The past 20 years have seen a dramatic evolution in our approach to the diagnosis and management of pulmonary arterial hypertension (PAH). What was once a death sentence has now become a chronic disease partially amenable to medical and surgical management. A key factor to this success has been the development of a clinical classification system to help distinguish PAH from other forms of pulmonary hypertension (PH) and algorithms to guide with the diagnosis and management of PAH. Efforts to standardize the clinical care of patients with PAH have led to the formation of multidisciplinary PAH tertiary care programs that strive to offer medical care based on peer-reviewed evidence-based, and expert consensus guidelines. Furthermore, these tertiary PAH centers often support clinical and basic science research programs to gain novel insights into the pathogenesis of PAH with the goal to improve the clinical management of this devastating disease. In this article, we discuss the clinical approach and management of PAH from the perspective of a single US-based academic institution. We provide an overview of currently available clinical guidelines and offer some insight into how we approach current controversies in clinical management of certain patient subsets. We conclude with an overview of our program structure and a perspective on research and the role of a tertiary PAH center in contributing new knowledge to the field. (Circ Res. 2014;115:131-147.)

Key Word: pulmonary arterial hypertension
Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>6MWD</td>
<td>distance walked in 6 minutes</td>
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<tr>
<td>BTT</td>
<td>bridge to transplantation</td>
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<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
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<tr>
<td>CO</td>
<td>cardiac output</td>
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<tr>
<td>ECMO</td>
<td>extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>ERA</td>
<td>endothelin receptor antagonist</td>
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<tr>
<td>INO</td>
<td>inhaled nitric oxide</td>
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<tr>
<td>IPAH</td>
<td>idiopathic PAH</td>
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<tr>
<td>LAD</td>
<td>lung assist device</td>
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<tr>
<td>PAH</td>
<td>Pulmonary Arterial Hypertension</td>
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<tr>
<td>PDE-5i</td>
<td>phosphodiesterase-5 inhibitors</td>
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<tr>
<td>PH</td>
<td>pulmonary hypertension</td>
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<tr>
<td>PVR</td>
<td>pulmonary vascular resistance</td>
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<tr>
<td>RAP</td>
<td>right atrial pressure</td>
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<tr>
<td>RV</td>
<td>right ventricle</td>
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<tr>
<td>RVAD</td>
<td>right ventricular assist device</td>
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PAH tertiary care programs that strive to offer medical care based on peer-reviewed, evidence-based, and expert consensus guidelines. Furthermore, these tertiary PAH centers often support clinical and basic science research programs to gain novel insights into the pathogenesis of PAH with the goal to improve the clinical management of this devastating disease.

In this article, we discuss the clinical approach and management of PAH from the perspective of a single US-based academic institution. We provide an overview of currently available clinical guidelines (see Clinical Care of Patients With PAH in the Modern Era section) and offer some insight into how we approach current controversies in clinical management of certain patient subsets (see Emerging Practice Topics section). We conclude with an overview of our program structure and a perspective on research and the role of a tertiary PAH center in contributing new knowledge to the field (see Structure and Function of a PAH Program section).

Clinical Care of Patients With PAH in the Modern Era

The first priority when determining the optimal management strategy for a given patient is to identify what form of PH is responsible for the clinical presentation. The 2013 Nice clinical classification guidelines (Figure 1) represent an update of prior Dana Point classification scheme and provide a useful framework to help phenotype patients presenting with PH. Changes to the 2009 Dana Point classification are that persistent pulmonary hypertension of the newborn is categorized as a separate entity group 1 PAH because it carries more differences than similarities with other entities in group 1 PAH. Furthermore, pediatric PH is now comprehensively characterized to create a common classification for both adults and children. Moreover, congenital or acquired left-heart inflow/outflow obstructive lesions and congenital cardiomyopathies have been added to group 2. PH associated with chronic hemolytic anemia has been moved from group 1 PAH to group 5 (unclear/multifactorial mechanism) and segmental PH has been added to group 5. SMAD9, CAV1, and KCNK3 have been added to the list of genes found in hereditary PAH. New drugs and toxins have been identified that are definitely, likely, or possibly associated with PAH: benfluorex and SSRIs (selective serotonin reuptake inhibitors) have been classified as definite, dasatinib as likely, and interferon α and β and amphetamine-like drugs as possible (such as entemrine/topiratame to treat obesity, methylphenidate to treat attention deficit disorder, ropinirole for Parkinson disease, and mazindol to treat narcolepsy).

The main advantage of the Nice 2013 clinical classification is that it helps clinicians distinguish patients with group 1 PAH from other forms of PH because each of these forms has a different prognosis and demands a unique approach to management. The mechanistic understanding of the disease has advanced and imaging methods of the pulmonary vasculature and the heart have improved, identification of innovative biomarkers and new PH phenotype definitions have been suggested. In an official American Thoracic Society statement, these new PH phenotypes are mainly defined on the basis of the pathobiology. These proposed new phenotype include a mixed pre- and postcapillary PH, severe PH in respiratory disease, maladaptive right ventricular (RV) hypertrophy,
connective tissue disease–associated PAH, portopulmonary hypertension, HIV-associated PAH, PH in elderly individuals, PAH in children, metabolic syndrome, and long-term survivors. It is suggested that deep phenotyping of patients consisting of measuring and integrating genomics, transcriptomics, proteomics, metabolomics, cell biology, tissue functioning, and imaging will advance the understanding of mechanisms, which then could be used to guide targeted management strategies.

Current treatment algorithms use the clinical classification system to recommend specific medical and surgical interventions for a specific World Health Organization (WHO) group of PH, whereas they strongly caution against them in other forms of PH for which there is not enough clinical or scientific evidence to support their use. These clinical guidelines for the diagnosis and care of PH are based on state-of-the-art clinical and scientific knowledge reviewed by experts in the field, and they represent the best paradigm for guiding the clinical care of patients with PH in the modern era (Figure 2). Despite being a comprehensive resource for PAH practitioners, there are clinical scenarios that are not properly addressed by the current clinical guidelines because of lack of robust data or expert consensus. The result of such limitation is that practitioners are forced to make decisions on the basis of a single provider experience or local consensus. The 2013 Nice guidelines do not provide any consensus recommendations on issues such as best first-line agent or optimal combinations of therapies. To the best of our knowledge, there are no studies that demonstrate the superiority of a specific drug class or brand. Furthermore, research is lacking to identify potential best responders to a certain therapy that would require a comprehensive phenotyping of the patient, thereby leading to a current practice pattern that encourages costly sequential or up-front combination therapy of multiple PAH drugs without knowing which patient would benefit most. Finally, it must be stressed that current clinical guidelines are unclear as to how to best approach patients with clinical features of 2 or more PH phenotypes (eg, patients with scleroderma who present with PAH and interstitial lung disease) in which the choice of therapy remains controversial.

Despite the availability of a wide range of specialized therapies, mortality from PAH remains unacceptably high. Although it is true that survival has improved since the introduction of modern therapies, data from both the Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL) and French registries still demonstrate a disturbingly low survival of 67% during a 3-year period, compared with that reported by the National Institutes of Health Registry in 1991 of 47%. These sobering facts reflect an ongoing controversy surrounding the degree to which modern, noninvasive PAH therapy can improve survival. During the past 5 years, several meta-analyses collecting most of the clinical trial data published on PAH therapeutics have tried to answer this important question, but the reports are conflicting. Some studies claim evidence for a survival benefit, whereas others fail to confirm this observation even with combination therapy. Although combination therapy reduced time to clinical worsening, reduced mean pulmonary artery pressure and pulmonary vascular resistance (PVR), and increased 6-minute walk distance, it did not influence mortality. One possible explanation might be that the quality of most currently available clinical PAH studies is inconsistent, a limitation that should be addressed in the design of future clinical trials. Until then, most data seem to support a survival benefit for IV epoprostenol, but whether any of the other agents also share this distinction remains unclear.

In summary, the current clinical classification and treatment guidelines have helped improve the standardization of PAH care in the clinical setting and have identified areas where more research is necessary to cover gaps in our knowledge and improve the quality of care. In the next section, we discuss how our center adapts the guidelines to the evaluation and management of patients and share some of the approaches we take to respond to the challenges we face in our clinical practice.

Diagnosis and Management—The Stanford Approach

Any discussion of the management of PH needs to start with an accurate diagnosis and full characterization of the disease
phenotype. This includes categorizing the patient into the appropriate WHO group and making a full assessment of the patient’s functional class and other comorbid conditions. Although the diagnostic work-up is discussed in full in a separate article in this compendium, here, we will describe briefly our approach to patients who present to our clinic.

Patients are primarily referred to our clinic with echocardiograms that show an elevated right ventricular systolic pressure with or without evidence of right ventricular dysfunction and right heart failure. In our initial visit, in addition to full review of symptoms, we assess risk factors for the development of PH. In our clinic, a right ventricular systolic pressure >45 mm Hg initiates a comprehensive PH work-up. Specifically, patients are screened for any history or evidence of congenital heart disease, autoimmune diseases, liver disease, thromboembolic disease, stimulant use, underlying lung disease, heart disease, sleep-disordered breathing, and HIV infection. If the patient’s echocardiogram and symptoms reasonably suggest that the patient may have PH, a comprehensive work-up is initiated. Routine studies include a complete blood count, comprehensive metabolic panel, thyroid function, hepatitis serologies, HIV, and, when indicated, hypercoagulable panels are checked. If a screening antinuclear antibody is positive, a panel of autoimmune antibodies, including anti-dsDNA anti-scl-70, anticientromere, anti-RNP, anti-SSA, and anti-SSB, is checked. Screening ECG and chest radiograph are used to alert the clinician to coexisting cardiopulmonary diseases. Patients also undergo a full set of pulmonary function tests, a 6-minute walk test, noncontrast CT scan of the chest or CT angiogram if thromboembolic disease is suspected, and V/Q scan. With the advent of more powerful CT scanners, it is debatable whether CT angiogram or V/Q scanning is superior for diagnosis of thromboembolism. We rely on either as an initial screen, but if thromboembolism is still a likely diagnosis, we require a V/Q scan. Chest imaging is a vital part of our initial evaluation given the fact that some patients with substantial parenchymal disease can present with relatively normal (pseudonormalized) lung function. Patients are routinely referred for evaluation for possible sleep apnea. If there is a suggestion of a shunt such as history of childhood murmurs, cyanosis, findings of clubbing, or flow murmurs on examination, an echocardiogram with bubble study is performed. We then have the patient return to clinic within 4 weeks. At this second appointment, we review the results of the study, and only if all of the requisite studies are complete, do we proceed with scheduling of the right heart catheterization. In our previous experience, we found that if the right heart catheterization was performed as part of the initial work-up, patients would get started on therapy before their disease phenotype was completely characterized, and often, these studies would never be completed. In the initial heart catheterizations, in addition to pressure measurements, the patients also have a full saturation run (to look for intracardiac shunts) and a vasoreactivity challenge with inhaled nitric oxide (INO). Formally vasoreactive patients should be started on calcium channel blocker (CCB) therapy with careful follow-up evaluation and anticipation of a substantial clinical improvement (further discussed in Emerging Practice Topics section).

With increased awareness of PH, our clinic has received a growing number of referrals for patients with echocardiogram that show borderline elevations (35–44 mm Hg) in right ventricular systolic pressure. Some referrals come through screening protocols for patients with systemic sclerosis or for liver transplantation, whereas others are for patients in whom there is an incidental finding of elevated right ventricular systolic pressure. An exhaustive work-up might be inappropriate because there are no clear guidelines for the evaluation of patients with such borderline abnormalities on echocardiogram. Therefore, our group has devised a screening protocol that takes into consideration the patient’s RV function, symptoms, and risk factors for disease (Table 1). Ultimately, for patients with suspected WHO groups 2, 3, and 5 PH, the evaluation is focused on optimization of the underlying condition.

**Initial Therapy Selection**

The most recent guidelines provide only loose guidance in choice of initial therapy for WHO group 1 PAH. The consensus algorithm for initial therapy remains dependent primarily on WHO functional class (FC; likely because of medication labeling) and gives numerous options for each class with few recommendations for choosing one medication over another. This ambiguity may be understandable given the lack of head-to-head clinical trials. Therefore, the decisions around initial therapy are generally driven by local expertise, practice patterns, patient preference, and insurance considerations. The shift in recent clinical trials to a primary end point of long-term outcomes (ie, morbidity and mortality) rather than changes in surrogate markers such as changes in distance walked in 6 minutes (6MWD) or hemodynamic measures in short-term studies has added another factor to the decision-making dilemma. How a PAH clinician reconciles conclusions of pivotal trials with different end points (6MWD plus long-term extension data versus a morbidity and mortality) of approved therapeutics from the same class remains to be seen. We consider consensus documents classifying patients as either lower risk or higher risk as a guide for initial therapy, particularly helpful in decision making. Factors that have been shown to differentiate patients into high-risk groups include clinical evidence of RV failure, rapid progression of disease, WHO FC IV, low 6MWD, low VO2 (oxygen consumption) on cardiopulmonary exercise testing, the presence of a peri-cardial effusion, severe RV enlargement of dysfunction, right atrial pressure (RAP) >20 mm Hg, cardiac index (CI)<2.0 L/(min·m2), or significantly elevated B-type natriuretic peptide. We consider a 6MWD of <380 m worrisome and <200 m extremely concerning. Although no single factor can determine risk, an assessment of all of these factors can be used as an optimal guide for choosing initial therapy.

For patients with WHO FC II or III and low-risk features, current guidelines recommend initial therapy with oral agents—either phosphodiesterase-5 inhibitors (PDE-5i) or endothelin receptor antagonists (ERAs). In general, PDE-5is (sildenafil or tadalafil) are well tolerated, have minimal side effects, and do not require regular monitoring. The choice between sildenafil and tadalafil is difficult to make and mostly depends on compliance and insurance formulary...
considerations. Because these therapies can cause systemic hypotension, PDE-5is as a first line are avoided in patients with low baseline blood pressures, that is, systolic blood pressure <100 mm Hg. Moreover, drug–drug interactions should be carefully considered because PDE-5is are contraindicated in patients with active nitroglycerin use and those on protease inhibitors because of strong CYP3A4 inhibitory effects.17 Currently, there are 3 ERAs approved for initial PAH therapy in the United States: bosentan, ambrisentan, and macitentan. All of the ERAs are teratogenic, so monthly pregnancy tests are required for all women of child-bearing age. Transaminitis can occur with these medications, most commonly with bosentan that requires monthly liver function test monitoring. Although this is not required for ambrisentan or macitentan, our practice has been to check liver function tests (LFTs) at least every 3 months. Anemia is also a known side effect of these medicines, so checking hemoglobin level every 1 to 3 months is also recommended. Last, significant fluid retention may be a common side effect, but data from the large randomized, placebo-controlled trial of macitentan showed that the incidence of fluid retention was no different from the placebo group, suggesting that edema may not be a significant side effect for this medication.18 Because of the monthly LFT monitoring and the twice-a-day dosing with bosentan, ambrisentan and macitentan (dosed daily) might be preferable choices.

The soluble guanylate cyclase stimulator, riociguat, is an oral medication and has recently been approved for the treatment of idiopathic PAH (IPAH), heritable PAH, and connective tissue disease associated PAH. The pivotal A Study to Evaluate Efficacy and Safety of Oral BAY63-2521 in Patients With Pulmonary Arterial Hypertension (PATENT-1) trial demonstrated efficacy as both monotherapy and combination therapy.19 However, it is yet to be determined in what cases this drug will be used as initial therapy. It is a 3 times per day–dosed medication that makes medication compliance an issue. Also, compared with placebo, riociguat 2.5-mg TID was associated with higher rates of mild-to-moderate hypotension. The PATENT-1 study excluded patients with baseline systolic blood pressure <95 mm Hg and should not be used in patients on active nitroglycerin or PDE-I agents. Lastly, like ERAs, riociguat is thought to be teratogenic and requires monthly pregnancy tests in patients of child-bearing age.

Patients who present with WHO FC IV symptoms and high-risk features should be considered for parenteral prostacyclins as first-line therapy. Currently, there are 3 parenteral prostacyclins available in the United States: epoprostenol, room temperature stable epoprostenol, and treprostinil. The 2 forms of epoprostenol are given by continuous intravenous infusion, whereas treprostinil can be given intravenously or subcutaneously. Patients who elect to go onto this therapy need to be able to manage an indwelling catheter, mix the medication in
a sterile fashion, and manage the pump. Given the challenges associated with managing parenteral prostacyclins, some patients are not willing or are not an appropriate candidate for parenteral therapy. In these cases, we will start with oral or inhaled therapy, with the plan to add a second agent in quick succession. Currently, there are 3 inhaled prostacyclins available in the United States: iloprost and treprostinil. Inhaled iloprost is dosed at 6 to 9 treatments per day, whereas inhaled treprostinil is dosed ≤9 breaths 4 times per day. Cough is a common side effect with inhaled prostacyclins and at times can be severe.

Although initial monotherapy has been a well-studied approach in PAH, the use of up-front combination therapy continues to be an unanswered question. Sitbon et al recently reported the results of a pilot study of up-front triple therapy. Patients with newly diagnosed severe PAH were offered up-front treatment with epoprostenol, bosentan, and sildenafil in patients with severe PAH. This small cohort demonstrated significant improvement in 6MWD and hemodynamics, and survival at 3 years was 100%. Although promising, the reporting of the study was retrospective and uncontrolled. Currently, there are 2 randomized clinical trials testing up-front combination therapy. The AMBITION (A Study of First-Line Ambisentan and Tadalafil Combination Therapy in Subjects With PAH) trial (ClinicalTrials.gov identifier: NCT01178073) is an event-driven study evaluating up-front combination therapy with tadalafil and ambisentan compared with ambisentan or tadalafil alone. The CONFONT (ConbinatiON Up-FRONT tTherapy for PAH - A Phase 4, Randomized, Multicenter Study of Inhaled Treprostinil in Treatment naive Pulmonary Arterial Hypertension Patients Starting on Tadalafil) trial is a phase IV clinical study comparing up-front therapy with tadalafil and inhaled treprostinil compared with tadalafil alone (ClinicalTrials.gov identifier: NCT01305252). Results from these 2 trials are anticipated in the next 6 to 12 months.

Goals of Therapy and Treatment Optimization

Once patients are started on therapy, high-risk patients are re-evaluated every 2 to 3 months, whereas those with milder and more stable disease are seen every 4 to 6 months. At follow-up, patients are re-evaluated with an assessment of WHO FC, an echocardiogram, 6-minute walk test, and often an N-terminal pro B-type natriuretic peptide. Surveillance right heart catheter at our institution is performed every 1 to 2 years or sooner if clinical deterioration is suspected.

In the most recent guidelines, the following targets for therapy were suggested: (1) modified WHO FC I or II; (2) echocardiography/cardiac MRI of normal/near-normal RV size and function; (3) hemodynamic parameters showing normalization of RV function (RAP<8 mm Hg and CI>2.5–3.0 L/min/m²); (4) 6MWD of >380 to 440 m; (5) cardiopulmonary exercise testing, including peak oxygen consumption >15 mL/(min·kg) and ventilatory equivalent for carbon dioxide <45 L/min/L/min; and (6) normal B-type natriuretic peptide levels. These targets parallel the factors used to assess risk. In short, the goal of treatment is to shift a patient from a higher risk to a lower risk phenotype.

To achieve these goals, combination targeted PAH therapy, as well as optimization of supportive care, is essential. The efficacy of sequential combination PAH therapies is suggested by several placebo-controlled, randomized clinical trials in patients on stable monotherapy. Although the PACES (Addition of Sildenafil to Long-Term Intravenous Epoprostenol Therapy in Patients with Pulmonary Arterial Hypertension) and TRIUMPH-1 (Double Blind Placebo Controlled Clinical Investigation Into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients With Severe PAH) trials demonstrated an improvement in 6MWD with the addition of a second agent, others (such as STEP [Trial of Iloprost Inhaled Solution as Add-On Therapy With Bosentan in Subjects With Pulmonary Arterial Hypertension]) were formally negative but suggestive. Results of the COMPASS-2 (Effects of the Combination of Bosentan and Sildenafil Versus Sildenafil Monotherapy) trial, addition of bosentan to background sildenafil, will provide further guidance on impact of stepwise combination of PAH therapies.

In our practice, the decision to add therapy mirrors the current guideline recommendations. If patients continue to have WHO class III or IV symptoms, low 6MWD, and natriuretic markers on echocardiogram (ie, pericardial effusion), additional PAH-specific therapies are used. For patients exhibiting persistent high-risk features, we optimize the baseline and consider adding a second agent within 3 months of treatment initiation. In general, our second-line choice is usually either an oral agent, an ERA, or a PDE-5i, or inhaled prostacyclin. If patients are unable to reach these goals with dual therapy, we move to triple therapy with oral dual therapy and inhaled prostacyclins. If they continue to progress, the inhaled prostacyclin is switched to a parenteral prostacyclin in patients who are willing and capable of managing this form of therapy. For high-risk patients, parenteral prostacyclin is discussed and offered at every treatment decision point.

A discussion in treatment selection cannot be made without consideration of drug cost and insurance coverage. All PAH medical therapies are prohibitively expensive, and costs compound as patients are placed on combination therapies. Sildenafil is the least expensive drug therapy, estimated at $18-404 for inhaled treprostinil compared with tadalafil alone. Cost of hospital admission for central line placement and drug titration or management of a blood stream infection.
a few months, thus repeating the cycle of paperwork submission. At our center, it is a coordinator’s full-time job simply to track the authorizations, paperwork submission, and filing of appeal letters should the insurance deny coverage of medications. The intense administrative burden adds to the indirect cost of PAH treatment. The American College of Cardiology and the American Heart Association recently published a cost and value methodology to be applied in developing treatment guidelines and performance measures.26 Given limited healthcare resources, cost considerations and resource utilization should be evaluated alongside future PH treatment guidelines.

Supportive therapies are essential for symptom control and optimization of hemodynamics. In patients with chronic right-sided heart failure, symptoms and hemodynamics can be significantly improved with control of volume status. This is generally achieved with diuretic therapy. Observation of a low-sodium diet (<2 g sodium/day) can significantly decrease the degree of fluid retention. Digoxin can add some inotropic support for the failing right ventricle (RV).27 In our practice, this is often added as a supportive therapy when PAH-specific therapy has been optimized. Last, exercise training and pulmonary rehabilitation is an important strategy for improving exercise tolerance, symptoms, and quality-of-life measures.28 Patients are encouraged to attend a pulmonary rehabilitation program soon after successful initiation of PAH-specific therapies.

Specifying discrete treatment goals lends itself to the development of formal goal-oriented therapy protocols. Interestingly, to date, there has been only 1 study with a specified protocol in which therapy was added if one of the treatment goals was not met.29 Compared with historic controls, Hoeper et al29 showed that goal-directed therapy improved survival. However, this study is limited by its retrospective design and lack of appropriate control arm. As this study was conducted more than a decade ago, several new medications for PAH have been approved and new prognostic factors have been identified, making the specific protocol less relevant. However, the concept of goal-oriented therapy is a useful one. Future studies should address optimal risk stratification factors, weight of these factors in determining a goal, ideal assessment intervals, order of therapies, and timing of therapeutic interventions.

One risk assessment that may be useful in a goal-oriented protocol is the REVEAL risk score. The REVEAL Registry was used to develop and validate a prognostic score for 1-year survival.5,30 This score is derived from combination of demographics, WHO FC, vital signs, 6MWD, B-type natriuretic peptide, echocardiogram, pulmonary function test, and right heart catheterization findings but is easy to calculate and stratify patients into 1 of 5 risk groups, ranging from low risk to very high risk. Although the use of the risk score to guide therapy needs to be validated, this could potentially be used to guide initial and optimization of ongoing therapies. Changes in the risk score over time may be a useful target for goal-oriented therapy.31 However, clinicians must recognize that such risk scores (and their change) have not been validated in individual patients, and their use in such setting is debatable.

Timing of Referral for Transplantation
Current guidelines recommend that patients with an inadequate response to therapy be referred for lung transplantation. Our current practice has been to refer patients who have been started on triple therapy, including parenteral prostacyclins for transplant evaluation. In the current lung allocation scoring system, patients with PAH, based on their diagnosis, often have low scores at listing.33,34 Although patients with other lung diseases (pulmonary fibrosis, chronic obstructive pulmonary disease, and cystic fibrosis) have had a decrease in their wait time for transplant, there has been no change for patients with IPAH. The lung allocation scoring system has also led patients with IPAH to having a lower likelihood of being transplanted compared with those with idiopathic pulmonary fibrosis and to a great risk of death while on the waiting list.35,36

Emerging Practice Topics

Genetic Screening and Counseling of Patients With PH
Since the discovery of the association between heritable PAH and mutations in the bone morphogenetic protein receptor (BMPR)-2 gene,37,38 there has been tremendous progress in our understanding of the genetic basis of PAH. In recent years, there have been reports of association between heritable PAH and mutations in novel genes, such as caveolin-139 and KCNK3,40 discovered via application of modern genome sequencing technologies such as whole exome sequencing.41 These studies have fueled enthusiasm for the application of genomic technologies to the clinical setting as tools to help personalize the care of patients with PAH and improve our ability to predict likelihood of disease development in carriers of susceptibility genes. However, more research needs to be conducted to determine how best to analyze the large data sets generated by genome sequencing and determine associations between candidate genes and critical end points such as prognosis, disease severity, and response to therapy.

At our institution, we routinely screen all patients for a family history of PH and will only recommend genetic testing when there is a high index of suspicion. Genetic counseling is offered before testing because both the patient and the family need to be educated on the clinical and legal implications of finding specific gene mutations and the likelihood of mutation carriers developing PAH in their lifetime.42 We routinely follow asymptomatic high-risk mutation (eg, bone morphogenetic protein receptor 2) carriers with yearly echocardiograms and a visit to evaluate for the presence of symptoms pertaining to PAH and conduct psychological assessment for possible stress and anxiety caused by the genetic diagnosis.43

Follow-Up Vasoreactivity Testing
Acute vasoreactivity testing remains a key component of the initial work-up for PAH to identify subjects who will respond favorably to long-term treatment with high doses of calcium channel blockers. iNO is the compound of choice for the acute test but intravenous epoprostenol or adenosine may also be used as an alternative.44 Furthermore, inhaled iloprost has been able to identify patients who may benefit from long-term therapy with CCBs.45 A decrease in mean pulmonary artery pressure by ≥10 mm Hg to an absolute level of <40 mm Hg without a decrease in cardiac output (CO) is defined as a positive pulmonary vasodilator response,46 and only those
responders are considered for long-term treatment with CCB. Less than 15% of patients with IPAH are deemed responders during testing, and even fewer exhibit long-term responsiveness to CCB. Independent of whether CCB are started, vasoactivity to iNO predicts long-term survival in PAH. In our center, vasoreactive patients with PAH are initiated on CCB therapy with close follow-up with the expectation of substantial clinical improvement within 3 to 4 months. As choice of CCBs, long-acting amlodipine, nifedipine, and diltiazem are the preferred agents.

In addition to identifying patients who would respond to CCB therapy, baseline and follow-up vasoreactivity testing in all patients with PAH as part of every right heart catheter can offer valuable additional insight into their response to therapy and possible antiremodeling effects. Our group has shown that in addition to loss of vasoreactivity, vasoreactivity can also be gained (using the same definition as baseline testing) during the course of the disease in idiopathic, drug and toxins, and connective tissue disease–associated PAH (abstract AJRCCM 183;2011:A5747). In the rare case of a gain of vasoreactivity, we consider initiation of CCB therapy in addition to targeted PAH therapy, but it should be noted that this is an expert opinion-driven practice, is highly preliminary, and requires future clinical testing. Once vasoreactivity is lost, we typically stop CCBs and optimize targeted PAH therapy.

### Use of Anticoagulation in PAH

The use of anticoagulation in PAH has been a subject of debate for decades. Although there is evidence of in situ thrombosis in all forms of PAH and a recognized hypercoagulable state in severe PAH, most clinical studies suggesting a survival benefit of anticoagulation in PAH are retrospective or nonrandomized and small and mainly refer to patients with IPAH at a time before targeted PAH therapy was available. Given the increased risk of bleeding with anticoagulation in subgroups of PAH such as congenital heart disease, liver disease, and mixed connective tissue disease, the current treatment guidelines only recommend—based on expert opinion—that anticoagulation should be considered in patients with IPAH, heritable PAH, and anorexigen-induced PAH and leave it up to the discretion of the treating physician whether to extend this treatment to other forms of PAH.

This insecurity and reluctance to use anticoagulation is reflected in the fact that only around 50% to 60% of patients with IPAH and 40% with associated PAH are on anticoagulation, based on data from European (Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension [COMPERA]) and North America–based (REVEAL) PH registries. A recent analysis from the above-mentioned European prospective PH registry (COMPERA) of survival rates of >1200 patients with IPAH and other forms of PAH depending on their use of anticoagulation documented a significantly better 3-year survival in patients with IPAH (but not associated PAH) on anticoagulation compared with patients who never received anticoagulation. These data suggest that long-term anticoagulation confers a survival benefit even in the presence of PAH–specific therapies. This prospective registry is the largest series assessing the use of anticoagulation in PAH over a long observation period and further supports the recommendation to use anticoagulation in patients with IPAH. Based on these data, we usually start patients on anticoagulation regardless of the PAH subtype unless limited by anemia or prior bleeding events.

### β-Blockers in PAH

The use of β-blockers in PAH remains controversial. Although it is well established that neurohormonal system is activated in PAH, reluctance to use β-blockers in PAH is based on the idea that patients with PAH are highly dependent on their heart rate to maintain and increase their CO. Neurohormonal activation was therefore interpreted as a necessary compensatory response to maintain adequate cardiac contractility and blood pressure. Although initially beneficial, chronic activation of the neurohormonal system may be detrimental in the long run because it could result in a down-regulation of β1-adrenergic receptors, impairing the inotropic responsiveness of the heart.

Several preclinical studies in experimental rat models of PAH with RV failure, as well as of isolated RV hypertrophy and failure after pulmonary artery banding, have implicated beneficial effects of β-blockers on RV function and morphology. A retrospective study compared the clinical outcome of 94 patients with PAH with cardiac comorbidities with and without β-blockers. The authors found that β-blocker use was common (28%) in their cohort and not associated with worse outcomes (PAH-related hospitalization or all-cause mortality). However, the studied patient cohort did not reflect the normal PAH population (older age, coronary artery disease, etc).

Recently, a phase II clinical trial to test the safety and efficacy of the cardioselective β1-adrenergic blocker bisoprolol finished recruitment, and results are expected in the next few months (ClinicalTrials.gov identifier: NCT01246037. Principal Investigator A. Vork-Noordegraaf). Thirty patients with IPAH were randomized to either bisoprolol or placebo treatment in a double-blinded fashion. A crossover design (6 months β-blocker, 6 months placebo) was used to increase the power of the study and to assess long-term effects of bisoprolol treatment and withdrawal. As primary efficacy end point, improvement in RV function (reflected by RV ejection fraction) will be determined by cardiac MRI. Safety of bisoprolol treatment in patients with IPAH was not a primary end point but was regarded as a precondition for the study and thus closely monitored. We are currently not treating patients with PAH with β-blockers and are awaiting the clinical trial results to see whether a safe and effective dose of selective β-blockade can be recommended in select patients with PAH.

### Intensive Care Unit Care of Patients With PAH

Because of the generally tenuous clinical status of patients with PAH, clinicians should have a low threshold to admit such patients to a higher level care setting such as intensive care unit or cardiac care unit. The management of critically ill patients with PAH is especially challenging given that (1) assessment of presenting critical illness is confounded or even masked by right heart failure and (2) treatment of the acute critical illness may have paradoxically detrimental effect on
RV function and the underlying pulmonary vascular disease (Figure 3).

Presentation of critical illness in the setting of RV failure in PAH usually requires immediate hemodynamic evaluation.62,63 The volume status of the PH patient is notoriously elusive, and noninvasive estimates of central venous pressure estimates may be misleading. Therefore, central line placement with direct measurement of central venous pressure and mixed oxygen saturation is often necessary. A pulmonary arterial catheter can be useful in this setting but is not required.

The selection of inotropes and vasopressors is challenging in patients with PAH. In this regard, a major guideline is to maintain systemic vascular resistance greater than PVR. Unlike left ventricular coronary perforation that occurs solely during diastole, right ventricular coronary perforation occurs both during systole and during diastole.64 Thus, if the gradient shifts during systole to a state in which PVR exceeds systemic vascular resistance (ie, systolic pulmonary arterial pressure >systolic systemic arterial pressure), the result is right ventricular ischemia.65 Usually, this means that systolic systemic arterial pressure goals are higher in patients with PH than in patients without PH. Inotropes that have neutral or beneficial effects on PVR include dobutamine, milrinone, and epinephrine.62,63 We often use dobutamine compared with milrinone because of its shorter half-life in face of the risk of hypotension in both. We try to offset the potential drop in systemic vascular resistance with replacement-dose vasopressin, particularly in our patients with septic or liver PH, in whom vasopressin deficiency is common.65,66 No single inotrope or pressor is entirely contraindicated in the critically ill patient with PH, but each agent should be considered carefully.

iNO has been shown to acutely decrease PVR and improve CO in PH, especially in patients who undergo postcoronary bypass surgery or valve replacement.67,68 Its advantages are its short half-life, short onset of action, capacity to improve oxygenation by way of augmenting ventilation–perfusion matching, and capacity to unload an acutely failing RV. Most importantly, it has no detrimental effect on systemic vascular resistance. Its disadvantages are its significant cost; its potential to cause methemoglobinemia though usually at sustained, high doses; and its potential for tachyphylaxis. Also of note, on weaning iNO, rebound PH can occur,69,70 particularly in the absence of a replacement pulmonary vasodilator. In addition to using select inotropes and vasopressors, we routinely use iNO at 20 parts per million in the intensive care unit in our patients with hypotensive PH, and on weaning, we routinely start or restart a phosphodiesterase inhibitor as replacement therapy.

Intubation, on its own, acutely decreases right ventricular preload and increases afterload.71 This, in combination with the effects of agents of induction and sedation and the associated loss of sympathetic drive once work of breathing is relieved, can instigate sudden and at times irreversible hypotension.72 We often call on an experienced cardiac anesthesiologist to assist with intubation. Depending on the urgency and nature of the case, arterial line monitoring may be used before the event and fiberoptic awake intubation may be used to avoid overstimulation of sympathetic drive, which can incite an acute increase in PVR. After intubation, a low-tidal volume strategy73 to minimize increases in RV afterload is used with the aim to keep peak pressures <30 cm H2O. If oxygenation allows, the positive end-expiratory pressures should be limited to ≤10 cm H2O. Permissive hypercapnia should be avoided as
acidosis and hypercapnea can acutely increase PVR. Finally, a systemic oxygen saturation of >90% should be aimed for because hypoxia can likewise acutely increase PVR. 62,63,71

Perioperative Work-Up and Risk Stratification

Patients with PAH are at highest risk for any major procedure or surgery that is emergent, requires significant volume shifts (eg, intra-abdominal surgery), carries a substantial risk of pulmonary (clot or fat) thromboembolism, and mandates prolonged anesthesia. Additionally, WHO FC >II, right ventricular hypertrophy on transthoracic echocardiogram (TTE), right axis deviation on ECG, and higher mean pulmonary artery pressure portend worse postoperative morbidity and mortality. 74–76 The detrimental effect PH has on outcomes in cardiac surgery is well established. PH was the only baseline variable that predicted increased perioperative mortality in a large group of patients undergoing coronary artery bypass graft surgery (odds ratio 2.1). 77 Severe PH was independently associated with in-hospital mortality (adjusted odds ratio 6.9) and decreased 5-year survival (adjusted hazard ratio 2.4) in patients undergoing aortic valve replacement for severe PH. 73

The effect of PH on noncardiac surgery outcomes is less well studied, but there are data that suggest PH is a notable risk factor for poor outcomes. Morbidity rates range from 2% to 42% and include acute respiratory failure, acute heart failure, dysrhythmia, and prolonged intubation and intensive care unit stay. 74–76,79,80 Mortality rates range from 1% to 18%. We think that even minor procedures such as dental extractions or routine colonoscopies requiring conscious sedation should be taken seriously. Unexpected bleeding, sedation-related hypoxia or hypotension, or postprocedure pain can incite a sudden increase in PVR and acutely stress a chronically failing RV.

A thorough preoperative evaluation and discussion of risks and benefits in advance of surgery is critical. We ask all our patients to notify us of any anticipated procedure or surgery and generally advocate that they undergo major surgery at our center. We advise that any minor procedures be performed under local sedation only if possible. At minimum, we ensure risk stratification on the basis of recent (within 3–6 months) TTE, right heart catheterization, 6-minute walk test, and N-terminal pro B-type natriuretic peptide data. We also advise our patients to avoid elective surgery unless it is anticipated to dramatically improve quality of life. We optimize PAH-specific therapy and volume status as much as possible before surgery. We will often cancel or delay elective surgery until this optimization is complete. Finally, we thoroughly discuss the risks from a cardiopulmonary perspective with our patients and their families.

In all major surgical cases, we assemble a multidisciplinary team, including surgeons and cardiac anesthesiologists, and together formulate an approach to the perioperative care. This discussion focuses on the choice of induction and maintenance anesthetic agents, close intraoperative monitoring (eg, central venous catheter, arterial line, and transesophageal echocardiogram), plan for pulmonary vasoconstrictor therapy during and after surgery (eg, continuous iNO may need to replace patient-delivered inhaled prostacyclins while under general anesthesia), surgical strategy, anticipated surgical complications, and close postoperative monitoring. Invariably, we admit our PAH patients postoperatively to our service in the cardiac care unit for ≥24 hours of monitoring because some of the major cardiovascular implications of surgery only manifest a day or 2 after the procedure. We think that this vigilant approach best prepares the patient with complicated PAH and associated care team for perioperative obstacles.

Role of Extracorporeal Membrane Oxygenation, Ventricular Assist Devices, and Lung Assist Devices in PAH

In patients with PAH who eventually fail medical therapy, a few mechanical therapies exist that can play a role in RV salvage. Atrial septostomy is the iatrogenic creation of an atrial septal defect that serves to offload the RV in face of a high PVR. It is rooted in evidence that patients with PAH with Eisenmenger syndrome, as well as patients with a patent foramen ovale, tend to do better long term. 81,82 Typically performed by experienced interventional cardiologists using a blade septostomy approach with a series of balloon dilations, 83 atrial septostomy may increase CI, decrease RAP, and improve symptoms and exercise tolerance. 84 However, the risks of cardiac tamponade, arrhythmia, and refractory hypoxemia are substantial. Patients with severe PAH, defined by a markedly elevated PVR, maximal arterial oxygen saturations of 80% at rest, and severe right heart failure with low CO and high RAP are at higher risk for death. 85 Although this approach is used in some centers purely as a bridge to transplantation or palliative salvage therapy, there is evidence that earlier performance of atrial septostomy is safer and possibly more effective. 86 The key to patient candidacy for atrial septostomy is early selection in patients with moderate-to-severe disease where the procedure is considered elective rather than rescue therapy. 86

Extracorporeal membrane oxygenation (ECMO) or extracorporeal life support in conjunction with targeted PAH therapy is considered a mechanical–medical bridging therapy. Until recently, adverse effects of venoarterial ECMO (including deconditioning, bleeding, thromboembolism, limb ischemia, cerebral hypoxia, and pulmonary hemorrhage) have limited its use 87,88 in patients with PAH awaiting lung transplantation. Small but promising case series data are emerging from experienced ECMO centers. Rosenzweig et al, 89 for example, presented 6 patients with PAH from 2009 to 2012 who were placed on physiological venoarterial-ECMO with either bridge-to-transplant (BTT) or bridge-to-recovery intent. Bridge-to-recovery patients were deemed eligible for venoarterial-ECMO by the consensus of a multidisciplinary team of PAH specialists, cardiothoracic surgeons, ECMO–critical care specialists, and neurologists. The 2 transplant-eligible patients underwent successful BTT. Three of the 4 patients with bridge to recovery survived until ECMO decannulation. Notably, PAH medical therapy was typically down-titrated in patients with BTT to limit the hemodynamic side effects of PAH therapy on ECMO, whereas it was up-titrated in patients with bridge to recovery, highlighting the importance of specialized knowledge of potential medical–mechanical therapeutic interactions. Finally, an extubated, upper-body venoarterial-ECMO cannulation approach was used to allow for...
ambulation and participation in physical therapy and to avoid the deleterious impact of general anesthesia and intubation on the right heart. This upper-body strategy to venoarterial-ECMO is detailed by Abrams et al90 and Olsson et al91 who present generally successful results. Future studies are needed to evaluate the use and appropriateness of ECMO prospectively as either BTT or bridge-to-recovery intent.

Right ventricular assist devices (RVADs) have been successful in RV failure in the setting of biventricular heart failure, after left (L) VAD placement and after heart transplantation.92 Essentially, the RVAD is an internal device with its inflow cannula typically placed in the RA and its outflow cannula in the PA. Computational RVAD model data92 and 2 case reports88,93 of RVAD use in cardiogenic shock secondary to PAH demonstrate RV unloading by decreases in RAP and improvement in CO at the expense of increasing pulmonary artery pressure and pulmonary capillary wedge pressure. Increases in pulmonary artery pressure and pulmonary capillary wedge pressure in the RVAD model system seem to occur in an RVAD-flow dependent manner92 and hence low-flow support might be better tolerated. Given the intrinsic increased and fixed PVR in PAH, implementation of RVAD may be problematic given the theoretical concern for resulting pulmonary vascular damage.94 The use of RVAD therapy as bridge to recovery or transplantation will require further research and comparison with other mechanical support strategies and is not currently routinely performed in PAH.

The lung assist device (LAD) membrane oxygenator system, or Novalung, is a pumpless device that relies on the pressure gradient between the pulmonary artery and left atrium to function.95–97 Novalung is the most promising of the mechanical support strategies for PAH and is gaining momentum as RV salvage technology because of its ability to partially bypass the high-resistance pulmonary vascular bed. Novalung is connected to the heart and lungs in parallel, as opposed to in series as the RVAD system; this allows for the lowest resistance circuit possible. Essentially, the LAD’s inflow cannula is placed in the main PA and the outflow cannula in the LA, creating a shunt across the damaged pulmonary vasculature. It is an external device that typically receives >20% of total CO.95–97 Usually, this degree of blood flow is sufficient in removing carbon dioxide but not in improving oxygenation. Severe hypoxemia mandates LAD modifications97 that are challenging but technically feasible. Such approach importantly evades the requirement for intubation and mechanical ventilation. Schmid et al96 reported a case of a PAH patient who survived 62 days on an LAD before undergoing successful bilateral lung transplantation. Strueber et al95 reported 4 cases of patients with PH (3 patients with pulmonary veno-occlusive disease and 1 patient with CTEPH [chronic thromboembolic pulmonary hypertension]) who developed refractory cardiogenic shock and survived 8 to 30 days on a LAD until successful heart–lung or bilateral lung transplantation with dramatic improvements in hemodynamics, inotropic requirements, and gas exchange parameters in the interim. Of note, 2 of the 4 patients required ECMO on LAD implantation because of complications of general anesthesia. Therefore, it should be recognized that LAD implantation is not without risk and requires a skilled, multidisciplinary team experienced with both ECMO and LAD technologies. If the early experience with LAD strategy continues to show promise in larger series, it may address the dilemma of long transplant waiting times that are still common for patients with PAH in the post lung allocation scoring era.34,35 Regardless of the modality, the use of assist devices as a BTT in PAH remains extremely rare96 but promising for the future.

Structure and Function of a PAH Program

The structure and function of modern-day pulmonary vascular disease programs is highly specific to the environment in which they function. Community-based programs are typically set in private-practice models and thus are highly focused on the clinical care of patients with PAH with some involvement in pharmaceutical clinical trials. Academic programs, however, are usually a combination of clinical expertise along with basic, translational, or clinical research programs, depending on the depth and breadth of experience. Such as other academic programs, our mission in the Stanford Adult Pulmonary Hypertension Program is to provide excellent patient care, carry-out cutting-edge clinical–translational research, and provide an educational environment for training physicians in pulmonary vascular diseases. As such, we have developed a clinical service composed of 1 medical director, 5 attending physician (combination of clinical and basic research scientists), 2 nurse practitioners, 1 to 2 pulmonary vascular superfellows (postgraduate pulmonary or cardiology fellows training in pulmonary vascular diseases for 12 months), 1 medical social worker, 3 clinical research staff, and 3 patient coordinators. Although modest in size, to realize the educational and research goals of a rare disease program, we have established a multidisciplinary structure optimizing clinical care–research interactions (Figure 4). For example, during outpatient clinic visits, several research associates also attend clinic to screen clinical trials subjects, consent, and collect samples for database and biobank.

With the expansion of knowledge and subspecialization in pulmonary vascular diseases and advent of numerous therapeutics, it is vital that programs with specific expertise in PAH become organized and meet consensus recommendations of practice, particularly in terms of diagnostic methods. As such, the pulmonary hypertension care centers initiative led by the Pulmonary Hypertension Association is an organized attempt at harmonizing care provided to patients with PH in the United States. With the implementation of specific criteria and benchmarks, including quality and depth of center experience, degree of infrastructure, referral/care model, and commitment to research, the goal of the pulmonary hypertension care center is to improve overall quality of care and ultimately to improve outcomes (http://www.phassociation.org/PHCareCenters).

Research Perspective/Commitment as an Academic Institution

With the full recognition that care of patients with PAH occurs at variety of types of institutions (from community to major tertiary medical centers with or without academic programs), patients with such a rare and lethal cardiopulmonary disease...
should have access to cutting-edge clinical research—both clinical trials, as well as observation registries, and biobanking programs. These initiatives are usually instituted at academic centers where active, bidirectional collaboration between the basic and clinical scientists exist (Figure 4). A highly productive model would be based on mutual collaboration between bench science and clinicians in which active bidirectional collaboration would initiate laboratory-based approaches that ultimately can empower future therapeutic testing in the clinical environment. There are numerous global examples of such research pipeline, such as the repurposing of dichloroacetate\(^9\) (ClinicalTrials.gov identifier NCT01083524), imatinib,\(^9\)\(^-\)\(^10\) and FK506, which has recently taken place at our institution\(^12\) (ClinicalTrials.gov identifier NCT01647945).\

Prerequisites for success of translational research are a supportive institutional environment that fosters basic and clinician scientists to engage in research in PAH as well as a clinical team that is well connected with the research team and eager to translate scientific findings into the clinic. Two important tools that have facilitated clinical and translational research at our institution have been the clinical database and tissue biobank. The Vera Moulton Wall Center PH database was established in 2000 and has collected records of \(>1000\) patients with PH from 1996 to present. This relational database captures \(>300\) demographic, clinical, and research-related parameters, and it was originally designed on an Access platform that required clinical staff to collect and enter all data manually—a tremendously time-consuming process. With the implementation of electronic medical records, our database has now migrated to an Oracle platform with back-end access to electronic medical record, substantially reducing the manual data entry needs. Although it is difficult to report exact cost, we estimate the initial development and implementation of Vera Moulton Wall Center PH database cost \(\approx 250,000\), and this has required ongoing programming, upkeep, and server fees along with 1 full-time database manager support. Initiated in 2006, our tissue biobank has been tasked with collecting blood, urine, saliva, and exhaled breath condensate from control and patients with PH. Initially, we attempted to collect samples at baseline and every 6 months in any clinical environment. However, we found this process to be complex and usually incomplete, especially in the outpatient setting. We have now formulated a coordinated protocol that samples fasting subjects before cardiac catheterization, which not only allows for available hemodynamic correlates but also standardizes collection. The task of biobanking also creates the need for data management (ie, sample inventory and tracking). Until recently, we have used Freezerworks Unlimited software (Dataworks Development, Inc. Mountlake Terrace, WA) but have now integrated biobank data into our own database. Implementation and upkeep of our biobank has required 1 to 2 full-time research associate support beyond the basic facilities costs. Finally, it has been extremely useful that our research associates are integrated to the clinical workings of the service and have paging/call access for collection of samples at unusual times such as is customary with transplant tissue procurement. The availability of such infrastructure along with academic collaboration facilitate initiation of institution-based studies, which have the advantage of evaluating multiple clinical and translational research questions and may eventually lead to multicenter phase II/III trials when appropriate.

Although participation in multicenter clinical trials are encouraged, not every tertiary PAH center participates in every study. A national and international network and subsequent collaboration of PAH centers could allow for development of research infrastructure, including cross referrals and inclusion in clinical trials in a different center in close proximity. The ClinicalTrials.gov (www.clinicaltrials.gov) and Pulmonary Hypertension Association (http://www.phassociation.org/Patients/Research) are simple accessible platforms that provide overview and information about all trials for PAH and should be used as a reference for patients and physicians. During the clinic visit, the patient should ask the PAH physician about current clinical trials the individual might qualify for. The PAH physician then should explain the details of the trial, the proposed mechanism of action, whether a special subtype of PAH is targeted in the trial, and what risks and benefits might be for the patient. Although often not of immediate clinical benefit for a patient, participation in a clinical trial has the advantage of close follow-up by the PAH team, a possible earlier availability of a study drug, and knowing that by participating in a clinical trial, research in PAH is advanced with possible implications for future PAH treatments. Emerging new treatments and targets for PAH that are currently in clinical phase I–III trials are summarized in Table 2. Historically, major therapeutic clinical trials (both preclinical and pivotal studies) have been largely sponsored by the pharmaceutical industry. The success of the past 2 decades has been the advent and approval of therapeutics that have altered the course of PAH but are arguably not curative. These organizations have assumed great financial risks to bring therapeutics to the field and are positioned in an expert role in conduct of major multicenter, global clinical trials. We think that the time has come to foster a different brand of collaboration for

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Figure 4. Schematic depicting a clinical and research collaborative model build around pulmonary hypertension academic programs. NIH indicates National Institutes of Health; PH, pulmonary hypertension; and VAD, ventricular assist device.
rare disorders such as PAH—closer collaboration between industry, academic institutions, and governmental research institutions such as the United States National Institutes of Health. The advantage of collaborative trials conducted by an industry–National Institutes of Health collaborative would be combination of expertise in clinical trial design and management, organizational support, cost sharing, and establishment of early proof of concept clinical trials that offer the most potential for discovery of curative therapies but are deemed financially high risk. Such initiatives could also expedite novel clinical trial design to overcome the limitations of current studies. Ultimately, complacency with the current process of drug discovery may result in continued production of highly specific me-too drugs—only improving specific aspects of existing therapeutics. Ideally, an academic–industry collaborative would be tasked to better define disease modification as a necessary concept in the path to curative therapeutics and encourage the testing of such modalities.

The current era of PAH management is characterized by the increasing number of therapeutics, more clinical subspecialization, and more complex clinical decision making—a process in which not only the clinician but also the patient must actively participate. Initiatives such as large registries have transformed our clinical understanding and have allowed a deeper understanding of concepts such as risk stratification and early diagnosis. The next phase of growth for the field should come from refinement of practice standards, both scientifically through clinical studies and structurally. Initiatives, such as the Pulmonary Hypertension Association pulmonary hypertension care center to standardize practice patterns are highly relevant for countries (such as the United States), where the care of patients with PAH is not centralized (compared with those in France and the United Kingdom). Finally, development of future therapeutics should focus on characterization and testing of disease-modifying drugs.

**Table 2. Emerging Therapies**

<table>
<thead>
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<th>Drugs</th>
<th>Proposed Mechanism</th>
<th>NCT Identifier</th>
<th>Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sapropterin dihydrochloride (6R-BH4)</td>
<td>Increase nitric oxide</td>
<td>NCT00435331</td>
<td>Phase I</td>
</tr>
<tr>
<td>Selexipag</td>
<td>Non-prostanoid IP receptor agonist</td>
<td>NCT01106014</td>
<td>Phase III</td>
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<td>Inhaled nitric oxide</td>
<td>Increase nitric oxide</td>
<td>NCT01457781</td>
<td>Phase II</td>
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<td>Beet juice</td>
<td>Increase nitric oxide</td>
<td>NCT02000856</td>
<td>Phase I</td>
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<td>Apelin</td>
<td>Increase apelin levels with infusion</td>
<td>NCT01590108</td>
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<tr>
<td>Cardizem</td>
<td>Calcium channel blockade</td>
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<td>Inhaled nitrite</td>
<td>Increase nitric oxide</td>
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<td>Ranolazine</td>
<td>Inhibition of sodium current</td>
<td>NCT01757808</td>
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**Metabolism**

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<td>Dichloroacetate</td>
<td>Inhibition of pyruvate dehydrogenase kinase</td>
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<td>Anastrozole</td>
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<td>HIF activation, NO synthesis, β-adrenergic receptor recovery</td>
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<td>Improvement of endothelial function</td>
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<td>(−)-Epicatechin</td>
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BMPR2 indicates bone morphogenetic protein receptor 2; HIF, hypoxia inducible factor; IP, prostacyclin receptor; and NO, nitric oxide.

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A Patient Asks Questions…

You mentioned that there are 3 classes of medications available to me; which is the best? Will I eventually be in all of them? I am insured but will I be able to afford this?—treatments seem to be so expensive...

It depends on the severity of the disease at diagnosis, feasibility, the patient’s preference, the PH center’s expertise, and unfortunately insurance coverage, which drug a patient will be started on. If the patient is in WHO functional class II/III (in other words moderate to moderately severe disease), oral phosphodiesterase type 5 inhibitors (the first drug on this class approved in PAH was sildenafil, and others followed) or ERAs (the first drug on this class approved in PAH was bosentan and others followed) would be the current preferred choice. For WHO functional class IV (ie, severe disease), most PAH clinicians in the United States would choose an intravenous prostacyclin. No head-to-head study has been done to answer which drug is superior to another. Combination therapy (in other words use 2 or 3 classes of medications at the same time) is common and is currently evaluated as a first-line therapy (ie, start 2 classes of drugs from the beginning, instead of starting one and adding another later on).

In the United States, patient assist programs are in place for all available drugs to help with drug cost coverage. Patients should ask their physician and social worker for information about financial aid. In Canada and many European countries, approved therapies are covered for all patients at no or low cost.

Research is actively performed to discover which class of medications is potentially best for a given patient. This may dramatically facilitate our decision making for the best choice of therapy because more drugs are getting approved.

Should I be optimistic about the future? It seems that there are so many cures for PAH in animal research, but the currently available therapies do not cure the disease—why?

The research in humans with therapies developed in animals is called translational research, and we now know that it suffers not only in the PAH field but also across all the fields of medicine. It is a complicated, long, and often expensive process. The scientific community is now specifically focusing to increase the efficiency of transferring knowledge from animal research to patients, and young physicians and scientists are starting to gain the required skills. The field of PAH is still relatively new, and considering that it often takes 10 years to prove that a promising therapy in animals is also effective in humans, we expect to see many more new therapies entering clinical trials in the immediate future. New theories hold promise for the development of more effective drugs with fewer side effects than those caused by the currently available ones. Many promising drugs developed from animal studies and currently evaluated in clinical trials are reviewed in this compendium, and in addition to this, they are also listed in the next 2 articles.

You mentioned there will be many research trials in the future that I may consider. How should I be best informed on which one is the most promising?

The best resource to learn about clinical trials in PAH is the PH physician in a specialized PAH center. In addition, the ClinicalTrials.gov (www.clinicaltrials.gov) and Pulmonary Hypertension Association Web sites (http://www.phassociation.org/Patients/Research) are simple accessible platforms, which provide overview and information (in a language often appropriate to be understood by the average-informed patient) about all ongoing trials for PAH and should be used as a reference for patients and physicians alike.

For the case description, see introductory article by E.D. Michelakis, page 109.

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