



## Reigniting the TORCH: Chronic Obstructive Pulmonary Disease Mortality and Inhaled Corticosteroids Revisited

In 2007, the TORCH (Toward a Revolution in Chronic Obstructive Pulmonary Disease [COPD] Health) investigators, including myself, published the results of the first multinational randomized controlled trial to examine whether receiving an inhaled corticosteroid (ICS) and a long-acting  $\beta$ -agonist (LABA) could reduce the risk of dying compared with then-routine inhaled short-acting bronchodilator treatment (1). TORCH did not meet its prespecified level of statistical significance, with a famously marginal *P* value for treatment difference of 0.052. Subsequent editorials, textbooks, and treatment guidelines affirmed that inhaled drug therapy in general and regimes including ICS specifically did not modify the risk of death in patients with COPD. This situation is surprising, as there are ample data showing that these treatments reduce the risk of COPD exacerbations (2), a known risk factor for death (3), and a more recent systematic review found that inhaled treatment reduced the rate of decline of FEV<sub>1</sub> in COPD (4).

Many things may have contributed to the equivocal findings of TORCH, not the least of which being the statistical approach used in the study. TORCH was a landmark study in COPD with more than 6,000 participants potentially followed for 3 years. Inclusion was based on having a prebronchodilator FEV<sub>1</sub> of <60% predicted with no requirement for a history of previous exacerbations, which may not have identified a population at a sufficiently high risk of dying. TORCH was one of the last large trials to use short-acting bronchodilators as its comparator arm, which probably contributed to the differential patient withdrawal (5). However, given the disappointment and expense of conducting the TORCH study, it is unsurprising that funders have been reluctant to revisit this topic.

The last 2 years have seen things change. The development of single inhaler treatment with LABA + long-acting antimuscarinic (LAMA) drugs, which is now recommended for first line use in COPD (6), led to large trials to determine whether adding an ICS to this regime further reduced the exacerbation risk. These studies recruited patients with a significant exacerbation history who, coincidentally, were at higher risk of dying. Two studies, IMPACT (Informing the Pathway of COPD Treatment) and ETHOS (Efficacy and Safety of Triple Therapy in Obstructive Lung Disease), have shown that triple therapy was more effective than dual bronchodilators in preventing exacerbation and hospitalization and that mortality, which was prospectively defined as a secondary outcome, was lowest in the triple-treatment arms (7, 8). More detailed analysis of the mortality data from IMPACT has already been presented (9), and we now have new data

from Martinez and colleagues (pp. 553–564), the ETHOS trialists, published in this issue of the *Journal* (10).

The ETHOS investigators recruited 8,509 patients with COPD with a history of either two moderate exacerbations or one severe exacerbation in the previous year if their FEV<sub>1</sub> was >50% predicted or at least one of either type of exacerbation if the FEV<sub>1</sub> was below this threshold. Patients were randomized to receive a LAMA-LABA combination (glycopyrrolate/formoterol fumarate [GFF] 18/9.6  $\mu$ g) or an ICS-LABA (budesonide/formoterol fumarate [BFF] 320/9.6  $\mu$ g) or one of two doses of an ICS-LAMA-LABA (budesonide/glycopyrrolate/formoterol fumarate [BGF] 320/18/9.6  $\mu$ g [320 BGF] or 160/18/9  $\mu$ g). All inhalers were given twice daily from a metered-dose inhaler for 1 year. In the paper by Martinez and colleagues, the vital status of 387 patients not included in the original report was obtained, allowing an intention-to-treat analysis on 99.6% of the study population (10). Altogether, 170 deaths occurred in the year after randomization, predominantly from cardiovascular and respiratory causes. There was a 45% reduction in the risk of death among those receiving 320 BGF compared with GFF, the additional cases making little difference to the original estimate. The lower-dose regime of BGF was numerically, but not significantly, different from GFF and was no different from the ICS-LABA combination of BFF. These data complement those of the earlier IMPACT analysis, in which the once-daily combination of the more potent ICS fluticasone furoate and the LABA vilanterol was associated with fewer deaths irrespective of whether it was given with a LAMA (8). ETHOS used a Cox proportional hazard model adjusted for lung function and age, variables that were not used in the secondary Cox analysis in TORCH, which still showed a nominally significant difference, with a 19% reduction in risk (1). The ETHOS data suggest that a dose response of effectiveness may exist for mortality in a way not seen when exacerbations are the endpoint, with the number needed to treat for a mortality gain with 320 BFF being 80 patients per year.

The effect of stopping prior therapy on the risk of subsequently exacerbating have been extensively debated in relation to IMPACT (11, 12), and similar concerns would apply to the ETHOS data. The authors provide a robust defense of the validity of their findings for mortality by first using a novel tipping-point analysis to model how many deaths would be needed among the 30 patients lost to follow-up to make the difference between treatments no longer significant. Even if 8 of the 10 missing patients who received BGF died the day after their last contact, that treatment would still decrease mortality significantly. A further analysis based on excluding deaths in the first 90 days of study, which might have been precipitated by stopping treatment, did not change the primary findings. Unsurprisingly, patients who were receiving more therapy, including ICS, at randomization gained more benefit in the study from triple therapy, in keeping with other observations that patients receiving

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Originally Published in Press as DOI: 10.1164/rccm.202012-4300ED on December 16, 2020

ICS treatment are sicker (13). Similarly, those with a history of more exacerbations showed a larger reduction in mortality with 320 BGF. It is becoming clearer that the effect of either starting or stopping ICS on exacerbation risk is influenced by the blood eosinophil count (14, 15). In ETHOS, this appears to be true for mortality as well, with patients with a higher eosinophil count being at greater risk of dying when receiving GFF compared with 320 BGF. Further analysis of this potentially important observation is needed.

Several important lessons come from these positive studies of ICS and COPD mortality. First, large studies allow for more complex analyses than small ones, but to properly test their primary hypothesis, trialists need to focus on patient groups at the greatest risk of experiencing the events under study. Treatment that reduces mortality will only be seen to work in patients who are at risk of dying. Second, neither the drug, the delivery system, nor the dosage regime is crucial to preventing death with ICS–LAMA–LABA treatment, but the dose of the corticosteroid chosen may be. Finally, mortality is not different from other endpoints in COPD studies, and a therapy that decreases exacerbations is likely to reduce mortality if sufficient numbers of the right kind of patient are studied. So, belatedly, the flame lit by TORCH is burning brightly again and does offer hope to all those who have COPD after all. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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\*P.C. is Associate Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

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## Learning from the First Wave of the Pandemic in England, Wales, and Northern Ireland

The year 2020 has been one like no other for intensive care medicine owing to the coronavirus disease (COVID-19) pandemic. Many

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Originally Published in Press as DOI: 10.1164/rccm.202101-0089ED on January 21, 2021

countries experienced unprecedented demand on critical care resources during the first half of the year, with some respite over the summer, only to see demand rise again toward the end of the year (1).

In this issue of the *Journal*, Doidge and colleagues (pp. 565–574) describe how the characteristics and outcomes of patients with COVID-19 admitted to ICUs in England, Wales, and Northern Ireland changed over the first wave of the pandemic (2). This large study from the well-established United Kingdom registry group