31 GIORNATE CARDIOLOGICHE TORINESI

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Risk Stratification in patients with pulmonary hypertension.

Stefano Ghio
Divisione di Cardiologia
Fondazione IRCCS Policlinico S.Matteo, PAVIA

Machine Learning and Prediction in Medicine — Beyond the Peak of Inflated Expectations

Jonathan H. Chen, M.D., Ph.D., and Steven M. Asch, M.D., M.P.H.

N ENGL J MED 376;26

<Data-driven clinical predictions are routine in medical practice … but precise predictions about the distant future are often fundamentally impossible.>

<The so-called butterfly effect refers to the future's extreme sensitivity to initial conditions. Tiny variations, which seem dismissible as trivial rounding errors in measurements, can accumulate into massively different future events. Identical twins with the same observable demographic characteristics, lifestyle, medical care, and genetics necessarily generate the same predictions — but can still end up with completely different real outcomes.>

<An accurate prediction of a patient outcome does not tell us what to do if we want to change that outcome — in fact, we cannot even assume that it's possible to change the predicted outcomes.>

Assessing risk in pulmonary arterial hypertension: what we know, what we don't

Raymond L. Benza[1], Harrison W. Farber[2], Mona Selej[3,4] and Mardi Gomberg-Maitland[5]

Eur Respir J 2017; 50: 1701353

In a progressive disease like PAH, early and accurate risk prediction allows for the identification of patients who are more likely to progress rapidly, "rapid progressors".

- Risk stratification is especially important in settings where clinical PAH experience is not available and could facilitate early referral to a PAH centre.
- A risk stratification algorithm could also offer a more individualised treatment strategy for PAH patients; by identifying risk stratum, guiding clinical decision making and informing treatment options and goals.
- Risk prediction modelling can help physicians allocate treatment resources in settings where they are scarce.
- They can also be used to inform patients of their prognosis thereby allowing them to make informed decisions about treatment options.
- …. assist in the timely referral for lung transplantation.
- Lastly, risk model-derived equations can enhance clinical study design both by selecting the appropriate study cohort and serving as a study end-point.

First proposal in 1991 – NIH Equation

- NIH registry: Ann Intern Med 1991; 115:343
- J Sandoval et al: Circulation 1994; 89:1733

$A(x,y,z) = e^{(007325x)+(0526y)-(0.3275z)}$

(x=PAPm, y=RAP, z=CI)

Survival probability at 1, 2 or 3 years:

$P(1)=.75^{A}$

$P(2)=.65^{A}$

$P(3)=.55^{A}$

First proposal in 1991 – NIH Equation

- NIH registry: Ann Intern Med 1991; 115:343
- J Sandoval et al: Circulation 1994; 89:1733

Important message :

"Mortality in PPH is largely associated with hemodynamic variables that assess right ventricular function"

However:

never used in routine clinical practice: complex equation, based on invasive data, for many years useless (no possibility to adjust therapy according to risk).

2010 – REVEAL risk score

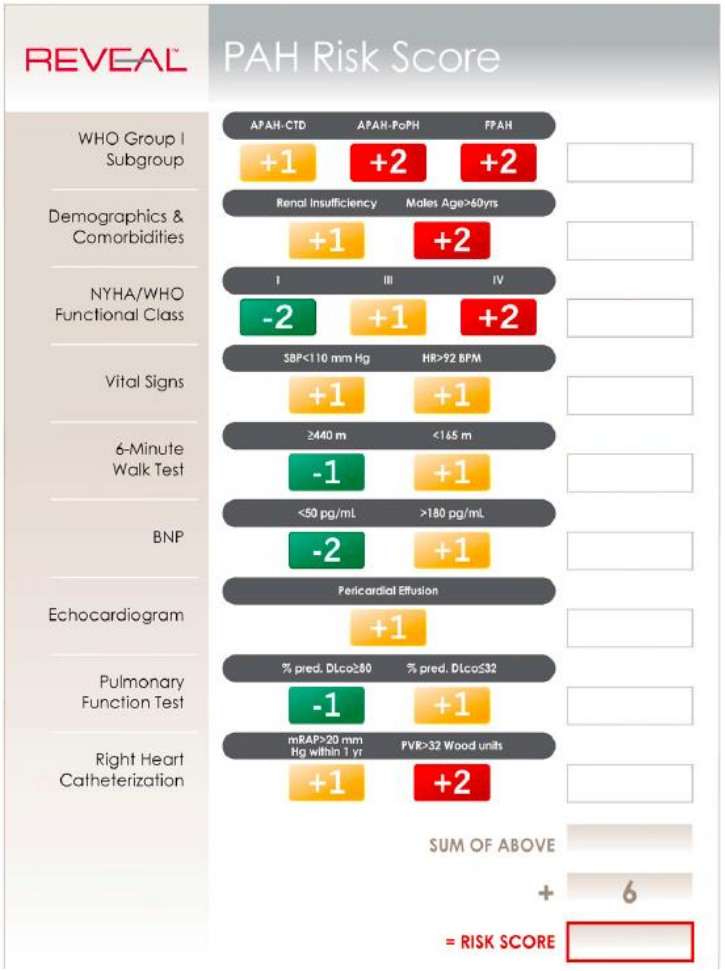
The REVEAL score

The REVEAL Registry Risk Score Calculator in Patients Newly Diagnosed With Pulmonary Arterial Hypertension

Raymond L. Benza, MD; Mardi Gomberg-Maitland, MD, FCCP; Dave P. Miller, MS; Adaani Frost, MD, FCCP; Robert P. Frantz, MD; Aimee J. Foreman, MA; David B. Badesch, MD, FCCP; and Michael D. McGoon, MD, FCCP

CHEST 2012; 141(2):354–362

In conclusion, the REVEAL Registry prognostic equation and simplified risk calculator, when applied to a cohort of recently enrolled patients with newly diagnosed PAH from the REVEAL Registry study, is accurate, well calibrated, and easy to use. The risk calculator has the potential to support decision making by clinicians and patients in everyday clinical practice and in future clinical research endeavors. Further research is needed, however, to prospectively assess the application of the tool in real-world clinical management.



2010 – REVEAL risk score

The REVEAL Score Calculator 2.0

Predicting Survival in Patients With Pulmonary Arterial Hypertension

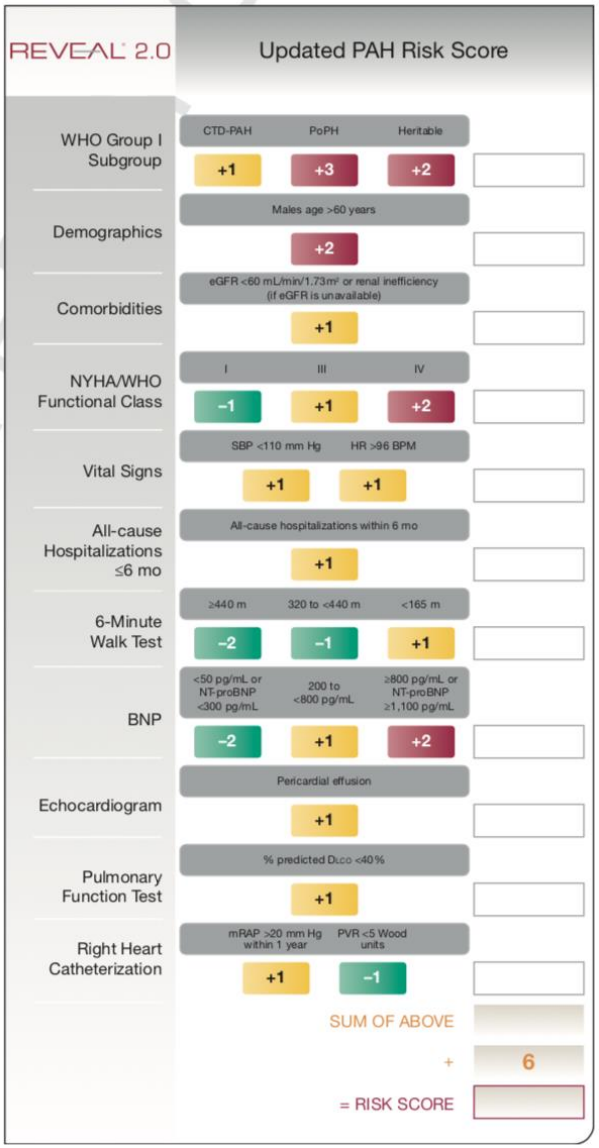
Check for updates

The REVEAL Risk Score Calculator 2.0 and Comparison With ESC/ERS-Based Risk Assessment Strategies

Raymond L. Benza, MD; Mardi Gomberg-Maitland, MD; C. Greg Elliott, MD; Harrison W. Farber, MD; Aimee J. Foreman, MA; Adaani E. Frost, MD; Michael D. McGoon, MD; David J. Pasta, MS; Mona Selej, MD; Charles D. Burger, MD; and Robert P. Frantz, MD

CHEST 2019; 156(2):323-337

c-statistic. Mortality estimates and discrimination were compared between REVEAL 2.0 and Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) and French Pulmonary Hypertension Registry (FPHR) risk assessment strategies. For this comparison, a three-category REVEAL 2.0 score was computed in which patients were classified as low-, intermediate-, or high-risk.



Not used in clinical practice (in Europe): reluctancy of physicians, maybe difficulty of associating a number with a risk.

- ESC/ERS Guidelines 2015 risk assessment Table.

Table 13 Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; CI = cardiac index; CMR = cardiac magnetic resonance; NT-proBNP = N-terminal pro-brain natriuretic peptide; pred. = predicted; RA = right atrium; RAP = right atrial pressure; SvO_2 = mixed venous oxygen saturation; VE/VCO_2 = ventilatory equivalents for carbon dioxide; VO_2 = oxygen consumption; WHO = World Health Organization.

[a]Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

Everything changes in autumn 2017!

- 3 different European groups publish abbreviated versions of the ESC/ERS 2015 Guidelines stratification approach.

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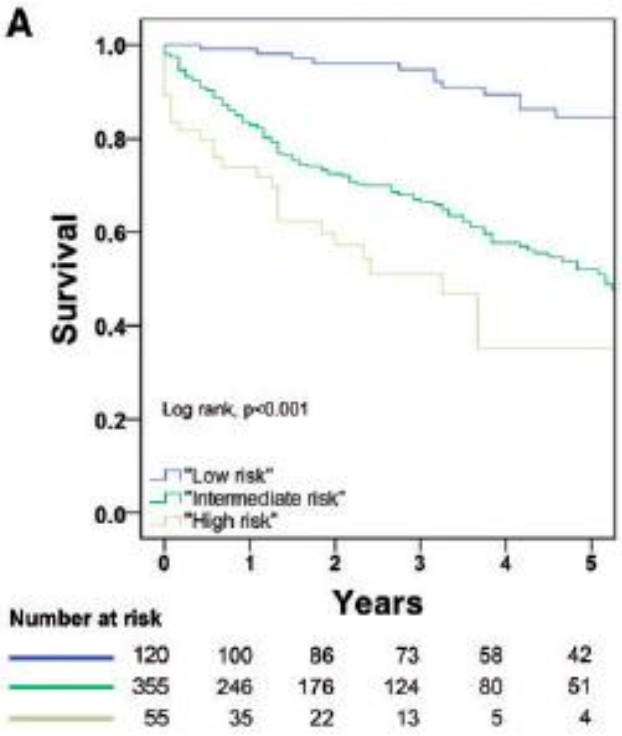
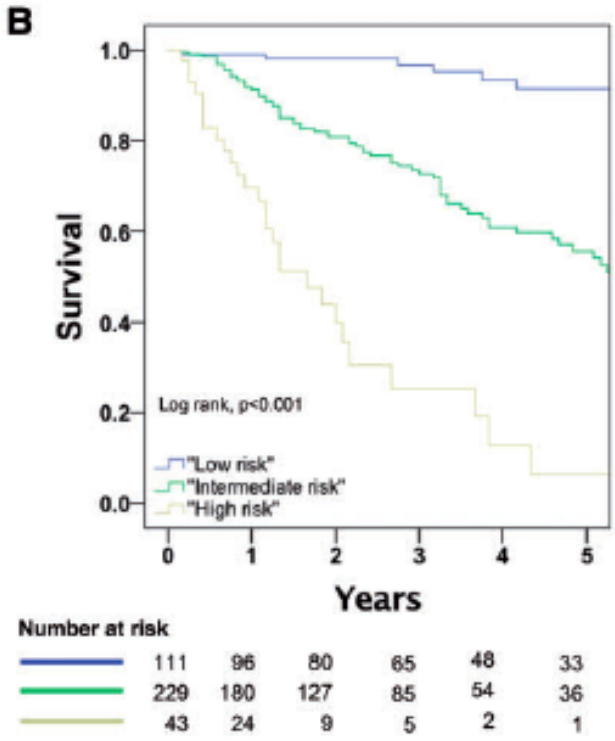
A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension

David Kylhammar[1]*, Barbro Kjellström[2], Clara Hjalmarsson[3], Kjell Jansson[4], Magnus Nisell[5], Stefan Söderberg[6], Gerhard Wikström[7], and Göran Rådegran[1], on behalf of SveFPH and SPAHR

Eur Heart J 2017; June 1

(A) baseline risk group = 530
(B) follow-up risk group = 383





Patients were categorized as 'Low', 'Intermediate', or 'High' risk according to cut-off values for FC, 6MWD, NT-proBNP, RA area, RAP, PE, CI, and SvO2

Each variable was graded from 1 to 3. Dividing the sum of all grades by the number of available variables rendered a mean grade.

Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model

Eur Respir J 2017; 50: 1700740

Marius M. Hoeper[1,2], Tilmann Kramer[3,4], Zixuan Pan[5], Christina A. Eichstaedt[5], Jens Spiesshoefer[6], Nicola Benjamin[5], Karen M. Olsson[1,2], Katrin Meyer[1], Carmine Dario Vizza[7], Anton Vonk-Noordegraaf[8], Oliver Distler[9], Christian Opitz[10], J. Simon R. Gibbs[11], Marion Delcroix[12], H. Ardeschir Ghofrani[13], Doerte Huscher[14], David Pittrow[15], Stephan Rosenkranz[3,4] and Ekkehard Grünig[2,5]

Variables from 1558 patients with newly diagnosed PAH enrolled into COMPERA: WHO class, 6MWT, BNP, CI, RAP, MVO2.

At least two were available in all 1588 patients (primary analysis set), at least three in 1580 (99.4%) patients, at least four in 1515 (95.3%) patients, at least five in 1312 (82.6%) patients and all six variables were available in 879 (55.4%) patients.

For each patient, the sum of all grades was divided by the number of available variables and rounded to the next integer to define the risk group. 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.

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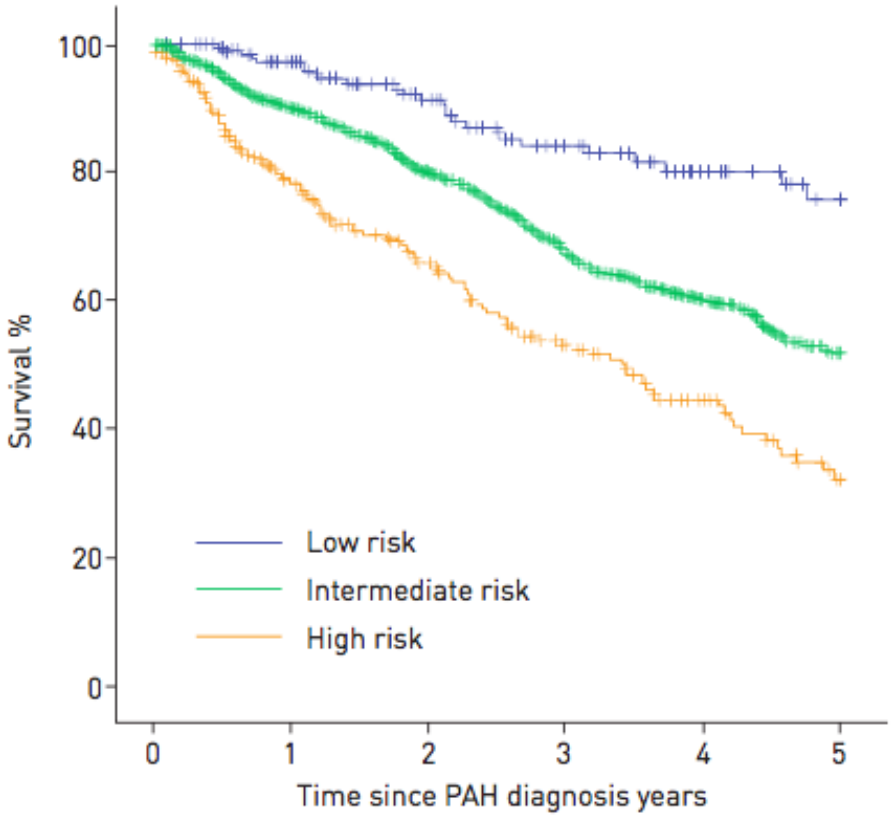

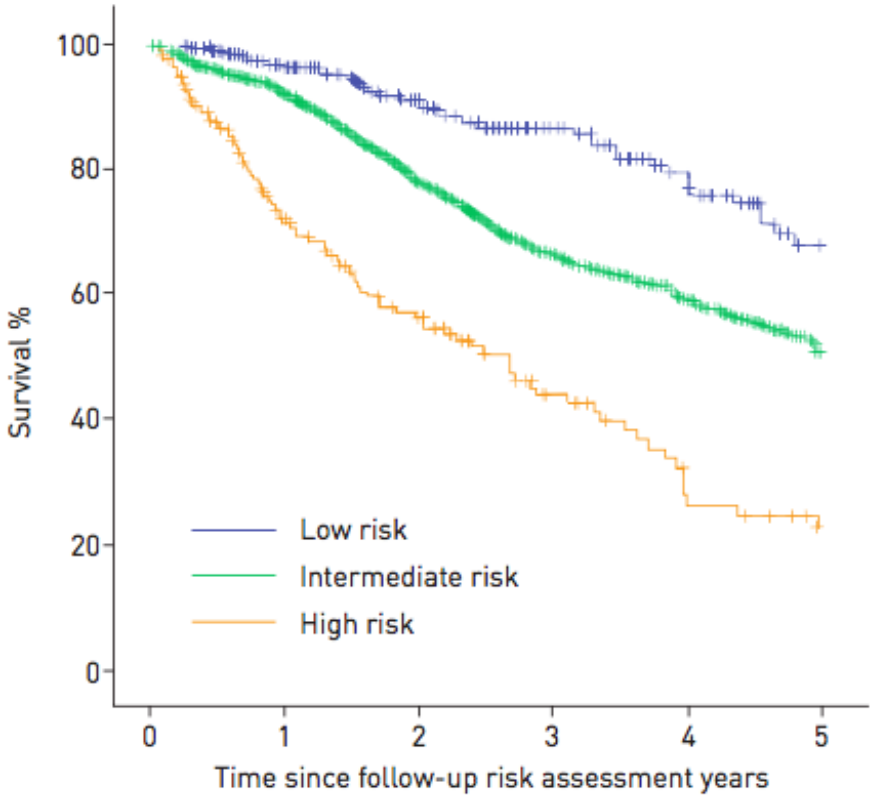

Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension

Athénaïs Boucly[1,2,3], Jason Weatherald[2,3,4], Laurent Savale[1,2,3], Xavier Jaïs[1,2,3], Vincent Cottin[5], Grégoire Prevot[6], François Picard[7], Pascal de Groote[8], Mitja Jevnikar[1,2,3], Emmanuel Bergot[9], Ari Chaouat[10,11], Céline Chabanne[12], Arnaud Bourdin[13], Florence Parent[1,2,3], David Montani[1,2,3], Gérald Simonneau[1,2,3], Marc Humbert[1,2,3] and Olivier Sitbon[1,2,3]

Eur Respir J 2017 50:1700889

1017 incident patients with idiopathic, heritable and drug-induced PAH between 2006 and 2016 were studied.

Four low-risk criteria were assessed: at diagnosis and at first re-evaluation

- WHO functional class I or II,
- 6MWD >440 m,
- right atrial pressure <8 mmHg
- cardiac index $\geqslant$2.5 L·min−1·m−2.

Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension

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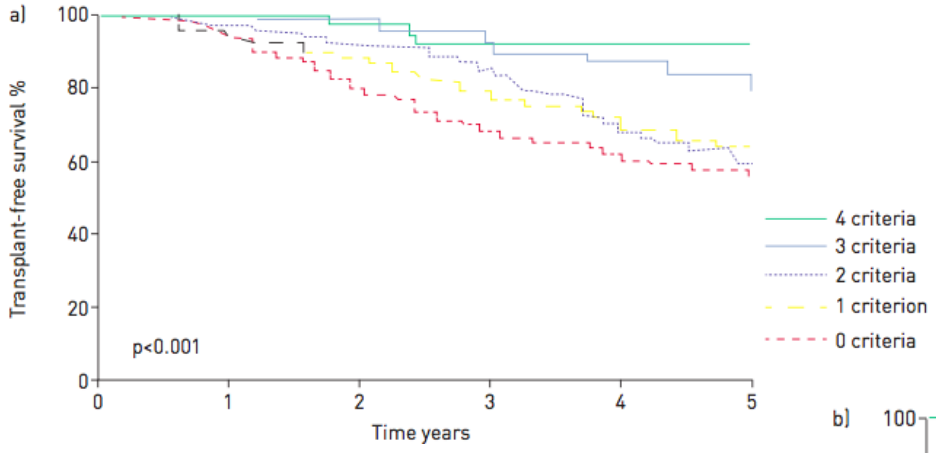
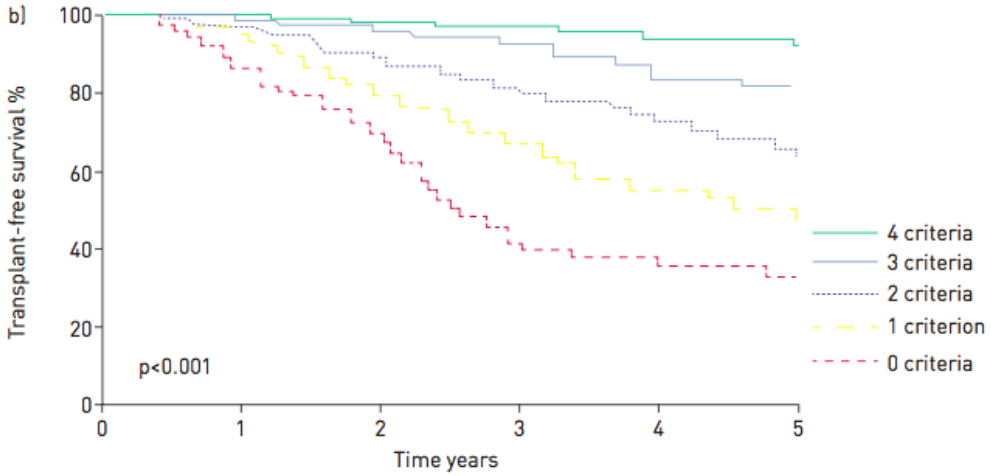
<this study helps validate the multidimensional approach to risk assessment recommended in the 2015 ERS/ESC guidelines in a large cohort of incident patients with PAH. Long-term prognosis was accurately determined using a simple quantification of **the number of low-risk criteria present at diagnosis and after treatment initiation** for WHO/NYHA functional class, 6MWD, RAP and cardiac index.>



Pts who maintained or achieved three or four low-risk criteria had excellent long-term transplant-free survival.



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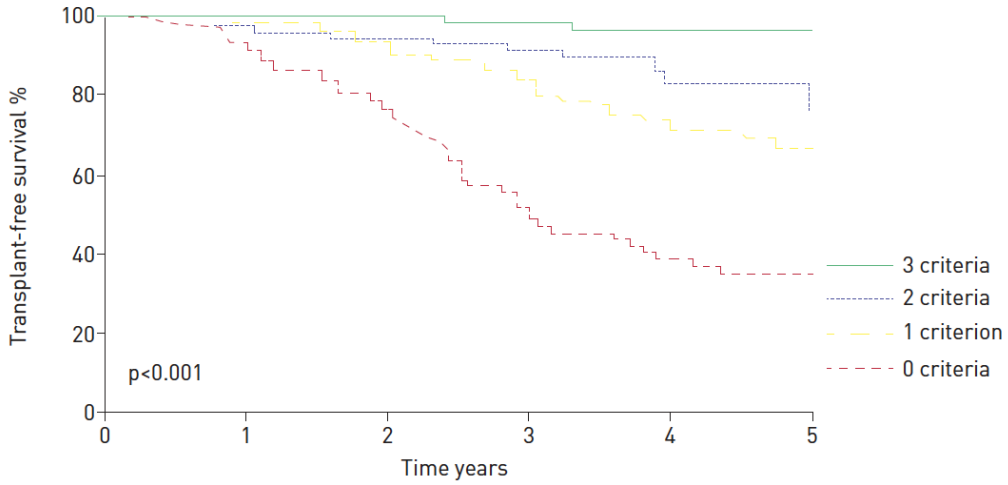


Patients at risk n						
3 criteria	115	97	81	63	38	26
2 criteria	145	116	95	72	36	21
1 criterion	175	136	101	62	38	24
0 criteria	168	117	76	39	23	11

FIGURE 4 Transplant-free survival according to the number of noninvasive low-risk criteria (World Health Organization/New York Heart Association functional class I–II; 6-min walking distance >440 m; brain natriuretic peptide <50 ng·L^{-1} or N-terminal pro-brain natriuretic peptide <300 ng·mL^{-1}) present at first re-evaluation (n=603).

<Survival was analysed using **three non-invasive low-risk criteria** (WHO/ NYHA functional class I–II, 6MWD >440 m, BNP <50 ng·L−1 or NT-proBNP <300 ng·L−1) **assessed at follow-up**.>

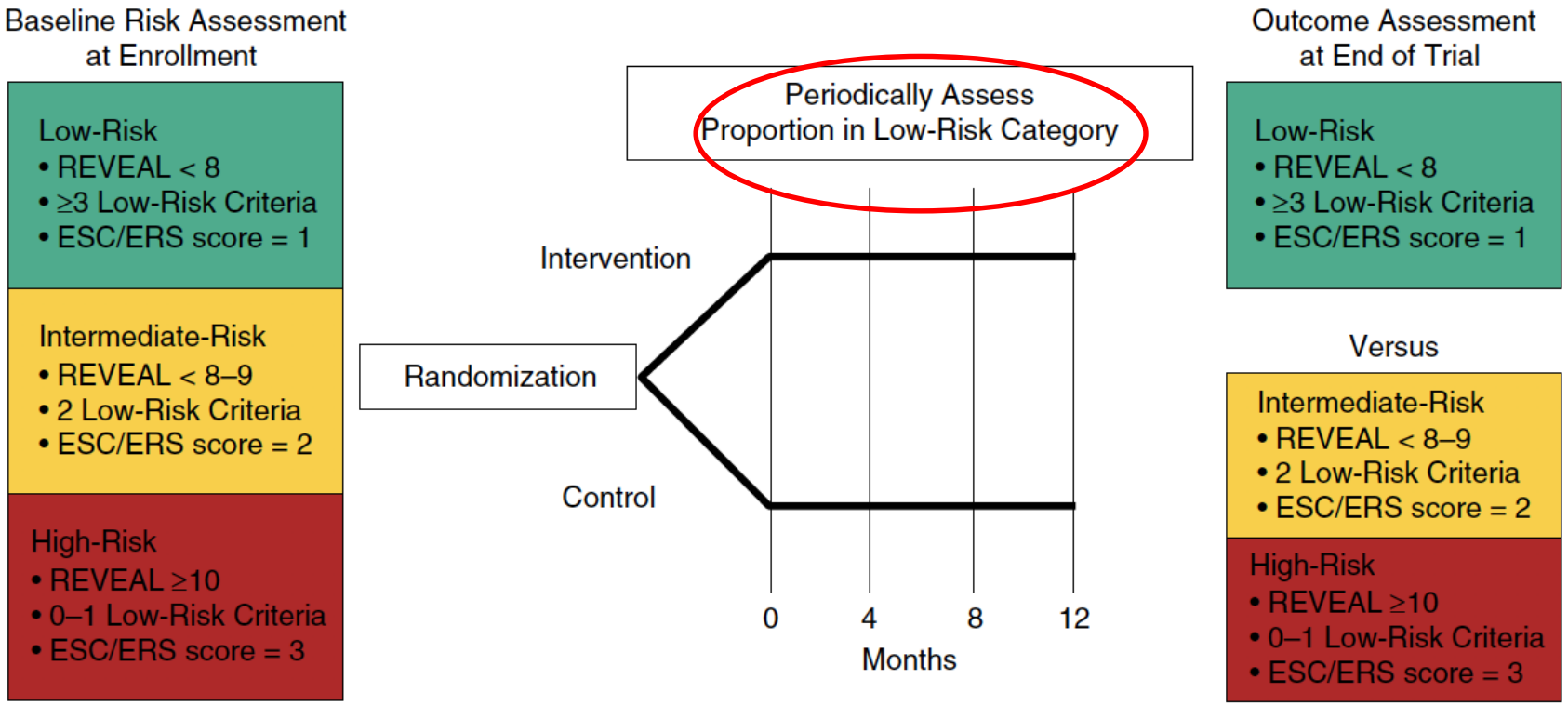
Pts who achieved three **non-invasive low-risk criteria**
had excellent long-term transplant-free survival.

The Low-Risk Profile in Pulmonary Arterial Hypertension

Time for a Paradigm Shift to Goal-oriented Clinical Trial Endpoints?

Jason Weatherald[1,2], Athénaïs Boucly[3,4,5], Sandeep Sahay[6], Marc Humbert[3,4,5], and Olivier Sitbon[3,4,5]

American Journal of Respiratory and Critical Care Medicine Volume 197 Number 7 | April 1 2018



Everything changes in autumn 2017!

European Risk Stratification tools

Very well accepted since the very first proposal:

1) Because risk stratification is easy to perform, based on a CLINICAL approach, even totally non-invasive (6MWT, BNP, WHO …);
2) and easy to understand (pts categorized as green/yellow/red) and easy thus TO USE;
3) because now we have more drugs in our armamentarium to individualise therapy.

Risk Stratification of pulmonary arterial hypertension.

Messages for clinicians:

WE MUST USE *risk stratification tools in our everyday clinical practice:*

1- calculating the RRS or assigning pts to a risk category (whichever),

2- then trying to optimize therapy accordingly,

(at each visit).

Risk Stratification of pulmonary arterial hypertension.
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No excuses.

- *because this is ethically correct, in the interest of the patients,*
- *because this will be a recommendation of the future Guidelines,*
- *because this is what makes us <experts> in PAH.*

Risk Stratification of pulmonary arterial hypertension.

Messages for clinicians:

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AFTER this, we may reason on how to improve the algorithms:

Because risk stratification is a CLINICIAN'S JOB.

These tools are meant to be improved! In each domain.

Table 13 **Risk assessment in pulmonary arterial hypertension**

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Improving Risk Assessment based on hemodynamics!

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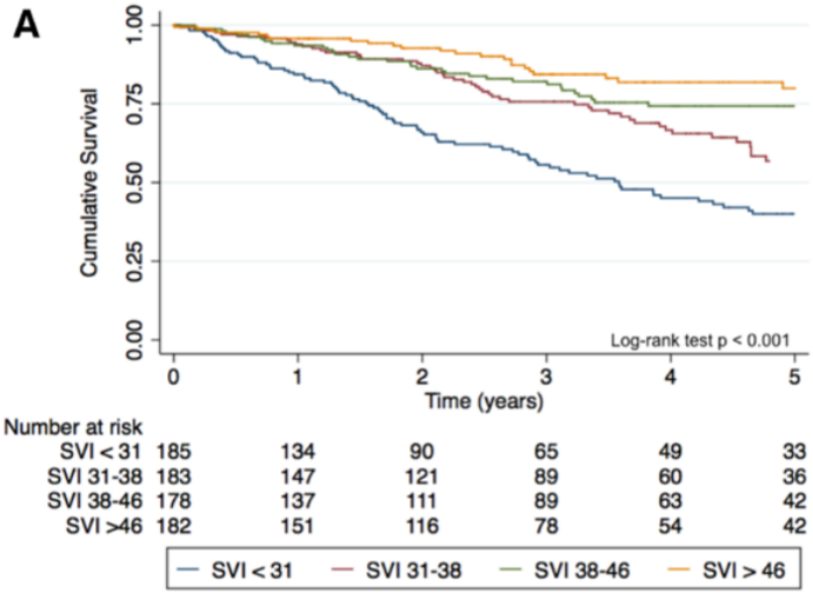
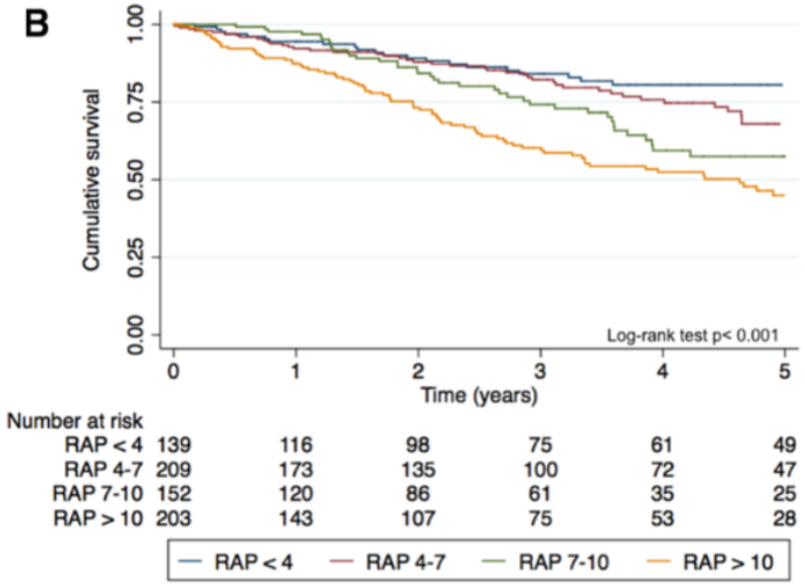
Prognostic Value of Follow-Up Hemodynamic Variables After Initial Management in Pulmonary Arterial Hypertension

Jason Weatherald,

Circulation. 2018;137:693–704.





981 patients, median follow-up duration of 2.8 years.

Baseline hemodynamic variables did not predict the risk of death or transplantation. After initial treatment, stroke volume index and right atrial pressure **at first follow-up** RHC: **SVi and RAP** were the strongest independent hemodynamic prognostic variables.

Prognostic Value of Follow-Up Hemodynamic Variables After Initial Management in Pulmonary Arterial Hypertension

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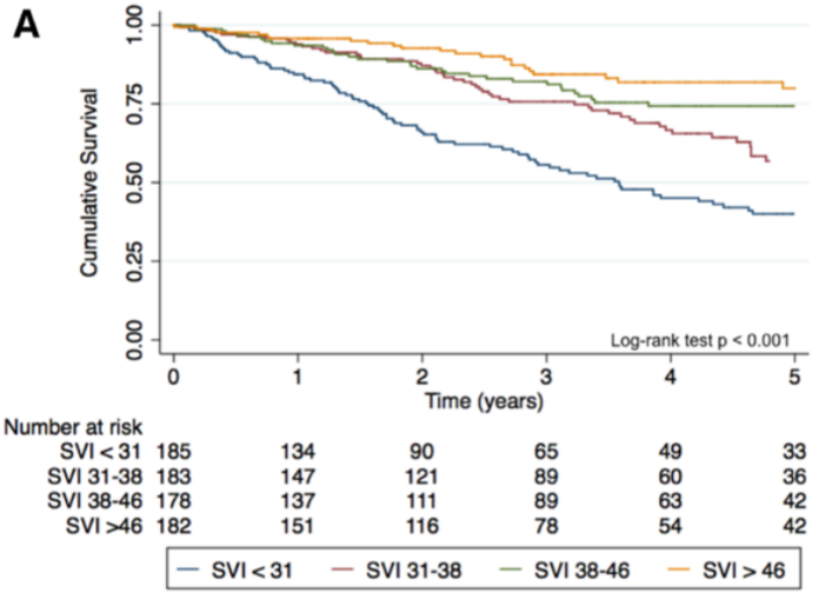

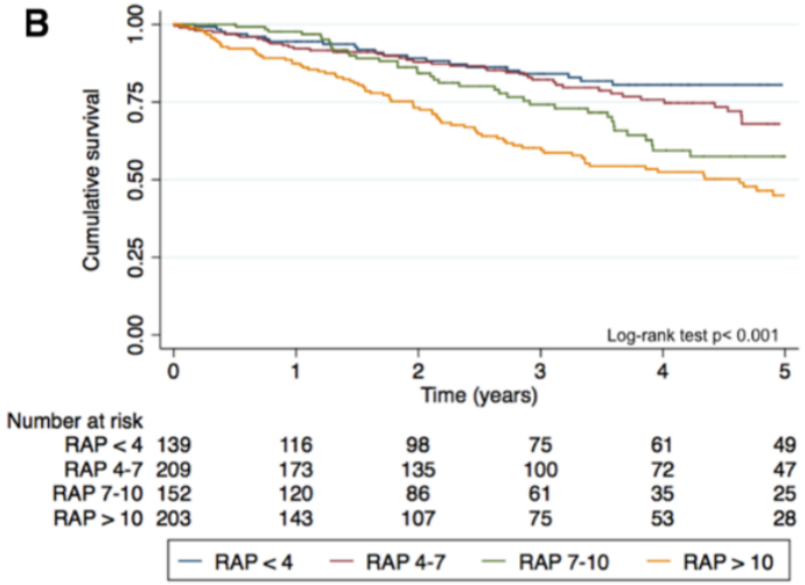

CONCLUSIONS: SVI and right atrial pressure were the hemodynamic variables that were independently associated with death or lung transplantation at first follow-up RHC after initial PAH treatment. These findings suggest that the SVI could be a more appropriate treatment target than cardiac index in PAH.

Improving Risk Assessment based on Imaging

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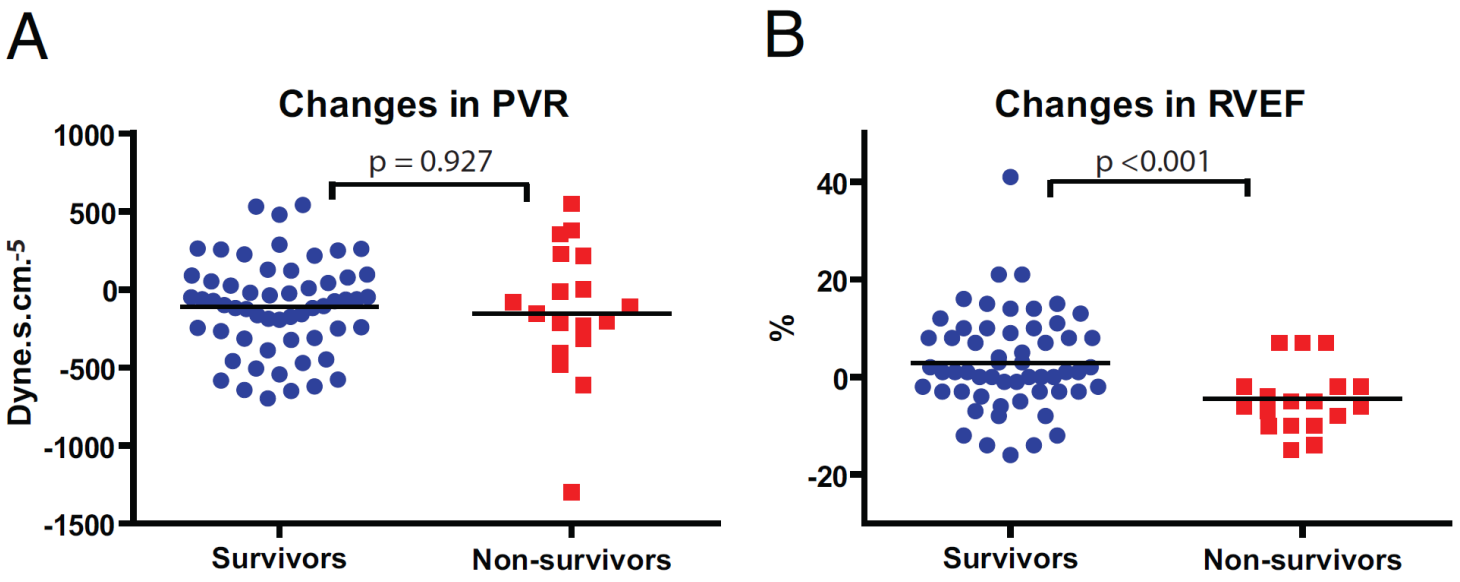
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Progressive Right Ventricular Dysfunction in Patients With Pulmonary Arterial Hypertension Responding to Therapy

van de Veerdonk *et al.* J Am Coll Cardiol 2011;58:2511–9

110 pts with incident PAH, undergoing RHC and CMR at baseline; 76 with fup data after 12 months of therapy



Changes in PVR and RVEF After 12 Months of Follow-Up According to Survival

A number of echo parameters have been associated with prognosis:

	Cut point	Univariate Predictors	Multivariate Predictors	Statistical Strength	Ref.
Right heart morphology					
IVS bulging		✓	✓	~	13
RA, cm^2		✓	✓	~	12
Tricuspid regurgitation		✓	✓	~	12
Δ RVEDA, cm^2	< -2.45	✓	✓	✓	35
Δ RA area, cm^2	< -1.3	✓	✓	✓	35
Δ LV-EIs	< -0.12	✓	✓	✓	35
RV systolic function					
TAPSE, mm	< 18	✓	✓	~	16
TAPSE, mm	≤ 15	✓	-	~	14
TAPSE-FU, mm	≤ 15	✓	-	~	17
TAPSE/PAPS		✓	✓	✓	18
TAPSE/PAPS		✓	✓	~	19
RVFAC, %	< 36.5	✓	✓	✓	15
IVC, cm/s	≤ 9	✓	✓	✓	22
RV dp/dt, mmHg/s	< 410	✓	✓	~	21
RV global strain, %		✓	✓	~	30
RV global strain, %	> -12.5	✓	✓	~	28
RVFWS, %	≥ -19	✓	✓	~	29
RV strain rate, s^{-1}	> -0.7	✓	✓	~	28
RVFWS/PAPS		✓	✓	~	19
RV filling pressure					
Pericardial effusion		✓	✓	~	11, 24
IVCd, (mm) + collapse, %	≥ 20,< 50	✓	✓	~	13, 26
M - E/A	≤ 1.0	✓	✓	~	24
E dec. time tricuspid, cm^2/s	≤ 300	✓	✓	~	24
E/E' tricuspid	> 6.8	✓	✓	~	25
RV Doppler index					
RV Doppler index	< 0.83	✓	✓	~	23
RV dyssynchrony					
RV-SD4, ms	> 23	✓	✓	✓	32
Pulmonary pressure					
PAPm, mmHg	≥ 49	✓	✓	~	13
PAPd, mmHg	≥ 29	✓	✓	~	13

Which is the best?

This search for the magic bullet is of limited value because only a

multiparametric approach

allows to understand the pathophysiology of the disease (and use it to stratify prognosis).

NIH equation is a multivariable equation

- NIH registry: Ann Intern Med 1991; 115:343
- J Sandoval et al: Circulation 1994; 89:1733

$A(x,y,z) = e^{(007325x)+(0526y)-(0.3275z)}$

(x=PAPm, y=RAP, z=CI)

Survival probability at 1, 2 or 3 years:

$P(1)=.75^{A}$

$P(2)=.65^{A}$

$P(3)=.55^{A}$

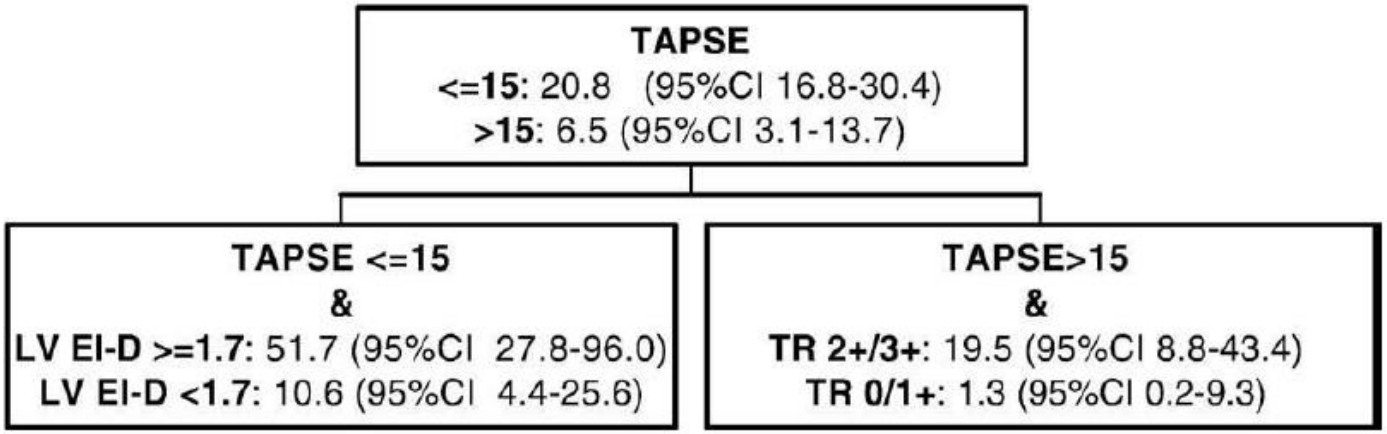
Prognostic relevance of the echocardiographic assessment of right ventricular function in patients with idiopathic pulmonary arterial hypertension

Stefano Ghio [a,*], Catherine Klersy [b], Giulia Magrini [a], Andrea Maria D'Armini [c], Laura Scelsi [a], Claudia Raineri [a], Michele Pasotti [a], Alessandra Serio [a], Carlo Campana [a], Mario Viganò [c]

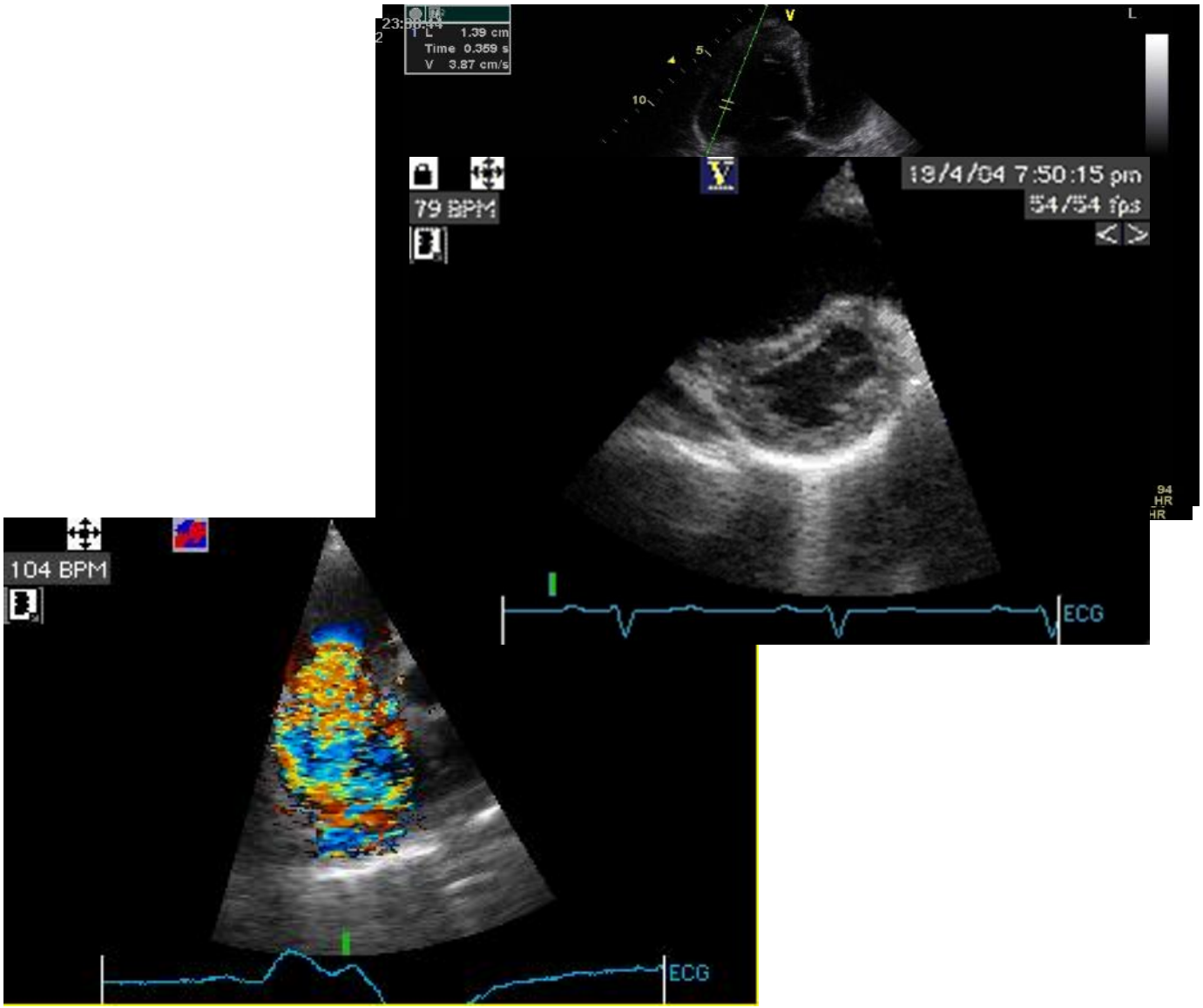
Int J Cardiol 2010;140:272–278

59 IPAH pts; median follow-up 52 months

Hierarchical analysis and mortality rate per 100 person year
Relevant findings



3 Echo indicators of RV function: TAPSE, Degree of TR, LV EI-d



Improving Risk Assessment based on biomarkers!

Table 13 **Risk assessment in pulmonary arterial hypertension**

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
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A number of biomarkers have been associated with prognosis:

Circulating biomarkers in pulmonary arterial hypertension: Update and future direction

Beatrice Pezzuto, MD,[a] Roberto Badagliacca, MD, PhD,[a] Roberto Poscia, MD, PhD,[a]
Stefano Ghio, MD,[b] Michele D'Alto, MD,[c] Patrizio Vitulo, MD,[d]
Massimilano Mulè, MD,[e] Carlo Albera, MD,[f] Maurizio Volterrani, MD,[g]
Francesco Fedele, MD, FESC,[a] and Carmine Dario Vizza, MD[a,g]

J Heart Lung Transplant 2015;34:282–305

The molecules evaluated to date, including markers of dysfunction and neurohormonal activation, myocardial injury, inflammation and oxidative stress, vascular damage and remodelling, end-organ failure, and gene expression, reflect the complex pathophysiology of PAH. However, not one of these shows all the characteristics of the ideal biomarker;

Risk Stratification in patients with pulmonary hypertension.

Let's start using risk stratification tools in everyday clinical practice.

We will soon learn that we clinicians are entitled to make research on how to improve risk stratification of PAH.

OSPITALE DI S. MATTEO
PAVIA