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PEER REVIEWED FEATURE
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COPD is complicated: the story of its comorbidities

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COPD is increasingly being considered a systemic disease because of the over-representation of an extraordinary range of comorbid conditions associated with biomarkers of systemic inflammation.

Key points

- **COPD is common, costly, and associated with many comorbidities, including heart disease, osteoporosis, mental health disorders, diabetes, renal dysfunction, anaemia, lung cancer and other respiratory conditions.**
- **Systemic inflammation is common to most of the observed chronic comorbid conditions, leading to a proposed unifying hypothesis that their association and consequences are due to systemic inflammation.**
- **Almost all people with moderate-to-severe COPD aged over 65 years are estimated to have at least one comorbidity.**
- **The implications of comorbidities in patients with COPD include diagnostic confusion, inappropriate use of treatment, and increased rates of hospitalisation and mortality.**
- **Clinical practice guidelines for COPD do not currently provide evidence-based guidance on how to account for the comorbid conditions.**

COPD – chronic obstructive pulmonary disease – has enormous global and national importance. It is the second most common cause of avoidable hospital admissions in Australia,[1] the third most common cause of morbidity globally,[2] will be the third most common cause of death by 2020,[3] and its economic impact is prodigious.[4]

WHAT IS COPD?

Learned bodies in Australia[1] and internationally[5] define COPD as a progressive but preventable disease caused by dysregulated inflammation, now recognised as systemic.[6,7] Inflammation is triggered by repeated exposure to multiple inhaled noxious agents or unregulated inflammatory remodelling of asthmatic airways,[6] resulting in chronic airway narrowing and parenchymal lung destruction (chronic airflow limitation and emphysema).[8]

Usually the inflammation in COPD is described as neutrophilic, which distinguishes it from the inflammation seen in asthma (eosinophil-predominant),[5] and resembles that seen in ageing.[9] This may have important therapeutic implications since corticosteroids are less effective in controlling neutrophilic inflammation. (These differences have recently been blurred by findings of non-eosinophilic asthma and non-neutrophilic COPD, leading to the idea that treatments could be targeted to the inflammatory cells rather than to the clinical features.[10])

Symptoms include daily cough and/or sputum production, breathing discomfort with tasks considered normal for age, easy fatigue, and reduced health-related quality of life. COPD is increasingly being considered a systemic disease[11] due to the over-representation of an extraordinary range of comorbid conditions, thought by many to be due to systemic spillover of the inflammation,[12] and a proportion of patients who demonstrate biomarkers of inflammation in the systemic circulation.[13] Alternatively, COPD and its comorbidities could be consequences of a systemic inflammatory (possibly autoimmune)

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disorder,[14] or an inflammatory phenomenon associated with obesity.[15] This article seeks to alert the wider medical community to the importance of these comorbidities and their impact in people with COPD.

EPIDEMIOLOGY AND IMPACT OF COPD

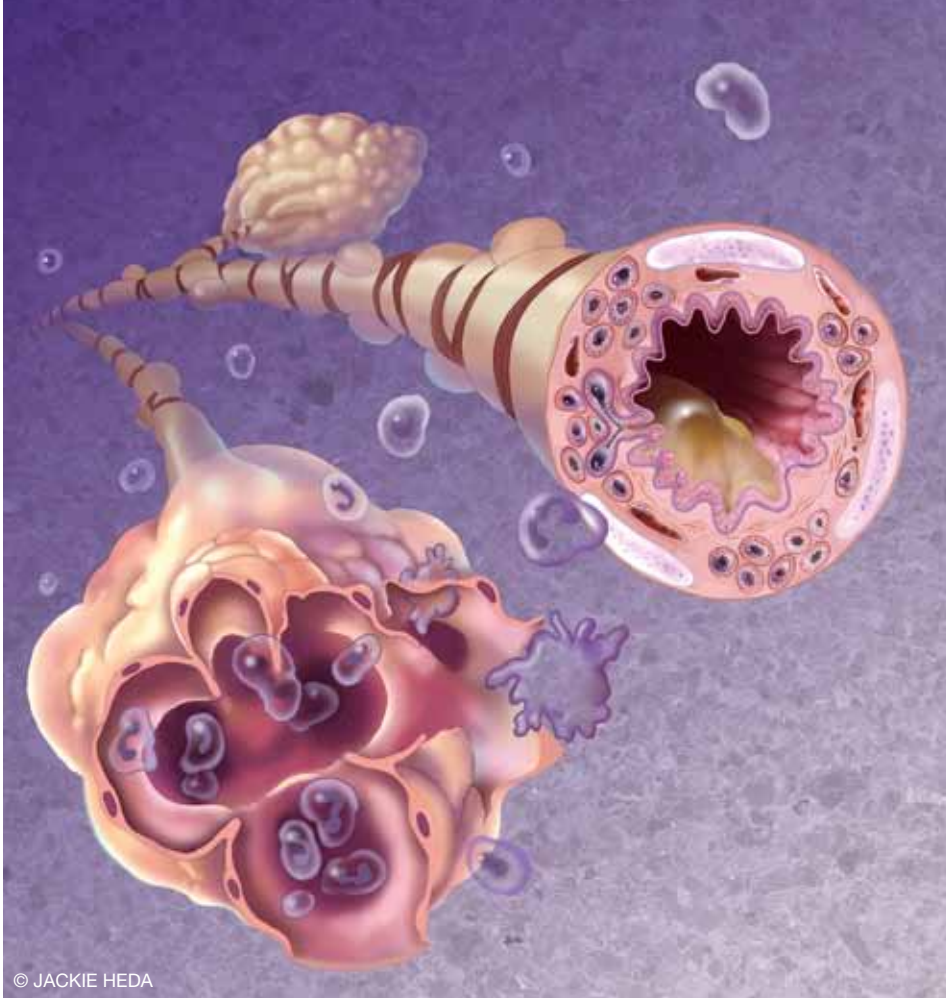
In Asian countries of the Asia-Pacific region, mortality and hospitalisation rates of people with COPD are even higher than in developed nations of the region.[16] In those developing nations males with COPD predominate, whereas in developed nations like Australia the trend is for prevalence and death rates to be almost equal in the sexes, and increasing in females.[16]

More than one in 10 people aged over 40 years has COPD.[17] About three in four of these have been smokers (or continue to smoke);[18] however, in some developing nations smoking is less prominent and biomass fuel pollution assumes greater importance, especially in women.[19] Other significant risk factors are second-hand smoke[20] and chronic (usually poorly controlled) asthma.[21]

Most people with COPD will die prematurely, usually after a prolonged decline in overall health. They may die, usually in hospital, of respiratory failure or, more commonly,[22] from one of the comorbid illnesses. Unfortunately many patients are only diagnosed with COPD when their disease has already begun to disable them or they have a severe exacerbation leading to hospitalisation. Greater awareness of this fact, a recognition of the clinical imperative to question adult patients more carefully and improved skills to undertake appropriate diagnostic tests or wider access to respiratory laboratories are pressing needs worldwide.[23]

COEXISTING MEDICAL CONDITIONS

The conditions often coexisting with COPD are mostly in epidemic proportions in themselves. Many of them share the same lifestyle or ageing factors. However, the associations addressed in this article go well beyond background prevalence rates, and each interacts with the other conditions to worsen their impact. One study has shown the median number of comorbidities in COPD is nine,[24] and comorbidity burden determines higher use of healthcare resources.[25] Systemic inflammation is common to most of the observed chronic conditions, leading to a proposed unifying hypothesis that their association and consequences are due to systemic inflammation.[26]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Patient data from the UK General Practice Research Database were analysed to quantify rates of comorbidities in 2699 patients with COPD compared with age-, sex-, practice- and time-matched controls. The authors of this study found that COPD is associated with many comorbidities, particularly cardiovascular, bone and other smoking-related conditions (Table).[27]

Heart disease

Not surprisingly, the most common comorbidity is heart disease – ischaemic coronary disease (IHD) and chronic heart failure (CHF) in particular, but arrhythmias also complicate medical care in patients with COPD, even allowing for background tobacco consumption. CHF is seen in about 20% of individuals with COPD,[28] and COPD occurs in up to 35% of patients with CHF[29] in studies that have used rigorous diagnostic criteria for each. COPD is an independent predictor of cardiovascular mortality in patients who also have hypertension.[30] In a large primary care survey in Madrid, people with coexisting COPD and heart disease were more disabled,

TABLE. INCREASED RISK OF COMORBIDITIES IN PATIENTS WITH COPD*[27]

Disorder	Relative risk
Pneumonia	16.00
Osteoporosis	3.14
Respiratory infection	2.24
Myocardial infarction	1.75
Angina	1.67
Fractures	1.58
Glaucoma	1.29

* Relative risk of comorbidities in 2699 patients with COPD compared with age-, sex-, practice- and time-matched controls without COPD (all except glaucoma p<0.05). Data from the UK General Practice Research Database (Soriano, et al).[27]

had worse quality of life and used more healthcare resources and their direct health care costs were substantially higher than those with COPD and no cardiac disease.[31]

Both COPD and worse lung function are independent and major cardiovascular risk factors[32] as well as predictors of cardiovascular death.[33] There is growing evidence that the main reason for this comorbidity is systemic inflammation,[34] in addition to the shared risk of smoking.

Mental health disorders

Mental health disorders are also overrepresented in patients with COPD. It may not be surprising that patients become despondent and frankly depressed, or that they assume avoidance behaviours. It is also not surprising that panic becomes entrenched when a person repeatedly becomes uncomfortably breathless.

Diagnosable depression and anxiety (either alone or together) occur at least five times as often in patients with COPD than in the general population.[35] In a large observational cohort 26% of patients with moderate to severe COPD had diagnosable depression,[36] with frequent symptoms and poor quality of life being the most important determinants. There is gross underdiagnosis of depression in the general population, and this is just as big an issue in COPD. The use of screening instruments suited to general practice is highly recommended, although clinical confirmation of abnormal scores and diagnosis of specific depression subtypes is equally important.[35]

Quite separately, cognitive function is impaired in patients with COPD (reported in 18.5% of subjects with COPD),[37] especially in those who have chronic hypoxaemia.[38]

Diabetes and osteoporosis

Diabetes is more common in patients with COPD compared with the general population (16.3%),[37] as is osteoporosis (16.9%).[37,39] In both cases, use of corticosteroids may be considered the cause, but the prevalence of both is excessive beyond the use of these drugs. Their development has been attributed to a range of pathophysiological mechanisms.

Osteoporosis may be caused by any combination of systemic inflammation, smoking (notably in women), hypoxaemia, vitamin D deficiency due to nutritional difficulties or lack of exposure to sunlight and reduced weight-bearing activity.[40]

Obesity and the metabolic syndrome

Obesity, elevated triglyceride and high-density lipoprotein cholesterol levels, elevated blood pressure and fasting hyperglycaemia (the metabolic syndrome) have been identified in 47% of patients with COPD compared with 21% of control patients without COPD.[41] Obesity has been linked to systemic inflammation and increased prevalence of cardiovascular disease.[15] In older patients with COPD who have relatively mild disease, however, high BMI is associated with significantly lower risk of mortality than those with normal BMI,[42] confirming previous observations from Dutch workers over many years.

On the other hand, it is recognised that cachexia is associated with greater risk of early death,[43] especially so in older patients with more severe COPD. This may reflect merely the energy consumption or reduced food assimilation that occurs in end-stage COPD, or high levels of systemic inflammation.

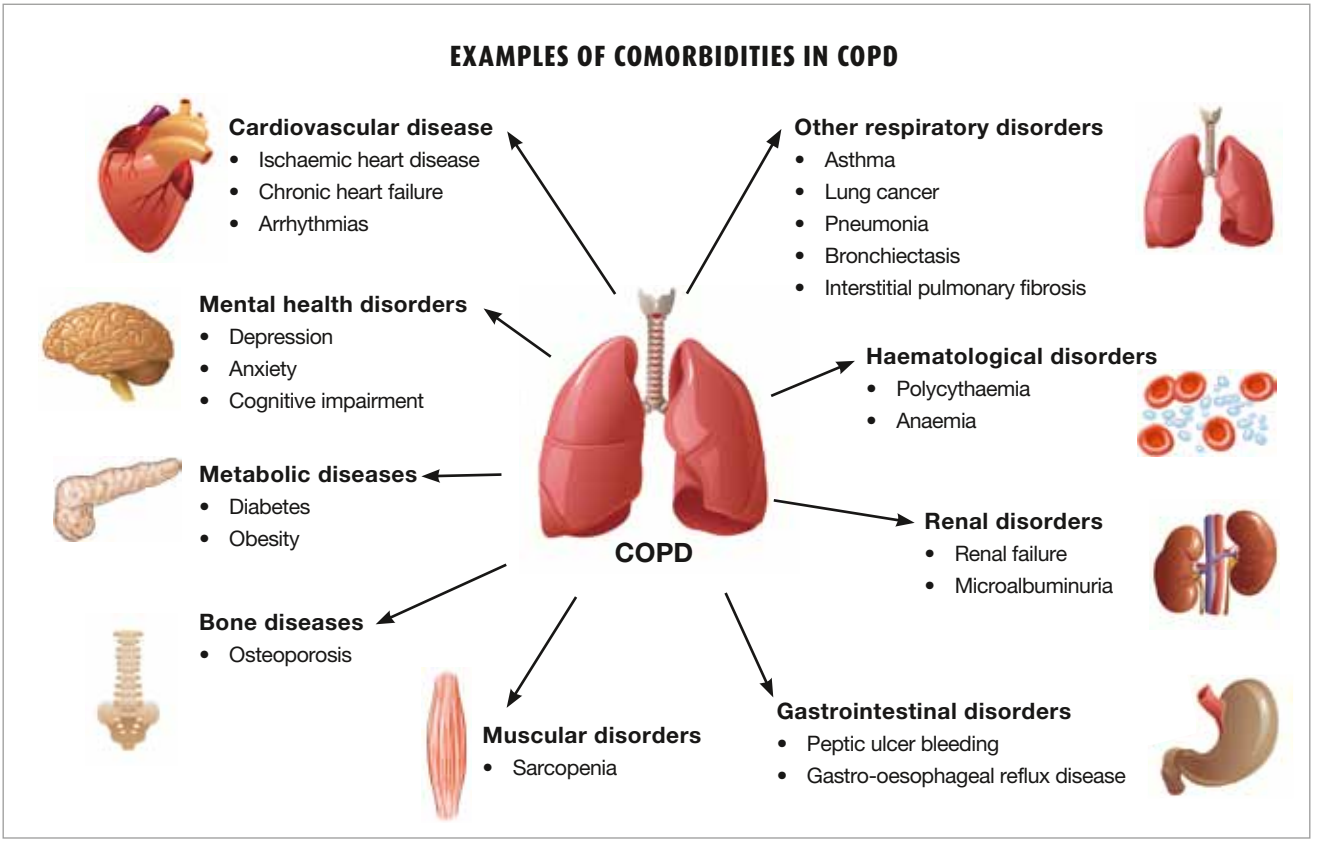
Polycythaemia, anaemia and renal failure

Secondary polycythaemia as a consequence of chronic hypoxia is now less often seen in patients with COPD and other conditions since appropriate long-term oxygen therapy has been more widely used. On the other hand, anaemia is increasingly being recognised. In a large Spanish population cohort, almost 10% of patients admitted to hospital with COPD had anaemia,[44] supporting an earlier systematic review.[45] This appears to be a consequence of systemic inflammation.

Linked with anaemia, renal failure is highly prevalent in patients with COPD,[46] and microalbuminuria is a common occurrence if sought, especially if those who have chronic hypoxaemia. Microalbuminuria can be reversed with long-term oxygen therapy.[47]

Muscular disorders

Muscle weakness is most usually thought to be due to atrophy secondary to inactivity



and poor nutrition,[48,49] but increasing evidence shows us that there is an almost specific form of COPD-associated sarcopenia, most probably a result of chronic systemic inflammation.[50] Skeletal weakness leads to fatigue[51] (along with depression and dyspnoea), a potent predictor of both poor quality of life and hospital readmissions of patients for COPD management.[52]

Gastrointestinal disorders

Gastric ulcers were once considered excessively common in patients with COPD, but since smoking rates have declined, and the diagnosis and treatment of peptic ulcer disease have improved, this comorbidity is not as prevalent. In a large Taiwanese database analysis, however, COPD was found to be a major independent risk factor for peptic ulcer bleeding, with almost a doubling of risk compared with age-matched controls.[53] Gastro-oesophageal reflux disease (GORD) is a vital condition to recognise as it is both more common and has greater importance to COPD progression and exacerbations than peptic ulcers.[54]

Other respiratory conditions

Other respiratory conditions occur more often with COPD.

- Smoking is now recognised to be responsible for some cases of interstitial pulmonary fibrosis.
- Bronchiectasis, a condition not due to smoking *per se* (even in those without cystic fibrosis), is increasingly identifiable on CT scans of the lungs of patients with COPD.
- Lung cancer is more common than could be predicted from the background smoking rate in people with COPD. FEV_1 has been proposed as a means of pre-screening risk of lung cancer in smokers because lung cancer is more often found in patients with a reduced FEV_1 independent of smoking history.[55]
- Asthma is even more common in those with COPD than in the general population, and itself can lead to COPD.[56]
- Patients with COPD are at increased risk of pneumonia.

Each of these conditions shares one or more clinical features with COPD. In turn, dyspnoea with exertion, chronic sputum production and recurrent lower respiratory infections (LRTI), haemoptysis, clubbing and weight loss, wheezing and exacerbations of respiratory symptoms can confuse the clinician as well as the patient and family.

Obstructive sleep apnoea, although not over-represented in patients with COPD,[57] compromises ventilation further when it coexists with COPD and increases the likelihood of worse respiratory and cardiovascular outcomes.

Some examples of the important comorbidities of COPD are illustrated in the box above.

IMPLICATIONS OF COMORBIDITIES IN COPD

Diagnostic confusion

Diagnostic confusion is not unusual when patients with COPD present with their symptom complex.[58] This is especially so when patients present with exacerbated symptoms, so pneumonia or pulmonary emboli might be missed in a patient who seems to have a COPD exacerbation. In addition, in patients with both COPD and heart failure, symptoms are shared (notably dyspnoea) and may cause diagnostic confusion for the patient as well as the doctor. Diagnostic investigations can also be confusing in such patients – notably chest x-ray cardiac size may be underestimated and echocardiographic images can be difficult to obtain when there is lung hyperinflation.

It behoves us to take extra care with our diagnosis as the outcomes hinge on correct medical management and the use of inappropriate drugs could make a patient worse. Take, for example:

- prescribing beta blockers for heart failure in a patient with asthma and COPD
- increasing doses of beta agonists or anticholinergic drugs for COPD too much in a patient with recurrent life-threatening cardiac arrhythmias and/or accelerating coronary artery narrowing
- assuming dyspnoea is due to COPD and ignoring anaemia
- patients taking increasing doses of sedatives or anxiolytics for panic when they have respiratory failure.

Treatments are tailored for uncomplicated COPD

Clinical practice guidelines for COPD (or any of the other conditions), while hinting at the comorbidities, cannot give evidence-based guidance for how to account for the comorbid conditions. The evidence within guidelines is mainly based on randomised controlled trials, and patients in these trials are as 'pure' as possible – i.e. with no comorbidities. Treatments are usually tailored for uncomplicated COPD – not a 'real-world' set of circumstances by any means.

Furthermore, the treatment applicable to one condition may complicate the others, and some treatments for stabilising a chronic condition may be underused, contributing to worse outcomes. Some examples are noted below.

- Beta blockers may be withheld when CHF or paroxysmal tachyarrhythmia coexists with COPD.
- Overuse of beta agonists or anticholinergics increases the risk of decompensation of CHF or tachyarrhythmia.
- Coexisting chronic renal failure may increase drug toxicity when CHF, arrhythmia or infections are being treated.
- Use of systemic corticosteroids may complicate the control of diabetes, contributing to the observed increased length of hospitalisation and mortality.[59]
- Use of inhaled corticosteroids (ICS) for mild to moderate COPD (i.e. when not indicated) appears to increase the risk of lower respiratory tract infection and/or pneumonia.[60]
- ICS interfere with bone metabolism, increasing the likelihood of osteoporotic skeletal fractures.[61]
- Cognitive impairment or mental health comorbidities contribute to poor medication adherence, particularly early response to exacerbating symptoms.[37]

Despite these issues, there is some encouraging evidence relating to cotreatments.

- Retrospective data in large cohorts suggest statins may have beneficial effects on COPD outcomes.[62,63]
- Use of cardioselective beta blockers for CHF or arrhythmia in patients with COPD is safe[64] and improves overall and COPD outcomes.[65,66]
- Large databases have attested to the safety of, and even improved cardiovascular outcomes from, tiotropium administered via HandiHaler.[67]
- Although traditionally avoided because of fears of respiratory depression, low-dose opioids have proven effective and safe in controlling intractable dyspnoea.[68]

Increased rates of hospitalisation, morbidity and mortality

The US National Hospital Discharge Survey, 1979-2001, which evaluated more than 47 million hospital discharges of patients aged 25 years or older with COPD found there was:[22]

- a significantly higher rate of hospitalisation of patients with important medical conditions (notably hypertension, ischaemic heart disease, pneumonia and diabetes) in those with COPD than in those without
- a significantly increased rate of in-hospital mortality from common medical conditions in patients with a codiagnosis of COPD than in those who had no such diagnosis.

Other studies have shown:

- length of hospital stay for COPD exacerbations is prolonged in patients with increasing numbers of comorbidities[69]
- patients seen in primary care have worse respiratory and general health-related quality of life during exacerbations, especially if there are more than three comorbidities[70]
- survival is significantly worse in patients with comorbid heart and lung disease,[22,71] irrespective of which condition developed first,[72] and especially so in those with more severe disease[29]
- the risk of death has been shown to be more than double in patients discharged from hospital following a diagnosed COPD exacerbation if they also had diabetes mellitus than in those without diabetes.[73]

Most costs relating to COPD are derived from hospital admissions, usually due to exacerbations. Exacerbations are not only costly to governments (and therefore society) but they also:

- are distressing for patients and their families

- worsen health-related quality of life for several weeks or months
- increase markedly the risk of further hospitalisations in the next year[74]
- increase depression and anxiety
- reduce physical activity, itself a risk factor for further exacerbations and permanent disablement.

In addition, exacerbations are now more deadly than myocardial infarctions, with reported in-hospital mortality as high as 7.4%,[75] and higher in those requiring ICU treatment (8 to 26%).[76] Exacerbations increase with advancing age: there is a 36% increase in hospitalisation rates for every five years after age 65 years.[77] After apparent recovery from exacerbations, studies from the UK, USA and Netherlands have shown that 14 to 20% of patients die within the next three months[78,79] and 23 to 43% within 12 months.[79,80]

CONCLUSION

Chronic noncommunicable diseases represent the new global epidemic. COPD ranks highly as a cause of death and prolonged disablement, with exacerbations consuming large amounts of our health budget. These exacerbations are more deadly than myocardial infarctions, and their severity is complicated by coexisting medical conditions.

All the chronic conditions that occur as comorbidities of COPD occur more often in patients with COPD than they do in the general age-matched population, and some estimates suggest almost all people with moderate-to-severe COPD aged over 65 years have at least one of these comorbidities. The most common are probably cardiovascular and osteoporosis, but mental health, endocrine, renal, haematological and other conditions occur in frequencies between 30 and 60% of people with COPD.

It is a matter of concern that there is no guidance from evidence-based guidelines for any chronic disease on how we should handle these circumstances, and patients are undeniably confused. Although this article documents the high prevalence and impacts of each comorbidity, and acknowledges the shortcomings of expert guidance, we can only await research that addresses the complexities, and demand that expert bodies develop clear integrated guidelines. MT

REFERENCES

References are included in the pdf version of this article available at www.medicinetoday.com.au.

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REFERENCES

1. Abramson MJ, Crockett AJ, Frith PA, et al. COPDX: an update of guidelines for the management of chronic obstructive pulmonary disease with a review of recent evidence. Med J Aust 2006; 184: 342-345.
2. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997; 349: 1436-1442.
3. Lopez AD, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: Current burden and future projections. Eur Respir J 2006; 27: 397-412.
4. Bustacchini S, Chiatti C, Furneri G, et al. The economic burden of chronic obstructive pulmonary disease in the elderly: results from a systematic review of the literature. Curr Opin Pulm Med 2011; 17(suppl): S35-S41.
5. Global Initiative for Chronic Obstructive Pulmonary Disease. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO workshop report 2008 update. Available online from: www.goldcopd.org (accessed May 2013).
6. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Lancet 2007; 370: 797-799.
7. Gan WQ, Man SF, Senthilselvan A, et al. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and meta-analysis. Thorax 2004; 59: 574-580.
8. Wouters EF. Local and systemic inflammation in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005; 2: 26-33.
9. Ito K, Barnes PJ. COPD as a disease of accelerated lung aging. Chest 2990; 135: 173-180.
10. Pavord ID, Shaw DE, Gibson PG, Taylor DR. Inflammometry to assess airway diseases. Lancet 2008; 372: 1017-1019.
11. Agusti A, Noguera A, Sauleda J, et al. Systemic effects of chronic obstructive pulmonary disease. Eur Respir J 2003; 21: 347-360.
12. Sinden NJ, Stockley RA. Systemic inflammation and comorbidity in COPD: a result of 'overspill' of inflammatory mediators from the lungs? Review of the evidence. Thorax 2010; 65: 930-936.
13. Agusti A, Edwards LD, Rennard SI, et al, for the ECLIPSE Investigators. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS ONE 2012; 7: e37483.
14. Agusti A, MacNee W, Donaldson K, Cosio M. Hypothesis: Does COPD have an autoimmune component? Thorax 2003; 58: 832-834.
15. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature 2006; 444: 875-880.
16. Tan WC, Seale JP, Ip M, et al. Trends in COPD mortality and hospitalization in countries and regions of Asia-Pacific. Respirology 2009; 14: 90-97.
17. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 2007; 370: 741-750.
18. Eisner MD, Anthonisen N, Coultas D, et al. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010; 182: 693-718.
19. Hu G, Zhou Y, Tian J, et al. Risk of COPD from exposure to biomass smoke: a metaanalysis. Chest 2010; 138: 3-6.
20. Qaseem A, Wilt T, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 2011; 155: 179-191.
21. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax 2009; 64: 728-735.
22. Holguin F, Folch E, Redd SC, Mannino DM. Comorbidity and mortality in COPD-related hospitalizations in the United States. 1979 to 2001. Chest 2005; 128: 2005-2011.
23. Hill K, Goldstein RS, Guyatt GH, et al. Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. CMAJ 2010; 182: 673-678.
24. Barr RG, Celli BR, Mannino DM, et al. Comorbidities, patient knowledge, and disease management in a national sample of patients with chronic obstructive pulmonary disease. Am J Med 2009; 122: 348-355.
25. Simon-Tuval T, Scharf SM, Maimon N, et al. Determinants of elevated healthcare utilization in patients with COPD. Respir Res 2011; 12: 7-14.

26. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009; 33: 1165-1185.
27. Soriano JB, Visick GT, Muellerova H, et al. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest 2005; 128: 2099-2107.
28. Hawkins NM, Petrie MC, Jhund PS, et al. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail 2009; 11: 130-139.
29. Mascarenhas J, Lourenco P, Lopes R, et al. Chronic obstructive pulmonary disease in heart failure. Prevalence, therapeutic and prognostic implications. Am Heart J 2008; 155: 521-525.
30. Mazza A, Zamboni S, Rubello D, et al. Chronic obstructive pulmonary disease and cardiovascular mortality in elderly subjects from the general population. Blood Press 2010; 19: 67-74.
31. Miguel-Diez J, Carrasco-Garrido P, Rejas-Gutierrez J, et al. The influence of heart disease on characteristics, quality of life, use of health resources, and costs of COPD in primary care settings. BMC Cardiovasc Dis 2010; 10: 8-16.
32. Stone IS, Barnes NC, Petersen SE. Chronic obstructive pulmonary disease: a modifiable risk factor for cardiovascular disease? Heart 2012; 98: 1055-1062.
33. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. Proc Am Thor Soc 2005; 2: 8-11.
34. Sin DD, Man SFP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular disease? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 2003; 107: 1514-1519.
35. Cafarella PA, Effing TW, Usmani ZA, Frith PA. Treatments for anxiety and depression in patients with chronic obstructive pulmonary disease: a literature review. Respirology 2012; 17: 627-638.
36. Hanania NA, Mullerova H, Locantore NW, et al. Determinants of depression in the ECLIPSE Chronic Obstructive Pulmonary Disease cohort. Am J Respir Crit Care Med 2011; 183: 604-611.
37. Schnell K, Weiss CO, Lee T. The prevalence of clinically-relevant comorbid conditions in patients with physician-diagnosed COPD: a cross-sectional study using data from NHANES 199-2008. BMC Pulm Med 2012; 12: 26-34.
38. Incalzi RA, Gemma A, Marra C, et al. Verbal memory impairment in COPD: its mechanisms and clinical relevance. Chest 1997; 112: 1506-1513.
39. Nuti R, Siviero P, Maggi S, et al. Vertebral fractures in patients with chronic obstructive pulmonary disease: the EOLO Study. Osteoporosis Int 2009; 20: 989-998.
40. Ionescu AA, Schoon E. Osteoporosis in chronic obstructive pulmonary disease. Eur Respir J Suppl 2003; 46: 64s-75s.
41. Marquis K, Maltais F, Duguay V, et al. The metabolic syndrome in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil 2005; 25: 226-232.
42. Burgel P-R, Paillasseur J-L, Caillaud D, for the Initiatives BPCO Scientific Committee. Clinical COPD phenotypes: a novel approach using principal component and cluster analyses. Eur Respir J 2010; 36: 531-539.
43. Vestbo J, Prescott E, Almdal T, et al. Body mass, fat-free body mass, and prognosis in patients with chornic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. Am J Respir Crit Care Med 2006; 173: 79-83.
44. Barba R, Casasola GGD, Marco J, et al. Anemia in chronic obstructive pulmonary disease: a readmission prognostic factor. Curr Med Res Opin 2012; 28: 617-622.
45. Yohannes AM, Ershler WB. Anemia in COPD: a systematic review of the prevalence, quality of life, and mortality. Respir Care 2011; 56: 644-652.
46. Incalzi R, Corsonello A, Pedone C, et al. Chronic renal failure: a neglected comorbidity of COPD. Chest 2012; 137: 831-837.
47. Casanova C, de Torres JP, Navarro J, et al. Microalbuminuria and hypoxemia in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010; 182: 1004-1010.
48. Schols AMWJ, Soeters PB, Dingemans AMC, et al. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. Am Rev Respir Dis 1993; 147: 1151-1156.
49. Bernard S, Leblanc P, Whittom F, et al. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998; 158: 629-634.
50. Sin DD, Man SF. Skeletal muscle weakness, reduced exercise tolerance, and COPD: is systemic inflammation the missing link? Thorax 2006; 61: 1-3.
51. Mador MJ. Muscle mass, not body weight, predicts outcome in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002; 166: 787-789.
52. Paddison JS, Effing TW, Quinn S, Frith PA. Fatigue in COPD: association with functional status and hospitalisations. Eur Respir J 2013; 41: 565-570.
53. Huang K-W, Luo J-C, Leu H-B, et al. Chronic obstructive pulmonary disease: an independent risk factor for peptic ulcer bleeding: a nationwide population-based study. Alim Pharmacol Ther 2012; 35: 796-802.
54. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010; 363: 1128-1138.
55. Wasswa-Kintu S, Gan WQ, Man SF, et al. Relationship between forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. Thorax 2005; 60: 570-575.
56. Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. Chest 2004; 126: 59-65.
57. McNicholas WT. Chronic obstructive pulmonary disease and obstructive sleep apnea: overlaps in pathophysiology, systemic inflammation, and cardiovascular disease. Am J Respir Crit Care Med 2009; 180: 692-700.
58. Ho KK, Pinsky JL, Kannell WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993; 22(4 Suppl A): 6A-13A.
59. Parappil A, Depczynski B, Collett P, Marks GB. Effect of comorbid diabetes on length of stay and risk of death in patients admitted with acute exacerbation of COPD. Respirology 2010; 15: 918-922.
60. Singh S, Loke YK. Risk of pneumonia associated with long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease: a critical review and update. Curr Opin Pulm Med 2010; 16: 118-122.
61. Yang IA, Fong KM, Sim EH, et al. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2007; CD002991.
62. Young RP, Hopkins R, Eaton TE. Potential benefits of statins on morbidity and mortality in chronic obstructive pulmonary disease: a review of the evidence. Postgrad Med J 2009; 85: 414-421.
63. Bartziokas K, Papaioannou AI, Minas M, et al. Statins and outcome after hospitalization for COPD exacerbation: a prospective study. Pulm Pharmacol Ther 2011; 24: 625-631.
64. Salpeter SR, Ormiston TM, Salpeter EE, et al. Cardioselective beta-blockers for chronic obstructive pulmonary disease: a meta-analysis. Respir Med 2003; 97: 1094-1101.

65. Rutten FH, Zuithoff NP, Hak E, et al. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. Arch Intern Med 2010; 170: 880-887.
66. Short PM, Lipworth SI, Elder DH, et al. Effect of beta-blockers in treatment on chronic obstructive pulmonary disease: a retrospective cohort study. BMJ 2011; 342: d2549.
67. Celli B, Decramer M, Leimer I, et al. Cardiovascular safety study of tiotropium in patients with COPD. Chest 2010; 137: 20-30.
68. Abernethy AP, Currow DC, Frith PA, et al. Randomised, double-blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. BMJ 2003; 327: 523-528.
69. Agboado G, Peter J, Donkin L. Factors influencing the length of hospital stay among patients resident in Blackpool admitted with COPD: a cross-sectional study. BMJ Open 2013; 2: e000869.
70. Jones PW, Brusselle G, Dal Negro RW, et al. Health-related quality of life in patients by COPD severity within primary care in Europe. Respir Med 2010; 105: 57-66.
71. Sidney S, Sorel M, Queensberry CP, et al. COPD and incident cardiovascular hospitalizations and mortality: Kaiser Permanente Medical Care Program. Chest 2005; 128: 2068-2075.
72. Dalal AA, Shah M, Lunacsek O, Hanania NA. Clinical and economic burden of patients diagnosed with COPD with comorbid cardiovascular disease. Respir Med 2011; 105: 1516-1522.
73. Gudmundsson G, Gislason T, Lindberg E, et al. Mortality in COPD patients discharged from hospital: the role of treatment and co-morbidity. Respir Res 2006; 7: 109-115.
74. Garcia-Aymerich J, Monso 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.
75. Roche N, Zureik M, Soussan D, et al. Predictors of outcomes in COPD exacerbation cases presenting to the emergency department. Eur Respir J 2008; 32: 953-961.
76. Patil SP, Krishnan JA, Pechtzin N, et al. In-hospital mortality following acute exacerbation of chronic obstructive pulmonary disease. Arch Intern Med 2003; 163: 1180-1186.
77. Niewoehlner DE, Lokhnygina Y, Rice K, et al. Risk indexes for exacerbations and hospitalizations due to COPD. Chest 2007; 131: 20-28.
78. Roberts CM, Lowe D, Bucknall CE, et al. Clinical audit indicators of outcome following admission to hospital with exacerbation of chronic obstructive pulmonary disease. Thorax 2002; 57: 137-141.
79. Connors AF, Dawson NV, Thomas C, et al. Outcomes of exacerbations of severe chronic obstructive lung disease. Am J Respir Crit Care Med 1996; 154: 959-967.
80. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbations of COPD. Chest 2003; 124: 459-467.