

*Canadian Agency for  
Drugs and Technologies  
in Health*



*Agence canadienne  
des médicaments et des  
technologies de la santé*

## **Evidence Update: Asthma and COPD**

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**CADTH is a not-for-profit, independent,  
National agency providing unbiased  
evidence to support decision-making in all  
sectors of health care**



# What is a Health Technology?

**Any medical intervention utilized in health treatment and maintenance across the whole spectrum of medical and health practices.**

## **Designed to:**

- Improve health
- Prevent, diagnose or treat disease
- Aid in rehabilitation or long term care

## **Includes:**

- Drugs and Vaccines
- Blood products
- Diagnostic tests
- Devices and equipment
- Medical and surgical procedures

# CADTH's Programs

**HTA** Health Technology Assessment



= Assessment



= Advice



= Recommendation



= User tools

**CDR** Common Drug Review



**COMPUS** Canadian Optimal Medication Prescribing and Utilization Service



# Additional CADTH Services

- Free access to reports: [www.cadth.ca](http://www.cadth.ca)
- Drug Interventions Database: [www.rxforchange.ca](http://www.rxforchange.ca)
- Rapid Response Service (Health Technology Inquiry Service)  
(self web access to database coming soon!)
- Local Liaison Officer support to aid interpretation of evidence, link with others pan-Canadian, and place new requests for information as needed



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## Health Technology Inquiry Service

Health Technology Assessment HTA



### HTIS Topic Summary

March 2010

Devices and Systems					
#	Technology	Question	Level	Date Complete	Org Type
1	Intermittent Pneumatic Compression Stockings and Thromboembolytic Deterrent Stockings for Perioperative Patients: Clinical Effectiveness and Guidelines*	<p>1. What are the evidence-based guidelines regarding patient indications and timing of use for intermittent pneumatic compression stockings and/or thromboembolytic deterrent stockings during a surgery that requires general anesthesia?</p> <p>2. What are the evidence-based guidelines regarding the use of both intermittent pneumatic compression stockings and thromboembolytic deterrent stockings compared to using one or the other during surgery that requires the delivery of anesthesia?</p> <p>3. What is the clinical effectiveness of placing intermittent pneumatic compression stockings and/or thromboembolytic deterrent stockings before the delivery of general anesthesia?</p> <p>4. What is the evidence regarding the need to use both intermittent pneumatic compression stockings and thromboembolytic deterrent stockings?</p>	Level 1	March 1	HOS

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TECHNOLOGY REPORT

20 HTA  
Issue 122  
November 2009

Long-Acting Beta<sub>2</sub>-Agonist and Inhaled  
Corticosteroid Combination Therapy for Adult  
Persistent Asthma: Systematic Review of Clinical  
Outcomes and Economic Evaluation



Supporting Informed Decisions



# Overview

- Review the evidence comparing tiotropium to ipratropium in patients with COPD
- Discuss issues related to adherence and outcome measures in asthma
- Review the evidence on combination therapy with long-acting beta-agonists (LABA) and inhaled corticosteroids (ICS) in asthma

# HTIS request: COPD

## The Issue

- Contacted by a drug plan manager via e-mail
- New Canadian guidelines recommended tiotropium (Spiriva®) as first line therapy in moderate to severe COPD
- Existing drug plan policy limited tiotropium to patients who continue to be symptomatic after an adequate trial of ipratropium
  - Ipratropium 12 puffs per day for 2 to 4 months
- Is there enough evidence to warrant a policy change?

# HTIS request: COPD

What is the clinical effectiveness of tiotropium compared with ipratropium for the treatment of patients with moderate to severe COPD?

# HTIS request: COPD

## Inclusion criteria

- **Patients:** adults with moderate to severe COPD
  - **Moderate:** shortness of breath from COPD causing the patient to stop after walking about 100 m on level ground
  - **Severe:** shortness of breath leaving the patient too breathless to leave the house, or breathless after undressing, or in the presence of chronic respiratory failure or clinical signs of right heart failure\*

\*Canadian Thoracic Society - Can Respir J Vol 15 Suppl A Jan/Feb 2008

# HTIS request: COPD

## Inclusion criteria

- **Interventions:** tiotropium, ipratropium
- **Outcomes:** pulmonary function, chronic activity related dyspnea, health status
- **Study design:** HTA, systematic reviews, meta-analyses, RCTs
- **Search:**
  - 2003 to present
  - PubMed, Cochrane Library, University of York databases
  - Focused Internet search for unpublished studies and HTAs

# HTIS request: COPD

## Results - Voshaar 2008

- Randomized double blind, 12 week study
- Moderate to very severe COPD
- >40 years of age,  $\geq 10$  pack-year history smoking
- Tiotropium 5 or 10  $\mu\text{g}$  daily (Respimat Soft Mist Inhaler), ipratropium 36  $\mu\text{g}$  four times daily MDI, or placebo
- Mean trough FEV<sub>1</sub>, other spirometry measures, use of rescue medication, symptoms

Respir Med 2008 Jan;102(1):32-41

# HTIS request: COPD

## Results – Voshaar 2008

- 719 patients, 69% male, mean age 64 years, COPD for 10 years
- Increase in FEV<sub>1</sub> significantly larger with tiotropium (5 and 10 µg) than ipratropium
- Inconsistent results on other spirometric measures
- Tiotropium 10 µg reduced use of rescue medication compared to ipratropium
- No difference in symptom relief

Respir Med 2008 Jan;102(1):32-41

# HTIS request: COPD

## Results – Hsu 2006

- Randomized double blind, 4 week duration
- Moderate to very severe COPD
- >40 years of age,  $\geq 10$  pack-year history smoking
- Tiotropium 18  $\mu\text{g}$  daily (HandiHaler®) or ipratropium 40  $\mu\text{g}$  four times daily MDI
- Change in trough FEV<sub>1</sub>, other spirometry measures, use of rescue medication, symptoms

J Formos Med Assoc 2006 Sept;105(9):708-14.

# HTIS request: COPD

## Results – Hsu 2006

- 199 patients, 98% male, age range 55 to 90 years
- Change in trough FEV<sub>1</sub> after 4 weeks therapy significantly larger in tiotropium vs ipratropium group
- Use of rescue medication similar
- No difference between groups on patient symptom questionnaire

J Formos Med Assoc 2006 Sept;105(9):708-14.

# HTIS request: COPD

## Limitations

- 2 RCTs, ~900 patients
- Duration of treatment 4, 12 weeks
- Respimat Soft Mist product not available in Canada
- Short term outcomes focused on lung function
- Limited data on patient-centered outcomes

# HTIS request: COPD

## Conclusions

### Patients with moderate to severe COPD treated with tiotropium versus ipratropium

- Tiotropium showed larger increases in FEV<sub>1</sub> after 4 or 12 weeks
- Results of other spirometric measures were similar between groups
- No differences in symptoms of COPD
- Functional capacity or quality of life were not assessed
- Unclear if gains were clinically important to patient

# Other evidence on tiotropium for COPD

## Cochrane systematic review 2008

- Tiotropium was compared to placebo, ipratropium or LABA
- 9 RCTs included
- Tiotropium reduced the odds of
  - Exacerbation OR 0.74 [95% CI 0.66 to 0.83]
  - Hospitalization OR 0.64 [0.51 to 0.82]
- Dry mouth was increased with tiotropium

Barr RG, Bourbeau J, Camargo CA. Tiotropium for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.:CD002876. DOI:10.1002/14651858.CD002876.pub2

# HTIS request: COPD

Question for the Health Technology Inquiry Service?

Contact Brendalynn Ens

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Tel: 306 655-6486

# Case Study - Asthma Management

# Asthma Case Study

**KC, a 22 year old female university student**

**Arrives at your pharmacy with a new prescription for Symbicort 100, 2 inhalations twice daily**

## **History**

- Asthma x 15 years, non-smoker
- Previous prescriptions for Ventolin MDI and Pulmicort 200 ug Turbuhaler
- Short course of oral prednisone 1 month ago
- Oral contraceptives

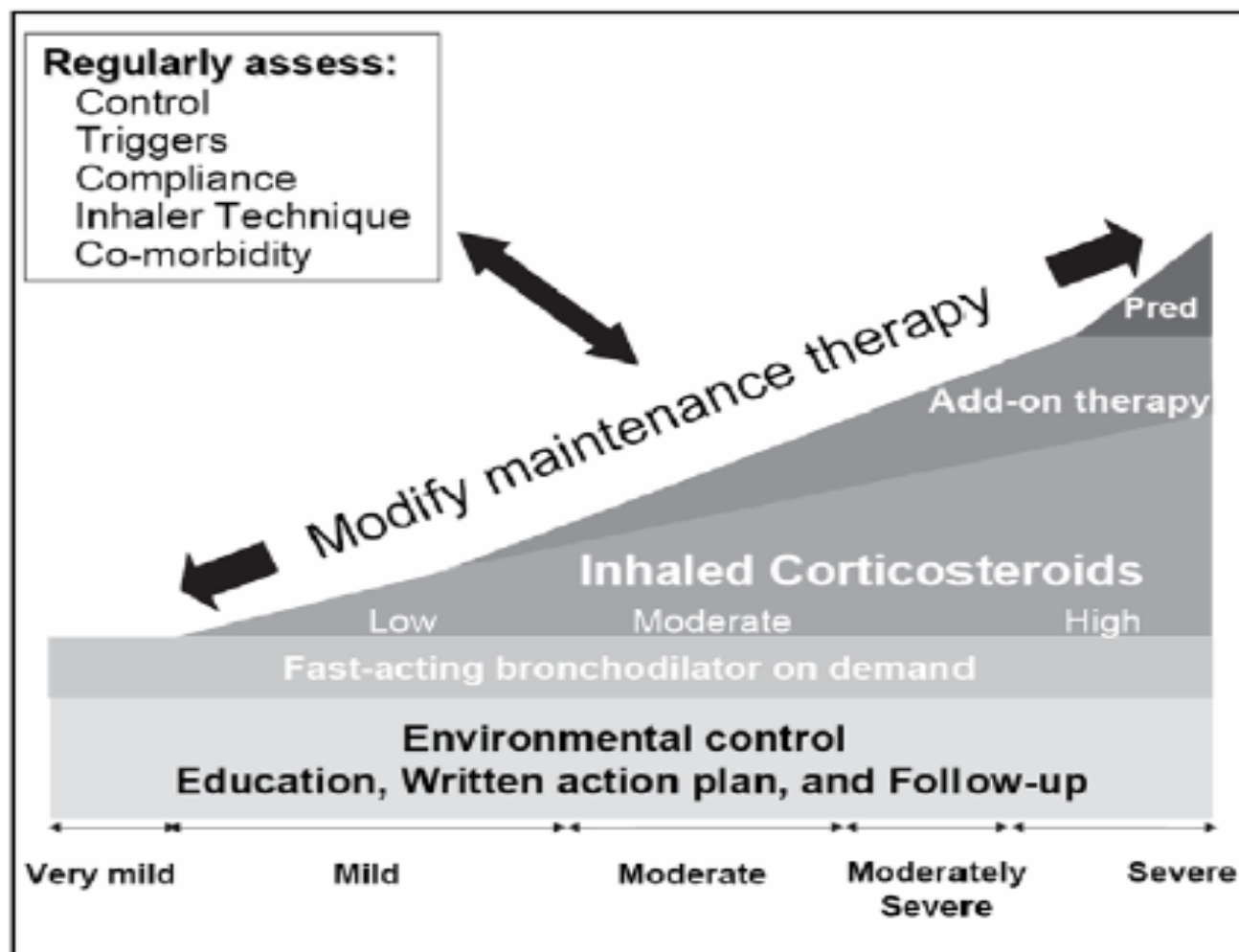
# Asthma Case Study

- You ask if she has been experiencing more symptoms from her asthma lately
- She states she had a real bad attack about a month ago and her doctor wants to switch to a different inhaler
- She is unsure about this new prescription and doesn't want to be taking too many medications
- She has heard that steroids can have a lot of side effects and is worried about the long term effects

# Asthma Case Study

- When asked how often she uses her Pulmicort she says she takes it almost every day
- Looking at her medication profile you see she has filled 5 Ventolin inhalers in the last year (average 3 puffs per day)
- In the same time frame her Pulmicort has been filled only twice (50% of expected refills)
- With further questioning she admits to only using Pulmicort when her asthma is really bad
- She knows she shouldn't use so much Ventolin but she doesn't want to be on steroids

**Figure 1: Continuum of Asthma Management\***



Pred = prednisone.

\*This information was originally published in the *Canadian Respiratory Journal* 2004;11(Supp A):9A-18A.

# Targets for Asthma Control

- Daytime symptoms <4 days per week
- Nighttime symptoms <1 night per week
- Physical activity normal
- Absence from work none
- Exacerbations mild, infrequent
- Need for SABA <4 doses per week
- FEV<sub>1</sub> or PEF ≥90% personal best
- PEF diurnal variation <10% to 15%

Lougheed M et al. Canadian Thoracic Society Asthma Management Continuum- 2010 Consensus Summary for children six years of age and over, and adults. *Can Respir J* 2010;19(1):15-24.

# Adherence to Inhaled Corticosteroids (ICS)

- Prevalence of poor adherence 30% to 80%
- Poor adherence contributes to poor asthma control, increased mortality and hospitalization rates, decreased quality of life and reduced lung function
- Self reported adherence is often over-estimated
- Ivanova 2008 compared self reported adherence to prescription refills
  - 21% and 55% reported adherence of >80% using two different self-report methods
  - 3% achieved good adherence based on prescription refills
- Gamble 2009 assessed patients with uncontrolled severe asthma
  - All patients reported good adherence; 35% filled half of their prescriptions

Ivanova J et al. Am J Manag Care 2008;14(12):801-9. Gamble J et al. Am J Resp Crit Care Med 2009;180:817-22.

# Adherence to ICS

Ponieman et al. 2009

- Cohort study investigated the impact of positive and negative beliefs about ICS on adherence among asthmatic patients
- 49% worried about side effects, 37% feared addiction, or ICS would stop working if used all the time (32%)
- Concerns about side effects or feeling the treatment regimen was hard to follow lowered odds of adherence (OR 0.52)
- Belief that ICS are important to use when asymptomatic quadrupled odds of regular adherence
- Being confident in ability to use ICS doubled odds of adherence

Ponieman et al. Ann Allergy Asthma Immunol 2009;103:38-42

# Asthma Case Study

**Will combination therapy with LABA and ICS help to improve KC's asthma control?**

**Is combination therapy steroid sparing?**

# LABA+ICS versus ICS monotherapy

## T E C H N O L O G Y R E P O R T



Long-Acting Beta<sub>2</sub>-Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation

Bond K, Coyle D, O’Gorman K, Colye K, Spooner C, Lemiere C, Vandermeer B, Tjosvold L, Rowe BH. *Long Acting Beta2-agonists and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma*. CADTH 2009



# LABA+ICS versus ICS monotherapy

## Research Questions

- What is the clinical efficacy and adverse effects of LABA plus ICS compared to ICS monotherapy in patients with persistent asthma:
  - Steroid naïve
  - Previously treated with ICS
- Is there evidence that LABA plus ICS has a steroid sparing effect?
- What is the comparative efficacy of salmeterol-fluticasone versus formoterol-budesonide?
- What is the cost effectiveness of LABA plus ICS?

# LABA+ICS versus ICS monotherapy

## Included studies

- 107 RCTs
- median N=429 (IQR 199 to 582)
- 88% double blind
- most trials high methodological quality
- Intermittent to severe asthma
- Low to high dose ICS
- 8 to 52 week duration (median 12 weeks)
- Majority of patients were adults (range 4 to 87 years)

# LABA+ICS versus ICS monotherapy

## Outcomes

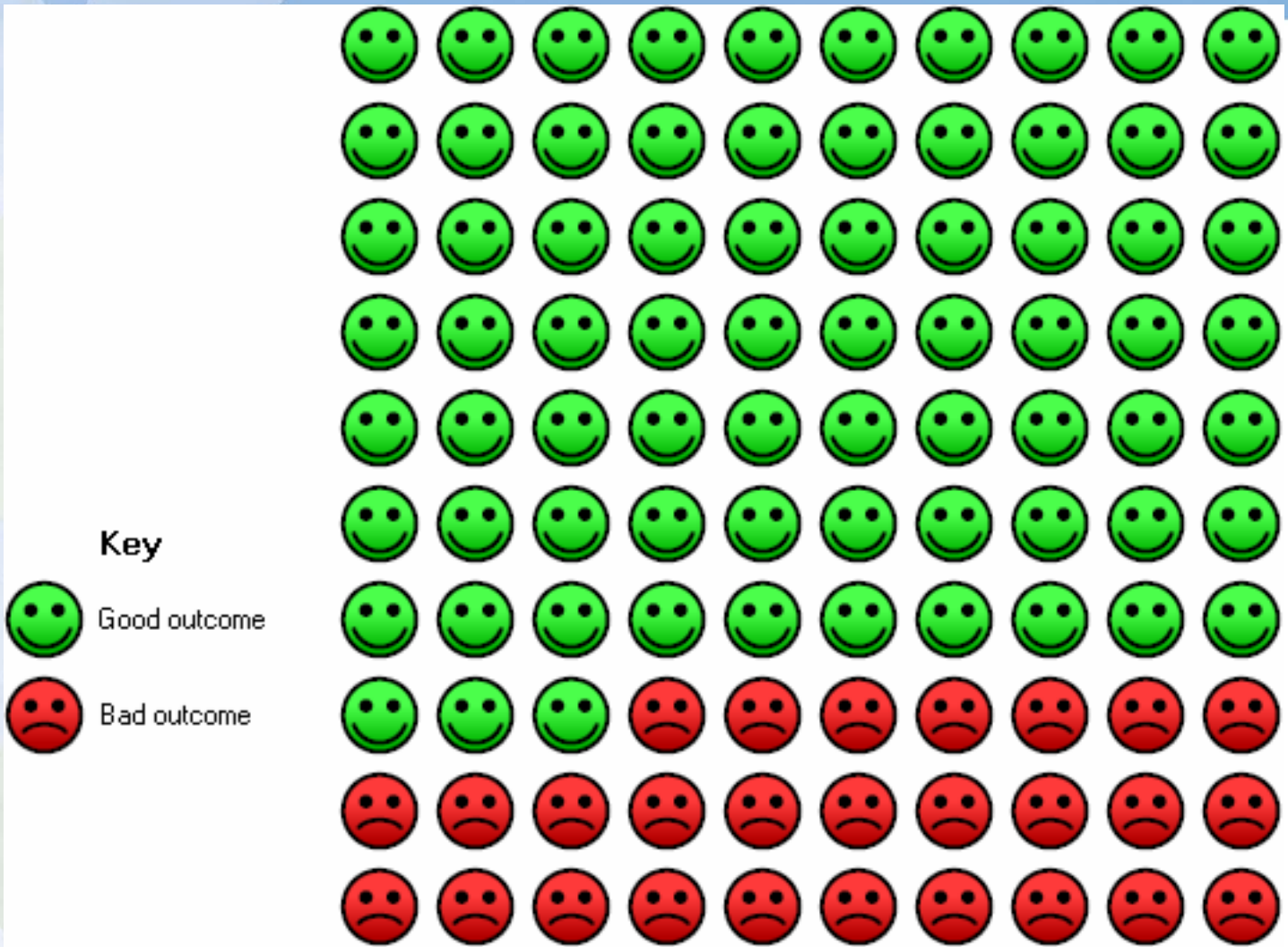
- Pulmonary function, asthma symptom control, asthma-related quality of life, adverse events
- Clinical importance of many outcomes may be questioned
- With large studies small differences between groups may become statistically significant
- Defined minimal clinically important difference (MCID) for each outcome
- MCID is the smallest difference in an outcome measure that patients would perceive as beneficial

# Results

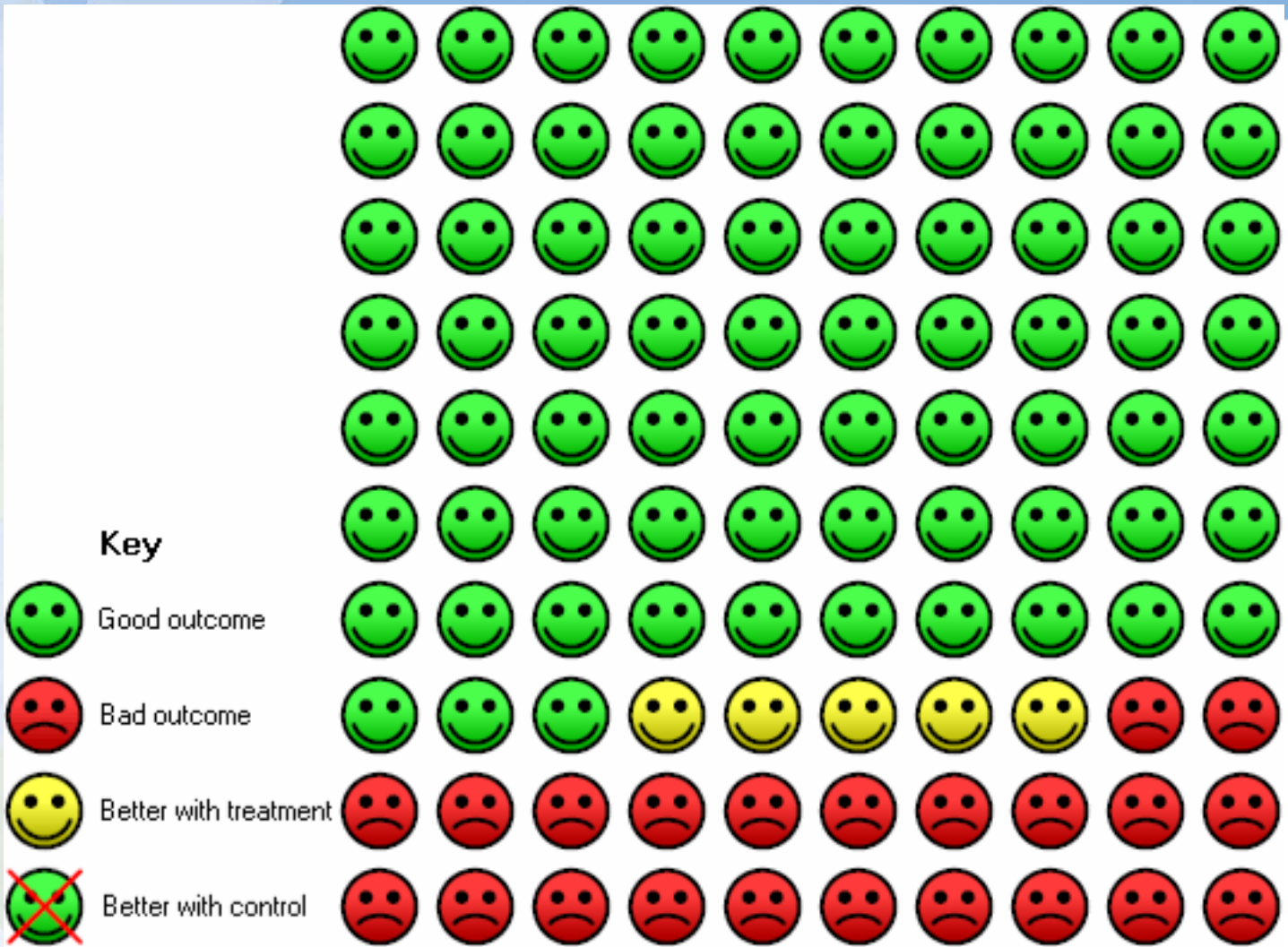
## LABA+ICS versus similar or higher dose ICS

- Improved am and pm PEF
- Increased the number of symptom free days
- Increased the number of days of optimal control
- Reduction in SABA use not considered clinically important
- Differences in asthma quality of life measure not considered to be clinically important
- LABA+ICS reduced the number of patients experiencing exacerbations and total number of exacerbations
- NNT to prevent 1 exacerbation = 19 or 23

# NNT to prevent 1 exacerbation



# NNT to prevent 1 exacerbation



# Results

## Steroid sparing effects of LABA+ICS

- 12 RCTs of patients previously treated with ICS, randomized to same dose ICS or LABA plus reduced dose ICS
- Pulmonary function measures were equivalent between treatments
- No difference in the number of patients with exacerbations
- LABA+ICS reduced mean ICS dose and increased symptom free days although confidence intervals suggest equivalence
- Treatments were equivalent in terms of asthma quality of life

# Results

## Adverse effects of LABA+ICS versus ICS

- Assessed 10 key safety measures (Death, serious adverse events, treatment withdrawal, worsening asthma, common side effects)
- 79 RCTs including 30,000 patients
- No difference between treatments for 9 outcomes
- Worsening asthma reduced by 22% with use of LABA+ICS (95% CI 10% to 34%)
- Not able to draw conclusions about the effect of LABA+ICS on asthma-related deaths

# LABA+ICS versus ICS monotherapy

## Conclusions

- LABA+ICS reduces exacerbations compared to same or higher dose ICS monotherapy (NNT 19 or 23)
- Combination therapy improved other asthma control or pulmonary function measures however the clinical importance was not always clear
- No difference in asthma quality of life
- Some evidence of a steroid sparing effect however the limited number of studies and wide confidence intervals prevent strong conclusions
- Treatments may be considered equivalent in terms of safety for all but the rarest side effects (death)

# Asthma Case Study

## Patient KC

- What can you tell KC about the effectiveness of LABA+ICS?
- Can you help her understand both the benefits and risks associated with regular use of ICS, and the consequences of poor adherence to controller medications?
- What other factors may be affecting KC's asthma control?



***Questions?***

# For More Information



CADTH web site: [www.cadth.ca](http://www.cadth.ca)