

Fernando J. Martinez, M.D.*
New York-Presbyterian Hospital/Weill Cornell Medical Center
New York, New York

On behalf of all the authors

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Angels Dancing on the Tip of a Needle: Interpreting Clinical Trials in Chronic Obstructive Pulmonary Disease

St. Thomas Aquinas was a distinguished medieval scholar who successfully reconciled Christian theology with Aristotelian philosophy. Sadly, he is best known today for the taunts of his critics who likened him to someone counting the number of angels who could stand on a needle tip, a metaphor for debating topics of no consequence when more urgent matters need attention. In this issue of the *Journal*, Han and colleagues (pp. 1237–1243) conduct a further analysis of the data from the very large 1-year IMPACT (Informing the Pathway of COPD Treatment) trial comparing the effectiveness of different inhaled combination treatments (long-acting antimuscarinic [LAMA] + long-acting β_2 -agonist [LABA] bronchodilators, LABA + inhaled corticosteroids [ICS], and LABA + LAMA + ICS) given in single inhalers once daily (1). The primary outcome measure in IMPACT was the rate of exacerbation, and triple therapy was more effective in exacerbation prevention than the bronchodilators alone.

Large clinical trials are required because the expected difference between treatments is small and/or the events of interest are clinically important but infrequent. Given the time (and expense) of conducting these investigations, secondary analyses, ideally prespecified before treatment unblinding, are conducted either to generate new hypotheses or, as in the case of the paper by Han and colleagues, to test the robustness of the primary result (1). In an accompanying editorial, Prof. Suissa, a long-standing critic of many studies of ICS in chronic obstructive pulmonary disease (COPD), outlines his concerns about the completeness of the data reporting and analysis, and the distinguished study authors rebut his assertions in a second editorial comment. Are they simply counting angels?

The new analysis highlights some important features of the IMPACT population. Among the 71% using ICS before study randomization, lung function and health status were rather worse than ICS-naïve subjects, but the reported exacerbation history was similar in each group. The observed exacerbation rate after randomization was significantly higher in those taking ICS beforehand, irrespective of the

treatment to which they were randomized. This is in keeping with other analyses showing that patients taking ICS are more likely to report exacerbations than those not doing so, irrespective of their prior exacerbation history (2). It seems that clinicians do identify some patients who benefit from ICS treatment! Indeed, those taking the least intense baseline treatment (LAMA alone) showed no benefit from triple treatment, although whether this reflects their disease severity or the smaller sample size of this group is unclear. The cumulative event plots resolve the previous confusion around the misinterpreted time to first event plots (3) about whether the benefit of triple therapy is maintained, and this point is further emphasized by the analysis of data from 30 days after randomization where a positive treatment signal is still seen in the triple therapy group.

Suissa views the present study as an ICS withdrawal study, although only 14% of patients had ICS stopped for the study. The IMPACT patients were sicker than those in either the INSTEAD (4) or even the WISDOM (Withdrawal of Inhaled Steroids during Optimal Bronchodilator Management) (5) studies to which he refers, with over 50% of IMPACT patients having two or more moderate or severe events and approximately a quarter reporting hospitalization in the year before randomization. This emphasizes the importance of understanding which patients have been studied and explains apparently contradictory results between different trials. Even the extreme view that the difference in treatments is driven by exacerbations occurring when ICS treatment is stopped implies that ICS were doing something useful beforehand. Identifying appropriate therapy is key to personalized treatment selection, but the suggestion that prior asthma explains the positive signal seems optimistic, especially as we have no knowledge of what led to an initial diagnosis of asthma before it was amended to COPD. Blood eosinophil count and exacerbation history both predict relapse when ICS are stopped (6), and the IMPACT group have already shown how important eosinophil counts can be in a population at high risk for exacerbation based on their history at study entry (7).

Karl Popper believed that science proceeds by a process of refutability. Any hypothesis can only be considered correct until evidence emerges that it cannot adequately explain. By that standard, the hypothesis that taking ICS in addition to optimized inhaled bronchodilators in patients meeting the entry criteria for the IMPACT study seems to be intact. Robust

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and thoughtful challenges like those of Suissa are needed to ensure that those advocating a treatment have not made significant errors. On balance, that does not seem to have happened in these new analyses. Clinicians can be confident that in appropriately selected patients with COPD with a history of exacerbations despite taking long-acting inhaled bronchodilators, and especially in those with blood eosinophilia, regular ICS treatment can reduce the risk of further moderate and severe events. They should note that many doctors had worked this out before their patients entered the IMPACT study and that the results have been very carefully scrutinized. Surely St. Thomas would have approved. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Peter Calverley, M.B. Ch.B.*
University of Liverpool
Liverpool, United Kingdom

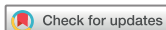
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Novel Phenotypes in Respiratory Failure: Same As It Ever Was

A central challenge in clinical studies of acute respiratory distress syndrome (ARDS) is its inherent heterogeneity (1). As documented in the landmark LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) (2) trial, patients with ARDS present with a spectrum of abnormalities in gas exchange and respiratory mechanics, a spectrum of clinical severity, and a spectrum of outcomes. Indeed, for this reason the Berlin (3) definition of ARDS has been criticized as being overly broad. A major focus of ARDS clinical research has therefore been identification of subphenotypes or endotypes within ARDS that can be used to design trials and tailor treatment. To date, however, no subphenotype has been demonstrated to predict treatment response or improve outcomes in a prospective trial. Crucially, despite its limitations, the Berlin definition does identify populations of patients that benefit from particular treatments. Volume- and pressure-limited ventilation, when applied to the broad population who meet the Berlin definition, reduces mortality (4). This is likely true even in the setting of relatively normal respiratory system mechanics. For example, a reanalysis of ARMA (Ventilation with Lower Tidal Volumes as Compared with

Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome) trial data by Hager and colleagues (5) showed that reduced V_T is associated with reduced mortality even when plateau pressures (P_{plats}) are not high. In the two decades since the publication of that landmark trial, initial suspicion (6) of low V_T ventilation has therefore given way to widespread consensus that most patients with ARDS by the Berlin definition benefit from a lung-protective approach.

However, we are reminded in the book of Ecclesiastes (Eccles 1:9) that what has been will be again. The global pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has brought renewed attention to the phenomenon of respiratory failure with relatively preserved mechanics and has led some to suggest that coronavirus disease (COVID-19) respiratory failure, despite nearly always meeting the Berlin definition (7, 8), is characterized by novel subtypes of ARDS. Furthermore, it has been asserted that for some patients with COVID-19 ARDS, deviation from standard lung-protective settings (in particular, by the use of larger V_T s) is potentially beneficial (9). Advocates point to observations of preserved respiratory system compliance (C_{rs}) in the setting of severely impaired gas exchange in COVID-19 as suggestive of a novel pathophysiology, perhaps related to endothelial dysfunction and impaired hypoxic vasoconstriction (10). In this issue of the *Journal*, however, Panwar and colleagues (pp. 1244–1252) point out that such phenotypes were easily identifiable the pre-COVID-19 era (11).

The authors undertake reanalysis of data from LUNG SAFE. They define several categories of C_{rs} impairment and attempt to

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