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Understanding the People Excluded from Chronic Obstructive Pulmonary Disease Clinical Trials

The return on investment, an important consideration in financial decisions, can also be applied to considerations in clinical trial design. Confidence in detecting treatment effects and creating generalizable results is higher when the outcomes to be modified occur frequently and are largely independent of the baseline characteristics of the subjects recruited (1, 2). However, trials in chronic noncommunicable diseases like chronic obstructive pulmonary disease (COPD) are more challenging as important outcomes like exacerbations and mortality are less frequent, do not affect all participants, and vary with the underlying disease severity (3, 4). Given the expense and complexity of a modern randomized clinical trial, sponsors have, understandably, focused on patients in which these outcomes are most likely to be present. In turn, this has led to the reasonable criticism that the results reported are not applicable to most patients seen with COPD in office practice who are likely to be much less impacted by their COPD (5, 6).

In this issue of the *Journal,* Çolak and colleagues (pp. 271–280) hypothesize that patients with COPD excluded from randomized clinical trials (RCTs) experience high rates of exacerbation and mortality compared with symptomatic smokers (7). To test their hypothesis, the authors identified a cohort of participants with a smoking history and respiratory symptoms within the Copenhagen General Population Study. COPD was defined within this cohort on the basis of $FEV_1/FVC < 70\%$ on prebronchodilator spirometry. The COPD group was furthermore divided into those who would be eligible for clinical trials and those who would be ineligible. Care was taken to identify the most commonly used criteria identified for RCT eligibility: $FEV_1 < 80\%$ predicted, smoking history ≥ 10 years, and no history of self-report or medical encounters for asthma. On the basis of these criteria, three groups were compared: *1)* individuals with a smoking history without COPD; *2)* patients with COPD not eligible for clinical trials; and *3)* patients with COPD eligible for clinical trials. The primary outcomes of interest were severe exacerbation, defined by emergency department or hospital visit with a primary diagnosis of COPD, and mortality. Cox proportional hazards regression was used to model time to severe exacerbation and all-cause mortality among the three groups.

Among the 7,516 participants in the Copenhagen General Population study with COPD, 4,228 (56%) participants would have been ineligible for RCTs on the basis of having comorbid asthma, a smoking history of less than 10 years, or $FEV_1 \geq 80\%$ predicted. Ineligible patients were generally similar in age to those suitable for

inclusion, but in general, they formed an intermediate group between individuals with smoking history and no airflow obstruction and potential trial participants. Of note, 35% of the ineligible COPD participants had a history of comborbid asthma. The COPD ineligible for clinical trial group was more symptomatic (mMRC ≥ 2, chronic mucus hypersecretion, wheezing and cough), had a higher risk of exacerbation (HR 7.45 [5.41–10.3]) and a greater risk of dying (HR 1.21 [1.11–1.31]) than those in the group consisting of symptomatic individuals without airflow obstruction. As expected, the highest risk of exacerbation and mortality was in the COPD eligible for clinical trial group (HR 29.0 [21.1–39.8] and HR 1.67[1.54–1.81]).

The analyses of the subgroups of ineligible individuals provide some intriguing data. As illustrated in Figure 5 of Colak and colleagues (7), the risk of having a hospitalized exacerbation rose in people with a history of comorbid asthma but without an effect on mortality. This is in keeping with previous observations about asthma–COPD overlap (ACO) (8, 9). By contrast, Figure 6 of Colak and colleagues (7) shows that having an FEV_1 below 80% predicted predicts both exacerbation and mortality risk, irrespective of the presence of comorbid asthma. These data help inform the debate about the utility of ACO as a diagnostic category (10). Multiple different definitions of ACO have been proposed (10, 11), but as defined by Colak and colleagues, self-reported and/or hospital-confirmed asthma in people with a history of cigarette smoking was associated with worse outcomes when the FEV_1 was below 80% predicted. Although the inclusion of individuals hospitalized with an asthma exacerbation may have biased the outcomes observed, a similar pattern was seen when the individuals defined by self-reported asthma were examined. The Copenhagen data suggest that using this definition, sufficient patients are available to better define the optimal treatment of ACO.

Strengths of this study include its size with 20,000 symptomatic individuals with smoking history followed for a median of 8 years without a loss to follow-up and the representative nature on the basis of this whole population dataset. Inevitably there are some limitations. As the authors acknowledge, they have only prebronchodilator spirometry available, which might lead to a reclassification of some patients with asthma from the eligible to the ineligible group. However, this appears unlikely to change any of the conclusions drawn here. Similarly, the ethnic mix of a north European country is not necessarily relevant to a US population in which some racial and ethnic groups are consistently underrepresented in clinical trials (12). Further studies to establish the outcomes in these patient populations are needed.

Randomized controlled trials primarily study whether an intervention works, and the Danish data show that the customary entry criteria for RCTs are effective in selecting individuals more likely to experience important outcomes within an acceptable time period. However, a majority of the people with COPD identified among individuals with a smoking history would not be allowed to enter such clinical trials. Nonetheless, these people go on to

experience more severe exacerbations and are more likely to die than individuals with smoking history and without airflow obstruction. This emphasizes that COPD severity within a population is a continuous variable and that, over time, this illness is not trivial among those not considered clinically severe enough to be included in a treatment trial. The challenge for the future will be to conduct appropriate treatment trials in this less severe population that is also commonly encountered in our clinical practice (13). ∎

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⊖ Turning the Page on Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome due to Severe COVID-19

The role of venovenous extracorporeal membrane oxygenation (ECMO) in the management of severe acute respiratory distress syndrome (ARDS) has been assessed by randomized controlled trials, meta-analyses, and a *post hoc* Bayesian analysis (1–6). This body of literature supports the beneficial effect of this intervention for severe ARDS refractory to protective mechanical ventilation. Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can develop ARDS being ECMO a therapeutic option for severely affected patients. Given that the mentioned evidence precedes the ongoing pandemic, the effectiveness of ECMO in COVID-19–related ARDS represents an important priority to be addressed.

Early reports during the pandemic suggested an alarmingly high mortality with ECMO in patients with COVID-19 (7). These studies were limited by the inclusion of unselected populations and the lack of adequate controls. Shaefi and colleagues conducted an emulated target trial using observational data to assess the efficacy of ECMO versus conventional mechanical ventilation in the context of COVID-19 (Table 1) (8). They included patients with severe hypoxemia and observed a reduction in mortality with ECMO (hazard ratio, 0.55; 95% confidence interval, 0.41–0.74). More recently, Urner and colleagues performed an emulated target trial including patients with severe hypoxemia, also observing a reduction of 60-day mortality associated with ECMO (relative risk, 0.78; 95% confidence interval, 0.75–0.82) (Table 1) (9).