Chronic Obstructive Pulmonary Disease Is Just One Component of the Complex Multimorbidities in Patients with COPD

In the last decade, there have been an increasing number of studies on chronic diseases concomitant with individual chronic disease (e.g., chronic obstructive pulmonary disease [COPD], heart failure, obesity, and osteoporosis) (1, 2), suggesting that the term “comorbidity” should probably be changed to “multimorbidity.” Indeed, there is very little evidence that one chronic disease dominates and is the cause of the other concomitant chronic disorders; rather, it is more likely that various chronic diseases develop simultaneously in response to common risk factors (e.g., smoking, alcohol, aging, pollution, inactivity, and diet). The number of studies on multimorbidities has increased exponentially in the last few years (3), indicating the importance of the topic and highlighting the tremendous impact that multimorbidities have on health and social systems and on medical education (1–3).

The interest in understanding the association of COPD with various chronic diseases has been prompted by the common dominant risk factor, that is, smoking, which is the major risk for both respiratory and cardiovascular chronic diseases as well as cancer. Most clinical studies have reported the association between COPD and single comorbidities (e.g., chronic heart failure or coronary artery disease) after actively searching them with specific clinical investigations or biomarkers (4, 5). In contrast, most epidemiologic studies have investigated the comorbidities of COPD by looking at clinical records, health care utilization, or large databases of insurance companies or public health services (6, 7).

This issue of the Journal contains two important articles that address the concept of multimorbidity (8, 9).

The most interesting aspect of the study on comorbidities of COPD by Vanfleteren and colleagues, published in this issue of the Journal (pp. 728–735), is the active search for multiple chronic conditions in patients with COPD using a standardized, guideline-directed approach (8). This approach enabled the investigators to prospectively and carefully assess the prevalence and severity of chronic concomitant disorders in a clinical population of patients with moderate to very severe COPD. Indeed, the prevalence of concomitant disorders reported in this study is among the highest reported (97.7%, i.e., almost all patients with COPD had at least one concomitant chronic disorder), and, more important, a large proportion of these concomitant disorders were not known to the patients and thus undiagnosed. Albeit starting from a search of comorbidities of one disease, that is, COPD, this pivotal study provides one of the best representations of the concept of multimorbidity. Indeed, in Figure 3 of the article, each of the 13 chronic disorders searched is plotted against the other 12, clearly showing the interdependence and simultaneous occurrence of these conditions. These results are very similar to those recently reported in the Lancet on multimorbidities, in particular as regards the significant increase of other concomitant disorders in the four most common chronic disease (coronary heart disease, diabetes, COPD, and cancer), with a similar trend in both most affluent and most deprived countries (2).

The strong clinical message of this elegant study is that each patient presenting with COPD should be carefully and actively investigated for concomitant chronic disorders, particularly the most frequent and undiagnosed disorders, that is, hyperglycemia, atherosclerosis, hypertension, dyslipidemia, and osteoporosis. In
fact, although the symptoms and exacerbations of COPD can be treated pharmacologically with inhaled bronchodilators and steroids and phosphodiesterase type 4 inhibitors, these treatments do not change the natural course of the disease (10). In contrast, the consequences of most of the concomitant metabolic and cardiovascular chronic diseases may be prevented and reversed by pharmacologic treatments (11–13). Interestingly, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, antiplatelet drugs, and statins seem to modify the natural course of COPD in patients who are treated with them because of concomitant cardiovascular or metabolic disorders (14). Unfortunately, the published data on the safety and efficacy of these drugs in patients with COPD are retrospective or mainly cover elderly patients with mild to moderate COPD whose cardiovascular or metabolic disorders dominate.

Another very interesting aspect of the article is the careful collection of clinical and functional features and imaging that provided the necessary database for a rigorous cluster analysis. This analysis identified five markedly different clinical comorbidity phenotypes—cardiovascular, metabolic, psychological, less comorbidity, and cachectic—that are indistinguishable from the degree of airway obstruction (FEV1) or from any clinical, functional, or multidimensional severity score. Considering that the prevalence and severity of concomitant disorders were independent not only of FEV1 but also of exercise tolerance, smoking history, long-term oxygen therapy (LTOT), quality of life, and the composite assessment of disease severity (BODE score), the discovery of these phenotypes suggests that clinical parameters (comorbid disorders) rather than functional ones (e.g., lung function, exercise testing, and symptom scores) should be used as criteria for (1) identifying phenotypes, (2) assessing severity and prognosis of the disease, and (3) measuring response to treatment. In this respect, it is likely that the cardiovascular, metabolic, and psychological phenotypes would be more sensitive to pharmacologic and lifestyle intervention than the less-comorbidity and cachectic phenotypes (14, 15). Further studies are required to determine whether these five phenotypes have different prognoses and/or responses to treatment, and to determine how to integrate the concept of different phenotypes identified by different concomitant diseases into COPD guideline development (15).

The findings of clinical and epidemiologic studies on comorbidities of COPD clearly show that metabolic and cardiovascular comorbidities carry a particularly high weight in these patients. Therefore, both specific respiratory COPD treatments and metabolic and cardiovascular treatments must be considered for the long-term management of patients with COPD. This is a complex approach that becomes a rule for patients with the most severe stages of COPD (requiring long-term oxygen therapy), who almost invariably have several severe comorbidities (16). The same investigators who recently reported the comorbidities and causes of death in a large population of patients with severe COPD requiring long-term oxygen therapy (16) report in this issue of the Journal (pp. 715–720) the effects of both respiratory and nonrespiratory drugs on mortality in the same population (9). In their longitudinal observational trial, the authors found that only antiplatelet drugs (mainly aspirin) significantly improve survival, whereas none of the other respiratory drugs (bronchodilators and inhaled corticosteroids or their combination) or nonrespiratory drugs (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics) had significant effects. Surprisingly, β-blockers were associated with a worse prognosis. The authors also confirmed previous observations that systemic steroids are associated with a worse prognosis (17), even though they were unable to dissociate this effect from the confounding feature of disease severity.

The significant 14% risk reduction of mortality by antiplatelet drugs is the most intriguing result of this study. COPD is known to be associated with increased platelet activation (18, 19) (Figure 1), and thromboembolism is a major cause of death of patients admitted to the hospital for severe exacerbations of COPD (20). A recent study cohort in an elderly population with COPD highlighted that, independent of the effects of smoking, atherosclerotic plaques are very common: 60% of never-smokers and 80% of ex-smokers and current smokers with COPD. Atherosclerotic plaques are more vulnerable to rupture due to their lipid core, thus generating major cardiovascular events (21). Therefore, antiplatelet drugs may improve survival through their antithrombotic effect (22). Platelet activation in patients with COPD is associated with hypoxia and hemodynamic stress, through changes in their structure, which lead to increased activation of cyclooxygenase-1 with thromboxane formation (23) and increased aggregation in hypoxic patients with COPD. Together, these factors may enhance platelet activation during an acute exacerbation and may explain the association between lower respiratory tract infection and acute myocardial infarction (24). It seems possible, therefore, that the prolonged use of antiplatelet agents may reduce atherothrombosis and the related risk in the COPD population, with the potential role of new drugs as thromboprophylaxis agents during relapse of the illness (25). Long-term oxygen therapy, the only treatment that improves survival in hypoxic patients with COPD (26), may also prevent hypoxia-induced platelet activation and blood clotting, and part of its clinical benefit may come from a reduction of atherothrombotic fatal events (5, 27, 28).

The other important and surprising finding of this study is that long-term use of β-blockers increases the risk of mortality by 19%. Despite the fact that β-blockade in the COPD population seems not to exacerbate symptoms or the level of airway obstruction (29), and that most studies showed clear beneficial effects in patients with COPD treated with β-blockers because of concomitant chronic cardiovascular diseases (15, 29) the long-term effect

![Figure 1](Image 303x545 to 548x737)
of β-blockade on pulmonary function and quality of life is still unclear, particularly in the patients with the most severe COPD. Indeed, no previous study has carefully looked at the effects of β-blockers in patients with severe or very severe COPD requiring LTOT (15, 29–31). In the Swedish study (9), mortality risk with β-blocking agents was reduced in those patients who were also using long-term β-agonist plus inhaled corticosteroids. This could indicate that long-acting bronchodilation may counteract some of the adverse respiratory effects of β-blockers. However, it cannot be ruled out that β-blockade specifically damages those patients with COPD with lower respiratory reserve (29–31). Indeed, the literature so far suggests that patients with severe or very severe COPD die more frequently from respiratory causes than do patients with more preserved ventilatory function (20, 32).

In conclusion, these two studies, taken together, suggest that patients with multimorbidity represent the norm rather than the exception, and that COPD is just one component, and not necessarily the most important, of multimorbidity, particularly in patients with severe COPD who require LTOT. Management of patients with several chronic diseases is now the most important task facing the medical community and presents a fundamental challenge to the single-disease focus that pervades medicine (33). Pulmonologist, internists and community and presents a fundamental challenge to the single- clinician who has responsibility for coordinating their complex care.

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

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Predicting the Development of Acute Respiratory Distress Syndrome
Searching for the “Troponin of ARDS”

Acute respiratory distress syndrome (ARDS) is the syndrome that defines critical care, much as coronary artery disease defines cardiology. Just as in coronary artery disease (1), a multifaceted approach, incorporating preventive strategies, early disease detection, and treatment may offer the best hope of reducing the burden of ARDS. We have had encouraging success in the area of prevention of ARDS in “at-risk” patients. Li and colleagues from the Mayo Clinic recently demonstrated that implementation of current approaches to preventing the development of ARDS, including optimal mechanical ventilation, aggressive resuscitation, reduction of transfusion, and prevention of common complications, reduced the incidence of ARDS in Olmsted County from 81 to 38.3 cases per 100,000 person-years (2). This decrease was driven by a decrease in hospital-acquired ARDS, suggesting that the preventive measures were effective.

Continuing the analogy to cardiology, early identification and treatment of patients with or at risk for coronary ischemia has been greatly facilitated by the availability of a number of biomarkers, particularly troponin. Many potential biomarkers of ARDS, including surfactant proteins, cytokines, and markers of pulmonary epithelial and endothelial injury, have been investigated, with some success. For example, combining a panel of biomarkers (IL-8, soluble tumor necrosis factor receptor-1, and surfactant protein-D) with APACHE II scores enhanced mortality prediction in patients with acute lung injury (ALI) (3). However, the identification of a clinically useful “troponin of ARDS” has proven elusive. The fact that acute myocardial infarction is a “disease” with a well-defined etiology and pathophysiology has greatly facilitated the identification of powerful diagnostic markers such as troponin. In addition, effective therapies exist for coronary artery disease, and their efficacy can be maximized by early diagnosis. ARDS, by contrast, is a syndrome—not a disease—and is diagnosed based on fulfillment of a set of “criteria” that themselves have a high sensitivity but low specificity for the pathologic condition of ARDS. In addition, ARDS has a complex multifactorial etiology, and an incompletely understood pathophysiology. Worse yet, there are no effective interventions for ARDS that if applied would harness the benefits of early ARDS detection. These issues all pose substantial challenges to the identification of a useful biomarker for ARDS.

In this issue of the Journal, Agrawal and colleagues (pp. 736–742) provide evidence for the utility of biomarkers, both alone and in combination with clinical prediction indices, in determining which critically ill patients will develop ARDS (4). They studied 230 patients presenting to the emergency department who required intensive care unit admission but did not have ALI. Furthermore, patients who developed ALI within the first 6 hours were excluded from analysis, to reduce the likelihood of enrolling patients with established early disease. The plasma biomarkers angiopoietin-2 (Ang-2), von Willebrand factor, IL-8, and/or soluble receptor for advanced glycation end products (sRAGE) were chosen a priori based on their potential roles in the pathogenesis of ALI. Elevated Ang-2—but not von Willebrand factor, sRAGE, or IL-8—predicted the development of ARDS. Ang-2 performed comparably to the Lung Injury Prediction (LIP) score, a validated clinical prediction score (5). Interestingly, the addition of plasma Ang-2 measurements to the LIP score improved the prediction of ALI development. Although the LIP score has a high negative predictive value, its positive predictive value of 18% is low (5). This means that less than one in five patients with a high LIP score will develop ALI, restricting its utility as a tool for targeted early intervention. Combining raised Ang-2 with the LIP score improved the positive predictive value to 40%, suggesting that this combination may be a better prediction tool for targeting early intervention and therapy. Plasma Ang-2 demonstrates growing promise as a biomarker for ARDS (6) and sepsis (7). Ang-2 concentrations correlated with increases in pulmonary endothelial permeability and both presence and severity of ALI/ARDS in the critically ill patients with and without sepsis (8). Ang-2 concentrations mirrored disease severity and predicted the development of shock and death in emergency department patients with suspected infection (7). Biomarkers are perhaps most useful when they tell us something about the pathophysiology of the disease. A biomarker that both closely reflects disease presence and/or severity and mediates the responsible biologic processes links molecular mechanisms to diagnosis. Such a biomarker would both aid in the prediction and/or diagnosis of ARDS and focus therapeutic strategies on the key pathogenic mechanisms contributing to ARDS. Intriguingly, Ang-2 appears

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