HSN'S FORMULARY ALTERNATIVES FOR STABLE COPD

Which drug comes with which device?

Long-Acting Bronchodilators

LAMAs

- LONG ACTING MUSCARINIC ANTAGONISTS

  Blocks acetylcholine-mediated bronchoconstriction (M3)

  - Aclidinium
  - Glycopyrronium
  - Tiotropium
  - Umeclidinium

LABAs

- LONG ACTING BETA AGONIST

  Direct relaxant activity on airway smooth muscle (β_2)

  - Indacaterol
  - Formoterol
  - Olodaterol
  - Salmeterol
  - Vilanterol

Spina D. *Eur Clin Respir J*. 2015;2:26634.

Which did we already have on formulary?
Long-Acting Bronchodilators

LAMAs

- LONG ACTING MUSCARINIC ANTAGONISTS

  Blocks acetylcholine-mediated bronchoconstriction (M3)

  - Aclidinium
  - Glycopyrronium
  - Tiotropium
  - Umeclidinium

LABAs

- LONG ACTING BETA AGONIST

  Direct relaxant activity on airway smooth muscle (β_2)

  - Indacaterol
  - Formoterol
  - Olodaterol
  - Salmeterol
  - Vilanterol

Spina D. *Eur Clin Respir J*. 2015;2:26634.

LAMA Monotherapies

LAMAs	Brand Name	Device
Aclidinium	*Incruse*	Ellipta
Glycopyrronium	*Seebri*	Breezhaler
Tiotropium	*Spiriva*	HandiHaler Respimat
Umeclidinium	*Tudorza*	Genuair

Spina D. *Eur Clin Respir J*. 2015;2:26634.

LABA Monotherapies

LABA Monotherapies	Brand Name	Device	
Formoterol	*Oxeze*		**Turbuhaler**
Indacaterol	*Onbrez*		**Breezhaler**
Salmeterol	*Serevent*		**Diskus**

Spina D. *Eur Clin Respir J*. 2015;2:26634.

Fixed-Dose Combination (FDCs) LAMA/LABAs

LAMA	+	LABA	Combination Brand	Device
Umeclidinium		Vilanterol	Anoro	Ellipta
Tiotropium		Olodaterol	Inspilto	Respimat
Glycopyrronium		Indacaterol	Ultibro	Breezhaler
Aclidinium		Formoterol	Duaklir	Genuair

Singh D. *Br J Clin Pharmacol*. 2014;79:695-708.

Only Respimat **Device** Options

Respimat Options	Brand Name	Device
Tiotropium	**Spiriva**	
Tiotropium **Olodaterol**	**Inspiolto**	

*All options are ***2*** *inhalations* **once** a day*

Singh D. *Br J Clin Pharmacol*. 2014;79:695-708.

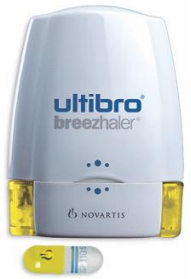
Only LAMA or LABA/LAMA Ellipta **Device** Options

Ellipta Options	Brand Name	Device
Umeclidinium	**Incruse**	
Umeclidinium + **Vilanterol**	**Anoro**	

*All options are **once** a day*

Singh D. *Br J Clin Pharmacol*. 2014;79:695-708.

Only Breezhaler **Device** Options

Breezhaler Options	Brand Name	Device
Glycopyrronium	**Seebri**	
Indacaterol	**Onbrez**	
Glycopyrronium + **Indacaterol**	**Ultibro**	

*All options are **once** a day*

Singh D. *Br J Clin Pharmacol*. 2014;79:695-708.

Only Genuair Options

Genuair Options	Brand Name	Device
Aclidinium	**Tudorza**	
Aclidinium + **Formoterol**	**Duaklir**	

*All options are **twice** daily*

Singh D. *Br J Clin Pharmacol*. 2014;79:695-708.

Let's See How I Did this Time!

- What drug (brand or generic) am I if I am…….?
  - Once a day
  - Respimat device
  - LAMA Monotherapy….

Let’s See How I Did this Time!

LAMAs	Brand Name	Device
Aclidinium	***Incruse***	
Glycopyrronium	***Seebri***	
Tiotropium	***Spiriva***	
Umeclidinium	***Tudorza***	

Spina D. *Eur Clin Respir J*. 2015;2:26634.

Let's See How I Did this Time!

LAMAs	Brand Name	Device
Aclidinium	*Incruse*	Ellipta
Glycopyrronium	*Seebri*	Breezhaler
Tiotropium	*Spiriva*	HandiHaler Respimat
Umeclidinium	*Tudorza*	Genuair

Spina D. *Eur Clin Respir J*. 2015;2:26634.

Let's See How I Did this Time!

- What drug (brand or generic) am I if I am……?
  - Twice a day
  - Genuair Device
  - LAMA/LABA COMBO…

Fixed-Dose Combination (FDCs) LAMA/LABAs

LAMA	+	LABA	Combination Brand	Device
Umeclidinium		Vilanterol	Anoro	
Tiotropium		Olodaterol	Inspilto	
Glycopyrronium		Indacaterol	Ultibro	
Aclidinium		Formoterol	Duaklir	

Singh D. *Br J Clin Pharmacol*. 2014;79:695-708.

Fixed-Dose Combination (FDCs) LAMA/LABAs

LAMA	+	LABA	Combination Brand	Device
Umeclidinium		Vilanterol	Anoro	Ellipta
Tiotropium		Olodaterol	Inspilto	Respimat
Glycopyrronium		Indacaterol	Ultibro	Breezhaler
Aclidinium		Formoterol	Duaklir	Genuair

Singh D. *Br J Clin Pharmacol*. 2014;79:695-708.

Let's See How I Did this Time!

- What drug (brand or generic) am I if I am…….?
  - Once a day
  - Ellipta device
  - LAMA Monotherapy….

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

Jadwiga A. Wedzicha, M.D., Donald Banerji, M.D., Kenneth R. Chapman, M.D., Jørgen Vestbo, M.D., D.M.Sc., Nicolas Roche, M.D., R. Timothy Ayers, M.Sc., Chau Thach, Ph.D., Robert Fogel, M.D., Francesco Patalano, M.D., and Claus F. Vogelmeier, M.D., for the FLAME Investigators*

N Engl J Med 2016; 374:2222-2234 | June 9, 2016 | DOI: 10.1056/NEJMoa1516385

BACKGROUND

Most guidelines recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid or a long-acting muscarinic antagonist (LAMA) as the first-choice treatment for patients with chronic obstructive pulmonary disease (COPD) who have a high risk of

MEDIA IN THIS ARTICLE

FIGURE 1

RELATED ARTICLES

EDITORIAL

Another Choice for Prevention of COPD Exacerbations

June 9, 2016 | J.F. Donohue

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD

Helgo Magnussen, M.D., Bernd Disse, M.D., Ph.D., Roberto Rodriguez-Roisin, M.D., Anne Kirsten, M.D., Henrik Watz, M.D., Kay Tetzlaff, M.D., Lesley Towse, B.Sc., Helen Finnigan, M.Sc., Ronald Dahl, M.D., Marc Decramer, M.D., Ph.D., Pascal Chanez, M.D., Ph.D., Emiel F.M. Wouters, M.D., Ph.D., and Peter M.A. Calverley, M.D., for the WISDOM Investigators*

N Engl J Med 2014; 371:1285-1294 | October 2, 2014 | DOI: 10.1056/NEJMoa1407154

Comments open through October 8, 2014

BACKGROUND

Treatment with inhaled glucocorticoids in combination with long-acting bronchodilators is recommended in patients with frequent exacerbations of severe chronic obstructive pulmonary disease (COPD). However, the benefit of inhaled glucocorticoids in addition to two long-acting bronchodilators has not been fully explored.

Full Text of Background

MEDIA IN THIS ARTICLE

FIGURE 1

Enrollment and

Let’s See How I Did this Time!

	Brand Name
Aclidinium	***Incruse***
Glycopyrronium	***Seebri***
Tiotropium	***Spiriva***
Umeclidinium	***Tudorza***

Spina D. *Eur Clin Respir J*. 2015;2:26634.

Let's See How I Did this Time!

LAMAs	Brand Name	Device
Aclidinium	*Incruse*	Ellipta
Glycopyrronium	*Seebri*	Breezhaler
Tiotropium	*Spiriva*	HandiHaler Respimat
Umeclidinium	*Tudorza*	Genuair

Spina D. *Eur Clin Respir J*. 2015;2:26634.

Short-Acting Bronchodilators (SAMA & SABA)

Class	Drug	Device	Dose	MOA	Onset	Duration	Cost
SABA	Salbutamol (Ventolin)	Diskus 200mcg	1 puff QID prn	Binds to β2 pulmonary receptors, which increases cAMP; cAMP responsible for the relaxation of bronchial smooth muscle	<5 min	4-6h	Diskus: $38 MDI: $17* Neb: $107* (LU: 265, 266, 267, 268)
		MDI 100mcg	1-2 puffs QID prn				
		Nebules 1.25, 2.5, 5mg/mL	2.5mg QID prn				
	Terbutaline (Bricanyl)	Turbuhaler 500mcg	1 puff QID prn				$20*
SAMA	Ipratropium (Atrovent)	MDI 20mcg	2 puffs QID prn	Binds to M3 pulmonary receptors, which blocks acetylcholine; resulting in relaxation of bronchial smooth muscle	<20 mins	6-8h	MDI: $33* Neb: $195* (LU: 265, 266, 267, 268)
		Nebules 250, 500mcg/2mL	1 neb QID prn				

* Denotes Ontario Drug Benefit coverage

Long-Acting Muscarinic Antagonists (LAMA)

Drug	Device	Dose	MOA	Onset	Duration	Cost
Tiotropium (Spiriva)	Handihaler 18mcg	1 cap inh once daily	Slow to dissociate from pulmonary M3 receptors, leading to long acting decreased smooth muscle contraction	5mins	24h	Both $87 (*Handihaler only covered)
	Respimat 2.5mcg	2 puffs once daily				
Aclindinium (Tudorza)	Genuair: 400mcg	1 puff BID		10mins	12h	$73*
Glycopyrronium (Seebri)	Breezehaler 50mcg	1 cap inh once daily		5mins	24h	$73*
Umeclidinium (Incruse)	Ellipta 62.5mcg	1 puff once daily		5-15mins	24h	$81

* Denotes Ontario Drug Benefit coverage

Long-Acting Beta-Agonists (LABA)

Drug	Device	Dose	MOA	Onset	Duration	Cost
Formoterol (Oxeze)				<5min	12h	Aerolizer: $69**
	Turbuhaler 6, 12mcg	6-12mcg inh BID	Slow to dissociate from pulmonary B2 receptors, leading to long acting bronchodilation			Turbuhaler: $63**
Salmeterol (Serevent)	Diskus 50mcg	1 puff BID		2h	12h	$77*(LU: 391)
Indacaterol (Onbrez)	Breezehaler 75mcg	1 cap inh once daily		<5min	24h	$65*(LU: 443)

* Denotes Ontario Drug Benefit coverage; **Denotes ODB coverage only for asthma

Combination Products

Class	Drug	Device	Dose	Cost
SABA+ SAMA	Salbutamol + Ipratropium (Combivent)	Nebules 2.5/0.5mg per 2.5mL	1 neb inh QID prn	$44*(generic coverage, 85% brand, LU: 256, 257, 258, 259)
		Respimat 20/100mcg	1 puff QID prn	$113
LAMA +LABA	Umeclidinium + Vilanterol (Anoro)	Ellipta 62.5/25 mcg	1 puff once daily	$107* (LU: 459)
	Glycopyrronium + Indacterol (Ultibro)	Breezhaler 50/110mcg	1 puff once daily	$105*(LU: 459)
	Tiotropium + Olodaterol (Inspiolto)	Respimat 2.5/2.5mcg	2 puffs once daily	$85
	Aclidinium + Formoterol (Duaklir)	Genuair 340/12mcg	1 puff BID	$98
LABA +ICS	Vilanterol + fluticasone (Breo)	Ellipta 25/100mcg	1 puff once daily	$153* (LU: 456)
	Salmeterol + fluticasone (Advair)	Diskus 50/100, 50/250, 50/500mcg	50/250mcg inhaled BID	$126**
	Formoterol + budesonide (Symbicort)	Turbuhaler 6/100, 6/200mcg	12/400mcg inh BID	$110**

*Denotes Ontario Drug Benefit coverage; **Denotes ODB coverage only for asthma

Questions you may have …

- Where do these agents fit in the treatment algorithm for patients with COPD?
- How does combination efficacy compare with monotherapy?
- What about inhaled corticosteroids (ICS)?

Presentation Outline

- **Clinical Drug Review**
  - **Introduction to HSN's New Formulary Review Process**
- **Available Devices**
  - **Personalized therapy**
- **Adherence**
  - **Ease of use**
  - **Device knowledge and competence**
- **Available Therapeutic Agents**
  - **Medication onset, mechanism of action, and goals of therapy for each agent**
  - **Introduction of Case Presentation**
- **Clinical Drug Review Case Presentation**
  - **Therapeutic Alternative Efficacy Data and Safety Data**

CLINICAL DRUG REVIEW CASE PRESENTATION

Meet SC

- 71 year old female, admitted 4 days ago for new onset T2DM (A1C 14%)
  - SC is being management on basal bolus insulin and her doses are being titrated daily
- She is eager to get her diabetes under control and taking to insulin administration well
- Lives at home alone, husband passed way in 2013
- 20 pack year history, quit 10 years ago, when she retired from teaching

SC's Chief Complaint

- 4 days after being admitted, the RN raises a concern with the MRP regarding symptoms of dyspnea on exertion.
- When SC walks to the washroom or up and down the hallway she takes frequent breaks to catch her breath.
- The patient's nurse asks SC if this is normal for her when she's at home?

History of Presenting Illness

- SC explains she walks 1 night a week with some friends and usually has to stop the group a few times to catch her breath.
  - SC said she would walk more often with her friends if it were not for her SOB
  - SC expressed her frustration with symptoms of fatigue when trying to exert herself

History of Presenting Illness

- SC denied a productive cough in the recent past or currently, but explained that she coughs often when she's SOB
- SC says she last saw her family doctor a year and a half ago and she doesn't recall her symptoms being as bad as they are currently

Exam, Labs, Investigation and Evaluation

- Troponin negative, ECG normal, CTA of Chest– No PE
- Vitals, CBC, Electrolytes normal: normal, RR at rest 19
- ABG: normal
- SpO2 Saturation: 93%
- CXR normal
- No wheezing or crackles; slightly prolonged expiration
- Dyspnea scale CAT score: 15
  - (> 10 is “**more symptoms**”)

SC's Past Medical History

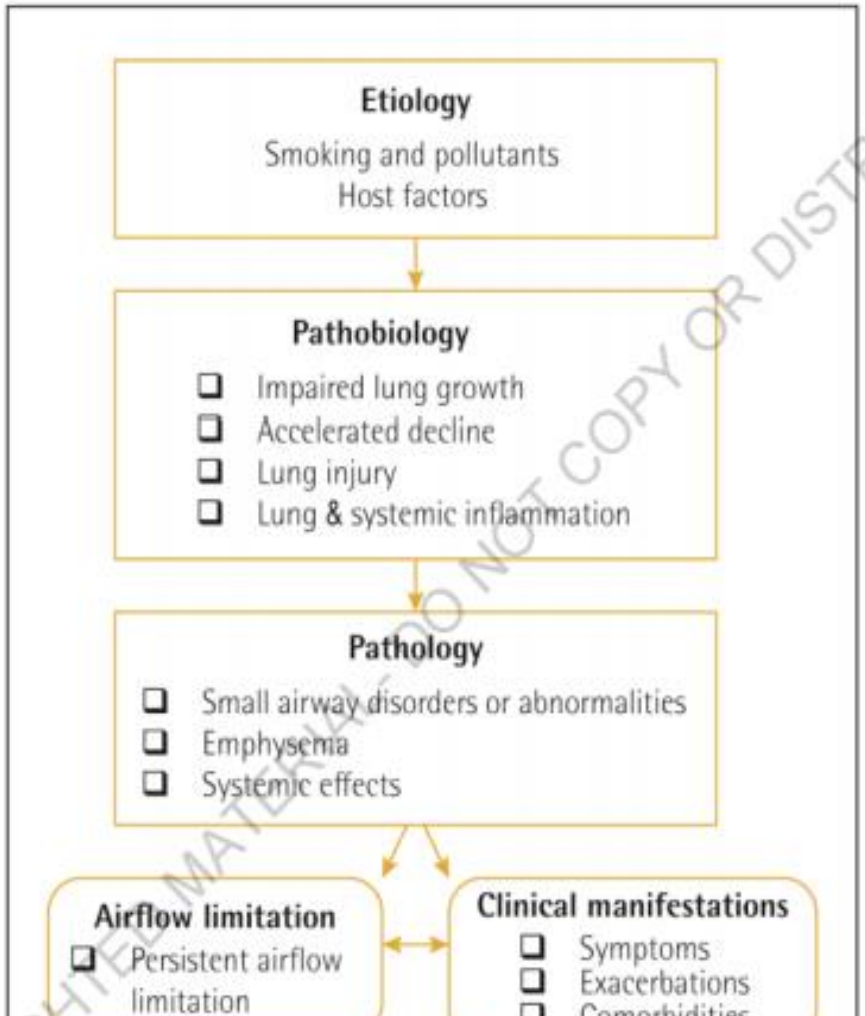
- Quit smoking 15 years ago when she retired from teaching
- Major Depression since (2012)
- Hypertension (2002)
- COPD diagnosed 20011, $FEV^1/FVC = 0.66$ (Sept 2014)
  - No exacerbation history, has never had a hospital admission or antibiotics for COPD
  - Demonstrated excellent inhaler technique, never misses dose
  - Other symptoms of dyspnea occur when SC goes up stairs

SC's Current Medications

- Salbutamol MDI 1-2 inhalations q6hrs PRN
- Escitalopram 10 mg po Daily
- Calcium 500 mg po BID
- Vitamin D3 1000 IU PO Daily
- Tiotropium 18 micrograms HandiHaler once daily
- Hydrochlorothiazide 25 mg po daily
- Amlodipine 5 mg po daily
- Insulin Glargine 16 units subQ at bedtime
- Insuline Glulisine 6 units subQ TIDCC

COPD Definition, Etiology, Pathophysiology…

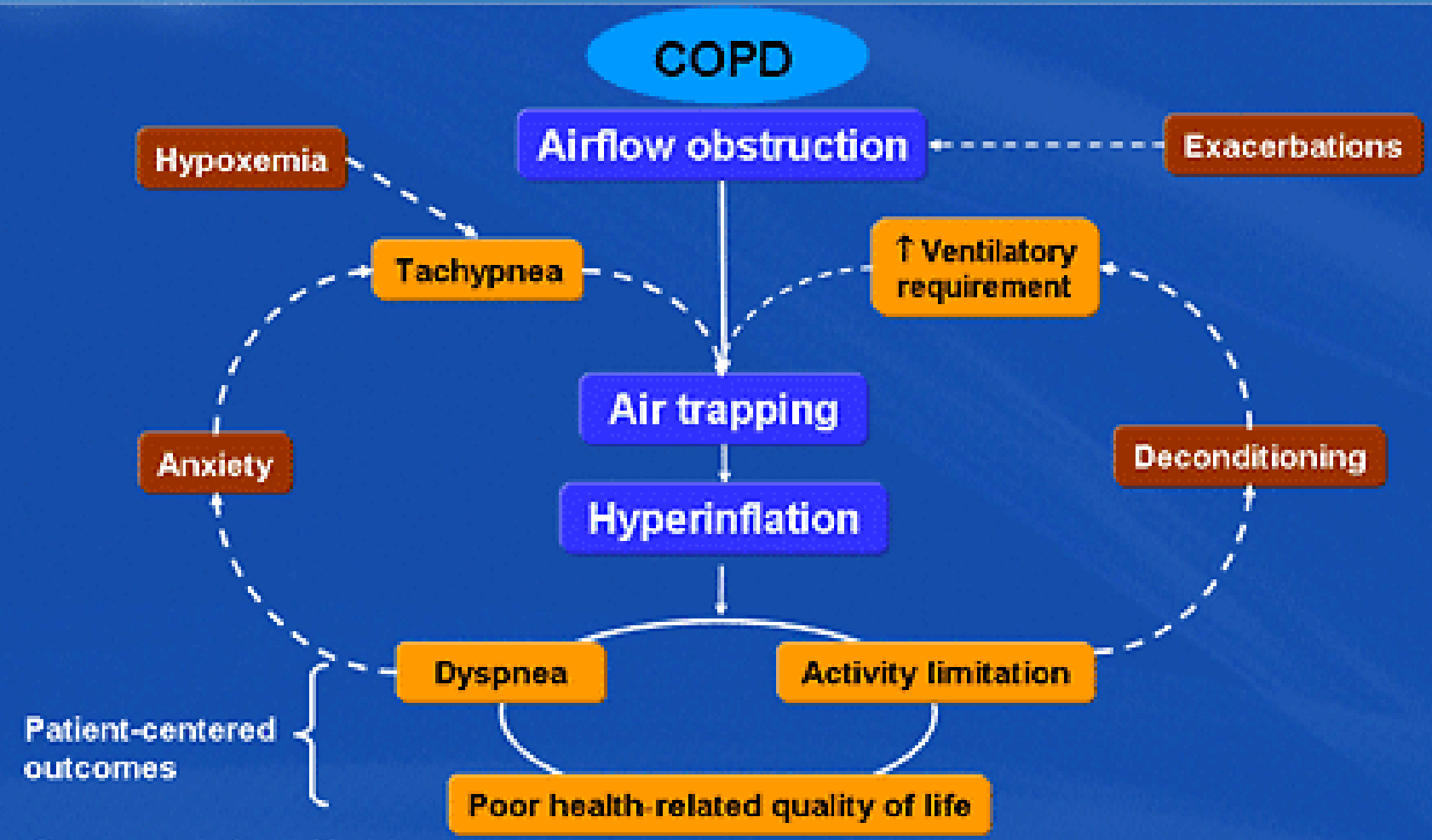
Figure 1.1. Etiology, pathobiology and pathology of COPD leading to airflow limitation and clinical manifestations



Burden of COPD

- In 2002 COPD was the fifth leading cause of death.
- Total deaths from COPD are projected to increase by more than 30% in the next 10 years unless urgent action is taken to reduce the underlying risk factors, especially tobacco use.
- Estimates show that COPD becomes in 2030 the third leading cause of death worldwide

Air Trapping Links Pathophysiology and Patient-Centered Outcomes in COPD



Cooper et al. *Am J Med*. In press.

Goals of Pharmacological Management of COPD

Reduce Symptoms

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

Reduce Risk

- Prevent and treat exacerbations
- Prevent disease progression
- Reduce mortality

http://www.goldcopd.org.

MRP's Assessment

- FVC/FEV1 < 0.7 standard for diagnosis
- FEV1 % Predicted: important prognostic tool

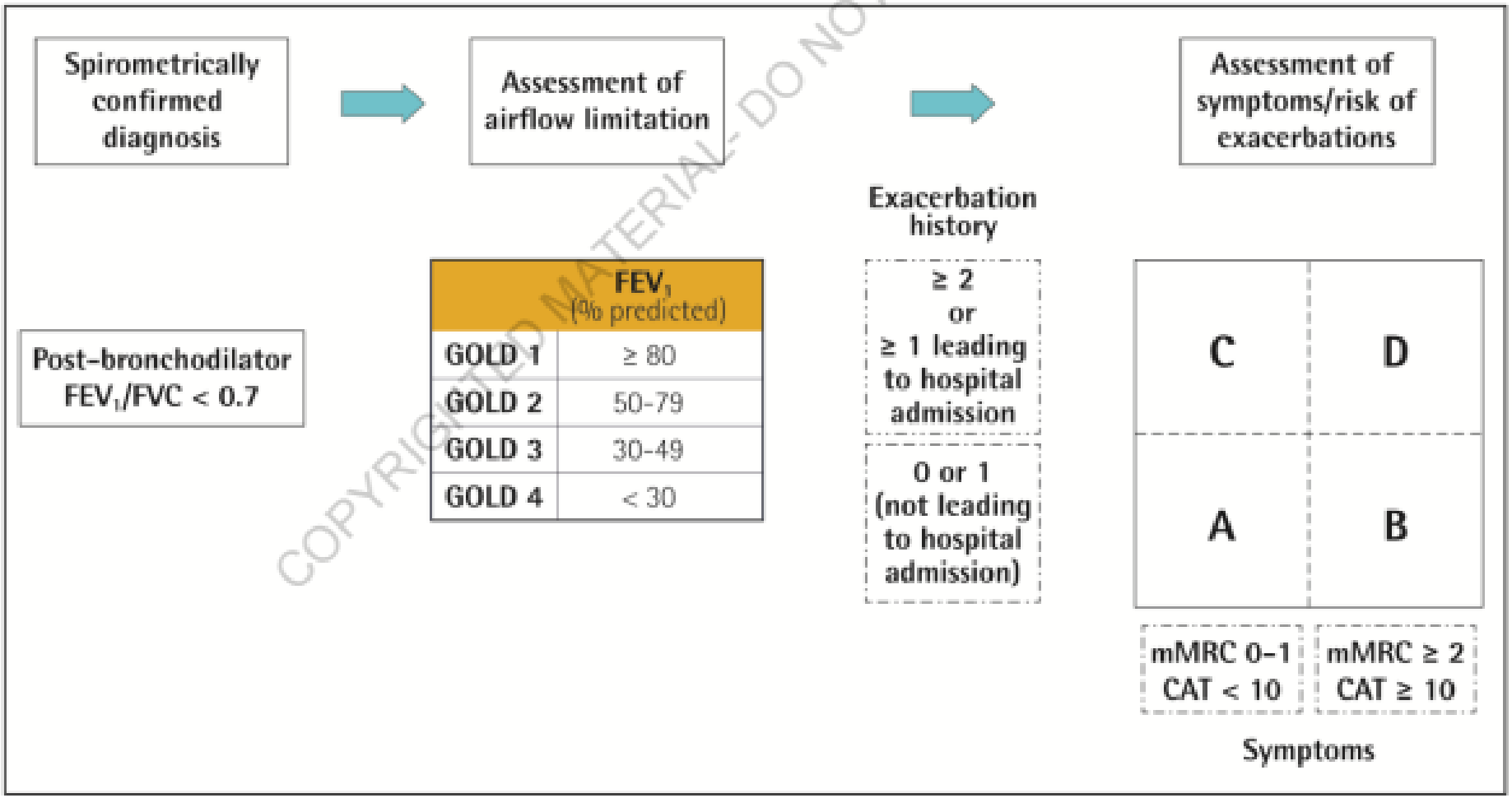
GOLD 2017 FEV1 not recommended to be used to make drug therapy treatment decisions as it can fluctuates too much and lacks sensitivity for guiding drug therapy decisions…….

- GOLD 2017 recommend treating based on
  - Symptom Scale (CAT or MMRC)

  and
  - Exacerbation history

GOLD 2017 Guidelines

Figure 2.4. The refined ABCD assessment tool



COPD Assessment Test (CAT)

Figure 2.3. CAT Assessment

For each item below, place a mark (✗) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy (0) (✗) (2) (3) (4) (5) I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE	

Reference: Jones et al. ERJ 2009; 34 (3): 648-54.

MMRC scale

Table 2.5. Modified MRC dyspnea scale[a]	
PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY) (Grades 0–4)	
mMRC Grade 0. I only get breathless with strenuous exercise.	❑
mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill.	❑
mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	❑
mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level.	❑
mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing.	❑

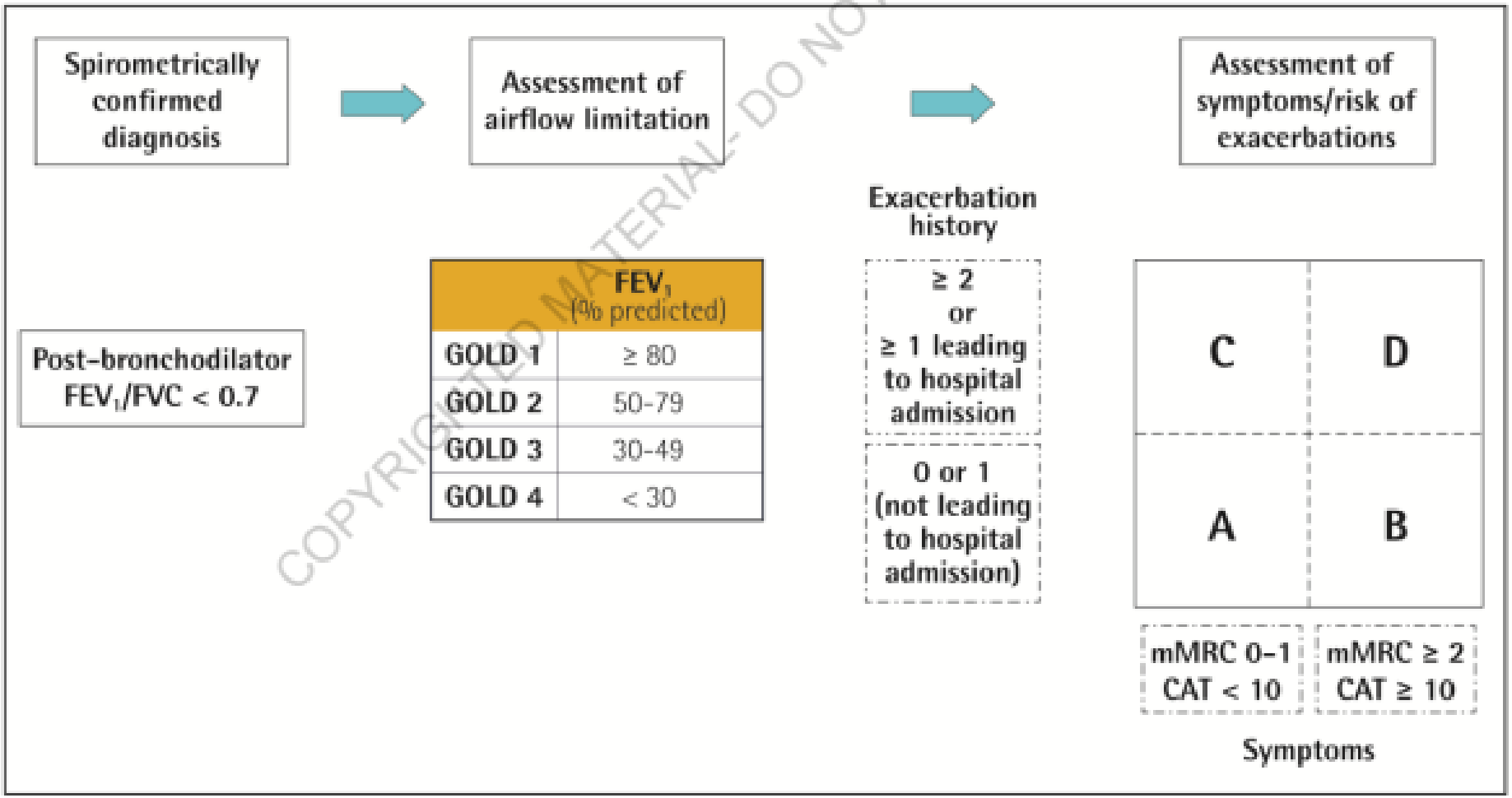
[a] Fletcher CM. BMJ 1960; 2: 1662.

COPD Assessment Test (CAT)

- GOLD 2017 defines "**more symptoms**" as a CAT > 10 or MMRC **≥** 2
- GOLD 2017 define "**less symptoms**" as CAT <10 or MMRC less than 2

GOLD 2017 Guidelines

Figure 2.4. The refined ABCD assessment tool



Assessment: GOLD B

- Group B patients have more significant symptoms but still low exacerbation risks.
  - Less than 2 exacerbation / year, none leading to hospitalization.

AND

  - "More Symptoms": CAT > 10 or MMRC **≥** 2
    - Dyspnea symptoms with ***mild*** exertion or symptoms of dyspnea interfering with daily activity
    - Short of breath when hurrying on level ground or walking up a slight hill

Problem

- Tiotropium has failed SC in meeting her goals of therapy for symptom management of COPD for a GOLD B patient
  - SC has a low exacerbation risk history and CAT > 10 indicating her persistent symptoms of dyspnea particularly in that she has to walk slower than her friends sometimes due to breathlessness and also symptoms of breathlessness in the morning when dressing.
- SC is experiencing symptoms of dyspnea that regularly interfere with her activities of daily living and she requires a switch to a more effective drug therapy to resolve or reduce these symptoms of dyspnea

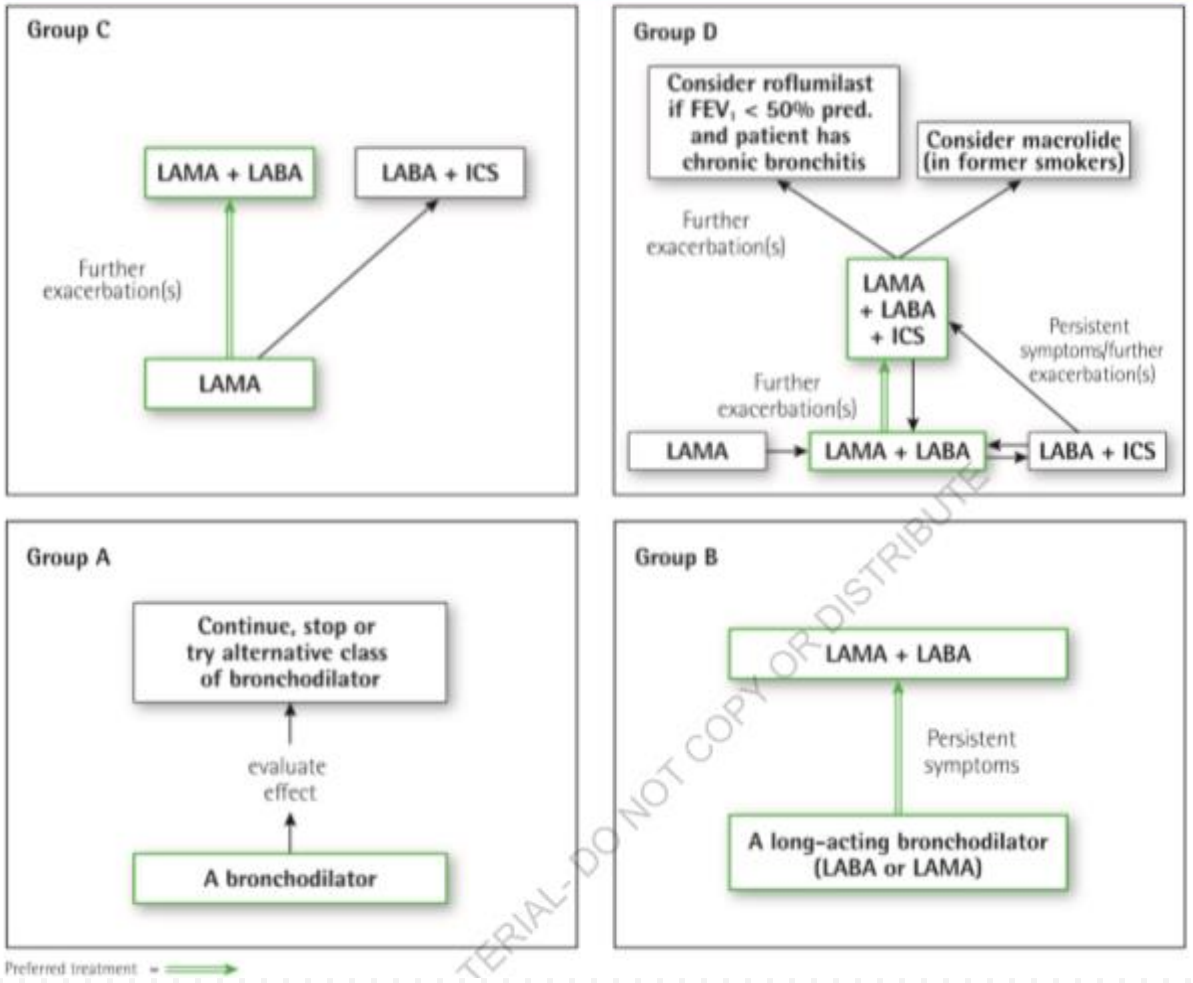
LAMA FAILURE!

Therapeutic Alternatives for SC

- *LABA Monotherapy
- *Different LAMA Monotherapy?
- *LABA + LAMA Combination
- ICS Monotherapy
- ICS/LABA Combination

GOLD 2017 Treatment Algorithm

Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]

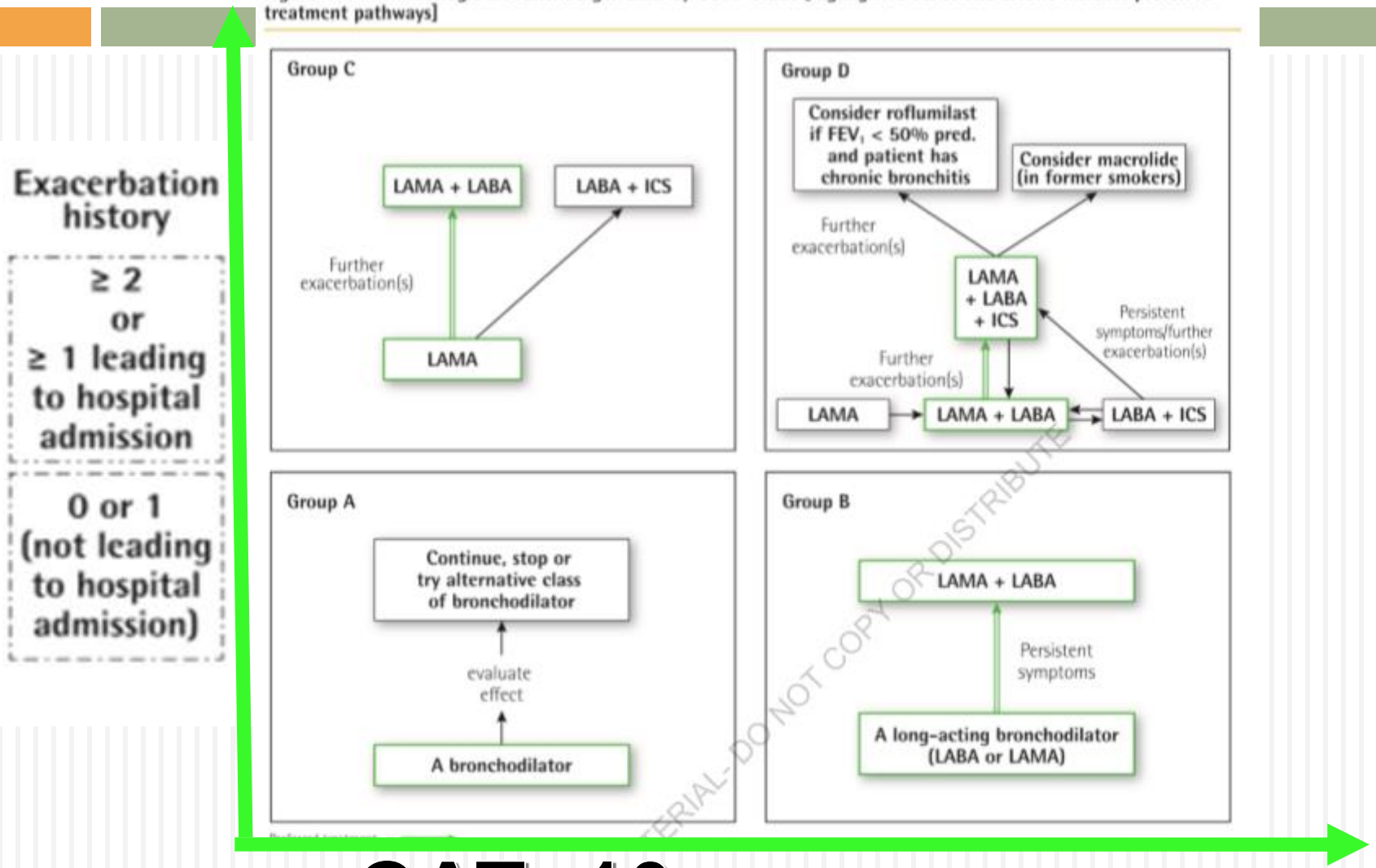


Increasing Exacerbation Risk

Increased Symptoms

GOLD 2017 Treatment Algorithm

Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]



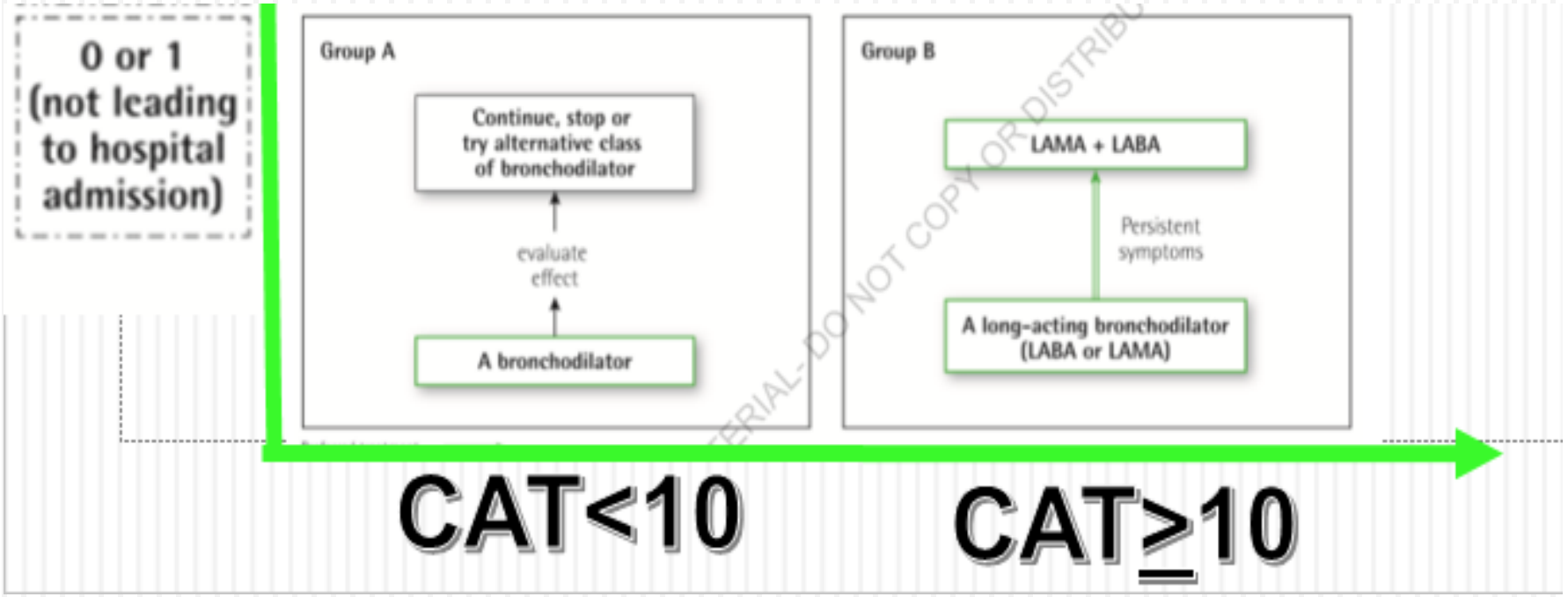
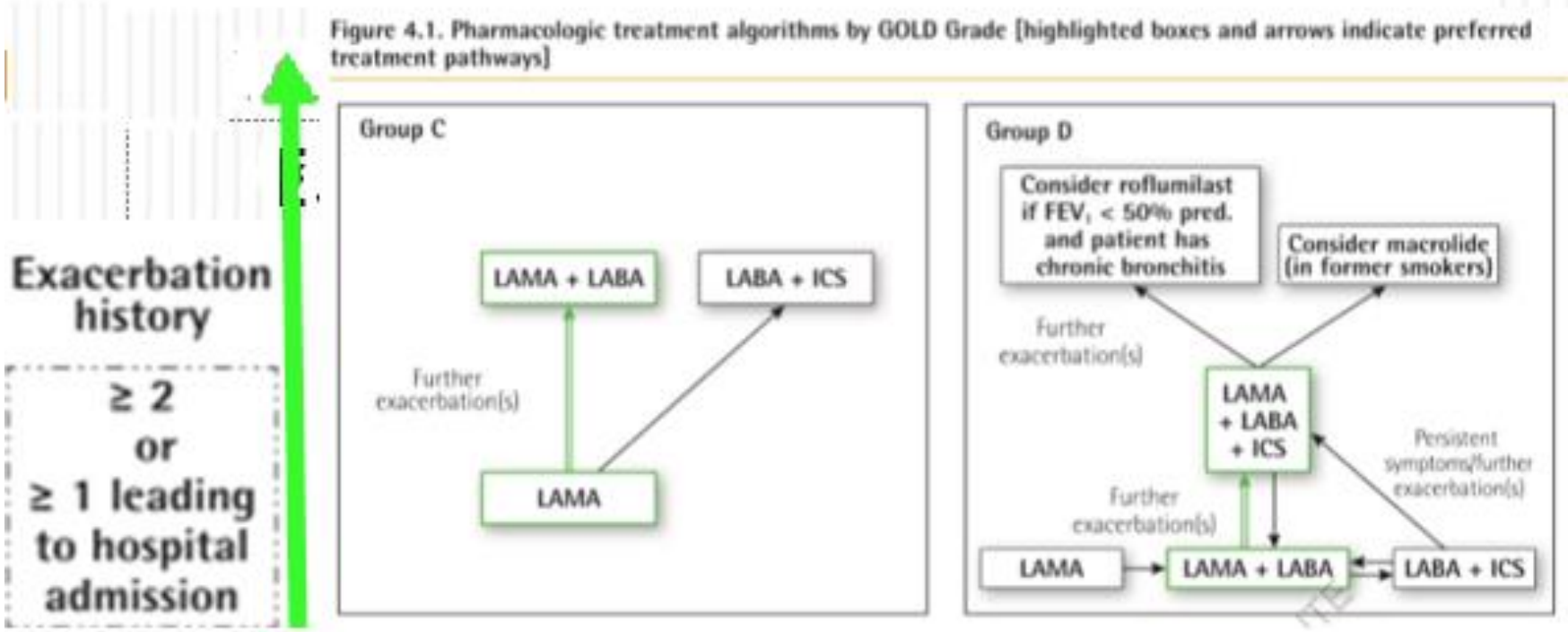

0 or 1 (not leading to hospital admission)
Group A
Continue, stop or try alternative class of bronchodilator
evaluate effect
A bronchodilator
Group B
LAMA + LABA
Persistent symptoms
A long-acting bronchodilator (LABA or LAMA)
CAT<10
CAT≥10

Figure 4.1. Pharmacologic treatment algorithms by GOLD Grade [highlighted boxes and arrows indicate preferred treatment pathways]



Guidelines: Canadian 2008

Canadian Thoracic Society recommendation for management of chronic obstructive pulmonary disease – 2008 update – highlights for primary care

Denis E O'Donnell MD[1*†], Paul Hernandez MD[2*†], Alan Kaplan MD[3], Shawn Aaron MD[4*], Jean Bourbeau MD[5*], Darcy Marciniuk MD[6*], Meyer Balter MD[7], Gordon Ford MD[8], Andre Gervais MD[9], Yves Lacasse MD[10], Francois Maltais MD[10], Jeremy Road MD[11], Graeme Rocker MD[2], Don Sin MD[11], Tasmin Sinuff MD[12], Nha Voduc MD[4]

DE O'Donnell, P Hernandez, A Kaplan, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2008 update – highlights for primary care. Can Respir J 2008;15(Suppl A):1A-8A.

Chronic obstructive pulmonary disease (COPD) is a major respiratory illness in Canada that is preventable and treatable but unfortunately

Recommandations de la Société thoracologie pour prendre en ch pulmonaire obstructive chroniq jour 2008 : Faits saillants des s

La maladie pulmonaire obstructive chronique (

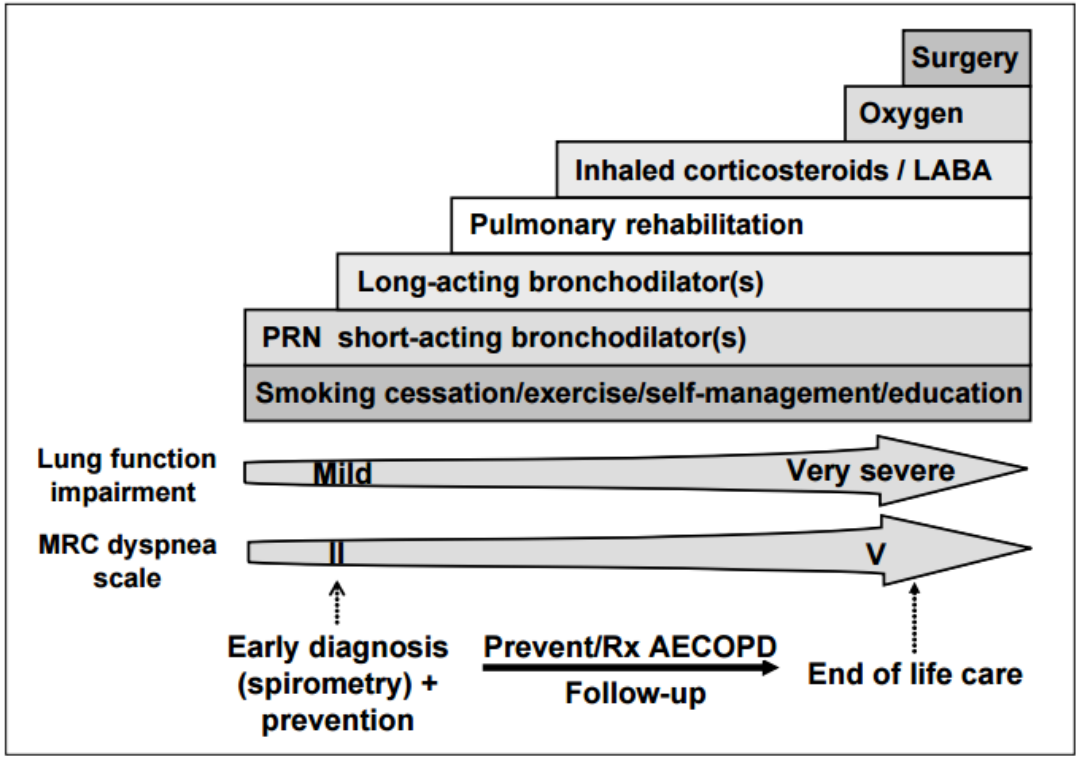


Figure 1) *A comprehensive approach to the management of chronic obstructive pulmonary disease (COPD). AECOPD Acute exacerbation of COPD; LABA Long-acting beta$_2$-agonist; MRC Medical Research Council; PRN As needed; Rx Treatment*

Efficacy Endpoints in 1º Literature

- FEV_1
- Health-related quality of life
- Symptom scales (CAT, MMRC, SGRQ)
- COPD exacerbations
- Mortality
- Exercise tolerance

Drug Class	Guideline Indication	Effectiveness	Safety	Convenience
LABA Monotherapy	+	+	+	++ 1-2 times per day
LAMA Monotherapy	+	+	+	++ 1-2 times per day
LABA + LAMA	++	++	+	++ 1-2 times per day
ICS Monotherapy	-	+	- Risk of pneumonia NNH 30	- Twice Daily Additional Device
ICS/LABA	- (Gold B)	+		

Head to Head Trials: Monotherapy with Long Acting Bronchodilators

Which LA**M**A or LA**B**A ?

- Tiotropium > LABA: 2 RCTs, 7384 pts
  - Tiotropium reduced exacerbation NNT 19. No difference in mortality or quality of life.
  - Tiotropium > salmeterol, placebo. 2 RCTs **Only** tiotropium > placebo for clinically important improved quality of life NNT 11 and reduced hospitalization NNT 10

Int J Chron Obstruct Pulmon Dis. 2013;8:405-23. *BMC Pulm Med*. 2014;14:4.

Head to Head Trials: LAMA VS LAMA

Int J 14;14:4.

Head to Head Trials: Monotherapy with Long Acting Bronchodilators

LAMA vs LAMA

- Umeclidinium = Aclidinium = Glycopyrronium = Tiotropium
- (FEV1 and symptoms of dyspnea)
  - Review 27 RCTs and 48,140 pts. (VS placebo)
    - The new LAMAs studied had at least comparable efficacy to tiotropium for FEV1, SGRQ, Exacerbations, Hospitalization
- Glycopyrronium vs Tiotropium 3 RCT
  - No statistical significance differences for
    - exacerbation, FEV1, SGRQ

Int J Chron Obstruct Pulmon Dis. 2013;8:405-23. *BMC Pulm Med*. 2014;14:4.

Respimat Data: Tiotropium

- Tiotropium Soft Myst Inhaler
  - Handihaler > Respimat. Systematic Review: 22 RCTs (23,309 pts)
    - NNH 143 for mortality for the Respimat
  - TIOSPIR (2.3 yrs, 17,135 pts): respimat mortality = handihaler; but healthy population is the criticism, FEV1 was > 60% predicted

1) Cochrane Database Syst Rev. 2014;7:CD009285. 2) Pulm Pharmacol Ther. 2014;;28:91- *Respir Med* 2010, **104:**1179-1188 3) Int J Chron Obstruct Pulmon Dis. 2013;8:221-30. doi: 10.2147/COPD.S31246. Epub 2013 Apr 3

LAMAs are considered equivocal

Drug Class	Guideline Indication	Effectiveness	Safety	Convenience
LABA Monotherapy	+	+	+	++ 1-2 times per day
LAMA Monotherapy	+	+	+	++ 1-2 times per day
LABA + LAMA	++	++	+	++ 1-2 times per day
ICS Monotherapy	-	+	- Risk of pneumonia NNH 30	- Twice Daily Additional Device
ICS/LABA	- (Gold B)	+		

Head to Head: LABA vs Steroid Monotherapy

- LABA vs Inhaled Steroid, Review 7 RCTs, 5997 pts
  - No difference in exacerbation or quality of life
  - Steroids increased pneumonia and approached statistically significant increased mortality
  - NNH 30 for pneumonia
  - NNH 27 for voice changes
  - NNH 30 for oral candidiasis
- **Gold 2017 Recommendation**
  - ICS/LAMA combination can be considered in patient with high risk history of exacerbation
  - Long-term ICS monotherapy no recommended

Drug Class	Guideline Indication	Effectiveness	Safety	Convenience
LABA Monotherapy	+	+	+	++ 1-2 times per day
LAMA Monotherapy	+	+	+	++ 1-2 times per day
LABA + LAMA	++	++	+	++ 1-2 times per day
ICS Monotherapy	-	+	- Risk of pneumonia NNH 30	- Twice Daily Additional Device
ICS/LABA	- (Gold B)	+		

Remaining Therapeutic Alternatives

LAMA	+	LABA	Combination Brand	Device
Umeclidinium		Vilanterol	Anoro	Ellipta
Tiotropium		Olodaterol	Inspilto	Respimat
Glycopyrronium		Indacaterol	Ultibro	Breezhaler
Aclidinium		Formoterol	Duaklir	Genuair

Singh D. *Br J Clin Pharmacol*. 2014;79:695-708.

Remaining Therapeutic Alternatives

LAMA + **LABA**

Efficacy/Safety Data

SPARK and SHINE Trial:

Glycopyrronium **Indacaterol**

Ultibro

•superior to tiotropium, indacaterol and glycopyrronium monotherapies for exacerbation reduction, FEV1, Dyspnea
•Incidence of serious adverse events was similar between groups.

Trial by Donahue and Systematic Review

Umeclidinium **Vilanterol**

Anoro

•Superior to monotherapies for FEV 1, symptoms of dyspnea and Exacerbation
•Regarding safety issues, the incidence of AEs, CVEs, and mortality on treatment was similar across treatments.

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Remaining Therapeutic Alternatives

LAMA + **LABA**

Efficacy/Safety Data

Aclidinium **Formoterol**

Duaklir

ACLIFORM, AUGENT Trails, and Systematic Review:

• superior to monotherapies to FEV1 and superior to placebo for symptoms of dyspnea, and exacerbation.
•In both trials, adverse effects were no different than placebo.

Tiotropium **Olodaterol**

Inspiolto

TORNADO Trial and Systematic Review

•Tiotropium + olodaterol respimat versus montherapies was found to be superior for FEV1 and symptoms of dyspnea.

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Remaining Therapeutic Alternatives

LAMA + LABA

Glycopyrronium / Indacaterol

Ultibro

Umeclidinium / Vilanterol

Anoro

Aclidinium / Formoterol

Duaklir

Tiotropium / Olodaterol

Inspiolto

Device Convenience

Advantages
- Rattling or whirring = correct inhalation
- Low inspiratory effort needed

Disadvantages
- Multi-step process: May difficult for patients with poor manual dexterity or cognitive impairment
- Capsules are packaged in foil blisters; may be difficult to remove and are light and moisture sensitive

Advantages
- Provides visual and audible ("click") feedback when dose taken correctly
- Loading button lock to signal empty
- Simple to use and less errors during dose preparation

Disadvantages
- Requires sharp, forceful inhalation of breath to get full dose • bitter taste

Advantages
- Simple to use; one step to open and load dose
- Displays exact number of remaining doses with large numbers

***Disadvantages* <u>* ONLY TWICE A DAY OPTION*</u>**
- No way to determine if proper inspiratory effort is being achieved from protective packaging •Requires sharp, forceful inhalation of breath

Advantages
- Slower actuation may improve technique vs. MDI
- Loading base locks to signal empty

•Disadvantages
- Requires reasonable strength to spring-load dose
- Incorrect rate of inhalation results in cough

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PLAN

1) Glycopyrronium/Indacaterol 110/50 microgram inhaled once daily.

2) Discontinue tiotropium Handihaler

3) Continue with salbutamol as ordered prn

3) Community pharmacist to review device technique at every refill and inquire about adverse effects at the same time.

4) Educate SC immediately on non-pharmacologic interventions that address behavioural risk factors such as avoiding smoking among other environment and occupation triggers, increase physical activity, ensuring adequate sleep and healthy diet.

Monitoring

Parameter	Desired /Observed Change
Efficacy: Dyspnea symptoms	No increase in symptoms, well controlled with pharmacotherapy, less frequent as a function of long acting bronchodilator. No interference with daily activities and less than 2 on MMRC
Efficacy: salbutamol usage	Reduce to 1-3 times per week or less
Efficacy: Exacerbation severity and frequency	None

Monitoring

Parameter	Desired /Observed Change
Safety: Ultibro Side Effects	Ultibro adverse effect: cough, heartburn, sore mouth, sore throat, upset stomach.
Efficacy: Device technique demonstration	Able to demonstrate proper technique
Efficacy: Exercise tolerance and increase physical activity	Increased physical activity and improve exercise tolerance specially shortness of breath during minimal exertion or while performing daily activities.

Clinical PEARLS Summary

- Inappropriate device choices for your patients severely limit the success of therapy.
- New devices, LAMAs, LABAs, and LAMA/LABA combinations are now available to help accommodated your COPD patient's needs.
- Evidence exist supporting LAMA/LABA efficacy superior to LAMA or LABA monotherapies

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Thank You For Coming this AM!

March 15th…….

Only Ellipta **Device** Options

Ellipta Options	Brand Name	Device
Vilanterol /Fluticasone	**Breo**	
Umeclidinium	**Incruse**	
Umeclidinium Vilanterol	**Anoro**	

*All options are **once** a day*

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Only Respimat **Device** Options

Respimat Options	Brand Name	Device
Tiotropium	**Spiriva**	
Tiotropium **Olodaterol**	**Inspiolto**	
Ipratropium **Salbutamol**	**Combivent**	

*All options are ***2*** *inhalations* **once** a day*

Singh D. *Br J Clin Pharmacol*. 2014;79:695-708.

Monotherapy vs Placebo	Efficacy				Safety
	FEV1	SGDQ Mean	Exacerbation	Death	
Indacaterol 13 RCTs (9961 pts)	**149**	**3.6**	**NNT 30**	**ns**	•Withdrawal NNT 19 vs placebo • AE: Nasopharyngitis, tremor, cough, headache, nausea
Formoterol 10 RCTs (4564 pts)	**45**	**2.66**	**ns**	**ns**	•Withdrawal NNT 15 vs placebo • AE:Diarrhea, headache, tremor, palpitations, URTI, cough
Salmeterol 14 RCTs (8973 pts)	**101**	**1.64**	**NNT 22**	**ns**	•Withdrawal NNT 29 vs placbo •Haedache, HTN, dry mouth nasopharyngitis, cough
Aclidinium 12 RCT (9547 pts)	**90**	**2.3**	**ns**	**ns**	•Withdrawal NNT 35 vs placebo • AE: Diarrhea, dry mouth, cough, headache, vomiting
Glycopyrronium 2 RCTs (1888 pts)	**112**	**3.32**	**NNT 14**	**ns**	•Withdrawal NNT 14 vs placebo •Placebo AE>glycopyrronium • AE: Dry mouth, cough, URTI, flushing heachache, flushing
Umeclidinium 4 RCTs (2,121 pts)	**140**	**4.7-7.9**	**ns**	**ns**	•Withdrawal NS vs placebo •AE: tachycardia, blurred vision, urinary retention, dry mouth and abdo pain, cough
Tiotropium 22 RCTs (23,309)	**119**	**2.89**	**NNT 16**	**ns**	•Withdrawal NNT 19 vs placebo •AE: dry mouth, cough, constipation, urinary retention, headache
Inhaled Steroids	**70**	**1.22**	**NNT 22**	**ns**	•No withdrawal data •Oral Candidiasis (NNH 27), Voice change (NNH 34), Bruising (NNH 32), Pneumonia (NNH 30)

GOLD C: ICS/LABA or LAMA

- Group C patients have few symptoms but a high risk of exacerbation.
  - FEV1 less than 50% predicted
  - One hospitalized exacerbation in the last year or 2 or more exacerbations per year.
- Symptoms: stop for breath after walking 100m or a few minutes on level ground.

GOLD C: ICS/LABA or LAMA

- ICS should not be prescribed before this stage as the risks of pneumonia and fractures outweigh the potential benefits.

Head to Head: ICS/LABA (blue)

	Combination Therapy Head to Head	Efficacy				Safety
		FEV1	SGDQ Mean	Exacerbation	Death	
ICS/LABA RCTs	ICS/LABA vs Plac	**90-160**	**2.9-4.1**	NNT 22	**NNT 53**	Pneumonia NNH 70
	ICS/LABA vs ICS	**50-110**	0.3-2.8	NS	**NNT 75**	-
	ICS/LABA vs LABA	70	1.58	NNT 23	NS	Pneumonia NNH 48
	ICS/LABA vs Tio	NS (40% patient drop out from study)				
	Fluticasone + Vilanterol vs Vil	10.-20	-	NS	NS	Pneumonia, hoarse throat, fractures
LAMA/LABA RCTs	Tio/LABA vs either	70	1.61	NS	NS	NS
	Umeclidinium/ Vilanterol (vs either)	**60-110**	-	NNT 42	NS	Withdrawal NNT 19
	Glycopyrronium/ Indacaterol vs Tio*	**60-100**	2.2-2.6	NNT 19-25	NS	NS

Head to Head: Combination Therapy (ICS, LABA, LAMA)

	Combination Therapy Head to Head	Efficacy				Safety
		FEV1	SGDQ Mean	Exacerbation	Death	
ICS/LABA RCTs	ICS/LABA vs Plac	**90-160**	**2.9-4.1**	NNT 22	**NNT 53**	Pneumonia NNH 70
	ICS/LABA vs ICS	**50-110**	0.3-2.8	NS	**NNT 75**	-
	ICS/LABA vs LABA	70	1.58	NNT 23	NS	Pneumonia NNH 48
	ICS/LABA vs Tio	NS (40% patient drop out from study)				
	Fluticasone + Vilanterol vs Vil	10.-20	-	NS	NS	Pneumonia, hoarse throat, fractures
LAMA/LABA RCTs	Tio/LABA vs either	70	1.61	NS	NS	NS
	Umeclidinium/ Vilanterol (vs either)	**60-110**	-	NNT 42	NS	Withdrawal NNT 19
	Glycopyrronium/ Indacaterol vs Tio*	**60-100**	2.2-2.6	NNT 19-25	NS	NS

GOLD D: 3X Therapy

- Adding Fluticasone/Salmeterol to Tiotropium

  Review, 6 RCTs, 1268 patients

  - FEV1 improved 55 mL
  - Exacerbation NNT 18
  - SGRQ: 4.63
  - Any adverse events: NNH 20

  Bottom-Line: Adding dual therapy to Tiotropium will have what is likely a clinical insignificant change in FEV1 but improve COPD quality of life to small, meaningful level. It also reduces exacerbation for one in 18 people over ¾ of a year.

  European J Internal Med 2014; 25: 491–495

GOLD C/D: Summary

- **Place in therapy**:
  - First line: ICS/LABA or LAMA is recommended.
  - *Alternative choice*: LAMA/LABA or a LAMA with an ICS for persistent dyspnea symptoms or intolerance to an ICS (pneumonia, hoarseness, bones, bruising, drug interactions)
    - Evidence exist supporting LAMA/LABA efficacy non-inferior and even superior, in some case to LAMAs including tiotropium relative to FEV1, SGRQ, and exacerbations.

NEJM 2011; 364:1093-103. 2) Thorax 2003;58:399-404. 3) Am J Respir Crit Care Med. 2008;177:19-26. 4) Cochrane 2010;(5):CD007891. 5) Cochrane 2011;12: CD007033. 6) Ann Intern Med. 2011;155:179-191.

Adverse Events: Long Acting Bronchodilators

Adverse Events: LABA Serious Adverse Events

- One meta-analysis of COPD suggested a mix of Beta-agonists (vs placebo) increased respiratory death (NNH= 131)
- Subsequent studies of LABA (RCT and Meta-analysis) refute this.
- **Bottom-line:** No clear support of increased serious respiratory adverse events with LABA in COPD

N Engl J Med. 2009; 360: 1592-95. 2) J Gen Intern Med. 2006;21:1011-9. & ACP journal club 2007; 146: 19

GOLD C: ICS/LABA or LAMA

- LABA/Steroid = Placebo

2 RCTs, 3 year, 6112 pts, 4 arms:
Fluticasone vs salmeterol vs combo vs placebo

- LABA vs placebo Hospitalization NNT 32
- ICS/LABA vs placebo Mortality NNT 56
- ICS/LABA vs ICS NNT 44
- Most of the effect seems to come from the LABA

GOLD C: ICS/LABA or LAMA

- LABA/Steroid = Tiotropium (3 RCTs 1323 pts) salmeterol/ fluticasone 50/500ug BID vs tiotropium.
  - No difference in exacerbations or quality of life.
  - Drop-out high (39%) and no outcome on drop-outs.