Comorbidities in Chronic Obstructive Pulmonary Disease

Wissam M. Chatila[1], Byron M. Thomashow[2], Omar A. Minai[3], Gerard J. Criner[1], and Barry J. Make[4]

[1]Division of Pulmonary and Critical Care Division, Temple University School of Medicine, Philadelphia, Pennsylvania; [2]Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York; [3]Department of Pulmonary, Allergy, and Critical Care Medicine, Cleveland Clinic Foundation, Cleveland, Ohio; and [4]Division of Pulmonary Sciences and Critical Care Medicine, National Jewish Medical and Research Center, University of Colorado School of Medicine, Denver, Colorado

Comorbidities such as cardiac disease, diabetes mellitus, hypertension, osteoporosis, and psychological disorders are commonly reported in patients with chronic obstructive pulmonary disease (COPD) but with great variability in reported prevalence. Tobacco smoking is a risk factor for many of these comorbidities as well as for COPD, making it difficult to draw conclusions about the relationship between COPD and these comorbidities. However, recent large epidemiologic studies have confirmed the independent detrimental effects of these comorbidities on patients with COPD. On the other hand, many of these comorbidities are now considered to be part of the commonly prevalent nonpulmonary sequelae of COPD that are relevant not only to the understanding of the real burden of COPD but also to the development of effective management strategies.

Keywords: chronic bronchitis; obstructive lung disease; epidemiology

Comorbidities, defined as other chronic medical conditions, including coronary artery disease, diabetes mellitus, osteoporosis and muscle weakness, are common in chronic obstructive pulmonary disease (COPD), but their prevalence varies tremendously between studies (Table 1). van Manen and colleagues reported that over 50% of 1,145 patients with COPD had 1 to 2 comorbidities, 15.8% had 3 to 4 comorbidities, and 6.8% had 5 or more comorbid conditions (1). In another study that selected 200 patients with COPD from 1,522 patients in a managed care organization, Mapel and coworkers reported that the COPD cohort had an average of 3.7 comorbidities versus 1.8 for the control subjects, and only 6% of patients with COPD did not have another chronic medical condition (2). Unfortunately, the presence of both COPD and other comorbidities is often ominous and contributes significantly to poor health outcomes (3–6). Regarding patients with COPD with the major emphysema phenotype, no studies have compared the prevalence and impact of their comorbidities to other COPD phenotypes.

COPD, COMORBIDITIES, AND HOSPITALIZATIONS

COPD is a leading cause of hospitalizations in adults, particularly older adults (7). Comorbidities are a common cause, or a contributing cause, to many of these hospitalizations. In the Lung Health Study 12.8% of the 5,887 smokers were hospitalized, with 42% of the hospitalizations secondary to cardiovascular events or pulmonary complications (8). In the review by Holguin and colleagues, comorbidities were frequently reported in hospitalized patients with primary or secondary COPD diagnoses: hypertension 17%, cardiac disease 25%, diabetes 11%, pneumonia 12%; all higher than in the control group (6). In a study of over 45,000 patients with COPD, heart failure was the leading cause of hospitalization, followed by myocardial infarction and stroke (9). Curkendall and coworkers found that the prevalence of all cardiovascular diseases was higher in patients with COPD compared with control subjects, and that the risk of hospitalization and mortality due to cardiovascular causes was also elevated in patients with COPD (10). In another study of 270 hospitalized patients with COPD, Antonelli Incalzi and coworkers noted hypertension in 28%, diabetes in 14%, and ischemic heart disease in 10% (5). Kinnunen and colleagues found that comorbidities had an impact on the duration of COPD hospitalizations, and reported a mean length of stay of 7.7 days without any comorbidity compared with 10.5 days if a concurrent disease was present (11).

COPD, COMORBIDITIES, AND MORTALITY

COPD is the fourth leading cause of death in adults in the United States, and is projected to be the third most common cause of death by 2020 (12). Between 1970 and 2002, death rates due to stroke and heart disease decreased (63% and 52%, respectively), while death rates due to COPD increased 100% (13). Some studies evaluating the cause of death in patients with COPD suggest that patients are more likely to die of comorbid conditions than from COPD, whereas others revealed that COPD is the more likely cause of death (Table 2). Patient selection and severity of disease probably account for these reported differences.

Mannino and coworkers evaluated obstructive lung disease deaths in the United States from 1979 through 1993, and found that 2.5 million (8.2%) individuals had the diagnosis of COPD listed on their death certificate (14). Of these, 1.1 million (43.3%) had COPD listed as a cause of death. Between 1979 and 2001, there were 47 million hospital discharges (8.5% of all hospitalizations in adults) with a primary or secondary diagnosis of COPD (21% and 79%, respectively) (6). Their reported hospital mortality was 5.9%, with 37% related to respiratory failure, 25% related to pneumonia, and 43% related to heart disease (6). In the Canadian study by Huiart and colleagues of 2,553 COPD deaths, cardiovascular disease was a much more common cause of death than COPD (37.6% versus 14.3%) (15). Similarly, Sidney and coworkers found that over 3 years, patients with COPD were more likely to die, particularly from cardiovascular causes (9). There were 149 deaths in the Lung Health Study (2.5%), with 25% dying of cardiovascular disease. Lung cancer was the cause of 38% of the deaths, while other cancers accounted for 22% (8).

(*Received in original form September 4, 2007; accepted in final form September 27, 2007*)

The National Emphysema Treatment Trial (NETT) is supported by contracts with the National Heart, Lung, and Blood Institute (N01HR76101, N01HR76102, N01HR76103, N01HR76104, N01HR76105, N01HR76106, N01HR76107, N01HR76108, N01HR76109, N01HR76110, N01HR76111, N01HR76112, N01HR76113, N01HR76114, N01HR76115, N01HR76116, N01HR76118, and N01HR76119), the Centers for Medicare and Medicaid Services (CMS), and the Agency for Healthcare Research and Quality (AHRQ).

Correspondence and requests for reprints should be addressed to Wissam Chatila, M.D., Division of Pulmonary and Critical Care Division, Temple University School of Medicine, 3401 N Broad Street, Philadelphia PA, 19140. E-mail: chatilw@tuhs.temple.edu

Proc Am Thorac Soc Vol 5. pp 549–555, 2008
DOI: 10.1513/pats.200709-148ET
Internet address: www.atsjournals.org

TABLE 1. CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND THE PREVALENCE OF COMORBIDITIES (%)

Source	n	Arthritis	Cardiac	HTN	Diabetes	Lipids	Psych	GI	Cancer	Osteoporosis
van Manen and colleagues (1)	1,145	36	13	23	5	—	9	15	6	—
Mapel and colleagues (2)	200	22	65	45	12	—	17	32	18	—
Soriano and colleagues (114)	2,699	28	22	—	—	—	10	26	4	—
Sidney and colleagues (9)	45,966	—	18	18	2	9	—	—	—	—
Walsh and Thomashow (115)	3,000	70	50	52	16	51	38	62	4	32

Definition of abbreviations: — = no available data; GI = gastrointestinal disturbances; HTN = hypertension.

RELATIONSHIP BETWEEN COPD AND COMORBIDITIES

Smoking, aging, and other factors such as polypharmacy, medication interactions, lack of treatment of comorbidities (16), diagnosis coding accuracy (17), and lack of specific case definitions for comorbidities (18) add to the complexity of studying comorbidities and outcomes in patients with COPD. β-Blockers may worsen lung function in a subset of patients with COPD, but their avoidance in many patients with COPD may contribute to increased cardiovascular events, especially in those at risk. In contrast, bronchodilators may contribute to tachyarrhythmias. Inhaled anticholinergics may affect intraocular pressure or bladder function. Inhaled corticosteroids may predispose to cataracts, skin bruising, and, potentially in high doses, osteoporosis. Systemic corticosteroids are frequently overused in the population with COPD, and may contribute to osteoporosis, diabetes, hypertension, muscle dysfunction, and adrenal insufficiency (19). Despite these limitations, mounting evidence has identified links between some comorbidities and COPD, such as its association with cardiovascular disease, even after allowing for common factors (20–23), with much focus on the pivotal role of systemic inflammation that characterizes many chronic medical diseases (21).

Pulmonary Embolism

Pulmonary embolism (PE) may be a more common comorbid condition of COPD than was previously thought, but the data are limited and contradictory to date. A diagnosis of PE could easily be missed in COPD, since the main presenting symptoms of PE overlap with those of a COPD exacerbation. Some evidence points to the importance of considering PE in patients who present with acute exacerbation of COPD with no obvious cause (24–26). In a study of 211 consecutive patients admitted for severe exacerbation of COPD of unknown origin and undergoing spiral CT or ultrasonography, Tillie-Leblond and colleagues reported that 25% of patients had PE (24). The authors further reported that a low Geneva score, which reflects a low clinical suspicion for PE, was insufficient to exclude the diagnosis of PE. Monreal and colleagues reported that 14% of patients in a symptomatic PE registry had COPD (25). In contrast, Rutschmann and coworkers recently reported a low incidence of PE in 123 consecutive patients admitted for acute exacerbation of COPD: 6.2% of patients with a clinical suspicion of PE, and only 1.3% of those with low suspicion (26).

Pneumonia

COPD is more frequently associated with pneumonia compared with other chronic diseases. Of 707 patients presenting with community-acquired pneumonia, 19% had COPD. Moreover, in 10% of the cases, pneumonia led to the new diagnosis of COPD. As expected, COPD contributes to longer hospital stays, increased intensive care admissions, and mortality (33). Pneumonia is viewed by some as part of the spectrum of COPD exacerbations; however, there are important differences between pneumonia and acute COPD exacerbations without pneumonia. Lieberman and colleagues evaluated and compared exacerbations in patients with COPD with and without pneumonia, and found that those with pneumonia had more abrupt onset of symptoms, more severe illness, longer length of stay, and higher rates of ICU admission and death (27). In addition, interventions that are effective at reducing the risk of exacerbations, such as salmeterol and fluticasone, may actually increase the risk of pneumonia (28). Distinguishing COPD exacerbations from pneumonia may be important for management purposes. In general, the literature supporting antibiotic usage in acute exacerbations of COPD shows a modest benefit at best. In contrast, prompt antibiotic delivery is associated with striking benefits in patients with pneumonia (29, 30). Corticosteroids are standard of care for acute exacerbations of COPD (31), with well-documented and important clinical benefits, but their role in the management of patients with COPD with pneumonia is less defined (32).

Lung Cancer

Lung cancer is an important cause of mortality in COPD. Studies relying on national databases for secondary diagnoses

TABLE 2. REPORTED CAUSES OF MORTALITY IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (%)

Author	Site	Patients with COPD Dying	Cause: COPD (%)	Cause: Cardiovascular (%)	Cause: Malignancy (%)	Cause: Other Respiratory (%)
Mannino and colleagues (14)	United States	1.1 million	43	26	8	—
Hansell and colleagues (17)	England	312,000	60	26	8	4
Camilli and colleagues (116)	Tucson	86	23	42	9	26
Huiart and colleagues (15)	Canada	2,000	14	38	—	—
Anthonisen and colleagues (8)	United States	149	< 15	25	60	—
Zielinski and colleagues (41)	Europe	215	38	27	7	21
Waterhouse and colleagues (120)	Europe	103	49	22	21	—
Keistinen and colleagues (118)	Europe	973	22	37	21	4
Vilkman and colleagues (117)	Europe	1,070	30	37	20	—
Celli and colleagues (119)	United States, Spain, Venezuela	162	61	14	12	—

on death certificates in Europe and the United States reported that 7 to 10% of COPD deaths are related to lung cancer (14, 17). In comparison, studies that followed patients with COPD prospectively found lung cancer as the cause of death in 7% and 38% of cases (8, 41). Patients with COPD with comorbid conditions, including lung cancer, have higher hospitalization and mortality rates (6, 34, 36, 42, 43). Lange and coworkers, and Hole and colleagues, reported hazard ratios as high as 3.9 and 4.4 for lung cancer mortality in patients with the lowest lung function independent of smoking status (34, 42).

Lung cancer and COPD seem to be casually linked by the pathobiology of COPD rather than COPD being an epimarker of a greater exposure to smoking (23). Although smoking causes COPD and lung cancer, airways obstruction has a greater risk on developing lung cancer than status or degree of smoking (34, 35). In the presence of moderate to severe airways obstruction, the incidence of lung cancer was almost as high among ex-smokers (6.8%) as among current smokers (10.8%) (23). Moreover, the risk of developing lung cancer has been shown to be proportional to the severity of airways obstruction. Compared with smokers with normal lung function, hazard ratios for developing lung cancer for patients with mild to moderate and severe COPD ranged between 1.4 and 2.7 and 2.8 and 4.4, respectively (23, 34). Even small reductions in lung function in smokers were associated with a significant increase in the risk of lung cancer, but this relationship may be less pronounced in men than in women (35–37). The risk of lung cancer was 3.5-fold higher for women than men at similar levels of FEV_1 (35).

The relationship between lung cancer and obstructive lung disease suggests a possible overlap in their biology. The mechanisms that are potentially involved seem to revolve around a particular histologic subtype, namely squamous cell carcinoma, and may be different between men and women. Malhotra and coworkers demonstrated no relationship between the severity of airflow obstruction and risk of having adenocarcinoma (38), which is the leading histologic subtype in women with lung cancer. In contrast, squamous cell carcinoma has a strong association with smoking, and the presence of COPD increases the risk by 2.5 and 3.5 times of having this subtype (39, 40).

Musculoskeletal Dysfunction

Musculoskeletal dysfunction (MSD) contributes to exercise limitation and disability in COPD (44–46). Coronell and colleagues (47) recently demonstrated that patients with COPD have a decreased ability to sustain repetitive muscular contractions and that their muscles fatigue rapidly. Qualitative changes in the activity of aerobic enzymes (48) and muscle fiber atrophy have been reported in patients with COPD (49). Moreover, MSD may be one of the systemic manifestations of COPD that have some bearing on survival and other comorbidities such as osteoporosis (50). Some studies demonstrated lower survival rates in underweight patients (44–46), while others suggested that loss of fat-free mass may be a more accurate measure of functional debilitation than the more traditional measure such as body mass index (51).

Patients with COPD have many reasons to have MSD, including periods of relative inactivity, use of systemic glucocorticoids, malnutrition, and possibly systemic inflammation and oxidative stress (52, 53). Cardiopulmonary function shows a significant decline with bed rest, including increased resting and submaximal heart rates and reduced maximum oxygen uptake (54, 55). There is also a 1 to 1.5% per day loss of muscle strength with prolonged bed rest (56). Nutritional status in patients with advanced COPD can be also compromised, with some patients becoming overtly cachectic or undernourished (57, 58). In addition, ongoing systemic inflammation and oxidative stress may potentially contribute to muscle wasting and reduced exercise tolerance. Pinto-Plata and coworkers reported that CRP levels were elevated in patients with COPD and correlated inversely with 6-minute walk distance (59). In another study of 102 patients with severe COPD, higher CRP levels were associated with poorer quality of life and reduced exercise endurance (60). Current recommendations in the management of MSD revolve around minimizing deconditioning, enrolling in pulmonary rehabilitation, and avoiding systemic corticosteroids (61). So far, results of nutritional supplementation and hormonal replacement have not been encouraging (62–66).

Osteoporosis

Patients with COPD are at an increased risk of osteoporosis because of their age, limited physical activity (67), low BMI (68), smoking, hypogonadism, malnutrition, and use of corticosteroids (69, 70). Males in their mid to late 60s with a smoking history of greater than 60 pack-years have a prevalence rate of vertebral fractures similar to, and possibly greater than, postmenopausal women greater than or equal to 65 years old (70). Limited studies suggest a significant association between COPD and osteoporosis independent of corticosteroids (70–72). In a study of 28 patients with advanced COPD, Shane and colleagues found a very high incidence of both osteoporosis and osteopenia (73). The prevalence rate of vertebral fractures was 29% in patients with COPD. In another study of 62 patients with severe COPD, 68% had osteoporosis or osteopenia and 24% had previously undiagnosed compression fractures (74), Systemic corticosteroids remain the most common cause of drug-related osteoporosis, and a meta-analysis concluded that the use of more than 6.25 mg prednisone daily led to decreased BMD and increased fracture risk (75). In contrast, the effects of the long-term use of inhaled corticosteroids on BMD remain debatable (69, 76–79).

Dietary supplementation with calcium, vitamin D, and life style modification with enrollment in a pulmonary rehabilitation program may be helpful (Table 3). The use of bisphosphonates is appealing, but their effectiveness has not been demonstrated in COPD. A recent nonrandomized study found a significant improvement in BMD and osteoporosis rates in a group of patients with emphysema who underwent lung volume reduction surgery compared with those who refused the surgery (80). The study was limited due to lack of information on medication use and other bone interventions. Nonetheless, the finding of increased BMD in a subgroup of surgery patients who contin-

TABLE 3. MANAGEMENT OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITH OSTEOPOROSIS OR AT HIGH RISK FOR OSTEOPOROSIS

1. Screening of high-risk patients: men and women with a significant smoking history, those with advanced chronic obstructive pulmonary disease, and those being treated with continuous high-dose inhaled glucocorticoids or low-to-medium dose inhaled glucocorticoids with frequent courses of oral glucocorticoids
2. Dietary supplementation with calcium (recommended daily allowance 1,000–1,500 mg) and vitamin D (recommended daily allowance 400–800 IU) as needed
3. Lifestyle modification and enrollment in a pulmonary rehabilitation program
4. Risedronate (5 mg/d) or alendronate (5 or 10 mg/d) are recommended as first-line therapy for the prevention and treatment of osteopenia and osteoporosis
5. Screening for metabolic abnormalities and hormonal deficiencies

ued systemic steroids suggests that bone health could be improved with effective COPD treatment strategies.

Gastroesophageal Reflux

An increased prevalence of gastroesophageal reflux (GER) disease and other esophageal disorders has been reported in COPD (81–83). Mokhlesi and coworkers recently reported an increased prevalence of GER symptoms among patients with COPD compared with control subjects (19% versus 0%; $P < 0.001$) (81). They noted that GER symptoms were more common in those with an FEV_1 less than or equal to 50%, as compared with those with an FEV_1 greater than 50% ($P = 0.08$). A recent study of 42 patients with severe COPD using 24-hour esophageal pH monitoring reported that 62% had pathological GER, and notably 58% of these 26 patients reported no symptoms of GER (84). On the other hand, a retrospective study found an increased risk of COPD in those with GER (85). Despite this evidence, the exact nature and significance of this relationship remains clouded by a paucity of evidence. The impact of GER on COPD is currently undefined. Hypotheses include that aspiration of *Helicobacter pylori* or its exotoxins may amplify the airway inflammation (86), or that increased rates of COPD exacerbations are related to GER symptoms.

METABOLIC CHANGES

Diabetes Mellitus

The reported prevalence of diabetes among patients with COPD ranges from 1.6 to 16% (Table 1). As in COPD, smoking has been established as a risk factor for diabetes (87–90), but quitting for more than 5 to 10 years mitigates that risk (89). The evidence for an interaction between diabetes and COPD is supported by studies that demonstrate reduced lung function as a risk factor for the development of diabetes (91–93). In addition, TNF-α, IL-6, and CRP, which are elevated in COPD, are also increased in diabetes (94–97). The impact of glucocorticoids on the management of diabetes during COPD exacerbations and the effect of diabetes control on COPD outcomes is of great clinical concern. In one study, mortality was found to be significantly higher in patients having poor glycemic control who were hospitalized for acute COPD exacerbation (98), and even after discharge, diabetes remained a risk factor for mortality (99). It is uncertain if tighter glucose control can improve COPD outcome.

Dyslipidemia

Smoking causes an increase in low-density lipoprotein (LDL)-C, triglycerides, and very low-density lipoprotein (VLDL) and a decrease in high-density lipoprotein (HDL) (100, 101), but lipid profiles have not been well characterized in COPD. Studies on dyslipidemia in COPD are limited (Table 1) and have generally relied on questionnaire or diagnostic codes to determine frequency. Therefore, it is unknown if dyslipidemia is another independent factor that could explain the increased risk of cardiovascular morbidity and mortality in COPD.

Regardless of cholesterol levels, robust evidence supports the role of CRP levels in predicting cardiovascular disease (102), and when CRP is added to the Global Initiative for Obstructive Lung Disease (GOLD) criteria or pulmonary function testing, the combined scores have greater predictive power for cardiovascular morbidity than either single assessment (103, 104). Consequently, it is expected to observe a significant reduction in cardiovascular disease with statin therapy in smokers (25 to 35%), but it is unclear if this reduction in morbidity is more prominent in those with COPD (105).

Anemia

Untreated hypoxemia is associated with secondary erythrocytosis, but like other chronic diseases, COPD potentially could affect hematopoesis. The observed hematopoietic suppression in chronic inflammatory diseases is likely mediated by three different mechanisms: shortened red blood cell survival, bone marrow erythropoietin resistance, and dysregulation of iron homeostasis (106). Underlying factors influencing these aforementioned mechanisms are thought to be related to smoking (and smoking-related morbidities), malnutrition, and probably the systemic inflammation that accompanies COPD. Systemic inflammation in COPD has been characterized by elevations in levels of IL-6, IL-8, CRP, and TNF-α, (22) with the latter two mediators potentially contributing to a reduction in red blood cells lifespan, impaired iron utilization, and increased erythropoietin resistance (106). A recent study by John and colleagues showed significantly higher CRP and erythropoietin levels in anemic compared with nonanemic patients with COPD (107). They also found a strong inverse correlation between hemoglobin and erythropoietin ($r = -0.84$) in anemic patients with COPD only, supporting further the association between inflammation and erythropoietin resistance (107).

Anemia is common in COPD and is associated with higher comorbidity, mortality, and health costs (96, 108, 110). In a cohort of 2,524 patients with COPD on long-term oxygen therapy, 13% of men and 8% of women were reported to have anemia (108). Recently, Mannino and coworkers presented data indicating anemia is present in one third of 2,404 patients with COPD (109). Two additional large studies reported the anemia prevalence to be 21% and 23% (110, 111). Risk factors for anemia with COPD include older age, severity of airways obstruction, lower BMI, and having other comorbidities (108). Small intervention studies suggest that correcting anemia in patients with COPD by blood transfusion improves physiologic and clinical parameters (112, 113), but it is uncertain if pharmacologic therapy in anemic patients with COPD can raise their hemoglobin levels or have an impact on their long-term outcome.

CONCLUSIONS

For years the relevance and impact of comorbidities on COPD was not well understood. The emerging evidence on the detrimental interrelationship of comorbidities and COPD is mounting, but this area of research is in its early stages. It is yet to be determined if nonpulmonary interventions such as those that reduce the systemic inflammatory burden, improve anemia, prevent osteoporosis, reverse malnutrition, or the like, will alter the natural history of COPD. In addition, more studies are needed to better define the burden of COPD on various comorbidities and to discover the influence of various COPD treatment strategies on these comorbidities.

***Conflict of Interest Statement*:** W.M.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.M.T. is on an Advisory Board for Boehringer Ingelheim (BI) and Pfizer. He attended one Advisory Board meeting in 2006. He is also on the speaker's bureaus for BI, Pfizer, and GlaxoSmithKline. O.A.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.J.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.J.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

References

1. van Manen JG, Bindels PJ, IJzermans CJ., van der Zee JS, Bottema BJ, Schade E. Prevalence of comorbidity in patients with a chronic airway obstruction and controls over the age of 40. *J Clin Epidemiol* 2001;54: 287–293.

2. Mapel DW, Hurley JS, Frost FJ, Petersen HV, Picchi MA, Coultas DB. Health care utilization in chronic obstructive pulmonary disease: a case-control study in a health maintenance organization. *Arch Intern Med* 2000;160:2653–2658.
3. Patil SP, Krishnan JA, Lechtzin N, Diette GB. In-hospital mortality following acute exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med* 2003;163:1180–1186.
4. Almagro P, Calbo E, Ochoa de Echaguen A, Barreiro B, Quintana S, Heredia JL, Garau J. Mortality after hospitalization for COPD. *Chest* 2002;121:1441–1448.
5. Antonelli Incalzi R, Fuso L, De Rosa M, Forastiere F, Rapiti E, Nardecchia B, Pistelli R. Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997;10:2794–2800.
6. 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.
7. Mannino DM. COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. *Chest* 2002;121:121S–126S.
8. Anthonisen NR, Connett JE, Enright PL, Manfreda J, Lung Health Study Research Group. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med* 2002;166:333–339.
9. Sidney S, Sorel M, Quesenberry CP Jr, DeLuise C, Lanes S, Eisner MD. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 2005;128: 2068–2075.
10. Curkendall SM, DeLuise C, Jones JK, Lanes S, Stang MR, Goehring E Jr, She D. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol* 2006;16:63–70.
11. Kinnunen T, Saynajakangas O, Tuuponen T, Keistinen T. Impact of comorbidities on the duration of COPD patients' hospital episodes. *Respir Med* 2003;97:143–146.
12. Petty TL. Definition, epidemiology, course, and prognosis of COPD. *Clin Cornerstone* 2003;5:1–10.
13. Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970–2002. *JAMA* 2005;294:1255–1259.
14. Mannino DM, Brown C, Giovino GA. Obstructive lung disease deaths in the United States from 1979 through 1993. An analysis using multiple-cause mortality data. *Am J Respir Crit Care Med* 1997;156:814–818.
15. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. *Chest* 2005;128:2640–2646.
16. Redelmeier DA, Tan SH, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. *N Engl J Med* 1998; 338:1516–1520.
17. Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *Eur Respir J* 2003;22:809–814.
18. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. *Eur Respir J* 2006;28:1245–1257.
19. Barr RG, Celli BR, Martinez FJ, Ries AL, Rennard SI, Reilly JJ Jr, Sciurba FC, Thomashow BM, Wise RA. Physician and patient perceptions in COPD: the COPD Resource Network Needs Assessment Survey. *Am J Med* 2005;118:1415.
20. 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.
21. Agusti A. Thomas A. Neff lecture. Chronic obstructive pulmonary disease: a systemic disease. *Proc Am Thorac Soc* 2006;3:478–481.
22. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004;59:574–580.
23. Mannino DM, Aguayo SM, Petty TL, Redd SC. Low lung function and incident lung cancer in the United States: data From the First National Health and Nutrition Examination Survey follow-up. *Arch Intern Med* 2003;163:1475–1480.
24. Tillie-Leblond I, Marquette CH, Perez T, Scherpereel A, Zanetti C, Tonnel AB, Remy-Jardin M. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med* 2006;144:390–396.
25. Monreal M, Munoz-Torrero JF, Naraine VS, Jimenez D, Soler S, Rabunal R, Gallego P; RIETE Investigators. Pulmonary embolism in patients with chronic obstructive pulmonary disease or congestive heart failure. *Am J Med* 2006;119:851–858.
26. Rutschmann OT, Cornuz J, Poletti PA, Bridevaux PO, Hugli O, Qanadli SD, Perrier A. Should pulmonary embolism be suspected in exacerbation of chronic obstructive pulmonary disease? *Thorax* 2007;62: 121–125.
27. Lieberman D, Lieberman D, Gelfer Y, Varshavsky R, Dvoskin B, Leinonen M, Friedman MG. Pneumonic vs nonpneumonic acute exacerbations of COPD. *Chest* 2002;122:1264–1270.
28. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J. TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775–789.
29. Meehan TP, Fine MJ, Krumholz HM, Scinto JD, Galusha DH, Mockalis JT, Weber GF, Petrillo MK, Houck PM, Fine JM. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA* 1997;278:2080–2084.
30. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med* 2004; 164:637–644.
31. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C. *et al.*: Global Initiative for Chronic Obstructive Lung Disease. *Am J Respir Crit Care* 2007;176:532–555.
32. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, Della Porta R, Giorgio C, Blasi F, Umberger R, *et al*. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005;171:242–248.
33. Pifarre R, Falguera M, Vicente-de-Vera C, Nogues C. Characteristics of community-acquired pneumonia in patients with chronic obstructive pulmonary disease. *Respir Med* 2007; 10.1016/j.rmed.2007.05.011 (in press).
34. Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Ventilatory function and chronic mucus hypersecretion as predictors of death from lung cancer. *Am Rev Respir Dis* 1990;141:613–617.
35. Wasswa-Kintu S, Gan WQ, Man SF, Pare PD, Sin DD. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. *Thorax* 2005;60: 570–575.
36. Van den Eeden SK, Friedman GD. Forced expiratory volume (1 second) and lung cancer incidence and mortality. *Epidemiology* 1992;3:253–257.
37. Islam SS, Schottenfeld D. Declining FEV1 and chronic productive cough in cigarette smokers: a 25-year prospective study of lung cancer incidence in Tecumseh, Michigan. *Cancer Epidemiol Biomarkers Prev* 1994; 3:289–298.
38. Malhotra S, Lam S, Man SF, Gan WQ, Sin DD. The relationship between stage 1 and 2 non-small cell lung cancer and lung function in men and women. *BMC Pulm Med* 2006;6:2.
39. Nomura A, Stemmermann GN, Chyou PH, Marcus EB, Buist AS. Prospective study of pulmonary function and lung cancer. *Am Rev Respir Dis* 1991;144:307–311.
40. Papi A, Casoni G, Caramori G, Guzzinati I, Boschetto P, Ravenna F, Calia N, Petruzzelli S, Corbetta L, Cavallesco G, *et al*. COPD increases the risk of squamous histological subtype in smokers who develop non-small cell lung carcinoma. *Thorax* 2004;59:679–681.
41. Zielinski J, MacNee W, Wedzicha J, Ambrosino N, Braghiroli A, Dolensky J, Howard P, Gorzelak K, Lahdensuo A, Strom K, *et al*. Causes of death in patients with COPD and chronic respiratory failure. *Monaldi Arch Chest Dis* 1997;52:43–47.
42. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996;313:711–715. (discussion 715–6).
43. Eberly LE, Ockene J, Sherwin R, Yang L, Kuller L, Multiple Risk Factor Intervention Trial Research Group. Pulmonary function as a predictor of lung cancer mortality in continuing cigarette smokers and in quitters. *Int J Epidemiol* 2003;32:592–599.
44. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1791–1797.
45. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160:1856–1861.
46. Gray-Donald K, Gibbons L, Shapiro SH, Macklem PT, Martin JG. Nutritional status and mortality in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;153:961–966.
47. Coronell C, Orozco-Levi M, Mendez R, Ramirez-Sarmiento A, Galdiz JB, Gea J. Relevance of assessing quadriceps endurance in patients with COPD. *Eur Respir J* 2004;24:129–136.

48. Maltais F, Simard AA, Simard C, Jobin J, Desgagnes P, LeBlanc P. Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med* 1996;153:288–293.
49. Gosker HR, Engelen MP, van Mameren H, van Dijk PJ, van der Vusse GJ, Wouters EF, Schols AM. Muscle fiber type IIX atrophy is involved in the loss of fat-free mass in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2002;76:113–119.
50. Bolton CE, Ionescu AA, Shiels KM, Pettit RJ, Edwards PH, Stone MD, Nixon LS, Evans WD, Griffiths TL, Shale DJ. Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170:1286–1293.
51. Vestbo J, Prescott E, Almdal T, Dahl M, Nordestgaard BG, Andersen T, Sorensen TI, Lange P. Body mass, fat-free body mass, and prognosis in patients with chronic 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.
52. Koechlin C, Couillard A, Cristol JP, Chanez P, Hayot M, Le Gallais D, Prefaut C. Does systemic inflammation trigger local exercise-induced oxidative stress in COPD? *Eur Respir J* 2004;23:538–544.
53. Oudijk EJ, Lammers JW, Koenderman L. Systemic inflammation in chronic obstructive pulmonary disease. *Eur Respir J Suppl* 2003;46:5s–13s.
54. Stremel RW, Convertino VA, Bernauer EM, Greenleaf JE. Cardiorespiratory deconditioning with static and dynamic leg exercise during bed rest. *J Appl Physiol* 1976;41:905–909.
55. Hung J, Goldwater D, Convertino VA, McKillop JH, Goris ML, DeBusk RF. Mechanisms for decreased exercise capacity after bed rest in normal middle-aged men. *Am J Cardiol* 1983;51:344–348.
56. Muller EA. Influence of training and of inactivity on muscle strength. *Arch Phys Med Rehabil* 1970;51:449–462.
57. Donahoe M, Rogers RM, Wilson DO, Pennock BE. Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989;140:385–391.
58. Openbrier DR, Irwin MM, Rogers RM, Gottlieb GP, Dauber JH, Van Thiel DH, Pennock BE. Nutritional status and lung function in patients with emphysema and chronic bronchitis. *Chest* 1983;83: 17–22.
59. Pinto-Plata VM, Mullerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, Celli BR. C-reactive protein in patients with COPD, control smokers and non-smokers. *Thorax* 2006;61:23–28.
60. Broekhuizen R, Wouters EF, Creutzberg EC, Schols AM. Raised CRP levels mark metabolic and functional impairment in advanced COPD. *Thorax* 2006;61:17–22.
61. Minai OA, Maurer JR, Kesten S. Comorbidities in end-stage lung disease. *J Heart Lung Transplant* 1999;18:891–903.
62. Creutzberg EC, Schols AM, Weling-Scheepers CA, Buurman WA, Wouters EF. Characterization of nonresponse to high caloric oral nutritional therapy in depleted patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:745–752.
63. Wilson DO, Rogers RM, Sanders MH, Pennock BE, Reilly JJ. Nutritional intervention in malnourished patients with emphysema. *Am Rev Respir Dis* 1986;134:672–677.
64. Efthimiou J, Fleming J, Gomes C, Spiro SG. The effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988;137:1075–1082.
65. Burdet L, de Muralt B, Schutz Y, Pichard C, Fitting JW. Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease: a prospective, randomized, controlled study. *Am J Respir Crit Care Med* 1997;156:1800–1806.
66. Ferreira IM, Verreschi IT, Nery LE, Goldstein RS, Zamel N, Brooks D, Jardim JR. The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. *Chest* 1998;114:19–28.
67. Reid IR. Osteoporosis–emerging consensus. *Aust N Z J Med* 1997;27: 643–647.
68. Incalzi RA, Caradonna P, Ranieri P, Basso S, Fuso L, Pagano F, Ciappi G, Pistelli R. Correlates of osteoporosis in chronic obstructive pulmonary disease. *Respir Med* 2000;94:1079–1084.
69. Gluck O, Colice G. Recognizing and treating glucocorticoid-induced osteoporosis in patients with pulmonary diseases. *Chest* 2004;125:1859–1876.
70. McEvoy CE, Ensrud KE, Bender E, Genant HK, Yu W, Griffith JM, Niewoehner DE. Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:704–709.
71. Iqbal F, Michaelson J, Thaler L, Rubin J, Roman J, Nanes MS. Declining bone mass in men with chronic pulmonary disease: contribution of glucocorticoid treatment, body mass index, and gonadal function. *Chest* 1999;116:1616–1624.
72. Katsura H, Kida K. A comparison of bone mineral density in elderly female patients with COPD and bronchial asthma. *Chest* 2002;122: 1949–1955.
73. Shane E, Silverberg SJ, Donovan D, Papadopoulos A, Staron RB, Addesso V, Jorgesen B, McGregor C, Schulman L. Osteoporosis in lung transplantation candidates with end-stage pulmonary disease. *Am J Med* 1996;101:262–269.
74. Jorgensen NR, Schwarz P, Holme I, Henriksen BM, Petersen LJ, Backer V. The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease-A cross sectional study. *Respir Med* 2007;101: 177–185.
75. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int* 2002;13: 777–787.
76. Suissa S, Baltzan M, Kremer R, Ernst P. Inhaled and nasal corticosteroid use and the risk of fracture. *Am J Respir Crit Care Med* 2004;169: 83–88.
77. Lee TA, Weiss KB. Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;169:855–859.
78. Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;343:1902–1909.
79. Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, Ohlsson SV. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *N Engl J Med* 1999;340:1948–1953.
80. Mineo TC, Ambrogi V, Mineo D, Fabbri A, Fabbrini E, Massoud R. Bone mineral density improvement after lung volume reduction surgery for severe emphysema. *Chest* 2005;127:1960–1966.
81. Mokhlesi B, Morris AL, Huang CF, Curcio AJ, Barrett TA, Kamp DW. Increased prevalence of gastroesophageal reflux symptoms in patients with COPD. *Chest* 2001;119:1043–1048.
82. Ducolone A, Vandevenne A, Jouin H, Grob JC, Coumaros D, Meyer C, Burghard G, Methlin G, Hollender L. Gastroesophageal reflux in patients with asthma and chronic bronchitis. *Am Rev Respir Dis* 1987; 135:327–332.
83. Andersen LI, Jensen G. Prevalence of benign oesophageal disease in the Danish population with special reference to pulmonary disease. *J Intern Med* 1989;225:393–402.
84. Casanova C, Baudet JS, del Valle Velasco M, Martin JM, Aguirre-Jaime A, de Torres JP, Celli BR. Increased gastro-oesophageal reflux disease in patients with severe COPD. *Eur Respir J* 2004;23:841–845.
85. el-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. *Gastroenterology* 1997;113:755–760.
86. Roussos A, Philippou N, Krietsepi V, Anastasakou E, Alepopoulou D, Koursarakos P, Iliopoulos I, Gourgoulianis K. Helicobacter pylori seroprevalence in patients with chronic obstructive pulmonary disease. *Respir Med* 2005;99:279–284.
87. Rana JS, Mittleman MA, Sheikh J, Hu FB, Manson JE, Colditz GA, Speizer FE, Barr RG, Camargo CA Jr. Chronic obstructive pulmonary disease, asthma, and risk of type 2 diabetes in women. *Diabetes Care* 2004;27:2478–2484.
88. Manson JE, Ajani UA, Liu S, Nathan DM, Hennekens CH. A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. *Am J Med* 2000;109:538–542.
89. Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *Int J Epidemiol* 2001;30:540–546.
90. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ* 1995;310:555–559.
91. Lazarus R, Sparrow D, Weiss ST. Baseline ventilatory function predicts the development of higher levels of fasting insulin and fasting insulin resistance index: the Normative Aging Study. *Eur Respir J* 1998;12: 641–645.
92. Engstrom G, Janzon L. Risk of developing diabetes is inversely related to lung function: a population-based cohort study. *Diabet Med* 2002; 19:167–170.

93. Engstrom G, Hedblad B, Nilsson P, Wollmer P, Berglund G, Janzon L. Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal cohort study. *J Intern Med* 2003;253:574–581.
94. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM, Insulin Resistance Atherosclerosis Study. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes* 2002; 51:1131–1137.
95. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001;286:327–334.
96. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes* 2004;53:693–700.
97. Chung KF. Cytokines in chronic obstructive pulmonary disease. *Eur Respir J Suppl* 2001;34:50s–59s.
98. Baker EH, Janaway CH, Philips BJ, Brennan AL, Baines DL, Wood DM, Jones PW. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax* 2006;61:284–289.
99. Gudmundsson G, Gislason T, Lindberg E, Hallin R, Ulrik CS, Brondum E, Nieminen MM, Aine T, Bakke P, Janson C. Mortality in COPD patients discharged from hospital: the role of treatment and co-morbidity. *Respir Res* 2006;7:109.
100. Villablanca AC, McDonald JM, Rutledge JC. Smoking and cardiovascular disease. *Clin Chest Med* 2000;21:159–172.
101. Craig WY, Palomaki GE, Haddow JE. Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. *BMJ* 1989;298:784–788.
102. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347: 1557–1565.
103. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005;2:8–11.
104. Lind P, Engstrom G, Stavenow L, Janzon L, Lindgarde F, Hedblad B. Risk of myocardial infarction and stroke in smokers is related to plasma levels of inflammation-sensitive proteins. *Arterioscler Thromb Vasc Biol* 2004;24:577–582.
105. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ, Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J Am Coll Cardiol* 2004;44:720–732.
106. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005;352:1011–1023.
107. John M, Hoernig S, Doehner W, Okonko DD, Witt C, Anker SD. Anemia and inflammation in COPD. *Chest* 2005;127:825–829.
108. Chambellan A, Chailleux E, Similowski T, ANTADIR Observatory Group. Prognostic value of the hematocrit in patients with severe COPD receiving long-term oxygen therapy. *Chest* 2005;128:1201–1208.
109. Mannino DM, Shorr AF, Doyle JJ, Stern LS, Dolgister M, Siegartel LR, Zilberberg MD. Prevalence of anemia in subjects with chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006;3:A615.
110. Halpern MT, Zilberberg MD, Schmier JK, Lau EC, Shorr AF. Anemia, costs and mortality in Chronic Obstructive Pulmonary Disease. *Cost Eff Resour Alloc* 2006;4:17.
111. John M, Lange A, Hoernig S, Witt C, Anker SD. Prevalence of anemia in chronic obstructive pulmonary disease: comparison to other chronic diseases. *Int J Cardiol* 2006;111:365–370.
112. Schonhofer B, Wenzel M, Geibel M, Kohler D. Blood transfusion and lung function in chronically anemic patients with severe chronic obstructive pulmonary disease. *Crit Care Med* 1998;26:1824–1828.
113. Schonhofer B, Bohrer H, Kohler D. Blood transfusion facilitating difficult weaning from the ventilator. *Anaesthesia* 1998;53:181–184.
114. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005;128:2099–2107.
115. Walsh JW, Thomashow BM. COPD and co-morbidities: results of COPD Foundation national survey. Paper presented at: COPD and co-morbidities: treating the whole patient. ATS 2006 San Diego International Conference; 2006 May 19–24; San Diego, CA.
116. Camilli AE, Robbins DR, Lebowitz MD. Death certificate reporting of confirmed airways obstructive disease. *Am J Epidemiol* 1991;133: 795–800.
117. Vilkman S, Keistinen T, Tuuponen T, Kivela SL. Survival and cause of death among elderly chronic obstructive pulmonary disease patients after first admission to hospital. *Respiration* 1997;64:281–284.
118. Keistinen T, Tuuponen T, Kivela SL. Survival experience of the population needing hospital treatment for asthma or COPD at age 50–54 years. *Respir Med* 1998;92:568–572.
119. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005–1012.
120. Waterhouse JC, Fishwick D, Anderson JA, Claverley PMA, Burge PS. What caused death in the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study? [abstract]. *Eur Respir J* 1999;14: 387s.