Update in Pulmonary Arterial Hypertension with Congenital Heart Diseases: Management in Daily Practice – Children and Adults

Prof. Ioannis Lekakis

Athens – Greece

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Introduction

- **PAH is a severe condition in children and in adults:**
  - **Associated with a particularly poor prognosis if left untreated**
    - **Median survival 10 months compared with 2.8 years in adults**

- **Unfortunately, studies of PAH-CHD therapies are few in children, and treatment of paediatric PAH is generally guided by the adult treatment algorithm, with some adaptations**

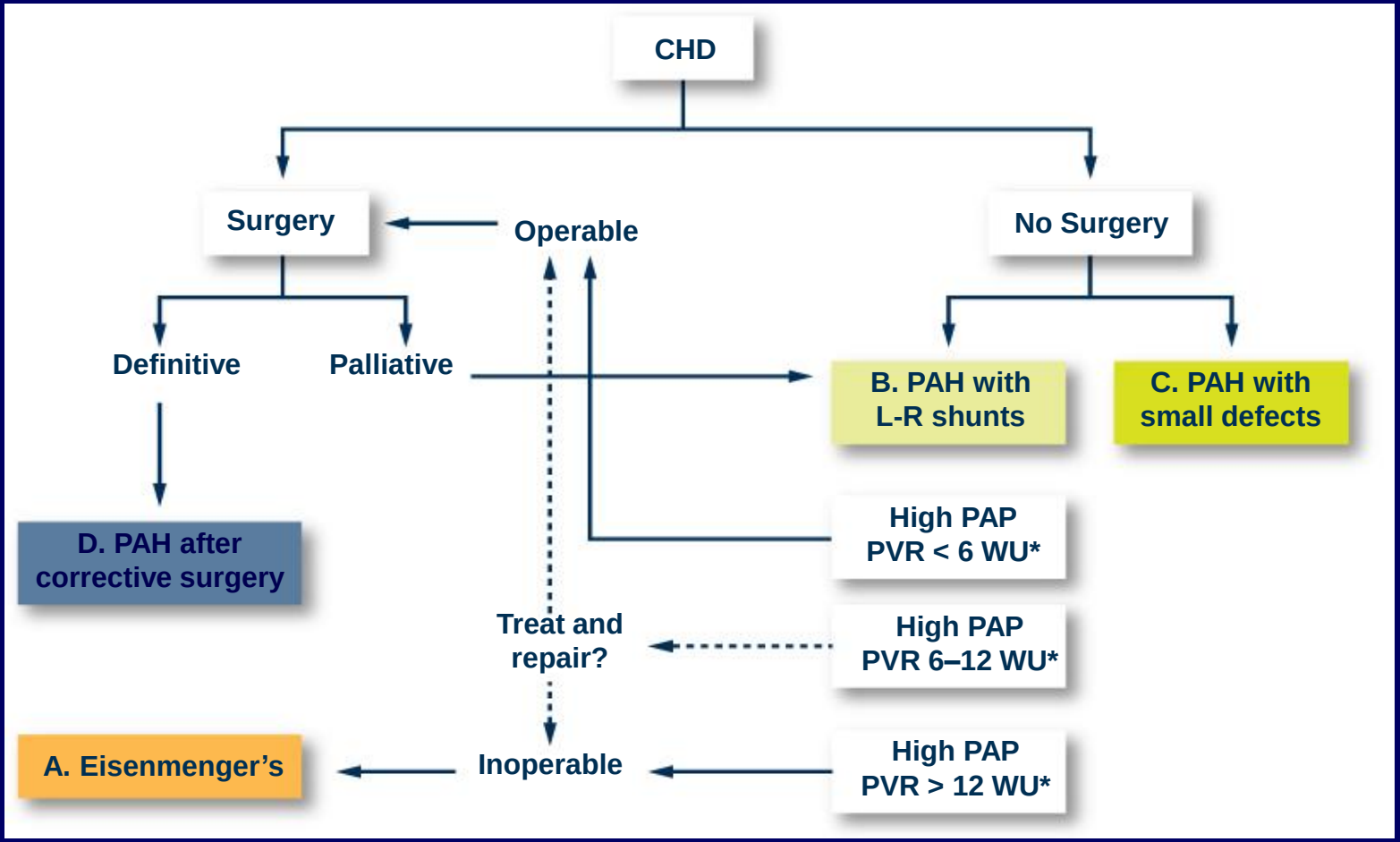
- **Due to advances in diagnosis and surgical treatments, there is a progressive 'aging' of CHD patients, many with complex cardiac lesions**

- **Even in those operated PAH-CHD children, complications and evolution of the PAH may occur**

- **Further research is required to develop appropriate treatment strategies, formulations and doses for PAH-CHD in children**

Widlitz and Barst. *Eur Resp J* 2003
D'Alonzo et al. *Ann Int Med* 1991

Management of patients with PAH-CHD



Galiè et al. *Eur Heart J* 2009; Baumgartner et al. *Eur Heart J* 2010; expert opinion

Epidemiology of PAH-CHD

- Understanding the epidemiology of paediatric PH is essential to guide management decisions, but such epidemiological data are scarce

- Euro Heart Survey (adults with CHD): of 1,877 patients with septal defects, 28% had PH and 7.1% had Eisenmenger´s syndrome

- In a recent study, the prevalence of PAH-CHD in 1,824 patients with septal defects was 6.1% and 3.5% had Eisenmenger´s syndrome

- In general population, the prevalence of PAH-CHD can be extrapolated from data of registries:
  - French Registry: 5 to 25 PAH cases per million adults (11.3% PAH-CHD)
  - Scottish Registry: 26 to 52 PAH cases per million (24% PAH-CHD)
  - Therefore, in Western countries may range between 0.6 (low French) and 12.5 (high Scottish) cases per million (25%-50% affected with ES)...

Engelfriet P et al. *Eur Heart J* 2005; 26: 2325–2333.
Engelfriet P et al. *Heart J* 2007; 93: 682-687.
Humbert M et al. *Am J Resp Crit Care Med* 2006; 173: 1023-1030.
Peacock A.J et al. *Eur Respir J* 2007; 30: 104-109

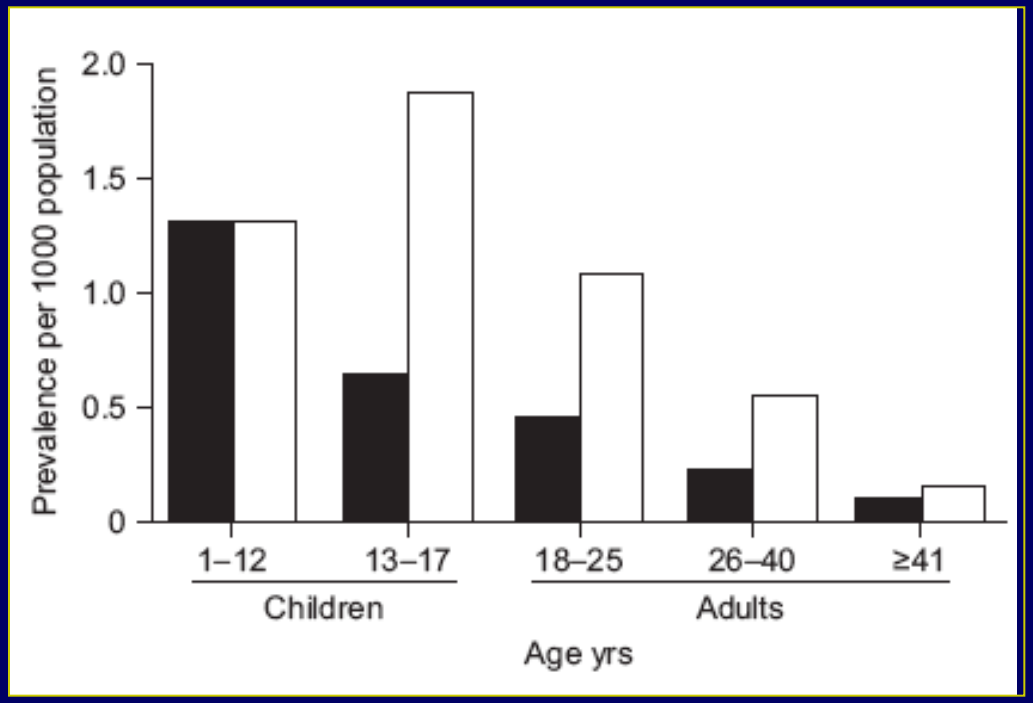
However, PAH-CHD patients are far to all detected...

▪ If we start from the known CHD prevalence	0,3%	3’000 ppm
▪ The prevalence of septal defects	24% of CHD	720 ppm
▪ VSD	10,2%	
▪ ASD	8,9%	
▪ AVSD	2,9%	
▪ DORV	2,0%	
▪ The prevalence of PAH in SD	6% of SD	43 ppm calculated prevalence

% derived from: Vander Velde et al. *European Journal of Epidemiology* 2005; 20: 549–557.

In the Last Years, More Patients with CHD Survive Into Adulthood

Canadian general population



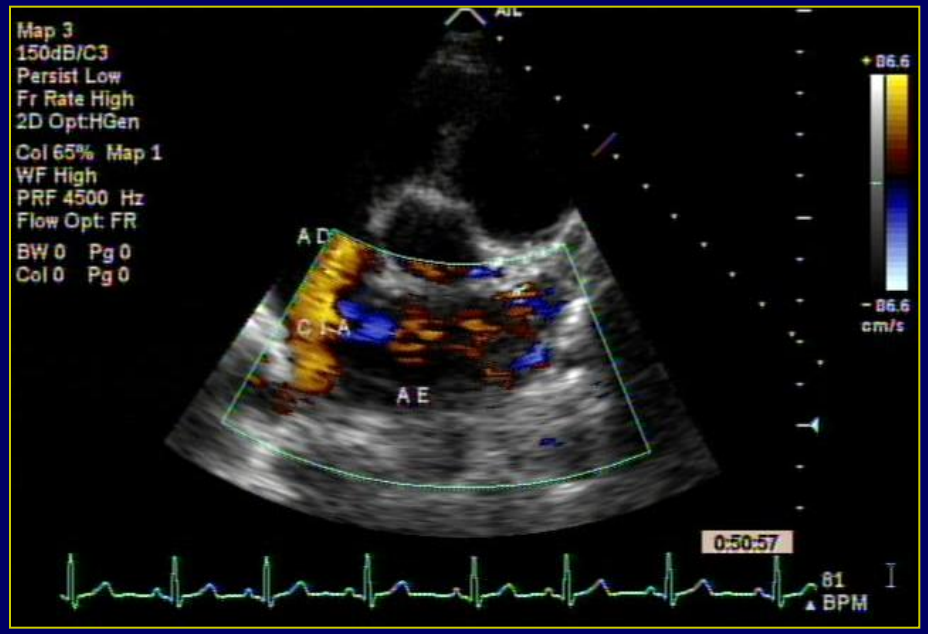
- No change was observed in the prevalence of CHD in children between 1985 and 2000, but many more patients survived into adulthood in 2000
- In fact, there was an 85% increase in adult prevalence between 1985 and 2000 with the largest increase occurring in adolescents and young adults

Marelli A.J et al. *Circulation* 2007; 115: 163–172.

And More CHD-PAH Patients Have More Complexed Lesions

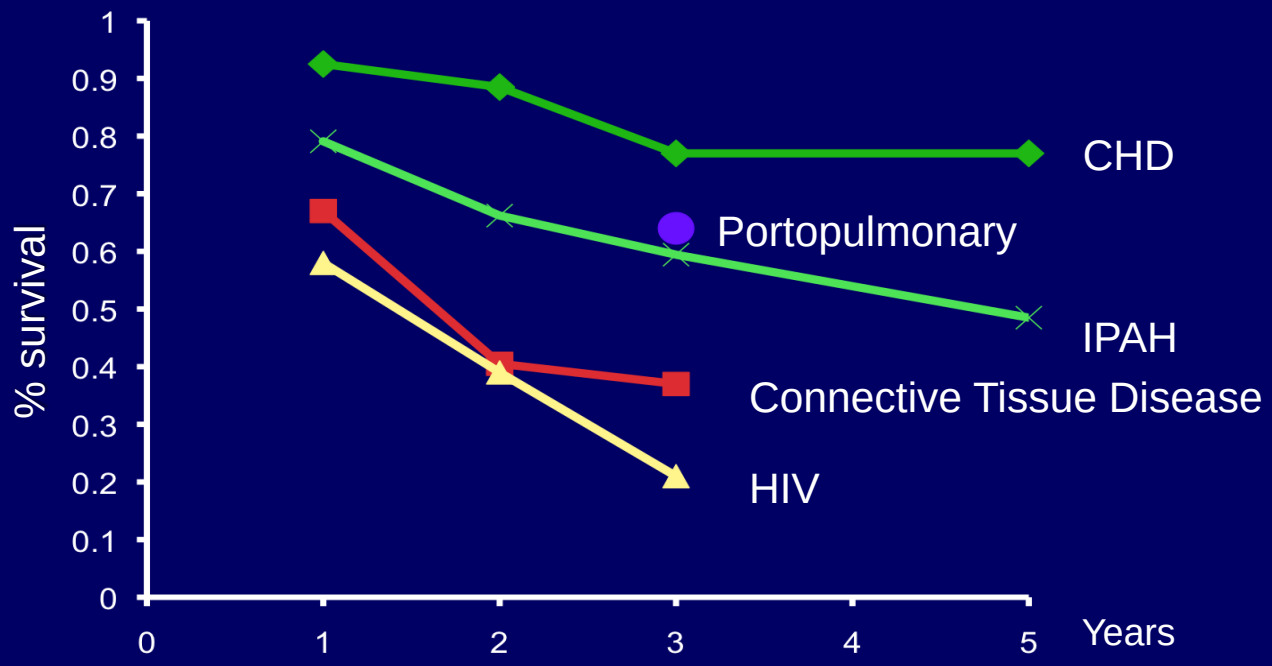
- In parallel with changes in the demographics of CHD, there have been corresponding shifts in the demographics of PAH-CHD

- These changes are toward not only more adult patients, but also fewer adult CHD patients with PAH and simple cardiac lesions and increased numbers of patients with more complex lesions and PAH



Diller GP, Gatzoulis MA. *Circulation* 2007; 115: 1039–1050.
Marelli A.J et al. *Circulation* 2007; 115: 163–172.
Gatzoulis M.A et al. *Eur Respir Rev* 2009; 18: 154–161.

Survival in Patients with CHD-PAH is Better...



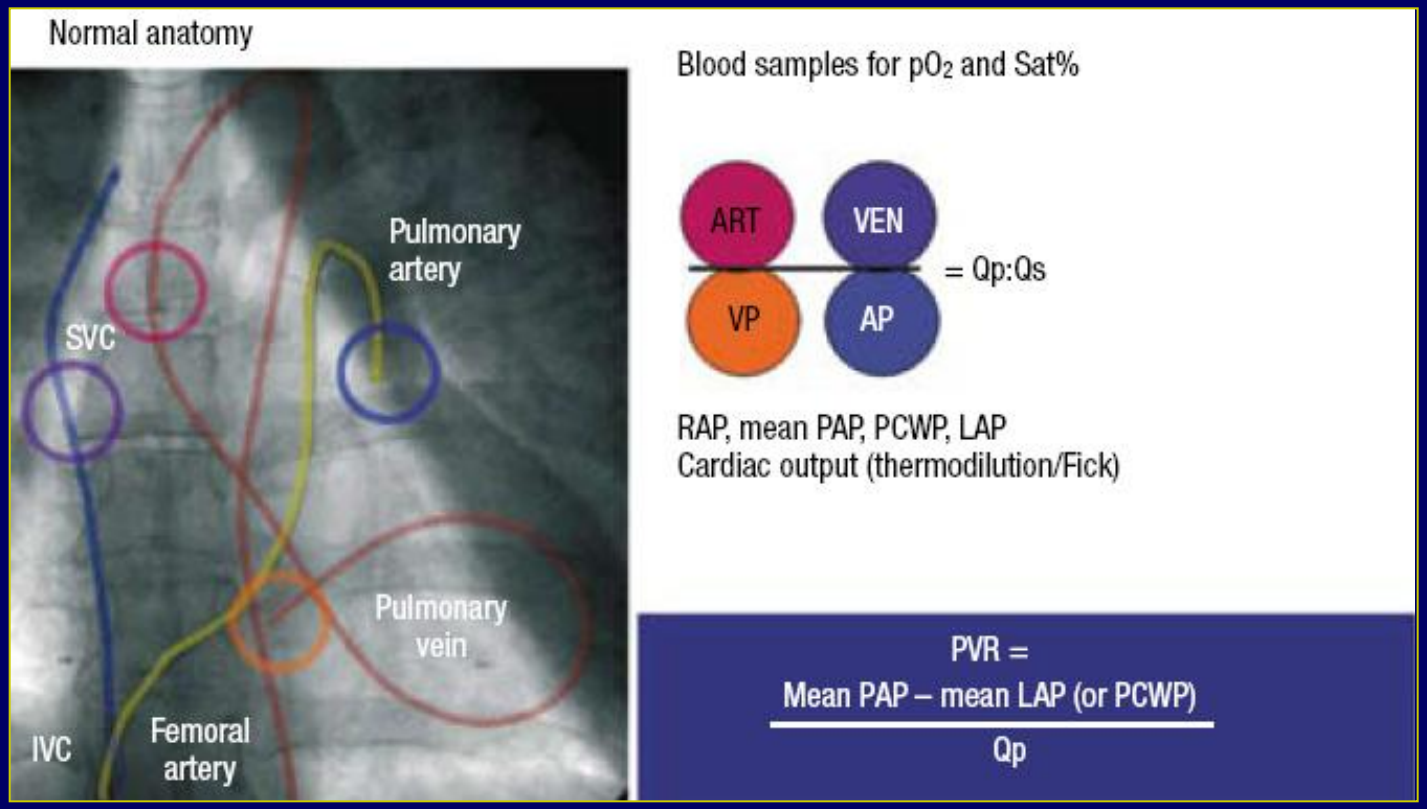
- **Given the inherent prognostic significance for CHD patients of a diagnosis of PAH, it is important to screen CHD patients who are at risk of developing the condition, especially since effective treatments for Eisenmenger's syndrome have become available**

McLaughlin VV et al. *Chest* 2004; 126: Suppl. 1, 78S–92S.
Mulder BJM et al. *Eur Respir Rev* 2010; 19(118): 308–313.

But, How To Find the CHD-PAH Patients?

Invasive Diagnosis of PAH-CHD

Cardiac Catheterization



Ingram Schulze Neick National & UK Centre for Pulmonary Hypertension in Children, Great Ormond Street Hospital, London, United Kingdom

Beghetti M, Tissot C. *Rev Esp Cardiol* 2010; 63(10): 1179-93

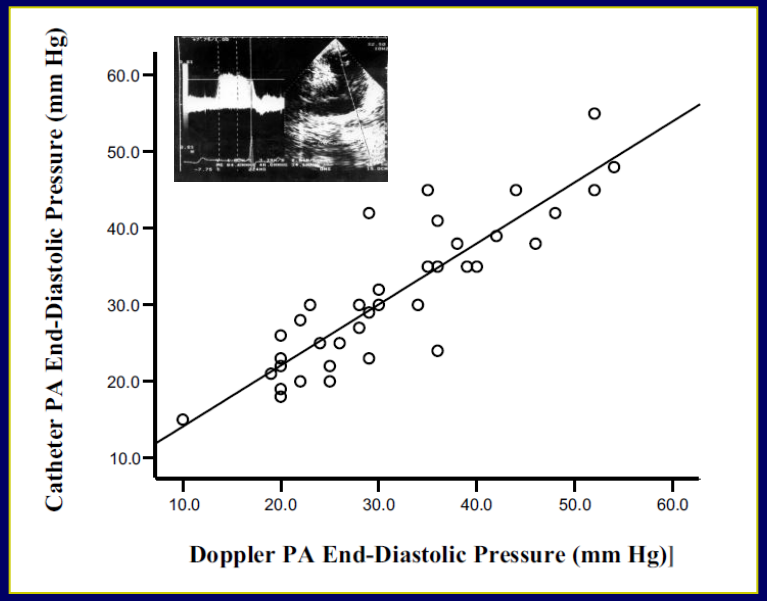
Prognosis Factors in Children
Caution: Right Heart Catheterization
Weighted Risk and Prognosis Value

Right heart catheterization in children has:

- a clear diagnostic role,
- its prognostic utility is not proven and requires validation…

- Children, their caregivers and their clinicians are reluctant to repeat catheterization due to the inherent risk associated with the procedure and the requirement for anaesthesia, even when performed in expert centres
- **Doppler Echocardiography** might be an appropriate way to evaluate treatment efficacy in children and estimate hemodynamics

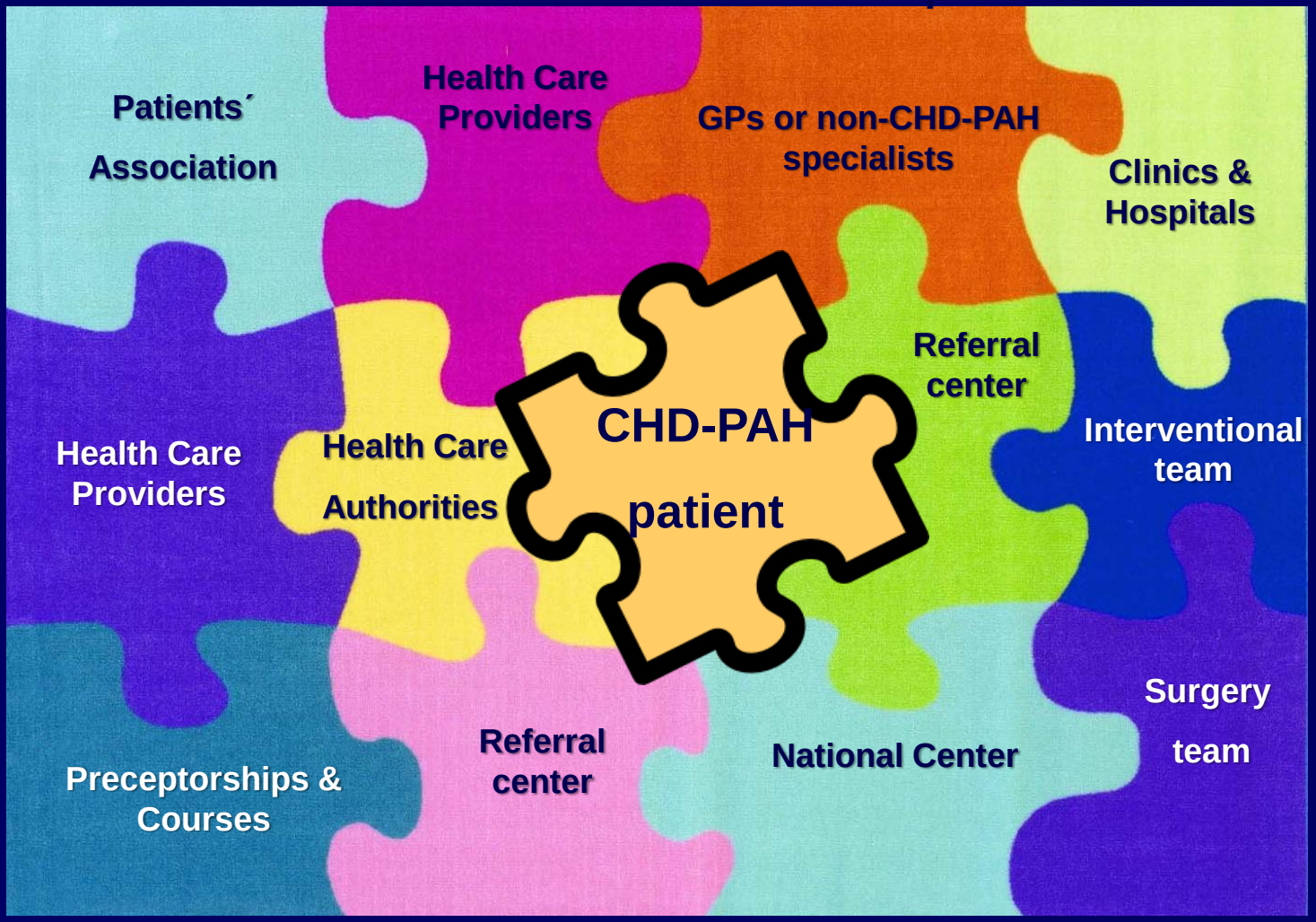
Pulmonary artery (PA) end-diastolic pressure measured by catheterization and Doppler echocardiography correlate (r=0.86, $r2$=0.77, y=2.128, p<0.0001)



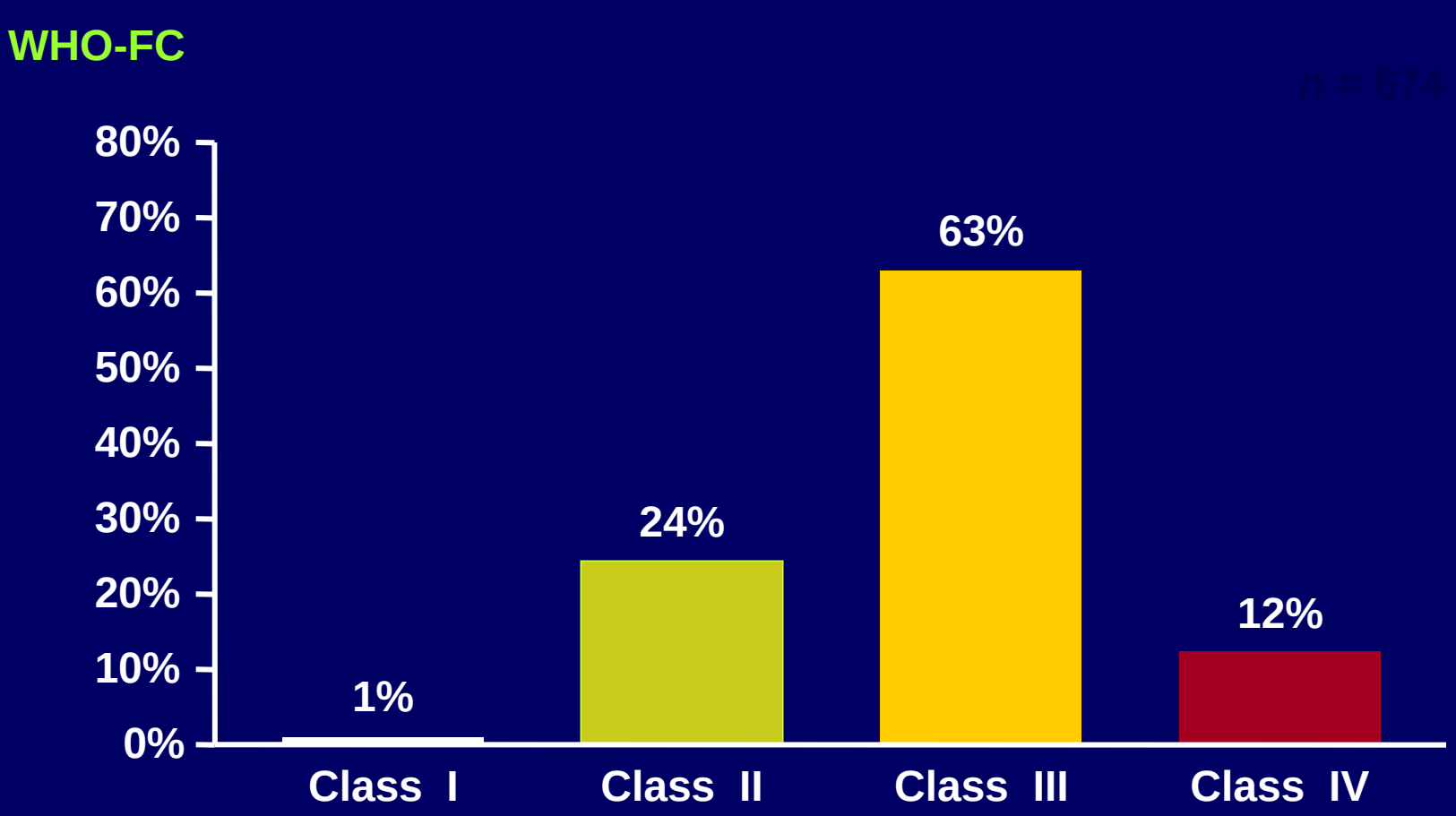
Atiq et al. *Asian Cardiovasc Thorac Ann* 2008;16:221-225

The Network for CHD-PAH Patients Starts with…

And It Is Essential for the Diagnosis, Treatment and Follow-Up of CHD-PAH Patients…



Unfortunately, Diagnosis of PAH Is Still Done Too Late…



Humbert M et al. *Am J Respir Crit Care Med* 2006;173:1023

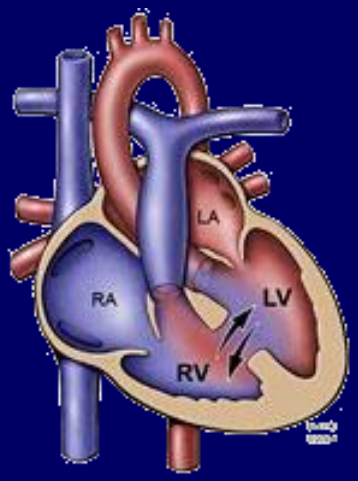
Humbert M et al. *Am J Respir Crit Care Med* 2006;173:1023

Targeted Strategies

- In the last years, many randomized controlled studies have demonstrated the efficacy and safety of the three classes of drugs used as *Advanced Therapies* for PAH patients: *PROSTANOIDS, ENDOTHELIN RECEPTOR ANTAGONISTS AND PHOSPHODIESTERASE-5 INHIBITORS*

- Target: endothelial dysfunction and vasoconstriction

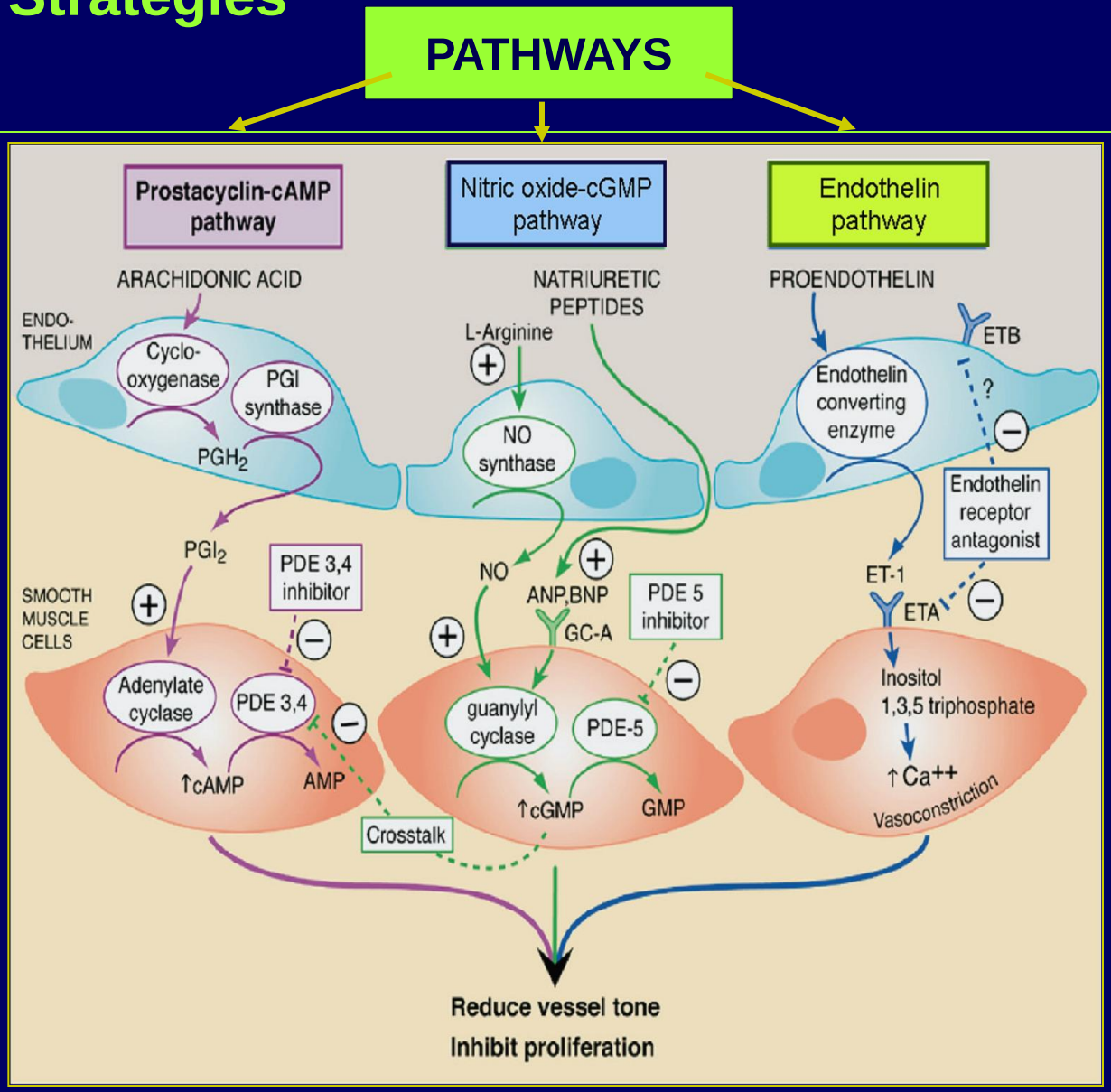
- But unfortunately, few randomized controlled studies have evaluated the effect of these drugs in PAH associated with CHD patients…



- Up to now, there is only one randomized, controlled study in Eisenmenger´s syndrome patients (very difficult to include, because of the very slow progression of the disease)…

Simonneau G et al. *Am J Respir Crit Care Med* 2002; 165: 800-4.
Rubien L.J et al. *N Engl J Med* 2002; 346: 896-903.
Galiè N et al. *J Am Coll Cardiol* 2006; 47: 2049-56.
Rosenzberg E.B et al. *J Am Coll Cardiol* 2006; 47: 2049-56.
Barst R et al. *Am J Resp Crit Care Med* 2004; 169: 441-7.
Galiè N et al. *Drugs* 2008; 68(8): 1049-1066.

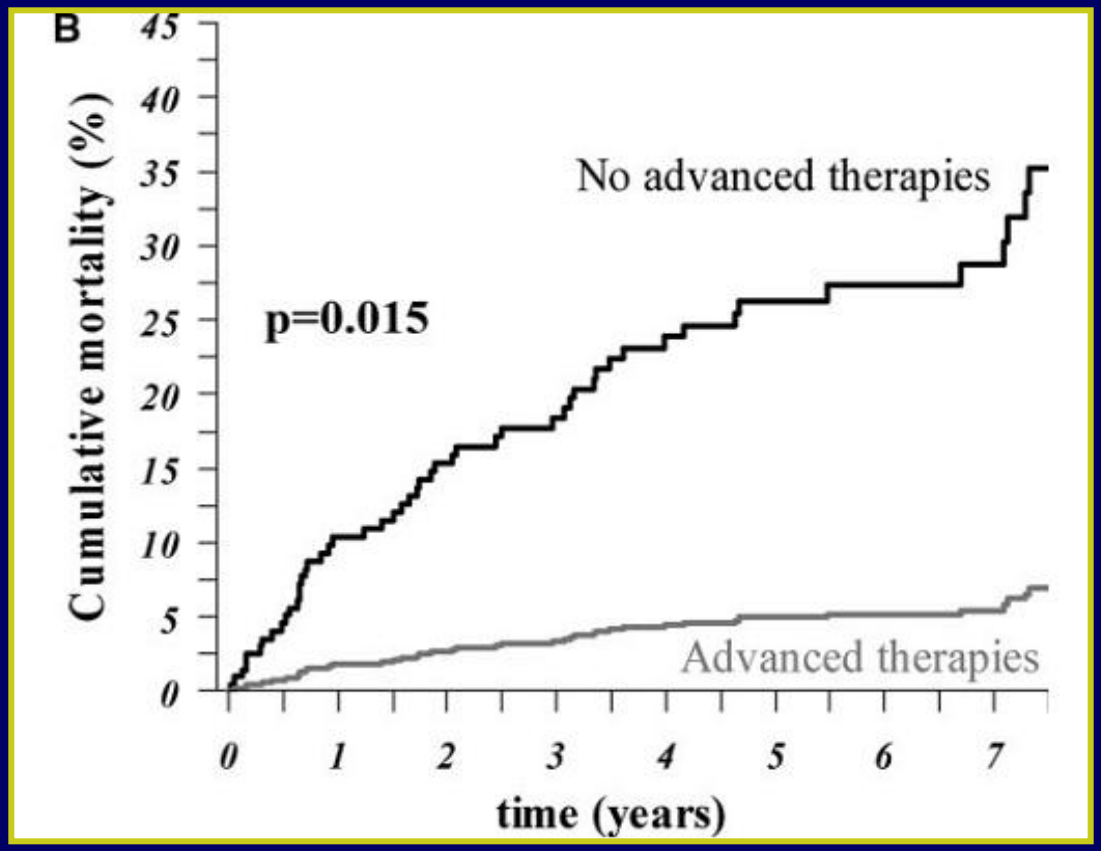
Targeted Strategies



Humbert M et al. *N Engl J Med* 2004; 351:1425-36

Advanced Therapy
Improved Survival in Eisenmenger's Syndrome

Cumulative Mortality with and w/o Advanced Therapy



- With adjustment for differences in clinical and demographic characteristics:
- Patients on AT at lower risk of death adjusted hazard ratio:
  0.16 (95% CI: 0.04, 0.71)

Dimopoulos et al. *Circulation* 2010;121:20-25

Targeted Therapies:
Few studies investigated specifically PAH-CHD population

	Author/Study/ (year publication)	Form, dosages	Study Design	Patients Population (n)	PH typologies	Patients PAH-CHD (n)	Patients PAH-CHD (in % patients)	End-Points	Follow-up	Outcome 6-MWT
Epoprostenol	Rosenzweig et al. (1999)	IV 82 ng/kg/min	Retrospective	20	PAH-CHD mixed Adult and Children	20	100%		1 year	+ 52 m
	Fernandes et al.	IV 14 ng/kg/min	Retrospective	8	PAH-CHD Eisenmenger	8	100%		3 months	+ 281 m
Treprostenil	Simonneau et al. (2002)	SC 9.3 ng/kg/min	Randomised, double blind, placebo-controlled	470	PAH	108	23%		12 weeks	+ 16 m
Iloprost	Olschewski et al. AIR (2002)	inhaled median daily dose: 30 µg	Randomised, double blind, placebo-controlled	213	PAH,CETPH	0	0%		16 weeks	+ 36 m
Sildenafil	Galiè et al. SUPER-1 (2005)	20 to 80 mg tid	Randomised, double blind, placebo-controlled	278	PAH	19	7%		12 weeks	+ 45 m (20 mg tid)
	Humpl et al. (2005)	0,5 mg / kg	Open label, prospective	14	IPAH, PAH-CHD Eisenmenger	9	64%		1 year	+156 m
	Singh et al. (2005)	100 mg tid	Randomised, placebo-controlled, double-blind, crossover	20	IPAH, PAH-CHD Eisenmenger	10	50%		1,5 month	+ 98 m
	Chau et al. (2007)	25 to 50 mg tid	Open label, prospective	13	IPAH, PAH-CHD Eisenmenger	7	54%		6 months	+ 28 m
	Tay et al. (2010)	20 mg tid	Open label, prospective	12	PAH-CHD Eisenmenger	12	100%	6-MWT/WHO/ Echocardiography/ QoL	3 months	+45 m
Tadalafil	Galiè et al. PHIRST (2009)	2,5 to 40 mg oad	Randomised, double blind, placebo-controlled	405	PAH	49	12%		16 weeks	+ 33 m (40 mg)
	Mukhopadhyay et al. (2006)	1 mg/kg up to 40 mg oad	Open label, prospective	16	PAH-CHD Eisenmenger	16	100%	WHO/SaO_2/ Haemodynamics	12 weeks	+43 m
	Barahni et al. (2007)	20 and 40 mg oad	Randomised, double blind, placebo-controlled, crossover	11	PAH-CHD Eisenmenger	11	100%	6-MWT/Borg/sPAP	4 weeks	+136 m
Ambrisentan	Galiè et al. ARIES-1 & 2 (2008)	1 to 10 mg oad	Randomised, double blind, placebo-controlled	394	PAH	0	0%		12 weeks	+ 51 m + 59 m
	Zuckerman et al. (2011)	5, 10 mg oad	Open label, retrospective	17	PAH-CHD Eisenmenger	17	100%	6-MWT/SaO_2/WHO/ Haemodynamics	2,5 years	+28 m
Bosentan	Rubin et al. BREATHE-1 (2002)	125 mg bid	Randomised, double blind, placebo-controlled	213	PAH	0	0%		16 weeks	+ 44 m
	Galiè et al. BREATHE-5 (2006)	125 mg bid	Randomised, double blind, placebo-controlled	54	PAH-CHD Eisenmenger	54	100%	6-MWT/SpO_2	16 weeks	+ 43 m
	Gatzoulis et al. BREATHE-5 OLE (2008)	125 mg bid	Open label extension BREATHE-5	37	PAH-CHD Eisenmenger	37	100%		40 weeks	+ 61 m
	Schulze-Neick et al. (2005)	125 mg bid	Open label, prospective	33	PAH-CHD	33	100%	6-MWT/WHO	2,1 year	+ 72 m
	Gatzoulis et al. (2005)	125 mg bid	Open label, prospective	10	PAH-CHD Eisenmenger	10	100%	6-MWT/SpO_2	3 months	+ 99 m
	D'Alto et al. (2007)	125 mg bid	Open label, prospective	22	PAH-CHD	22	100%	6-MWT/WHO/ Haemodynamics	1 year	+ 67 m
	Apostolopoulo et al. (2007)	125 mg bid	Open label, prospective	18	PAH-CHD	18	100%	6-MWT/SpO_2/WHO	2 years	return to baseline
	Sitbon et al. (2006)	125 mg bid	Retrospective	27	PAH-CHD	27	100%		15 months	+ 66 m
	Benza et al. (2006)	125 mg bid	Retrospective	24	PAH-CHD	24	100%		1 year	+ 31 m
	Diller et al. (2007)	125 mg bid	Retrospective	18	PAH-CHD	18	100%		29 months	+ 79 m

Adapted from Diller G-P and Baumgartner H. *Int J Clin Pract.* 2010; 64(Suppl 165): 13-2

Targeted Therapies:
Studies investigating PAH-CHD population

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limitations: retropective studies, limited population

limitations: open label, limited population

limitations: open label, limited population

limitations: limited population, duration

limitations: open label, limited population

only double-blind study on large population, with long-term follow

Adapted from Diller G-P and Baumgartner H. Int J Clin Pract. 2010; 64(Suppl 165): 13-22

ESC/ERS Recommendations for PAH Associated with Congenital Cardiac Shunts

Statement	Class[a]	Level[b]
The ERA bosentan is indicated in WHO-FC III patients with Eisenmenger's syndrome	I	B
Other ERAs, phosphodiesterase type-5 inhibitors, and prostanoids should be considered in patients with Eisenmenger's syndrome	IIa	C
In the absence of significant haemoptysis, oral anticoagulant treatment should be considered in patients with PA thrombosis or signs of heart failure	IIa	C
The use of supplemental O_2 therapy should be considered in cases in which it produces a consistent increase in arterial oxygen saturation and reduces symptoms	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered usually when the haematocrit is > 65%	IIa	C
Combination therapy may be considered in patients with Eisenmenger's syndrome	IIb	C
The use of CCBs is not recommended in patients with Eisenmenger's syndrome	III	C

Galiè N et al. *European Heart Journal* 2009; 30, 2493–2537.

- **ERAs: One RCT is available with specific drug therapy: bosentan has been shown to improve 6MWT and decrease PVR after 16 weeks of treatment in WHO-FC III patients. The long-term follow-up (40 weeks) showed sustained improvement. Bosentan is currently approved in Europe for WHO-FC III Eisenmenger's syndrome patients. No studies are available with the use of other ERAs in this setting.**

- **PDEi-5: Anecdotal experiences with the PDEi-5 sildenafil and tadalafil show favorable functional and haemodynamic results in patients with PAH associated with CHD and Eisenmenger's syndrome.**

- **Prostanoids: The use of i.v. epoprostenol has been reported in Eisenmenger's syndrome patients, with favorable effects on haemodynamics and exercise capacity, although central lines expose the patients to the risk of paradoxical embolism and sepsis.**

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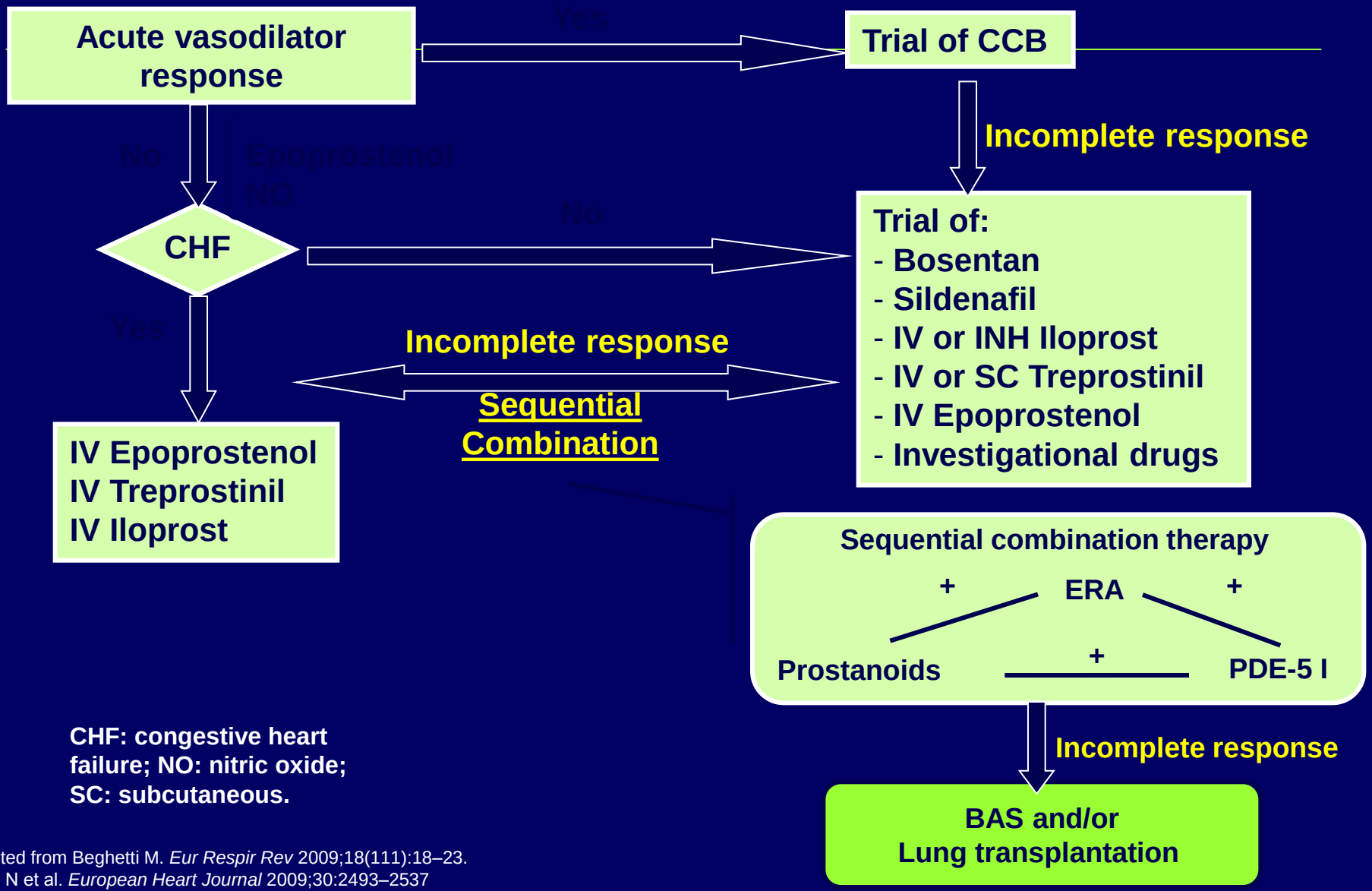
But, what about patients with WHO-FC I, II and IV ???

Galiè N et al. *European Heart Journal* 2009; 30, 2493–2537.

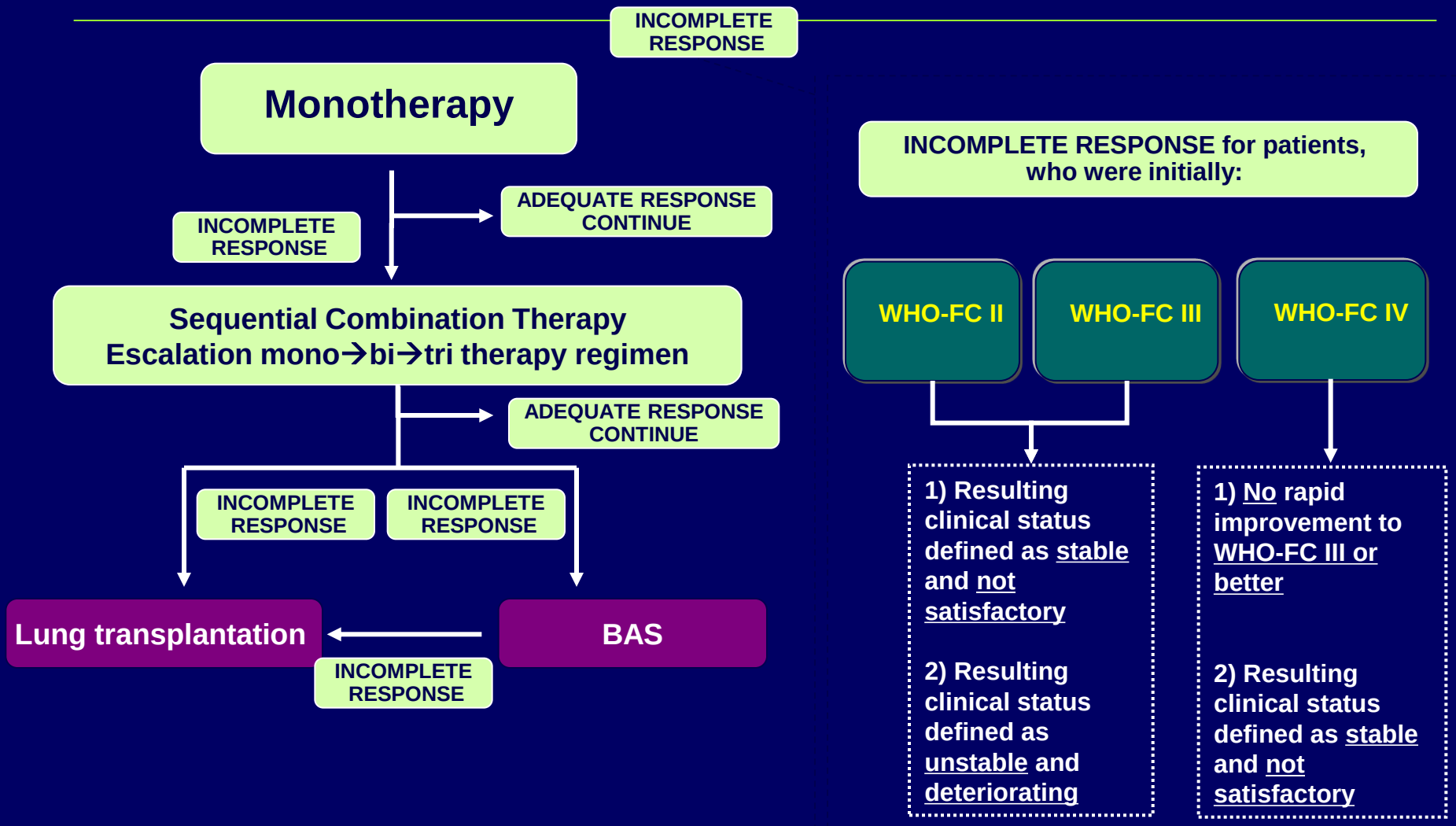
Current Algorithm: Treatment of PAH



CHF: congestive heart failure; NO: nitric oxide; SC: subcutaneous.

Adapted from Beghetti M. *Eur Respir Rev* 2009;18(111):18–23.
Galiè N et al. *European Heart Journal* 2009;30:2493–2537

Sequential Combination Therapy / Defining 'Incomplete Clinical Response'



Adapted from Beghetti. *Eur Respir Rev* 2009;18(111):18–23
Galiè N et al. *European Heart Journal* 2009;30:2493–2537

And How To Determine Severity, Prognosis and To Monitor Patients with Advanced Therapies???

Better Prognosis	Determinants of Prognosis	Worse Prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of Progression	Rapid
No	Syncope	Yes
I, II	WHO-FC	IV
Longer (> 500 m)*	6MWT	Shorter (< 300 m)
VO_2max > 15 ml/min/kg	CPET	VO_2max < 12 ml/min/kg
Normal or near-normal	BNP/NT-proBNP plasma levels	Very elevated and rising
No pericardial effusion TAPSE > 2.0 cm	Echocardiographic findings†	Pericardial effusion TAPSE < 1,5 cm
RAP < 8 mmHg and CI ≥ 2.5L/min/m^2	Haemodynamics	RAP > 15 mmHg or CI ≤ 2.0 L/min/m^2

*Depending on age
† TAPSE and pericardial effusion have been selected because they can be measured in the majority of the patients
For abbreviations refer to the list of acronyms and abbreviations

What Would You Consider to Monitor PAH-CHD Patients, specially children?

- Frequency?
- Parameters?
- Echo?
- Right Heart Catheterization?
- BNP / NT-ProBNP?
- Cut-Off Values?

EHJ/ERJ guidelines 2009

THANK YOU!