Risk and Prevention of Cardiovascular Events after Exacerbations of Respiratory Symptoms in Patients with COPD

Chronic obstructive pulmonary disease (COPD) is often associated with cardiovascular diseases, particularly ischemic heart disease, heart failure (HF), and atrial fibrillation (AF) (1–3). Both concomitant cardiovascular diseases and exacerbations of COPD (ECOPDs) increase the rates of future moderate ECOPDs (M-ECOPD) and/or hospitalized ECOPDs (H-ECOPD), cardiovascular events, and death (4, 5), particularly immediately after severe H-ECOPDs (6) (Figure 1). The high mortality and morbidity in this group of patients, especially those hospitalized in pulmonology, internal and/or emergency medicine, or geriatric departments, have unfortunately never been studied in long-term randomized clinical trials and thus are not adequately addressed in guidelines (7). ECOPDs are a broad group of events, potentially including respiratory, cardiovascular, infectious, and other acute events, suggesting that they should be renamed "exacerbations of respiratory symptoms in patients with COPD" (4, 8).

In this issue of the *Journal*, Graul and colleagues (pp. 960–972) report a retrospective analysis of a large primary care–derived English COPD cohort in which they evaluated the occurrence of cardiovascular events occurring over a median of 2.4 years of follow-up after M-ECOPDs or H-ECOPDs (9). The authors observed an increased rate of cardiovascular events that peaked immediately (1–14 d) after H-ECOPDs and 14–30 days after M-ECOPDs but persisted beyond the first year irrespective of ECOPD severity. Scaling these findings up to the wider COPD population, the authors calculated that approximately 28 people might experience at least one cardiovascular event for every 100 H-ECOPDs and 22 for every 100 M-ECOPDs. The large size of the population examined permitted the analysis of both the primary outcome (a composite score of acute coronary syndrome [ACS]; arrhythmias, particularly AF; acute HF; ischemic stroke; and pulmonary hypertension), and of the individual components (ACS, acute HF, AF, ischemic stroke, and pulmonary hypertension). Similar results and conclusions, albeit collected using different methods in a primary care–derived Canadian database were just reported by Hawkins and colleagues (10).

The present study is currently being extended using routinely collected electronic healthcare records or claims databases in different countries to further characterize this very high risk group, constituting patients with COPD recruited after ECOPDs, particularly H-ECOPDs, with particular focus on cardiovascular events (11). The study by Hawkins and colleagues (10) is part of the same program (11).

The excellent study by Graul and colleagues (9) confirms and extends the results of previous studies, particularly *1*) focusing on the importance of nonfatal potentially preventable and treatable cardiovascular events; *2*) showing differences in the time course and severity of a composite score of nonfatal cardiovascular events (primary outcome) after M-ECOPDs versus H-ECOPDs; and *3*) showing prolonged (>1 yr) increases in both the composite score and most individual components after both M-ECOPDs and H-ECOPDs. The major strengths of the study are *1*) the very well characterized population of patients with COPD identified in a primary care database linked to hospital data, using a previously validated diagnosis of COPD; *2*) the link to hospital records to identify cardiovascular events; *3*) the strict inclusion and exclusion criteria for the distinction between exacerbators and nonexacerbators; and *4*) the large sample size, which allowed analyses of both the composite outcome and its individual components. Although data on individual components of the score are interesting, we should be aware that they often represent only the tip of the iceberg, as they often do not occur alone, but are rather associated with the other components (e.g., ACSs are often associated with HF) (12).

The major limitation of this study and that of Hawkins and colleagues (10) is the use of the current definition of severity of ECOPDs (7), which is based on the use of healthcare resources (medications and/or hospitalization). This may be inaccurate when distinguishing between exacerbations of symptoms due to acute respiratory and/or cardiovascular and/or other causes (4, 8). The use of this definition may have identified as ECOPDs the occurrence of cardiovascular events or vice versa. In addition, the stringent inclusion criteria of this study (9) might have resulted in a population with more severe disease (*see below*), thus limiting the generalizability of the results. Prospective carefully conducted randomized clinical trials are urgently required to better characterize exacerbations of respiratory symptoms and to identify the size of this bias and its clinical consequences (4, 8, 13).

The prevalence of ECOPDs at the start of follow-up in this highly selected population was higher (68.4%) than in a previous study that used the same database (14), and in the study of Hawkins and colleagues (10), whereas the distribution of M-ECOPDs (81.3%) versus H-ECOPDs (18.7%) was similar to that seen in previous studies. Interestingly, the increased rate of nonfatal cardiovascular events was not dramatically higher after H-ECOPDs (28 of 100) than after M-ECOPDs (22 of 100). M-ECOPDs represent the vast majority of ECOPDs and are seen almost exclusively in primary care centers with limited resources compared with hospitals, potentially explaining the unexpected high rates of cardiovascular events. Thus, specific follow-up protocols and treatment strategies should be considered also for M-ECOPDs.

The authors explain the rationale for focusing on nonfatal cardiovascular events and for excluding deaths in their main analysis, even if acknowledging that including deaths in the composite score increased the observed incidences of the event. In clinical practice, the association of both M-ECOPDs and H-ECOPDs with remarkably increased nonfatal cardiovascular events and deaths, particularly during hospitalization and in the first month of follow-up (Figure 1), should prompt healthcare practitioners to act now without waiting for evidence (15), not only by planning a careful specific cardiologic strategy but by implementing an interventional plan similar to that

Originally Published in Press as DOI: 10.1164/rccm.202401-0040ED on February 6, 2024

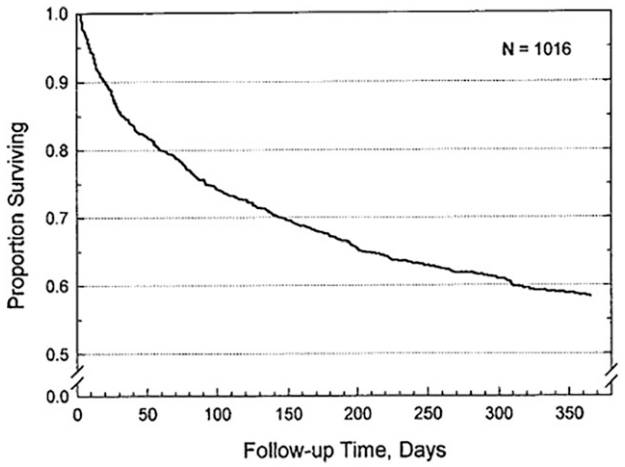

Figure 1. One-year survival among 1,016 patients after severe acute exacerbations of chronic obstructive pulmonary disease. The Kaplan-Meier survival estimates over the 365 days after study entry are shown. Although moderate hospital mortality (11%) was seen, there was considerable mortality in the months after the index admission. Reprinted by permission from Reference 6.

recommended by cardiologists in the aftermath of myocardial infarction (16). The comprehensive global respiratory and cardiovascular risk reduction strategy should include the optimization of COPD prevention and management (7) as well as cardiovascular lifestyle adaptations, risk factor management, cardiorespiratory rehabilitation programs, and even the implementation of cardioprotective pharmacologic treatment, possibly including lipid management to enhance the control of lipid concentrations. Such strategies might improve the overall survival of these patients (7, 16). ■

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

Acknowledgment: Writing support (in the form of editing content for grammar and journal style) was provided by David Young of Young Medical Communications and Consulting Ltd.

Bianca Beghe, M.D., Ph.D.
Department of Medicine
University of Modena and Reggio Emilia
Modena, Italy

Antonio Spanevello, M.D.
Istituti Clinici Scientifici Maugeri IRCCS
and
Department of Medicine and Surgery
University of Insubria
Varese-Como, Italy

Leonardo M. Fabbri, M.D.
Department of Translational Medicine
University of Ferrara
Ferrara, Italy

ORCID ID: 0000-0001-8894-1689 (L.M.F.).

References

1. Roversi S, Fabbri LM, Sin DD, Hawkins NM, Agustí A. Chronic obstructive pulmonary disease and cardiac diseases: an urgent need for integrated care. *Am J Respir Crit Care Med* 2016;194:1319–1336.
2. Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? *Eur Respir Rev* 2018;27:180057.
3. Fabbri LM, Celli BR, Agustí A, Criner GJ, Dransfield MT, Divo M, *et al.* COPD and multimorbidity: recognising and addressing a syndemic occurrence. *Lancet Respir Med* 2023;11:1020–1034.
4. Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook RD, Criner GJ, *et al.* Differential diagnosis of suspected chronic obstructive pulmonary disease exacerbations in the acute care setting: best practice. *Am J Respir Crit Care Med* 2023;207:1134–1144.
5. Müllerova H, Maselli DJ, Locantore N, Vestbo J, Hurst JR, Wedzicha JA, *et al.* Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort. *Chest* 2015;147:999–1007.
6. Connors AF Jr, Dawson NV, Thomas C, Harrell FE Jr, Desbiens N, Fulkerson WJ, *et al.* Outcomes following acute exacerbation of severe chronic obstructive lung disease: the SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med* 1996;154: 959–967.
7. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease; 2024 [accessed 2024 Jan 8]. Available from: https://goldcopd.org/2023-gold-report-2/.
8. Beghé B, Verduri A, Roca M, Fabbri LM. Exacerbation of respiratory symptoms in COPD patients may not be exacerbations of COPD. *Eur Respir J* 2013;41:993–995.
9. Graul EL, Nordon C, Rhodes K, Marshall J, Menon S, Kallis C, *et al.* Temporal risk of non-fatal cardiovascular events post COPD exacerbation: a population-based study. *Am J Respir Crit Care Med* 2024;209:960–972.
10. Hawkins NM, Nordon C, Rhodes K, Talukdar M, McMullen S, Ekwaru P, *et al.* Heightened long-term cardiovascular risks after exacerbation of chronic obstructive pulmonary disease. *Heart* [online ahead of print] 4 Jan 2024; DOI: 10.1136/heartjnl-2023-323487.
11. Nordon C, Rhodes K, Quint JK, Vogelmeier CF, Simons SO, Hawkins NM, *et al.* Exacerbations of COPD and Their Outcomes on Cardiovascular Diseases (EXACOS-CV) programme: protocol of multicountry observational cohort studies. *BMJ Open* 2023;13: e070022.
12. Harjola VP, Parissis J, Bauersachs J, Brunner-La Rocca HP, Bueno H, Čelutkienė J, *et al.* Acute coronary syndromes and acute heart failure: a diagnostic dilemma and high-risk combination. A statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;22: 1298–1314.
13. Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook R, Criner GJ, *et al.* An updated definition and severity classification of chronic obstructive pulmonary disease exacerbations: the Rome proposal. *Am J Respir Crit Care Med* 2021;204:1251–1258.
14. Whittaker H, Rubino A, Müllerová H, Morris T, Varghese P, Xu Y, *et al.* Frequency and severity of exacerbations of COPD associated with future risk of exacerbations and mortality: a UK routine health care data study. *Int J Chron Obstruct Pulmon Dis* 2022;17: 427–437.
15. Fabbri LM, Beghé B, Agusti A. Cardiovascular mechanisms of death in severe COPD exacerbation: time to think and act beyond guidelines. *Thorax* 2011;66:745–747.
16. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, *et al.*; ESC Scientific Document Group. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111–188.