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Editorial

Fibrinogen and COPD: Now what?

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Abbreviations: COPD Biomarker Qualification Consortium, **CBQC**; hazard ratio, **HR**; confidence interval, **CI**; cardiovascular disease, **CVD**

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Introduction

It is often said that chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous disease.[1] Not that often, however, are the meanings of *complex* and *heterogeneous* defined. *Complex* means that COPD has different intra and extra-pulmonary components, both at the molecular, structural, functional and clinical levels, whereas *heterogeneous* means that not all these components are present in all patients or, in a given patient, that these components may change over time.[2] Given that these different domains of the disease can influence its clinical course and may require specific treatment, it follows that it is important to identify and validate *biomarkers* that inform on their presence or absence, as well as on their potential response to treatment.[3,4] In this issue of *Chronic Obstructive Pulmonary Diseases: Journal of COPD Foundation*, Mannino et al[5] present evidence to qualify fibrinogen as a biomarker for risk stratification of COPD patients. This is an important report not only because of its scientific content but also because of the way it has been developed, since it has been produced by the COPD Biomarker Qualification Consortium (CBQC),[6] a successful example of public-private partnership to be exported to other areas of medical research.[7]

Fibrinogen is an acute phase soluble plasma glycoprotein and the principal protein of vertebrate blood clotting.[8] Normal fibrinogen levels in blood are between 150 and 350 mg/dL.[8] Mannino et al used a cohort of 6376 COPD patients from publically and industry funded studies in the CBQC to explore the value of fibrinogen values higher than 350 mg/dL to predict the risk of hospitalizations from exacerbations and death.[5] They found that almost half of the patients had increased fibrinogen values (≥ 350 mg/dL) and that this was associated with an increased risk of future hospitalization because of COPD exacerbations (hazard ratio (HR): 1.64; 95% confidence interval (CI): 1.39–1.93) and all-cause mortality (HR: 1.94; 95% CI: 1.62–2.31).[5] Authors conclude that these results support the use of high fibrinogen values to identify high risk COPD patients both in clinical practice and as a way to enrich for this phenotype in future clinical trials in COPD.[5]

These results are in line with other previous studies showing that a proportion of, but not all, COPD patients have evidence of persistent systemic inflammation (including fibrinogen) and that this is associated with

poor outcomes.[9] As with any good research study, though, this particular one[5] also raises more questions than offers answers. First, the origin of systemic inflammation in some patients with COPD continues to be obscure.[10] Second, fibrinogen is a well established biomarker of cardiovascular disease (CVD),[11] and CVDs are one of the main (if not the main) cause of death in COPD and a frequent comorbidity in these patients.[12, 13] Although authors report on all-cause mortality,[5] it is not surprising therefore, that high fibrinogen levels predict death in COPD. It is less straightforward, though, that high fibrinogen levels predict the risk of hospitalization because of an exacerbation of COPD. Although fibrinogen levels can increase during exacerbations of COPD,[8] it is unclear why high levels when clinically stable should predict the risk of severe exacerbation, unless we consider that these episodes might involve a cardiovascular component.[14] Alternatively, it is also plausible that systemic fibrinogen levels might mirror an enhanced pulmonary production of this protein[15] since CR3, a complement receptor that recognizes bacterial antigens and is present on neutrophils, NK cells, and macrophages, binds fibrinogen,[16] and thus provides a potential link of fibrinogen levels with pulmonary inflammation. Third, what can we do to treat these patients and reduce their future risk of hospitalization and death is also unclear. Yet, several alternatives may be considered. On the one hand, optimal treatment of COPD is unavoidable.[1] On the other, proper treatment of CVD risk factors are also a must. In this context, although statins do not reduce exacerbations of COPD in patients without a CV indication for them,[17] their beneficial effect in the rest of COPD patients (actually the majority) is well established.[18,19] The effect of other potential therapeutic alternatives for COPD patients with systemic inflammation, including anti-inflammatory treatment, regular physical activity, dietary changes and/or anti-oxidants agents, among others, deserve further research. Finally, the results of this study[5] support the proposal of a *control panel* for the management of COPD,[20] where the identification, treatment and monitoring of several COPD *treatable traits*, including validated biomarkers such as fibrinogen, may allow us to better understand the complexity and heterogeneity of COPD and, as a result, progress towards personalized medicine in these patients.[2, 21]

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