ing group supported the conservative positions and limited the changes to the removal of exercise criteria of PH, retaining the simple and universally recognized definition based on resting PAP ≥25 mm Hg. Another area that did not change much despite earlier expectations was the approach to echocardiographic diagnosis of PH. When compared with the Venice consensus, which offered an option of making an echocardiographic diagnosis of "mild PH," we may have even taken a step back. The current document limits the statement to a prudent: "it appears reasonable to consider TJV >2.8 m/s and TIPG ≥31 mm Hg at rest as elevated, except in elderly and/or very obese patients." In addition to collecting and digesting new evidence in PAH, the objective of future meetings must involve providing clearer indications about when to proceed to right heart catheterization and when to consider echocardiography as sufficient evidence of PH, particularly in the presence of clear causative factors such as lung or left heart disease. Professor Robert Naeije's suggestion to create and prospectively validate a noninvasive score assessing the "probability of PAH" and assisting in the decision whether to perform right heart catheterization seems very timely.

New evidence that could be useful in identification of an optimal set of goals to be achieved by PAH therapy would be most welcomed before the next world meeting, which should preferably be dedicated to the entirety of the pulmonary circulation rather than just PH. ■

Updated Evidence-Based Treatment Algorithm in Pulmonary Arterial Hypertension

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Ernst von Romberg, a German physician, described an autopsy in 1891 as "pulmonary vascular sclerosis"; however, only with the introduction of intravenous epoprostenol in 1995 have disease-specific targeted medical therapies for pulmonary arterial hypertension (PAH) become available. Furthermore, significant advances in the treatment of PAH have occurred during the past 15 years, with 8 medical therapies now approved. These agents target the prostacyclin pathway, the nitric oxide (NO) pathway, and the endothelin (ET-1) pathway. In addition, combination trials have demonstrated additive or synergistic benefit by targeting 2 or 3 of these pathways (**Figure 1**).

At the 4th World Symposium on Pulmonary Hypertension in Dana Point in early 2008, both uncontrolled and controlled clinical trials with different compounds and procedures were reviewed and compared to define

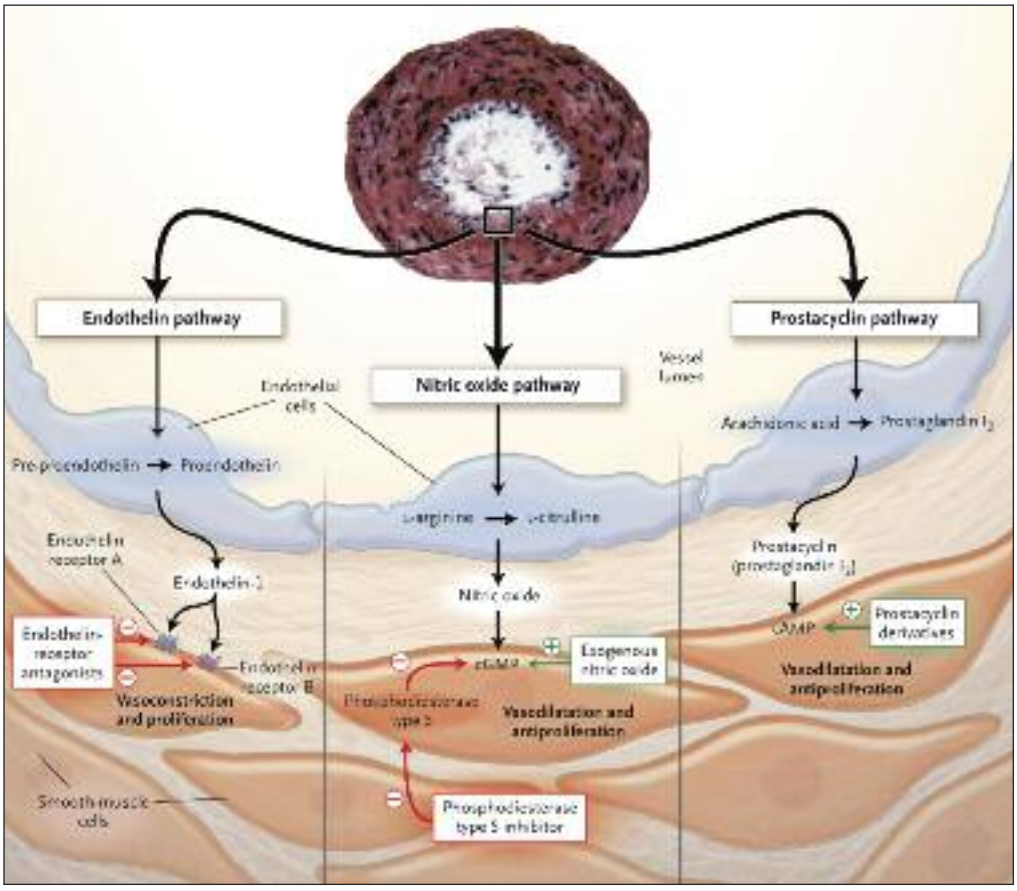

Figure 1. Pathways now defined for the treatment of PAH. (reprinted with permission from Humbert M, et al. *New Engl J Med*. 2004;351:1425-1436).

Key Words—idiopathic, calcium channel blockers, functional class, atrial septostomy, lung transplantation

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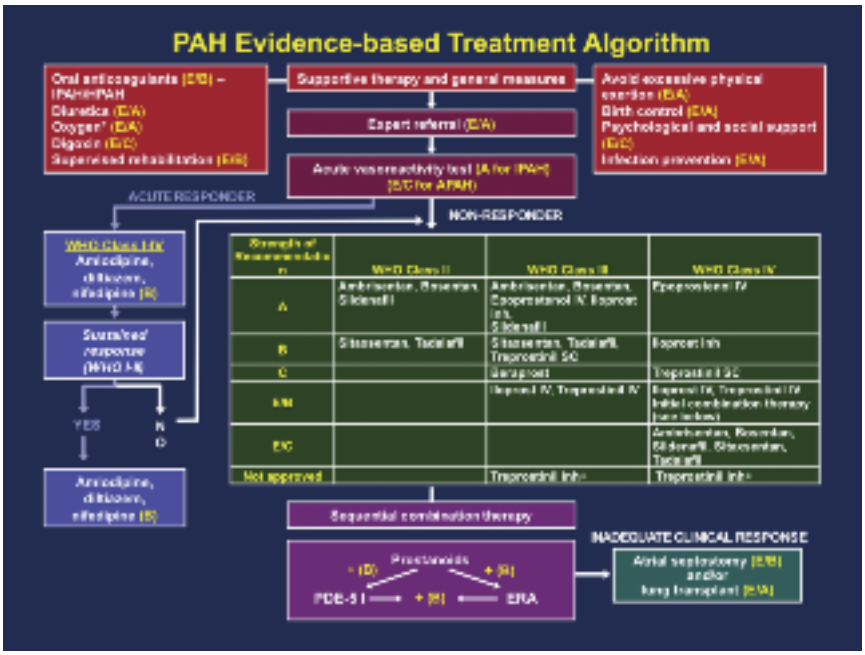

Figure 2. Algorithm of the quality of evidence and the magnitude of the treatment effect.

the risk-benefit profiles for PAH therapeutic options. The objective of the Medical Treatment Task Force at the Dana Point meeting was to review all the randomized controlled trials (RCTs) performed in PAH and to propose an evidence-based updated treatment algorithm that would incorporate the currently available therapies. These clinical studies included compounds targeting 3 pathways in the pathobiology of PAH; ie, the NO pathway, the ET-1 pathway, and the prostacyclin pathway.

Nineteen RCTs with 8 compounds as monotherapy have been completed to date in PAH patients. In addition, 5 RCTs testing the combination of agents have been completed. Approximately 5000 patients have participated in these studies to date to develop effective treatments for PAH and, ultimately, to find a cure for PAH.

A grading system incorporating both the quality of evidence and the magnitude of the treatment effect was utilized in developing the PAH treatment algorithm (**Figure 2**). The algorithm included drugs approved by regulatory agencies for the treatment of PAH and/or drugs available on the market for other indications. The different treatments that have been evaluated were studied primarily in idiopathic or heritable PAH, and in PAH associated with connective tissue diseases or with anorexigen use. Extrapolation to the other PAH subgroups should be done with caution.

Oral anticoagulation remains proposed for idiopathic and heritable forms of PAH, whereas diuretic treatment and supplemental oxygen are indicated in cases of fluid retention and hypoxemia, respectively. High doses of calcium channel blockers remain indicated only in the minority of patients who are responders to acute vasoreactivity testing. Nonresponders to acute vasoreactivity testing, or responders who remain NYHA functional class III, should be considered candidates for treatment with either an oral PDE-5I or an oral ERA. Continuous intravenous administration of epoprostenol remains the treatment of choice in NYHA functional class IV patients. Combination therapy is recommended for patients treated with either PDE-5I or ERA monotherapy who remain NYHA functional class III. Both atrial septostomy and lung transplantation are indicated for refractory patients or where medical treatment is unavailable.

The conclusions derived from the clinical trials over the past 15 years will allow us to treat patients with an evidence-based treatment strategy. In addition, we look forward with enthusiasm to reviewing ongoing and future clinical trials in 2013 at the 5th World Symposium on Pulmonary Hypertension in Paris with the next update to follow in evidence-based PAH treatment strategies to further improve outcomes for PAH. ■