Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 62, No. 25, Suppl D, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.10.030

INTRODUCTION

The Fifth World Symposium on Pulmonary Hypertension

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Sometimes pivotal events can be identified in the history of a disease that mark the borders of different eras in the diagnosis or treatment. One of these pivotal events in the history of pulmonary arterial hypertension (PAH) was the publication in 1996 of the paper of Barst et al. (1) on continuous intravenous epoprostenol therapy for primary pulmonary hypertension. For the first time, a medical therapy was shown to reduce substantially the mortality of a disease defined as the "kingdom of the near dead" (2). In her outstanding career, Dr. Barst made considerable contributions to the additional pivotal events in the PAH history, which can be identified in the World Symposia on Pulmonary Hypertension (WSPH) that has been held since 1973. The influence of Dr. Barst spanned every aspect of the disease from pediatrics to adulthood and from genetics to randomized, controlled trials (RCTs). Her interventions in the discussions were unmistakable and full of energy and passion, and this passion also characterized her last days when the energy was fading. We miss her, and we would like to remember her with the last gift she has left us: the example of a physician and a scientist fully engaged in her activity until the end of her life. Even if she was not able to personally attend the meeting, we dedicate the 5th WSPH to her memory.

The achievements of the different WSPH have marked the progress made on this condition. The first WSPH was held in Geneva, Switzerland, in 1973 and was organized by the World Health Organization because of an epidemic of PAH cases due to the use of aminorex, an anorexigen drug (3). A simple clinical classification was proposed at this meeting (primary, secondary, and associated pulmonary hypertension [PH]) together with the hemodynamic definition of the disease as a mean pulmonary arterial pressure ≥25 mm Hg. The well-known National Institutes of Health Registry on primary pulmonary hypertension was launched after this first symposium (4).

The second WSPH was held 25 years later in 1998 in Evian, France. There were multiple reasons for starting the modern series of WSPH, including the availability of 2 very effective treatments such as epoprostenol (1) and high doses of calcium channel blockers in patients responding to acute vasoreactivity tests (5). A more comprehensive clinical classification, including 5 groups, was proposed for the first time at the symposium, and this facilitated both clinical practice and the clinical research.

In fact, in the third WSPH, which was held in Venice, Italy, in 2003, there were already 3 classes of drugs effective in the treatment of PAH (prostanoids, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors), and a specific treatment algorithm was proposed (6). The clinical classification was refined, including the familial form characterized by the *BMPR2* gene mutations (7).

The fourth WSPH was held in Dana Point, California, in 2008. New management strategies were introduced such as the treatment of mildly symptomatic patients and the combination and goal-oriented treatment strategies (8). The RCT design was also discussed, including the need to use time to clinical worsening as primary endpoint in phase III registration studies (9).

The fifth WSPH was held in Nice, France, from February 27 to March 1, 2013; the findings and recommendations of 129 worldwide experts divided into 12 task forces operating for 12 months were discussed in front of an audience of ~1,000 physicians and representatives of the industry, patient associations, and regulatory agencies.

The main conclusions of the task forces and the meeting discussions are reported in the 13 articles published in this supplement of the *Journal of the American College of Cardiology*.

The Pathology and Pathobiology Task Force reports the increasingly recognized importance of venous disease in PH as well as the disordered metabolism and mitochondrial structure, inflammation, and dysregulation of growth factors leading to a proliferative, apoptosis-resistant state of the pulmonary vascular cells (10).

The Genetics and Genomics Task Force confirms a 75% mutation detection rate for the known genes (*BMPR2*, *ALK1*,

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Manuscript received October 18, 2013; accepted October 22, 2013.

Endoglin, *SMAD-9*, *CAV1*) in familial PAH patients (11). New-generation sequencing techniques have allowed the identification of a new recently reported gene encoding the potassium channel KCNK3 (12). The importance of genetic testing and counseling and genomic studies is also discussed.

The clinical and prognostic importance of the right ventricle adaptation to the increased afterload in PH patients is outlined by the Task Force on Pathophysiology: "adaptive" and a "maladaptive" right ventricle phenotypes are described with specific molecular, structural, and hemodynamic characteristics (13).

An updated clinical classification, for the first time the same for adult and pediatric patients, is proposed by the specific Task Force (14). Changes includes the individual categorization of the persistent PH of neonates; the addition of congenital diseases in groups 2, 3, and 5; and the shifting of PH associated with chronic hemolytic anemias from group 1 to group 5. New drugs potentially inducing PH are also listed.

The Task Force for Definitions and Diagnosis provides a new hemodynamic definition of PAH, including pulmonary vascular resistance, and a more accurate and standardized zero level for the transducer at right heart catheterization (15). The term "borderline PH" is discouraged and the definition of PH on exercise is still considered not possible. Indications for screening strategies in asymptomatic patients and an updated diagnostic algorithm are also provided.

The Task Force on Epidemiology and Registries describes the basic methodology by which PAH registries have been conducted and review key insights provided by registries (16). An analysis on the utility of data to predict the survival outcomes is also discussed.

An updated treatment algorithm is provided by the Task Force on Standard of Care including new published data concerning rehabilitation, combination therapy, new compounds (17–19), and lung transplantation (20,21). The importance of the effect of the drugs on patient outcome is also outlined (22).

The Task Force on Treatment Goals for PH confirms the need to analyze multiple goals for defining the success of therapy including symptoms, exercise capacity and the right ventricular function (23). Specific absolute values for the relevant parameters are also provided.

The Task Force on New Trial Designs and Potential Therapies for PAH confirms the need to adopt a morbidity and mortality primary endpoint in future phase 3 randomized, controlled trials (24). No surrogate endpoints are identified in PAH and correlates may be included in phase 2 studies. Different novel drugs in very early stages of development are also reported.

The Task Force on Chronic Thromboembolic Pulmonary Hypertension provides new diagnostic and treatment algorithms for this condition (25). Pulmonary endoarterectomy is confirmed as the treatment of choice for the affected patients, and medical therapy is used in nonoperable ones and in those with persistent PH after surgery (26).

The Task Force on PH due left heart disease and due to lung diseases recommends that the term "out of proportion" PH should be abandoned in both conditions (27,28). A new nomenclature for PH due to left heart disease and the use of the diastolic gradient (diastolic pulmonary pressure − mean pulmonary artery wedge pressure) for the identification of patients with a pre-capillary PH component is reported (27). Similarly, new definitions are provided for PH due to lung diseases (28). Targeted therapies have not provided convincing benefits in both conditions (27,28).

The Task Force on Pediatric PH proposes new diagnostic and treatment algorithms adapted for this group of patients (29). The general structure is similar to the algorithms used in the adults but takes into consideration the specific characteristics and requirements of the pediatric patient population.

In conclusion, this supplement of the *Journal of the American College of Cardiology* provides the cutting-edge knowledge in the different fields of PH, as discussed in the fifth WSPH.

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Key Words: Fifth World Symposium ▪ pulmonary arterial hypertension ▪ pulmonary hypertension.