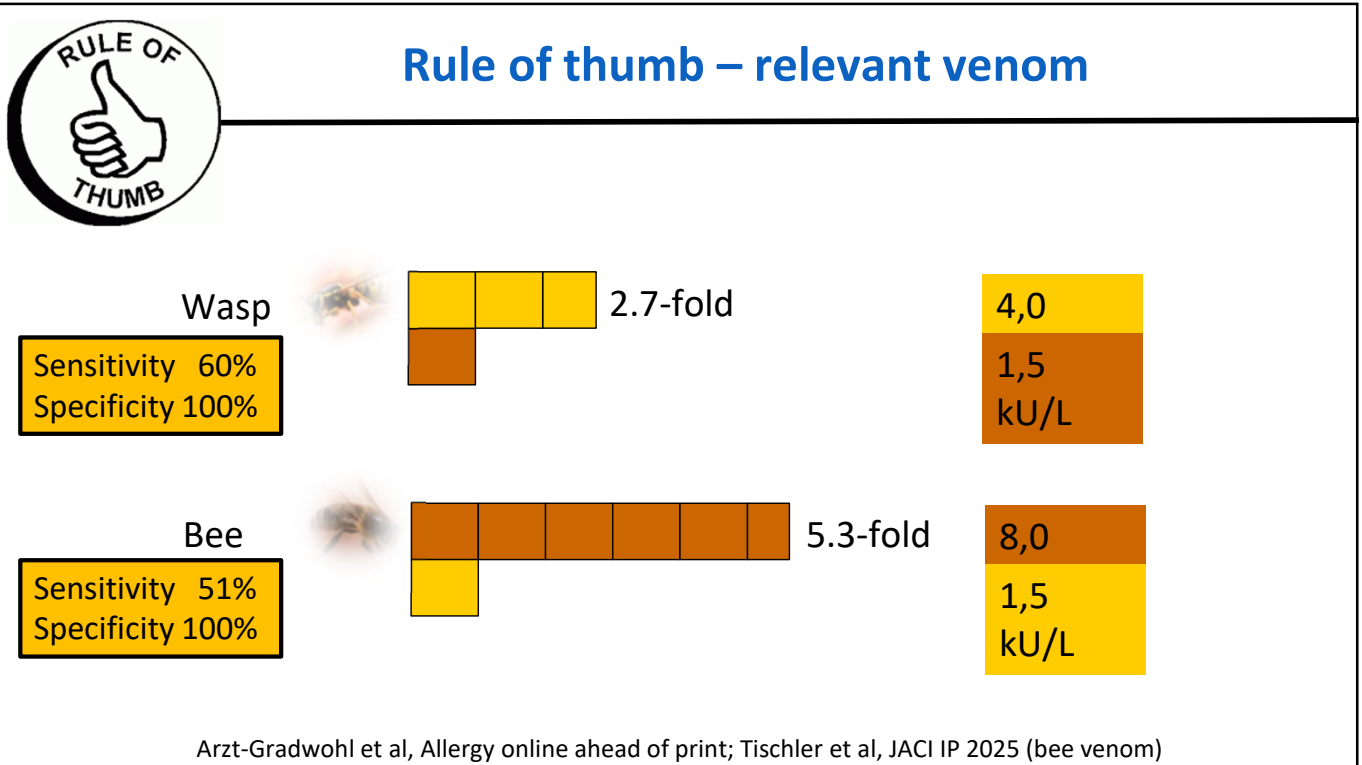
Arzt-Gradwohl et al, Allergy online ahead of print

Allergens and potential cross-reactive allergens

| | | | | |
|----------|-----------------------------|-----|---------|-------------------------|
| Api m 1 | Phospholipase A2 * | 54% | Ves v 1 | Phospholipase A1 |
| Api m 2 | Hyaluronidase * | | Ves v 2 | Hyaluronidase * |
| Api m 3 | Acid phosphatase * | 54% | Ves v 3 | Dipetidylpeptidase IV * |
| Api m 4 | Melittin | | Ves v 5 | Antigen 5 |
| Api m 5 | Dipetidylpeptidase IV * | 40% | Ves v 6 | Vitellogenin * |
| Api m 6 | Protease inhibitor | | | |
| Api m 7 | CUB serine protease * | | | |
| Api m 8 | Carboxylesterase * | | | |
| Api m 9 | Carboxypeptidase * | | | |
| Api m 10 | Icarapin * | | | |
| Api m 11 | Major royal jelly protein * | | | |
| Api m 12 | Vitellogenin * | | | |

www.allergen.org & www.allergome.org





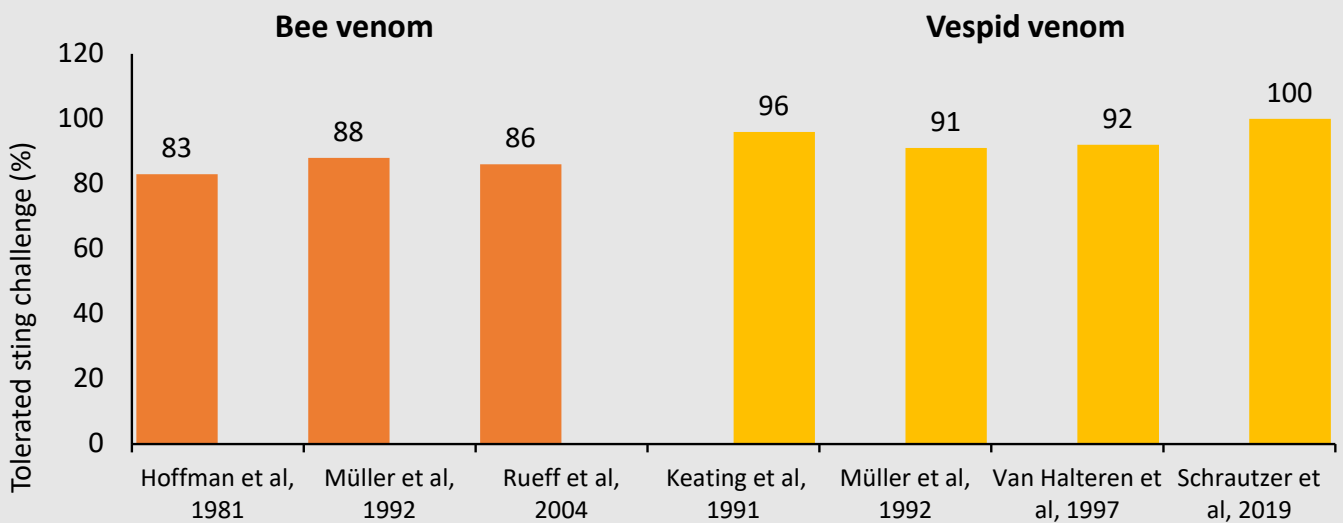
Summary – diagnosis

- Sensitivity of the diagnostics with bee venom is always lower
- sIgE determination and intradermal tests have comparable sensitivity
- Molecular allergy diagnosis: limited benefit due to low sensitivity
- Lowering the cut-off in patients with low tIgE (<30) is useful
- Combination of tests (sIgE & skin tests) increases sensitivity

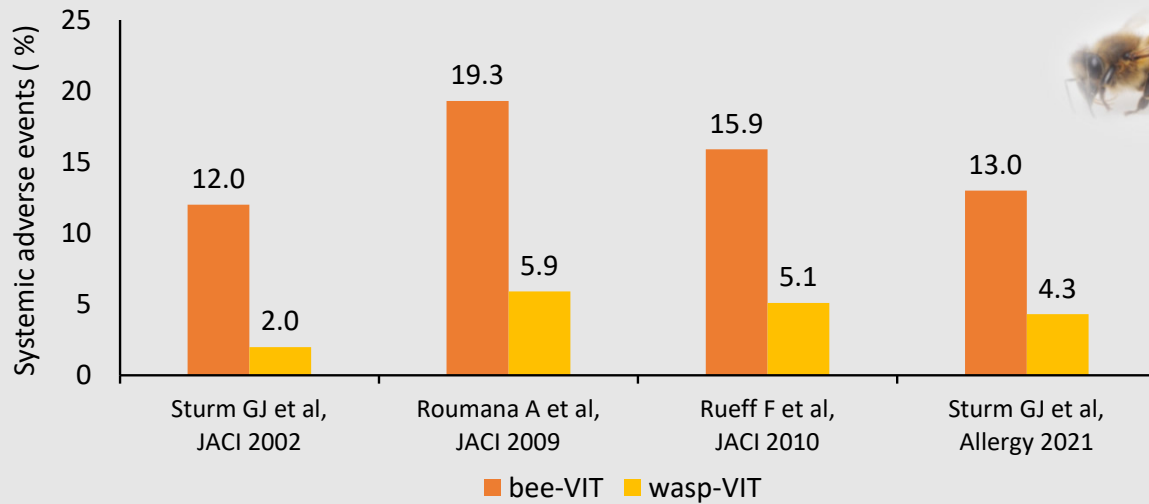


Therapy

VIT is highly effective

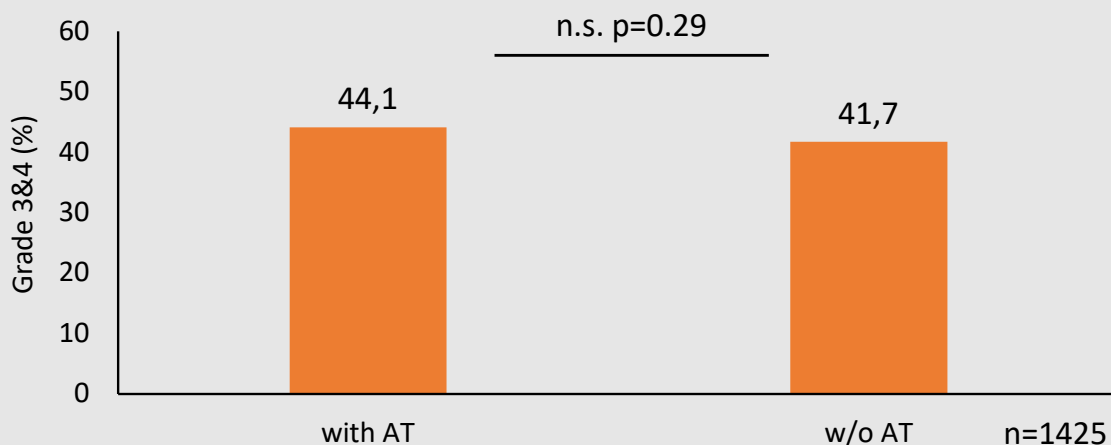


Bee venom: Risk factor #1 for adverse events



Bee venom: 3.1 – 6.0-fold higher risk for systemic adverse events

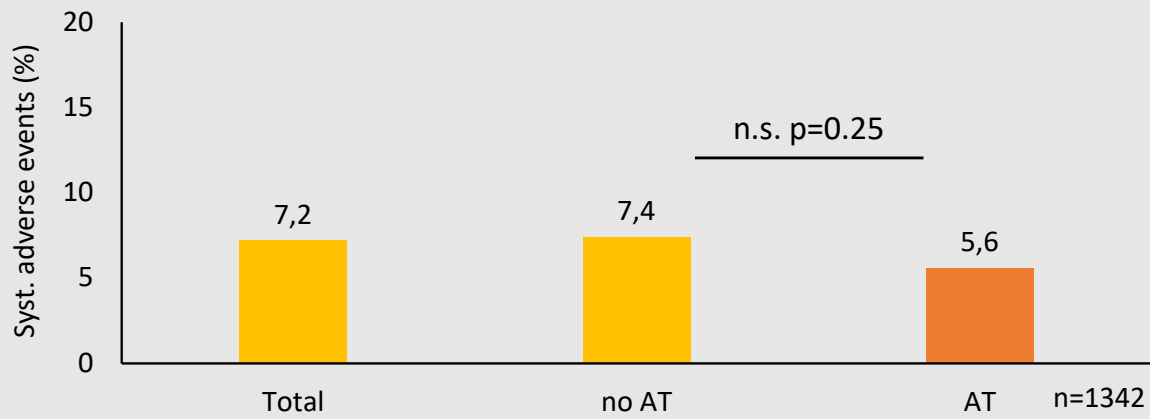
ACE inhibitors & β -Blocker: Influence on initial reaction



Sturm GJ et al, *Allergy* 2021.

Antihypertensive drugs do not aggravate sting reactions

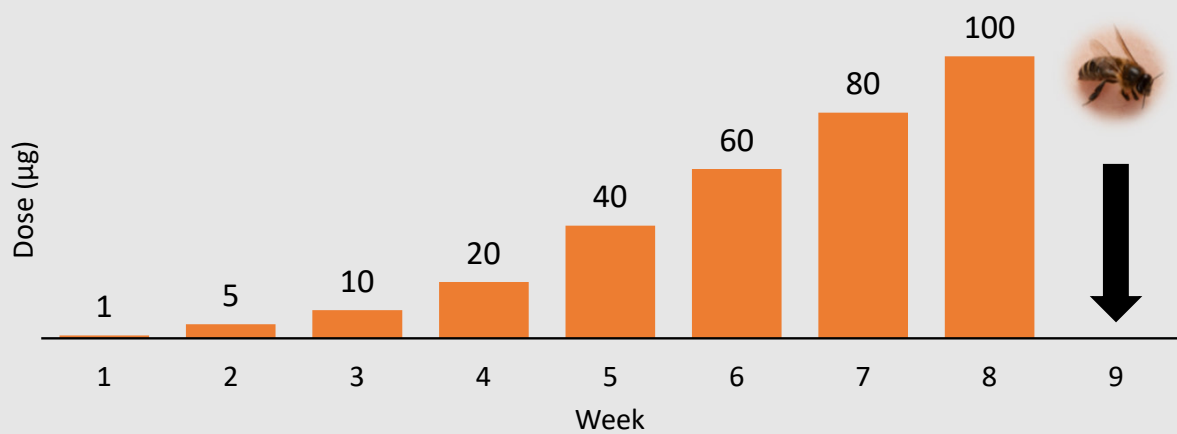
ACE inhibitors & β -Blocker: systemic adverse events



Sturm GJ et al, *Allergy* 2021.

- 338 (25%) of 1342 patients took antihypertensive drugs
- Adverse events not more frequent (even lower)

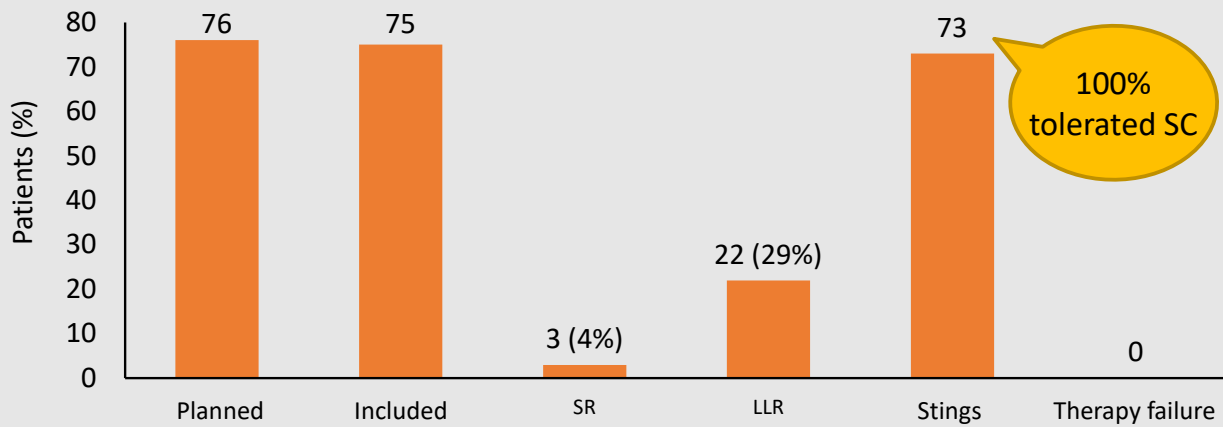
7-week up dosing protocol with depot venom preparations



EudraCT number 2015-002769-44.

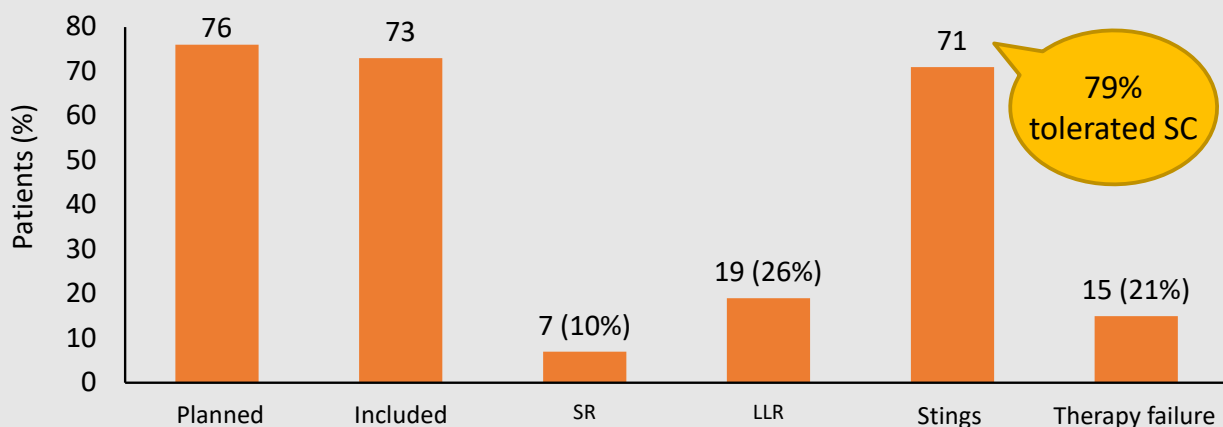


7-week up-dosing protocol – vespid venom



Schrautzer C et al, *Allergy* 2020.

7-week up-dosing protocol – bee venom



Arzt-Gradwohl, Cerpes U et al, *Allergy* 2025

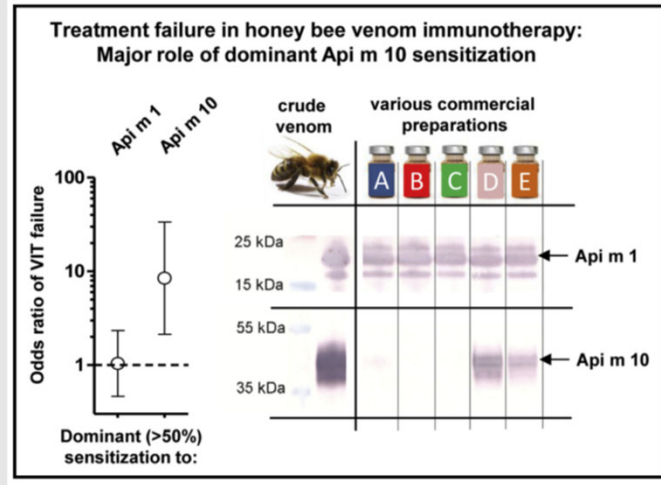
Predominant Api m 10 sensitization: Risk for treatment failure?

- 115 patients allergic to bee venom
- 79 responder
- 36 treatment failure

Findings:

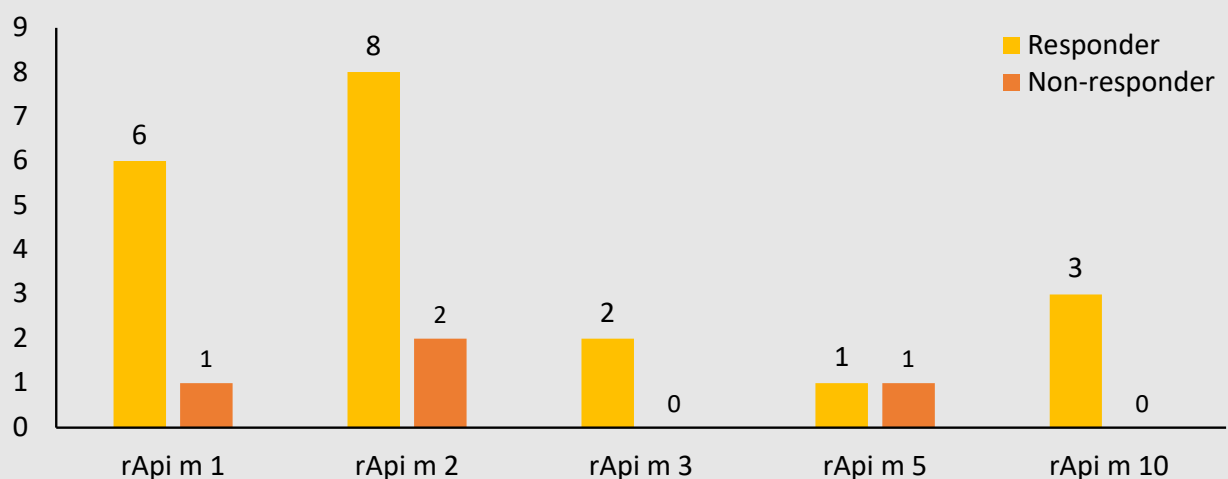
- 8-fold higher risk for therapy failure
- **Some venom preparations:** higher amount of Api m 10

GRAPHICAL ABSTRACT



Frick M... Jakob T, *JACI* 2016.

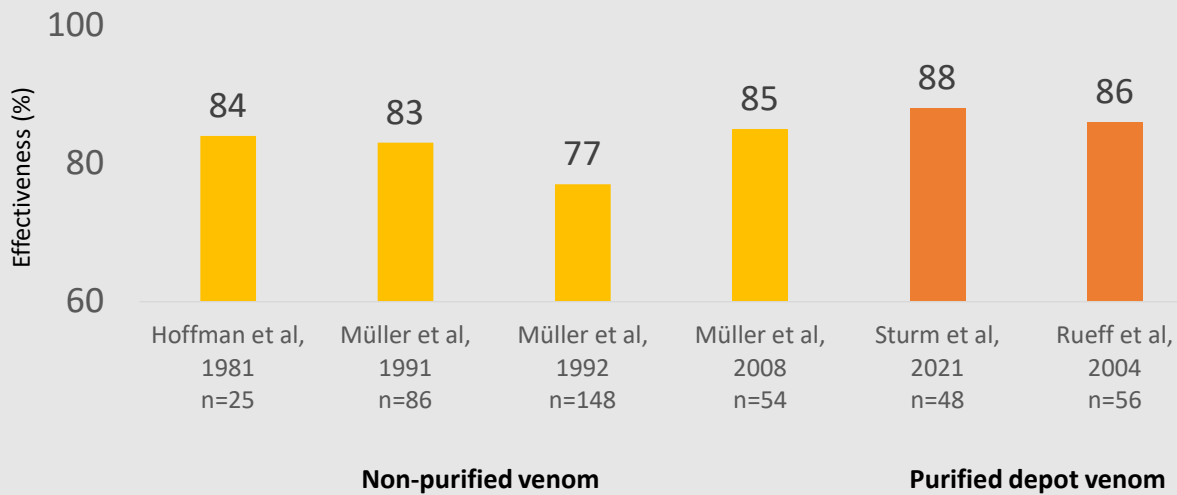
Treatment failure with depot bee venom preparation



Sturm GJ et al, *Allergy* 2022

Other predominant sensitizations might also contribute to treatment failure

No evidence that non-purified bee venom is superior



Why the Api m 10 story didn't fully convince us

1

Data did not support that purified venoms were less effective

2

Fragile evidence due to low number of patients

3

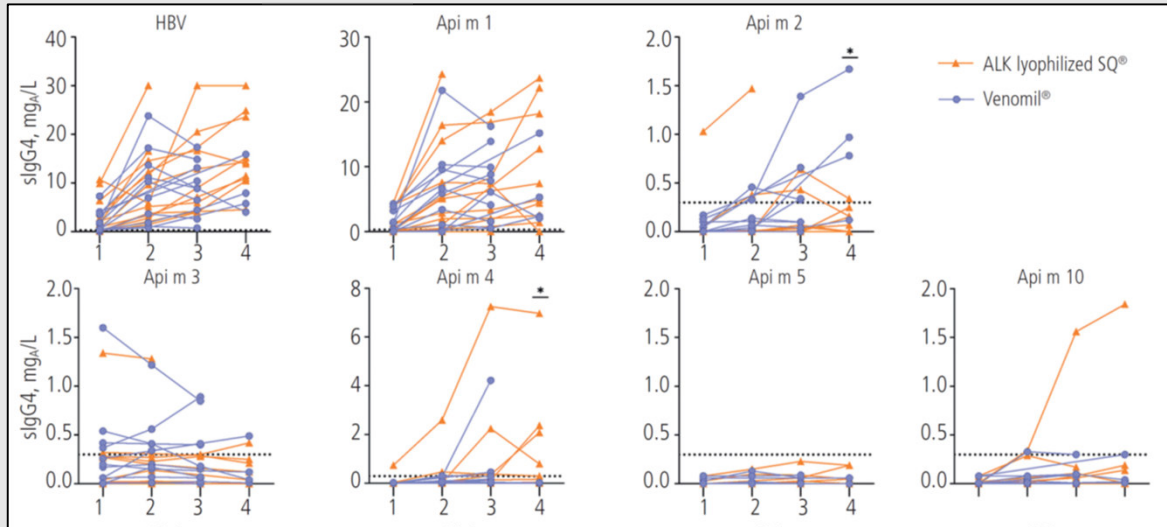
Other predominant sensitizations appeared to matter as well

4

No evidence from the literature that non-purified venom is superior



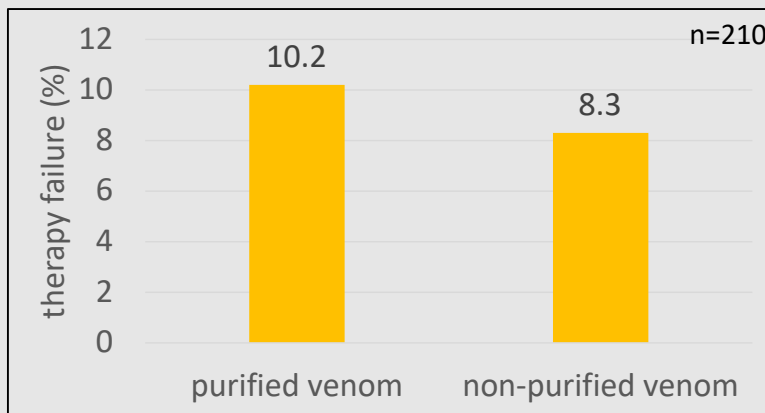
Coming full circle



No IgG4 induction against low-abundant allergens, independent of the venom used

Blank S.....Jakob T, //ACI online ahead of print.

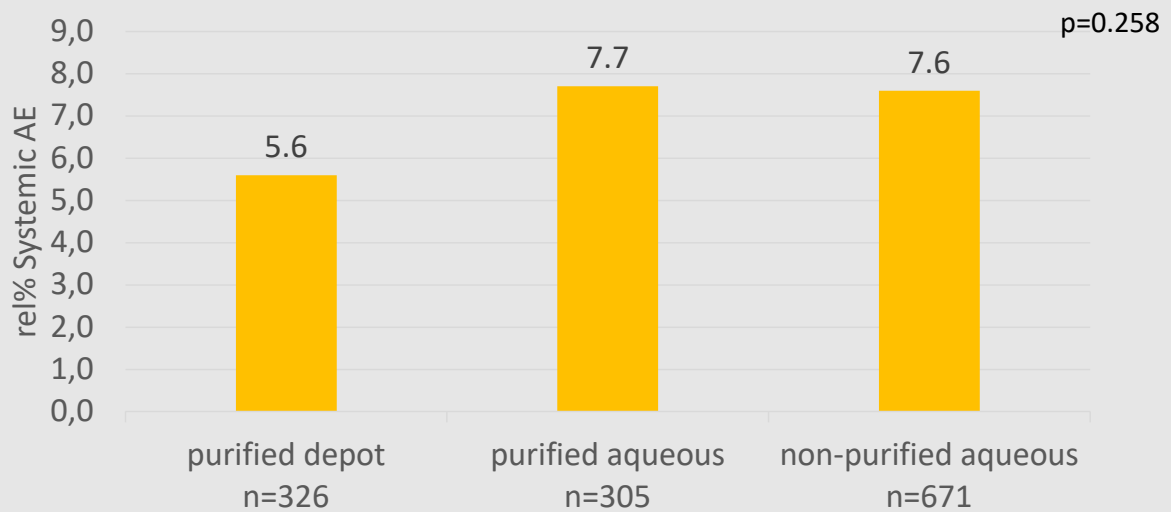
No difference in effectiveness



OR: 1.25; 95% CI: 0.42-3.98; p=0.804

Arzt-Gradwohl et al, J Investig Allergol Clin Immunol 2023

No difference in the frequency of systemic AE



Arzt-Gradwohl et al, J Investig Allergol Clin Immunol 2023



Summary – treatment

- Venom immunotherapy is highly effective; trend to shorter protocols
- Most important risk factor for adverse events: treatment with bee venom
- ACEI and betablockers are safe in patients with venom allergy
- Bee venom: predominant sensitizations to minor allergens may be a risk factor for treatment failure
- Comparable effectiveness of available venom preparations