Experts analyze the New ACCP Clinical Practice Guidelines

Pulmonary Arterial Hypertension: Diagnostic Considerations

[Editor's note: Editor-in-Chief Victor Tapson, MD, interviewed a select panel of experts in pulmonary hypertension to obtain their review and comments on the new evidence-based clinical practice guidelines of the American College of Chest Physicians. Please see the Editor's Memo for more information.]

Echocardiography

The American College of Chest Physicians (ACCP) Clinical Practice Guidelines emphasize the use of echocardiography in pulmonary arterial hypertension (PAH) with much of the discussion involving the estimate of right ventricular systolic pressure. There is a bit less focus on the use of echo to evaluate right ventricular size and function and how to best evaluate these parameters. Though there may not be large, prospective trials for an evidence base, can you give us your thoughts on how you think we should assess the right ventricle? Dr Hinderliter, do you believe that these recommendations or future research should focus more on how to characterize right ventricular function so it can be more consistently implemented in clinical practice?

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As indicated in the ACCP consensus guidelines, Doppler echocardiography is the "test of choice" for noninvasive measurement of pulmonary arterial pressure in patients in whom PAH is clinically suspected. In studies performed by experienced sonographers, pulmonary arterial systolic pressure can be accurately estimated from the velocity of the tricuspid regurgitant jet in most (though not all) patients. Similarly, a comprehensive echocardiogram is invaluable in assessing cardiac causes of PAH, such as left ventricular systolic or diastolic dysfunction, valvular heart disease, or intracardiac shunts. Echocardiography is strongly recommended for these indications.

Less widely recognized—and probably underemphasized in the clinical practice guidelines—is the value of echocardiography in assessing end-organ manifestations of severe PAH. Right ventricular failure is the most common cause of death in patients with PAH, and the results of several observational studies suggest that echocardiographic evaluation of right ventricular structure and function can provide important prognostic information.[1-3] Investigators at the Mayo Clinic have developed a Doppler-derived index of right ventricular myocardial performance that represents the sum of isovolumetric contraction and relaxation times divided by the ejection time. When retrospectively measured in 53 patients with idiopathic PAH, this index of global right ventricular function was a potent and independent predictor of cardiac death and lung transplantation.[1]

Abnormalities in the Doppler flow velocity patterns of right ventricular ejection (due to increased right ventricular impedance) and left ventricular filling (due to abnormal ventricular interaction) are common findings in patients with severe PAH. In a cohort of 26 patients with PAH described by Eysmann et al[2] a short right ventricular acceleration time (<62 ms) and a ratio of early to late transmitral flow velocities (E/A) <1 were associated with reduced survival. Raymond et al[3] reported that two structural manifestations of right ventricular decompensation—right atrial enlargement and displacement of the ventricular septum—were indicative of a poor prognosis in 81 patients with idiopathic PAH and Class III or Class IV symptoms. A planimetered right atrial area in the apical four-chamber view exceeding 20 cm^2/m and a value >2 for the end-diastolic eccentricity index—a simple measure of septal displacement measured from the parasternal short axis view—were associated with a 2-year mortality of between 40% and 50%. The presence of a pericardial effusion, a common finding in patients with severe PAH that reflects an elevated right atrial pressure, was a powerful and independent predictor of mortality in the studies by both Eysmann et al and Raymond et al.

Several important limitations of these studies should be acknowledged. They were relatively small; they evaluated patients with idiopathic PAH, and their relevance to patients with PAH associated with portal hypertension, collagen vascular disease, or other systemic disease is unclear; they were conducted in an era when our therapeutic armamentarium for treating PAH was limited; and they did not evaluate a number of novel measures of right ventricular function (eg, tricuspid annular velocity by tissue Doppler[4]) and cardiac remodeling (eg, the relative sizes of the right and left ventricles[5]) of potential value. Nonetheless, the very consistent theme that has emerged is that echocardiographic evidence of right ventricular failure is an ominous finding. Additional research to further define the role of echocardiography in assessing prognosis and guiding therapy in patients with PAH would be of value.

In patients with severe idiopathic PAH, however, there is ample evidence to support a comprehensive echocardiographic examination to assess the extent of target organ disease as an important component of the routine evaluation. The assessment by an experienced echocardiographer of the degree of right ventricular enlargement and dysfunction, utilizing simple measures—the presence of a pericardial effusion, an E/A ratio <1, a right ventricular acceleration time <62 ms, a planimetered right atrial size >20 cm^2/m, and a diastolic eccentricity index <2—or more complex parameters, such as the Doppler right ventricular index, can complement the clinical evaluation in assessing prognosis and guiding therapy.

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The Role of Electrocardiography

Dr Ahearn, do you agree with the ACCP recommendation that, in patients with a suspicion of PAH, electrocardiography should be performed to screen for cardiac anatomic and arrhythmic problems though it lacks sensitivity as a screening tool for PAH, but contributes prognostic information in patients with known PAH?

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Electrocardiography is a noninvasive, widely available test that should be performed in all patients with cardiovascular complaints. In patients with established PAH, electrocardiography has a limited role in monitoring patients except for acute arrhythmic and ischemic events. In patients undergoing evaluation of their symptoms, however, it is important to recognize the limitations of the test. In our investigation of 61 patients with significant PAH, 8 (13%) had normal findings on electrocardiography, though these patients tended to have less severe disease. Other common electrocardiographic indicators correlated poorly with hemodynamic and clinical parameters. Thus, the ACCP recommendation that electrocardiography is inadequate as a screening tool is correct.

The most definitive prognostic information available on electrocardiography in PAH comes from a study by Bossone and colleagues in which they retrospectively analyzed the initial electrocardiographic findings in 51 untreated patients with PAH.[1] Despite the limitations of this type of study design, these data suggest that electrocardiographic findings consistent with right ventricular hypertrophy bode a worse prognosis. No meaningful data are available on the use of electrocardiography to monitor response to treatment.

In summary, I agree with the ACCP recommendations on the use of electrocardiography. A key point is that electrocardiography is an inadequate tool to exclude PAH. Electrocardiographic criteria for right ventricular hypertrophy can be of prognostic significance, but these probably do not add much

value to other more robust predictors of mortality (for example, hemodynamic values and exercise capacity). There is no established role for electrocardiography in monitoring PAH therapy.

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Implantable Hemodynamic Monitoring

Preliminary work with the use of implantable hemodynamic monitoring devices in PAH is very exciting. Because there is not yet enough evidenced-based work in the form of large clinical trials with these devices, there was no discussion about them in the ACCP recommendations. Dr. Benza, you have been very involved with research in this area. What has your experience been thus far? Do you think they have a future for the PAH patient? If so, what kind of patient would you consider?

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The impaired vascular compliance caused by PAH leads to a progressive increase in pulmonary vascular resistance. As a result, right ventricular pressure and afterload dramatically increase, leading to eventual right heart failure. It is this decline in right ventricular performance that closely ties to mortality in patients with PAH and that is best predicted by serial assessments of hemodynamics. Unfortunately, these serial assessments require frequent invasive procedures that affect patient comfort and are costly. The ability to reliably measure these hemodynamic parameters on line without repeated procedures would, therefore, be a significant advancement in the field. Let me offer some background about this technology and how it can be used. I will include a few selected references also.

The Chronicle® (Medtronic, Inc., Minneapolis, Minnesota) consists of an implantable hemodynamic monitor (IHM) with a memory for continuous storage of data from a pressure sensor lead (Medtronic, Inc.) positioned in the right ventricle. Continuous hemodynamic variables such as right ventricular systolic, diastolic, and estimated pulmonary artery diastolic pressure, pre-ejection and systolic time intervals, as well as heart rate are derived by the IHM from each cardiac cycle. The estimated pulmonary artery diastolic pressure is derived from the right ventricular pressure waveform at maximum dP/dt, the time of pulmonary valve opening. Mean artery pulmonary pressure is calculated based on the collected variables. Measured values are stored continuously as the median or median and range (6th and 94th percentiles) over each storage interval. The storage interval can be programmed to high-resolution data (2-second storage interval) or low-resolution data (1-hour storage interval), with several programmable steps in between. Activity counts allow for an estimate of the patient's daily activities. The absolute pressure, measured by the pressure sensor in the right ventricle, requires correction for atmospheric pressures by an external pressure reference device (Medtronic, Inc.).

Patients with an IHM routinely send long-term, continuous, hemodynamic information from home via an Interactive Remote Monitor to the Internet-based Chronicle Information Network. Healthcare staff log on to the Network using a personal user identification and password. Trend plots and summary tables of all hemodynamic variables, as well as triggered events, sample pressure waveforms, and user-entered notes are available in the application.[1]

A series of patient studies have been performed to verify the feasibility of continuous hemodynamic monitoring in congestive heart failure patients and devices for remote transfer and use of these data. Several acute studies support the ability to reliably estimate pulmonary artery diastolic pressures from the right ventricular pressure signal. The results of several separate studies in heart failure patients who received systems for long-term hemodynamic monitoring support the technical feasibility and the long-term accuracy and stability of these systems. These findings set the stage to determine the potential clinical value of implantable hemodynamic monitoring and its impact on the care of patients with heart failure. An early research study designed to optimize diuretics showed that the Chronicle IHM was a sensitive tool for volume changes.[2] Findings in 32 patients implanted with a Chronicle IHM described hemodynamic changes that preceded patient symptoms in the case of a mild decompensation (not hospitalized) by at least 24 hours and preceding a severe decompensation (hospitalized) by 4 ± 2 days.[3] The authors concluded that if the changes had been detected at an early stage and medication regimens changed, periods of decompensation and subsequent hospitalization might have been avoided.

Hemodynamic response to submaximal walk and bike tests were compared to symptom-limited exercise tests in patients previously receiving an IHM. Changes in pressures ranged from 72% to 79% and in S_vO_2 from 80% to 91 % of the maximal tests.[4] Observations from monitoring of daily activity can, when compared to data from submaximal exercise tests, give a good estimate on how heavy daily activity is for a patient. Comparisons over time can then serve as an indicator of deterioration or improvement. Case studies describing hemodynamic changes under such circumstances as beta-blocker titration, anesthesia, and pacemaker optimization have also been published or are in press.

In the setting of PAH, a study using the IHM to guide therapy in 5 patients with pulmonary hypertension on inhaled iloprost has now been published[5] and several other small studies in which therapy has been guided by the IHM are in press. PAH is becoming an increasingly recognizable entity as emerging therapies and screening of at-risk populations have evolved over the last several years. PAH therapies are targeted directly to reduction of pulmonary pressure and resistance. Frequent monitoring of clinical status and hemodynamics is essential particularly in the first year of therapy to achieve and maintain optimal therapy that improves functional class and prognosis. Today, this monitoring of hemodynamics still requires repeated catheterizations. Use of the Chronicle IHM system in this patient population has the potential to allow more precise and individualized titration of drugs by providing data during rest and

exercise in the hospital and during normal activities during daily living.

Can you tell us about the ongoing pilot study?

A PAH pilot study is in progress and is designed as a prospective, multicenter, nonrandomized study to assess the feasibility and safety of implanting and using an IHM in patients diagnosed with PAH. A maximum of 24 patients will be included in the study. The aim is to show that continuous pressure monitoring by the IHM provides accurate hemodynamic data in patients with PAH and can be used to optimize treatment with approved therapies.

To be included in the study, patients must be 18 years old or older and newly diagnosed with PAH; if diagnosed earlier, the patient should be on stable PAH therapy for at least 3 months. The patient must also be in functional class II-IV, have a PA systolic pressure >50 mm Hg (echo), low probability of pulmonary embolism, total lung capacity >70%, and be willing to comply with the study protocol. Patients will be excluded if the PAH is related to left-to-right shunt, sickle cell anemia, HIV infection, schistosomiasis, or parenchymal pulmonary disease. Other exclusion criteria are left ventricular dysfunction, 6-minute walk <50 or >450 meters, pulmonary occlusive disease, presence of other implantable device (pacemaker or ICD), septal defect, mechanical right heart valve, and stenotic mitral, tricuspid, or pulmonary valve. Before the start of treatment it is typical to test the patient's pulmonary vasodilator response to prostacyclin, adenosine, or nitric oxide during invasive monitoring in order to predict prognosis and guide therapy choices.

Let me offer a bit of background information on the pilot study patients so far. Sixteen PAH patients have been enrolled and have had a monitor implanted to date. The mean age is 48 ± 15 years (range, 19 to 74), 14 are women, and the majority of patients are in WHO class III (14 in III, 2 in IV). Baseline pulmonary artery pressure (PAP) measured at rest was 89 ± 38 mm Hg (range, 28 to 137) and 38 ± 15 mm Hg (range, 14 to 65) for systolic and diastolic pressures, respectively, and the mean PAP was 62 ± 25 mm Hg (range, 21 to 99). Before the start of treatment the patients performed a 6-minute hall walk test. The average walked distance was 328 ± 100 meters (range, 79 to 476) resulting in an increase in systolic (37%), diastolic (40%), and mean (45%) pulmonary artery pressures.[6-9]

Treatment with oral bosentan was started in 7 patients, with subcutaneous treprostinil in 6 patients, and with intravenous epoprostenol in 1 patient. One patient, already treated with calcium channel blockers was not considered in need of any additional treatment and another patient died before treatment could be initiated.

All patients are asked to send data from their IHMs to the Chronicle Information Network once a week to allow easy and quick access to data review for the clinical staff in charge of the patient's treatment. Compliance with the protocol has been high and most patients have sent data on a weekly basis or more often.

Results from individual patients or the total study population are not available yet; analysis will be completed when 24 patients have been included in the study and followed for a minimum of 3 months of PAH treatment. Case-by-case observations of the hemodynamic trends displayed on the IHM Chronicle Information Network have led to adjustments and medication changes.

Dr. Benza, what is the future of implantable hemodynamic monitoring?

There is the potential for future technological improvement in these devices. Implementation of an oxygen sensor in the IHM system would offer new diagnostic possibilities. Cardiac output measurements using a modified Fick method would be an option, and measurements of oxygen consumption and demand could be useful, especially in the PAH population. The possibility of estimating flow using measurements from the IHM is undergoing investigation. Despite improvements in medical care, mortality remains high in PAH and no cure for the disease is available. As new treatments are evaluated, we are continuously reminded about the close link between the efficacy of these drugs, including improvement in symptoms, improvement in quality of life, and prolonged survival. This performance is best as gauged by improvement in related hemodynamics. The IHM, which reads pressures in the right ventricle as well as estimating the pulmonary artery pressure, should be able to adequately reflect the impact of the disease on heart function and help guide the need for earlier intensification in medical therapies in order to prevent the insidious development of right heart failure. Continuous ambulatory monitoring with the Chronicle IHM might be helpful to assure efficacy as well as safety in guiding these therapies. I am including a few selected references about this technology.

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Cardiopulmonary Exercise Testing

Although cardiopulmonary exercise testing (CPET) is discussed in the ACCP chapter, the actual recommendation is really for 6-minute walk testing. Dr Oudiz, how do feel about this? Would CPET be a better endpoint for clinical trials?

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I believe that both the ACCP recommendations[1] and the proceedings of the 2003 Venice consensus meeting[2] have predominantly relied on the 6-minute walk test as the exercise test of choice, mostly because it has been the endpoint used in nearly all of the recent multicenter trials of PAH treatments. The most recent multicenter therapeutic trial using CPET as the primary endpoint was the STRIDE 1 (sitaxsentan) trial.[3] Oddly enough, CPET did not perform as well as an endpoint as did its surrogate, the 6-minute walk test. One question that we are addressing is why the surrogate outperformed CPET. We suspect that the answer is related to inexperience in interpretation of the CPET studies (in patients with PAH) at the individual study sites and/or the fact that a core CPET lab was not used.

Going forward, as newer therapies and strategies for combination therapies are being considered, the pulmonary hypertension community is aware of the need for a better, perhaps more sensitive endpoint than the 6-minute walk test as a useful clinical marker of disease severity, mainly to better assess response to therapy in clinical trials. I believe that CPET can be useful in this regard, in that it provides physiologic data regarding disease severity,[4,5] the mechanism of improvement (or deterioration) in response to therapeutic interventions,[6] as well as prognostic data.[4,5]

How often should the 6-minute walk or other exercise testing be performed?

We generally have patients undergo exercise testing at all regular follow-up visits. We do both 6-minute walk tests and CPET. Unless there is a clinical change, we do not do CPET more often than twice a year. If there is a change in clinical status in the interim, we often do CPET to confirm the change and determine its physiologic nature.

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Pulmonary Arterial Hypertension: Therapeutic Considerations

Calcium-Channel Blockers

The recent ACCP consensus statement on medical therapy of PAH offers the following recommendation regarding the vasodilator response at catheterization: "Patients with IPAH, in the absence of right-heart failure, demonstrating a favorable acute response to vasodilator (defined as a fall in mean pulmonary artery pressure of at least 10 mm Hg to <40 mm Hg, with an increased or unchanged cardiac output), should be considered candidates for a trial of therapy with an oral calcium-channel antagonist. Level of evidence: low; benefit: substantial; grade of recommendation: B." Dr Gaine, how does this recommendation fit into your usual practice?

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This is a very useful new recommendation. In the past, before we had effective oral therapy for PAH, calcium-channel blockers were often used in an attempt to delay the need for intravenous epoprostenol therapy. Under the new evidence-based recommendations, unless patients have a true response to the vasodilator trial, calcium-channel blockers are avoided.

If someone without right ventricular failure had a mean pulmonary artery pressure of 65 mm Hg and it decreased to 50 mm Hg (ie, did not go to 40 mm Hg or below), would you consider calcium-channel blocker therapy?

A drop in mean pulmonary artery pressure from 65 mm Hg to 50 mmHg is no longer considered a favorable response. Calcium-channel blockers rarely contribute much long-term benefit in this setting.

Do you use calcium-channel blocker therapy in patients with PAH but without any vasodilator response, for example, to control systemic hypertension?

Whenever I see systemic hypertension in a patient with PAH, I look for underlying medical conditions such as obstructive sleep apnea. When treatment is required, I prefer to use an angiotensin-receptor antagonist rather than calcium-channel blockers. The negative inotropic effect of calcium-channel blockers, as well as peripheral edema can be troublesome in PAH patients.

Do you ever add additional therapy (eg, an endothelin antagonist) to the calcium-channel blocker in a stable patient with a good vasodilator response?
If calcium-channel blockers are demonstrated to achieve the same result as the vasodilator trial, then I generally stick with monotherapy as long as the patient is stable and asymptomatic. However, I have added either sildenafil or bosentan in patients who had a favorable response to a vasodilator trial, but who have been unable to tolerate sufficient calcium-channel blocker therapy to achieve a consistent mean pressure below 40 mmHg.

The ACCP recommends acute vasodilator testing with a short-acting agent such as epoprostenol, adenosine, or inhaled nitric oxide. Which vasodilator do you use for acute testing and why?
I use inhaled nitric oxide. It is very safe, well tolerated, and its actions are specific to the pulmonary circulation.

Treating Class II PAH Patients

Dr. Schilz, the recommendation for class II PAH patients made by the ACCP group is of necessity not terribly specific, since we don't have an extensive evidence base to guide us. What is your general approach to these patients? Do you use endothelin antagonists in these patients? How do you decide?

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The recently published guidelines represent an extremely careful and extensive review of the current scientific knowledge relating to the diagnosis and treatment of patients with PAH. Although data continue to accumulate almost on a weekly basis, several important questions remain unanswered.

One such question concerns the recommendations for treatment of World Health Organization (WHO) class II patients (PAH patients who have slight limitation of physical activity). Narrow and specific recommendations based on scientific evidence are available with regard to patients who are vasoreactive according to specific guidelines and testing performed at the time of right-heart catheterization. These class II patients, assuming they have no contraindications, can be treated with calcium-channel antagonists as long as they achieve and maintain excellent functional status while receiving those agents. Most adult class II patients probably will not demonstrate vasoreactivity. Substantial evidence does not exist to clarify the treatment of such patients.

Scientific evidence supporting any particular treatment of these patients is lacking for at least two reasons. One is that previous trials have typically included few class II patients. The other is that the duration of the therapeutic trials that have included class II patients may have been insufficient to detect important long-term effects in this "functional" patient group.

My current approach to class II patients is to assess for potential vasoreactivity and treat with calcium-channel antagonists as defined in the guidelines for the rare patient demonstrating response. I will consider the use of warfarin in nonresponders if no contraindications to its use exist. I believe (as I think many PAH physicians do) that additional treatment of such patients is important given what we know about the progressive nature of PAH. Practically then, at least four potential agents can be considered. In alphabetical order, these are bosentan, epoprostenol, sildenafil, and treprostinil. Outside the United States, aerosolized iloprost may also be available. Of these, only treprostinil currently has Food and Drug Administration (FDA) labeling for use in class II patients.

Issues that I consider in treating WHO class II patients include:

- Availability of trials and potential for enrollment. The ACCP guidelines underline the importance of such trials.
- Patient contraindications to therapy (ie, pregnancy or liver disease may preclude the use of bosentan).
- Insurance concerns. Payment for all regimens is a reality. Different patients have different plans that may or may not limit coverage to labeled indications or certain agents.
- Ability to deliver or monitor therapy. Infusion therapy with prostacyclin agents, although widely delivered, may not be appropriate for some patients. Similarly, the need to reliably monitor liver enzyme values monthly may not be practical for some.
- Route of administration. Oral administration is obviously attractive compared with infusion therapies as far as ease of delivery is concerned.

If all else is equal and the patient is a candidate for any therapy, I believe that initial monotherapy with bosentan or perhaps sildenafil is reasonable. Bosentan has an advantage in terms of being well known, with increased clinical experience and a well-defined dosing scheme. The use of sildenafil is less well defined. If oral regimens are not possible in a patient, I consider infusion therapy with treprostinil or epoprostenol.

Regardless of the initial therapy, patients must be followed closely for efficacy and safety of the regimen. I see patients approximately every 12 weeks. Exercise testing, echocardiography, and repeat right-heart catheterization are important in determining clinical improvement, stabilization, or deterioration. In patients whose condition improves, therapy is continued. Patients who deteriorate should be considered for alternate or additional therapy. Patients whose condition remains unchanged present another dilemma in clinical practice. The good news is that they have not changed, and the bad news might be that they have not changed. If a patient whose condition is unchanged has significant functional limitations that are troublesome or has substantially elevated pulmonary pressures, I tend to favor more or alternate therapy.

I want to underline the concept that robust scientific literature does not exist to support these approaches. At least two trials may give us more information to guide therapy in this setting. First, the EARLY trial, a current trial of bosentan in just such patient populations, may provide some of the important information that currently is lacking with regard to the use of this agent in WHO class II patients. In addition, though not a trial specifically for class II patients, a large, multicenter trial recently evaluated the use of sildenafil in patients with PAH and preliminary results suggest benefit. Results were announced at the annual American College of Chest Physicians meeting in October. In addition, the STRIDE II trial is evaluating sitaxsentan and bosentan and includes not just class III and IV patients but also class II.

A question beyond our current search defining therapies for WHO class II patients with PAH is what the *optimal* initial and subsequent therapy might be. This will not be answered in either of these trials, since direct comparisons with other available agents will not be performed. I remain extremely optimistic, given the continued advances in the treatment of PAH. However, many important questions remain and will require our continued commitment to answer.

Treating Class III PAH Patients

The ACCP group made the following recommendation regarding the therapeutic approach to the class III patient with PAH: Patients with PAH in functional class III who are not candidates for, or who have failed, CCB therapy are candidates for long-term therapy with:
Endothelin-receptor antagonists (bosentan). Level of evidence: good; benefit: substantial; grade of recommendation: A. IV epoprostenol. Level of evidence: good; benefit: substantial; grade of recommendation: A. Subcutaneous treprostinil. Level of evidence: fair; benefit: intermediate; grade of recommendation: B. Inhaled iloprost. Level of evidence: fair; benefit: intermediate; grade of recommendation: B. Beraprost. Level of evidence: good; benefit: conflicting; grade of recommendation: I.

Dr Hill, is your general approach the same as that presented in the above recommendations? How do you decide whether to use epoprostenol, treprostinil, or bosentan?

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Iona Preston, MD, codirects our Pulmonary Hyper-

tension Center at Tufts-New England Medical Center, and I have asked her to join me in answering. Although we agree in principle with the ACCP guidelines for functional class III PAH patients, we often don't follow them. First, we divide functional class III patients into two subcategories; IIIA and IIIB. IIIA patients are limited in their activities of daily living, but have been stable for at least several months. IIIB patients have similar functional limitations, but have had progressive symptoms over the previous several months. We consider endothelin-receptor antagonists like bosentan to be the agents of first choice for class IIIA patients, but don't feel comfortable administering them to IIIB patients (or class IV patients, for that matter) because these patients aren't sufficiently stable to wait out the 2 to 3 months that can elapse before a substantial favorable response occurs.

We prefer prostacyclins for IIIB patients, because in our experience these provide the greatest chance of a rapid, favorable response. We often start therapy in these patients with subcutaneous treprostinil in preference to intravenous epoprostenol because of the convenience and safety advantages. If patients can't tolerate the infusion site pain, we convert treatment to intravenous epoprostenol.

Our institution has a busy liver transplant center, and we have a fair number of patients with portopulmonary hypertension. Although there are case reports in the literature of patients with portopulmonary hypertension successfully treated with endothelin-receptor antagonists, we prefer subcutaneous treprostinil for such patients in functional class III, because we want to avoid adding potential liver toxins to their medical regimen. Our experience is that such patients respond very well to treprostinil.

Our center is also participating in multicenter trials to evaluate the efficacy and safety of sitaxsentan and ambrisentan. We enter some class IIIA patients into these trials because we believe there is a great need for more therapeutic choices and more efficacious medications. Thus, class IIIA patients who wish to try promising new investigational agents are entered into one of these trials.

Some of our class IIIA and IIIB patients have started receiving sildenafil as a first-line therapy. Some were enrolled in the Pfizer-supported multinational pivotal phase III trial of sildenafil and continue to use the drug as a sole therapy, now up to 2 years later. Others had difficulty obtaining insurance coverage for other agents (a patient with sarcoidosis, for example) and still others requested sildenafil after reading about it on the Internet or in the media, deciding that they preferred it to other currently available therapies. These patients were counseled that sildenafil has not yet been proven to be safe and effective for the treatment of PAH, nor has it been approved by the FDA for this indication. In our experience, most private insurers and Medicaid in the New England region will reimburse for sildenafil to treat PAH. As much as possible, we obtain free samples for those who are unable to get insurance coverage. Our anecdotal experience using sildenafil for class III PAH patients has been favorable, and the preliminary results of the pivotal trial support our experience.

Treatment for Class IV Patients

The ACCP recommendation for treatment of PAH patients with WHO class IV symptoms are as follows: Patients with PAH in functional class IV who are not candidates for, or who have failed, CCB therapy are candidates for long-term therapy with intravenous epoprostenol (treatment of choice). Level of evidence: good; benefit: substantial; grade of recommendation: A. Other treatments available for patients with PAH and functional class IV include, in no hierarchical order: Endothelin-receptor antagonists (bosentan). Level of evidence: fair; benefit: intermediate; grade of recommendation: B. Subcutaneous treprostinil. Level of evidence: fair; benefit: intermediate; grade of recommendation: B. Inhaled iloprost. Level of evidence: low; benefit: small; grade of recommendation: C.

Dr. Klinger, how do you decide the approach for the class IV patient with PAH? Is your general approach the same as the above recommendations?

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For the most part, I adhere to the guidelines that recommend continuous intravenous infusion of epoprostenol for class IV PAH patients. The most important finding in this group is compromised right ventricular function. Patients with poor functional status secondary to impaired right ventricular function are a perilous group with significant near-term mortality. Prostacyclin derivatives are unique in that they have a significant inotropic effect in addition to being potent pulmonary vasodilators. Hemodynamics can be misleading. Some patients have impressive pulmonary arterial pressures, but maintain adequate cardiac output. I'm not likely to favor prostacyclins in class III patients just because of high pulmonary artery pressures, but patients with clinical evidence of decompensated right-heart failure, ascites, severe peripheral edema, or severe pressure overload or hypokinesis on echocardiography always have me a little worried. We were recently referred a patient by the cardiologist reading echocardiograms. He had come across an echo that revealed severe right ventricular dilation and hypokinesis. The peak pulmonary artery pressure was estimated to be 80 mm Hg, but they just didn't like the way the right ventricle moved. Interestingly, the patient complained of only moderate dyspnea on exertion, but her right-heart catheterization findings confirmed severely impaired right ventricular function with a cardiac index less than 1.8. In general, I like to see these patients treated with epoprostenol as soon as possible. The approach should be to stabilize their condition and then consider transition to oral therapy if they respond better than anticipated.

The recommendations (algorithm and its footnotes) indicate that epoprostenol is generally the first-line therapy. Are there settings in which you'd consider another drug?

Some patients just aren't good candidates for intravenous infusion therapy. For example, patients at high risk for central line infection or those who struggle with aseptic technique. Under these circumstances, I do consider alternative therapies. Theoretically, treprostinil should be as effective as epoprostenol if dosed aggressively. Although the data from controlled trials in terms of functional response and survival have not been as impressive, I have had class IV patients do well with treprostinil.

Some patients simply refuse or are incapable of managing continuous infusion therapy. In this situation, oral therapy may be the only option. I've been slightly more impressed with the response to sildenafil than with endothelin-receptor antagonists in the few class IV patients I've treated this way. This may be because of the lack of an immediate hemodynamic effect with the latter drugs.

Finally, there is the occasional patient who may be better suited for an alternative therapy. One of my patients progressed from WHO class III to class IV while receiving calcium-channel blockers and an endothelin-receptor antagonist. She developed progressive hypoxemia and became difficult to oxygenate despite continuous high flow oxygen. On repeat catheterization, she had a similar vasodilator response to epoprostenol and to inhaled nitric oxide, but her oxygenation was considerably worse with epoprostenol. We participate in a long-term home inhaled nitric oxide program and were able to offer this option to the patient. She did remarkably well for over a year on inhaled nitric oxide and an endothelin antagonist.

So, there are certain situations in which I find treatments other than epoprostenol to be appropriate for initial therapy in class IV patients. However, these are the exceptions to the rule and for the great majority of my patients I still recommend doing everything possible to get them to undergo intravenous infusion therapy first.

Considering Sildenafil

Dr. Gossage, a recommendation has been made by the ACCP group with regard to the use of sildenafil. As you know, since this publication, additional data have been made available: In patients with PAH who have failed or are not candidates for other available therapy, treatment with sildenafil should be considered. Level of evidence: low; benefit: intermediate; grade of recommendation: C. What are your thoughts about this recommendation?

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I basically agree with the ACCP recommendation, though recently published trials will likely result in an upgrading of the recommendation. The ACCP recommendations were based on data published predominantly before 2003 and as such, did not include any randomized trials. These studies collectively showed an improvement in exercise tolerance and pulmonary artery pressure, although a study by Bhatia and colleagues, did not show a persistence of the hemodynamic effects.[1] Following finalization of the ACCP recommendations, Sastry and colleagues published a randomized crossover study of 22 patients with PPH, which is the only randomized trial to be published, thus far.[2] They showed a 44% increase in exercise time with sildenafil, and a statistically nonsignificant decrease in systolic pulmonary artery pressure. The preliminary results of the much-awaited SUPER-1 trial were presented at the recent ACCP meeting. In this study, sildenafil patients showed a 45 to 50 m increase in 6-minute walk distance, an improvement in functional class, and a 5 mm Hg decrease in mean pulmonary artery pressure ($P = .09$). If the full report of the trial holds up to scrutiny, I would foresee that the recommendation for sildenafil will be upgraded to B or perhaps even A.

Do you use this drug?

Yes. I have used sildenafil in perhaps 5% to 8% of my patients with PAH. My results have been mixed but I have had one excellent success in a woman with portopulmonary hypertension who did not tolerate doses of epoprostenol above 14 ng/kg/min because of side effects. Following initiation of sildenafil at 25 mg tid, I was able to wean her off epoprostenol over 3 months. At 22 months after stopping epoprostenol, she has had a persistent hemodynamic and functional response.

How do you decide when to use it or add it?

Up to this point, I have been fairly cautious in my use of sildenafil. I have reserved it mainly for patients with WHO class III-IV PAH who meet one of the following scenarios: 1) patients with intolerable side effects from other treatments, such as the woman in the above vignette, 2) patients who have contraindications to other treatments, 3) patients in whom all other reasonable treatments have failed, and 4) patients who are not candidates for treatment with bosentan, treprostinil, and epoprostenol. So I have basically followed the ACCP recommendations for its use. I have also tried sildenafil in one patient with PVOD, but it was not successful. Following full publication of the SUPER-1 data, I would expect to use it more frequently, especially in class II patients.

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Relative Merits of Different Endothelin Antagonists

Dr. Channick, at the present time no clinical data are available comparing different endothelin antagonists to each other. Thus, the ACCP could not suggest one drug over another. At present, bosentan, a nonspecific (dual-receptor) endothelin antagonist is FDA-approved for use. At present, do you feel that endothelin antagonists specific for the A receptor will have advantages over the nonspecific drugs?

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Although the existing data for two selective endothelin-A (ET-A) receptor antagonists, sitaxsentan and ambrisentan, are favorable, there are not sufficient data to suggest that they are more effective than the currently approved dual-receptor antagonist bosentan. Arguments can be made on both sides, for A receptor or A, B receptor antagonism. But the proof is in the clinical data, both short and long term. As of now, most of those data are with bosentan, which has been shown to improve exercise capacity, functional class, hemodynamics, quality of life, and survival, as well as prevent clinical worsening. Time will tell whether ET-A antagonists can reach or exceed the high bar that bosentan has established.

Discontinuing Epoprostenol

Dr. Frost, the ACCP recommendations discuss at length the data on treatment with epoprostenol for PAH but don't address the issue of its potential safe discontinuation in favor of oral therapy. You have recently published in this area; could you brief us on your patient selection and general approach to this?

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I will explain the rationale behind the decision to try to transition patients from epoprostenol to bosentan, and how we achieved this transition. The benefits of epoprostenol therapy are well known and clearly stated in the ACCP guidelines. When epoprostenol therapy was introduced for the treatment of PAH, it was for most patients the only therapeutic option. However, while life-saving, it is not innocuous. Complications of therapy include diarrhea, nausea, headache, flushing, leg pain, jaw pain, a reduced quality of life, hospitalizations, morbidity, and occasionally mortality (due to drug interruption and infection).

The development and release of the oral endothelin receptor antagonist bosentan has changed first-line therapy in many patients with PAH. Many patients currently receiving epoprostenol would have received this drug as their first line of therapy if it had been available at the time of their original diagnosis. That is, stable class II or III patients do not normally require epoprostenol, and since bosentan has been extensively evaluated in such patients with PAH, it appeared reasonable to consider such patients for this drug with cautious weaning from epoprostenol. Needless to say, it was a question raised by many PAH patients. The next question was which patients to transition and how to accomplish this.

Our approach to this process (it may differ at different centers) is as follows: We considered patients who had achieved sustained benefit with epoprostenol and had improved to WHO functional class II (or early III). Patients who were unstable either acutely or chronically were not considered for transition. It was also extremely important that the patients understood that a trial of epoprostenol cessation was all about making them feel better, that is, about having equivalent functional capacity but less risk and inconvenience. Any worsening of symptoms or deterioration in function was to mean that the transition was to be aborted immediately, and epoprostenol therapy was to be resumed or increased. As this was an unexplored area, the patients were also advised that should they deteriorate it was possible they would not immediately return to their pretransition functional state, even if epoprostenol was resumed. Not unexpectedly, many epoprostenol patients still wanted to try to achieve the transition.

Pulmonologists and cardiologists treating patients with PAH routinely use noninvasive criteria (symptoms, World Health Organization functional class, 6-minute walk tests, and echocardiography) to evaluate patients, to assess their response to therapy, and to govern titration of epoprostenol. It therefore seemed reasonable to use these same noninvasive parameters to follow patients as they came off one medicine while starting another.

The bosentan studies suggest that improvement in functional parameters appears to be achieved after one month of initial-dose therapy (62.5 mg q12h) followed by one month of full-dose therapy (125 mg q12h) with little further improvement reported afterward. A potential risk of starting bosentan in patients receiving Flolan would theoretically be an increase in epoprostenol-associated symptoms. Patients were monitored in the hospital during the initial weaning process and this was completed on an outpatient basis. At one month, the standard increase in bosentan from 62.5 mg q12h to 125 mg q12h was undertaken in an outpatient monitored setting. Patients were then given individual instructions to gradually decrease their epoprostenol dosage and it was weaned completely over one month. If their symptoms, examination, echocardiogram, and walk test remained stable during this down-titration and observation period, the infusion catheter was removed and they were followed closely thereafter.

Approximately half of the 23 patients (11) were successfully transitioned to bosentan therapy, although two patients subsequently developed liver function abnormalities necessitating drug cessation (one resumed epoprostenol, one patient transitioned to sitaxsentan). Most of the patients who successfully stopped their epoprostenol have remained on oral therapy now for over one year. To permit 40% of patients previously committed to continuous

intravenous infusion therapy to replace it with a pill, while not perfect, is a tremendous boost to their quality of life. It is important to emphasize that these transitions are best carried out by centers experienced at using these drugs. Long-term follow-up will determine whether or not patients will be able to remain off epoprostenol.

When to Use Treprostinil

Dr. Bourge, you have extensive experience with subcutaneous treprostinil. How do you decide which patients should receive this drug versus epoprostenol or bosentan, and what has been your overall experience?

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The University of Alabama, Birmingham, Pulmonary Vascular Disease group has extensive experience with the use of subcutaneous treprostinil. With this use, we also have extensive experience with addressing the primary cause of discontinuation of the drug, local site pain. It is interesting that about two thirds of our patients tolerate the drug over the long term. We do not find that the local site pain effects are necessarily dose-related (at least at a dosage above about 2.3 ng/kg/min), and it appears that the timing of the subjective severity of the symptoms is also very variable.

Some patients have symptoms early on and cannot tolerate the drug, while some have the onset of severe site pain symptoms late in the course of therapy, as late as 9 to 12 months after drug initiation. We utilize most published forms of site pain control, including the use of lidocaine patches, Emla cream, and a variety of other methods, including the limited use of topical local steroids and the limited use of both nonopioid (preferred) or even opioid pain medication.

In general, we prescribe all of our drugs after careful patient education regarding the risks, potential benefits, and lifestyle modifications inherent in each drug's use. For class IIIa or IIIb patients we usually (after intense education) offer oral bosentan as the first-line drug, depending on the hemodynamics. If the cardiac index is very low and/or the RA pressure very high, we often start with a prostenoid (most patients choose to try subcutaneous treprostinil instead of intravenous treprostinil).

We add a second drug (such as bosentan or treprostinil) to the subcutaneous or oral drug that the patient is taking if symptoms or side effects of the first drug are not tolerated and we think it will have to be discontinued, or if the cardiac index remains low despite an adequate trial of the first drug (usually 3 months). We have reported our generally favorable results in using combination therapy, and believe it is safe and efficacious, if the second drug is started cautiously and titrated slowly.

PAH Treatment in Germany

Dr. Olschewski, you have extensive experience treating patients with PAH. Do the ACCP guidelines apply in general to your practice in Germany? How do you decide which drug to use?

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The ACCP recommendations are only partly applicable to our clinical practice in Germany. The development of PAH treatment in Germany has been different from that in the United States and the approval situation is also different. For example, intravenous epoprostenol was never used in considerable numbers of patients in Germany and has never been approved in our country. Instead, inhaled iloprost or intravenous iloprost was the drug of first choice until bosentan became available. The recommendation of bosentan (grade A) is applicable in our country and fits our practice. In contrast, intravenous epoprostenol is not approved, is extremely expensive, and having a practical alternative, is hardly used in German patients. While intravenous iloprost is more widely used, it is approved only for peripheral artery occlusive disease. It is not mentioned in the ACCP Clinical Practice Guidelines as it was not tested in randomized controlled studies. Subcutaneous treprostinil is not approved and does not play a major role in Germany.

In contrast, inhaled iloprost plays a considerable role as the only approved alternative to bosentan and as a suitable combination partner to any other PAH therapy. In Germany, there has been extensive experience with the use of inhaled iloprost since 1994 and the benefit is considered substantial by most experts, including for patients who are severely ill. The ACCP recommendation (intermediate benefit) does not reflect the result of the double-blind, controlled Aerosolized Iloprost Randomized (AIR) study, which showed an improvement in 6-minute walk test results similar to that seen with intravenous epoprostenol and bosentan (PPH +59 m).[1] Beraprost was used off-label with enthusiasm by some German centers since 1997 but it turned out that the long-term results were disappointing, particularly in severe disease states. As it is not approved, it plays no major role in clinical practice. In contrast, sildenafil plays a role although it has not been approved for PAH. It is mostly used in combination with approved drugs where these are not sufficient.

There are ongoing clinical trials in the United States with iloprost, and completed trials in Europe. Do you feel that this drug will be used increasingly?

Inhaled iloprost has a place in the management of PAH in Germany. Since bosentan was introduced, it is no longer the drug of first choice because of the practical difficulties (six to nine inhalations per day) and a high-tech nebulizing device necessitating training of the patient and personnel. I am sure there will be increasing use of inhaled iloprost as an alternative to intravenous prostanoid therapy when bosentan

is not effective or stopped because of side effects. The advantages compared to epoprostenol and subcutaneous treprostinil are substantial with regard to systemic side effects and the risk of catheter-related complications. I am quite sure the drug will be increasingly used.

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Combination Therapy

Dr. Fagan, the ACCP group could not make a specific recommendation on the use of combination therapy for PAH patients because we don't have an extensive evidence base to guide us. What is your general approach to combination therapy? Do you use epoprostenol together with bosentan? How about sildenafil? How do you decide?

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The potential for combination therapy in PAH is very appealing but to date the data supporting this are limited. Broadly speaking, we consider combination therapy in two general groups of patients. First, for patients who have been receiving treatment with aggressive therapy (ie, epoprostenol) and who have had a very good clinical response, we consider adding additional therapy with the goal of withdrawing epoprostenol and using a less complicated, less risky therapy. Second, when patients have evidence of significant clinical worsening while receiving aggressive treatment, usually with epoprostenol, we will consider combination therapy with the hope of stabilizing or reversing disease progression.

Thus far we have the most experience with the addition of bosentan to treatment with epoprostenol. As was suggested by the BREATHE-2 trial, the combination appears to be safe and we have not experienced significant adverse events with this combination.[1] Occasionally we decrease the dose of epoprostenol with the initiation of bosentan to lessen the possibility of side effects, especially hypotension. As to the success of combination treatment, we have had a few patients who have discontinued epoprostenol with addition of bosentan who have remained clinically stable. It is less clear if we have achieved additional benefit in very ill patients in whom we have added bosentan to epoprostenol. Some patients seem to have some improvement while others do not.

In patients who were treated initially with bosentan and who demonstrate clinical worsening, we have generally added epoprostenol as the next therapy. The decision on whether to continue bosentan is difficult, but we generally continue both until the patient has initiated and tolerated epoprostenol for several weeks and then consider whether to continue bosentan or not.

Our experience with other combinations such as addition of sildenafil to other therapy is very limited at present. A large clinical trial recently evaluated the use of sildenafil in patients with PAH and preliminary results suggest benefit. This will likely open the doors to further exploration of combination therapy.

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Treatment Options in Portopulmonary Hypertension

Drs. Sulica and DePalo, the ACCP Evidence-Based Clinical Practice Guidelines offer a lengthy discussion of the complexities of portopulmonary hypertension and suggestions with regard to therapy. However, based on the small sample size of most clinical studies, no formal recommendations are made with regard to the therapeutic approach to this entity. How do you address it?

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Let us first offer some background on this entity. Portopulmonary hypertension is a subtype of PAH defined by an elevated pulmonary artery pressure and increased pulmonary vascular resistance in association with porto-systemic shunts. In patients with end-stage liver disease, it must be distinguished from increased pulmonary artery pressure due to hyperdynamic circulatory states or to fluid overload. Patients with portopulmonary hypertension have a particular hemodynamic profile characterized by a higher cardiac output compared to patients with idiopathic PAH with a similar degree of pulmonary pressure elevation. Cardiopulmonary complications and right ventricular failure are the main cause of death in approximately two thirds of patients with portopulmonary hypertension. The pathophysiology and pathological findings are similar to other categories of PAH, thereby allowing similar therapies to be used. However, the presence of liver disease modifies most treatment considerations, explaining why portopulmonary hypertension patients have been excluded from multicenter PAH treatment trials and the consequent lack of evidence-based recommendations.

Moderate-to-severe pulmonary hypertension significantly increases the mortality of orthotopic liver transplantation. The estimated prevalence of portopulmonary hypertension in patients presenting for liver transplantation is 10% to 15%. While in the typical PAH patient, the primary goal of thera-

py is right ventricular functional improvement, for portopulmonary hypertension patients, rapid reduction in pulmonary pressure is also important for transplant eligibility. During evaluation for orthotopic liver transplantation, the main objective is to reduce and keep mean pulmonary arterial pressure <35 mm Hg and pulmonary vascular resistance <240 dyne sec cm^{-5}. The degree of right ventricular dysfunction is also important for surgical outcome; therefore, echocardiography with dobutamine stress test and fluid challenge are employed preoperatively to determine the right ventricular reserve. Follow-up with echocardiography and right-heart catheterization is performed every 6 months in patients with portopulmonary hypertension on the liver transplant waiting list to assure maintenance of hemodynamic eligibility. Therapeutic choices in patients with portopulmonary hypertension depend not only on consideration of liver transplantation, but also on other aspects of the disease. Most information regarding the treatment options in portopulmonary hypertension comes from case series and case reports.

How does the diagnosis of portopulmonary hypertension affect your treatment decision compared with patients with other causes of PAH? Which drugs do you use?

Continuous intravenous epoprostenol has led to improved pulmonary hemodynamics in several case series of patients with portopulmonary hypertension, leading to successful transplantation in these patients. Epoprostenol has been also used in patients who developed de novo portopulmonary hypertension after liver transplantation. Long-term administration of epoprostenol results in augmentation of cardiac output in idiopathic PAH and adjustments in the epoprostenol rate are tailored to avoid the drug-induced high flow state. Since CO is elevated at baseline in patients with portopulmonary hypertension, further increases related to therapy can prove deleterious and difficult to interpret and manage. In patients with portopulmonary hypertension, specific adverse effects of prostacyclin therapy have been described, including thrombocytopenia and pancytopenia, either from splenomegaly and hypersplenism (which are potentially worsened by therapy) or related to an autoimmune phenomenon. The continuous monitoring of blood cell counts is critically important in the follow-up of these patients to avoid bleeding complications or overwhelming infections.

Epoprostenol administration is cumbersome and requires a serious commitment. Patients must be able to reconstitute their own drug and to follow strict administration recommendations. These skills can be compromised in patients with fluctuating mental status from hepatic encephalopathy and appropriate family and social support is an important consideration before initiation of epoprostenol therapy. Epoprostenol is reserved for patients with more severe portopulmonary hypertension.

Treprostinil is a prostacyclin analogue with a longer half-life compared to epoprostenol, thereby allowing subcutaneous administration by continuous infusion. Advantages over epoprostenol include easier administration and avoidance of line sepsis and of rebound pulmonary hypertension in cases of abrupt drug discontinuation. Although the landmark treprostinil trial in PAH did not include portopulmonary hypertension patients, a large retrospective series of portopulmonary hypertension patients demonstrated hemodynamic, functional, and survival benefit (compared to historical controls) at 8-month follow-up. There were no instances of significant effect of treprostinil on liver function tests or on platelet counts. Control of pain and reactions at the infusion site related to treprostinil administration remains a difficult problem. Although various local measures are employed, some patients require systemic pain management (including opioids). This can be associated with increased complications in patients with advanced liver disease. Patients receiving treprostinil have been successfully activated for orthotopic liver transplantation.

What about endothelin receptor antagonists?

Clinical trials with endothelin receptor antagonists in patients with PAH have demonstrated beneficial effect on symptoms, WHO functional class, hemodynamics, and right ventricular function. An important advantage of these drugs is oral administration. Because of the potential for liver toxicity, endothelin receptor antagonists are currently not recommended for portopulmonary hypertension. Although there is no formal recommendation from the ACCP, the document emphasizes that "most experts would likely recommend avoiding the oral endothelin antagonist bosentan in this population." Approximately 10% of the PAH patients treated with bosentan have developed reversible elevations in hepatic transaminases, but no cases of fulminant liver injury were reported in clinical trials or postmarketing. Of note, recent case reports have demonstrated the safe use of bosentan in portopulmonary hypertension.

Is sildenafil an option in this disease?

The theoretical lack of hepatotoxicity and the ease of oral administration render sildenafil treatment an attractive potential therapeutic alternative in patients with portopulmonary hypertension, particularly in light of the data in PAH presented at the ACCP meeting in October. However, both sildenafil plasma levels and duration of action are altered in the presence of advanced liver disease and the optimal dosing regimen is not established in portopulmonary hypertension.

How about conventional therapy with anticoagulation, diuretics, and calcium-channel blockers?

As with the above therapies, there are no randomized controlled trials in patients with portopulmonary hypertension with conventional therapies. Warfarin anticoagulation is recommended by experts in patients with PAH to counteract in-situ thrombosis. The role of anticoagulation in portopulmonary hypertension is unknown and potentially hazardous given the already present increased risk of bleeding. It is not recommended in portopulmonary hypertension. In a select group of idiopathic PAH patients who demonstrate acute vasoreactivity during vasodilator administration, oral calcium-channel blocker therapy is associated with long-term benefit. There are no studies on calcium-channel blockade

in portopulmonary hypertension, but experts advocate the role of a vasodilator trial in portopulmonary hypertension evaluation as a guide to the vasoactive perioperative management of orthotopic liver transplantation. The ACCP suggests that in vasodilator responders calcium-channel blockers are appropriate to consider, but that high-dose challenges should probably be avoided. Diuretics are used to avoid fluid overload states and oxygen supplementation is given to keep the arterial oxygen saturation >90%.

In conclusion, current recommendations for portopulmonary hypertension therapy are scarce and incomplete and mainly based on expert opinion with moderate strength of recommendation (E/B). Severity of the disease and impact on the outcome of liver transplantation should serve as strong motivators for future treatment trials in this particular group of PAH patients. I offer a few selected references on this topic.[1-7]

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Severe PH Associated with LVDD

Dr. Rubenfire, the ACCP recommendations do not offer recommendations for certain patients based on the lack of clinical data. One such area involves patients with clear left ventricular diastolic dysfunction who have a very high pulmonary artery pressure. Could you offer your thoughts on how you approach such patients?

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Not only are there not enough clinical data regarding the evaluation of severe pulmonary hypertension in association with left ventricular diastolic dysfunction (LVDD), treatment is more a trial and error art form than evidence based. As you are inferring, severely elevated pulmonary artery pressures are not commonly found with isolated LVDD, but we see at least one or two patients a month in the setting of left ventricular hypertrophy with what I would call disproportionate pulmonary hypertension.

Classic examples of left ventricular pathology associated with isolated diastolic dysfunction that can result in severe pulmonary hypertension include:

- Chronic hypertension with left ventricular concentric hypertrophy
- Hypertensive combined with ischemic heart disease
- Hypertensive heart disease with diabetes
- Hypertrophic cardiomyopathy
- Hypertensive hypertrophic cardiomyopathy of the elderly
- Aortic stenosis with a normal ejection fraction

In my experience severe pulmonary hypertension in hypertensive heart disease is more common in elderly diabetes and obesity, but there is no gender difference in aortic stenosis.

Multifactorial pulmonary hypertension is the rule more often than the exception in pulmonary hypertension associated with LVDD. It is important to follow the guidelines for assessing pulmonary hypertension in patients with disproportionately high pulmonary artery pressure and obvious LVDD associated with left ventricular hypertrophy. The most common aggravating conditions are obstructive sleep apnea, hypoxemia and COPD, pulmonary embolism, and a missed atrial septal defect. On the other hand, scleroderma-related disorders with pulmonary arterial hypertension can have significant resting or exercise associated increase in the pulmonary capillary wedge pressure due to LVDD. Each of the mechanisms for pulmonary hypertension can contribute and create a disproportionate increase in pulmonary artery pressure. For example, chronically elevated pulmonary capillary wedge pressures and pulmonary congestion associated with a hypertrophic cardiomyopathy can lead to pulmonary hemosiderosis/fibrosis, abnormal diffusion capacity, hypoxemia, and hypertrophy of pulmonary arterioles. Hypoxemia associated with chronic lung disease and sleep apnea can worsen left ventricular diastolic and systolic function.

Why does severe pulmonary hypertension occur in some patients with LVDD? I suspect it is related to the very long time course seen in hypertensive and hypertrophic cardiomyopathies perhaps accompanied by a genetic susceptibility, somewhat akin to high flow in atrial septal defects. Another analogy would be rheumatic mitral stenosis in which long-standing elevation of the pulmonary venous pressure leads to disproportionate pulmonary hypertension in about 20% of patients.

There are certain features of pulmonary hypertension associated with left ventricular hypertrophy, aortic stenosis, and other causes of LVDD that are not well characterized or understood. These include a disproportionate increase in systolic pulmonary arterial pressure (sPA) [usual sPA = 2 diastolic PA (dPA), with LVDD sPA ≥3 x dPA] or wide PA pulse pressure; a relatively small gradient between the dPA pressure and pulmonary capillary wedge pressure; modest pulmonary vasodilator reserve to inhaled nitric oxide; and a significant response to intravenous or sublingual nitroglycerin.

The four major determinants of the pulmonary artery pressures include the stroke volume, compliance or elastance of the pulmonary artery and major branches, resistance provided by the pulmonary arterioles and pulmonary venous pressure, and the reflectance wave.

The right ventricular stroke volume is usually normal in hypertensive and hypertrophic cardiomyopathies. The resistance is predominantly from hypertrophy and increased tone of the pulmonary arterioles (abnormal endothelial function and increased endothelin) and pulmonary venous pressure reflecting the high left ventricular filling and end-diastolic pressures. The natural history of increasing left ventricular hypertrophy over decades in hypertensive heart disease and obstructive and nonobstructive cardiomyopathy promotes a gradual increase in pulmonary arterial pressures with an exaggerated rapid progression in some. In long-standing and severe forms of left ventricular hypertrophy the resting left ventricular filling and end diastolic pressures are usually 15 to 18 mm Hg and 25 to 30 mm Hg, respectively, and the pulmonary capillary wedge pressure is 18 to 25 mm Hg. The latter rises to 25 to 40 mm Hg with modest exercise.

What are the therapeutic implications of the hemodynamic assessment in pulmonary hypertension associated with LVDD? Severe pulmonary hypertension in the setting of aortic stenosis and hypertrophic cardiomyopathy is associated with a poor prognosis and increased risk of surgery, but should not preclude the surgical approach. We have used intravenous nitroglycerin to demonstrate significant reversibility of pulmonary hypertension in the setting of aortic stenosis with and without coronary disease, which has helped in the decision to operate. Intravenous nitroglycerin can rapidly reduce the left ventricular filling pressure and pulmonary capillary wedge pressure, which can be followed by a sudden reduction of sPA, dPA, and mPA with minimal change in CO, suggesting the pulmonary hypertension is reversible.

In patients demonstrating pulmonary vasodilator reserve, my approach is to keep them as dry as possible without undo hypotension, use spironolactone to reduce myocardial fibrosis as in CHF trials, ACE or ARB inhibitors to regress left ventricular hypertrophy, and long-acting and sublingual nitrates to reduce symptoms and increase exercise tolerance. The vasodilator reserve to inhaled nitric oxide in pulmonary hypertension associated with LVDD is useful to help in understanding the pathogenesis and is an interesting finding. I have too little experience to characterize the distribution of the magnitude of response. Trials using endothelin antagonists and prostacyclin in patients with CHF have failed, perhaps in part because the pulmonary vasoconstriction has protected the lungs and left ventricle. It's important to control the heart rate, particularly in atrial fibrillation so as to allow an adequate left ventricular filling time. Beta blockers, verapamil, and diltiazem are effective for rate slowing with the addition of digoxin in atrial fibrillation. There are reports of beta blockers and calcium-channel blockers (nifedipine) lowering left ventricular filling pressures by enhancing the rate of isovolumetric diastolic relaxation in LVDD and regressing LVH, but the clinical effects are not consistent. Short to intermediate-term trials can be used to determine their potential value.

Examining the Use of Anticoagulants

Dr. Bourge, the ACCP consensus included several recommendations on anticoagulation therapy for PAH patients: 1. Patients with IPAH should receive anticoagulation with warfarin. Level of evidence: fair; benefit: intermediate; grade of recommendation: B. 2. In patients with PAH occurring in association with other underlying processes, such as scleroderma or congenital heart disease, anticoagulation should be considered. Level of evidence: expert opinion; benefit: small/weak; recommendation: E/C. With regard to your current practice of anticoagulation in these patients, do you prescribe anticoagulants in all patients with idiopathic PAH in the absence of contraindications?

Unless there is a strong contraindication, we routinely give anticoagulants all patients with PAH. There is fair to good anecdotal evidence to support this practice.

Do you prescribe anticoagulants for patients with CREST/scleroderma? If not, would you use anticoagulants in a patient with scleroderma and very severe PAH requiring intravenous epoprostenol?

We consider those patients with CREST/scleroderma as at the same risk for thrombosis in situ as all patients with PAH, and generally use the same criteria for anticoagulation. The evidence to support this practice is not as strong, however.

How about patients with congenital heart disease and pulmonary hypertension?

One cannot lump all patients with congenital heart disease together. If there is a repaired shunt and pulmonary hypertension, then we tend to do so, unless there is a contraindication such as recurrent hemoptysis. If there is an unrepaired shunt, then it depends on the pulmonary arterial pressure and other comorbid problems (there are not many data in this population however).

What is your target/range INR? Does it depend on the patient?

We aim for an INR of 2.0 to 2.5, unless there is a comorbid problem with a recommendation for a higher INR (such as atrial fibrillation).