Asthma Year in Review

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Disclosures

Grant support – GSK

I will not be discussing off-label use for any drugs or devices

Objectives

- Review findings from, and strengths/limitations of recent significant publications in asthma

- Discuss how these findings may impact daily clinical practice when caring for patients with asthma

Outline

- Are LABAs safe in asthma?
- Is as-needed ICS/LABA an effective strategy is mild asthma?
- Can escalation of ICS dose early in ‘yellow zone’ of asthma action plan abort exacerbations?
- New treatment for severe asthma

Background: LABA safety concerns

1993: Serevent nationwide surveillance study (SNS)

- A 16-week RCT in the UK, evaluating Salmeterol vs. Salbutamol in ~ 25,000 participants, found a small, not statistically significant, increase in asthma-related deaths in Salmeterol group

2006: Salmeterol Multicenter Asthma Research Trial (SMART)

- 28-week RCT in ~ 26,000 participants evaluated Salmeterol vs. placebo added-on to usual therapy
- Interim analysis revealed a small but statistically significant increase in serious asthma related events in African American subjects

Castle et al. BMJ 1993; 306:1034-1037
Nelson et al. Chest 2006; 129: 15-26

Background

- 2005: FDA required black-box warning regarding increased asthma related deaths for all LABAs
- 2011-2016: FDA mandated LABA safety studies
- 2016: 4 parallel trials with 41,297 patients (3 studies > age 12, & 1 age 4-11)
  - No significant increase in risk of serious asthma events with LABA used in combination with ICS (Hazard ration 1.10; 95% CI 0.85-1.44)
  - Significant reduction in exacerbations (Hazard ratio 0.79-0.89)
- 2017: 'black box warning' removed!

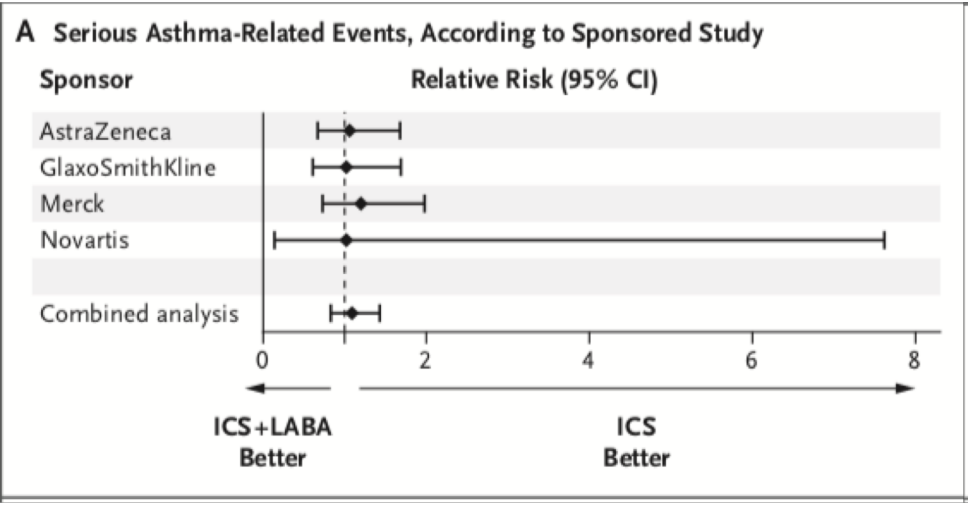
The NEW ENGLAND JOURNAL of MEDICINE

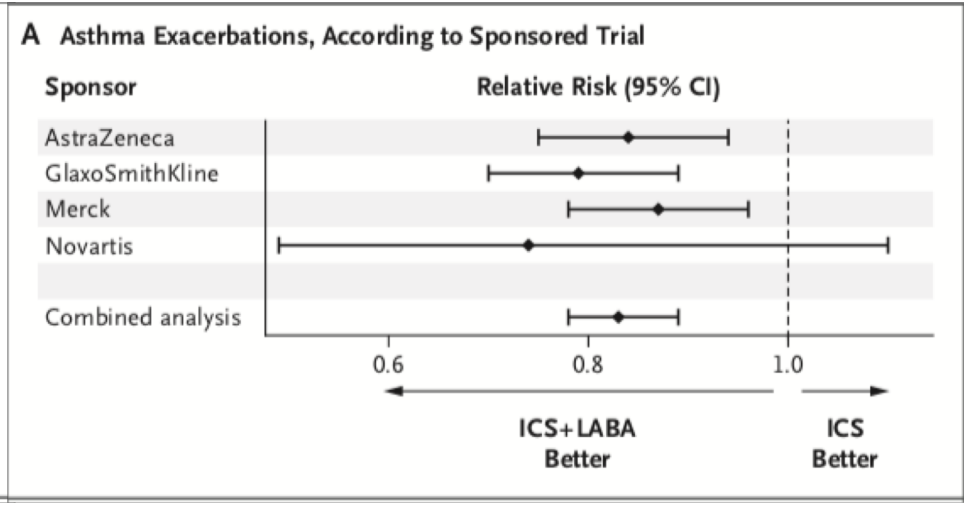
ORIGINAL ARTICLE

Combined Analysis of Asthma Safety Trials of Long-Acting β_2-Agonists

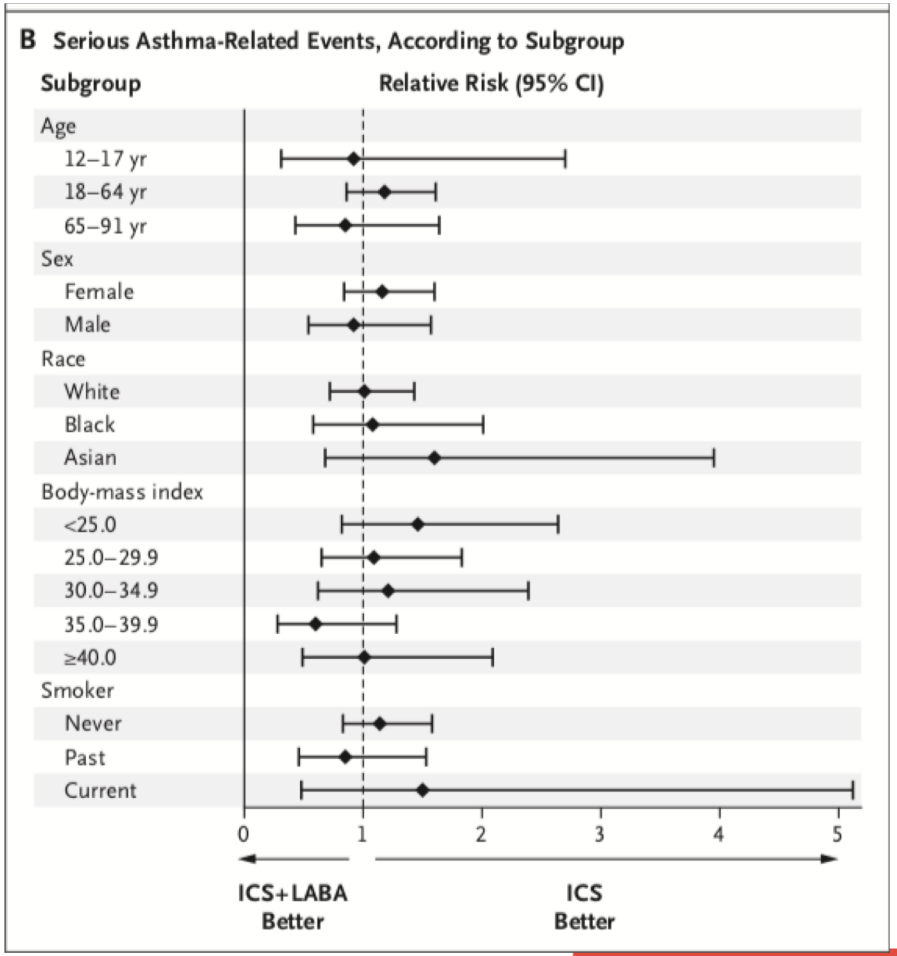
William W. Busse, M.D., Eric D. Bateman, M.B., Ch.B., M.D.,
Arthur L. Caplan, Ph.D., H. William Kelly, Pharm.D., Paul M. O'Byrne, M.B.,
Klaus F. Rabe, M.D., Ph.D., and Vernon M. Chinchilli, Ph.D.

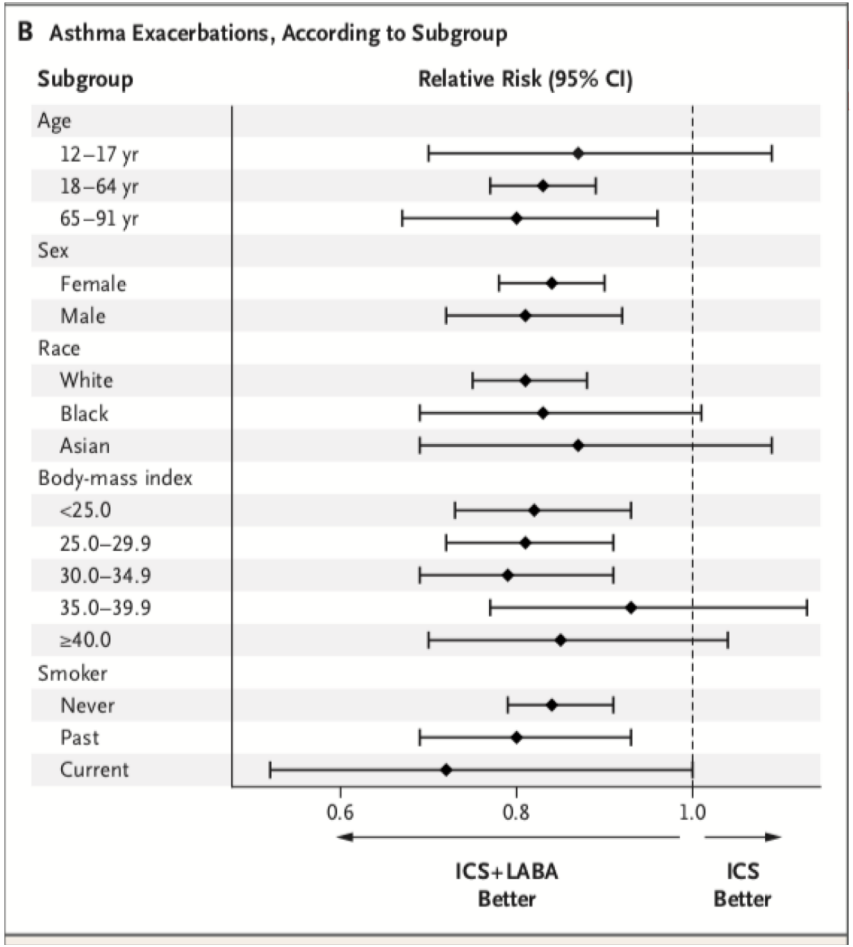
June 2018





Busse et al NEJM 2018; 378: 2497





Busse et al NEJM 2018; 378: 2497

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 17, 2018 VOL. 378 NO. 20

Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Paul M. O'Byrne, M.B., J. Mark FitzGerald, M.D., Eric D. Bateman, M.D., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Stefan Ivanov, M.D., Ph.D., and Helen K. Reddel, M.B., B.S., Ph.D.

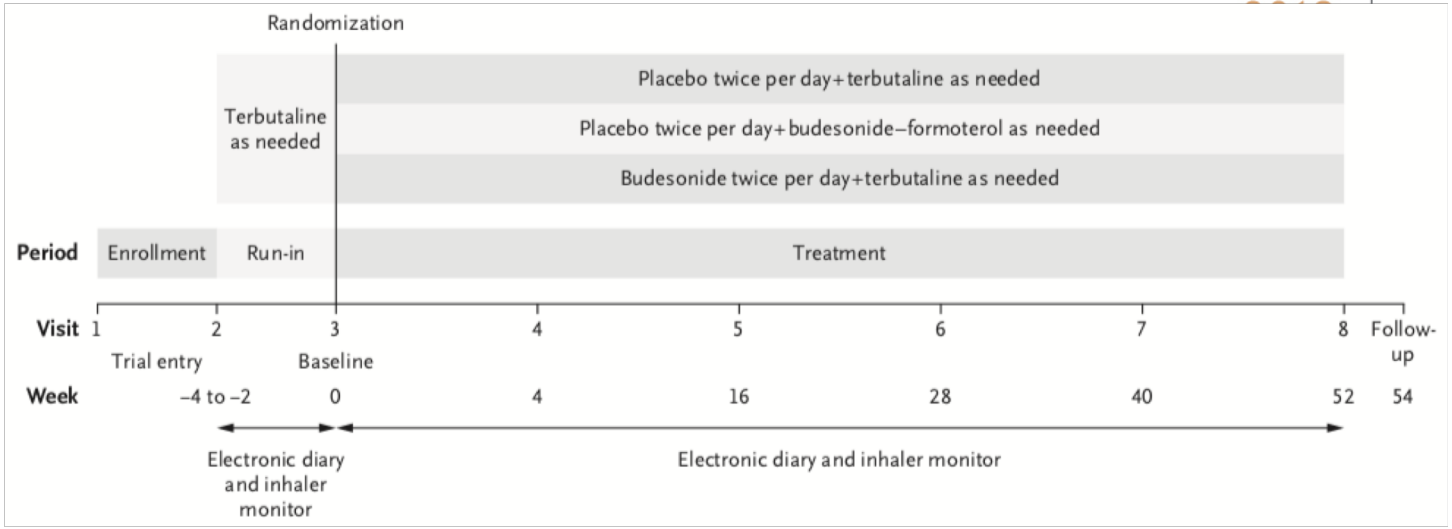
As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma

Eric D. Bateman, M.D., Helen K. Reddel, M.B., B.S., Ph.D., Paul M. O'Byrne, M.B., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Agnieszka Siwek-Posluszna, M.D., and J. Mark FitzGerald, M.D.

Background

- Mild asthma occurs in 50-75% of patients with asthma
- Symptoms may not be burdensome but airway inflammation is often present
- These patients are at risk of exacerbations and event asthma related death
- Guidelines recommend regular use of inhaled steroids as maintenance but poor adherence is a major problem, leading to undertreatment of airway inflammation
- At the same time, patients rely heavily on SABAs for symptom relief.

SYGMA 1: Budesonide/Formoterol given as needed in mild asthma



52 week double blind RCT, age > 12 years

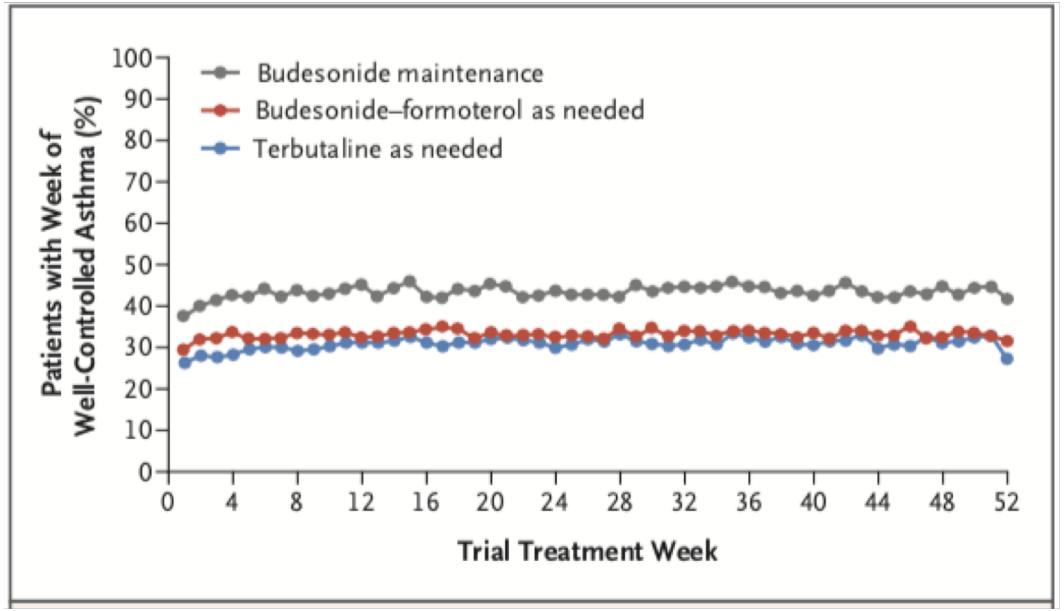
GINA Step 2 (either uncontrolled on SABA alone, or controlled on Step 2)

Primary outcome: electronically recorded weeks with well controlled asthma (electronic diary and digital inhaler) with as needed ICS/Formoterol compared to terbutaline alone

Secondary outcome: non inferiority of ICS/Formoterol to fixed dose ICS

O'Byrne PM et al. NEJM 2018; 378: 1865

SYGMA 1: Budesonide/Formoterol given as needed in mild asthma



In terms of weeks of well controlled asthma, budesonide-formoterol was:

Superior to as needed terbutaline

Inferior to Budesonide maintenance

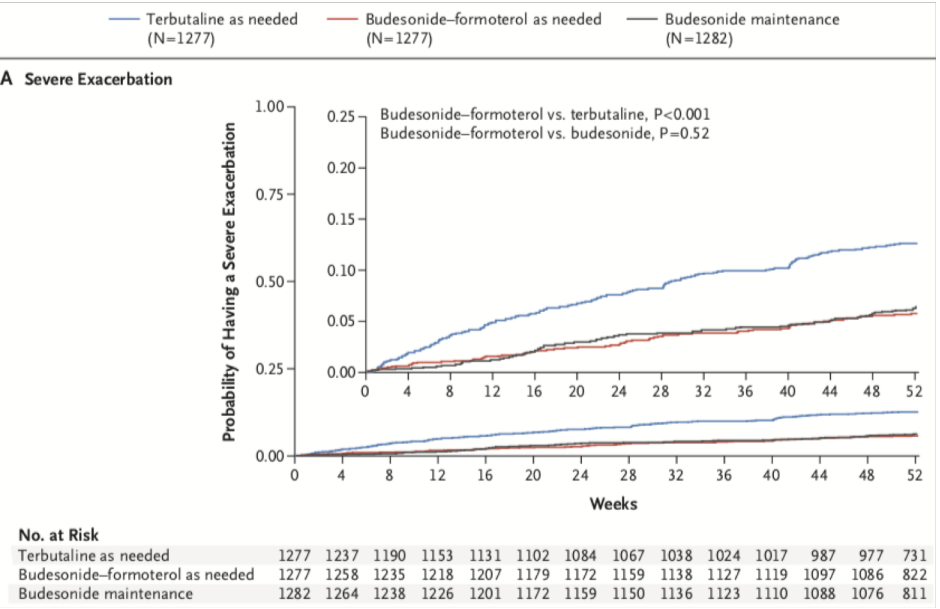
O'Byrne PM et al. NEJM 2018; 378: 1865

SYGMA 1: Budesonide/Formoterol given as needed in mild asthma

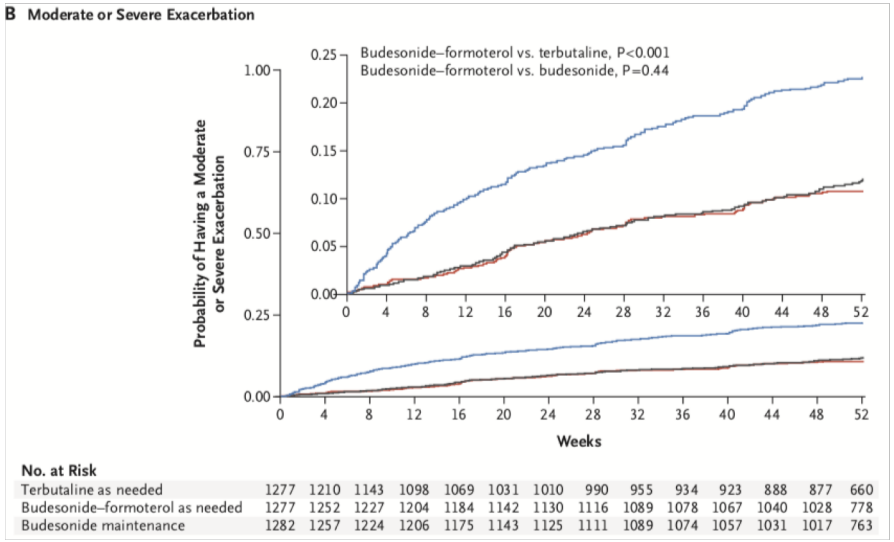
CHEST Congress 2019 | Thailand Bangkok | 10-12 April

Time to First Exacerbation.

P values were not controlled for multiple comparisons. Insets show the same data on an enlarged y axis.



No. at Risk															
Terbutaline as needed	1277	1237	1190	1153	1131	1102	1084	1067	1038	1024	1017	987	977	731
Budesonide–formoterol as needed	1277	1258	1235	1218	1207	1179	1172	1159	1138	1127	1119	1097	1086	822
Budesonide maintenance	1282	1264	1238	1226	1201	1172	1159	1150	1136	1123	1110	1088	1076	811



No. at Risk															
Terbutaline as needed	1277	1210	1143	1098	1069	1031	1010	990	955	934	923	888	877	660
Budesonide–formoterol as needed	1277	1252	1227	1204	1184	1142	1130	1116	1089	1078	1067	1040	1028	778
Budesonide maintenance	1282	1257	1224	1206	1175	1143	1125	1111	1089	1074	1057	1031	1017	763

In terms of exacerbations:

As-needed budesonide/formoterol was <u>non-inferior to maintenance ICS</u> with <u>1/5th of the ICS dose</u> (57 ug vs. 340 ug)

O'Byrne PM et al. NEJM 2018; 378: 1865

SYGMA 2: Budesonide/Formoterol given as needed in mild asthma

CHEST Congress 2019 | Thailand Bangkok | 10-12 April

<u>Parallel study to SYGMA 1 but Pragmatic design:</u>

no daily reminders to use maintenance inhalers

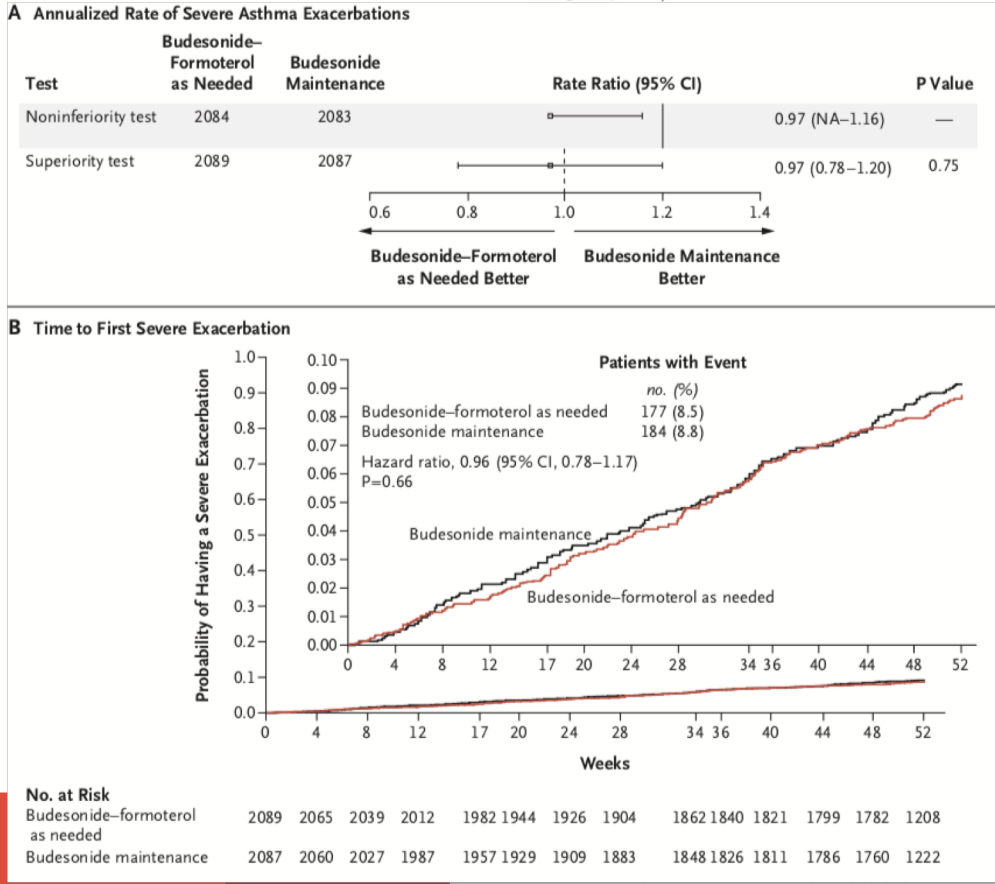
only 2 mid-trial visits

no diary, no PEF monitoring

<u>Remote digital monitoring of inhaler use</u>

BFC non-inferior to fixed dose ICS and ICS lower similar to SYGMA 1

Higher than anticipated adherence



Bateman ED et al. NEJM 2018; 378: 1877

Can exacerbations be prevented with early escalation in ICS dose?

The NEW ENGLAND JOURNAL of MEDICINE

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Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations

Tricia McKeever, Ph.D., Kevin Mortimer, Ph.D., Andrew Wilson, M.D., Samantha Walker, Ph.D., Christopher Brightling, Ph.D., Andrew Skeggs, B.Sc., Ian Pavord, F.Med.Sci., David Price, F.R.C.G.P., Lelia Duley, M.D., Mike Thomas, Ph.D., Lucy Bradshaw, M.Sc., Bernard Higgins, Ph.D., Rebecca Haydock, B.Sc., Eleanor Mitchell, B.A., Graham Devereux, Ph.D., and Timothy Harrison, M.D.

Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations

D.J. Jackson, L.B. Bacharier, D.T. Mauger, S. Boehmer, A. Beigelman, J.F. Chmiel, A.M. Fitzpatrick, J.M. Gaffin, W.J. Morgan, S.P. Peters, W. Phipatanakul, W.J. Sheehan, M.D. Cabana, F. Holguin, F.D. Martinez, J.A. Pongracic, S.N. Baxi, M. Benson, K. Blake, R. Covar, D.A. Gentile, E. Israel, J.A. Krishnan, H.V. Kumar, J.E. Lang, S.C. Lazarus, J.J. Lima, D. Long, N. Ly, J. Marbin, J.N. Moy, R.E. Myers, J.T. Olin, H.H. Raissy, R.G. Robison, K. Ross, C.A. Sorkness, and R.F. Lemanske, Jr., for the National Heart, Lung, and Blood Institute AsthmaNet*

Background

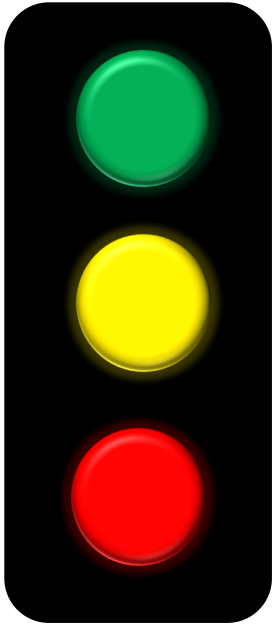
Acute exacerbations of asthma cause considerable illness and costs related to asthma

Asthma action plans have been shown to improve asthma control

Limited guidance for change in asthma medications for early loss of asthma control 'yellow zone' = Zone 2

2016 Cochrane review concluded that doubling ICS dose not efficacious

Quadrupling the dose of ICS identified as potentially efficacious in a single study previously



Quadrupling ICS dose to abort exacerbations

Pragmatic unblinded randomized trial in adults and adolescents

N = 1922, age > 16, > 1 exacerbation in past 12 months

Primary outcome: Time to first severe exacerbation (OCS or urgent medical visit)

Table 1. Zone 2 of Asthma Self-Management Plans Used by the Two Groups.

Quadrupling Group	Non-Quadrupling Group
Indication of deteriorating asthma control (one or more)	**Indication of deteriorating asthma control (one or more)**
You need your reliever inhaler more than usual.	Your need your reliever inhaler more than usual.
You have more difficulty sleeping because of your asthma.	You have more difficulty sleeping because of your asthma.
Your peak flow is below [80% of your normal level].	Your peak flow is below [80% of your normal level].
Action	**Action**
Use your reliever inhaler to relieve your symptoms and quadruple your inhaled glucocorticoid dose as described. Once your symptoms or peak flow have returned to normal or after a maximum of 14 days, return to your normal treatment. If your symptoms get worse, follow Zone 3 instructions.	Use your reliever inhaler to relieve your symptoms and continue your inhaled glucocorticoid medication at your normal dose. If your symptoms get worse, follow Zone 3 instructions.
Start to record your morning peak flow, symptoms, and medication in the trial diary.	Start to record your morning peak flow, symptoms, and medication in the trial diary.
Telephone your research nurse to arrange a trial visit.	Telephone your research nurse to arrange a trial visit.

McKeever T et al. N Engl J Med 2018;378:902

Quadrupling ICS dose to abort exacerbations

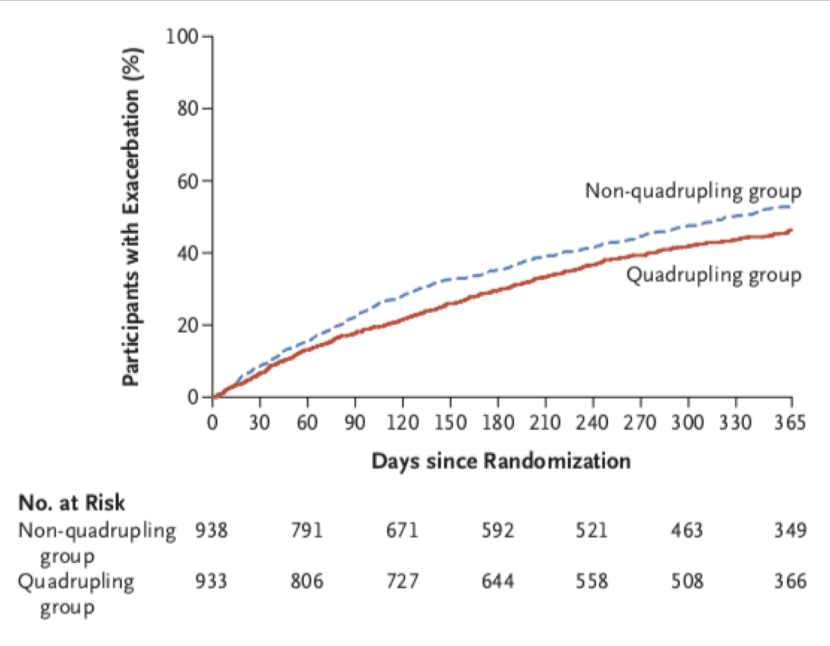


Figure 2. Kaplan–Meier Curves for the Time to the First Severe Asthma Exacerbation, According to Assigned Group.

58% of participants had a zone 2 event

45% in intervention vs. 52% in control group

RR 0.81

Increased laryngeal adverse effects

McKeever T et al. N Engl J Med 2018;378:902

Quintupling ICS dose to prevent exacerbation in children

Run-in Phase: 4 Wk	Treatment Phase: 48 Wk		
	Randomized treatment group	Daily *except* during 7-day yellow zone	Daily *only* during 7-day yellow zone
Fluticasone 44 μg/inhalation, 2 inhalations twice daily	Low dose	Fluticasone 44 μg/inhalation, 2 inhalations twice daily	Fluticasone 44 μg/inhalation, 2 inhalations twice daily
	High dose	Fluticasone 44 μg/inhalation, 2 inhalations twice daily	Fluticasone 220 μg/inhalation, 2 inhalations twice daily

Randomized, blinded study

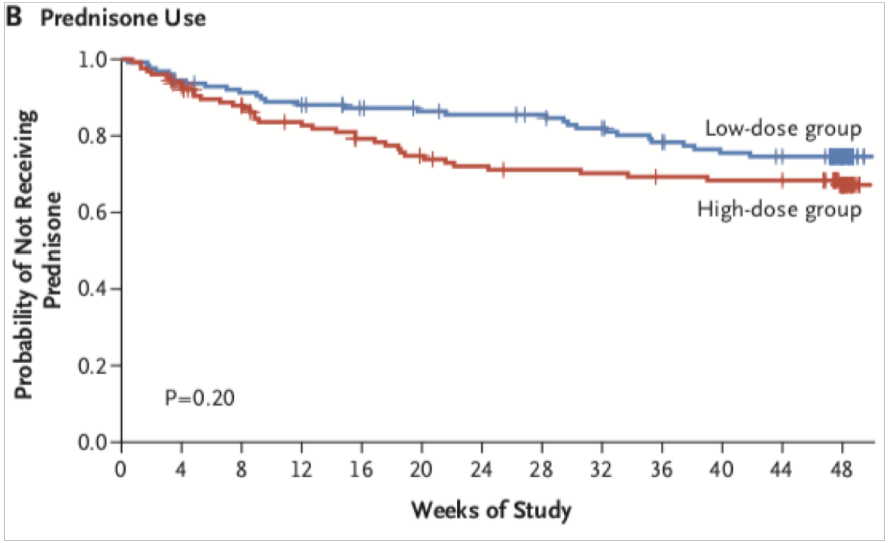
Children ages 5-11 years

Mild-to-moderate doctor diagnosed asthma

Step 2 therapy of NAEPP-EPR3

Jackson DJ et al. N Engl J Med 2018;378:891

Quintupling ICS dose to prevent exacerbation in children



No difference in number of exacerbations, ED visits, hospitalization, treatment failure

Systemic levels of steroids in high dose group and possible decreased linear growth in children < 7

Jackson DJ et al. N Engl J Med 2018;378:891

The NEW ENGLAND JOURNAL of MEDICINE

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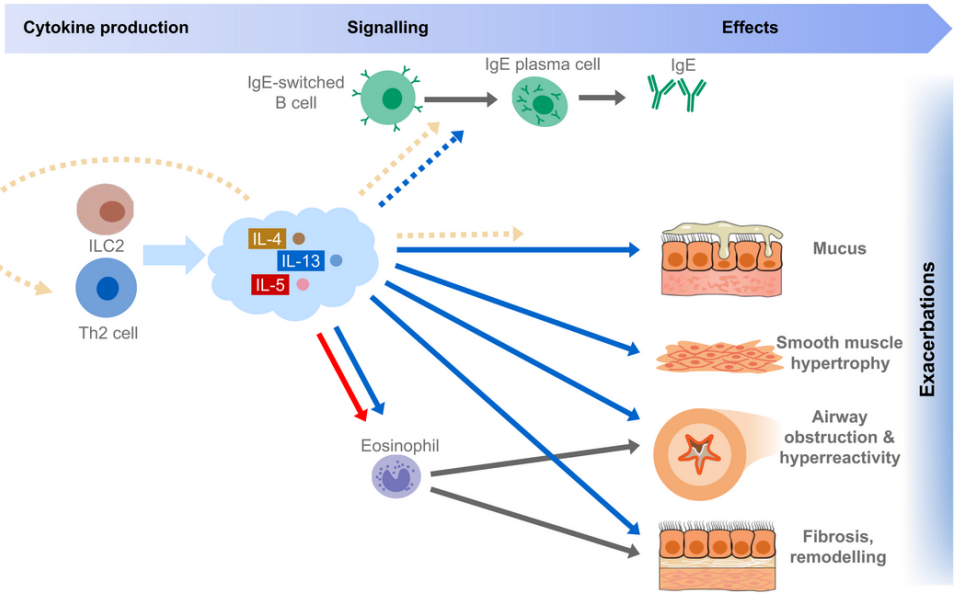
Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper

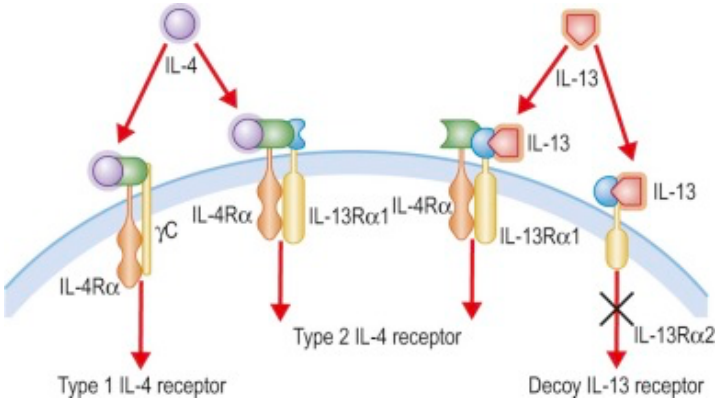
Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

Klaus F. Rabe, M.D., Ph.D., Parameswaran Nair, M.D., Ph.D., Guy Brusselle, M.D., Ph.D., Jorge F. Maspero, M.D., Mario Castro, M.D., Lawrence Sher, M.D., Hongjie Zhu, Ph.D., Jennifer D. Hamilton, Ph.D., Brian N. Swanson, Ph.D., Asif Khan, M.B., B.S., M.P.H., Jingdong Chao, Ph.D., Heribert Staudinger, M.D., Ph.D., Gianluca Pirozzi, M.D., Ph.D., Christian Antoni, M.D., Ph.D., Nikhil Amin, M.D., Marcella Ruddy, M.D., Bolanle Akinlade, M.D., Neil M.H. Graham, M.B., B.S., M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Ariel Teper, M.D.

Background - Dupilumab



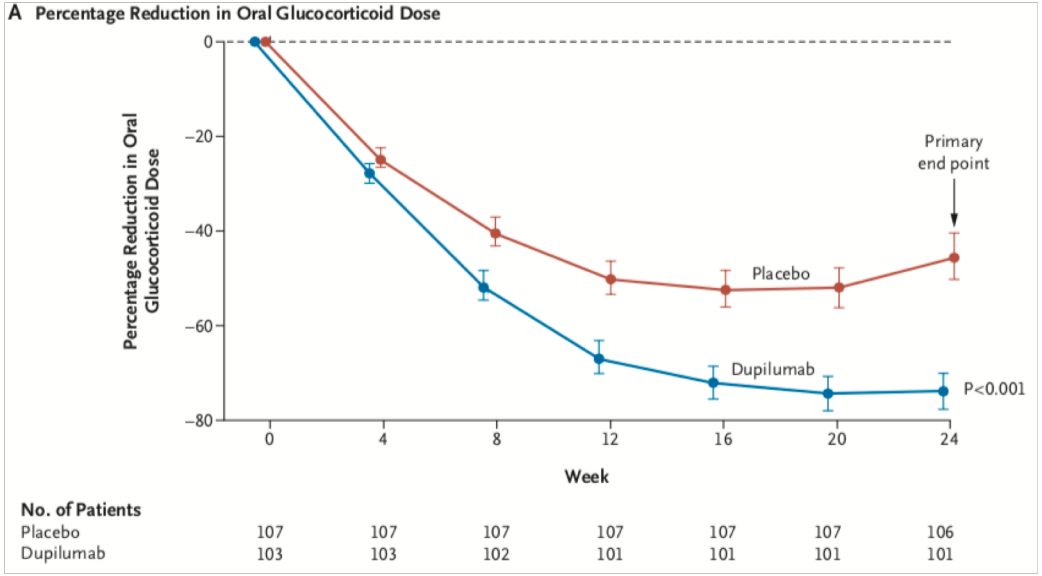
- IL-4 and IL-13 bind to a shared subunit, IL-4Rα
- Dupilumab, a human monoclonal IgG4 antibody, binds to IL-4Rα, blocking both IL-4 and IL-13 signaling
- IL-4 and IL-13 pathways have unique and overlapping function



Middleton's allergy essentials
Robinson et al. Clinical & Experimental Allergy 2017

Dupilumab & OCS-dependent Asthma

- 210 patients with OCS dependent asthma
- Dupilumab vs. placebo after an OCS optimization run-in period
- Tapering week 4-20 then stable for 4 weeks
- Primary endpoint: % reduction in OCS at week 24



Rabe et al NEJM 2018; 378:2486

Dupilumab & OCS-dependent Asthma

Table 2. Overview of Adverse Events during 24-Week Intervention Period and Injection-Site Reactions (Safety Population).*

Event	Placebo Group (N = 107)	Dupilumab Group (N = 103)
	number (percent)	
Any adverse event	69 (64)	64 (62)
Any serious adverse event	6 (6)	9 (9)
Any adverse event leading to death	0	0
Any adverse event leading to permanent discontinuation of trial regimen	4 (4)	1 (1)
Adverse event occurring in ≥5% of patients in either group†		
Viral upper respiratory tract infection	19 (18)	9 (9)
Bronchitis	6 (6)	7 (7)
Sinusitis	4 (4)	7 (7)
Influenza	6 (6)	3 (3)
Eosinophilia‡	1 (1)	14 (14)
Injection-site reaction§	4 (4)	9 (9)
≥1 measurement of blood eosinophil count >3000 cells/mm^3	1 (1)	13 (13)

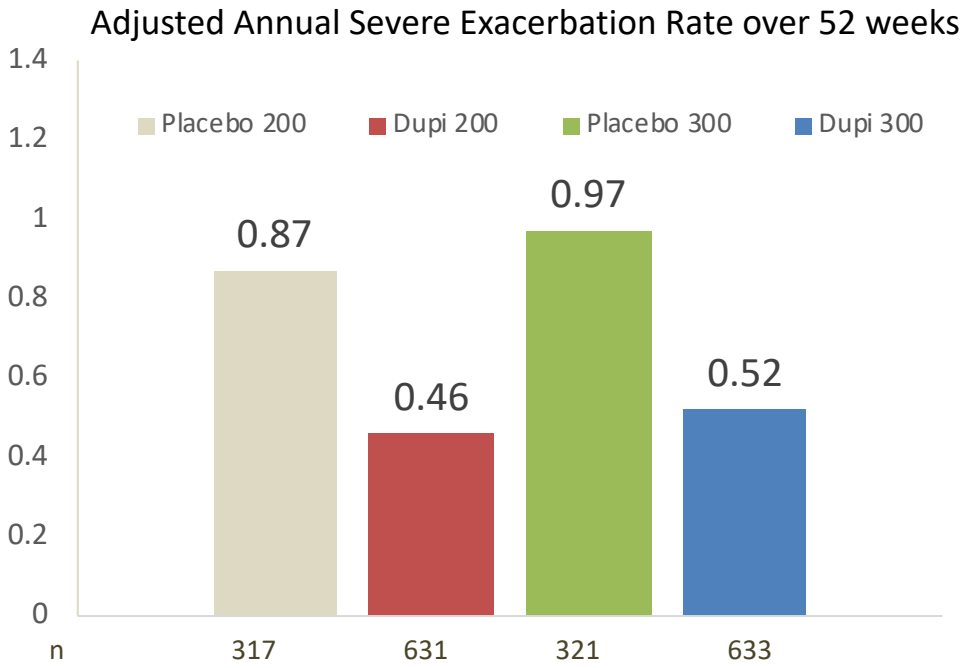
Rabe et al NEJM 2018; 378:2486

Dupilumab & mod-severe uncontrolled asthma

1902 patients

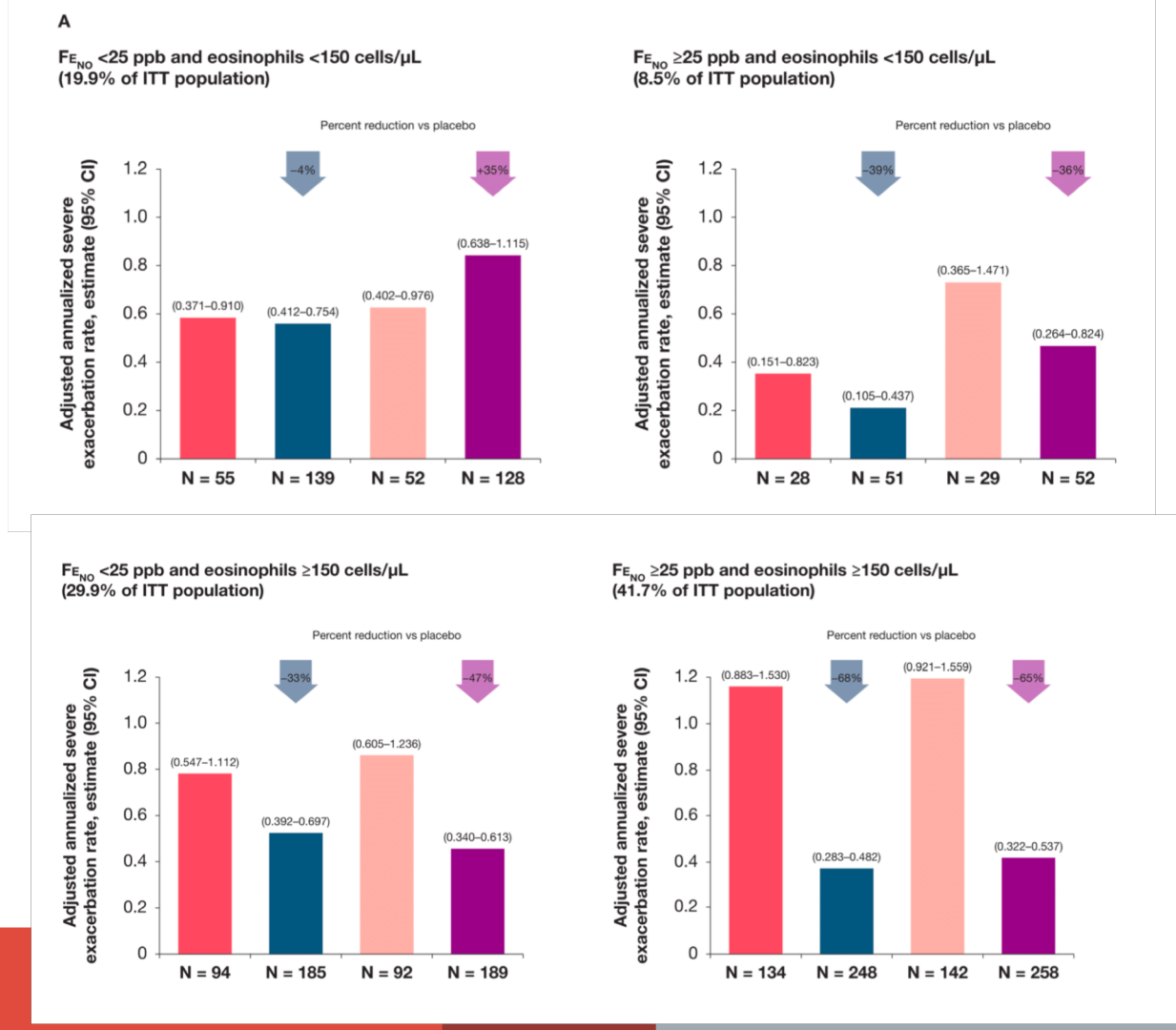
Adolescents & adults

200 vs 300 mg dupilumab SC q 2 weeks



Castro et al NEJM 2018; 378:2486

Effect of dupilumab by baseline Eos and FeNO



Castro et al. NEJM 2018 ; 378:2486

Summary

- Reassuring data on safety of LABA in asthma when used in combination with ICS
- More evidence for formoterol containing ICS/LABA as ‘SMART’ strategy
- Escalation of ICS dose during ‘yellow’ zone
  - Not effective in children
  - Small benefit in adults
- New class of biologic – dupilumab – effective in reducing exacerbation and OCS dependence. Effect size larger in patients with elevated FeNO or blood eos

Honorable mentions

- Inadequate assessment of adherence to maintenance medication leads to loss of power and increased costs in trials of severe asthma therapy. Results from a systematic literature review and modelling study. European Respiratory Journal 2019; DOI: 10.1183/13993003.02161-2018
- Refractory airway type 2 inflammation in a large subgroup of asthmatic patients treated with inhaled corticosteroids. JACI 2019; 143: 104.
- Managing Asthma in Pregnancy (MAP) trial: FENO levels and childhood asthma. JACI 2018; 142: 1765
- Asthma Is a Risk Factor for Respiratory Exacerbations Without Increased Rate of Lung Function Decline. CHEST 2018; 153: 368
- Associations of Asthma and Asthma Control With Atrial Fibrillation Risk. Results From the Nord-Trøndelag Health Study (HUNT). JAMA 2018; 3: 721
- Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. Lancet Respir Med. 2019; 7: 46.
- Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. JACI 2018. doi: 10.1016/j.jaci.2018.09.033.