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The Leeds Teaching Hospitals 
NHS Trust

Asthma and COPD Update – New Inhalers and Risk Issues

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Medicines Management
and Pharmacy Services

UKCPA
CLINICAL PHARMACY ASSOCIATION

RESPIRATORY
GROUP

Declarations of Interest

- Payment received for educational events and conference sponsorship from:
 - Almirall
 - AstraZeneca
 - Boehringer Ingelheim
 - Chiesi
 - GSK
 - Napp
 - Novartis
 - Pfizer
 - Teva



Asthma & COPD: Inhalers in **2010**

Bronchodilators

SABAs

- Salbutamol (7+ devices)
- Terbutaline (1 device)

SAMAs

- Ipratropium (2 devices)

LABAs

- Formoterol (2 devices)
- Salmeterol (2 devices)

LAMAs

- Tiotropium (2 devices)

Corticosteroids

ICS

- Beclometasone (4 devices)
- Beclometasone extra-fine (3 devices)
- Budesonide (3 devices)
- Ciclesonide (1 device)
- Fluticasone propionate (2 devices)
- Mometasone (1 device)

ICS/LABA

- Fostair (1 device)
(beclometasone/formoterol)
- Seretide (2 devices)
(fluticasone propionate/salmeterol)
- Symbicort (1 device)
(budesonide/formoterol)



Asthma & COPD: Inhalers in 2018

Bronchodilators

SABAs

• Salbutamol	(6 devices)
• Terbutaline	(1 device)

SAMAs

• Ipratropium	(1 devices)
---------------	-------------

LABAs

• Formoterol	(4 devices)
• Salmeterol	(2 devices)
• Indacaterol	(1 device)
• Olodaterol ▼	(1 device)
• † Vilanterol	

LAMAs

• Acclidinium ▼	(1 device)
• Glycopyrronium	(1 device)
• Tiotropium	(3 devices)
• Umeclidinium ▼	(1 device)

LABA/LAMAs

• Anoro ▼ (vilanterol/umeclidinium)	(1 device)
• Duaklir ▼ (formoterol/aclidinium)	(1 device)
• Spiolto ▼ (olodaterol/tiotropium)	(1 device)
• Ultibro ▼ (indacaterol/glycopyrronium)	(1 device)

Corticosteroids

ICS

• Beclometasone	(2 devices)
• Beclometasone extra-fine	(3 devices)
• Budesonide	(3 devices)
• Ciclesonide	(1 device)
• † Fluticasone furoate	
• Fluticasone propionate	(2 devices)
• Mometasone	(1 device)

ICS/LABA

• Aerivio (fluticasone propionate/salmeterol)	(1 device)
• AirFluSal (fluticasone propionate/salmeterol)	(2 devices)
• Aloflute (fluticasone propionate/salmeterol)	(1 device)
• Combisal (fluticasone propionate/salmeterol)	(1 device)
• DuoResp (budesonide/formoterol)	(1 device)
• Flutiform (fluticasone propionate/formoterol)	(2 devices)
• Fobumix (budesonide/formoterol)	(1 device)
• Fostair (beclometasone/formoterol)	(2 devices)
• Relvar (fluticasone fuorate/vilanterol)	(1 device)
• Sereflo (fluticasone propionate/salmeterol)	(1 device)
• Seretide (fluticasone propionate/salmeterol)	(2 devices)
• Sirdupla (fluticasone propionate/salmeterol)	(1 device)
• Symbicort (budesonide/formoterol)	(2 devices)

ICS/LABA/LAMA

• Trelegy ▼ (fluticasone fuorate/vilanterol/umeclidinium)	(1 device)
• Trimbow ▼ (beclometasone/formoterol/glycopyrronium)	(1 device)

†Not available as monotherapy

Inhalers are not all the same

Aerosol

MDI



Small Vol. Spacer



Large Vol. Spacer



Soft Mist Inhaler



Autohaler



Easi-Breathe



K-haler



Dry Powder Inhaler (DPI)

Single dose DPI - Blister

Accuhaler



Ellipta



Forspiro



Single dose DPI - Capsule

Aeroliser



Breezhaler



HandiHaler



Zonda



Reservoir Multidose DPI

Easyhaler



Genuair



NEXThaler



Novolizer



Spiromax



Turbohaler



Twisthaler



Novel Therapies in COPD

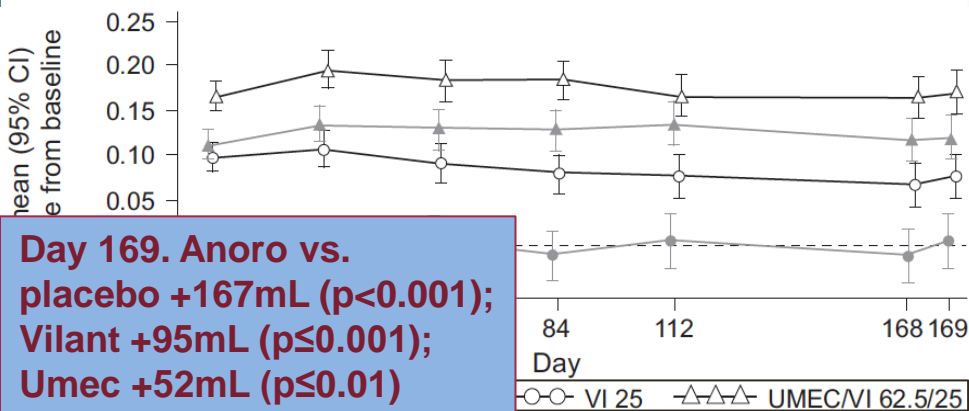
LABA/LAMA - Dual Long-Acting Bronchodilators

ICS/LABA/LAMA – Triple therapy combination inhalers



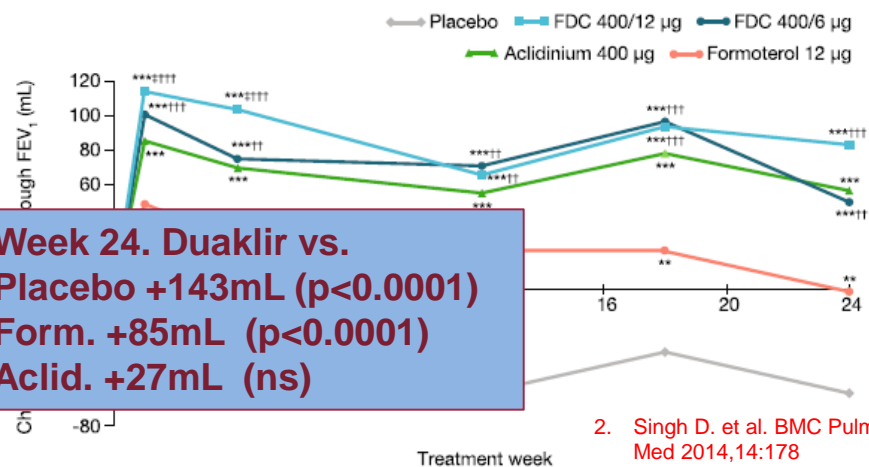
LABA/LAMA: Effect on lung function

1. Anoro Ellipta (vilanterol / umeclidinium)



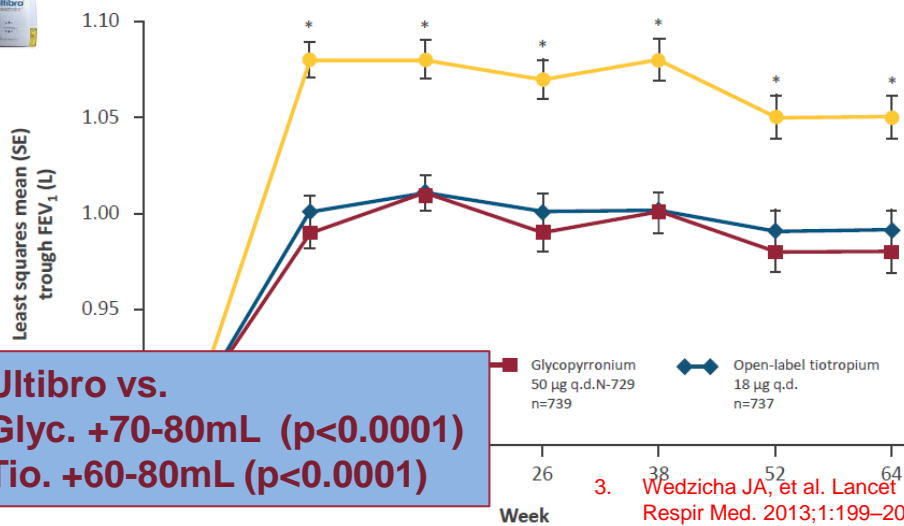
1. Donohue JF et al. *Respir Med* 2013;107:1538-46

2. Duaklir Genuair (formoterol / acclidinium)



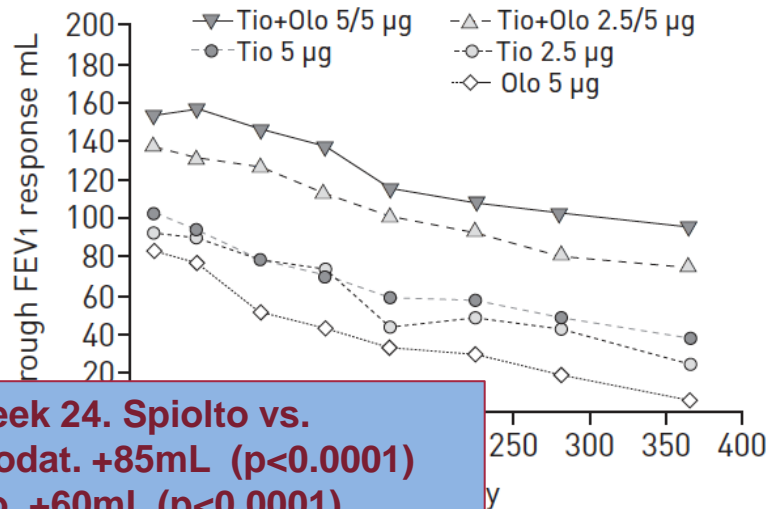
2. Singh D. et al. *BMC Pulm Med* 2014,14:178

3. Ultibro Breezhaler (indacaterol / glycopyrronium)



3. Wedzicha JA, et al. *Lancet Respir Med.* 2013;1:199-209

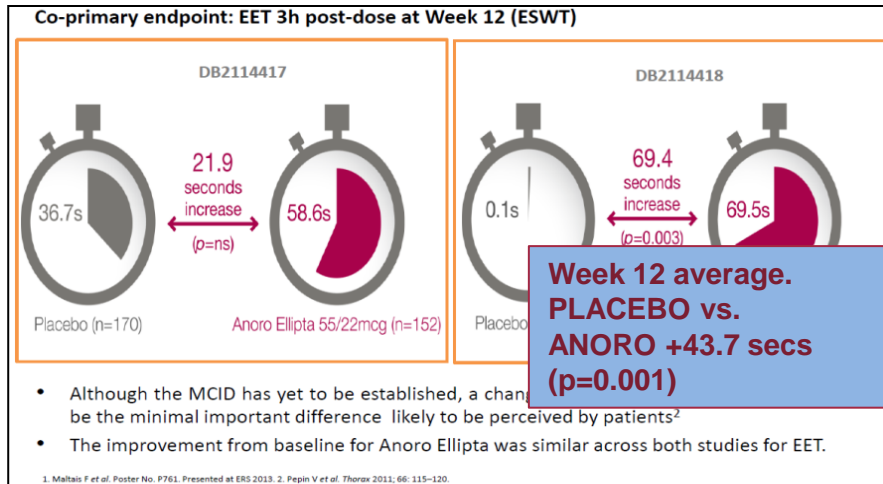
4. Spiolto Respimat (olodaterol / tiotropium)



4. Buhl R et al. *Eur Respir J* 2015; 45: 869-871

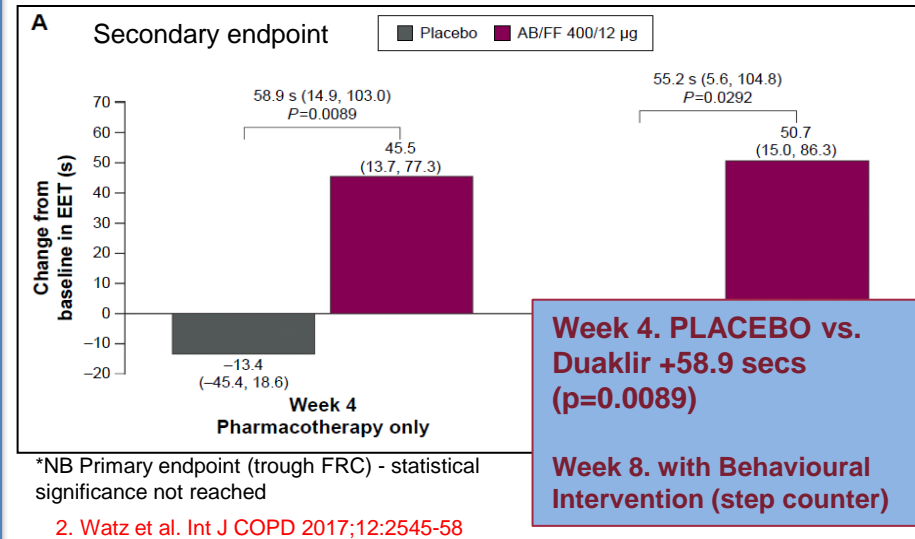
LABA/LAMA: Exercise Tolerance

1. Anoro Ellipta (vilanterol / umeclidinium)

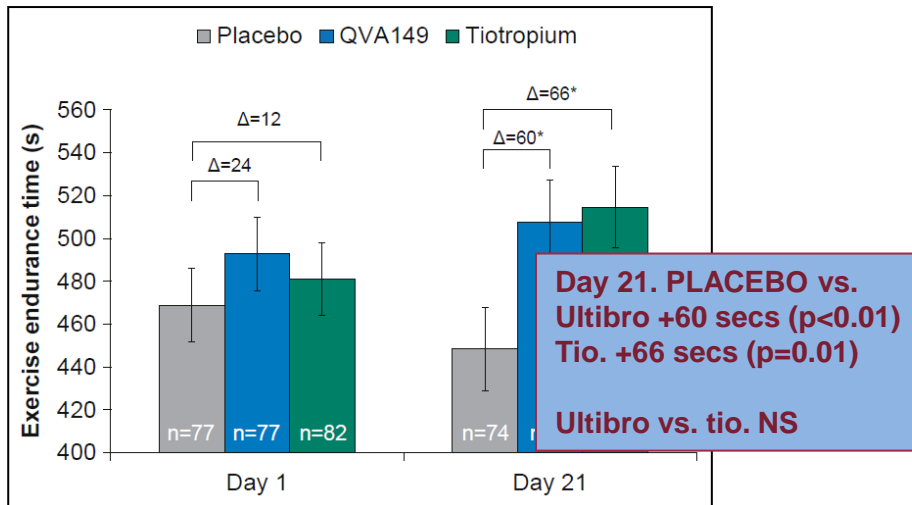


1. Maltais et al. Ther Adv Respir Dis 2014;8:169-81

2. Duaklir Genuair (formoterol / acclidinium)

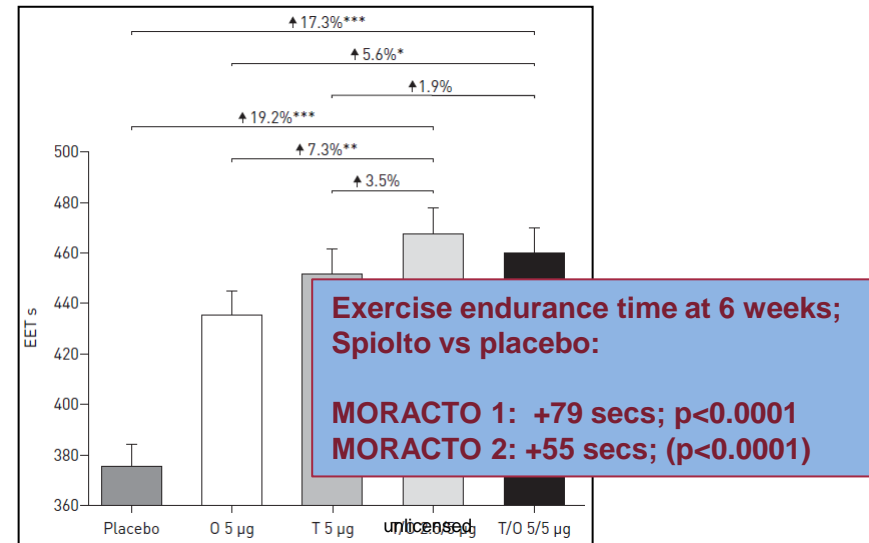


3. Ultibro Breezhaler (indacaterol / glycopyrronium)



3. Beeh K, et al. Respir Med. 2014;108:584-92

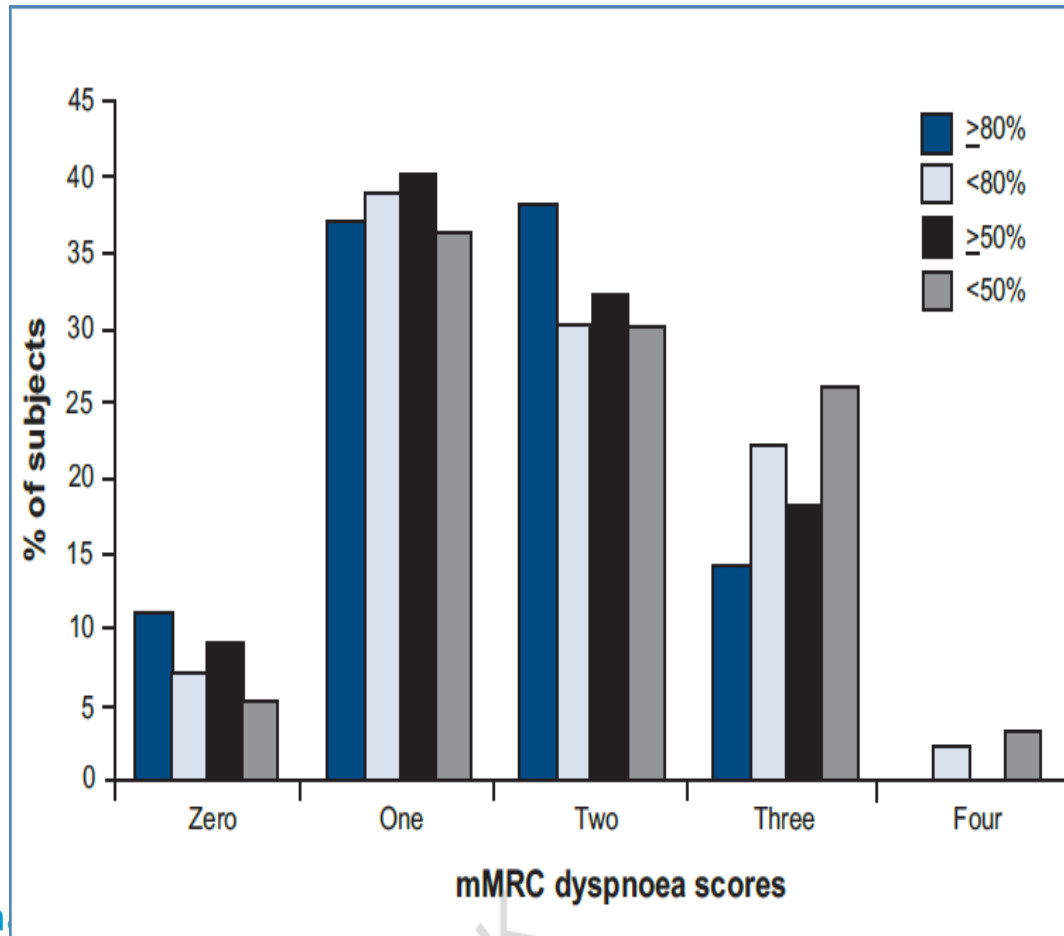
4. Spiolto Respimat (olodaterol / tiotropium)



4. O'Donnell et al. Eur Respir J 2017;49:1601348

Most COPD patients remain breathless despite using one long-acting bronchodilator

This is independent of Lung Function.



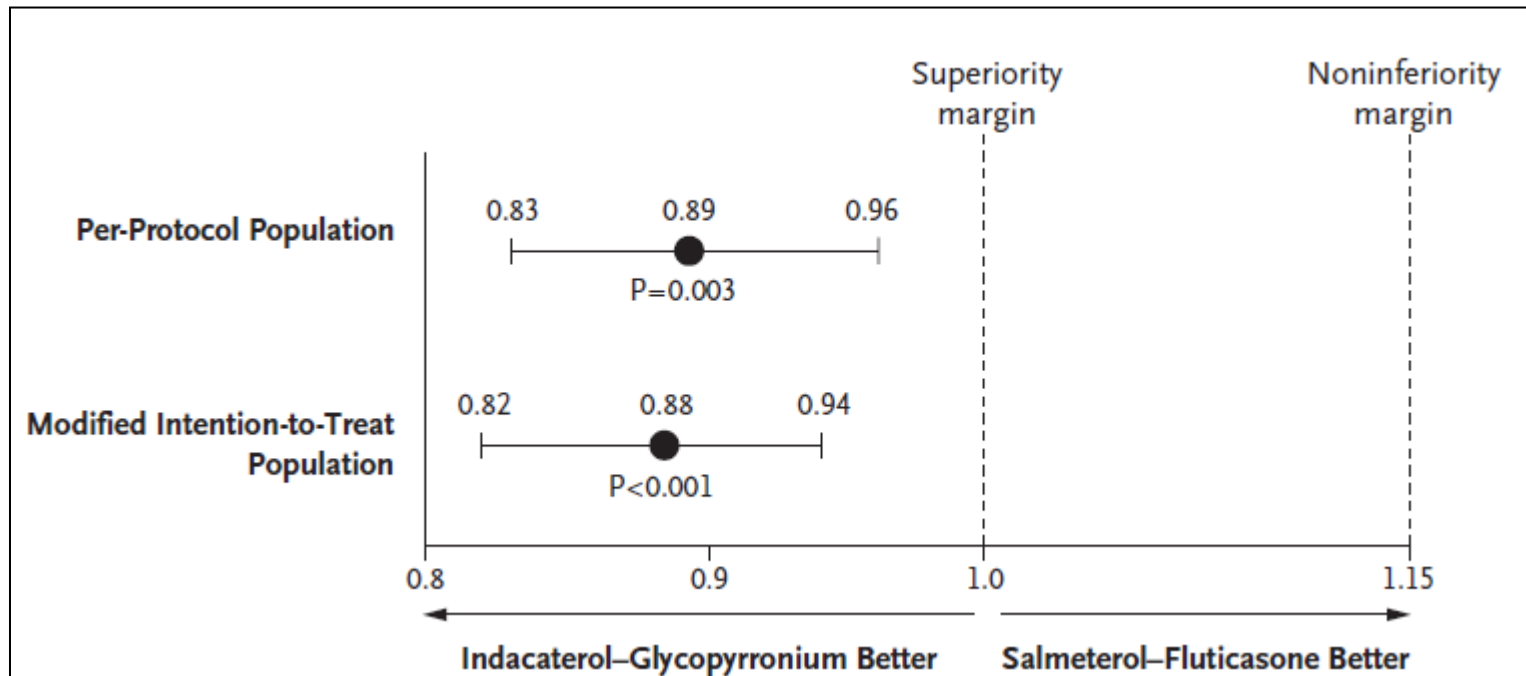
FLAME Study

Ultibro 110/50 Breezhaler vs. Seretide 500 Accuhaler, 52-week Exacerbation Study

COPD

- mMRC ≥ 2
- FEV1 25%-60% predicted (post-bronchodilator)
- At least 1 COPD exacerbation in past year (Tx with OCS and/or Abx)

Non-inferiority and Superiority for Ultibro vs. Seretide



New COPD drugs

Triple therapy (ICS/LABA/LAMA)



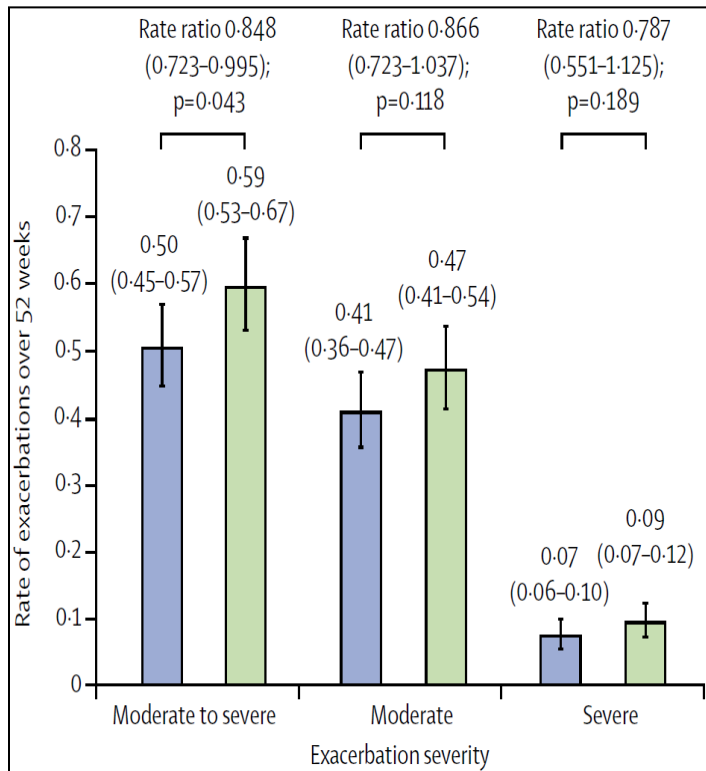
Trimbow pMDI

Beclometasone 87mcg / Formoterol 5mcg / Glycopyrronium 9mcg (delivered dose)



TRIBUTE Study: Trimbow MDI vs. Ultibro Breezhaler

- Primary Endpoint: Rate of moderate to severe exacerbations over 52 weeks.
- Population: Severe/v. severe COPD ($FEV_1 < 50\%$), CAT score ≥ 10 & at least 1 mod-sev exacerbation in the last 12 months, despite ICS+LABA, ICS+LAMA, LABA+LAMA, or LAMA (but not ICS+LABA+LAMA).
- *64%-66% taking ICS prior to study; 18%-20% had ≥ 2 mod-sev exacerbations; 13.5% reversibility to SABA*



Trimbow superior to Ultibro:

- 15% reduction in annual rate of mod-severe exacerbations.
- Absolute reduction: 0.09 exacerbations per patient per year.

Greatest effects* for Trimbow vs. Ultibro in COPD patients with

- Chronic bronchitis (RR 0.752; $p=0.01$) vs. emphysema (RR 0.995; $p=0.974$)
- Higher ($\geq 2\%$) eosinophil count (RR 0.806; $p=0.029$) vs. lower ($< 2\%$) counts (0.943; $p=0.685$)

No difference in Pneumonia for Trimbow vs. Ultibro.

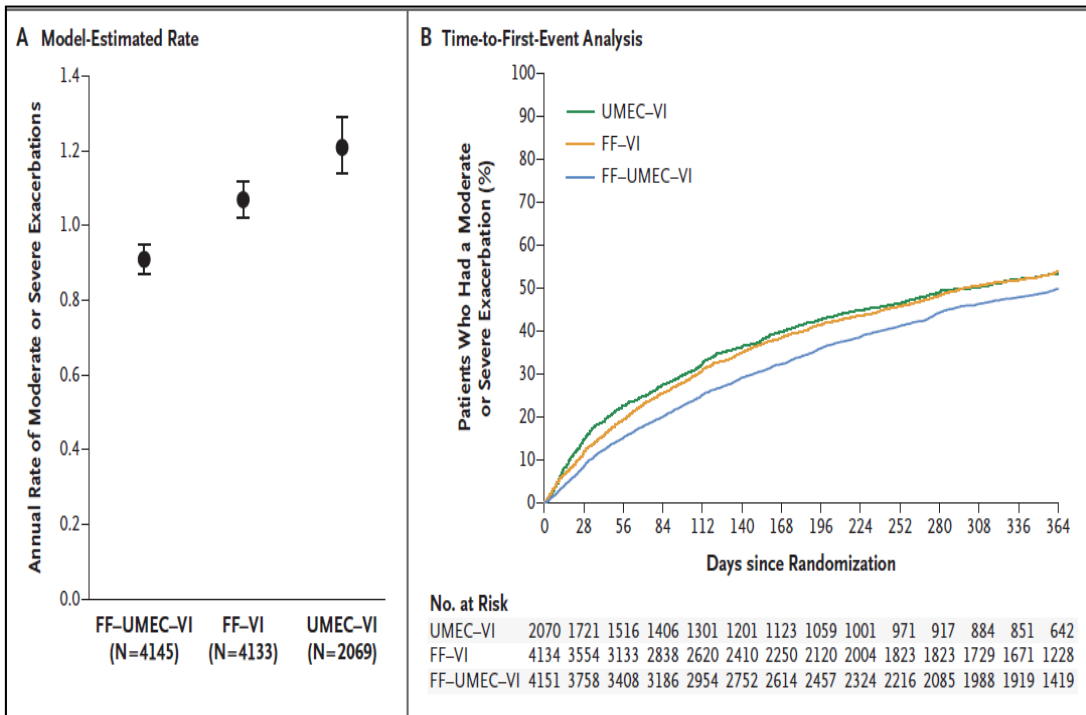
Trelegy Ellipta

Fluticasone furoate 92mcg / umecclidinium 55mcg / vilanterol 22mcg (delivered dose)



IMPACT Study: Trelegy Ellipta vs. Relvar Ellipta vs. Anoro Ellipta

- Primary Endpoint: Rate of moderate to severe exacerbations over 52 weeks.
- Population: moderate COPD (FEV₁50-80%) & at least 2 mod./ 1 sev. Exac. in the last 12 months; or severe COPD (FEV₁<50%) & at least 1 mod./sev. Exac. in the last 12 months, despite any COPD medication
- *70% taking ICS prior to study; 77% had ≥2 mod. ±≥1 sev. Exacs. in past 12 months; 18% reversibility to salbutamol*



Exacerbations: Trelegy was superior to Relvar & Anoro:

- 15% *relative* reduction vs. Relvar
 - *ARR*: 0.16 mod-sev. exac per pt per yr
- 25% *relative* reduction vs. Anoro
 - *ARR*: 0.3 mod-sev. exac per pt per yr
- Superiority irrespective of eosinophil count

Pneumonia Risk

- 50% *relative* increase in pneumonia vs. Anoro
 - *ARR*: 35 additional first pneumonias per 1000 patient-years

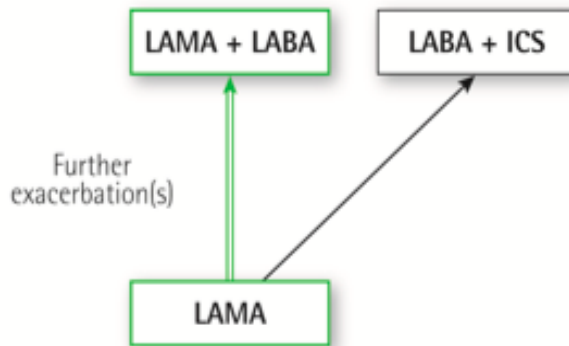
How does this affect COPD Guidelines?

GOLD 2018 vs. NICE (draft) 2018

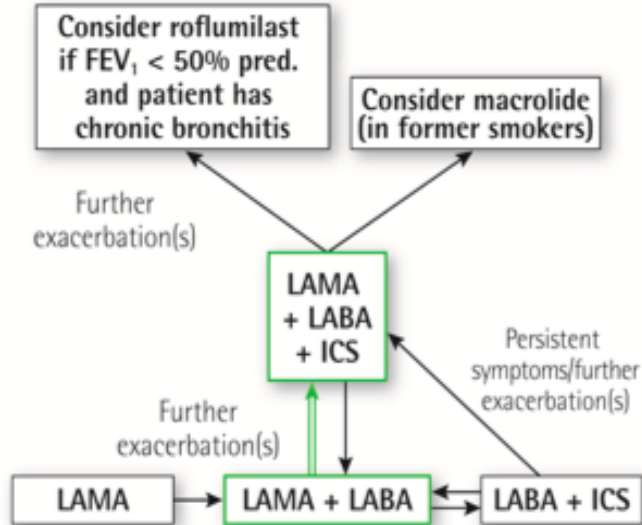


GOLD (2018) Pharmacotherapy

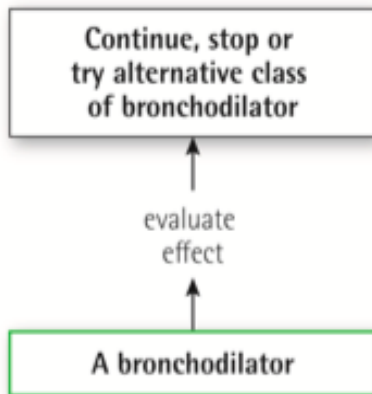
Group C Symptoms - Exac's +



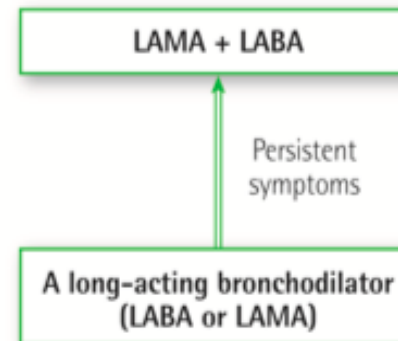
Group D Symptoms + Exac's +



Group A Symptoms - Exac's -



Group B Symptoms + Exac's -



Preferred treatment = →

NICE (draft) 2018 – treatment algorithm

Inhaled therapies

Offer SABA or SAMA

Person still breathless or has exacerbations despite treatment?

No asthmatic features*

Offer LABA + LAMA

Asthmatic features*

Consider LABA + ICS

For ALL inhaled therapies:

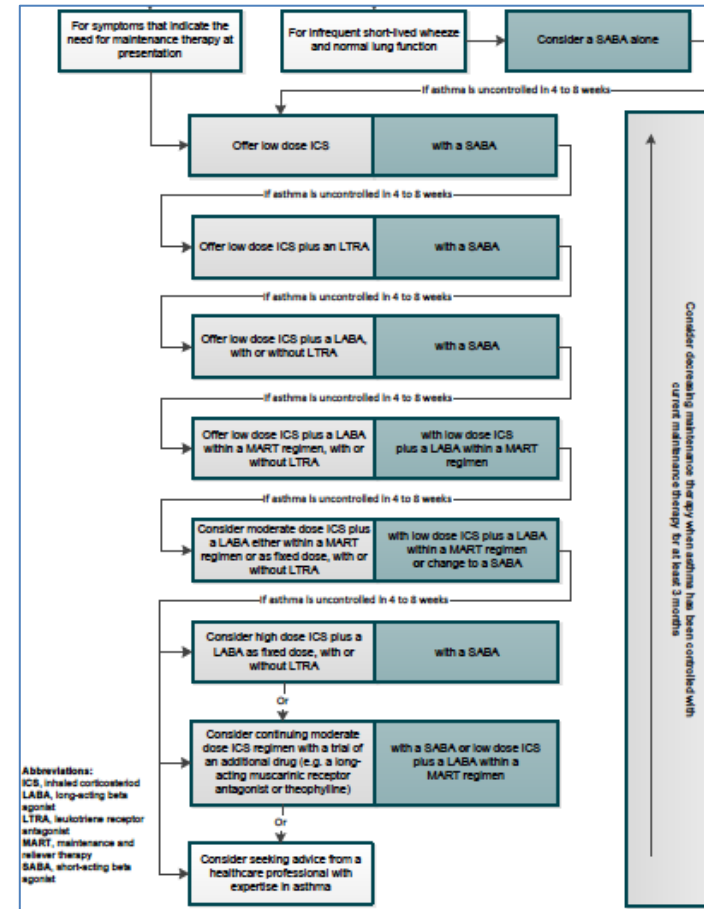
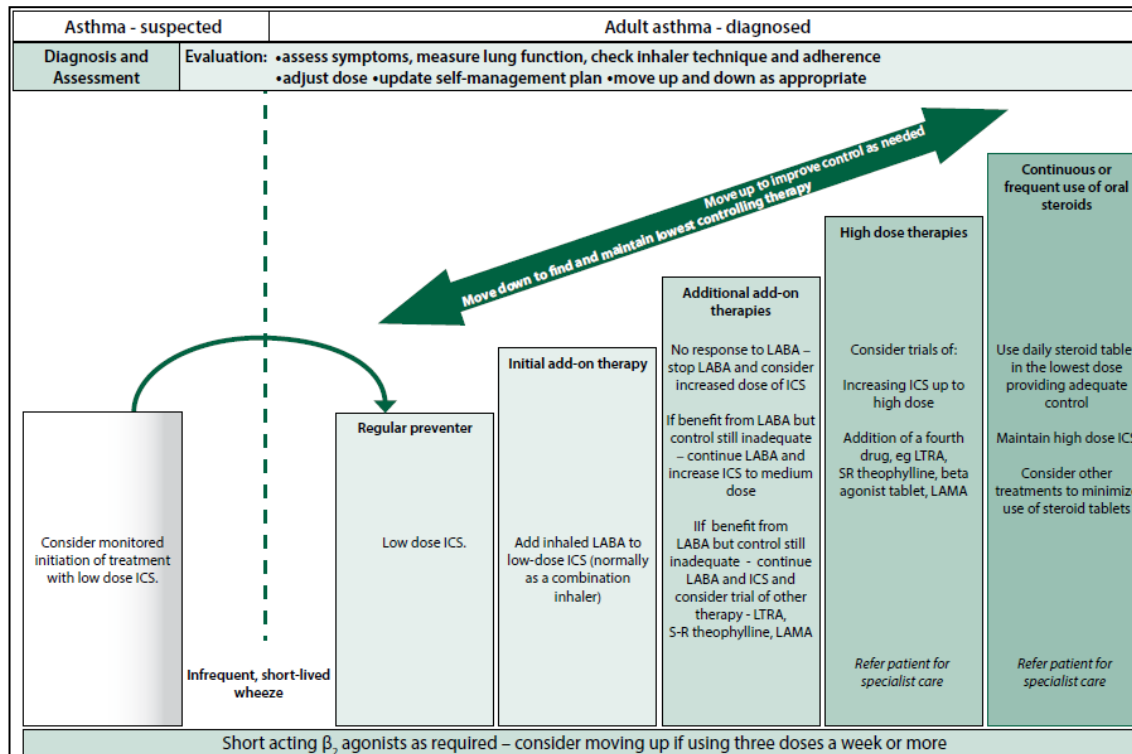
Train people in correct inhaler technique, and assess inhaler technique and adherence throughout treatment

Person still breathless or has exacerbations despite further treatment?

Consider
LAMA + LABA + ICS

Comparison of Asthma Guidelines

BTS/SIGN 2016 vs. NICE 2017



Differences between BTS/SIGN and NICE

Issue	BTS/SIGN (2016)	NICE (2017)
Diagnosis	Structured clinical history & examination. +ve response to Tx without objective testing.	Structured clinical history & examination. Emphasis on objective testing (PFTs, FeNO).
'Mild Asthma'	Low dose ICS.	SABA prn.
First-line add-on to low dose ICS	Add LABA.	Add LTRA.
'MART' Therapy	Consider if exacerbations on mod-dose ICS.	Recommended for all if uncontrolled on low-dose ICS.



Potential Risks in Asthma and COPD Treatment

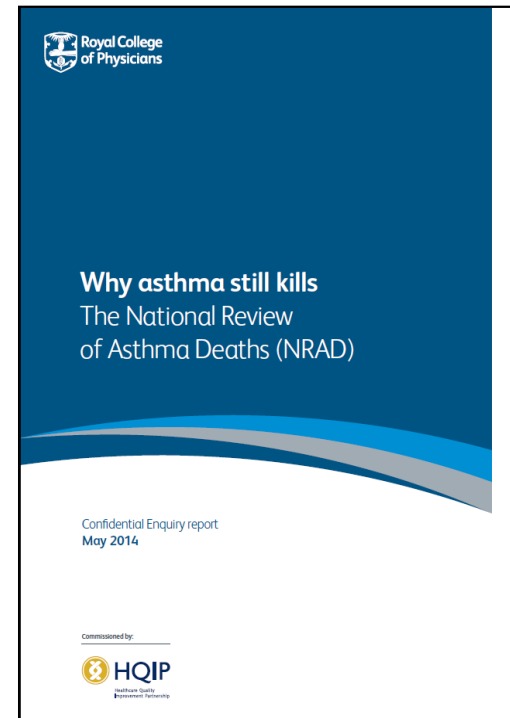
- National Review of Asthma Deaths
- Generic prescribing
- MHRA DSUs
- Pneumonia
- Over-prescribing of ICS
- Inhaler technique
- Poor adherence



National Review of Asthma Deaths

Analysis of 195 deaths (Feb 2012 – Jan 2013):

- 43%: no asthma review in 12 months
- 57%: no specialist care
- 67%: no asthma action plan
- 80%: sub-optimal Rx of preventers
- 39%: Rxed 12+ SABAs in 12 months



Safety concerns can arise with all inhalers – recent cases

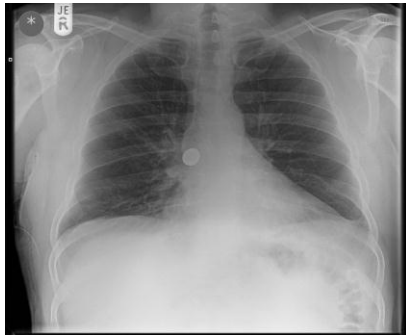


npj | Primary Care Respiratory Medicine www.nature.com/npjprm

ARTICLE OPEN

Is the 'blue' colour convention for inhaled reliever medications important? A UK-based survey of healthcare professionals and patients with airways disease

Monica Fletcher¹, Jane Scullion², John White³, Bronwen Thompson⁴ and Toby Capstick⁵



Foreign body inhalation from salbutamol inhaler
(*BMJ Case Rep.* 2014; 2014: bcr2013202248)



Braltus Zonda Safety Concern

Two patients in North Derbyshire have incorrectly put the capsule into the mouthpiece of their Braltus Zonda inhaler instead of into the central chamber, putting them at risk of choking.

Wiltshire CCG. *Script Medicines Management Newsletter.* May 2017. Issue 117



9 Apr 2016

Just found this. Switched to Sirdupla last week, have bad reaction: more wheezing + coughing + sore throat. Was fine on Seretide

← ↻ ♥

Any other #asthmatics have probs with DuoResp Spiromax inhalers? Powder makes me wheeze. Used to have Symbicort (same drug) with no probs.

31 Mar 2015 09:14



Drug Safety Update



MHRA

Braltus (tiotropium): risk of inhalation of capsule if placed in the mouthpiece of the inhaler

Train patients to place the Braltus capsule in the correct chamber of the Zonda inhaler. We have received reports of patients who have inhaled a Braltus capsule from the mouthpiece into the back of the throat, resulting in coughing and risking aspiration or airway obstruction.

May 2018

Pressurised metered dose inhalers (pMDI): risk of airway obstruction from aspiration of loose objects

Remind patients to check and remove the mouthpiece cover properly before inhaling a dose and to shake the inhaler to remove loose objects that may have become trapped in the inhaler during storage. The mouthpiece cover should be replaced securely after use. We have received reports of patients who have inhaled objects into the back of the throat, resulting in coughing. In some cases, objects were aspirated, causing airway obstruction.

July 2018

Generic Prescribing

- **Budesonide/formoterol**



Symbicort
Turbohaler



DuoResp
Spiromax



Fobumix
Easyhaler

- **Beclometasone/formoterol**



pMDI



NEXThaler

- **Fluticasone/salmeterol**



Seretide
Accuhaler



AirFluSal
Forspiro



Aerivio
Spiromax



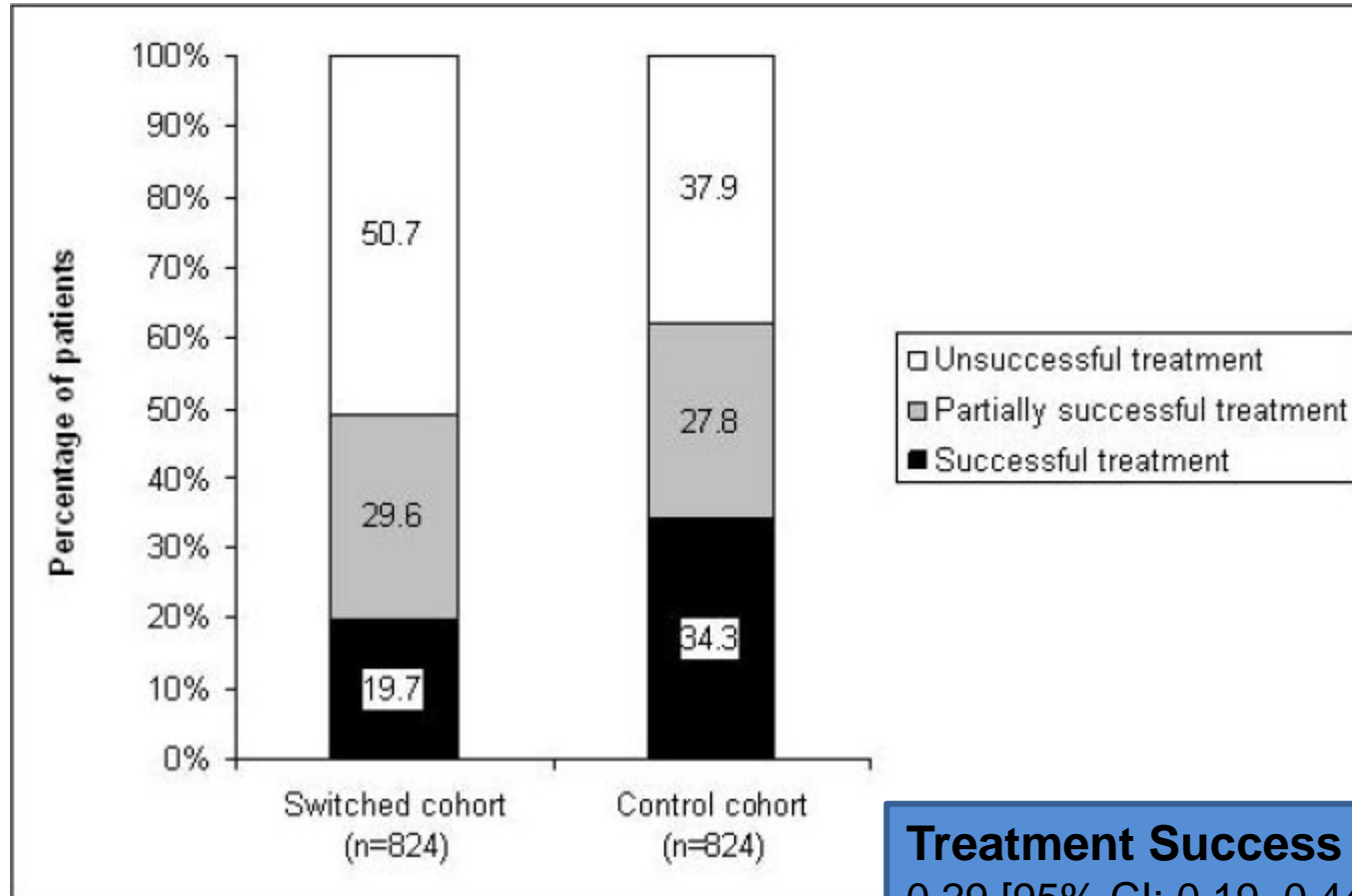
Generic prescribing of inhalers should be avoided as this might lead to people with asthma being given an unfamiliar inhaler device which they are not able to use properly.

BTS/SIGN Asthma Guidelines 2016

1.2.16 When prescribing long-acting drugs, ensure people receive inhalers they have been trained to use (for example, by specifying the brand and inhaler in prescriptions). [2018]

NICE COPD Guidelines (DRAFT) 2018

Switching Inhaler Devices: Effect of unconsented switch (Asthma)



Treatment Success OR:
0.29 [95% CI: 0.19, 0.44; p<0.001)



Pneumonia Risk with ICS

- COPD: Class effect for all ICS
 - No evidence of lower risk with any ICS compared to any other¹
 - (lack of comparative studies; different patient populations in studies)
 - IMPACT:² pneumonia rate of 95.8 (Trelegy) vs. 61.2 (Anoro) per 1000 patient-years (diff = 34.6).
 - TRIBUTE:³ pneumonia rate of 45 (Trimbow) vs. 41 (Ultibro) per 1000 patients-years (diff = 4).
 - Suggests 9-fold increased risk of pneumonia for Trelegy vs. Trimbow.
 - But: IMPACT recruited population with more severe disease and frequent exacerbators.
- Limited evidence for increased risk in asthma
 - Possible additional 1.44 pneumonias per 1,000 patient-years of treatment.⁴



Asthma: Overuse of ICS

Dose - response curve for inhaled corticosteroids

Top of clinical dose response curve:

Clenil Modulite 200mcg 2 puffs BD
Qvar 100mcg 2 puffs BD

Flutiform 125/10 MDI 2 puffs BD
Fostair 100/6 MDI 2 puffs BD
Seretide 125 MDI 2 puffs BD
Seretide 250 Accuhaler 1 puff BD
Symbicort 200/6 Turbohaler 2 puffs BD

90% effect achieved at doses:

Clenil Modulite 100mcg 2 puffs BD
Qvar 50mcg 2 puffs BD

Flutiform 50/5 MDI 2 puffs BD
Fostair 100/6 MDI 1 puff BD
Seretide 50 MDI 2 puffs BD
Seretide 100 Accuhaler 1 puff BD
Symbicort 100/6 Turbohaler 2 puffs BD

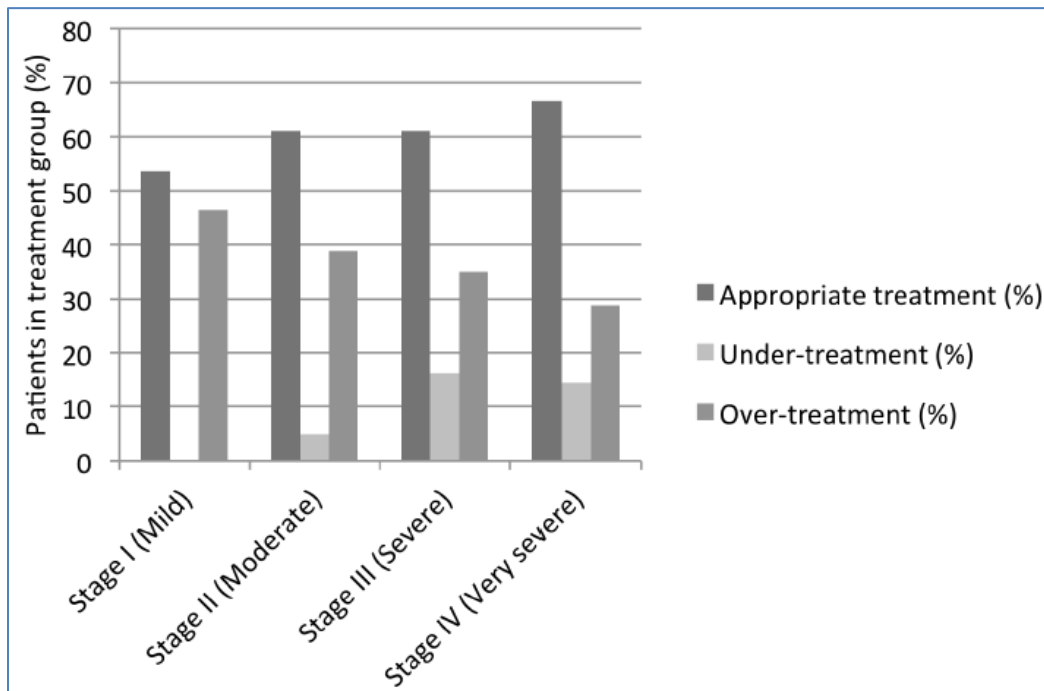
0 50 100 200 400 600 800 1000

Daily dose of inhaled steroid (FP ug)

1. Masoli M et al. Thorax 2004; 59:16-20
2. Holt S et al. BMJ 2001; 323:253-256

COPD: Overuse of ICS

- 41 London General Practices
- 3,537 patients with COPD diagnosis. 709 (29%) did not have COPD on spirometry.



Overall:

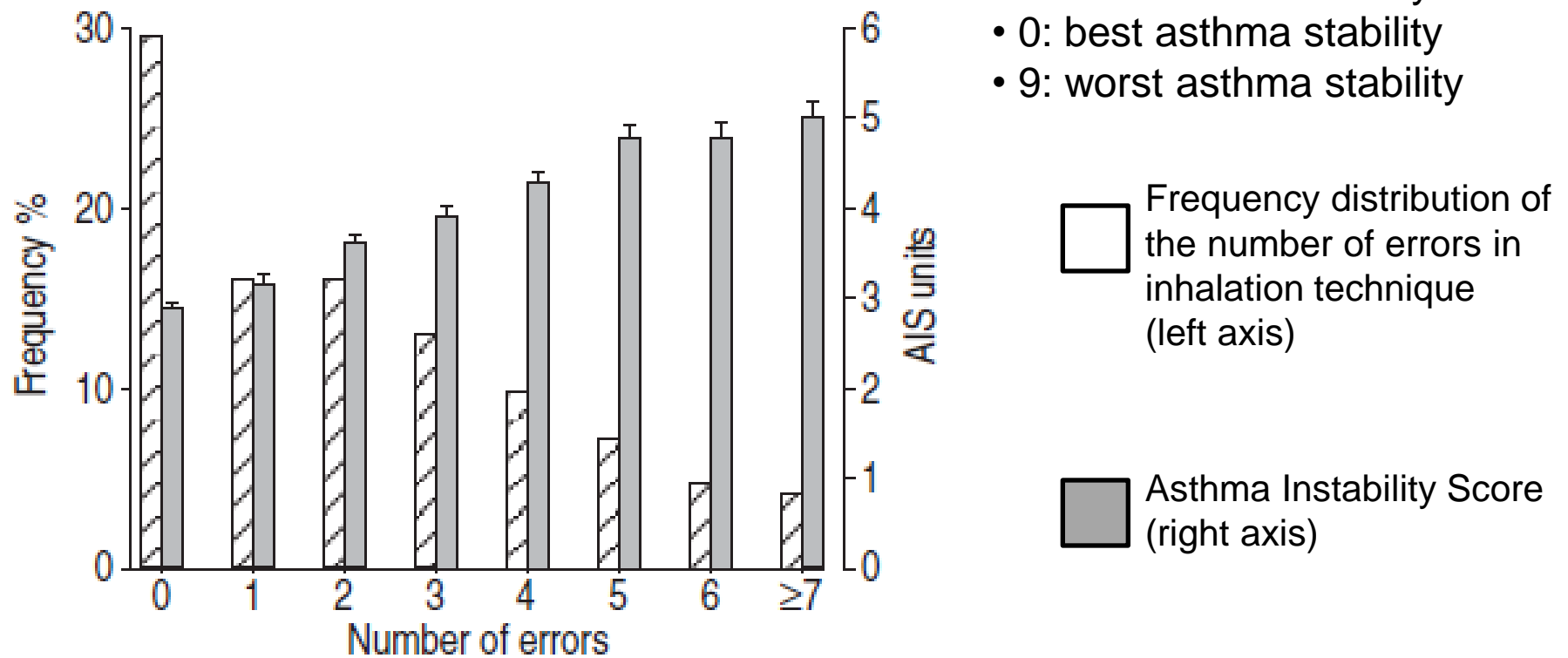
- 8.6% under-treated
- 38% over-treated

Inappropriate ICS Rx:

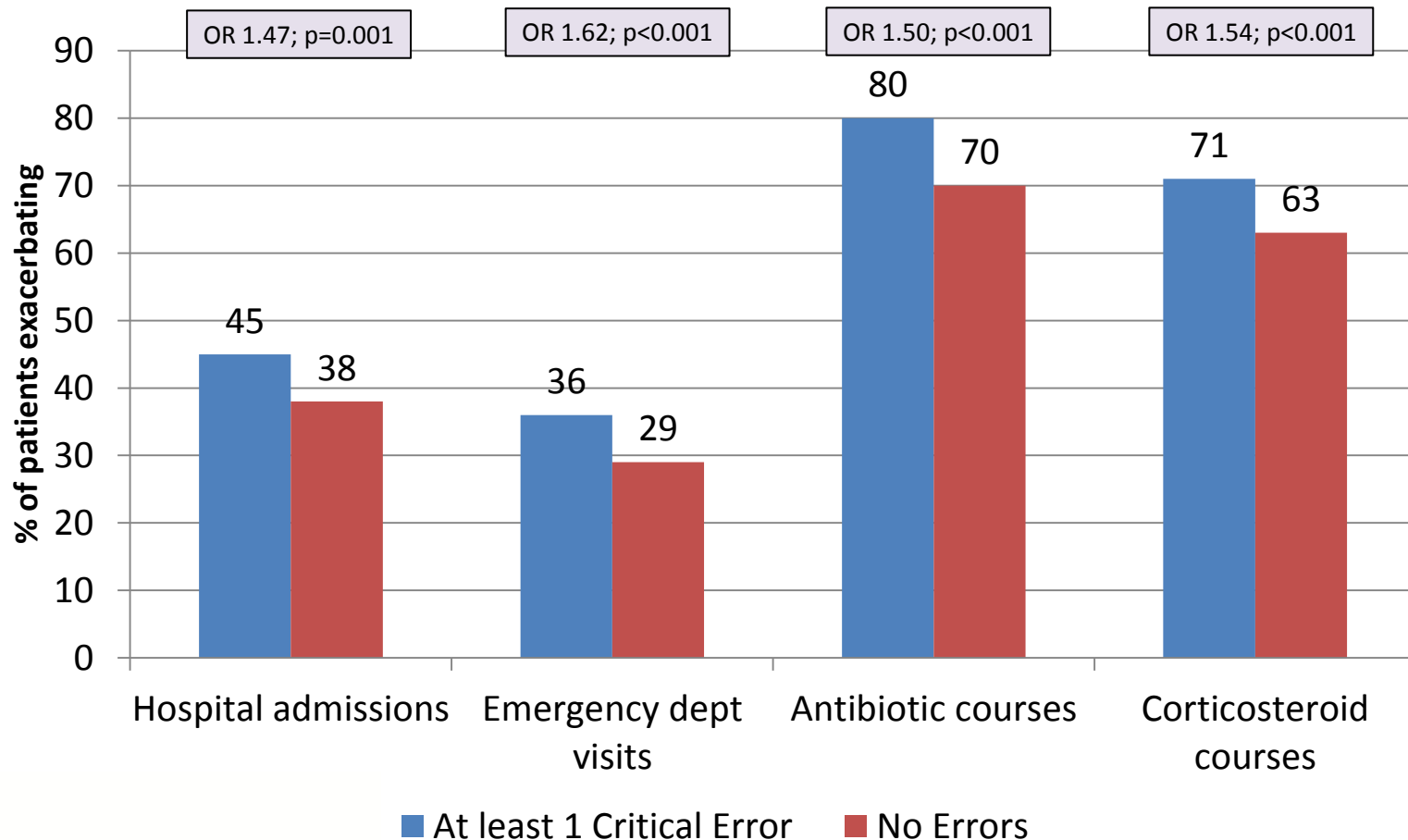
- 38% in GOLD stage I & II
- 33.6% in GOLD stage III & IV non-exacerbators.
- 12 serious pneumonias in 897 inappropriately treated.

Inhaler technique:

Misuse of Inhalers is Associated with Decreased Asthma Stability



Association Between Inhaler Technique and COPD exacerbations



The Good Old days



- 50-75% of patients make errors using common inhaler devices (Accuhaler, pMDI, Turbohaler).¹
- Between 1:3 and 1:10 patients make '*critical*' (serious) errors using these inhalers.¹
- **8%** of healthcare professionals can use a pMDI correctly.²



Risks of Non-Adherence

- National Review of Asthma Deaths 2014:
 - 80% had evidence of poor adherence from prescription records
 - 38% collected <4 preventer inhalers in previous the 12 months
- Increased hospitalisation rates
- Increased symptoms and reduced QoL



Can we improve adherence?

- Medical concordance interview
 - 37% of non-concordance patients improved
 - Reduced daily ICS
 - Reduced prednisolone courses
 - Reduced hospital admissions
- Subsequent nurse-led interventions
 - 62% of non-concordance patients improved
 - Reduced oral maintenance steroid



Summary

- **Sup-optimal** prescribing and use of respiratory medicines is widespread amongst **patients** and **healthcare professionals**.
- **New inhaled drugs & devices** provide opportunities for greater patient choice & may assist in medicines optimisation.
- **Patient involvement** in prescribing decisions is essential.
- **Greater Cost Savings** can be achieved through **cost-effective & rational prescribing** rather than by simple script switches.

