Acute Asthma

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Disclosures

- Honoraria for CME talks: AZ, BI
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- No of label discussions

Objectives

- To review the causes of poor asthma control
- To recognize asthma exacerbations/worsenings
- To understand the management of asthma exacerbations

Asthma Epidemiology

- One of the most common chronic diseases in the world
  - Estimated worldwide prevalence is 300 million
- In 2014, 2.4 million Canadians reported having been diagnosed with asthma
- Every day in Canada:
  - **317** people are diagnosed with asthma
  - **290** people suffer an asthma attack that requires emergency care
- The economic burden of asthma across Canada is estimated at $52 billion annually

Asthma Epidemiology

- Asthma mortality has decreased in the past decade
  - Most deaths occur in those > age 65 years
  - Higher mortality rates in the US among African Americans, Hispanics and those of lower SES

Goals of Asthma Management

- Symptom control
- Lowest dose of medications to achieve control
- Prevention of exacerbations
- Normal functional capacity
- Prevent mortality
- Prevent side effects of medications

Understanding Asthma Control

- Critical in determining the next steps in disease management
  - Step up therapy
  - Step down therapy
- Critical for patients to develop an awareness of ideals i.e. not just adapting to chronic symptoms
  - Leads to better management of exacerbations/worsenings
  - Better self-management

CTS Asthma Control Criteria

Characteristic	Frequency or Value (Canadian guidelines)
Daytime symptoms	< 4 days/week
Night-time symptoms	< 1 night/week
Physical activity	Normal
Exacerbations	Mild, infrequent
Absence from work, school, or daycare due to asthma	None
Need for prn fast-acting beta-agonist	< 4 doses/week
FEV_1 or PEF	≥ 90% of personal best or predicted
PEF diurnal variation	< 10% to 15% diurnal variation

Balter MS, Bell AD, Kaplan AG, et al. CMAJ 2009; 181(12):915-22.

30 Second Asthma Test

How do you know if your asthma is well managed?

Take the 30 Second Asthma Test®:

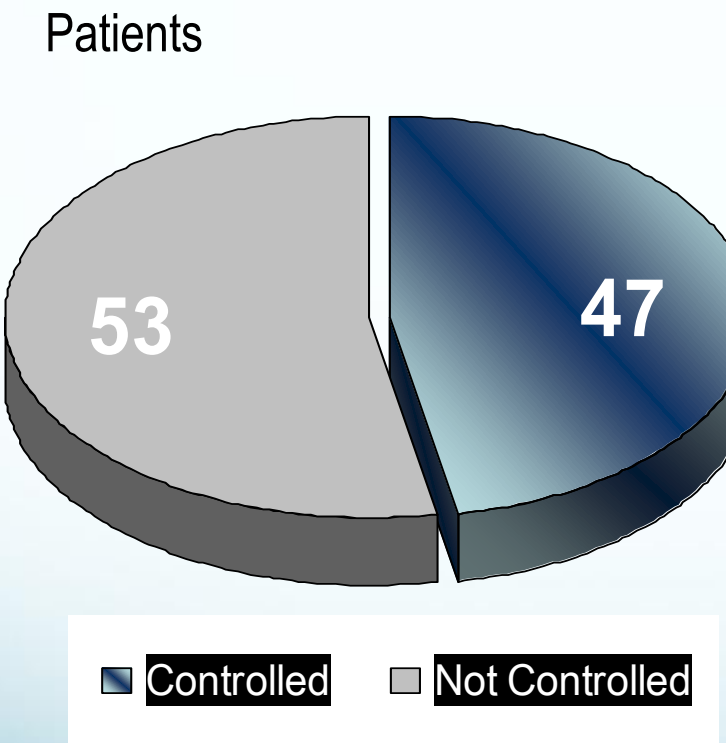
Do you cough, wheeze, or have a tight chest because of your asthma? (4 or more days a week)	☐ YES	☐ NO
Does coughing, wheezing, or chest tightness wake you at night? (1 or more times a week)	☐ YES	☐ NO
Do you stop exercising because of your asthma? (In the past 3 months)	☐ YES	☐ NO
Do you ever miss work or school because of your asthma? (In the past 3 months)	☐ YES	☐ NO
Do you use your rescue medication (blue puffer) 4 or more times a week? (Except 1 dose per day for exercise)	☐ YES	☐ NO

If you answer YES to one or more questions, talk to your doctor or certified asthma educator about how you can better manage your asthma.

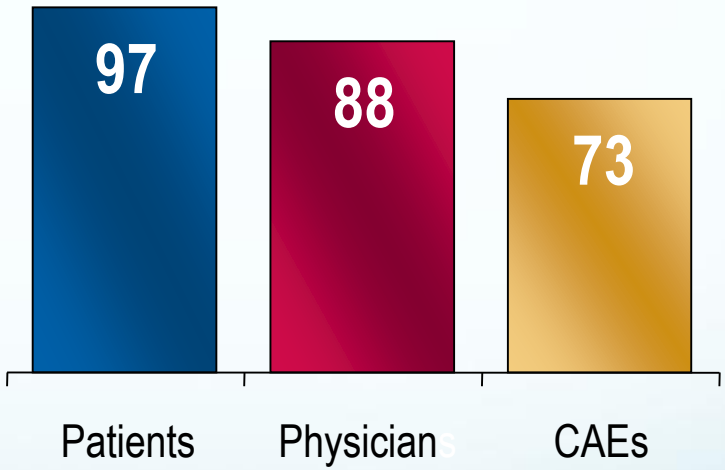
The 30 Second Asthma Test® is a registered trademark, used under license by GlaxoSmithKline Inc.

Actual vs. Perceived Control

Actual Asthma Control



Perceived Asthma Control



Consequences of Uncontrolled Asthma

- Uncontrolled asthma can:
  - Increase likelihood of future asthma attacks[1,2]
  - Lead to preventable deaths[3]
  - Reduce patient quality of life[2]
  - Increase healthcare utilization[2]
  - Have significant social and economic effects[2,4,5]

References: 1. Balter M, et al. *Can Resp J* 2008;15 Suppl B:1B–19B. 2. The Lung Association, Asthma Control in Canada™ Survey, 2016.
3. Royal College of Physicians. *Why asthma still kills: the National Review of Asthma Deaths (NRAD) Confidential Enquiry report.* London: RCP, 2014.
4. Conference Board of Canada. Cost Risk Analysis for Chronic Lung Disease in Canada 2012.
5. Sadatsafavi M, et al. *Chest* 2014;145:787–793.

Identifying Uncontrolled Asthma-SERENA

- Multi-centre, cross-sectional, 6-month observational study in asthma patients on ICS/LABA therapy in clinical practice

	All Patients N=396	Controlled 9.1% (N=36)	Partially Controlled 39.5% (N=154)	Uncontrolled 51.3% (N=202)
Exacerbation (n)	64.5% (253)	22.2% (8)	50.0% (77)	83.17% (168)
Admission to ED	18.6% (72)	8.33% (3)	9.15% (14)	27.78% (55)
Unscheduled visits	49.9% (193)	8.33% (3)	38.6% (59)	66.2% (131)

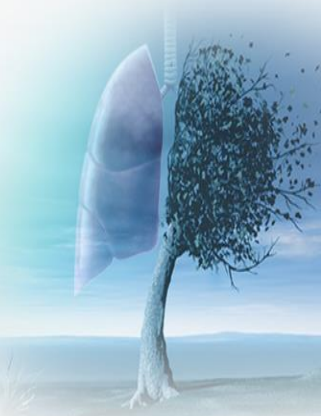
- Highlights the importance of a periodic assessment by a validated asthma control instrument and exacerbations/health care contacts

Corrado A, *et al. Respiratory Med*. 2013;107:1659-1666.

Common causes of poor asthma control

- Suboptimal use of medications
  - Under prescription
  - Poor adherence
- Comorbidities
- Poor inhaler technique
- Poor environmental control
- Lack of continuity of care
- Insufficient use of objective measurement of airflow obstruction leading to over or under estimation of asthma control

DEFINING CONTROLLED ASTHMA: GINA MANAGEMENT STRATEGY[1]



Potentially modifiable independent risk factors for flare-ups (exacerbations):

- Uncontrolled asthma symptoms
- High SABA use (with increased mortality if >1 x 200-dose canister/month)
- Inadequate ICS: not prescribed ICS; poor adherence, incorrect inhaler technique
- Low FEV_1, especially if <60% predicted
- Major psychological or socioeconomic problems
- Exposures: smoking; allergen exposure if sensitized
- Comorbidities: obesity, rhinosinusitis; confirmed food allergy
- Sputum or blood eosinophilia; elevated FENO (in adults with allergic asthma)
- Pregnancy

Having one or more of these risk factors increases the risk of exacerbations even if symptoms are well controlled

1. GINA. Global Strategy for Asthma Management and Prevention, 2017. Available at www.ginasthma.org. Accessed April 4, 2018.
© 2018, Global Initiative for Asthma, available from www.ginasthma.org, reprinted with permission.

SABA Use: A Key Marker of Asthma Control

- Good control means < 4 inhalations per week of rescue therapy*
- One rescue inhaler contains approximately 200 inhalations
- Therefore…1 salbutamol inhaler should last approximately 1 year*

*Excluding 1 dose/day before exercise

Over-reliance on Rescue Medication

In uncontrolled patients:

Use of reliever medication ≥4 times/week: **43%**

24% stated that relievers should be used regularly

Do not take ICS: **33%**

26% stated that controllers should be used as needed

ICS, inhaled corticosteroid.

TRAC, The Reality of Asthma Control in Canada.

Telephone interviews were conducted between April and August 2004 with adults 18 to 54 years of age who had been diagnosed with asthma more than 6 months prior to the survey, who did not have chronic obstructive pulmonary disease, and who had a smoking history of fewer than 20 pack years (n=893).

Adapted from FitzGerald JM, *et al. Can Respir J.* 2006;13(5):253–59.

Inappropriate and Excessive use of SABA

Inappropriate SABA use is associated with a:

- 45% increase in risk of asthma-related hospitalization
- 25% increase in asthma-related emergency department visits[1]

- Inappropriate SABA use is less likely if:
  - GPs are advised on prescribing SABAs, which can reduce reliever use without compromising asthma control[2]
  - Patients receive the appropriate amount of ICS[3]

References: 1. Fitzgerald JM, et al. *Respir Med* 2017;131:135–140. 2. Wong MD, et al. *Ann Pharmacother* 2010;44:623–629. 3. Tavakoli M, et al. *BMC Pulm Med* 2018;18:33.

Patient Perception

- Perception of asthma severity was tested by methacholine challenge in 32 patients with stable asthma
  - FEV1 was reduced by 30%
  - Patients were asked: “If you were at home and felt this way would you use your inhaler?”
    - 56 % answered “Yes”
    - 44 % answered “No”

Hardie Journal of Asthma 2002
Rubinfeld & Pain. Lancet. 1976

Improving Asthma Control

- Medication compliance/adherence
- Education
- Regular FU
- Manage comorbidities
- Environmental controls
- Stop smoking
- Ensure correct diagnosis

Strategies to Improve Adherence

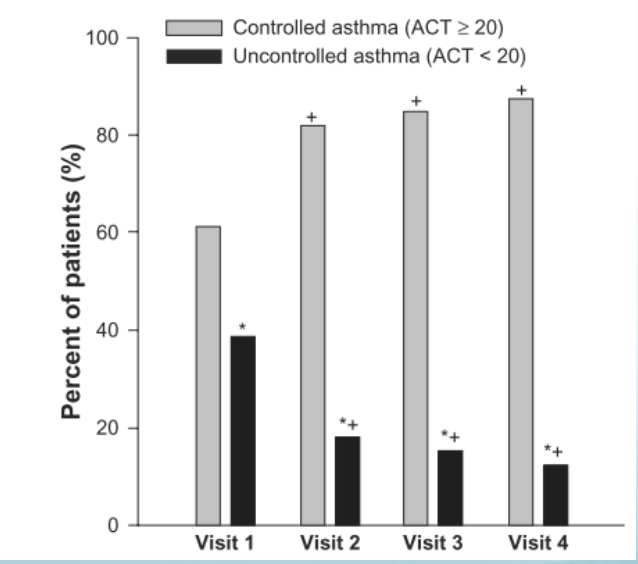
- Focus on patient education
  - ensure language at appropriate level
  - write it down
  - consider referral to an asthma educator
- Encourage self-monitoring
- Use a written asthma action plan
- Monitor adherence to medication regimen and proper inhaler techniques
- Combination therapy may improve compliance

National Heart, Lung, and Blood Institute National Asthma Education and Prevention Program Expert Panel. Guidelines for the Diagnosis and Management of Asthma Full Report, 2007.
Stoloff SW, et al. J Allergy Clin Immunol 2004; 113:245-51.

Follow-Up Key to Improving Asthma Control Rates

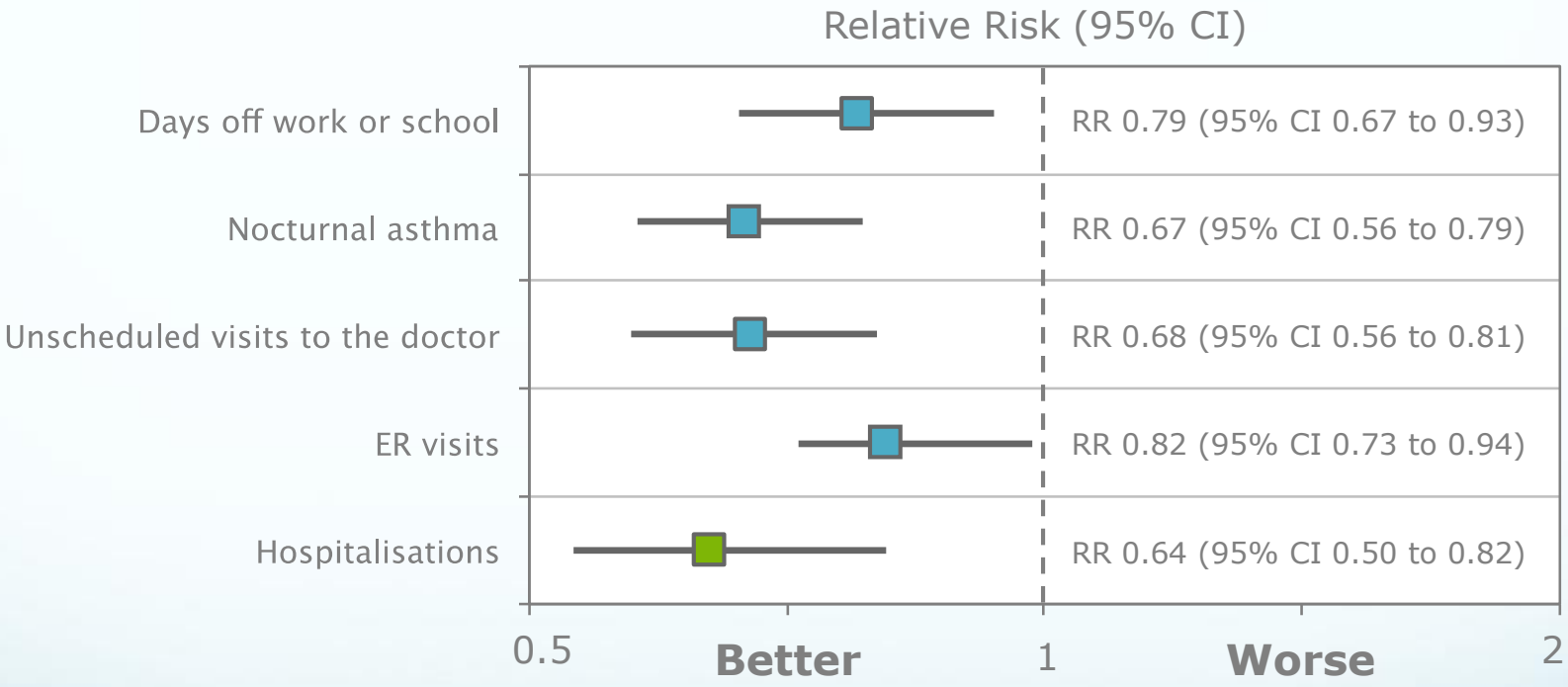
- With follow-up asthma control rate increased from 61.5% to 87.0% after 6 months, regardless of patient demographics, smoking, educational, or employment status.

Asthma control improvement between visits.



Yildiz F, on behalf of the Asthma Inhaler Treatment Study Group. *J Asthma Allergy*. 2013;6:93-101.

Self-Management Education vs. Usual Care Leads to a Reduction in Various Health Outcomes



RR: relative risk
CI: confidence interval

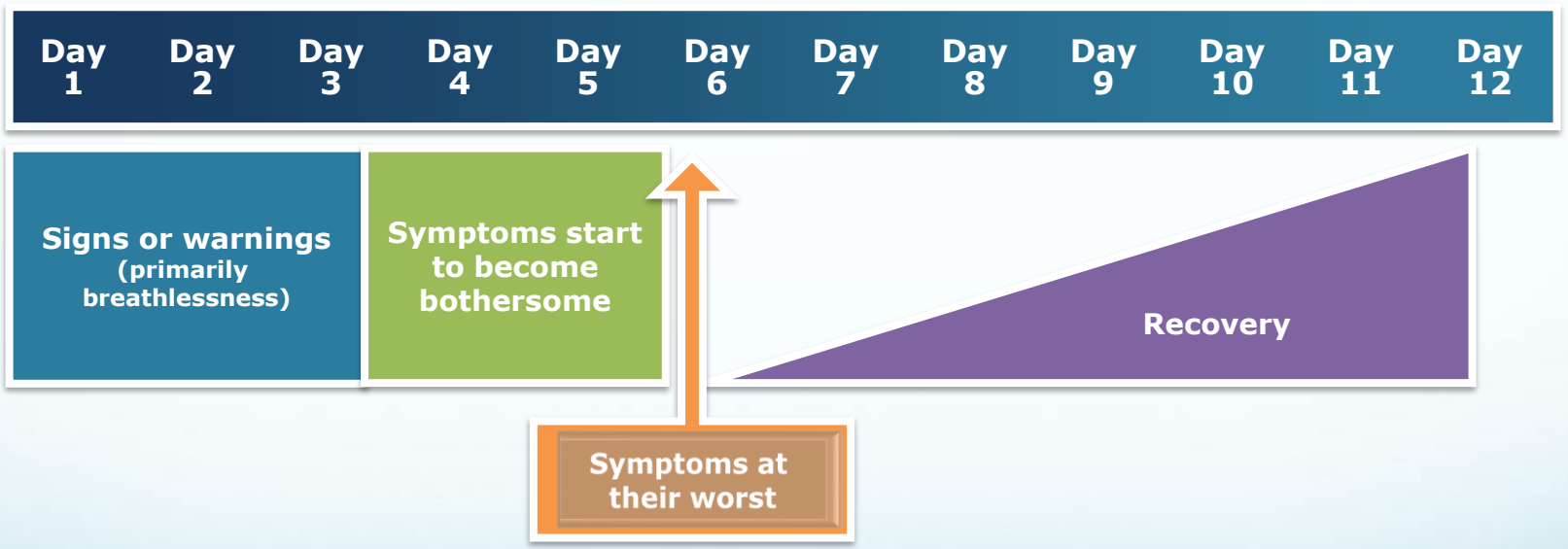
Cochrane Database review to assess the effects of asthma self-management programmes, when coupled with regular health practitioner review, on health outcomes in adults with asthma. Thirty six trials, which compared self-management education with usual care, were included.

Gibson PG, *et al*. *Cochrane Database Syst Rev*. 2003;(1):CD001117.

Asthma Worsenings/Exacerbations

Even Patients with Well-controlled Asthma Experience Periods of Asthma Worsenings* that Require Management

- Most patients report experiencing early warning signs before an asthma worsening, however proper intervention does not always occur



*asthma worsening is an increase in symptoms that:
- are considered "bothersome"
- affect normal functioning or sleep
- lead to an increase in rescue medication

Balter M, *et al*. *Can Resp J* 2008;15(Suppl B):1B-19B.

Asthma Exacerbations

- Episodes of progressively increasing SOB, wheezing, cough and chest tightness
- Usually have a progressive onset
  - Some people can have acute onset of severe symptoms
- Marked by significant decrease in PEFR or FEV_1

Acute Asthma

- Hallmark features of acute asthma attack are :
  - Airway narrowing due to inflammation
  - Increased bronchiolar smooth muscle tone
- Consequences
  - Increased flow resistance
  - Hyperinflation
  - V/Q mismatch
  - Eventually respiratory failure due to ↑ WOB, gas exchange inefficiency and respiratory muscle exhaustion

Investigations

- Objective measurement of obstruction
  - PEFR
  - FEV_1
- CXR
  - If no improvement in symptoms in 6-12 hrs
  - Sign or symptoms of pneumothorax
- ABG/VBG
  - only in patients with 0_2 sats < 90% or in patients starting to fatigue
- Early response to therapy is a very important predictor of outcome
  - PEF >40% of normal after 30 mins of treatment is a predictor of a good outcome

Principles of Acute Management

- Assess the severity
- Assess for possible triggers
- Bronchodilators
- Systemic steroids if needed
- Frequent assessment of response to therapy
- Ensure education and FU plan

Management of Exacerbations

- Depends on severity
- Milder exacerbations with improvement after several doses of beta-agonist do not need to be referred to an acute care setting
- In milder exacerbations increasing the dose of inhaled steroids at the first sign can prevent more severe attacks
  - May avoid need for oral steroids

Home Management

- Beta agonist
  - MDI with spacer
  - 2-8 puffs every 20 mins for the first hour to assess response
  - Then every 3-4 hours 2-4 puffs
  - If no response then to ED
- Inhaled corticosteroid (ICS)
  - Quadruple dose of ICS
  - Careful of fixed dose ICS/LABA combos
- If on ICS/LABA (Budesonide/formoterol) as maintenance and rescue then may increase to 8-12 puffs in a day

Management of Exacerbation in hospital/ED

- Oxygen if hypoxemic
  - Improves hypoxic vasoconstriction
  - Oxygen delivery to respiratory muscles
  - Humidification may be of benefit
- Inhaled β-agonists (Salbutamol)
  - Relax smooth airways muscle and ↓ bronchial mucosal edema
  - May be given continuously until obstruction improves or toxicity develops (tachycardia, arrhythmias, tremor)
    - Evidence supports high and repeated doses
    - MDI with spacer or nebulized equivalent

Management of exacerbation in hospital/ED

- Anticholinergics (Ipratropium)
  - Addition decreased hospital admission rates and improved lung function
  - Ipratropium 4 puffs q 10 mins or 500 ug q 20 mins for 3 doses and then increase interval
  - Addition of ipratropium to a large dose of nebulized albuterol lead to greater improvement in FEV1 than albuterol alone (48%)
  - Alternating therapies can decrease side effects of beta-agonists

Corticosteroids

- Benefit clearly demonstrated in randomized control trials in acutely ill asthmatic studies
  - Slowness of response does not diminish importance

    Fanta Am J Med 1983;74:845
  - Early treatment dramatically reduces need for hospitalization
  - Potentiate β responsiveness of airway smooth muscle, reduce mucosal edema and inflammatory cell infiltrate and decrease mucous secretion

Corticosteroids Dosing

- Severe attack (hospitalized)
  - Methylprednisolone 1mg/kg/dose IV q 6-8 hrs
  - Equivalent oral dosing is as effective
- Outpatients
  - Prednisone 0.5-1 mg/kg daily for 7-10 days
- Once oral meds started they should be continued for 1 week and not tapered or stopped before pt is seen in follow-up
- All patients should be started on inhaled steroids prior to discharge from hospital

Management of exacerbation in hospital/ED

- MgSO4
  - Benefit unclear in literature but minimal side-effects
  - 1-2 grams over 20 mins or inhaled may reduced admission rates
- Theophylline
  - IV aminophylline does not have additional benefit over beta-agonists
  - Can be reserved for patients not responding to standard therapy
  - Continue in patient already on the medication

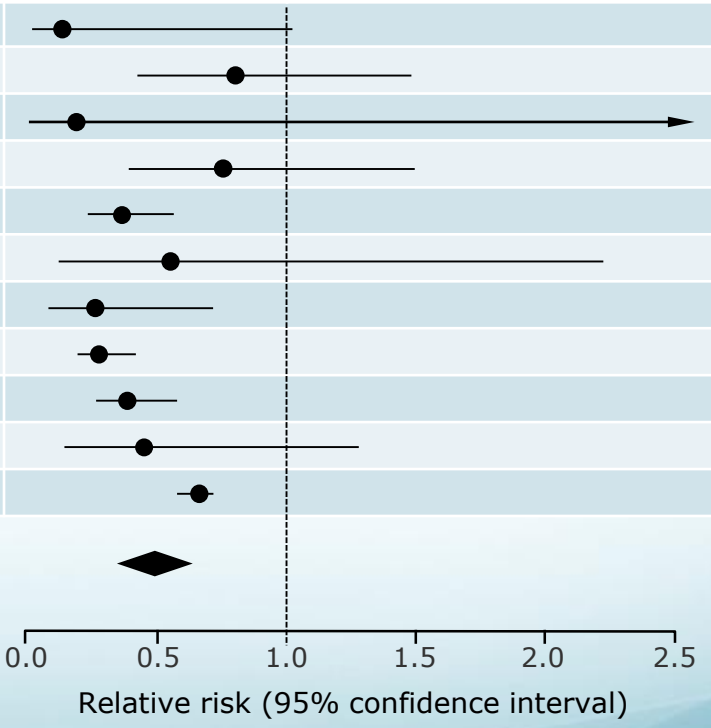
Disposition

- If not response to therapy, hypercapnia or fatigue developing
  - Likely need ICU and intubation
- Good response to treatment and PEFR>60% of personal best
  - Discharge with follow-up with the week
- In between clinical judgment of needs step-down unit or regular ward

Prevention of Exacerbations and Worsenings

ICS Monotherapy Reduces Exacerbations by Nearly 55%*

Study	Participants, No.	Age (year) Mean (SD)*	FEV, % Predicted, Mean (SD)*
Juniper, 1990	32	39 (14)	91 (13)
Haahtela, 1991	103	38 (12)	87 (14)
Osterman, 1997	75	34	NR
Nathan, 1999	258	30 (12)	79 (12)
Malmstrom, 1999	508	36	66 (11)
Kavuru, 2000	172	37	64
Lazarus, 2001	110	31 (11)	94 (9)
Nathan, 2001	227	40	76
O'Byrne, 2001	465	31	90 (15)
Busse, 2001	227	NR	66
Pauwels, 2003	7241	24 (15)	86 (14)



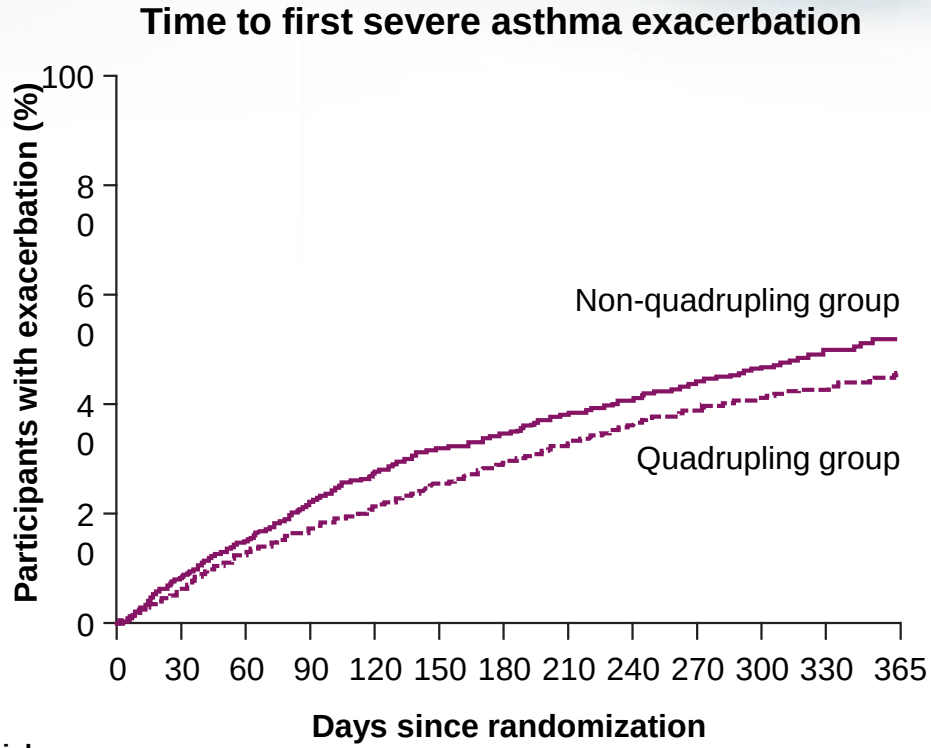
Pooled summary
(RR, 0.46; 95% CI, 0.34–0.62;
Test for heterogeneity: χ^2 =32.15, p<.001)

*compared with placebo or short-acting beta$_2$-agonist.
Higher-dose therapy was associated with fewer exacerbations compared with the lower dose (RR, 0.77;95% CI, 0.67–0.89).

Sin DD, *et al*. *JAMA.* 2004;292:367–76.

Severe Exacerbations: Quadrupling ICS[1]

- Quadrupling ICS resulted in fewer participants reporting severe exacerbations vs non-quadrupling (45% vs 52%, respectively)
  - Time to first exacerbation: HR 0.81 (95% CI: 0.71–0.92; p=0.002)
- Rate of AEs was higher in the quadrupling group
  - Local effects of ICS

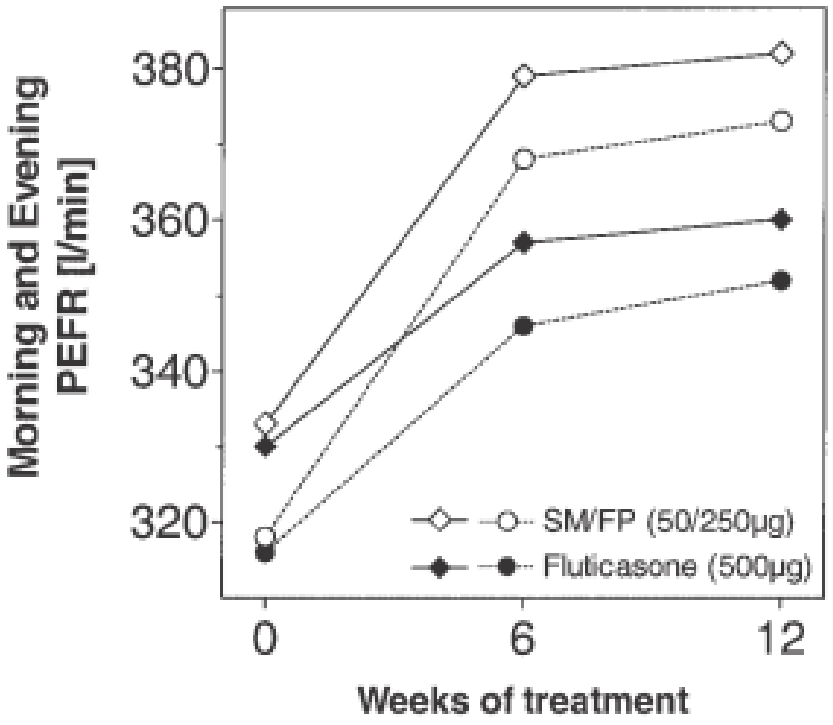


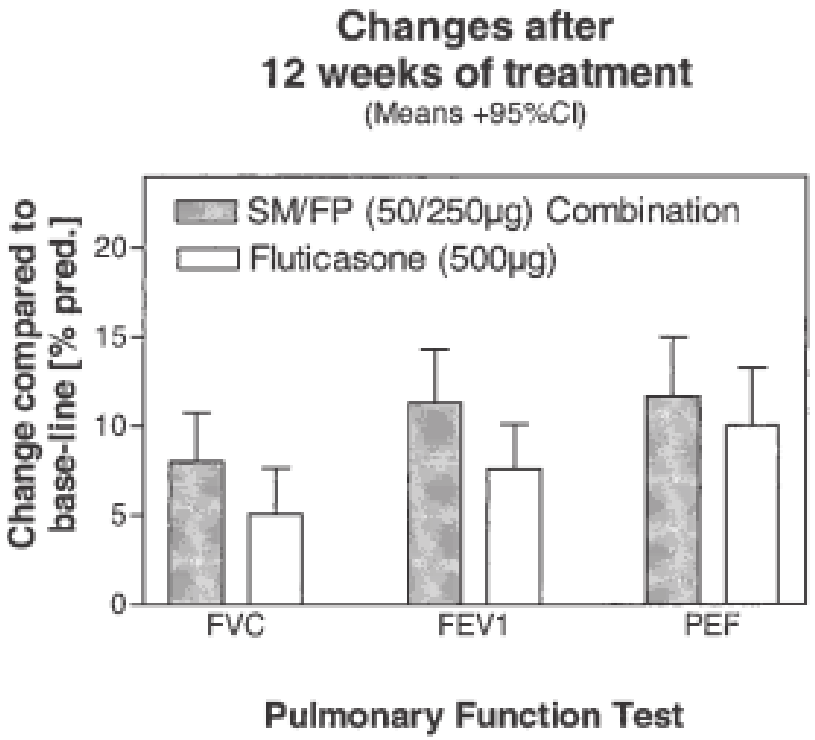
No. at risk							
Non-quadrupling group	938	791	671	592	521	463	349
Quadrupling group	933	806	727	644	558	508	366

AE, adverse event; CI, confidence interval; HR, hazard ratio; ICS, inhaled corticosteroid

Reference: 1. McKeever T, et al. *N Engl J Med* 2018;378:902–910.

ICS/LABA Combination Better than Double Dose ICS Monotherapy



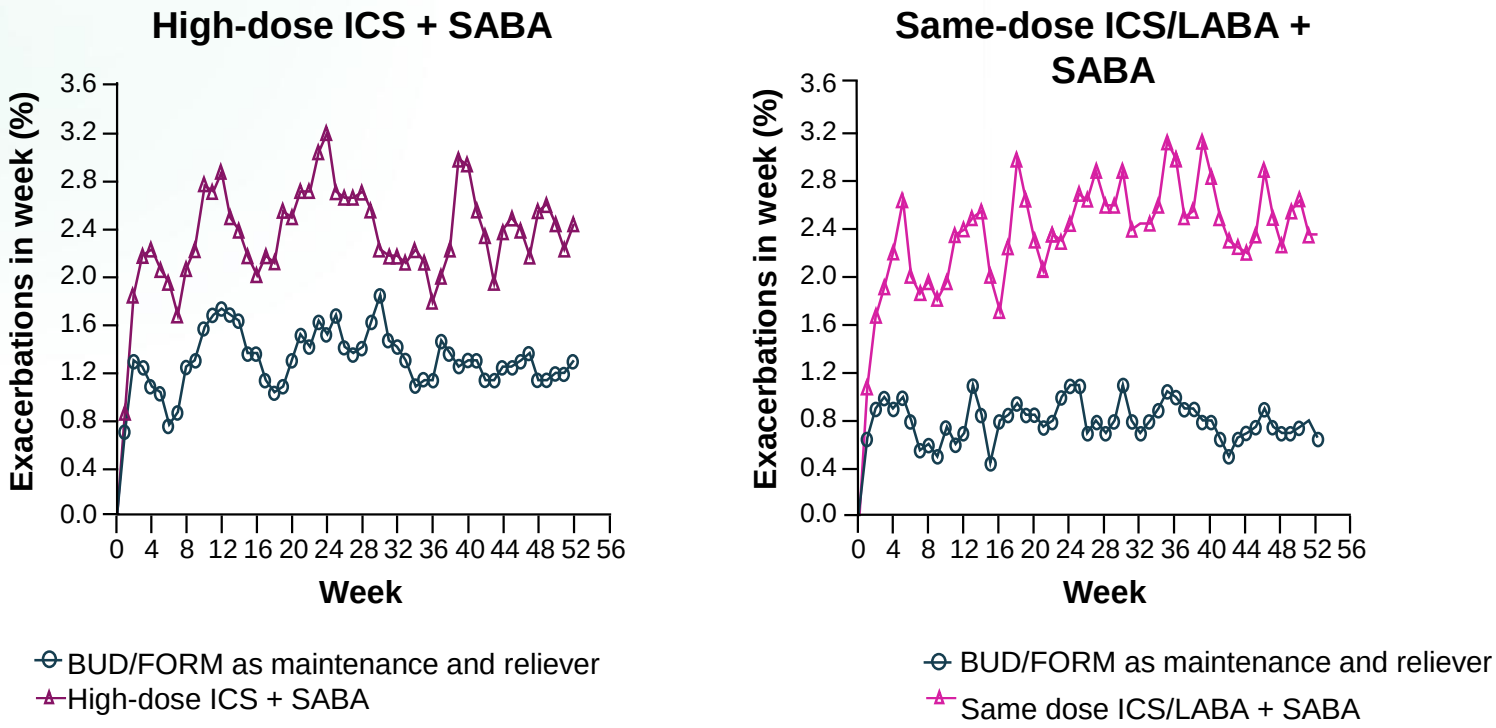


FEV_1, forced expiratory volume in one second; FP, fluticasone propionate; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; PEF, peak expiratory flow;
PEFR, peak expiratory flow rate; SM, salmeterol; pred., predicted.

Bergmann KC, et al. *Swiss Med Wkly.* 2004;134:50–58

Severe Exacerbations: A Retrospective Pooled Analysis[1]

BUD/FORM maintenance and reliever therapy reduced exacerbations compared with high-dose ICS + SABA, and same-dose ICS/LABA + SABA



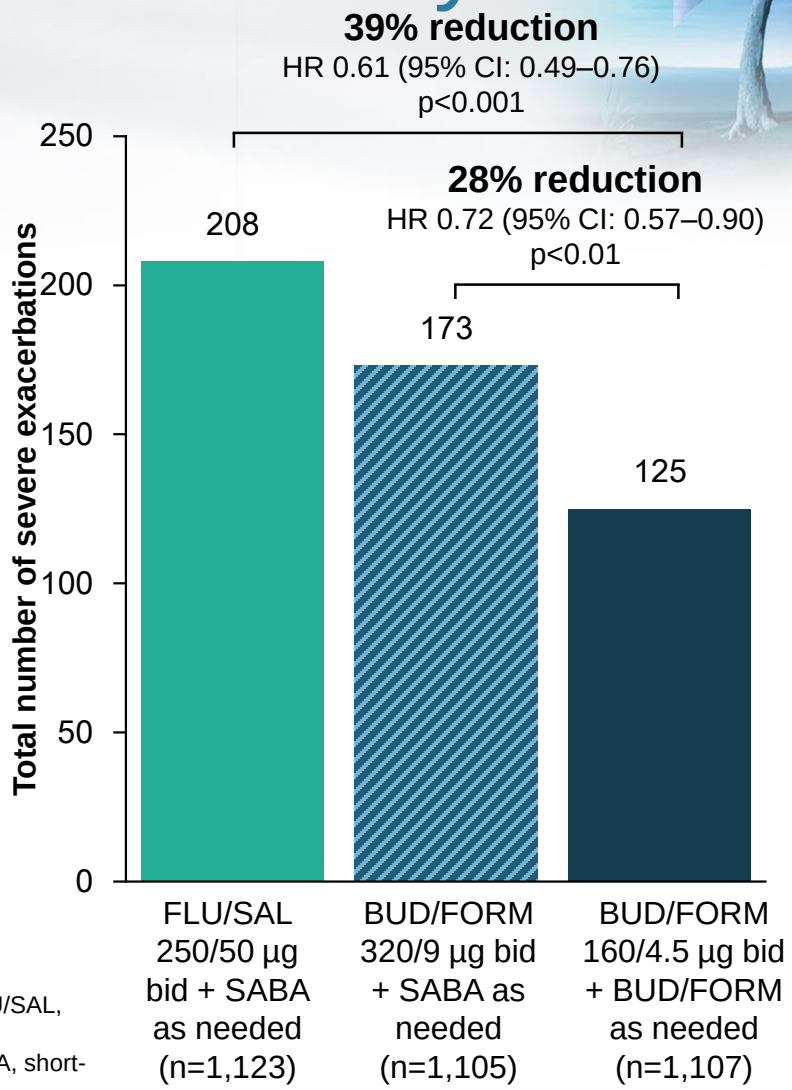
/FORM, budesonide/formoterol; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist

Reference: 1. Bateman ED, et al. *J Allergy Clin Immunol* 2010;125:600–608.

Severe Exacerbations: 6-Month Randomized Study

BUD/FORM maintenance and reliever therapy:

- Reduced the number of severe exacerbations by 39%
- Prolonged the time to first severe exacerbation
- Reduced days requiring oral steroids due to exacerbations

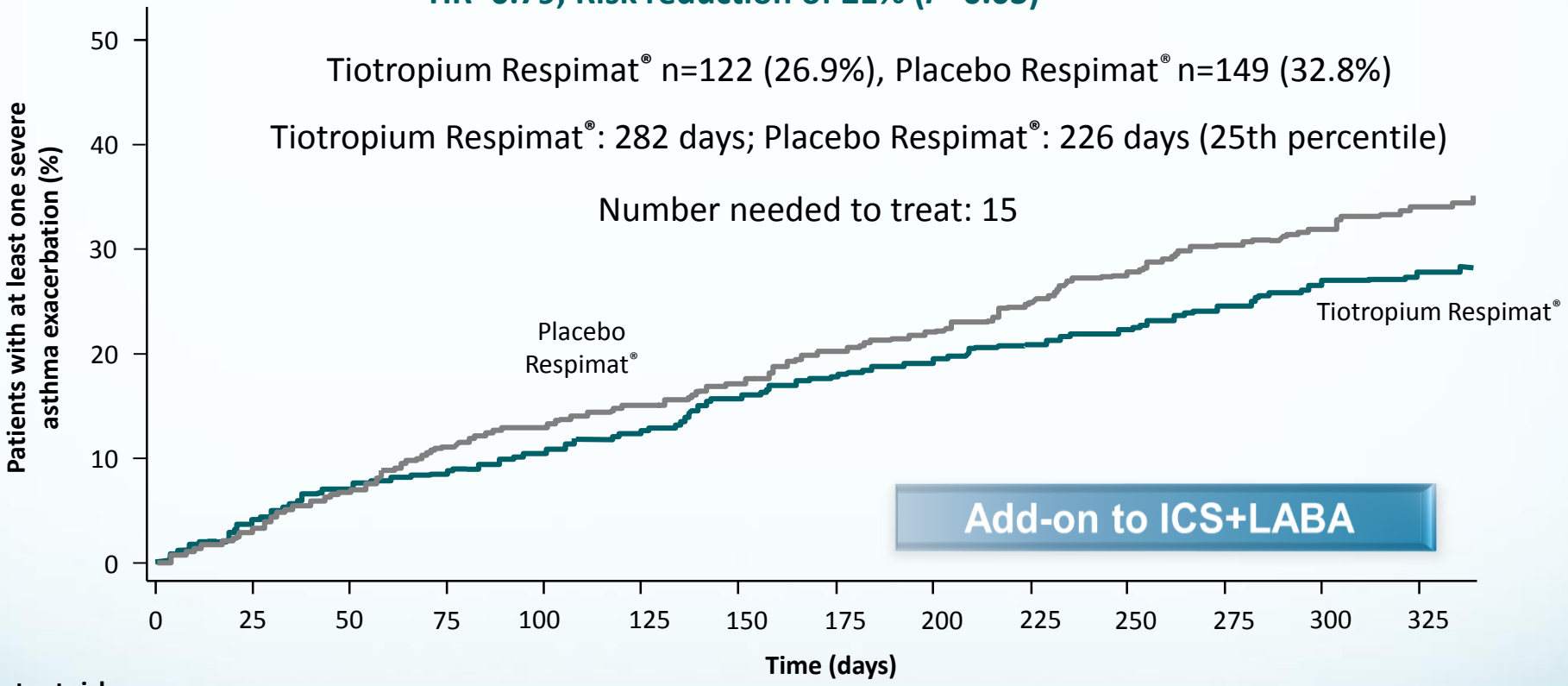


bid, twice daily; BUD/FORM, budesonide/formoterol; CI, confidence interval; FLU/SAL, fluticasone/salmeterol;
HR, hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; SABA, short-acting β_2-agonist

Reference: 1. Kuna P, et al. *Int J Clin Pract* 2007;61:725–736.

Time to first severe asthma exacerbation-pooled

HR=0.79; Risk reduction of 21% (*P*=0.03)



Patients at risk														
Placebo Respimat®	454	435	412	388	379	367	356	339	332	319	303	290	282	272
Tiotropium Respimat®	453	430	409	401	389	378	363	353	348	339	331	319	308	298

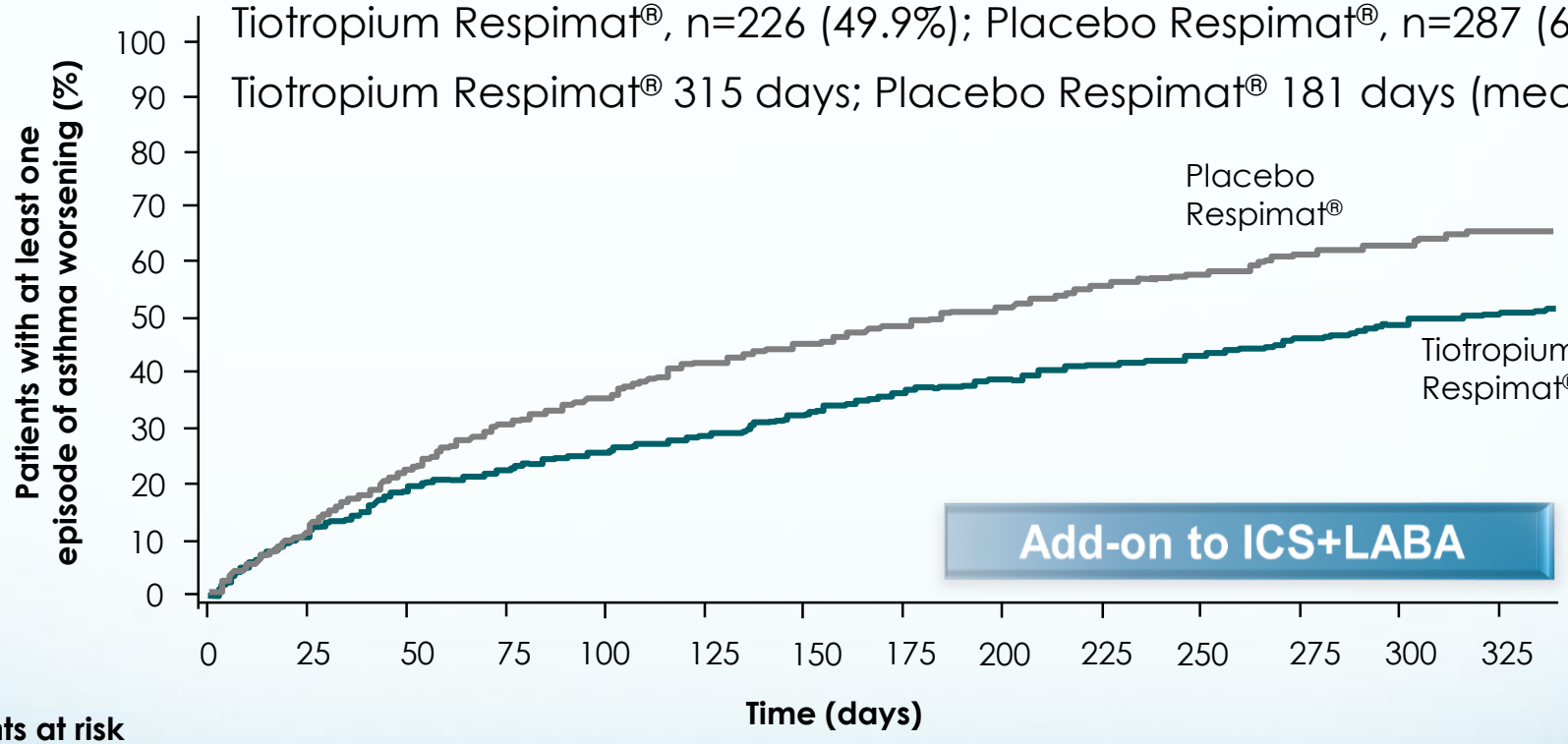
Kerstjens HAM et al. Tiotropium in Asthma poorly controlled with standard combination therapy. NEJM 2012;367:1198-1207.
HR, hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist

Time to first asthma worsening

HR=0.69; Risk reduction of 31% (*P*<0.001)

Tiotropium Respimat®, n=226 (49.9%); Placebo Respimat®, n=287 (63.2%)

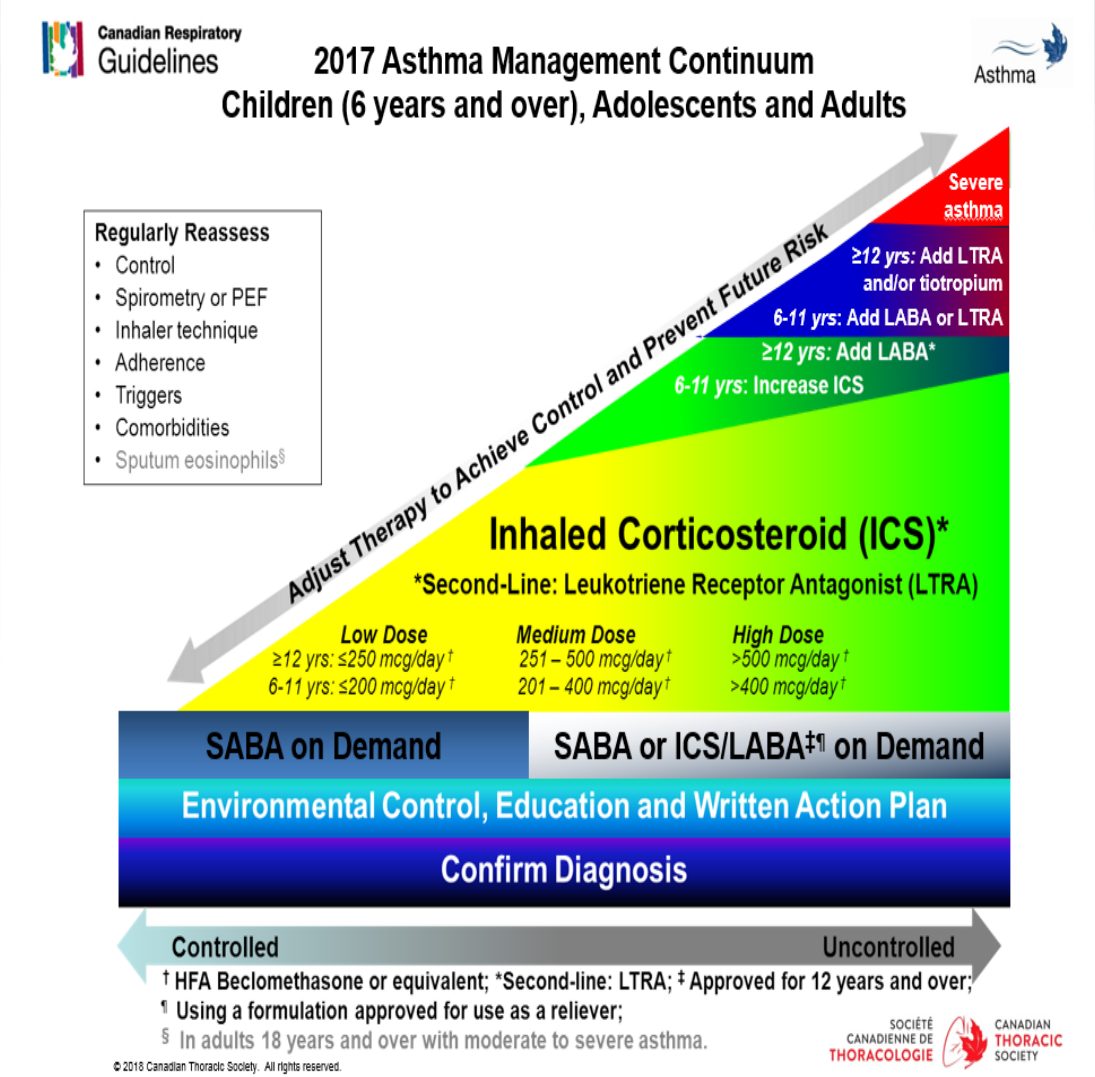
Tiotropium Respimat® 315 days; Placebo Respimat® 181 days (median)



Patients at risk														
Placebo Respimat®	454	393	345	302	280	250	236	219	207	190	180	163	154	146
Tiotropium Respimat®	453	396	357	339	323	306	290	272	263	251	241	227	212	203

Kerstjens HAM et al. Tiotropium in Asthma poorly controlled with standard combination therapy. NEJM 2012;367:1198-1207.
HR, hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist

CTS Asthma Management Continuum[1]



Reference: 1. Lougheed MD, et al. *Can Respir J* 2012;19:e81-e88. © 2018, Canadian Thoracic Society, reproduced with permission.

Why sudden increase in severity or exacerbations?

Change in Severity of Symptoms

- New environmental exposure
- New job exposure
- Medications
- GERD
- Sinusitis
- Post-nasal drip
- Vocal cord dysfunction
- Airway lesion
- Wrong diagnosis

Confirm Diagnosis of Asthma

- A re-assessment of a current diagnosis of asthma may be needed
  - Use objective measurements with either
    - Spirometry - evidence of reversibility, or
    - Methacholine challenge - an assessment of airway hyper-responsiveness[1]
- In a recent Canadian study of 613 participants with physician-diagnosed asthma within the previous 5 years, 203 (33%) did not have current asthma
  - 12 (2%) participants had serious cardiorespiratory conditions previously misdiagnosed as asthma[2]

Alternative Causes of Symptoms Suggestive of Asthma in Adults

- Other obstructive lung diseases
- Chronic rhinosinusitis
- Gastroesophageal reflux disease
- Hyperventilation syndrome & panic attacks
- Vocal-cord dysfunction
- Infections
- Mechanical obstruction of the airways
- Medications (ACE inhibitors)
- Non-obstructive lung disease
- Extrapulmonary disease

Kaplan AG, Balter MS, Bell AD, et al. CMAJ 2009; 181(10):E210-E220.

Take Home Points

- Assessment of asthma control at all visits is essential
- Goal is to achieve symptom control and prevent exacerbations
- Take a systematic approach to determining cause of poor asthma control
- Recognize asthma worsenings/exacerbations early to up titrate therapy to prevent hospitalization

Questions?