

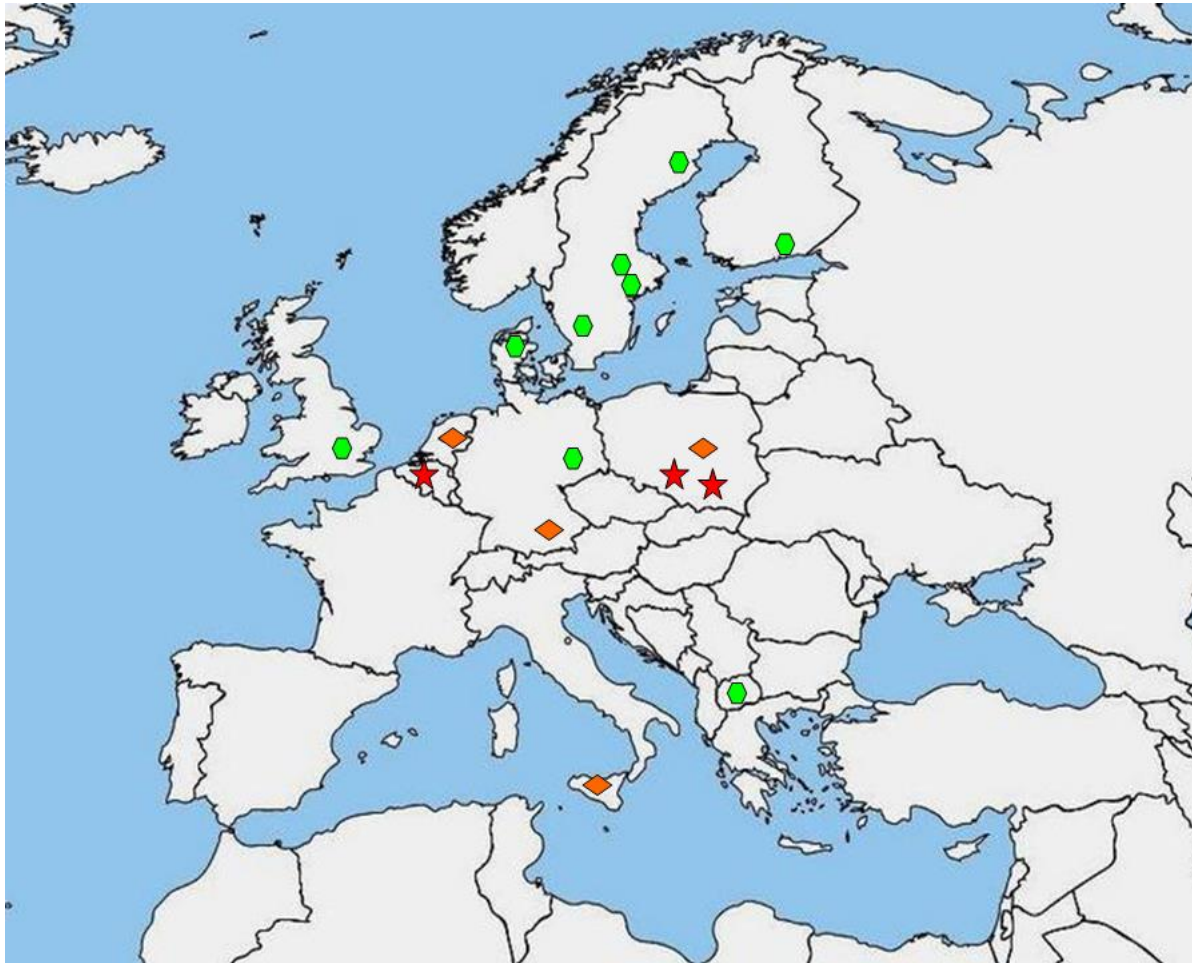
Globale Aanpak van Chronische Rhinosinusitis Met en Zonder Neuspoliepen

PROF. Dr Philippe GEVAERT

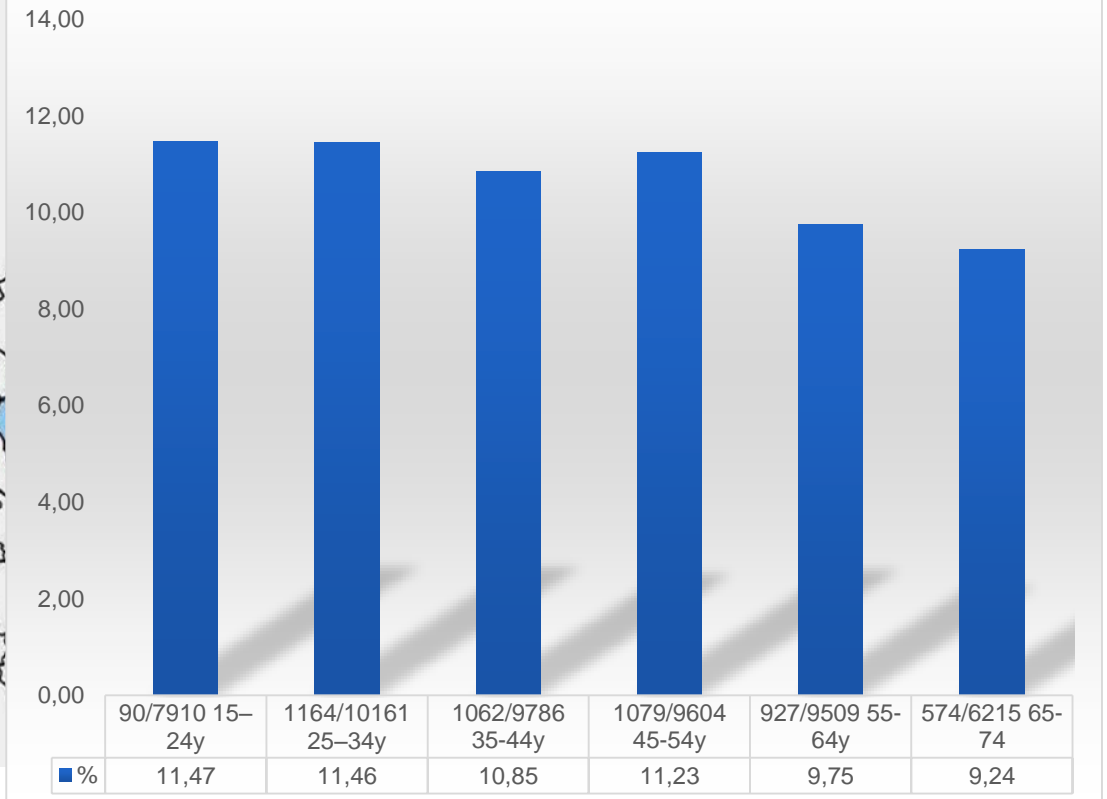
PREVALENCE CRS

Prevalence of CRS: **10,9%**

- ranging from **6,7%** in Helsinki
- to **19,7%** in Krakow

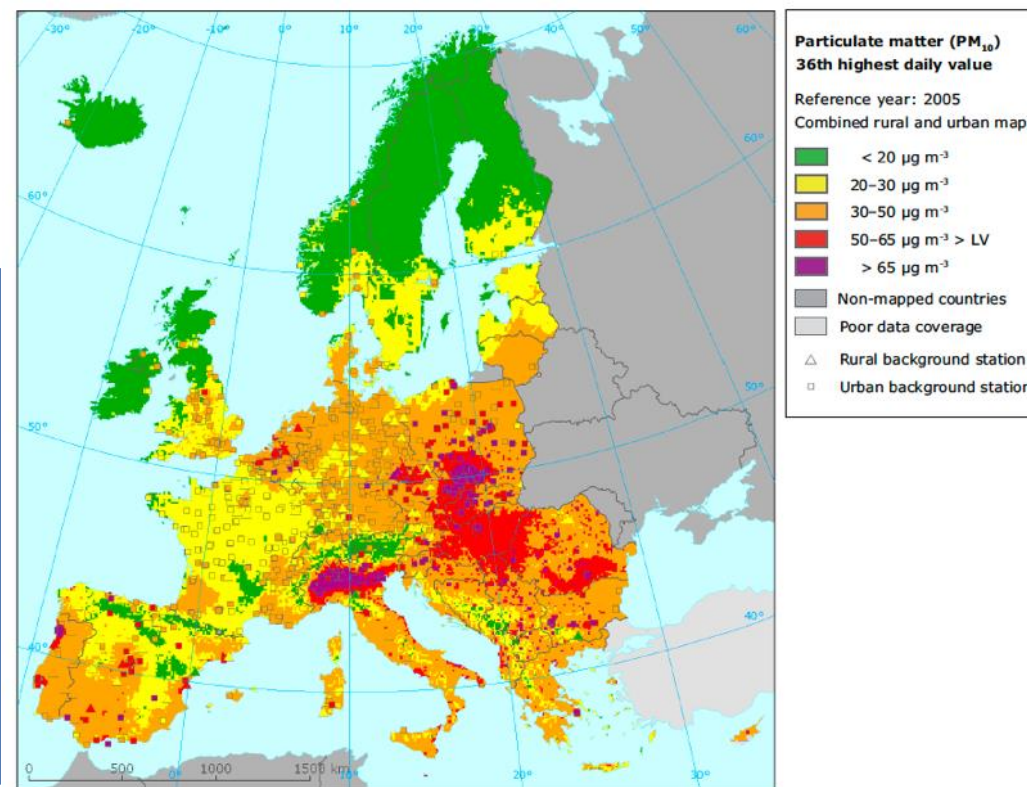


Age vs CRS %



RISICOFACTOREN CRS IN EUROPA

	unadj. OR*	adj. OR**	[95% CI]	p
age				
15-24				
25-34	0.87	0.76	[0.55 - 1.04]	0.086
35-44	0.68	0.66	[0.48 - 0.89]	0.006
45-54	0.65	0.61	[0.45 - 0.83]	0.001
55-64	0.59	0.63	[0.46 - 0.87]	0.004
65-74	0.48	0.50	[0.34 - 0.73]	<0.001
smoking status				
non smoker				
past smoker	1.15	1.28	[1.03 - 1.59]	0.027
current smoker	1.71	1.87	[1.51 - 2.32]	<0.001
current allergic rhinitis				
none				
intermittent	1.95	1.74	[1.38 - 2.19]	<0.001
persistent	5.91	5.55	[4.46 - 6.91]	<0.001
current asthma	2.88	1.92	[1.46 - 2.54]	<0.001
eczema history	2.06	1.61	[1.31 - 1.97]	<0.001
gender: female	0.99	0.92	[0.78 - 1.10]	0.38



EUROPEAN POSITION PAPER ON RHINOSINUSITIS AND NASAL POLYPS (EPOS) 2012



*Fokkens W.J., Lund V.J.,
Mullol J., Bachert C.,
et al.*



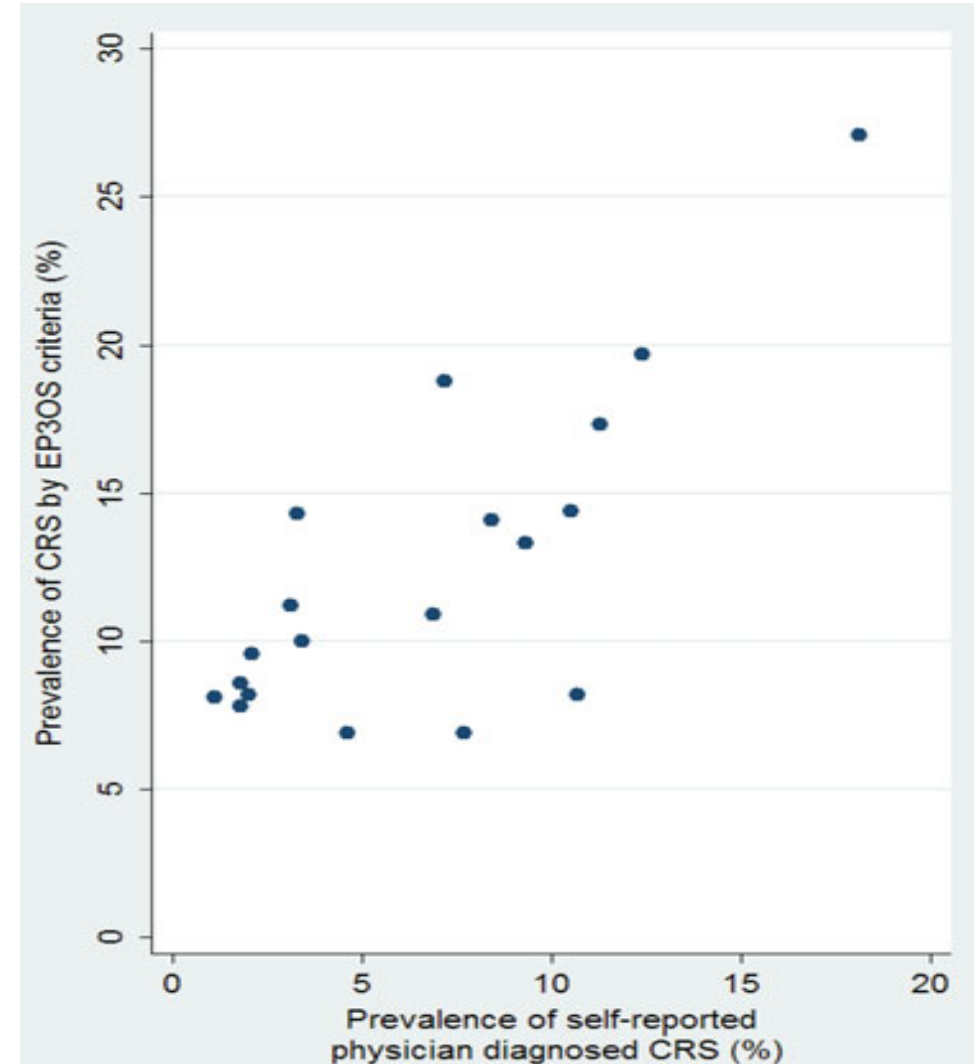
PREVALENCE CRS FOLLOWING EPOS / SELF REPORTED DE PHYSICIAN DIAGNOSED



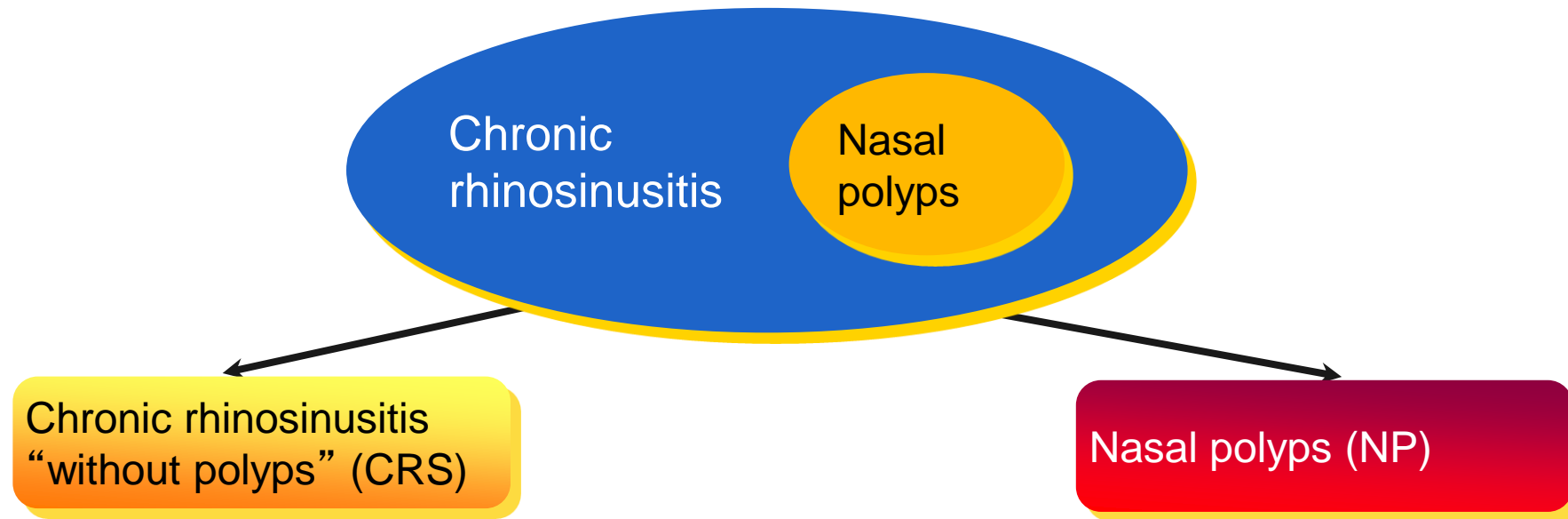
Diagnosis of Rhinosinusitis Based on symptoms:
Two or more symptoms, one of which should be either

- nasal blockage/obstruction/congestion or
- nasal discharge: anterior/post nasal drip;
- ± facial pain/pressure,
- ± reduction or loss of smell

ACUTE < 12 weeks
CHRONIC > 12 weeks



Hastan D Allergy 2011



All the same?

CHRONIC RHINOSINUSITIS WITH AND WITHOUT NASAL POLYPS

Chronic rhinosinusitis



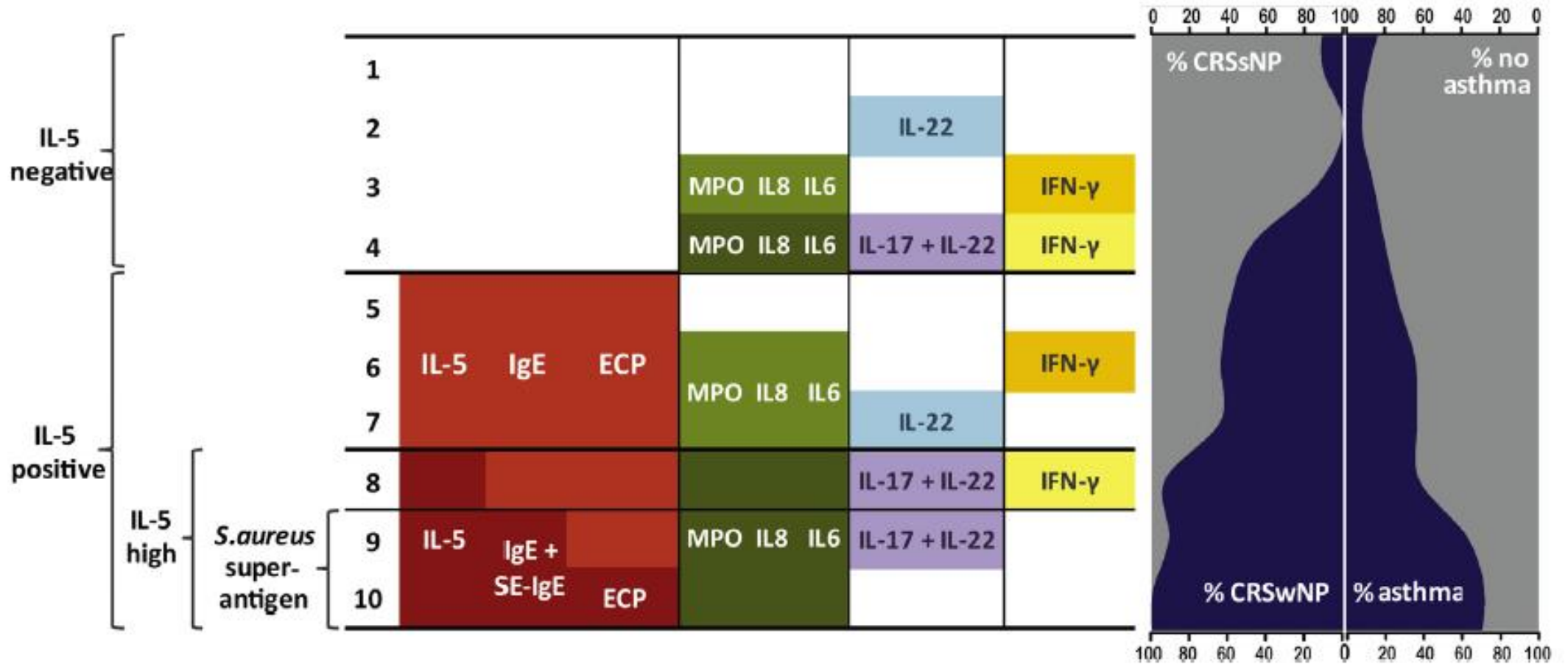
Nasal Polyps



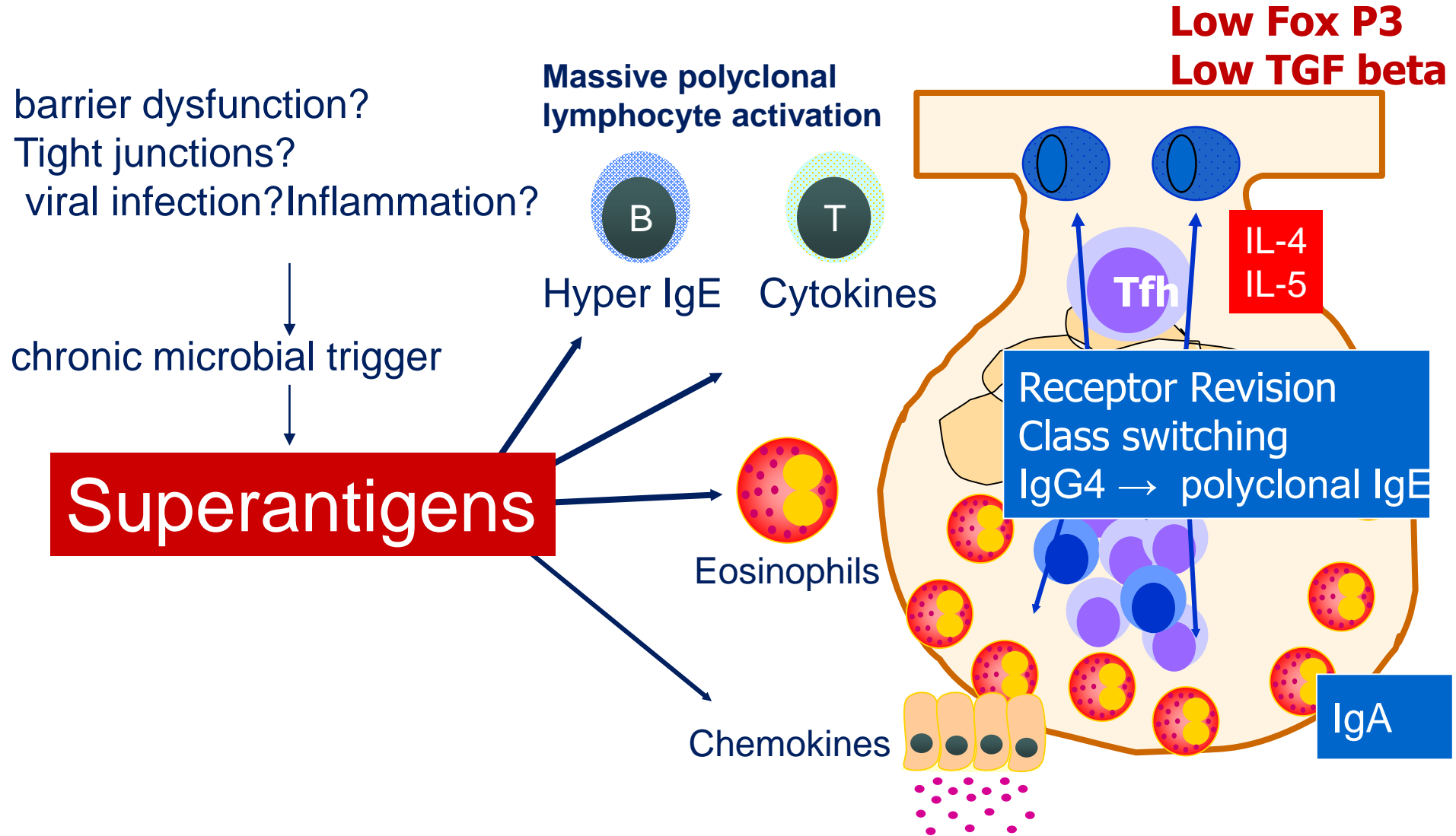
CHRONIC RHINOSINUSITIS WITH AND WITHOUT NASAL POLYPS

	Chronic Sinusitis	Nasal Polyposis
Facial pain/pressure	Yes	Rarely
Facial congestion/fullness	Yes	Yes
Nasal obstruction/blockage	Yes	Yes
Nasal discharge/purulence/postnasal drip	Yes	Yes
Hyposmia/anosmia	Rarely	Yes
Blood eosinophils	No	Often
Asthma	Rarely	Often
Aspirin hypersensitivity	Rarely	Typical

Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers



SUPERANTIGENS IN NASAL POLYPOSI



S Aureus superantigens = disease modifiers

CASUS I



- Man , 42 jaar
- Hoofdpijn tussen ogen, PND
- PND en hoesten+++
- Op en af sinds januari 2012
- Endoscopie:
 - mucoïde secreties
- CT scan:
 - Partiele sluiëring van sinussen

Nasal saline irrigations for the symptoms of chronic rhinosinusitis (Review)

Harvey R, Hannan SA, Badia L, Scadding G

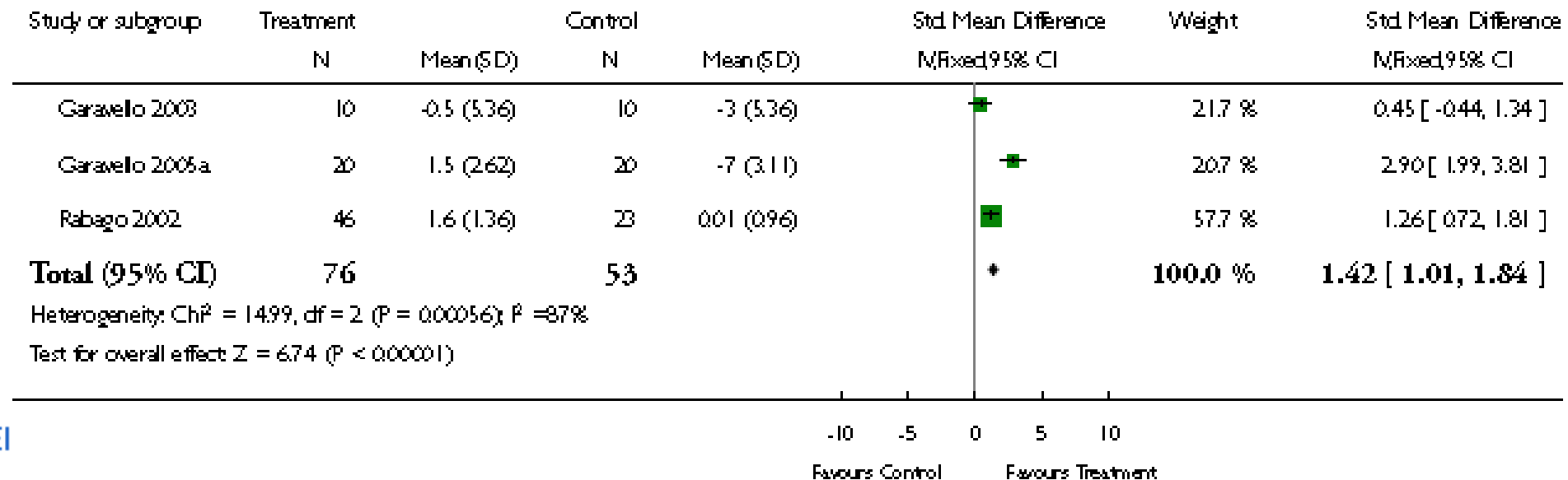


Analysis 1.1. Comparison 1 A: Comparison of saline versus no treatment, Outcome 1 Symptom scores.

Review: Nasal saline irrigations for the symptoms of chronic rhinosinusitis

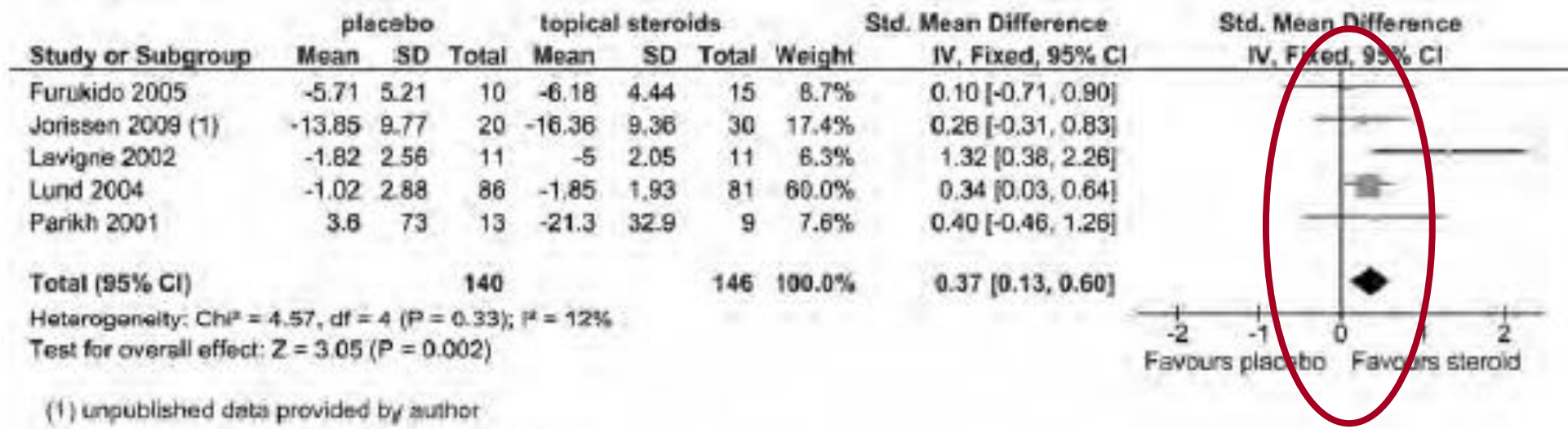
Comparison: 1 A: Comparison of saline versus no treatment

Outcome: 1 Symptom scores

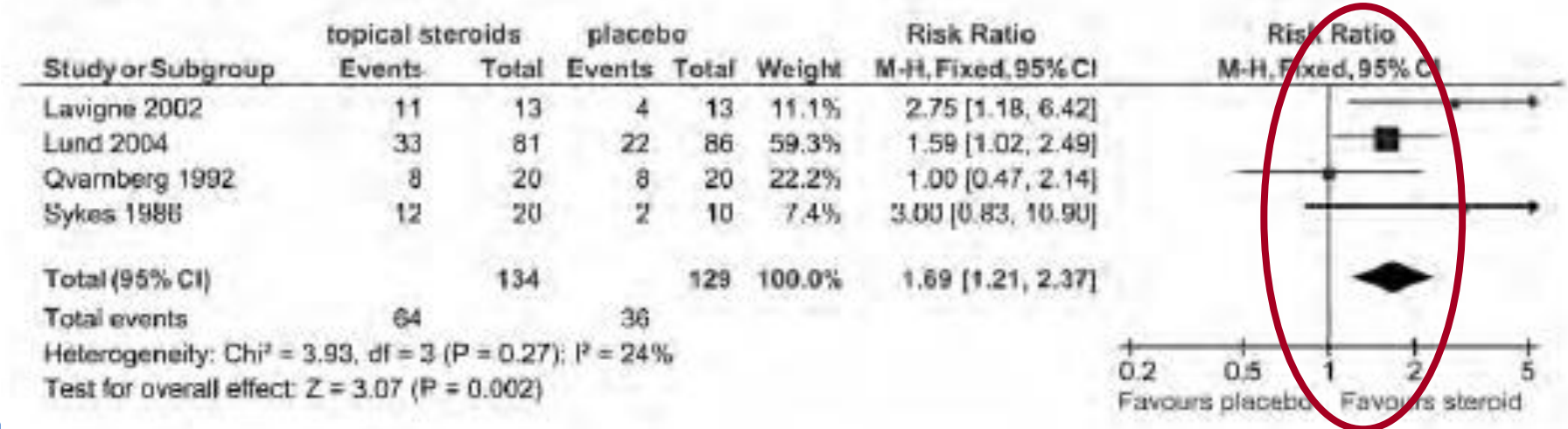


TREATMENT OF CRSSNP WITH INTRANASAL CORTICOSTEROIDS

A Symptom scores



B Proportion of patients responding to treatment



NO EVIDENCE FOR SHORT TERM ANTIBIOTIC TREATMENTS FOR CRS

Table 6.2.1. "Short Term" Antibiotics in CRSsNP.

Study	Drug	Number	Time/Dose	Effect on symptoms	Evidence
Huck 1993 ⁽¹⁶⁸³⁾ .	ceflaclor vs. amoxicillin	56 acute rhinosinusitis 25 recurrent rhinosinusitis 15 chronic maxillary sinusitis	2x 500mg 3x500mg for 10 days	clinical improvement: acute rhinosinusitis 86% recurrent rhinosinusitis 56% chronic maxillary sinusitis no statistics	1b (-)*
Legent 1994 ⁽¹⁶⁸²⁾	ciprofloxacin vs. amoxicillin clavulanate	251	9 days	nasal discharge disappeared: ciprofloxacin 60% amoxicillin clavulanate 56% clinical cure: ciprofloxacin 59% amoxicillin clavulanate 51% clinical cure: ciprofloxacin 59% amoxicillin clavulanate 51% bacteriological eradication: ciprofloxacin 91% amoxicillin clavulanate 89%	1b (-)
Namyslowski 2002 ⁽¹⁶⁸¹⁾	amoxicillin clavulanate vs. cefuroxime axetil	206	875/125mg for 14 days 500mg for 14 days	clinical cured: amoxicillin clavulanate 5% cefuroxime axetil 88% bacterial eradication: amoxicillin clavulanate 65% cefuroxime axetil 68% clinical relapse: amoxicillin clavulanate 0/ 98 cefuroxime axetil 7/89	1b (-)

**Only short term broad spectrum antibiotics
for acute exacerbations of CRS**

LONG TERM TREATMENT WITH ANTIBIOTICS IN CRS

Table 6.2.2. Placebo controlled RCTs in long-term treatment with antibiotics in chronic rhinosinusitis without polyps ⁽¹⁷⁰⁸⁾ and in a mixed population CRS ⁽¹⁷⁰⁹⁾.

Study	Drug	N=	Time/dose	Effect symptoms	Level of evidence
Wallwork 2006 ⁽¹⁷⁰⁸⁾	Roxithromycin	64	12 weeks/150 mg daily	Significant effect on SNOT-20 score, nasal endoscopy, saccharine transit time, and IL-8 levels. CRSsNP population. Improved or cured in treatment group was 67% vs 22% in placebo group. In a subgroup with normal IgE levels 93% were improved or cured in the treatment group.	1b
Videler 2011 ⁽¹⁷⁰⁹⁾	Azithromycin placebo controlled	60	12 weeks/500 mg week	No significant effect. Response rate was 44% in treatment group vs 22% in placebo group.	1b (-)

In CRSsNP there is some evidence to use long-term, low-dose macrolide antibiotics for 12 weeks
Selecting patients with normal serum IgE could improve response rate

CHRONIC RHINOSINUSITIS IN DE HUISARTSPRAKTIJK

- Nasale douching / spoeling met zoutwater
 - 1 liter flessenwater (kamertemperatuur/ ideaal 37° C)
+ 9 gram zeezout (keukenzout)
= 2 koffielepels of 1 soeplepel
 - Goed mengen
 - Beide neusgaten spoelen boven lavabo
2 x dag met 250ml met
20ml spuit of neuskannetje of spoelsystemen



- spoelen en snuiten
- Nasale Corticosteroiden: 2x2/d, **minstens 8 weken (dan evt CT scan)**

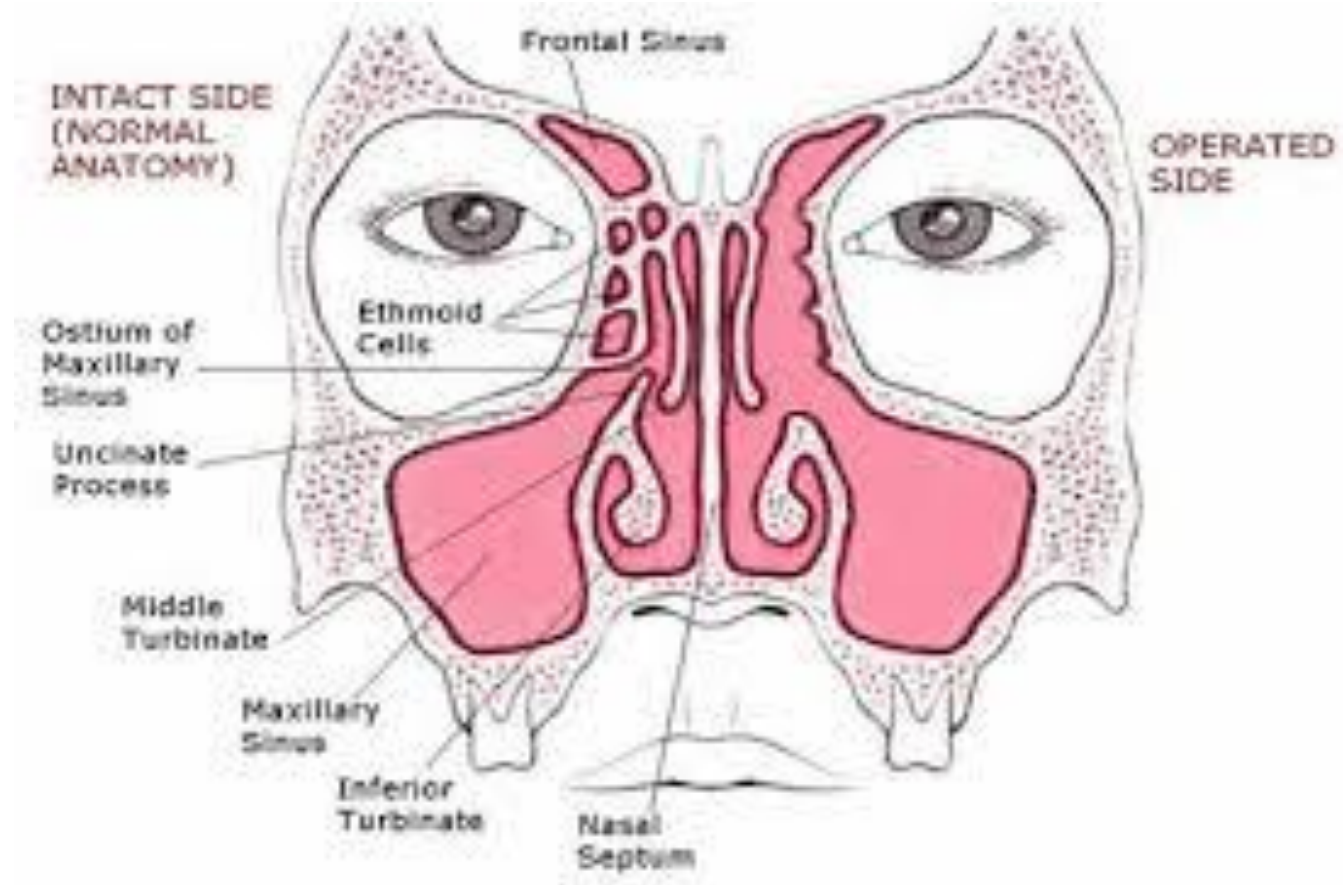
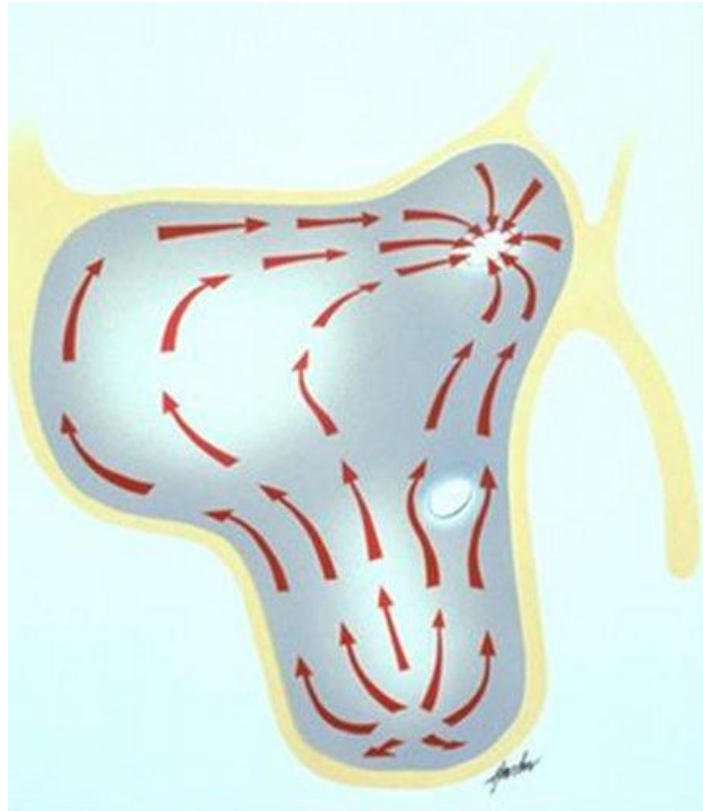
CHRONIC RHINOSINUSITIS BIJ DE NKO-ARTS

- Nasal douching/Saline
- Nasal Corticosteroids: 2x2/d



- Antibiotics: long-term Macrolides ?!?!?!
Clarithromycine 250mg/d(3 months)
- FESS (functionele endoscopische sinus chirurgie)

FESS OPERATIE: FUNCTIONAL ENDOSCOPIC SINUS SURGERY



CRSsNP in adults management scheme for ENT-specialists

2 symptoms: one of which should be nasal obstruction or discoloured discharge
+/- frontal pain, headache
+/- smell disturbance
ENT examination including endoscopy
consider CT scan
check for allergy
consider diagnosis and treatment of co-morbidities eg. asthma

consider other diagnosis
unilateral symptoms
bleeding
crusting
cacosmia

orbital symptoms:
peri-orbital oedema/erythema
displaced globe
double or reduced vision
ophthalmoplegia

severe frontal headache
frontal swelling
signs of meningitis
neurological signs

mild
VAS 0-3
no serious mucosal disease
at endoscopy

moderate/severe
VAS >3-10
mucosal disease at endoscopy

topical steroids
nasal saline irrigation

no improvement
after 3 months

topical steroids
nasal saline irrigation
culture
consider long term antibiotics
(if IgE is not elevated)

CT scan

urgent investigation
and intervention

improvement

follow-up +
nasal saline irrigation
topical steroids

CT scan
if not done before

consider
surgery

no improvement

follow up +
topical steroids
nasal saline irrigation
culture
consider long term antibiotics

consider
surgery



CASUS III

- Man 46 jaar
- aanhoudende “verkoudheid”, geen reuk
- Anafylaxie na inname pijnstiller
- Intrinsiek astma

- SPT en RAST: negatief
- Totaal IgE: 340 kU/l

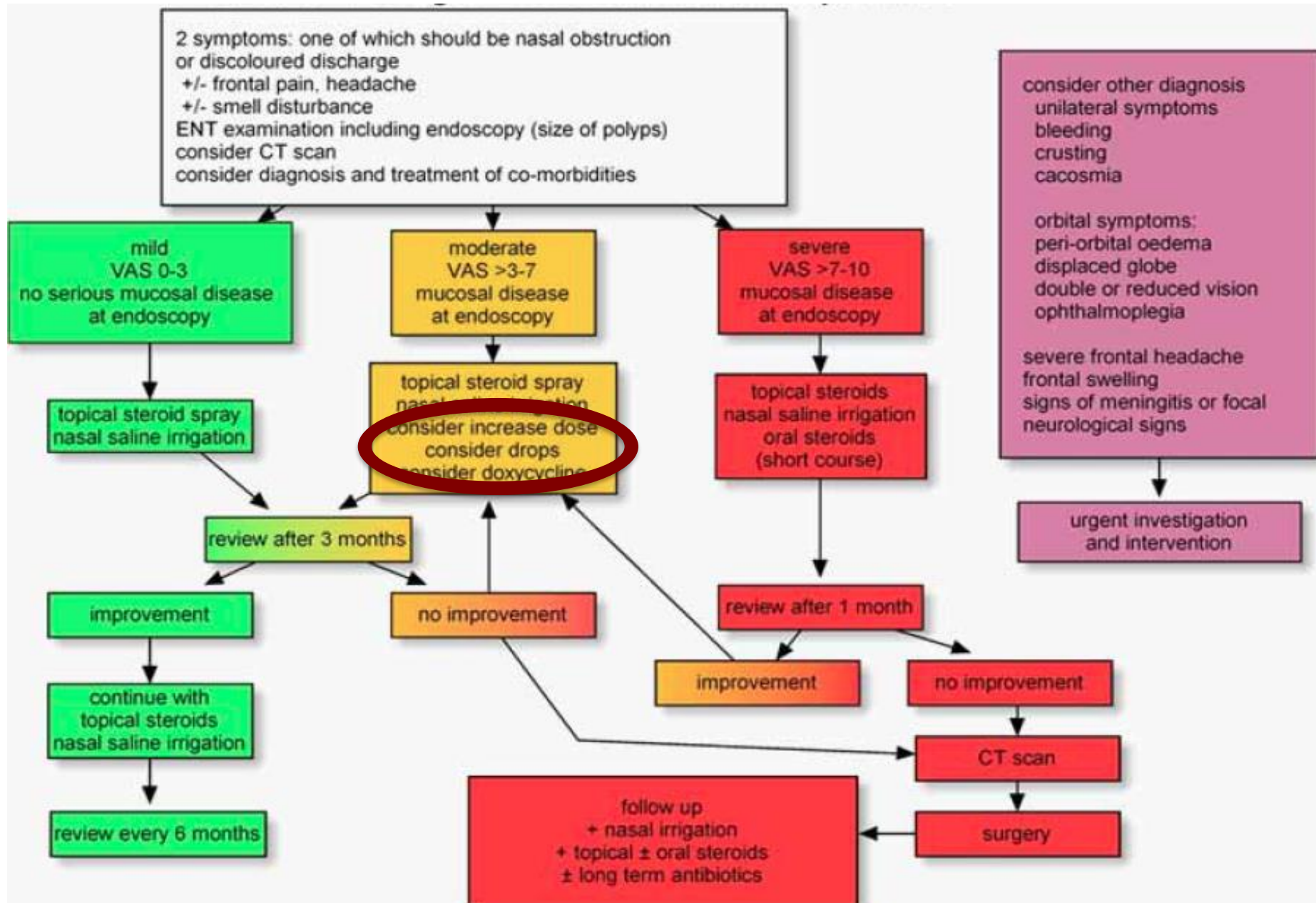
- Nasale polypose
(Astma Polypose Aspirin)

Behandeling?

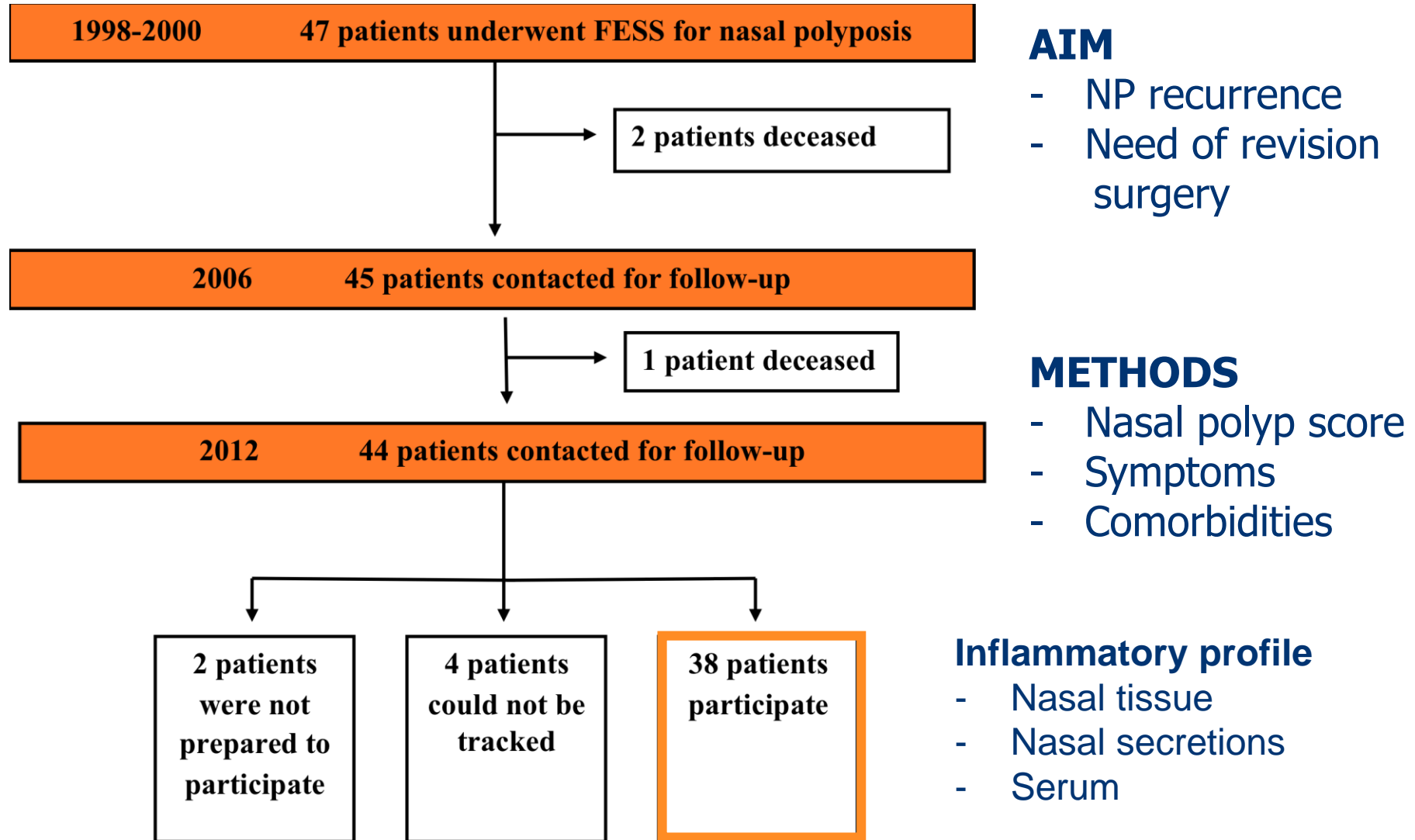
HISTORIEK

- Man 46 jaar
- 1997 aanhoudende “verkoudheid”
- Anafylaxie na inname pijnstiller
- 1998 FESS omwille van neuspoliepen
- 12/1999 FESS omwille van orbitaflegmoon
- 24/02/2000 FESS omwille van neuspoliepen
- 29/10/2009 FESS omwille van neuspoliepen

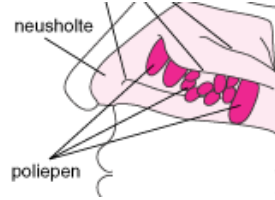
MANAGEMENT OF NASAL POLYPOSIS FOLLOWING EPOS



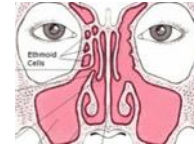
STUDY DESIGN: PROSPECTIVE 12-YEAR FOLLOW-UP STUDY AFTER ESS



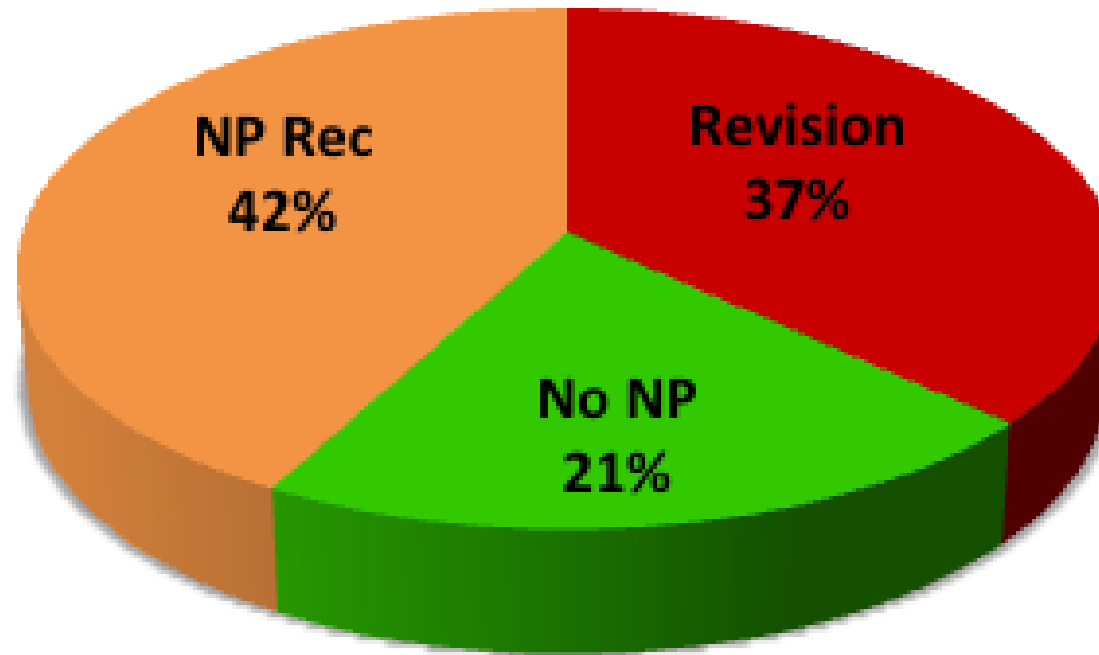
12-YEAR FOLLOW-UP STUDY AFTER ESS



NP RECURRENCE
30/38
78.9%

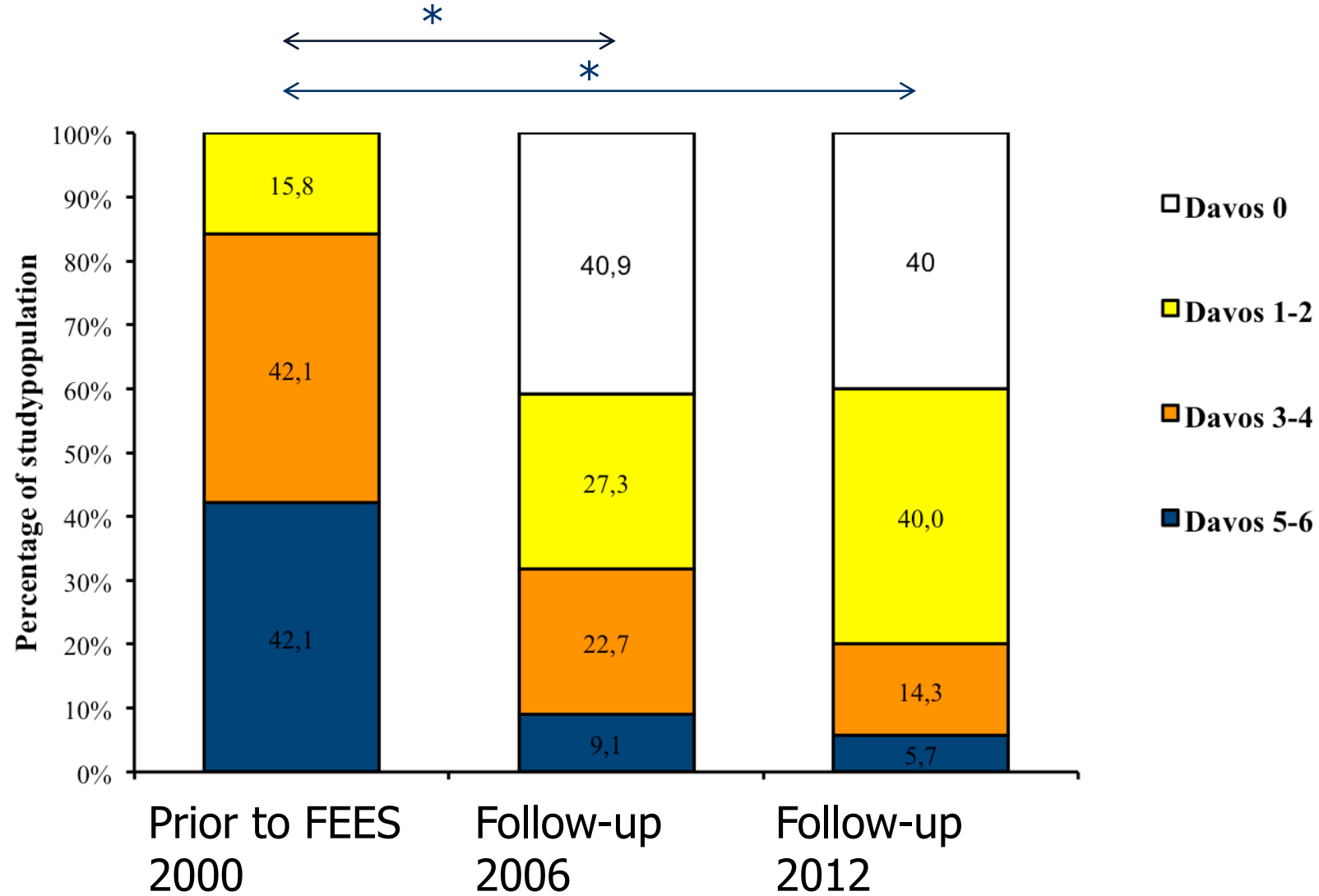


REVISION SURGERY
14/38
36.8%

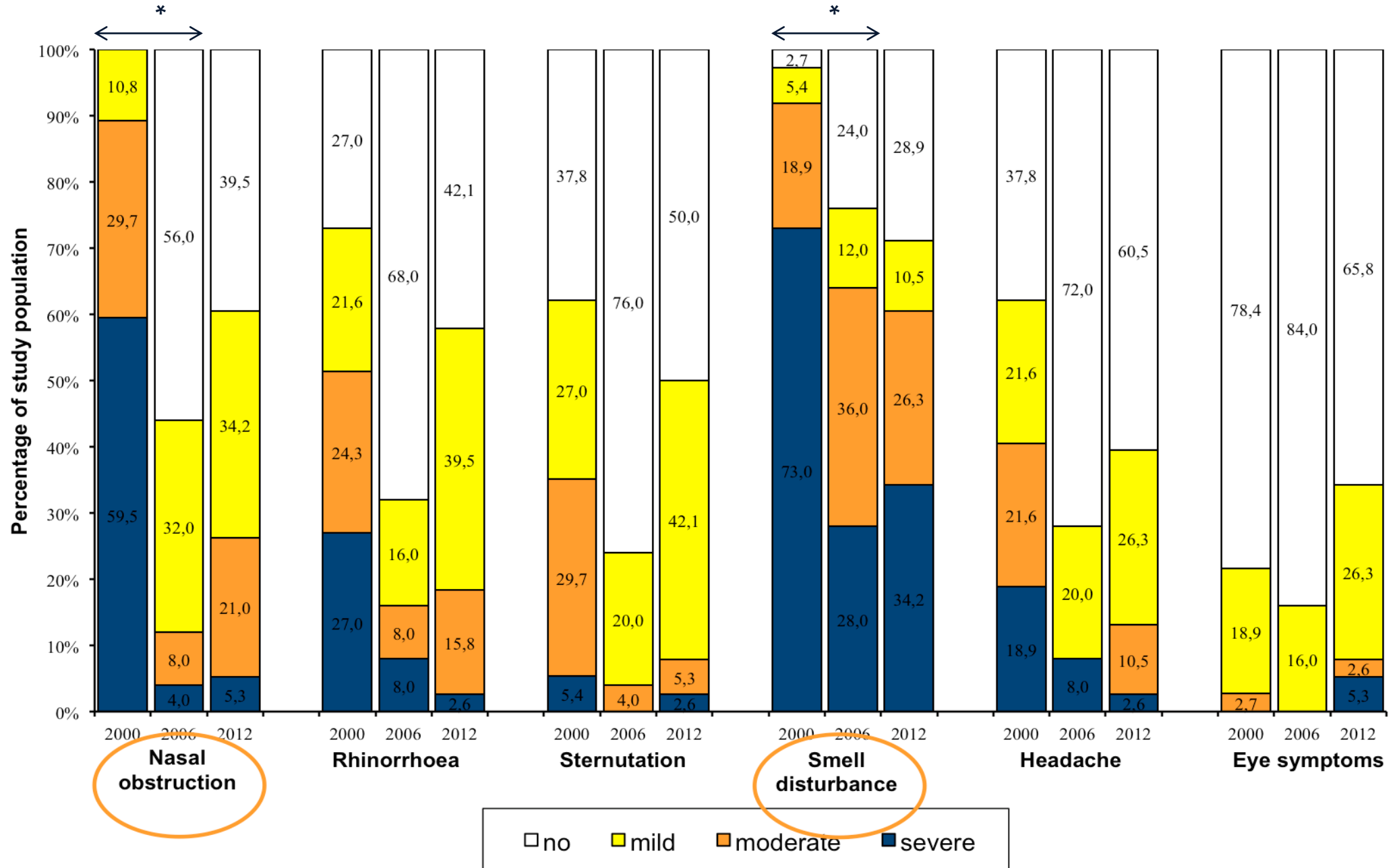


**No NP
recurrence**

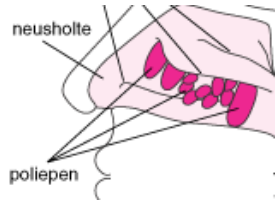
ENDOSCOPIC NASAL POLYP SCORE



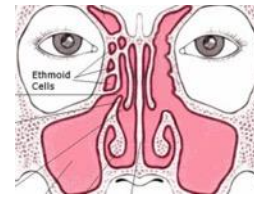
Symptom control 12-year after ESS



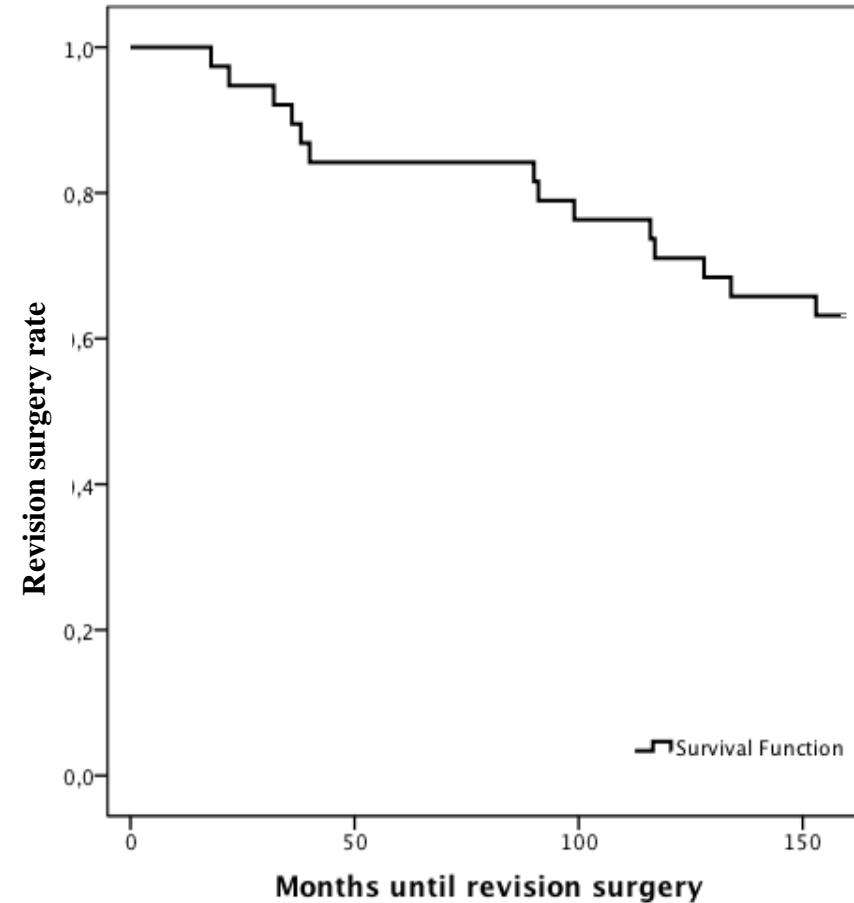
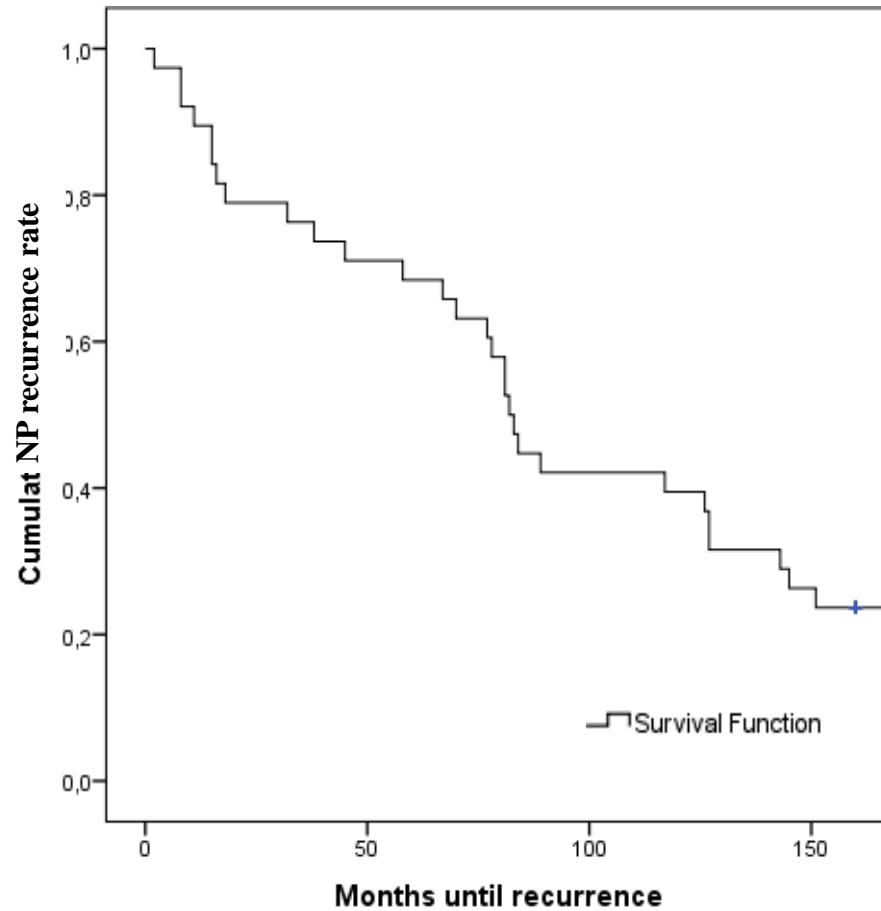
12-YEAR FOLLOW-UP STUDY AFTER ESS



NP RECURRENCE

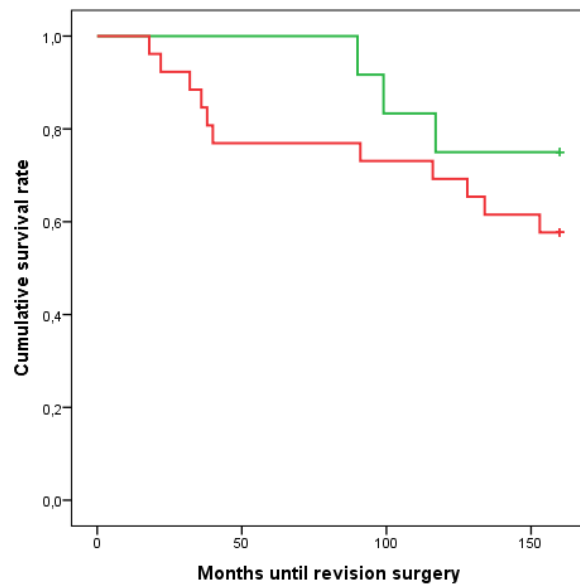


NEED OF REVISION SURGERY

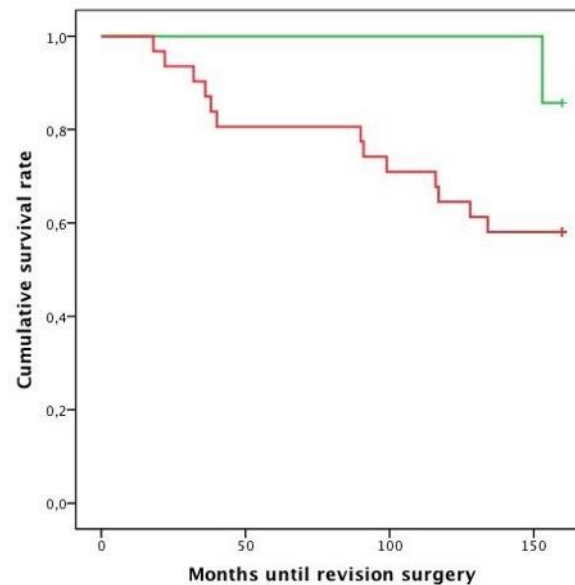


NEED FOR REVISION SURGERY 2000-2012: PREDICTORS?

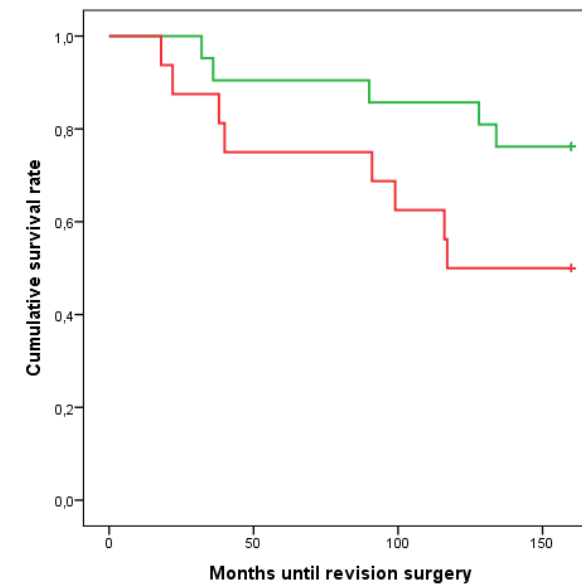
Tissue IL-5



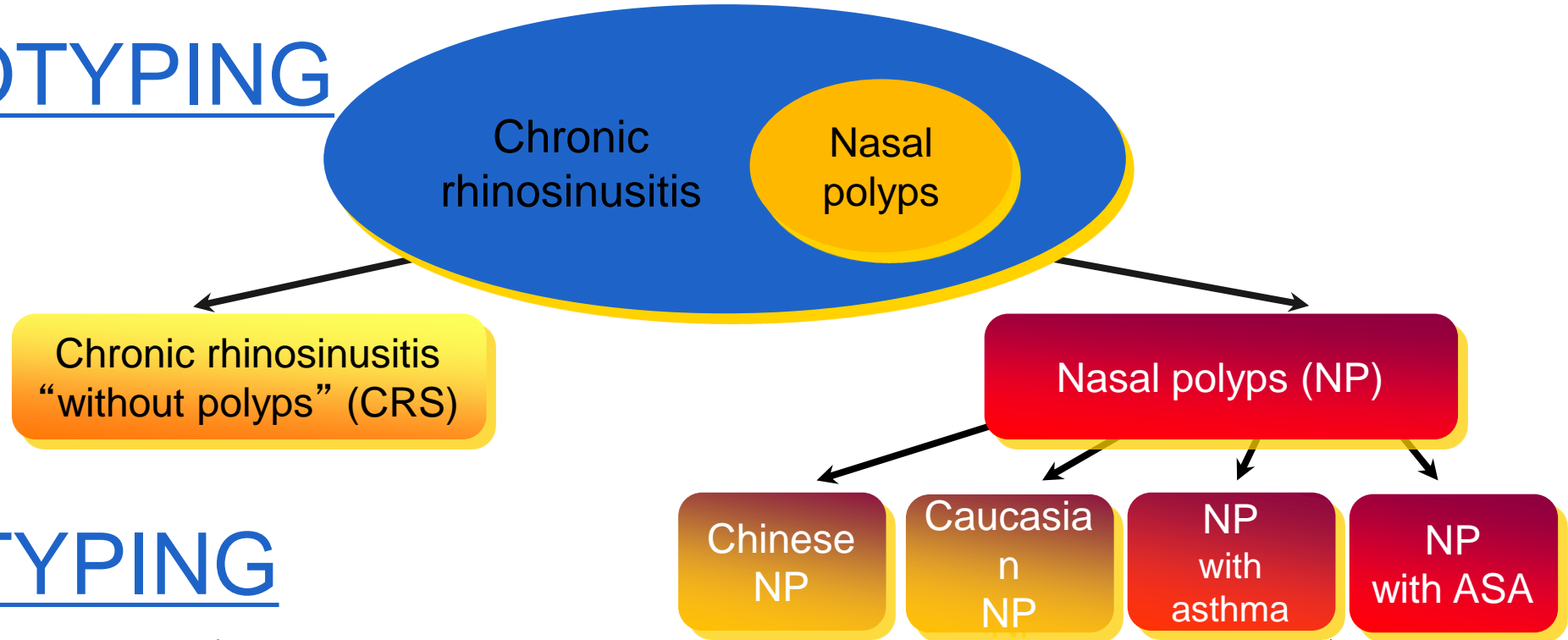
Tissue IgE



Tissue IgE to SAE



PHENOTYPING



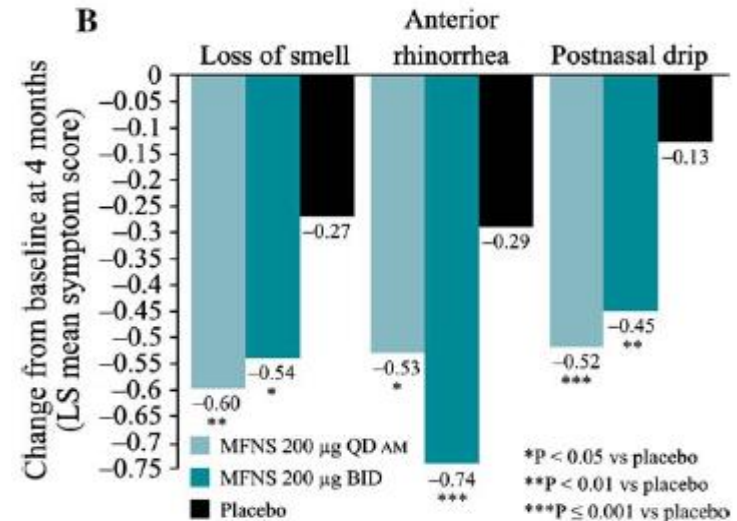
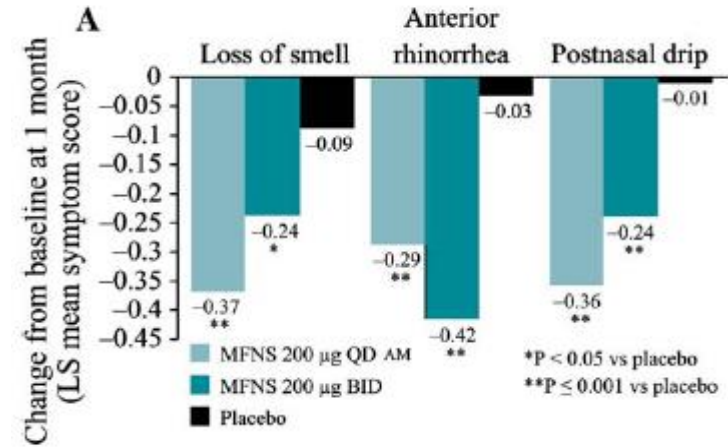
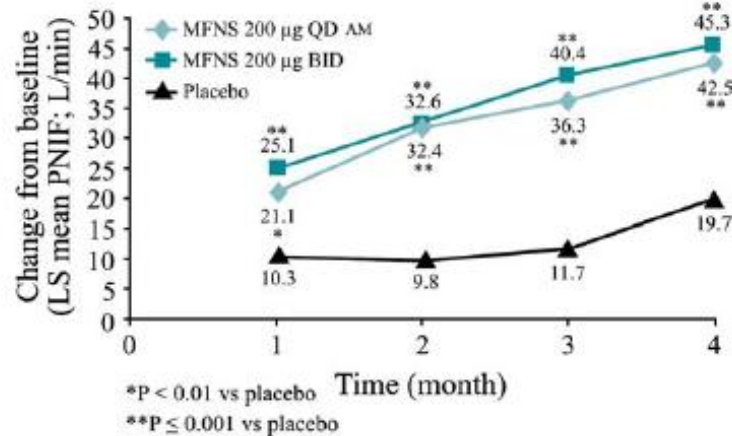
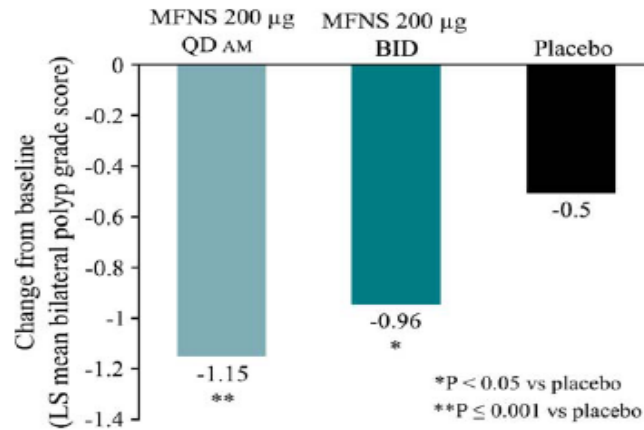
ENDOTYPING



Efficacy and safety of mometasone furoate nasal spray in nasal polyposis

Catherine Butkus Small, MD,^a Jaime Hernandez, MD,^b Antonio Reyes, MD,^c
 Eric Schenkel, MD,^d Angela Damiano, MD,^e Paul Stryszak, PhD,^f Heribert Staudinger,
 MD,^f and Melvyn Danzig, PhD^f Valhalla, NY, Medellin and Cali, Colombia, Philadelphia, Pa,
 and Kenilworth, NJ *J Allergy Clin Immunol* 2005;116:1275-81

N=354



NASAL CORTICOSTEROID DROPS IN NASAL POLYPS

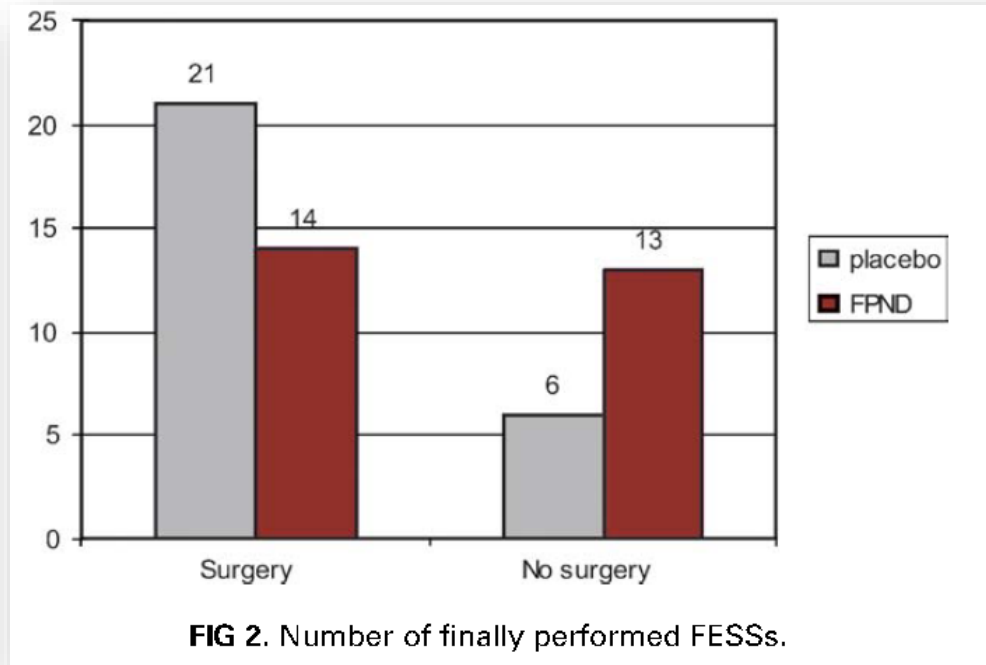
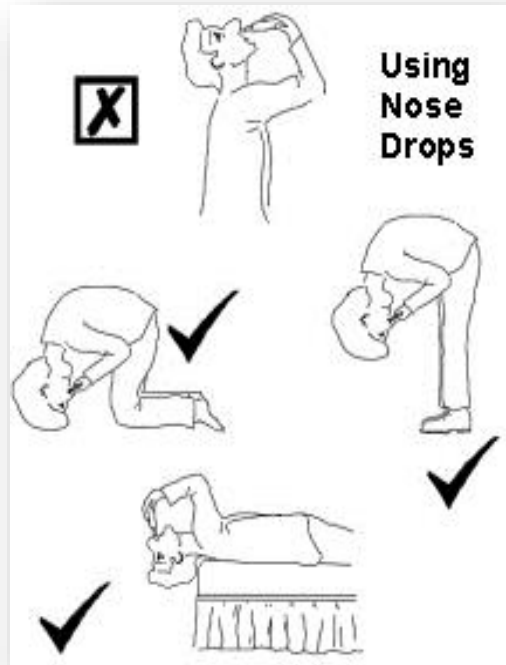


FIG 2. Number of finally performed FESSs.

Double-blind, placebo-controlled study with nasal GCS drops

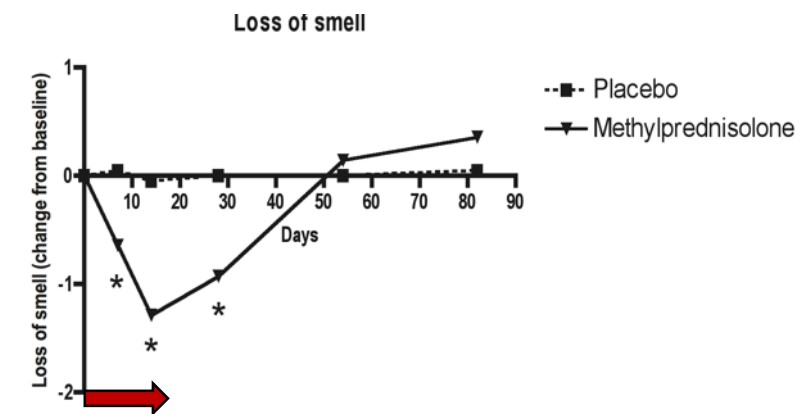
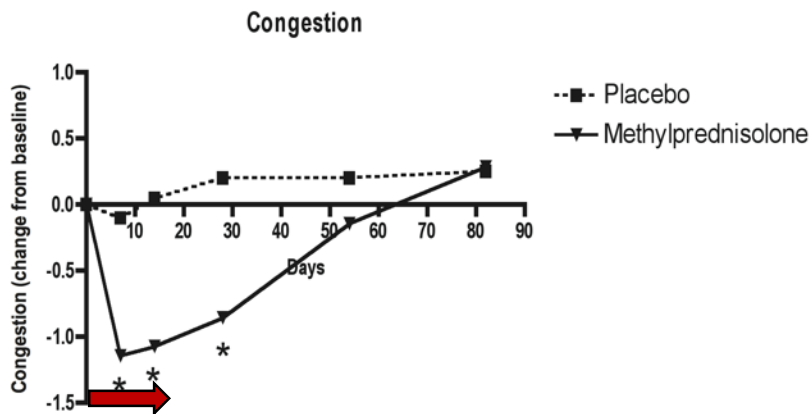
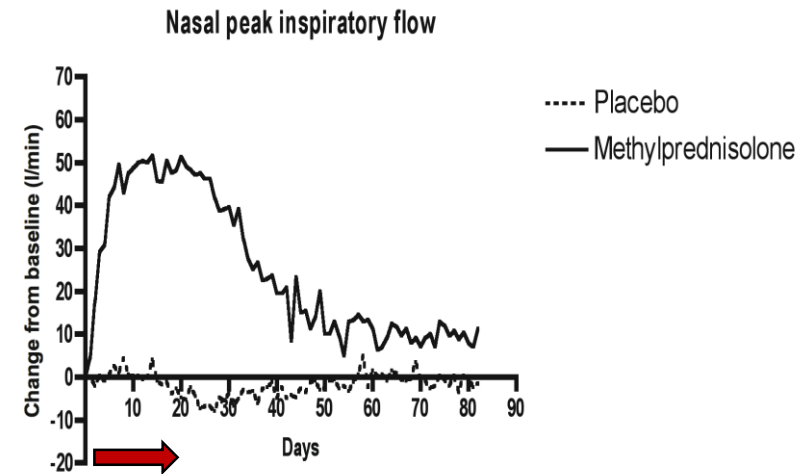
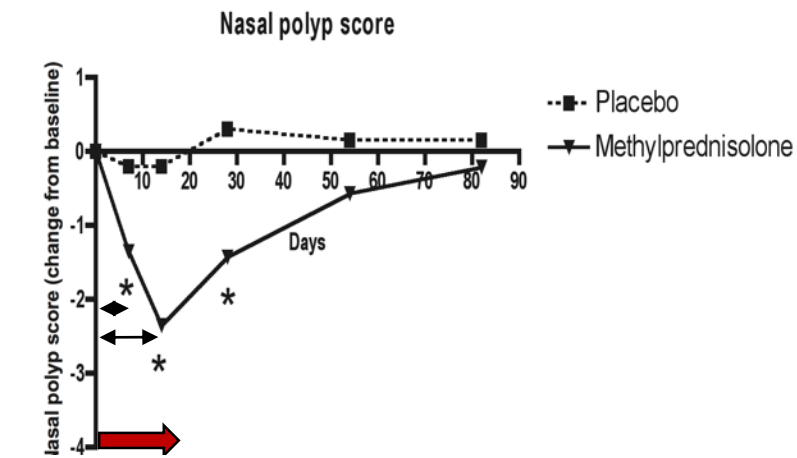
- After 12-weeks: ↓ nasal blockage, ↓ peak nasal inspiratory flow
- ↓ polyp volume (CT score)
- ↓ need for sinus surgery

Aukema, Mulder, Fokkens; JACI 2005

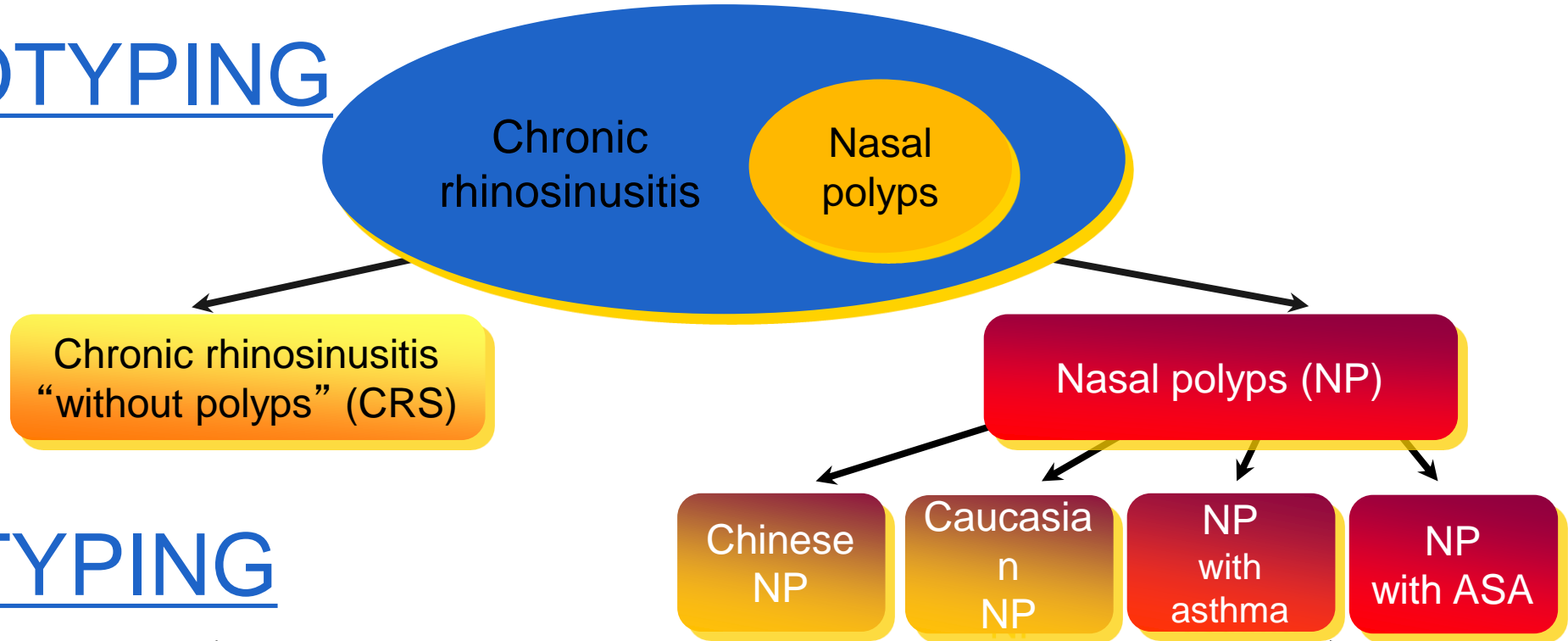


ORAL STEROIDS IN NASAL POLYPS: A 3-MONTH DOUBLE BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

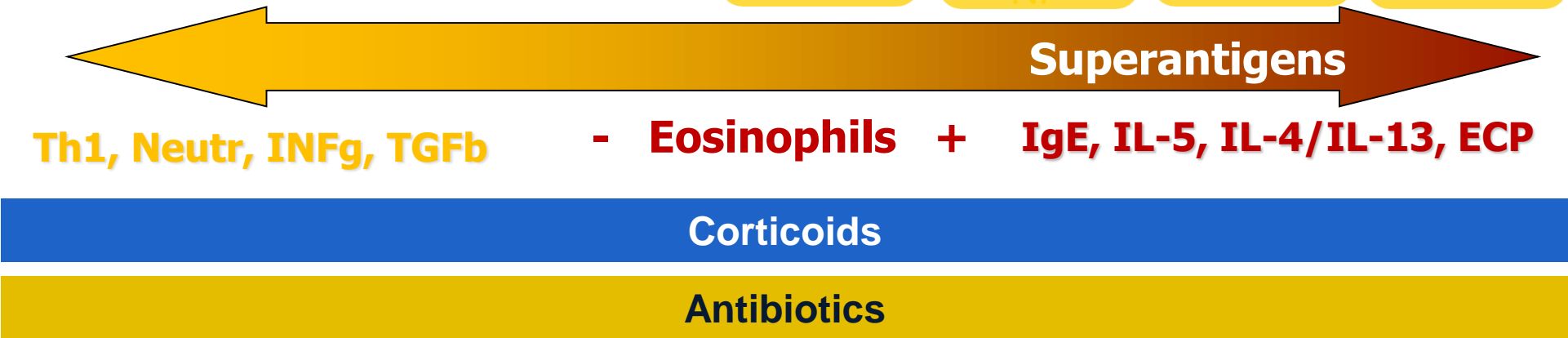
DBPC IN 32 PATIENT WITH NASAL POLYPS, 20DAYS METHYLPREDNISOLON (DAY 1-5 32 MG, DAY 6-10 16 MG, DAY 11-20 8 MG)



PHENOTYPING

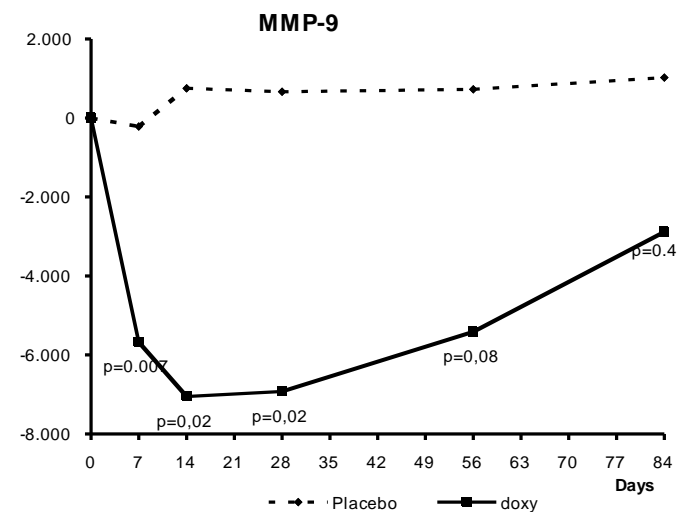
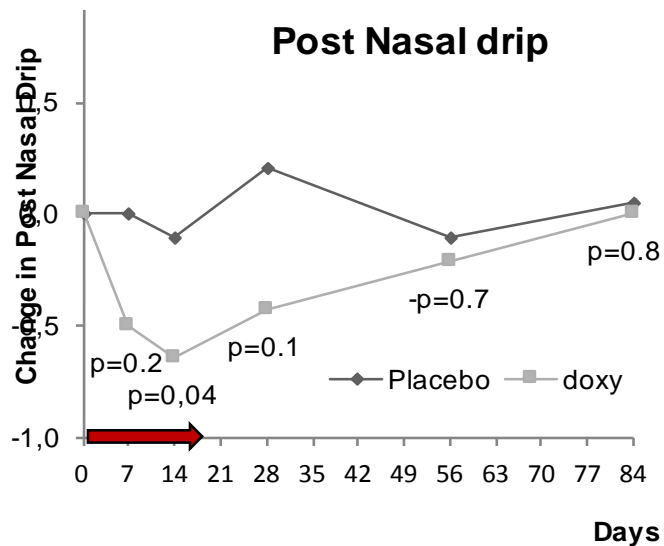
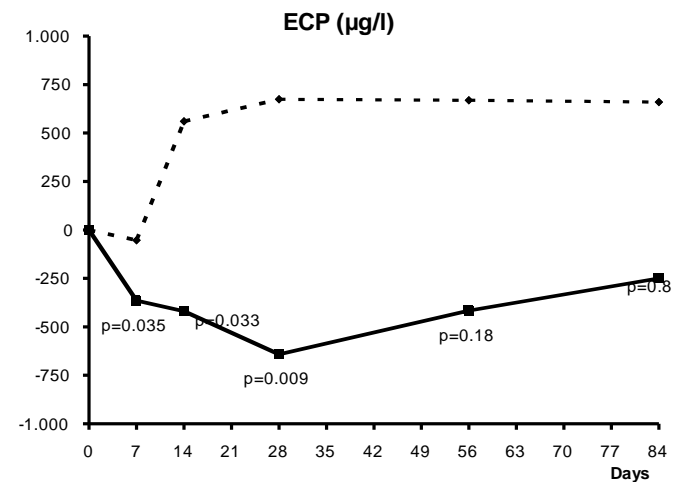
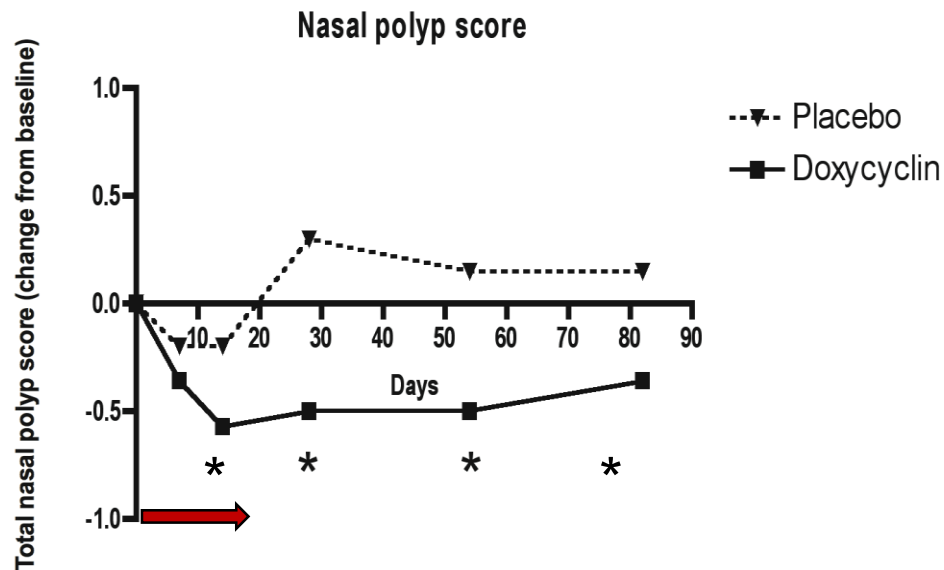


ENDOTYPING

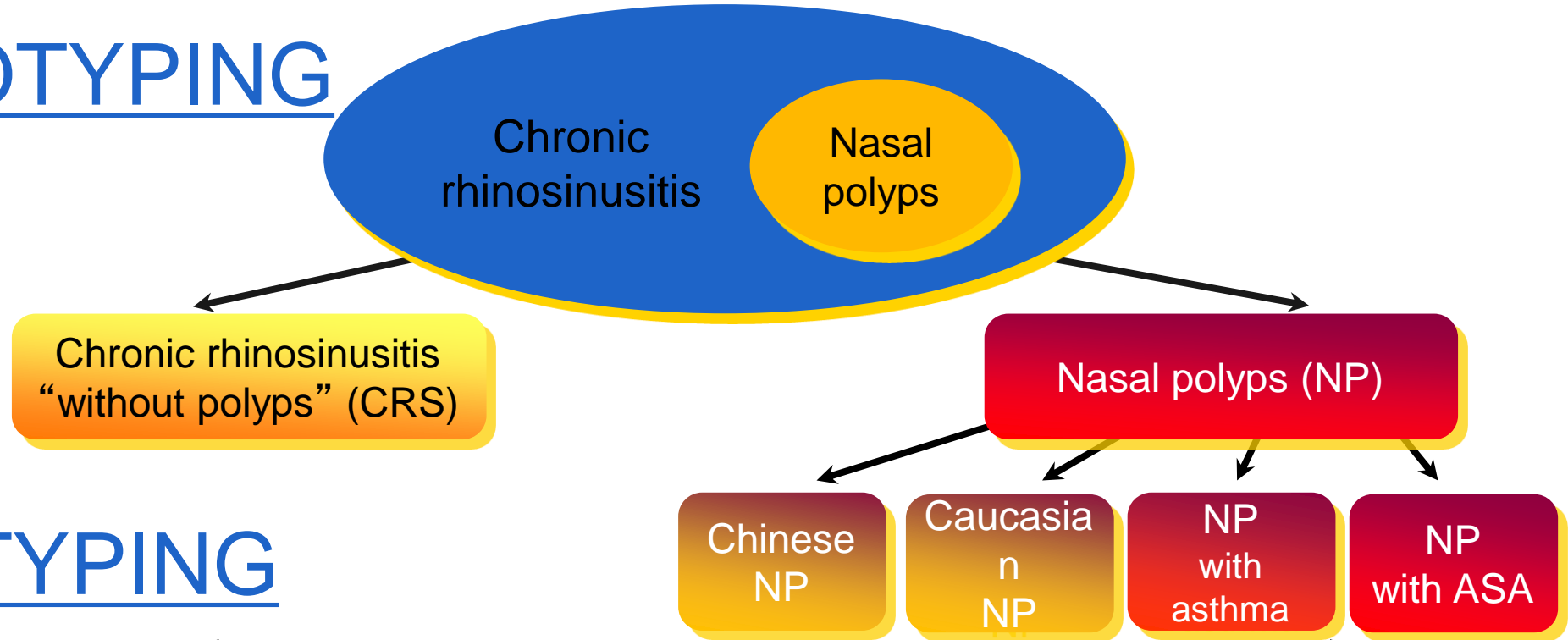


DOXYCYCLINE REDUCES NASAL POLYP SIZE, POST NASAL DRIP, MMP9, ECP, MPO IN A DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, MULTICENTER TRIAL.

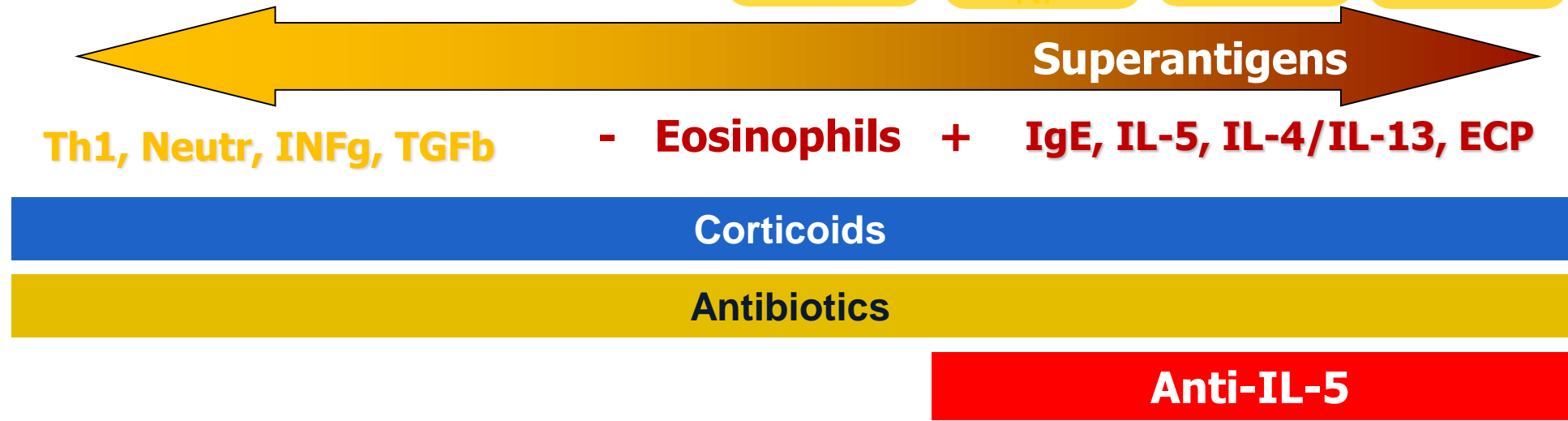
20 DAYS DOXYCYCLINE (100MG/D) REDUCES PND



PHENOTYPING



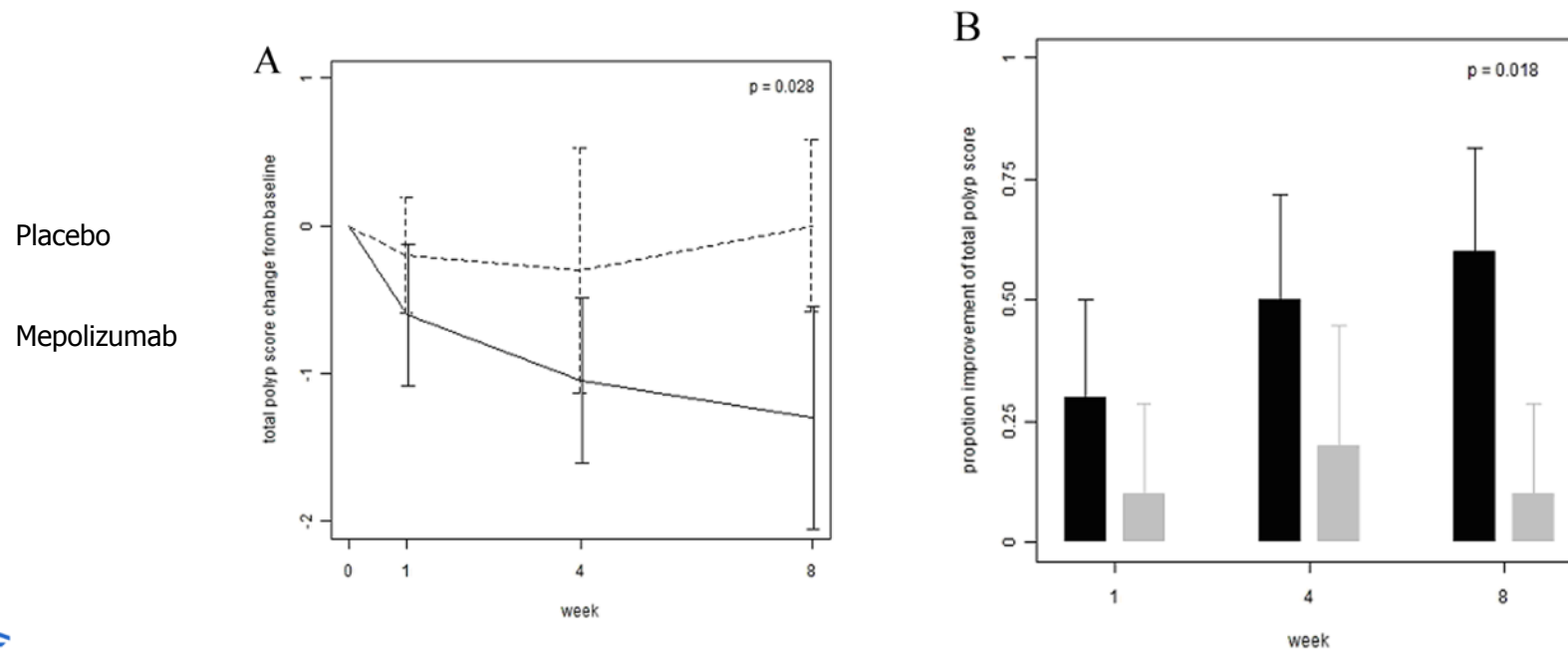
ENDOTYPING



ANTI-IL5 IMPROVES TOTAL NASAL POLYP SCORE IN 50% OF PATIENTS

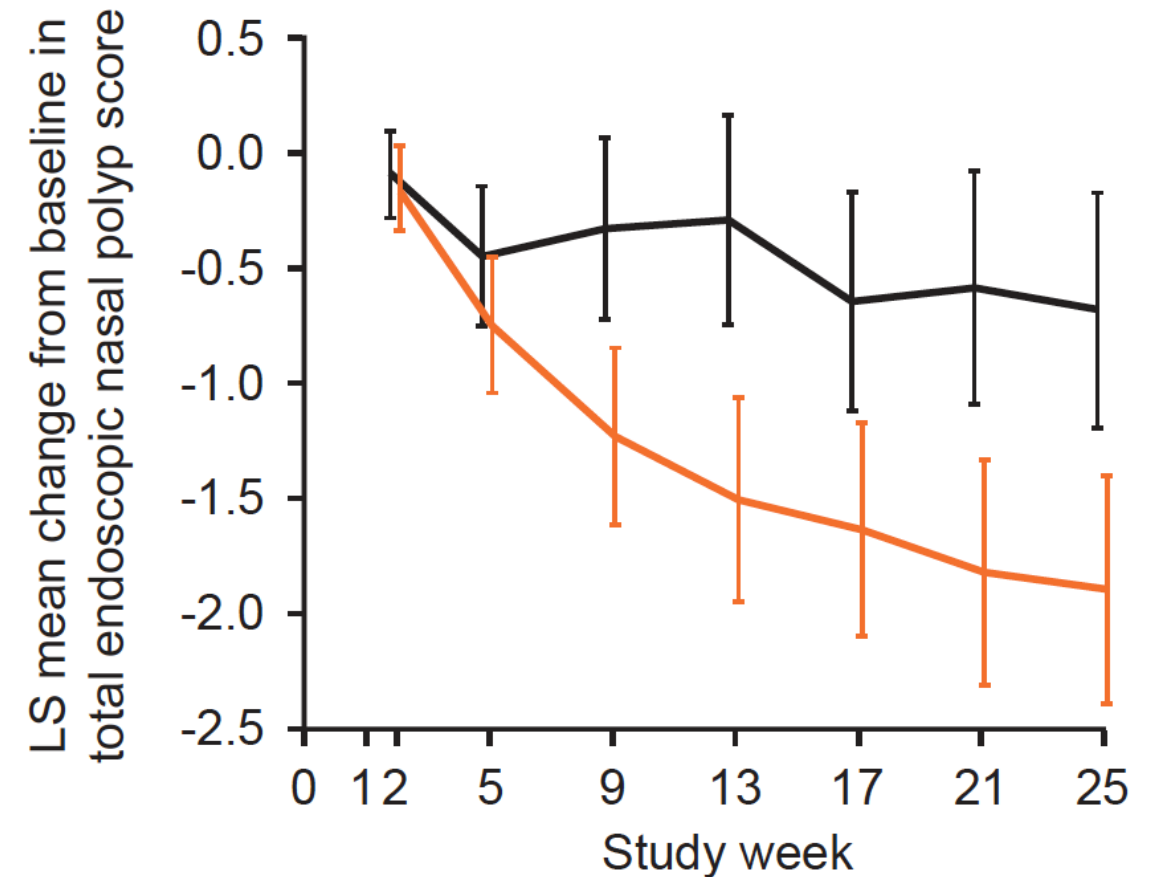
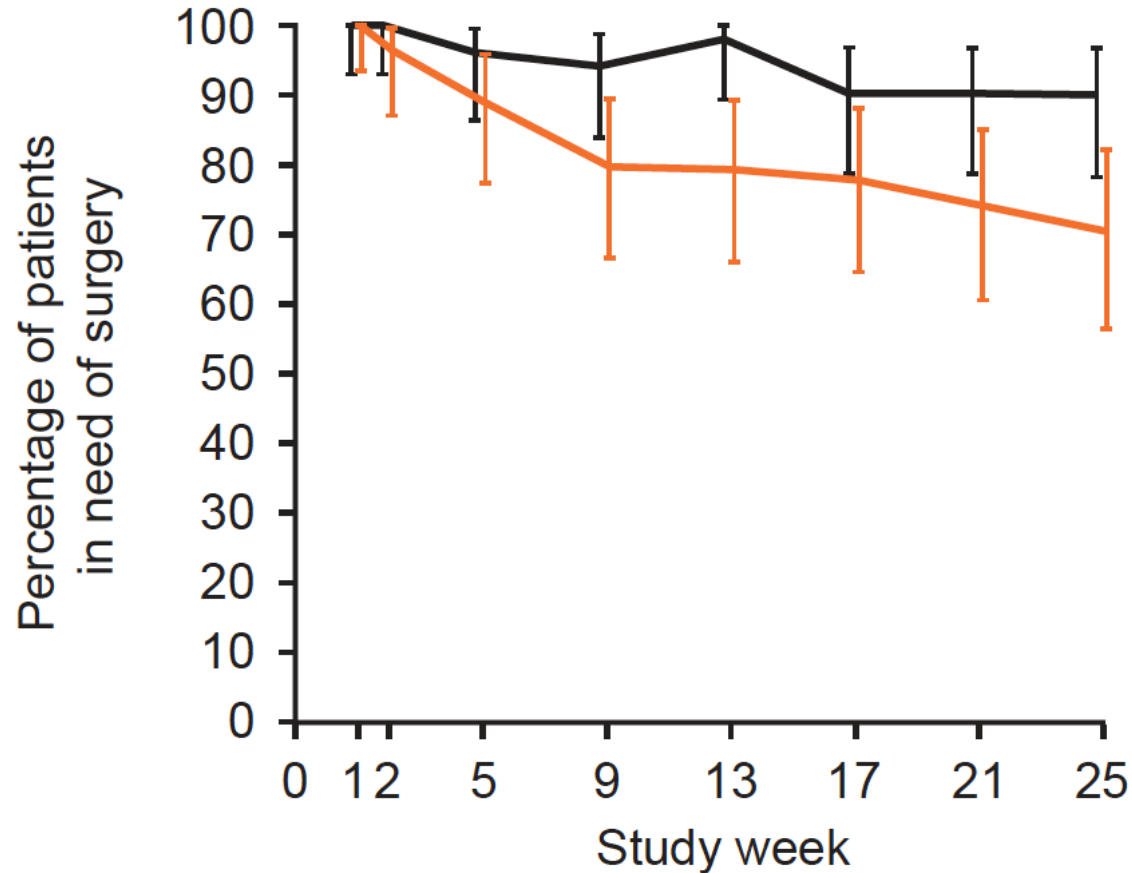
Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis

Philippe Gevaert, MD, PhD,^{a*} Nicholas Van Bruaene, MD,^{a*} Tom Cattaert, PhD,^{b,c} Kristel Van Steen, PhD,^{b,c} Thibaut Van Zele, MD, PhD,^a Frederic Acke, MD,^a Natalie De Ruyck, MSc,^a Katrien Blomme, MSc,^a Ana R. Sousa, PhD,^d Richard P. Marshall, MD, PhD,^d and Claus Bachert, MD, PhD^a *Ghent and Liège, Belgium, and Stevenage, United Kingdom*

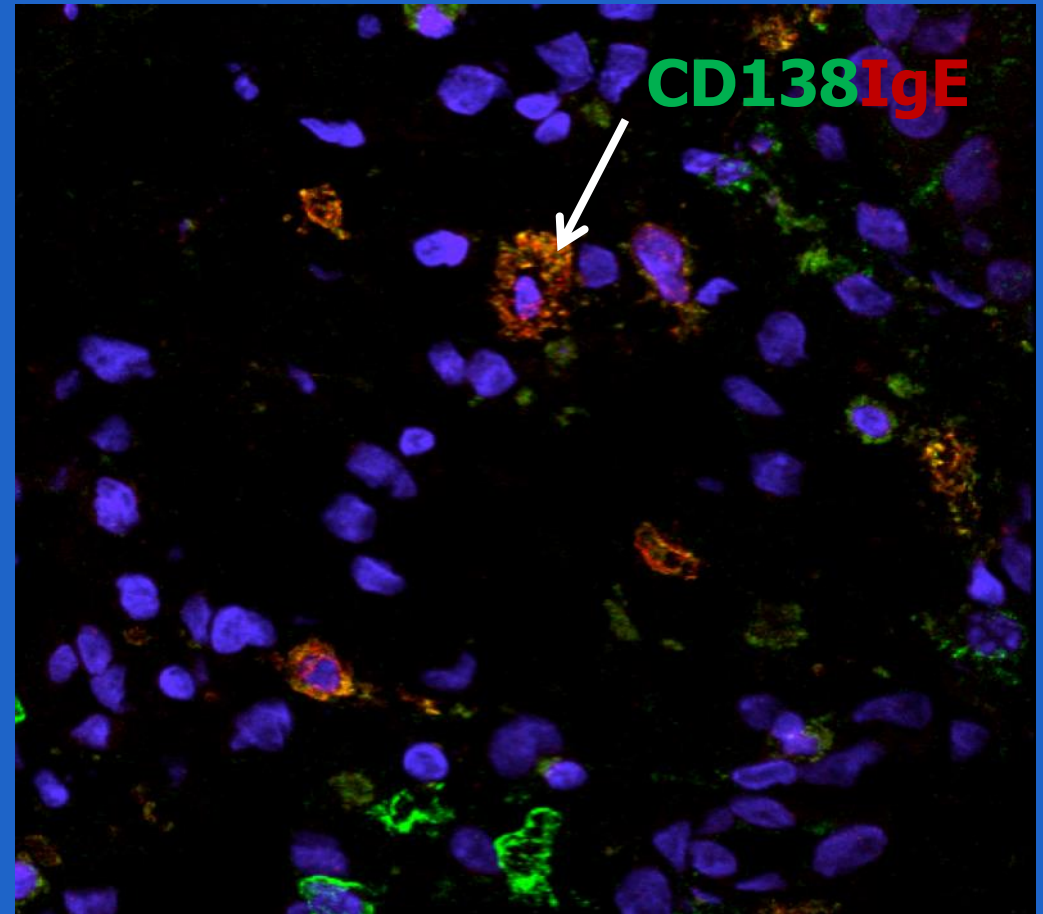
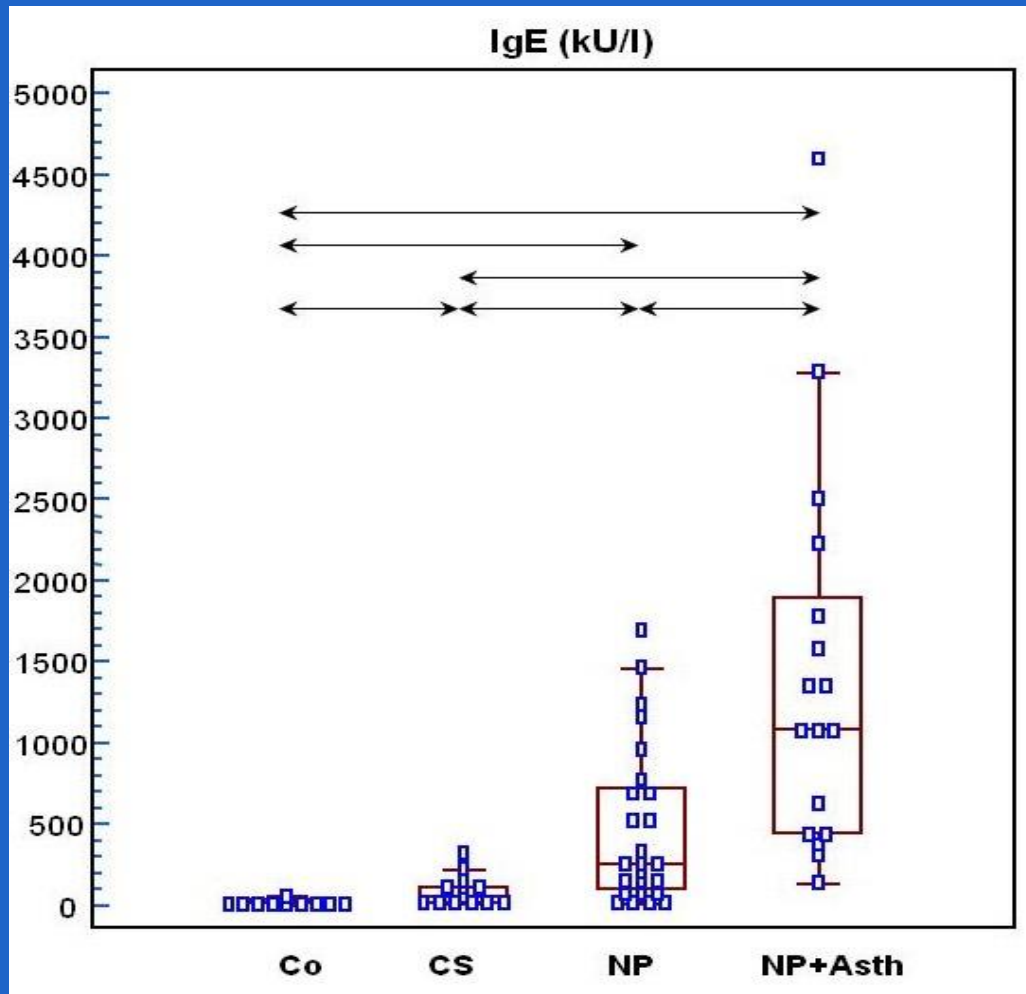


REDUCED NEED FOR SURGERY IN SEVERE NASAL POLYPOSIS WITH MEPOLIZUMAB: RANDOMISED TRIAL

CLAUS BACHERT PHD^{1,2}, ANA R. SOUSA PHD³, VALERIE J. LUND MD⁴, GLENIS K. SCADDING MD⁴, PHILIPPE GEVAERT MD¹, SHUAIB NASSER MD⁵, STEPHEN R. DURHAM MD⁶, MARJOLEIN E. CORNET MD⁷, HARSHA H. KARIYAWASAM PHD⁴, JANE GILBERT MSC⁸, DAREN AUSTIN PHD³, AOIFE C. MAXWELL PHD⁹, RICHARD P. MARSHALL PHD³, WYTSKE J. FOKKENS PHD⁷

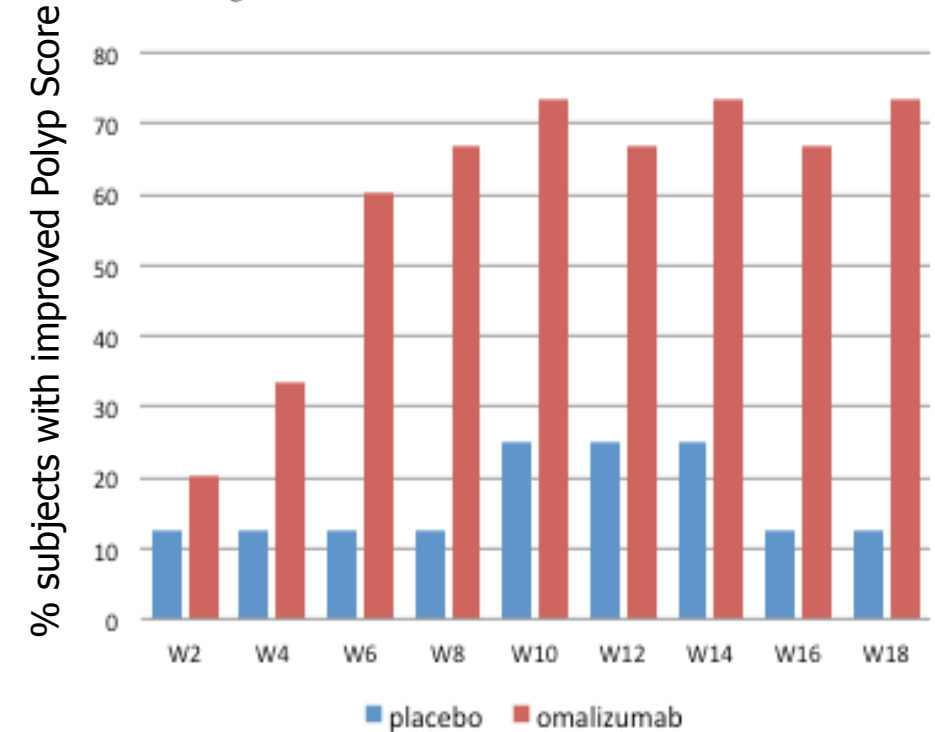
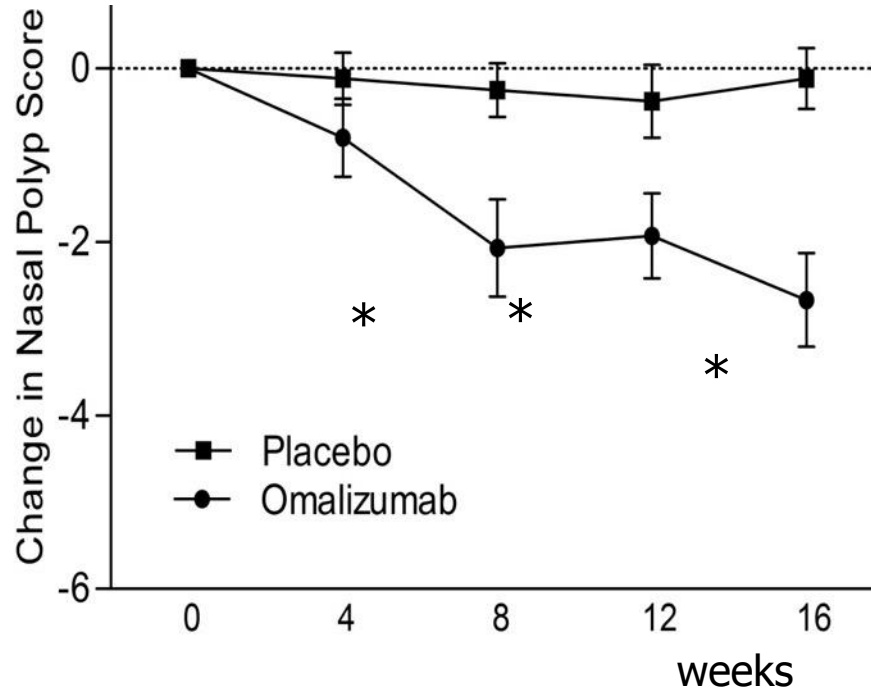


LOCAL IGE IN NASAL POLYPS



Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma

Philippe Gevaert, MD, PhD,^{a*} Lien Calus, MD,^{a*} Thibaut Van Zele, MD, PhD,^a Katrien Blomme, MSc,^a Natalie De Ruyck, MSc,^a Wouter Bauters, MD, PhD,^b Peter Hellings, MD, PhD,^c Guy Brusselle, MD, PhD,^d Dirk De Bacquer, MD, PhD,^e Paul van Cauwenberge, MD, PhD,^a and Claus Bachert, MD, PhD^a *Ghent and Leuven, Belgium*



Results of mixed model (Compound Symmetry covariance matrix/ Time categorical)

Treatment

P=0.004

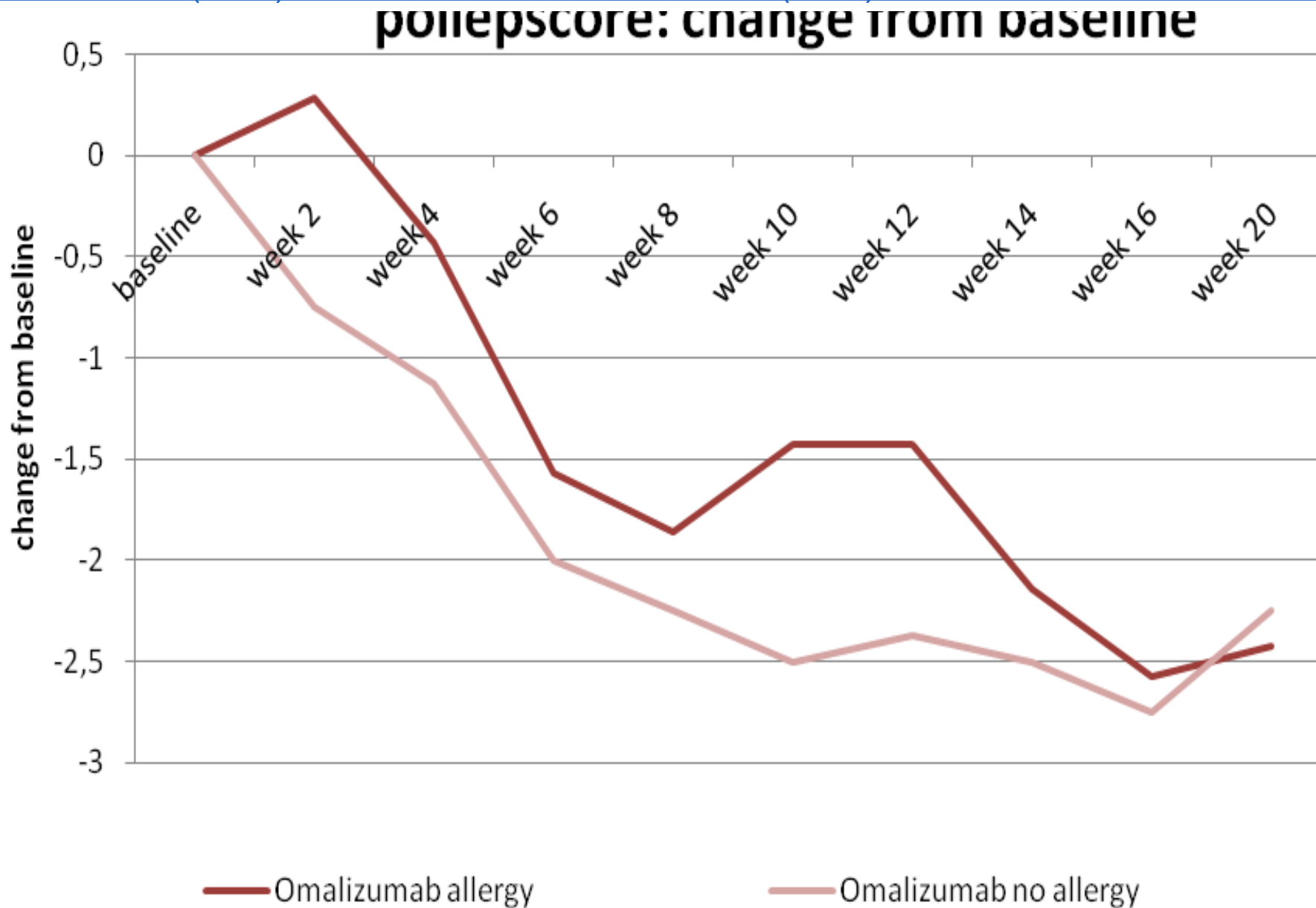
Time

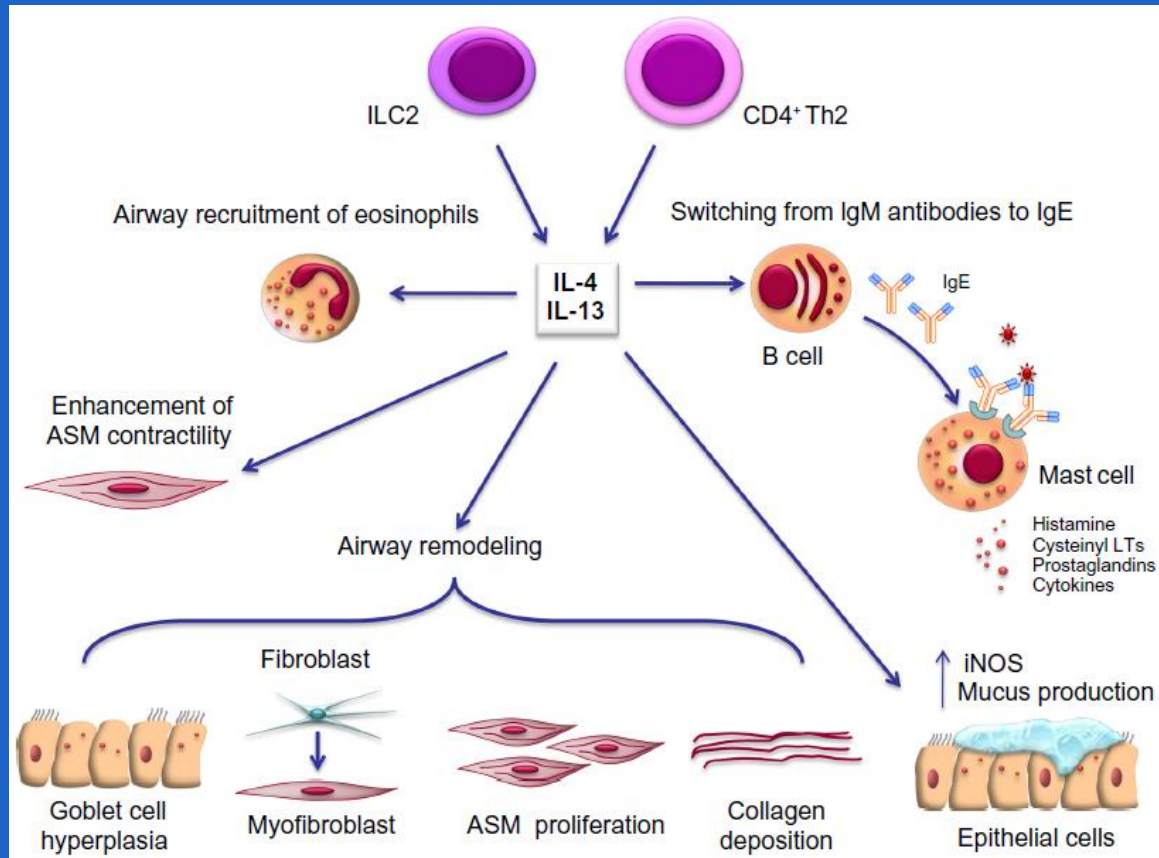
P<0.0001

Time*Treatment

P=0.0009 $F_{4,84} = 5.15$

CHANGE IN TOTAL NASAL POLYP SCORE ALLERGIC (N=7) VERSUS NON ALLERGIC (N=8) POLYPOSIS WITH ASTHMA





ANTI-IL-13 AND ANTI-IL-4R α

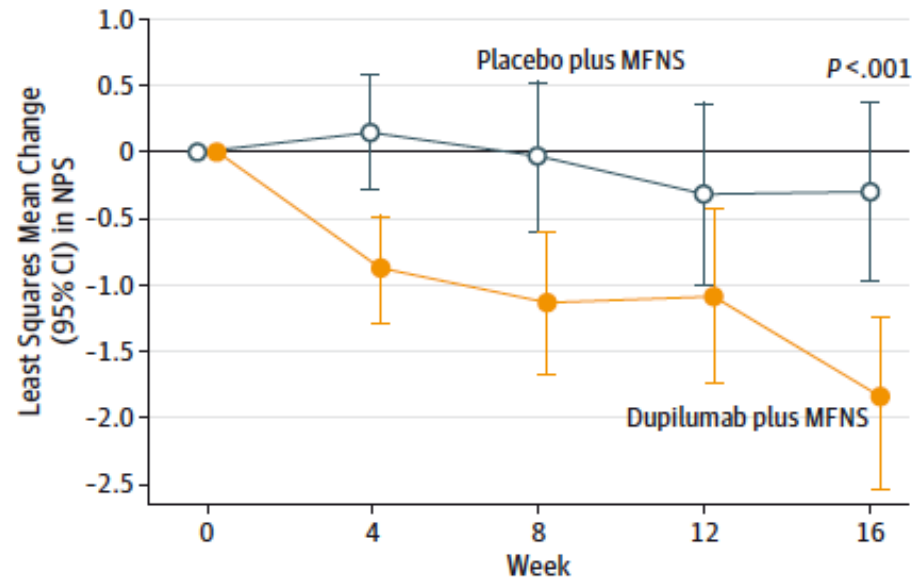
Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis

A Randomized Clinical Trial

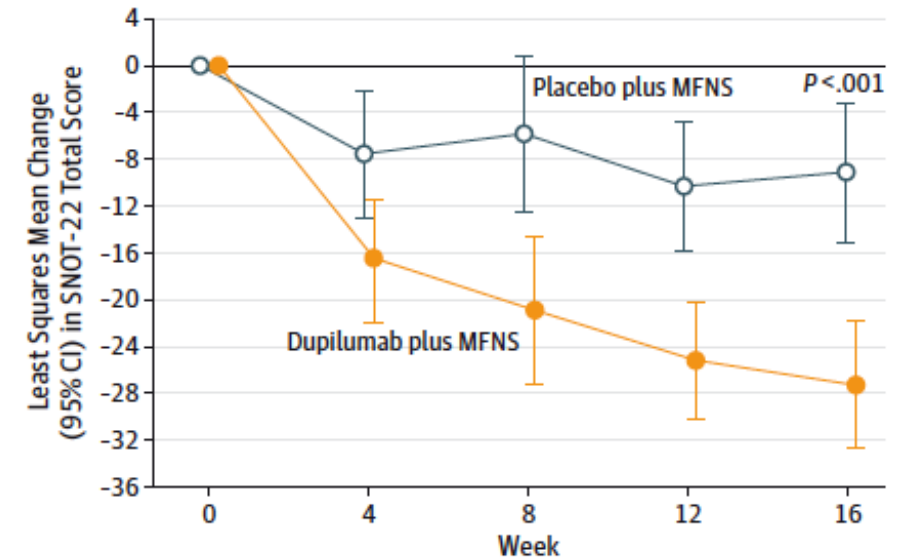
Claus Bachert, MD, PhD; Leda Mannent, MD; Robert M. Naclerio, MD; Joaquim Mullol, MD, PhD; Berrylin J. Ferguson, MD; Philippe Gevaert, MD, PhD; Peter Hellings, MD, PhD; Lixia Jiao, PhD; Lin Wang, PhD; Robert R. Evans, PharmD; Gianluca Pirozzi, MD, PhD; Neil M. Graham, MD, MPH; Brian Swanson, PhD; Jennifer D. Hamilton, PhD; Allen Radin, MD; Namita A. Gandhi, PhD; Neil Stahl, PhD; George D. Yancopoulos, MD, PhD; E. Rand Sutherland, MD, MPH

Figure 2. Primary and Secondary End Points for All Patients

A Endoscopic nasal polyp score (NPS) by treatment group



A 22-Item SinoNasal Outcome Test (SNOT-22) total score by treatment group



No. of patients

Placebo plus MFNS	30	29	26	25	23
Dupilumab plus MFNS	30	30	27	26	29

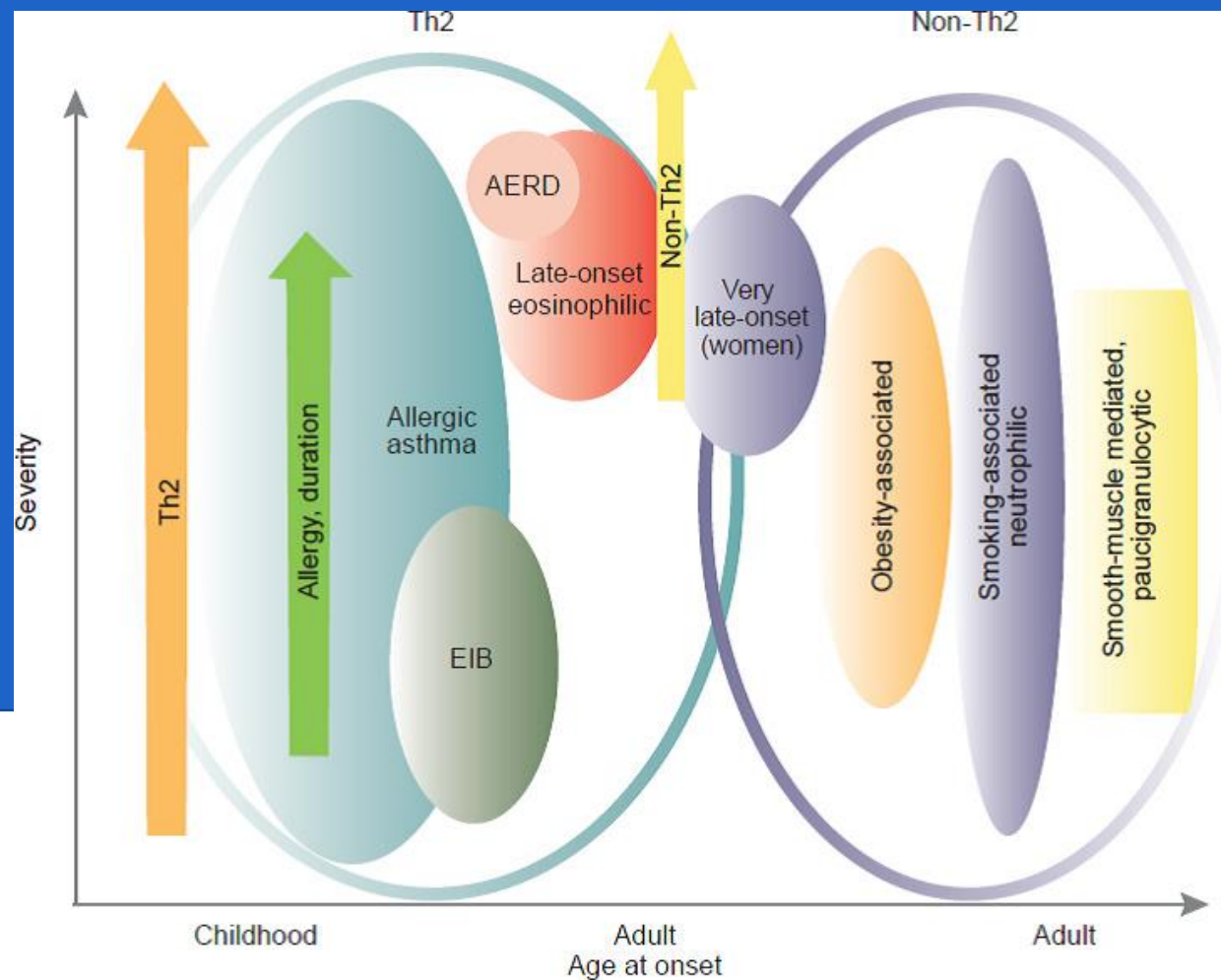
BEHANDELING VAN NEUSPOLIEPEN IN DE PRAKTIJK



- Spoelen met zout water
- Nasale corticosteroiden
 - GCS sprays: 2x/d, symptomen↓
 - GCS druppels: symptomen↓, surgery↓↓
- Orale corticosteroiden: snel en effectief
snel recidief en bijwerkingen
- Antibiotica:
 - Antibiotica zalf of spoelingen (bactroban)
 - Long-term antibiotica: clarithromycine 250 mg/d for 8w
doxycycline 100 mg/d for 8w
- Toekomst: Omalizumab (anti-IgE) bij NP met astma!
Reslizumab en Mepolizumab (anti-IL5)
Dupilumab (anti-IL4R/13R)

UNITED AIRWAYS REVISITED:

TREATMENT OF LATE ONSET SEVERE AIRWAY INFLAMMATION WITH BIOLOGICALS



Prof Dr Claus Bachert
Prof Dr Philippe Gevaert
Prof Dr Thibaut Van Zele

Dr Nan Zhang
Dr Koen Van Crombruggen
Dr Olga Krysko
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