Update on the Management of COPD:
Advantages and Limitations of Management.

John KOLBE

Emeritus Professor of Medicine
Dept of Medicine, FMHS
University of Auckland
&
President, ISIM.

International Society of Internal Medicine

THE UNIVERSITY OF AUCKLAND
Te Whare Wānanga o Tāmaki Makaurau
NEW ZEALAND

Global Initiative for Chronic Obstructive Lung Disease

2023 Teaching Slide Set

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease

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Commonly Used Maintenance Medications in COPD*

Table 3.3

Generic Drug Name	Inhaler Type	DELIVERY OPTIONS			Duration of Action
		Nebulizer	Oral	Injection	
$BETA_2$-Agonists					
Short-acting (SABA)					
Fenoterol	MDI	✓	pill, syrup		4-6 hours
Levalbuterol	MDI	✓			6-8 hours
Salbutamol (albuterol)	MDI & DPI	✓	pill, syrup, extended release tablet	✓	4-6 hours 12 hours (ext. release)
Terbutaline	DPI		pill	✓	4-6 hours
Long-acting (LABA)					
Arformoterol		✓			12 hours
Formoterol	DPI	✓			12 hours
Indacaterol	DPI				24 hours
Olodaterol	SMI				24 hours
Salmeterol	MDI & DPI				12 hours
Anticholinergics					
Short-acting (SAMA)					
Ipratropium bromide	MDI	✓			6-8 hours
Oxitropium bromide	MDI				7-9 hours
Long-acting (LAMA)					
Aclidinium bromide	DPI,				MDI 12 hours
Glycopyrronium bromide	DPI		solution	✓	12-24 hours
Tiotropium	DPI, SMI, MDI				24 hours
Umeclidinium	DPI				24 hours
Glycopyrrolate		✓			12 hours
Revefenacin		✓			24 hours
Combination Short-Acting $Beta_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)					
Fenoterol/ipratropium	SMI	✓			6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓			6-8 hours
Combination Long-Acting $Beta_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)					
Formoterol/aclidinium	DPI				12 hours
Formoterol/glycopyrronium	MDI				12 hours
Indacaterol/glycopyrronium	DPI				12-24 hours
Vilanterol/umeclidinium	DPI				24 hours
Olodaterol/tiotropium	SMI				24 hours
Methylxanthines					
Aminophylline			solution	✓	Variable, up to 24 hours
Theophylline (SR)			pill	✓	Variable, up to 24 hours
Combination of Long-Acting $Beta_2$-Agonist Plus Corticosteroid in One Device (LABA+ICS)					
Formoterol/beclometasone	MDI, DPI				12 hours
Formoterol/budesonide	MDI, DPI				12 hours
Formoterol/mometasone	MDI				12 hours
Salmeterol/fluticasone propionate	MDI, DPI				12 hours
Vilanterol/fluticasone furoate	DPI				24 hours
Triple Combination in One Device (LABA+LAMA+ICS)					
Fluticasone/umeclidinium/vilanterol	DPI				24 hours
Beclometasone/formoterol/glycopyrronium	MDI, DPI				12 hours
Budesonide/formoterol/glycopyrrolate	MDI				12 hours
Phosphodiesterase-4 Inhibitors					
Roflumilast			pill		24 hours
Mucolytic Agents					
Erdosteine			pill		12 hours
Carbocysteine†			pill		
N-acetylcysteine†			pill		

*Not all formulations are available in all countries. In some countries other formulations and dosages may be available. †Dosing regimens are under discussion.
MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler. Note that glycopyrrolate & glycopyrronium are the same compound.

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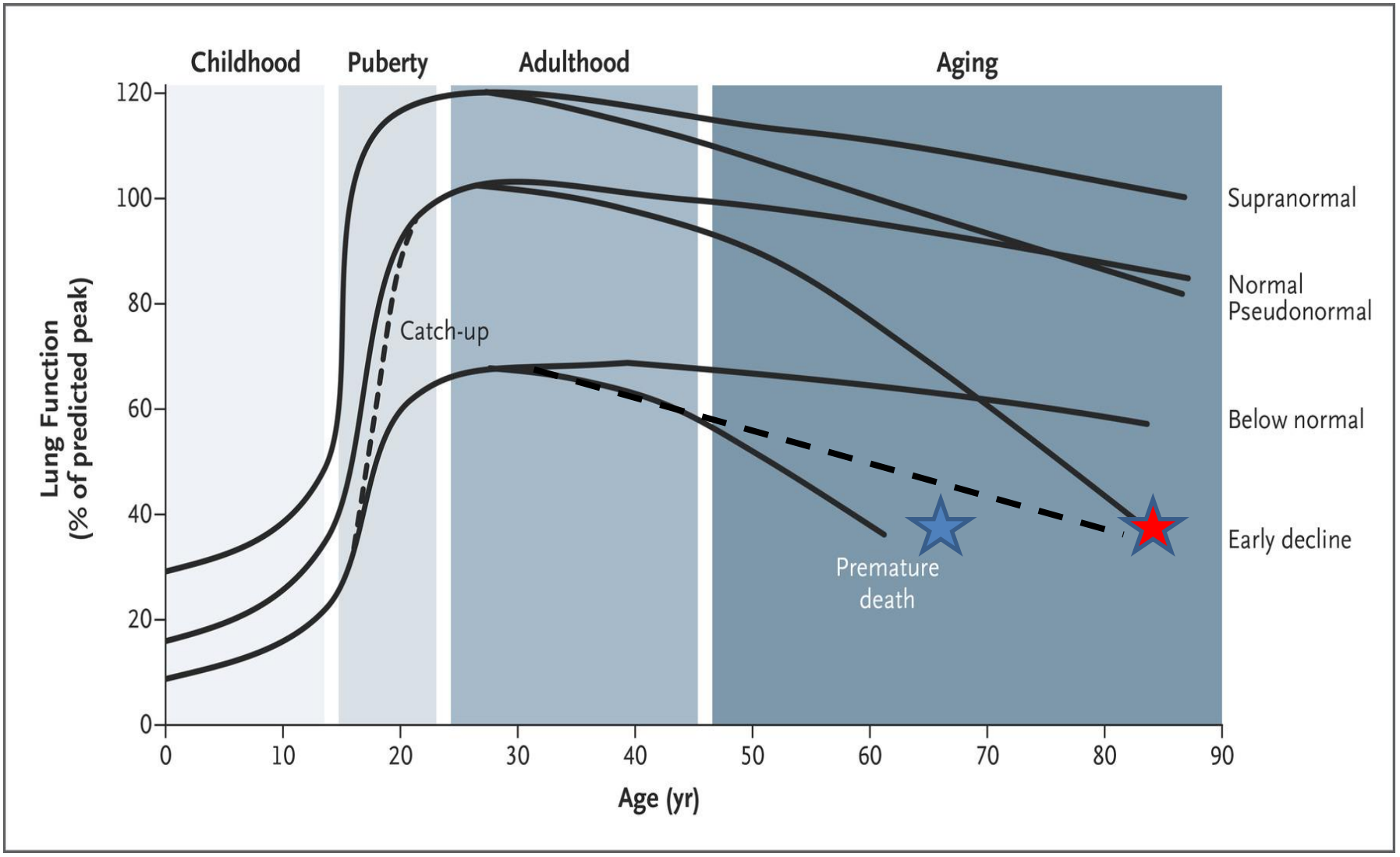
Development of COPD.



Proposed Taxonomy (Etiotypes) for COPD

Table 1.1

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others ★
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma ★
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

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Management Approaches to COPD.

- **Symptom Reduction**
  - reduce symptoms
  - improve exercise tolerance
  - improve health status

- **Reduce Medium/Long-term Outcomes**
  - reduce exacerbations
  - reduce disease progression
  - reduce mortality

COPD Management; Non- Pharmacologic

Evidence that non-pharmacologic therapies are under-used, particularly in primary care, but they have the greatest impact

- **Smoking cessation**
  - only intervention to slow rate of decline in FEV1
- **Influenza Vaccination**
  - cost-effective and of proven benefit
- **Pneumococcal vaccination**
  - less evidence but recommended

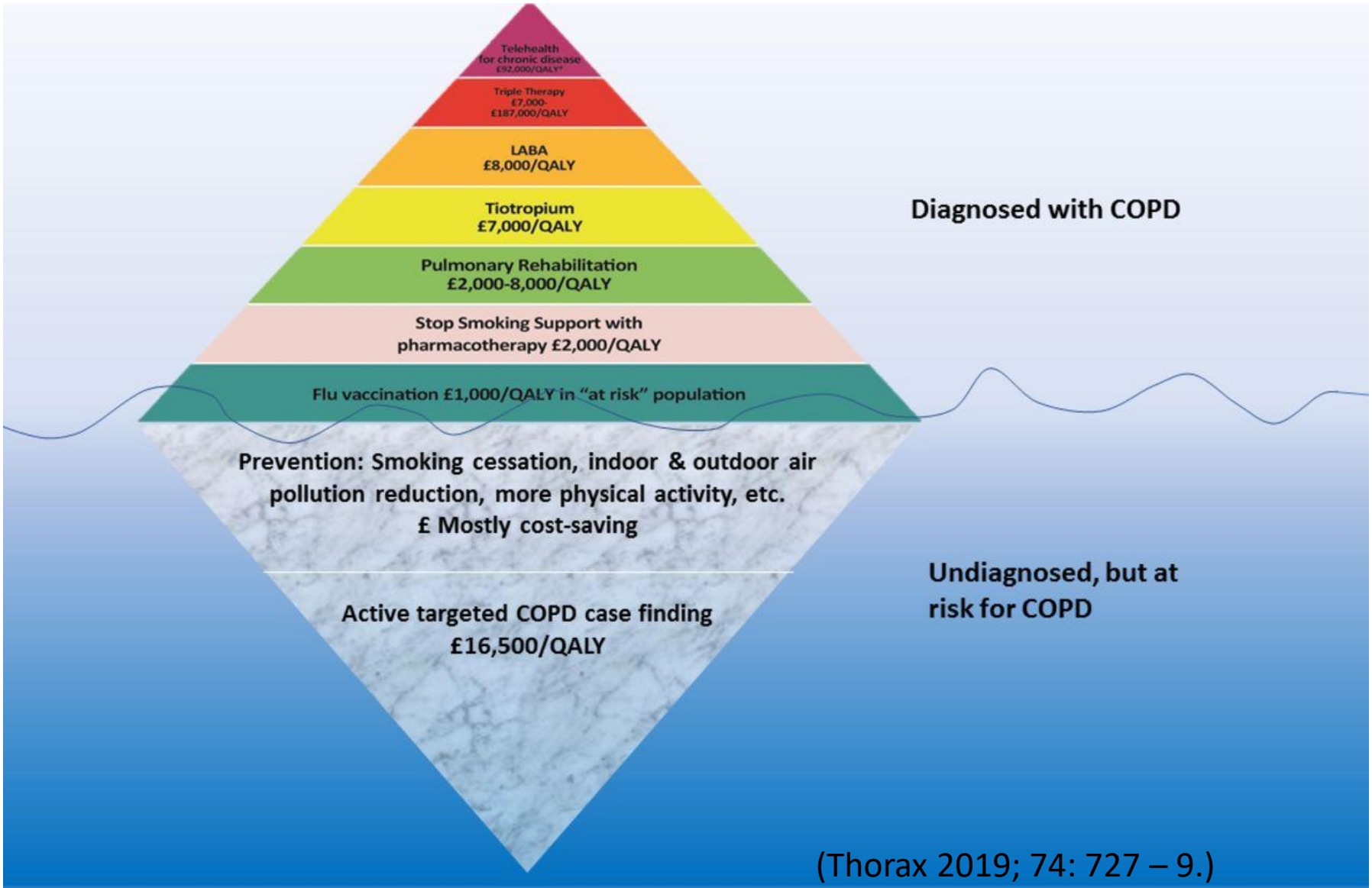
COPD Management; Non- Pharmacologic cont.

- **LTOT**
  - only (?) treatment shown to reduce mortality
  - only in those with severe hypoxemia
  - no benefit in those with moderate hypoxaemia (PaO_2 > 7.3 kPa)
  - Risk of mis-classification if decision based on pulse oximetry Sat O_2

- **Pulmonary Rehabilitation**
  - largest improvements in exercise capacity and HRQL
  - IMT in assoc with PR does not improve outcomes
  - PR after HA, saving of US$ 5700/patient over lifetime
  - >US$ 1 billion potential savings in US
  - UNDERUSED
  - Predictors of non-adherence;
    - social isolation,
    - lack of COPD-associated social support. and
    - other non-adherence.

(BTS Clinical Statement on Pulmonary Rehabilitation: Thorax 2023; 78: (Suppl 4) S2-S15.)

“Bang for Buck” in COPD Management.



(Thorax 2019; 74: 727 – 9.)

COPD Pharmacologic Treatment: LABAs & LAMAs;

Initial therapy with bronchodilator(s)

Generalizations:

(based on Cochrane Reviews, Respirology 2015; 20 :1153-1159, NEJM 2019, etc, etc)

- LAMAs > SAMAs
- All LABAs are approx equal
- All LAMAs are approx equal
- LAMAs approx = LABAs (in terms of HRQL)

(Possibly LAMAs better at preventing exacerbations)

- LAMA + LABA > LABA or LAMA

– LAMA + LABA (prob) > LABA + ICS.
– (?) LAMA + LABA + ICS > any two. (Impact Study)

COPD Pharmacologic Treatment: LABAs & LAMAs;

- So, in the clinic
  - Trial one or other (LAMA or LABA),
  - Assess response (in meaningful terms)
  - Then add the other
  - Assess response.

  - **Other factors to consider:**
    - Advantage of once vs twice daily use

  - **Importance of preparation and delivery systems**
    - Need for spacer ie pMDI
    - Ease of use
    - Same vs different devices
    - Combined in single device.

Other COPD Management Issues.

- No risk of un-opposed LABAs (or LAMAs) in COPD
- COPD is not contraindication to use of B blockers

- **No good indication for widespread use of ICS in COPD**; currently used in >80% !!
- Use of ICS may be associated with serious adverse effects; specifically **pneumonia**

(Following pneumonia, mortality increased for >1 year; due to cardio-vascular causes; common risk factors for COPD and IHD ……? opportunity to screen)

- (Slow) Withdrawal of ICS can be safely undertaken

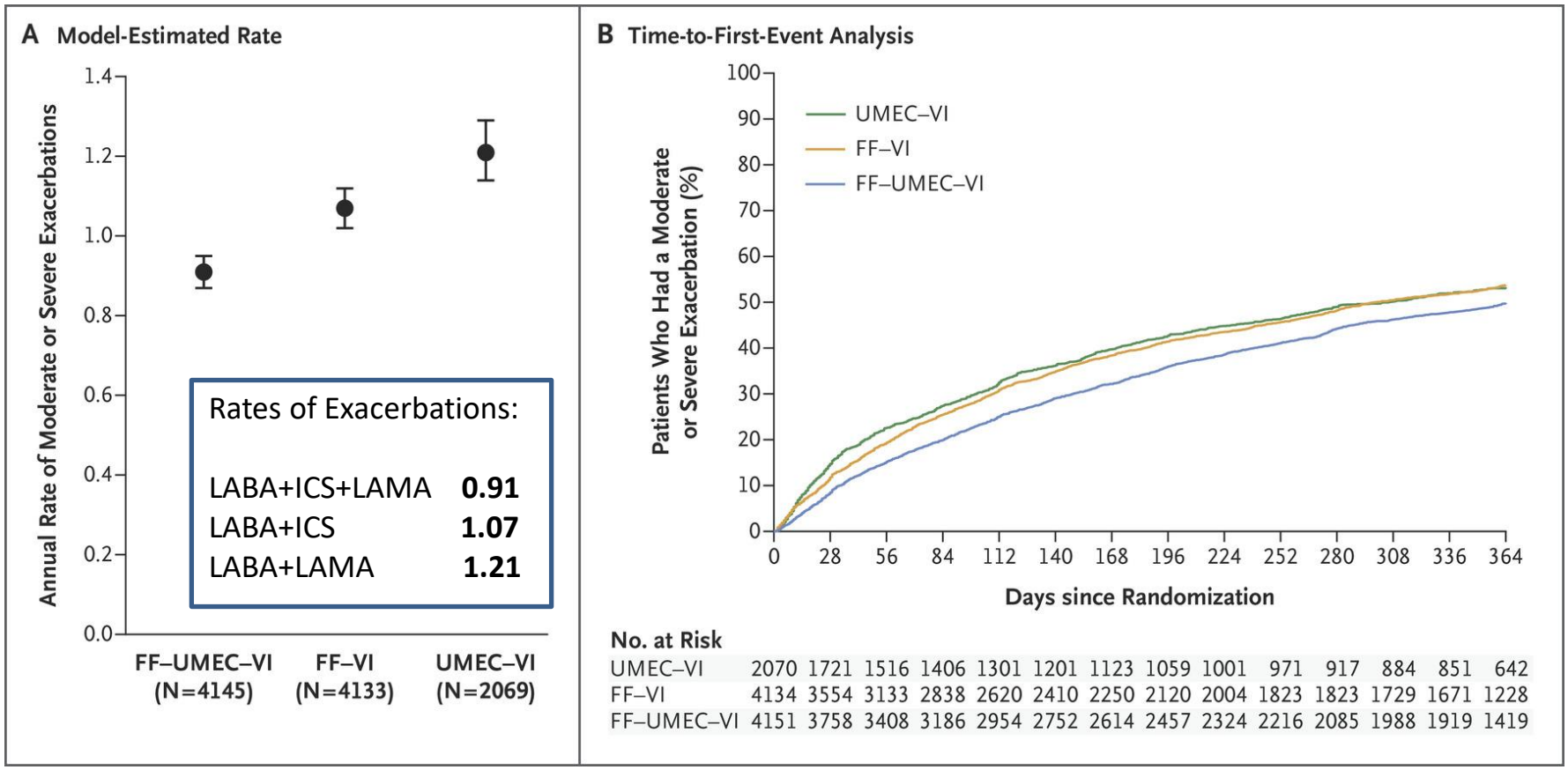
- There may be a sub-group of COPD patients that benefit from ICS but …..

GOLD Recommendations.

“Blood eosinophil counts may identify patients with a greater likelihood of a beneficial response to ICS.

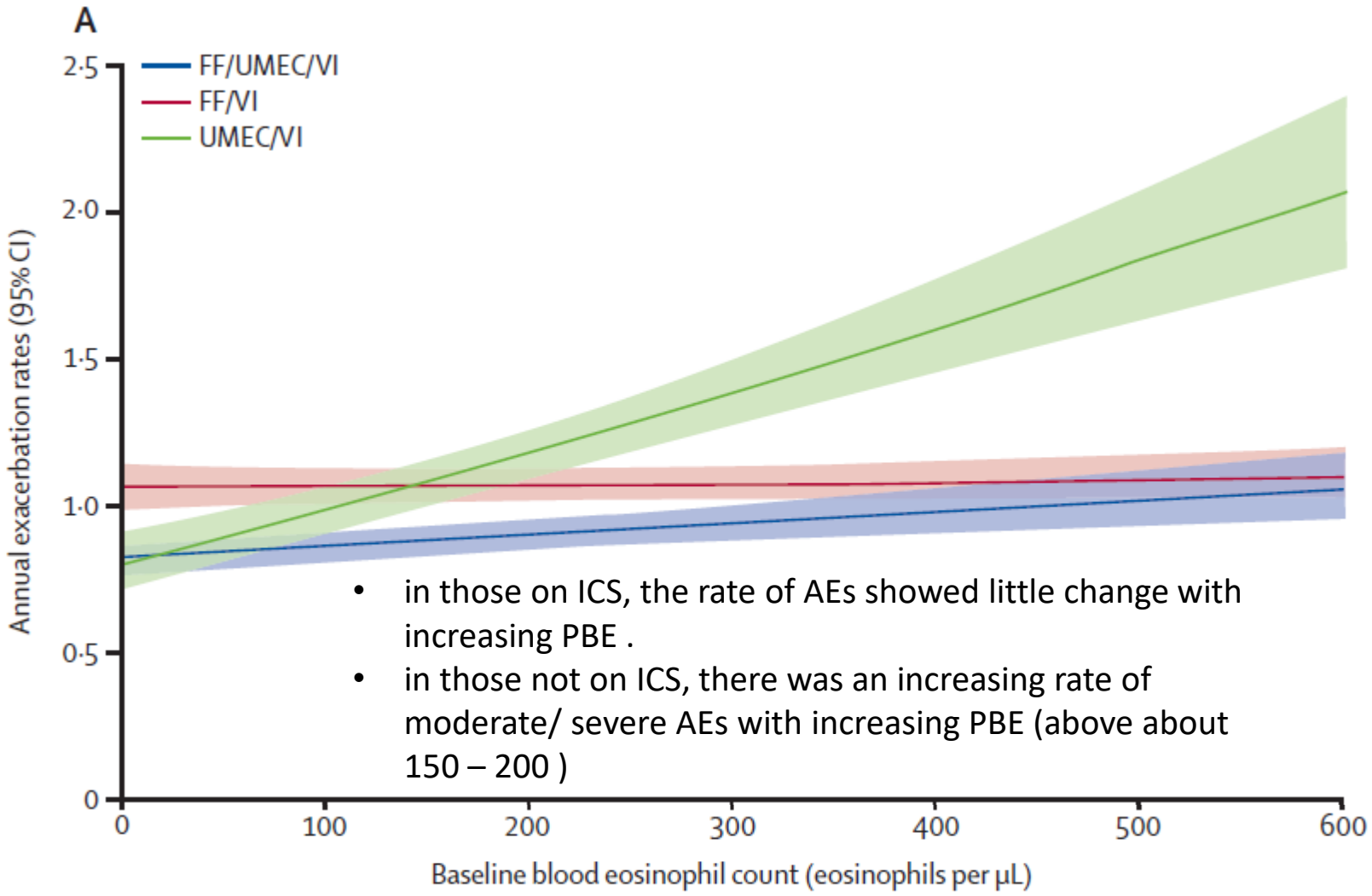
For patients with **one exacerbation per year, a peripheral blood level >= 300 eosinophils/ul** identifies patients more likely to respond to LABA/ICS treatment.

For patients with >= 2 exacerbations per year or at least one severe exacerbation requiring hospitalisation in the prior year, LABA/ICS treatment can be considered at a blood eosinophil counts >= 100 cells/ul, as ICS effects are more pronounced in patients with greater exacerbation frequency and/or severity.”



(N Engl J Med 2018; 378:1671-1680)

Magnitude of Benefits of Therapy Based on PBE count.



- in those on ICS, the rate of AEs showed little change with increasing PBE .
- in those not on ICS, there was an increasing rate of moderate/ severe AEs with increasing PBE (above about 150 – 200)

(N Engl J Med 2018; 378:1671-1680)

ICS and PBE in COPD

- Inherent variability of PBE count
- Relationship of PBE to response is a continuum (not adequately described by dichotomising PBE)
- Biologically implausible that there is a “magic” number that predicts response to ICS
- Should not focus on a dichotomy; cut points are a guide at best

- Need to consider other factors that may predict response ie multi-factorial dependence.

Peripheral Blood Eosinophil Count

Low: <200

Likely unresponsive to ICS

Use LABA + LAMA.

Moderate/High ; > 200

(Higher the count , more likely to respond to ICS)

Consider other factors indicating benefit:

- Rate of previous AEs
- History of asthma

Consider factors indicating potential harm:

- Risk of pneumonia
- NTM infection
- Risk of other adverse events.

- multifactorial considerations are the basis of personalised medicine
- incorporate the concept of PBE as a biomarker
- use Clinical Judgment !

Messages.

- Etiology wider than cigarette smoking
- Non-pharmacological managements have greatest impacts
- Bronchodilator therapy has priority; preferably LAMA + LABA
- Limited role for ICS.

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Thank You.

So…….

- COPD represents irreversible pulmonary damage
- Management is primarily “palliative”
- Importance of shared decision-making
- Importance of “rehabilitation” to regain/retain functional capacity
- Strategies to reduce dyspnoea: use of hand-held fans, opiates

COPD-Bronchiectasis Overlap.

- May often be based on radiologic appearances; other factors effect the B:A ratio

- Genuine co-existence
- Similarities in pathology; neut inflammation
- More likely to have PA infection, more frequent exacerbatiions, more sputum, higher morbidity
- In COPD , those with Bx phenotype may benefit from Bx treatments eg ACTs, nebuised HTS.

Effect Size of Interventions: Health Related Quality of Life.

Intervention	HRQL; Change in Total SGQ Score.
<u>DRUGS</u> LABA	- 2.3 *
LABA + ICS	- 2.9 *
LABA + Tio vs Tio	- 1.6 *
LABA + Tio + ICS vs Tio	- 2.5 *
<u>Non-Pharmacologic Interventions</u> Rehabilitation	- 6.1 *
Smoking Cessation	- 2.9 to -11

LABA = Long-acting B agonist
ICS = Inhaled corticosteroid
Tio = Tiotropium

(* based on results of Cochrane Reviews)

Eosinophils and COPD.

- In COPD, increased peripheral blood eosinophils;
  - associated with accelerated decline in lung function
  - associated with increased risk of exacerbations
  - **predict the response to ICS** (wrt prevention of acute exacerbations)

Publications >> Clarity

COPD Management.