

The Value of Real World evidence

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Wiesbaden, Germany***



Disclosure

Clinical studies:

- ALK-Abello, Danmark, Allergopharma, Germany, Artu-Biologicals, Netherlands, Bencard, Great Britain, Bionorica, Germany, Biomay, Austria, Boehringer Ingelheim, Germany, Cytos, Switzerland, HAL, Netherlands, Hartington, Spain, GSK, Great Britain, Leti, Spain, Lofarma, Italy, Novartis, Switzerland, MEDA, Germany, MSD, USA, Phadia / Thermofisher, Sweden, Optima, Germany, Roxall, Germany; DFG; BMBF, EU-Kommission; VW-Stiftung; Fresenius-Stiftung; Hochschulfond BW

Lecturing fee:

- ALK-Abello, Danmark, Allergopharma, Germany, Bencard, Great Britain, Bionorica, Germany, Boehringer Ingelheim, Germany, Cytos, Switzerland, HAL, Netherlands, Hartington, Spain, GSK, Great Britain, Leti, Spain, Lofarma, Italy, Novartis, Switzerland, MEDA, Germany, MSD, USA, Phadia / Thermofisher, Sweden, Optima, Germany, Roxall, Germany

Scientific advice:

- ALK-Abello, Danmark, Allergopharma, Germany, Bionorica, Germany, Boehringer Ingelheim, Germany, Cytos, Switzerland, Hartington, Spain, GSK, Great Britain, Leti, Spain, Lofarma, Italy, Novartis, Switzerland, MEDA/Mylan, USA/Germany

Health Research

biomedical basic research

experimental,
animal,
preclinical,
ex vivo / in vitro

experiments



clinical research

clinical studies
Phase I-III

Controlled
trials

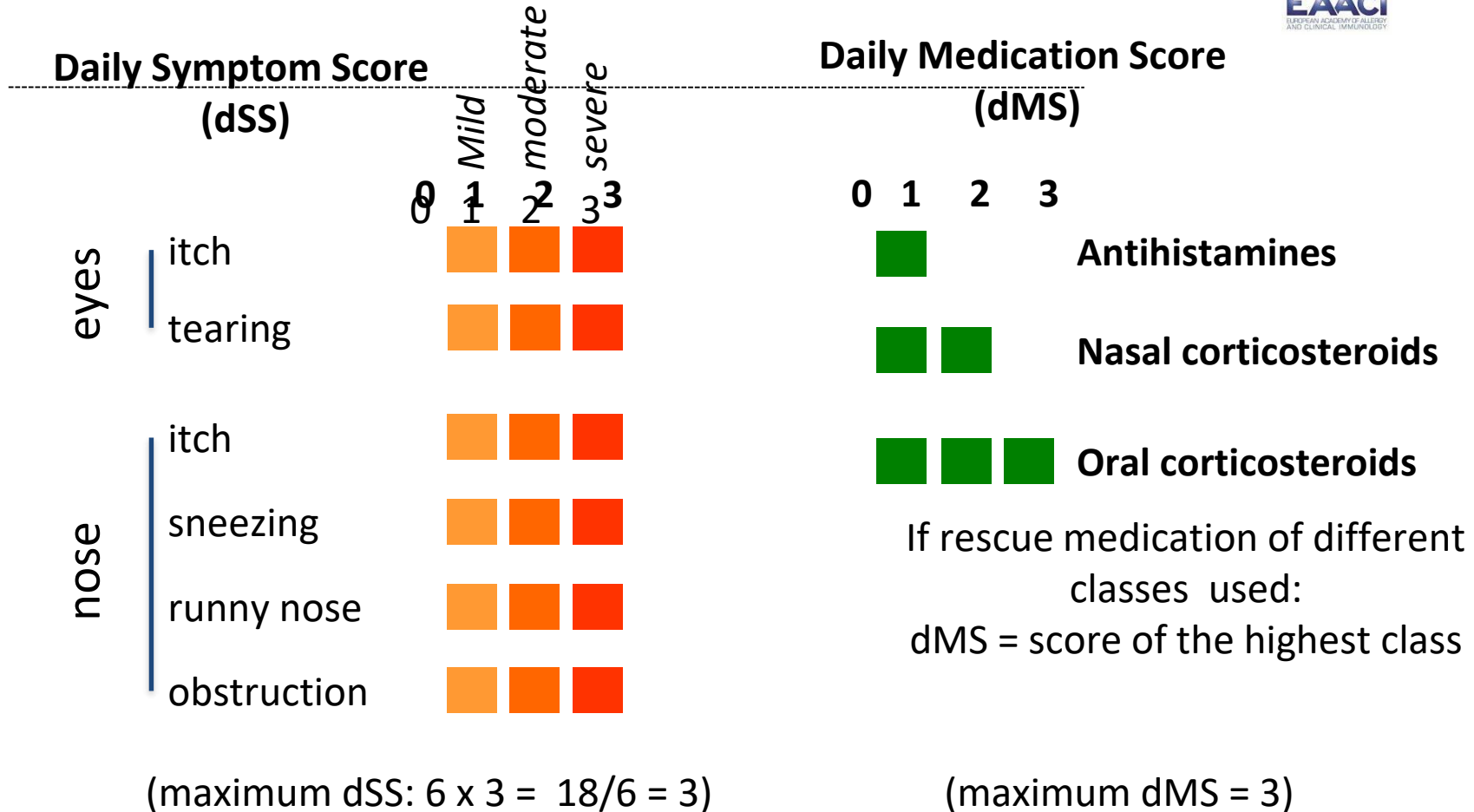


healthcare research

observational
studies,
Public Health-
research,
epidemiology,
Health economics

„Real-world“-
trials

Combined Symptom and Medication Score (CSMS)



Primary endpoint: CSMS = dSS + dMS (range 0-6)

Patient needs in AR

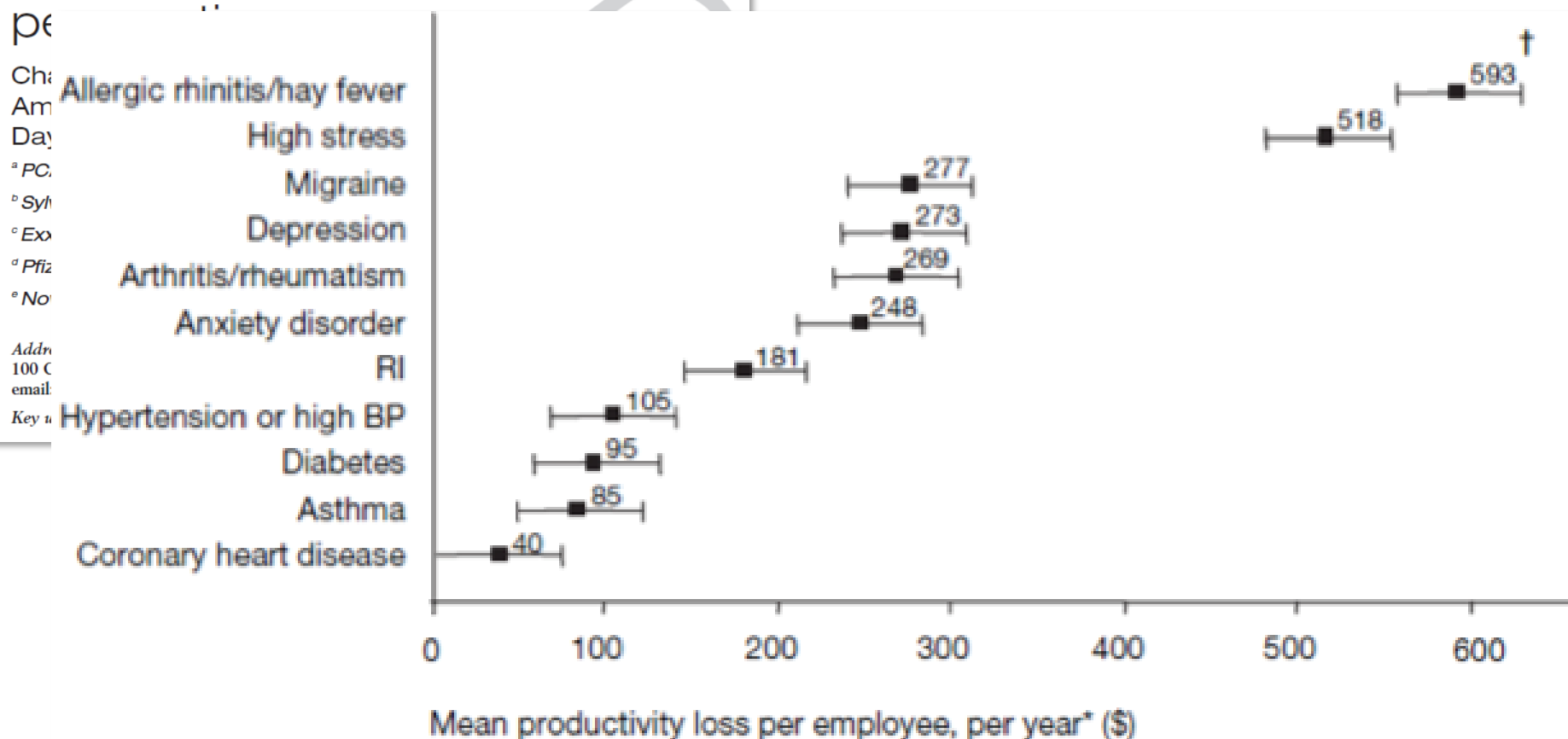
A new instrument for the assessment of patient-defined benefit in the treatment of allergic rhinitis

N. Franzke¹, I. Schäfer¹, K. Jost¹, C. Blome¹, S. J. Rustenbach¹, K. Reich², M. Reusch³, M. Maurer⁴ & M. Augustin¹

¹CVderm – German Center for Health Services Research in Dermatology, Institute for Health Services Research in Dermatology, University Clinics of Hamburg; ²Dermatologikum Hamburg; ³Dermatology Practice Niendorf, Hamburg; ⁴Department of Dermatology and Allergy, Allergie-Centrum-Charité/ECARF, Charité – Universitätsmedizin Berlin, Berlin, Germany

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Needs	% quite/very important*	Mean*	SD*
...to be able to stay outdoors without symptoms	93.2	3.7	0.6
...to no longer have a runny or stuffed up nose	90.4	3.6	0.7
...to be healed of all symptoms	89.2	3.6	0.8
...to be able to breathe through my nose more freely	88.5	3.5	0.8
...to not have itching on the eyes, nose or palate anymore	85.4	3.6	0.7
...to not have sneezing impulses	77.7	3.2	1.1
...to have an easily applicable treatment	77.5	3.4	0.9
...to have confidence in the therapy	76.7	3.5	0.8
...to not have burning or watery eyes anymore	76.0	3.6	0.8
...to feel less fatigued or groggy	75.5	3.5	0.8
...to be able to engage in normal leisure activities	69.9	3.4	0.8
...to be less dependent on doctor and clinic visits	64.1	3.2	1.1
...to be able to sleep better	61.8	3.4	0.9
...to have fewer side effects	61.2	3.2	1.1
...to be more productive in everyday life	60.2	3.2	0.9
...to have fewer out-of-pocket treatment expenses	59.2	3.0	1.3
...to be able to concentrate better at work	56.9	3.3	0.9
...to have no fear that the disease will become worse	50.0	3.2	1.0
...to need less time for daily treatment	50.0	2.9	1.3
...to experience a greater enjoyment of life	47.6	3.4	0.9
...to feel less depressed	46.1	3.3	1.1
...to feel less irritated	43.7	3.1	1.1
...to feel more comfortable showing yourself	33.3	2.8	1.2
...to be less burdened in your partnership	33.0	2.7	1.4
...to be able to have a normal sex life	27.5	2.7	1.4



Pollen concentration in nature vs challenge chamber

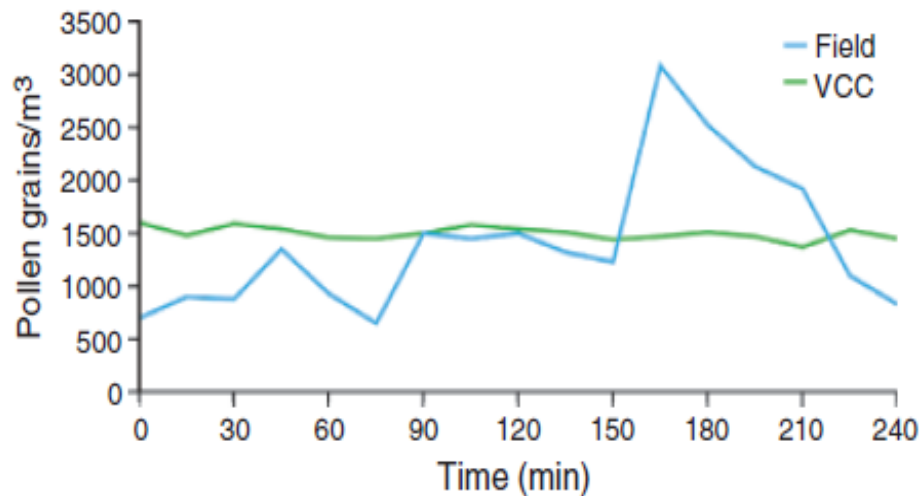


Fig. 9. Fluctuation of grass pollen count during 4 h in a park setting and in the Vienna Challenge Chamber (VCC).

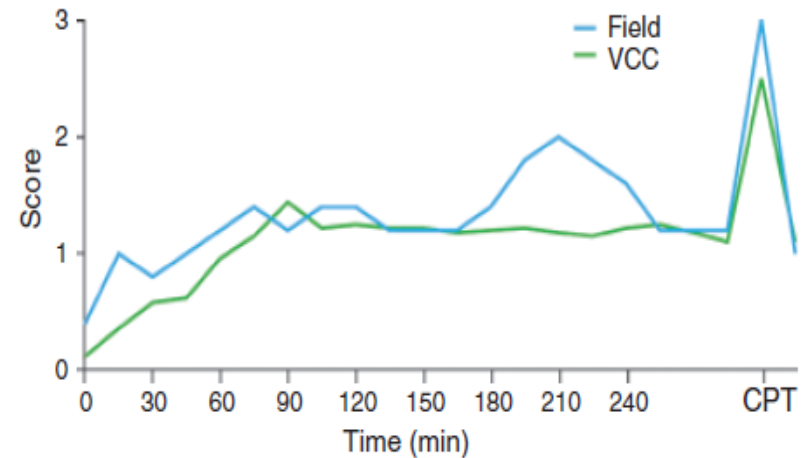
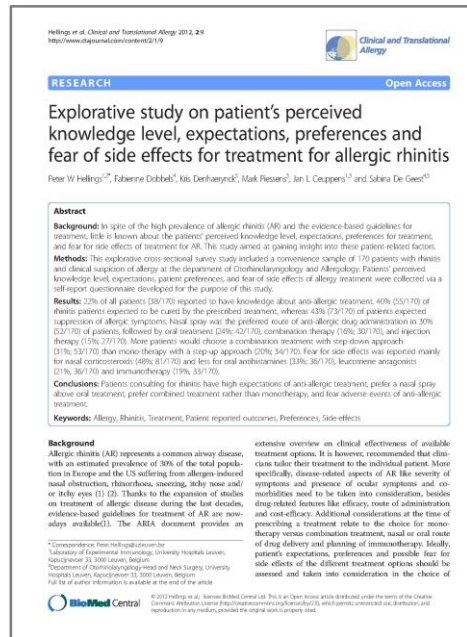


Fig. 10. Comparison of subjective eye itching using the conjunctival provocation test (CPT). This symptom was scored every 15 min on a 0-3 scale, in subjects studied in the Vienna Challenge Chamber (VCC) or in a park setting.

AR patients have high expectations from treatment



- **40%:** expected to be cured by Tx
- **43%:** expected suppression of symptoms
- Preferred therapy
 - Nasal spray: **30%**
 - Oral treatment : **24%**
 - Combination: **16%**
- Approach
 - **31%:** combination Tx with step-down approach
 - **20%:** mono-therapy with step-up approach

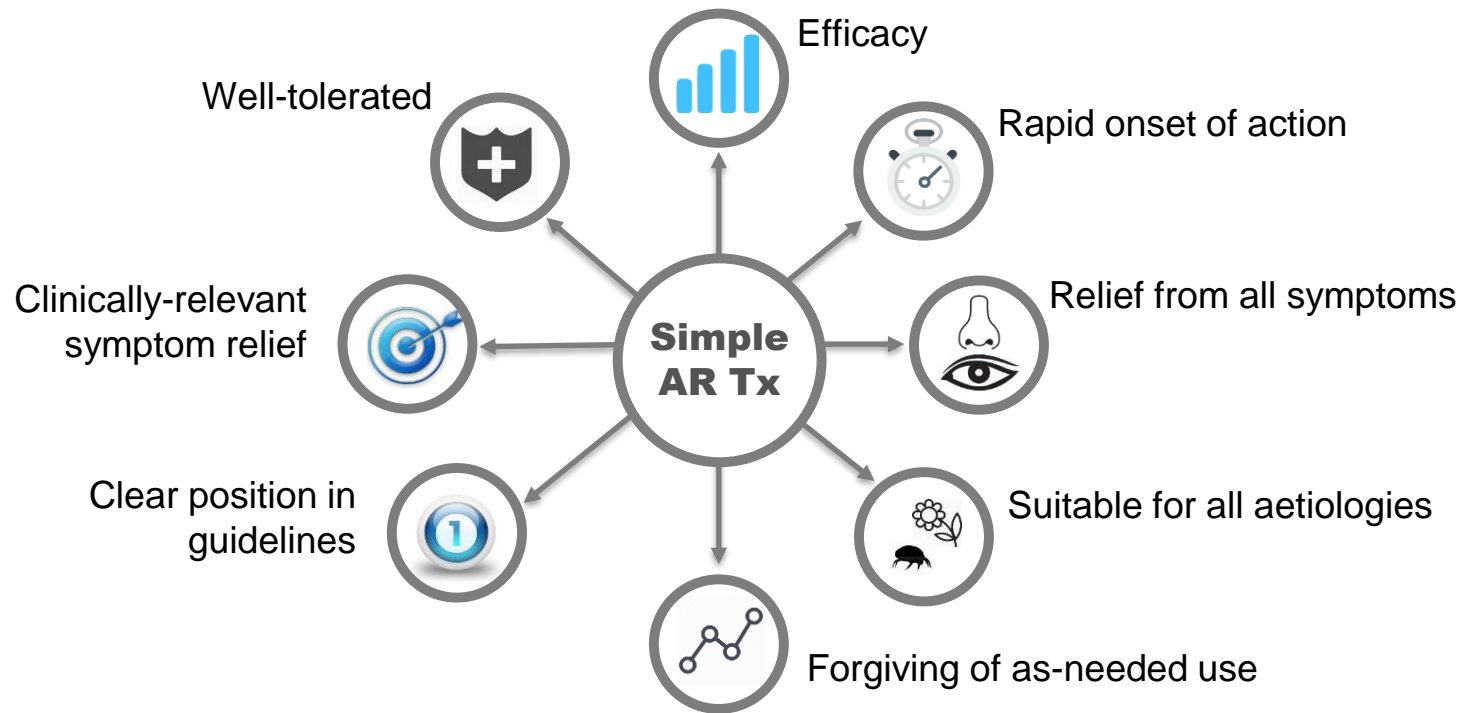
The AR landscape in the Real World is complex



1. Marple et al, Otolaryngol Head & Neck Surg 2007;
2. Price et al, Clin Transl Allergy 2015; 3. Data on file;
4. Canonica et al, Allergy 2007; 5. Schatz et al, Allergy 2007; 6. Hellings et al, Allergy 2013; 7. Scadding et al, Rhinol 2018; 8. Bachert et al, Clin Transl Allergy 2018; 9. Hellings et al, Clin Transl Allergy 2012; 10. Acaster et al, EAACI 2012; 11. Brozek et al, JACI 2017; 12. Scadding et al, Clin Exp Allergy 2017; 13. Bousquet et al, JACI 2016

AR: allergic rhinitis; Tx: treatment

What patients want: simplification of AR treatment



AR: allergic rhinitis; Tx: treatment

Disorganized AR treatment in real-life¹



- Perceived knowledge exceeds actual knowledge

- **29%** of patients NOT know class of allergy medication they were taking¹



- Changing treatments

- **26%** of patients are constantly trying different medications to find one that 'works'¹



- Confusion

- **42%** of patients are confused by all the different AR medications¹



- Non-compliance

- **64%** of patients fail to take their AR medication consistently¹
 - As needed use is associated with more breakthrough symptoms²

A single medication with a more rapid onset of action would be advantageous

1. Marple et al, Otolaryngol Head & Neck Surg 2007; 2. Khan et al, J Laryngol Otol 2010
AR: allergic rhinitis

Reasons for non-compliance

Main causes for general non-compliance^{1,2}

1. Frequency and complexity of treatment

2. Adverse events (real or imagined)

3. Poor communication

4. Psychosocial factors

5. Rejection of diagnosis

Improving compliance with treatment³

1. Keep it simple

2. Deliver it effectively

3. Avoid its problems

4. Call it medicine (not drug)

5. Provide it readily (samples)

6. Review its usage

7. Link it with lifestyle

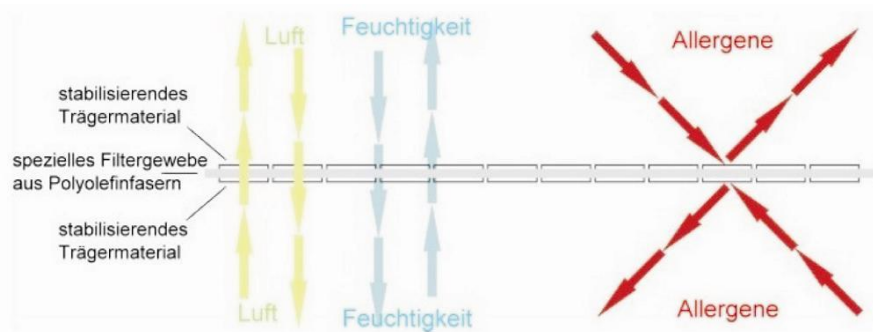
8. Put it in writing

9. Support is psychosocially

10. Minimize its cost

- Therapeutic principals in allergies

- > Allergen avoidance
- > Symptomatic therapy
- > specific immunotherapy



Avoidance of mite allergen is not effective

- 1122 patients with asthma (18 – 50 years)
- 65% sensitization to house dust mites
- DBPC, Encasings, endpoint: PEF

	Intervention	Control
PEF	411.0 + 93.2	415.5 + 93.4
Symptoms	1.35 + 0.76	1.35 + 0.77
QoL	33.1 + 16.3	32.6 + 16.9

- PEF: \emptyset difference
- Symptoms: \emptyset difference
- ICS: \emptyset difference
- allergen-concentration after
12 month: no difference
between verum and Placebo

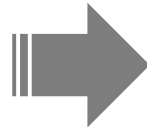


Conclusion: Allergen-impermeable covers, as a single intervention for the avoidance of exposure to dust-mite allergen, seem clinically ineffective in adults with asthma.

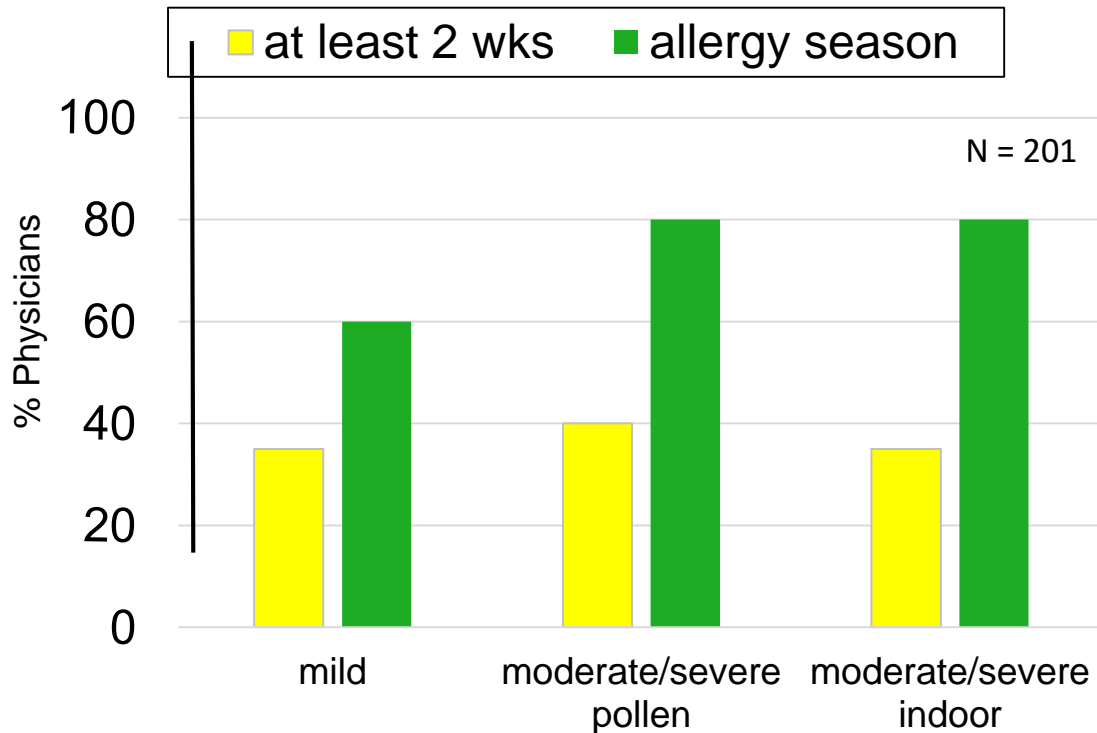
Simplicity of treatment is a desired attribute & key to success

Evidence exists in the literature for:

- Determinants of treatment outcomes^{1,2}
- Determinants of treatment compliance^{3,4}
- But NOT what constitutes a simple treatment



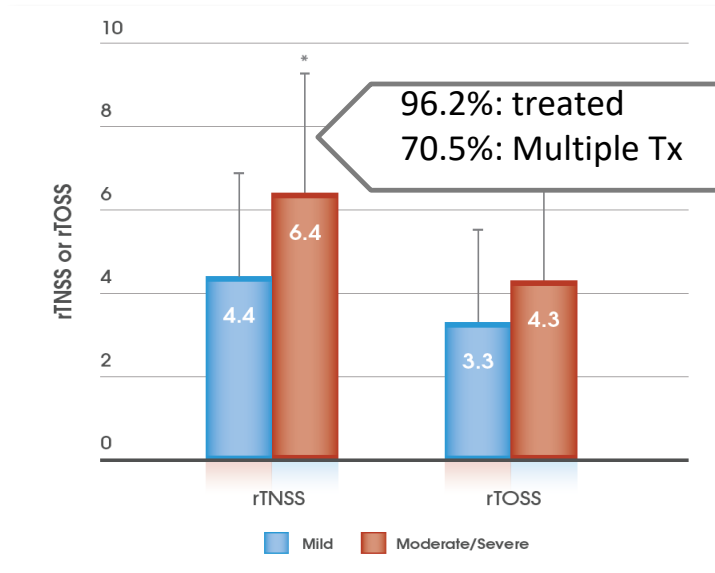
What we prescribe: Continuous treatment



AR treatments are most often prescribed for continuous use during the whole allergy season

Breakthrough symptoms

- Patients frequently experience breakthrough symptoms whilst on therapy¹
 - Need for a more rapidly acting AR treatment for fast relief when symptoms breakthrough



- In Europe **32.8%** of patients report moderate-to-severe nasal and ocular symptoms on therapy²

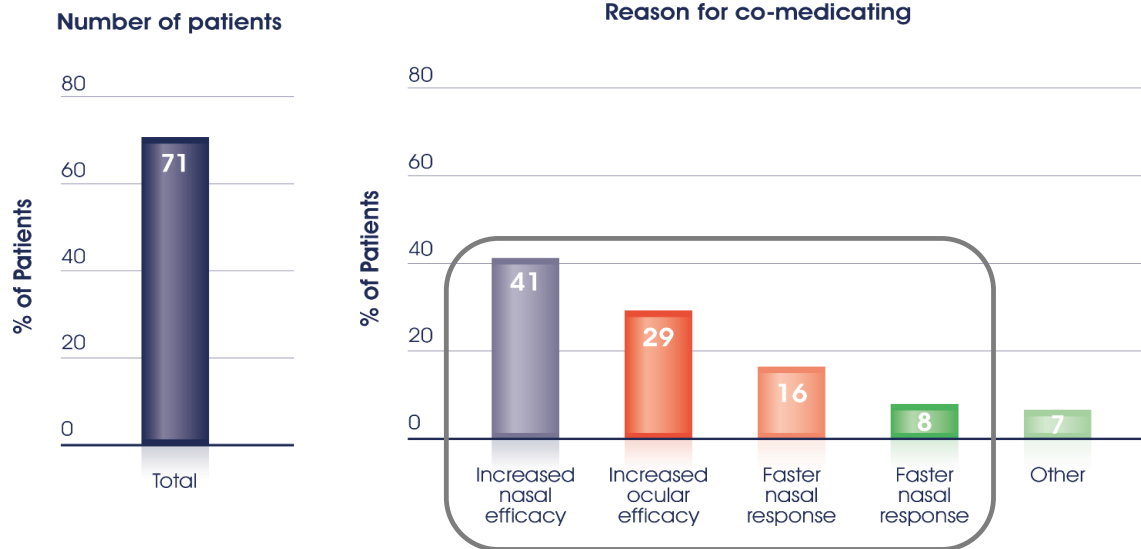


- In the U.S. **44.0%** of patients report suffering from nasal and ocular symptoms on treatment
 - **23.7%** report symptom severity as moderate/severe³

1. Price et al, Clin Transl Allergy, 2015; 2. Canonica et al, Allergy 2007; 3. Schatz et al, Allergy 2007
Tx: treatment; rTNSS: reflective total nasal symptom score; rTOSS: reflective total ocular symptom score

Patients co-medicate searching for better & faster symptom relief

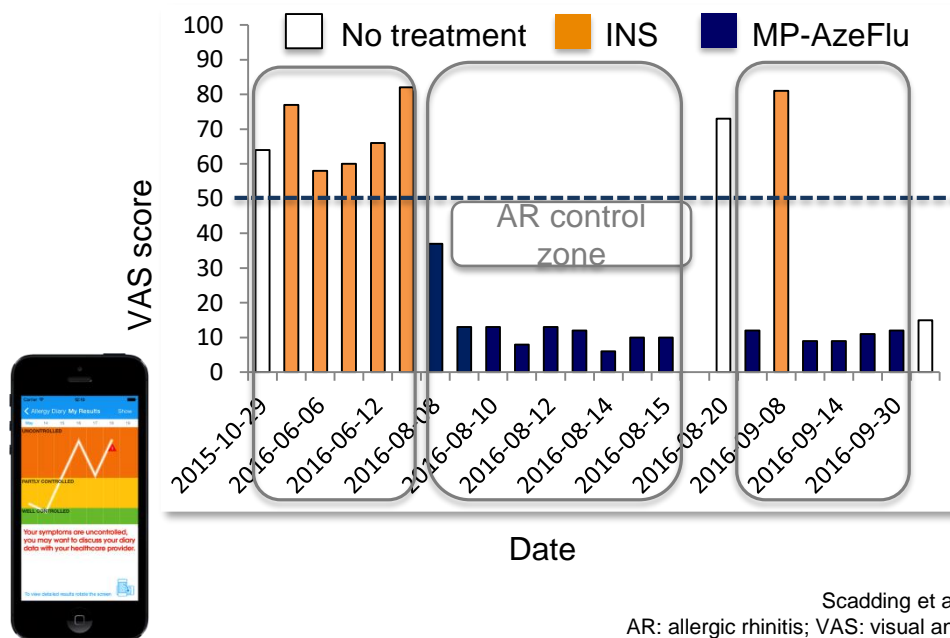
% moderate/severe patients on ≥ 2 AR medications



Price et al, Clin Transl Allergy 2015
AR: allergic rhinitis

Rapid AR treatment switching in real life

- The true AR world as revealed by *Allergy Diary*
- AR treatment options and VAS scores from User 1 (Sweden)

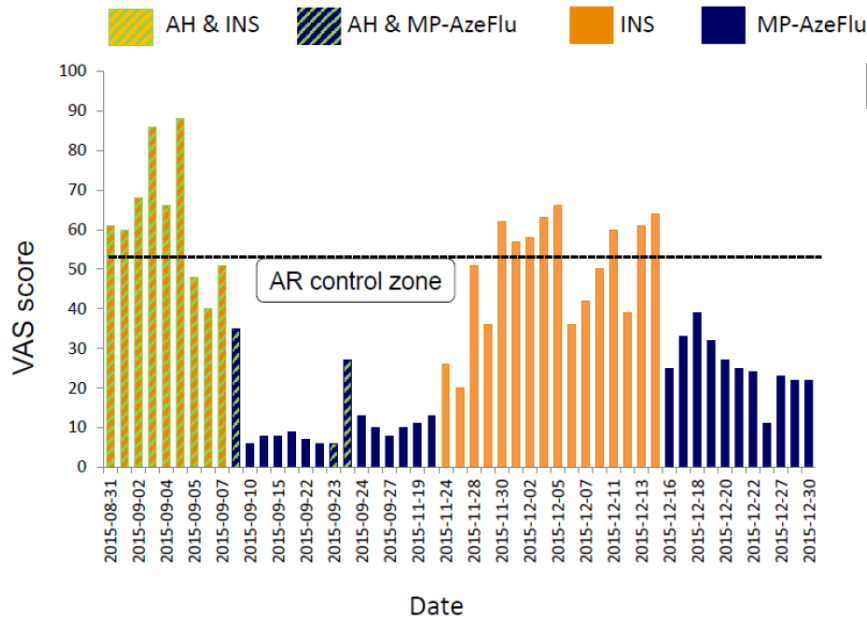


- Patients rapidly switch AR treatment
 - If it's not working they switch
- Lack of control on INS monotherapy
- AR control achieved on MP-AzeFlu
- Users stop treatment when symptoms are well-controlled
- Users do not log symptoms every day

Patients need a treatment which has a more rapid onset AND is more effective than an INS

Rapid switching & poly-pharmacy in real life

- AR treatment options and VAS scores from User 2



- Polypharmacy use
 - AH + INS
- Rapid switching
- Control achieved with MP-AzeFlu
- Lack of control on AH + INS or INS monotherapy

Patients need a single treatment which has a more rapid onset AND is more effective than an INS



Bachert et al, Clin Transl Allergy 2018;In press

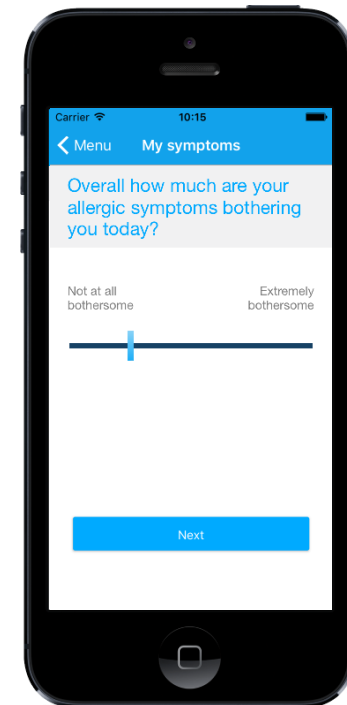
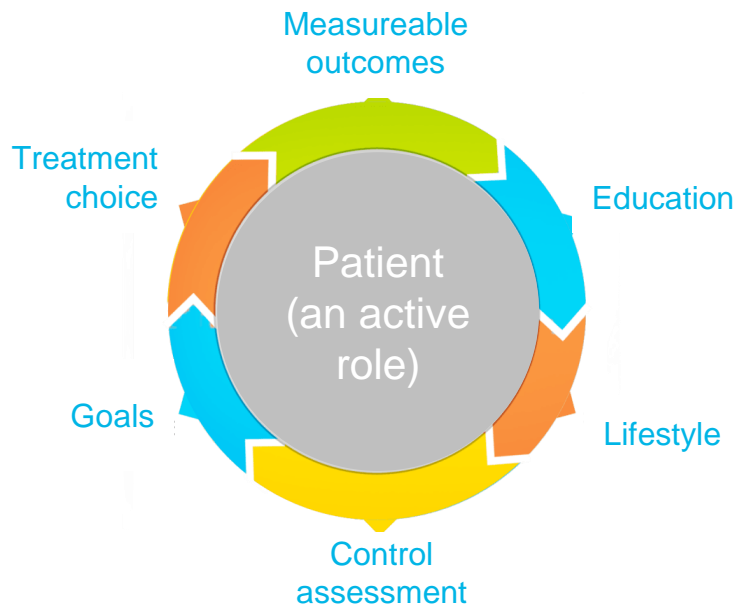
AR: allergic rhinitis; VAS: visual analogue scale; AH: anti-histamine; INS: intranasal corticosteroid



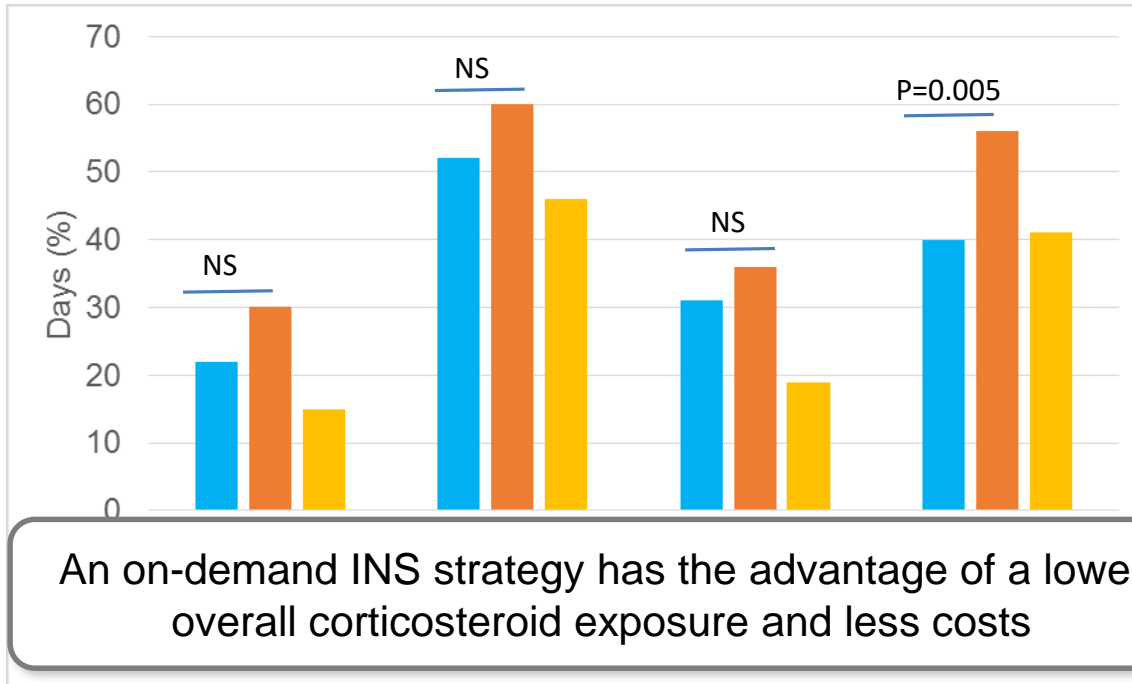
ARIA Phase 3:

The *Allergy Diary* strengthens change management

- Patient empowerment & the finger approach



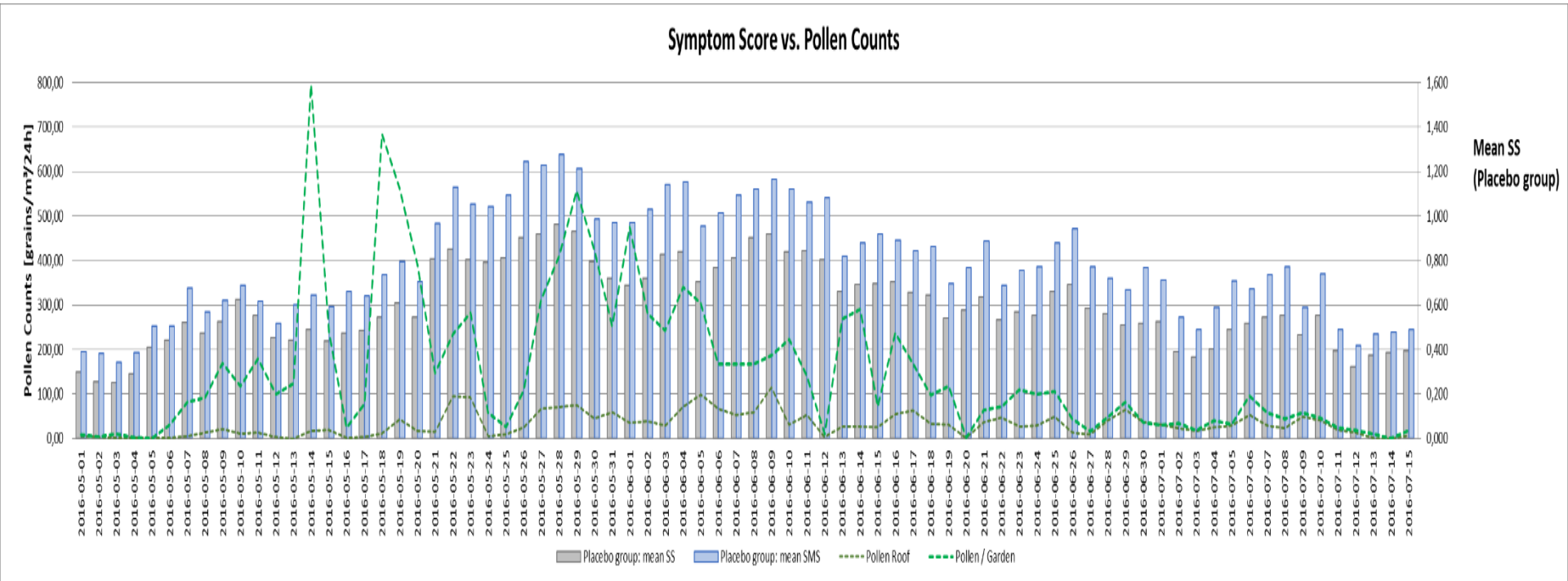
Efficacy of continuous vs on demand treatment is debated



- % symptom-free days in favour of INS on demand (30% vs 22%)
- % symptom-free eye symptoms significantly in favour of INS on demand (40% vs 56%)
- INS on demand group used 61% less fluticasone ($p < 0.0001$)







Wartna et al, Allergy 2017
INS: intranasal corticosteroid; AH: anti-histamine

Pollen concentration vs symptoms



courtesy Petra Zieglmayer, Vienna

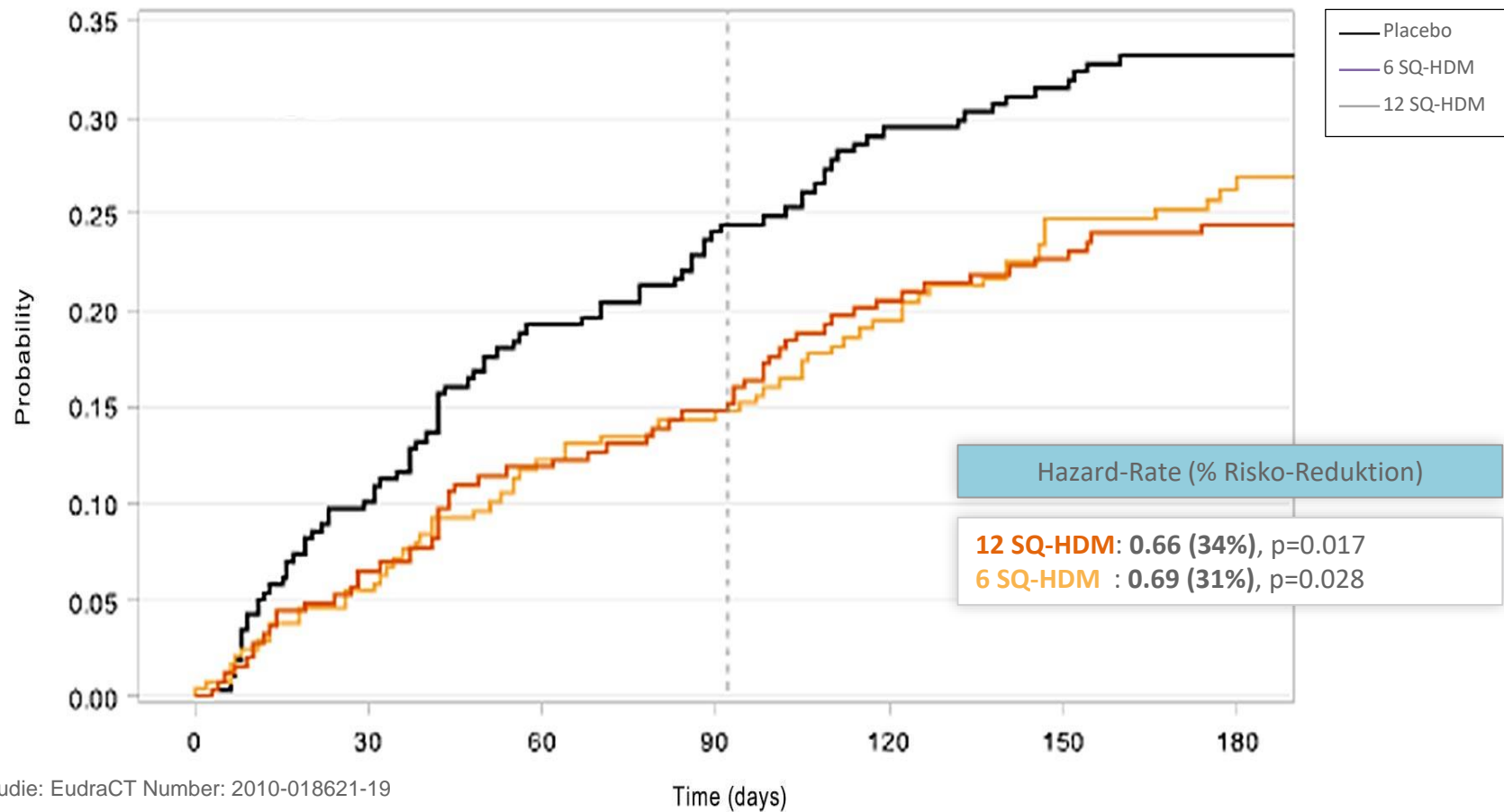
Current state of play: onset of action by drug class

OAH	INAH	INS	INS + OAH	MP-AzeFlu
			 	
LOR: 75 mins ¹ CET: 60 mins ¹ DES: 150 mins ² FEX: 60 mins ³ BIL: 60 mins ⁴	AZE: 15 mins ¹ OLO: 30 mins ⁵	FF: 8 hrs ⁶ FP: 8 hrs MF: 12 hrs ⁷ BUD: 12 hrs ⁸	FP + LOR: 150 mins ⁹	MP-AzeFlu: 5 mins ⁹

1. Tenn et al Allergy Asthma Clin Immuno 2018; 2. Horak et al, Curr Med Res Opin 2006; 3. Berkowitz et al, Allergy Asthma Proc 2004; 4. Horak et al, Inflamm Res 2010; 5. Patel et al, Allergy Asthma Proc 2007; 6. Kaiser et al, JACI 2007; 7. Nasonex SPC <https://www.medicines.org.uk/emc/medicine/9748>; 8. Fokkens et al, AAAI 2002; 9. Bousquet et al, JACI Pract 2018

SLIT in (uncontrolled) Asthma

Time until mean or severe asthma-exacerbation



Original article

Cost effectiveness analysis of immunotherapy in patients with grass pollen allergic rhinoconjunctivitis in Germany

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**Excellent
cost effectiveness of Allergen-
Immunotherapy (AIT)
in Allergic Rhinitis**

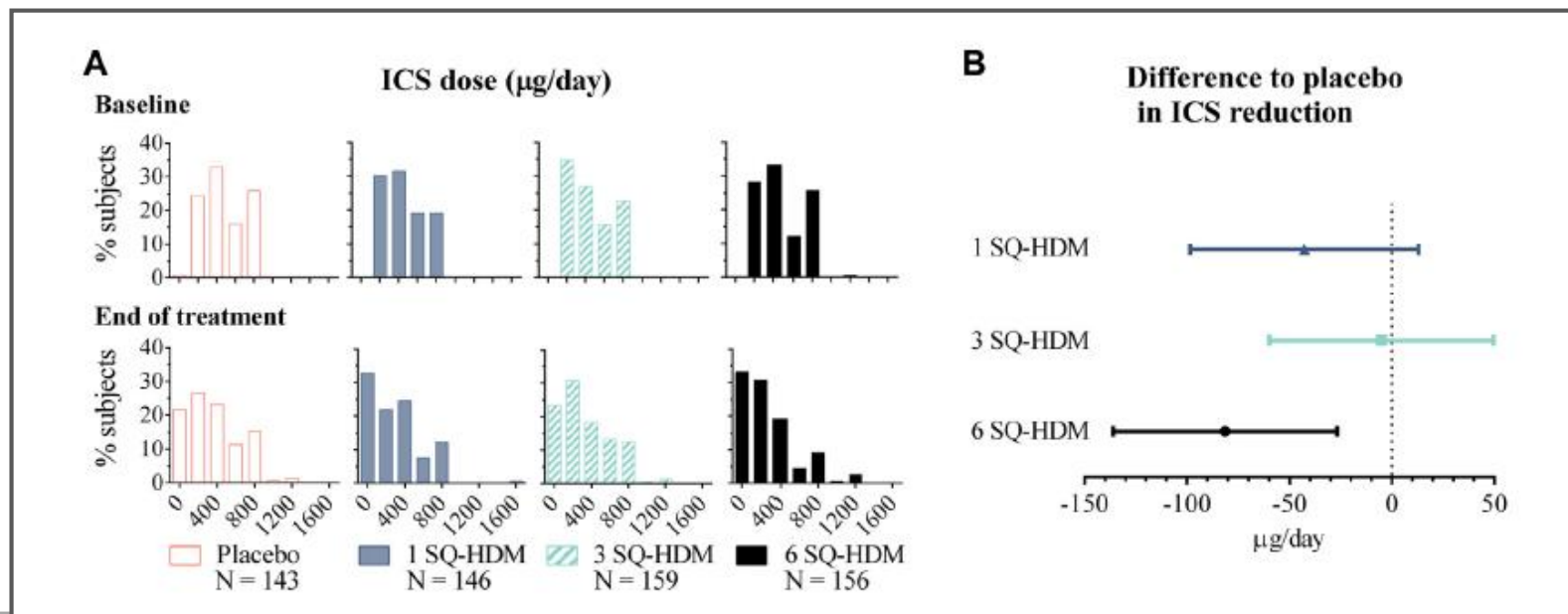
Methods:

The costs and outcomes of 3-year treatment were assessed over 3 years using a Markov model. Treatment efficacy was estimated using an indirect comparison of available clinical trials with placebo as a common comparator. Estimates for immunotherapy discontinuation, occurrence of asthma, health state utilities, drug costs, resource use, and healthcare costs were derived from published sources. The analysis was conducted from the insurer's perspective including public and private health insurance payments and co-payments by insurers. Outcomes were reported as quality-adjusted life years (QALYs) and symptom-free days. The uncertainty around incremental model results was tested by means of extensive deterministic univariate and probabilistic multivariate sensitivity analyses.

**Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control:
A randomized, double-blind, placebo-controlled trial**

Background: Investigations meeting **current standards are limited** for the effect of house dust mite (HDM) allergy immunotherapy in asthmatic patients.

Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: A randomized, double-blind, placebo-controlled trial



Background: Investigations meeting current standards are limited for the effect of house dust mite (HDM) allergy immunotherapy in asthmatic patients.

Conclusion: *Efficacy in mild-to-moderate asthma of 6 SQ-HDM relative to placebo was demonstrated by a **moderate** statistically significant reduction in the ICS dose required to maintain asthma control.*

Long-lasting effects of sublingual immunotherapy according to its duration: A 15-year prospective study

Maurizio Marogna, MD,^a Igino Spadolini, MD,^b Alessandro Massolo, BS,^c Giorgio Walter Canonica, MD,^d and Giovanni Passalacqua, MD^d *Varese, Florence, and Genoa, Italy, and Calgary, Alberta, Canada*

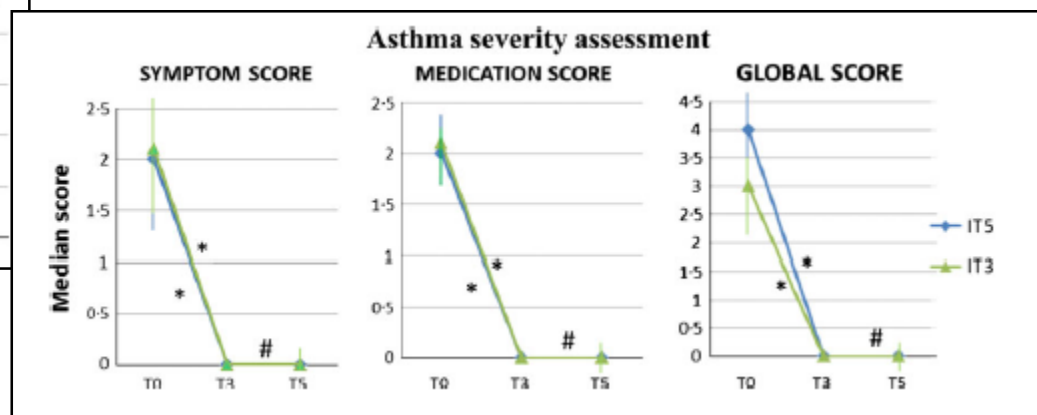
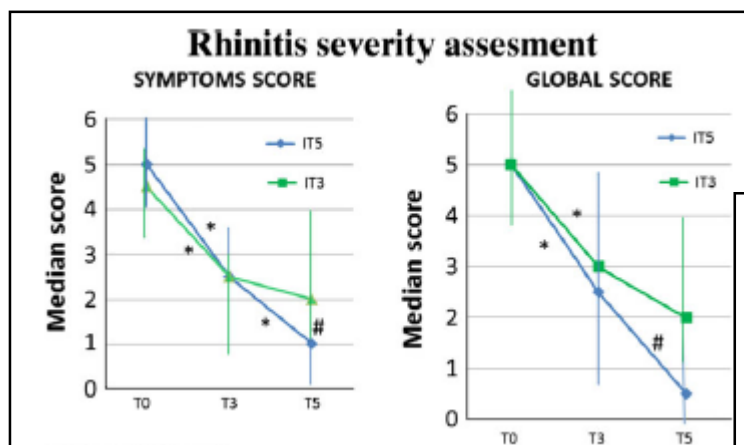
Data on the long-term effects of sublingual immunotherapy (SLIT) **are sparse**, and the optimal duration of treatment is a matter of debate.

Long-lasting effects of sublingual immunotherapy according to its duration: A 15-year prospective study

Maurizio Marogna, MD,^a Igino Spadolini, MD,^b Alessandro Massolo, BS,^c Giorgio Walter Canonica, MD,^d and Giovanni Passalacqua, MD^d *Varese, Florence, and Genoa, Italy, and Calgary, Alberta, Canada*

Data on the long-term effects of sublingual immunotherapy (SLIT) are sparse, and the optimal duration of treatment is a matter of debate.

Optimal duration of allergen immunotherapy in children with dust mite respiratory allergy



Conclusions: Three years of SCIT induced significant improvement in children with dust mite respiratory allergy, **but a 5-yr course** added clinical improvement in rhinitis.

How adherent to sublingual immunotherapy prescriptions are patients?

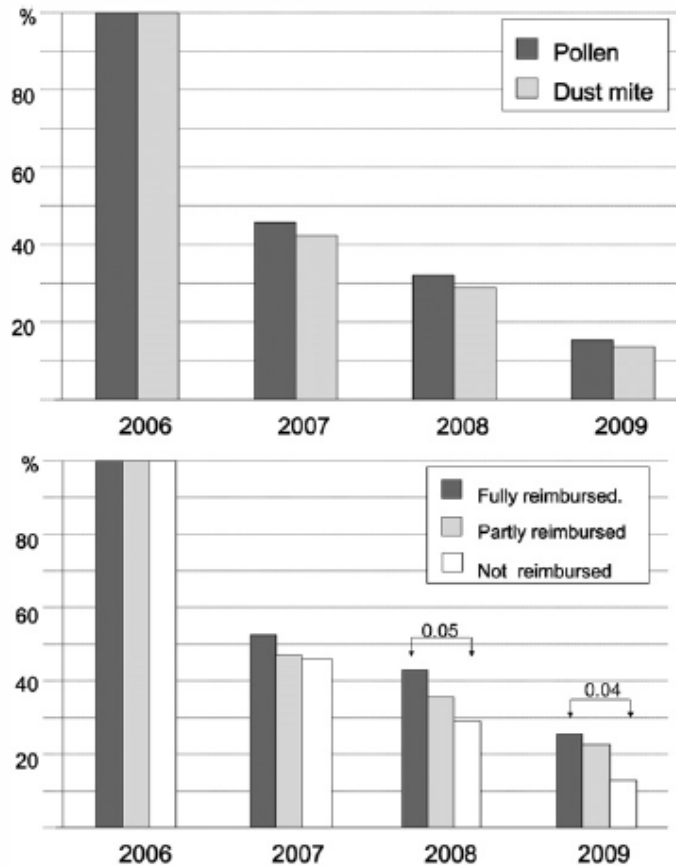
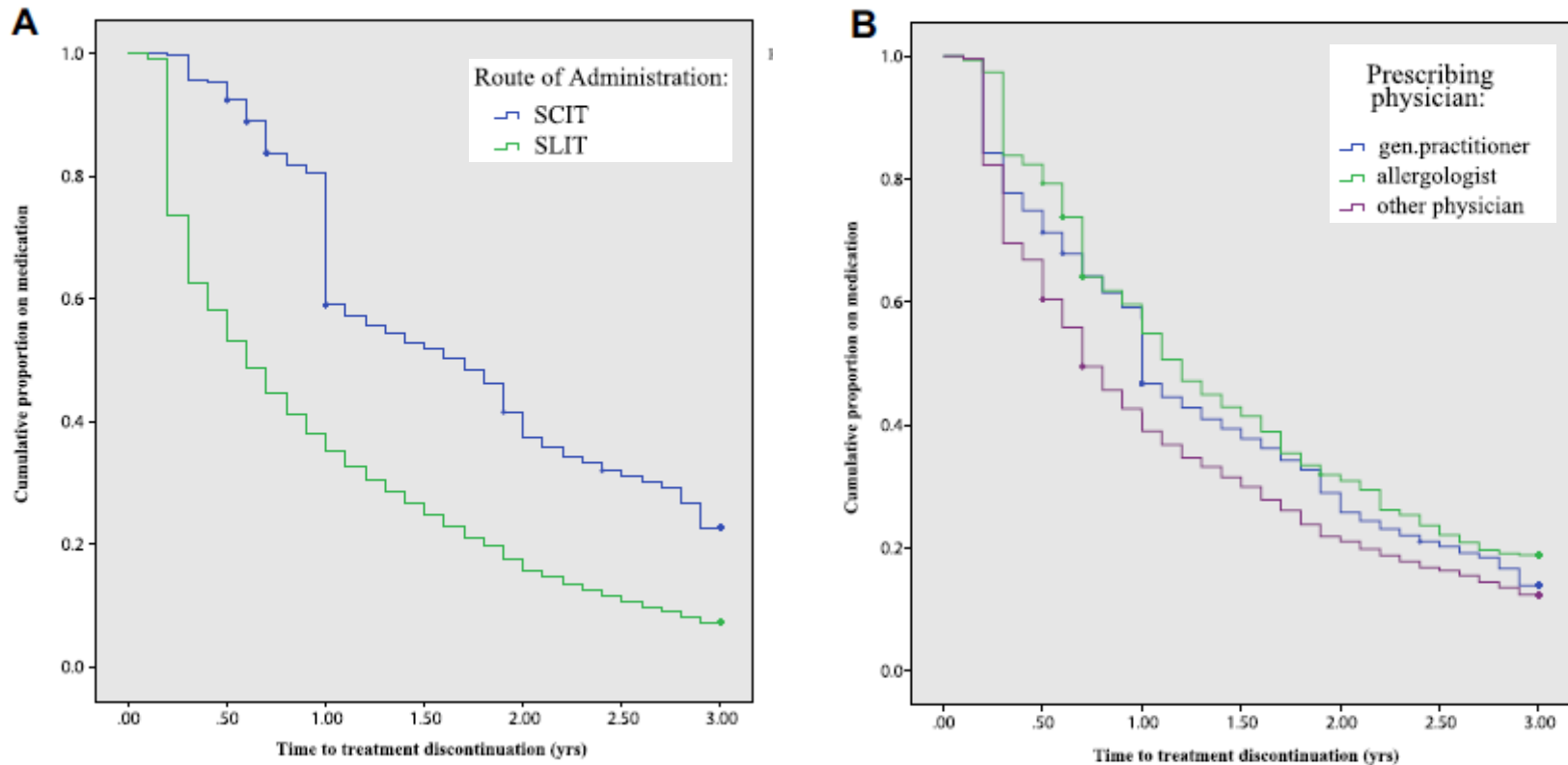


FIG 1. Percentages of SLIT treatments still ongoing at 1, 2, and 3 years after the initial prescription. *Upper panel,* Percentages for pollens and house dust mite SLITs. *Lower panel,* Percentages according to the reimbursement modality. Significant *P* values are indicated above the bars.

Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy

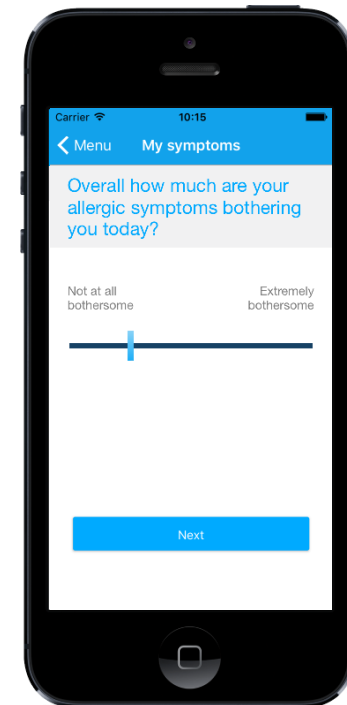
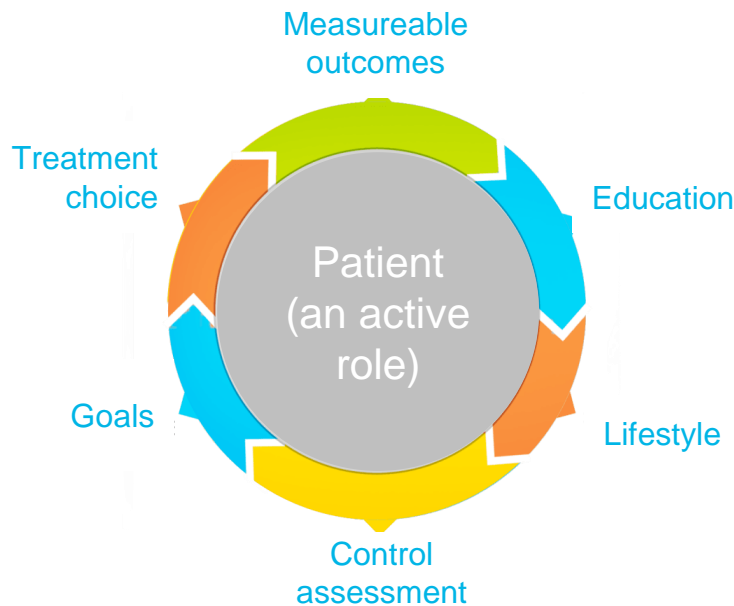


Clinical implications: Efforts to increase persistence with allergen immunotherapy in real life are urgently needed because large amounts of money are currently being misspent as a result of premature discontinuation of treatment.

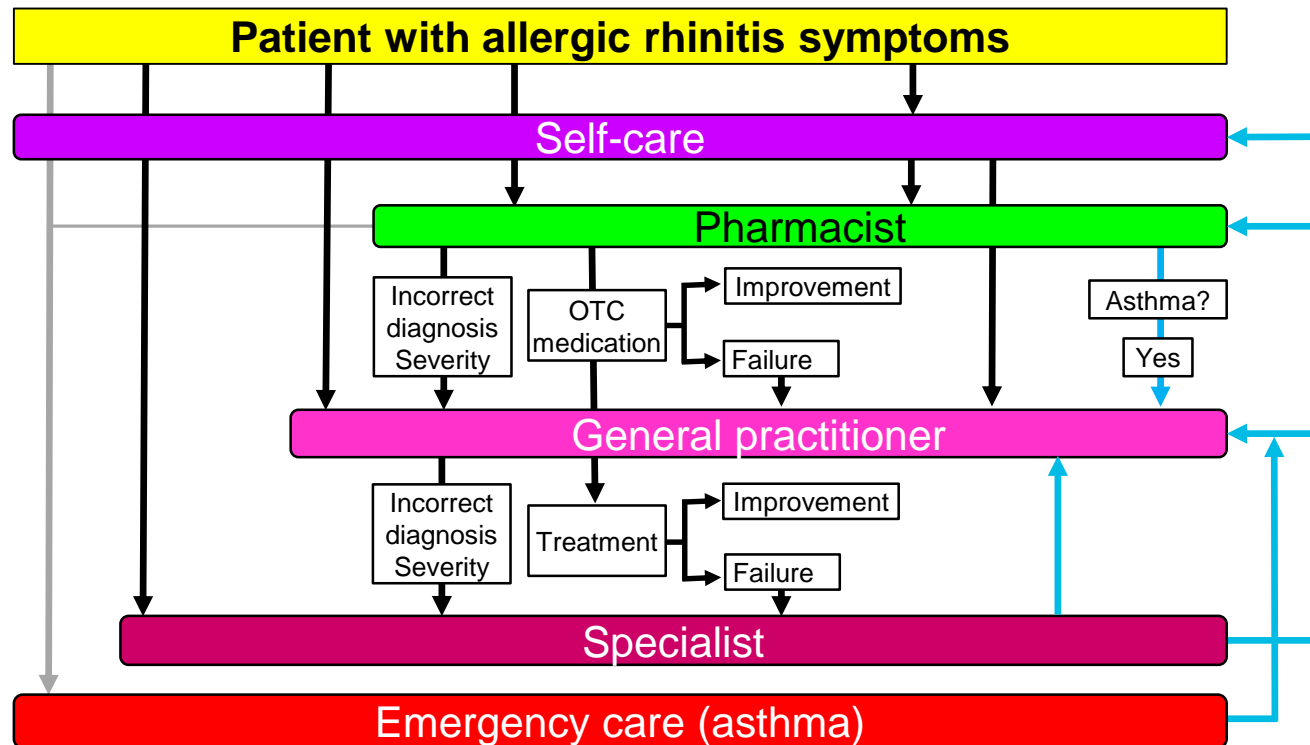


ARIA Phase 3: The *Allergy Diary* strengthens change management

- Patient empowerment & the finger approach



ARIA real World approach for care pathways in rhinitis and asthma



Bousquet et al, Eur Respir J 2014
OTC: over the counter



Guidelines are based on evidence derived from RCTs: real life data should be considered

- RCTs

- Continuous treatment
- Defined treatment start and end time points
- Homogenous patient population
- Adherence to protocol is required
- Success of treatment
 - Superiority to placebo
 - Measured using symptom scores

- Real life

- Intermittent treatment
- Heterogeneous patient population
- Non-adherence is common
- Success of treatment
 - ??
 - ??

Real life data should be incorporated into the next generation guidelines

RCT: randomized controlled trial



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Carrier 12:26

< Medication Nasal Done

QUICK SEARCH

Dymista (fluticasone propionate/
azelastine)

I The I'm

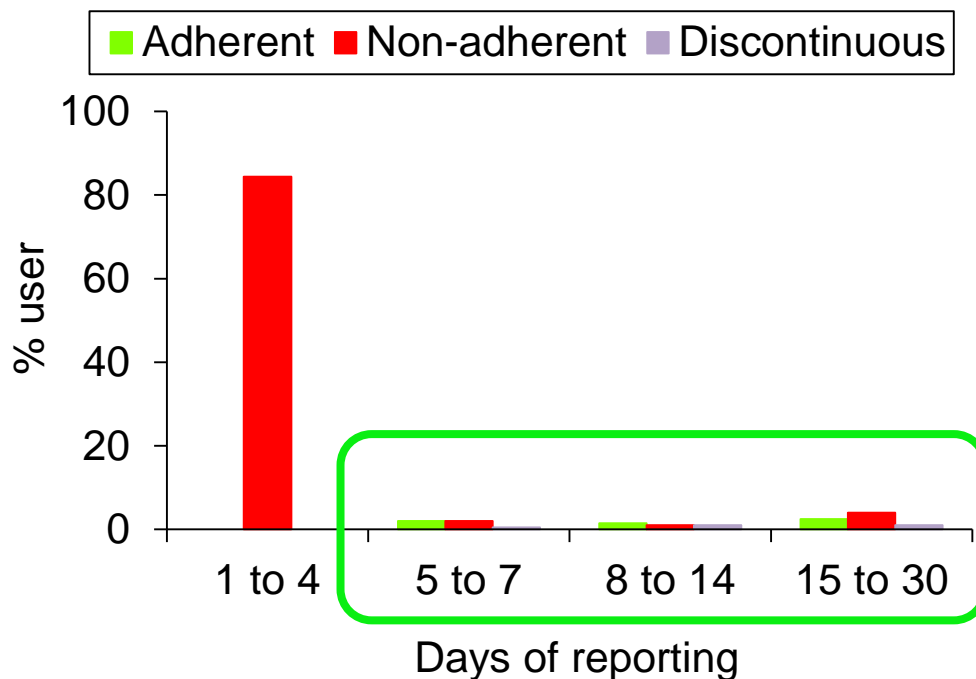
Q W E R T Y U I O P

A S D F G H J K L

↑ Z X C V B N M

123 smiley space return

MACVIA: Contre les Maladies pour un Vieillissement Actif; MASK: Mobile Airways Sentinel Network



2,850 users
 Adherence
 ≥ 5 days
 70% same treatment
 6% users

Most patients use their treatment for ≤ 4 days and are non-adherent

mHealth approach for care pathways

Patient with allergic rhinitis symptoms

Self-care

Pharmacist

General practitioner

Specialist

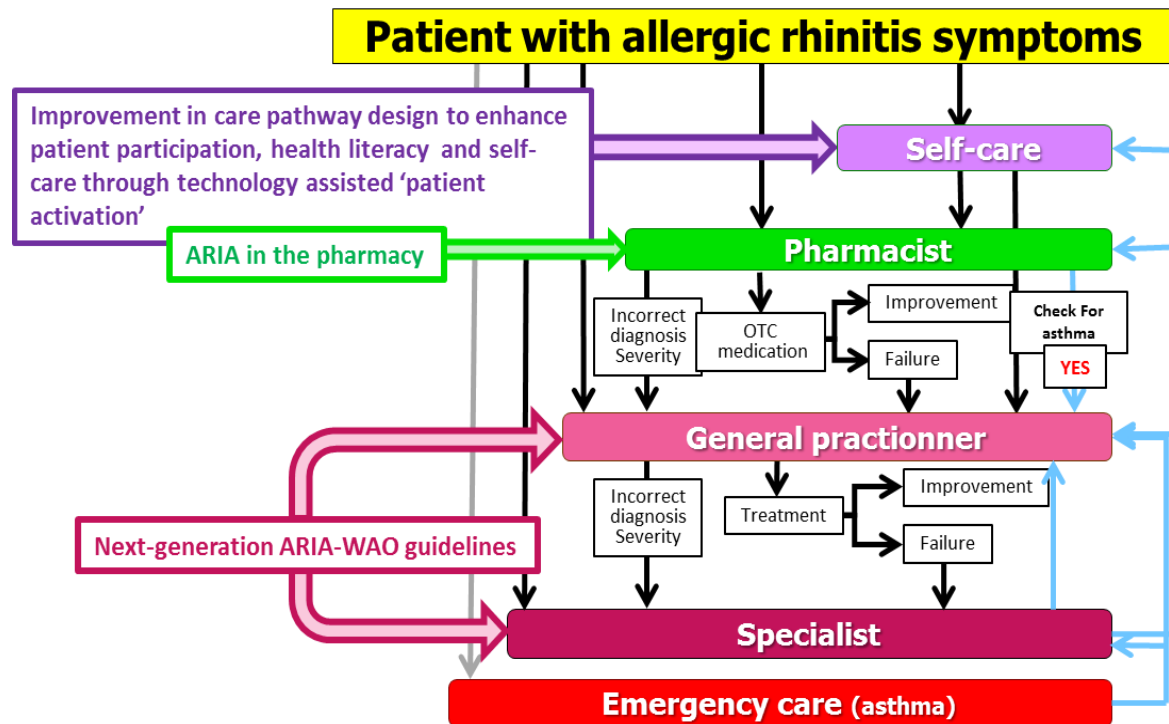
Emergency care (asthma)

Goals

1. Develop for each step an mHealth tool
2. cell phone for self-care
3. interoperable tablet for pharmacists and physicians
4. Patient's personal data with maintained privacy



Stepwise approach for next generation care pathways



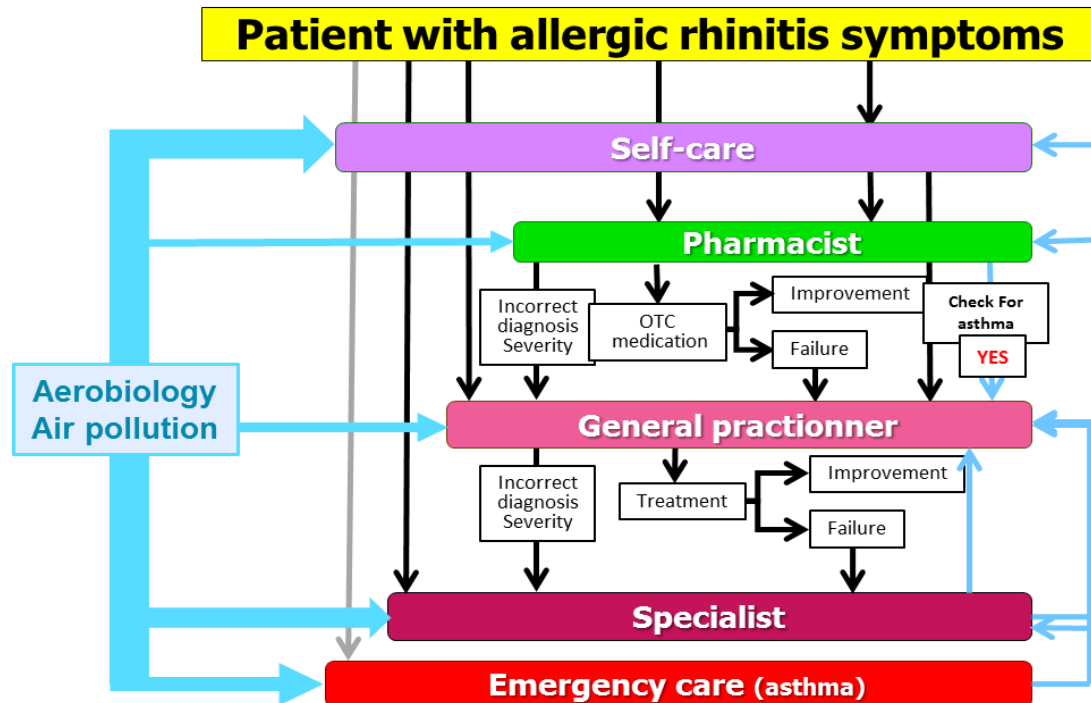
Goals

1. For each step develop a document with a 4-pages pocket-guide
2. Include mHealth for each step
3. From one step to the next one
4. When to go to the next step
5. Stepwise approach for management
6. Develop machine learning to optimize ICPs

OTC: over the counter; ICP: integrated care pathway



Embedding environment in next generation care pathways



Goals

1. Embedding environmental data
2. Prevention of symptoms and asthma (self-care)
3. Assess if severity of symptoms is associated with allergens or pollution
4. Predict emergency care visits
5. Develop machine learning to optimize ICPs

OTC: over the counter; ICP: integrated care pathway



EAACI
EUROPEAN ACADEMY OF ALLERGY
AND CLINICAL IMMUNOLOGY

RHINA  European
Rhinallergy
Meeting



EAACI
EUROPEAN ACADEMY OF ALLERGY
AND CLINICAL IMMUNOLOGY

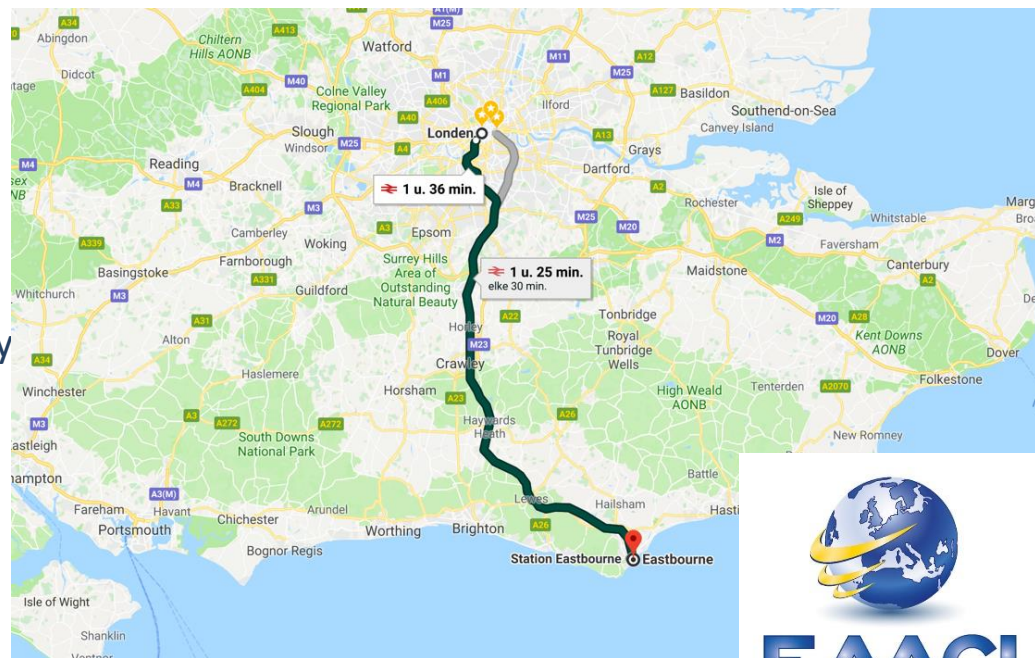
European Rhinallergy meeting

Focus on allergen specific
immunotherapy and biologicals

21 - 23 March 2019

Eastbourne, United Kingdom

- Local OC: M Shamji, S Durham, C Hopkins, G Scadding
- EAACI OC: P Gevaert, L Klimek, JL Fauquert, L Jacobsen, O Palomares Gracia, P Hellings, I Agache
- ENT Section & Interest groups: Immunotherapy
Biologicals
- EAACI congresses: C Schmidt-Weber



EAACI
EUROPEAN ACADEMY OF ALLERGY
AND CLINICAL IMMUNOLOGY



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AND CLINICAL IMMUNOLOGY