Patients enrolled into TRIBUTE had, on average, more severe airflow limitation but fewer previous exacerbations than patients in IMPACT. These differences alone are unlikely to explain the marked disparity in infection risk. A more likely reason for increased pneumonias is that fluticasone furoate is much more lipophilic than beclometasone dipropionate and its active metabolite, beclometasone 17-monopropionate. Increased lipophilicity with fluticasone furoate results in longer retention in lung tissue, which is evident in its prolonged lung absorption kinetics when comparing inhaled and intravenous routes.[4] Prolonged lung retention and immunosuppression could increase susceptibility to infection in the presence of impaired mucociliary clearance and altered lung microbiome in COPD (figure).

In medical school, students are taught *primum non nocere*—first, to do no harm. This axiom applies to single triple inhalers for COPD in which there appear to be important class differences with respect to the benefit–risk of inhaled corticosteroid moieties.

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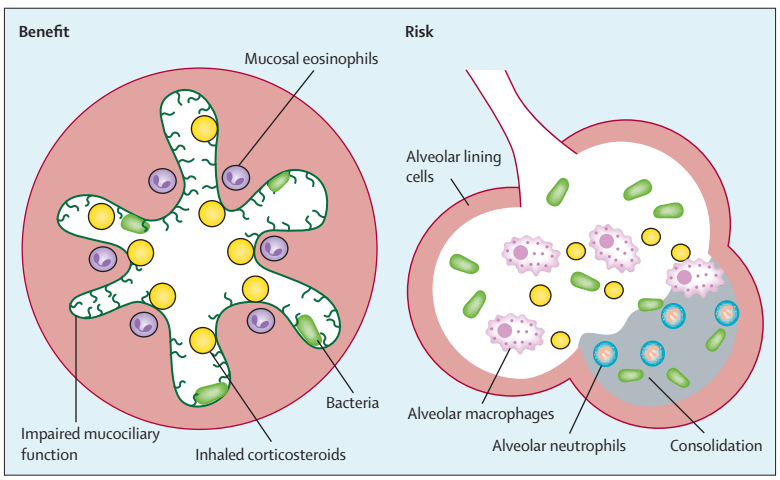

Figure: **The effects of inhaled corticosteroid moiety of single-inhaler triple therapy in chronic obstructive pulmonary disease**
Benefits include attenuation of bronchial mucosal eosinophilic inflammation resulting in reduced exacerbations and risks include altered microbiome along with prolonged alveolar inhaled corticosteroid retention and local immunosuppression resulting in an increased risk of pneumonia.

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Authors' reply

We thank Eric Marchand for his comment and query. On the basis of previous studies,[1,2] Marchand questions whether the withdrawal of inhaled corticosteroids (ICS) in a proportion of patients randomised to a combination of a long-acting β-agonist and a long-acting anticholinergic (LABA/LAMA) in the TRIBUTE study[3] could be responsible for the observed difference in moderate-to-severe exacerbation rates. To address this issue, we have done a stratified analysis according to previous use of ICS/LABA and LABA/LAMA in the 2 months before screening. Although such subgroup analyses have reduced statistical power, we found better efficacy of the triple combination of beclometasone dipropionate, formoterol fumarate, and glycopyrronium (BDP/FF/G) over the dual therapy of indacaterol plus glycopyrronium bromide (IND/GB) in patients previously treated with LABA/LAMA (rate reduction 24%) than in patients previously treated with ICS/LABA (rate reduction 11%). Thus, the difference in exacerbation rate between groups in the TRIBUTE study is unlikely to be attributable to ICS withdrawal at study entry. Indeed, we found that the adjusted rate of exacerbation (patient per year) was higher in patients previously on LABA/LAMA randomised to IND/GB (0·74) than in patients previously on LABA/ICS randomised to IND/GB (0·57).

Mathieu Molimard and colleagues wonder whether the distribution of exacerbations per patient in the two treatment groups of the study could have influenced the statistical output of the study, as reported in previous analyses.[4] Here, we provide

	BDP/FF/G n=764	IND/GB n=768
0	491 (64%)	480 (63%)
1	171 (22%)	170 (22%)
2	69 (9%)	67 (9%)
3	20 (3%)	31 (4%)
4	8 (1%)	15 (2%)
5	1 (<1%)	3 (<1%)
6	1 (<1%)	1 (<1%)
7	3 (<1%)	1 (<1%)

Data are n (%). BDP/FF/G=beclometasone dipropionate, formoterol fumarate, and glycopyrronium. IND/GB=indacaterol and glycopyrronium bromide.

Table: **Number of moderate-to-severe exacerbations in chronic obstructive pulmonary disease during the study (intention-to-treat population)**

the distribution of moderate-to-severe chronic obstructive pulmonary disease (COPD) exacerbations in the two treatment groups in the TRIBUTE trial (table). No outlier patient with an exceptional number of events was observed in the reference group; this finding reinforces the primary endpoint result. Even when patients with more than four events were excluded from the analysis, the favourable outcome for BDP/FF/G versus IND/GB was maintained (adjusted exacerbation rate [patients per year] of 0·479 for BDP/FF/G *vs* 0·571 for IND/GB; adjusted rate ratio of 0·838 [95% CI 0·717–0·980], p=0·027).

We thank Brian Lipworth and colleagues for their comments on the benefit–risk rates of single-inhaler triple therapy for COPD. Indeed, in the TRIBUTE study we found no difference in the incidence of pneumonia (4%) between the two patient groups treated with either extrafine BDP/FF/G or IND/GB. We cannot speculate on the effect on pneumonia if the combination contains fluticasone furoate.

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Free to breathe hard in the Tour de France

In the Vuelta a España in September, 2017, a urine sample from the British cyclist Chris Froome returned an adverse analytical finding, a concentration of salbutamol higher than 1000 ng/mL, the highest concentration by the World Anti-Doping Agency (WADA). The case lasted several months, and just 2 days before the 2018 Tour de France, the case was resolved by the world governing body of cycling, the Union Cycliste Internationale (UCI), which considered Froome to be innocent and free to compete in the race. Controversially, similar previous cases (eg, that of Alessandro Petacchi or Diego Ulissi) led to official sanctions by the UCI. The issue is also contentious because Froome's team has not made available the scientific arguments used in his defence.

Meta-analytical evidence for an enhancing effect of systemic β2 agonists on maximal aerobic performance is weak, but these compounds might benefit sprint or anaerobic performance[1] and have some muscle anabolic effects.[2] According to WADA, exceeding the aforementioned cutoff would theoretically rule out therapeutic drug usage against asthma or bronchospasm through inhalations at the permitted doses (ie, ≤800 μg/12 h or 1600 μg/24h, with one single puff delivering a dose of about 100 μg), and suggests systemic administration, which is banned in sports. However, several confounding variables might result in the detection of abnormally high amounts of salbutamol despite therapeutic drug usage.

The combination of exercise and dehydration (eg, during a cycling stage) affects urine salbutamol concentrations and increases the risk of exceeding the WADA threshold after inhalation of maximal permitted doses, even after correction for urine-specific gravity.[3] The results of one study might also support an athlete's innocence.[4] On the basis of a pharmacokinetic model of salbutamol absorption and clearance, the authors concluded that establishing the administered dose from a single untimed urine sample is impossible.[4] This could lead to incorrect assumptions of violation, with urine samples of 15·4% of 1000 virtual subjects who had inhaled therapeutic salbutamol doses surpassing the threshold.[4]

Despite the controversy surrounding the resolution of Froome's case and the long history of doping in cycling, an optimistic vision of professional cycling is not necessarily naive. Athletes' temptation for banned substances will always exist, but using doping agents with a clear ability to manipulate sports capabilities, notably those enhancing oxygen supply to working muscles, the main limiting factor for endurance performance, is becoming increasingly difficult—cyclists' haematocrit values now resemble those reported in the so-called pre-erythropoietin era.[5] The ability to endure a gruelling training regime distinguishes cycling champions.

We declare no competing interests.

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