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**Title:** Association of $\beta_2$-adrenoreceptor genotypes with prevention of COPD exacerbations by tiotropium or salmeterol in the POET-COPD® trial

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**Body:** Background: $\beta_2$-adrenoreceptor (ADRB2) polymorphisms are found at positions B16 (G16R) and B27 (Q27E). The POET-COPD® trial allowed assessing the effects of these polymorphisms on exacerbations in patients treated with tiotropium (Tio) or salmeterol (Sal). Methods: RCT comparing Tio 18 µg qd vs Sal pMDI 50 µg bid over 1 y. 7376 COPD patients aged ≥40 y, with a smoking history ≥10 pack-y, postBD $FEV_1$ ≤70% pred., $FEV_1$/FVC ratio ≤0.7, ≥1 exacerbation in past year. Results: Genotype distribution and baseline characteristics of 5125 patients (69.5%) (Tio 2564; Sal 2561) who consented to genotyping were balanced between groups. Exacerbations in the Tio group were unaffected by B16 or B27 genotypes. While B27 did not affect Sal outcomes, B16 significantly modified the efficacy of Sal: The fraction of patients with ≥1 exacerbation was 32.3% in R16R, 39.8% in G16R, and 42.1% in G16G carriers (log rank P-values vs R16R: 0.0130 and 0.0018, respectively). Among R16R carriers, exacerbation risk was similar between groups, while for G16G and G16R, Tio was more effective than Sal.

| ADRB2 | Tio % | Sal % | HR (95% CI) Tio vs Sal | Treatment by genotype interaction |
|---|---|---|---|---|
| G16G | 37 | 37 | 0.76 (0.66,0.88) | |
| G16R | 46 | 47 | 0.83 (0.73,0.95) | P=0.0381 |
| R16R | 17 | 16 | 1.08 (0.86,1.37) | |
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|---|---|---|---|---|
| Q27Q | 34 | 32 | 0.86 (0.73,1.01) | |
| Q27E | 46 | 48 | 0.85 (0.75,0.97) | P=0.7312 |
| E27E | 20 | 20 | 0.78 (0.64,0.95) | |

Conclusions: In R16R carriers (16.5% of patients), Sal prevented exacerbations as effectively as Tio. In the majority of patients (83.5%), Tio was superior to the $\beta_2$-AR agonist due to the limited benefit from the latter in G16G or G16R patients, while Tio was equally efficacious in all B16 genotypes. Funded by Boehringer Ingelheim/Pfizer.