WREN Convocation September 2010

Macrolide treatment for “chlamydial asthma”: Evidence for enrollment bias in an effectiveness trial

A WREN Study

DL Hahn, M Grasmick, S Hetzel

Acknowledgements

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What this talk covers

- Rationale for macrolide treatment for asthma
  - Atypical infections are common and ?causal
- Definition of effectiveness trials in asthma
  - Currently lacking for guideline therapies
- Results of current RCT: AZMATICS
  - Challenges to external validity

Rationale for macrolide treatment

- Atypical infection potentially causal
  - Inception
  - Severity
- *C. pneumoniae*
  - Attributable risk ~50%
    - Seroepidemiology
    - PCR from BAL
    - Treatment trial results

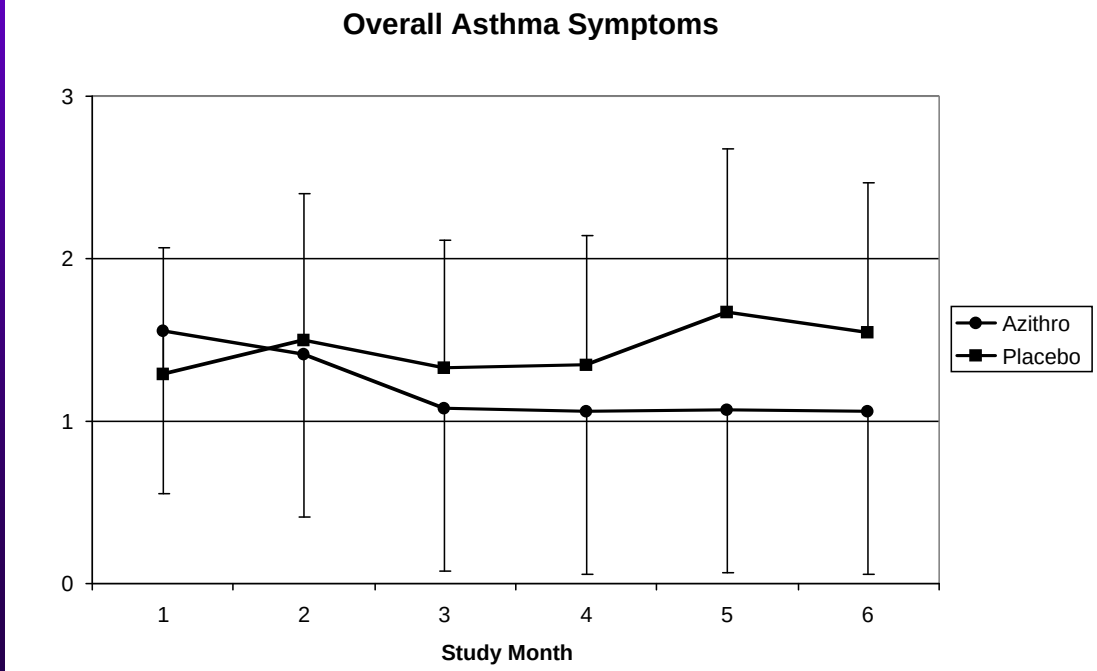
Rationale for macrolide treatment

OPEN ACCESS Freely available online

PLOS CLINICAL TRIALS

Secondary Outcomes of a Pilot Randomized Trial of Azithromycin Treatment for Asthma

David L. Hahn[1*], Mary Beth Plane[2], Olaimatu S. Mahdi[3], Gerald I. Byrne[3]



Clinically significant improvement*:

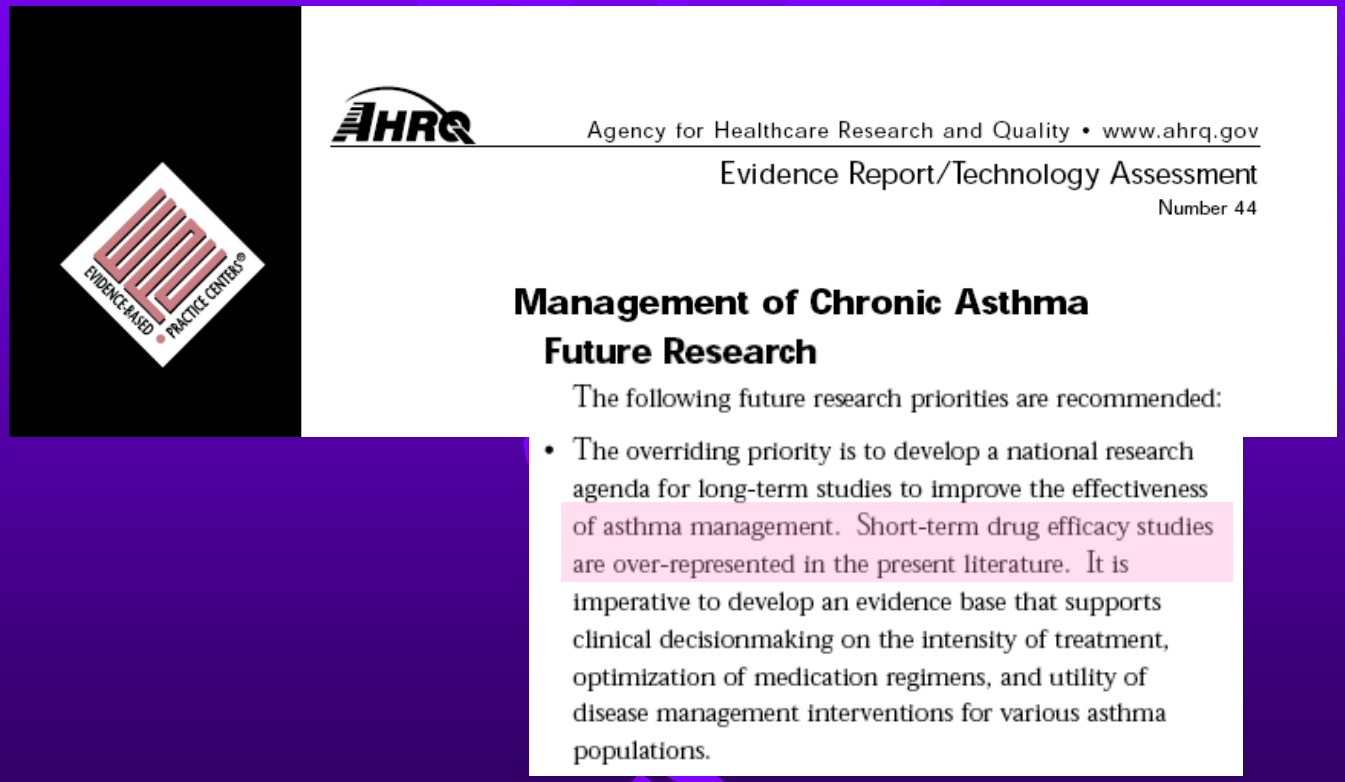
53% v 13% (P=0.03)

*≥1 unit AQLQ increase and/or
≥50% rescue BD decrease

Effectiveness: Definition

- Externally valid
- Internally valid
- Patient-oriented outcomes
- Preferably long term

Effectiveness trials in asthma



Agency for Healthcare Research and Quality • www.ahrq.gov

Evidence Report/Technology Assessment

Number 44

Management of Chronic Asthma

Future Research

The following future research priorities are recommended:

- The overriding priority is to develop a national research agenda for long-term studies to improve the effectiveness of asthma management. Short-term drug efficacy studies are over-represented in the present literature. It is imperative to develop an evidence base that supports clinical decisionmaking on the intensity of treatment, optimization of medication regimens, and utility of disease management interventions for various asthma populations.

Aronson N et al. Management of Chronic Asthma. Evidence Report/Technology Assessment Number 44: Agency for Healthcare Research and Quality: AHRQ Publication No. 01-E044, September 2001

AZMATICS: Design

- Long term (1-yr) effectiveness trial
- Adjunctive azithromycin (weekly for 12 weeks)
- Patient-oriented outcomes (sx, QOL, control, med use etc)
- Final outcome assessment (48 weeks)
  - Long after active treatment was completed
  - “Anti-inflammatory” mechanism not plausible at 24-48 weeks

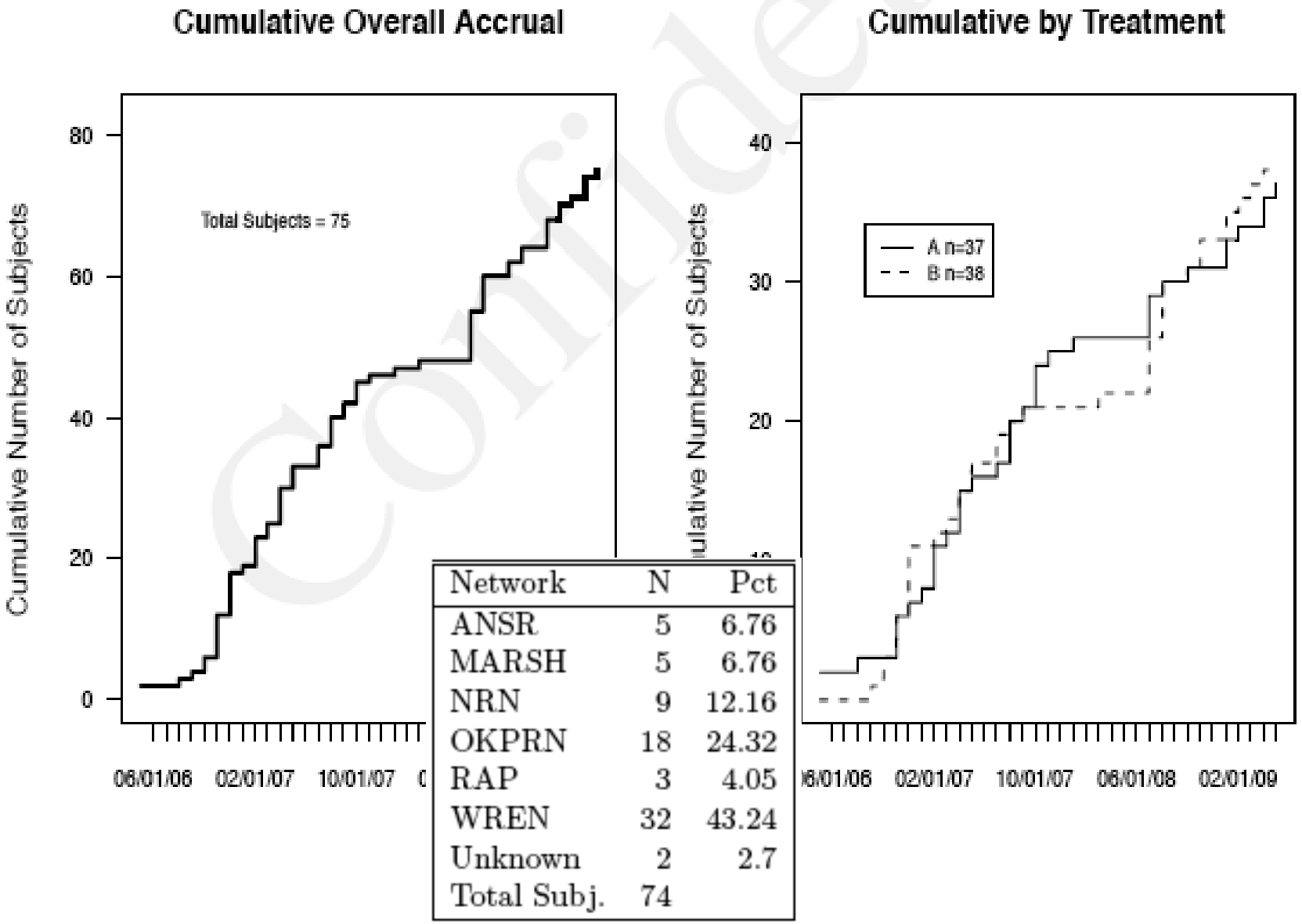
AZMATICS: Challenges

- "Approved but not funded": NIH
- Internet enrolment & follow up
  - Low cost
  - PBRNs, voluntary, nationwide
  - Patient-reported outcomes
  - Motivated (+), uncompensated (+/-), unsupervised (-)
  - No biomarkers, no PFTs, limited staff (-)

AZMATICS: Challenges

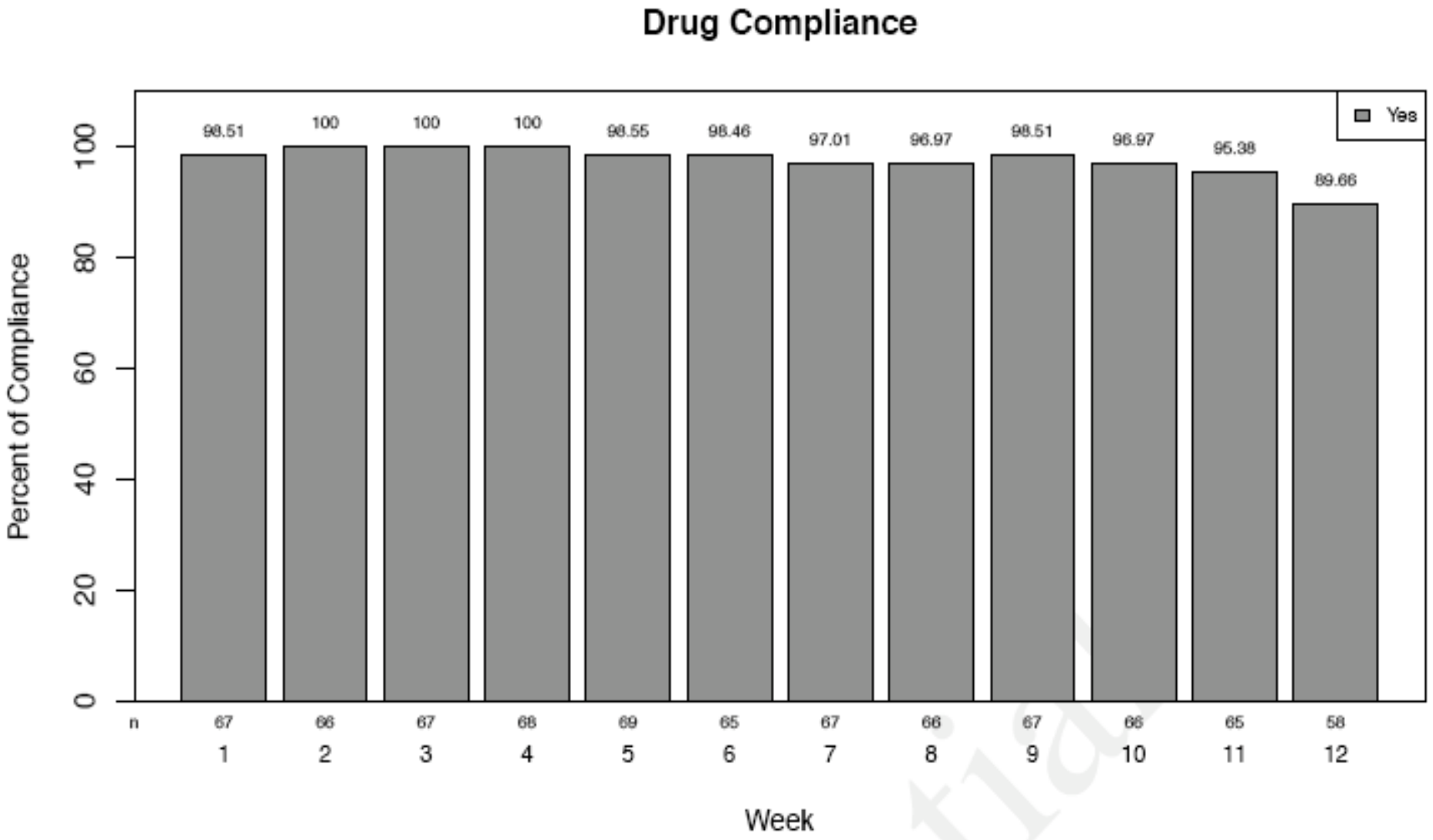
- Eligibility limited
  - Internet-savvy subjects
- Unanticipated effects of Clinical Trial registration*
  - Self-referral via Internet
    - <clinicaltrials.gov>; <asthmastory.com>
    - Prior experience with azithromycin (see email)
- Open-Label (OL) arm implemented

*Hahn DL. An unanticipated effect of clinical trial registration.*BMJ online at http://www.bmj.com/cgi/eletters/325/7376/1314#178926* 2007.



Network	N	Pct
ANSR	5	6.76
MARSH	5	6.76
NRN	9	12.16
OKPRN	18	24.32
RAP	3	4.05
WREN	32	43.24
Unknown	2	2.7
Total Subj.	74	

Fig. 1: Accrual by Month


Drug Compliance
Yes
Percent of Compliance
0
20
40
60
80
100
98.51
100
100
100
98.55
98.46
97.01
96.97
98.51
96.97
95.38
89.66
n
67
66
67
68
69
65
67
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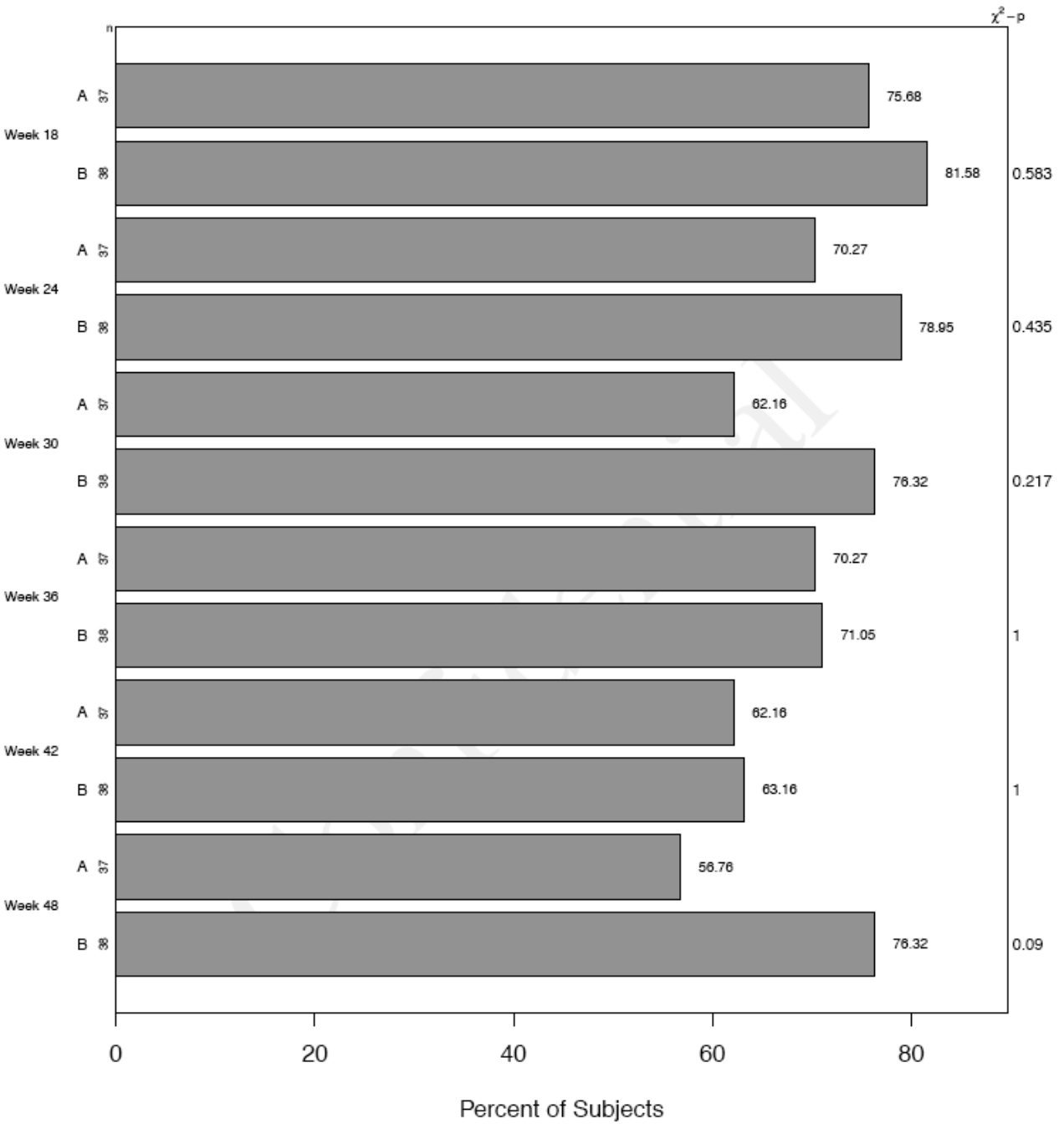
65
58
1
2
3
4
5
6
7
8
9
10
11
12
Week


Follow Up Compliance by Week
n
χ^2 – p
Week 18
A 37 75.68
B 38 81.58 0.583
Week 24
A 37 70.27
B 38 78.95 0.435
Week 30
A 37 62.16
B 38 76.32 0.217
Week 36
A 37 70.27
B 38 71.05 1
Week 42
A 37 62.16
B 38 63.16 1
Week 48
A 37 56.76
B 38 76.32 0.09
0
20
40
60
80
Percent of Subjects

Baseline characteristics.1

	Randomized N=75	Open Label N=22	P-value
Age, median, Min-max	47 20-80	48 22-77	0.73
Gender, %M	68%	45%	0.08
Smoking, % Curr/Prev/No	15%/41%/ 44%	0%/27%/ 73%	0.03
Chronic Sinusitis, %	33%	77%	0.0004
ST, % 0/1-3/4+, %	53% 8%/19%/ 72%	86% 32%/42%/ 26%	0.006 0.004

Baseline characteristics.2

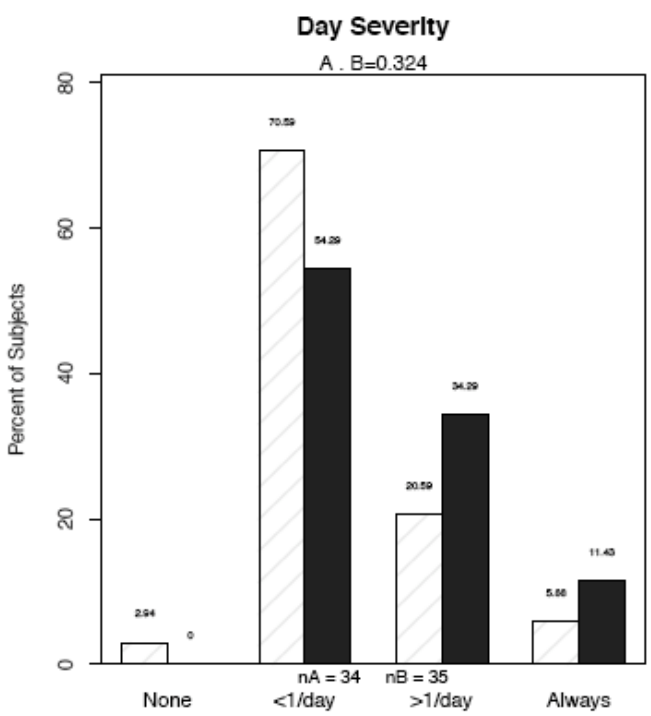
Asthma severity

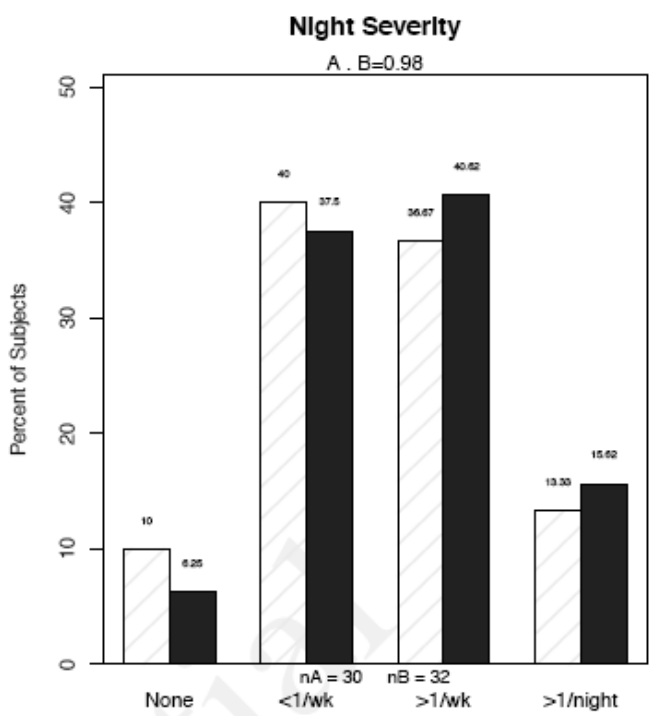
	Randomized N=75	Open Label N=22	P-value
Hospitalized Previous 2y	3%	9%	0.02
Day Severity Mild/Mod/Sev	64%/28%/ 8%	32%/36%/ 32%	0.01
Night Severity Mild/Mod/Sev	51%/37%/ 12%	50%/18%/ 32%	0.02

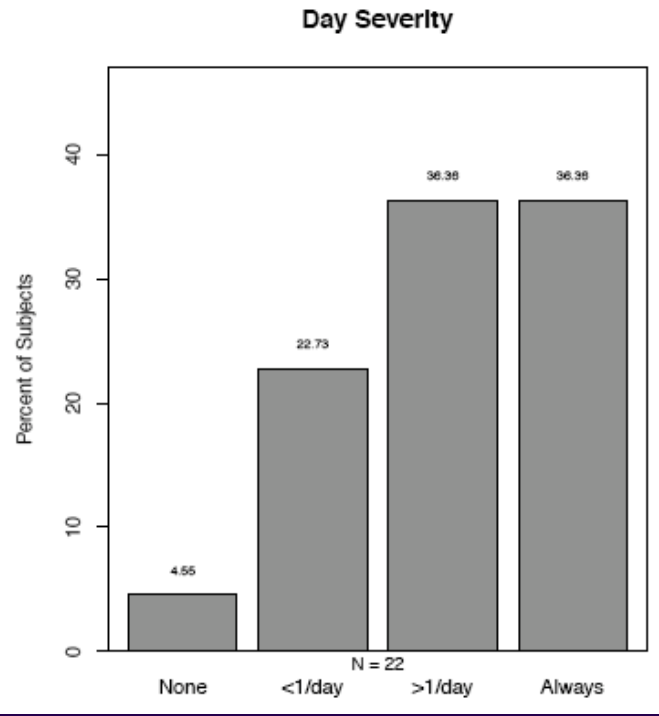
Asthma symptom frequency

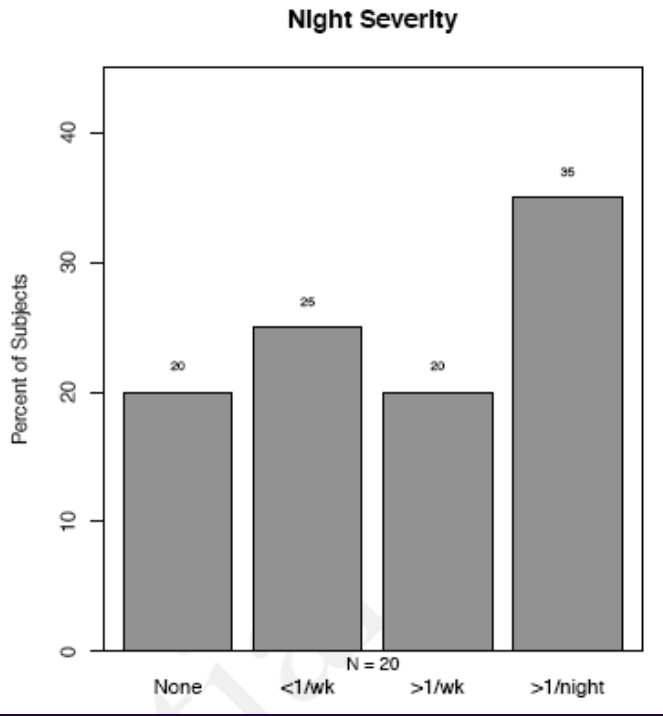
Randomized subjects

Open-label subjects

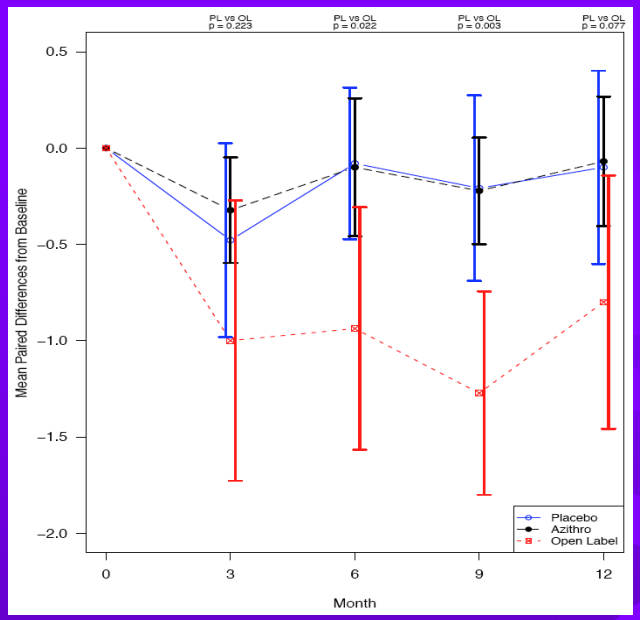




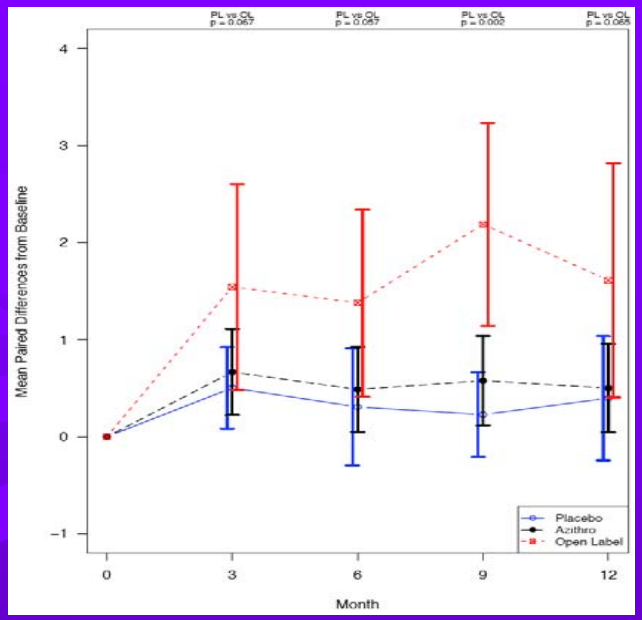




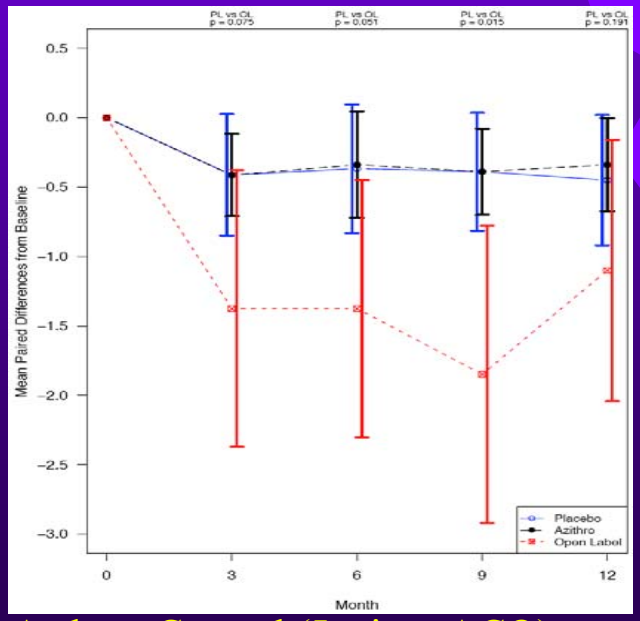
Results



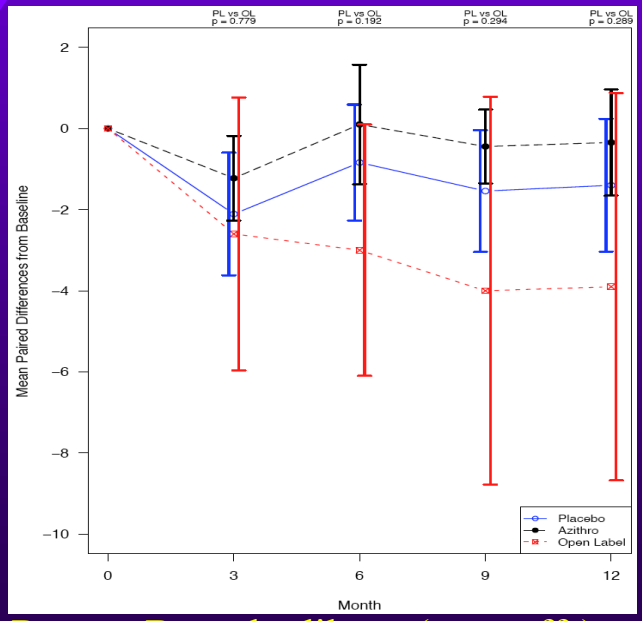
Asthma Symptoms (5-point scale)



Asthma QOL (Juniper AQLQ)



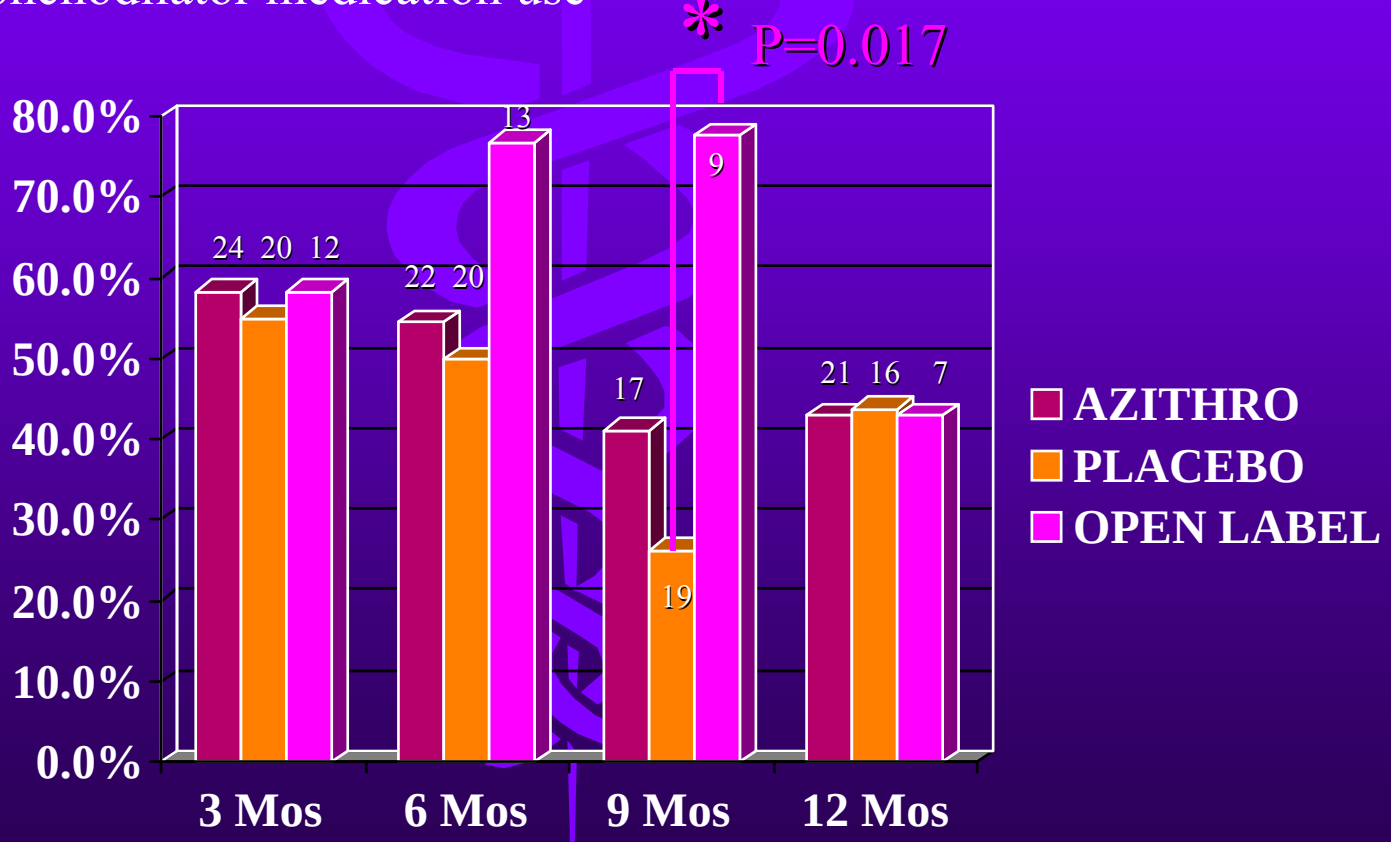
Asthma Control (Juniper ACQ)



Rescue Bronchodilator (no. puffs)

Improved v Not Improved

Subjects with no increase in controller medication use:
≥1 unit increase in AQLQ and/or ≥50% decrease in rescue bronchodilator medication use



Summary

- Subjects with severe treatment-resistent asthma - who declined to be randomized - demonstrated clinically important improvement lasting at least 6 months after completing open-label azithromycin.
- Subjects with milder asthma - who agreed to randomization - did not demonstrate comparable benefit.

Strengths

- Effectiveness RCT design
- Remarkable completion rate given lack of resources
- Demonstrates feasibility of effectiveness RCTs in community practices/primary care

Limitations

- No objective markers
  - Biomarkers
  - Pulmonary function
- Completion <80%
- Underpowered for subgroup analyses

Conclusions

- The results of this trial are inconclusive.
  - "Open label" results were due to placebo effects OR
  - The RCT was biased towards a null effect because of systematic (self-) exclusion of subjects most likely to benefit.
- In AZMATICS, this "enrollment bias" was unanticipated and accounted for.
- In NIH clinical trials, "enrollment bias" is purposeful, unaccounted for, and results in degraded guideline treatment recommendations.

Appendices

Guideline treatment trials: Lacking external validity

Typical exclusions:

- No comorbidity
- FEV1 50-85 %predicted
- ≥12% reversibility
- Current non-smoking
- Past hx <10 pack years

Additional exclusions:

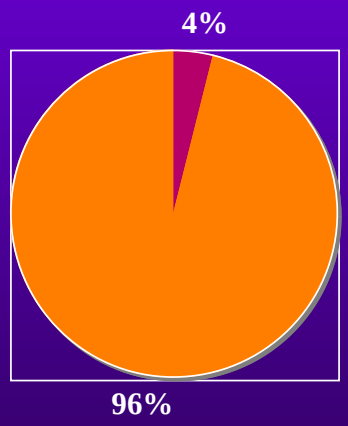
- Being symptomatic
- Regular use of inhaled steroids

Herland et al. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease?. Respiratory Med 2005; 99:11-19

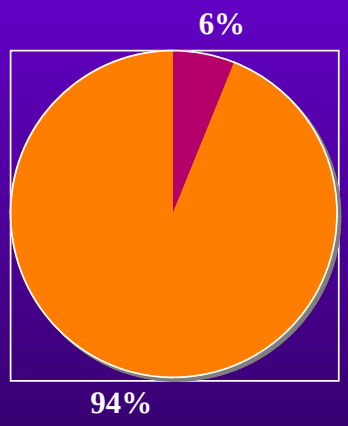
Guideline treatment trials: Lacking external validity

The proportion of people with asthma eligible for the major RCTs (n=17) cited in the Global Initiative for Asthma (GINA) guidelines.

- Current asthma



- Current asthma on treatment

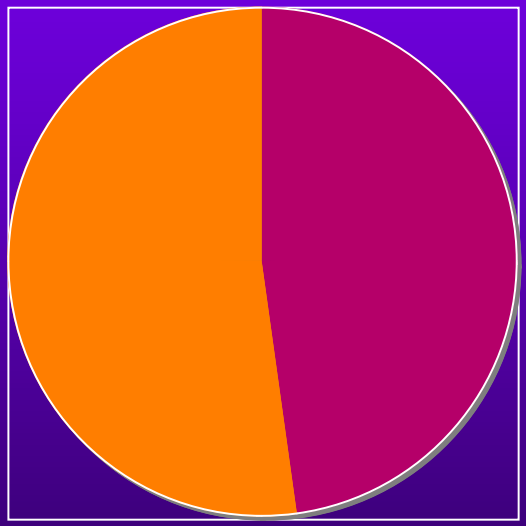


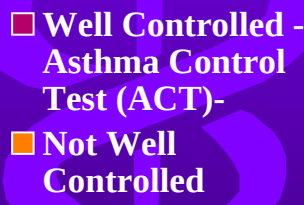
Eligible
Ineligible

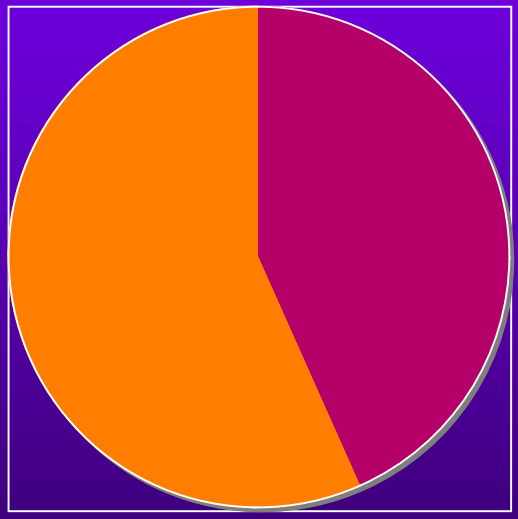
Travers et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply?. Thorax 2007;62:219-223

Guideline treatment for asthma is inadequate

Asthma prevalence = 6.1% (France,Germany, Italy, Spain and UK, 2008)







All asthma

Treated asthma

Demoly et al. Update on asthma control in five European countries. Eur Respir Rev 2010

Guideline treatment for asthma is inadequate

Not Well Controlled asthma (vs Controlled asthma):

- More activity limitations (40.8% vs 1.5%)
- More breathlessness ≥3 times weekly (72.5% vs 5.4%)
- More sleep difficulties ≥1 times weekly (60.3% vs 4.6%)
- More rescue medication ≥2-3 times weekly (77.4% vs 15.9%)
- More healthcare utilization (17.4% vs 9.9%)
- More absenteeism (12.2% vs 5.5%)
- More work impairment (30.0% vs 15.4%)
- Decreased quality-of-life (P<.001)

Demoly et al. Update on asthma control in five European countries. Eur Respir Rev 2010

Guideline treatment is ineffective in smokers

No patient-oriented benefits of inhaled steroids in smokers

• Pedersen et al. Eosinophil and neutrophil activity in asthma in a one-year trial with inhaled budesonide. The impact of smoking. *Am J Respir Crit Care Med* 1996;**153:**1519-1529.

• Chalmers et al. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002;**57:**226-230.

• Chaudhuri et al. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med* 2003;**168:**1308-1311.

• Tomlinson et al. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax* 2005;**60:**282-287.

• Lazarus et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007;**175:**783-790.

Guideline treatment is also less effective in non-smokers with severe asthma*

Severe (versus Not Severe) Asthma associated with:

- Steroid resistance.
- More pneumonia.
- Fewer eosinophils and less skin test positivity.
- Longer disease duration.
- Lower lung function.

These are all characteristics of *Chlamydia*-associated "infectious asthma."

- Hahn DL. Infectious asthma: A reemerging clinical entity? *J Fam Pract* 1995;41:153-157.

*Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2007;**119**:405-413.