PAH Evaluation of Severity: Comments and Proposals

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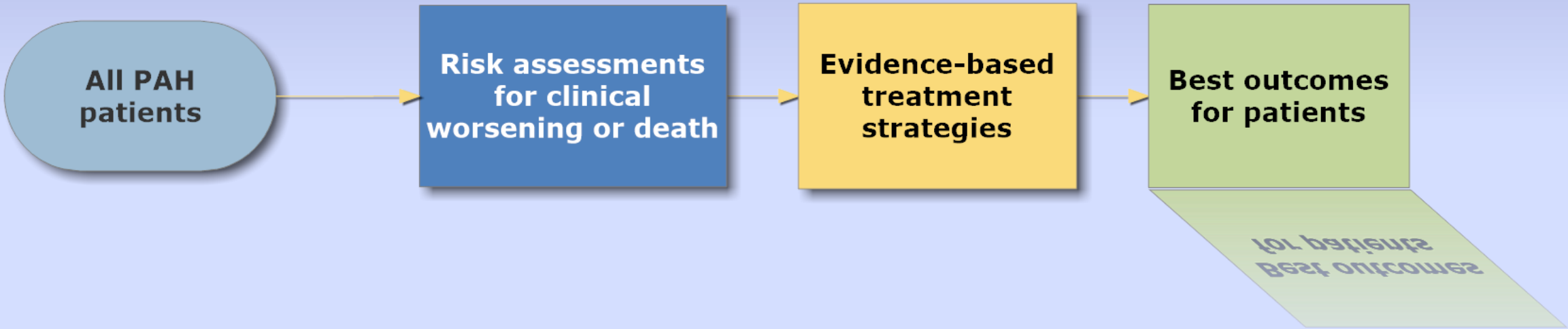
The rationale for evaluation of PAH severity

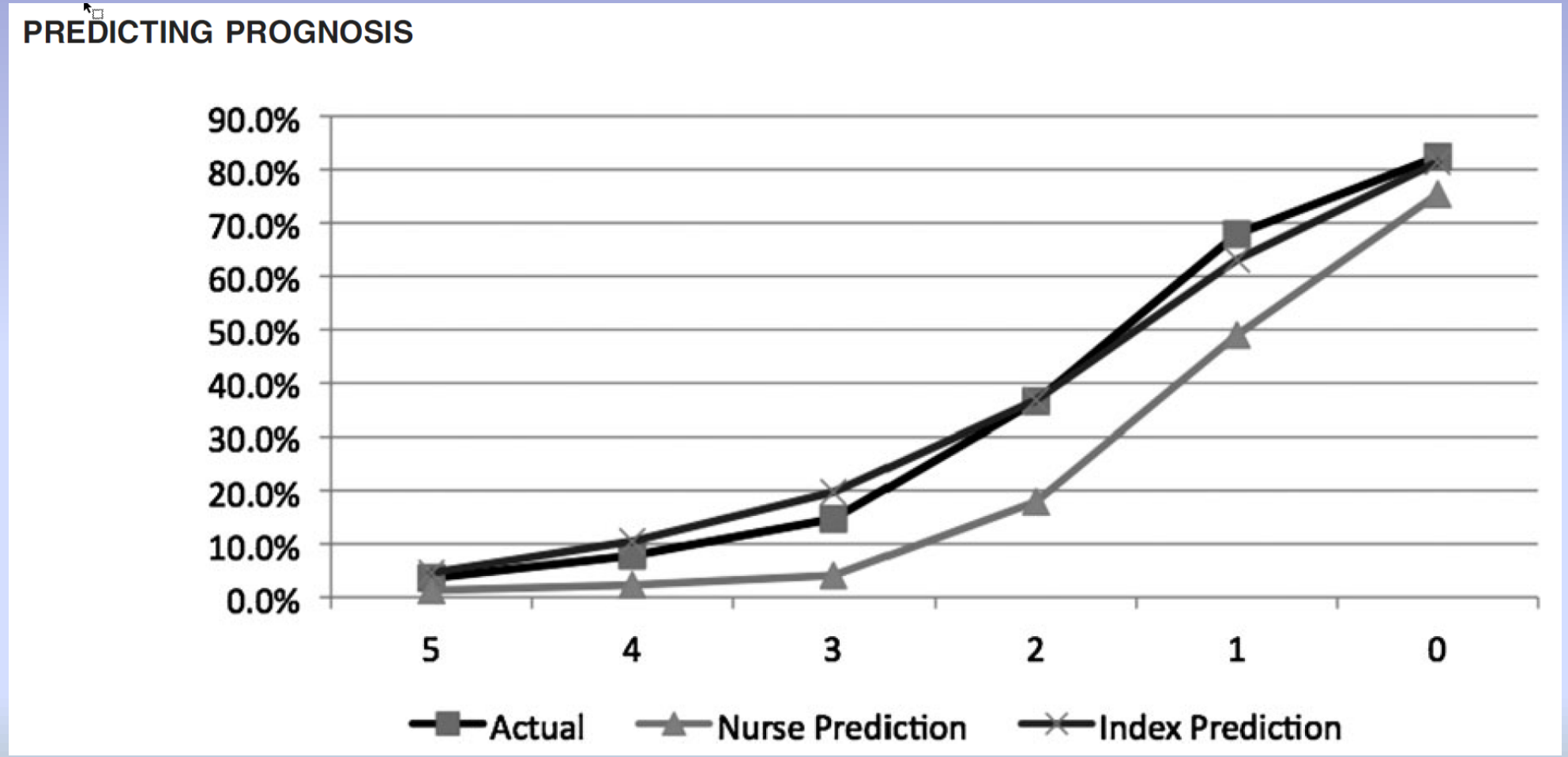


Physicians' prognostication may be inaccurate

- Eighty percent of physician's predictions of prognosis were inaccurate (365 physicians in 504 terminally ill patients):
  - 60% overoptimistic
  - 17% overpessimistic
- The greater the experience of the physician, the greater the prognostic accuracy
- A stronger the doctor-patient relationship is associated with lower prognostic accuracy

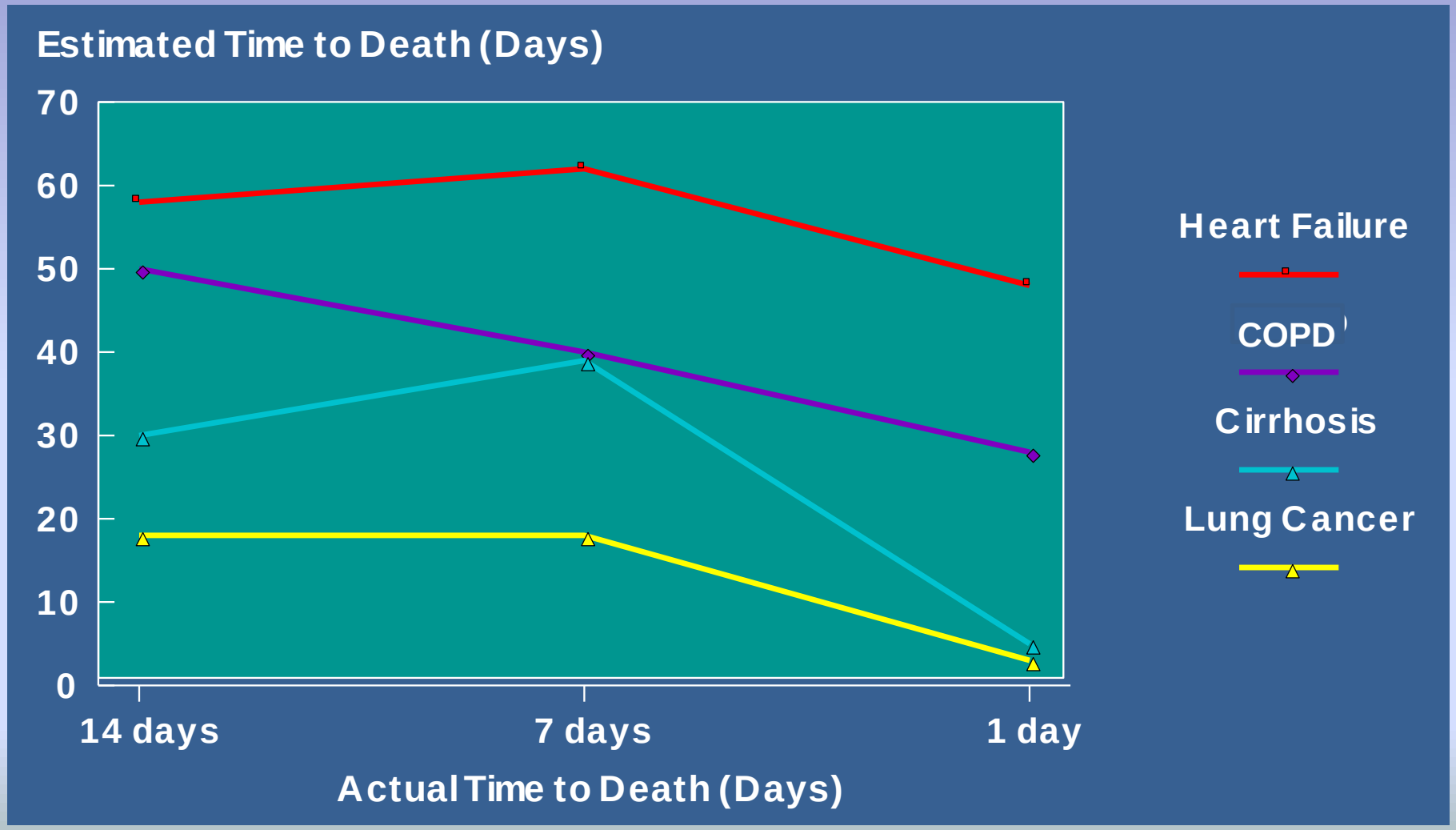
Christakis NA & Lamont EB BMJ 2000;320:469-472

Nurses prognostication underestimates 7 day mortality in hospice patients by up to 19%



Casarett DJ et al J Pall Med 2012;15:703-708

Physician prediction of outcome based on disease severity in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT)



Knaus WA et al Ann Intern Med 1995;122:191-203

The ESC/ERS Pulmonary Hypertension Guidelines recommend multi-parameter assessment to stratify patients based on risk

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 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	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%

The use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

Evidence for variables used to assess disease severity in PAH

	Prognostic Implications at Baseline (Ref. #)	Prognostic Implications at Follow-Up (Ref. #)	Comments
Exercise tolerance			
NYHA FC	(2,4,9,10)	(2,9,10)	
6MWD	(2–4,10,61)		
Peak VO_2	(24)		
Hemodynamics			
RAP	(2,9,10,24,40,50,61,62)	(9)	In some studies, higher PAPm was associated with better survival (10,63)
PAPm	(1,4)		
PVR	(24)	(9)	
CO/CI	(2,3,9,24,40,50,61)	(2,9)	
SvO_2	(2,24,64)	(2,64)	

	Prognostic Implications at Baseline (Ref. #)	Prognostic Implications at Follow-Up (Ref. #)	Comments
Echocardiographic variables			
TAPSE	(40)		
RV strain	(65)		
RA area	(40)		
Pericardial effusion	(4,40)		
Biomarkers			
BNP/NT-proBNP	(2,4,5,62)	(2,5,66)	
Troponin	(62)		
Uric acid	(24,67,68)		
CRP	(69)		
$PaCO_2$	(61)	(61)	
MRI parameters			
SV index	(8)		
RVEDVI	(8)		
LVEDV	(8)		
RVEF	(44)	(44)	
RVAC		(70)	

BNP = B-type natriuretic peptide; CI = cardiac index; CO = cardiac output; CRP = C-reactive protein; LVEDV = left ventricular end-diastolic volume; MRI = magnetic resonance imaging; NYHA FC = New York Heart Association functional class; NT-proBNP = N-terminal pro–B-type natriuretic peptide; 6MWD = 6-min walk distance; $PaCO_2$ = partial arterial pressure of carbon dioxide; PAPm = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; RA = right atrial; RAP = right atrial pressure; RVEDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVFAC = right ventricular fractional area change; SV = stroke volume; SvO_2 = mixed venous oxygen saturation; TAPSE = tricuspid annular plane systolic excursion; VO_2 = oxygen consumption.

McLaughlin VV et al J Am Coll Cardiol 2013;62:D73-D81

ACCF / AHA Expert Consensus on Pulmonary Hypertension: determinants of prognosis in PAH

Determinants of Risk	Lower Risk (Good Prognosis)	Higher Risk (Poor Prognosis)
Clinical evidence of RV failure	No	Yes
Progression of symptoms	Gradual	Rapid
WHO class†	II, III	IV
6MW distance‡	Longer (greater than 400 m)	Shorter (less than 300 m)
CPET	Peak VO_2 greater than 10.4 mL/kg/min	Peak VO_2 less than 10.4 mL/kg/min
Echocardiography	Minimal RV dysfunction	Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement
Hemodynamics	RAP less than 10 mm Hg, CI greater than 2.5 L/min/m^2	RAP greater than 20 mm Hg, CI less than 2.0 L/min/m^2
BNP§	Minimally elevated	Significantly elevated

Reprinted from McLaughlin and McGoon (99). *Most data available pertains to IPAH. Little data is available for other forms of PAH. One should not rely on any single factor to make risk predictions. †WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class. ‡6MW distance is also influenced by age, gender, and height. §As there is currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and gender may influence BNP, absolute numbers are not given for this variable.

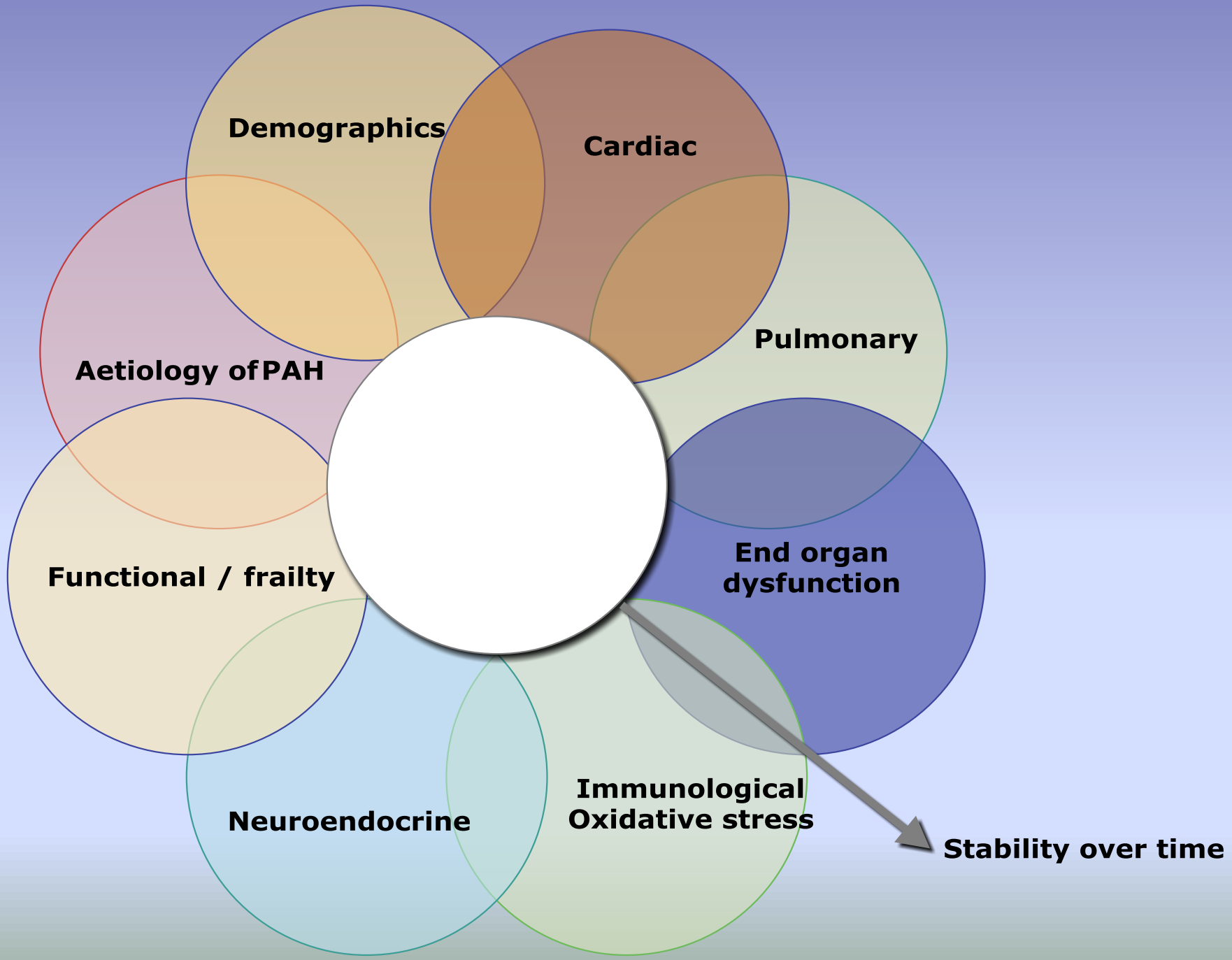
6MW indicates 6-minute walk; BNP, brain natriuretic peptide. CI, cardiac index; CPET, cardiopulmonary exercise testing; peak VO_2, average peak oxygen uptake during exercise; RAP, right atrial pressure; RV, right ventricle; and WHO, World Health Organization.

McLaughlin VV et al J Am Coll Cardiol 2009;53:1573-1619

World Symposium 2013: reasonable goals for PAH therapy

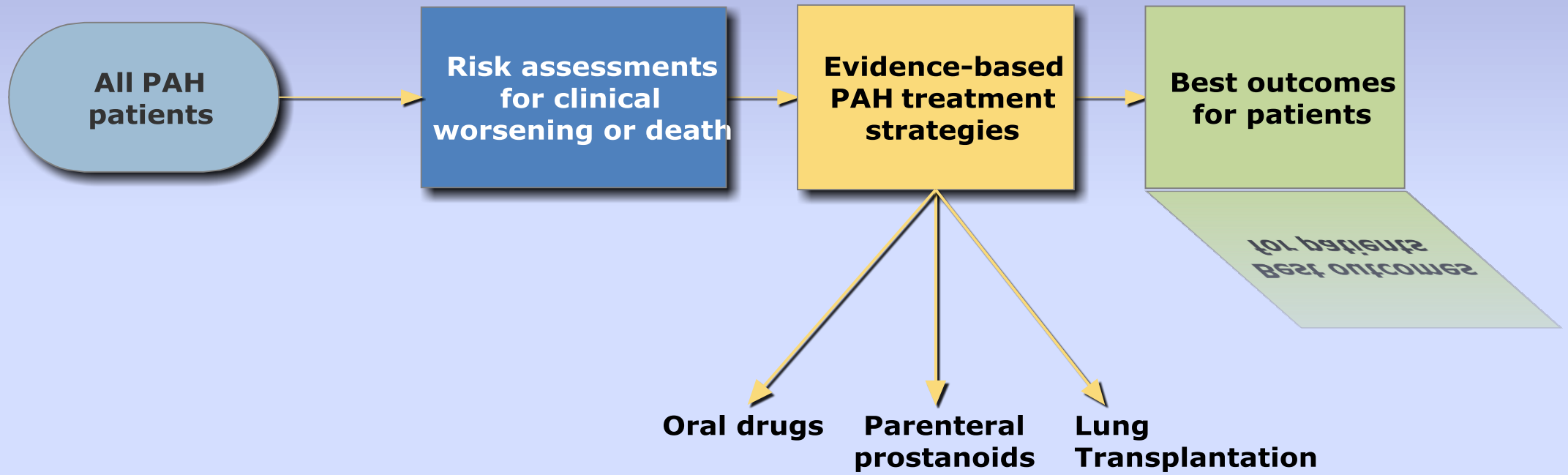
- Modified NYHA FC I or II
- Echocardiography/CMR of normal/near-normal RV size and function
- Haemodynamic parameters showing normalization of RV function (RAP <8 mm Hg and CI >2.5 to 3.0 l/min/m2)
- 6MWD of >380 to 440 m (which may not be aggressive enough)
- Cardiopulmonary exercise testing, including peak oxygen consumption >15 ml/min/kg and EqCO2 <45 l/min/l/min
- Normal BNP levels

McLaughlin VV et al J Am Coll Cardiol 2013;62:D73-D81

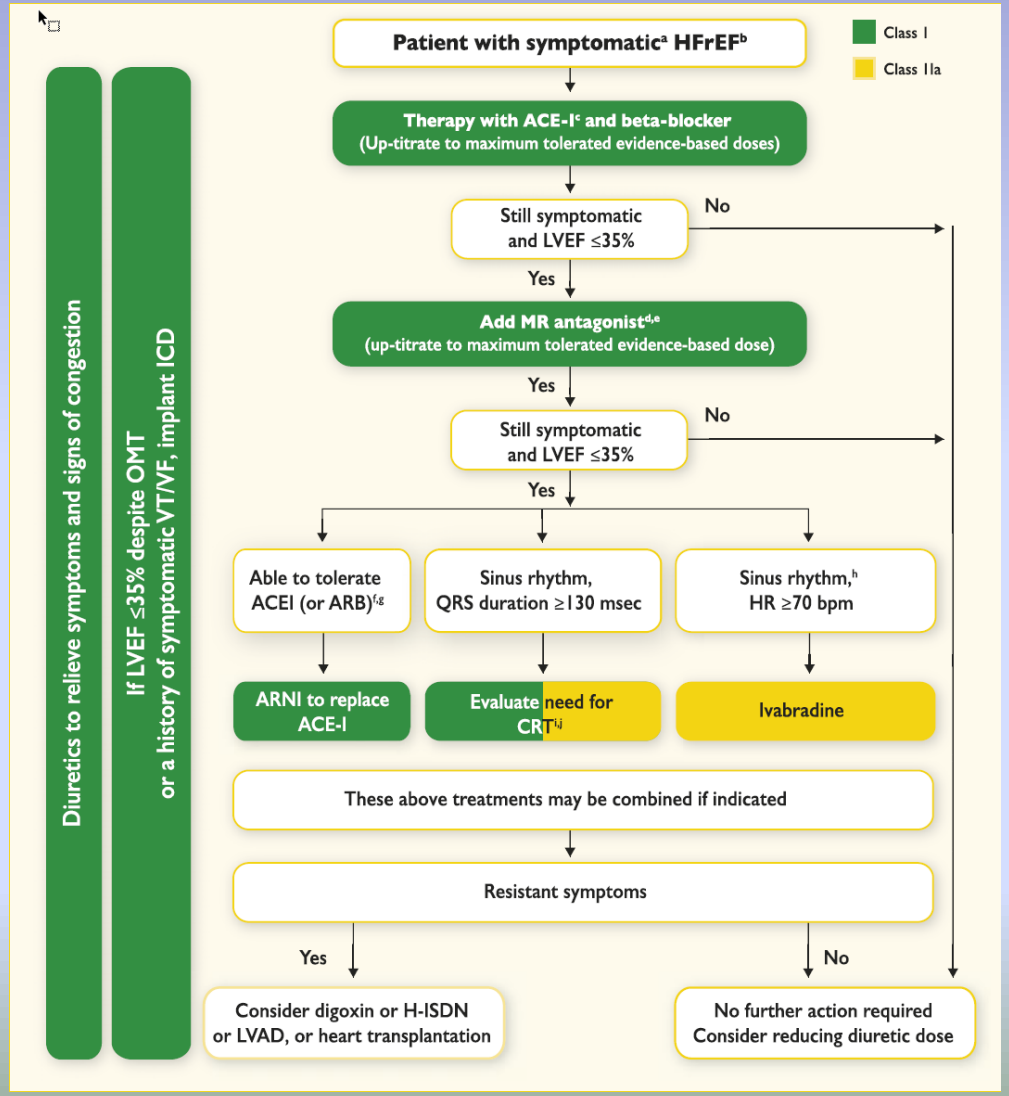


Adapted from Haddad F et al JACC Cardiovasc Imaging 2016;9:630

Shall we still need an assessment of severity if we use initial combination therapy in PAH?



How do other diseases assess severity and use this to guide clinical management?



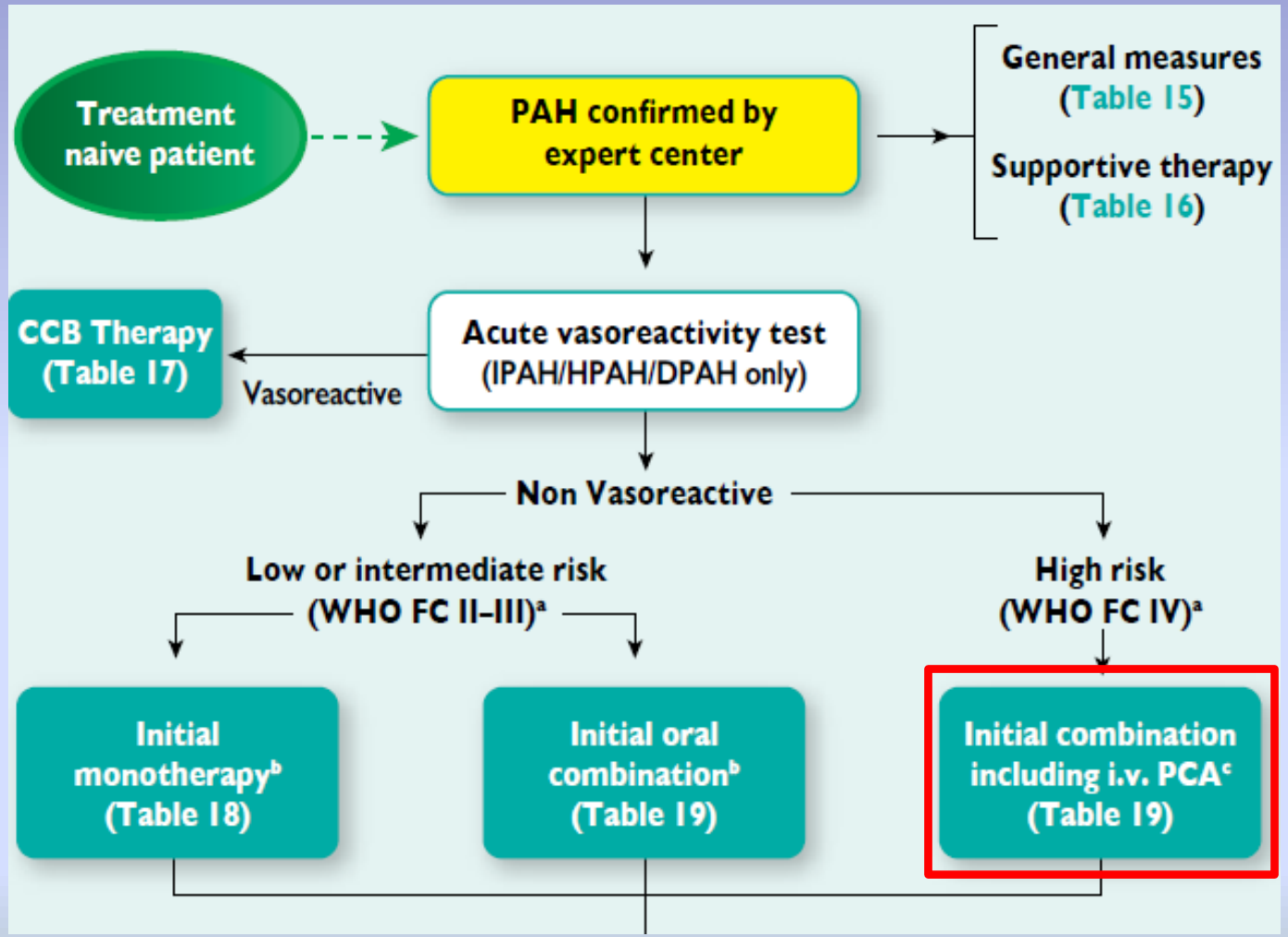
Ponikowski P et al
Eur J Heart Failure (2016)18, 891–975

32-year-old female with 9 months worsening breathlessness

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	
Progression of symptoms			Rapid
Syncope	No		
WHO functional class			IV
6MWD		165–440 m	
Cardiopulmonary exercise testing			Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels		BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	
Imaging (echocardiography, CMR imaging)			RA area >26 cm^2 Pericardial effusion
Haemodynamics			RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

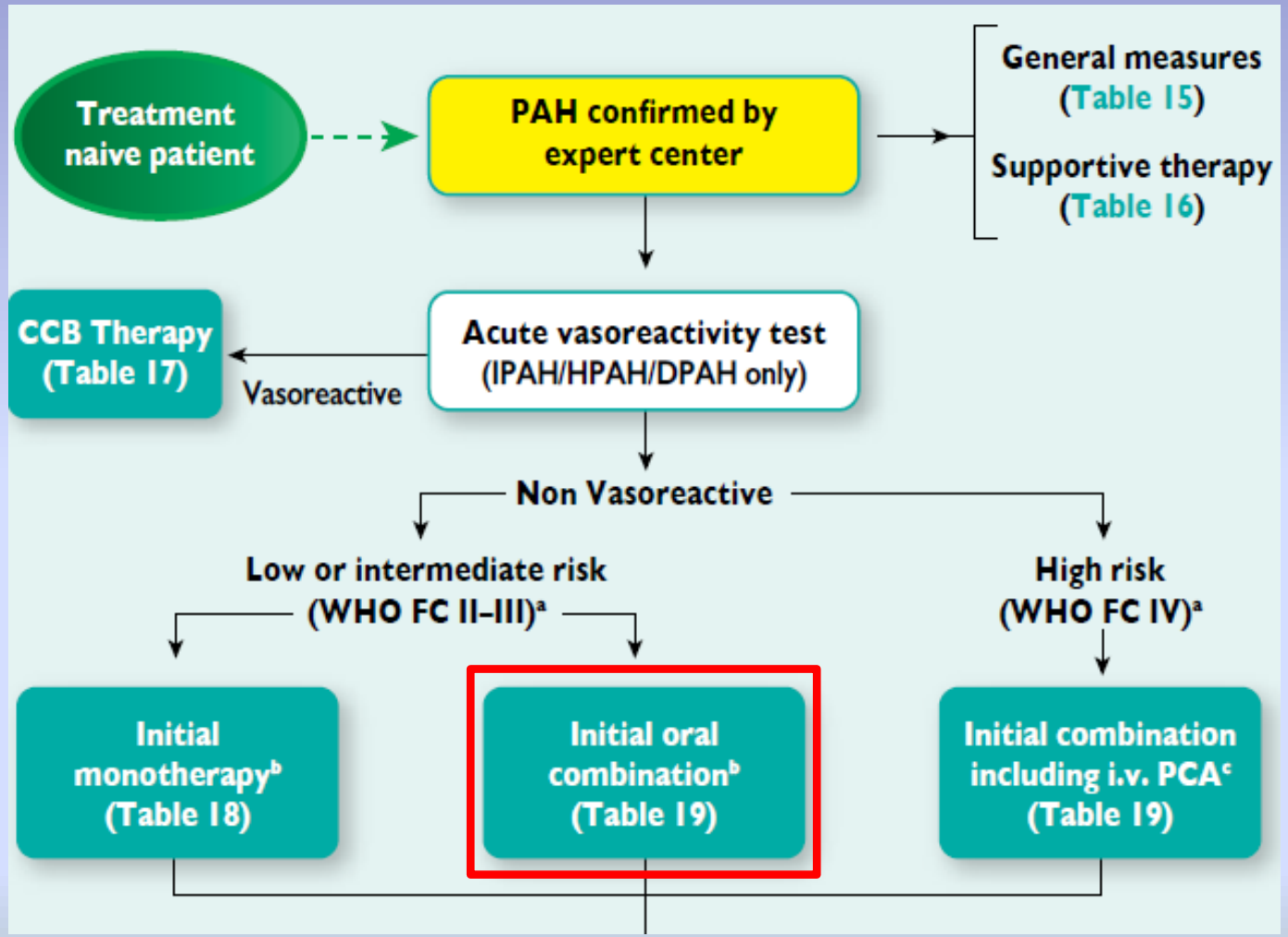
Adapted from Galie N et al Eur Heart J 2016;37:67-119 & Eur Respir J 46:903-75

Treatment Algorithm for Pulmonary Arterial Hypertension



Galie N et al Eur Heart J 2016;37:67-119 & Eur Respir J 46:903-75

Treatment Algorithm for Pulmonary Arterial Hypertension



Galie N et al Eur Heart J 2016;37:67-119 & Eur Respir J 46:903-75

32-year-old female with 9 months worsening breathlessness

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

Adapted from Galie N et al Eur Heart J 2016;37:67-119 & Eur Respir J 46:903-75

32-year-old female with 9 months worsening breathlessness

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	
Progression of symptoms	No		
Imaging (echocardiography, CMR imaging)		No or minimal, pericardial effusion	
Haemodynamics		RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	

Symptoms alone may underestimate risk.
Six-minute walk test distance may underestimate peak exercise performance and risk in some individuals.
Not all measurements are of equal value for assessing risk in an individual.

Adapted from Galie N et al Eur Heart J 2016;37:67-119 & Eur Respir J 46:903-75

28 year old male with 2 years worsening breathlessness @ baseline

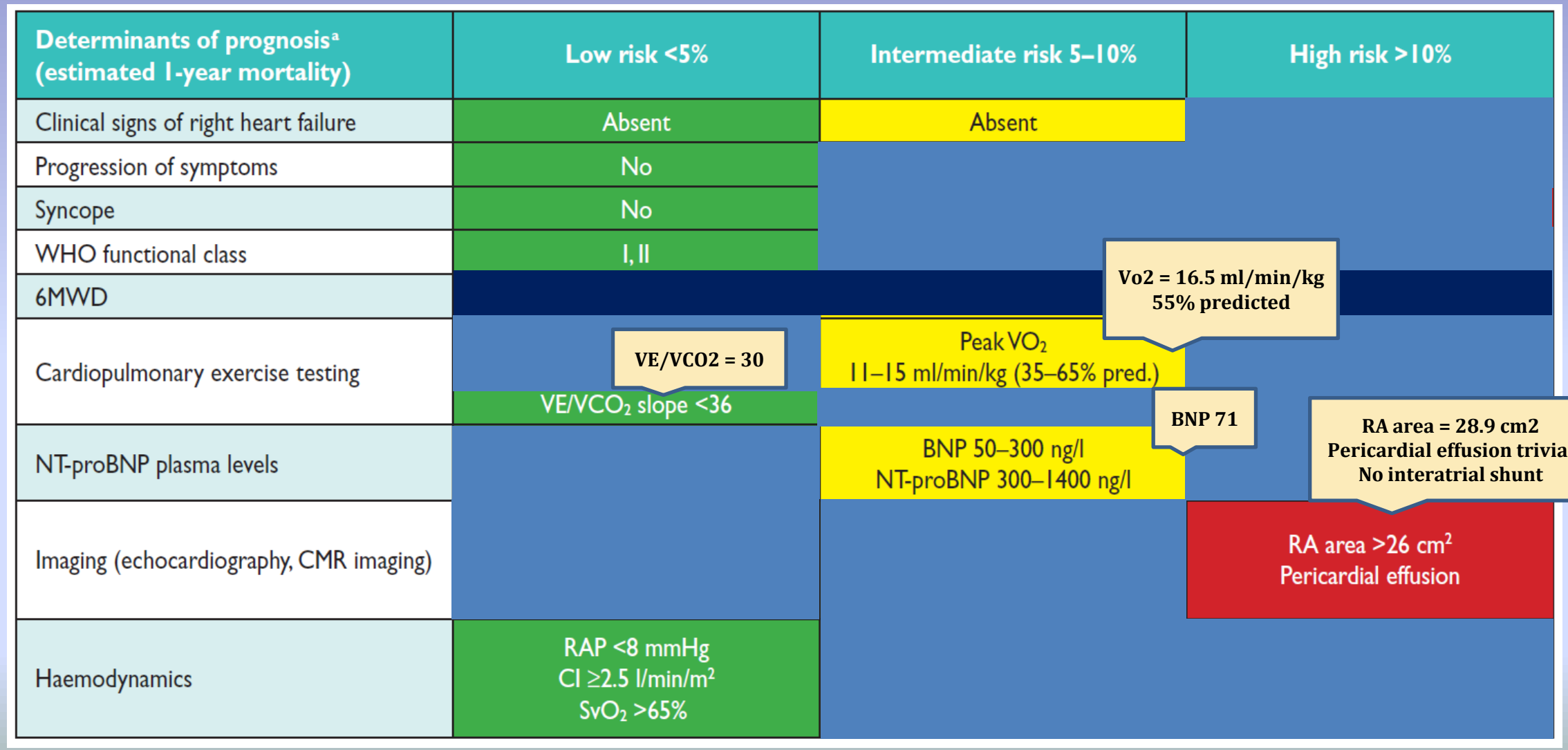
Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	
Progression of symptoms		Slow	
Syncope			Repeated syncope[c]
WHO functional class		III	
6MWD			<165 m
Cardiopulmonary exercise testing			
NT-proBNP plasma levels			BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)			RA area >26 cm^2 Pericardial effusion
Haemodynamics		RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	

144 m

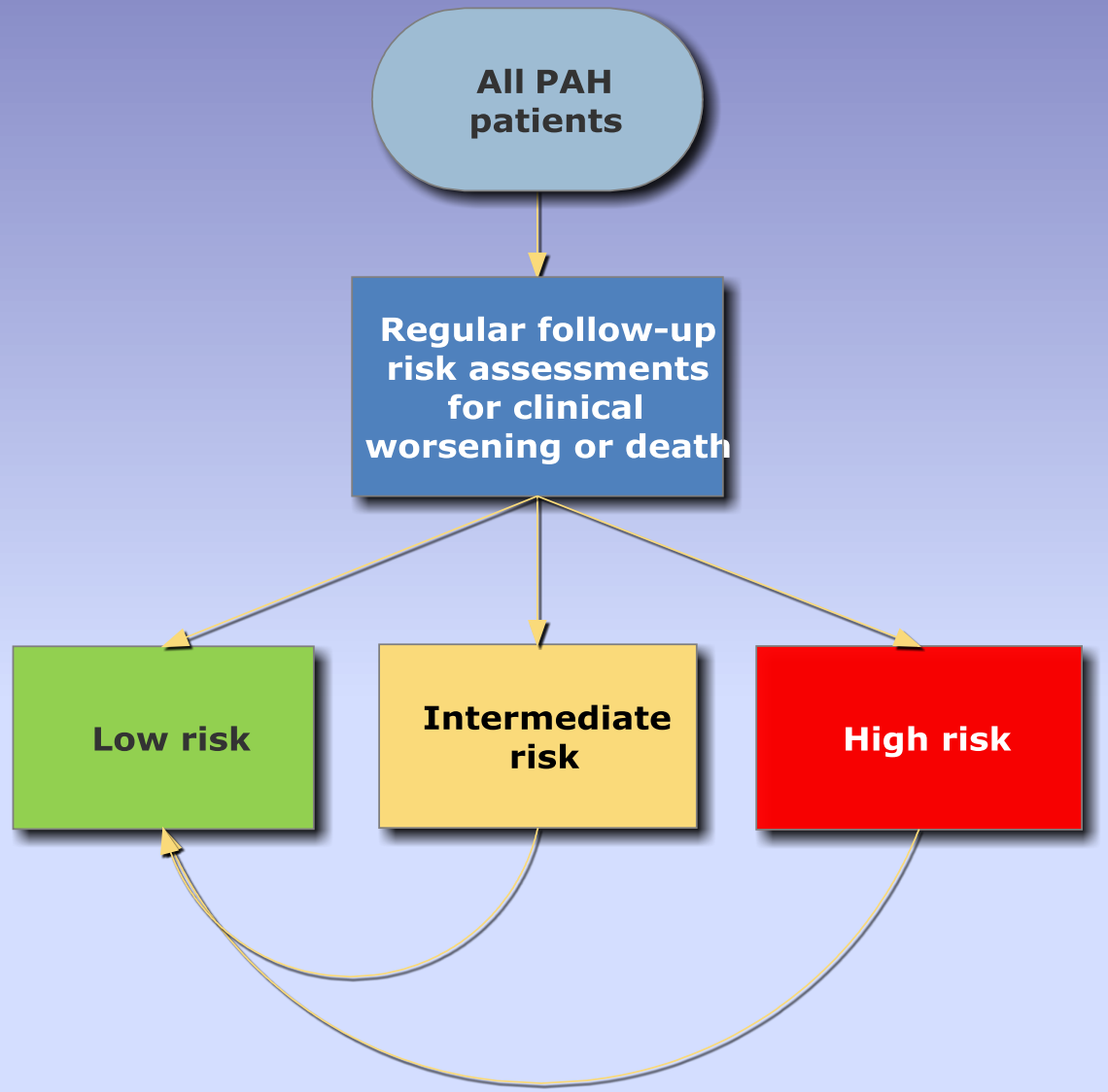
BNP 822

Adapted from Galie N et al Eur Heart J 2016;37:67-119 & Eur Respir J 46:903-75

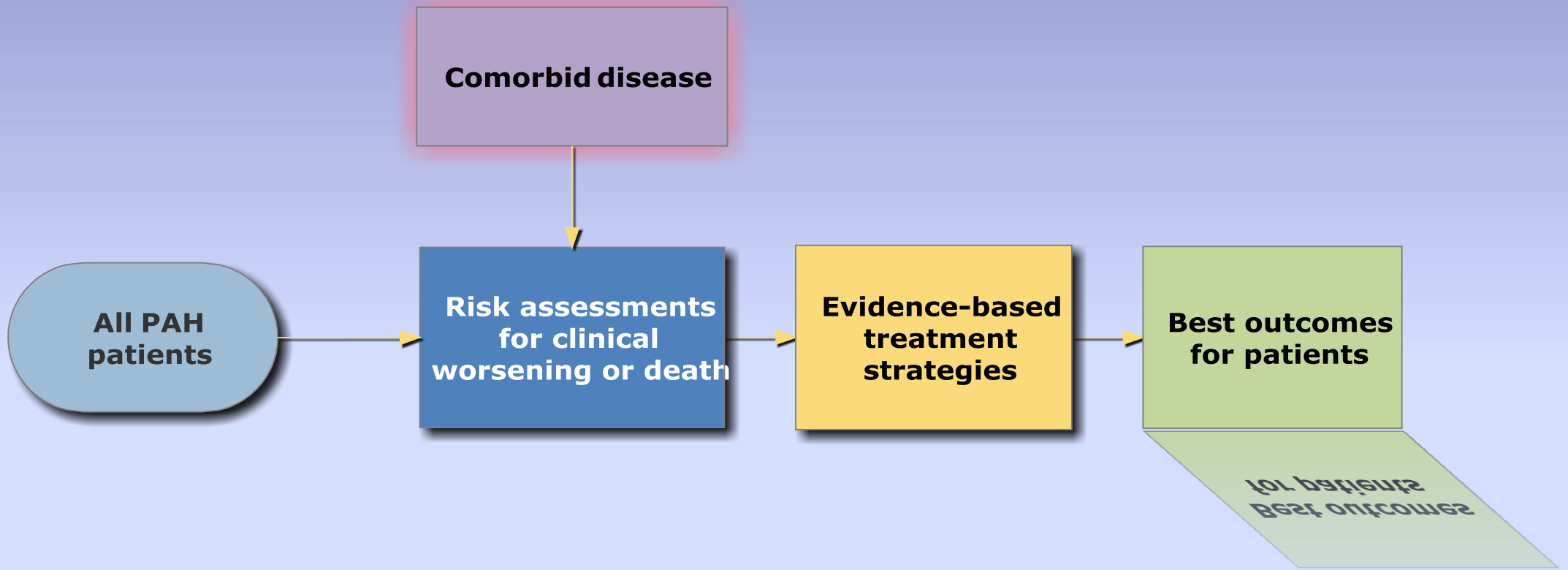
29 year old male with 2 years worsening breathlessness @ one year on dual oral combination therapy



Adapted from Galie N et al Eur Heart J 2016;37:67-119 & Eur Respir J 46:903-75



Risk at follow-up on treatment may not be the same as at baseline



“There is uncertainty about the effectiveness of interventions for people with multimorbidity”

Smith SM, Wallace E, O’Dowd T, Fortin M. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD006560. DOI: 10.1002/14651858.CD006560.pub3.

AMBITION enrollment criteria

Key enrollment criteria:

- Pulmonary Arterial Hypertension (PAH)
  - IPAH/HPAH; APAH (HIV, CTD, Drugs and Toxins, repaired simple CHD)
- Functional Class II or III
- Treatment naïve
- Age 18-75 years
- Baseline 6MWD 125-500m

Amendment 2:

- To reduce likelihood of enrolling subjects with PH due to covert diastolic dysfunction

Original Protocol Criteria (Intent to Treat (ITT))

- PVR ≥ 240 dyn•s/cm^5
- PAWP or LVEDP ≤ 15 mmHg
- No exclusion of subjects with risk factors for left ventricular disease

Amendment 2 Changes (Primary Analysis Set (PAS)) N = 500

- PVR ≥ 300 dyn•s/cm^5
- PAWP lowered to ≤ 12 mmHg in subjects with PVR ≥ 300 but < 500 dyn•s/cm^5
- PAWP or LVEDP ≤ 15 mmHg if PVR ≥ 500
- Exclusion of subjects with ≥ 3 of the following risk factors for left ventricular disease:
  - BMI ≥ 30 kg/m^2
  - History of essential hypertension
  - Diabetes mellitus (any type)
  - History of significant CAD (PCI, MI, CABG, stable angina, at least 1 vessel CAD)

Galie N et al *N Engl J Med* 2015;373:834-44

AMBITION inclusion criteria

7. Subject must meet all of the following pulmonary function tests completed no more than 24 weeks before the Screening visit:
   i. Total lung capacity (TLC) ≥60% of predicted normal and
   ii. Forced expiratory volume in one second (FEV1) ≥55% of predicted normal
8. Subject must walk a distance of ≥125m and ≤500m at the screening visit
9. Subject, with or without supplemental oxygen, must have a resting arterial oxygen saturation (SaO2) ≥88% as measured by pulse oximetry at the Screening Visit.

NB: subjects with portopulmonary hypertension and PVOD are NOT eligible for the study

Galie N et al *N Engl J Med* 2015;373:834-44

Multivariate model of predictors of mortality in systemic sclerosis APAH and other CTD APAH

Risk Score Characteristic	HR	95% CI	*P* Value
SSc-APAH			
Men aged >60 y	2.222	1.421-3.474	<.001
NYHA FC III	1.326	1.002-1.756	.049
NYHA FC IV	2.938	1.921-4.492	<.001
Systolic BP≥110 mm Hg	1.334	1.034-1.723	.027
6MWD<165 m	2.252	1.614-3.142	<.001
BNP<50 pg/mL	0.450	0.209-0.966	.040
BNP>180 pg/mL	2.082	1.617-2.682	<.001
mRAP>20 mm Hg within 1 y	1.910	1.003-3.637	.049
PVR>32 Wood units	14.567	3.464-61.262	<.001
Non-SSc-CTD-APAH			
NYHA FC III	1.679	1.067-2.641	.025
NYHA FC IV	5.427	2.588-11.383	<.001
6MWD≥440 m	0.293	0.118-0.732	.009
BNP>180 pg/mL	2.466	1.589-3.826	<.001

Chung L et al Chest 2014;146(6):1494 - 1504

Assessment of disease severity in other forms of PAH: Monitoring and prognosis in adult Eisenmenger's syndrome

Better prognosis	Determinants of prognosis	Worse prognosis
No	Right ventricular failure[a]	Yes, guarded
No	Syncope[b]	Uncertain
I, II	WHO functional class[c] [42]	III, IV
Longer (>350 m)	6MWD [24,25]	Shorter (<300 m)
>85%	Oxygen saturation [24,25]	<85% *or* a drop of >2%/year
Transferrin saturation ≥20%	Iron deficiency [60]	Transferrin saturation < 20%
Normal or near normal	BNP plasma levels[d]	>30 pmol/L
TAPSE ≥ 1.5 cm	Echocardiographic findings[e]	TAPSE < 1.5 cm
RA area < 25 cm^2		RA area ≥ 25 cm^2
RA/LA < 1.5		RA/LA ≥ 1.5
RAP < 8 mm Hg and CI ≥ 2.5 L/min/m^2	Haemodynamics[f]	RAP > 15 mm Hg and CI ≤ 2.0 L/min/m^2

BNP, brain natriuretic peptide; CI, cardiac index; LA, left atrium; RA, right atrium; RAP, right atrial pressure; 6MWD, 6-minute walk distance; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization.

[a] Presence or absence of right ventricular failure in PAH is deemed to carry a worse or better prognosis respectively. However, in patients with ES right ventricular failure is a late and ominous sign and thus of limited value for early prognostication.

[b] Syncope in patients with ES and chronic cyanosis can be vasovagal, due to autonomic nervous dysfunction; therefore, if syncope is present, its prognostic value is assumed to be uncertain.

[c] Overall 5-year mortality amongst aduts with ES was higher in functional class III patients compared with patients in functional class I or II (14.1% versus 32.2%; log rank p = 0.006) [42]

[d] A plasma BNP value of >30 pmol/L has been shown to convey a 4.5-fold greater mortality risk in ES patients (normal values < 20 pmol/L) [61].

[e] Echocardiographic parameters specific for ES patients; a composite score, including tricuspid annular plane systolic excursion < 1.5 cm, ratio of right ventricular effective systolic to diastolic duration ≥ 1.5, right atrial area ≥ 25 cm^2 and a ratio of right atrial to left atrial area ≥ 1.5 was highly predictive of clinical outcome (area under the curve 0.90 ± 0.01) [62].

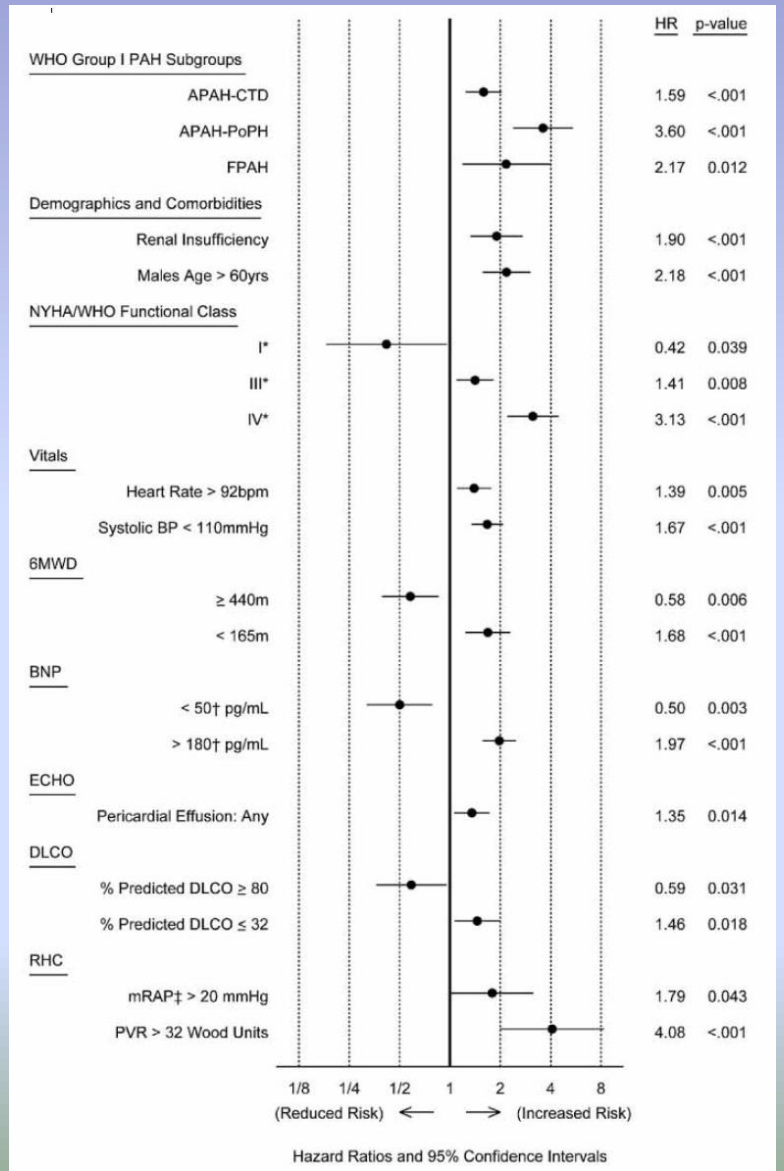
[f] Baseline haemodynamic assessment, including measurement of pulmonary vascular resistance, is the norm in most tertiary centres. Repeated, serial haemodynamic assessments are not, however, routinely recommended for patients with ES. Acute vasoreactivity studies during baseline haemodynamic assessment may convey prognostic information [63].

Gatzoulis MA et al Int J Cardiol 2014;177:340-347.

Alternative severity assessment strategies to the ESC / ERS guidelines

- Create a risk score from a registry

REVEAL Cox proportional hazards for multivariable model of survival limited to terms in the final stepwise model



APAH indicates associated PAH;
ECHO, echocardiogram;
FPAH, familial PAH;
mRAP, mean right atrial pressure;
PoPH, portopulmonary hypertension;
RHC, right heart catheterization.

*Reference category: NYHA/WHO functional class (Fn) II or missing.
†If N-terminal proBNP is available and BNP is not, listed cut points are replaced with 300 pg/mL and 1500 pg/mL.
‡Restricted to tests performed within 1 year of enrollment; otherwise, the indicator is set to 0.

Benza RL et al Circulation 2010;122:164-172

REVEAL Risk Score

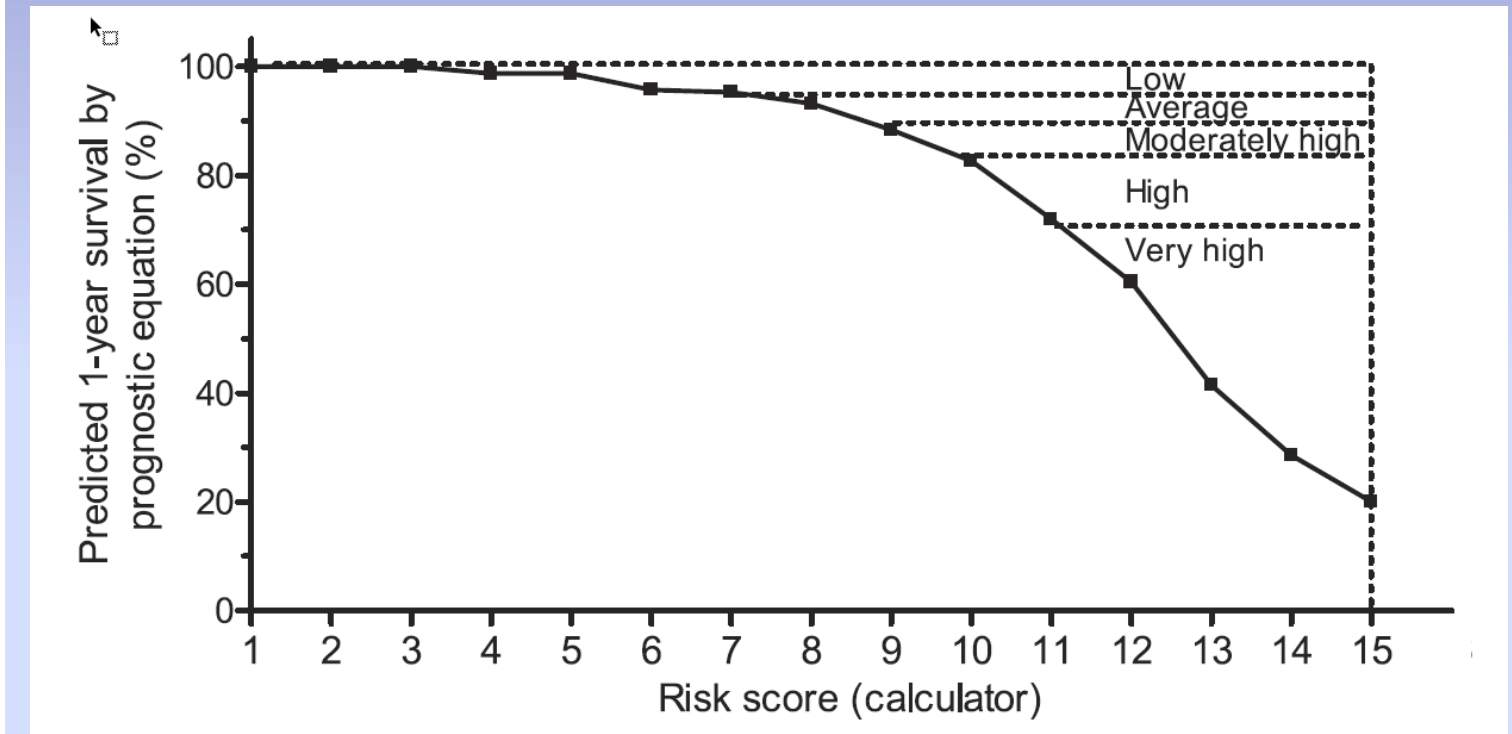
REVEAL™ PAH Risk Score

WHO Group I Subgroup	APAH-CTD +1	APAH-PoPH +2	FPAH +2
Demographics & Comorbidities	Renal Insufficiency +1	Males Age>60yrs +2	
NYHA/WHO Functional Class	I -2	III +1	IV +2
Vital Signs	SBP<110 mm Hg +1	HR>92 BPM +1	
6-Minute Walk Test	≥440 m -1	<165 m +1	
BNP	<50 pg/mL -2	>180 pg/mL +1	
Echocardiogram	Pericardial Effusion +1		
Pulmonary Function Test	% pred. DLco≥80 -1	% pred. DLco≤32 +1	
Right Heart Catheterization	mRAP>20 mm Hg within 1 yr +1	PVR>32 Wood units +2	

SUM OF ABOVE

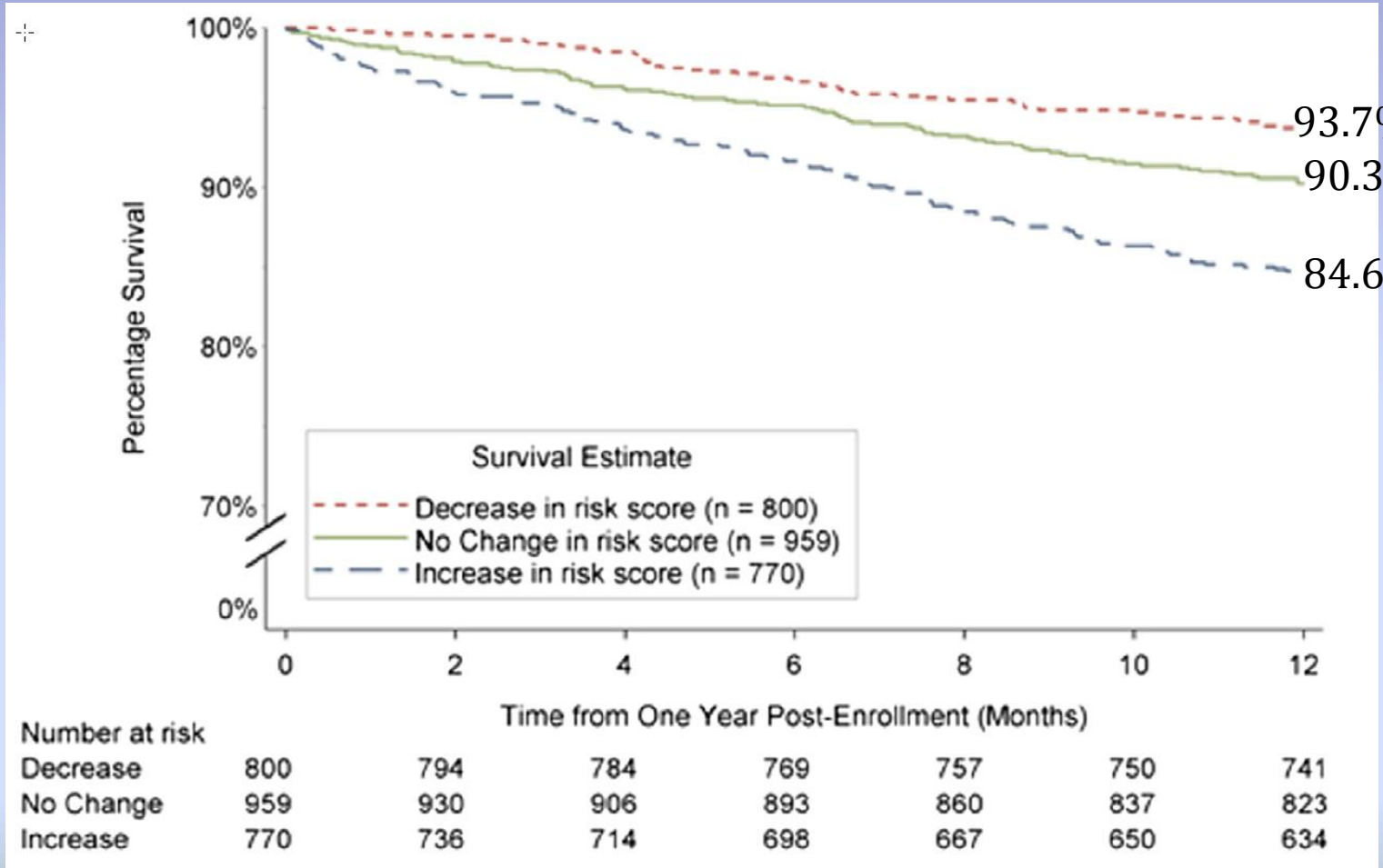
\+ 6

= RISK SCORE



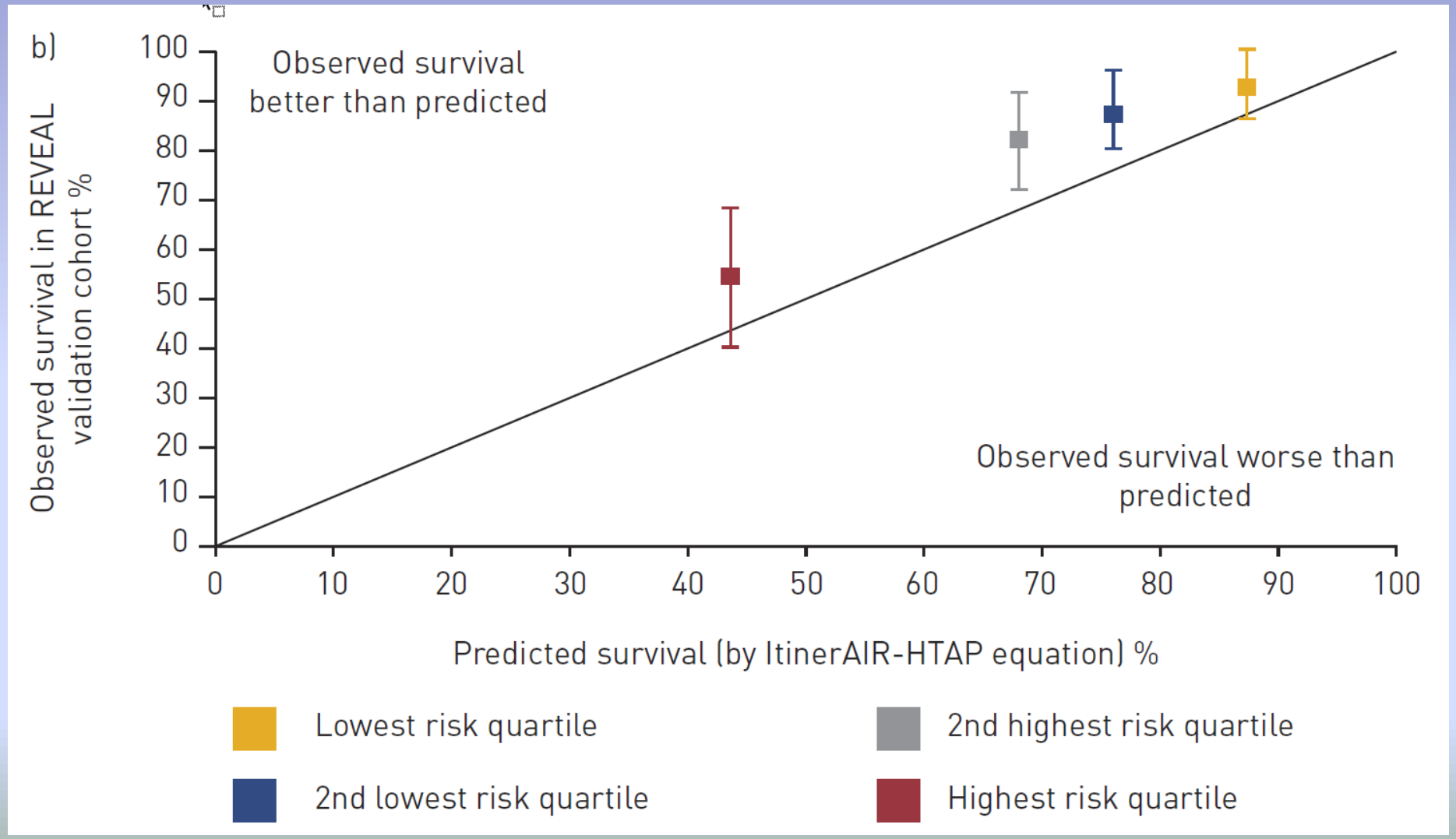
Benza RL et al Chest 2012;141:354-162

Serial change in REVEAL Risk Score after 1 year alters prognosis



Benza RL et al Chest 2012;141:354-162

Comparison of REVEAL and French registries: observed versus predicted 3-year survival using the FPHN ItinérAIR-HTAP equation in the REVEAL validation cohort



Sitbon O, *et al. Eur Respir J* 2015; 46:152-64.

Alternative severity assessment strategies to the ESC / ERS guidelines

- **Create a risk score from a registry; limitations include**:
  - Immortal time bias requires correction in some registries
  - Missing data
  - Lack of serial data in some registries
  - Generalisability of the risk score outside the registry population

Alternative severity assessment strategies

- **Create a risk score from a registry, limitations include**:
  - Immortal time bias requires correction in some registries
  - Missing data
  - Lack of serial data in some registries
  - Generalisability of the risk score outside the registry population
- **Use a large database to predict outcome by matching patient's phenotype**
  - Meta-analysis of registries
  - Meta-analysis of patient-level clinical trial data
  - Machine learning and "big data"

Heart Failure Risk Calculator

MAGGIC

Meta-Analysis Global Group in Chronic Heart Failure

The Heart Failure Risk Calculator presents 1 and 3 year all-cause mortality estimates for people with heart failure, as developed and presented in Pocock et al. "Predicting survival in heart failure: a risk score based on 39372 patients from 30 studies" Eur Heart J 2012 doi:10.1093/eurheartj/ehs337.

The intended audience for the Risk Calculator is health care professionals knowledgeable in cardiology and the management of people with heart failure.

The model was constructed from research data collected from 1980-2006 and may not be indicative of current or future trends in heart failure management. The variability in risk between studies and cohorts is greater than that explained by known risk factors. True risk within any centre may be higher or lower than the stated estimates for 1 and 3 year mortality.

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Te Whare Wānanga o Tāmaki Makaurau

Heart Foundation

University of Glasgow

Age	18-110
Gender	Female
Diabetes	○ Yes ○ No
COPD	○ Yes ○ No
Heart failure diagnosed within the last 18 months	○ Yes ○ No
Current smoker	○ Yes ○ No
NYHA Class	1
Receives beta blockers	○ Yes ○ No
Receives ACEi/ARB	○ Yes ○ No
BMI calculate BMI	10-50 kg/m^2
Systolic blood pressure	50-250 mmHg
Creatinine	20-1400 µmol/L
Ejection fraction	1-95 %

Risk factor	Addition to risk score								Risk score
Ejection fraction (%)	<20 +7	20–24 +6	25–29 +5	30–34 +3	35–39 +2	40+ 0			
Extra for age (years)	<55	56–59	60–64	65–69	70–74	75–79	80+		
EF < 30	0	+1	+2	+4	+6	+8	+10		
EF 30 - 39	0	+2	+4	+6	+8	+10	+13		
EF 40 +	0	+3	+5	+7	+9	+12	+15		
Extra for Systolic blood pressure (mm Hg)	<110	110–119	120–129	130–139	140–149	150+			
EF < 30	+5	+4	+3	+2	+1	0			
EF 30 - 39	+3	+2	+1	+1	0	0			
EF 40 +	+2	+1	+1	0	0	0			
BMI (kg / m^2)	<15 +6	15–19 +5	20–24 +3	25–29 +2	30+ 0				
Creatinine (µmol/l)	<90 0	90–109 +1	110–129 +2	130–149 +3	150–169 +4	170–209 +5	210–249 +6	250+ +8	
NYHA Class	1 0	2 +2	3 +6	4 +8					
Male				+1					
Current smoker				+1					
Diabetic				+3					
Diagnosis of COPD				+2					
First diagnosis of heart failure in the past 18 months				+2					
Not on beta blocker				+3					
Not on ACEI/ARB				+1					
								Total risk score =	

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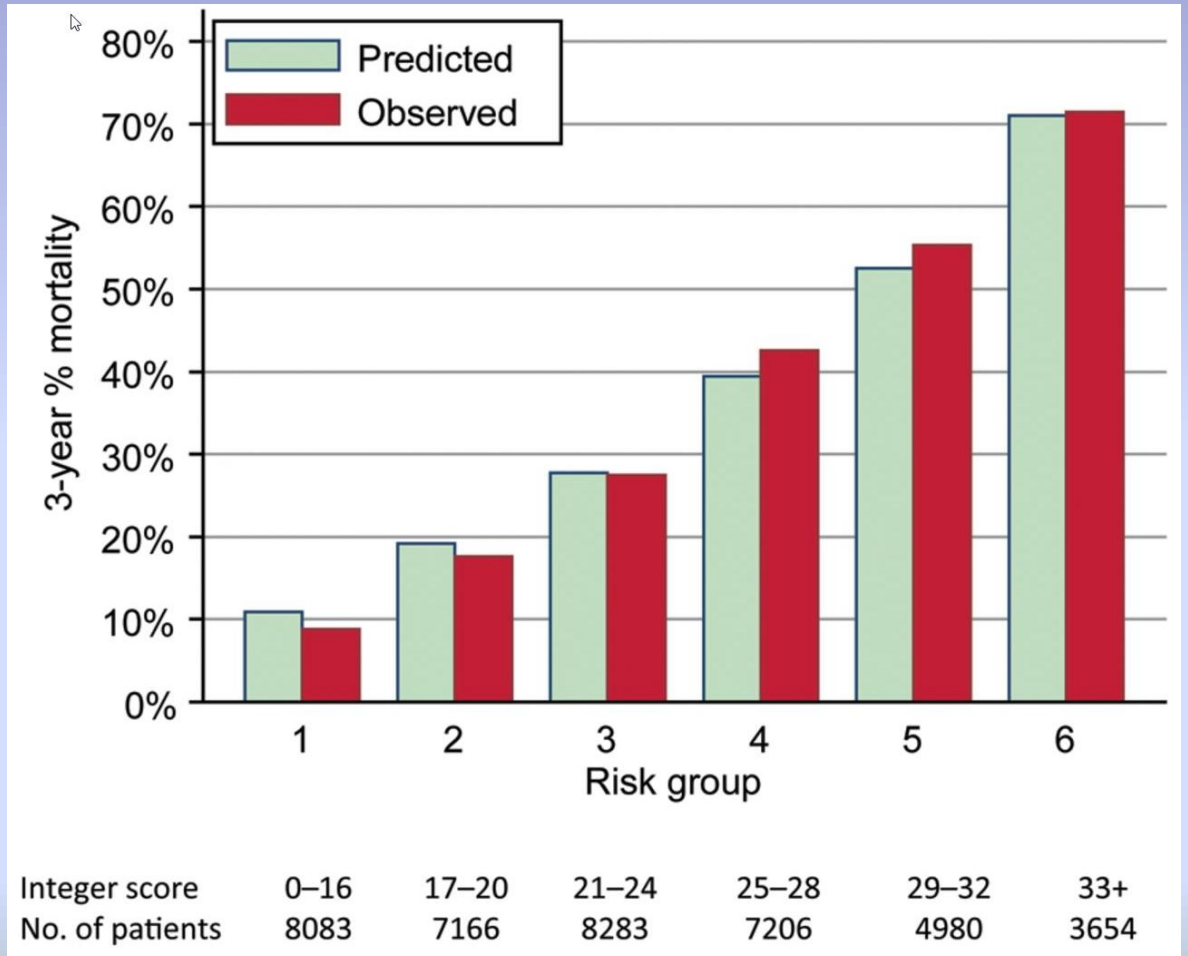
MAGGIC: observed versus predicted 3 year mortality in six risk groups



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Conclusions

- A risk assessment tool may be better than asking the patient's doctor or nurse to predict outcome
- A selection of risk assessment tools combining multiple measurements are recommended for PAH patient management
- Different forms of PAH may require different assessments to describe severity
- Comorbid diseases may make the assessment of PAH severity more difficult
- Future alternatives has been discussed