Depression: Beyond Description As an Important Comorbidity in Pulmonary Arterial Hypertension—The Next Steps

Deborah H. McCollister, RN, BSN
Lead Clinical Research Coordinator
Pulmonary Hypertension Center
University of Colorado Denver
Aurora, CO

Philippe Weintraub, MD
Psychiatry
University of Colorado Denver
Aurora, CO

David B. Badesch, MD
Professor of Medicine
Clinical Director
Pulmonary Hypertension Center
University of Colorado Denver
Aurora, CO

The recent identification of depression as an important comorbidity in pulmonary arterial hypertension (PAH)[1,2] is leading to a broad array of efforts to further refine our understanding of this disorder, enhance patient and provider education about it, and encourage prompt recognition, appropriate diagnosis, and treatment of affected individuals. We will provide an update on the nature and extent of the problem, and describe ongoing and future efforts to address this very important determinant of quality of life and possible long-term outcome in patients with PAH.

PAH is a rare and debilitating disease characterized by progressive increases in pulmonary arterial pressure and pulmonary vascular resistance, leading to right ventricular failure and death.[3-7] As there is no cure, the primary goal of disease management remains to alleviate symptoms and prolong survival. Although treatment of patients with PAH with agents such as prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors have been shown to improve exercise capacity,[7,8] many patients still experience diminished quality of life, severe limitations in mobility requiring lifestyle modifications, and the potential for social isolation. The substantial physical burden imposed by PAH may result in loss of employment, adding to concern about paying for expensive therapies. Thus, patients with PAH frequently accumulate a number of life stressors that have been associated with, and make them more vulnerable to, development of depression.[9]

According to the World Health Organization (WHO), depression is the leading cause of disability as measured by years lived with a disability, and organizations such as the Institute of Medicine emphasize that depression screening and treatment should be a priority for US medicine in the 21st century.[10] Patients with depression and/or chronic illnesses, such as poorly controlled diabetes[11,12] and cardiovascular disease,[13-15] have an increased risk of adverse outcomes and high health care costs.[16] Recognizing the complex interplay between depression and chronic medical illness, and addressing it with collaborative interventions involving nurses who provide guideline-based patient-centered simultaneous management of depression and chronic disease has been shown to improve outcomes.[16]

Applying what has been learned about the interaction between chronic medical disease and depression to patients with PAH will likely improve treatment response and the quality of our patients' lives.

HIGH PREVALENCE OF COMORBID DEPRESSION IN PAH

A study performed at 2 large PAH referral centers showed that depression is common in PAH patients, with 55% of subjects demonstrating depressive symptoms.[2] This study utilized a simple and well-validated instrument, the Patient Health Questionnaire-8 (PHQ-8),[17] to determine the prevalence and severity of depressive symptoms in patients with PAH. The PHQ-8 is a useful measure for establishing the presence of depressive symptoms in primary care patients and those with medical illness; it also has the capability of identifying not only those with major depressive disorder (MDD) but "at-risk" patients with clinically significant subsyndromal depression that may also need treatment.

Data from the REVEAL registry, a multicenter observation cohort study of

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Correspondence: Deb.McCollister@ucdenver.edu
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WHO Group I PAH, demonstrated that 25% of patients report a history of depression.[18] This registry relied on self-reporting a history of depression, as opposed to utilization of a standardized instrument like the PHQ-8, which has good sensitivity and specificity for the detection of depressive symptoms. The difference between this self-reported frequency of a history of depression elicited in a nonstandard way, and the much higher prevalence of depressive symptoms detected using a measure like the PHQ-8, illustrates the importance of using well-validated instruments when performing routine screening of PAH patients for depressive symptoms.

Another interesting recently reported finding from the REVEAL registry was that depression occurred more frequently among females than males with PAH.[19] This finding highlights the particular importance of screening women with PAH for the presence of depressive symptoms.

THE EFFECT OF DEPRESSION IN PAH

Even with the likely underestimate of depressive symptoms using unsystematically obtained self-report data in the REVEAL registry,[18] an analysis showed that of the most frequent comorbid conditions experienced by PAH patients (including hypertension, thyroid disease, and obesity), clinical depression is the strongest predictor for the development of medical disability.[20] Another study describing the human responses to PAH found that it produced anxiety, depression, panic attacks, impairments in cognition and memory, and reductions in physical functioning.[21] The adverse effects of depression on PAH may also be mediated by sleep disturbances. A recent study by Batal et al suggests that poor sleep quality is common in patients with pulmonary hypertension (PH) and correlates with depression, dyspnea, and poor quality of life.[22]

Undiagnosed comorbid depression makes it difficult for the provider to properly evaluate the patient,[23] and likely decreases treatment adherence. The presence of depression might also affect reporting of symptoms and make it more difficult for the provider to determine the correct plan of care. Furthermore, the presence of depression might interfere with functional assessment of the patient. For example, the utility of the 6-minute walk test, which is one of the noninvasive standards for evaluating functional capacity in PH, may be reduced in individuals with comorbid depression because slower walking may be due not only to worsening disease but also lack of motivation from depression, which may, additionally, cause reduced compliance with taking medications. These confounding effects of depression on test performance may lead to an erroneous impression of worsening disease and the consequent unnecessary prescription of expensive therapies with potential side effects.

In summary, the interplay between PAH and depression is complex and multifaceted, with the potential for important negative effects on medical disability, medication adherence, reporting of functional status, sleep quality, and emotional responses to the disease. The development of depressive symptoms likely has an important effect on quality of life, and may also prove to affect outcomes, such as survival, although further studies are needed to determine if this is true.

ARE WE DOING WHAT IS NECESSARY TO PROMPTLY DIAGNOSE DEPRESSION IN PATIENTS WITH PAH?

In spite of the frequency of depression as a comorbidity in patients with PAH, formal screening and treatment of depressive disorders is not currently a common practice in most PH referral centers.[23,24] A majority of patients are seen in their respective PH clinics every 3 to 6 months, making the PAH provider well positioned to recognize and address concurrent psychiatric illness. Unfortunately, however, inadequate assessment for depression and other comorbid psychiatric disorders is the rule rather than the exception. In a busy PH practice, clinic time with each patient is limited, patients need to be assessed rapidly, tests need to be ordered, and very little time remains to be spent addressing the patient's psychosocial needs. In addition, PAH providers may lack the training to adequately address their patients' psychiatric disorders.

POTENTIAL EFFECT OF A SCREENING INSTRUMENT FOR DETECTION OF DEPRESSIVE SYMPTOMS IN PAH

Routine screening of PH patients for depression is likely to improve detection of depression in this patient population.[23] Without a plan for screening and referral, depression may be underdiagnosed and undertreated by PAH providers. Our recent study[2] found that 69% of patients with mild-to-moderate depressive symptoms were not on antidepressant therapy, and 50% of patients with severe depressive symptoms were not taking an antidepressant. Patients who are emotionally distressed may choose not to seek help for fear of stigmatization, or they may wish to attempt to solve the problem on their own. Depression may be insidious in onset, and patients as well as providers may struggle to discriminate between changes in mood and changes in their state of health. Patients followed for years in their PH clinic may transition through different stages of coping with their disease, and ongoing assessment is necessary to detect these potentially important changes, which often represent the onset of depression and/or other psychiatric disorders.

Several simple screening tools exist for the detection of depressive symptoms, including the 2-, 8-, and 9-item Patient Health Questionnaires (PHQ-2, PHQ-8, and PHQ-9).[17,25,26] The PHQ-8 and -9 have been found to be both sensitive and specific for diagnosing major depressive disorder. These tools take only several minutes to administer and could be integrated into standard inpatient and outpatient evaluations. Patients can complete the questionnaire while in the waiting room, and the provider can then review the results.

THE EMERGING IMPORTANCE OF PATIENT-REPORTED OUTCOMES IN CLINICAL RESEARCH

Although much of the care we provide our PAH patients is focused on increasing longevity, many of our treatments are specifically designed to improve symptoms

and function, 2 essential components of health-related quality of life. In most cases, the best way to measure symptoms and functional status is by direct patient query. In contrast to self-evident outcomes of illness such as survival, patient-reported outcomes (PROs) represent the patient's perspective on the influence of disease and its treatment on his or her everyday functioning and well being. By definition, PROs are a measurement of any aspect of a patient's health status that comes directly from the patient (ie, without the interpretation of the patient's responses by a physician or other care provider).[27]

While quality of life assessments have been used for years as secondary outcome measures in clinical trials, including some of those in PAH,[28-33] such assessments may be underutilized in the application of evidence-based therapy. Patient-reported outcome measures (PROMs) provide a means of gaining insight into the way patients perceive their health and the affect of treatments or adjustments to lifestyle on their quality of life. Patients can complete these assessments. PROMs have been used in the management of a variety of disease states, and their application in the area of PAH is likely to increase. Since depression can have significant influence on quality of life in patients with PAH, it will be important to determine what patients report in terms of the effects of their medical disease on mood, appetite, happiness, and satisfaction.

The development of an effective PRO instrument depends on its ability to measure what it sets out to measure, and whether it can be demonstrated to be valid, reliable, sensitive, and specific. Because of the time, effort, and cost associated with creating a new PRO instrument, PRO instruments used in PAH are generally borrowed from those used for other disease states. Examples of PROs that have commonly been used in PAH clinical research studies include the Short Form 36 (SF-36),[34,35] the Minnesota Living with Heart Failure Questionnaire (MLHFQ),[36] and the EuroQol (EQ-5D),[37] to name a few. While these generic tools enable comparisons to be made across disease states, a more sensitive and specific tool for health-related quality of life might address the unique challenges our patient population faces. A more recently developed and approved PRO is the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR),[38] the first of its kind to be developed exclusively with the PAH patient in mind. Of most importance for any future PAH instrument developed will be its ability to detect change in reported outcomes over time. In PAH patients, change in functioning may be gradual, and an instrument sensitive to this change would be useful in determining longitudinal effect on decline or improvement.

With the release of the 2006 US Food and Drug Administration's Guidance for Industry document entitled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims," there has been an increasing visibility of these measures in clinical trials. For example, between January 2005 and December 2008, Rahimi et al reported an increase of nearly double to 16% for the number of cardiovascular disease studies that utilized PROs.[39] We are likely to see this same trend in PAH clinical trials, as benefits that are considered meaningful to a patient can be viewed as valuable to the success of a newly developed drug and its maker. Nonetheless, the importance lies in the increased recognition and evaluation of previously underrecognized outcomes such as quality of life.

INTERNATIONAL INTEREST IN THE RECOGNITION OF DEPRESSION IN PAH

Recognizing the important influence that depression and general distress can have as a comorbidity in PAH, the Pulmonary Hypertension Association (PHA) has recently initiated an international survey studying emotional effect in this disease state. This project has leadership in Europe and the United States, and will hopefully lead to a better understanding of what patients sense as the effect of depression on their ability to cope with PAH. The key research objective is to understand the emotional effect of living with PAH, both from a patient's and a caregiver's perspective. These qualitative insights will feed into an online quantitative survey that will be designed to allow for the quantification of these needs. Ultimately, the objective will be to empower affected persons to not only recognize the attendant emotional needs of PAH, but to make them aware that help is available.

REFERRAL FOR CARE OF DEPRESSION

The practice of universal depression screening of PH patients should be accompanied by a plan for referral for further evaluation and treatment if needed. This might involve communication with the patient's primary care provider, or perhaps referral to a specialist, such as a psychiatrist. Such a plan ensures that affected patients would undergo a more thorough evaluation for depression, and would have resources available for treatment if needed, including pharmacologic and/or psychotherapeutic options. The choice of therapy may depend on available resources and patient preferences. An important component of any evaluation includes assessment of risk for suicide, which is a major complication of depression.

Colleagues in the area of oncology are taking the lead in recognizing the importance of prompt recognition and referral of psychosocial issues. Starting in 2012, all cancer programs seeking accreditation from the American College of Surgeons Commission on Cancer (CoC) will be required to screen and evaluate patients to identify psychosocial issues impeding patient progress during treatment and survivorship. The new standard will additionally require that all CoC-accredited oncology programs either have psychosocial services onsite or be equipped to link patients to the proper resources.[40]

TREATMENT

When a patient is found on screening to have symptoms suggestive of clinically significant depression, a system to ensure appropriate evaluation, treatment, and follow-up is essential.[23] Because of the stigma often associated with a diagnosis of depression and mental disorders in general, it is important for the provider to

provide psycho-education to the patient, emphasizing that, like PAH, depression is a medical illness with significant morbidity and mortality, as well as being a potential risk factor for worse prognosis of the primary medical illness. It should also be identified to patients that recovering from depression is not simply a question of will since it is believed, based on current research data, that genetic, biological, psychological, and/or social factors can lead to brain abnormalities, as in nonpsychiatric disorders, that cannot be alleviated without treatment.

Patients suspected of having depression on screening should undergo a formal evaluation to establish if a depressive disorder is present and determine the appropriate type and level of treatment when clinically indicated. An important component of any evaluation includes assessment of risk for suicide, which is a major complication of depression. In addition, depressed individuals frequently suffer from other psychiatric illnesses, such as anxiety disorders and substance dependence, which may be contributing to or exacerbating the depression.

Given the heterogeneity in the types of factors leading to depression, the wide range in depression severity, the tremendous variability in treatment response, and the higher rates of treatment resistance in those with chronic medical illness, multiple treatment options need to be available to optimally treat each patient. To some extent, choice of psychotherapy and/or medications may depend on available resources and patient preferences. In addition, providers vary in their knowledge and comfort level when it comes to prescribing antidepressant medication for their patients.

For many milder cases of depression requiring only medication management, the primary care physician may be able to provide treatment. In more complex, severe cases with extensive psychiatric comorbidity and concerns about suicide, referral to a psychiatrist or other mental health professional is indicated. In some practices, there are mental health professionals onsite to evaluate and treat patients. In other settings, close relationships are sometimes forged between primary care physicians and mental health professionals, which can help to effectively coordinate the treatment of the patient's primary medical illness and comorbid depression.

Currently, there are multiple FDA-approved medications for treatment of major depressive disorder, and psychosocial treatments, such as cognitive-behavioral therapy and interpersonal therapy, have been shown to be highly efficacious in the treatment of this illness.

Promising new interventions with less of an evidence base are also proliferating and should be considered as possible interventions. For example, there has been a growing recognition that patients with severe, chronic medical illnesses may benefit from support groups in which other individuals with the same illness can have a positive therapeutic effect because of their capacity to have empathy for the patient's suffering that only comes from having the same illness. Other individuals with the illness may also be able to offer guidance on how they have learned to cope with many of the challenges that individuals with PAH face. And in the age of the Internet, online chat rooms may also enable patients to share their experiences and decrease their sense of isolation.

Another promising, potentially beneficial new intervention for depression is exercise, which has also been shown to reduce stress and anxiety.[41] The REVEAL registry shows that some of our patients are overweight, with an average BMI of 28.9.[18] A randomized, 15-week, closely monitored program of daily exercise done in patients with severe PH was completed by Mereles at al,[42] and showed that exercise capacity and quality of life can be significantly enhanced using an exercise training program. Accordingly, it is logical to presume that exercise may be efficacious for the treatment of comorbid psychiatric disorders experienced by our patients, but future studies are needed to assess its efficacy and safety in patients with PAH and to determine the best type and intensity of exercise that will optimally alleviate symptoms of depression in our patients.

Another important aspect of successful treatment of depression in PAH is the coordination of care for both medical and psychiatric disorders. A recent study by Katon el al[16] illustrates the importance of collaborative intervention involving proactive follow-up by nurse care managers working closely with physicians, integrating the management of medical and psychological illnesses, and using individualized treatment regimens guided by treat-to-target principles. By using such a strategy, each patient has an individualized care plan and target goal to reach. Treatment protocols guide the adjustments of commonly used medicines, and increased nursing support is provided for self-care in patients who do not achieve their specified goals. For example, the authors utilized the PHQ-9 scale to evaluate depression. If upon evaluation, a patient fails to show an improvement in depression symptoms by means of PHQ-9 score, the health care team intervenes, providing education that encompasses self-monitoring, behavioral activation, goal setting, and problem solving to improve medication adherence and self-care. The patient then receives self-care materials such as a depression manual and video on depression care, a booklet and other materials on chronic disease management, and self-monitoring devices appropriate to his or her chronic condition. Weekly case management team meetings with nurses and providers present allow for review of medications and adjustment if necessary to achieve the patient's specific clinical goals. Such intervention improved medical outcomes and depressive symptoms in depressed patients with diabetes, and/or coronary heart disease.

THE FUTURE

Important unanswered questions include: What are the associations between depressive symptoms and functional capacity? Is depression a risk factor for worsening PAH, as has been shown in heart failure, a secondary event elicited by the inevitable decline in functional capacity, or can it be both a cause of and reaction to advancing illness? Would treatment of depression in PAH make a difference in survival? If, as has been found in left heart disease, the occurrence of depressive

symptoms in patients with PAH has a significant influence on functional status and quality of life, as well as risk for worsening of symptoms, early detection of depression and implementation of appropriate treatment could have a significant effect on overall outcomes in our patients. Is there a preferred medication treatment for PAH patients? Are nondrug therapies (ie, cognitive-behavioral therapy, interpersonal therapy, supportive therapy, psycho-education, support groups, pulmonary rehabilitation, counseling) as effective or more so than drug therapy in our patients? Is a combination of medication and psychosocial treatments necessary to achieve good outcomes as has been shown in certain subgroups of depressed individuals without medical illness?

CONCLUSION

The recent identification of depression as an important comorbidity in patients with PAH mandates the development of interventions for this disorder based on what we have learned about the adverse effect of depression on treatment outcome for other chronic medical illnesses. Increased awareness through patient and provider education, formal screening, prompt recognition, accurate and timely diagnosis, appropriate referral, and a collaborative, coordinated approach to treatment of patients with depressive symptoms will likely improve their quality of life.

References

1. Löwe B, Gräfe K, Ufer C, et al. Anxiety and depression in patients with pulmonary hypertension. *Psychosom Med*. 2004;66(6):831-836.
2. McCollister DH, Beutz M, McLaughlin V, et al. Depressive symptoms in pulmonary arterial hypertension: prevalence and association with functional status. *Psychosomatics*. 2010;51(4): 339-339.e8.
3. Simonneau G, Rubin LJ, Galiè N, et al; PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med*. 2008;149(8):521-530.
4. Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med*. 2004;351(16):1655-1665.
5. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. *Circulation*. 2006;114(13): 1417-1431.
6. McLaughlin V, Humbert M, Coghlan G, Nash P, Steen V. Pulmonary arterial hypertension: the most devastating vascular complication of systemic sclerosis. *Rheumatology (Oxford)*. 2009;48(Suppl 3):iii25-iii31.
7. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009; 53(17):1573-1619.
8. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest*. 2007; 131(6):1917-1928.
9. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry*. 1999;156(6):837-841.
10. Adams K, Corrigan JM (eds.). Priority Areas for National Action: Transforming Health Care Quality. Washington, DC: The National Academies Press, 2003.
11. Mezuk B. Depression and type 2 diabetes mellitus: a call to explore the common cause hypothesis. *Arch Intern Med*. 2011;171(11):1040-1041.
12. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care*. 2008;31(12):2383-2390.
13. Lippi G, Montagnana M, Favaloro EJ, Franchini M. Mental depression and cardiovascular disease: a multifaceted, bidirectional association. *Semin Thromb Hemost*. 2009;35(3):325-336.
14. Rumsfeld JS, Havranek E, Masoudi FA, et al; Cardiovascular Outcomes Research Consortium. Depressive symptoms are the strongest predictors of short-term declines in health status in patients with heart failure. *J Am Coll Cardiol*. 2003;42(10):1811-1817.
15. Rumsfeld JS, Magid DJ, Plomondon ME, et al. History of depression, angina, and quality of life after acute coronary syndromes. *Am Heart J*. 2003; 145(3):493-499.
16. Katon WJ, Lin EH, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med*. 2010;363(27):2611-2620.
17. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord*. 2009;114(1-3):163-173.
18. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest*. 2010; 137(2):376-387.
19. Shapiro S, Traiger GL, Turner M, McGoon MD, Wason P, Barst RJ. Gender Differences in the Diagnosis, Treatment, and Outcome of Patients With Pulmonary Arterial Hypertension Enrolled in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL). *Chest*. 2011 Jul 14. [Epub ahead of print]
20. Hill W, Abbott C, Durst L, et al. Predicting Medical Disability In Patients With Pulmonary Arterial Hypertension. *Am J Respir Crit Care Med.* 2011;183:A5940.
21. Matura LA, Carroll DL. Human responses to pulmonary arterial hypertension: review of the literature. *J Cardiovasc Nurs*. 2010;25(5):420-427.
22. Batal O, Khatib OF, Bair N, Aboussouan LS, Minai OA. Sleep quality, depression, and quality of life in patients with pulmonary hypertension. *Lung*. 2010;189(2):141-149.
23. McCollister DH, Weintraub P. Depresion and pulmonary arterial hypertension: Should we be screening for depressive symptoms? *Adv Pulmonary Hypertens*. 2010;8(4):223-227.
24. McCollister DH. Screening pulmonary hypertension patients for depression. *Int J Clin Pract Suppl*. 2011;(174):4-5.
25. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.
26. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care*. 2003;41(11):1284-1292.
27. Food and Drug Administration. Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *Federal Register*. 2009;74:65132-65133.
28. Gihl A. Health-related quality of life in pulmonary arterial hypertension. *Adv Pulmonary Hypertens*. 2010;8(4):215-222.
29. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med*. 1996; 334(5):296-302.
30. Olschewski H, Simonneau G, Galiè N, et al; Aerosolized Iliprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med*. 2002;347(5):322-329.
31. Simonneau G, Barst RJ, Galie N, et al; Treprostinil Study Group. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002; 165(6):800-804.
32. Barst RJ, Langleben D, Frost A, et al; STRIDE-1 Study Group. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2004;169(4):441-447.
33. Galiè N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol*. 2005;46(3):529-535.
34. Stewart AL, Hays RD, Ware JE Jr. The MOS short-form general health survey. Reliability and validity in a patient population. *Med Care*. 1988; 26(7):724-735.
35. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual

framework and item selection. *Med Care*. 1992; 30(6):473-483.
36. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. *Am Heart J*. 1992;124(4):1017-1025.
37. EuroQol–a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy*. 1990;16(3):199-208.
38. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res*. 2006;15(1):103-115.
39. Rahimi K, Malhotra A, Banning AP, Jenkinson C. Outcome selection and role of patient reported outcomes in contemporary cardiovascular trials: systematic review. *BMJ*. 2010;341:c5707.
40. American College of Surgeons. Cancer Program Standards 2012: Ensuring Patient-Centered Care. http://www.facs.org/cancer/coc/programstandards2012.html. Accessed January 22, 2012.
41. Dunlop BW, Self RL. Exercise for depression: efficacy, safety and clinical trial implications. *Psychopharmacol Bull*. 2008;41(4):65-75.
42. Mereles D, Ehlken N, Kreuscher S, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation*. 2006; 114(14):1482-1489.