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**Title:** The bronchitic phenotype is associated with frequent exacerbations in COPD irrespective of chronic bacterial airway infection

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**Body:** BACKGROUND Despite its therapeutic relevance, the relationship between chronic sputum production (SP) and airway bacterial infection in COPD remains poorly defined. We hypothesize that the risk of future events differs between patients with and without chronic bacterial infection within those categorized as bronchitic phenotype in stable COPD METHODS We prospectively evaluated 638 patients with stable COPD for  $\geq 6$  weeks,  $> 10$  PY and GOLD II-IV seeking care in pulmonary tertiary hospitals in 8 European countries and included in the PROMISE cohort. SP and microbiology were assessed at baseline and each semi-annual visit for a median observation time of 24 months RESULTS At baseline, spontaneous sputum samples were obtained in 241 (65.0%) of the 371 patients reporting chronic bronchitis. Potentially pathogenic bacteria were isolated in 54 (30.7%) and ruled out in 122 cases with representative sputum specimens. The annual deterioration of dyspnea scores and lung function, health-related QoL, peripheral oxygenation and exercise capacity were similar in patients with and without

chronic bacterial airway infection. Conversely, patients with SP presented higher annual exacerbation rates, irrespective of the presence or absence of chronic bacterial airway infection. In the multivariable regression analysis, SP with positive (OR 2.39,  $p=0.004$ ) and negative (OR 1.58,  $p=0.032$ ) microbiology, and FEV1% pred (OR 0.99,  $p=0.0093$ ) but not age adjusted Charlson score (OR 0.92,  $p=0.091$ ) remained independently associated with frequent exacerbations ( $\geq 2$ /year) CONCLUSION Spontaneous SP is associated with higher exacerbation rates independently of chronic bacterial airway infection.