Title: Inhaled fluticasone propionate (FP) restores angiogenesis in the airway lamina propria of current smokers with COPD: A randomized controlled trial

Body: Introduction: We have previously reported that in smokers with COPD, compared with non-smoking controls, the bronchial mucosa in larger airways is hyper-vascular in the reticular basement membrane (Rbm) and epithelium, but hypo-vascular in the lamina propria (LP), Rbm vessels stained for vascular endothelial growth factor (VEGF) and transforming growth factor-β1 (TGF-β1) were increased. Rbm hyper-vascularity may be related to epithelial-mesenchymal transition (EMT), a likely pre-cancerous condition. Objective: To examine the effect of inhaled FP on changes in blood vessels in endobronchial biopsies (Ebb) from COPD patients. Methods: This study derived from a double-blinded randomised controlled trial in 34 subjects to compare the effect of inhaled FP (0.5 mg twice daily for 6 months) versus placebo on vascular remodelling in mild to moderate COPD (median age 61 years old, 17 current smokers). Ebb, before and after treatment, were stained with anti-factor VIII antibody, VEGF and TGF-β1. Results: There was a strong trend for increase in the number of LP vessels per mm² with ICS, but not with placebo [median (range) 289 (158-585) before vs. 386 (213-444) after ICS, p = 0.08 and 277 (200-641) before vs. 295 (173-377) after placebo, p = 0.5]. This ICS effect was significant in current smoking COPD [median (range) 219 (158-437) before vs. 356 (213-413) after ICS, p < 0.05]. Vessels in the Rbm did not respond to treatment in either group. Conclusions: Inhaled FP has the potential to restore angiogenic activity in LP to normal in current smokers with COPD, but no anti-angiogenic activity in the Rbm.