

COPD – Management



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Disclosures

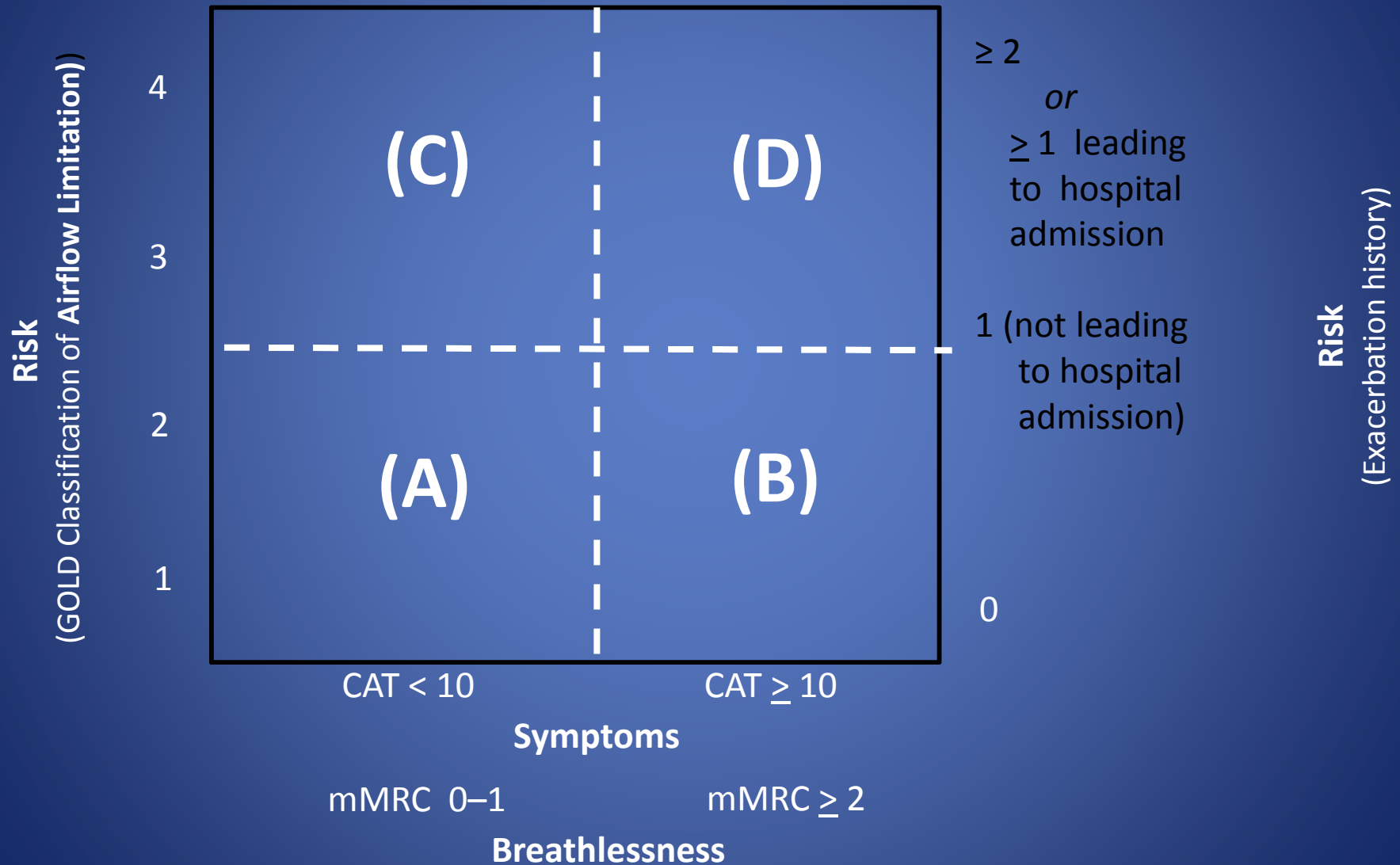
- Advisory bodies – GSK, Astra Zeneca, Pfizer, Boehringer Ingelheim, Bayer, Novartis.
- Travel grants – GSK, Astra Zeneca, Cipla

COPD-Unmet needs/Conundrums

- Failure of prevention
- Underdiagnosis and misdiagnosis
- Underutilisation of Spirometry
- Overuse of ICS
- “Non-smoking” COPD
- Lack of public awareness of the term COPD
- COPD vs Asthma – different diseases or continuum.

- COPD is a heterogeneous disorder
- COPD and comorbidities
- Real world studies

Combined Assessment of COPD



Therapeutic Options: Key Points

- Smoking cessation has the greatest capacity to influence the natural history of COPD. Health care providers should encourage all patients who smoke to quit.
- Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.
- All COPD patients benefit from regular physical activity and should repeatedly be encouraged to remain active.

Global Strategy for Diagnosis, Management and Prevention of COPD

Therapeutic Options: Risk Reduction

- Encourage comprehensive **tobacco-control policies** with clear, consistent, and repeated nonsmoking messages.
- Emphasize primary prevention, best achieved by elimination or reduction of **exposures in the workplace**. Secondary prevention, achieved through surveillance and early detection, is also important.
- Reduce or avoid **indoor air pollution** from biomass fuel, burned for cooking and heating in poorly ventilated dwellings.
- Advise patients to monitor public announcements of **air quality** and, depending on the severity of their disease, avoid vigorous exercise outdoors or stay indoors during pollution episodes.

Therapeutic Options: Key Points

- Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.
- None of the existing medications for COPD has been shown conclusively to modify the long-term decline in lung function.
- Influenza and pneumococcal vaccination should be offered depending on local guidelines.

Global Strategy for Diagnosis, Management and Prevention of COPD

Therapeutic Options: COPD Medications

Beta₂-agonists

Short-acting beta₂-agonists

Long-acting beta₂-agonists

Anticholinergics

Short-acting anticholinergics

Long-acting anticholinergics

Combination short-acting beta₂-agonists + anticholinergic in one inhaler

Combination long-acting beta₂-agonist + anticholinergic in one inhaler

Methylxanthines

Inhaled corticosteroids

Combination long-acting beta₂-agonists + corticosteroids in one inhaler

Systemic corticosteroids

Phosphodiesterase-4 inhibitors

Global Strategy for Diagnosis, Management and Prevention of COPD

Therapeutic Options: Bronchodilators

- Bronchodilator medications are central to the symptomatic management of COPD.
- Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.
- The principal bronchodilator treatments are beta₂-agonists, anticholinergics, theophylline or combination therapy.
- The choice of treatment depends on the availability of medications and each patient's individual response in terms of symptom relief and side effects..

Global Strategy for Diagnosis, Management and Prevention of COPD

Therapeutic Options: Bronchodilators

- Long-acting inhaled bronchodilators are convenient and more effective for symptom relief than short-acting bronchodilators.
- Long-acting inhaled bronchodilators reduce exacerbations and related hospitalizations and improve symptoms and health status.
- Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

Therapeutic Options: Inhaled Corticosteroids

- Regular treatment with inhaled corticosteroids improves symptoms, lung function and quality of life and reduces frequency of exacerbations for COPD patients with an $FEV_1 < 60\%$ predicted.
- Inhaled corticosteroid therapy is associated with an increased risk of pneumonia.
- Withdrawal from treatment with inhaled corticosteroids may lead to exacerbations in some patients.

Therapeutic Options: Combination Therapy

- An inhaled corticosteroid combined with a long-acting beta₂-agonist is more effective than the individual components in improving lung function and health status and reducing exacerbations in moderate to very severe COPD.
- Combination therapy is associated with an increased risk of pneumonia.
- Addition of a long-acting beta₂-agonist/inhaled glucocorticosteroid combination to an anticholinergic (tiotropium) appears to provide additional benefits.

Therapeutic Options: Systemic Corticosteroids

- Chronic treatment with systemic corticosteroids should be avoided because of an unfavorable benefit-to-risk ratio.

Therapeutic Options: Phosphodiesterase-4 Inhibitors

- In patients with severe and very severe COPD (GOLD 3 and 4) and a history of exacerbations and chronic bronchitis, the phosphodiesterase-4 inhibitor, roflumilast, reduces exacerbations treated with oral glucocorticosteroids.

Therapeutic Options: Theophylline

- Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators and is not recommended if those drugs are available and affordable.
- There is evidence for a modest bronchodilator effect and some symptomatic benefit compared with placebo in stable COPD. Addition of theophylline to salmeterol produces a greater increase in FEV₁ and breathlessness than salmeterol alone.
- Low dose theophylline reduces exacerbations but does not improve post-bronchodilator lung function.

Therapeutic Options: Other Pharmacologic Treatments

Influenza vaccines can reduce serious illness.

Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older and for COPD patients younger than age 65 with an $FEV_1 < 40\%$ predicted.

The use of *antibiotics*, other than for treating infectious exacerbations of COPD and other bacterial infections, is currently not indicated.

Therapeutic Options: Rehabilitation

- All COPD patients benefit from *exercise training programs* with improvements in exercise tolerance and symptoms of dyspnea and fatigue.
- Although an effective pulmonary rehabilitation program is 6 weeks, the longer the program continues, the more effective the results.
- If exercise training is maintained at home, the patient's health status remains above pre-rehabilitation levels.

Therapeutic Options: Other Treatments

Oxygen Therapy: The long-term administration of oxygen (> 15 hours per day) to patients with chronic respiratory failure has been shown to increase survival in patients with severe, resting hypoxemia.

Ventilatory Support: Combination of noninvasive ventilation (NIV) with long-term oxygen therapy may be of some use in a selected subset of patients, particularly in those with pronounced daytime hypercapnia.

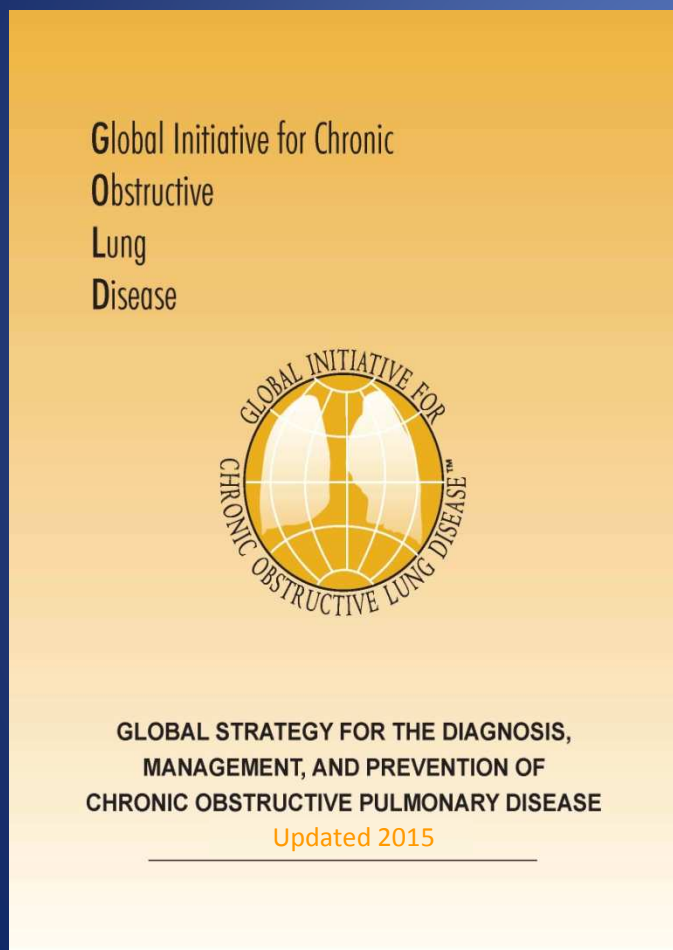
Therapeutic Options: Surgical Treatments

Lung volume reduction surgery (LVRS) is more efficacious than medical therapy among patients with upper-lobe predominant emphysema and low exercise capacity.

LVRS is costly relative to health-care programs not including surgery.

In appropriately selected patients with very severe COPD, *lung transplantation* has been shown to improve quality of life and functional capacity.

Global Strategy for Diagnosis, Management and Prevention of COPD, 2015: Chapters



- n Definition and Overview
- n Diagnosis and Assessment
- n Therapeutic Options
- n Manage Stable COPD**
- n Manage Exacerbations
- n Manage Comorbidities
- n Asthma COPD Overlap
Syndrome (ACOS)

Manage Stable COPD: Goals of Therapy

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

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Non-pharmacologic

Patient Group	Essential	Recommended	Depending on local guidelines
A	Smoking cessation (can include pharmacologic treatment)	Physical activity	Flu vaccination Pneumococcal vaccination
B, C, D	Smoking cessation (can include pharmacologic treatment) Pulmonary rehabilitation	Physical activity	Flu vaccination Pneumococcal vaccination

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

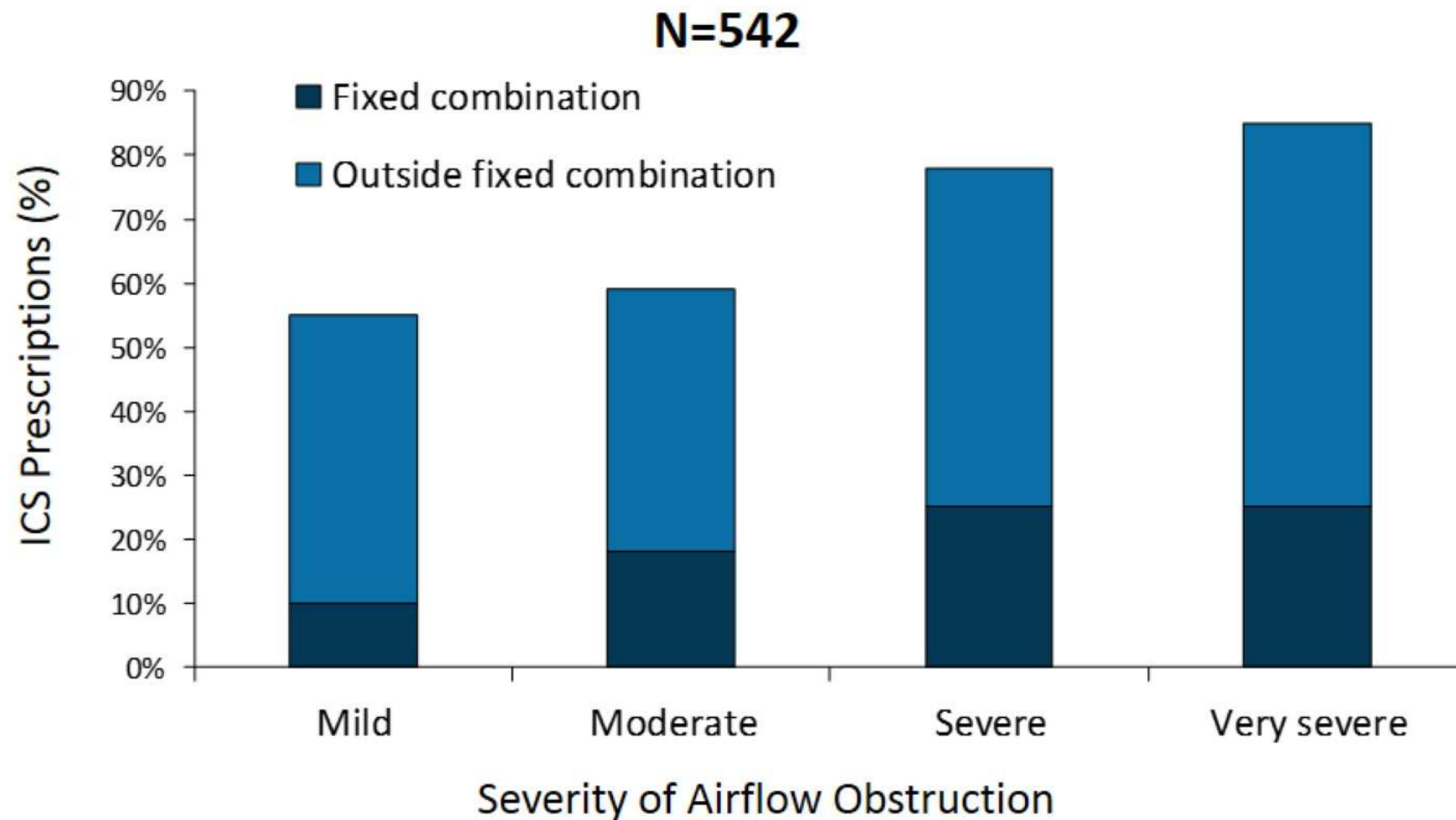
(Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.)

Patient	Recommended first choice	Alternative choice	Other Possible Treatments
A	SAMA prn or SABA prn	LAMA or LABA or SABA and SAMA	Theophylline
B	LAMA or LABA	LAMA and LABA	SABA and/or SAMA Theophylline
C	ICS + LABA or LAMA	LAMA and LABA or LAMA and PDE4-inh. or LABA and PDE4-inh.	SABA and/or SAMA Theophylline
D	ICS + LABA and/or LAMA	ICS + LABA and LAMA or ICS+LABA and PDE4-inh. or LAMA and LABA or LAMA and PDE4-inh.	Carbocysteine N-acetylcysteine SABA and/or SAMA Theophylline

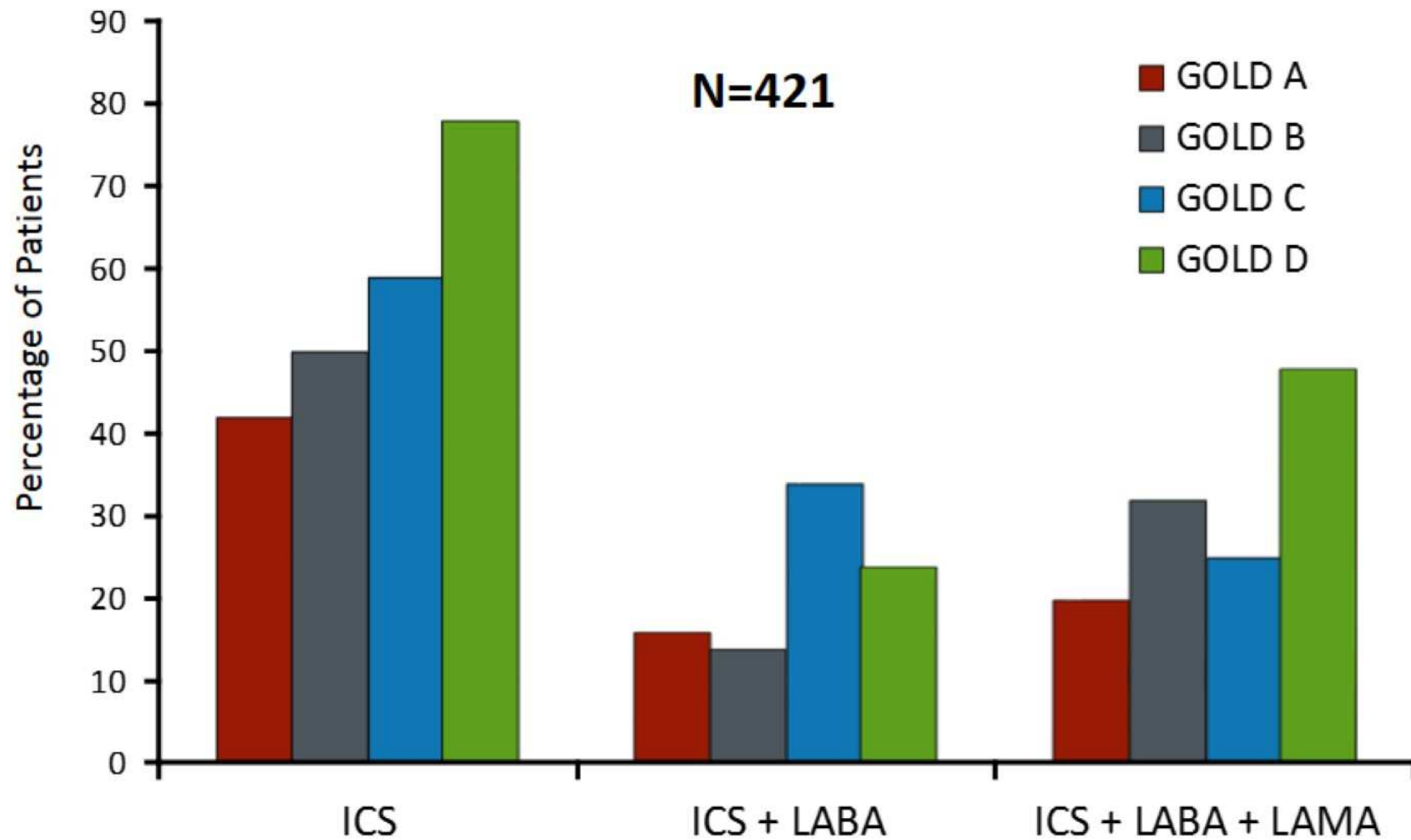
Updated GOLD Recommendations: First-line Pharmacologic Therapy for Stable COPD

Patient Group	GOLD Recommendation	Other Approaches?
A Low risk Fewer symptoms	SAMA <i>or</i> SABA	LAMA <i>or</i> LABA?
B Low risk More symptoms	LAMA <i>or</i> LABA	LAMA and LABA?
C High risk Fewer symptoms	ICS + LABA <i>or</i> LAMA	When to use ICS?
D High risk More symptoms	ICS + LABA <i>and/or</i> LAMA	When to use ICS?

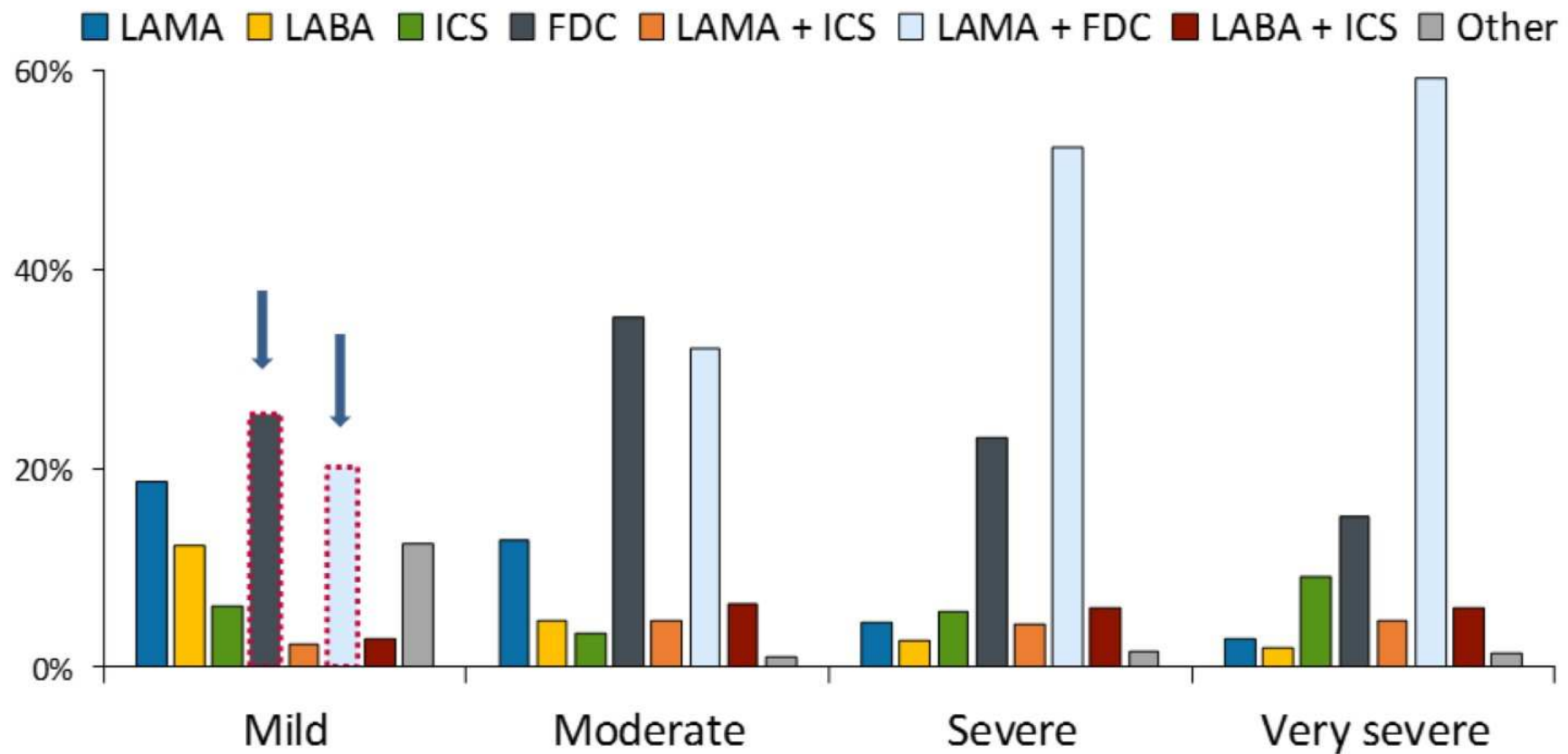
Real-Life ICS Use in COPD: Adherence to Guidelines in France



Real-Life ICS Use in COPD According to 2011 GOLD Classification

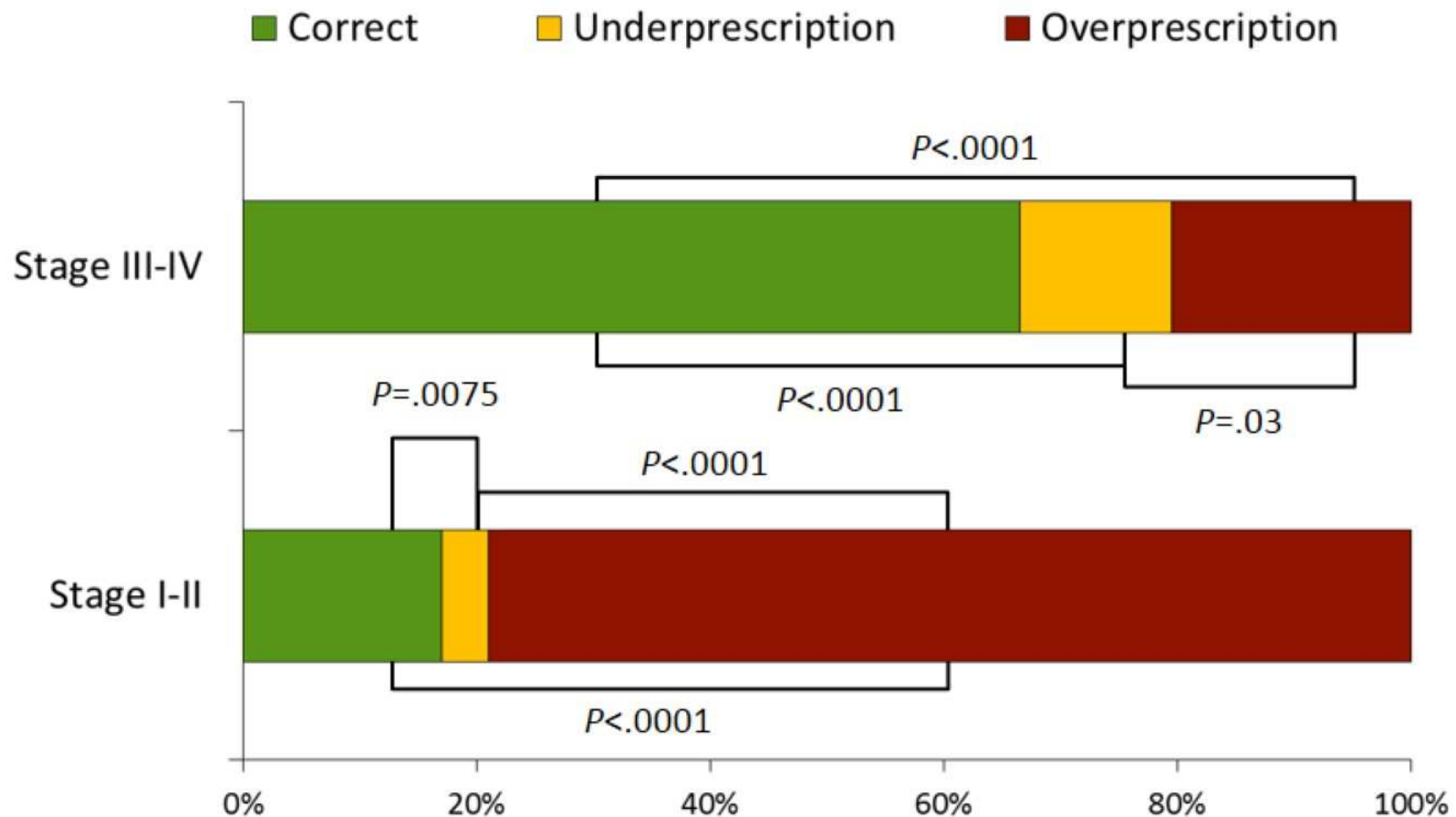


Concordance Between Real-Life COPD Treatment and Recommendations



Correct, Under-, and Overprescription of COPD Treatment According to GOLD 2008

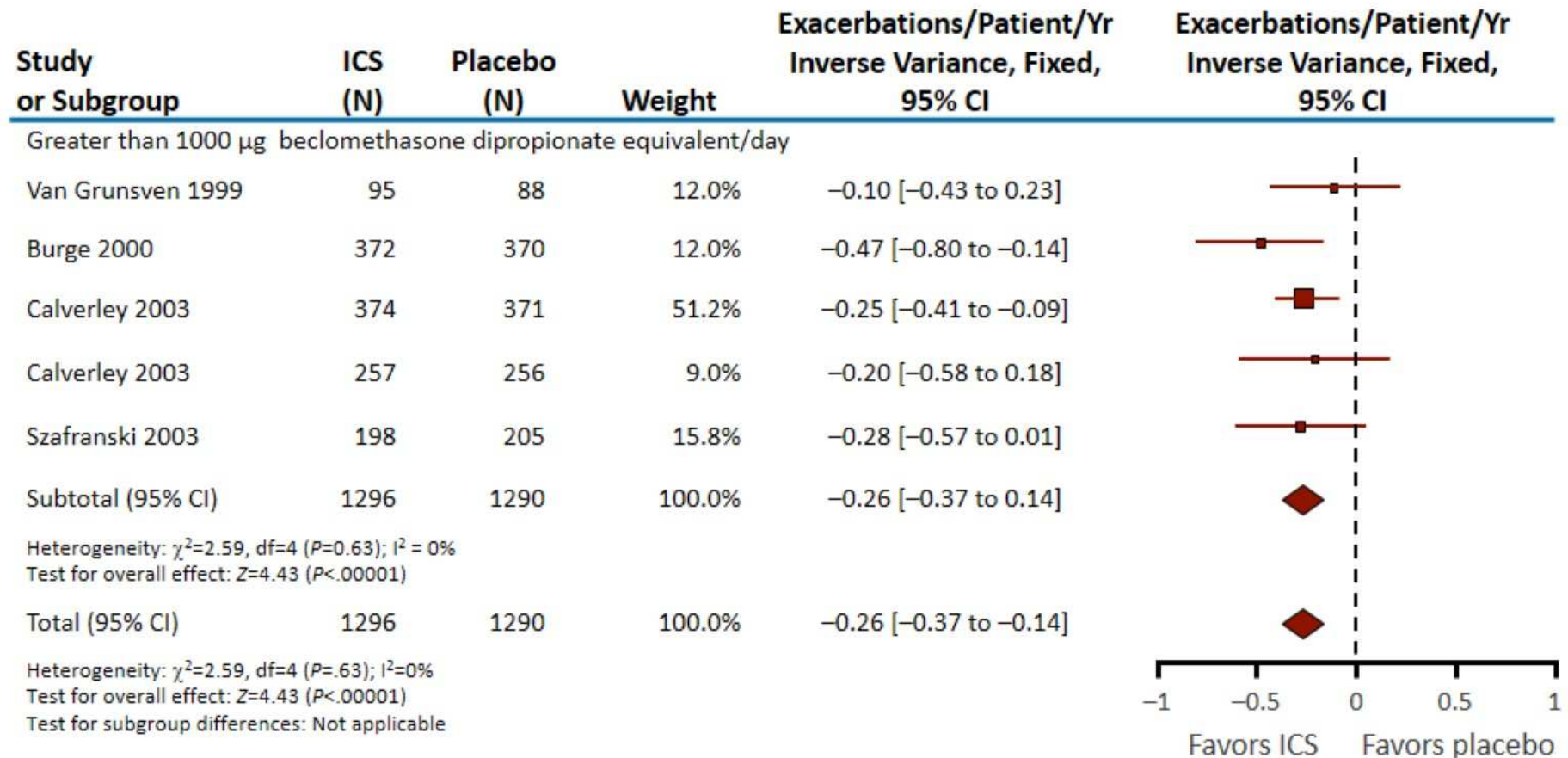
3792 Patients Treated Regularly With at Least 1 Drug



Considerations When Switching or Stepping Up Therapy

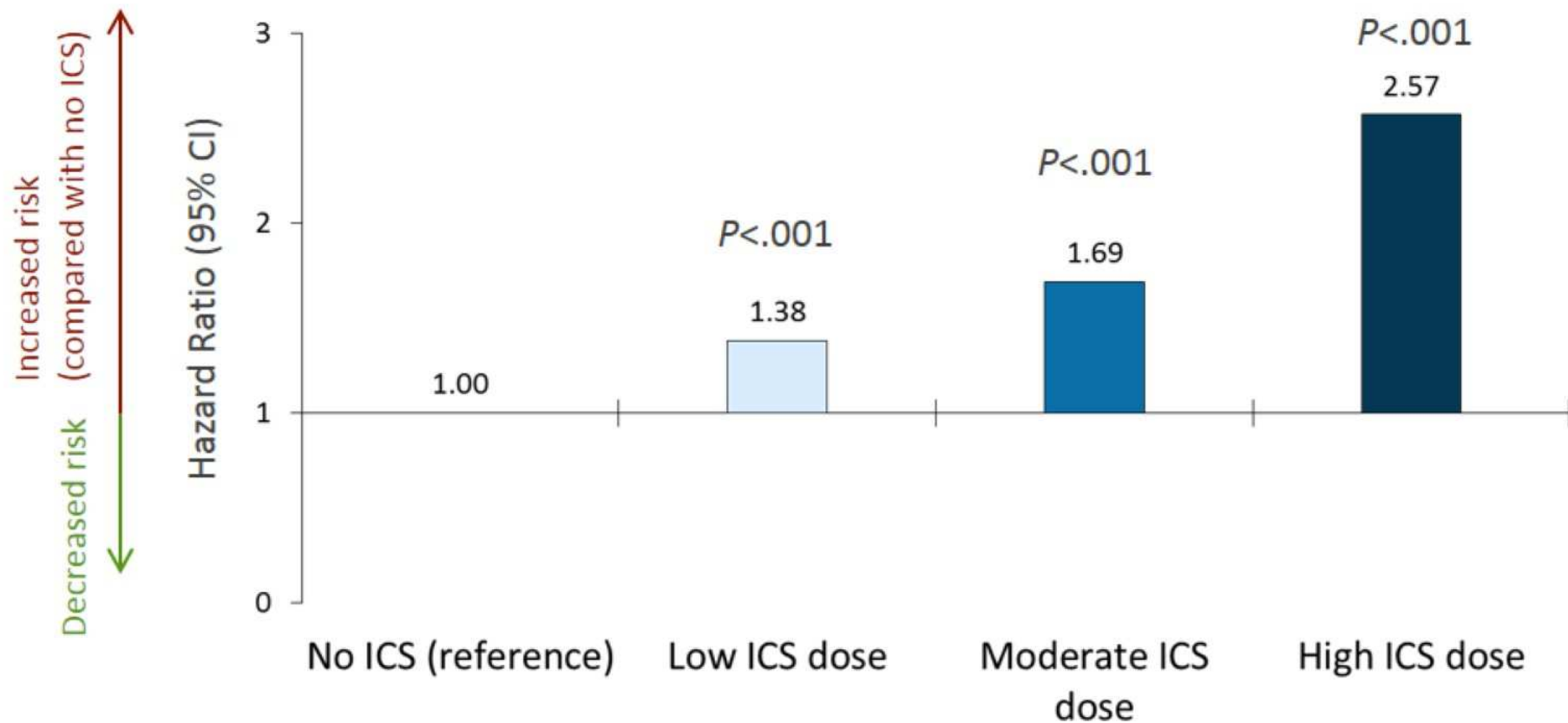
- Frequency of exacerbations
- Predominant problem with regular symptoms
- Exercise limitation
- Convenience to the patient

Effect of ICS on Preventing COPD Exacerbations

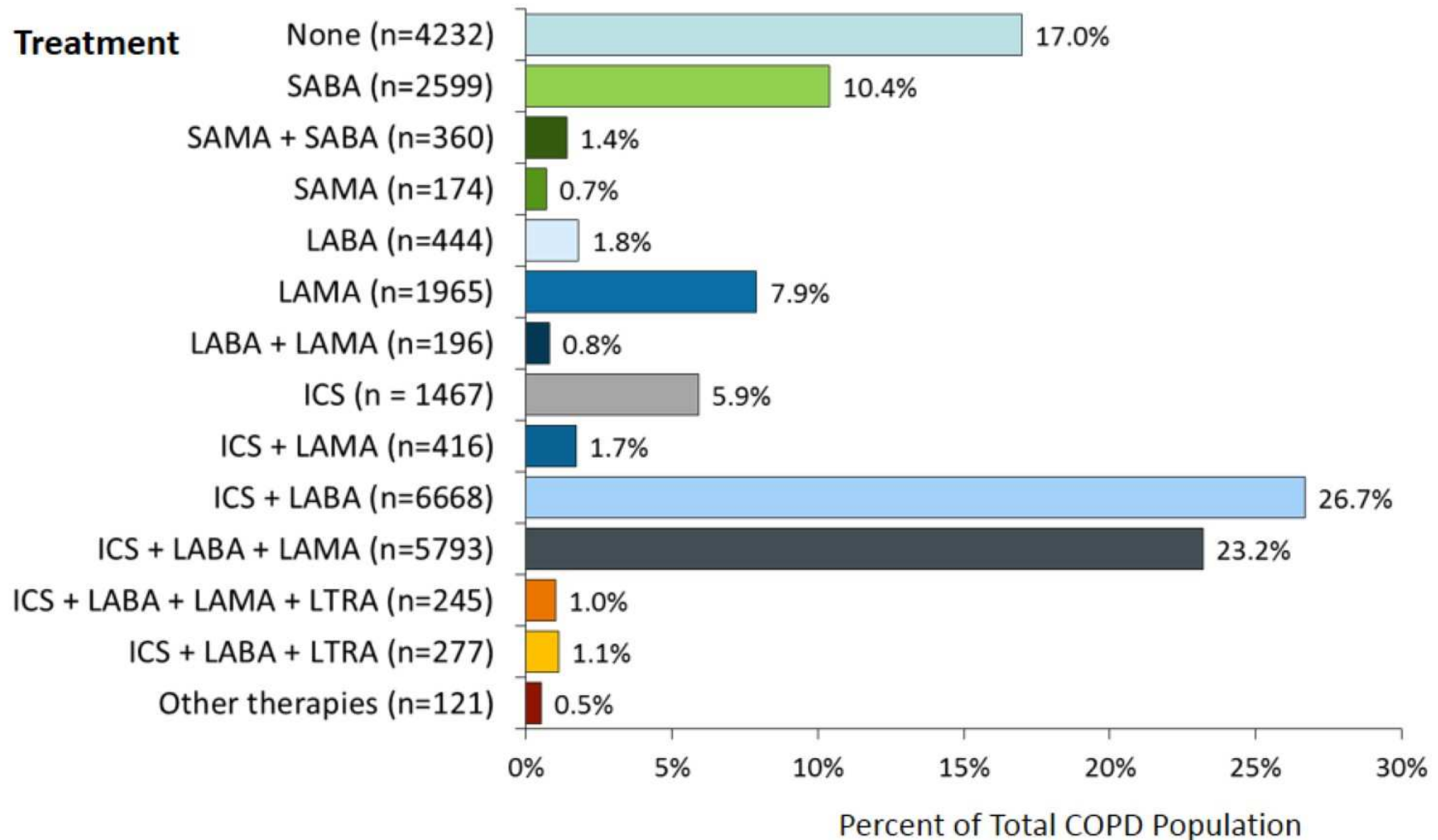


The mean difference for this analysis was -0.26 exacerbations/patient/yr with ICS (2586 participants)

Use of ICS and Risk for Pneumonia: Dose-Response Relationship

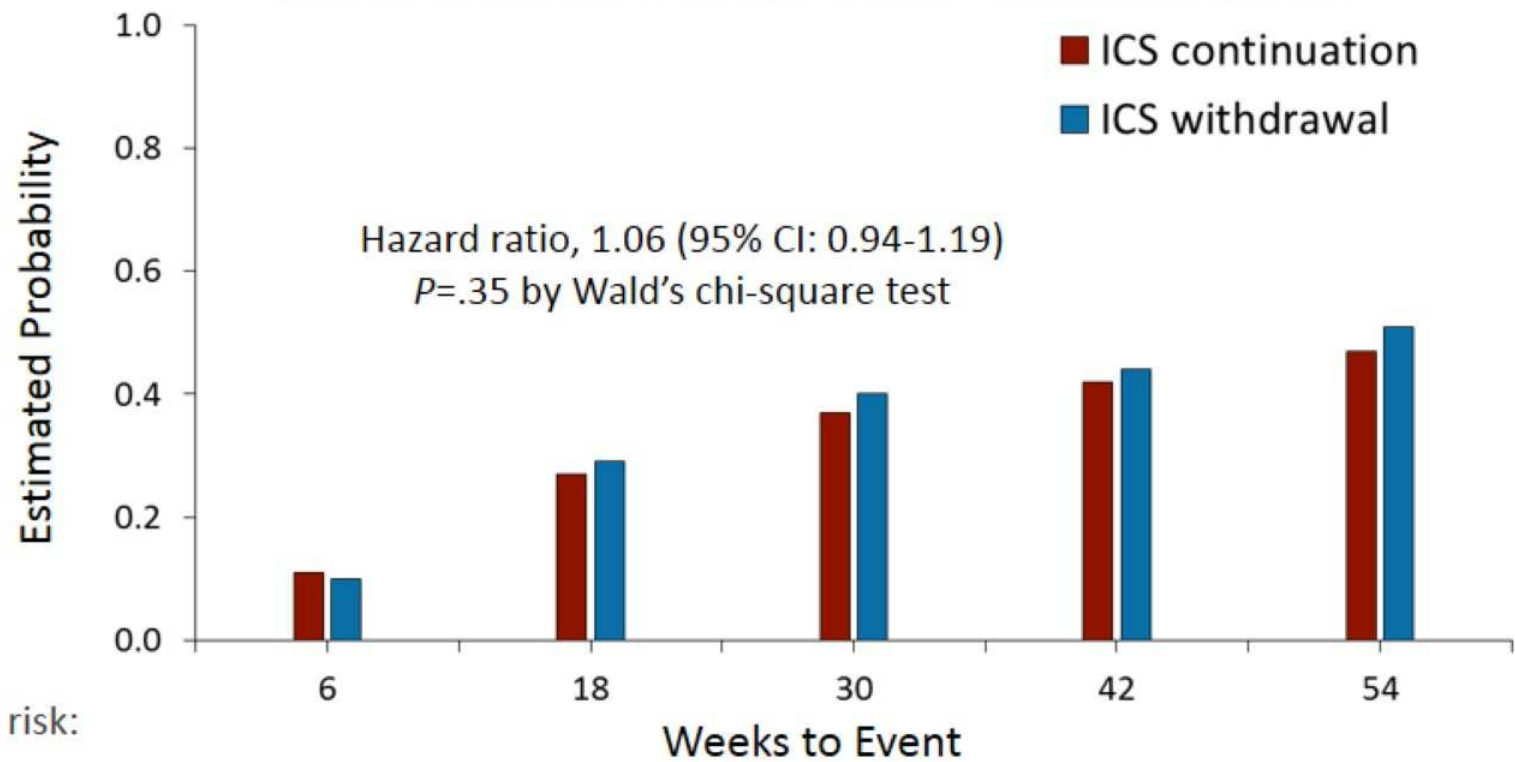


Real-World Management for COPD Population in the United Kingdom



ICS Withdrawal and Exacerbations in Patients With Severe COPD: WISDOM

Moderate or Severe COPD Exacerbation



Number at risk:

	0	6	18	30	42	54
ICS continuation	1243	1059	827	694	615	14
ICS withdrawal	1242	1090	825	688	607	19

A PCP Approach to Monotherapy for COPD

- Some patients with mild COPD may benefit from short-acting bronchodilator monotherapy over the short term
- Most patients will need regular treatment with a long-acting bronchodilator, whether LABA or LAMA
- An initial choice could be an ultra-long-acting once-daily LABA or a LAMA
- If the patient is not controlled on monotherapy, one could step up to dual LABA/LAMA therapy

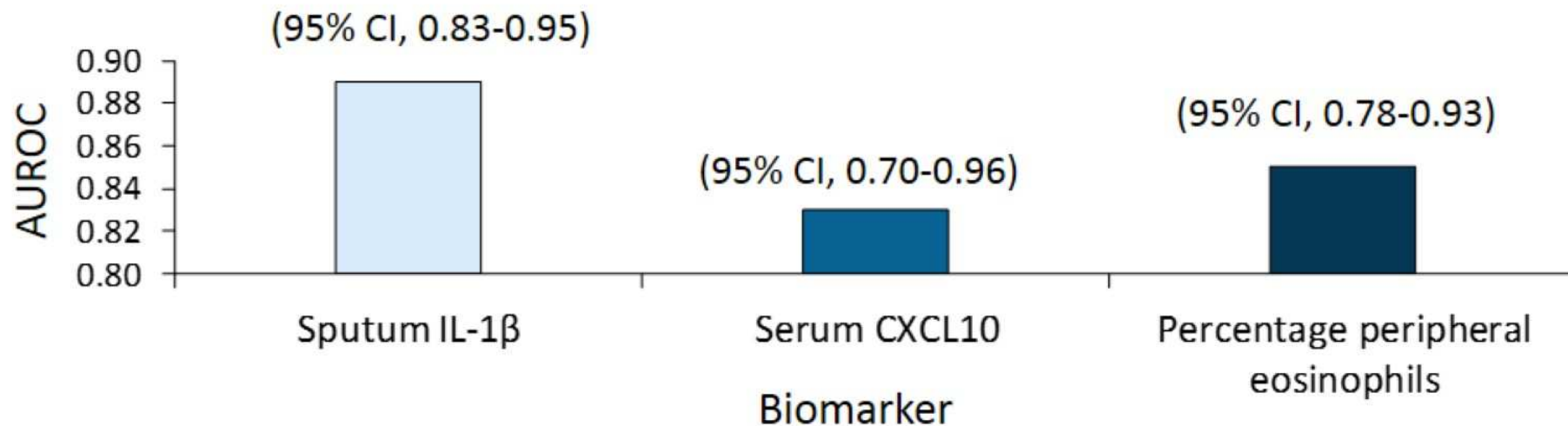
A Pulmonologist's View of COPD Treatment

- Two main pharmacotherapeutic approaches:
 - 1) Bronchodilators
 - 2) Anti-inflammatory, ICS
- For airflow limitation, 2 bronchodilators have a greater effect than 1
- If airflow limitation causes dyspnea, bronchodilation can be proportional to the degree of dyspnea
- Symptoms have to be expressed in relation to activity
- If, despite adequate bronchodilator treatment, there are COPD exacerbations, ICSs are indicated

Move Towards Phenotype-Directed Treatment?

- Observational, 1-year study of 182 exacerbations in 86 patients identified 4 distinct biologic COPD exacerbation phenotypes: bacterial-, viral-, or eosinophilic-predominant and “pauci-inflammatory”

Biomarkers Best Identifying Clinical Phenotypes



Take-Home Messages

- Many different treatments are available, including bronchodilators, short-acting, long-acting, ultra-long acting, and ICS
- Bronchodilator monotherapy has a role in mildly symptomatic patients
- Clinicians need to encourage physical activity in patients
- Highly symptomatic patients may have dual bronchodilator treatment, and those who continue to have exacerbations could be prescribed a LABA/ICS combination
- High burden of symptoms and exacerbations despite treatment could warrant triple therapy

Take-Home Messages (cont)

- Characterize patients in terms of symptoms and exacerbations
- Future management will involve biomarkers, and the challenge will be to combine them with clinical characteristics to offer optimal targeted treatment
- Remember to emphasize the need for smoking cessation, to check that the patient uses the inhaler properly, and to identify and treat comorbidities
- Many patients receive ICS/LABA inappropriately, and future efforts could identify those patients who may benefit from ICS



Thank you

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Available and Emerging LABA and LAMA Bronchodilators for COPD

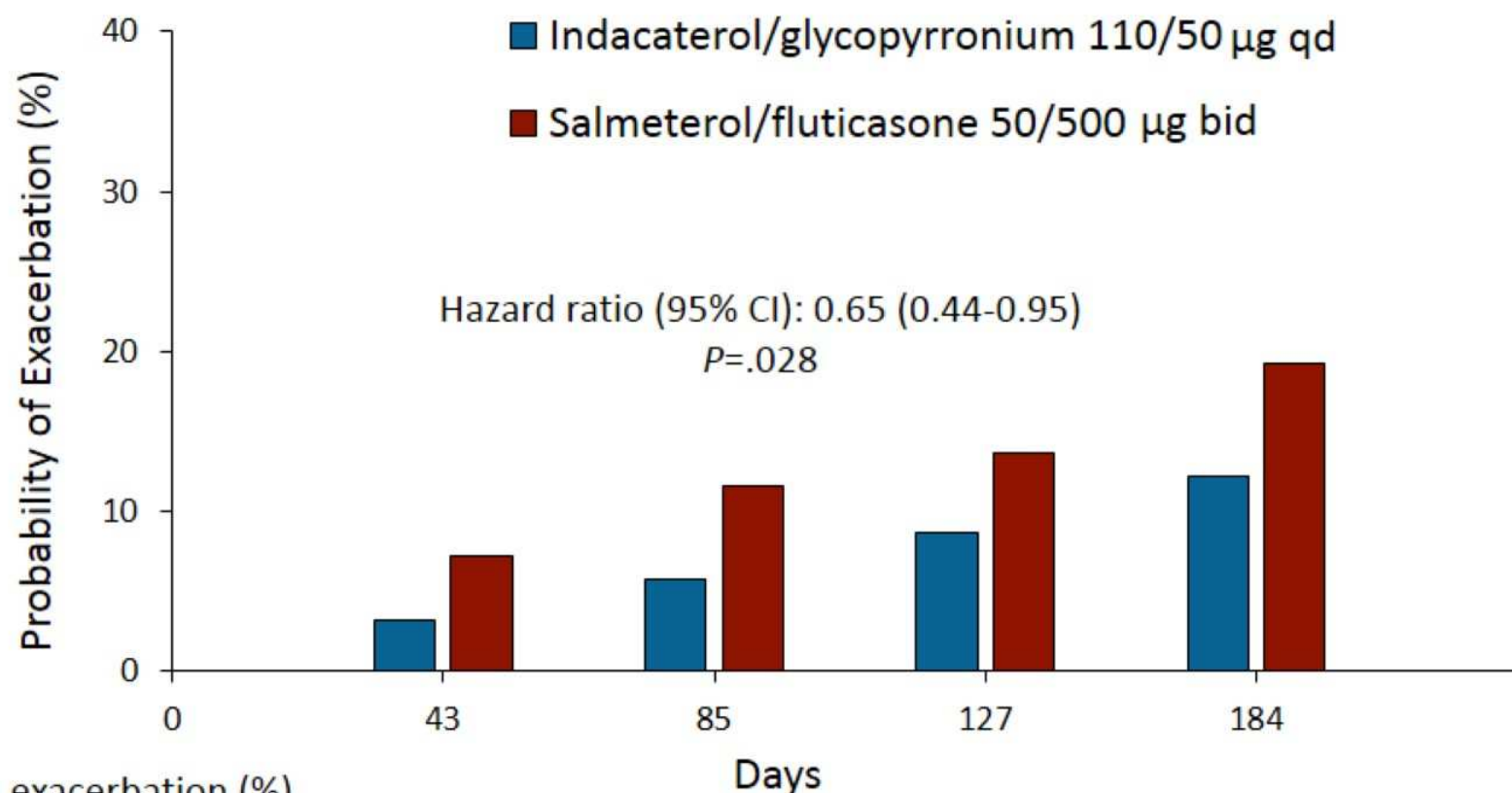
Agents

- **LABAs (twice daily)**
 - Formoterol
 - Salmeterol
- **LAMAs (twice daily)**
 - Acclidinium
- **LABAs (once daily)**
 - Indacaterol
 - Olodaterol
 - Vilanterol
- **LAMAs (once daily)**
 - Glycopyrronium
 - Tiotropium
 - Umeclidinium

LABA/LAMA Combinations

- Once daily
 - Indacaterol/glycopyrronium
 - Vilanterol/umeclidinium
 - Olodaterol/tiotropium
- Twice daily
 - Formoterol/acclidinium
 - Formoterol/glycopyrrolate

Time to First Moderate or Severe COPD Exacerbation for Indacaterol/Glycopyrronium vs Salmeterol/Fluticasone

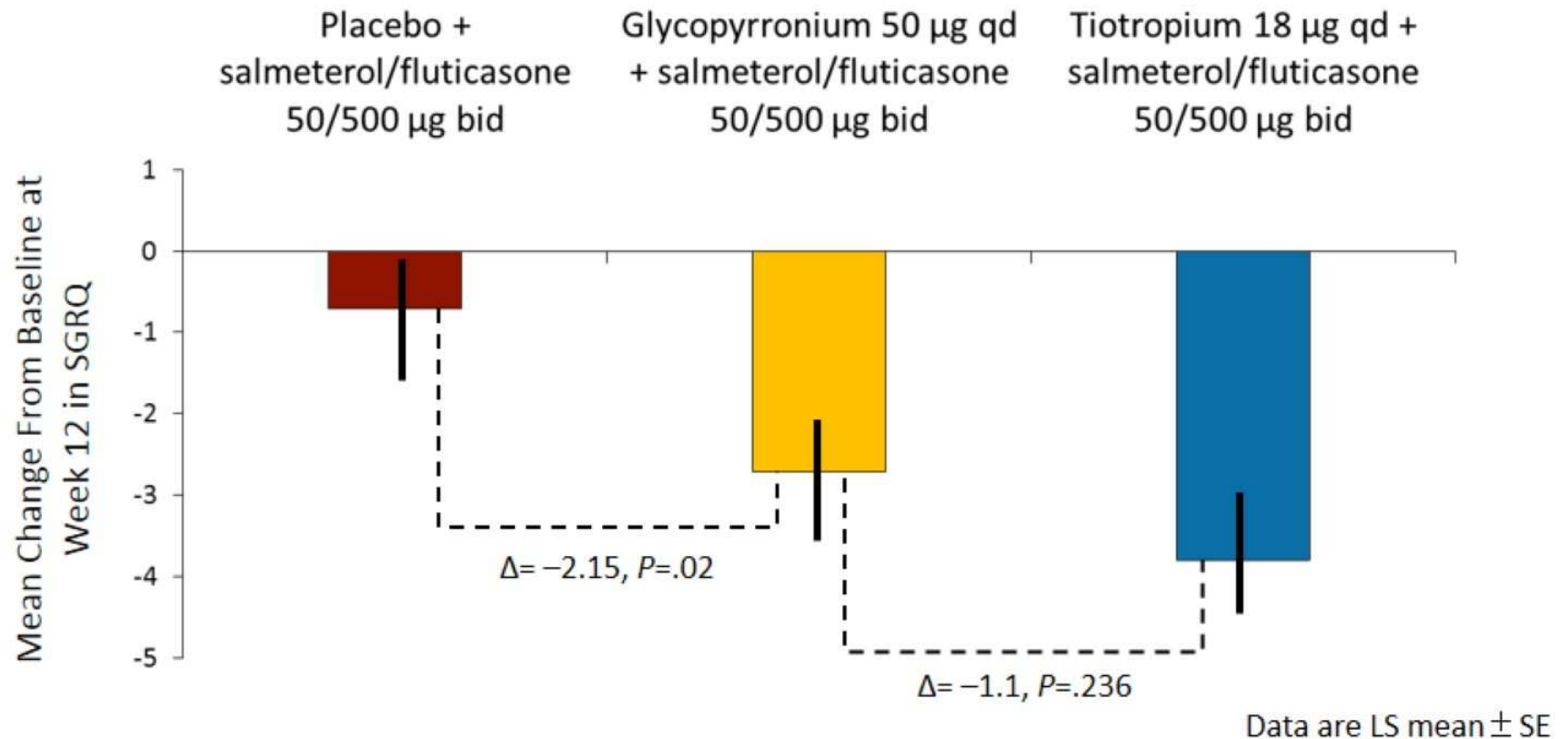


Patients with exacerbation (%)

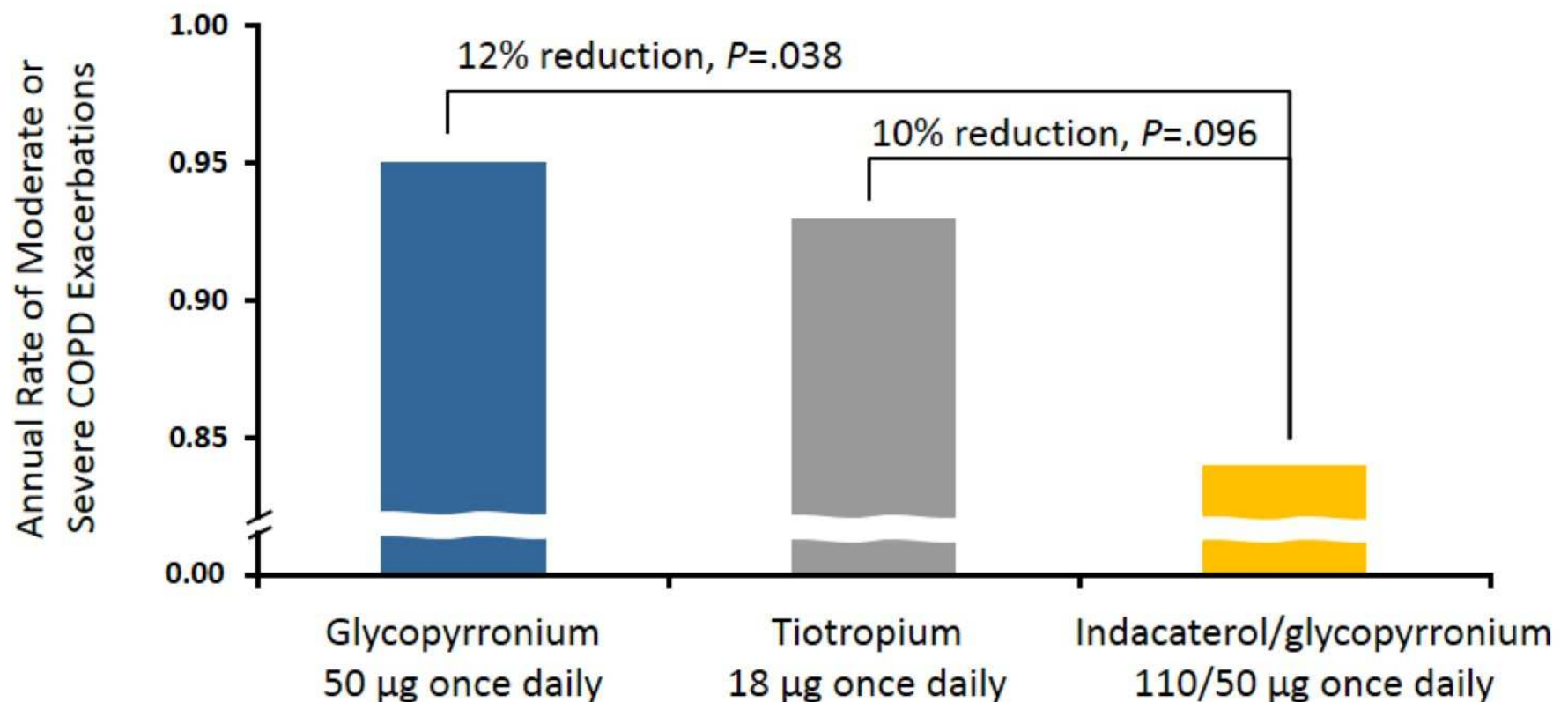
	0	43	85	127	184
Indacaterol/glycopyrronium	0	12 (3.3)	20 (5.5)	31 (8.6)	43 (12.1)
Salmeterol/fluticasone	0	24 (6.6)	38 (10.5)	48 (13.4)	67 (18.9)

Improvements in SGRQ Score for Salmeterol/Fluticasone With or Without Glycopyrronium or Tiotropium

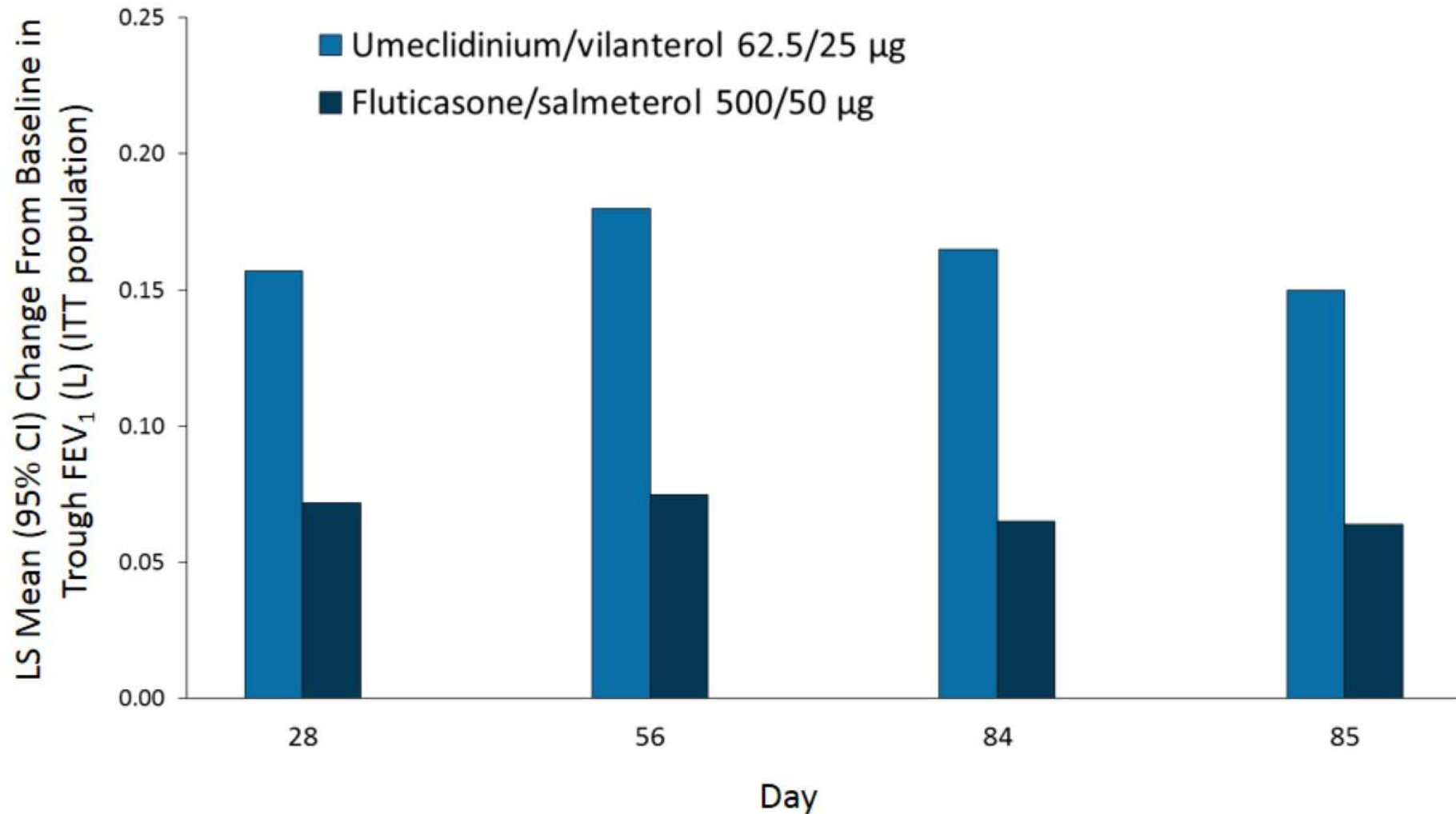
- Significant improvement with glycopyrronium + salmeterol/fluticasone vs salmeterol/fluticasone alone ($P=.02$)
- No significant treatment difference between glycopyrronium + salmeterol/fluticasone and tiotropium + salmeterol/fluticasone



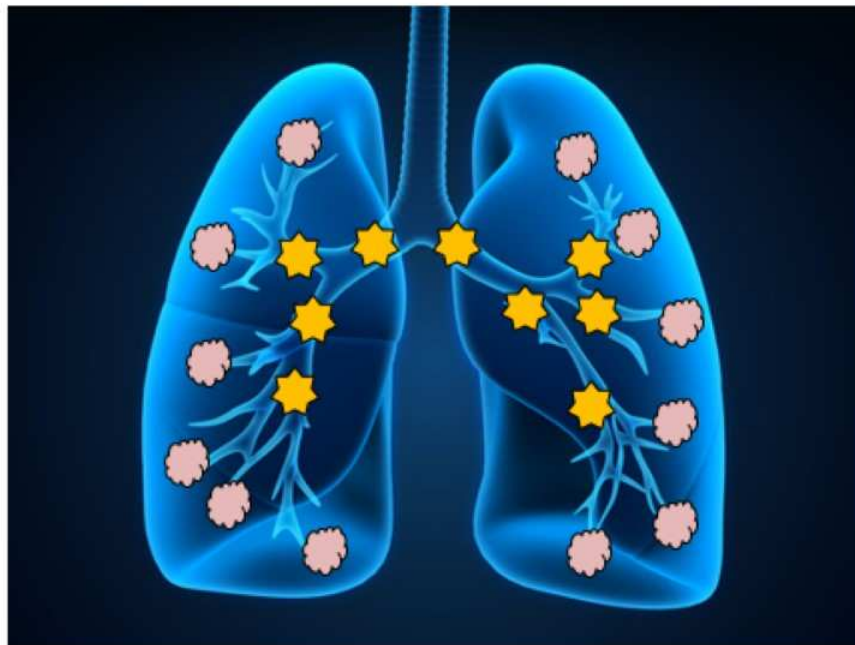
Annualized Rate of Moderate or Severe Exacerbations: SPARK



Lung Function Improvement With Umeclidinium/Vilanterol vs Fluticasone/Salmeterol



β_2 -Agonists and Muscarinic Antagonists in COPD: Sites of Action



★ Muscarinic receptors

Antimuscarinic agents

- More effective in the proximal airways^[a]
- Inhibit bronchoconstrictor effect of acetylcholine at M_3 muscarinic receptors located on airway smooth muscle^[b]
- Nonselective agents also block M_1 and M_2 receptors^[c]

🌸 β_2 -adrenergic receptors

β_2 -agonists

- More effective in the distal airways^[a]
- Directly activate β_2 receptors in bronchioles, leading to increase in cAMP, relaxation of smooth muscle, and bronchodilation^[d]

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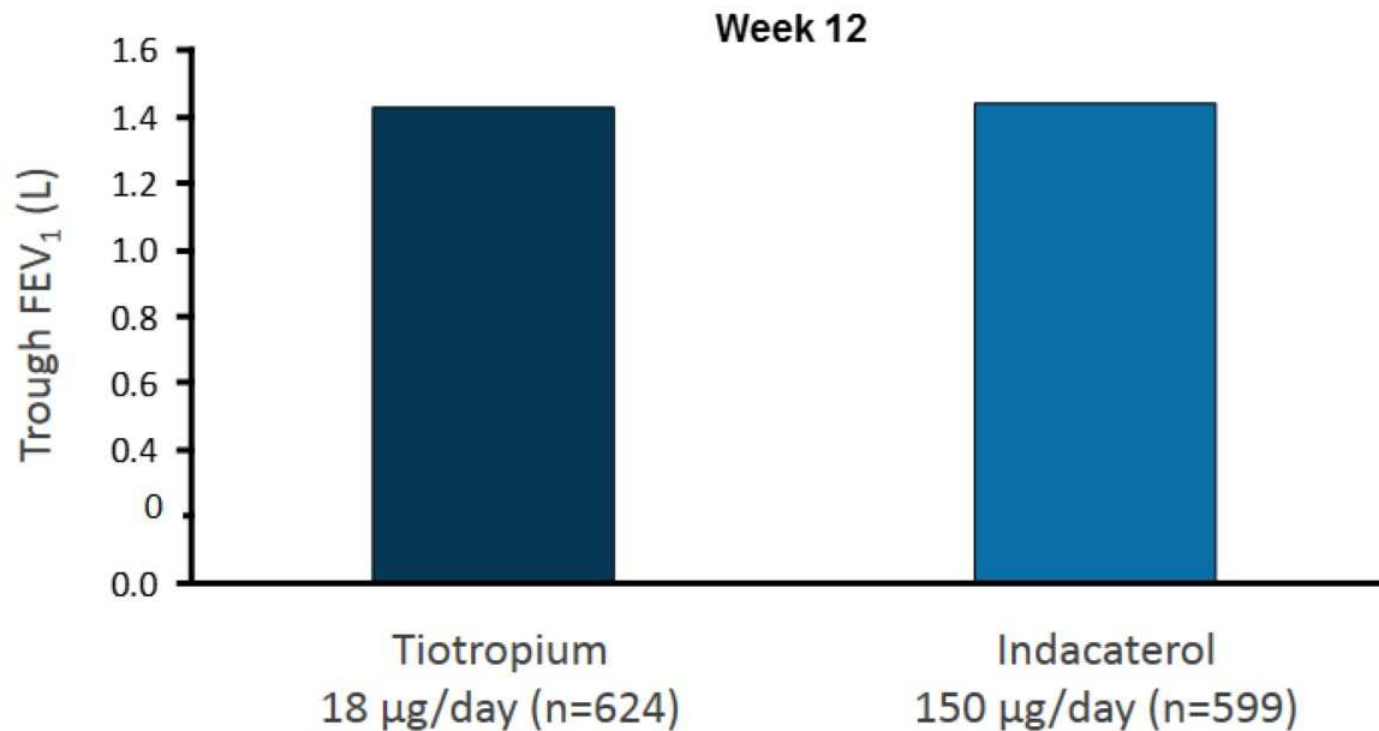
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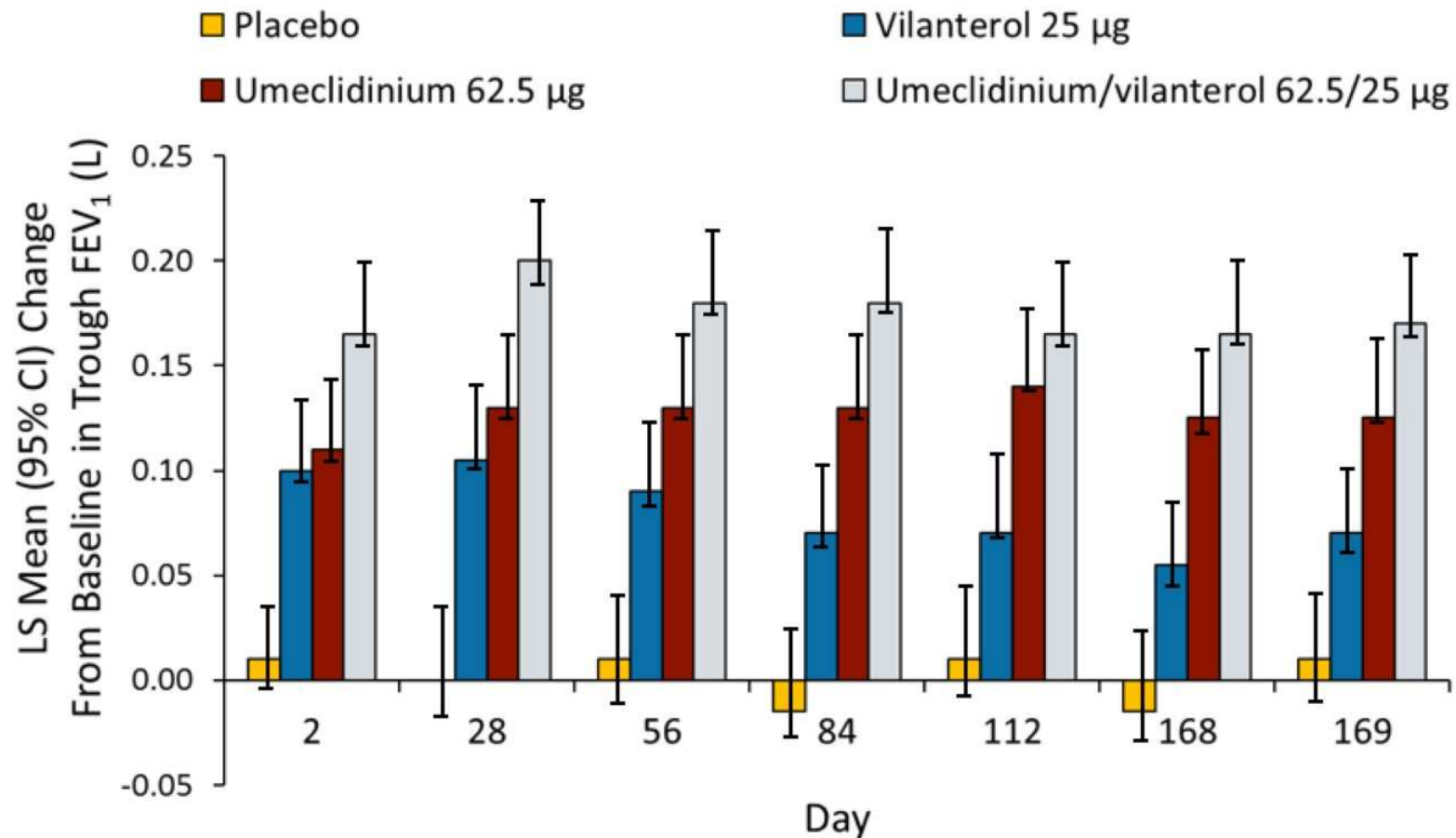
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Effect of Indacaterol vs Blinded Tiotropium on Trough FEV₁: INTENSITY

- Study met its primary objective of noninferiority of indacaterol to tiotropium in effect on “trough” FEV₁ ($P=.001$)



Single Dose of Umeclidinium/Vilanterol vs Single-Agent Components or Placebo



* $P < .04$ vs single components