

Treatment Option for Mild Asthma

순천향의대 호흡기내과

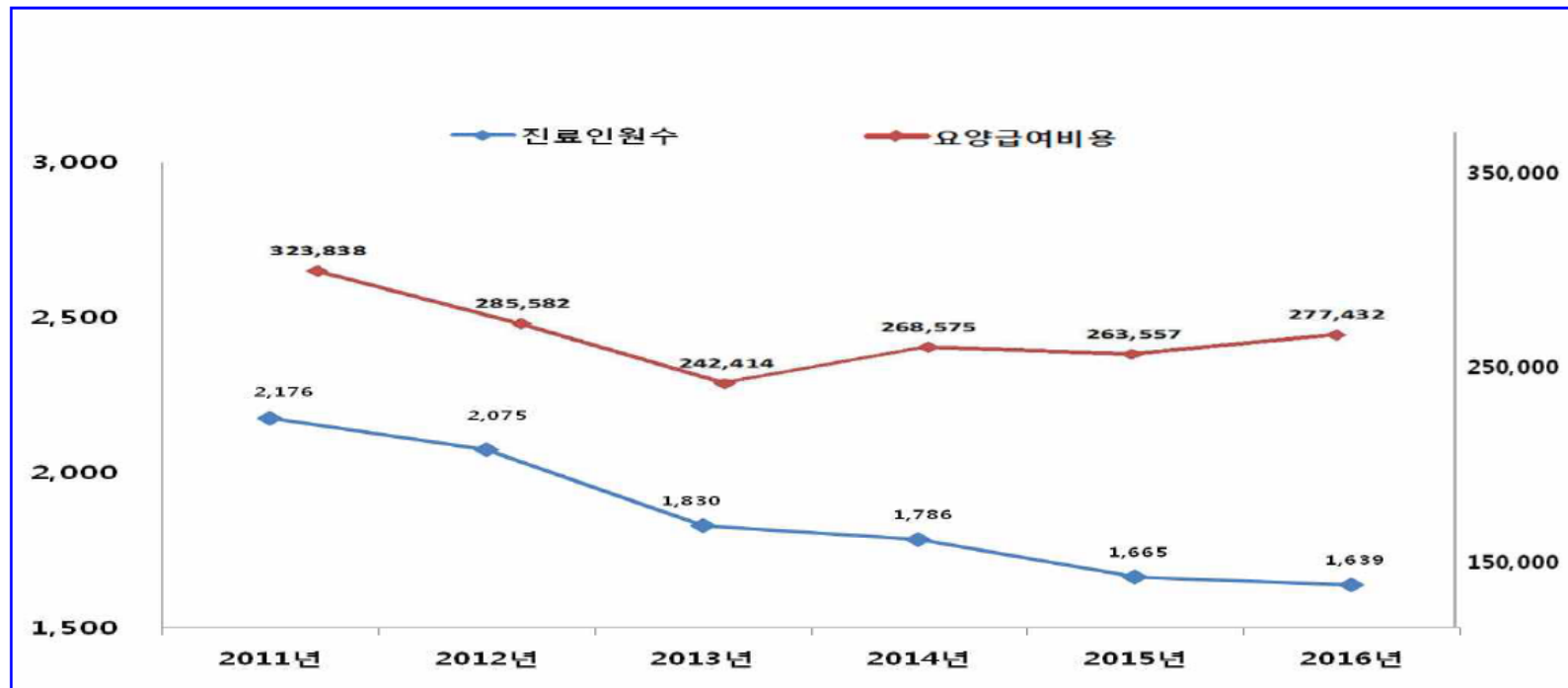
나주옥

Contents

1. Definition & prevalence of mild asthma
2. Treatment option for mild asthma in 2018 GINA guideline
3. Paradigm shift in the treatment of mild asthma
4. Suggestion for mild asthma treatment & 2019 GINA

○ 천식은 의료자원 소모가 많은 질환으로 관리가 중요함

- 천식 유병율: 2.7%(19세 이상), 2.5%(19세 이상 표준화), 5.7%(65세 이상)⁽²⁾
- 환자수 163만 명(총 진료인원의 3.43%), 진료비용 2,774억 원(총 진료비용의 0.34%)⁽³⁾



[천식 진료현황]

Definition of mild asthma

- Mild asthma, often termed mild intermittent or mild persistent asthma, is defined by the Global Initiative in Asthma (GINA) management strategy as **patients who meet the criteria for step 1 and step 2 treatment strategies**

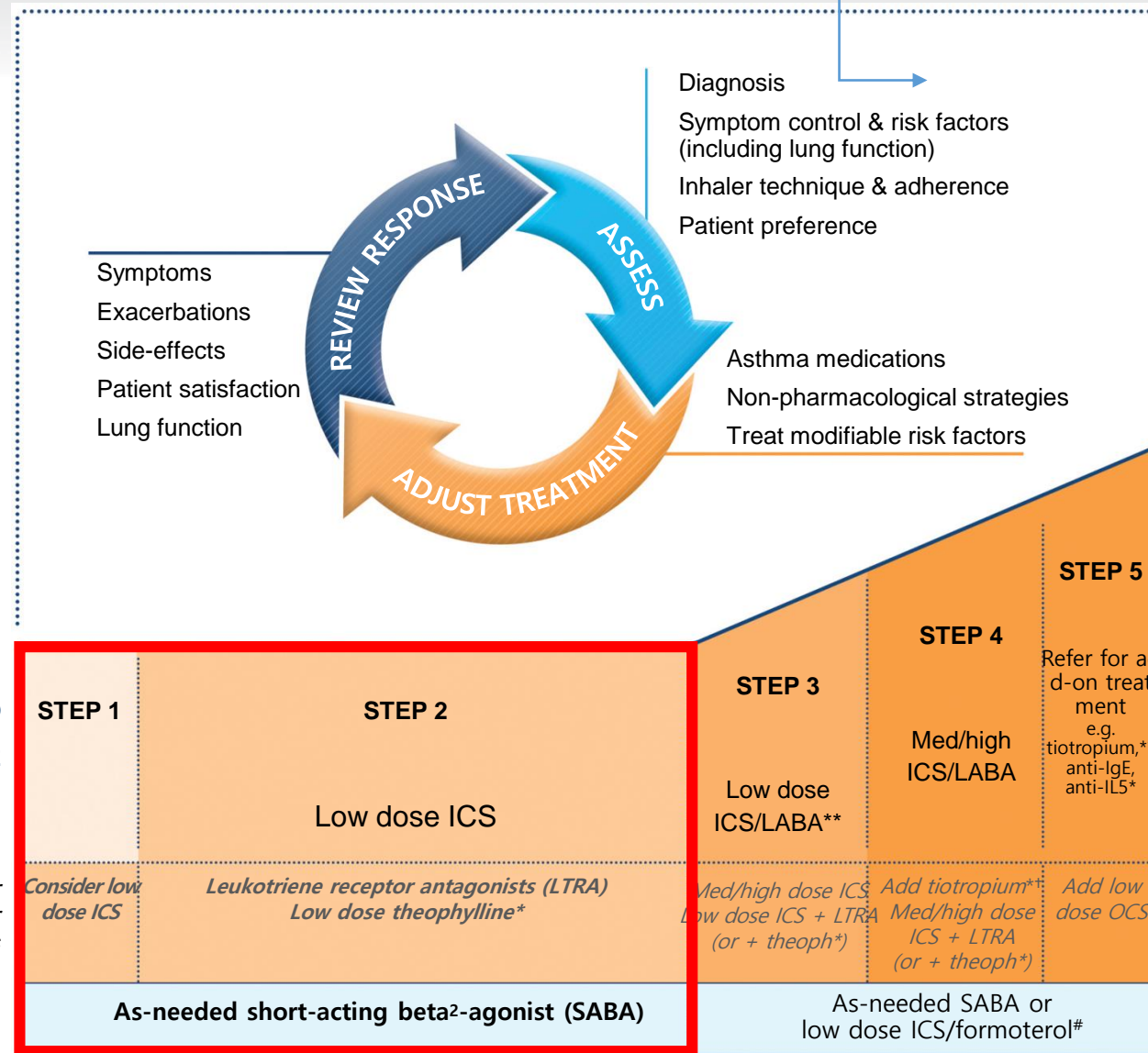
Assessing asthma severity

- Asthma severity is assessed retrospectively from the level of treatment required to control symptoms & exacerbations
- Assess asthma severity after patient has been on controller treatment for several months
- Severity is not static
 - it may change over months or years, or as different treatments become available

• **Categories of asthma severity**

- **Mild asthma: well-controlled with Steps 1 or 2 (as-needed SABA or low dose ICS)**
- Moderate asthma: well-controlled with Step 3 (low-dose ICS/LABA)
- Severe asthma: requires Step 4/5 (moderate or high dose ICS/LABA ± add-on), or remains uncontrolled despite this treatment

GINA 2018 Stepwise management - pharmacotherapy



#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

권장되는 첫 조절제

| 증상 | 선호되는 첫 조절제 |
|--|--|
| 월 1회 이하의 주간증상 혹은 SABA사용 지난 한 달 야간증상 (-) 급성악화 위험요인 (-) 지난 1년간 급성악화 (-) | - 조절제 필요 없음(prn SABA only) |
| 증상 거의 없지만 한 개 이상 급성악화 위험요인 : 폐기능 저하, 경구스테로이드 복용력이 필요한 급성 악화, 중환자실 입원 | - 저용량 ICS |
| 월 2회 이상-주 2회 이하의 주간증상 혹은 월 1회 이상 야간증상 | - 저용량 ICS |
| 주 3회 이상의 주간증상 혹은 SABA 사용 | - 저용량 ICS - LTRA 혹은 테오필린 (효과 적음) |
| 매일 주간 증상 혹은 주 1회 이상의 야간증상 | - 중간/고용량 ICS - 저용량 ICS/LABA |
| 중증의 조절되지 않은 천식 혹은 급성악화 | - 단기간의 경구스테로이드 + 조절제 (고용량 ICS 혹은 중간용량 ICS/LABA) |

Step 1

Step 2

Step 3

Step 4,5

Estimation of the prevalence of mild asthma (40%-70%)

| Reference | Asthma definition | Population | Frequency | Prevalence (over the whole population) |
|--|---|---|---|---|
| Credes (France) (6) | Asthma life, or CPAM table, or asthma treatment, or physiotherapist | Whole population $n = 16\ 389$ | Intermittent: 49% Mild persistent: 29% Moderate persistent: 11% Severe persistent: 10% | Intermittent: 2.9% Mild persistent: 1.7% Moderate persistent: 0.6% Severe persistent: 0.6% |
| Zureik et al. (International) (10) | Recent asthma 12 months ECRHS | Whole population $n = 17\ 089$ | Mild: 50% Moderate: 29% Severe: 21% | Mild: 3.3% Moderate: 1.9% Severe: 1.4% |
| Liard et al. (France) (7) | Asthma diagnosed by GP | Asthmatic patients Transversal study $n = 4362$ Age: 16–45 | Intermittent: 13% Mild persistent: 26.6% Moderate persistent: 35.6% Severe persistent: 24.8% | |
| Rabe et al. AIRE Study (International) (8) | Current asthma diagnosed by GP (12 months or treatment) | Asthmatic patients Transversal study $n = 7786$ adults $n = 3153$ children | Intermittent: 22–54% Mild persistent: 12–20% Moderate persistent: 16–27% Severe persistent: 11–32% | |

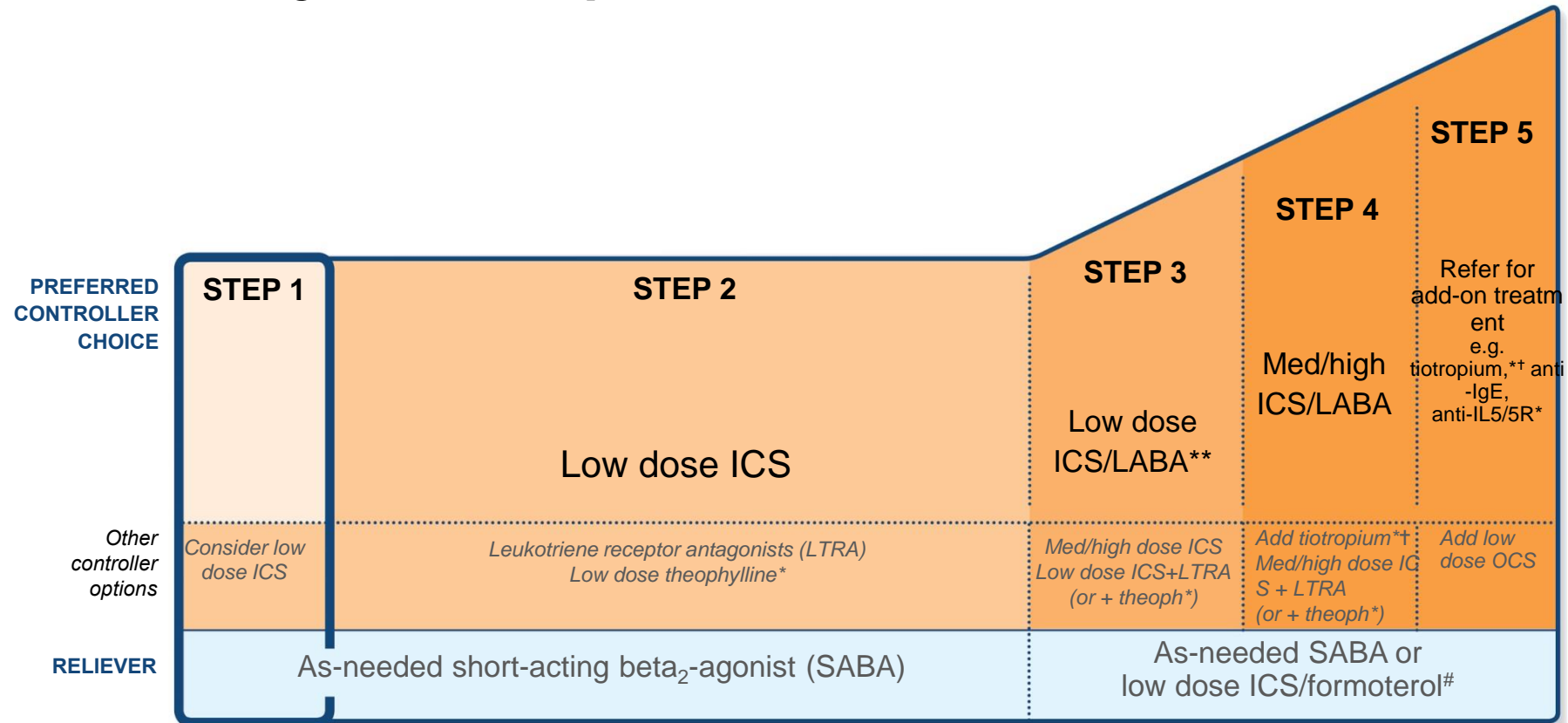
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Initial controller treatment for adults, adolescents

- Start controller treatment early
- **Indications for regular low-dose ICS - any of:**
 - Asthma symptoms more than twice a month
 - Waking due to asthma more than once a month
 - Any asthma symptoms plus any risk factors for exacerbations
- **Consider starting at a higher step if:**
 - Troublesome asthma symptoms on most days
 - Waking from asthma once or more a week, especially if any risk factors for exacerbations
- **If initial asthma presentation is with an exacerbation:**
 - Give a short course of oral steroids and start regular controller treatment
 - (e.g. high dose ICS or medium dose ICS/LABA, then step down)

Step 1 – as-needed inhaled SABA (very few patients)



Step 1 – as-needed reliever inhaler



- Preferred option
 - : as-needed inhaled short-acting beta₂-agonist (SABA)
- Insufficient evidence about the safety of treating asthma with SABA alone
- This option should be reserved for patients (Evid B)

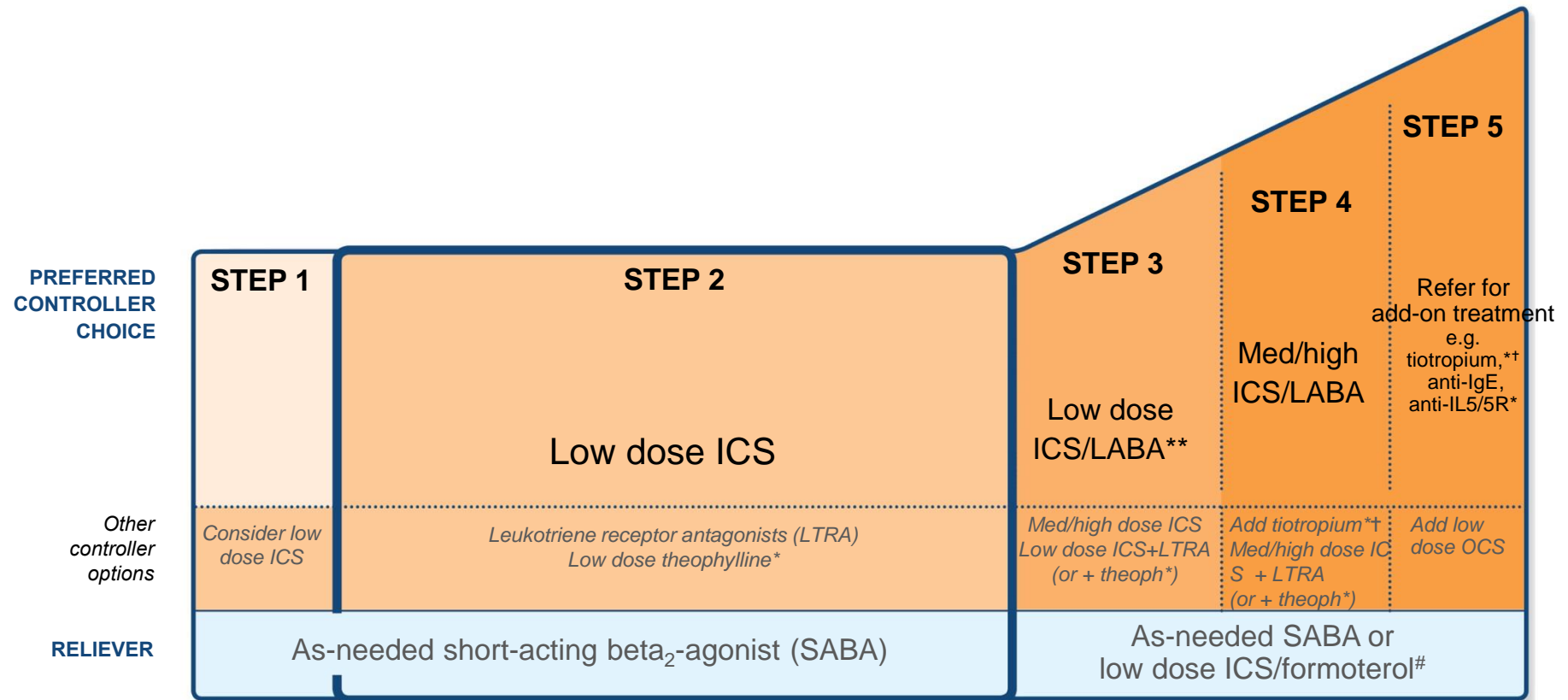
infrequent symptoms (less than twice a month) of short duration,
no night waking due to asthma
normal lung function (fev1 >80% personal best or predicted)
no risk factors for exacerbations
no previous 12 months exacerbation

Risk factors for exacerbations



- Uncontrolled asthma symptoms
- ◆ **Additional risk factors, even if the patient has few symptoms:**
 - High SABA use (≥ 3 canisters/year)
 - Having ≥ 1 exacerbation in last 12 months
 - Low FEV₁; higher bronchodilator reversibility
 - Incorrect inhaler technique and/or poor adherence
 - Smoking
 - Obesity, chronic rhinosinusitis, pregnancy, blood eosinophilia
 - Elevated FeNO in adults with allergic asthma taking ICS
 - Ever intubated for asthma

Step 2 – low-dose controller + as-needed inhaled SABA



Step 2 – Low dose controller + as-needed SABA

- Low dose ICS reduces symptoms, reduces risk of exacerbations, asthma-related hospitalization and death

• Other options

- Leukotriene receptor antagonists (LTRA) with as-needed SABA
 - Less effective than low dose ICS, especially for preventing exacerbations
 - some patients with both asthma and allergic rhinitis, or if patient will not use ICS
- Combination low dose ICS/LABA with as-needed SABA
 - Reduces symptoms and increases lung function compared with ICS
 - More expensive, and does not further reduce exacerbations
- Intermittent ICS with as-needed SABA for purely seasonal allergic asthma with no interval symptoms
 - Start ICS immediately symptoms commence, and continue for 4 weeks after pollen season ends

Treatment steps – changes in 2018

- Step 1

- It is explained that the reason ICS should be considered for patients with mild asthma (rather than prescribing SABA alone) is to reduce their risk of serious exacerbations

- *(Pauwels, Lancet 2003; O'Byrne AJRCCM 2001; Reddel Lancet 2017)*

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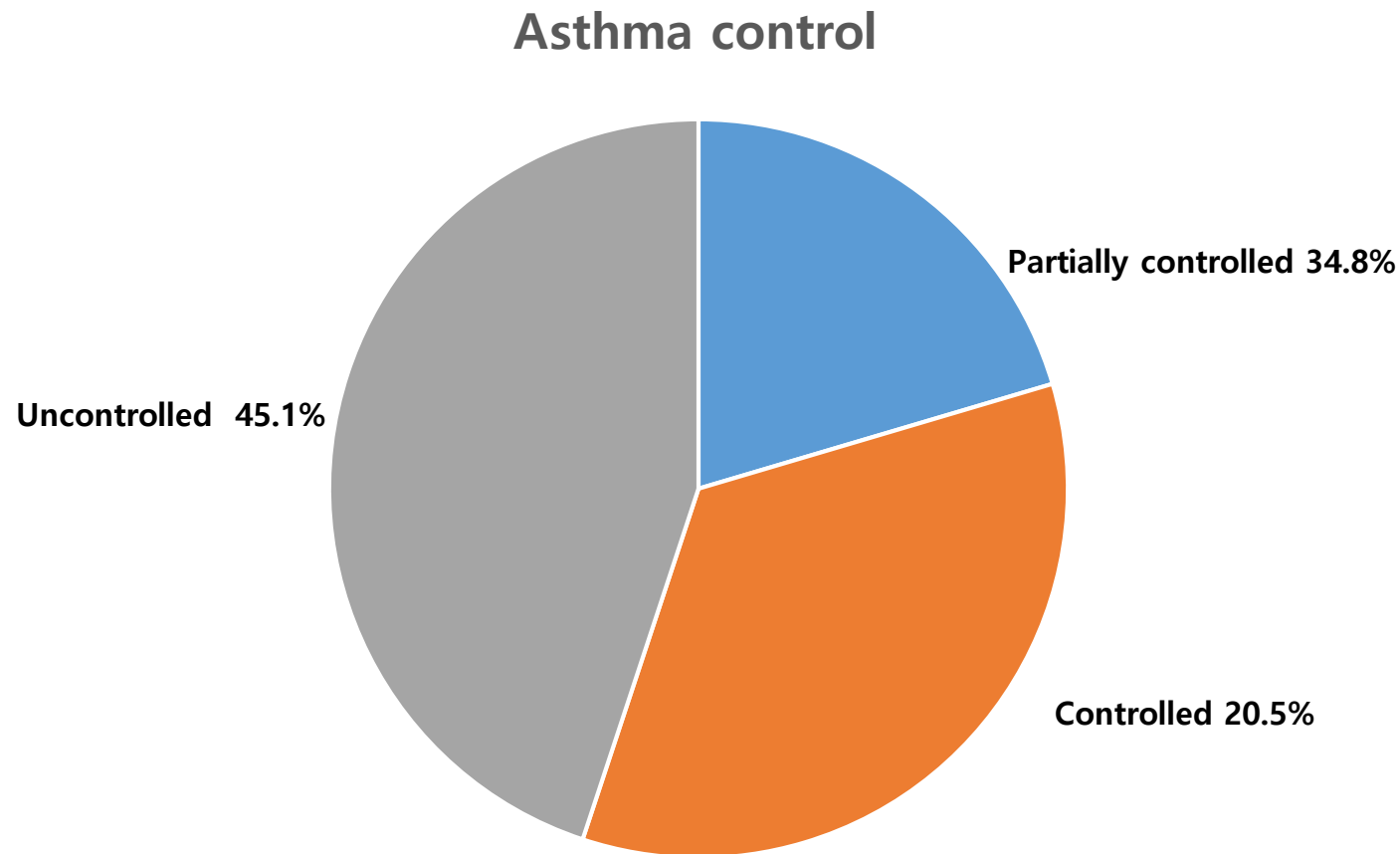
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Dilemma for treatment of mild asthma

Overuse SABA vs Underuse ICS

Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey

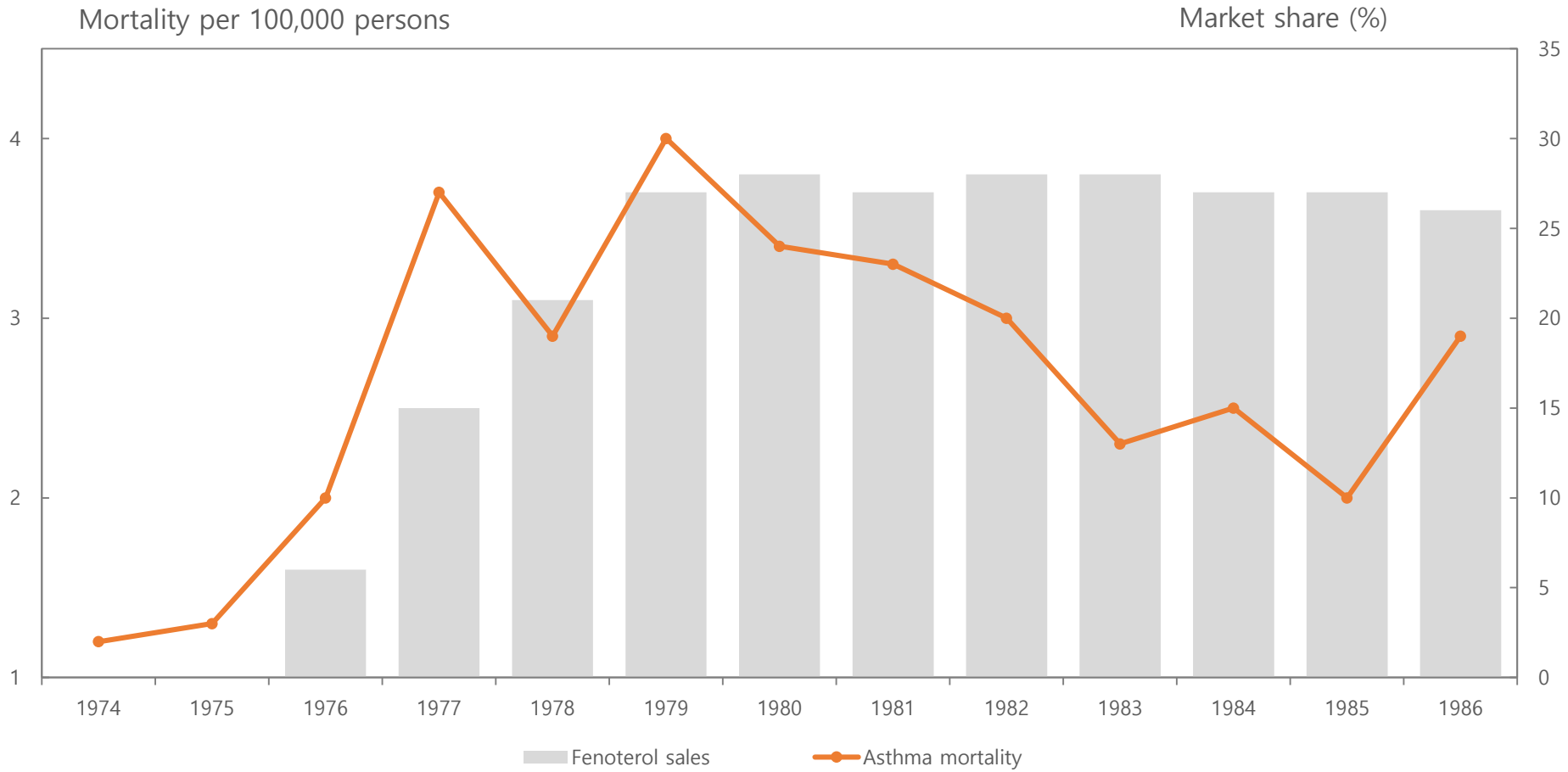
David Price¹, Monica Fletcher² and Thys van der Molen³

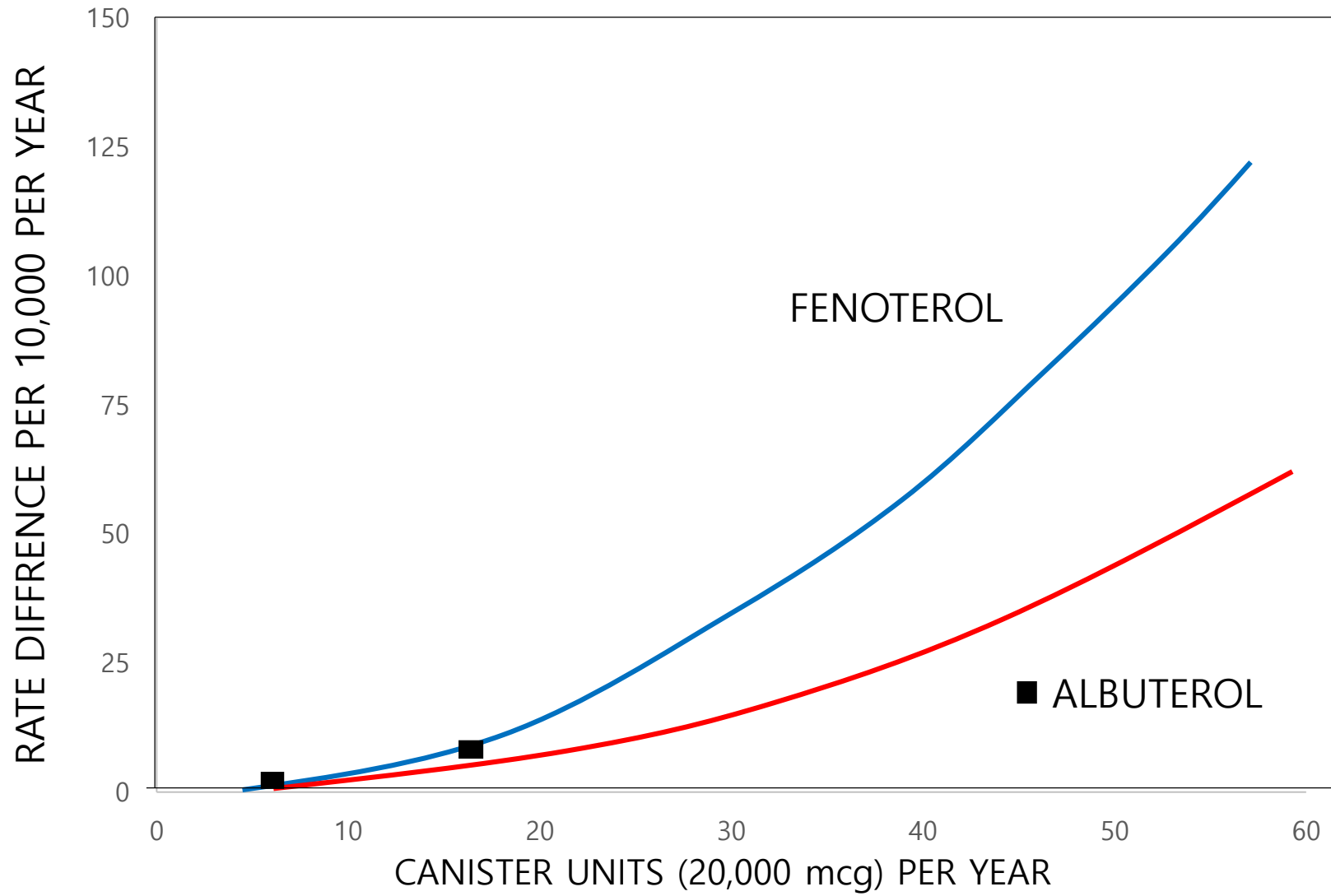


Indicators of asthma symptoms and exacerbations overall and by GINA-defined control levels

| | Overall (N = 8,000) | GINA-defined asthma control | | | Correlation with control, <i>r</i> |
|--|---------------------|-----------------------------|----------------------------------|--------------------------|------------------------------------|
| | | Controlled (n = 1,604) | Partially controlled (n = 2,785) | Uncontrolled (n = 3,611) | |
| <i>Control and indicators of symptoms</i> | | | | | |
| Days with symptoms ^a | | | | | |
| None | 1,622 (20.3) | 1,037 (64.7) | 544 (19.5) | 41 (1.1) | 0.600 ^b |
| ≥1 day | 6,378 (79.7) | 567 (35.3) | 2,241 (80.5) | 3,570 (98.9) | |
| ≥3 days | 3,343 (41.8) | 0 | 449 (16.1) | 2,894 (80.1) | |
| Normal activities affected by symptoms ^a | | | | | |
| None | 3,360 (42.0) | 1,604 (100) | 1,455 (52.2) | 301 (8.3) | 0.708 ^b |
| ≥1 day | 4,640 (58.0) | 0 | 1,330 (47.8) | 3,310 (91.7) | |
| Night-time awakening ^a | | | | | |
| None | 3,639 (45.5) | 1,604 (100) | 1,606 (57.7) | 429 (11.9) | 0.683 ^b |
| ≥1 day | 4,361 (54.5) | 0 | 1,179 (42.3) | 3,182 (88.1) | |
| Reliever inhaler use ^a | | | | | |
| Not used | 2,143 (26.8) | 1,083 (67.5) | 894 (32.1) | 166 (4.6) | 0.679 ^b |
| ≥1 time | 5,509 (68.9) | 407 (25.4) | 1,738 (62.4) | 3,364 (93.2) | |
| ≥3 times | 3,430 (42.9) | 0 | 610 (21.9) | 2,820 (78.1) | |
| ≥10 times | 518 (6.5) | 0 | 85 (3.1) | 433 (12.0) | |
| <i>Acute exacerbations</i> | | | | | |
| Oral steroid use for worsening asthma ^c | | | | | |
| Not used | 4,484 (56.1) | 1,224 (76.3) | 1,924 (69.1) | 1,336 (37.0) | 0.332 |
| ≥1 course | 3,516 (44.0) | 380 (23.7) | 861 (30.9) | 2,275 (63.0) | |
| Days off work/education ^{cd} | | | | | |
| None | 4,150 (62.5) | 1,163 (85.7) | 1,772 (77.1) | 1,215 (40.8) | 0.389 |
| ≥1 day | 2,485 (37.5) | 194 (14.3) | 525 (22.9) | 1,766 (59.2) | |
| Antibiotic use for an asthma-associated condition ^c | | | | | |
| None | 3,033 (37.9) | 925 (57.7) | 1,250 (44.9) | 858 (23.8) | 0.278 |
| ≥1 course | 4,967 (62.1) | 679 (42.3) | 1,535 (55.1) | 2,753 (76.2) | |
| Emergency department visit due to asthma ^c | | | | | |
| None | 6,090 (76.1) | 1,485 (92.6) | 2,421 (86.9) | 2,184 (60.5) | 0.317 |
| ≥1 visit | 1,910 (23.9) | 119 (7.4) | 364 (13.1) | 1,427 (39.5) | |
| Overnight hospitalisation due to asthma ^c | | | | | |
| None | 7,066 (88.3) | 1,579 (98.4) | 2,695 (96.8) | 2,792 (77.3) | 0.284 |
| ≥1 stay | 934 (11.7) | 25 (1.6) | 90 (3.2) | 819 (22.7) | |

Prn SABA 문제점



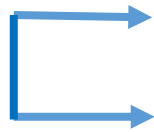


ICS in mild asthma

: Recommendation in even step 1 ??

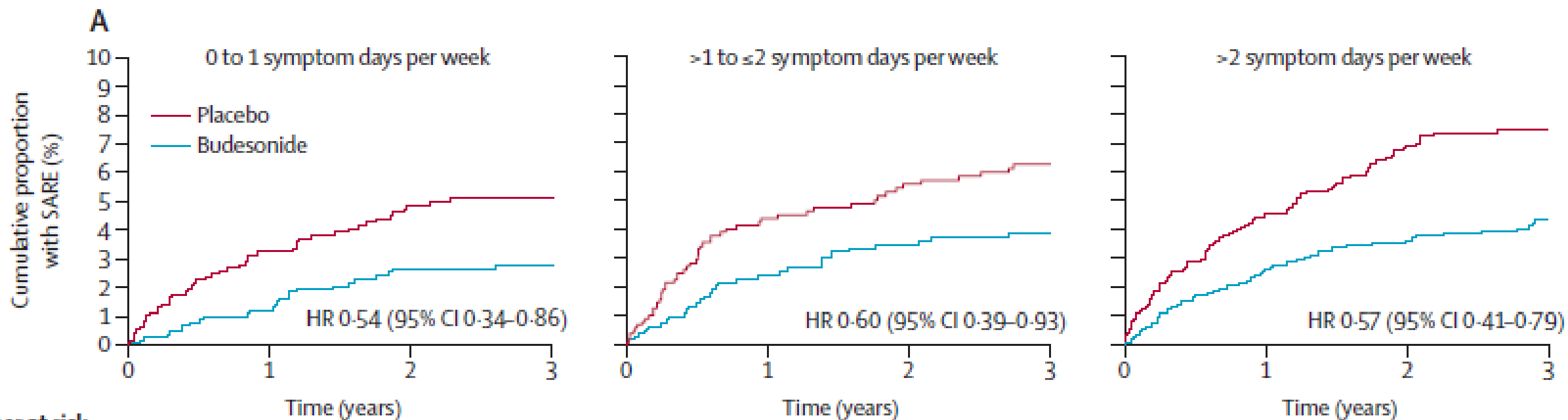
Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study

Helen K Reddel, William W Busse, Søren Pedersen, Wan C Tan, Yu-Zhi Chen, Carin Jorup, Dan Lythgoe, Paul M O'Byrne

Mild asthma randomized
(Total 7138 patients)  once daily, inhaled budesonide 400 µg
placebo.

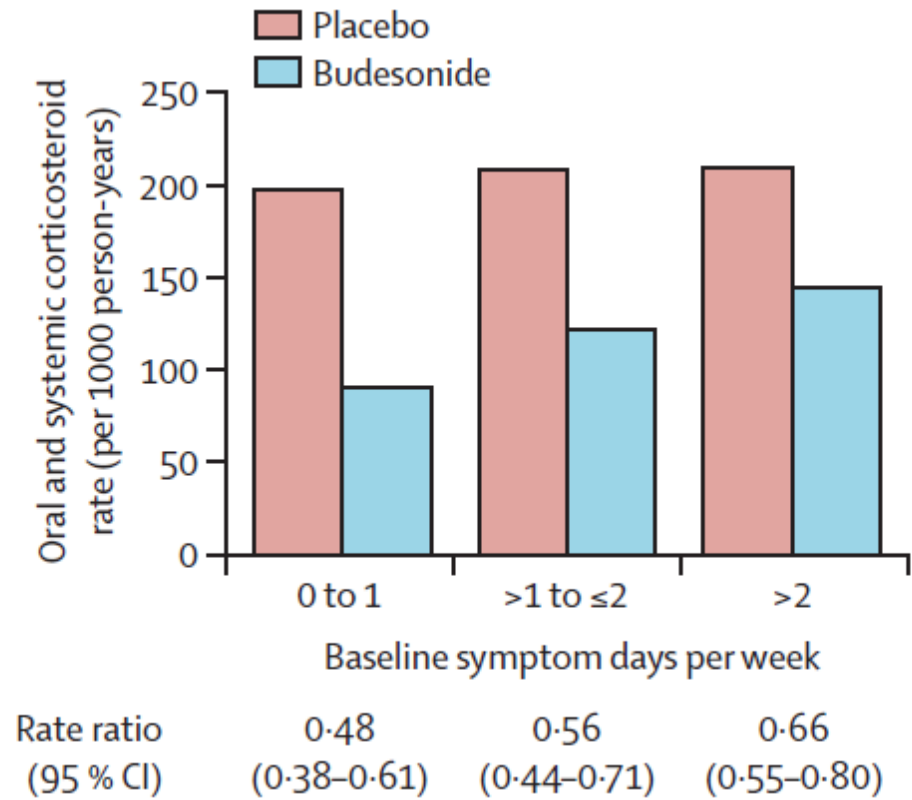
Coprimary outcomes

- 1) time to first severe asthma-related event
(SARE; hospital admission, emergency treatment, or death)
- 2) change from baseline in lung function after bronchodilator



Number at risk

| | | | | | | | | | | | | | | | | | | | | | |
|------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|------|------|-----|
| Placebo | 1082 | 932 | 881 | 836 | 797 | 766 | 409 | 963 | 836 | 779 | 746 | 711 | 671 | 371 | 1516 | 1287 | 1201 | 1147 | 1089 | 1047 | 561 |
| Budesonide | 1102 | 978 | 927 | 880 | 843 | 814 | 457 | 951 | 836 | 794 | 740 | 715 | 691 | 352 | 1524 | 1355 | 1264 | 1196 | 1152 | 1095 | 574 |



A Prebronchodilator FEV1 (% predicted)

Baseline symptom days per week

Mean difference (95% CI)

$P_{\text{interaction}}$

Year 1

>2

1.91 (1.01 to 2.81)

>1 to ≤2

2.48 (1.36 to 3.60)

0.48

0 to 1

2.72 (1.66 to 3.78)

Year 3

>2

1.53 (0.61 to 2.45)

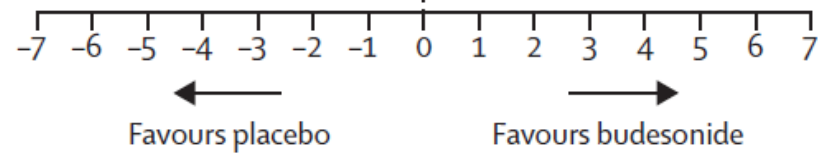
>1 to ≤2

1.41 (0.25 to 2.57)

0.43

0 to 1

2.34 (1.26 to 3.42)

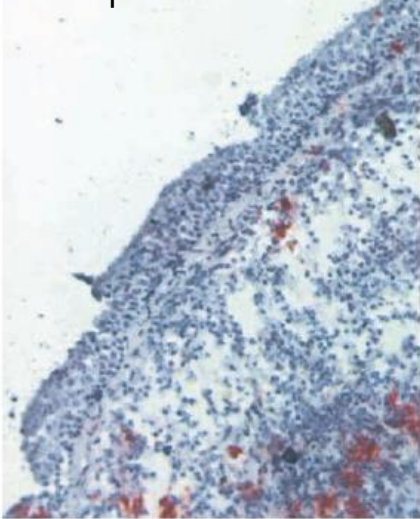


Conclusion

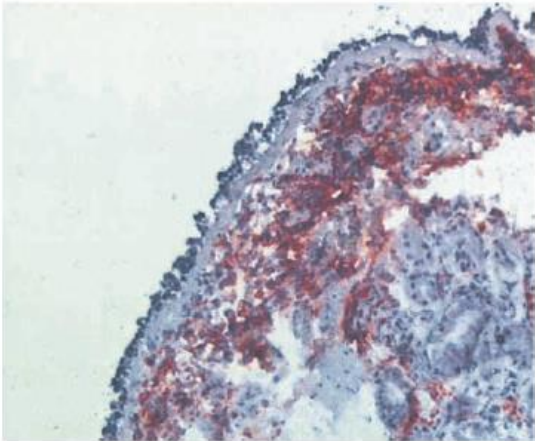
- Long-term, once-daily, low-dose budesonide treatment reduces the risk of severe asthma exacerbations by half, reduces long-term decline in lung function, and improves asthma symptoms in patients with mild, recent-onset asthma.
- These beneficial effects were seen even in patients with infrequent baseline symptoms, who would not previously have been considered for ICS treatment.

Airway Inflammation Is Present during Clinical Remission of Atopic Asthma

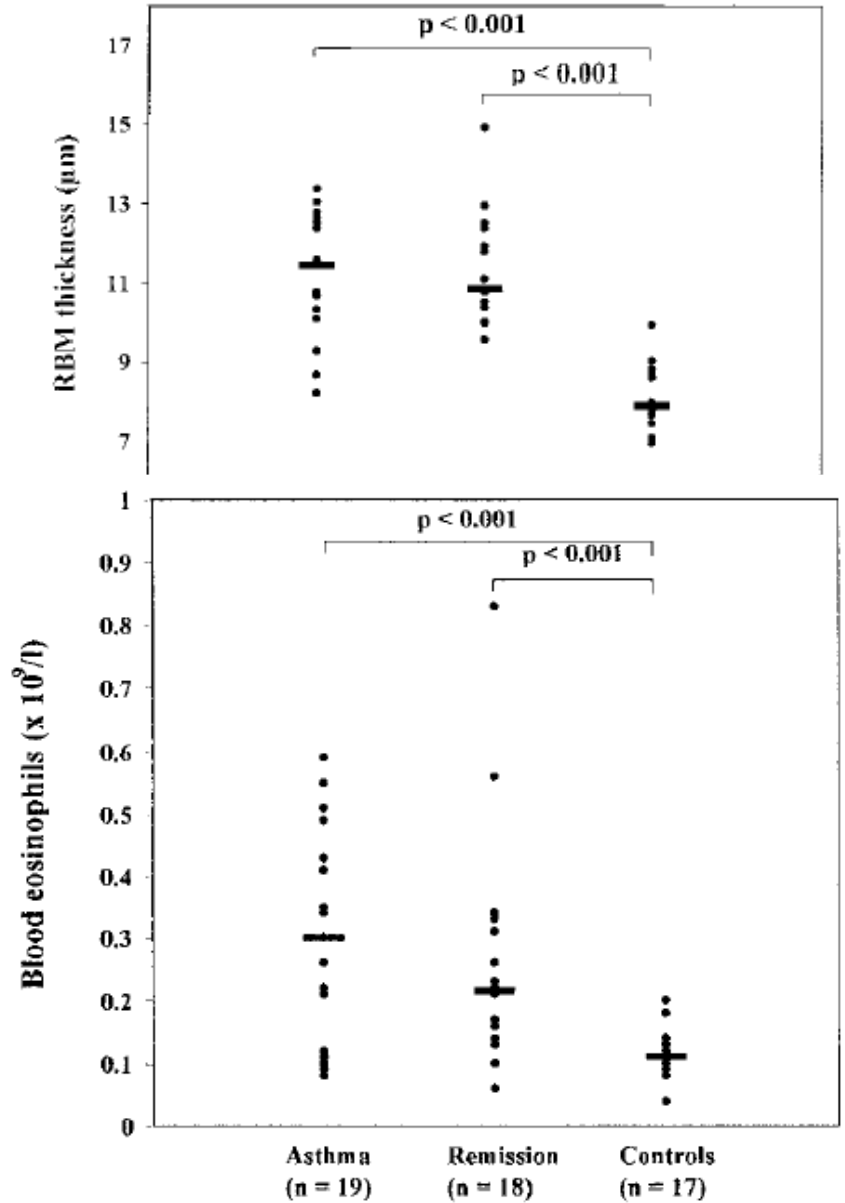
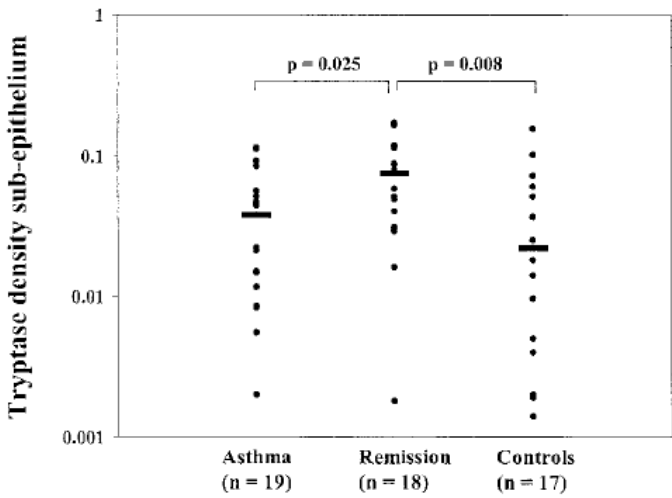
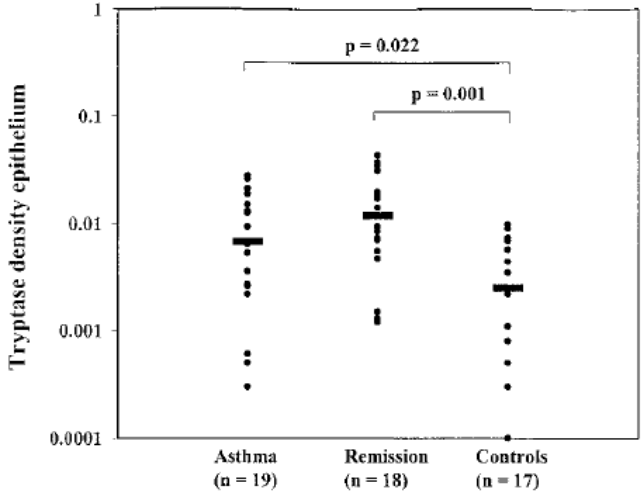
Major basic protein of bronchial biopsy



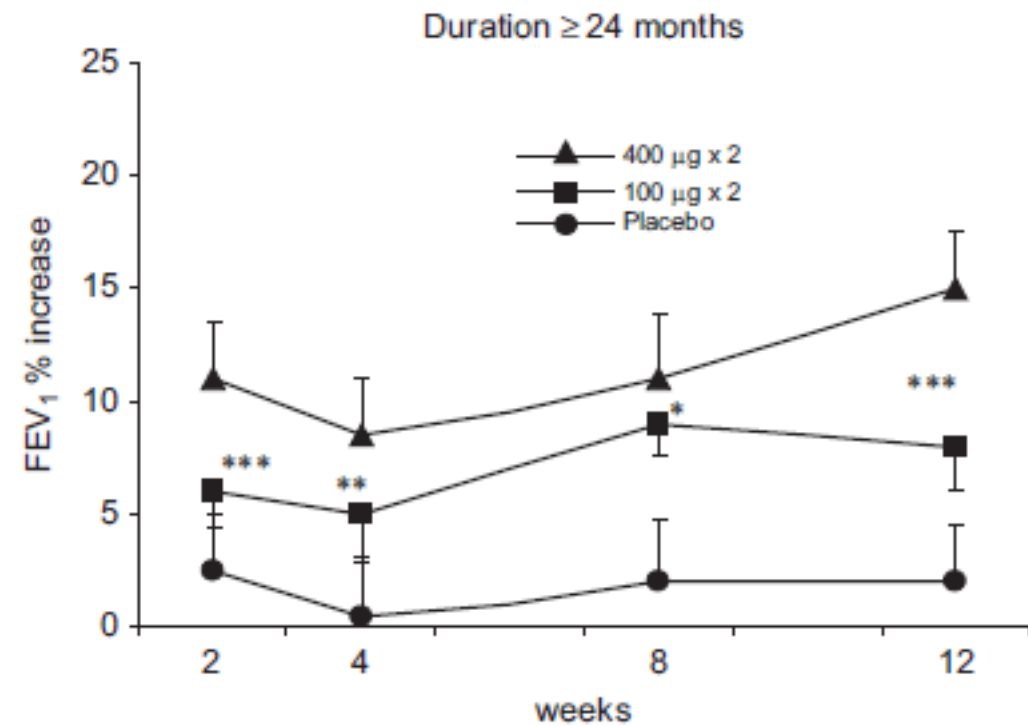
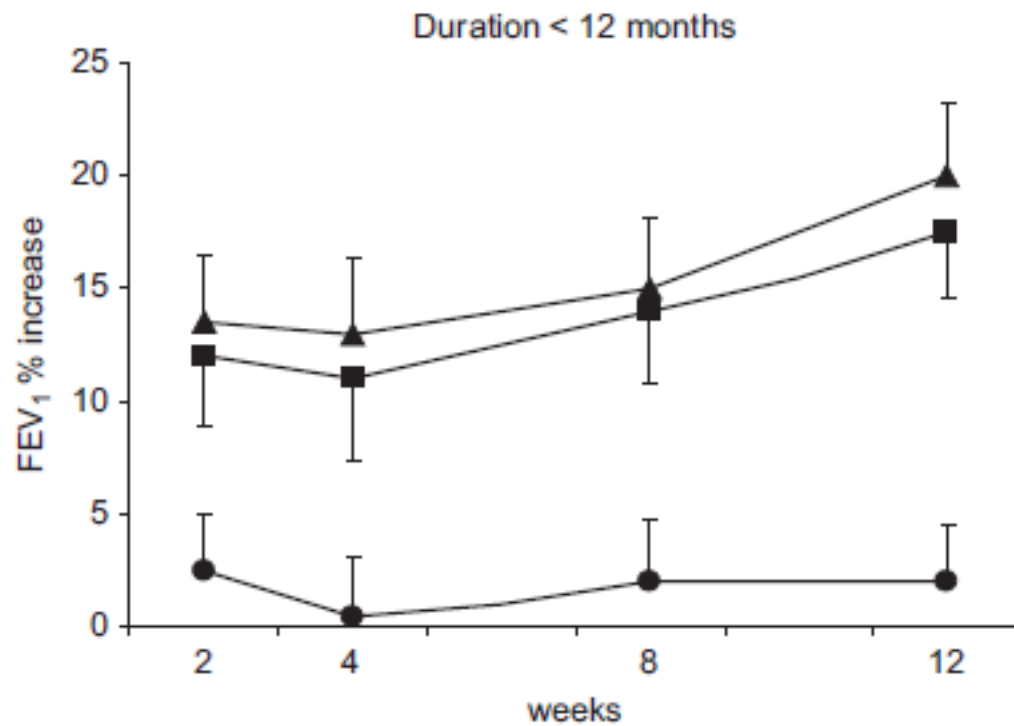
Healthy control



clinical remission of asthma



Effect of disease duration on dose response of inhaled budesonide in asthma

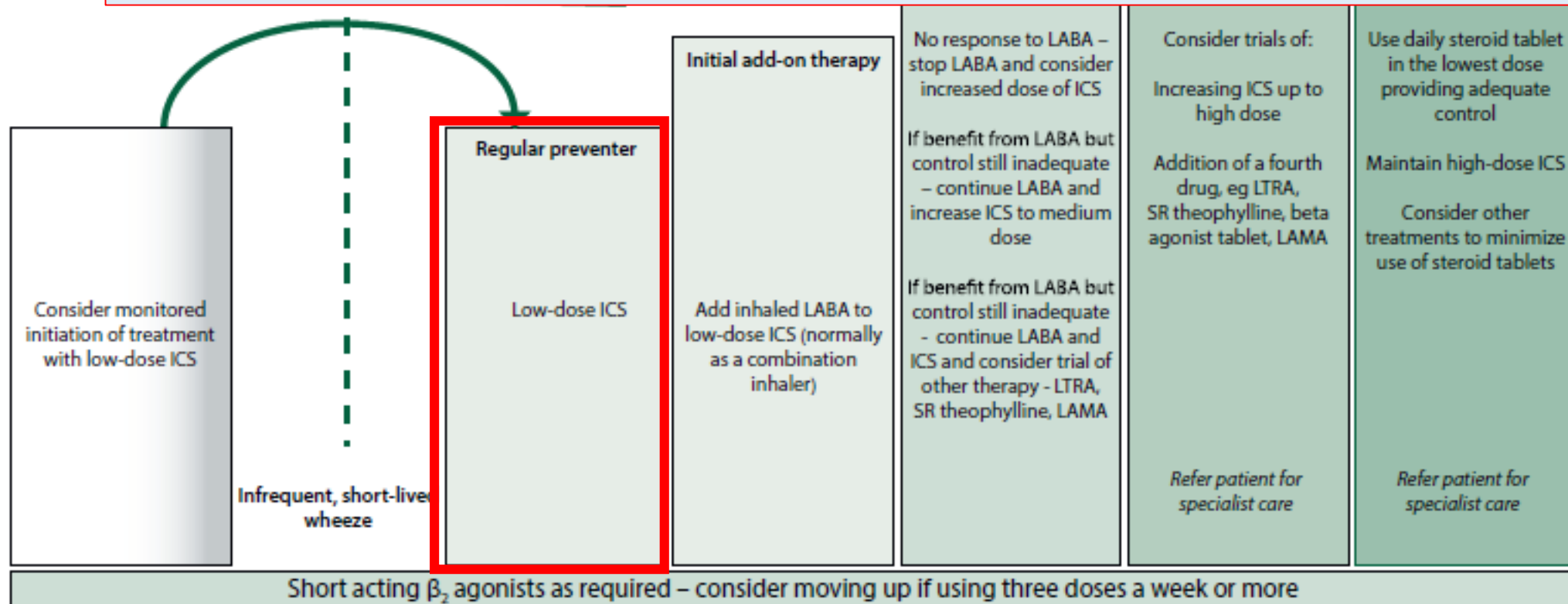


Recommendation of ICS at step 1

1. Ongoing airway inflammation and remodeling in adolescents in clinical remission of atopic asthma
2. Elevated FENO levels and bronchial biopsy evidence of airway inflammation in mild intermittent asthma
3. Bronchoconstriction generates excessive mechanical forces within the airways that distort tissue cells
4. Early initiation of low-dose ICS leads to a greater improvement in lung function

ICS considered

- asthma attack in the last 2 years,
- using SABA 3 times a week or more
- symptomatic 3 times a week or more
- waking 1 night a week

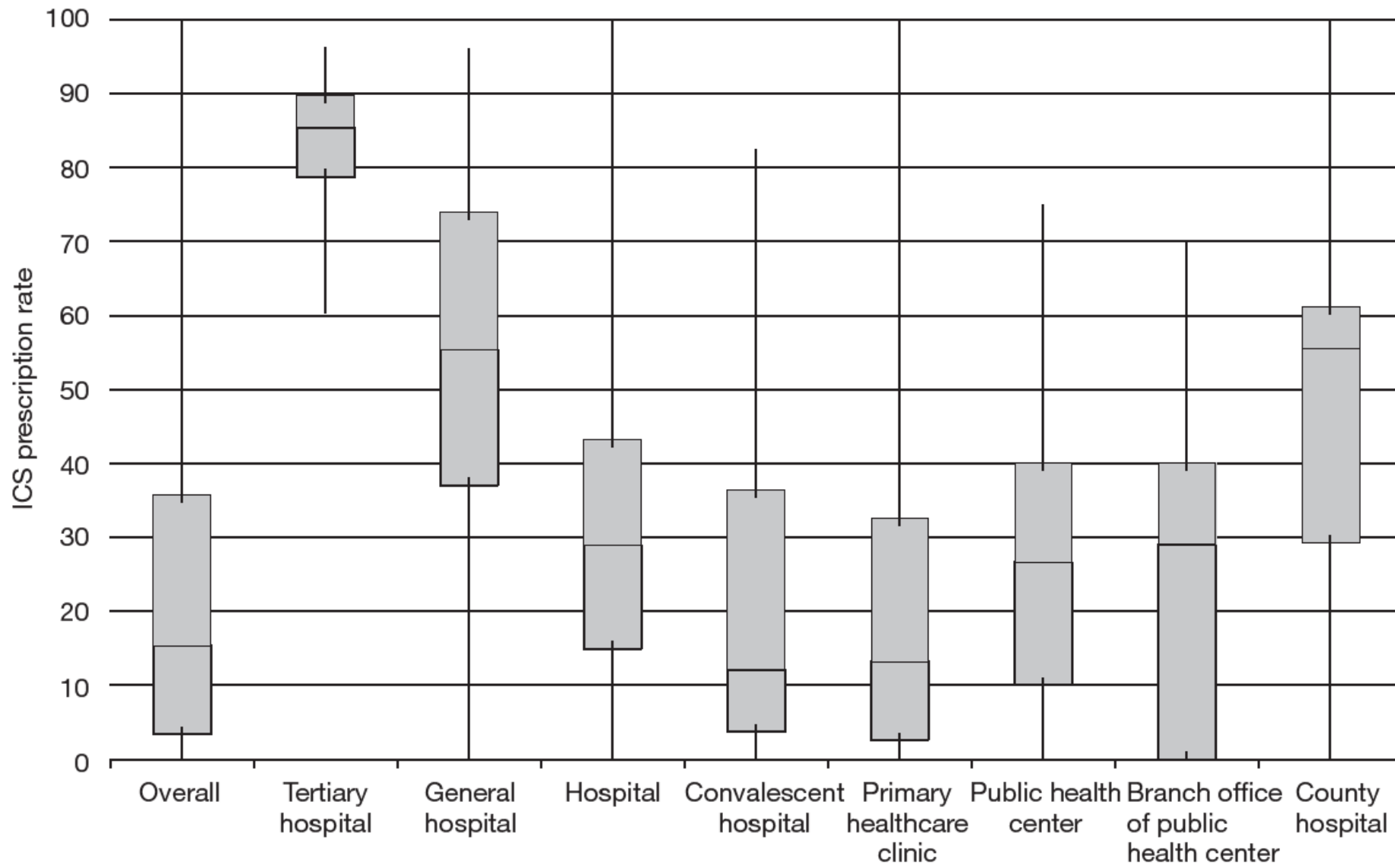


Problem in ICS use ?!!



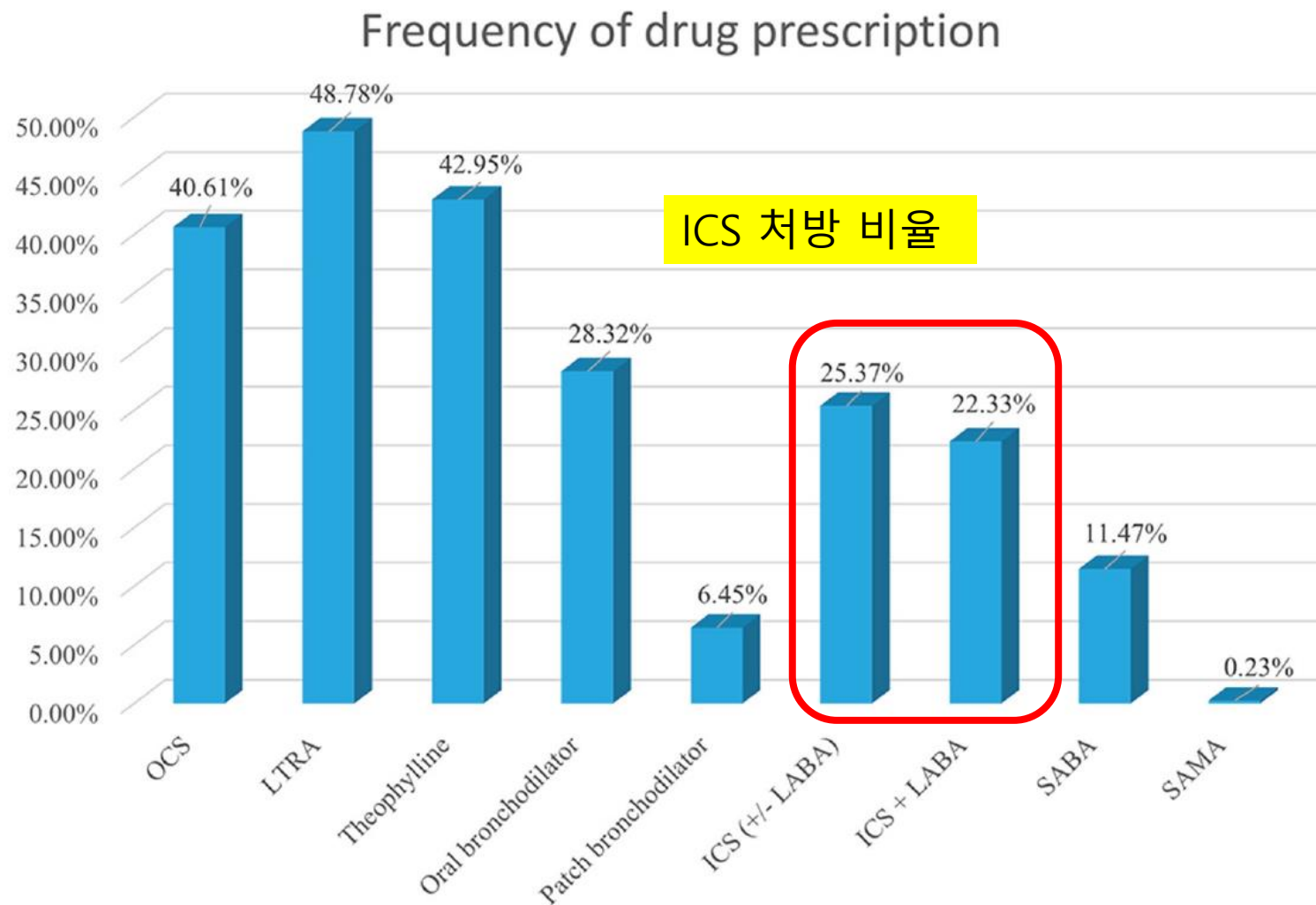
Inhaled corticosteroids improve lung function, airway hyper-responsiveness and airway inflammation but not symptom control in patients with mild intermittent asthma: A meta-analysis

WEI DU¹, LING ZHOU¹, YINGMENG NI¹, YUANYUAN YU¹, FANG WU² and GUOCHAO SHI¹



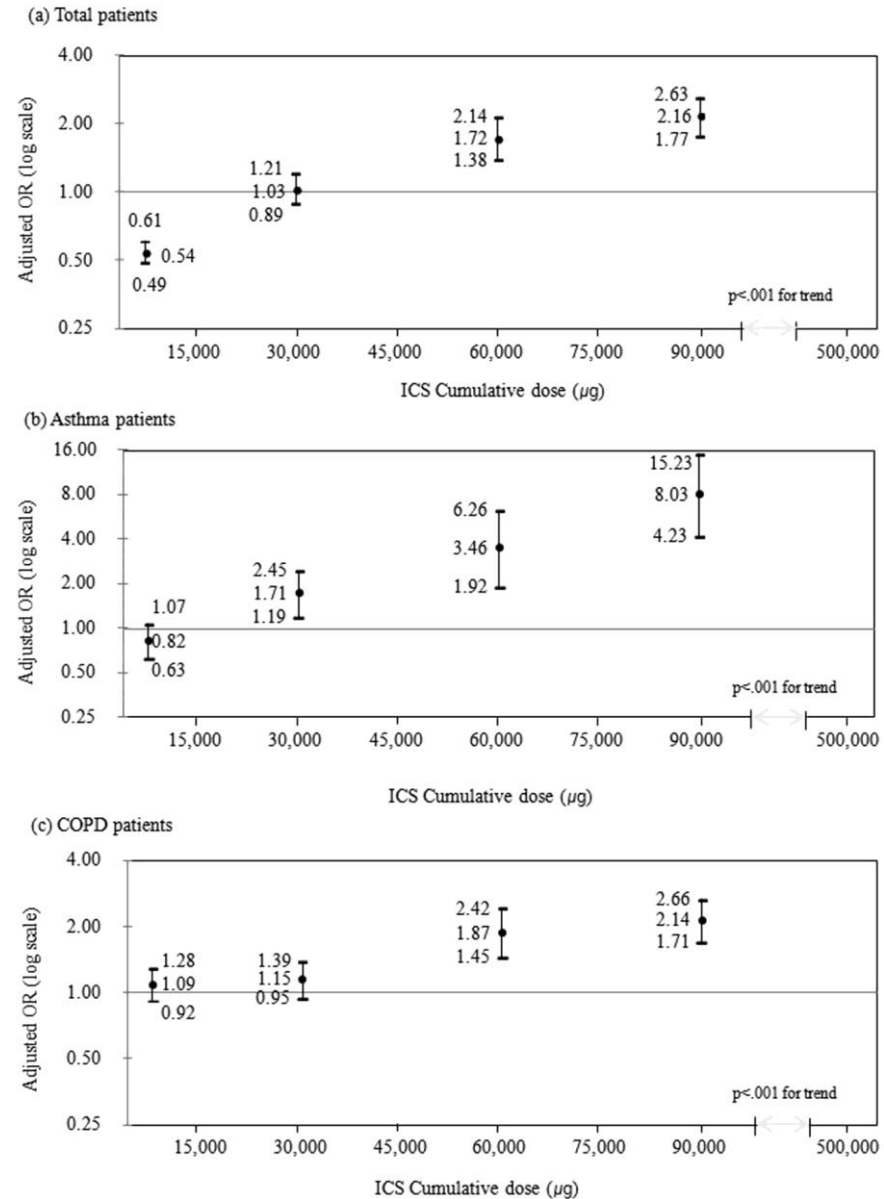
Current status of asthma care in South Korea: nationwide the Health Insurance Review and Assessment Service database

Joon Young Choi¹, Hyoung Kyu Yoon², Jae Ha Lee³, Kwang Ha Yoo⁴, Bo Yeon Kim⁵, Hye Won Bae⁵, Young Kyoon Kim¹, Chin Kook Rhee¹

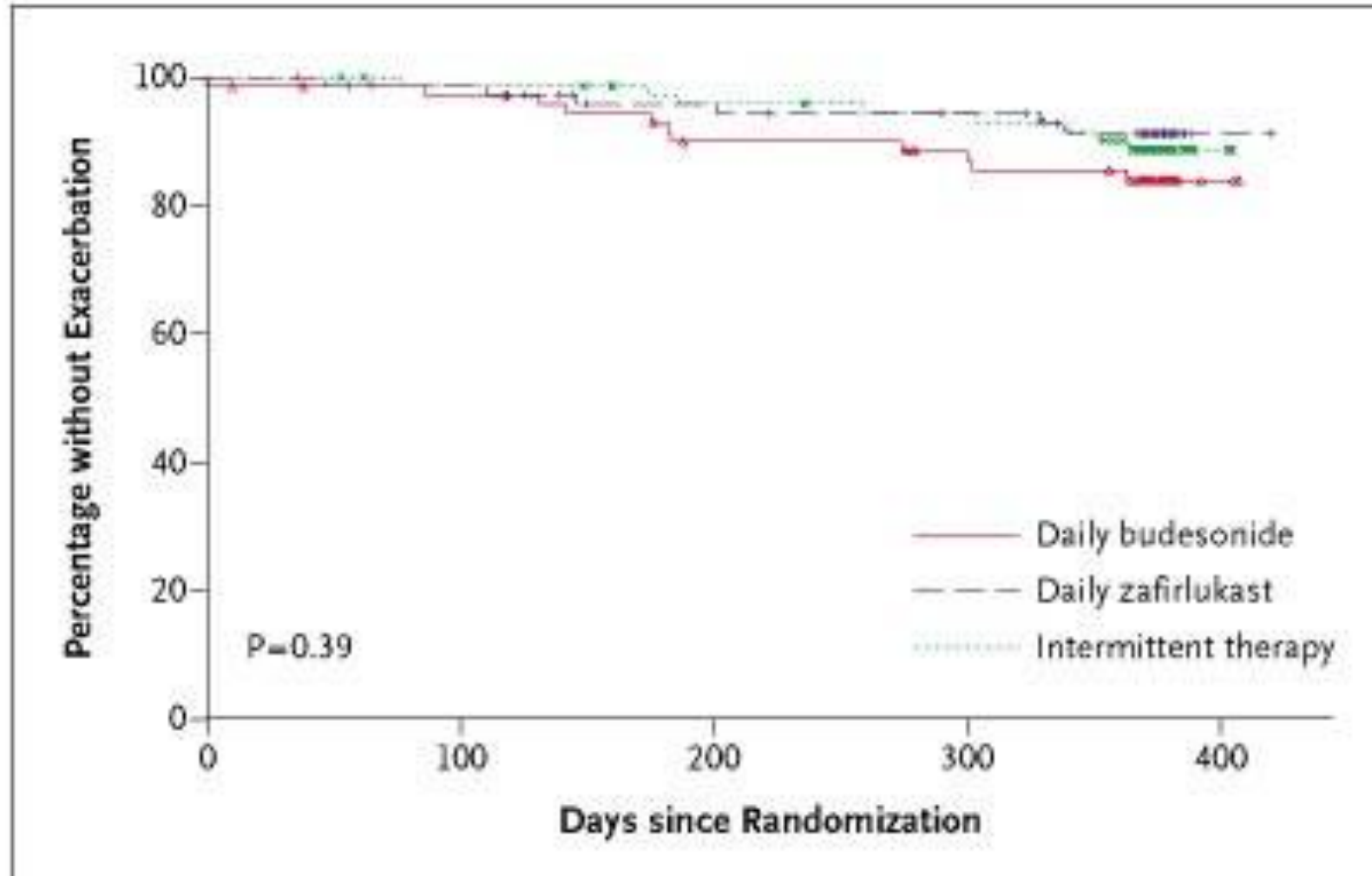


| | NTM-PD cases [#] | Controls [†] | Crude OR (95% CI) | p-value | Adjusted OR* (95% CI) | p-value |
|--------------------------------------|---------------------------|-----------------------|-------------------|---------|-----------------------|---------|
| All OLD | | | | | | |
| No ICS use | 592 (20.0) | 4175 (35.2) | 1.0 (reference) | | 1.0 (reference) | |
| Prior ICS use | 469 (15.8) | 2647 (22.3) | 1.30 (1.14–1.48) | 0.001 | 0.94 (0.80–1.11) | 0.465 |
| Current ICS use | 1905 (64.2) | 5029 (42.4) | 2.87 (2.59–3.19) | <0.001 | 1.86 (1.60–2.15) | <0.001 |
| Fluticasone | 1576 (53.1) | 3779 (31.9) | 3.18 (2.85–3.54) | <0.001 | 2.09 (1.80–2.43) | <0.001 |
| Budesonide | 291 (9.8) | 1070 (9.0) | 2.05 (1.75–2.40) | <0.001 | 1.19 (0.97–1.45) | 0.089 |
| Other ICS [†] | 38 (1.28) | 180 (1.5) | 1.59 (1.11–2.28) | 0.012 | 1.29 (0.86–1.93) | 0.223 |
| ICS cumulative dose in 1 year | | | | | | |
| No use | 592 (20.0) | 4175 (35.2) | 1.0 (reference) | | 1.0 (reference) | |
| Low dose | 546 (18.4) | 2769 (23.4) | 1.43 (1.26–1.63) | <0.001 | 1.06 (0.90–1.24) | 0.486 |
| Moderate dose | 781 (26.3) | 2615 (22.1) | 2.27 (2.01–2.56) | <0.001 | 1.48 (1.27–1.74) | <0.001 |
| High dose | 1047 (35.3) | 2292 (19.3) | 3.58 (3.17–4.03) | <0.001 | 2.28 (1.94–2.68) | <0.001 |
| Asthma only | | | | | | |
| | 219 | 872 | | | | |
| No ICS use | 81 (37.0) | 398 (45.6) | 1.0 (reference) | | 1.0 (reference) | |
| Prior ICS use | 55 (25.1) | 236 (27.1) | 1.18 (0.80–1.74) | 0.406 | 1.23 (0.74–2.03) | 0.428 |
| Current ICS use | 83 (37.9) | 238 (27.3) | 1.76 (1.23–2.51) | 0.002 | 1.56 (0.93–2.62) | 0.095 |
| ACOS | | | | | | |
| | 910 | 3633 | | | | |
| No ICS use | 146 (16.0) | 1033 (28.4) | 1.0 (reference) | | 1.0 (reference) | |
| Prior ICS use | 135 (14.8) | 837 (23.0) | 1.16 (0.90–1.48) | 0.261 | 0.83 (0.61–1.12) | 0.228 |
| Current ICS use | 629 (69.1) | 1763 (48.5) | 2.60 (2.13–3.18) | <0.001 | 1.74 (1.32–2.28) | <0.001 |
| COPD only | | | | | | |
| | 1837 | 7346 | | | | |
| No ICS use | 365 (19.9) | 2744 (37.3) | 1.0 (reference) | | 1.0 (reference) | |
| Prior ICS use | 279 (15.2) | 1574 (21.4) | 1.40 (1.18–1.65) | <0.001 | 0.98 (0.79–1.20) | 0.827 |
| Current ICS use | 1193 (64.9) | 3028 (41.2) | 3.20 (2.79–3.66) | <0.001 | 1.96 (1.62–2.36) | <0.001 |

Dose-dependent relationship between cumulative doses of inhaled corticosteroid (ICS) and diagnosis of tuberculosis (TB).

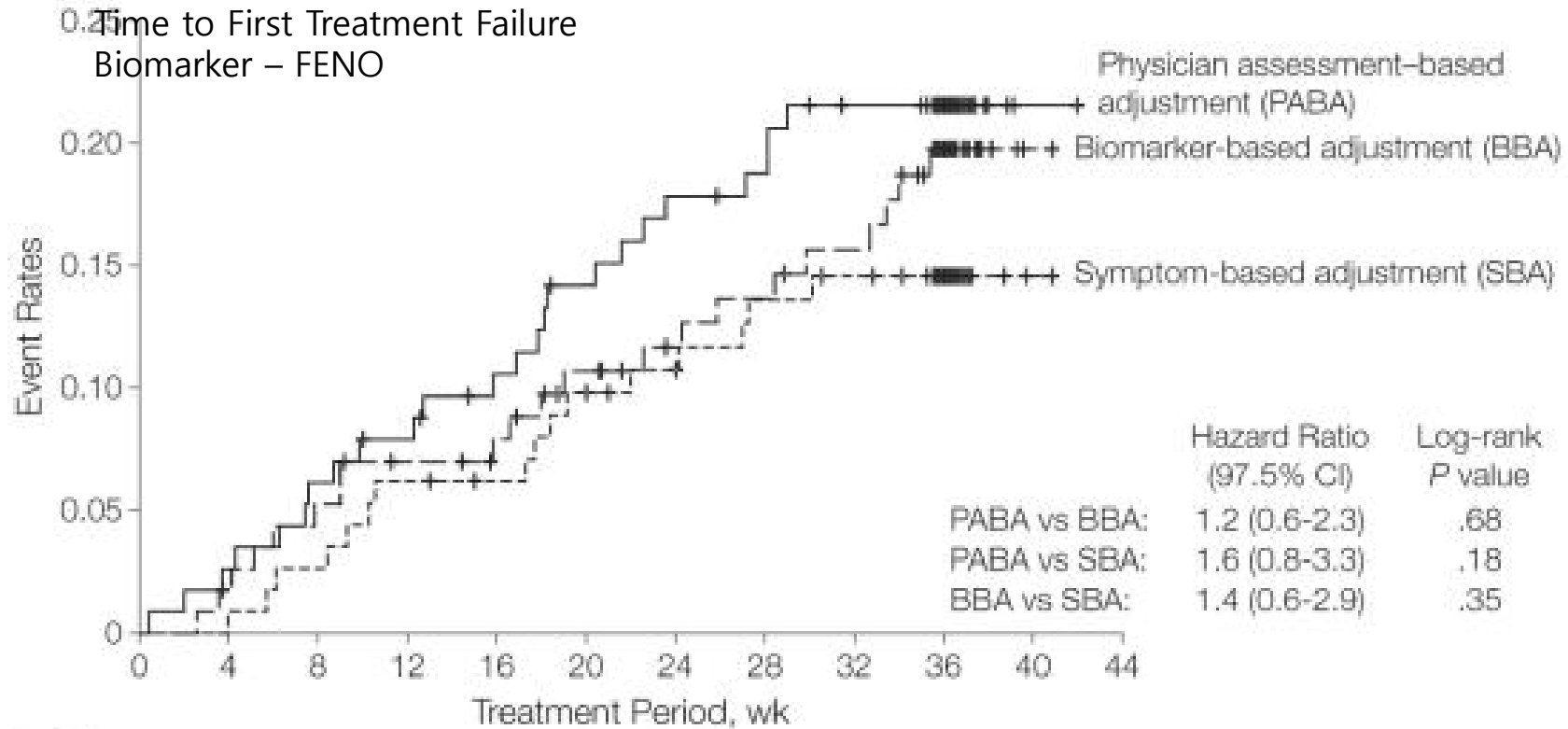


Daily versus *As-Needed* Corticosteroids for Mild Persistent Asthma



There was no significant difference among the groups ($P=0.39$).

Comparison of Physician-, biomarker-, and symptom-based strategies for adjustment of ICS therapy In adults with asthma



| No. at risk | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 |
|-------------|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|
| PABA | 114 | 111 | 107 | 104 | 99 | 94 | 90 | 88 | 82 | 60 | 1 | 0 |
| BBA | 115 | 112 | 108 | 104 | 101 | 94 | 89 | 87 | 83 | 58 | 1 | 0 |
| SBA | 113 | 113 | 110 | 106 | 104 | 100 | 95 | 90 | 87 | 68 | 1 | 0 |

ICS/fast acting LABA
as needed in mild asthma

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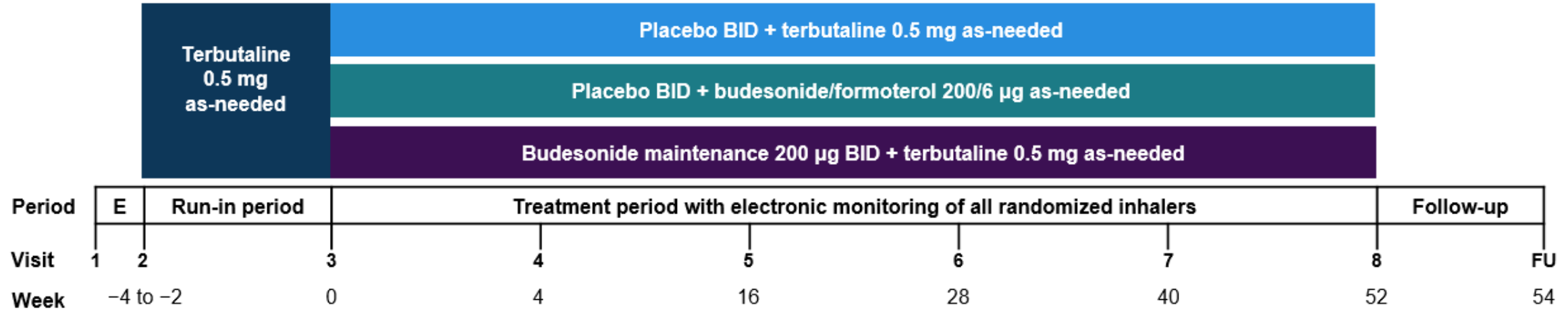
Inhaled Combined Budesonide–Formoterol as Needed
in Mild Asthma

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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.



Symbicort Given as needed in Mild Asthma

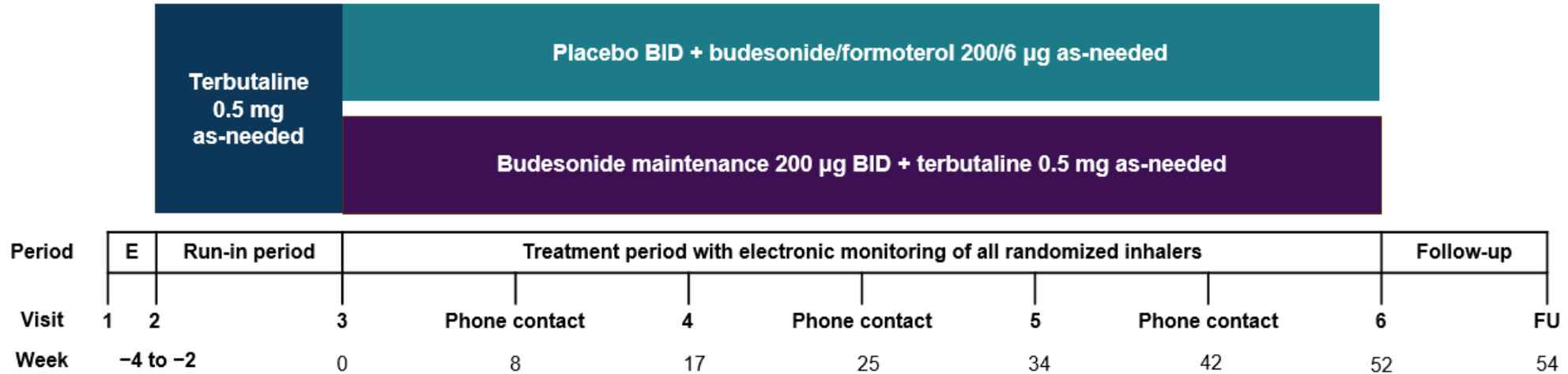
SYGMA 1: budesonide/formoterol as-needed vs. terbutaline as-needed



| SYGMA 1 ^{1,2} | |
|------------------------|---|
| Primary Objective | <p>Show superiority: budesonide/formoterol as-needed vs. terbutaline as-needed</p> <p>Primary endpoint: WCAW (well-controlled asthma weeks)</p> |
| Secondary Objectives | <ol style="list-style-type: none"> Efficacy of budesonide/formoterol as-needed vs. budesonide maintenance BID + terbutaline as-needed Efficacy of budesonide/formoterol as-needed vs. terbutaline as-needed and budesonide maintenance BID + terbutaline as-needed <ul style="list-style-type: none"> WCAW: budesonide/formoterol as-needed vs. budesonide maintenance BID + terbutaline as-needed (non-inferiority) Annualised severe asthma exacerbation rate Pre- and post-bronchodilator FEV₁ ACQ-5 and AQLQ score ICS use (or exposure) and rescue medication use |

ACQ-5 = Asthma Control Questionnaire-5
AQLQ = Asthma Quality of Life Questionnaire

SYGMA 2: budesonide/formoterol as-needed vs. budesonide maintenance BID + terbutaline as-needed



SYGMA 2^{1,3}

Show non-inferiority: budesonide/formoterol as-needed vs. budesonide maintenance BID + terbutaline as-needed

Primary endpoint: Annualised severe asthma exacerbation rate (steroid, ER, hospitalization)

1) Efficacy of budesonide/formoterol as-needed vs. budesonide maintenance BID + terbutaline as-needed

- Pre- and post-bronchodilator FEV₁
- ACQ-5 and AQLQ score
- ICS use (or exposure) and rescue medication use

Adherence: Inhaled Therapies Electronically Monitored Throughout; Patients Received Twice-daily Reminders (SYGMA 1)

| | SYGMA 1 ¹ | | | SYGMA 2 ² | |
|--------------|--|--|--|--|--|
| | Terbutaline 0.5mg As-needed (n=1277) | Budesonide/Formoterol 200/6 µg As-needed (n=1277) | Budesonide Maintenance 200 µg BID + Terbutaline 0.5 mg As-needed (n=1282) | Budesonide/Formoterol 200/6 µg As-needed (n=2089) | Budesonide Maintenance 200 µg BID + Terbutaline 0.5 mg As-needed (n=2087) |
| Adherence, % | | | | | |
| Mean (SD) | 79.0 (23.3) | 79.1 (23.0) | 78.9 (22.4) | 64.0 (30.0) | 62.8 (29.4) |
| Median | 85.6 | 85.7 | 85.1 | 67.7 | 66.9 |
| Min, Max | 0, 186 | 0, 196 | 0, 176 | 0, 230 | 0, 186 |

Adherence to maintenance therapy was 63–79%,^{1,2} while real-world adherence to maintenance therapy has been shown to be 29–46%³

1. O'Byrne PM et al. *N Engl J Med.* 2018;378:1865-1876; 2. Bateman ED et al. *N Engl J Med.* 2018;378:1877-1887; 3. Foster JM et al. *J Allergy Clin Immunol.* 2014;134:1260–1268.

SYGMA 1 & 2 Primary Objectives for Both SYGMA 1 and 2 Were Met

| | | |
|----------------------|--|--|
| SYGMA 1 ¹ | Terbutaline 0.5mg As-needed (n=1272) | Budesonide/ Formoterol 200/6 µg As-needed (n=1269) |
|----------------------|--|--|

Mean % of WCAW per patient 31.1 34.4

Budesonide/formoterol as-needed vs. terbutaline as-needed

Odds ratio
(2-sided 95% CI) **1.14**
(1.00, 1.30)

P-value **0.046**

| | | |
|----------------------|--|--|
| SYGMA 2 ² | Budesonide/ Formoterol 200/6 µg As-needed (n=2084) | Budesonide Maintenance 200 µg BID + Terbutaline 0.5 mg As-needed (n=2083) |
|----------------------|--|--|

Severe^a exacerbation rate
LS Mean (2-sided 95% CI) 0.11 (0.10, 0.13) 0.12 (0.10, 0.14)

Budesonide/formoterol as-needed vs. budesonide maintenance BID + terbutaline as-needed

Rate ratio
(1-sided 95% CI)^b **0.97**
(1.16)

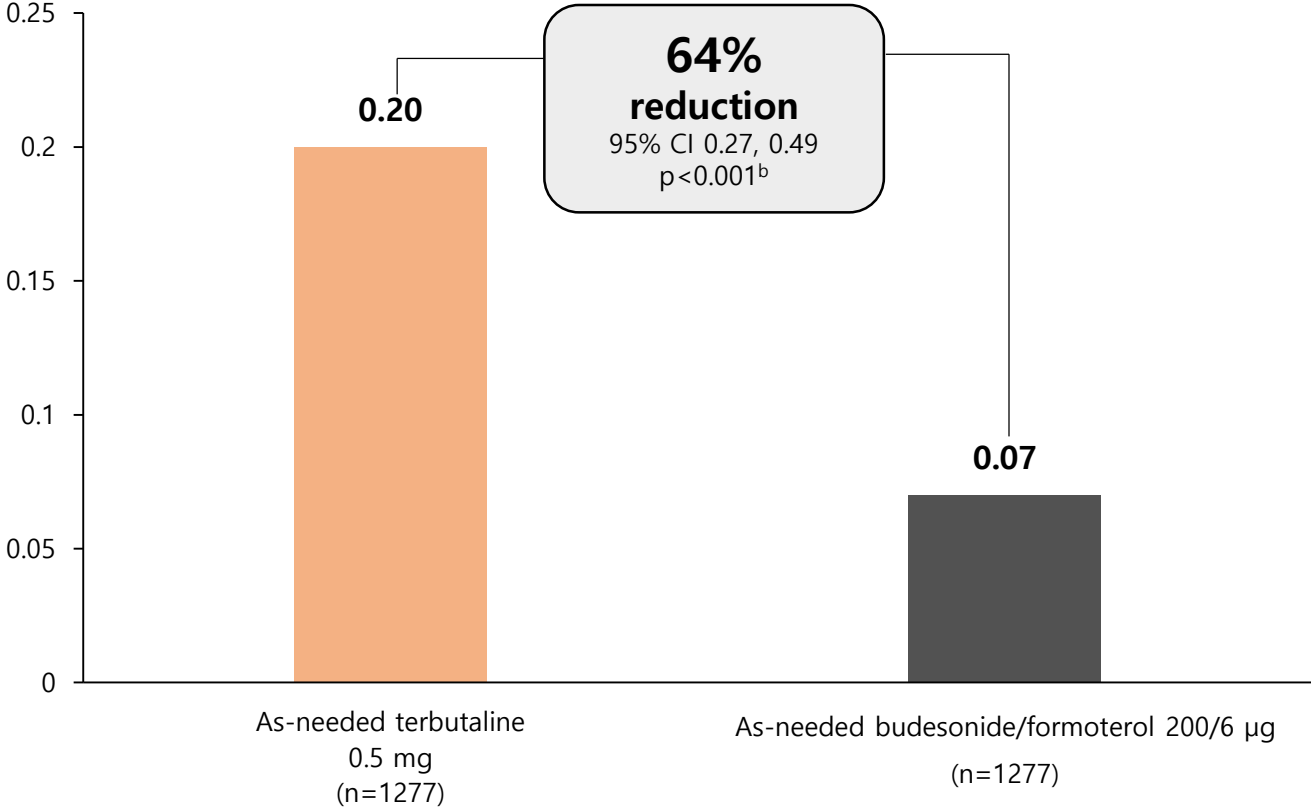
P-value NA

Budesonide/formoterol as-needed was *superior* to terbutaline as-needed on WCAW and increased the odds of a week being a WCAW by 14%¹

Budesonide/formoterol as-needed was *non-inferior* to budesonide maintenance BID for annual rate of severe exacerbations²

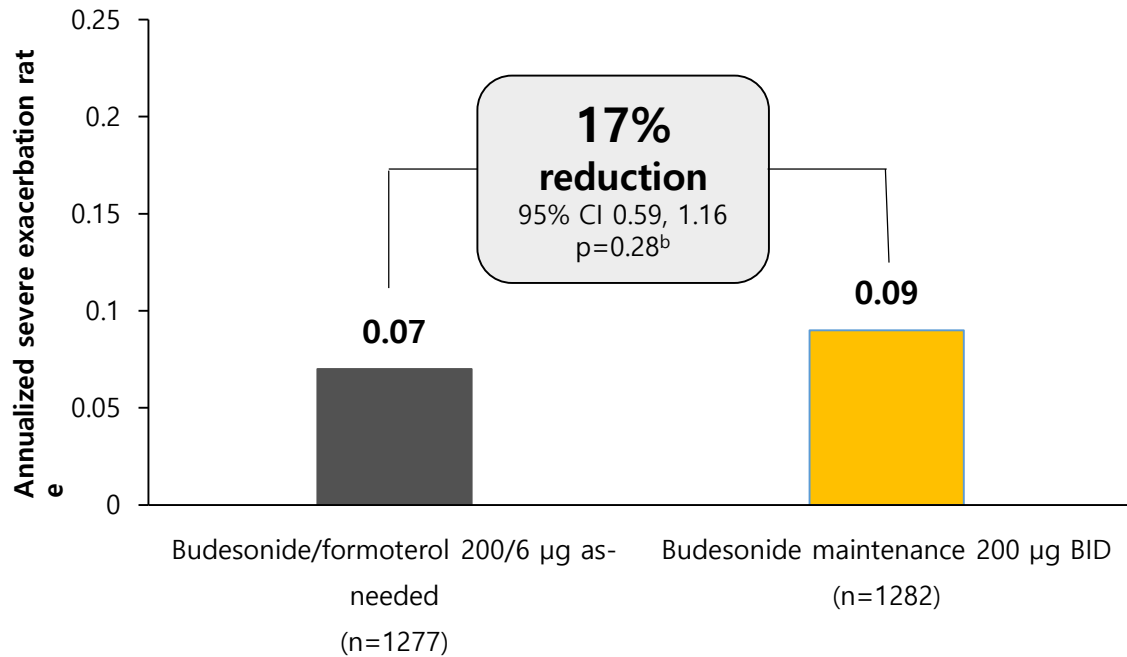
1. O'Byrne PM et al. *N Engl J Med.* 2018;378:1865-1876; 2. Bateman ED et al. *N Engl J Med.* 2018;378:1877-1887; 3. O'Byrne PM et al. *Trials.* 2017;18:12. <https://doi.org/10.1186/s13063-016-1731-4>; 4. Accessed February 22, 2018.

SYGMA 1 Secondary Endpoint: Patients on Budesonide/Formoterol As-needed had a 64% Lower Severe Exacerbation Rate Compared to Terbutaline As-needed Only

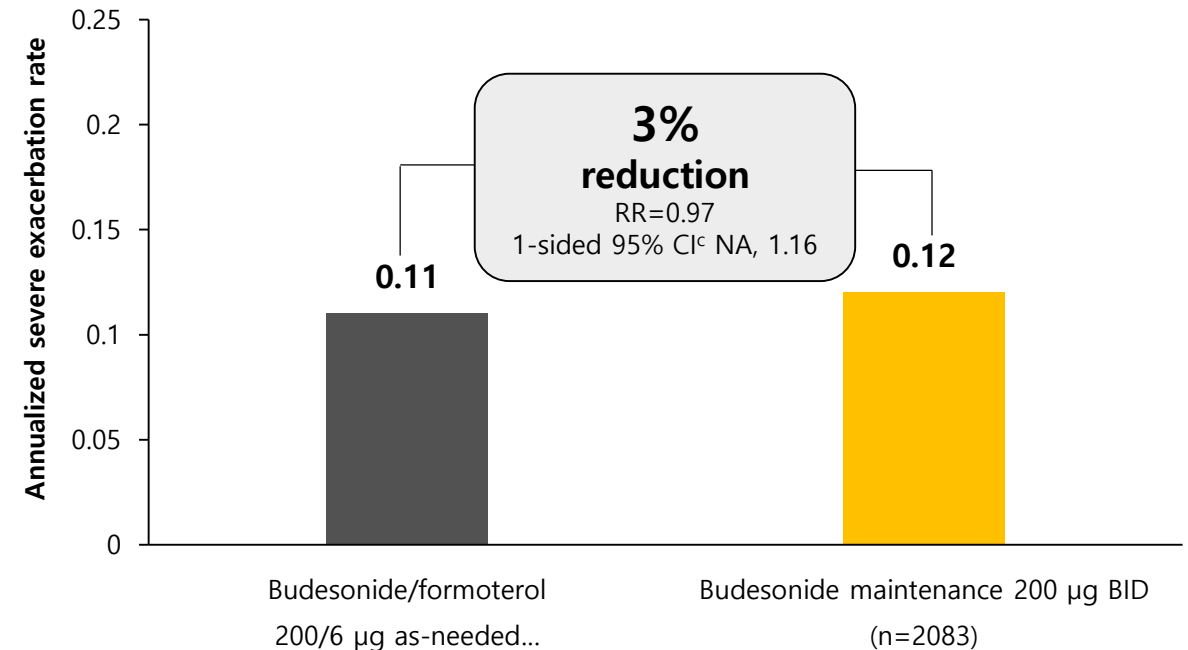


SYGMA 1 & 2: Patients on Budesonide/Formoterol As-needed had a Comparable Risk of Severe Exacerbations to Those on Maintenance Budesonide

SYGMA 1 Secondary Endpoint¹

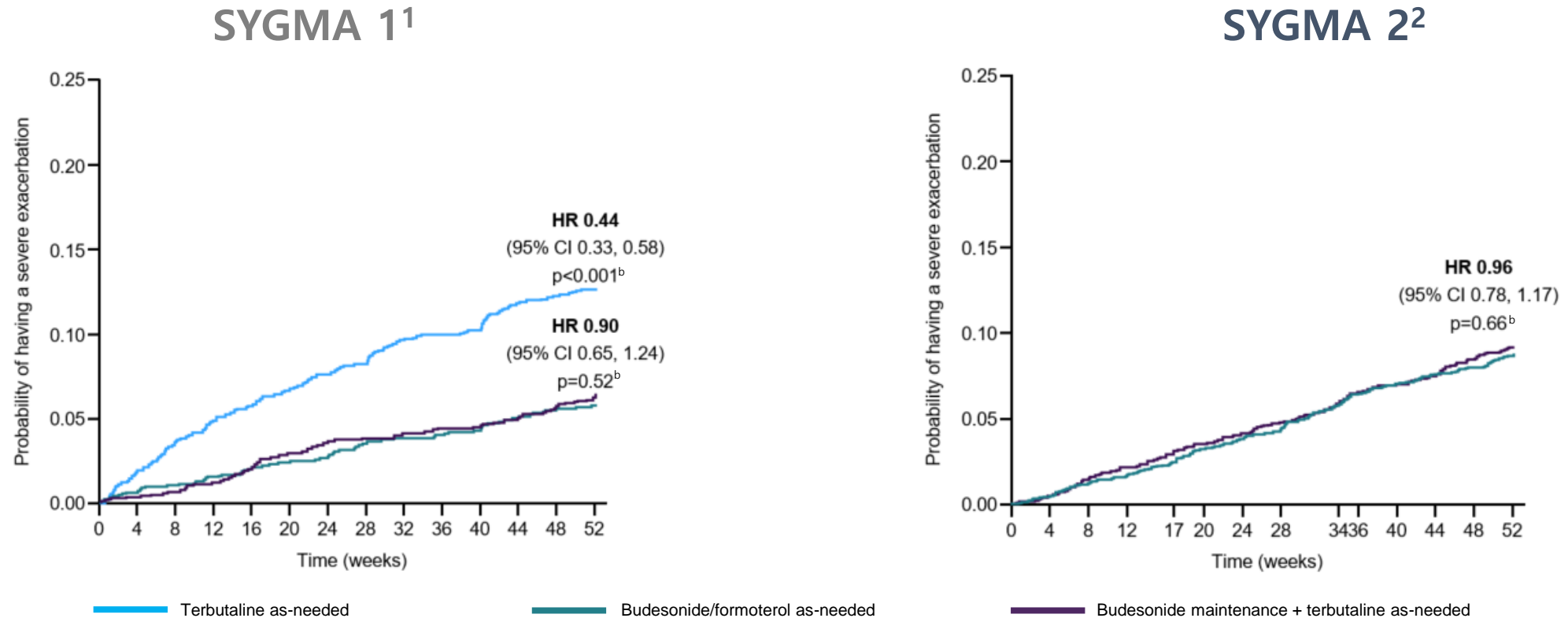


SYGMA 2 Primary Endpoint²



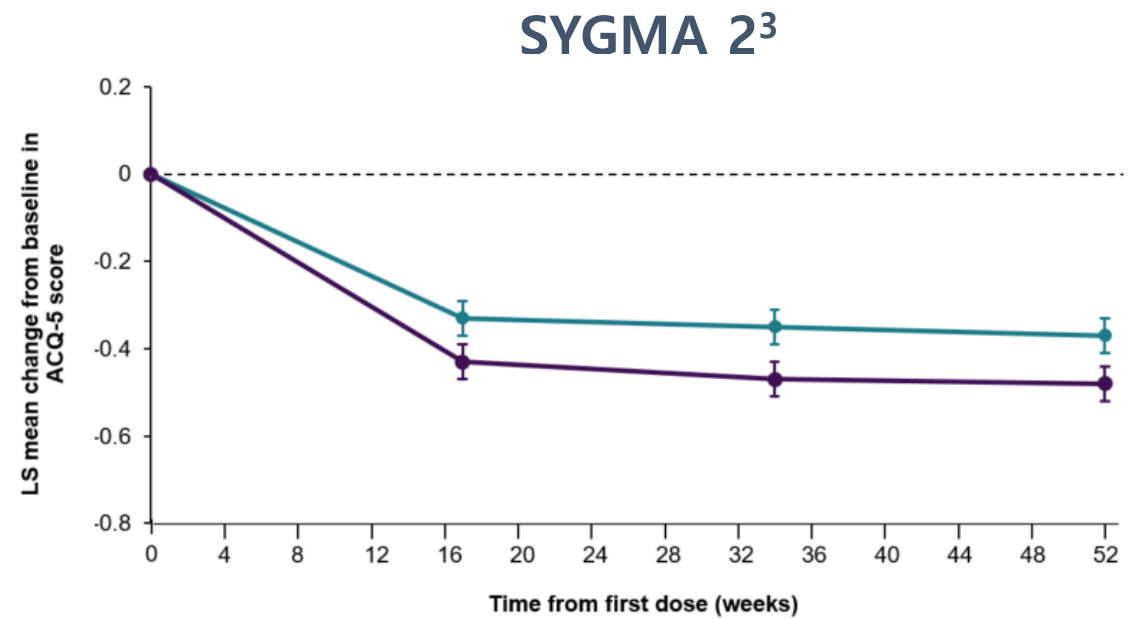
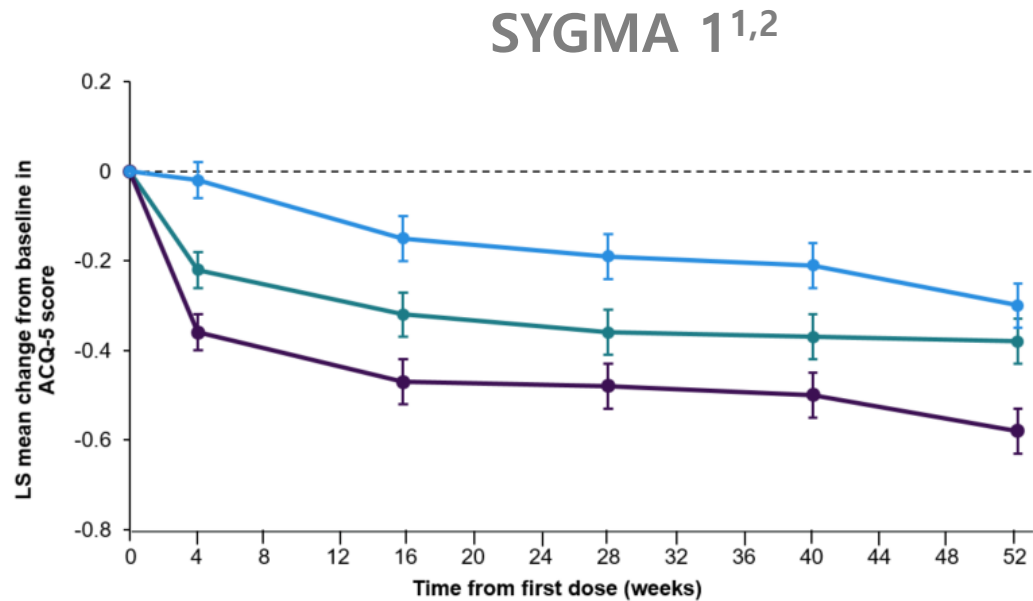
Budesonide/formoterol as-needed was similar to budesonide maintenance BID in both SYGMA 1 & 2 at preventing severe exacerbations^{1,2}

SYGMA 1 & 2 Secondary Endpoint: Time to First Severe Exacerbation



Budesonide/formoterol as-needed was **non-inferior** to budesonide maintenance BID and **superior** to terbutaline as-needed in prolonging the time to first severe exacerbation^{1,2}

SYGMA 1 & 2 Secondary Endpoint: Change From Baseline in ACQ-5



— Terbutaline as-needed

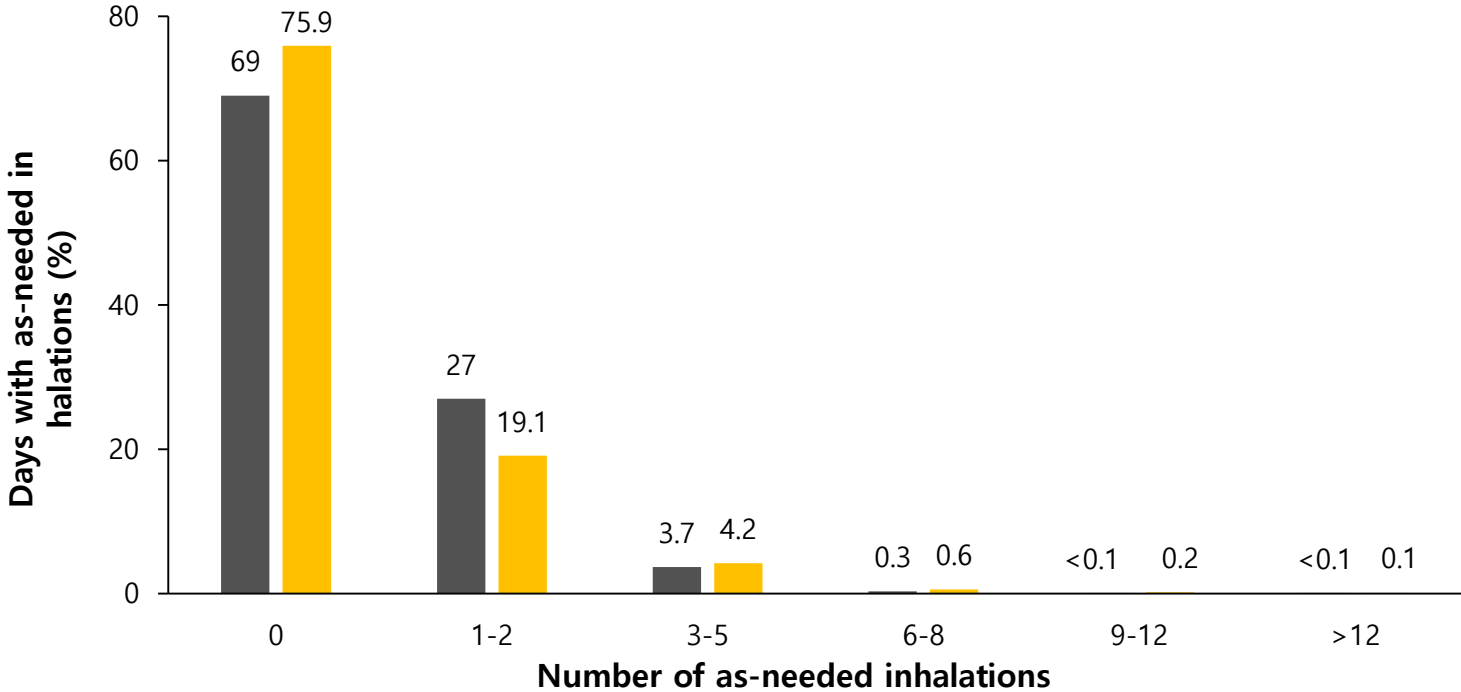
— Budesonide/formoterol as-needed

— Budesonide maintenance + terbutaline as-needed

Note: Minimal important difference = 0.5.⁴

ACQ-5 = Asthma Control Questionnaire-5; LS = least-squares. 1. O'Byrne PM et al. Article and supplementary appendix. *N Engl J Med.* 2018;378:1865-1876; 3. Bateman ED et al. *N Engl J Med.* 2018;378:1877-1887; 4. Juniper EF et al. *J Clin Epidemiol.* 1994;47:81-87; 5. Juniper EF et al. *Respir Med.* 2005;99:553-558.

SYGMA 2 Percentage of Days With As-needed Inhalations¹

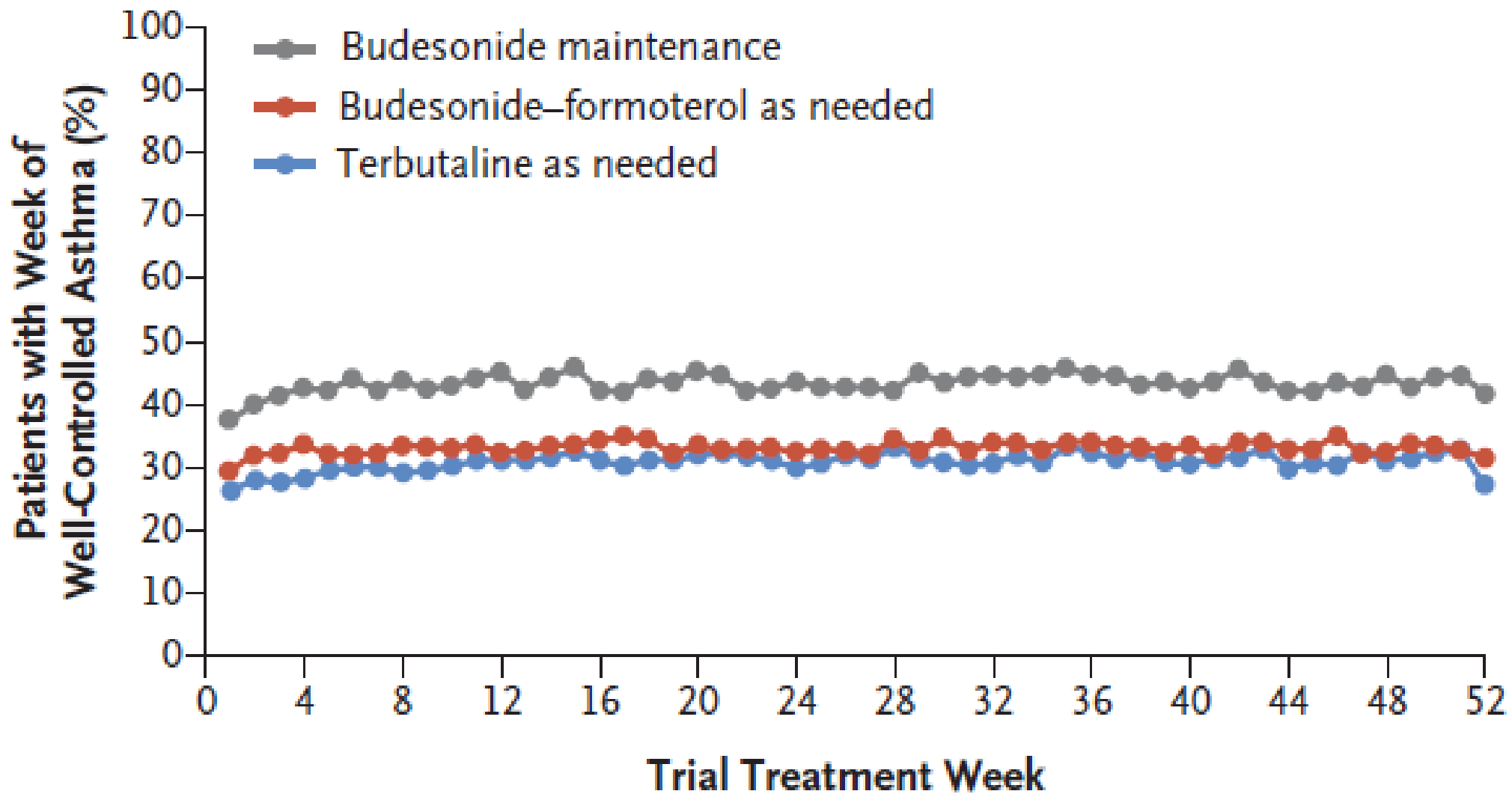


~70% of days required no as-needed inhalations (average ~0.5 as-needed inhalations per day)

| | Budesonide/Formoterol 200/6 µg As-needed (n=2089) | Budesonide Maintenance 200 µg BID + Terbutaline 0.5 mg As-needed (n=2087) |
|---|---|---|
| As-needed inhalations per day, mean (SD) | 0.52 (0.55) | 0.49 (0.70) |

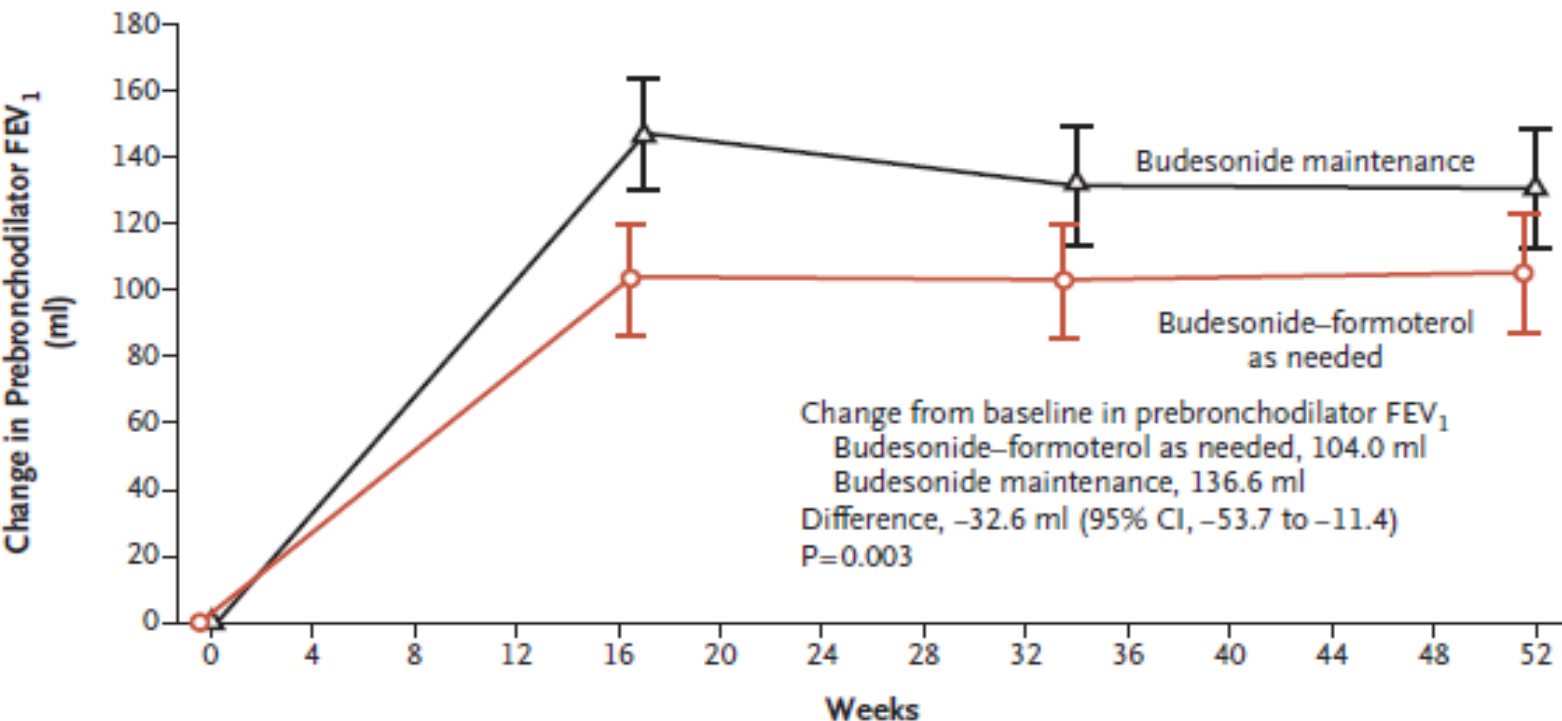
1. Bateman ED et al. Article and supplementary appendix. *N Engl J Med.* 2018;378:1877-1887

SYGMA 1 Secondary Endpoint: Budesonide/Formoterol As-needed was Inferior to Budesonide Maintenance BID on WCAW



SYGMA 1 & 2 Secondary Endpoint: Change From Baseline in Pre-BD FEV₁

A Change in Prebronchodilator FEV₁ from Baseline

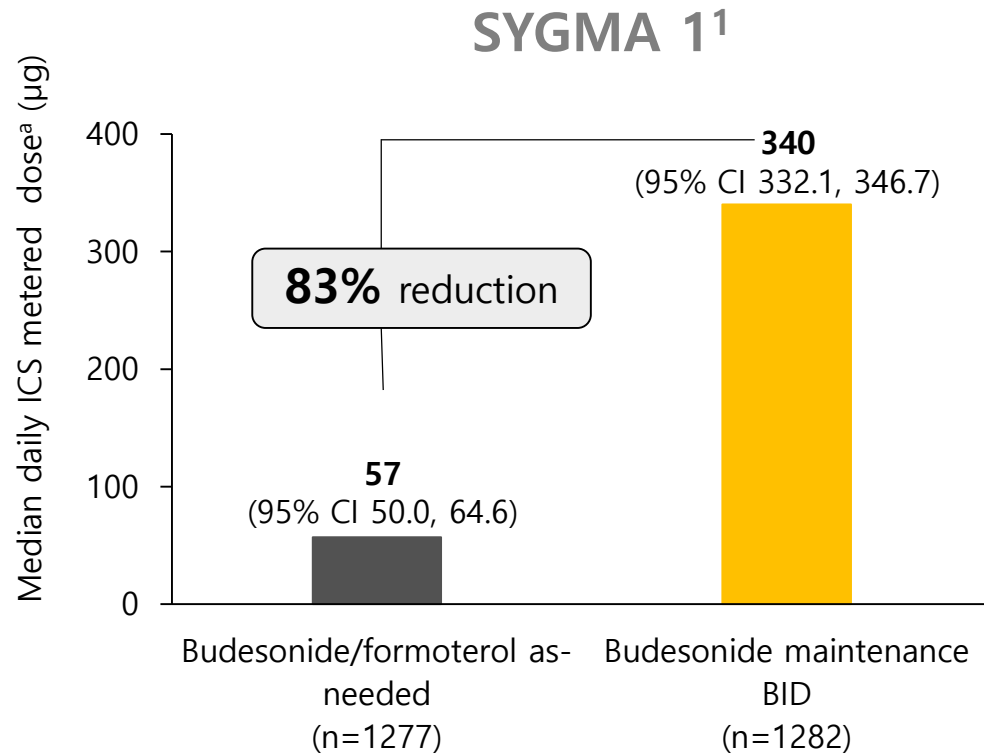


No. of Patients

| | | | |
|---------------------------------|------|------|------|
| Budesonide-formoterol as needed | 1984 | 1932 | 1914 |
| Budesonide maintenance | 1953 | 1908 | 1880 |

1. O'Byrne PM et al. Article and supplementary appendix. *N Engl J Med.* 2018;378:1865-1876; 2. Bateman ED et al. Article and supplementary appendix. *N Engl J Med.* 2018;378:1877-1887;

SYGMA 1 & 2: Budesonide/Formoterol As-needed Achieved Comparable Risk of Severe Exacerbations With >75% Lower Steroid Load



Budesonide/formoterol as-needed achieved comparable risk of severe exacerbations to budesonide BID with a >75% lower inhaled steroid load over 1-year study period^{1,2}

SYGMA 1 & 2 Conclusions

- In mild asthma, as-needed budesonide.formoterol provided superior asthma-symptom control to as-needed terbutaline, assessed according to electronically recorded weeks with well-controlled asthma, but was inferior to budesonide maintenance therapy.
- Exacerbation rates with the two budesonide-containing regimens were similar and were lower than the rate with terbutaline. Budesonide-formoterol used as needed resulted in substantially lower glucocorticoid exposure than budesonide maintenance therapy.

- In mild asthma, budesonide-formoterol used as needed was noninferior to twice-daily budesonide with respect to the rate of severe asthma exacerbations during 52 weeks of treatment but was inferior in controlling symptoms.
- Patients in the budesonide.formoterol group had approximately one quarter of the inhaled glucocorticoid exposure of those in the budesonide maintenance group.

A paradigm shift in the treatment of mild asthma?

Wei Tang¹, Lin Sun¹, J. Mark FitzGerald²

- ◆ As needed use of budesonide-formoterol was non-inferior to the budesonide maintenance treatment in terms of reducing exacerbations with no need to routinely use a twice daily medication and greatly reduced the exposure to ICS.
- ◆ SABA PRN should not be considered as the primary treatment for mild asthma.

Suggested definition of **persistent controller Users**

Asthma patients requiring a controller medication(s) persistently even under controlled

Asthma patients with a high risk of exacerbation even under controlled

Low FEV1, especially if < 60% predicted

Allergen exposure if sensitized; confirmed food allergy

Sputum or blood eosinophilia; elevated FeNO in adults with allergic asthma

Uncontrolled comorbidities like obesity or rhinosinusitis

Pregnancy

Ever intubated or in intensive care unit for asthma

≥1 severe exacerbation in last 12 months

Asthma patients who have failed the trial of a controller discontinuation

Step-wise asthma treatment comparing a current guideline to strategies for solutions of asthma treatment dilemma

| Step | Current guideline* | | Strategy 1 | | Strategy 2 | |
|--------|---------------------------|---|---------------------------|----------------|---|----------|
| | Preferred controller | Reliever | Preferred controller | Reliever | Preferred controller | Reliever |
| Step 1 | None | SABA as needed | Low-dose ICS [†] | SABA as needed | Patient-adjusted, symptom-driven, intermittent-to-regular treatment with low-dose ICSs/rapid-onset LABAs [†] | |
| Step 2 | Low-dose ICSs | | | | | |
| Step 3 | Low-dose ICSs/LABAs | | | | | |
| Step 4 | Medium/high ICS/ LABA | SABA as needed or low-dose ICSs/ rapid-onset LABAs [§] | | | Same as the current guideline (see the column of Current guideline) | |
| Step 5 | Refer to add-on treatment | | | | | |

*Adopted and modified from the Korean Asthma Guideline 2014, according to the Creative Commons license Korean Academy of Tuberculosis and Respiratory Diseases⁶. [†]For persistent controller users. [†]The strategy might be applied from the step 1 to some cases of the step 2 in the Asthma Guideline. [§]Formoterol is an example.

Dilemmas and New Paradigms in Asthma Management

- Treatment in Step 1: SABA or LABA (Fast Acting)/ICS?

ICS/LABA can be more effective as on-demand treatment than a SABA alone, because it helps to reduce inflammation and the risk of exacerbations.

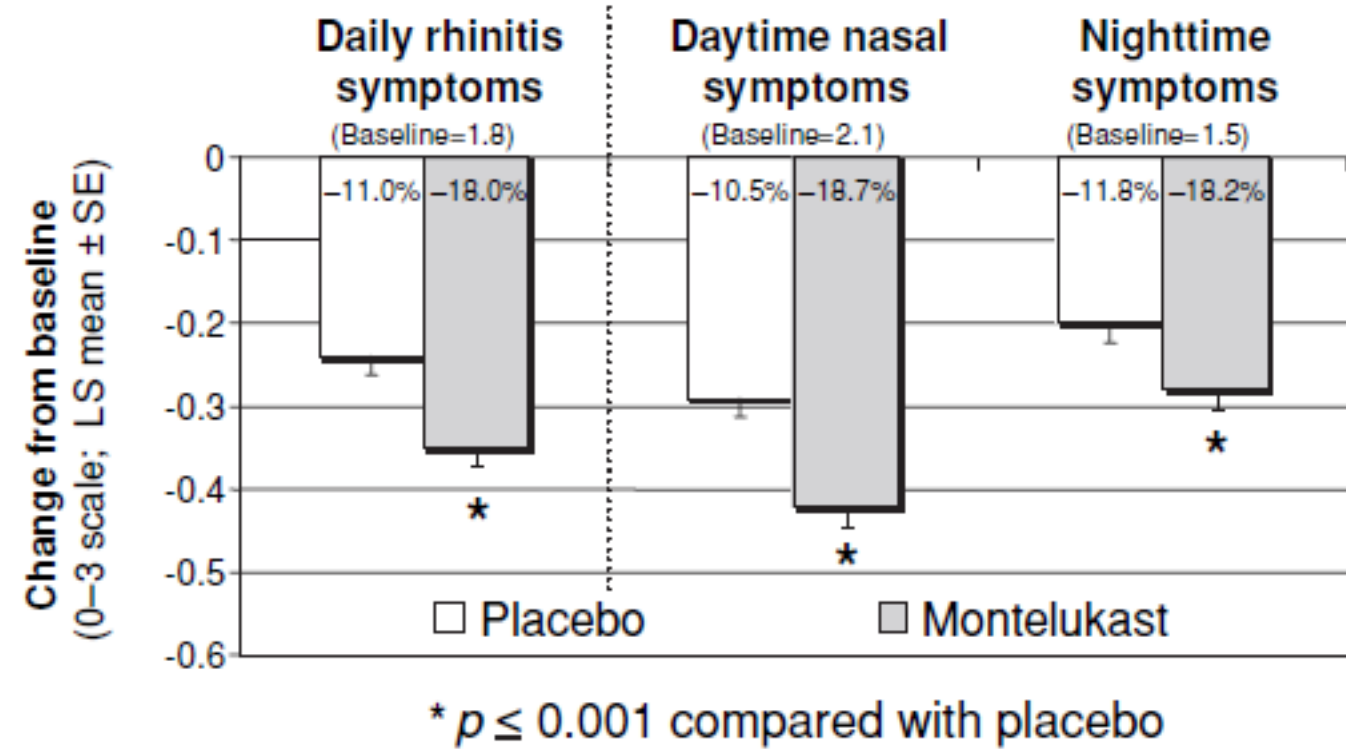
- Step 2, Carrying Over Habits From Step 1

ICS/LABA therapy has proven to be more effective than SABA monotherapy as needed in step 2 and plays a role in improving adherence to ICSs.

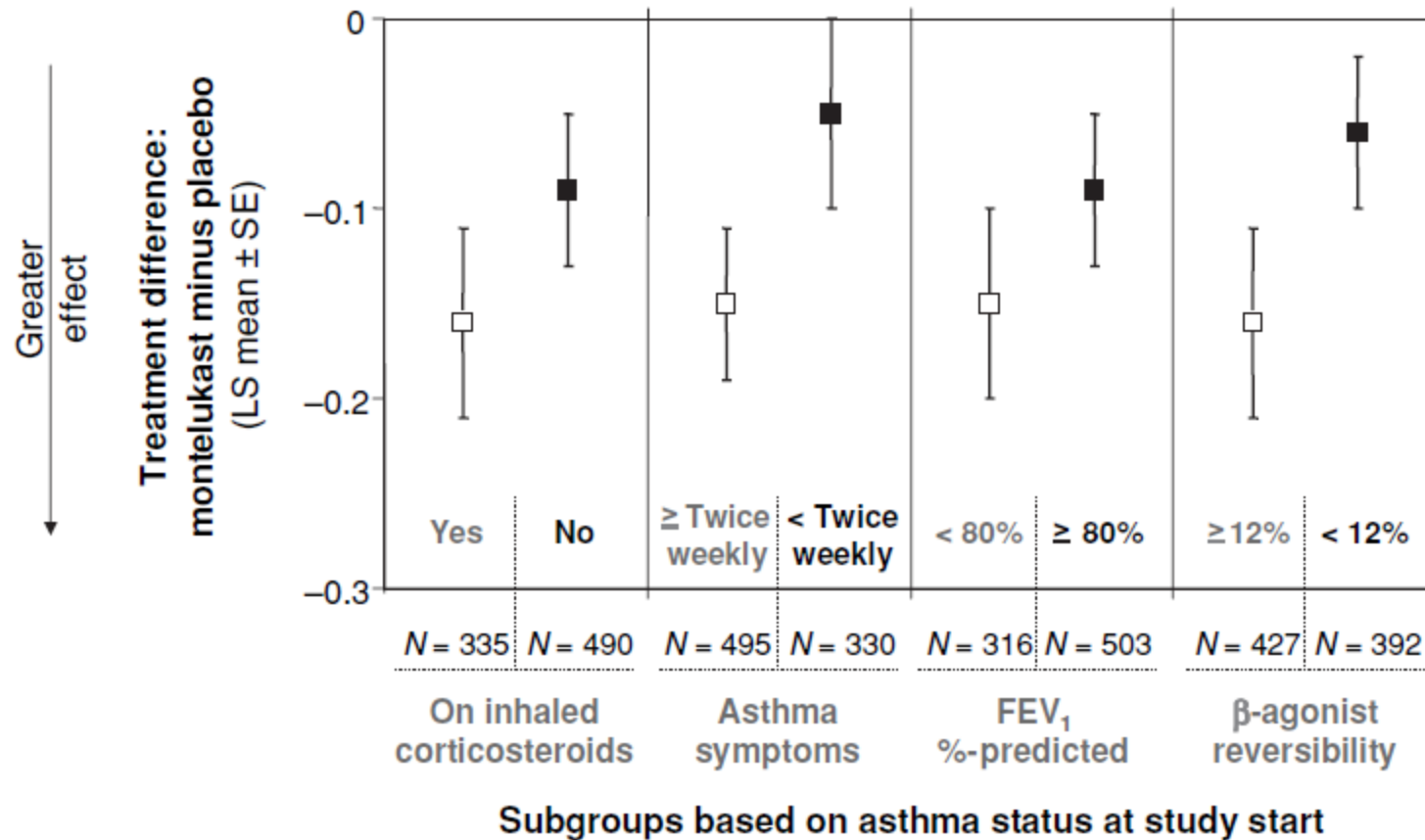
LTRA vs ICS

- Leukotriene receptor antagonists are less effective than ICS especially for exacerbation (Evidence A).
- LTRA may be appropriate for initial controller treatment
 - ① patients who are unable or unwilling to use ICS;
 - ② patients who experience intolerable side-effects from ICS
 - ③ patients with concomitant allergic Rhinitis

The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis



Treatment effect of montelukast on the Daily Rhinitis Symptoms score



Low dose ICS/LABA as the initial maintenance controller treatment

- Reduces symptoms and improves lung function compared with low dose ICS alone.
- More expensive and does not further reduce the risk of exacerbations compared with ICS. (Evidence A).
- Sustained-release theophylline
: weak efficacy in asthma(Evid B), side effect common

Contents

1. Definition & prevalence of mild asthma
2. Treatment option for mild asthma in 2018 GINA guideline
3. Paradigm shift in the treatment of mild asthma
4. Suggestion for mild asthma treatment in 2019 GINA

Mild Asthma treatment option

- prn SABA
- low dose ICS + prn SABA
- **As needed ICS + rapid onset LABA**
- Leukotriene receptor antagonist
- Low dose theophylline less likely
- Low dose ICS/LABA maintenance less likely

POCKET GUIDE FOR ASTHMA MANAGEMENT AND PREVENTION

(for Adults and Children Older than 5 Years)



A Pocket Guide for Health Professionals
Updated 2019

BASED ON THE GLOBAL STRATEGY FOR ASTHMA

Major change in GINA 2019 recommendation for mild asthma

- No longer recommendation starting with SABA only treatment
- All asthma patient should receive ICS containing regimen for preventing exacerbation and symptom control
 - 1) As needed low dose ICS + formoterol
 - 2) If not available, low dose ICS taken whenever SABA is taken
 - 3) Maintenance and reliever with ICS + formoterol
- Evidence only in budesonide + formoterol

Recommended treatment in mild asthma 2019 GINA

| | Step 1 | Step 2 |
|---|---|---|
| Preferred controller to prevent exacerbation and control symptom | As needed low dose ICS + formoterol | Daily low dose ICS As needed low dose ICS + formoterol |
| Other controller option | <ul style="list-style-type: none"> low dose ICS taken whenever SABA is taken | <ul style="list-style-type: none"> LTRA low dose ICS taken whenever SABA is taken |
| Preferred reliever | As needed low dose ICS + formoterol | |
| Other reliever options | As needed SABA | |

GINA 2019

Adults & adolescents 12+ years

Personalized asthma management:

Assess, Adjust, Review response

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

Asthma medication options:

Adjust treatment up and down for individual patient needs

PREFERRED CONTROLLER

to prevent exacerbations and control symptoms

Other controller options

PREFERRED RELIEVER

Other reliever option

| | STEP 1 | STEP 2 | STEP 3 | STEP 4 | STEP 5 |
|--|---|--|---|--|---|
| | As-needed low dose ICS-formoterol* | Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol* | Low dose ICS-LABA | Medium dose ICS-LABA | High dose ICS-LABA |
| | Low dose ICS taken whenever SABA is taken † | Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA is taken † | Medium dose ICS, or low dose ICS+LTRA # | High dose ICS, add-on tiotropium, or add-on LTRA # | Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R |
| | As-needed low dose ICS-formoterol* | As-needed low dose ICS-formoterol* | As-needed low dose ICS-formoterol ‡ | As-needed low dose ICS-formoterol ‡ | Add low dose ICS, but consider side-effects |
| | As-needed short-acting β ₂ -agonist (SABA) | | | | |

* Off-label; data only with budesonide-formoterol (bud-form)

‡ Low-dose ICS-form is the reliever for patients prescribed

경청해주셔서 감사합니다!!

