2 DEVICES, ONE CONSISTENT RESULT : LESSON LEARNT FROM *UPLIFT* AND *TIOSPIR* TRIALS

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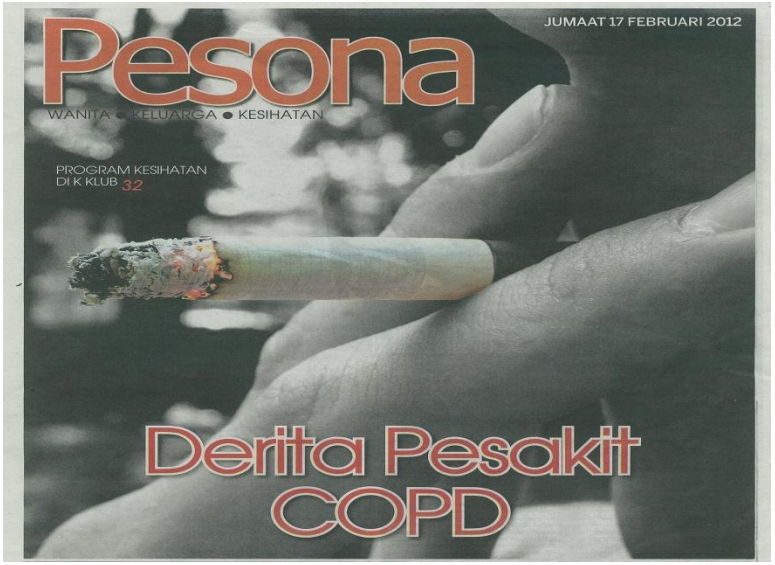
COLUMBIA ASIA
21st Century Healthcare

LINCOLN UNIVERSITY COLLEGE

WORLD BURDEN OF COPD

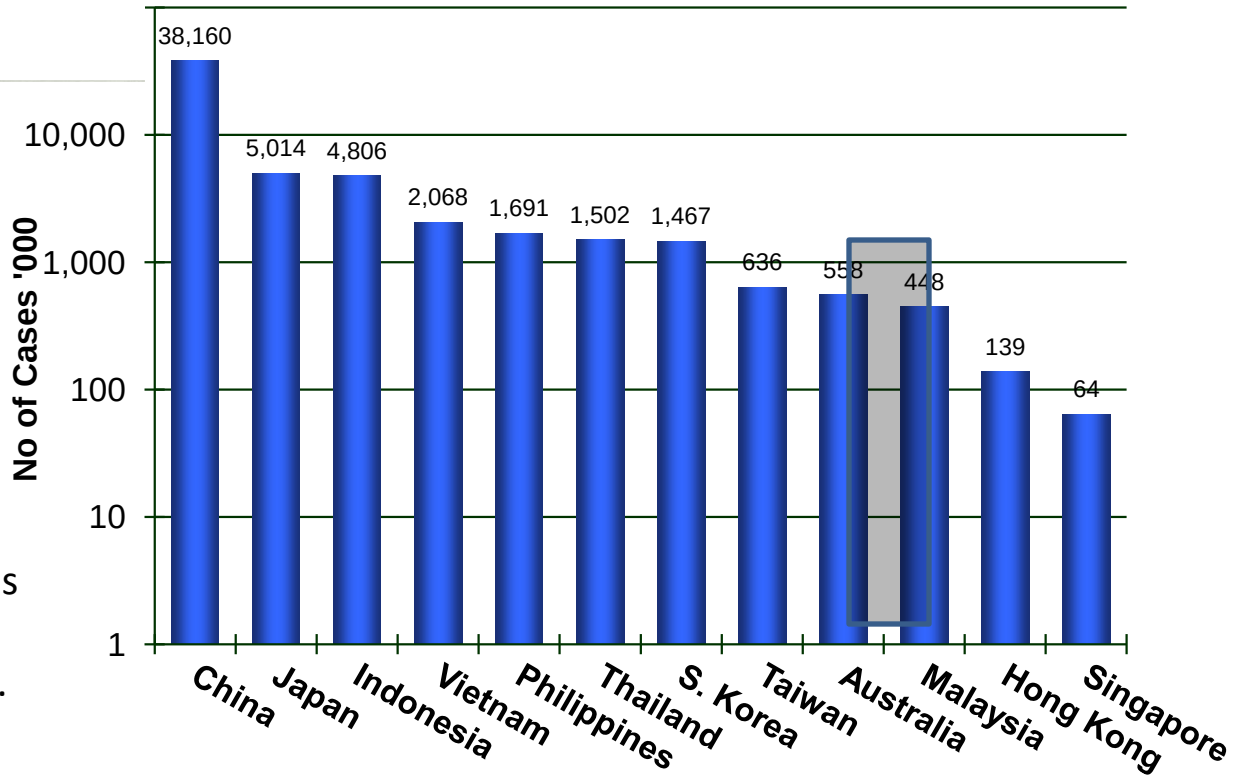
- Chronic obstructive pulmonary disease (COPD) is ***a major global health burden*** in both developed and developing countries.
- The disease is predicted to become ***the third leading*** cause of worldwide disease burden by 2030.[1]
- COPD is also the ***leading respiratory cause*** of days lost from work,[2] and three quarters of COPD patients report difficulty in simple day-to-day activities such as dressing and walking up stairs.[3]

1. WHO: *World Health Statistics 2008*. Available fromhttp : // ww.who.int/whois/EN_WHO8
2. European Respiratory Society/European Lung Foundation: *European Lung White Book*. European Respiratory: Society Journals Limited; 2003.
3. Vermeire P: The burden of chronic obstructive pulmonary disease. *Respir Med* 2002, 96(Suppl C):S3–S10



½ A MILLON OF MALAYSIANS ARE SUFFERING FROM COPD

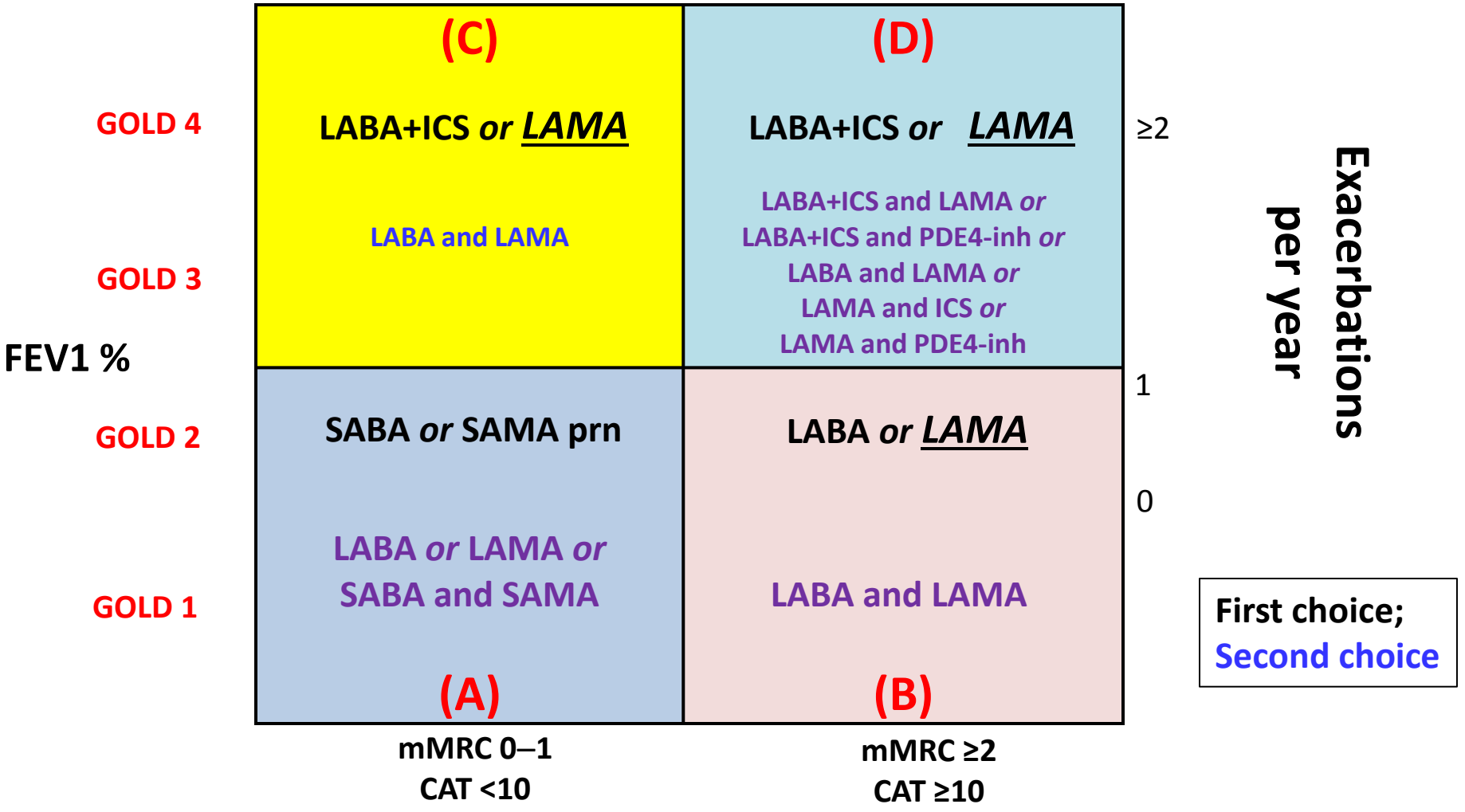
Number of COPD Cases Model Projections of Moderate-Severe COPD in population aged ≥ 30 yrs.*



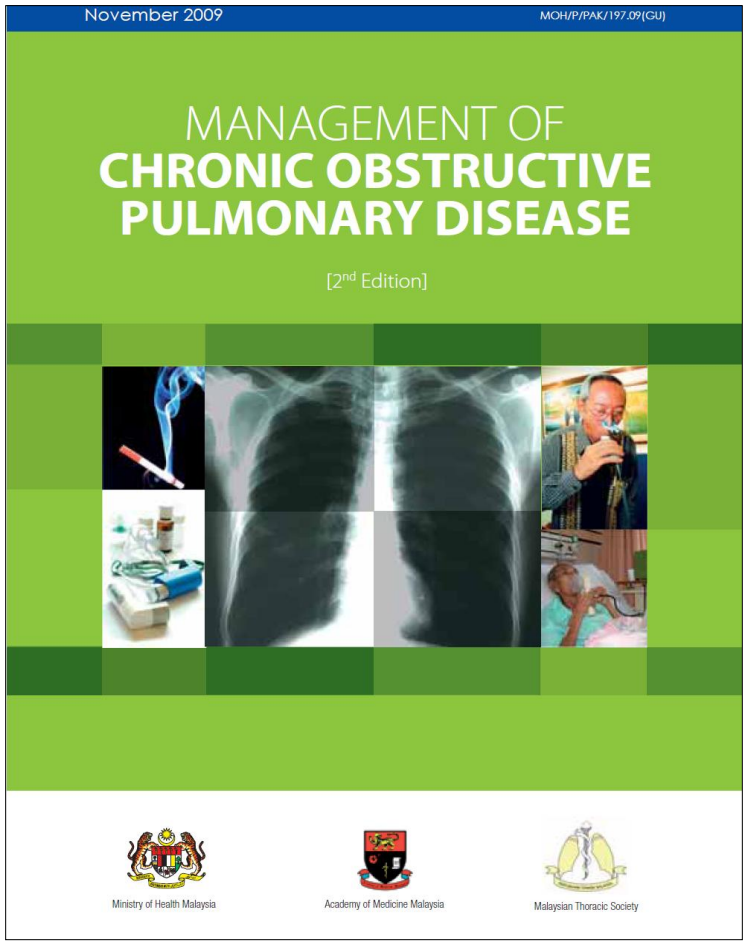
*Regional COPD Working Group. Trends in COPD mortality and hospitalizations in countries and regions of Asia-Pacific. Respirology .2009; 14:90-97

COPD: PHARMACOLOGIC THERAPY (FIRST CHOICE)

Based on combined assessment of airflow limitation, symptoms and exacerbations



*Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of **preference**



- A few studies have suggested that tiotropium produces superior bronchodilation as compared to the LABAs.[1,2] (Level I)

1. Donohue JF, van Noord JA, Bateman ED, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest 2002; 122:47-55.*

2. Van Noord JA, Aumann J, Janssens E, et al. Comparison of tiotropium qd, formoterol bid and both combined qd in patients with COPD. *Eur Respir J 2005; 26,214-222.*

TIOTROPIUM *(SPIRIVA)*

- **The first long acting anti Muscarinic / cholinergic agent (LAMA, LAAC) recommended by GOLD for maintenance therapy for COPD.**
- **Last 12 years, Tiotropium showed:**
  - **Reduction in lung function declines in moderate and moderately severe patients**
  - **Improved quality of life**
  - **Decreased number of exacerbations**
  - **Reduction in all caused- mortality**
  - **No increase in CV side effects**

TIOTROPIUM INHALATION DEVICES

HandiHaler®

Respimat® SMI

- **Patients can choose between single- and multidose device**
- **Both devices well established in most countries with HandiHaler® being the most prescribed COPD maintenance drug device worldwide**

1. SPIRIVA® SmPC. Boehringer Ingelheim 2013; 2. SPIRIVA® Respimat® SmPC. Boehringer Ingelheim 2013

SUPPORTING EVIDENCE

- ***UPLIFT STUDY*** **(Understanding Potential Long-term Impacts on Function with Tiotropium)**

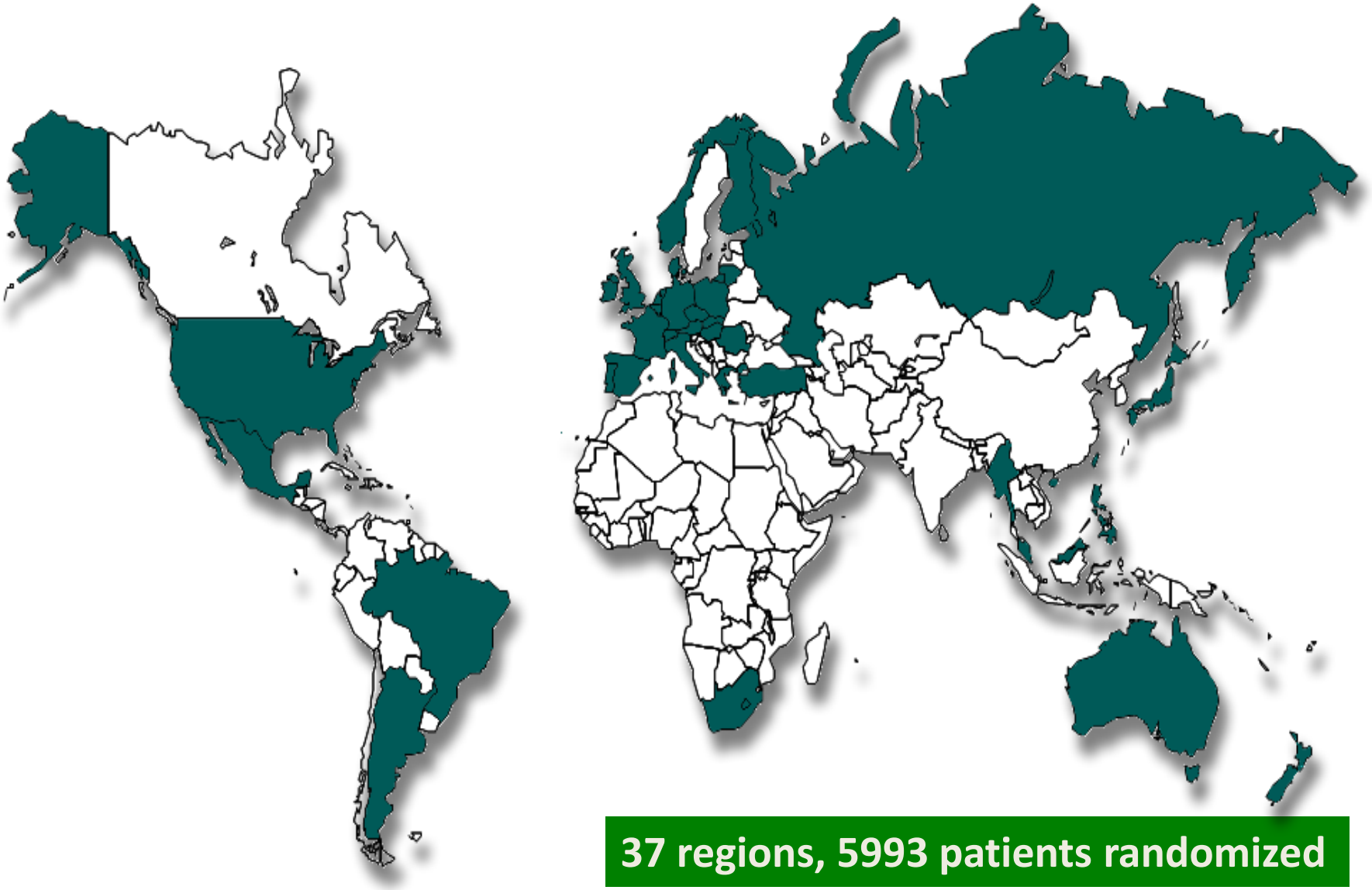
- ***TIOSPIR STUDY*** **(The Tiotropium Safety and Performance In Respimat®)**

UPLIFT®

UNDERSTANDING POTENTIAL LONG-TERM IMPACTS ON FUNCTION WITH TIOTROPIUM

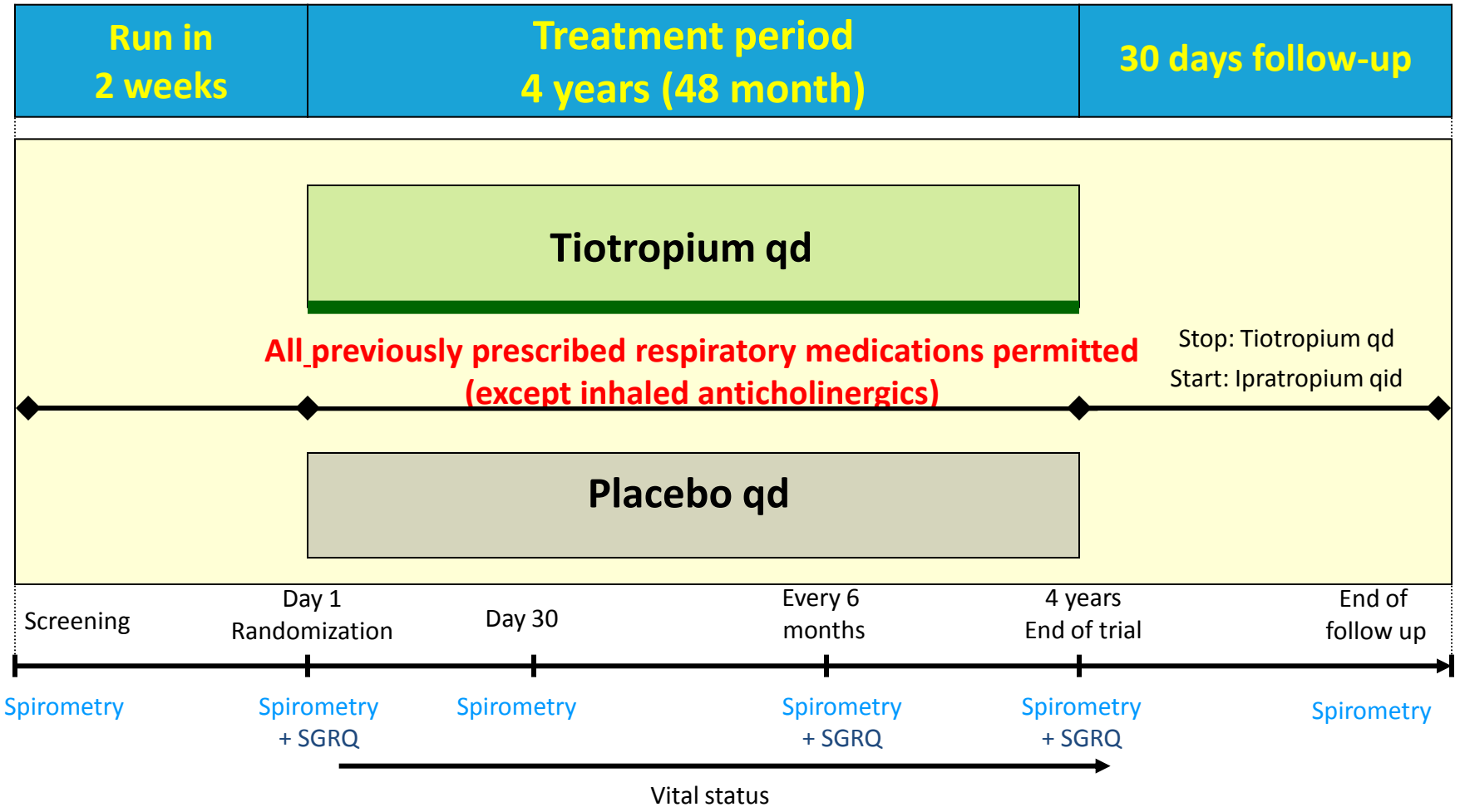
- **5993 patients randomized to tiotropium or usual care for 4 years**
- **Outcome = trough FEV_1**

UPLIFT : Understanding Potential Long-term Impacts on Function with Tiotropium Study



37 regions, 5993 patients randomized

STUDY DESIGN



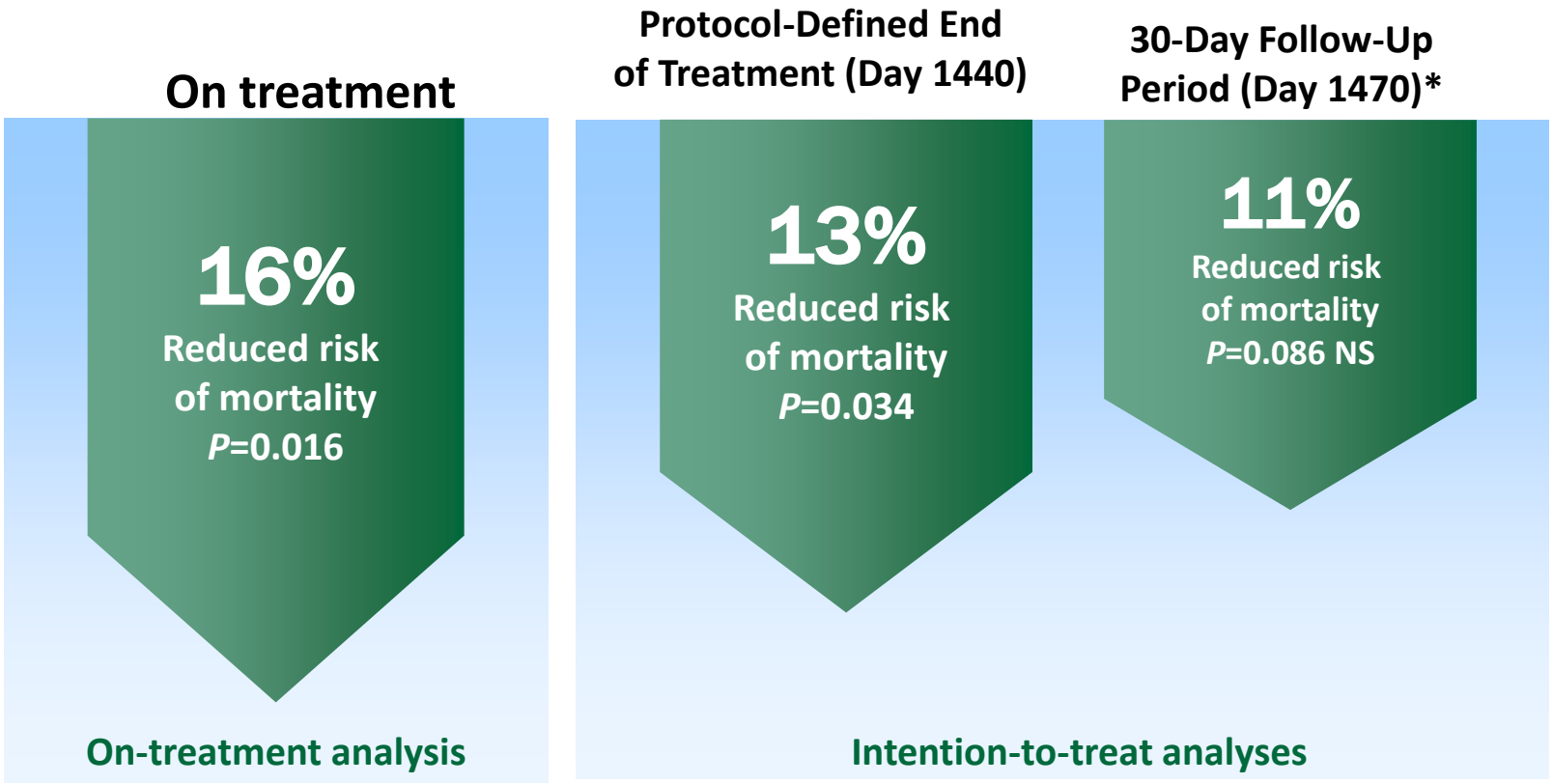
Summary of Result- Efficacy

- Improvement in FEV_1, FVC and SVC maintained throughout study
  - No effect on rate of decline of FVC and SVC.
- Improvement in SGRQ maintained throughout study
  - Tiotropium group similar to baseline after 4 years treatment
- Reduction in number of exacerbations and reduction in risk for exacerbation and hospitalization for exacerbations

Summary - Safety

- Reduced mortality
- Evidence for reduced cardiac morbidity
  - No increased risk for stroke or myocardial infarction
- Reduced lower respiratory morbidity
  - Decreased risk for adverse event reports of dyspnea, exacerbations, respiratory failure
  - No increased risk of pneumonia

UPLIFT: Reduced Risk of Mortality



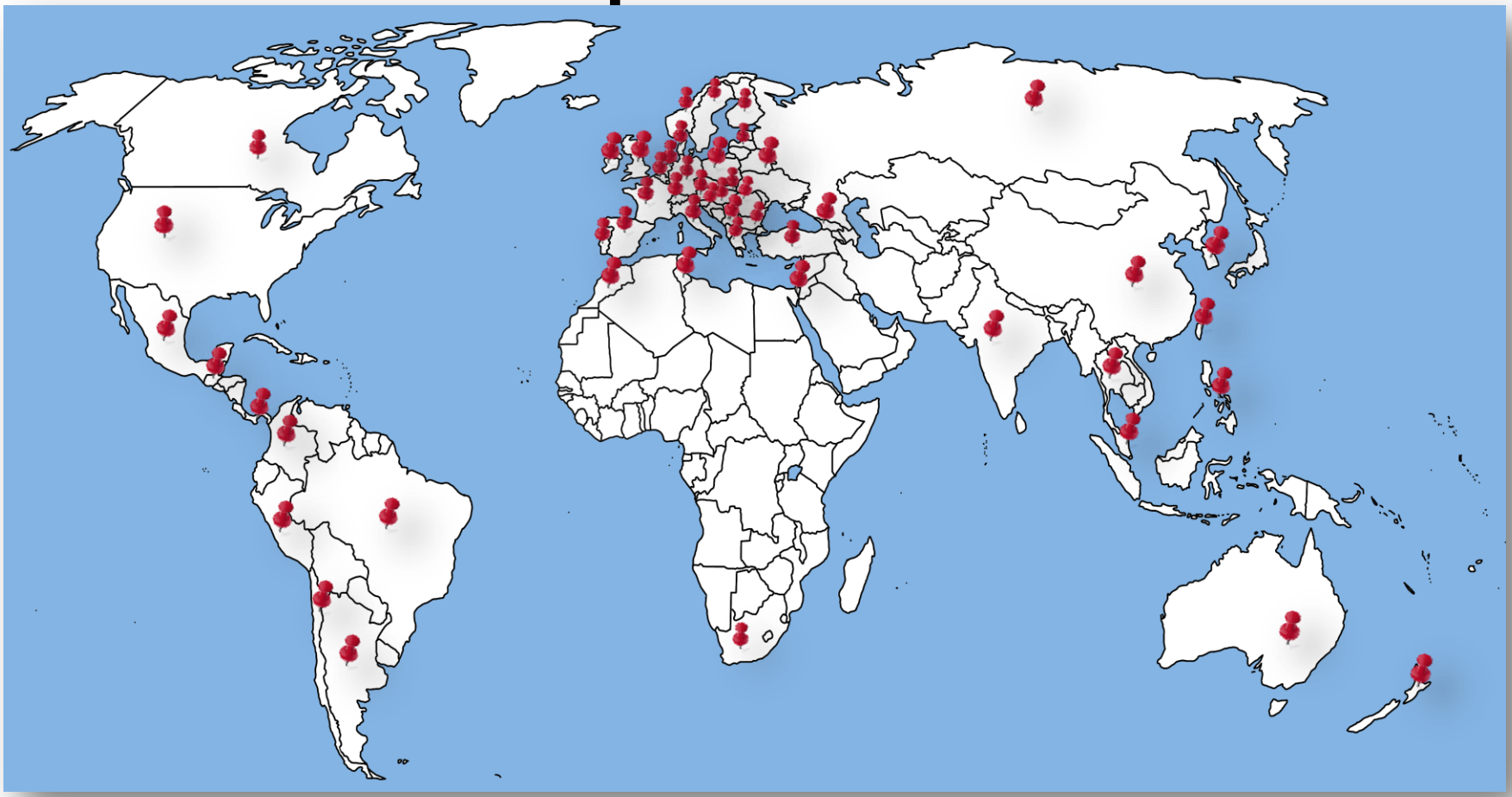
- 16% lower mortality risk with tiotropium while patients received study medication
- Effect extended to end of treatment period (day 1440), as defined by protocol
- Effect became non-significant within the 30-day follow-up period (day 1470), when according to protocol, patients were discontinued from their study medication

Tashkin DP et al. *N Engl J Med.* 2008;359:1543-1554.

TIOSPIR

The Tiotropium Safety and Performance in Respimat® Trial

The Tiotropium Safety and Performance in Respimat® Trial



Countries: 50, Sites/centres: 1202, Patients: 17,183 randomized ,17,135 treated, 77% completed with 99.7% vital status follow up.
Enrollment: May 2010 to April 2011. Trial completed: May 2013

Wise RA, et al. *N Engl J Med.* 2013;369.DOI:10.1056/NEJMoa1303342.

- Tiotropium delivered via the Respimat soft mist inhaler has been shown to be associated with a significantly increased risk of mortality compared with placebo. Caution is urged until further studies designed to compare delivery devices and doses are reported.

1. Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ 2011;342:d3215
2. Karner C, Chong J, Poole P . Tiotropium versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2012 Jul 11;7:CD009285
3. Beasley R, Singh S, Loke YK, Enright P, Furberg CD. Call for worldwide withdrawal of tiotropium Respimat mist inhaler. BMJ 2012 Nov 345:e7390.520.

Objective of Study

- To compare the ***efficacy*** and ***safety*** of tiotropium delivered via ***Respimat®*** with tiotropium delivered via ***HandiHaler®***

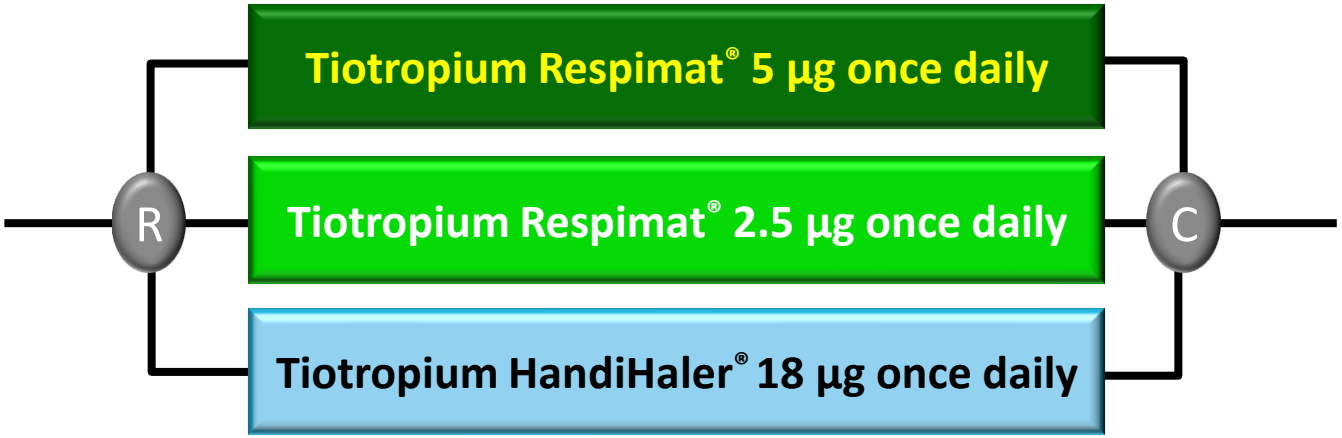
Wise RA, et al. *Respir Res.* 2013;14:40. Wise RA, et al. ERS 2013.

Summary of Study Design

- Design:
  - Multicentre, randomized, active-controlled, double-blind, parallel-group trial.
  - Treatment arms:
    - Tiotropium Respimat® 5 µg (two inhalations of 2.5 µg, once daily)
    - Tiotropium Respimat® 2.5 µg (two inhalations of 1.25 µg, once daily)
    - Tiotropium HandiHaler® 18 µg (once daily)
- Patients :
    - Age ≥40 years, with a smoking history of ≥10 pack-years
    - Moderate to severe COPD (FEV_1 ≤70% predicted; FEV_1/FVC ratio ≤0.70)
- Sample size : 17,135 patients

Study Design

- Treatment time is 2-3 years, dependent on fatal events observed*



*Event-driven trial designed to end when approximately 1266 deaths reported.

C, close of study once the planned 1266 events have been reached;

Wise RA, et al. *Respir Res.* 2013;14:40.

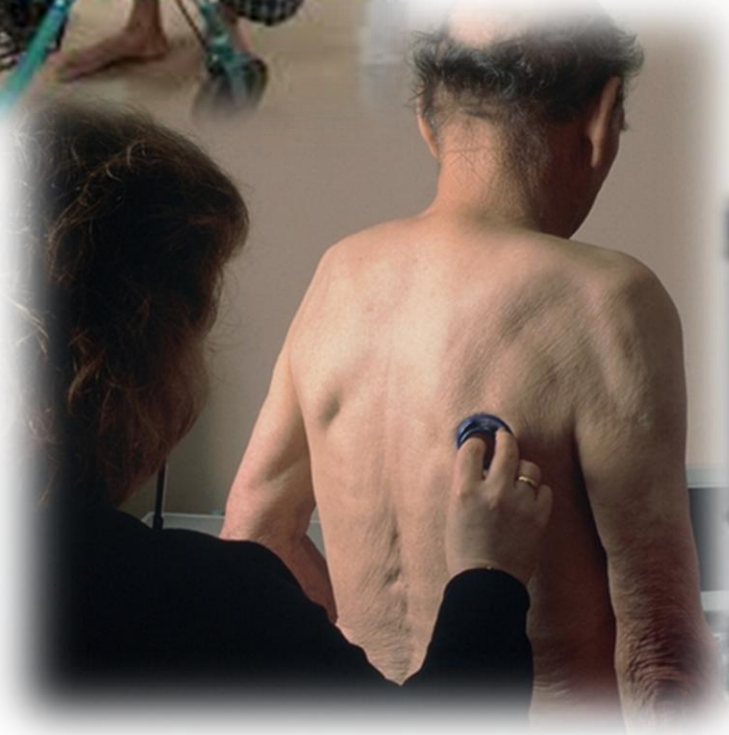
Unique Characteristics of TIOSPIR study

- One of the largest COPD trials ever performed
- Designed to provide a precise estimate of rare but relevant outcomes, mortality as well as exacerbations
- Compared the same active-treatment tiotropium in different marketed delivery systems and doses
- Absence of a placebo group, and patients were permitted to use their usual background treatments for COPD except other inhaled anticholinergics
- Event-driven trial with treatment continuing until approximately 1266 fatal events had occurred (ie, no set treatment period, but estimated 2-3 years)

Wise RA, et al. *Respir Res.* 2013;14:40. Wise RA, et al. ERS 2013.

ENDPOINT RESULTS

1. SAFETY
2. EFFICACY



TIOSPIR Overall summary and conclusions (I)

- Tiotropium Respimat® was not associated with higher mortality compared to HandiHaler®, including patients with prior cardiac disease and cardiac arrhythmia at baseline
- No difference was observed between treatment groups in time to first exacerbation, time to first severe (hospitalized) exacerbation or exacerbation frequency
- Overall, there were no differences between treatment groups in terms of serious AEs, nonfatal and fatal MACE, nor incidence of arrhythmias during the study

Wise RA, et al. *N Engl J Med.* 2013;369.DOI:10.1056/NEJMoa1303342.

AE, adverse event; MACE, major adverse cardiovascular event; MI, myocardial infarction

Variable	Respimat® 2.5 µg (N=5730)	Respimat® 5 µg (N=5711)	HandiHaler® 18 µg (N=5694)	Comparison	HR (95% CI)	*P*-value
Mortality (vital status follow-up), n (%)	440 (7.7)	423 (7.4)	439 (7.7)	Respimat® 5 µg versus HandiHaler	0.96 (0.84,1.10)	*
				Respimat® 2.5 µg versus HandiHaler	1.00 (0.87,1.14)	*
Rate of events (per 100 patient-years)	3.35	3.22	3.36			
Mortality (on treatment), n (%)	359 (6.3)	326 (5.7)	357 (6.3)	Respimat® 5 µg versus HandiHaler®	0.91 (0.79,1.06)	
				Respimat® 2.5 µg versus HandiHaler®	1.00 (0.86,1.16)	

Incidence of death from any cause was similar across treatment groups

*Test for noninferiority was statistically significant (*P*<0.05).

Variable	Tiotropium Respimat® 2.5 µg (N=5730)	Tiotropium Respimat® 5 µg (N=5711)	Tiotropium HandiHaler® 18 µg (N=5694)	Comparison	HR (95% CI)	P-value
Adjudicated primary cause of death, n (%)						
CV death (fatal MACE)	119 (2.1)	113 (2.0)	101 (1.8)	Respimat® 5 µg versus HandiHaler®	1.11 (0.85, 1.45)	0.44
				Respimat® 2.5 µg versus HandiHaler®	1.17 (0.90, 1.53)	0.24
MI	10 (0.2)	11 (0.2)	3 (0.1)			
Sudden death*	82 (1.4)	67 (1.2)	68 (1.2)			
Other CV†	17 (0.3)	21 (0.4)	19 (0.3)			
Stroke	10 (0.2)	14 (0.2)	11 (0.2)			
Respiratory‡	143 (2.5)	148 (2.6)	155 (2.7)			
Neoplasms	110 (1.9)	100 (1.8)	95 (1.7)			
Death, undetermined/ unknown	35 (0.6)	27 (0.5)	37 (0.6)			
Other	33 (0.6)	35 (0.6)	51 (0.9)			
Mortality in patients with history of cardiac arrhythmia (vital status follow-up), n (%)§	79 (13.1)	65 (10.6)	78 (12.9)	Respimat® 5 µg versus HandiHaler®	0.81 (0.58, 1.12)	
				Respimat® 2.5 µg versus HandiHaler®	1.02 (0.74, 1.39)	

Causes of death, including from CV causes, were similar across treatment groups

Anticholinergics. The most important effect in COPD patients of anticholinergic medications, such as ipratropium, oxitropium and tiotropium bromide, appears to be blockage of acetylcholine's effect on muscarinic receptors. Current short-acting drugs block M2 and M3 receptors and modify transmission at the pre-ganglionic junction, although these effects appear less important in COPD[207]. The long-acting anticholinergic tiotropium has a pharmacokinetic selectivity for the M3 and M1 receptors[208]. The bronchodilating effect of short-acting inhaled anticholinergics lasts longer than that of short-acting beta$_2$-agonists, with some bronchodilator effect generally apparent up to 8 hours after administration[191]. Among long-acting anticholinergics, acclidinium has a duration of at least 12 hours[552] whereas tiotropium and glycopyrronium have a duration of action of more than 24 hours[209-211]. Tiotropium reduces exacerbations and related hospitalizations, improves symptoms and health status[212] (**Evidence A**), and improves the effectiveness of pulmonary rehabilitation[213] (**Evidence B**). In a large, long-term clinical trial on patients with COPD, there was no effect of tiotropium added to other standard therapies on the rate of lung function decline and no evidence of cardiovascular risk[214]. In another large trial, tiotropium was superior to salmeterol in reducing exacerbations although the difference was small[215,517]. The long-acting anticholinergics aclidinium and glycopyrronium seem to have similar action on lung function and breathlessness as tiotropium, whereas far less data are available for other outcomes[552, 558].

GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE,

UPDATED 2014

2013

Adverse effects. Anticholinergic drugs are poorly absorbed which limits the troublesome systemic effects seen with atropine[216]. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of the mouth. Twenty-one days of inhaled tiotropium, 18 mcg/ day as a dry powder, does not retard mucus clearance from the lungs[144]. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal relationship. Some patients using ipratropium report a bitter, metallic taste. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported and requires further investigation[217,218]. Tiotropium delivered via the Respimat soft mist inhaler has been shown to be associated with a significantly increased risk of mortality compared with placebo. Caution is urged until further studies designed to compare delivery devices and doses are reported[219,518,519]. Use of solutions with a facemask has been reported to precipitate acute glaucoma, probably by a direct effect of the solution on the eye.

2014

Adverse effects Anticholinergic drugs are poorly absorbed which limits the troublesome systemic effects seen with atropine[216]. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of the mouth. Twenty-one days of inhaled tiotropium, 18 mcg/ day as a dry powder, does not retard mucus clearance from the lungs[144]. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal relationship. Some patients using ipratropium report a bitter, metallic taste. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported and requires further investigation[217,218]. Tiotropium delivered via the Respimat® soft mist inhaler was associated with a significantly increased risk of mortality compared with placebo in a meta-analysis[519]; however, the findings of the TIOSPIR® trial showed that there was no difference in mortality or rates of exacerbation when comparing tiotropium in a dry-powder inhaler to the Respimat® inhaler[559]. Use of solutions with a face mask has been reported to precipitate acute glaucoma, probably by a direct effect of the solution on the eye.

DEVICE

RESPIMAT®

Soft Mist™ Inhaler

Device-related Factors That Influence the Success of Inhaled Respiratory Medication

Particle size[1-2]

- MMAD <10 µm allows particles to deposit in airways
- MMAD 2-5 µm required to reach peripheral airways and alveolar regions

Aerosol velocity[3]

- Influences extent of lung deposition; rapid drug cloud expulsion (MDIs) can result in preferential deposition of drug in the oropharynx
- There may be difficulty in synchronizing inhaler actuation and inspiration

Device internal resistance[4]

- Defines the patient's maximal inspiratory flow rate
- Inadequate delivery technique can lead to suboptimal clinical response[5]

1. Dalby R, et al. *Int J Pharm.* 2004;283:1-9. 2. Barnes PJ. *Pulmonary Pharmacology*, Chapter 36. 3. Hochrainer D, et al. *J Aerosol Med.* 2005;18:273-282. 4. Chrystyn H. *J Clin Pract.* 2007;61:1022-1036. 5. Vincken W, et al. *Prim Care Respir J.* 2010;19:10-20.

Advantages and Limitations of Inhaler Devices

Device	Advantages	Limitations
pMDI	▶ Convenient and relatively inexpensive[2] ▶ Can be used in patients with low inspiratory flow rate[1] ▶ HFA-pMDI – reliable and effective in delivering inhaled medication[1]	▶ Requires coordination of actuation and inhalation[1,2]
DPI	▶ Breath-actuated so no need for actuation and inhalation coordination[1,2]	▶ Requires high inspiratory flow rates[2] ▶ Sensitive to humidity[1]
SMI	▶ "Best of both worlds": minimal coordination required (as for DPIs) and no/hardly any inspiratory effort needed (as for pMDIs) ▶ Propellant-free[2] ▶ High lung / low oropharyngeal deposition due to slow-moving aerosol[2] ▶ High fine-particle fraction[2] ▶ Efficient drug delivery even with poor inhalation technique[2,3]	▶ Relatively expensive

1. Beaucage D, Nesbitt S. Using Inhalation devices. In: Bourbeau J, Nault D, Borycki E, eds. Comprehensive management of COPD. Hamilton, Ontario, Canada: BC Decker, 2002:83-107;
2. Hodder R, Price D. *Int J COPD.* 2009;4:381-390; 3. Brand P, et al. *Int J COPD.* 2008;3:763-770.

COMPARISON OF "IDEAL" INHALER CRITERIA

Design characteristics of the ideal inhaler	MDI	DPI	Respimat® SMI
Majority of aerosol cloud <5.8 μm in size			✓
Low cloud velocity		✓	✓
Slow release of aerosol		✓	✓
Cloud generation independent of patient inspiratory flow rate	✓		✓
Breath actuated/simple coordination		✓	✓
Dosing and delivery independent of external conditions	✓		✓
Absence of propellants to avoid environmental effects		✓	✓
Simple to operate	✓	✓	✓
Convenient and portable	✓	✓	✓
Robust	✓	✓	✓
Multiple doses to reduce preparation time	✓	✓	✓
Include a dose counter/indicator	✓	✓	✓
Contains other feedback aids to reassure patients of correct drug delivery		✓	
Ease of use in young children	✓		✓

MDI, metered-dose inhaler; DPI, dry powder inhaler; SMI, Soft Mist™ inhaler

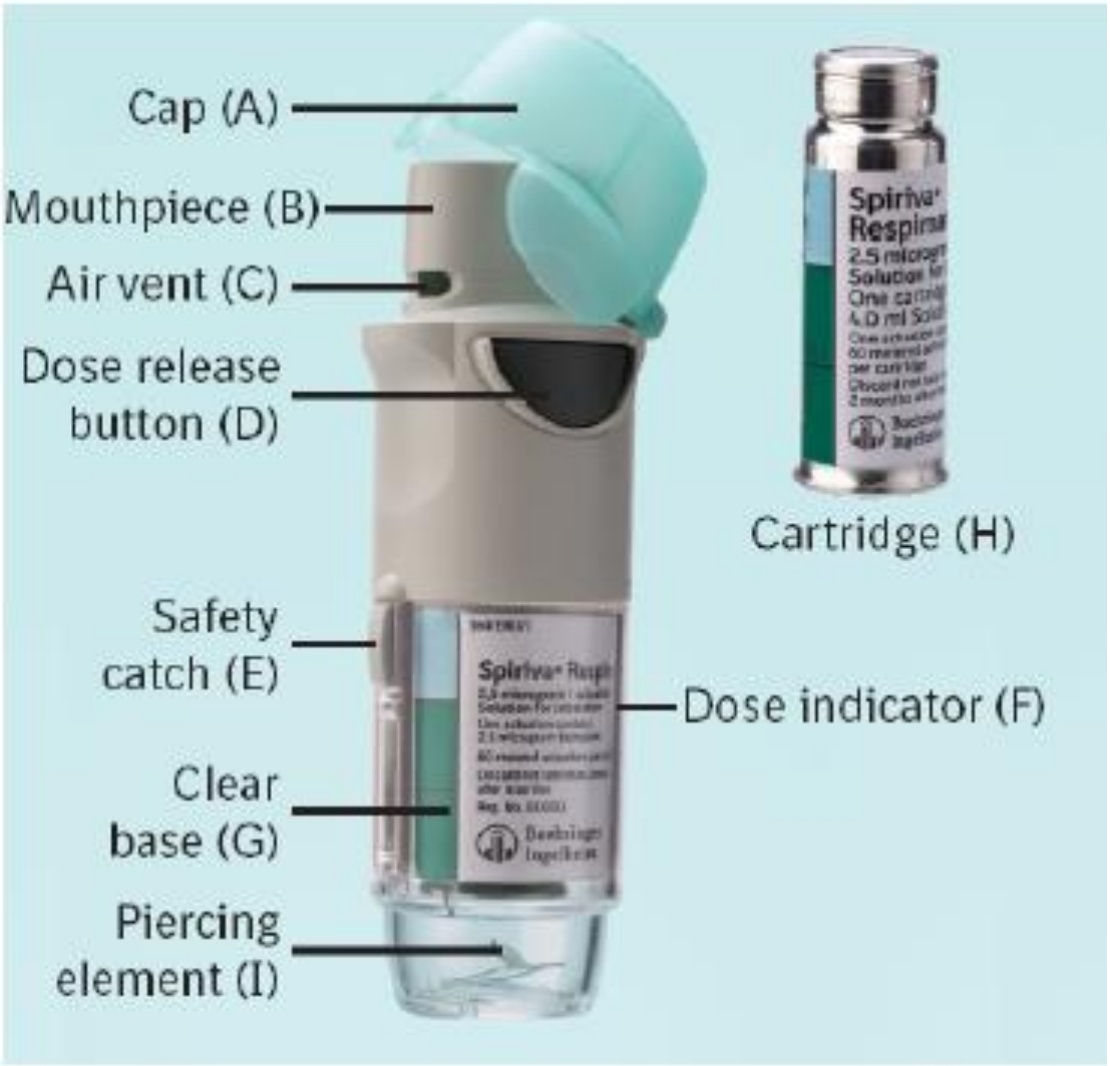
Ari A, et al. *Expert Rev Respir Med.* 2011;5:561-572. Chrystyn H. *Int J Clin Pract.* 2007;61:1022-1036; Dalby R, et al. *Int J Pharm.* 2004;283:1-9. Ganderton D. *J Aerosol Med.* 1999;12(Suppl 1):S3-S8. Hochrainer D, et al. *J Aerosol Med.* 2005;18:273-282. Vincken W, et al. *Prim Care Respir J.* 2010;19:10-20.

Respimat® SMI

- A new-generation, propellant-free inhaler developed as an innovative approach to inhalation therapy
- Delivers a metered dosage of medication as a fine mist
- Designed to overcome problems such as:
  - Limited drug deposition in the lung
  - Reliance on adequate patient coordination for effective inhalation
- Spiriva: delivered dose 2.5 µg per puff

www.respimat.com

Components of Respimat® SMI

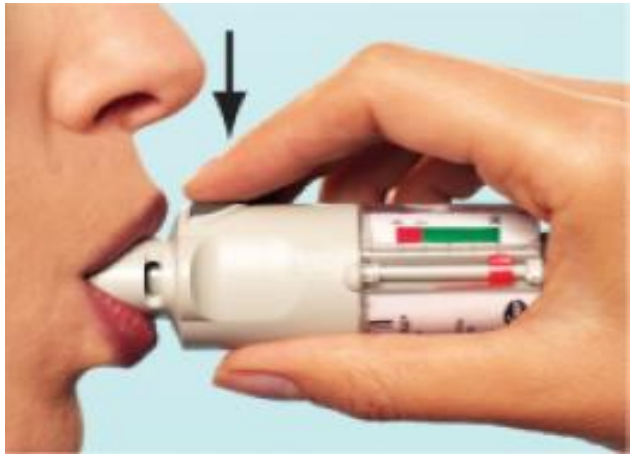


SMI, Soft Mist™ Inhaler

RESPIMAT is as easy as…

T – urn

O – pen



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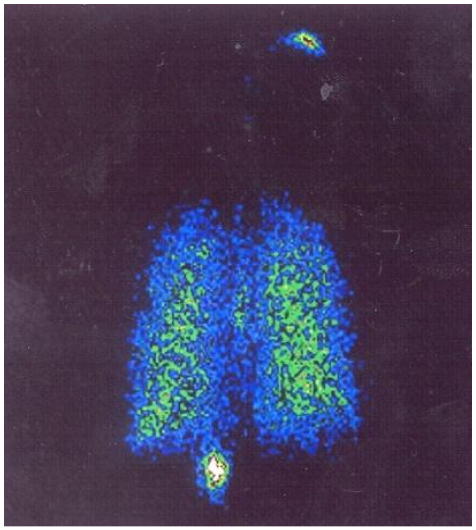
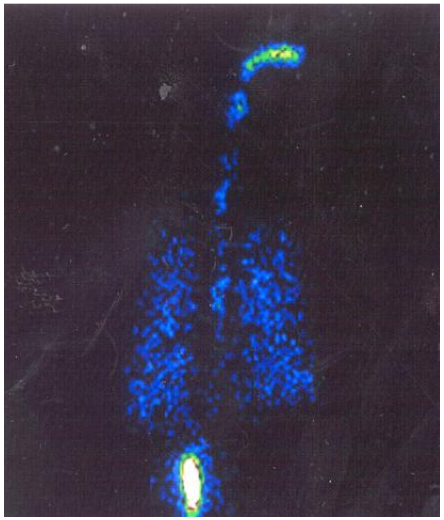
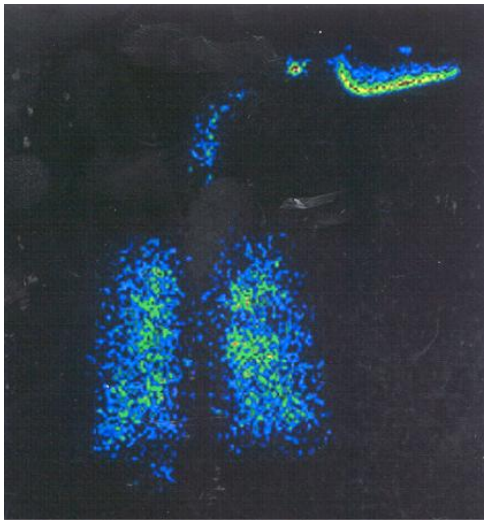
Respimat® SMI Performance Comparison Versus Other Inhalers

Respimat® SMI : Higher Lung Deposition With Versus CFC-pMDI





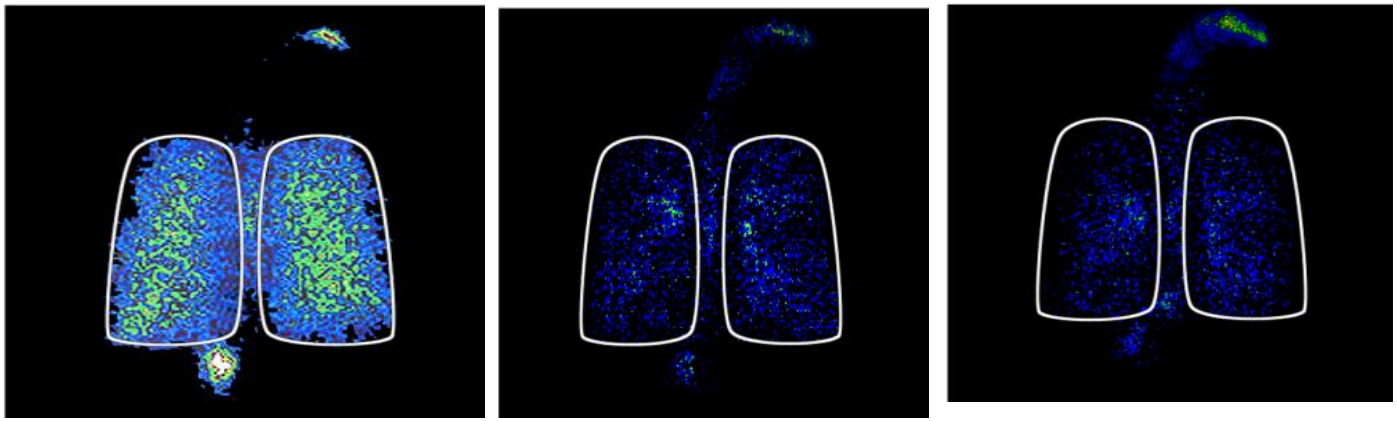


Deposition of fenoterol and flunisolide	Respimat®	MDI	MDI plus Aerochamber
Lung deposition (%)	39.2	11.0	9.9
Oropharyngeal deposition (%)	37.1	71.7	3.6

CFC-pMDI, chlorofluorocarbon pressurized metered-dose inhaler; MDI, metered-dose inhaler; SMI, Soft Mist™ Inhaler

Newman SP, et al. *Chest* 1998;113;957-963

Respimat® SMI : Higher Lung Deposition Versus Turbuhaler



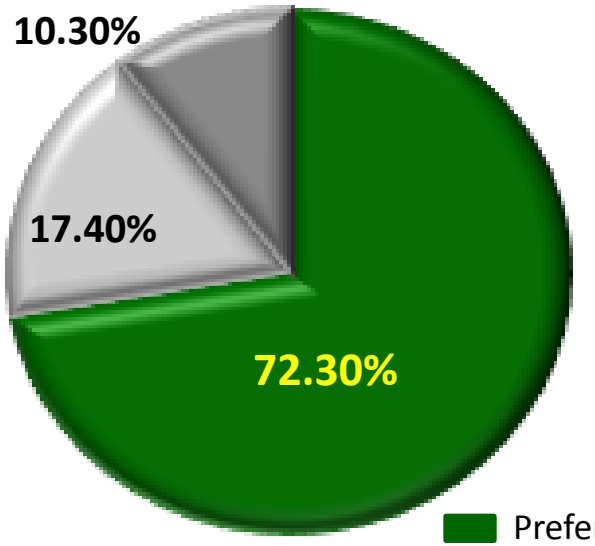
Deposition of budesonide	Respimat® (30 L/min)	Turbuhaler® Fast Inspiratory Q (60 L/min)	Turbuhaler® Low Inspitatory Q (30 L/min)
Lung deposition (%)	51.6	28.5	17.8
Oropharyngeal deposition (%)	19.3	49.3	40.5

Q, flow; SMI, Soft Mist™ Inhaler

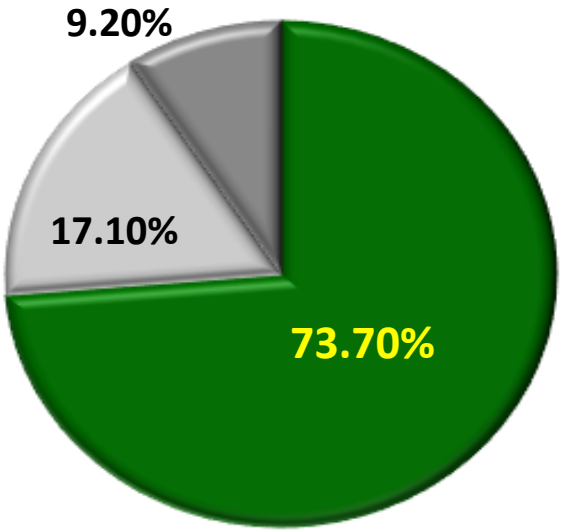
Pitcairn G, et al. *J Aerosol Med*. 2005;18:264-272

Is Respimat® Well Accepted in Asthma and COPD Patients ?

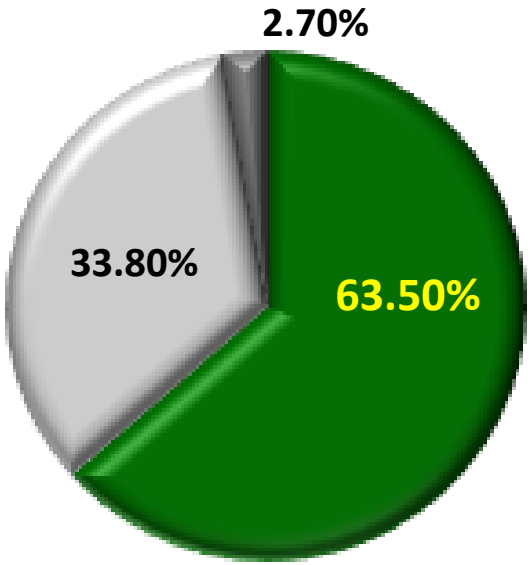
A: versus pMDI
Clinical study[2] (n=224)



B: versus Turbuhaler
Clinical study[3] (n=153)



C: versus Diskus
Observational study[4] (n=150)



Preferred Respimat® SMI
Preferred other inhaler
No preference for either device, or no reply

COPD, chronic obstructive pulmonary disease; PASAPQ, Patient Satisfaction and Preference Questionnaire; pMDI, pressurized metred-dose inhaler; SMI , Soft Mist™ inhaler

1. Hodder R, et al. *Int J COPD*. 2009;4:381-390. 2. Schürmann W, et al. *Treat Respir Med*. 2005;4:53-61. 3. Hodder R, et al. *Int J COPD*. 2009;4:225-232. 4. Freytag F, et al. *Am J Respir Crit Care Med*. 2007;175:A639.

Patient Satisfaction Summary

Patients:

- Find Respimat® SMI easy to use
- Find Respimat® SMI easy to assemble
- Show increased willingness to continue using Respimat® SMI
- Prefer Respimat® SMI over HFA-MDI, Turbuhaler® and Diskus®


THANK YOU