Risk Stratification—What's My Risk? A Practitioner's Tool

Ioana R. Preston, MD
Pulmonary, Critical Care and Sleep Division
Tufts Medical Center
Boston, MA

At the 6th World Symposium on Pulmonary Hypertension, the task force on clinical risk stratification and medical therapy in pulmonary arterial hypertension (PAH) reviewed the latest developments published in the field of therapeutics since the previous meeting and presented their consensus opinions to an audience of 1376 participant attendees between February 27 and March 1, 2018, in Nice, France. After participants' input was incorporated, the final recommendations were published in the *European Respiratory Journal*.[1]

In the past several years, treatment for PAH was based on several parameters to determine the severity of the disease and risk of progression and poor outcome. These parameters included New York Heart Association Functional Class (NYHA FC), exercise capacity represented by the 6-minute walk distance (6MWD), and echocardiographic and hemodynamic measurements. Until recently, the guidelines for initiation and escalation of therapy relied mostly upon NYHA FC.[2] However, data from 3 independent registries demonstrate the importance of a methodical risk assessment and treatment strategy in PAH patients. All registries prove that, in order to obtain a good outcome (assessed as event-free survival at 1 year), patients need to achieve a low-risk status.

DEVELOPMENT OF RISK ASSESSMENT TOOLS FROM VARIOUS REGISTRIES

The task force evaluated several risk scores developed from the US and European registries: the French Pulmonary Hypertension Network (FPHN) registry risk equation,[3,4] the US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) risk equation[5] and risk score,[6,7] the Swedish PAH Register,[8] and the COMPERA Registry.[9] They also evaluated the PH connection equation,[10,11] the Scottish composite score,[12] and the previous 2015 European Society of Cardiology and the European Respiratory Society PH guidelines.[2] We will briefly review the main 3 risk scores (FPHN, Swedish/COMPERA, and REVEAL), and point out some of their differences, advantages, and disadvantages for the practitioner. All risk calculators demonstrated good discrimination for long-term outcome.

The Swedish/COMPERA Risk Calculator

The Swedish PAH Register[8] and COMPERA[9] studies included both idiopathic and associated PAH patients and applied a risk score at baseline and at the first follow-up. A table of the variables is presented in Table 1. The risk calculator assigns a score of 1, 2, or 3 to each criterion (1 = low risk, 2 = intermediate risk, and 3 = high risk) and calculates the mean of the available variables.

The French Risk Calculator

In the FPHN registry,[13] risk assessment was performed in incident idiopathic, heritable, and drug-induced PAH patients according to the presence of 4 low-risk criteria: (1) NYHA FC I or II, (2) 6MWD > 440 m, (3) right atrial pressure < 8 mm Hg, and (4) cardiac index ≥ 2.5 L/min/m^2. Patients were classified according to the number of low-risk criteria present at baseline or at the time of reevaluation. As exploratory analyses, the additive value of brain

Table 1. Variables used in the Swedish/COMPERA calculator[a]

Variables	Low risk, score = 1	Intermediate risk, score = 2	High risk, score = 3
NYHA FC	I/II	III	IV
6MWD, m	>440	165–440	<165
BNP, ng/L	<50	50–300	>300
NT-proBNP, ng/L	<300	300–1400	>1400
RAP, mm Hg	<8	8–14	>14
CI, L/min/m^2	≥2.5	2.0–2.4	<2.0
SvO_2, %	>65	60–65	<60

Abbreviations: 6MWD = 6-minute walk distance; BNP = brain natriuretic peptide; CI = cardiac index; NT-proBNP = N-terminal precursor of brain natriuretic peptide; NYHA FC = New York Heart Association Functional Class; RAP = right atrial pressure; SvO_2 = mixed venous saturation.

[a]Adapted from Hoeper et al.[9]

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Correspondence: ipreston@tuftsmedicalcenter.org.
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natriuretic peptide (BNP) < 50 ng/L or N-terminal pro-BNP (NT-proBNP) < 300 ng/L plasma levels or mixed venous saturation (SvO_2) > 65% as low-risk criteria was assessed in the subsets of patients for whom these data were available.

The REVEAL Risk Calculator

The initial score was developed from a US-based cohort of 2716 PAH patients, used 12 modifiable and nonmodifiable parameters measured at baseline, and provided the 12-month likelihood of survival (5 strata) in incident and prevalent idiopathic and associated PAH patients.[5] The REVEAL score has been validated in incident patients.[14] If used at follow-up, the equation can predict outcome at 1 additional year.[7] The REVEAL 2.0 score is an updated variation using fewer parameters and is more user friendly.[15] Although at the time of the symposium the updated version had not been published, here, we present the updated version in Table 2.

COMPARISON OF VARIOUS RISK ASSESSMENT TOOLS

The 3 risk calculators provide good discrimination for low, intermediate, and high risk (Table 3), REVEAL 2.0 having the highest discrimination score. The FPHN risk assessment strategy provides an accurate and easy identification of patients with an excellent long-term survival. The French score is the easiest to apply, having only 4 variables obtained noninvasively, although it has been developed only in idiopathic, heritable, and drug-induced PAH. The goal of the French score is to identify patients who do not need escalation of care. The downside is that a minority of patients achieve this very low-risk status, and the French calculator does not give any insights as to how to modify the treatment of those patients who do not fall into the very low-risk category. On the other hand, the other scores have been tested in both idiopathic and associated PAH. REVEAL 2.0 has the most variables and is the only one to include all-cause hospitalizations within the previous 6 months and the presence of renal failure, both of which have been shown to impact mortality.[16,17]

Table 2. Variables included in the updated REVEAL 2.0 risk calculator[a]

Variables			
WHO Group I subgroup	CTD-PAH	POPH	Heritable
	+1	+3	+2
Demographics	Male age > 60 years		
	+2		
Comorbidities	eGFR < 60 mL/min/1.73 m^2 or renal inefficiency (if eGFR is unavailable)		
	+1		
NYHA FC	I	III	IV
	–1	+1	+2
Vital signs	SBP < 110 mm Hg		HR > 96 BPM
	+1		+1
Hospitalizations	All-cause hospitalizations within 6 months		
	+1		
6MWD	≥440 m	320 to < 440 m	< 165 m
	–2	–1	+1
BNP or NT-proBNP	BNP < 50 pg/mL or NT-proBNP < 300 pg/mL	200 to <800 pg/mL	BNP ≥ 800 pg/mL or NT-proBNP ≥ 1100 pg/mL
	–2	+1	+2
Echocardiogram	Pericardial effusion		
	+1		
Pulmonary function test	D_LCO < 40% predicted		
	+1		
Hemodynamics	mRAP > 20 mm Hg within 1 year		PVR < 5 Wood units
	+1		–1

Abbreviations: D_LCO = diffusion capacity for carbon monoxide; CTD-PAH = connective tissue disease associated pulmonary arterial hypertension; eGFR = estimated glomerular filtration rate; HR = heart rate; POPH = portopulmonary hypertension; PVR = pulmonary vascular resistance; SBP = systolic blood pressure; WHO = World Health Organization. For other abbreviations, see Table 1.

[a]Adapted from Benza RL, Gomberg-Maitland M, Elliott CG, et al.[15]

Table 3. Comparisons between the risk calculators[a]

	REVEAL 2.0	Swedish PAH Register	COMPERA	French PH Network
Variables	12	8	8	4
Patients at baseline, n	2529	530	1588	1017
Patients at follow up, n		383	1094	1017
Type of PAH	IPAH, APAH	IPAH, APAH	IPAH, APAH	IPAH
Definition of low risk/ intermediate/high	6/7–8/9–12	Low: <1.5	Low: <1.5	Low: 3 or 4
1 year mortality by risk group (low/intermediate/ high), %	2.0/5.0/60.0–10.0	1.0/7.0/26.0	2.8/9.9/21.2	1.0/NA/13.0–30.0

Abbreviations: APAH = associated pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; NA = not applicable.

[a]Adapted from Galié et al.[1]

In conclusion, there is strong relationship between risk stratification and outcome. The recently developed risk assessment tools help guide the treatment strategy for PAH based on disease severity as assessed by a multiparametric risk stratification approach. These risk scores are intended to complement the clinician's clinical judgment for any individual patient. Clinicians can now apply various risk scores in everyday practice depending on the type of PAH patient and choose the appropriate combination therapy or monotherapy (for a minority of patients). Further treatment escalation is required if low-risk status (considered as treatment goal) is not achieved in structured follow-up assessments.

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