

# Acute exacerbation of COPD: is it the “stroke of the lungs”?

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**Abstract:** Chronic obstructive pulmonary disease (COPD) is one of the top five major causes of morbidity and mortality worldwide. Despite worldwide health care efforts, costs, and medical research, COPD figures demonstrate a continuously increasing tendency in mortality. This is contrary to other top causes of death, such as neoplasm, accidents, and cardiovascular disease. A major factor affecting COPD-related mortality is the acute exacerbation of COPD (AECOPD). Exacerbations and comorbidities contribute to the overall severity in individual patients. Despite the underestimation by the physicians and the patients themselves, AECOPD is a really devastating event during the course of the disease, similar to acute myocardial infarction in patients suffering from coronary heart disease. In this review, we focus on the evidence that supports the claim that AECOPD is the “stroke of the lungs”. AECOPD can be viewed as: a Semicolon or disease’s full-stop period, Triggering a catastrophic cascade, usually a Relapsing and Overwhelming event, acting as a Killer, needing Emergent treatment.

**Keywords:** COPD, acute exacerbation, stroke

## Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide<sup>1</sup> despite increased health care efforts, financial costs, and research concerning its early diagnosis and proper management. COPD epidemiology continues to display a steep increasing trend in mortality, contrary to the other leading causes of death like cancer and cardiovascular disease.<sup>2</sup> The most relevant event affecting COPD mortality is the acute exacerbation of COPD (AECOPD), a catastrophic event during the clinical course of the disease.<sup>3</sup>

The frequency and severity of AECOPD is the major modifier of the management and outcome of COPD. This was the reason that Global Initiative for Chronic Obstructive Lung Disease (GOLD) current initiatives emphasized it even in its COPD definition.<sup>3</sup> The GOLD definition of AECOPD is characterized by clinical empiricism, but is too vague to be useful in the clinical interpretation of COPD patients developing acute exacerbations.

The fact is that COPD prevalence, which is on the rise in developing and developed countries, results in enlarged direct and indirect costs of COPD on the health care systems worldwide. According to several reports, in the US, direct costs have escalated from \$18 billion in 2002 to \$29.5 billion in 2010, consisting mainly of hospital expenses, whereas indirect costs account for 27%–61% of the total costs, with the higher estimates shown by studies focusing on working age populations.<sup>4–6</sup> Average costs for individuals retiring early due to COPD have been estimated to be \$316,000 per individual.<sup>7</sup> In Europe, a remarkable annual cost of €38.7 billion

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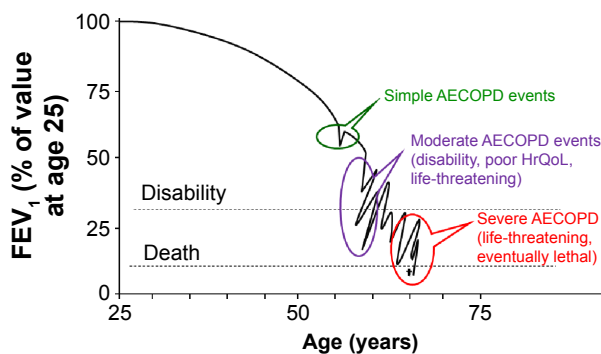
was caused by COPD.<sup>8</sup> Hospitalizations are the greatest contributor to total COPD costs, and account for up to 87% of the total COPD-related costs.<sup>9</sup> Exacerbations are the main cause of the hospital admissions and subsequently account for between 40% and 75% of COPD's total health care costs, despite improvement in new maintenance medications.<sup>10,11</sup> The health care systems worldwide need to endorse the health policies aiming at prevention and appropriate management of COPD exacerbations.

In this review, we focus on the evidence that supports the claim that AECOPD, especially when accompanied by respiratory failure and leads to hospitalization, is the “stroke of the lungs” leading to accelerated loss of lung function and contributes remarkably to increase in morbidity and mortality. We present an overview of the effects of an acute exacerbation in the disease's clinical course, characterized by triggering a catastrophic cascade that is actually a killer, especially when it presents as a relapsed event.

## Semicolon or disease's full-stop period

Contrary to the common perception that lung function decline is a gradual steady process that can be visualized by the Fletcher–Peto diagram,<sup>12</sup> evidence shows that lung function decline is not a constant, stable process. It is the accumulated result of mild losses during steady state and sharp losses, due to acute exacerbations, that accelerate as exacerbations become more frequent and more severe over time, during the disease's natural course (Figure 1).

Even since the end of the 1970s, exacerbations have been implicated as a possible independent factor associated with lung function decline.<sup>13</sup> But only after large cohort studies



**Figure 1** Fletcher–Peto diagram modified: lung function decline is not a constant, stable process.

**Notes:** It is the accumulated result of mild losses during steady state and sharp losses, due to acute exacerbations that accelerate as exacerbations become more frequent and more severe over time, during the natural course of the disease.

**Abbreviations:** AECOPD, acute exacerbation of chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; HrQoL, health-related quality of life.

were performed, the relationship between exacerbations and forced expiratory volume in 1 second (FEV<sub>1</sub>) decline was established. The Lung Health Study reported that each additional exacerbation was associated with a greater annual decline of 7 mL.<sup>14</sup> The London COPD cohort study investigators showed a greater annual decline of 8 mL in frequent exacerbators, compared to non-exacerbation-prone patients.<sup>15</sup> Patients with higher rates of exacerbations showed more rapid lung function decline in the UPLIFT study also.<sup>16</sup> This exacerbation frequency–lung function decline relationship has also been reported in ex-smokers.<sup>17</sup>

Part of this decline may be attributed to increased airway inflammation caused by exacerbations,<sup>18</sup> systemic inflammation,<sup>19</sup> and incomplete symptomatic and physiological resolution, as observed in a significant percentage of COPD patients after an acute exacerbation.<sup>20</sup> Exacerbations may contribute to as much as 25% of lung function decline.<sup>21</sup>

If no further exacerbations occur in the following 6-month period, health status seems to recover to levels similar to those in patients with no exacerbations. But this is not a common rule.<sup>22</sup> In the SUPPORT study, a prospective cohort of 1,016 patients with an exacerbation of COPD and a PaCO<sub>2</sub> of 50 mmHg or more were enrolled.<sup>23</sup> At 6 months, only 26% of the cohort was both alive and capable of reporting a good, very good, or excellent quality of life.<sup>23</sup>

If recurrent events occur, they inhibit full recovery and accelerate health status deterioration.<sup>24,25</sup> Exacerbations show seasonal distribution<sup>26</sup> and tend to cluster together in time, suggesting a high-risk period of 8 weeks for recurrent exacerbations after the initial exacerbation.<sup>27</sup> The European Respiratory Society (ERS) COPD audit survey revealed high 90-day readmission rates across Europe, reaching almost 40%.<sup>28</sup> The time period after an exacerbation is also a high-risk period for all-cause mortality.<sup>29</sup>

## Triggering a catastrophic cascade

There is a striking similarity in the catastrophic pathophysiologic cascade triggered by acute COPD exacerbations and acute myocardial infarctions (MIs) (Table 1). The latter, in the context of coronary heart disease (CHD), lead to more symptoms, recurrent events,<sup>30</sup> worsening of extraction fraction, lower ability for exercise, more frequent hospital admissions,<sup>31</sup> lower quality of life scores,<sup>32</sup> and increased mortality.<sup>33</sup> Acute exacerbations of COPD lead to more symptoms, lung function decline,<sup>14,15</sup> lower exercise capacity,<sup>34</sup> higher hospitalization rates,<sup>35,36</sup> lower quality of life,<sup>37</sup> as well as poorer prognosis.<sup>38,39</sup>

**Table 1** Similarities in the catastrophic pathophysiologic cascade triggered by acute myocardial infarctions and acute COPD exacerbations

Diseases	More symptoms	Higher hospitalization rates	Lower quality of life	Lower exercise capacity	Poorer prognosis
Coronary disease (myocardial infarctions)	√ <sup>30</sup>	√ <sup>31</sup>	√ <sup>32</sup>	√ <sup>31</sup>	√ <sup>33</sup>
COPD (acute exacerbation)	√ <sup>14, 15</sup>	√ <sup>35, 36</sup>	√ <sup>37</sup>	√ <sup>34</sup>	√ <sup>38, 39</sup>

**Abbreviation:** COPD, chronic obstructive pulmonary disease.

COPD and vascular diseases do not just share common risk factors like smoking and aging.<sup>40</sup> The crosstalk between COPD exacerbations and acute events of vascular diseases is impressive, only as COPD has been reported as a contributing factor for endothelial inflammation,<sup>41,42</sup> it may induce arterial stiffness, aggravate atherosclerosis,<sup>43</sup> and increase the risk of cardiovascular disease. Reduced lung function correlates with a higher cardiovascular mortality<sup>44,45</sup> and the risk of ventricular arrhythmias.<sup>46</sup> A reduced FEV<sub>1</sub> has been considered a prognostic marker for cardiovascular and all-cause mortality,<sup>47</sup> which may increase as much as 28% for every 10% decrement in FEV<sub>1</sub> value.<sup>48</sup> In a study analyzing, over a 2-year period, 25,857 patients with COPD from the Health Improvement Network database, COPD exacerbation was associated with a significant increase in risk for MI during a 5-day postexacerbation period.<sup>49</sup> The presence of COPD is reported to worsen the long-term outcomes in patients who underwent percutaneous coronary intervention or coronary artery bypass graft.<sup>50,51</sup> In a study of 81,191 MI patients, of whom 4,867 (6%) had a baseline COPD hospital discharge diagnosis, the COPD patients were reported to have a significantly higher 1-year mortality.<sup>52</sup>

## Relapsing event

Recurring acute events is no coincidence. Acute COPD exacerbations are among the strongest predisposing factors for future exacerbations, as recognized even in smaller cohort studies.<sup>53</sup> Our knowledge regarding AECOPD management was widely extended by large cohort studies like TORCH,<sup>54</sup> UPLIFT,<sup>55</sup> and ECLIPSE,<sup>56</sup> which illustrated that exacerbation frequency increases alongside disease severity. But the rate at which exacerbations occur highlights a distinct phenotype of patients, recognized by the ECLIPSE study, in moderate and severe COPD.<sup>56</sup> Besides disease progression, increased exacerbation frequency may be attributed to inadequate treatment, intrinsic factors like lower airway bacterial load,<sup>57,58</sup> lower levels of physical activity,<sup>59</sup> or exposure to environmental triggers, especially viral or bacterial infections.<sup>60</sup> The frequent exacerbator, a distinct and well-described phenotype of the disease, tends to have reduced responses to treatment for acute

exacerbations concerning inflammatory indices and quality of life,<sup>61</sup> and higher airway inflammation in the steady state and quicker elevation of systemic inflammation levels over time.<sup>62</sup> Acute vascular events such as MI tend to present a similar pattern of relapse.<sup>30</sup> In a study of 3,010 patients with first episode of MI, 30-day readmission rate after discharge was as high as 18.2%,<sup>63</sup> 42.6% of which was associated with a new MI event, while COPD presence was also related to an increased risk of readmission.<sup>63</sup> The postinfarction period is a high risk period for new-onset atrial fibrillation (AF) as well as all-cause mortality.<sup>64</sup>

## Overwhelming

AECOPD is not considered just an acute event characterized by worsening of the patient's respiratory symptoms; it presents an overwhelming situation leading to more frequent serious adverse events.

Patients participating in the UPLIFT study<sup>55</sup> were observed over a 4-year period, and exacerbations or adverse events were recorded throughout the period in patients receiving the study drug. The researchers of the UPLIFT study examined in a later time point this large clinical trial database (5,992 COPD patients) to assess the relationship between exacerbations and the occurrence of nonrespiratory morbidity recorded as adverse events.<sup>65</sup> A total of 3,960 patients had an exacerbation and were analyzed. Non-lower Respiratory Serious Adverse Events' (NRSAsEs) incidence rates (IRs; per 100 patient-years) were recorded before and after the first exacerbation. Comparison of IR 30 days before and after an exacerbation showed significant changes (20.2 vs 65.2 with RR [95% confidence interval] =3.22 [2.40–4.33]). Similar IR changes were observed for the 180-day period (13.2 vs 31.0 with RR [95% confidence interval] =2.36 [1.93–2.87]). The top three common NRSAsEs were cardiac, other respiratory conditions, and gastrointestinal. All NRSAsEs including cardiac events were more frequent after the first exacerbation, irrespective of the cardiac comorbidity of the patient at baseline.

The combination of worsening respiratory symptoms and increased systemic events after exacerbations, particularly

shortly after the event, has a dramatic impact in patients' quality of life and feelings. This impact was studied by a qualitative interview-based study, which was conducted to gain an insight into patients' comprehension and experience of COPD exacerbations and to explore their perspective on the burden of exacerbations.<sup>66</sup> Patients (n=125) with moderate-to-very severe COPD with two or more exacerbations during the previous year underwent a 1-hour face-to-face interview with a trained interviewer. Although commonly used by physicians, only 1.6% of patients understood the term "exacerbation", preferring to use simpler terms such as "chest infection" or "crisis" instead. About two-thirds of patients stated that they were aware when an exacerbation was imminent and, in most cases, symptoms were consistent among exacerbations. Some patients (32.8%) did not report any recognizable warning signs. At the onset of an exacerbation, self-administering their medication was reported by 32.8% of the patients.

The majority of patients (64.8%) cited that exacerbations affected their mood, causing a variety of negative feelings such as anxiety, isolation, depression, irritability/bad temper, anger, and guilt. Overall, patients most commonly reported lack of energy, depression, and anxiety when describing their feelings about exacerbations. These effects seem to have adverse consequences in their personal and family relationships, leading to prevention of social activities and isolation. It is remarkable that physicians tended to underestimate the psychological impact of exacerbations, when compared to patient reports.

It is also remarkable that patients with coronary disease experienced the same feelings as COPD patients, as reported by The Heart and Soul Study.<sup>67</sup> Out of 1,024 participants, 201 (20%) had depressive symptoms. Depressive participants were more likely to report at least mild symptom burden (60% vs 33%), mild physical limitation (73% vs 40%), mildly diminished quality of life (67% vs 31%), and fair or poor overall health (66% vs 30%). Depressive symptoms were strongly related to greater physical limitation, greater symptom burden, worse quality of life, and worse overall health, when using multivariate analyses adjusting for cardiac function and other patient characteristics.

Based on the aforementioned data, depressive symptoms, after a heart attack, are strongly associated with patient-reported health status in patients with coronary disease, which is similar to the case of COPD patients after an acute exacerbation of the disease.

## Killer

According to GOLD guidelines, exacerbations of COPD requiring hospitalization are associated with significant mortality.<sup>3</sup>

In-hospital mortality of COPD patients admitted for a hypercapnic exacerbation with acidosis is ~10%.<sup>23,68,69</sup> In the SUPPORT study,<sup>23</sup> as aforementioned, 1,016 patients were enrolled, who were admitted with an exacerbation of COPD and a PaCO<sub>2</sub> of 50 mmHg or more. The 60-day, 180-day, 1-year, and 2-year mortality was high (20%, 33%, 43%, and 49%, respectively) and at 6 months, only 26% of the cohort was both alive and capable of reporting a satisfactory quality of life.

Similar results were reported in another study where 205 consecutive patients hospitalized with AECOPD were prospectively assessed and were followed up for 3 years.<sup>68</sup> In total, 17 patients (8.3%) died in hospital and the overall 6-month mortality rate was 24%, with 1-, 2-, and 3-year mortality rates of 33%, 39%, and 49%, respectively.<sup>68</sup>

The 1-year mortality rates after an AECOPD seem to be affected by the presence of respiratory failure.<sup>69</sup> In a cohort of 171 patients, the mortality rate during hospitalization was 8%, going up to 23% after 1 year of follow-up.<sup>69</sup> Despite a comparable in-hospital mortality rate (6%), the 1-year mortality rate was reported to be significantly higher for patients admitted to the intensive care unit due to respiratory failure (35%).

The high rates of mortality after an AECOPD have been also reported in the ERS COPD audit survey.<sup>28</sup> The ERS COPD audit was a cross-sectional, multicenter study that analyzed the outcomes of COPD patients admitted to hospital with an exacerbation across Europe. Finally, 16,000 patients and 400 centers across 13 European countries were included in this project. Mortality among COPD patients discharged from hospital and within 90 days of the initial admission date was 6.1% (5.8% in males and 6.8% in females). The composite mortality rate (in-hospital plus 90 days follow-up period) was 11.1%.

Similarly, the incidence rates of sudden cardiac death and recurrent ischemic events post-MI were examined in a large cohort study.<sup>70</sup> Between 1979 and 1998, 2,277 MIs occurred (57% in men). After 3 years, the event-free survival rate was 94% for sudden cardiac death and 56% for recurrent ischemic events. Both outcomes were more frequent with older age and greater comorbidity.<sup>70</sup> As the authors concluded, in the community, recurrent ischemic events are frequent post-MI, while sudden cardiac death is less common. Thus, a COPD exacerbation is related to higher mortality rates than an MI in the general population.

## Emergency

AECOPD is a severe medical condition demanding immediate action.<sup>3</sup> The initial management includes: assessment of

medical history and clinical signs of severity, administration of supplemental oxygen therapy, increasing the dose or/and frequency of inhaled bronchodilators, and addition of oral or intravenous corticosteroids and antibiotics (oral or intravenous) if signs of bacterial infection are present.<sup>3</sup>

In cases of acute respiratory acidosis, noninvasive mechanical ventilation (NIV) is considered. NIV has been shown to improve severity of breathlessness and acute respiratory acidosis and decrease the respiratory rate, work of breathing, complications such as ventilator-associated pneumonia, and the length of hospitalization.<sup>3</sup> More importantly, NIV decreases the intubation rates and mortality.<sup>71,72</sup> If a patient is unable to tolerate NIV, or in case of NIV failure, invasive mechanical ventilation is mandated. Indications of initiating invasive mechanical ventilation include respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, massive aspiration, severe ventricular arrhythmias, severe hemodynamic instability, and persistent inability to remove respiratory secretions.<sup>3</sup> At all times of the management of an acute exacerbation, the medical staff has to monitor the fluid balance and nutrition of the patient; subcutaneous heparin or low-molecular-weight heparin must be considered, and most importantly, associated conditions (eg, heart failure, arrhythmias) must be identified and treated.<sup>3</sup>

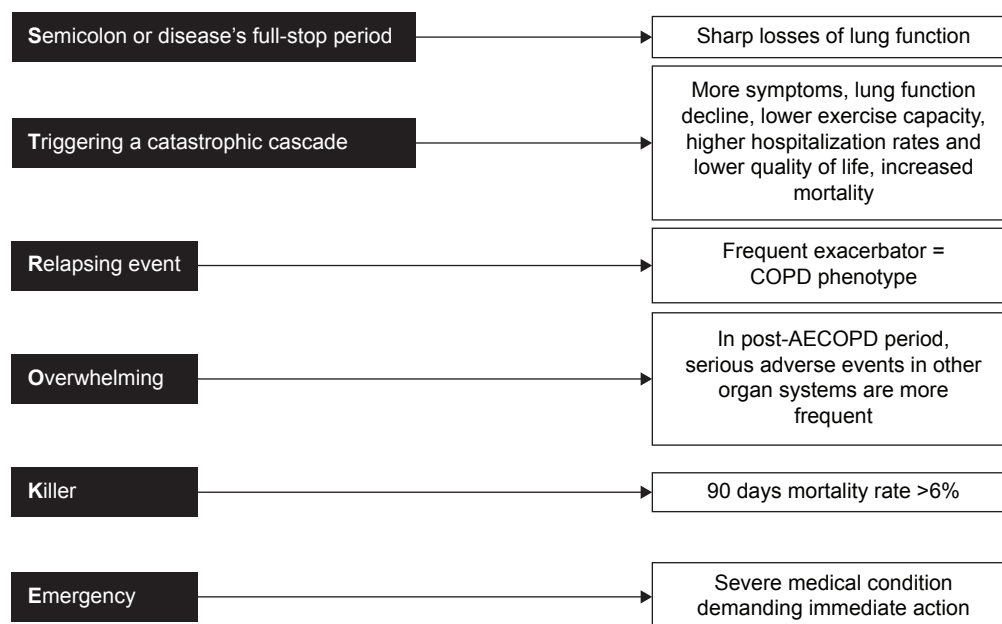
When an acute exacerbation has to be managed, a serious problem is that the COPD patient is rarely only “COPD patient”. Comorbidities are frequent in COPD and 12 of them negatively influence survival.<sup>73</sup> For example, COPD

and CHD share a common major risk factor, which is smoking. The coexistence has been reported as high as 30% or even higher in COPD patients.<sup>74</sup> In some studies of COPD patients’ medical records, the undiagnosed cases of CHD have reached 70%.<sup>75</sup> Also, AF and COPD are two common morbidities and often coexist.<sup>76</sup> The presence and severity of COPD are associated with increased risk for AF/atrial flutter and nonsustained ventricular tachycardia. The prevalence of AF and nonsustained ventricular tachycardia among COPD patients has been reported to be as high as 23.3% and 13.0%, respectively.<sup>77</sup> Hypertension, diabetes and metabolic syndrome, cachexia, myopathy, mental disorders, osteoporosis, and chronic renal failure are also common comorbidities in COPD patients.<sup>78</sup> Finally, studies show that up to 94% of COPD patients have at least one comorbid disease and up to 46% have three or more.<sup>79</sup> Thus, during an AECOPD, the coexistence of comorbidities creates a “lethal cocktail” that has to be faced by the physicians.

## Conclusion

Despite the underestimation by the physicians and the patients themselves, AECOPD is a really catastrophic event in the natural course of the disease, similar to acute MI in patients suffering from CHD (Table 1).

AECOPD can be considered as the “stroke of the lungs” and it can be viewed as: a Semicolon or disease’s full-stop period, Triggering a catastrophic cascade, usually a Relapsing and Overwhelming event, acting as a Killer, needing Emergent treatment (Figure 2).



**Figure 2** AECOPD is the “stroke of the lungs”.

**Abbreviation:** AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

Acknowledging the pivotal role of AECOPD in progression of the disease is crucial in order to design and incorporate a multimodality preventive approach that focuses not only on prevention of exacerbations, but also on the comorbidities that can transform even a minor respiratory exacerbation into a potentially lethal event.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Resp Crit Care Med.* 2007;176(6):532–555.
- WHO. *Chronic Obstructive Pulmonary Disease (COPD)*. Geneva: World Health Organization; 2011. Available from: [www.who.int/respiratory/copd](http://www.who.int/respiratory/copd). Accessed January 3, 2016.
- Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease*; revised 2014. Available from: <http://www.who.int/respiratory/copd/management/en/>. Accessed January 3, 2016.
- Ornek T, Tor M, Altin R, et al. Clinical factors affecting the direct cost of patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease. *Int J Med Sci.* 2012;9(4):285–290.
- Patel JG, Nagar SP, Dalal AA. Indirect costs in chronic obstructive pulmonary disease: a review of the economic burden on employers and individuals in the United States. *Int J Chron Obstruct Pulmon Dis.* 2014;9:289–300.
- National Heart, Lung, and Blood Institute. *Morbidity and Mortality 2009: Chart Book on Cardiovascular, Lung and Blood Diseases*. Bethesda: National Institutes of Health; 2009.
- Fletcher MJ, Upton J, Taylor-Fishwick J, et al. COPD uncovered: an international survey on the impact of chronic obstructive pulmonary disease [COPD] on a working age population. *BMC Public Health.* 2011;11:612.
- Halpin DM, Miravittles M. Chronic obstructive pulmonary disease: the disease and its burden to society. *Proc Am Thorac Soc.* 2006;3(7):619–623.
- Darnell K, Dwivedi AK, Weng Z, Panos RJ. Disproportionate utilization of healthcare resources among veterans with COPD: a retrospective analysis of factors associated with COPD healthcare cost. *Cost Eff Resour Alloc.* 2013;11:13.
- Hilleman D, Dewan N, Malesker M, Friedman M. Pharmacoeconomic evaluation of COPD. *Chest.* 2000;118(5):1278–1285.
- Teo W, Tan WS, Chong W, et al. Economic burden of chronic obstructive pulmonary disease. *Respirology.* 2012;17(1):120–126.
- Fletcher EC, Peto R. The natural history of chronic airflow obstruction. *Br Med J.* 1977;1:1645–1648.
- Kanner RE, Renzetti AD Jr, Klauber MR, Smith CB, Golden CA. Variables associated with changes in spirometry in patients with obstructive lung diseases. *Am J Med.* 1979;67:44–50.
- Kanner RE, Anthonisen NR, Connett JE. Lower respiratory illnesses promote FEV<sub>1</sub> decline in current smokers but not ex-smokers with mild obstructive pulmonary disease: Results from the lung health study. *Am J Respir Crit Care Med.* 2001;164:358–364.
- Donaldson GC, Seemungal TAR, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax.* 2002;57:847–845.
- Halpin DM, Decramer M, Celli B, Kesten S, Liu D, Tashkin DP. Exacerbation frequency and course of COPD. *Int J Chron Obstruct Pulmon Dis.* 2012;7:653–661.
- Makris D, Moschandreas J, Damianaki A, et al. Exacerbations and lung function decline in COPD: new insights in current and ex-smokers. *Respir Med.* 2007;101:1305–1312.
- Bhowmik A, Seemungal TA, Sapsford RJ, Wedzicha JA. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax.* 2000;55:114–120.
- Groenewegen KH, Dentener MA, Wouters EF. Longitudinal follow-up of systemic inflammation after acute exacerbations of COPD. *Respir Med.* 2007;101:2409–2415.
- Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2000;161:1608–1613.
- Wedzicha JA, Donaldson GC. Exacerbations of chronic obstructive pulmonary disease. *Respir Care.* 2003;48:1204–1213.
- Bourbeau J, Ford G, Zackon H, Pinsky N, Lee J, Ruberto G. Impact on patients' health status following early identification of a COPD exacerbation. *Eur Respir J.* 2007;30:907–913.
- Connors AF, Dawson NV, Thomas C, 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.* 1996;154:959–967.
- Spencer S, Jones PW. Time course of recovery of health status following an infective exacerbation of chronic bronchitis. *Thorax.* 2003;58:847–852.
- Spencer S, Calverley PM, Burge PS, Jones PW. Impact of preventing exacerbations on deterioration of health status in COPD. *Eur Respir J.* 2004;23:698–702.
- Donaldson GC, Wedzicha JA. The causes and consequences of seasonal variation in COPD exacerbations. *Int J Chron Obstruct Pulmon Dis.* 2014;9:1101–1110.
- Hurst J, Donaldson GC, Quint J, Goldring J, Baghai-Ravary R, Wedzicha J. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2009;179:369–374.
- Crinion S, Cotter O, Kennedy B, et al. COPD exacerbations – a comparison of Irish data with European data from the ERS COPD audit. *Ir Med J.* 2013;106:270–272.
- Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest.* 2003;124:459–467.
- Adabag AS, Therneau TM, Gersh BJ, Weston SA, Roger VL. Sudden death after myocardial infarction. *JAMA.* 2008;300:2022–2029.
- Chaudhry SI, Khan RF, Chen J, et al. National trends in recurrent AMI hospitalizations 1 year after acute myocardial infarction in Medicare beneficiaries: 1999–2010. *J Am Heart Assoc.* 2014;3(5):e001197.
- Hawkes AL, Patrao TA, Ware R, Atherton JJ, Taylor CB, Oldenburg BF. Predictors of physical and mental health-related quality of life outcomes among myocardial infarction patients. *BMC Cardiovasc Disord.* 2013;13:69.
- Zaman S, Kovoov P. Sudden cardiac death early after myocardial infarction: pathogenesis, risk stratification, and primary prevention. *Circulation.* 2014;129(23):2426–2435.
- Donaldson GC, Wilkinson TM, Hurst JR, Perera WR, Wedzicha JA. Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2005;171:446–452.
- Dewan NA, Rafique S, Kanwar B, et al. Acute exacerbations of COPD. Factors associated with poor treatment outcomes. *Chest.* 2000;117:662–671.
- Garcia-Aymerich J, Monsó E, Marrades RM, et al. Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation. EFRAM study. *Am J Respir Crit Care Med.* 2001;164:1002–1007.
- Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1998;157:1418–1422.

38. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*. 2005;60(11):925–931.
39. Domingo-Salvany A, Lamarca R, Ferrer M, et al. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2002;166:680–685.
40. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ*. 1994;309:901–911.
41. Takahashi T, Kobayashi S, Fujino N, et al. Increased circulating endothelial microparticles in COPD exacerbation susceptibility. *Thorax*. 2012;67:1067–1074.
42. Takahashi T, Kobayashi S, Fujino N, et al. Annual FEV<sub>1</sub> changes and numbers of circulating endothelial microparticles in patients with COPD: a prospective study. *BMJ Open*. 2014;4:e004571.
43. McAllister DA, Maclay JD, Mills NL, et al. Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007;176:1208–1214.
44. Löfdahl CG. COPD and co-morbidities, with special emphasis on cardiovascular conditions. *Clin Respir J*. 2008;2(Suppl 1):59–63.
45. Sin DD, Wu L, Man SF. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest*. 2005;127:1952–1959.
46. Engström G, Wollmer P, Hedblad B, Juul-Möller S, Valind S, Janzon L. Occurrence and prognostic significance of ventricular arrhythmia is related to pulmonary function: a study from 'men born in 1914,' Malmö, Sweden. *Circulation*. 2001;103:3086–3091.
47. Mannino DM, Watt G, Hole D, et al. The natural history of chronic obstructive pulmonary disease. *Eur Respir J*. 2006;27:627–643.
48. Quint JK, Herrett E, Bhaskaran K, et al. Effect of beta blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records. *BMJ*. 2013;347:f6650.
49. Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest*. 2010;137:1091–1097.
50. Selvaraj CL, Gurm HS, Gupta R, Ellis SG, Bhatt DL. Chronic obstructive pulmonary disease as a predictor of mortality in patients undergoing percutaneous coronary intervention. *Am J Cardiol*. 2005;96:756–759.
51. Leavitt BJ, Ross CS, Spence B, et al. Long-term survival of patients with chronic obstructive pulmonary disease undergoing coronary artery bypass surgery. *Circulation*. 2006;114(1 Suppl):I430–I434.
52. Andell P, Koul S, Martinsson A, et al. Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction. *Open Heart*. 2014;1(1):e000002.
53. Hisebø GR, Bakke PS, Aanerud M, et al. Predictors of exacerbations in chronic obstructive pulmonary disease – Results from the Bergen COPD cohort study. *PLoS One*. 2014;9(10):e109721.
54. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356:775–789.
55. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543–1554.
56. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363:1128–1138.
57. Donaldson GC, Seemungal TA, Patel IS, Lloyd-Owen SJ, Wilkinson TM, Wedzicha JA. Longitudinal changes in the nature, severity and frequency of COPD exacerbations. *Eur Respir J*. 2003;22:931–936.
58. Patel IS, Seemungal TAR, Wiks M, Lloyd-Owen SJ, Donaldson GC, Wedzicha JA. Relationship between bacterial colonization and the frequency, character and severity of COPD exacerbations. *Thorax*. 2002;57:759–764.
59. Esteban C, Arostegui I, Abusto M, et al. Influence of changes in physical activity on frequency of hospitalization in chronic obstructive pulmonary disease. *Respirology*. 2014;19:330–338.
60. Seemungal T, Harper-Owen R, Bhowmik A, et al. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001;164:1618–1623.
61. Chang C, Yao W. Time course of inflammation resolution in patients with frequent exacerbations of chronic obstructive pulmonary disease. *Med Sci Monit*. 2014;20:311–320.
62. Donaldson GS, Seemungal TA, Patel IS, et al. Airway and systemic inflammation and decline of lung function in patients with COPD. *Chest*. 2005;128:1995–2005.
63. Dunlay SM, Weston SA, Killian JM, Bell MR, Jaffe AS, Roger VL. Thirty-day rehospitalizations after acute myocardial infarction: a cohort study. *Ann Intern Med*. 2012;157(1):11–18.
64. Bang CN, Gislason GH, Greve AM, et al. New-onset atrial fibrillation is associated with cardiovascular events leading to death in a first time myocardial infarction population of 89,703 patients with long-term follow-up: a nationwide study. *J Am Heart Assoc*. 2014;3(1):e000382.
65. Halpin DM, Decramer M, Celli B, Kesten S, Leimer I, Tashkin DP. Risk of nonlower respiratory serious adverse events following COPD exacerbations in the 4-year UPLIFT® trial. *Lung*. 2011;189:261–268.
66. Kessler R, Stahl E, Vogelmeier C, et al. Patient understanding, detection, and experience of COPD exacerbations: an observational, interview-based study. *Chest*. 2006;130:133–142.
67. Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: The heart and soul study. *JAMA*. 2003;290(2):215–221.
68. Gunen H, Hacievliyagil SS, Kosar F, et al. Factors affecting survival of hospitalised patients with COPD. *Eur Respir J*. 2005;26(2):234–241.
69. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest*. 2003;124(2):459–467.
70. Jokhadar M, Jacobsen SJ, Reeder GS, Weston SA, Roger VL. Sudden death and recurrent ischemic events after myocardial infarction in the community. *Am J Epidemiol*. 2004;159:1040–1046.
71. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 1995;333(13):817–822.
72. Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet*. 1993;341(8860):1555–1557.
73. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;186(2):155–161.
74. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc*. 2005;2(1):8–11.
75. Brekke PH, Omland T, Smith P, Søyseth V. Underdiagnosis of myocardial infarction in COPD – Cardiac Infarction Injury Score (CIIS) in patients hospitalised for COPD exacerbation. *Respir Med*. 2008;102(9):1243–1247.
76. Huang B, Yang Y, Zhu J, et al. Clinical characteristics and prognostic significance of chronic obstructive pulmonary disease in patients with atrial fibrillation: Results from a multicenter atrial fibrillation registry study. *J Am Med Dir Assoc*. 2014;15(8):576–581.
77. Konecny T, Park JY, Somers KR, et al. Relation of chronic obstructive pulmonary disease to atrial and ventricular arrhythmias. *Am J Cardiol*. 2014;114(2):272–277.
78. Tsiligianni IG, Kosmas E, Van der Molen T, Tzanakis N. Managing comorbidity in COPD: A difficult task. *Curr Drug Targets*. 2013;14(2):158–176.
79. Fumagalli G, Fabiani F, Forte S, et al. INDACO project: a pilot study on incidence of comorbidities in COPD patients referred to pneumology units. *Multidiscip Respir Med*. 2013;8(1):28.

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