What we shouldn't do in COPD
To do or not to do, so many questions!

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Disclosures

None relevant to this paper

What we shouldn't do in COPD just a few, in random order

Include asthma patients in COPD trials

Give inhaled steroids to so many COPD patients

Exclude respiratory disease in smokers with normal spirometry

Repeat spirometry regularly

Switch drugs within classes of inhaled R/

Screen for COPD in asymptomatic smokers

Add theophyllin to ICS/LABA in COPD

Use blood eosinophyl levels to predict effects of ICS in COPD

Test new drugs against placebo

Trust pharmaceutical companies

Expect patients to use prescribed drugs properly

Implement currently available e-health selfmanagement apps

Confuse questionnaires with proper medical history-taking

Diagnose ACOS

Expect drugs to cure the disease

Treat without changing the patient's behavior

What we shouldn’t do in COPD

Give inhaled steroids to so many patients

They have not been shown to be effective in mild-to-moderate disease and in the absence of exacerbatons

They have not been properly tested in severe disease

- asthma inadequately excluded
- patients undertreated with LABA + LAMA
- various irrelevant outcome measures

How come over 70% of COPD patents are on ICS??

What we shouldn't do in COPD

Trust pharmaceutical companies:

withholding relevant safety information

comparing their drugs to low doses of other

not publishing negative outcomes

chosing irrelevant (composite) outcome measures

using taxpayer's money for their own profits

spending research money on marketing

manipulating knowledge transfer and education

Marcia Angell: The Truth About The Drug Companies

Peter Gøtzsche: Deadly Medicines and organised crime

What we shouldn’t do in COPD

Diagnose ACOS

You have asthma with normal lungfunction or reversible airflow obstruction or with persistent airflow obstruction due to undertreated inflammation or smoking

Or

You have COPD in patients who do not and did not have asthma

Don’t include asthma patients in COPD-trials!

Exclusion criteria:

Current asthma

many early ICS-in-COPD-trials

Diagnosis of asthma, non-COPD respiratory disorders….

- Calverley et al, N Eng J Med 2007; 356:775-789 (TORCH)

Respiratory disorders other than COPD…

- Vestbo et al. Lancet 2016; 387: 1817–1826 (SUMMIT)

Patients with any history of asthma.

- Wedzicha et al. N Engl J Med. 2016 Jun 9;374(23):2222-34 (FLAME)

Personal observation

The more likely the sponsor wants to show an effect of ICS in COPD, the more likely one will find patients with asthma in the trial, with positive effects on whatever one is trying to prove.

The more likely the sponsor wants to show benefits of (more) bronchodilators, the better asthma will be excluded.

Don’t test new drugs against placebo

If it is a new beta-adrenergic or anticholinergic, it is surely going to do something

We need proof that is either better, safer or cheaper than what is already available

Don’t spend taxpayers’ money or waste time of researchers and patients on useless studies. It is unethical, has nothing to do with progress of science but is only about money, it is marketing, not research

Test against best currently available!!

Do not test new drugs against placebo

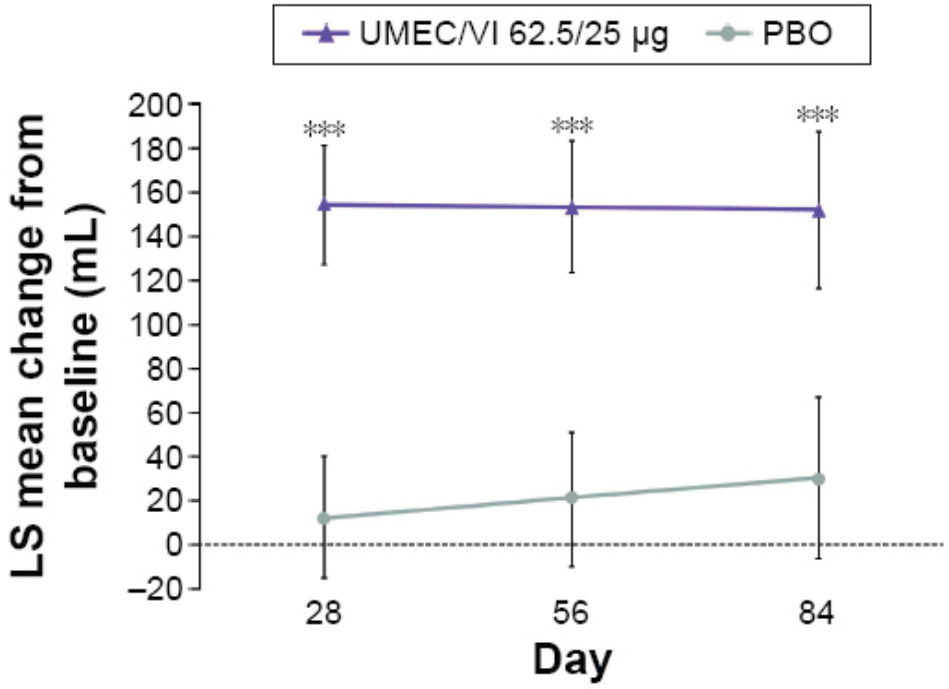
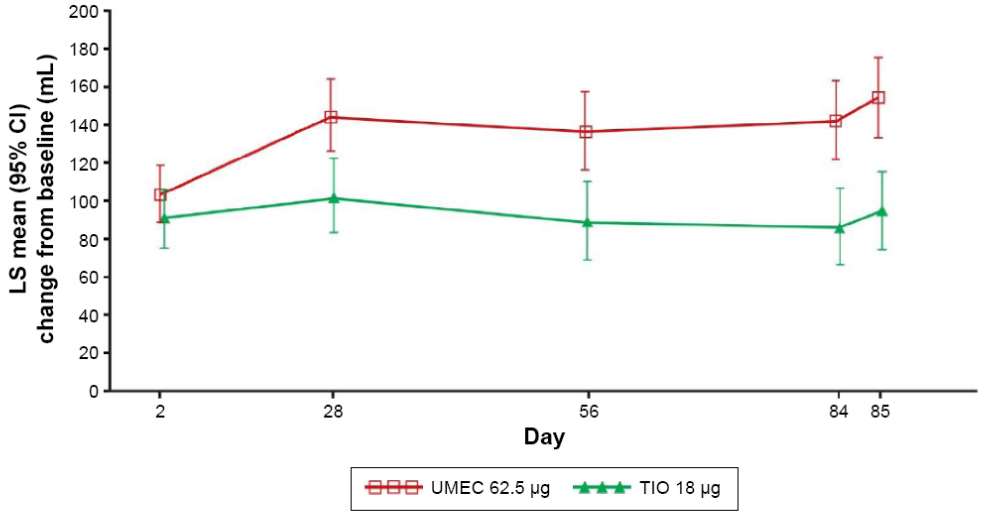


Figure 3 LS mean (95% CI) change from baseline in trough FEV_1 (mL) over time (ITT population).
Note: ***$P<0.001$.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ITT, intent-to-treat; LS, least squares; PBO, placebo; UMEC, umeclidinium; VI, vilanterol.

Effect of LABA/LAMA compared with placebo

Siler et al, Intern J of COPD 2016; 11:971-979

This what we should do:



Day	2		28		56		84		85	
	UMEC	TIO	UMEC	TIO	UMEC	TIO	UMEC	TIO	UMEC	TIO
n_1	485	484	485	484	485	484	485	484	485	484
n_2	469	471	453	454	425	432	402	420	392	416
LS mean change from baseline (mL), (SE)	103 (8)	91 (8)	144 (10)	102 (10)	136 (11)	89 (11)	142 (11)	86 (11)	154 (11)	95 (11)
Difference vs TIO (95% CI)	13 (–9, 35)	–	42 (14, 69)	–	46 (17, 76)	–	56 (26, 85)	–	59 (29, 88)	–
P-value	0.254		0.003		0.002		<0.001		<0.001	

Figure 2 LS mean change from baseline in trough FEV_1 (mL) (PP population).
Notes: n_1, number of patients with analyzable data for ≥1 time points. n_2, number of subjects with analyzable data at the current time point.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; LS, least squares; PP, per-protocol; SE, standard error; TIO, tiotropium; UMEC, umeclidinium.

Compare an old LAMA with a new LAMA

no differences for TDI, SGRQ, and CAT scores. similar tolerability and safety profiles.

Feldman et al, Int J Chron Obstruct Pulmon Dis 2016; 11: 719–730.

Don’t exclude repiratory disease in symptomatic smokers with normal spirometry!

COPD is excluded in case of normal spirometry

Please correct FEV1/FVC for age (LLN) instead of 0.7 to exclude subects with normal aging of the lung

Many smokers with normal spirometry have symptoms

Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function

Prescott G. Woodruff, et al for the SPIROMICS Research Group*

N Engl J Med 2016; 374:1811-1821

Design, n = 2736

Healthy non-smokers aged 40 – 80 with normal spirometry

or

Current or ex-smokers (> 20 pack-years) with normal spirometry

- Relevant and significant differences in:
- CAT-scores,
- Activity limitation
- Exacerbatie rate
- Brochodilator response
- Use of respiratory medication
- HR-CT airway wall thickness and emphysema

Conclusions

….respiratory symptoms and exacerbations are common in current or former smokers who have spirometric values that are generally considered to be within the normal range.

Many of these patients are already being treated with respiratory medications despite a lack of data from clinical trials. This finding suggests that the current use of spirometry to define who should receive a diagnosis of COPD may not adequately cover the breadth of symptomatic smoking-related lung disease.

Clinical trials that are directed at this large and understudied population may provide better insight into appropriate treatment strategies for these patients.

Don’t add theofyllin to ICS/LABA in COPD

Hypothesis:

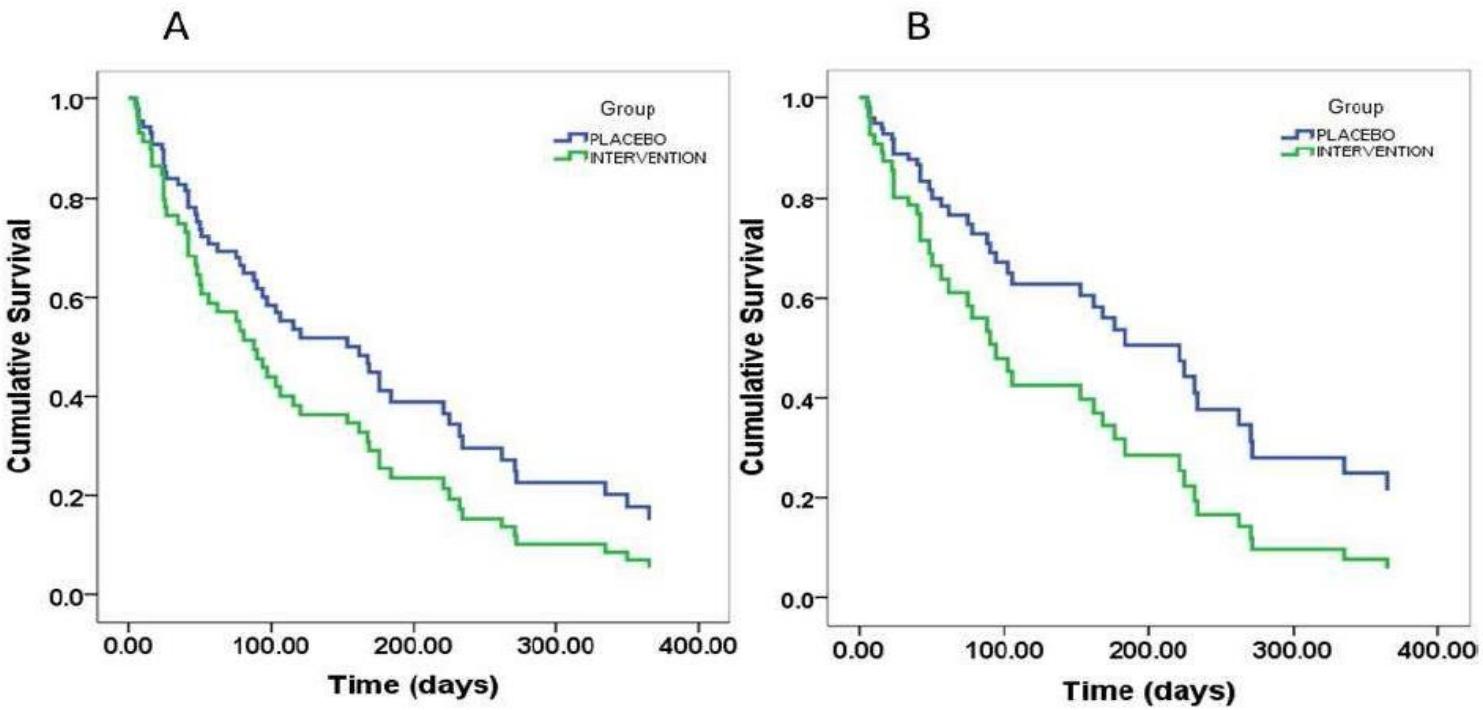
a decreased concentration of HDAC in peripheral lung tissue from patients with COPD.

HDAC suppresses inflammatory gene expression, so a decrease may contribute to inflammatory responses, and may be central to the pathogenesis of COPD.

HDAC-2 is vital to the ability of corticosteroids to turn off inflammatory genes.

Lung concentrations of HDAC-2, or perhaps polymorphisms of the genes, may confer varying degrees of steroid resistance (ineffectiveness) in patients with COPD.

Don’t add theophyllin to ICS/LABA in COPD



Kaplan Meier
Time to 1st AE
A = PP
B = ITT

No effect on inflammatory markers, on HDAC or on AE frequency

Oral Low-Dose (2 dd 100 mg) Theophylline on Top of Inhaled Fluticasone-Salmeterol Does Not Reduce Exacerbations in Patients with Severe COPD.

Cosio et al. Chest 2016, epub ahead of print

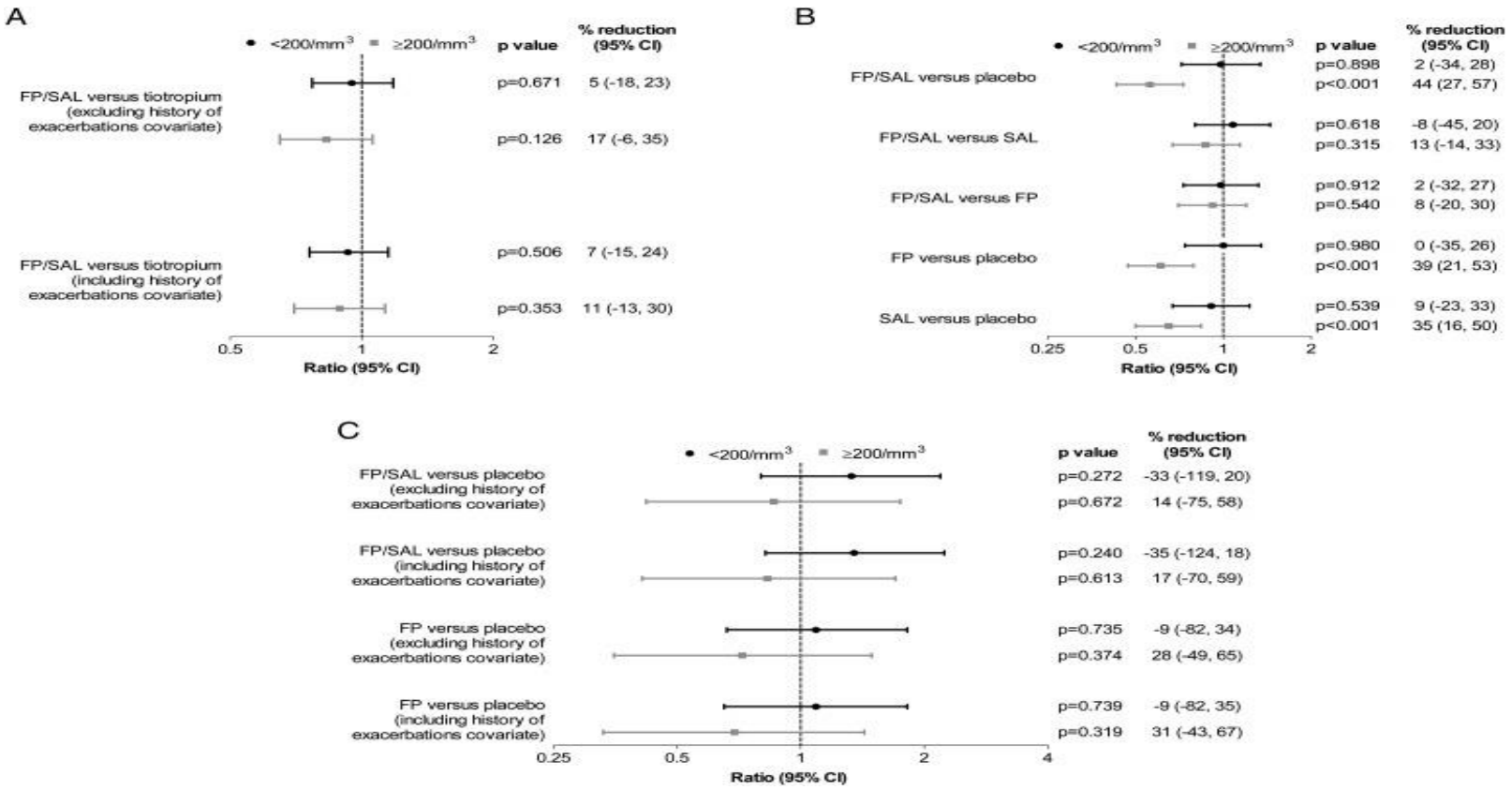
Blood eosinophils and ICS in COPD?

Blood eosinophils and inhaled corticosteroid/long-acting β-2 agonist efficacy in COPD

Ian Pavord et al, Thorax 2016

“A retrospective analysis of data from three randomised, controlled trials of at least 1-year duration supported the hypothesis that there is greater response to fluticasone propionate/salmeterol, compared with placebo or long-acting anti-muscarinic agents, in individuals with a pretreatment blood eosinophil level of ≥2% compared with those with a pretreatment blood eosinophil level of <2%”.

Use blood eo's to predict effects if ICS



"Blood eosinophil levels represent a potentially important biomarker that could aid treatment decision-making in patients with moderate-to-severe COPD. Prospective studies are required to explore these findings further."

Pavord et al, Thorax 2016 Feb; 71(2): 118–125.

Blood eo's to predict effects of ICS in COPD?

My advice: take a proper history and ask for asthma in the past, allergies and family to exclude asthma or to initiate ICS!

Questionnaires in COPD (and Asthma)?

Questionnaires help in assessing burden of disease, are not meant to establish a diagnosis

ACQ

CCQ

ACT

CDQ

SGRQ

etc.

It takes a proper diagnosis to diagnose a disease!

Don’t screen for COPD!

US Preventive Services Task Force Recommendation Statement

KQ7: Does treatment for asymptomatic adults identified with mild to moderate COPD through screening improve health-related quality of life or reduce morbidity or mortality?

Guirguis-Blake et al, JAMA 2016; 315(13):1378-1393

Screening for COPD?

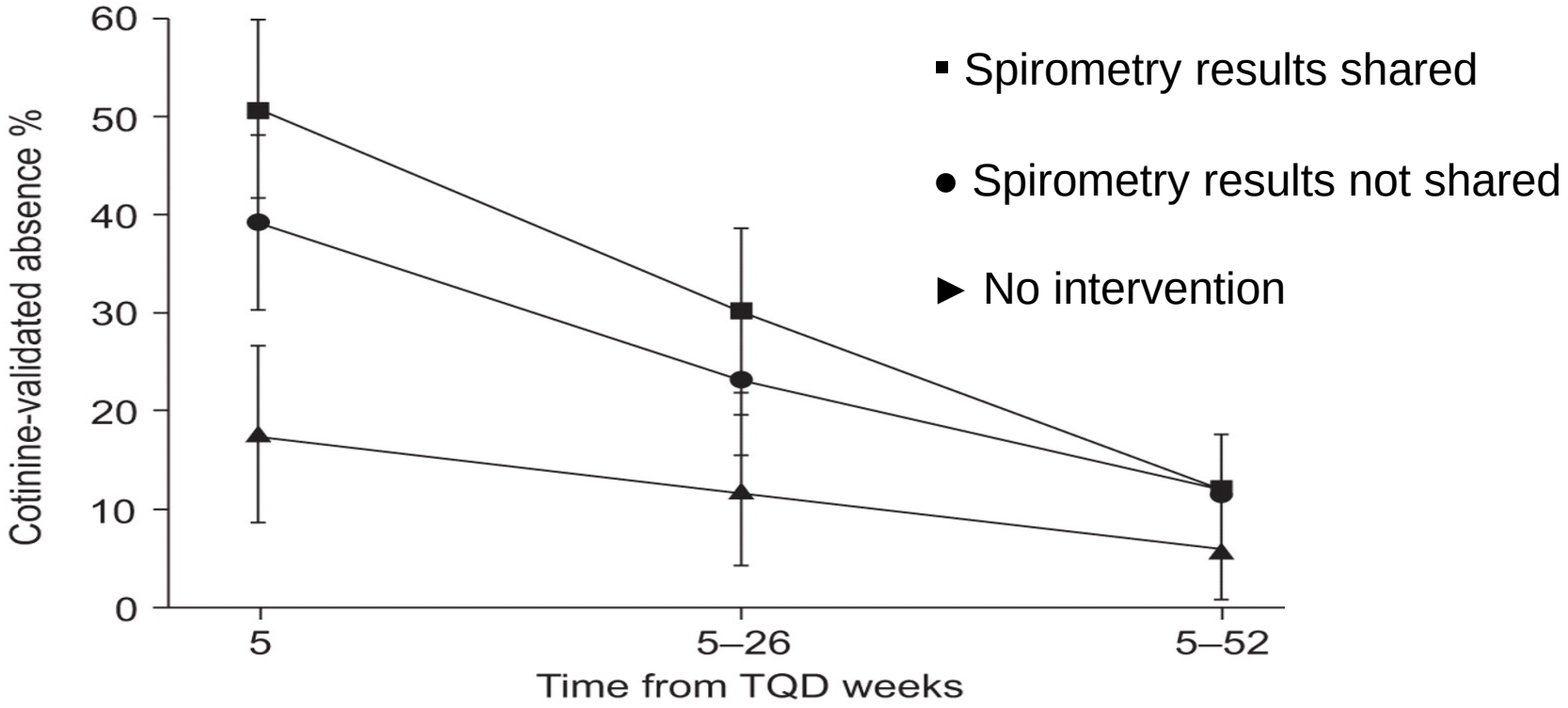
There was no direct evidence available to determine the benefits and harms of screening asymptomatic adults for COPD using questionnaires or office-based screening pulmonary function testing or to determine the benefits of treatment in screen-detected populations. Indirect evidence suggests that the CDQ has moderate overall performance for COPD detection.

Among patients with mild to moderate COPD, the benefit of pharmacotherapy for reducing exacerbations was modest.

Guirguis-Blake et al, JAMA 2016; 315(13):1378-1393

Screening for COPD?

KQ5a: Does screening for COPD increase smoking cessation rates among asymptomatic adults compared with usual care? Not really!



Kotz et al, ERJ 2009

Don’t expect patients to use drugs properly

Treatment adherence with inhaled drugs is thought to be poor

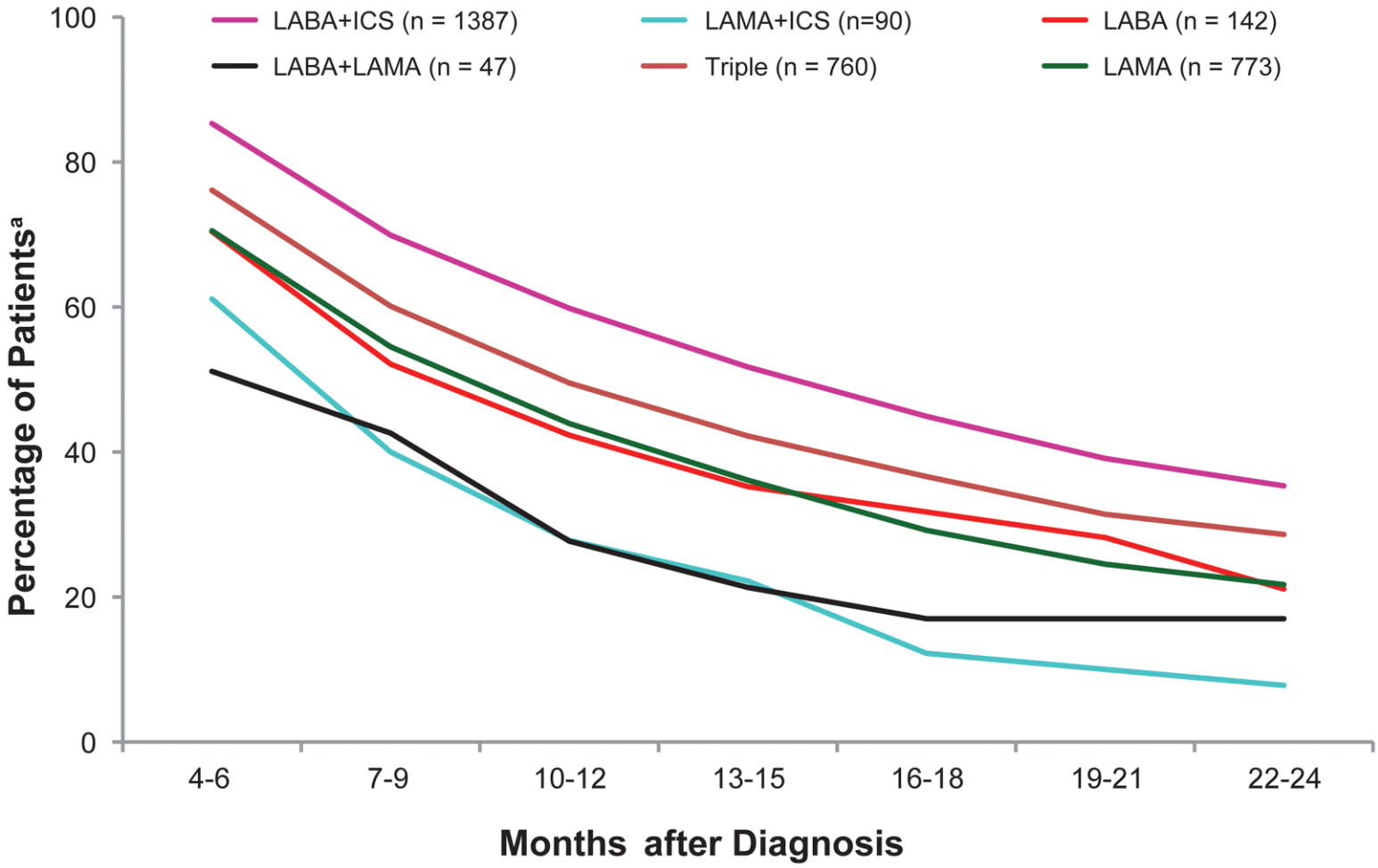
Even more so in asthma than in COPD

Adherence is thought to benefit from once daily

There is a multitude of devices out there, which is not really helping!

And a lack of robust clinical data to support decision making

Use of R/ after establishing diagnosis



Wurst et al. PLoS One 2014

Factors influencing proper use

Patient's age

Cognitive status

Visual aquity

Manual dexterity

Manual strength

Ability to coordinate

Patient preference

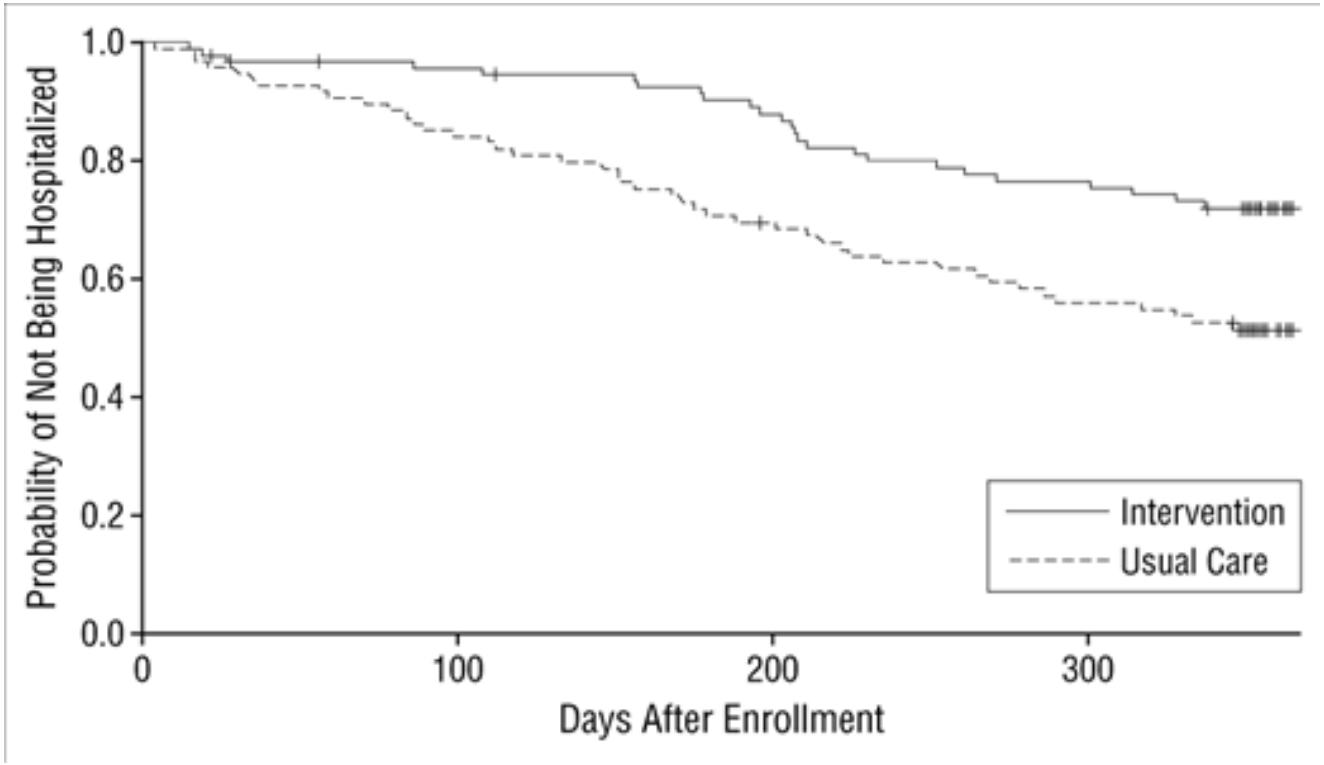
Guidelines offer limited guidance regarding choice of devices

Cazzola and Rogliani, ERS monograph 2014

Don’t use self management action plans to reduce mortality in COPD

Reduction of Hospital Utilization in Patients With Chronic Obstructive Pulmonary Disease

A Disease-Specific Self-management Intervention



Bourbeau et al, JAMA Intern Med 2003

Selfmanagement in COPD Cochrane 2014

Self management interventions in patients with COPD are associated with improved health-related quality of life as measured by the SGRQ, a reduction in respiratory-related and all cause hospital admissions, and improvement in dyspnoea as measured by the (m)MRC.

No statistically significant differences were found in other outcome parameters.

However, heterogeneity among interventions, study populations, follow-up time and outcome measures makes it difficult to formulate clear recommendations regarding the most effective form and content of self management in COPD.

What we shouldn’t do in COPD

We do a lot to improve outcomes in COPD

Smoking cessation, exercise and inhaled bronchodilators are definitely effective in COPD

Many other things, however are not.

Thank you for your attention