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A pooled analysis of mortality in patients with COPD receiving triple therapy versus dual bronchodilation

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Rationale

Recent studies report a possible mortality benefit of treatment with long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA)/inhaled corticosteroid (ICS) versus LAMA/LABA combinations in patients with highly symptomatic COPD and a history of exacerbations (≥1 moderate or severe exacerbation in the previous year). We compared the time to all-cause mortality with LAMA/LABA/ICS versus LAMA+LABA in a population of patients with predominantly moderate-to-severe COPD and a predominantly lower exacerbation risk.

Methods

Data were pooled from patients who participated in six phase 3/4 randomized controlled trials (TONADO 1/2, DYNAGITO, WISDOM, UPLIFT and TIOSPIR) and received treatment with either LAMA/LABA/ICS (n=11,891) or LAMA+LABA (n=3,156). There was no withdrawal of prior treatment at randomization in either arm, and the LAMA/LABA/ICS group were receiving ICS prior to study entry. The analysis was on-treatment and all data were censored at 52 weeks. To address any imbalance in characteristics between treatment arms, analyses were performed in a propensity score (PS)-matched cohort with age, sex, geographical region, smoking status, post-bronchodilator forced expiratory volume in 1 second (FEV_1) percent predicted, exacerbation history, body mass index and time since diagnosis as covariates. Patients were PS-matched to those who received LAMA+LABA during the treatment period and had not previously received ICS. Cox proportional

hazard regression models adjusting for covariates (see Figure) were used to assess time to all-cause mortality.

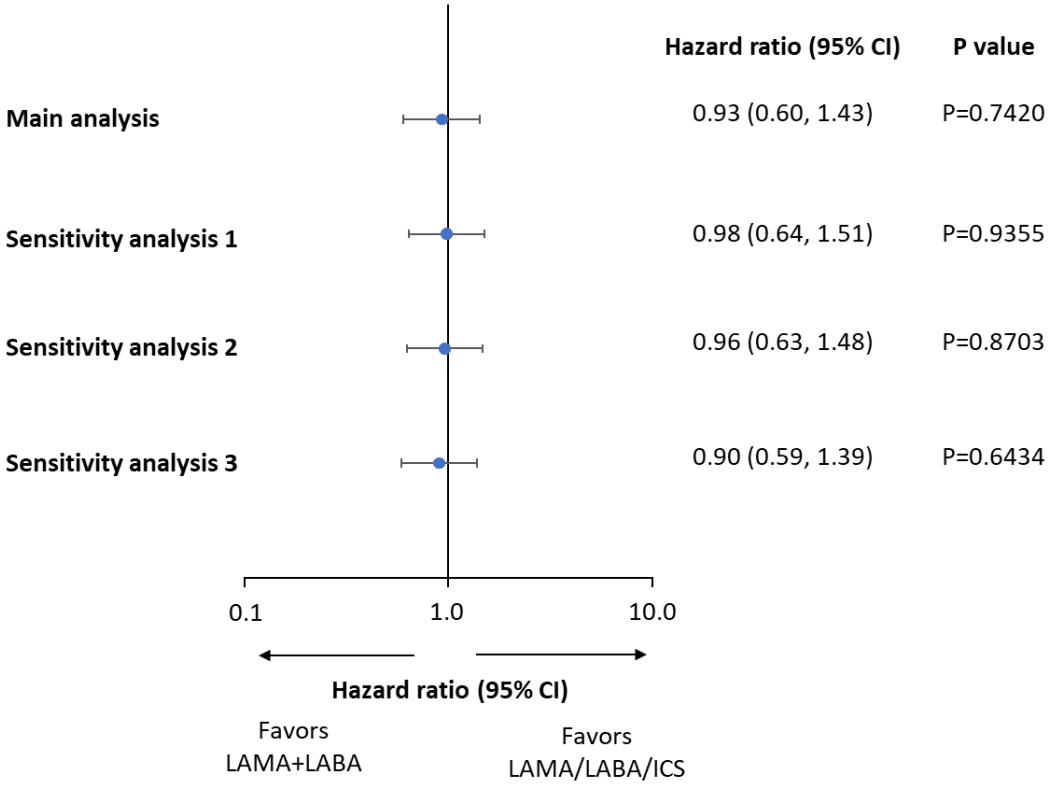
Results

After propensity score matching, there were 3,133 patients in both the LAMA+LABA and LAMA/LABA/ICS treatment groups. Baseline characteristics and comorbidities were well balanced between groups (LAMA+LABA vs. LAMA/LABA/ICS: male: 71.7% vs. 71.3%; age, mean±SD: 65.5±8.8 years vs. 65.8±8.6 years; FEV_1% predicted, mean±SD: 48.6±13.2% vs. 48.4±13.5%). Groups were composed mostly of infrequent exacerbators (patients with ≥2 COPD exacerbation in prior year: 24.7% vs. 25.4%). Overall, there were 41 (1.3%) deaths in the LAMA+LABA group and 48 (1.5%) in the LAMA/LABA/ICS group. No significant difference in the time to death was observed between treatment groups (Figure; hazard ratio 0.93; 95% confidence intervals 0.60, 1.43; P=0.742). Sensitivity analyses using three additional models with different covariates showed similar results (Figure).

Conclusions

This pooled analysis of over 6,000 PS-matched patients showed no differences in mortality between LAMA+LABA and triple therapy in patients with moderate-to-very severe COPD and predominantly low risk of exacerbations.

Figure. Time to all-cause mortality over 52 weeks for patients treated with LAMA+LABA versus LAMA/LABA/ICS



Results were obtained by fitting a Cox proportional hazard regression model with treatment, region, smoking status, FEV_1% predicted (post bronchodilator) and number of COPD exacerbations as covariates (main analysis); with treatment, study, age and sex as covariates (sensitivity analysis 1); with treatment, study, age, sex and number of COPD exacerbations as covariates (sensitivity analysis 2); or with treatment, study, age, sex, region, smoking status, FEV_1% predicted (post bronchodilator), number of COPD exacerbations, BMI and diagnosis duration as covariates (sensitivity analysis 3).

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist.