RISK STRATIFICATION IN PAH
IMPACT IN PROGNOSIS AND TREATMENT

Eftychia Demerouti MD, MSc, PhD
Cardiologist
Onassis Cardiac Surgery Center
NAME OF COMPANIES WITH WHICH RELATIONSHIP EXISTS
Actelion Pharmaceuticals Ltd
Elpen
Galenica
Menarini
Servier Hellas

NAME OF RELATIONSHIP
Consultant
Grants
Advisory Board Member

At diagnosis, measurements of hemodynamic variables, pulmonary function, and gas exchange variables were taken in addition to information on demographic variables, medical history, and life-style. Patients were followed for survival at 6-month intervals.

Variables associated with poor survival included a New York Heart Association (NYHA) functional class of III or IV, elevated mean RAP, elevated mean PAP, decreased CI, and decreased diffusing capacity for carbon monoxide (DL_{CO}).

Mortality an equation using three variables: mPAP, mean RAP, and C.I., each of which was shown to contribute independently toward the prediction of risk of death.
1-, 2-, and 3-year survival estimates were 85.7%, 69.5%, and 54.9%, respectively, for incident cases.
In this analysis of 2716 patients

1-year survival was 91% from the date of enrollment

1- and 3-year survival rates from the time of PAH diagnosis were 87.7% and 72.1%, respectively

Individual survival analysis identified the following as significantly and positively associated with survival:

- female gender,
- NYHA class I/II,
- greater 6MWT,
- lower RAP, and
- higher CO.

Multivariable analysis showed that

being female,

having a greater 6MWT, and exhibiting higher CO

were jointly significantly associated with improved survival.

Cox proportional-hazards estimates for multivariable model of survival, limited to terms included in the final stepwise model.

### WHO Group 1 PAH Subgroups

- **APAH-CTD**: HR 1.59, p-value < .001
- **APAH-PoPH**: HR 3.60, p-value < .001
- **PAH**: HR 2.17, p-value 0.012

### Demographics and Comorbidities

- **Renal Insufficiency**: HR 1.90, p-value < .001
- **Males Age > 60 yrs**: HR 2.18, p-value < .001

### NYHA/WHO Functional Class

- **I**
- **II**
- **III**
- **IV**: HR 3.13, p-value < .001

### Vitals

- **Heart Rate > 92bpm**: HR 1.39, p-value 0.005
- **Systolic BP < 110mmHg**: HR 1.67, p-value < .001

### 6MWD

- **≥ 440m**: HR 0.58, p-value 0.006
- **< 165m**: HR 1.68, p-value < .001

### BNP

- **< 50 pg/mL**: HR 0.50, p-value 0.003
- **> 180 pg/mL**: HR 1.97, p-value < .001

### ECHO

- **Pericardial Effusion: Any**: HR 1.35, p-value 0.014

### DLCO

- **% Predicted DLCO ≥ 60**: HR 0.59, p-value 0.031
- **% Predicted DLCO ≥ 52**: HR 1.46, p-value 0.018

### RHC

- **mRAP > 20 mmHg**: HR 1.79, p-value 0.043

### PVR > 32 Wood Units

- **HR 4.08, p-value < .001**

**Hazard Ratios and 95% Confidence Intervals**
A Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) analysis over a 12-month period

Although extensive data have been collected on treatments being administered to patients enrolled in REVEAL Registry, specific therapies were not included as candidate predictors of survival in the equation, and the score has not been evaluated as a tool to monitor treatment response

THE PROGNOSTIC IMPACT OF FOLLOW-UP ASSESSMENTS IN PATIENTS WITH IDIOPATHIC PAH

109 IPAH
At baseline and 3-12 months after initiation of PAH-targeted therapy, were followed for a median 38 months

WHO I,II or III,IV
C.I. < or > 2.5 l/min/m2
SvO2 < or > 65%
NT-proBNP < or > 1800 pg/ml

### Variables Used in Clinical Practice to Determine Response to Therapy and Prognosis in PAH

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adequate Response</th>
</tr>
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<tbody>
<tr>
<td>FC</td>
<td>I, II</td>
</tr>
<tr>
<td>6MWD</td>
<td>≥380 to 440 m</td>
</tr>
<tr>
<td>CPEX</td>
<td>VO₂ &gt; 15 mL/kg/min or VE/VCO² &lt; 45 L/min/L/min</td>
</tr>
<tr>
<td>BNP</td>
<td>Normal or near normal</td>
</tr>
<tr>
<td>Echo/CMR</td>
<td>Normal or near normal RV size and function</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RA &lt; 8 mm Hg and Cl &gt; 2.5 to 3 L/min/m²</td>
</tr>
</tbody>
</table>
The individual criteria in the ESC/ERS table are not weighted according to relative importance (e.g. CTD). The cut-points for each variable are based on previous studies, including those from REVEAL, and consensus expert opinion.

Data collected 2006-2016 for incident IPAH, HPAH, drug induced PAH (N 1017)

At a median follow-up of 34m, 238 (23%) pts had died. The No of low-risk criteria at diagnosis (p<0.01) and at first reevaluation (p<0.01) Discriminated the risk of death or LTx.
Risk Assessment and Survival: The French Registry (cont)

Survival According to the Number of Low-Risk Criteria at Baseline

Survival According to the Number of Low-Risk Criteria at Follow-Up*

Patients with all criteria at low risk at baseline had a 5-year survival > 90%

*Median (IQR) interval between diagnosis and first re-evaluation was 4.4 (3.6-6.4) months. Bouchy A, et al. Eur Respir J. 2017;50:1700889.
a normal BNP/NTpro-BNP level had 98% sensitivity to exclude the presence of either RAP >8 mmHg, cardiac index <2.5 L·min⁻¹·m⁻² or both
‘It must also be noted that the haemodynamic risk assessment criteria were still independent predictors of transplant-free survival in the overall analysis population and provide important diagnostic and prognostic information in PAH patients with signs of clinical worsening.

It remains unknown whether the addition of other noninvasive modalities, such as echocardiography or cardiopulmonary exercise testing to the three noninvasive criteria assessed in our study could further improve the prognostic utility of a noninvasive risk assessment tool’.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariable Analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>P</td>
</tr>
<tr>
<td>WHO/NYHA FC I-II</td>
<td>0.47</td>
<td>(0.32, 0.71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6MWD &gt;440m</td>
<td>0.32</td>
<td>(0.17, 0.60)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BNP &lt;50 ng/L or NT-proBNP &lt;300 ng/mL</td>
<td>0.31</td>
<td>(0.19, 0.52)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

RHC if discrepancy between these 3 parameters and for those more intermediate and high-risk.

3 low-risk criteria at follow-up, excellent survival >25% at 5 years and more.

THE PROGNOSTIC VALUE OF FOLLOW UP HEMODYNAMIC VARIABLES AFTER INITIAL MANAGEMENT IN PAH

Weatherald J¹, Boucly A², Chemla D³, Savale L², Peng M⁴, Jevnikar M², Jais X², Taniguchi Y², O'Connell C², Parent F², Sattler C², Hervé P², Simonneau G², Montani D², Humbert M², Adir Y⁵, Sitbon O².

Incident patients with idiopathic, drug and toxin-induced or heritable PAH enrolled in the French pulmonary hypertension registry between 2006-2016 who had a follow-up RHC

Among patients who had 2 (n=355) or 3 (n=193) low-risk prognostic features at follow-up, including

a cardiac index ≥ 2.5 L/min/m²,
6MWD > 440 m and either
NYHA I or II functional class,
Lower SVI was still associated with higher rates of death or lung transplantation (p<0.01)

SVI and RAP were the hemodynamic variables independently associated with death or lung transplantation at first follow-up RHC after initial PAH treatment.

Calculations were made from baseline assessments and from follow-up assessments between 3 months and 2 years after the initiation of medical therapy for PAH.
Haemodynamic follow-up data were available for only 386 (35%) of pts.

Patients with all three noninvasive low-risk criteria had a 2-, 3- and 5-year survival of 100%, 99% and 97%, respectively.
Comprehensive Risk Stratification at Early Follow-Up Determines Prognosis

- n=530; follow-up assessments at a median of 4 months (n=383)
- Survival better ($P<0.001$) for those with a higher (baseline) proportion of variables at low risk
- Patients in the low-risk group at follow-up had a reduced mortality risk (HR = 0.2 [95% CI: 0.1, 0.4; in multivariable analysis adjusted for age, sex and PAH subset]), as compared with patients in the intermediate or high-risk groups

Findings demonstrate validity of comprehensive risk assessments and goal of reaching a low-risk profile

GUIDELINES FOR RISK STRATIFICATION IN PAH

Achievement of a low-risk profile as treatment response

<table>
<thead>
<tr>
<th>Determinants of prognosis* (estimated 1-year mortality)</th>
<th>Low risk &lt;5%</th>
<th>Intermediate risk 5–10%</th>
<th>High risk &gt;10%</th>
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</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncopeb</td>
<td>Repeated syncopec</td>
</tr>
<tr>
<td>WHO functional class</td>
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<tr>
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<td>Cardiopulmonary exercise testing</td>
<td>Peak VO\textsubscript{2} &gt;15 ml/min/kg (&lt;65% pred.) VE/VO\textsubscript{2} CO\textsubscript{2} slope &lt;36</td>
<td>Peak VO\textsubscript{2} 11–15 ml/min/kg (35–65% pred.) VE/VO\textsubscript{2} CO\textsubscript{2} slope 36–44.9</td>
<td>Peak VO\textsubscript{2} &lt;11 ml/min/kg (&lt;35% pred.) VE/VO\textsubscript{2} CO\textsubscript{2} slope ≥45</td>
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<td>NT-proBNP plasma levels</td>
<td>BNP &lt;50 ng/l</td>
<td>BNP 50–300 ng/l</td>
<td>BNP &gt;300 ng/l</td>
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<td>CI ≥2.5 l/min/m\textsuperscript{2} SvO\textsubscript{2} ≥65%</td>
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Regular follow-up every 3-6 months
Panel of data derived from clinical assessment, exercise tests, biochemical markers echocardiography & hemodynamics
Importantly, in all three European studies and a recent REVEAL study, patients who improved to a **lower-risk profile at follow-up had better outcomes** than those who did not improve.

In all three European studies, a **minority of patients actually achieved a low-risk profile** by the time of follow-up assessment:

- 30% in the Swedish study by Kylhammar et al.,
- 24% in the COMPERA study by Hoeper et al., and
- 41.5% in the French study by Boucly et al.
However, a low-risk profile has not yet been rigorously tested as a clinical outcome in a trial setting. Because PAH is a rare disease, it is difficult to power clinical trials to demonstrate an effect on mortality.

Instead, hemodynamic variables, the 6-minute walking distance, and composite endpoints including death and other important clinical morbidity events have been used in PAH clinical trials. Such endpoints overlook the importance of achieving a low-risk status as opposed to achieving clinical stability or delaying clinical events such as hospitalizations.

A low-risk profile is clinically meaningful and warrants further validation as a potential surrogate outcome. With the emergence of precision medicine and molecular phenotyping, **better patient selection and a valid surrogate endpoint** could increase the efficiency, statistical power, and impact of future clinical trials in PAH.

Neither AN EQUATION nor A CUBE will perfectly define an individual’s risk assessment.

EVERY tool has inherent weakness and none have been studied prospectively.

WE ALL SEEK THE SAME END:
A TOOL IN WHICH CHANGE IN SCORE BY TREATMENT CHOICES IS ASSOCIATED WITH CHANGE IN OUTCOME

WOMAN 35 Y.O.
CASE
# Case: Risk Stratification

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<td>RAP 8–14 mmHg CI 2.0–2.4 l/min/m² SvO₂: 60–65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 l/min/m² SvO₂ &lt;60%</td>
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BASELINE RISK ASSESSMENT
- multiparameter
PAH aetiology
Important to identify pts
Truly at high risk or those
Who need most intensive approach

FIRST REASSESSMENT
3-6 mo later
If not low risk,
Treatment modification

Close Follow-up
6-12mo
RHC included at least 12 m

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|             | $< 45 \text{ L/min/L/min}$             |
| BNP         | Normal or near normal                   |
| Echo/CMR    | Normal or near normal RV size and function |
| Hemodynamics| RA<8 mm Hg and CI>2.5 to 3 L/min/m²     |
RV FUNCTION PREDICTS SURVIVAL

Treatment

RV afterload ➔ RV function ➔ RV contractility ➔ RV function

Degree

PAH and its response to PH-specific therapy

FOLLOW THE RV...THE PATIENT WILL GO THE WAY OF THEIR RV

Time, mo/y

UNCOPLED
‘Combining machine-learning software with the best human clinician ‘hardware’
Will permit delivery of the care that outperforms what either can do alone’


INDIVIDUALIZED APPROACH AT EXPERT CENTERS

providing the Best therapeutic strategy
THANK YOU FOR YOUR ATTENTION
We suggest that a minimum of 3 variables be included when using the ESC/ERS tool

one of which should be a **direct indicator of right ventricular function** (i.e. hemodynamic
variables, BNP/NT-proBNP, or an imaging-derived measure of RV function)

Unlike REVEAL, the ESC/ERS tool has not yet been validated in prevalent patients more than 1
year from diagnosis, which were the majority of participants in recent phase III studies of
macitentan and selexipag

It is also of interest whether other hemodynamic variables such as the stroke volume index, and cardiac
magnetic resonance imaging derived or echocardiography-derived measures of RV function improve
discrimination of risk within the first year and can refine the definition of "low-risk", prior to adoption of
these risk tools as a trial endpoint
## Risk Stratification

<table>
<thead>
<tr>
<th>European Registries</th>
<th>the analyses were retrospective</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>there was significant loss to follow-up</td>
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</table>

<table>
<thead>
<tr>
<th>French</th>
<th>None examined risk assessment in prevalent cohorts</th>
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<tbody>
<tr>
<td></td>
<td>has not yet been studied in PAH associated with other medical conditions (i.e. CTD)</td>
</tr>
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<tr>
<th>Sweden</th>
<th>Do not cover all ages</th>
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<tr>
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<th>Loss of patients at follow up</th>
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- **Unavailability of key parameters of risk**
- **Loss of patients at follow up**
- **The degree to which Assessed variables were contemporaneous**
# Survival in Registries

<table>
<thead>
<tr>
<th>Registry (Ref. #)</th>
<th>Study Cohort</th>
<th>1 yr, %</th>
<th>3 yrs, %</th>
<th>5 yrs, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. NIH (17,18)</td>
<td>Inc</td>
<td>NA</td>
<td>PAH 68</td>
<td>IPAH 48</td>
</tr>
<tr>
<td>U.S. PHC (19)</td>
<td>Prev and Inc</td>
<td>84</td>
<td>PAH 67</td>
<td>IPAH NA</td>
</tr>
<tr>
<td>French (9,21,22)</td>
<td>Prev and Inc</td>
<td>Ent 87</td>
<td>Ent 67</td>
<td>Ent 58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prev 88</td>
<td>Prev 71</td>
<td>Prev 69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inc 88</td>
<td>Inc 51</td>
<td>Inc 55</td>
</tr>
<tr>
<td>Chinese (23)</td>
<td>Inc</td>
<td>NA</td>
<td>PAH 68</td>
<td>IPAH 39</td>
</tr>
<tr>
<td>U.S. REVEAL (8,24-33)</td>
<td>Prev and Inc</td>
<td>85</td>
<td>PAH 68</td>
<td>IPAH 74</td>
</tr>
<tr>
<td>Spanish (34)</td>
<td>Prev and Inc</td>
<td>NA</td>
<td>PAH 89</td>
<td>IPAH 77</td>
</tr>
<tr>
<td>UK (6,35)</td>
<td>Inc</td>
<td>79*</td>
<td>PAH 57*</td>
<td>IPAH 73</td>
</tr>
<tr>
<td>Mayo (38)</td>
<td>Prev and Inc</td>
<td>81</td>
<td>PAH 61</td>
<td>IPAH NA</td>
</tr>
<tr>
<td>Compera (39)</td>
<td>Inc</td>
<td>NA</td>
<td>PAH 88.2</td>
<td>IPAH 89.7</td>
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<tr>
<td>GIESSEN</td>
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</table>
Baseline and Serial Brain Natriuretic Peptide Level Predicts 5-Year Overall Survival in Patients With Pulmonary Arterial Hypertension: Data From the REVEAL Registry

Overall Survival was compared in patients with low (≤340 pg/mL) vs high (>340 pg/mL) BNP at baseline.

Baseline BNP threshold of 340 pg/mL strongly predicted survival up to 5-years in patients with PAH. A BNP reduction at 1 year since enrollment was associated with decreased mortality risk, while an increase in BNP at 1 year was associated with an increased mortality risk, supporting BNP as a surrogate marker of PAH survival.