Cancun, December 5, 2011

ALLERGIC RHINITIS: Evidence Based Medicine

Prof. ***Giorgio Walter Canonica***

Allergy and Respiratory Diseases Department
University of Genoa

Past President

1° vice President

Disclosure of Interests of G.W.Canonica

Prof. Giorgio Walter CANONICA , in the last five years, has been:
-scientific consultant as a single scientist or in national/international boards,
-researcher in scientific trials in his university or in collaboration with other research institutions,
-speaker in scientific meetings, seminars and educational activities devoted to specialists, general practitioners and other healthcare professionals,
totally or partially supported by the following commercial companies:

-A.Menarini
-Alk-Abello'
-Almirall
-Allergy Therapeutics
-Anallergo
-AstraZeneca
-Boeringher Ingelheim
- Chiesi Farmaceutici
- Danone
- Faes
- Glaxo Smith Kline
- Hal
- Lallemand
- Lofarma
- Merck Sharp & Dome
- Nycomed Takeda
- Novartis
- Pfizer
- Sanofi
- SigmaTau
- Stallergenes
- Thermo Fisher
- URIACH
- Valeas


OPINION

Opinion Based Medicine

Table 2. Opinion-based medicine

Physicians always try to base their decisions on the best available evidence, all too often this evidence represents:

- extrapolations from physiopathology
- conditioning from pre- and postgraduate training,
- clinical experience
- logic, rather than established facts

Bousquet J. et al.,Allergy 2004

Opinion Based Medicine

1991

POSITION PAPER

ITALIAN SOCIETY of ALLERGY
& CLINICAL IMMUNOLOGY

IMMUNOTERAPIA SPECIFICA delle ALLERGIE

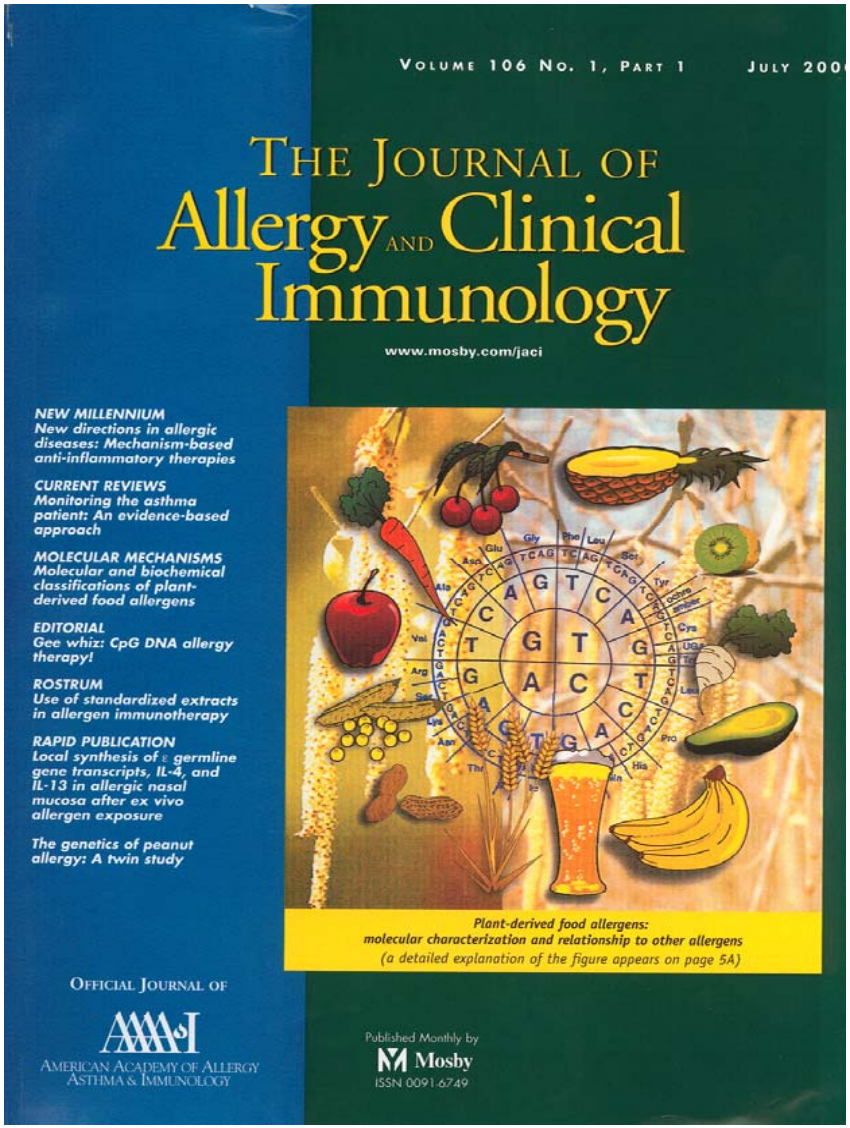
G.W.CANONICA

SLIT:

..... Risk of severe reactions

DUE TO THE RAPID ABSORPTION

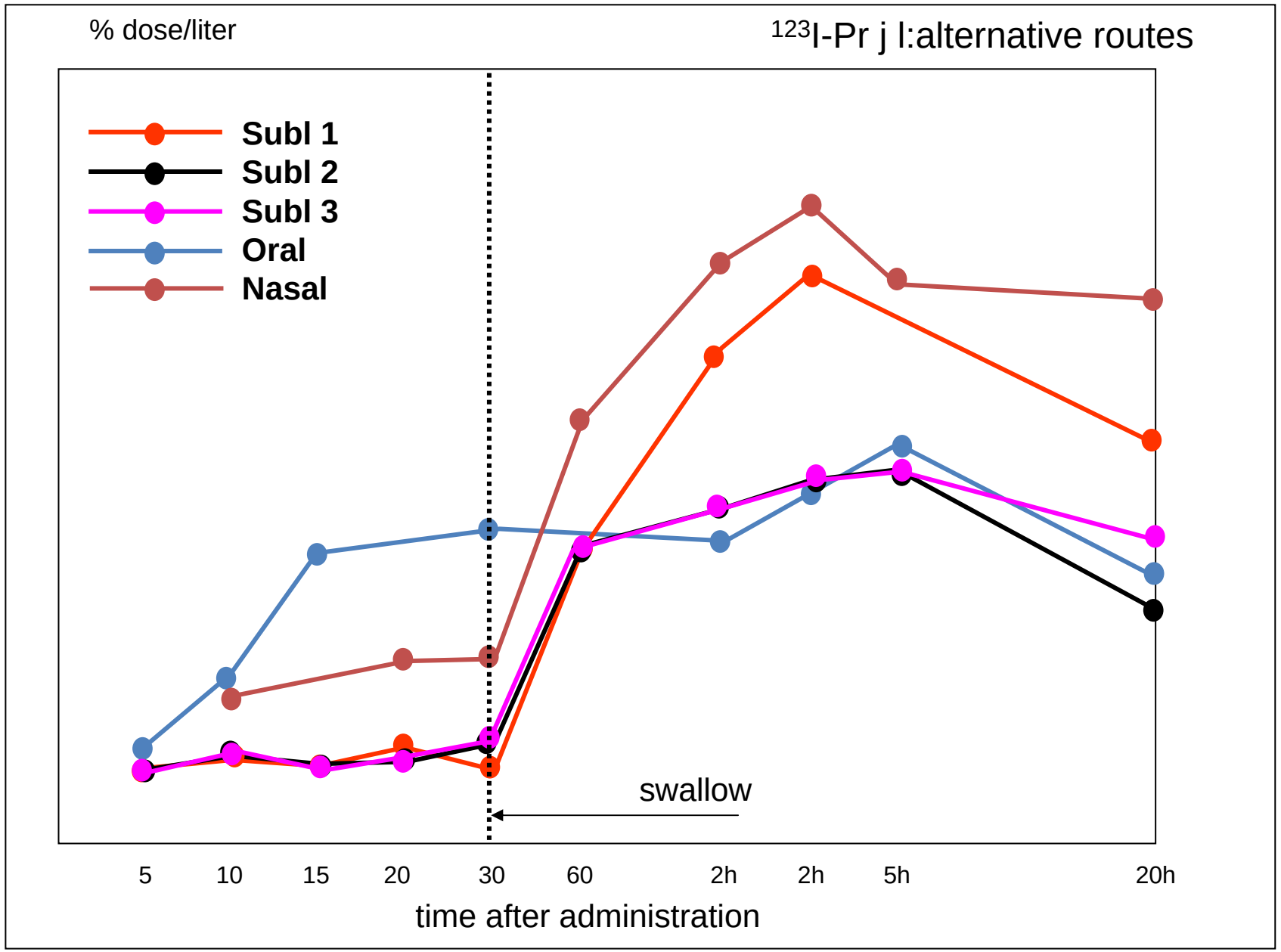
of the allergen.....



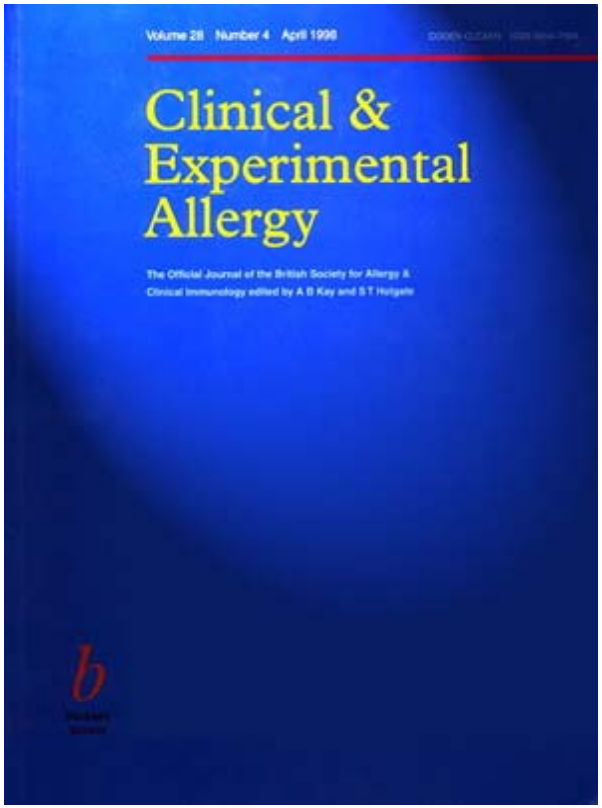
Absorption and distribution kinetics of the major *Parietaria Judaica (Par J 1)* allergen administered by non-injectable to healthy humans beings.

M.Bagnasco, G.Mariani, G.Passalacqua, C.Motta, M.Bartolomei, P. Falagiani, G.Mistrello, G.W. Canonica

JACI 1997; 100:199



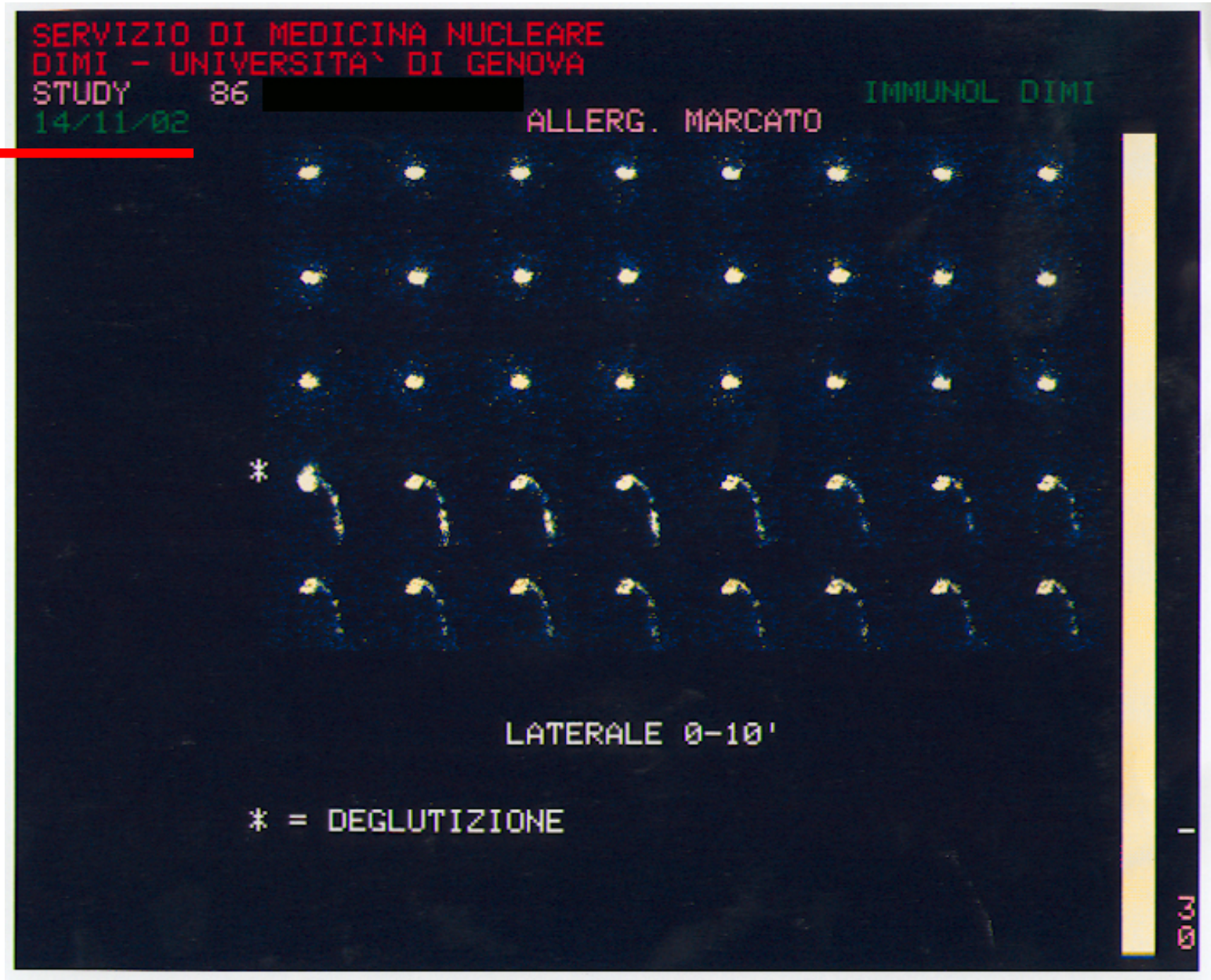
Bagnasco et al. J.A.C.I. 1997



Pharmacokinetics of an allergen and a Monomeric Allergoid for oromucosal immunotherapy in allergic volunteers

Bagnasco M., et al

Clin Exp.Allergy 2001



Der p1 monomeric allergoid. *Allergic volunteer*

E.B.M.

Evidence Based Medicine

Guyatt GH
ACP J Club 1991
Mar-Apr

McMaster University
Inspiring Innovation and Discovery

20 years

EDITORIAL

Evidence-Based Medicine

An internist sees a 70-year-old man whose main problem is fatigue. The initial investigation reveals a hemoglobin of 90 g/L. The internist suspects iron deficiency anemia. How might she proceed?

The way of the past

When faced with this situation during her training just a few years earlier, the internist was told by the attending physician that one ordered serum ferritin and transferrin saturation and proceeded according to the results. She now follows this path. If both results come back below the laboratory's lower limit of normal, she will make a diagnosis of iron deficiency anemia, and investigate and treat accordingly. If both results

She faxes the citation to the library at the local hospital and picks up the article when she does rounds the next morning. She reviews the paper and finds that it meets criteria she has previously learned about validating a diagnostic test (2) and that the results are applicable to patients like hers.

The study shows that she should order a serum ferritin level, but not transferrin saturation, which is less powerful and adds no useful information. She also finds that her laboratory's normal range for the test is misleading. The internist estimates the pretest likelihood of iron deficiency and orders the test. When the result is available, she uses data from the article to determine the sensitivity and specificity associated with the

mal management of the individual patient (3).

For the clinician, evidence-based medicine requires skills of literature retrieval, critical appraisal, and information synthesis.* It also requires judgment of the applicability of evidence to the patient at hand and systematic approaches to make decisions when direct evidence is not available. The primary purpose of *ACP Journal Club* is to help make evidence-based medicine more feasible for internists by extracting new, sound clinical evidence from the morass of the biomedical literature so that practitioners can get at it.

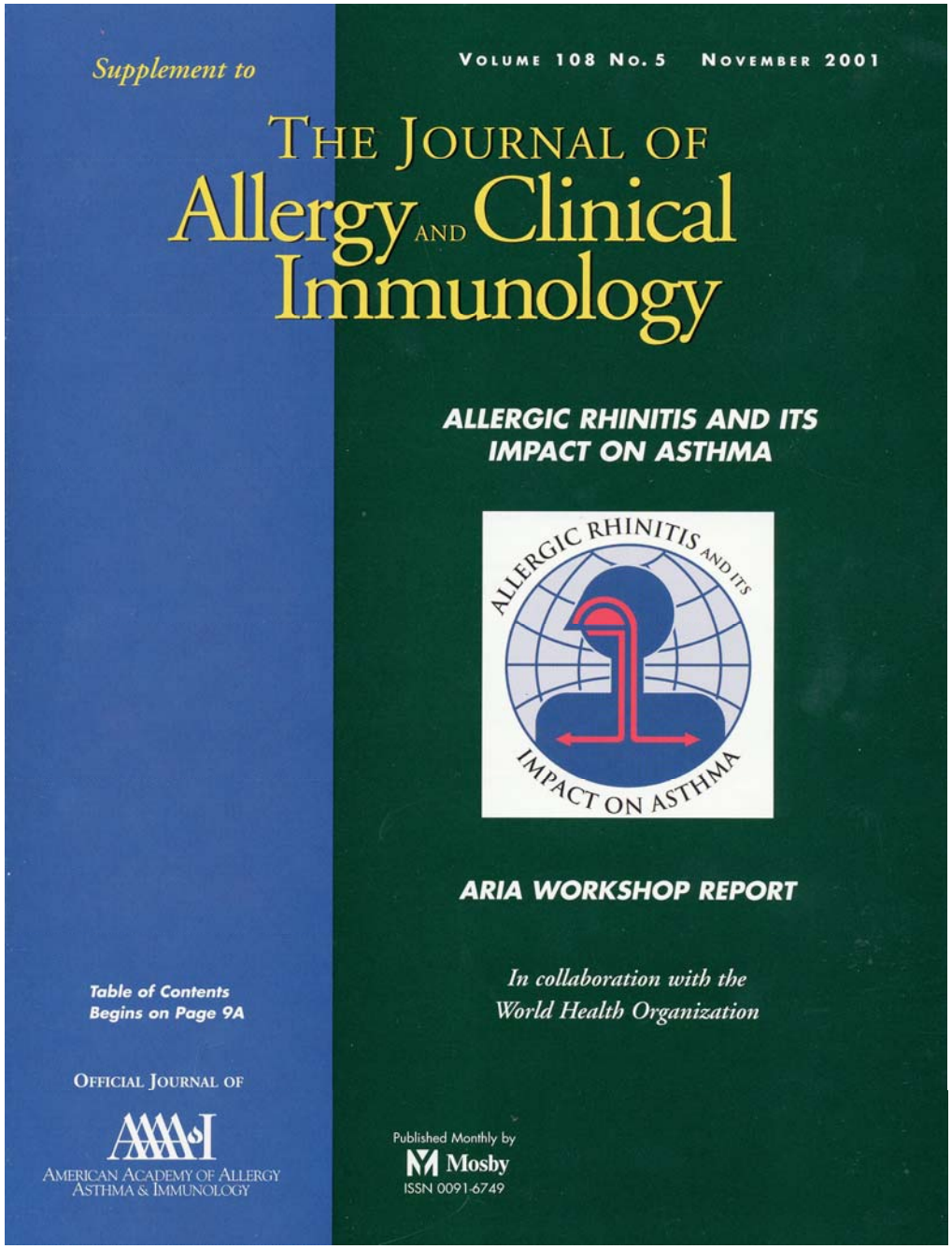
Gordon H. Guyatt, MD, MSc

Evidence-Based Medicine

A New Approach to Teaching the Practice of Medicine

Evidence-Based Medicine Working Group

JAMA, November 4, 1992—Vol 268, No. 17


Supplement to
VOLUME 108 NO. 5 NOVEMBER 2001
THE JOURNAL OF
Allergy AND Clinical
Immunology
ALLERGIC RHINITIS AND ITS
IMPACT ON ASTHMA
ALLERGIC RHINITIS AND ITS
IMPACT ON ASTHMA
ARIA WORKSHOP REPORT
In collaboration with the
World Health Organization
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Begins on Page 9A
OFFICIAL JOURNAL OF
AAAAI
AMERICAN ACADEMY OF ALLERGY
ASTHMA & IMMUNOLOGY
Published Monthly by
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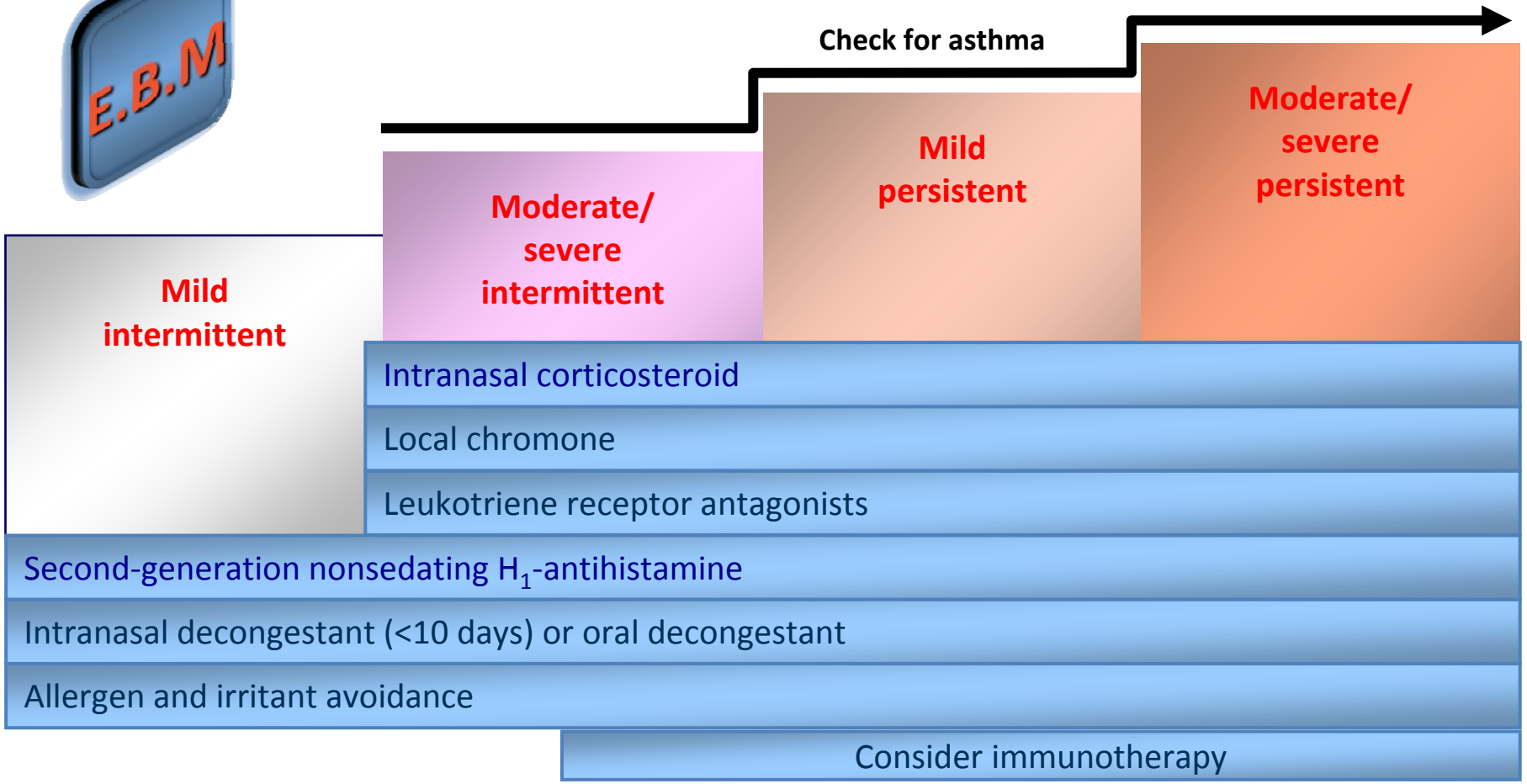
ISSN 0091-6749


E.B.M

ARIA Guidelines: Recommendations for Management of Allergic Rhinitis



Bousquet et al. *J Allergy Clin Immunol*. 2001;108(5 suppl):S147.
At: http://www.whiar.org.

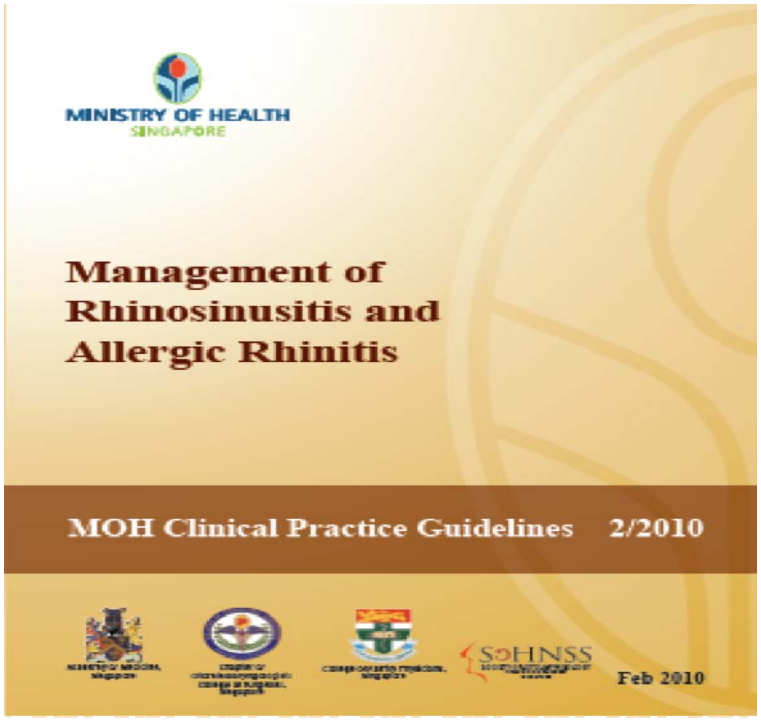
Strength of Evidence for Treatment of Rhinitis: ARIA 2008

Intervention	IAR Adult	IAR Children	PER Adult	PER Children
Oral anti-H_1	A	A	A	A
Intranasal anti-H_1	A	A	A	A
Intranasal CS	A	A	A	A
Intranasal chromone	A	A	A	A
Antileukotriene	A	A	B	
Subcutaneous SIT	A	A	A	A
Sublingual/nasal SIT B	A	A	A	B
Allergen avoidance	D	D	D	B

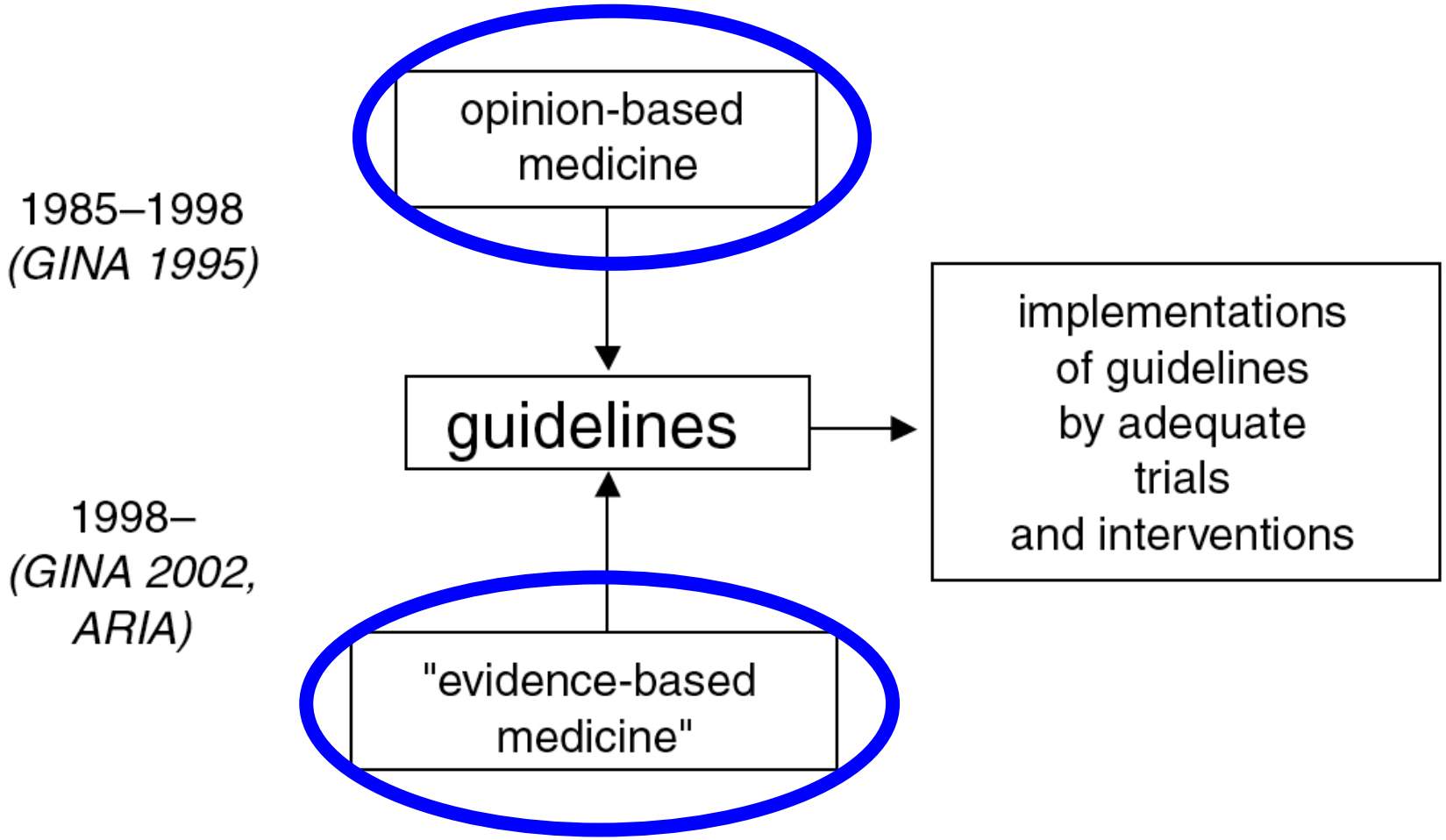
Bousquet et al. *Allergy*. 2008;63(suppl 86):8.


ALLERGIC RHINITIS AND ITS
IMPACT ON ASTHMA


E.B.M


MINISTRY OF HEALTH
SINGAPORE
Management of Rhinosinusitis and Allergic Rhinitis
MOH Clinical Practice Guidelines 2/2010
SOHNSS
Feb 2010

From OBM to EBM



Bousquet J. et al.,Allergy 2004

From EBM to recommendation

Evidence-based medicine

Clinical recommendations on efficacy for an intervention

Clinical guidelines

Developing guidelines

Paul G Shekelle, Steven H Woolf, Martin Eccles, Jeremy Grimshaw

Classification schemes

Category of evidence:
Ia—evidence for meta-analysis of randomised controlled trials
Ib—evidence from at least one randomised controlled trial
IIa—evidence from at lease one controlled study without randomisation
IIb—evidence from at lease one other type of quasi-experimental study
III—evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV—evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Strength of recommendation:
A—directly based on category I evidence
B—directly based on category II evidence or extrapolated recommendation from category I evidence
C—directly based on category III evidence or extrapolated recommendation from category I or II evidence
D—directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

metanalysis

Opinion Based

EAACI/GA²LEN/EDF Guidelines for Management of Urticaria

Zuberbier et al. *Allergy.* 2006;61:321-331.

EAACI / WAO / GA²LEN / EDF Guidelines

3rd International Consensus Meeting on Urticaria

Urticaria 2008

WORLD ALLERGY ORGANIZATION

Allergy 2009: 64: 1417–1426

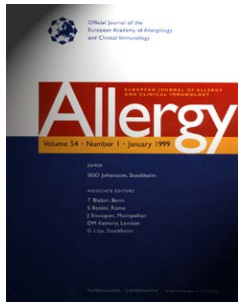
DOI: 10.1111/j.1398-9995.2009.02179.x

Position paper

EAACI/GA²LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria

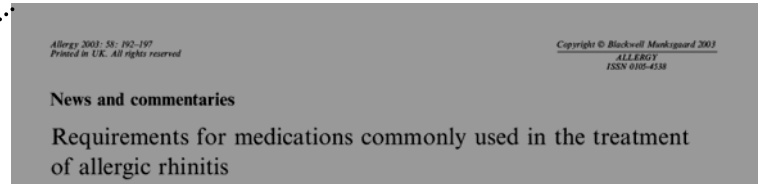
This guideline, together with its sister guideline on the management of urticaria [Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Giménez-Arnau AM et al. EAACI/GA²LEN/EDF/WAO Guideline: Management of urticaria. Allergy, 2009; **64**:1427–1443] is the result of a consensus reached during a panel discussion at the 3rd International Consensus Meeting on Urticaria, *Urticaria 2008*, a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-funded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF) and the World

T. Zuberbier[1], R. Asero[2], C. Bindslev-Jensen[3], G. Walter Canonica[4], M. K. Church[1], A. Giménez-Arnau[5], C. E. H. Grattan[6], A. Kapp[7], H. F. Merk[8], B. Rogala[9], S. Saini[10], M. Sánchez-Borges[11], P. Schmid-Grendelmeier[12], H. Schünemann[13], P. Staubach[14], G. A. Vena[15], B. Wedi[7], M. Maurer[1]



2009

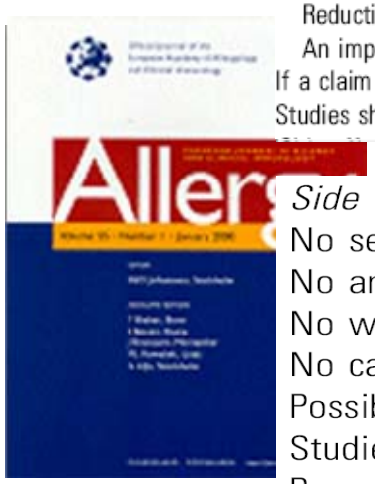
ARIA/EAACI Requirements for Antihistamines in the Treatment of AR



Efficacy

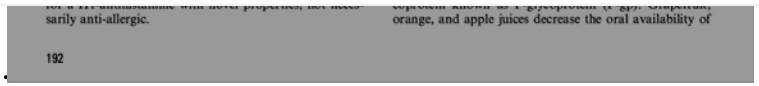
Effective in the treatment of intermittent and persistent rhinitis as defined in the ARIA document
Effective for all nasal symptoms including nasal obstruction
Improvement of eye symptoms
If a claim for asthma is made
- Improvement of asthma symptoms (short term studies)
- Reduction of asthma exacerbations (long term studies)
- An improvement of the pulmonary function tests, although in pollen-induced bronchial symptoms, FEV_1 and peak flow rates are usually not altered.

If a claim for a preventive effect is proposed, appropriate trials should be conducted
Studies should be carried out in young children and elderly patients to assess efficacy



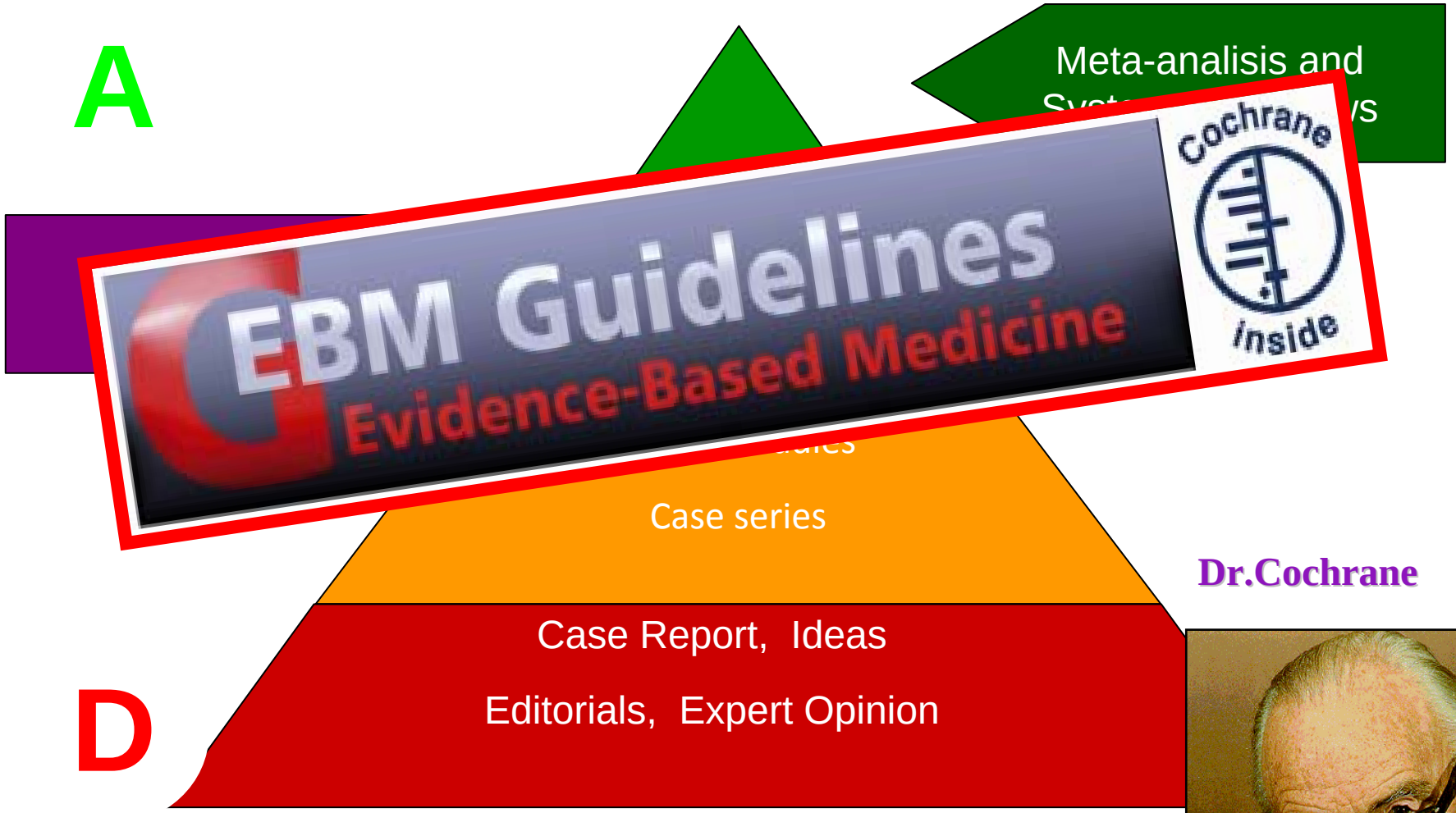
Side effects

No sedation or cognitive or psychomotor impairment
No anti-cholinergic effects
No weight gain
No cardiac side effects
Possible use in pregnancy and breast feeding
Studies should be carried out in young children and elderly age patients to assess safety
Prospective postmarketing safety analyses should be conducted



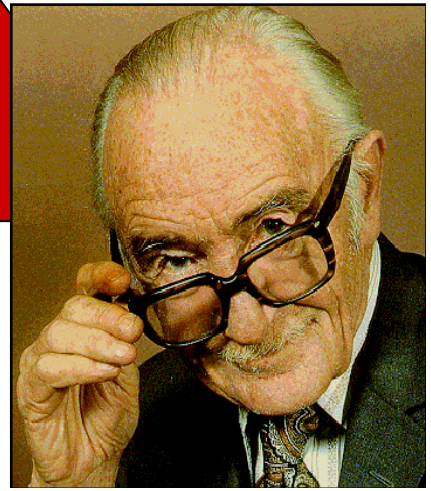
Bousquet. *Allergy*. 2003;58:192.
Bousquet. *Allergy*. 2004;59(suppl 77):4.
Bousquet et al. *Allergy*. 2008;63(suppl 86):8.

GUIDELINES



EBM Hierarchy

Dr.Cochrane



Review article

Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis*

D. R. Wilson[1], M. Torres Lima[2], S. R. Durham[2]

Intranasal corticosteroids versus topical H_1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-an

Anahi Yáñez, MD* and Gustavo J. Rodrigo, MD†

Inhaled magnesium sulfate in the treatment of acu

Blitz M, Blitz S, Beasely R, Diner BM, Hughes R, Knopp JA,

Allergen immunotherapy for asth

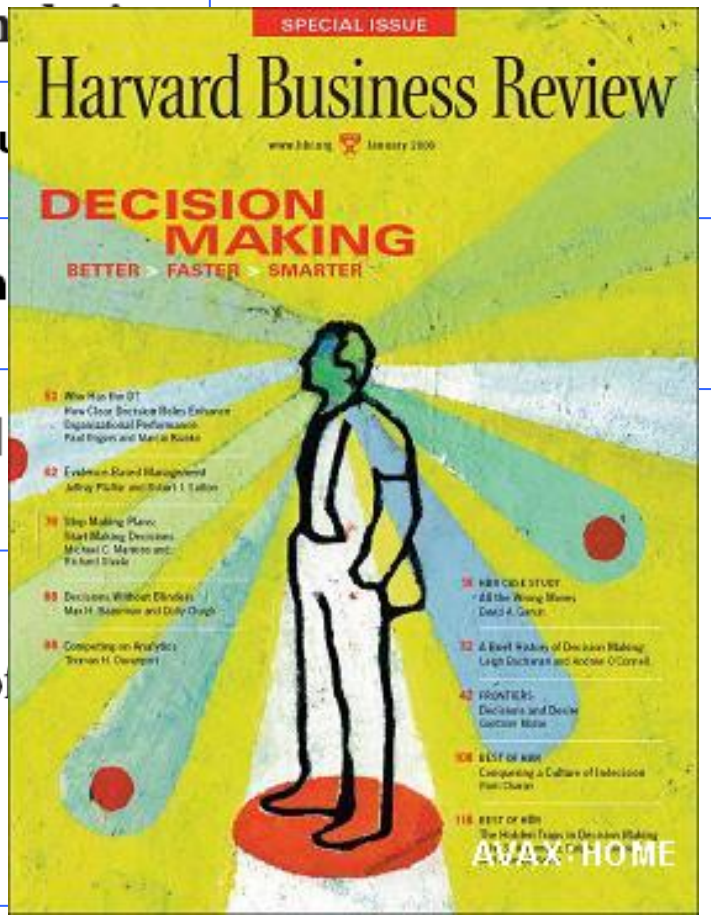
Abramson MJ, Puy RM, Weiner JM

Anti-IgE for chronic asthma in adults and

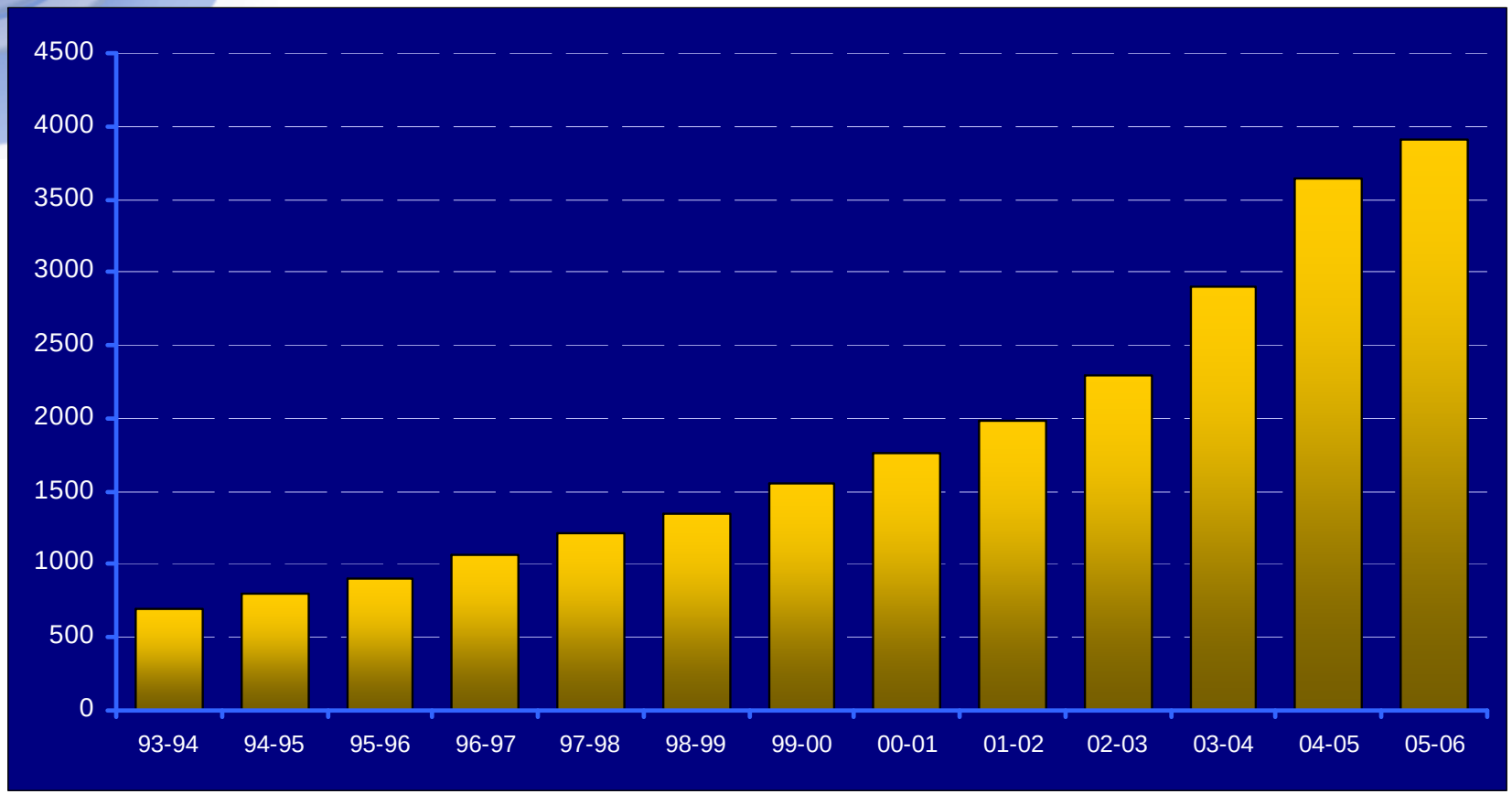
Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH

Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis o randomized, placebo-controlled, double-blind trials

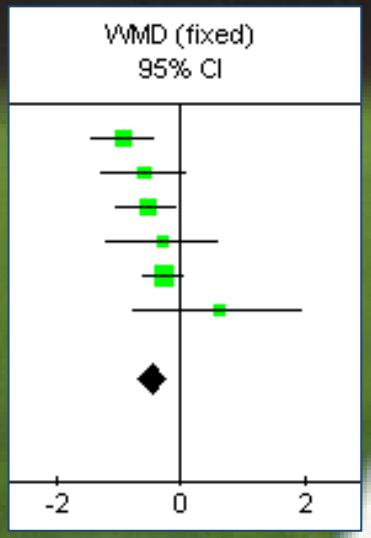
Martin Penagos, MD, MSc*†; Enrico Compalati, MD*; Francesco Tarantini, MD*; Rodrigo Baena-Cagnani, MD*; Jose Huerta, MD‡; Giovanni Passalacqua, MD*; and Giorgio Walter Canonica, MD*

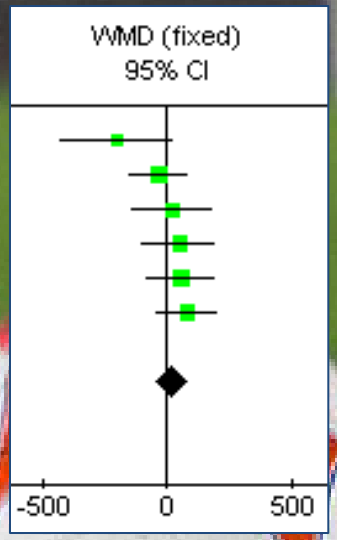


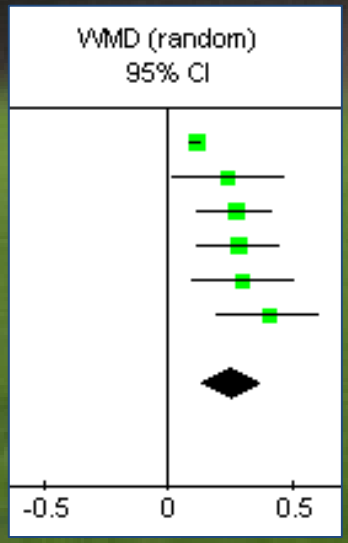
Number of Published Metanalysis Studies



METANALYSIS - Forrest Plot





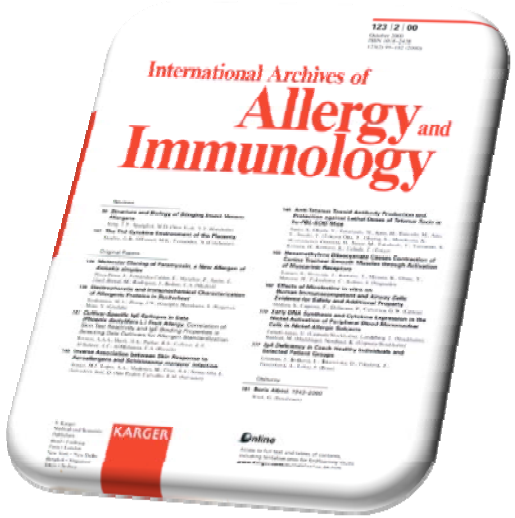


GOAL!!!!

NO

OUT

Systematic review on the efficacy of fexofenadine in seasonal allergic rhinitis: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials.



2011

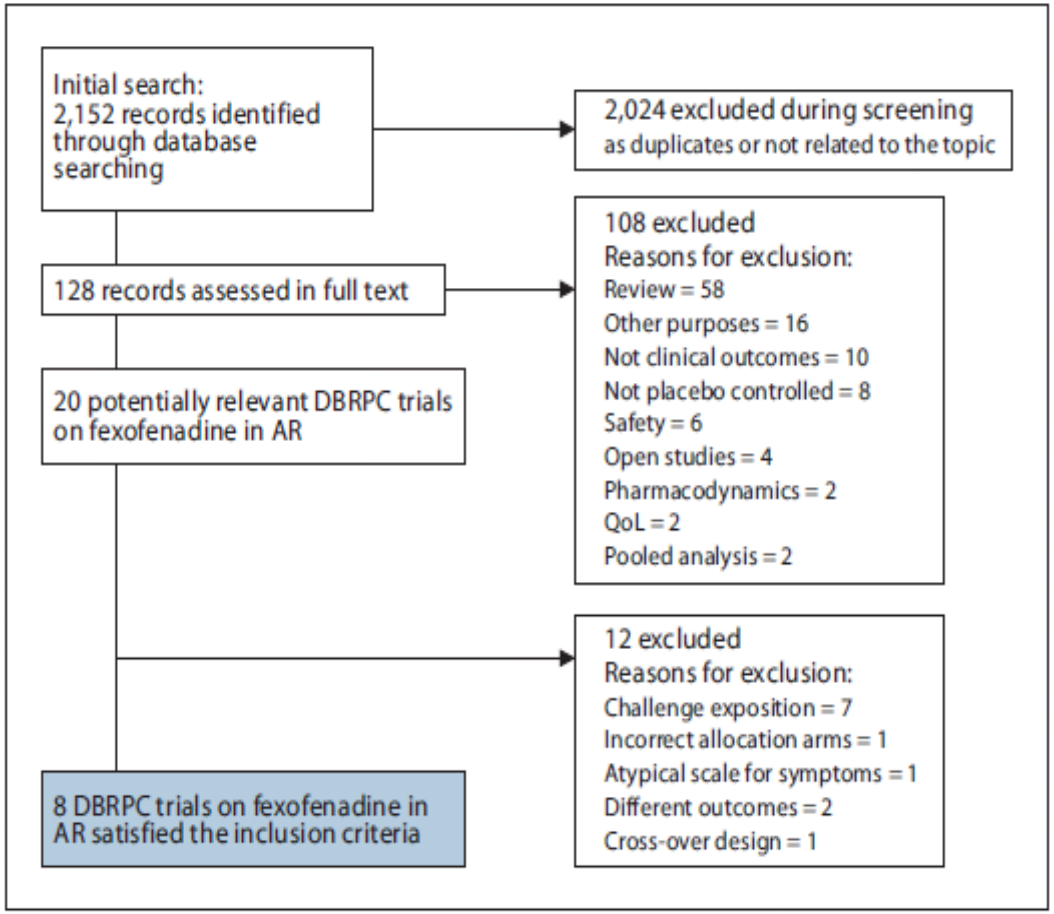
COMPALATI E [1], BAENA-CAGNANI R [2-3], PENAGOS M [1], BADELLINO H [2-3], BRAIDO F [1], GÓMEZ RM [3], CANONICA GW [1], BAENA-CAGNANI CE [1-2-3].

[1] ALLERGY & RESPIRATORY DISEASES CLINIC. DIMI. UNIVERSITY OF GENOA. ITALY.
[2] CENTRE OF RESPIRATORY MEDICINE AND ALLERGY. CHUTRO CLINIC. CORDOBA. ARGENTINA
[3] CIMER. CENTRE FOR INVESTIGACION IN RESPIRATORY MEDICINE. FACULTY OF MEDICINE. CATHOLIC UNIVERSITY OF CORDOBA, CORDOBA, ARGENTINA.

Methods

- All double-blind, placebo-controlled randomized trials assessing the efficacy of fexofenadine in AR were searched in ***OVID, MEDLINE, EMBASE*** databases up to December 2007
- Outcomes were extracted from original articles; when this information was not available, authors of each trial were contacted
- Some graphics were digitalized. ***RevMan 5 program*** was used to perform the analysis.
- ***GradePro 3.2.2*** was used to assess the quality of the evidence for paediatric population.

Methods


Initial search:
2,152 records identified through database searching
2,024 excluded during screening
as duplicates or not related to the topic
128 records assessed in full text
108 excluded
Reasons for exclusion:
Review = 58
Other purposes = 16
Not clinical outcomes = 10
Not placebo controlled = 8
Safety = 6
Open studies = 4
Pharmacodynamics = 2
QoL = 2
Pooled analysis = 2
20 potentially relevant DBRPC trials on fexofenadine in AR
12 excluded
Reasons for exclusion:
Challenge exposition = 7
Incorrect allocation arms = 1
Atypical scale for symptoms = 1
Different outcomes = 2
Cross-over design = 1
8 DBRPC trials on fexofenadine in AR satisfied the inclusion criteria

Methods

	Study quality							Study features				Subjects		
Reference	**Study design**	**Concealment of allocation**	**Blinding**	**Quality score***	**Dropout rate (%)**	**Overall quality assessment (Risk of bias)**	**Intervention**	**Control group**	**Active FEX dose analysed in this review**	**Duration (median), days**	**ITT analysis: (active/placebo)**	**Population**	**Age (mean), years**	**Disease classification as reported by the author**
Wahn et al. (36)	DBRPC Parallel 2 arms	B	B	3/5	3.7	Medium	FEX 30	PL	30mg/bid	15	935 (464/471)	Children	8.8 ±1.6 (5-12)	SAR.
Bronsky et al. (37)	DBRPC parallel 4 arms	B	B	3/5	6	Medium	FEX 40/60/120	PL	120mg/bid	14	589 (137/138)	Children-adult	34 ± 10 (12-65)	SAR.
Casale et al. (38)	DBRPC Parallel 3 arms	B	B	3/5	1.2	Medium	FEX 180/120	PL	180mg/od	14	864 (282/292)	Children-adult	33 ± 12 (12-65)	SAR.
Van Cauwenberge et al. (39)	DBRPC Parallel 3 arms	B	B	3/5	3.9	Medium	FEX 120	PL, LO10mg	120mg/od	14	688 (232/225)	Children-adult	30.9 ± 11.51 (12-75)	SAR.
Berstein et al. (40)	DBRPC Parallel 4 arms	B	B	3/5	9%	Medium	FEX 60/120/240	PL	120mg/bid	14	575 (144/141)	Children-adult	32 ± 10 (12-65)	SAR.
Howarth et al. (41)	DBRPC Parallel 4 arms	B	B	3/5	14%	Medium	FEX 120/180	PL, CZ 10mg	180 mg/od	14	842 (202/201)	Children-Adult	33 (13-68)	SAR.
Schapowal et al (42)	DBRPC Paralle 3 arms	B	B	3/5	8.2%	Medium	FEX 180	PL, Butterbur Ze339	180 mg/od	14	330 (113/107)	Adult	38.6±14 (18-80)	SAR.
Berger et al (43)	DBRPC parallel 3 arms	A	A	5/5	3.4%	Low	FEX 180	PL, Desloratdine 5mg	180 mg/od	15	722 (288/244)	Children-Adult	34.5±14.09 (12-84)	SAR.

FEX, fexofenadine; CZ, cetirizine; LO, loratadine; PL, placebo; DBRPC, randomized clinical trial, double-blind; bid, two times daily; od, once daily

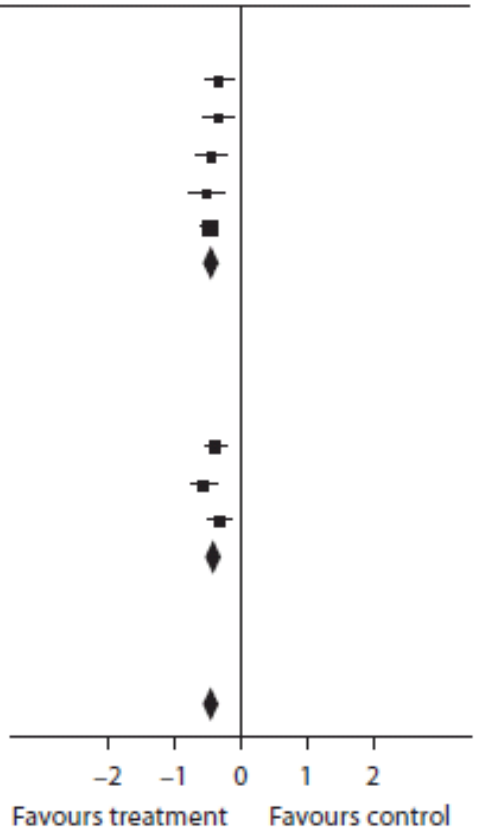
Results

- **Of 2152 identified articles, *20 were potentially relevant trials*. Eight studies satisfied inclusion criteria and were included in the meta-analysis. The main reasons for exclusion were: not natural exposition, strong study limitations, atypical outcome measurement, design for other outcomes, not placebo-controlled, single blind studies. *Seven trials investigated a mixed population of adults and children, one only children and one only adults*.**
- **In 1,833 patients receiving fexofenadine**
- **1,699 placebo**

12-24h Reflective TSS

a

Study or subgroup	Fexofenadine mean	SD	total	Placebo mean	SD	total	weight, %	Std. mean difference IV, fixed, 95% CI
1.1.1 12-hour reflective TSS								
Berger	6.26	2.37	260	7.03	2.37	126	9.8	−0.32 (−0.54, −0.11)
Bernstein	6.55	2.4	144	7.32	2.37	141	8.3	−0.32 (−0.56, −0.09)
Bronsky	6.5	2.11	137	7.45	2.11	138	7.9	−0.45 (−0.69, −0.21)
Schapowal	6.63	4.81	113	9.16	4.81	107	6.2	−0.52 (−0.79, −0.26)
Wahn	4.86	2.15	463	5.86	2.16	469	26.6	−0.46 (−0.59, −0.33)
Subtotal (95% CI)			1,117			981	58.8	−0.42 (−0.51, −0.34)
Heterogeneity: $\chi^2 = 2.50$, d.f. = 4 ($p = 0.65$); $I^2 = 0\%$								
Test for overall effect: $Z = 9.51$ ($p < 0.00001$)								
1.1.2 24-hour reflective TSS								
Casale	6.07	1.85	282	6.78	1.88	292	16.5	−0.38 (−0.55, −0.22)
Howarth	4.1	2.34	202	5.4	2.34	201	11.4	−0.55 (−0.75, −0.36)
Van Cauwenberge	4.56	2.56	232	5.42	2.81	225	13.2	−0.32 (−0.50, −0.14)
Subtotal (95% CI)			716			718	41.2	−0.41 (−0.51, −0.30)
Heterogeneity: $\chi^2 = 3.07$, d.f. = 2 ($p = 0.22$); $I^2 = 35\%$								
Test for overall effect: $Z = 7.66$ ($p < 0.00001$)								
Total (95% CI)			1,833			1,699	100.0	−0.42 (−0.49, −0.35)
Heterogeneity: $\chi^2 = 5.62$, d.f. = 7 ($p = 0.58$); $I^2 = 0\%$								
Test for overall effect: $Z = 12.21$ ($p < 0.00001$)								
Test for subgroup differences: $\chi^2 = 0.05$, d.f. = 1 ($p = 0.82$); $I^2 = 0\%$								

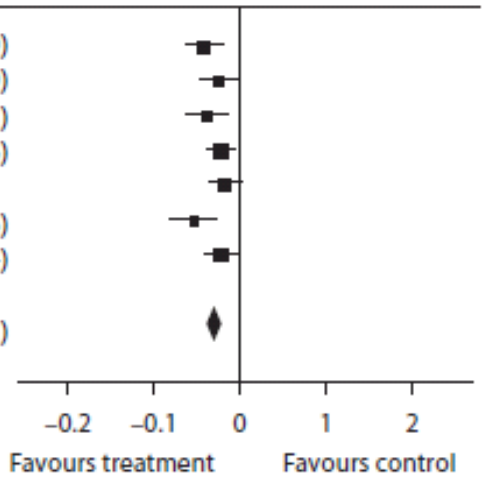


Morning instantaneous TSS

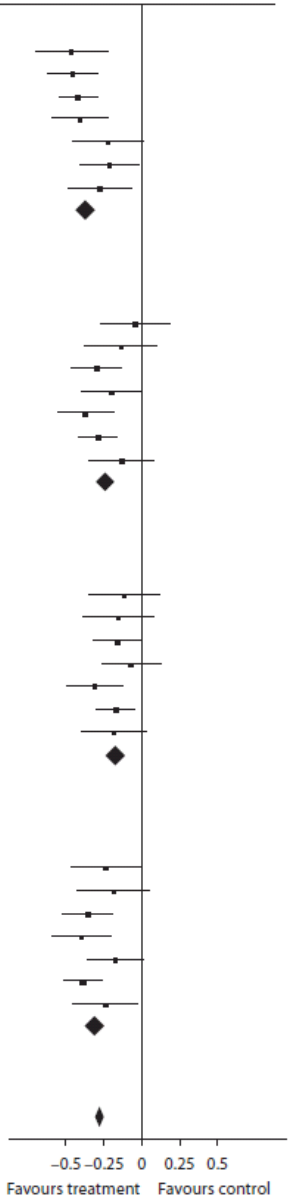
b

Study or subgroup	Fexofenadine mean	SD	total	Placebo mean	SD	total	weight, %	Std. mean difference IV, fixed, 95% CI
Berger	6.04	2.07	260	6.91	2.07	126	13.2	−0.42 (−0.63, −0.20)
Bernstein	6.81	2.28	144	7.36	2.37	141	11.2	−0.24 (−0.47, −0.00)
Bronsky	6.58	2.11	137	7.38	2	138	10.7	−0.39 (−0.63, −0.15)
Casale	6.33	1.85	282	6.74	1.88	292	22.6	−0.22 (−0.38, −0.06)
Howarth	4.2	2.34	202	4.6	2.34	201	15.9	−0.17 (−0.37, 0.03)
Schapowal	20.2	12.34	113	26.8	12.34	107	8.4	−0.53 (−0.80, −0.26)
Van Cauwenberge	4.46	2.71	232	5.06	2.73	225	18.0	−0.22 (−0.40, −0.04)
Total (95% CI)			1,370			1,230	100.0	−0.28 (−0.36, −0.21)

Heterogeneity: $\chi^2 = 8.06$, d.f. = 6 ($p = 0.23$); $I^2 = 26\%$
Test for overall effect: $Z = 7.15$ ($p < 0.00001$)



Study or subgroup	Fexofenadine mean	SD	total	Placebo mean	SD	total	weight, %	Std. mean difference IV, fixed, 95% CI
1.3.1 Sneezing								
Bronsky	1.49	0.58	137	1.76	0.58	138	2.1	−0.46 (−0.70, −0.22)
Casale	1.34	0.5	282	1.57	0.51	292	4.3	−0.45 (−0.62, −0.29)
Wahn	1.2	0.67	463	1.48	0.67	464	7.0	−0.42 (−0.55, −0.29)
Van Cauwenberge	1.14	0.75	232	1.45	0.78	225	3.5	−0.40 (−0.59, −0.22)
Bernstein	1.5	0.72	144	1.66	0.71	141	2.2	−0.22 (−0.46, 0.01)
Howarth	1	1.42	202	1.3	1.42	201	3.1	−0.21 (−0.41, −0.02)
Berger	−0.49	0.58	260	−0.33	0.58	126	2.6	−0.28 (−0.49, −0.06)
Subtotal (95% CI)			1,720			1,587	24.8	−0.37 (−0.44, −0.30)
Heterogeneity: $\chi^2 = 7.06$, d.f. = 6 (p = 0.32); $I^2 = 15\%$								
Test for overall effect: Z = 10.42 (p < 0.00001)								
1.3.2 Rhinorrhea								
Bernstein	1.94	0.72	144	1.97	0.71	141	2.2	−0.04 (−0.27, 0.19)
Bronsky	1.98	0.58	137	2.06	0.58	138	2.1	−0.14 (−0.37, 0.10)
Casale	1.73	0.5	282	1.88	0.51	292	4.4	−0.30 (−0.46, −0.13)
Howarth	1.2	0.14	202	1.4	1.42	201	3.1	−0.20 (−0.39, −0.00)
Van Cauwenberge	1.28	0.78	232	1.57	0.78	225	3.5	−0.37 (−0.56, −0.19)
Wahn	1.4	0.69	463	1.6	0.69	464	7.1	−0.29 (−0.42, −0.16)
Berger	−0.61	0.38	260	−0.56	0.38	126	2.6	−0.13 (−0.34, 0.08)
Subtotal (95% CI)			1,720			1,587	25.1	−0.24 (−0.31, −0.17)
Heterogeneity: $\chi^2 = 7.64$, d.f. = 6 (p = 0.27); $I^2 = 22\%$								
Test for overall effect: Z = 6.81 (p < 0.00001)								
1.3.3 Nasal congestion								
Bernstein	2.09	0.6	144	2.16	0.59	141	2.2	−0.12 (−0.35, 0.12)
Bronsky	2.08	0.58	137	2.17	0.58	138	2.1	−0.15 (−0.39, 0.08)
Casale	1.96	0.5	282	2.04	0.51	292	4.4	−0.16 (−0.32, 0.01)
Howarth	1.4	1.42	202	1.5	1.42	201	3.1	−0.07 (−0.27, 0.13)
Van Cauwenberge	1.44	0.74	232	1.66	0.68	225	3.5	−0.31 (−0.49, −0.12)
Wahn	1.6	0.64	463	1.71	0.63	464	7.2	−0.17 (−0.30, −0.04)
Berger	−0.48	0.44	260	−0.4	0.44	126	2.6	−0.18 (−0.39, 0.03)
Subtotal (95% CI)			1,720			1,587	25.2	−0.17 (−0.24, −0.10)
Heterogeneity: $\chi^2 = 3.42$, d.f. = 6 (p = 0.75); $I^2 = 0\%$								
Test for overall effect: Z = 4.87 (p < 0.00001)								
1.3.4 Nasal itching								
Bernstein	1.59	0.72	144	1.76	0.71	141	2.2	−0.24 (−0.47, −0.00)
Bronsky	1.69	0.7	137	1.82	0.7	138	2.1	−0.19 (−0.42, 0.05)
Casale	1.51	0.5	282	1.69	0.51	292	4.4	−0.36 (−0.52, −0.19)
Howarth	1	0.14	202	1.4	1.42	201	3.1	−0.40 (−0.59, −0.20)
Van Cauwenberge	1.18	0.61	232	1.3	0.75	225	3.5	−0.18 (−0.36, 0.01)
Wahn	1.17	0.67	463	1.43	0.67	464	7.1	−0.39 (−0.52, −0.26)
Berger	−0.67	0.63	260	−0.52	0.63	126	2.6	−0.24 (−0.45, −0.02)
Subtotal (95% CI)			1,720			1,587	25.0	−0.31 (−0.38, −0.24)
Heterogeneity: $\chi^2 = 6.34$, d.f. = 6 (p = 0.39); $I^2 = 5\%$								
Test for overall effect: Z = 8.71 (p < 0.00001)								
Total (95% CI)			6,880			6,348	100.0	−0.27 (−0.31, −0.24)
Heterogeneity: $\chi^2 = 41.98$, d.f. = 27 (p = 0.03); $I^2 = 36\%$								
Test for overall effect: Z = 15.39 (p < 0.00001)								
Test for subgroup differences: $\chi^2 = 17.51$, d.f. = 3 (p = 0.0006), $I^2 = 82.9\%$								



sneezing

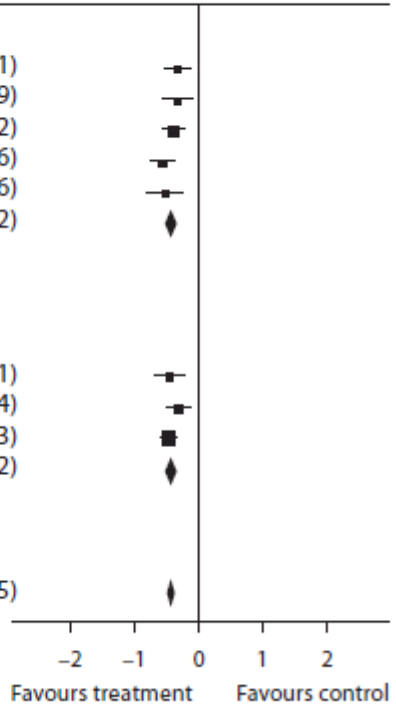
rhinorrea

nasal congestion

nasal itching

doses

Study or subgroup	Fexofenadine mean	SD	total	Placebo mean	SD	total	weight, %	Std. mean difference IV, fixed, 95% CI
1.5.1 >120 mg daily								
Berger	6.26	2.37	260	7.03	2.37	126	9.8	−0.32 (−0.54, −0.11)
Bernstein	6.55	2.4	144	7.32	2.37	141	8.3	−0.32 (−0.56, −0.09)
Casale	6.07	1.85	282	6.78	1.88	292	16.5	−0.38 (−0.55, −0.22)
Howarth	4.1	2.34	202	5.4	2.34	201	11.4	−0.55 (−0.75, −0.36)
Schapowal	6.63	4.81	113	9.16	4.81	107	6.2	−0.52 (−0.79, −0.26)
Subtotal (95% CI)			1,001			867	52.3	−0.42 (−0.51, −0.32)
Heterogeneity: $\chi^2 = 3.99$, d.f. = 4 ($p = 0.41$); $I^2 = 0\%$								
Test for overall effect: $Z = 8.77$ ($p < 0.00001$)								
1.5.2 120 mg or less daily								
Bronsky	6.5	2.11	137	7.45	2.11	138	7.9	−0.45 (−0.69, −0.21)
Van Cauwenberge	4.56	2.56	232	5.42	2.81	225	13.2	−0.32 (−0.50, −0.14)
Wahn	4.86	2.15	463	5.86	2.16	469	26.6	−0.46 (−0.59, −0.33)
Subtotal (95% CI)			832			832	47.7	−0.42 (−0.52, −0.32)
Heterogeneity: $\chi^2 = 1.62$, d.f. = 2 ($p = 0.44$); $I^2 = 0\%$								
Test for overall effect: $Z = 8.50$ ($p < 0.00001$)								
Total (95% CI)			1,833			1,699	100.0	−0.42 (−0.49, −0.35)
Heterogeneity: $\chi^2 = 5.62$, d.f. = 7 ($p = 0.58$); $I^2 = 0\%$								
Test for overall effect: $Z = 12.21$ ($p < 0.00001$)								
Test for subgroup differences: $\chi^2 = 0.01$, d.f. = 1 ($p = 0.93$), $I^2 = 0\%$								



ADVERSE EVENTS

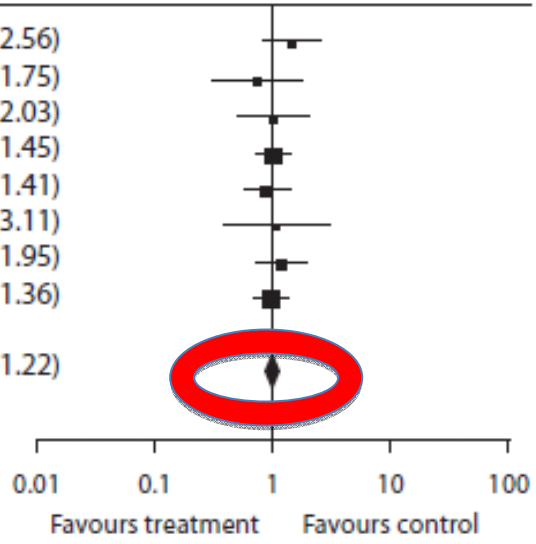
Reference	No. of patients reporting adverse events (active/placebo)	
	Total Patients	**Most commonly reported specific adverse events**
Wahn et al.	85/88	Headache (23/13), Epistaxis (7/5), Upper respiratory infection (7/5), Pharyngitis (6/1), Sinusitis (6/0), Nausea (5/1), Rash (5/3), Accidental injury (4/6), Asthma (3/9), Infection (1/5), Gastro-intestinal pain (1/5)
Bronsky et al.	18/18	Headache (10/9)
Casale et al.	86/88	Headache (30/22), Upper respiratory infection (9/9), Pharyngitis 6/9, Back pain (8/4), Pain (5/10)
Van Cauwemberge et al.	39/33	Headache (7/5), Drowsiness (4/3), Asthenia (1/1), Pharyngitis (3/1), Diarrhea (4/0), Nausea (1/3)
Berstein et al.	10/13	Headache (1/4), Throat irritation (1/2), Dry mouth (0/2), Cough (0/2), Leukopenia (1/1)
Howarth et al	50/53	Headache (8/15), Fatigue (3/2), Drowsiness (14/7)
Schapowal et al	8/7	Headache(0/1), Sedation (6/3), Common Cold (1/2), Sinus pain (1/0), Nausea (1/0)
Berger et al	52/19	Headache (11/2), Somnolence (3/0), Nausea (3/0), Upper respiratory infection (3/1)

Adverse effects

Study or subgroup	Fexofenadine events	Fexofenadine total	Placebo events	Placebo total	weight, %	Odds ratio M-H, fixed, 95% CI
Berger	52	288	19	144	8.1	1.45 (0.82, 2.56)
Bernstein	10	144	13	142	4.8	0.74 (0.31, 1.75)
Bronsky	18	137	18	138	6.1	1.01 (0.50, 2.03)
Casale	86	283	88	293	23.6	1.02 (0.71, 1.45)
Howarth	50	213	53	209	16.0	0.90 (0.58, 1.41)
Schapowal	8	113	7	107	2.6	1.09 (0.38, 3.11)
Van Cauwenberge	39	232	33	225	10.9	1.18 (0.71, 1.95)
Wahn	85	464	88	471	27.9	0.98 (0.70, 1.36)
Total (95% CI)		1,874		1,729	100.0	1.03 (0.87, 1.22)
Total events	348		319			

Heterogeneity: $\chi^2 = 2.68$, d.f. = 7 ($p = 0.91$); $I^2 = 0\%$

Test for overall effect: $Z = 0.31$ ($p = 0.75$)

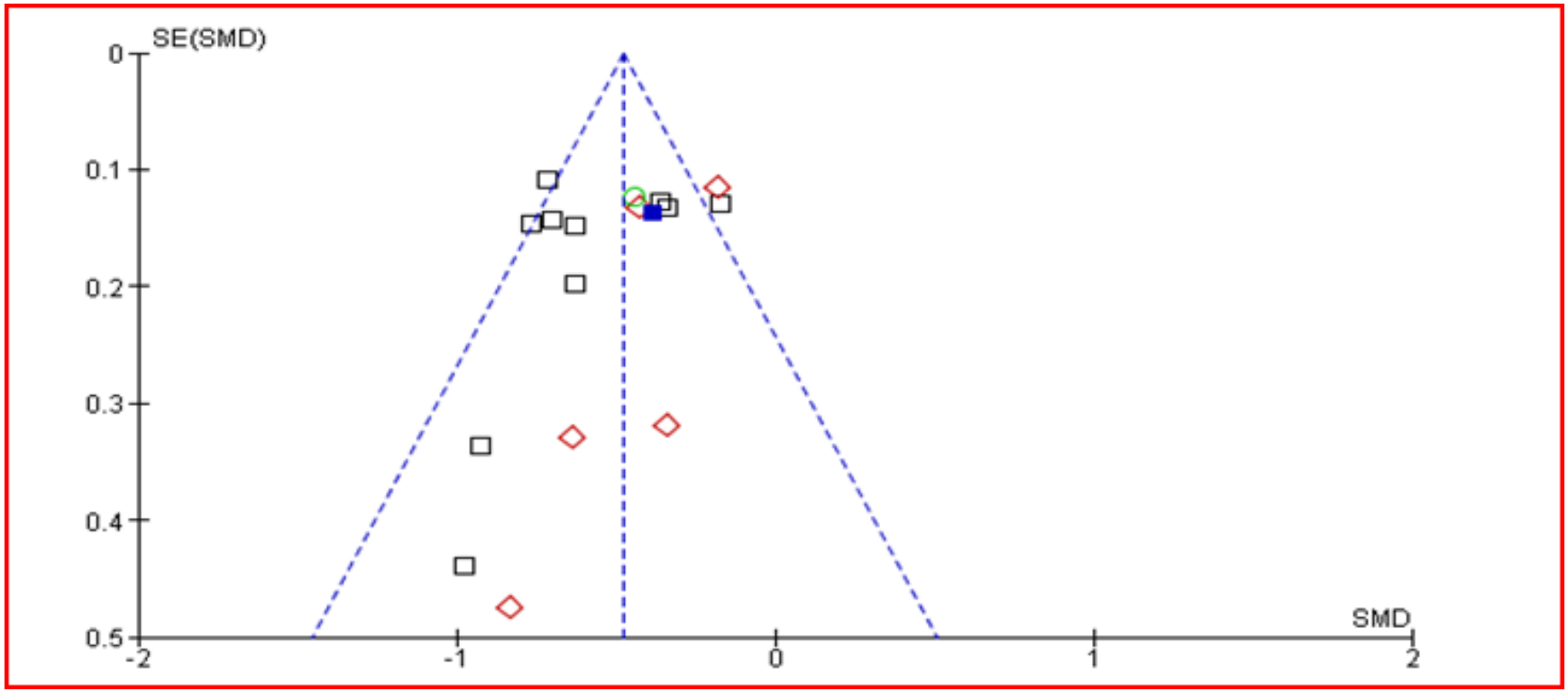


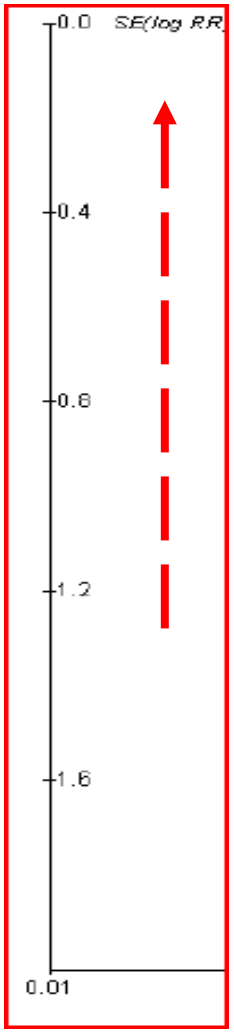
Is it GOAL???????????

Exploring Publication Bias:

Funnel Plot

You should use the funnel plot to investigate
the presence of publication bias in your review

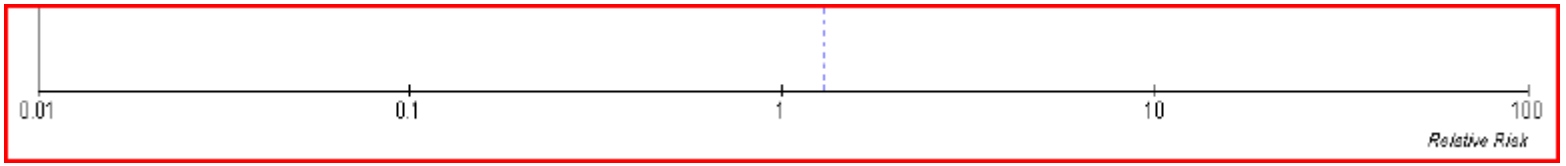




The vertical axis is some measure of the precision of the estimate of the treatment effect.

So the smaller the confidence interval, the more precise the study, and the further up the study is placed.

The horizontal axis measures the treatment effect

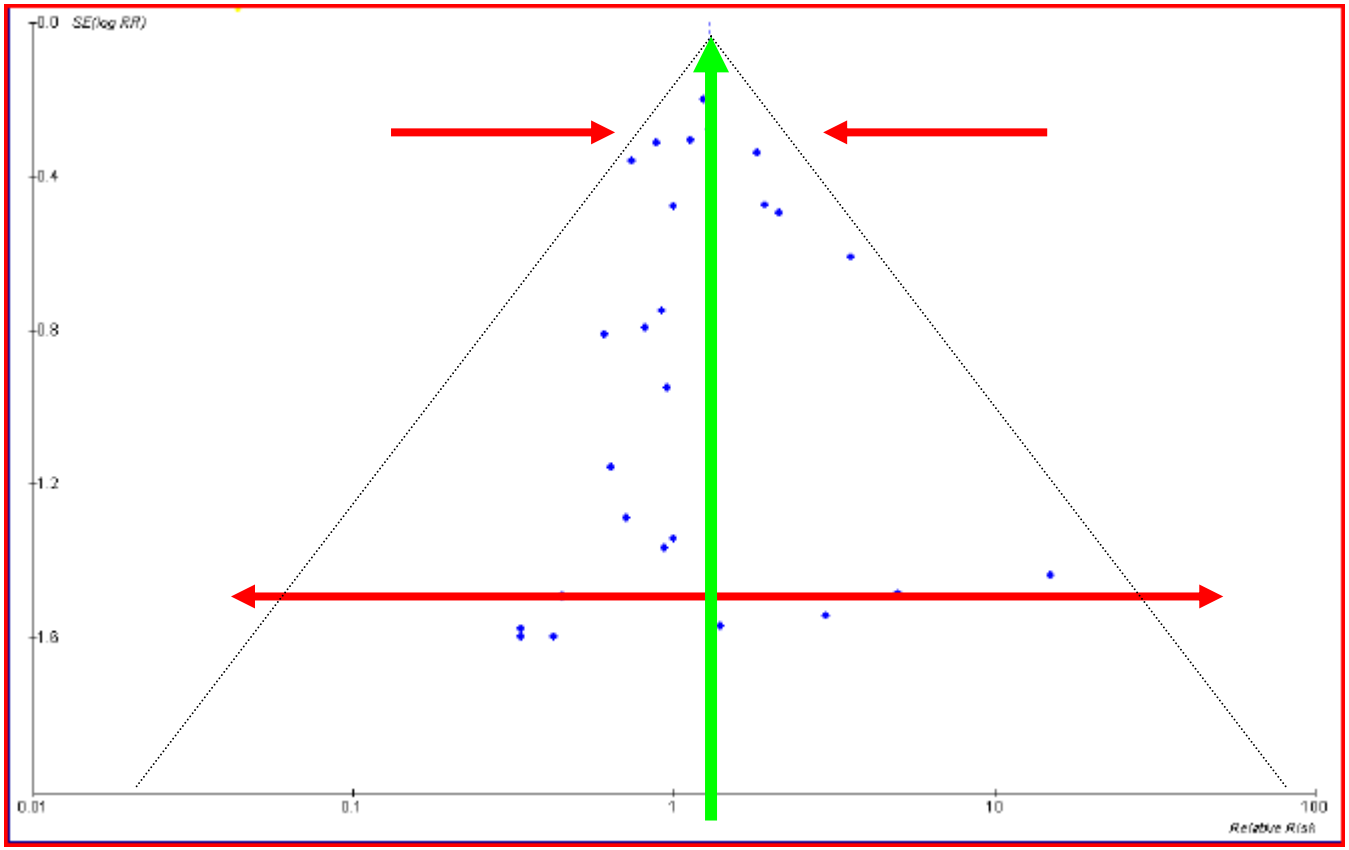


The point estimate from each study is then plotted…

…a vertical line added, where the pooled estimate from the meta-analysis lies

more precise studies

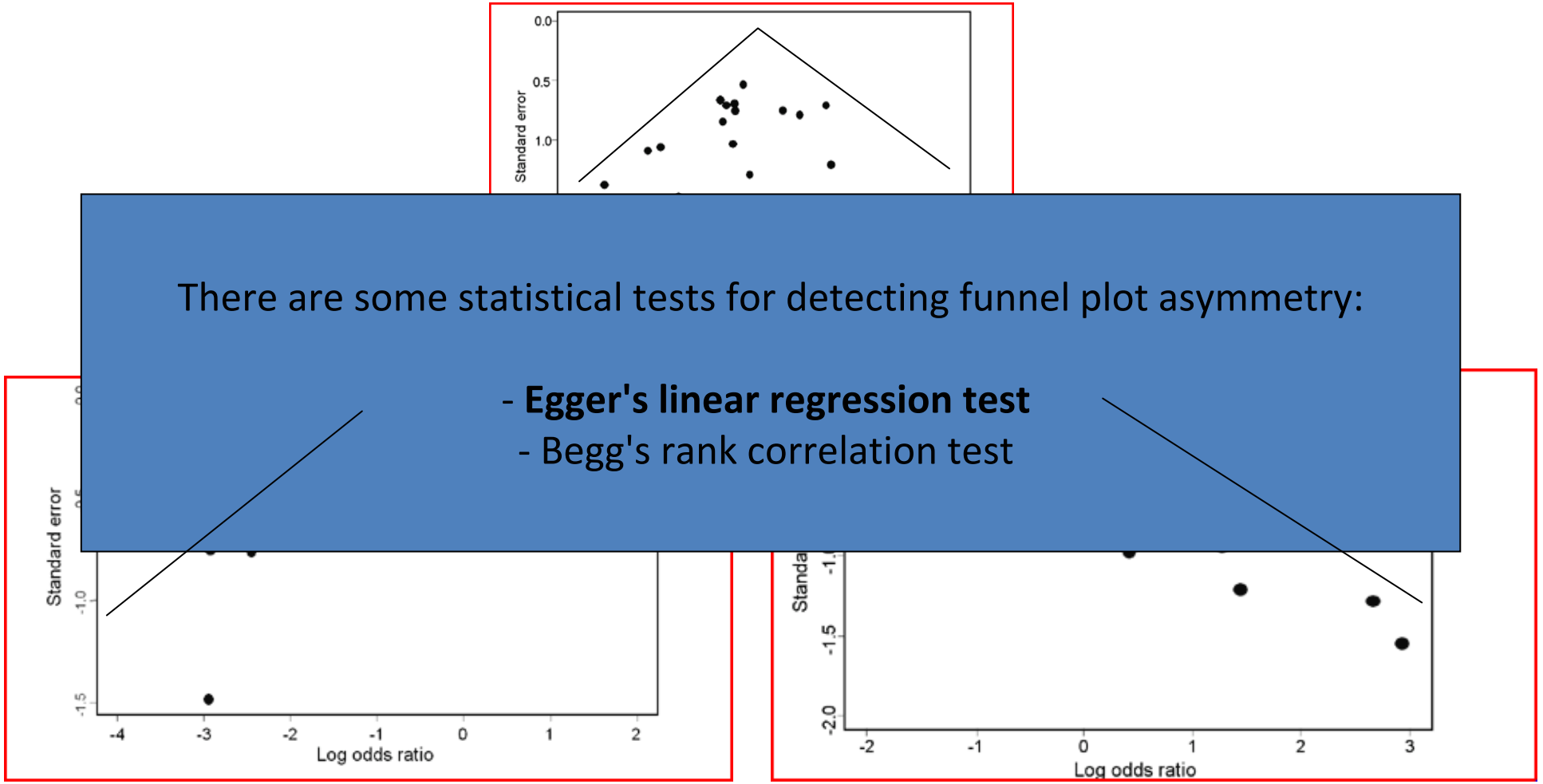
less precise studies



THE COCHRANE COLLABORATION®

Funnel plot **ASYMMETRY** may be due to:

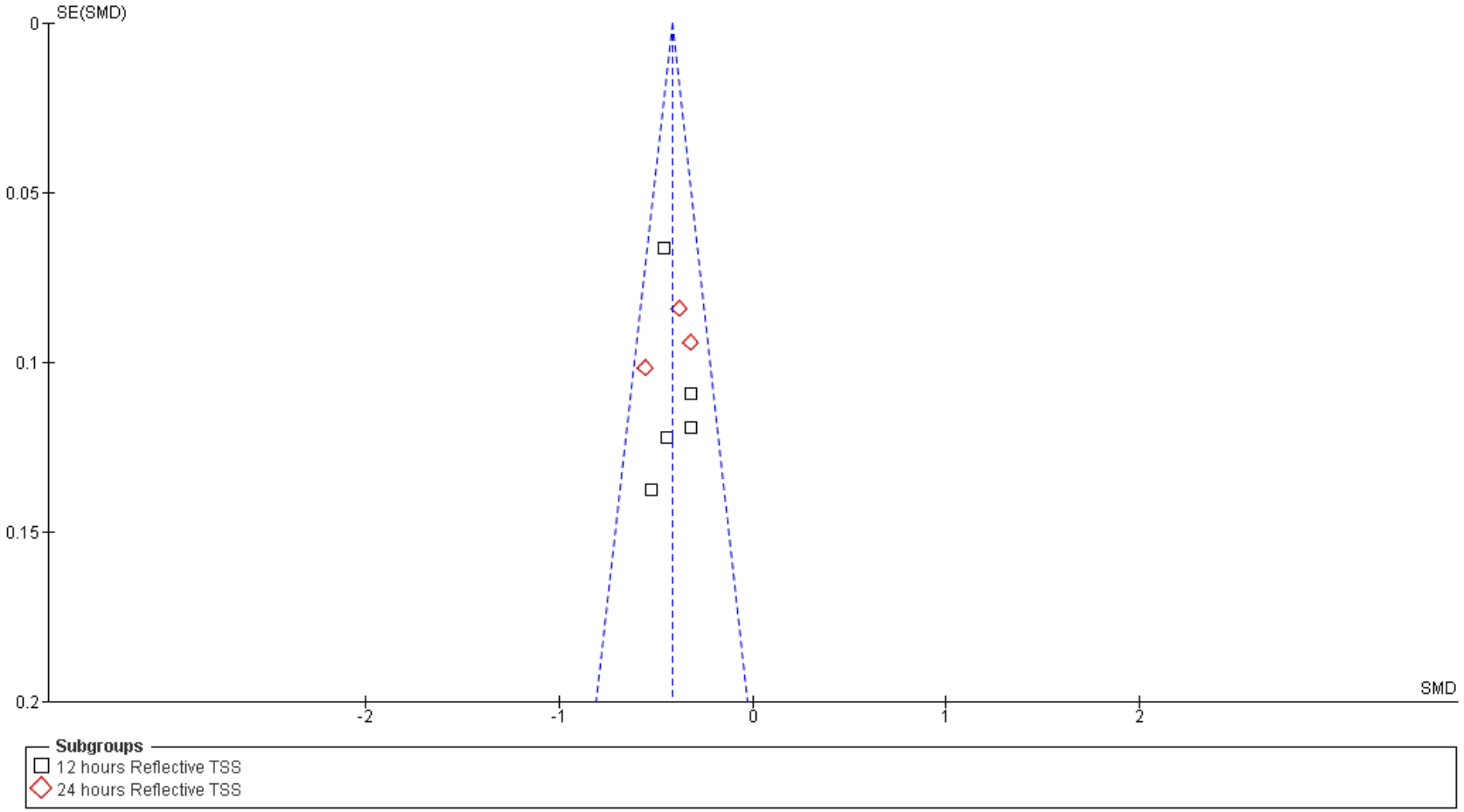
- *publication bias*
- clinical heterogeneity between studies
- methodological heterogeneity between studies.



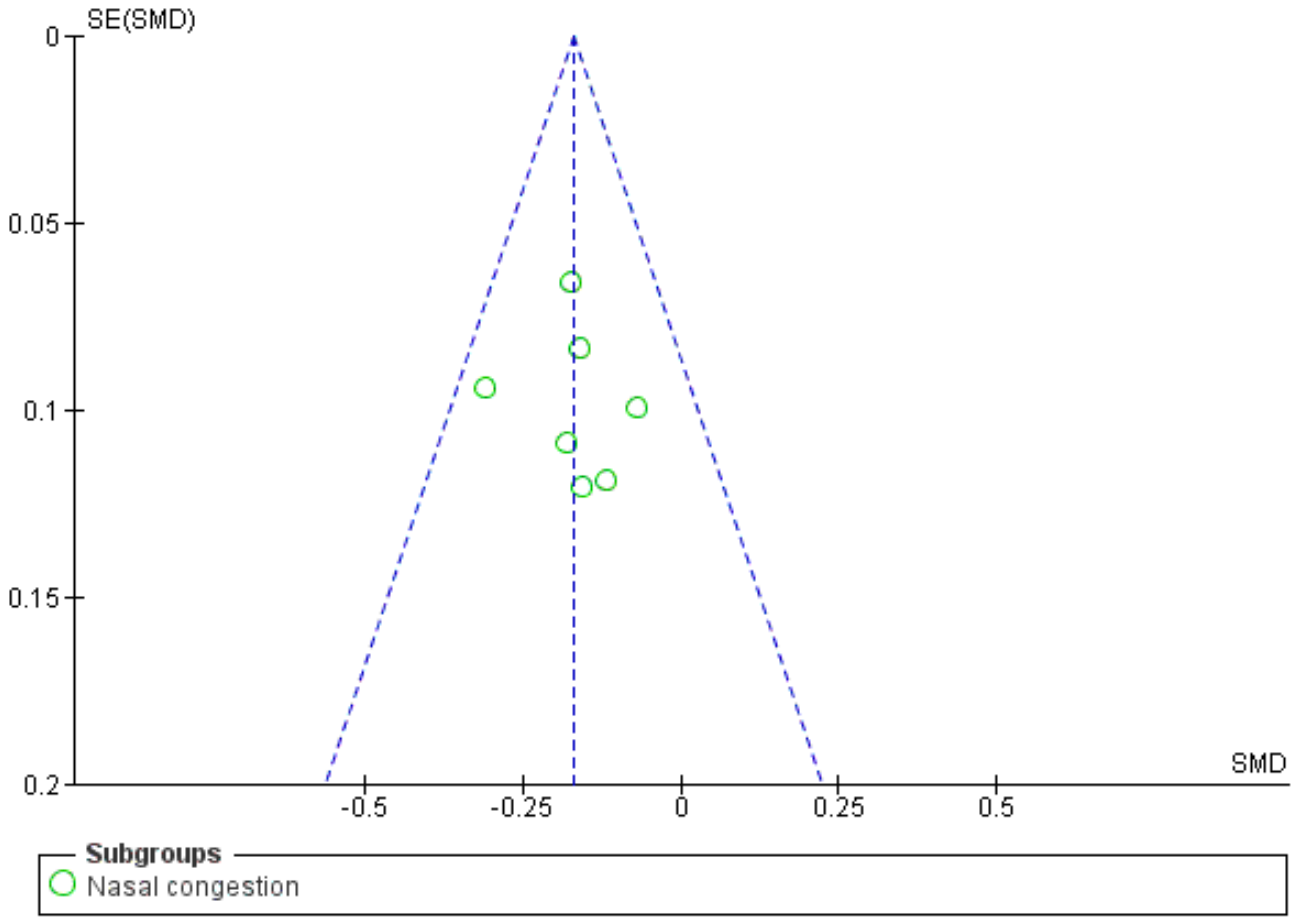
There are some statistical tests for detecting funnel plot asymmetry:

- **Egger's linear regression test**
- Begg's rank correlation test

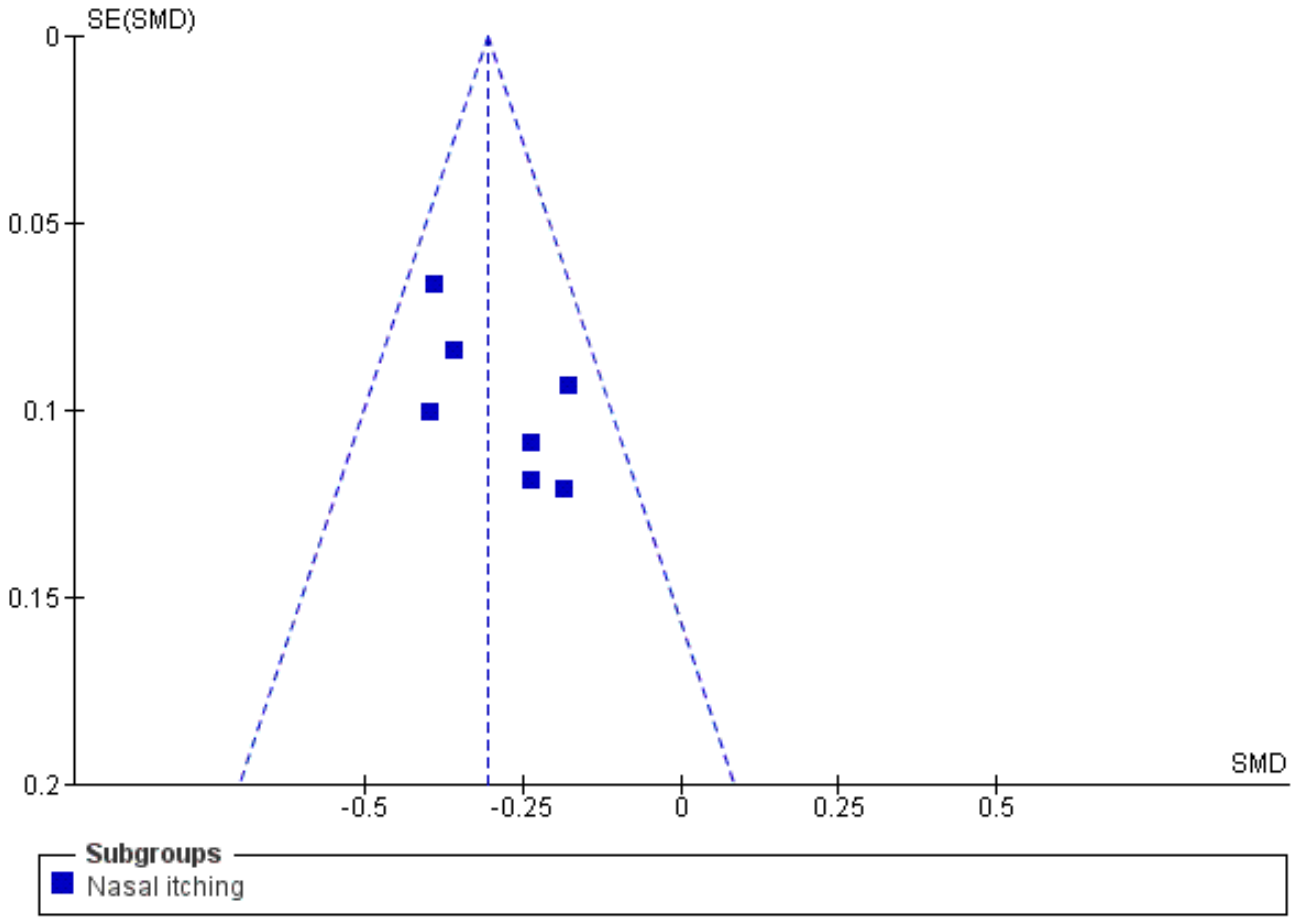
12-24 h reflective TSS



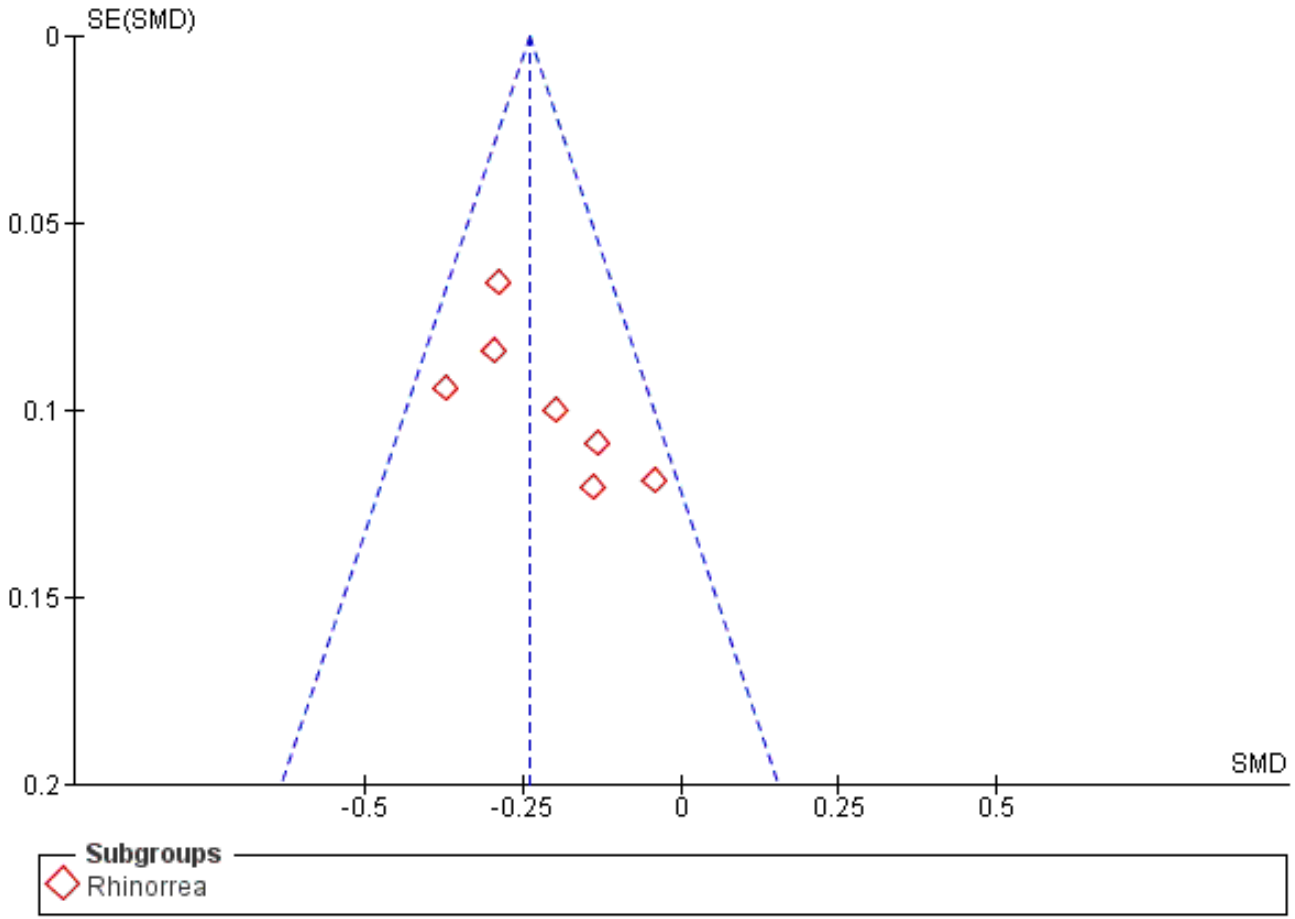
N.Congestion



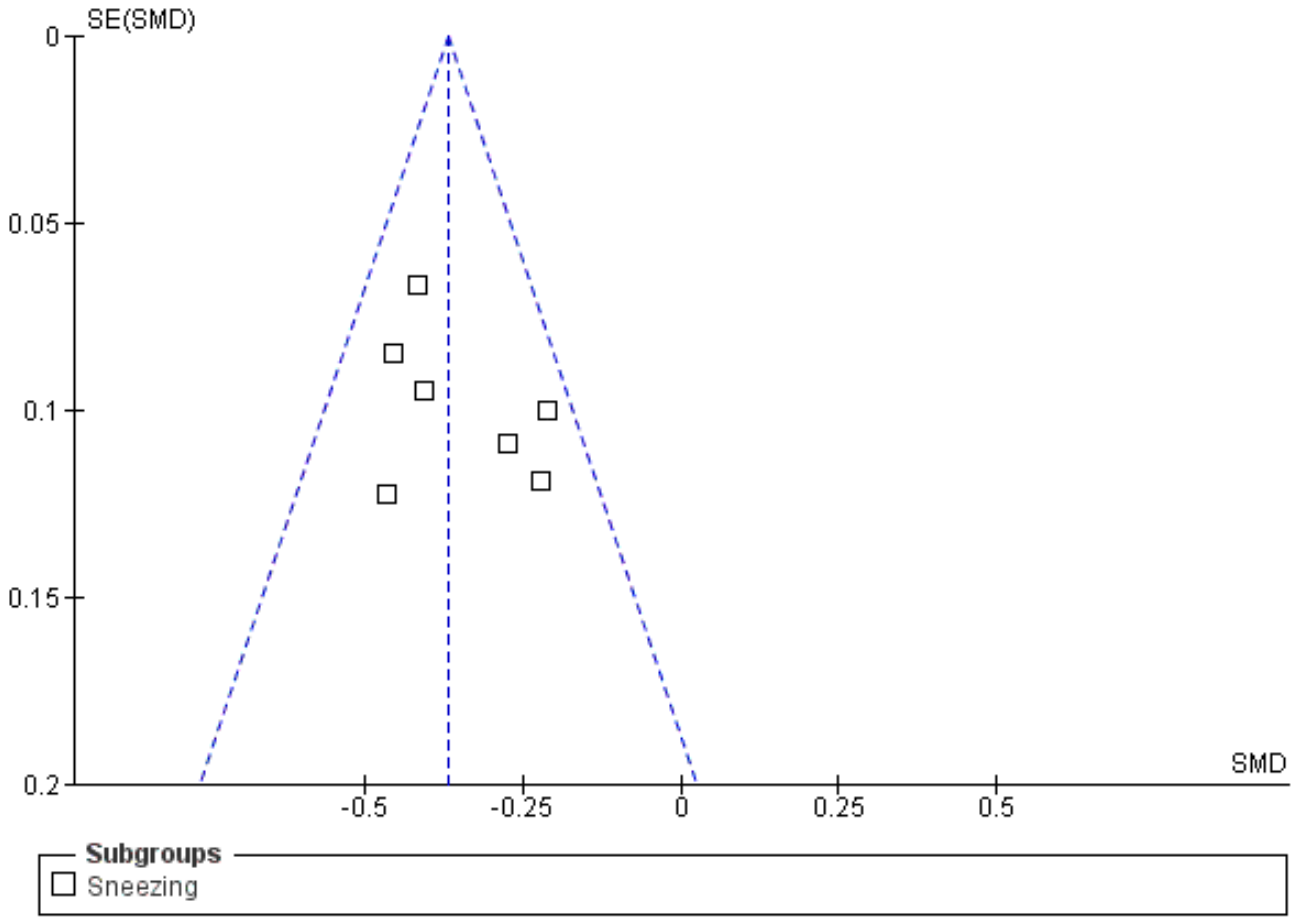
N.Itching


SE(SMD)
0
0.05
0.1
0.15
0.2
SMD
-0.5
-0.25
0
0.25
0.5
Subgroups
Nasal itching

Rhinorrea



Sneezing



CONCLUSIONS

This study has five major aspects: it represents the first attempt to evaluate the efficacy and safety of fexofenadine in the treatment of AR by means of meta-analysis of RCTs;

- **Consistency between positive results in terms of efficacy in TSS and in individual symptoms;**
- **Large population studied;**
- **Not relevant inter-study heterogeneity;**
- **Adverse events frequency was similar in both groups (placebo).**

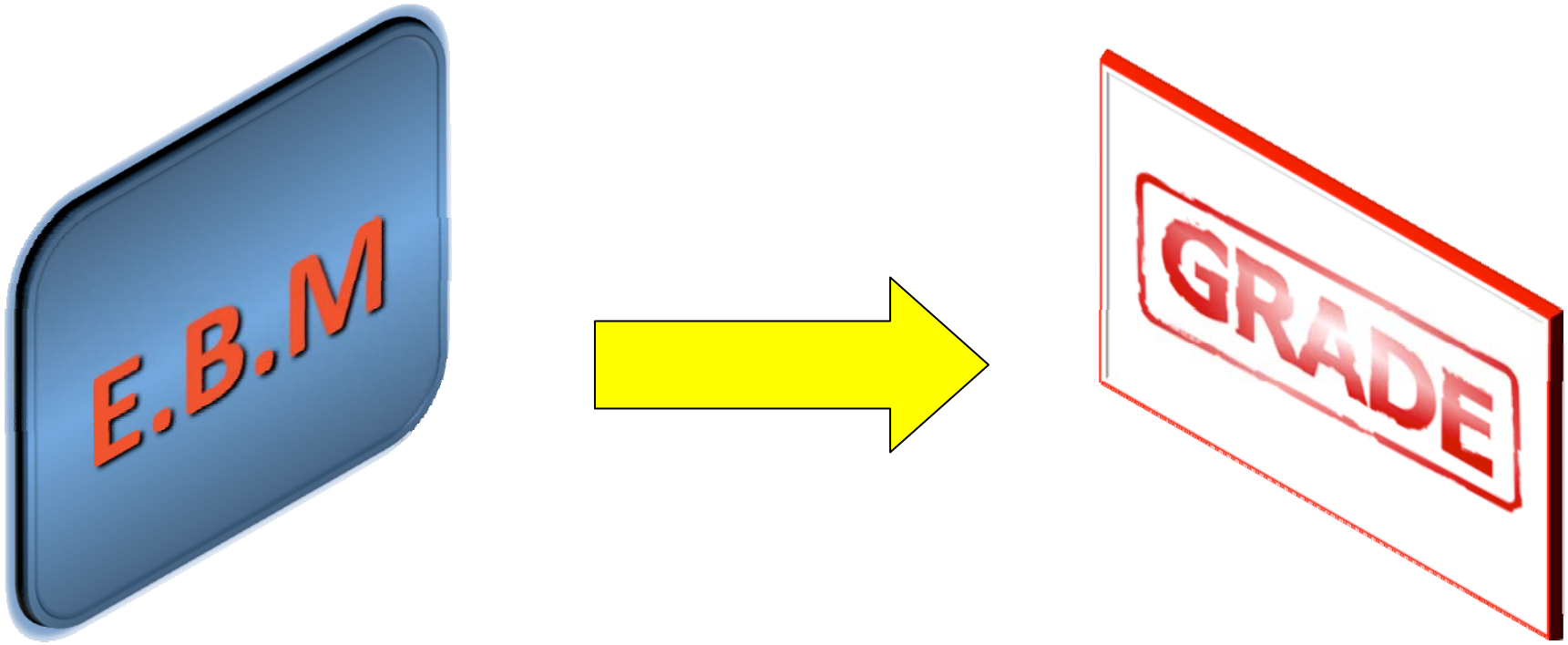
All these values encourage the recommendation of fexofenadine for AR.

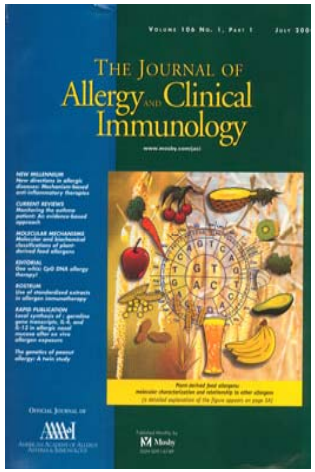
Treatment of allergic rhinitis (ARIA)

Allergic Rhinitis and its Impact on Asthma

mild intermittent	moderate severe intermittent	mild persistent	moderate severe persistent
	intra-nasal steroid		
	local cromone		
oral or local non-sedative H1-blocker			
intra-nasal decongestant (<10 days) or oral decongestant			
allergen and irritant avoidance			
		immunotherapy	

A general process in guidelines evolution





GRADE

J.A.C.I. September 2010

ALLERGIC RHINITIS AND ITS IMPACT ON ASTHMA

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 Revision

Jan L. Brożek, MD, PhD,[a] Jean Bousquet, MD, PhD,[b,c,d] Carlos E. Baena-Cagnani, MD,[e] Sergio Bonini, MD,[f,g] G. Walter Canonica, MD,[h] Thomas B. Casale, MD,[i] Roy Gerth van Wijk, MD, PhD,[j] Ken Ohta, MD, PhD,[k] Torsten Zuberbier, MD,[l] and Holger J. Schünemann, MD, PhD, MSc[a] *Hamilton, Ontario, Canada, Montpellier, France, Córdoba, Argentina, Rome, Naples, and Genoa, Italy, Omaha, Neb, Rotterdam, The Netherlands, Tokyo, Japan, and Berlin, Germany*

Brozek et al.,J.A.C.I. September 2010

Interpretation of Recommendations

TABLE I. Interpretation of strong and conditional (weak)* recommendations

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

*Guideline panels applying GRADE use the term "conditional" and "weak" synonymously.

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GRADE

ALLERGIC RHINITIS AND ITS IMPACT ON ASTHMA

Antihistamines

III. Pharmacologic treatment of AR

11. Should oral H_1-antihistamines be used for the treatment of AR?. *Recommendation.* In patients with AR, we recommend new-generation oral H_1-antihistamines that [illegible] interact with cytochrome P450 (strong recommendation | low-quality evidence). In patients [illegible] new-generation oral H_1-antihistamines that cause some sedation and/or interact with cytochrome P450 (conditional recommendation | low-quality evidence).

12. Should new-generation oral H_1-antihistamines versus old-generation oral H_1-antihistamines be used for the treatment of AR?. *Recommendation.* In patients with AR, we [illegible] old-generation oral H_1-antihistamines (strong recommendation | low-quality evidence).

13. Should oral H_1-antihistamines be used in preschool children with other allergic diseases for the prevention of wheezing or asthma?. *Recommendation.* In infants with atopic dermatitis and/or family history of allergy or asthma (at high risk of developing asthma), we suggest clinicians do **not** administer and parents do **not** use oral H_1-antihistamines for the prevention of wheezing or asthma (conditional recommendation | very low-quality evidence).

14. Should intranasal H_1-antihistamines be used for treatment of AR?. *Recommendation.* We suggest intranasal H_1-antihistamines in adults with seasonal AR (conditional recommendation | low-quality evidence) and in children with seasonal AR (conditional recommendation | very low-quality evidence). In adults and children with persistent AR, we suggest that clinicians do **not** administer and patients do **not** use intranasal H_1-antihistamines until more data on their relative efficacy and safety are available (conditional recommendation | very low-quality evidence).

15. Should newer oral H_1-antihistamines versus intranasal H_1-antihistamines be used for treatment of AR?. *Recommendation.* We suggest new-generation oral H_1-antihistamines rather than intranasal H_1-antihistamines in adults with seasonal AR (conditional recommendation | moderate-quality evidence) and in adults with persistent AR (conditional recommendation | very low-quality evidence). In children with intermittent or persistent AR, we also suggest new-generation oral H_1-antihistamines rather than intranasal H_1-antihistamines (conditional recommendation | very low-quality evidence).

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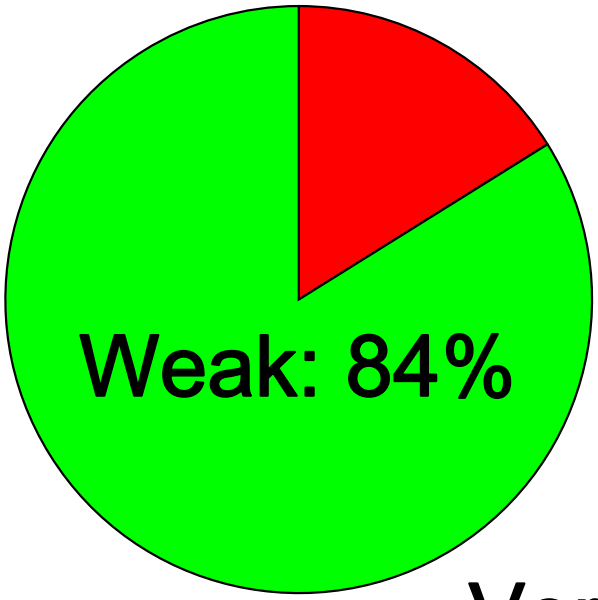
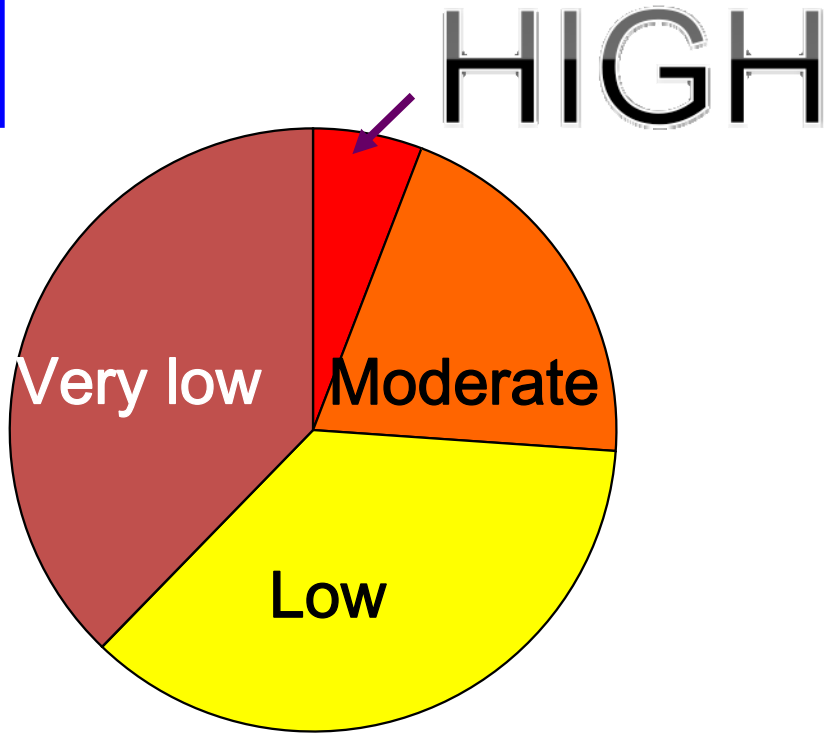


Very low

Strength of recommendation

GRADE 2010

Grade of evidence



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Clinical Implications

Clinical implications: Patients, clinicians, and policy makers can use these systematically developed and transparent recommendations to inform their judgments about the choice of the most appropriate treatment for patients with AR.

Take Home Message

FEXOFENADINE

Is fulfilling the ARIA criteria for Anti-H1

Is fulfilling the ARIA-GRADE recommendations

FEXOFENADINE

Ranks at the Top in E.B.M.

2011

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Evidence-Based Medicine in the EMR Era

Jennifer Frankovich, M.D., Christopher A. Longhurst, M.D., and Scott M. Sutherland, M.D.

EMR

2011

ELECTRONIC MEDICAL RECORD

STRIDE

STANFORD INTEGRATED DATABASE ENVIROMENT

2011

STRIDE

CTIVE

EVIDENCE-BASED MEDICINE IN THE

Results of Electronic Search of Patient Medical Records (for a Cohort of 98 Pediatric Patients with Lupus) Focused on Risk Factors for Thrombosis Relevant to Our 13-Year-Old Patient with Systemic Lupus Erythematosus.*

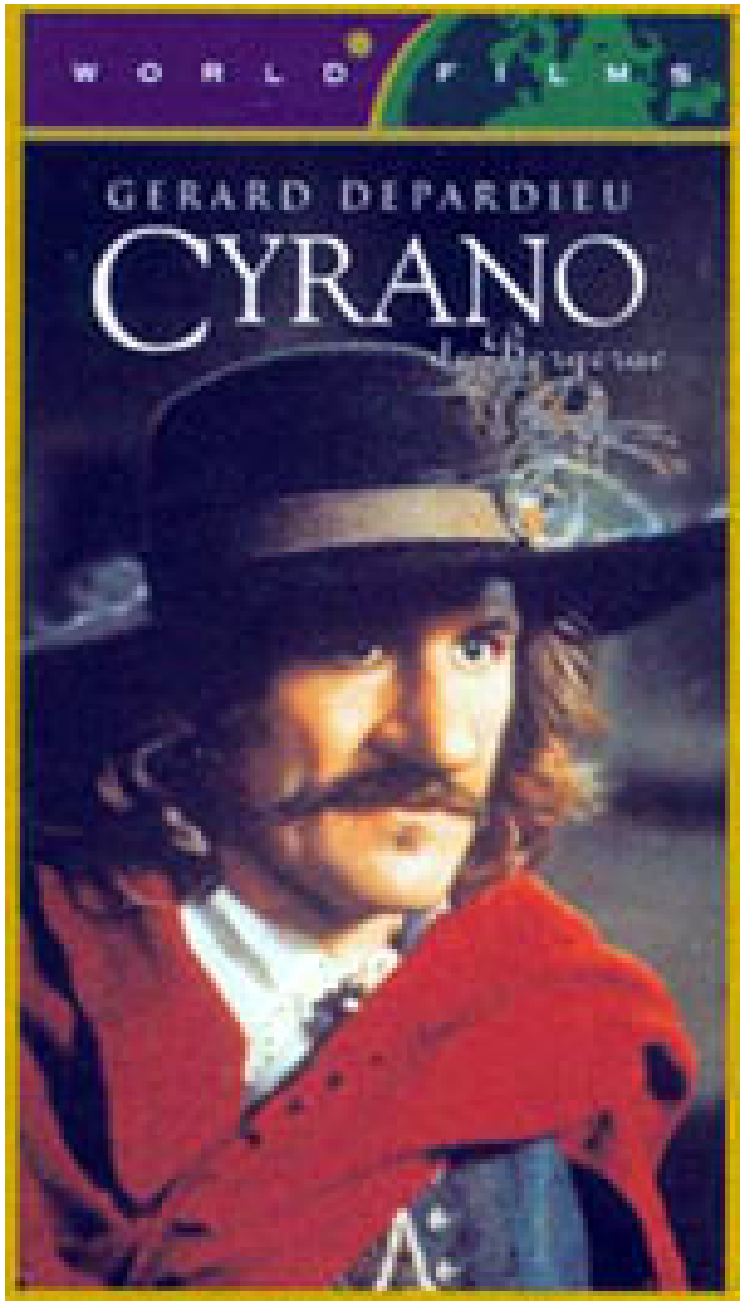
Outcome or Risk Factor	Keywords Used to Conduct Expedited Electronic Search	Prevalence of Thrombosis	Relative R (95% CI
		no./total no (%)	
Outcome — thrombosis	"Thrombus," "Thrombosis," "Blood clot"	10/98 (10)	Not applica
Thrombosis risk factor			
Heavy proteinuria (>2.5 g per deciliter)			
Present at any time	"Nephrosis," "Nephrotic," "Proteinuria"	8/36 (22)	7.8 (1.7–
Present >60 days	"Urine protein"	7/23 (30)	14.7 (3.3–9
Pancreatitis	"Pancreatitis," "Lipase"	5/8 (63)	11.8 (3.8–2
Antiphospholipid antibodies	"Aspirin"	6/51 (12)	1.0 (0.3–3

2011

NERO WOLFE
by Rex Stout

CONCLUSION

know. We will, however, know that we made the decision on the basis of the best data available — acting, as the fictional detective Nero Wolfe would say, "in the light of experience as guided by intelligence."[5] In the practice of medicine, one can't do better than that.



SO…WE CAN TREAT PROPERLY ALSO THE BIG NOSES

Thank You

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