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Coronary Artery Disease Is Under-diagnosed and Under-treated in Advanced Lung Disease

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Abstract

BACKGROUND—Coronary artery disease is a potentially treatable comorbidity observed frequently in both chronic obstructive pulmonary disease and interstitial lung disease. The prevalence of angiographically proven coronary artery disease in advanced lung disease is not well described. We sought to characterize the treatment patterns of coronary artery disease complicating advanced lung disease and to describe the frequency of occult coronary artery disease in this population.

METHODS—We performed a 2-center, retrospective cross-sectional study of patients with either chronic obstructive pulmonary disease or interstitial lung disease evaluated for lung transplantation. Medications and diagnoses before the transplant evaluation were recorded in conjunction with left heart catheterization results.

RESULTS—Of 473 subjects, 351 had chronic obstructive pulmonary disease, and 122 had interstitial lung disease. In subjects diagnosed clinically with coronary artery disease, medical regimens included a statin in 78%, antiplatelet therapy in 62%, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in 42%, and a beta-blocker in 37%. Ten percent were on no medication from these 4 classes. Fifty-seven percent of these subjects were on an antiplatelet agent as well as a statin, and 13% were on neither. Beta-blockers were less frequently prescribed in chronic obstructive pulmonary disease than interstitial lung disease (23% vs 58%, $P = .007$). Coronary angiography was available in 322 subjects. It demonstrated coronary artery disease in 60% of subjects, and severe coronary artery disease in 16%. Occult coronary artery disease and severe occult coronary artery disease were found in 53% and 9%, respectively. There were no

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significant differences in angiographic results between chronic obstructive pulmonary disease and interstitial lung disease, despite imbalanced risk factors.

CONCLUSIONS—Coronary artery disease is common in patients with advanced lung disease attributable to chronic obstructive pulmonary disease or interstitial lung disease and is under-diagnosed. Guideline-recommended cardioprotective medications are suboptimally utilized in this population.

Keywords

COPD; Coronary artery disease; Interstitial lung disease; Lung transplantation; Pulmonary fibrosis

Chronic obstructive pulmonary disease and interstitial lung disease are both conditions with limited therapeutic options, making the treatment of comorbidities particularly important. Coronary artery disease is a treatable comorbidity observed frequently in both chronic obstructive pulmonary disease[1,2] and interstitial lung disease.[3] It is a leading cause of death in both conditions.[4–8] The primary mechanisms proposed to explain the excess cardiovascular morbidity and mortality observed in chronic obstructive pulmonary disease and interstitial lung disease are similar and include systemic inflammation, hypercoagulability, platelet activation, and oxidative stress.[9,10] Current guidelines place considerable emphasis on antiplatelet agents and statins in patients with uncomplicated coronary artery disease with lesser indications for beta-blockers and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).[11] Guidelines in effect during the time of the study suggested that all patients with coronary artery disease should be treated with antiplatelet agents, beta-blockers, ACE inhibitors, or ARBs and, in most patients, statin therapy.[12]

The prevalence of angiographically proven coronary artery disease in advanced lung disease is not well described. Diagnosis of coronary artery disease in this population can be difficult, as its symptoms may be masked or mimicked by those of lung disease.[13,14] Noninvasive diagnostic modalities are hindered in advanced lung disease, and particularly in chronic obstructive pulmonary disease, by ventilatory limitations to exercise, poor tolerance of pharmacologic agents for stress testing, and poor echocardiographic windows attributable to interference from hyperinflation and cardiac posteromedial rotation.[15] Studies utilizing invasive assessments have mostly consisted of retrospective analysis of angiographic data in patients undergoing coronary angiography based on clinical suspicion of disease.[13,16,17]

Chronic obstructive pulmonary disease and pulmonary fibrosis comprise the 2 leading indications for lung transplantation.[18] The “gold standard” assessment for coronary artery disease in the pretransplant evaluation is coronary angiography, which is routinely performed as a part of clinical evaluation protocols without regard to symptoms or risk factor profiles. We hypothesized that in this advanced lung disease population, coronary artery disease would be common, underdiagnosed, and undertreated. We describe the case rate of coronary artery disease in this population, compare coronary artery disease and its treatment between patients with chronic obstructive pulmonary disease and interstitial lung disease, and assess characteristics associated with the disease and recommended therapies.

METHODS

This retrospective study was approved by the investigational review boards of the Johns Hopkins University and the University of Maryland School of Medicine. Patients over 40 years of age referred for lung transplant evaluation with a diagnosis of chronic obstructive pulmonary disease or interstitial lung disease whose medication lists were available in the prospectively maintained databases of each institution were considered for inclusion. Data

were collected in the context of clinical transplant evaluation protocols. Data abstracted from the medical record included demographics, anthropometrics, pulmonary function, medical comorbidities, medications, lipid profile values, and heart catheterization results. Hypertension, hyperlipidemia, and diabetes were defined by mention of those diagnoses in the medical record. A clinical diagnosis of coronary disease was determined by review of the medical record for mention of that diagnosis before the coronary angiography was performed in the context of the transplant evaluation protocol. Coronary angiography is performed at both sites in patients over 40 years of age as part of the transplant evaluation protocol without regard to symptoms or risk factor profiles. Angiography is generally one of the last tests performed in the transplant evaluation due to the invasive nature of the study, and so is often not done if contraindications to transplant are identified through other testing. Coronary angiographic results were stratified into 3 categories: severe disease, nonsevere disease, and no disease. Severe disease was defined as a stenosis occluding ≥50% of the left main coronary artery, ≥70% of another epicardial artery, or any occlusion for which an intervention was performed.

In presentation of guideline-recommended therapies for coronary artery disease, 4 classes of medication were tabulated and included: statins, beta-blockers, ACE inhibitors or ARBs, and aspirin or clopidogrel. Subjects with a diagnosis of coronary artery disease made before catheterization are herein described as having “clinically apparent” coronary artery disease, whereas those without a prior clinical diagnosis of coronary artery disease who were subsequently found at catheterization to have coronary artery disease are referred to as having “occult” coronary artery disease.

Case Definitions

Chronic obstructive pulmonary disease and interstitial lung disease diagnoses were abstracted from transplant evaluation summary sheets and confirmed by 2-physician review of the medical record. Due to the retrospective limitations of this study, it was not possible to confirm that all subjects diagnosed with idiopathic pulmonary fibrosis met American Thoracic Society consensus criteria.[19] Furthermore, in recognition of the limitations of a clinical diagnosis for subjects with idiopathic pulmonary fibrosis and other interstitial lung diseases,[20,21] end-stage pulmonary fibrotic conditions other than sarcoidosis were included and are referred to in this manuscript as interstitial lung disease.

Statistical Analysis

Continuous data are expressed with median values (inter-quartile range), and categorical data are presented as counts and percentages. Comparison of continuous variables was performed using Wilcoxon rank-sum tests. Categorical variables were compared using chi-squared or Fisher’s exact test. To examine correlates of coronary artery disease, potential confounders were identified based on biological plausibility and review of the literature. Variables with a corresponding *P*-value of .4 or lower in univariate analysis were then examined for inclusion in a multivariate model by using reverse stepwise multiple logistic regression with a threshold for inclusion in the final model of $P < .2$. Statistical significance was defined as a *P*-value ≤.05. Analyses were performed using Stata Statistical Software, Release 11.0 (Stata Corporation, College Station, Tex).

RESULTS

The study group consisted of 473 subjects, 351 with chronic obstructive pulmonary disease and 122 with interstitial lung disease (Table 1). Ninety-six percent of the chronic obstructive pulmonary disease subjects had forced expiratory volume in 1 second (FEV1)% predicted <50%, and 81% had FEV1% predicted <30%. Further pulmonary function assessments are

summarized in Supplementary Table 1 (online). Among interstitial lung disease subjects, 108 (89%) carried a diagnosis of idiopathic pulmonary fibrosis. The remaining 14 subjects carried the following diagnoses: nonspecific interstitial pneumonia (n = 3), acute interstitial pneumonia (n = 1), cryptogenic organizing pneumonia (n = 2), eosinophilic pneumonia (n = 1), interstitial lung disease associated with connective tissue disease (n = 6), and nonsarcoid granulomatous disease (n = 1). Interstitial lung disease subjects were older, more frequently male, had higher body mass indices and more diabetes mellitus. Chronic obstructive pulmonary disease subjects had more tobacco exposure.

Comparative analysis was performed between the group as a whole and the subgroup of subjects in whom angiographic data were available. Principal differences in subjects in whom no angiographic data were available included younger age, less diabetes, less hyperlipidemia, less supplemental oxygen use, less statin use, less pulmonary fibrosis, and less frequently listed for transplantation (Supplementary Table 2, online).

Angiographically Proven Burden of Disease

Coronary angiography revealed coronary artery disease in 60% of subjects. Sixteen percent of the cohort had severe coronary artery disease. All subjects with a clinical diagnosis of coronary artery disease before transplant evaluation who underwent angiography were confirmed to have coronary artery disease. No difference between chronic obstructive pulmonary disease and interstitial lung disease subjects was observed in the frequency of any coronary artery disease (59% vs 63%, $P = .54$) or severe coronary artery disease (15% vs 20%, $P = .54$). Frequency of occult coronary artery disease and occult severe coronary artery disease did not differ between chronic obstructive pulmonary disease and interstitial lung disease, and was found in 53% and 9%, respectively, in the cohort as a whole (Table 2). Results by study site were similar (data not presented). Clinical correlates to occult coronary artery disease were examined (Supplementary Table 3, online) and a multivariable logistic regression model performed poorly in predicting occult coronary artery disease (pseudo R^2 of 0.05).

Cardiovascular Medication Use

Overall, use of cardiovascular medications in subjects with clinically apparent or angiographically proven coronary artery disease was low. Statins were used in 46%, antiplatelet agents in 35%, ACE inhibitors or ARBs in 30%, and beta-blockers in 16%. These rates were only moderately higher than those of the cohort as a whole (Table 1). Compared with chronic obstructive pulmonary disease, a greater proportion of subjects with interstitial lung disease received statins (42% vs 24%, $P < .001$), beta-blockers (21% vs 5%, $P < .001$), and antiplatelet agents (34% vs 21%, $P = .003$) (Table 1). A clinical diagnosis of coronary artery disease was present in a larger proportion of interstitial lung disease subjects (20% vs 10%, $P = .007$).

In those subjects with clinically apparent coronary artery disease, 53% were on 2 or fewer cardioprotective medications, and 10% were on none (Table 3). Fifty-seven percent received both an antiplatelet agent and a statin, whereas 13% received neither. There were no between-group differences in statin prescriptions (78% vs 79%, $P = 1.0$), but beta-blocker therapy was prescribed less often in chronic obstructive pulmonary disease (23% vs 58%, $P = .007$). Calcium channel blocker therapy was prescribed to 37% of chronic obstructive pulmonary disease and 17% of interstitial lung disease subjects; $P = .14$.

Eighty-eight percent of patients with clinically apparent coronary artery disease carried the diagnosis of hypertension or took antihypertensive medications. Among these hypertensive patients with known coronary artery disease, hypertensive medications included ACE

inhibitor/ARB in 47%, beta-blocker in 42%, and calcium channel blocker in 31%. Beta-blockers were used less frequently in the chronic obstructive pulmonary disease patients (25% vs 70%, $P = .003$). Calcium channel blockers were frequently (70%) taken along with ACE inhibitor/ARB, but were taken rarely (19%) along with beta-blockers.

In subjects with severe occult coronary artery disease, cardioprotective medications were underutilized, with 88% of subjects taking 2 or fewer cardioprotective medications and 31% taking none. In this group, 58% used statins, 19% used antiplatelet agents, 15% used statin as well as antiplatelet agents, and 38% received neither. When medication use was compared with the cohort of clinically apparent coronary artery disease, utilization was lower for statins (58% vs 78%, $P = .05$), beta-blockers (8% vs 37%, $P = .008$), and aspirin (19% vs 62%, $P < .0001$).

DISCUSSION

Summary of Findings

In this study, we observe high rates of occult coronary artery disease in patients with advanced lung disease attributable to chronic obstructive pulmonary disease or interstitial lung disease. Guideline-recommended treatments for coronary artery disease were suboptimally utilized overall. Compared with subjects with interstitial lung disease, those with chronic obstructive pulmonary disease were less likely to receive statins, antiplatelet agents, or beta-blocker therapy.

Our results complement those of prior studies showing high rates of coronary artery disease in advanced lung disease[10,22] and are particularly comparable to observations from a smaller cohort of patients undergoing evaluation for lung transplantation.[3] In that study, the frequency of coronary artery disease in idiopathic pulmonary fibrosis was 65.8%, which was similar to the 60% rate observed in our study. The frequency of coronary artery disease observed in subjects with chronic obstructive pulmonary disease in that study, however, was significantly lower than that observed in their idiopathic pulmonary fibrosis cohort at (46.1% vs 65.8%, $P < .03$). In our study, the coronary artery disease rate in chronic obstructive pulmonary disease was similar to that of our interstitial lung disease cohort. The prior study reported the chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis groups to be similar in terms of risk factors for coronary artery disease other than tobacco use, whereas the risk factors for coronary artery disease in our study were imbalanced between groups. The difference between our results and those of this comparable study may reflect regional variations in referral practice, or different thresholds for the transplant selection programs to subject patients to the full transplant evaluation protocol.

Frequency of Occult Coronary Artery Disease

The value of routine angiography in the evaluation of patients for lung transplantation has been questioned based on a prior study concluding that only 8% of results affected medical management.[23] Furthermore, current literature comparing revascularization interventions to optimal medical therapy have demonstrated lack of mortality benefit outside of acute coronary syndromes[24] and lack of benefit before surgery.[25] It is possible that revascularization could actually lead to worse outcomes by virtue of the fact that the majority of patients mistakenly believe revascularization can fix coronary artery disease and reduce cardiovascular risk.[26] Consequently, adherence rates to optimal medical therapy is lower in patients undergoing revascularization.[27] While our study methods did not allow direct quantification of the effect of angiographic results on management, the high rates of occult coronary artery disease coupled with the low rates of optimal medical therapy

observed in our study suggest potential value of routine angiography not for the purpose of revascularization, but for medication optimization. Approximately half of patients not known to have coronary artery disease were found to have some degree of coronary artery disease at catheterization.

Given the imperfect adherence to guideline-recommended therapies in subjects with clinically apparent coronary artery disease, one could question whether the angiographic confirmation of coronary artery disease would substantially alter prescription rates. If these arguably suboptimal rates are nonetheless considered “usual care” in the cohort, the significantly lower rates of statin, beta-blocker, and aspirin use in the subjects with severe occult coronary artery disease imply potential benefit even in a background of imperfect adherence to guideline-recommended therapies.

Cardiovascular Medication Use

While the rates of optimal coronary artery disease treatment in the cohort as a whole were low, the even lower rates in chronic obstructive pulmonary disease compared with interstitial lung disease reaffirms previous observations of under-treatment in this condition, and may represent a major, modifiable risk factor for mortality in this population. Chronic obstructive pulmonary disease is independently associated with worse outcomes after coronary artery bypass surgery[28–31] and after percutaneous coronary interventions.[16,17,29] It has been suggested that underutilization of optimal medical therapy may contribute to this observation.[16]

A single-center study including 10,994 subjects undergoing percutaneous coronary intervention showed chronic obstructive pulmonary disease to be an independent predictor of in-hospital (hazard ratio [HR] 2.51, $P = .001$) and long-term (HR 2.16, $P < .0001$) mortality. In that study, 5.6% fewer chronic obstructive pulmonary disease subjects received beta-blocker therapy ($P < .0001$), despite 6.3% more subjects reporting a history of prior myocardial infarction ($P < .0001$).[17] A multicenter study of 10,908 subjects undergoing percutaneous coronary intervention reaffirmed these findings.[16] In adjusted modeling, chronic obstructive pulmonary disease was independently associated with increased risk of death (HR 1.3, $P = .04$) and revascularization (HR 1.22, $P = .03$) at 1 year. Notably, rates of cardioprotective medication use were significantly lower in the chronic obstructive pulmonary disease group, with 2.9% fewer patients taking aspirin ($P < .001$), 6.8% fewer taking statins ($P < .001$), and 20.5% fewer taking beta-blockers. This was despite a 9.8% higher rate of prior myocardial infarction.

The low rates of beta-blocker use in chronic obstructive pulmonary disease is likely attributable to the misperception among physicians that beta-blockers are not safe or tolerated in this population.[32,33] Data show that cardioselective beta-blockers are well tolerated in chronic obstructive pulmonary disease[34–37] and are associated with lower rates of exacerbations as well as mortality in chronic obstructive pulmonary disease.[38–40] Beta-blockers also are associated with decreased mortality compared with calcium channel-blockers,[41] and guidelines specifically advise that cardioselective beta-blockers should not be withheld because of chronic obstructive pulmonary disease.[14] Our data suggest a suboptimal pattern of favoring calcium channel blockers to beta-blockers in patients with advanced chronic obstructive pulmonary disease, in particular.

The lower rates of statin use in patients with chronic obstructive pulmonary disease compared with those with interstitial lung disease was observed despite higher measured low-density lipoprotein cholesterol levels and may be explained in part by the higher high-density lipoprotein cholesterol levels in patients with advanced chronic obstructive pulmonary disease.[42] These high high-density lipoprotein cholesterol levels likely affect

physician assessment of cardiac event risk, and may dissuade practitioners from prescribing statin therapy. The low rates of statin use overall also may reflect the under-diagnosis of coronary artery disease in this population.

Study Strengths and Limitations

This study carries the limitations of a retrospective study, but is improved by the fact that patients were prospectively enrolled through clinical evaluation protocols. While these protocols are designed to risk-stratify patients with chronic obstructive pulmonary disease or interstitial lung disease through coronary angiography without regards to symptoms or risk profile, the possibility of evaluation bias remains and is supported by the results presented in Supplementary Table 2 (online). The observed differences between the cohort as a whole and the subgroup with angiographic data available were not unexpected, however, as there are numerous contraindications to transplantation[43] that can prevent a referred patient from undergoing the angiographic portion of the transplant evaluation protocol. Occasional patients referred for evaluation are too well to benefit from transplantation and as such would not be subjected to invasive studies. The substantial minority of patients listed for transplant in the cohort without angiographic data suggest either imperfect application of clinical evaluation protocols, a proportion of missing angiographic data, or a combination of both. Due to the retrospective nature of the data, tabulation of reasons for or against the performance of angiography is not possible. Evaluation bias would certainly lead to an enriched sample with higher rates of coronary artery disease found at angiography, but a bias perhaps more likely to affect the observed results is referral bias. It is likely that patients with clinically apparent coronary artery disease are under-referred due to the perception of poor candidacy for transplantation. These patients, or those identified early as poor candidates based on coronary artery disease and thus denied transplantation without generation of a transplant summary sheet, would not be represented in the dataset. This would temper the results by under-representing the true burden of coronary artery disease. Regardless, the angiographic cohort remains a highly selected group of patients, and findings may not be generalizable.

In assessing the appropriateness of therapy for coronary artery disease, we acknowledge the ongoing controversy of whether all patients with known coronary artery disease should be treated with the 4 medication classes presented. The 2006 guidelines, which were the guidelines in effect during the majority of evaluations performed, recommended the consideration of ACE-inhibitor therapy for all patients with coronary artery disease (level 1B). Similarly, beta-blocker use is nearly universally accepted as beneficial after myocardial infarction, but in uncomplicated coronary artery disease, the data are somewhat less compelling and received only a class IIa indication,[12] which recognizes conflicting evidence but asserts that the weight of evidence/opinion is in favor of usefulness/efficacy. The updated 2011 guidelines[11] were not in effect during the period of these evaluations. These new guidelines give class I indications to antiplatelet agents as well as statins, and class II indications for both ACE-inhibitor and beta-blocker therapy in uncomplicated coronary artery disease. Re-evaluation of our data based on these current guidelines with attention to only the class I indications continues to demonstrate room for improvement in cardiovascular care.

As our data do not include a nonpulmonary control group, we can make no direct comparisons of under-treatment compared with a general population of patients with coronary artery disease. It is possible that coronary artery disease is similarly under-diagnosed and under-treated in patients with conditions other than advanced lung disease.

CONCLUSIONS

Coronary artery disease is common in patients with advanced lung disease attributable to chronic obstructive pulmonary disease or interstitial lung disease and is frequently not clinically apparent. Cardiovascular disease complicating advanced lung disease may represent a frequently overlooked opportunity to offer medical treatments with potential to improve survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Finkelstein J, Cha E, Scharf SM. Chronic obstructive pulmonary disease as an independent risk factor for cardiovascular morbidity. Int J Chron Obstruct Pulmon Dis. 2009; 4:337–349. [PubMed: 19802349]
2. Newman AB, Naydeck BL, Sutton-Tyrrell K, Feldman A, Edmundowicz D, Kuller LH. Coronary artery calcification in older adults to age 99: prevalence and risk factors. Circulation. 2001; 104:2679–2684. [PubMed: 11723018]
3. Nathan SD, Basavaraj A, Reichner C, et al. Prevalence and impact of coronary artery disease in idiopathic pulmonary fibrosis. Respir Med. 2010; 104:1035–1041. [PubMed: 20199856]
4. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. Chest. 2005; 128:2640–2646. [PubMed: 16236937]
5. Sin DD, Man SF. Impact of cancers and cardiovascular diseases in chronic obstructive pulmonary disease. Curr Opin Pulm Med. 2008; 14:115–121. [PubMed: 18303420]
6. 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. [PubMed: 14621089]
7. Mannino DM, Etzel RA, Parrish RG. Pulmonary fibrosis deaths in the United States, 1979–1991. An analysis of multiple-cause mortality data. Am J Respir Crit Care Med. 1996; 153:1548–1552. [PubMed: 8630600]
8. Panos RJ, Mortenson RL, Niccoli SA, King TE Jr. Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. Am J Med. 1990; 88:396–404. [PubMed: 2183601]
9. Fimognari FL, Scarlata S, Conte ME, Incalzi RA. 2008. Mechanisms of atherothrombosis in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2008; 3:89–96. [PubMed: 18488431]
10. Kizer JR, Zisman DA, Blumenthal NP, et al. Association between pulmonary fibrosis and coronary artery disease. Arch Intern Med. 2004; 164:551–556. [PubMed: 15006833]
11. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. J Am Coll Cardiol. 2011; 58:2432–2446. [PubMed: 22055990]
12. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update endorsed by the National Heart, Lung, and Blood Institute. J Am Coll Cardiol. 2006; 47:2130–2139. [PubMed: 16697342]
13. Gunes Y, Tuncer M, Guntekin U, et al. Reliability of symptoms suggestive of angina in patients with chronic obstructive pulmonary disease. Arq Bras Cardiol. 2009; 92:334–5. 364. [PubMed: 19629287]

14. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008; 29:2388–2442. [PubMed: 18799522]
15. Falk JA, Kadiev S, Criner GJ, Scharf SM, Minai OA, Diaz P. Cardiac disease in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008; 5:543–548. [PubMed: 18453369]
16. Enriquez JR, Parikh SV, Selzer F, et al. Increased adverse events after percutaneous coronary Iintervention in patients with COPD: insights from the National Heart, Lung, and Blood Institute Dynamic Registry. Chest. 2011; 140:604–610. [PubMed: 21527507]
17. 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. [PubMed: 16169353]
18. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report—2010. J Heart Lung Transplant. 2010; 29:1104–1118. [PubMed: 20870165]
19. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000; 161:646–664. [PubMed: 10673212]
20. Raghu G, Mageto YN, Lockhart D, Schmidt RA, Wood DE, Godwin JD. The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease: a prospective study. Chest. 1999; 116:1168–1174. [PubMed: 10559072]
21. Peckham RM, Shorr AF, Helman DL Jr. Potential limitations of clinical criteria for the diagnosis of idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis. Respiration. 2004; 71:165–169. [PubMed: 15031572]
22. Izbicki G, Ben-Dor I, Shitrit D, et al. The prevalence of coronary artery disease in end-stage pulmonary disease: is pulmonary fibrosis a risk factor? Respir Med. 2009; 103:1346–1349. [PubMed: 19362458]
23. Leibowitz DW, Caputo AL, Shapiro GC, et al. Coronary angiography in smokers undergoing evaluation for lung transplantation: is routine use justified? J Heart Lung Transplant. 1994; 13:701–703. [PubMed: 7947888]
24. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007; 356:1503–1516. [PubMed: 17387127]
25. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med. 2004; 351:2795–2804. [PubMed: 15625331]
26. Rothberg MB, Sivalingam SK, Ashraf J, et al. Patients' and cardiologists' perceptions of the benefits of percutaneous coronary intervention for stable coronary disease. Ann Intern Med. 2010; 153:307–313. [PubMed: 20820040]
27. Kulik A, Shrank WH, Levin R, Choudhry NK. Adherence to statin therapy in elderly patients after hospitalization for coronary revascularization. Am J Cardiol. 2011; 107:1409–1414. [PubMed: 21414595]
28. Clough RA, Leavitt BJ, Morton JR, et al. The effect of comorbid illness on mortality outcomes in cardiac surgery. Arch Surg. 2002; 137:428–432. [PubMed: 11926947]
29. Nishiyama K, Morimoto T, Furukawa Y, et al. Chronic obstructive pulmonary disease—an independent risk factor for long-term cardiac and cardiovascular mortality in patients with ischemic heart disease. Int J Cardiol. 2010; 143:178–183. [PubMed: 19368979]
30. Roques F, Nashef SA, Michel P, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg. 1999; 15:816–822. [PubMed: 10431864]
31. Rosenthal GE, Vaughan SM, Hannan EL. In-hospital mortality following coronary artery bypass graft surgery in Veterans Health Administration and private sector hospitals. Med Care. 2003; 41:522–535. [PubMed: 12665716]
32. Erdmann E. Safety and tolerability of beta-blockers: prejudices & reality. Indian Heart J. 2010; 62:132–135. [PubMed: 21180303]

33. Egred M, Shaw S, Mohammad B, Waitt P, Rodrigues E. Under-use of beta-blockers in patients with ischaemic heart disease and concomitant chronic obstructive pulmonary disease. QJM. 2005; 98:493–497. [PubMed: 15955798]
34. Kotlyar E, Keogh AM, Macdonald PS, Arnold RH, McCaffrey DJ, Glanville AR. Tolerability of carvedilol in patients with heart failure and concomitant chronic obstructive pulmonary disease or asthma. J Heart Lung Transplant. 2002; 21:1290–1295. [PubMed: 12490274]
35. Gold MR, Dec GW, Cocca-Spofford D, Thompson BT. Esmolol and ventilatory function in cardiac patients with COPD. Chest. 1991; 100:1215–1218. [PubMed: 1682112]
36. Camsari A, Arikan S, Avan C, et al. Metoprolol, a beta-1 selective blocker, can be used safely in coronary artery disease patients with chronic obstructive pulmonary disease. Heart Vessels. 2003; 18:188–192. [PubMed: 14520486]
37. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005; (4):CD003566. [PubMed: 16235327]
38. Rutten FH, Zuithoff NP, Hak E, Grobbee DE, Hoes AW. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. Arch Intern Med. 2010; 170:880–887. [PubMed: 20498416]
39. Andrus MR, Holloway KP, Clark DB. Use of beta-blockers in patients with COPD. Ann Pharmacother. 2004; 38:142–145. [PubMed: 14742808]
40. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. N Engl J Med. 1998; 339:489–497. [PubMed: 9709041]
41. Au DH, Bryson CL, Fan VS, et al. Beta-blockers as single-agent therapy for hypertension and the risk of mortality among patients with chronic obstructive pulmonary disease. Am J Med. 2004; 117:925–931. [PubMed: 15629731]
42. Reed RM, Iacono A, Defilippis A, Eberlein M, Girgis RE, Jones S. Advanced chronic obstructive pulmonary disease is associated with high levels of high-density lipoprotein cholesterol. J Heart Lung Transplant. 2011; 30(6):674–678. [PubMed: 21306919]
43. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2006; 25:745–755. [PubMed: 16818116]

CLINICAL SIGNIFICANCE

- Guideline-recommended therapies for secondary prevention of cardiovascular disease are underutilized in advanced lung disease.
- Ten percent of patients with advanced lung disease receive no guideline-recommended medication for known coronary artery disease.
- Over half of patients with advanced lung disease have occult coronary artery disease.

Table 1

Cohort Characteristics

	Cohort (n = 473)	COPD (n = 351)	ILD (n = 122)	*P*-Value
Demographics				
Age at evaluation (years)	59 (54–63)	58 (53–62)	61 (55–66)	.0002
Male sex (%)	47%	42%	61%	<.001
Caucasian race (%)	82%	86%	72%	<.001
BMI	26 (22–30)	25 (22–30)	29 (25–32)	.009
Diabetes mellitus	20%	14%	40%	<.001
Hypertension	52%	50%	55%	.33
Hyperlipidemia	28%	26%	35%	.04
Tobacco exposure (pack-years)	40 (25–70)	50 (35–75)	15 (0–35)	<.0001
Supplemental oxygen (%)	89%	89%	86%	.40
CAD clinical diagnosis	13%	10%	20%	.007
Lipid values				
Total cholesterol (mg/dL)	200 (165–234)	206 (178–243)	176 (147–215)	<.0001
Triglycerides (mg/dL)	103 (70–148)	93 (67–142)	117 (83–160)	.002
HDL-C (mg/dL)	62 (47–79)	69 (53–84)	49 (39–60)	<.0001
LDL-C (mg/dL)	110 (84–137)	114 (86–142)	100 (80–131)	.009
TC/HDL-C	3.1 (2.5–4.0)	2.9 (2.4–3.8)	3.7 (2.7–4.7)	<.0001
Medications				
Statin	29%	24%	42%	<.001
Beta-blocker	10%	5%	21%	<.001
Calcium channel blocker	24%	26%	20%	.20
ACE inhibitor or ARB	23%	22%	26%	.45
Aspirin	23%	20%	32%	0.008
Clopidogrel	3%	1%	7%	0.003

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HDL-C = high-density lipoprotein cholesterol; ILD = interstitial lung disease; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.

Data are expressed as medians (interquartile ranges) or as percentages. *P* values were obtained through Wilcoxon rank sum, chi-squared, or Fisher's exact tests as appropriate, and refer to comparison between COPD and ILD subgroups.

Table 2

Characteristics of Subjects with Available Coronary Angiographic Data

	Cohort (n = 322)	COPD (n = 215)	ILD (n = 107)	*P*-Value
Demographics				
Age at evaluation (years)	59 (54–64)	59 (54–63)	61 (55–66)	.003
Male sex (%)	48%	42%	61%	.001
Caucasian race (%)	82%	87%	71%	<.001
BMI	26 (22–30)	25 (22–30)	30 (26–33)	.003
Diabetes mellitus	24%	15%	41%	<.001
Hypertension	53%	53%	54%	.87
Hyperlipidemia	33%	33%	34%	.80
Tobacco exposure (pack-years)	40 (23–66)	51 (30–75)	15 (0–40)	<.0001
Supplemental O_2 use (%)	91%	93%	86%	.04
CAD clinical diagnosis	15%	13%	20%	.09
Lipid values				
Total cholesterol (mg/dL)	200 (165–233)	206 (173–243)	176 (147–215)	<.0001
Triglycerides (mg/dL)	101 (70–137)	89 (66–123)	116 (83–157)	.0002
HDL-C (mg/dL)	62 (45–79)	70 (54–85)	48 (38–60)	<.0001
LDL-C (mg/dL)	109 (84–137)	112 (85–142)	101 (81–130)	.03
TC/HDL-C	3.1 (2.5–4.0)	2.9 (2.4–3.6)	3.8 (2.7–4.8)	<.0001
Medications				
Statin	33%	30%	42%	.04
Beta-blocker	11%	6%	22%	<.001
Calcium channel blocker	24%	27%	17%	.04
ACE inhibitor or ARB	24%	23%	25%	.80
Aspirin	25%	22%	32%	.07
Clopidogrel	3%	1%	6%	.02
Coronary angiography				
CAD	60%	59%	63%	.54
Nonsevere CAD	44%	44%	43%	
Severe CAD	16%	15%	20%	
	Cohort (n = 274)	COPD (n = 188)	ILD (n = 86)	
Coronary angiography in subjects without clinically apparent CAD				
Occult CAD	53%	53%	53%	.96
Occult Severe CAD	9%	9%	12%	.41

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HDL-C = high-density lipoprotein cholesterol; ILD = interstitial lung disease; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.

Data are expressed as medians (interquartiles ranges) or as percentages. *P* values were obtained through Wilcoxon rank sum, chi-squared, or Fisher's exact tests as appropriate.

Table 3

Cardiovascular Medication Use

Clinically Apparent CAD*	Cohort (n = 60)	COPD (n = 36)	ILD (n = 24)	*P*-Value
Statin	78%	78%	79%	1.0
Beta-blocker	37%	23%	58%	.007
Calcium channel blocker	29%	37%	17%	.14
ACE inhibitor or ARB	42%	47%	33%	.42
Aspirin	62%	58%	67%	.59
Clopidogrel	15%	11%	21%	.46
Cardioprotective medications prescribed†				
0	10%	14%	4%	.14
1	13%	8%	21%	
2	30%	39%	17%	
3	38%	33%	46%	
4	8%	6%	13%	
	Cohort (n = 26)	COPD (n = 16)	ILD (n = 10)	
Severe occult CAD‡				
Statin	58%§	50%	70%	.43
Beta-blocker	8%§	6%	10%	1.0
ACE inhibitor or ARB	31%	25%	40%	.67
Aspirin	19%§	19%	20%	1.0
Clopidogrel	4%	0%	10%	.39
Cardioprotective medications prescribed†				
0	31%	31%	30%	.09
1	38%	50%	20%	
2	19%	6%	40%	
3	8%	13%	0%	
4	4%	0%	10%	

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease.

Percentages are rounded to the nearest decimal.

*Clinically apparent coronary disease refers to the subjects who carried the diagnosis of coronary artery disease before undergoing coronary angiography in the clinical evaluation protocol.

†Cardioprotective medication counts assigned up to 4 points for the following medications: statin, beta-blocker, ACE inhibitor or ARB, and aspirin or clopidogrel.

‡Severe CAD was defined as a stenosis occluding ≥50% of the left main coronary artery, ≥70% of another epicardial artery, or any occlusion for which an intervention was performed.

§$P = .05$ compared with frequency of use in clinically apparent CAD cohort.