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A Pooled Analysis of Mortality in Patients with COPD receiving Triple Therapy versus Dual Bronchodilation

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Introduction

For patients with COPD, the relative effects on survival of combination treatment with LAMA/LABA/ICS versus LAMA/LABA are widely debated[1–6]

Recent studies report a possible survival benefit of LAMA/LABA/ICS versus LAMA/LABA treatment in patients with highly symptomatic COPD and a history of exacerbations[a,1–3]

However, data are currently lacking for patients with moderate-to-severe COPD and a lower exacerbation risk

[a]≥1 moderate or severe exacerbation in the previous year.

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist.

1. Lipson DA, et al. Am J Respir Crit Care Med 2020; 201:1508–1516; 2. Lipson DA, et al. N Engl J Med 2018; 378:1671–1680;
3. Rabe KF, et al. N Engl J Med 2020; 383:35–48; 4. Suissa S, Ariel A. Eur Respir J 2018; 52:1801848;
5. Calzetta L, et al. Expert Rev Respir Med 2021; 15:143–152; 6. Han MK, et al. Expert Rev Respir Med 2021; 15:577–578.

Aim

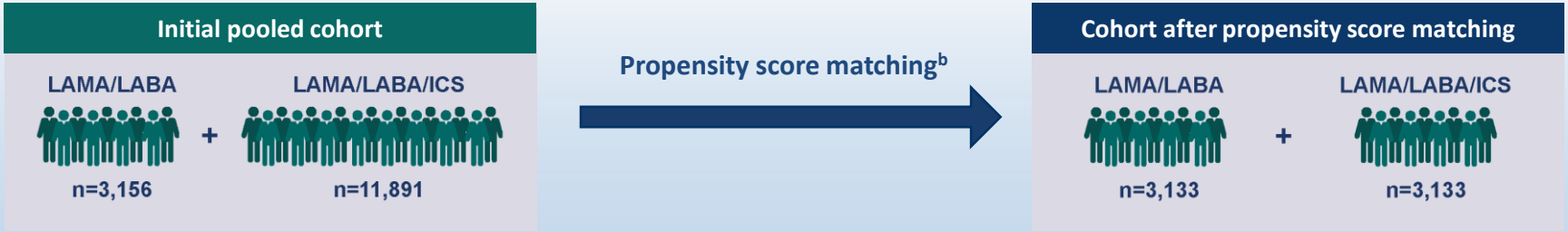
This pooled analysis compared the time to all-cause mortality with LAMA/LABA versus LAMA/LABA/ICS in a population of patients with moderate-to-very-severe COPD and a predominantly low exacerbation risk

Study design

Pooled data from six Phase III/IV trials

TONADO 1[1] | TONADO 2[1] | DYNAGITO[2] | WISDOM[3] | UPLIFT[4] | TIOSPIR[5,6]

Time to all-cause mortality was assessed in patients with moderate-to-very-severe COPD and a predominantly low risk of exacerbations[a]



- Analysis was on-treatment and limited to 52 weeks; patients were censored at the earliest date of treatment discontinuation or 52 weeks
- The LAMA/LABA/ICS group received ICS prior to study entry
- There was no withdrawal of prior ICS treatment at randomization in either arm

[a]After propensity score matching, >80% of patients had a low risk of exacerbations (≤1 exacerbation in prior year); [b]Patients were one-to-one propensity score matched for age, sex, geographical region, smoking status, post-bronchodilator forced expiratory volume in 1 second percent predicted, exacerbation history in previous year, body mass index and time since COPD diagnosis.

1. Buhl R, et al. Eur Respir J 2015; 45:969–979; 2. Calverley PMA, et al. Lancet Respir Med 2018; 6:337–344; 3. Magnussen H, et al. N Engl J Med 2014; 371:1285–1294; 4. Tashkin DP, et al. N Engl J Med 2008; 359:1543–1554; 5. Wise RA, et al. N Engl J Med 2013; 369:1491–1501; 6. Wise RA, et al. Respir Res 2013; 14:40.

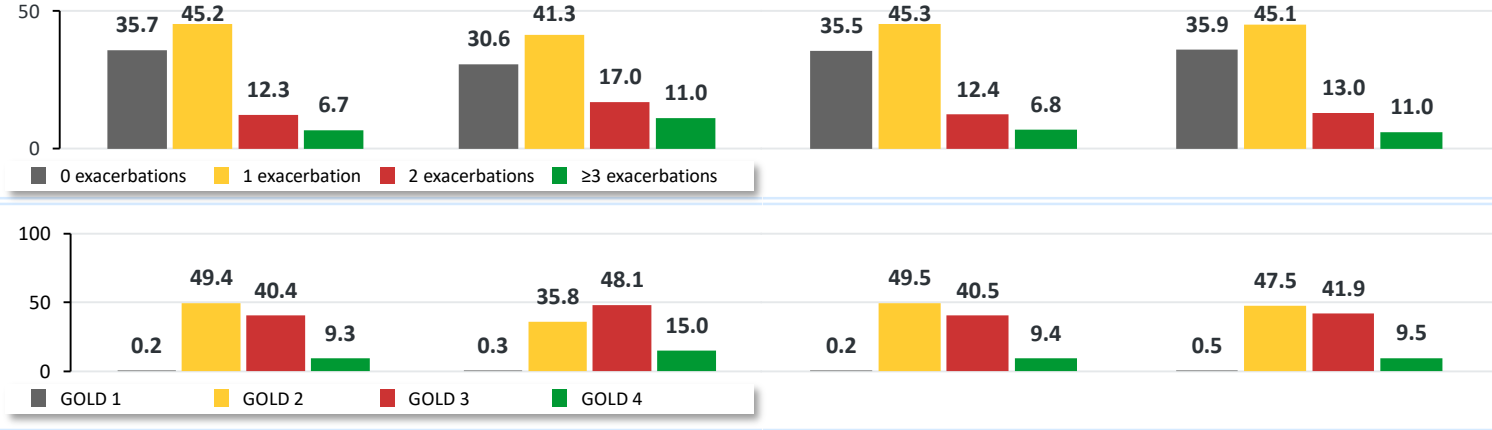
Baseline characteristics (1/2)

	Overall population		Cohort after propensity score matching	
	LAMA/LABA (n=3,156)	LAMA/LABA/ICS (n=11,891)	LAMA/LABA (n=3,133)	LAMA/LABA/ICS (n=3,133)
Sex, %				
Age, years	65.5 Mean; 8.8 SD	65.3 Mean; 8.6 SD	65.5 Mean; 8.8 SD	65.5 Mean; 8.7 SD
BMI, kg/m²	26.2 Mean; 5.5 SD	26.1 Mean; 5.5 SD	26.2 Mean; 5.5 SD	26.3 Mean; 5.6 SD
Smoking history current/former, %				

BMI, body mass index; SD, standard deviation.

Baseline characteristics (2/2)

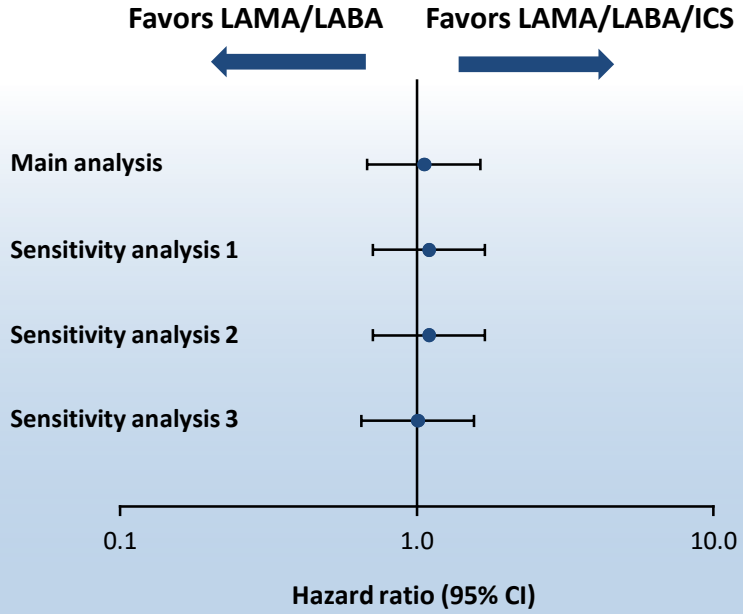
	Overall population		Cohort after propensity score matching	
	LAMA/LABA (n=3,156)	LAMA/LABA/ICS (n=11,891)	LAMA/LABA (n=3,133)	LAMA/LABA/ICS (n=3,133)
Post-BD FEV_1, L	1.3 Mean, 0.5 SD	1.2 Mean, 0.4 SD	1.3 Mean, 0.5 SD	1.3 Mean, 0.4 SD
% predicted FEV_1	48.6%, 13.2	44.7%, 24.5	48.6%, 13.2	48.4%, 13.3
COPD exacerbations in prior year,[a] %	35.7, 45.2, 12.3, 6.7	30.6, 41.3, 17.0, 11.0	35.5, 45.3, 12.4, 6.8	35.9, 45.1, 13.0, 11.0
GOLD category,[a] %	0.2, 49.4, 40.4, 9.3	0.3, 35.8, 48.1, 15.0	0.2, 49.5, 40.5, 9.4	0.5, 47.5, 41.9, 9.5



[a]Data were missing in ≤0.1% of patients for prior COPD exacerbations and <1% for GOLD status.
BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Time to all-cause mortality over 52 weeks[a]

No statistically significant difference in the time to death was observed between patients treated with LAMA/LABA versus LAMA/LABA/ICS

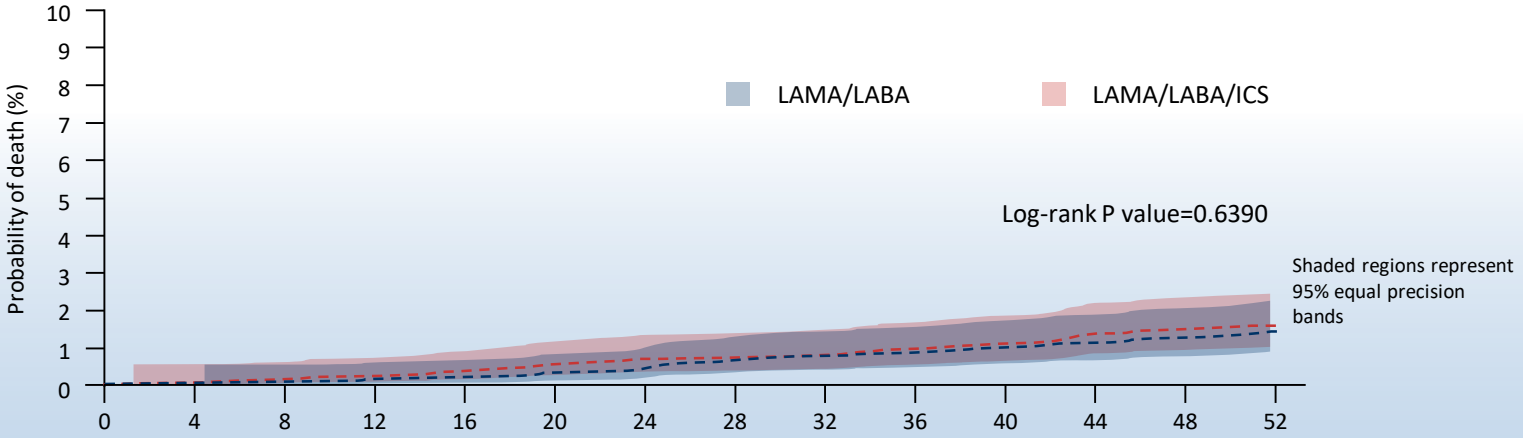


Hazard ratio (95% CI)	P value	Results were obtained by fitting a Cox proportional hazard regression model with the following covariates
1.06 (0.68, 1.64)	0.806	Treatment, study, region, smoking status, FEV_1% predicted (post bronchodilator) and number of prior COPD exacerbations
1.10 (0.71, 1.70)	0.675	Treatment, study, age and sex
1.10 (0.71, 1.70)	0.679	Treatment, study, age, sex and number of prior COPD exacerbations
1.01 (0.65, 1.56)	0.967	Treatment, study, age, sex, region, smoking status, FEV_1% predicted (post bronchodilator), number of prior COPD exacerbations, BMI and diagnosis duration

[a]This was an on-treatment analysis conducted in the propensity score-matched population.
CI, confidence interval.

Estimates of probability of all-cause death over 52 weeks[a]

No significant difference in all-cause mortality between the treatment arms over the duration of the study



Number at risk

LAMA/LABA	3,133	3,109	3,057	3,013	2,979	2,945	2,919	2,882	2,860	2,839	2,817	2,801	2,784	2,104
LAMA/LABA/ICS	3,133	3,116	3,044	2,990	2,956	2,915	2,886	2,857	2,837	2,816	2,793	2,769	2,754	2,342

At 52 weeks, there were 41 (1.3%) deaths in the LAMA/LABA arm and 45 (1.4%) in the LAMA/LABA/ICS arm

[a]This was an on-treatment analysis conducted in the propensity score-matched population.

Conclusions

This pooled analysis of over 6,000 patients showed no differences in survival between LAMA/LABA and LAMA/LABA/ICS in patients with moderate-to-very-severe COPD and a predominantly low risk of exacerbations[a]

An important limitation of our study is that the LAMA/LABA/ICS group received ICS prior to study entry, however this is similar to recent prospective randomized controlled trials, where over 65% of the study populations received prior ICS[1,2]

[a]There was no withdrawal of prior ICS treatment at randomization in either treatment arm.

1. Lipson DA, et al. N Engl J Med 2018; 378:1671–1680; 2. Rabe KF, et al. N Engl J Med 2020; 383:35–48.

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