

Treatment choices for patients with asthma or COPD

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Lead Nurse For Oxfordshire
Respiratory Service

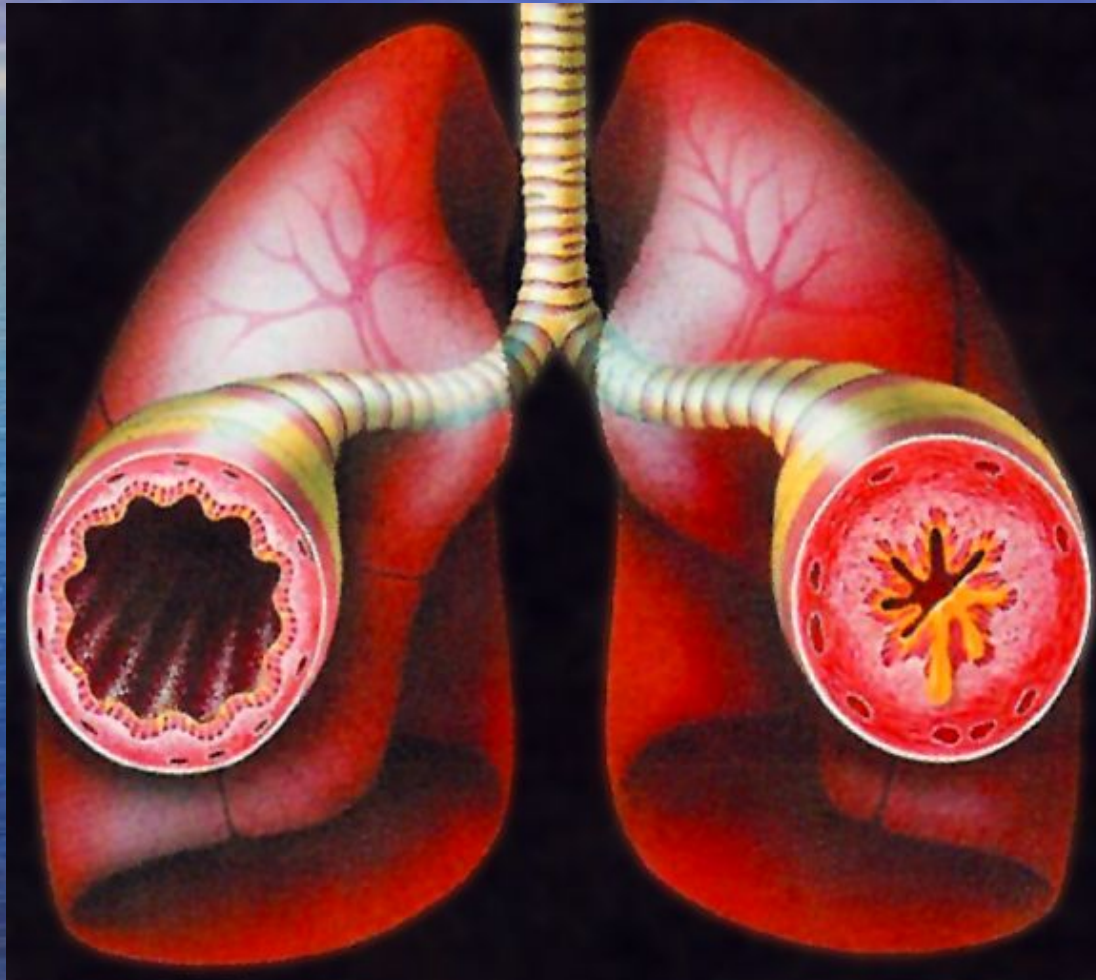
What is the difference?

- Is it all about ?–
 - Inhaled steroids
 - Long acting β_2 agonists
 - Short acting β_2 agonists
- Where do these fit in?
 - Short acting anticholinergics
 - Long acting anticholinergics

What is the difference?

- Used at different stages of the diseases
- Different doses
- Different outcomes
- Different licenced indications

Asthma



Basement
membrane

Epithelium

Mucous plug

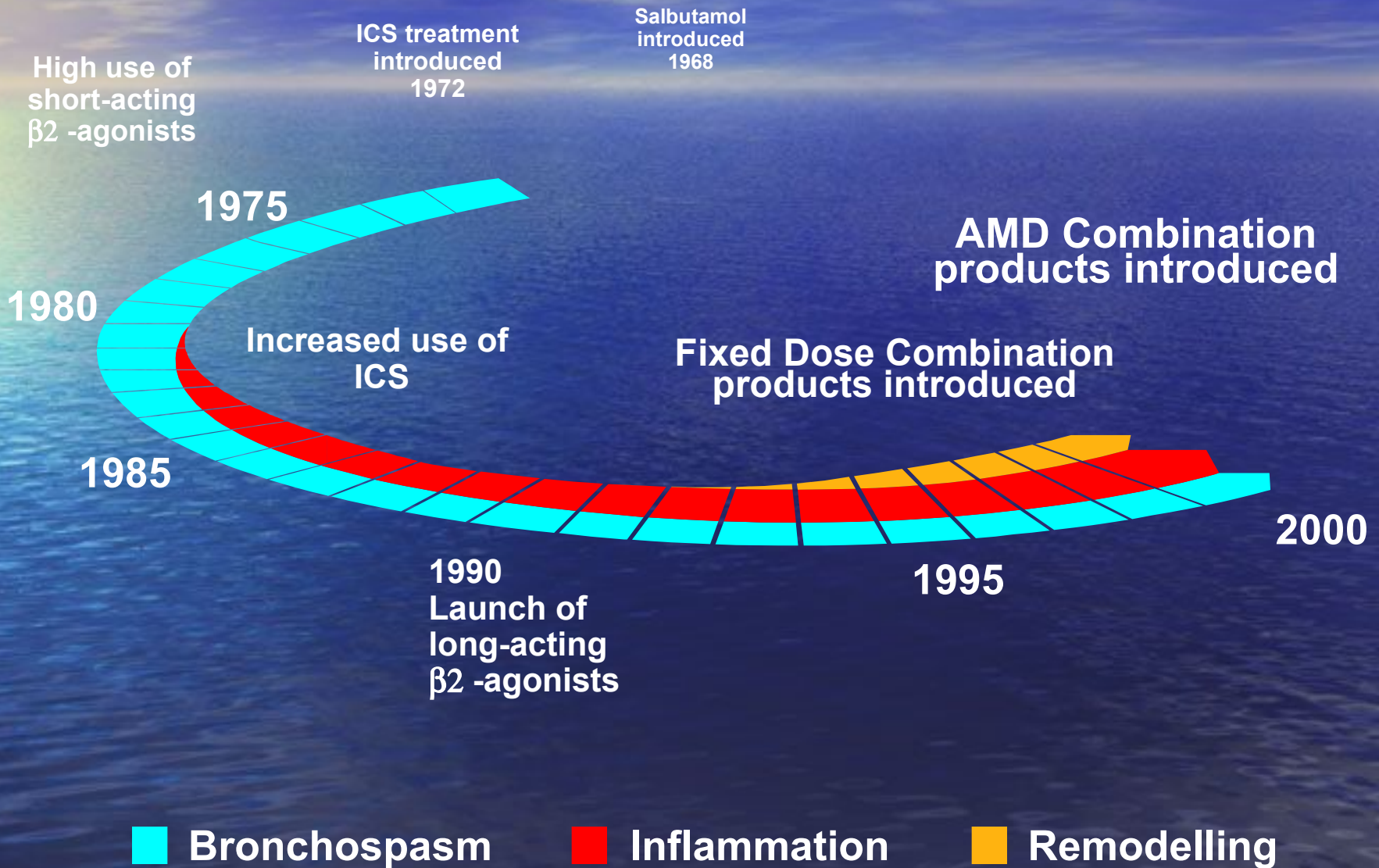
Smooth muscle

Mucous glands

Aims of asthma Treatment - 2008

- No daytime symptoms
- No Night time waking due to asthma
- No exacerbations
- No need for rescue β 2 agonist
- No activity limitation
- Normal lung function (FEV1 >80%)
- Minimal/no adverse effects for medication

Progression of asthma therapy



Inhaled short-acting β_2 agonist as required

appropriate to the
and reconsider
daily poor.

IN LOWEST CONTROLLING STEP

MOVE UP TO IMPROVE CONTROL AS NEEDED

200-800

appropriate
by patients

led
to

1. Add inhaled long-acting β_2 agonist (LABA)
2. Assess control of asthma:
 - good response to LABA - continue LABA
 - benefit from LABA but control still inadequate - continue LABA and increase inhaled steroid dose to 800 mcg/day* (if not already on this dose)
 - no response to LABA - stop LABA and increase inhaled steroid to 800 mcg/day.* If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or SR theophylline

STEP 3

Initial add-on therapy

Consider trials of:

- increasing inhaled steroid up to 2000 mcg/day*
- addition of a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, β_2 agonist tablet

STEP 4

Persistent poor control

Use daily steroid tablet in lowest dose providing adequate control

Maintain high dose inhaled steroid at 2000 mcg/day*

Consider other treatments to minimise the use of steroid tablets

Refer patient for specialist care

STEP 5

Continuous or frequent use of oral steroids

STEP 1

Mild intermittent asthma

SYMPTOMS

vs

TREATMENT

* BDP or equivalent

therapy

Stepping up treatment?

- Check compliance with existing therapies
- Check understanding
- Check Inhaler technique
- Eliminate trigger factors where possible

Adults

Patients should start at initial severity of their diagnosis if resp

Add inhaled steroid 200-800 mcg/day*
400 mcg is an appropriate starting dose for many patients

Start at dose of inhaled steroid appropriate to severity of disease.

MOVE DOWN

Inhaled short-acting β_2 agonist as required

STEP 1

Mild intermittent asthma

STEP 2

Regular preventer therapy

long-acting LABA
level of asthma
response to
continue LABA
on LABA but
if inadequate
LABA and
inhaled steroid
200 mcg/day* (if
on this dose)
add LABA
and increase
steroid to 800
mcg/day*
If control
adequate, institute
other therapies,
e.g. leukotriene
receptor
antagonist or SR
theophylline

STEP 3

Low-dose LABA on therapy

MOVING STEP

MOVE UP TO IMPROVE CONTROL AS NEEDED

Consider trials of:

- increasing inhaled steroid up to 2000 mcg/day*
- addition of a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, β_2 agonist tablet

STEP 4

Persistent poor control

Use daily steroid tablet in lowest dose providing adequate control

Maintain high dose inhaled steroid at 2000 mcg/day*

Consider other treatments to minimise the use of steroid tablets

Refer patient for specialist care

STEP 5

Continuous or frequent use of oral steroids

TREATMENT

* BDP or equivalent

Introducing inhaled steroids

- Adults or children
 - using inhaled beta 2 agonist 3 times a week or more
 - having symptoms 3 times a week or more
 - Waking at night once a week or more
- Consider in adults and children who have had an exacerbation requiring oral steroids in the last 2 years

Which inhaled steroid?

- Beclometasone –either
 - Qvar (100mcg – 400mcg daily in adults) or
 - Clenil modulate (200mcg-800 mcg daily in adults)
- Budesonide (200 – 800mcg daily in adults)
- Fluticasone (100 – 400mcg daily in adults)
- Ciclesonide (160mcg daily in adults)
- Mometasone (400 – 800mcg daily in adults)

Patients should start treatment at the step most appropriate to their initial severity of their asthma. Check concordance and diagnosis if response to treatment is unexpected

MOVE DOWN TO FIND AND MAINTAIN

Add inhaled steroid 400 mcg/day*
400 mcg is an appropriate starting dose for most patients.
Start at dose of inhaled steroid appropriate to severity of disease.

STEP 2
Regular preventive therapy

Inhaled short-acting β_2 agonist as required

STEP 1
Mild intermittent asthma

1. Add inhaled long-acting β_2 agonist (LABA)
2. Assess control of asthma:
 - good response to LABA - continue LABA
 - benefit from LABA but control still inadequate - continue LABA and increase inhaled steroid dose to 800 mcg/day* (if not already on this dose)
 - no response to LABA - stop LABA and increase inhaled steroid to 800 mcg/day. *If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or SR theophylline

STEP 3
Initial add-on therapy

GO UP TO IMPROVE CONTROL AS NEEDED

Options of:
- 800 mcg inhaled steroid
- 800 mcg/day*
- or a fourth drug
- leukotriene receptor antagonist, SR theophylline, or oral steroid

STEP 4
Persistent poor control

Use daily steroid tablet in lowest dose providing adequate control

Maintain high dose inhaled steroid at 2000 mcg/day*

Consider other treatments to minimise the use of steroid tablets

Refer patient for specialist care

STEP 5
Continuous or frequent use of oral steroids

* BDP or equivalent

Step 3: Initial add-on therapy

- The first choice as add-on therapy to inhaled steroids in adults and children(5-12 years) is an inhaled long-acting beta₂ agonist (LABA)
- Adding a LABA should be considered before going above a dose of 400 mcg BDP or equivalent and certainly before going above 800mcg
- Long-acting beta₂ agonists are effective at providing bronchodilation over a sustained period. They increase lung function, improve symptoms and reduce incidence of exacerbation
- LABAs are not licensed as monotherapy in the treatment of asthma

MHRA advice on LABA's

- **At present the benefits of long-acting β 2 agonists outweigh the risks, and it is important that patients take their asthma medicine as prescribed to them. Patients should discuss any concerns regarding their asthma treatment with their doctor. Feb 2008**

<http://www.mhra.gov.uk/Safetyinformation/GeneralSafetyinformationandadvice/Product-specificinformationandadvice/Asthma/index.htm>

Combination inhalers

Section 4.3.3. BTS 2008

- “there is no difference in efficacy in giving inhaled steroid and long-acting β_2 agonist in combination or in separate inhalers”
- “Once a patient is on stable therapy, combination inhalers have the advantage of guaranteeing that the long-acting β_2 agonist is not taken without inhaled steroid”

Supported by Oxfordshire guidance in prescribing
“Points Bulletin Oxfordshire PCT Vol 17(1) 09
May 2008”

LABA's and combinations

- Salmeterol 50mcg BD
- Formoterol 6-24mcg BD
- Seretide 50 / 125 / 250mcg 2 BD
- Symbicort 100/6 / 200/6 1-2 BD

GOAL

Gaining Optimal Asthma control

Primary endpoint:

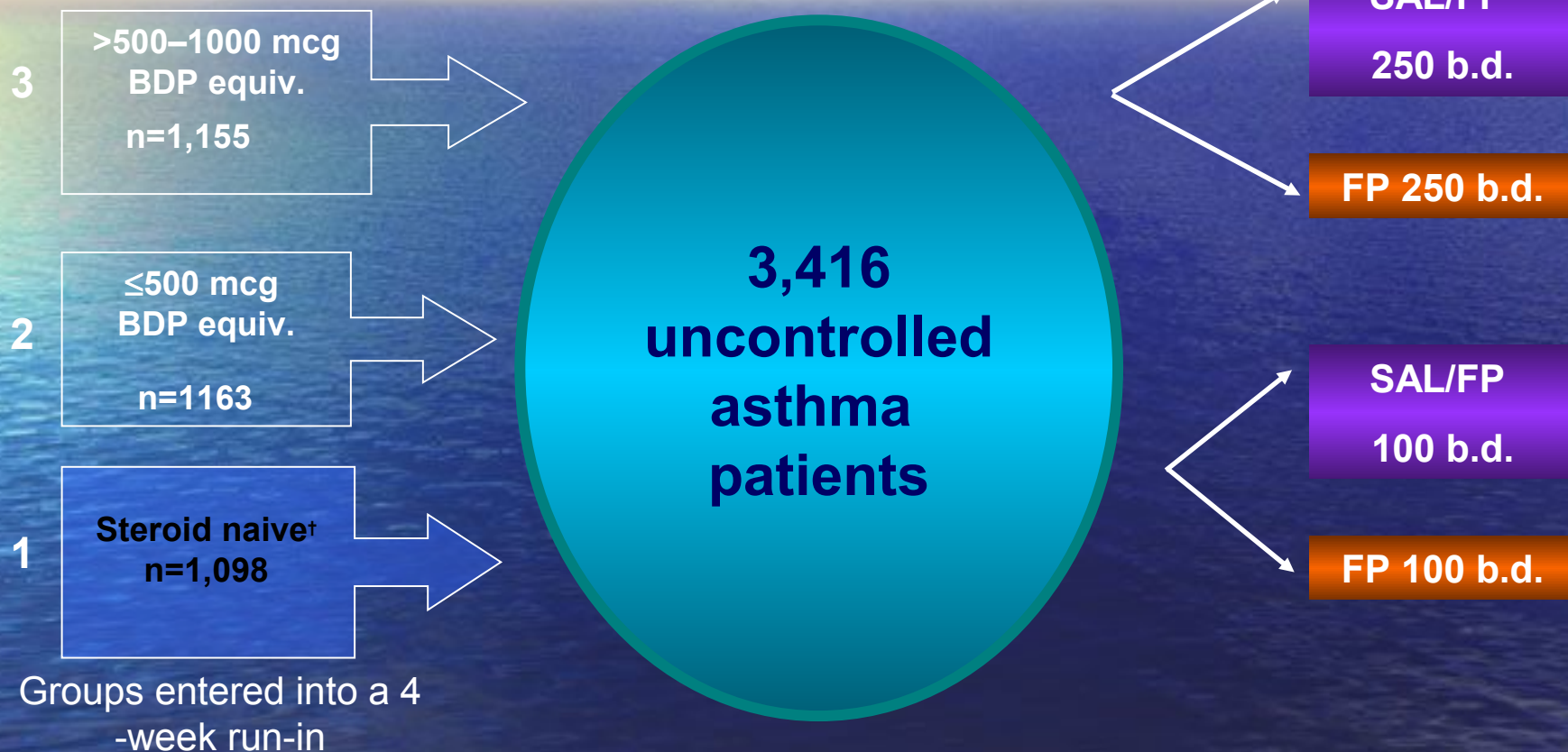
- Determine the proportion of patients who achieved **guideline-defined control** with SAL/FP (salmeterol/fluticasone propionate) compared to FP

Secondary Endpoints:

- Cumulative proportion of patients achieving control in phase II
- Dose of ICS and time to required to achieve first guideline-defined asthma week
- Proportion of patients who achieved Total Control
- Asthma Quality of Life Questionnaire
- Rate of exacerbations
- Morning predose FEV₁





GOAL study design

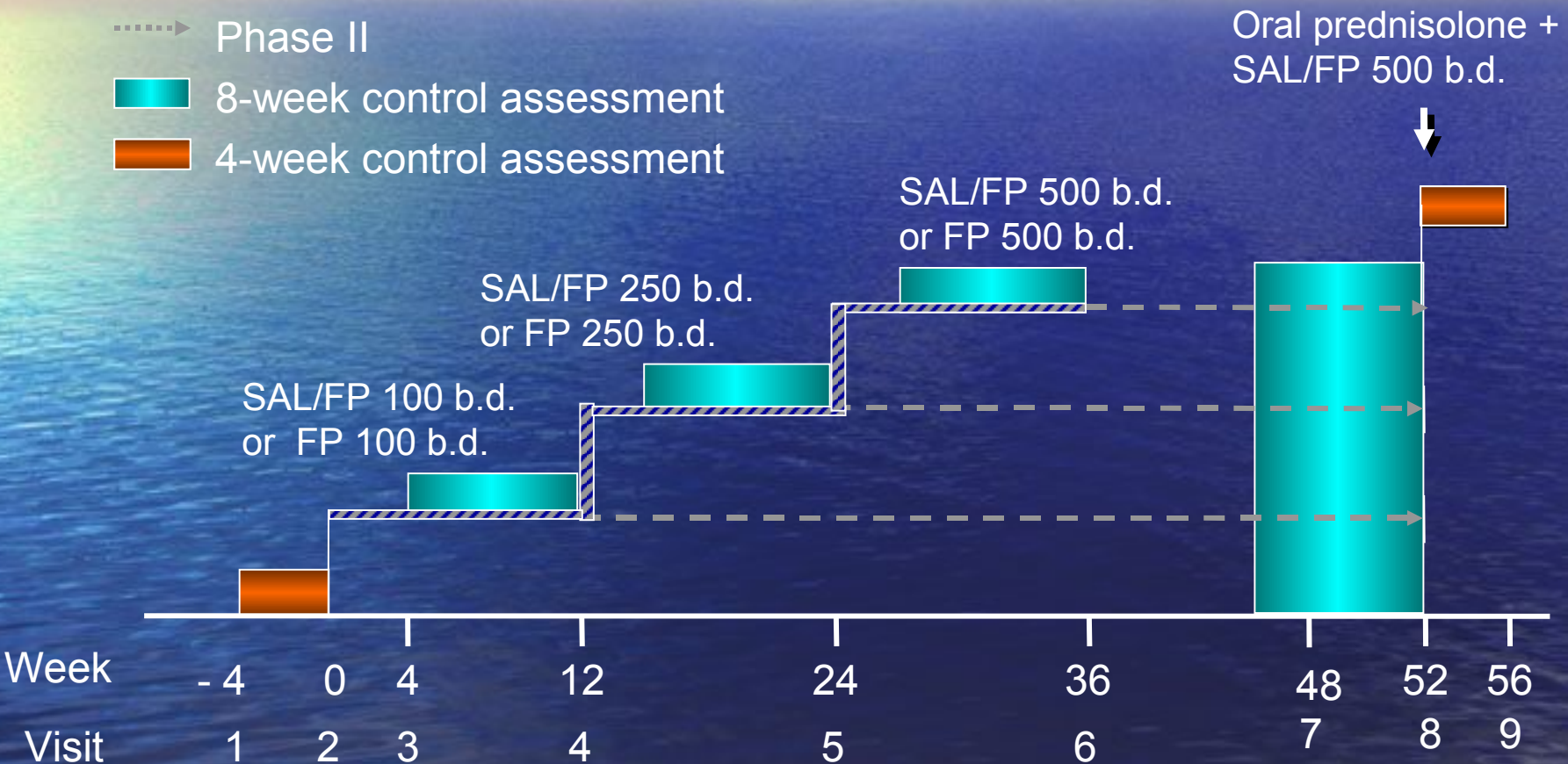
Study Strata – based on previous total daily dose of ICS



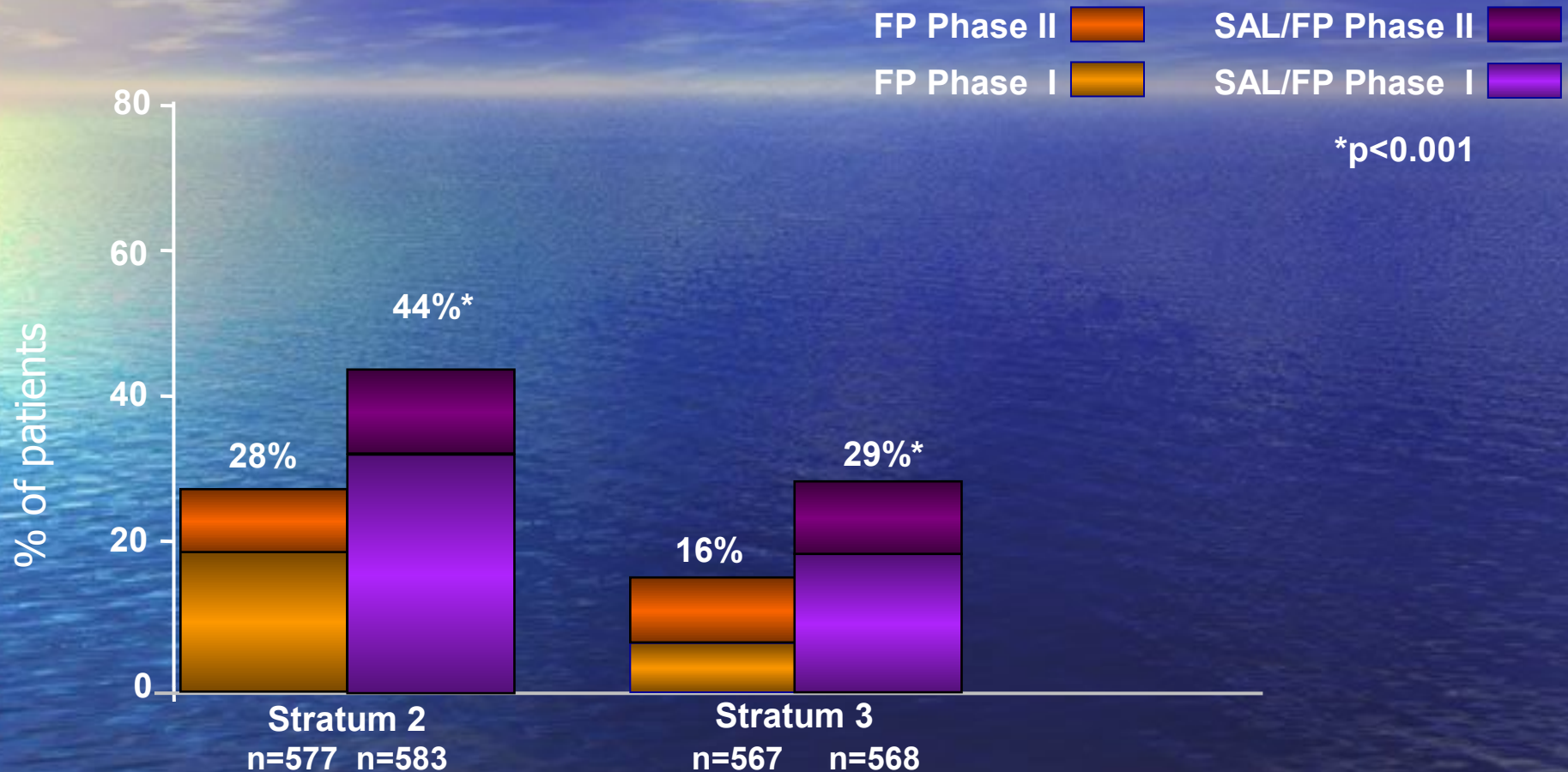
†Combination inhalers are not normally licensed for the treatment of steroid naïve patients

GOAL study plan stratum 1 and 2

-  Phase I
-  Phase II
-  8-week control assessment
-  4-week control assessment



Total Control: achieved with sustained treatment



Guideline-defined control: time to achieve control

Time to control (weeks)
- 50% of patients

FP

Seretide

Low dose ICS (S2)

7

2*

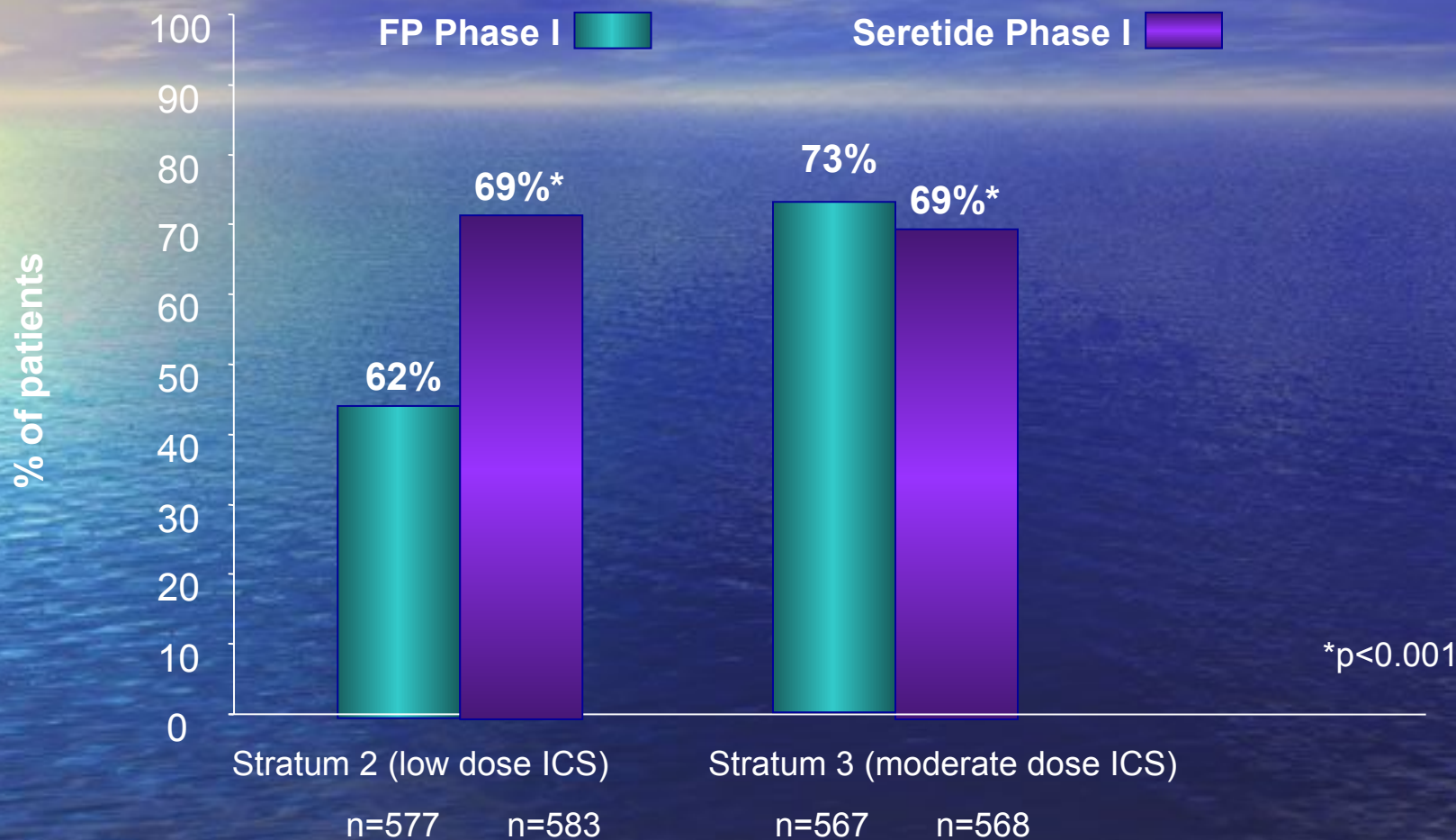
Moderate dose ICS (S3)

10

5*

* $p < 0.001$

Percentage of patients who still had Total Control at the end of 52 weeks



Boushey H *et al.* Abstract presented at the World Asthma Meeting, February 2004, Bangkok, Thailand.

GOAL conclusions

- Guideline-defined control is achievable and sustainable in a significant proportion of patients
- More patients achieve Guideline-defined control with SAL/FP than with FP alone, at a lower ICS dose
- SAL/FP compared with FP, more patients can achieve guideline-defined control:
 - Earlier
 - With fewer exacerbations
 - With more symptom free days
 - With more rescue free days
 - With a better quality of life

Symbicort "SMART"

A new approach to asthma
management for some of your
patients

What is Symbicort SMART®?

- The management of persistent asthma with a single inhaler as both maintenance and reliever medication
- Adult patients (18 years and over) take an adequate fixed maintenance dose, with additional reliever inhalations of Symbicort as needed
- The use of a separate reliever inhaler is NOT required*
- Symbicort SMART simplifies management



*A short-acting bronchodilator may be required for prophylaxis of exercise-induced asthma

Why is Symbicort[®] suitable for both maintenance and reliever therapy?

- Long acting beta agonist bronchodilators are not all the same
- Formoterol has rapid bronchodilator activity
 - Faster than salmeterol¹
 - Similar to salbutamol²
- Symbicort relieves bronchoconstriction faster than Seretide³

• Palmqvist *et al.* Eur Respir J 1997;
• Seberová E, Andersson A Respir. Med. 2000;
• Palmqvist M, *et al.* Pulm Pharmacol Ther 2001

Symbicort SMART[®] evidence base

Study	SMART	BUD §	Symbicort Fixed Dose §	Seretide §
Steam	200/12µg	400µg		
Step	400/12µg	800µg		
Stay	200/12µg	800µg	200/12µg	
Smile	400/12µg		* 400/12µg	
Compass	400/12µg		800/24µg	100/500µg
Cosmos	** 400-800/12-2 4µg			** 100/200-1000 µg

BUD: budesonide; § : plus SABA reliever medication; * : also LABA reliever medication;

** : dosage adjustable; Doses refer to total daily maintenance dose

Overall conclusions of Symbicort SMART studies

- Symbicort SMART consistently reduces the rate of severe exacerbations compared to other treatments
 - High-dose ICS + as needed SABA^{1 2 3}
 - Fixed dose Symbicort + as needed SABA or LABA⁴
 - Seretide + as needed SABA^{5 6}
- Symbicort SMART achieves this with
 - less use of reliever medication^{1 2 3 6}
 - a lower steroid load^{1 2 3 4 5}
- Symbicort SMART is potentially more convenient than multiple inhalers and is a significant therapeutic advance in the management of asthma

• Rabe *et al*, CHEST 2006

• Scicchitano *et al*, Curr Med Res Opin 2004

• O'Byrne *et al*, Am J Respir Crit Care Med 2005

4. Rabe KF *et al*. Lancet 2006

5. Kuna *et al*. Int J Clin Pract 2007.

6. Vogelmeier *et al*. Eur Respir J 2005

How to prescribe Symbicort SMART

This will depend upon the severity of asthma of the individual patient

- Primary Care – The majority of patients will be well controlled on:
 - **Symbicort 200/6, 1 inhalation bd plus as needed**
- Secondary care
 - Symbicort 200/6, 1 or 2 inhalations bd plus as needed

Adults

Patients should start treatment at the step most appropriate to the initial severity of their asthma. Check concordance and reconsider diagnosis if response to treatment is unexpectedly poor.

MOVE DOWN TO FIND AND MAINTAIN LOWEST CONTROLLING

Inhaled short-acting β_2 agonist as required

STEP 1
Mild intermittent asthma

Add inhaled steroid 200-800 mcg/day*
400 mcg is an appropriate starting dose for many patients

Start at dose of inhaled steroid appropriate to severity of disease.

STEP 2
Regular preventer therapy

1. Add inhaled long-acting β_2 agonist (LABA)
2. Assess control of

- good response to LABA - continue
- benefit from LABA control still inadequate - continue LABA, increase inhaled dose to 800 mcg if not already on this dose
- no response to LABA - stop LABA and increase inhaled steroid to 800 mcg/day.* If control still inadequate, trial of other therapies such as leukotriene receptor antagonist or SR theophylline

STEP 3
Initial add-on of LABA

STEP 4
Persistent poor control

Consider trials of:

- increasing inhaled steroid up to 2000 mcg/day*
- addition of a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, β_2 agonist tablet

NEEDED

steroid tablet dose providing control

high dose inhaled steroid 2000 mcg/day*

other treatments to the use of steroid

referral for specialist care

STEP 5
High dose inhaled steroid or frequent oral steroids

* 800 mcg or equivalent

SYMPTOMS vs

Adults

Patients should start treatment at the step most appropriate to the initial severity of their asthma. Check concordance and reconsider diagnosis if response to treatment is unexpectedly poor.

MOVE DOWN TO FIND AND MAINTAIN LOWEST CONTROLLING STEP

MOVE UP

Inhaled short-acting β_2 agonist as required

STEP 1
Mild intermittent asthma

Add inhaled steroid 200-800 mcg/day*
400 mcg is an appropriate starting dose for many patients

Start at dose of inhaled steroid appropriate to severity of disease.

STEP 2
Regular preventer therapy

1. Add inhaled long-acting β_2 agonist (LABA)
2. Assess control of asthma:
 - good response to LABA - continue LABA
 - benefit from LABA but control still inadequate - continue LABA and increase inhaled steroid dose to 800 mcg/day* (if not already on this dose)
 - no response to LABA - stop LABA and increase inhaled steroid to 800 mcg/day.* If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or SR theophylline

STEP 3
Initial add-on therapy

Consider

- increase up to 2l
- addition e.g. leukotriene antagonist β_2 agon

Persist

Use daily steroid tablet in lowest dose providing adequate control

Maintain high dose inhaled steroid at 2000 mcg/day*

Consider other treatments to minimise the use of steroid tablets

Refer patient for specialist care

SYMPTOMS vs TREATMENT

STEP 5
Continuous or frequent use of oral steroids

Children age 5-12 yrs

Patients should start treatment at the step most appropriate to the initial severity of their asthma. Check concordance and reconsider diagnosis if response to treatment is unexpectedly poor.

MOVE DOWN TO FIND AND MAINTAIN LOWEST CONTROLLING STEP

MOVE UP TO IMPROVE CONTROL AS NEEDED

Inhaled short-acting β_2 agonist as required

STEP 1

Mild intermittent asthma

Add inhaled steroid 200-400 mcg/day* (other preventer drug if inhaled steroid cannot be used) 200 mcg is an appropriate starting dose for many patients

Start at dose of inhaled steroid appropriate to severity of disease.

STEP 2

Regular preventer therapy

1. Add inhaled long-acting β_2 agonist (LABA)
2. Assess control of asthma:
 - good response to LABA
- continue LABA
 - benefit from LABA but control still inadequate
- continue LABA and increase inhaled steroid dose to 400 mcg/day* (if not already on this dose)
 - no response to LABA
- stop LABA and increase inhaled steroid to 400 mcg/day.*If control still inadequate, institute trial of other therapies, leukotriene receptor antagonist or SR theophylline

STEP 3

Initial add-on therapy

Increase inhaled steroid up to 800 mcg/day*

STEP 4

Persistent poor control

Use daily steroid tablet in lowest dose providing adequate control

Maintain high dose inhaled steroid at 800 mcg/day*

Refer to respiratory paediatrician

STEP 5

Continuous or frequent use of oral steroids

* BDP or equivalent

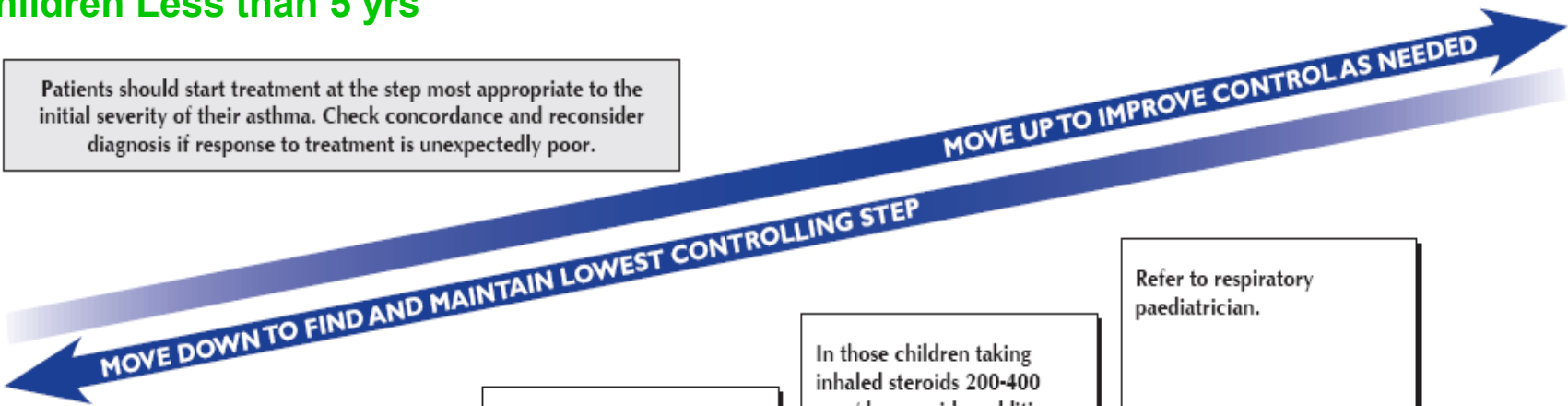
SYMPTOMS

vs

TREATMENT

Children Less than 5 yrs

Patients should start treatment at the step most appropriate to the initial severity of their asthma. Check concordance and reconsider diagnosis if response to treatment is unexpectedly poor.



Inhaled short-acting β_2 agonist as required

STEP 1

Mild intermittent asthma

Add inhaled steroid 200-400 mcg/day*† or leukotriene receptor antagonist if inhaled steroid cannot be used.

Start at dose of inhaled steroid appropriate to severity of disease.

STEP 2

Regular preventer therapy

In those children taking inhaled steroids 200-400 mcg/day consider addition of leukotriene receptor antagonist.

In those children taking a leukotriene receptor antagonist alone reconsider addition of an inhaled steroid 200-400 mcg/day.

In children under 2 years consider proceeding to step 4.

STEP 3

Initial add-on therapy

Refer to respiratory paediatrician.

STEP 4

Persistent poor control

SYMPTOMS vs TREATMENT

* BDP or equivalent
 † Higher nominal doses may be required if drug delivery is difficult

Asthma Control Test™ (ACT)

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

Score

All of the time

1

Most of the time

2

Some of the time

3

A little of the time

4

None of the time

5

- During the past 4 weeks, how often have you had shortness of breath?

More than once a day

1

Once a day

2

3 to 6 times a week

3

Once or twice a week

4

Not at all

5

1. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night, or earlier than usual in the morning?

4 or more nights a week

1

2 or 3 nights a week

2

Once a week

3

Once or twice

4

Not at all

5

- During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as salbutamol)?

3 or more times per day

1

1 or 2 times per day

2

2 or 3 times per week

3

Once a week or less

4

Not at all

5

- How would you rate your asthma control during the past 4 weeks?

Not controlled at all

1

Poorly controlled

2

Somewhat controlled

3

Well controlled

4

Completely controlled

5



Assessment: Royal College of Physicians of London three questions

IN THE LAST WEEK / MONTH

	YES	NO
"Have you had difficulty sleeping because of your asthma symptoms (including cough)?"	<input type="checkbox"/>	<input type="checkbox"/>
"Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?"	<input type="checkbox"/>	<input type="checkbox"/>
"Has your asthma interfered with your usual activities (e.g. housework, work, school, etc)?"	<input type="checkbox"/>	<input type="checkbox"/>
Date _____ / _____ / _____		

- Applies to all patients with asthma aged 16 and over.
- Only use after diagnosis has been established.

Goals of COPD management

NICE



GOLD²

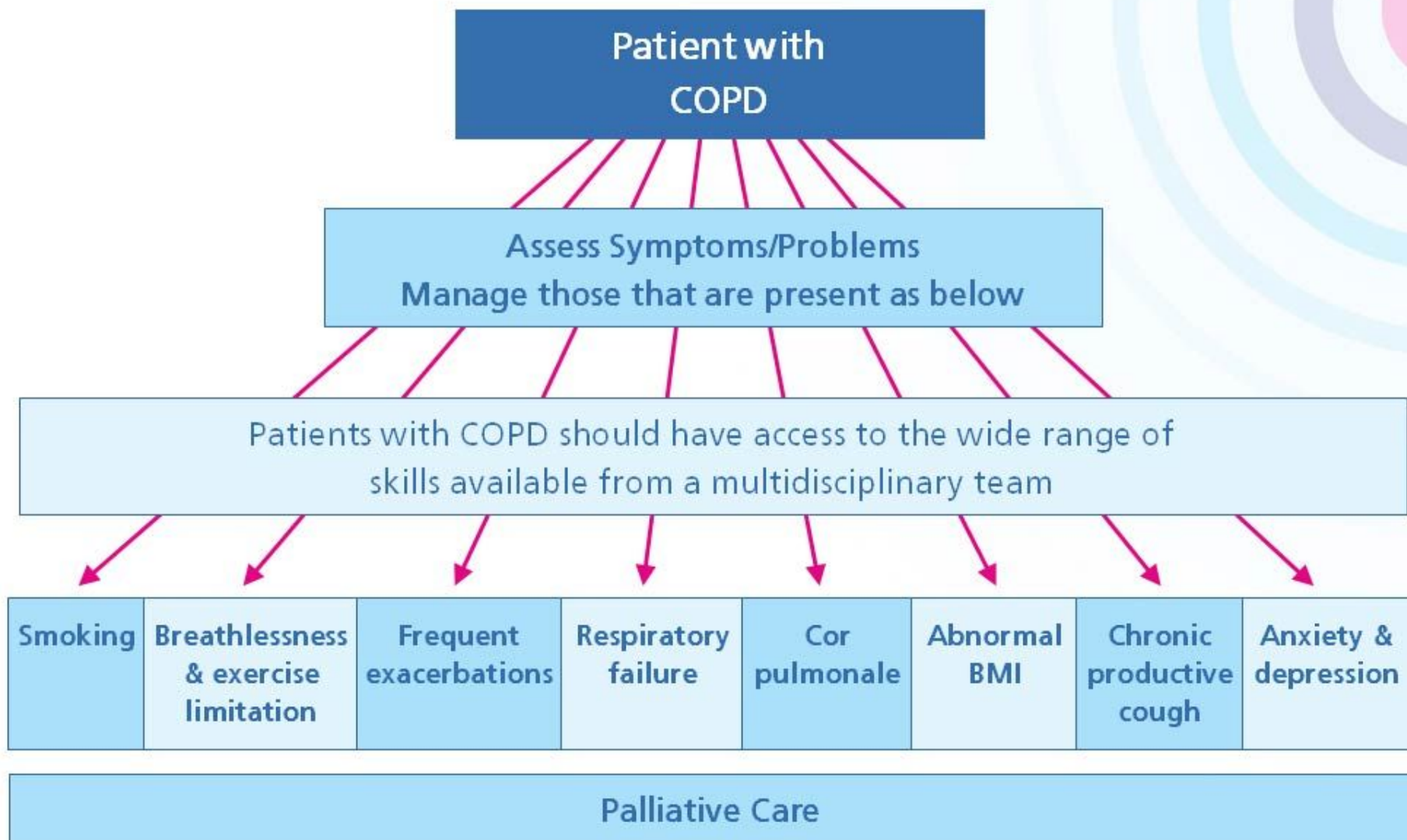
- Accurate diagnosis
- Stopping smoking
- Effective inhaled therapy
- Access to pulmonary rehab
- Prevent and treat exacerbations
- Multidisciplinary working

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Reduce mortality

1. NICE 2004

2. Pauwels RA *et al.* 2001.

MANAGEMENT OF STABLE COPD



BREATHLESSNESS AND EXERCISE LIMITATION

<i>Stop therapy if ineffective</i>	<ul style="list-style-type: none">• Use short-acting bronchodilator prn (beta₂-agonist or anticholinergic)
	<ul style="list-style-type: none">• If still symptomatic try combined therapy with a short-acting beta₂-agonist and a short-acting anticholinergic
	<ul style="list-style-type: none">• If still symptomatic use a long-acting bronchodilator (beta₂-agonist or anticholinergic)
	<ul style="list-style-type: none">• In moderate or severe COPD: If still symptomatic consider a trial of a combination of a long-acting beta₂-agonist and inhaled corticosteroid. Discontinue if no benefit after 4 weeks
	<ul style="list-style-type: none">• If still symptomatic consider adding theophylline
<ul style="list-style-type: none">• Offer pulmonary rehabilitation to all patients who consider themselves functionally disabled (usually MRC grade 3 and above)	
<ul style="list-style-type: none">• Consider referral for surgery: bullectomy, LVRS, transplantation	

Pharmacological treatment

- Can:
 - Improve and prevent symptoms
 - Reduce frequency and severity of exacerbations
 - Improve health status
 - Improve exercise tolerance

Commonly used formulations of inhaled therapy

- Short-acting
 - Short-acting β_2 agonists (SABA)
 - Short-acting anticholinergics
- Long-acting
 - Long-acting β_2 agonists (LABA)
 - Long-acting anticholinergics
- Inhaled corticosteroids (ICS)
 - Combination long acting β_2 agonist / corticosteroids (LABA / ICS)

What are you looking for?

- Less breathlessness
- Ability to be more active
- Better quality of life
- Improved health status
- Reduced mortality
- Reduction in exacerbations
- FEV_1 ?
 - Would not expect to see improvements in FEV_1 over time

Assessing benefits of prescribed therapy

- **Assess response by asking:**¹

“Has your treatment made a difference to you?”

“Can you do some things now that you couldn't do before, or the same things but faster?”

“Has your sleep improved?”

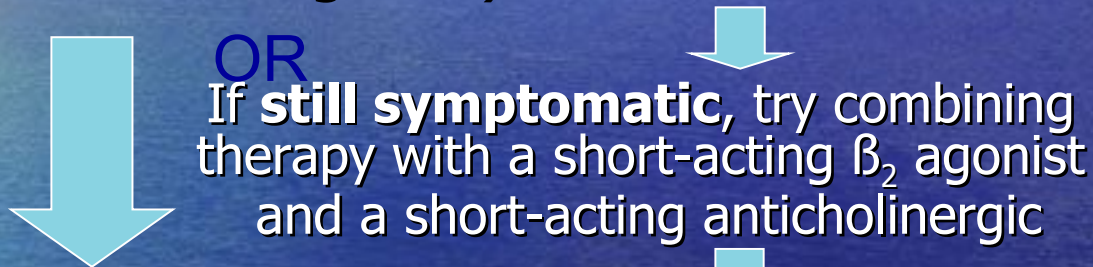
“Is your breathing easier in any way?”

“Can you do the same things as before but are now less breathless when you do them?”

- **Also ask about an activity that they would like to be able to do more easily, and assess any difference after treatment**

NICE management of stable COPD

Use short-acting bronchodilator (anticholinergic or β_2 agonist) as needed



If still symptomatic, use a long-acting bronchodilator (anticholinergic and / or β_2 agonist)

In moderate or severe COPD:
If **still symptomatic**, 2 or more exacerbations consider a combination of long-acting bronchodilators and inhaled corticosteroid

If still symptomatic, consider adding theophylline

β_2 agonists

- Short-acting
- Salbutamol, terbutaline
- Quick onset of action
- In COPD can be used regularly in addition to 'as needed'
- First line treatment in newly diagnosed COPD where breathlessness is the presenting symptom
- 'First aid' treatment for breathlessness at all stages of the disease



Long-acting β_2 agonists

- **Salmeterol, Formoterol**
- Reduce need for short acting rescue bronchodilators
- Improve quality of life
- May improve symptoms

Long-acting β_2 agonists

Action:

- Same as short-acting but last for 12 hours
- Salmeterol has slower onset of action than formoterol
- Side effects, cautions and interactions: same as short-acting but may also cause hypertension; elevated cardiac risk



Anticholinergics

- Inhibit muscarinic receptors
- Work by blocking parasympathetic nervous system
- Reduces contraction of airway smooth muscle (rather than causing bronchodilation)
- Reduce viscous mucus secretions
- Anticholinergic drugs act on cholinergic tone, the only reversible mechanism of COPD



In COPD, cholinergic tone contributes to airway narrowing (bronchoconstriction) and decreases the amount of air that can be exhaled (air trapping)

Short-acting anticholinergics

- Ipratropium bromide
- Should be used four-times a day
- Usually given in combination with salbutamol
- Non-selective binding to M_1 M_2 M_3 receptors in the smooth muscle
- (Combivent inhaler discontinued June 2008)



Long-acting anticholinergics

- Tiotropium 18 mcg dry power capsule
- Tiotropium 2.5 mcg soft mist inhaler (Respimat)
- Works on the parasympathetic nervous system¹



Inhaled corticosteroids

- In moderate to severe COPD
- ($FEV_1 < 50\%$ predicted)
- Reduce exacerbation rates
- Reduce rate of decline in health related quality of life
- All studies carried out on high dose
- Long-term side effects

Corticosteroids in COPD

- **Inhaled corticosteroids in combination with bronchodilators**
 - Evidence shows fewer exacerbations and slower reduction in health status
 - Recommended if:
 - $FEV_1 < 50\%$
 - 2 or more exacerbations in a year
 - Side effects: oral candidiasis, hoarse voice, skin bruising
- **Oral steroids**
 - Recommended for use in exacerbation when there is insufficient response to increased bronchodilators
 - Regular use not recommended in COPD
 - Numerous side effects with long term use of oral preparations

Combination inhalers

- **Symbicort 400 Turbohaler and Seretide 500 Accuhaler**
- Reduce exacerbation rates
- Reduce breathlessness
- Improve health status
- Improve lung function



**Inhaled steroids not licensed for use
in COPD except as combination**

Oral therapy in COPD

- Theophylline
 - Useful for some – Be aware of side effects and drug interactions
- Mucolytics
 - Thin mucus thus aiding expectoration. Reduce exacerbations when they work
- Antidepressants
 - Screen all severe patients for depression and anxiety

What do we know about improving survival in COPD?

- Smoking cessation^{1,2}
- Long term oxygen therapy^{3,4}
- Lung volume reduction surgery⁵
- Can pharmacotherapy improve survival?⁶

1. Anthonisen et al. *Annals of Internal Medicine*, 2005 142: 233-239, 2. NICE Guideline COPD. National Collaboration Centre for Chronic Conditions Thorax 2004, 3. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med* 1980, 4. MRC Working Party. *Lancet* 1981., 5. Fishman et al. *N Engl J Med* 2003., 6. Celli BR. Predicting mortality in chronic obstructive pulmonary disease: chasing the "Holy Grail". *Am J Respir Crit Care Med* 2006; **173**: 1298-1299

TORCH: main objectives

- **Primary objective**

- The effect of Seretide™ 500 Accuhaler™ vs control on all-cause mortality over 3 years in patients with moderate-to-severe COPD

- **Secondary objectives**

- The effect of Seretide™ 500 Accuhaler™ on the rate of moderate and severe exacerbations over 3 years
- The effect of Seretide™ 500 Accuhaler™ on health status (SGRQ) over 3 years
- Post-bronchodilator FEV₁

SGRQ = St. George's Respiratory
Questionnaire

Efficacy endpoints

- Mortality benefits are important, but may be of less relevance if other endpoints are not met
- Three pillars of COPD management
 - Exacerbations
 - Health status
 - Lung function

TORCH results: Summary

- **Seretide™ 500 Accuhaler™** shows a trend towards improved survival vs control over 3 years which is non-statistically significant
- **Seretide™ 500 Accuhaler™** shows sustained exacerbation reduction over 3 years vs control
- **Seretide™ 500 Accuhaler™** improves and sustains quality of life over 3 years vs control
- Patients feel better for longer on **Seretide™ 500 Accuhaler™** (vs control)

New Licence

Seretide™ 500 Accuhaler™ is now indicated for the symptomatic treatment of patients with COPD with a FEV₁ <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy ¹

1. Seretide SPC (July 5th 2007)

The logo for the INSPIRE study is centered on a white rectangular background. At the top, the word "INSPIRE" is written in a playful, rounded font. Each letter is a different color: 'I' is orange, 'N' is purple, 'S' is yellow, 'P' is purple, 'I' is yellow, 'R' is purple, and 'E' is orange. Below the text is a stylized illustration of a pair of lungs in shades of purple and blue, with white branching structures representing the bronchial tree. The entire logo is framed by two thick, curved lines: a purple one on the left and an orange one on the right, both curving upwards and then downwards.

INSPIRE

Investigating **N**ew **S**tandards
for **P**rophylaxis **I**n **R**eduction
of **E**xacerbations

INSPIRE study

Objectives

- Objective

- To study the relative effects of Seretide[®] 500 Accuhaler[®] b.d. (salmeterol 50mcg/fluticasone propionate 500mcg) and Spiriva[®] Handihaler[®] (tiotropium bromide) 18mcg o.d. on the rate of healthcare utilisation COPD exacerbations and related outcomes over 104 weeks in subjects with severe COPD.

Accuhaler and Seretide are registered trademarks of the GlaxoSmithKline group of companies

Spiriva and Handihaler are registered trademarks of Boehringer Ingelheim *et al.* J COPD 2007

Endpoints

- Primary Endpoint
 - Rate of healthcare utilisation exacerbations
- Other Endpoints
 - Rate of symptom-defined exacerbations
 - Time to withdrawal
 - Post-dose FEV₁
 - Health status as measured by SGRQ
 - All-cause mortality
 - Adverse events & AEs of special interest

FEV₁ = Forced Expiratory Volume in 1 second

SGRQ = St George's Respiratory Questionnaire

Overall Study Conclusions 1

- First head to head study of two of the main pharmacological agents used in the management of COPD.
- No differences between the treatments for exacerbation rate and lung function at 2 years.
 - Biggest diary card data set on exacerbations and different types of exacerbations produced to date
 - Nature of the exacerbations appears to be different

Overall Study Conclusions 2

- Patients on SFC compared with those on TIO had;
 - improved & sustained Health Status.
 - statistically significant reduction in all cause mortality
- More pneumonias were reported on SFC than on TIO
 - These do not appear to have led to increased mortality or detriment in health status
- This study provides important new findings for the understanding of COPD exacerbations.

UPLIFT®

- UPLIFT is a unique, 4-year, landmark trial involving nearly 6000 patients¹
- All patients were allowed to use all other respiratory medications, except inhaled anticholinergics. Patients were then randomised to receive tiotropium or placebo (control)¹
- 46% of patients in the trial were classified as having mild COPD as per NICE

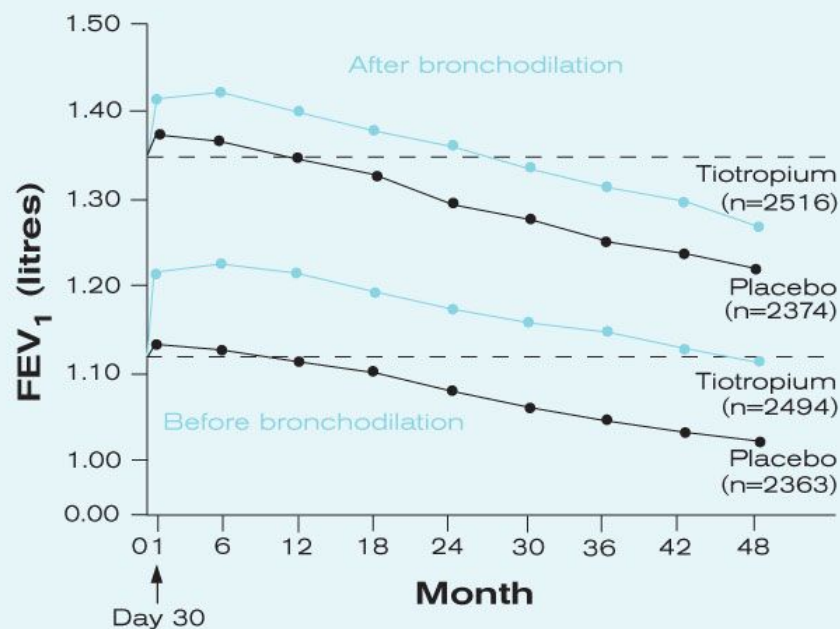


Uplift your expectations in COPD

SPIRIVA® (tiotropium) demonstrated long-term sustained improvements in lung function vs. control

- While SPIRIVA did not alter the rate of decline in lung function, the primary study endpoint, it achieved and sustained lung function improvements vs. control¹
- SPIRIVA sustained improvements vs. control for up to 4 years, delaying the clinical course of the disease¹

SPIRIVA achieved and sustained significant improvements in lung function (pre- and post-bronchodilator FEV₁) over 4 years vs. control¹



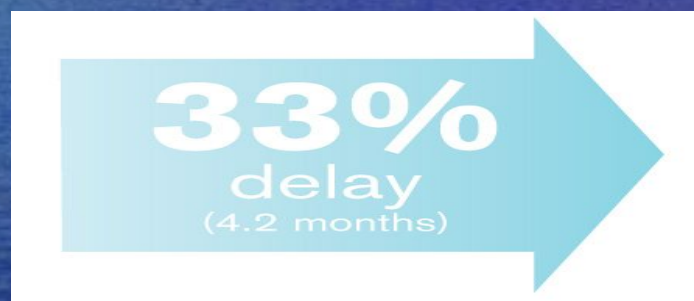
SPIRIVA achieved sustained long-term improvements in quality of life vs. control

- SPIRIVA sustained statistically significant improvements in quality of life (total SGRQ score) for up to 4 years vs. control¹
 - An improvement of ≥ 4 units is clinically significant
- Patients did not return to baseline SGRQ score over the 4 years of the study¹



SPIRIVA achieved a long-term reduction in COPD exacerbations vs. control

- SPIRIVA significantly delayed time to first exacerbation vs. control¹

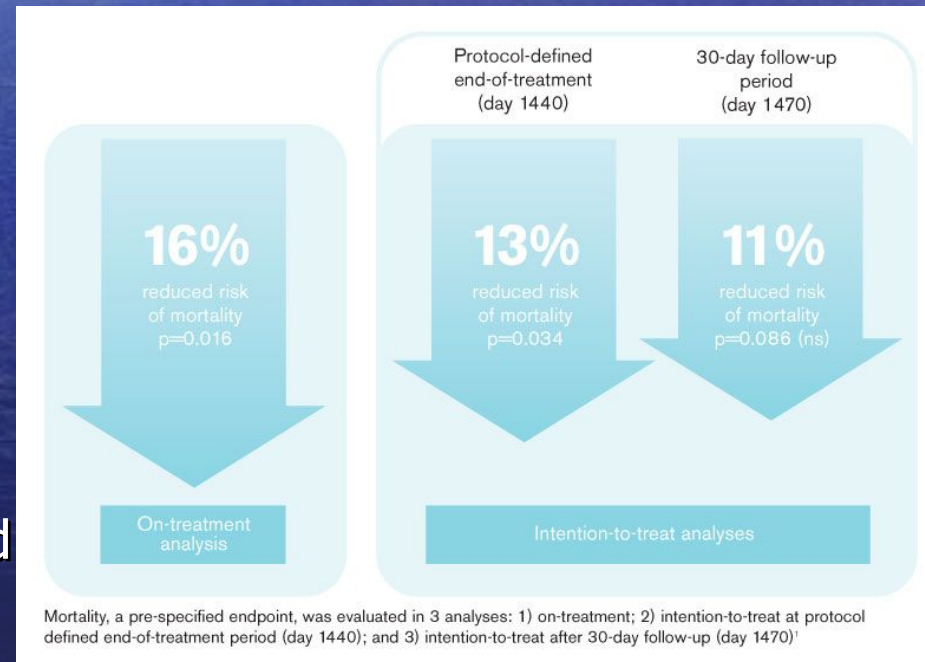


- SPIRIVA significantly reduced the risk of exacerbations for up to 4 years vs. control¹
 - 14% reduced risk of exacerbations ($p < 0.001$)
 - 14% reduced risk of exacerbations leading to hospitalisations ($p = 0.002$)



Whilst on treatment, SPIRIVA reduced the risk of mortality vs. control

- 16% lower mortality risk with SPIRIVA vs. control while patients received study medication¹
- Effect extended to end-of-treatment period (day 1440), as defined by protocol¹
- Effect became non-significant within the 30-day follow-up period (day 1470) when, according to protocol, patients were discontinued from their study



Uplift your expectations in COPD

Inhaler devices

Consider:

- Patient preference
- Ability, physical and cognitive
- Lifestyle
- Cost effective (e.g. Seretide MDI versus accuhaler)

Most patients can use inhalers given sufficient training

Check inhaler technique regularly

Nebulisers should not be given without specialist assessment

Which inhaler device would you consider for an elderly patient with RA and poor vision?



Aim of Inhaled therapy

Deliver high concentration of drugs directly to lungs & bronchioles while reducing systemic side effects

Pressurised metered dose inhalers

Think Eddy Stobart lorry doing 70 miles per hour on a country lane trying to round the bends!



Needs to be slowed down to negotiate the bends

Spacers

- Several types available
- Holding chamber & one way valve
- Reduces need for hand breath co-ordination
- Spacer should be compatible with MDI
 - BTS, 2003



Recommendations about spacers

Cleaning:

Clean no more than monthly as more frequent cleaning affects performance (due to a build up of static)

Clean with water and washing up liquid and leave to air dry

Wipe mouthpiece clean of detergent before use

NOTE – Volumatic (large volume) spacer discontinued in October 2005 and reintroduced in Feb 2006

Dry powder devices

Think Eddy Stobart lorry trying to round a country bend from stationary!!

Needs acceleration
to get around the bends



What the guidelines say

- In most cases bronchodilator therapy should be administered using a hand held inhaler device (including a spacer device if appropriate)
- Find the most suitable device (remember that not all drugs come in all devices)
- Patients must be trained in the use of the device and be able to demonstrate it's use satisfactorily
- Patients should be reassessed and re-taught correct technique regularly
- The dose of medication should be titrated to clinical response

NICE Guidelines (Thorax 2004)

In addition:

- Does the patient know what to take and when?
- Does the patient know how to store the medication safely?
- What is the patient actually doing with the drugs once home?

1 bag
Of drugs
From
Patients
Home!



Nebuliser collected this week!

