

In focus – The paediatric PAH population Clinicians Perspectives

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Paediatric PAH

- Complex condition associated with diverse cardiac, pulmonary and systemic diseases¹
- Associated with significant morbidity and mortality¹
- Shares some similarities with adult PAH, but also important differences^{2,3}
- PAH in children is rare
 - Several European registries have reported prevalence of IPAH ranging from 2.1-4.4 per million⁴⁻⁶

1. Hansmann G, *et al. Heart* 2016; 102 Suppl 2:ii86-100.

2. Bart RJ, *et al. Eur Respir J* 2011; 37:655-77.

3. Beghetti M and Berger RM. *Eur Respir Rev* 2014; 23:498-504.

4. Fraisse A, *et al. Arch Cardiovasc Dis* 2010; 103:66-74.

5. Moledina S, *et al. Heart* 2010; 96:1401-6.

6. van Loon RL, *et al. Circulation* 2011; 124:1755-64.

Definition

Table 1. PH: Definitions

PH

mPAP \geq 25 mm Hg in children >3 mo of age at sea level

PAH

mPAP \geq 25 mm Hg

PAWP <15 mm Hg

PVRI >2 WU/m²

IPAH or isolated PAH

PAH with no underlying disease known to be associated with PAH

Referred to as HPAH with positive family or genetic evaluation

PHVD

Broad category that includes forms of PAH but includes subjects with elevated TPG (mPAP–left atrial pressure or PAWP >6 mm Hg) or high PVRI as observed in patients with cavopulmonary anastomoses without high mPAP

HPAH indicates heritable pulmonary artery hypertension; IPAH, idiopathic pulmonary artery hypertension; mPAP, mean pulmonary artery pressure; PAH, pulmonary artery hypertension; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PHVD pulmonary hypertensive vascular disease; PVRI, pulmonary vascular resistance index; and TPG, transpulmonary pressure gradient.

Treatment of paediatric PAH

Children with PAH are currently being treated with PAH-specific therapies^{1,2}

Prognosis has improved due to the introduction of new therapies^{1,2}

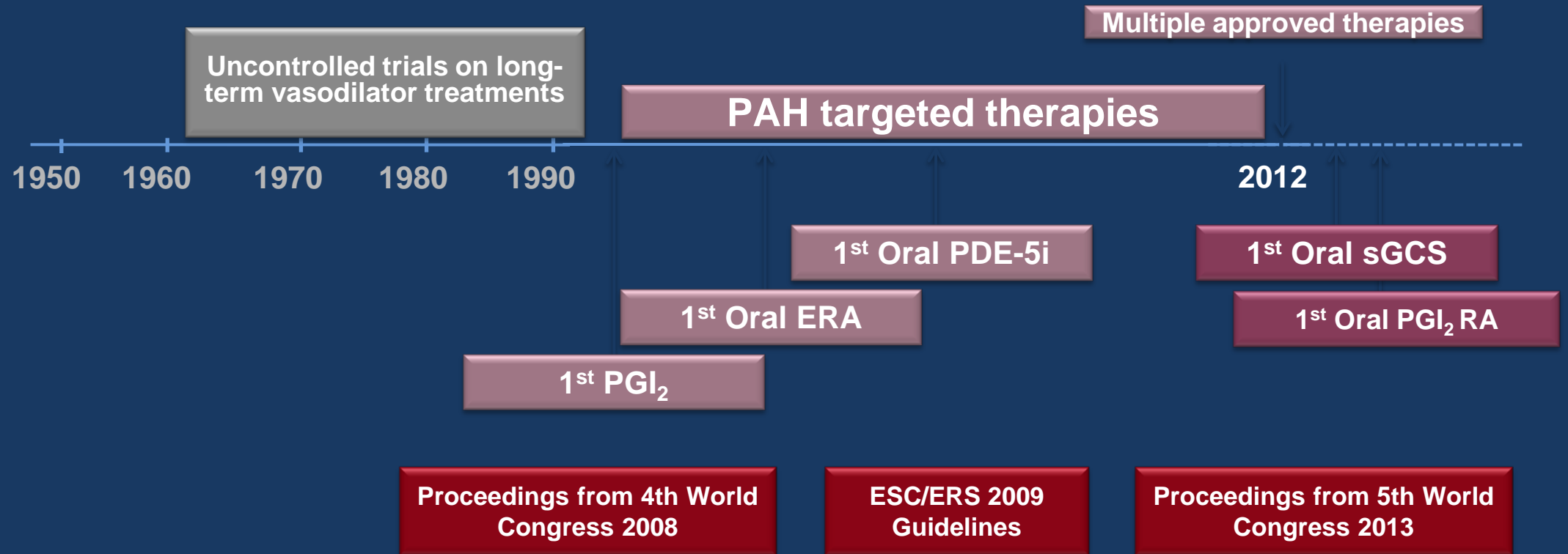
Paediatric formulations can offer ease of dosing and paediatric acceptability

Bosentan is currently the only PAH-specific therapy with an approved paediatric formulation

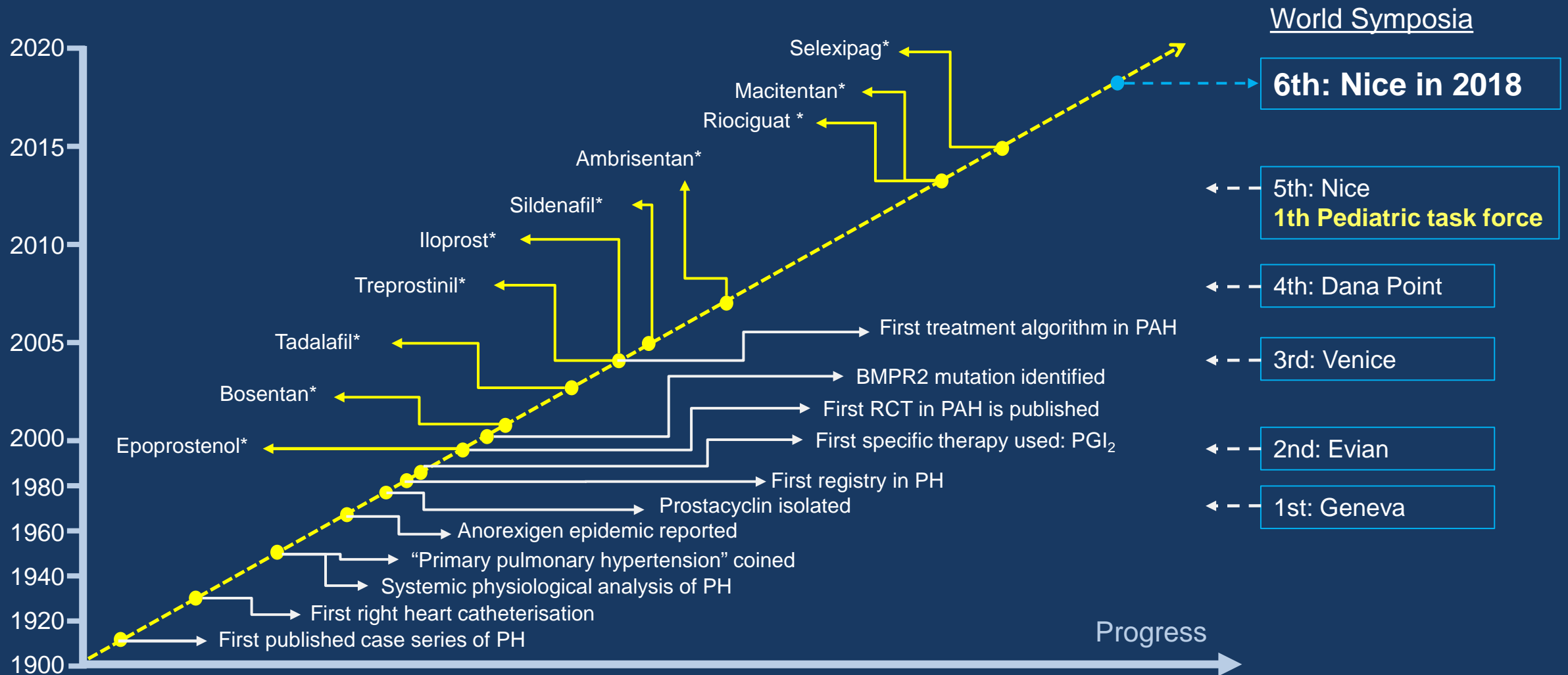
RCT data are lacking for paediatric populations and treatment decisions are often based on extrapolations from adult studies^{1,2}

Challenges exist when extrapolating from adult data, e.g. PK differences between adults and children have been demonstrated²

Adult: Evolution

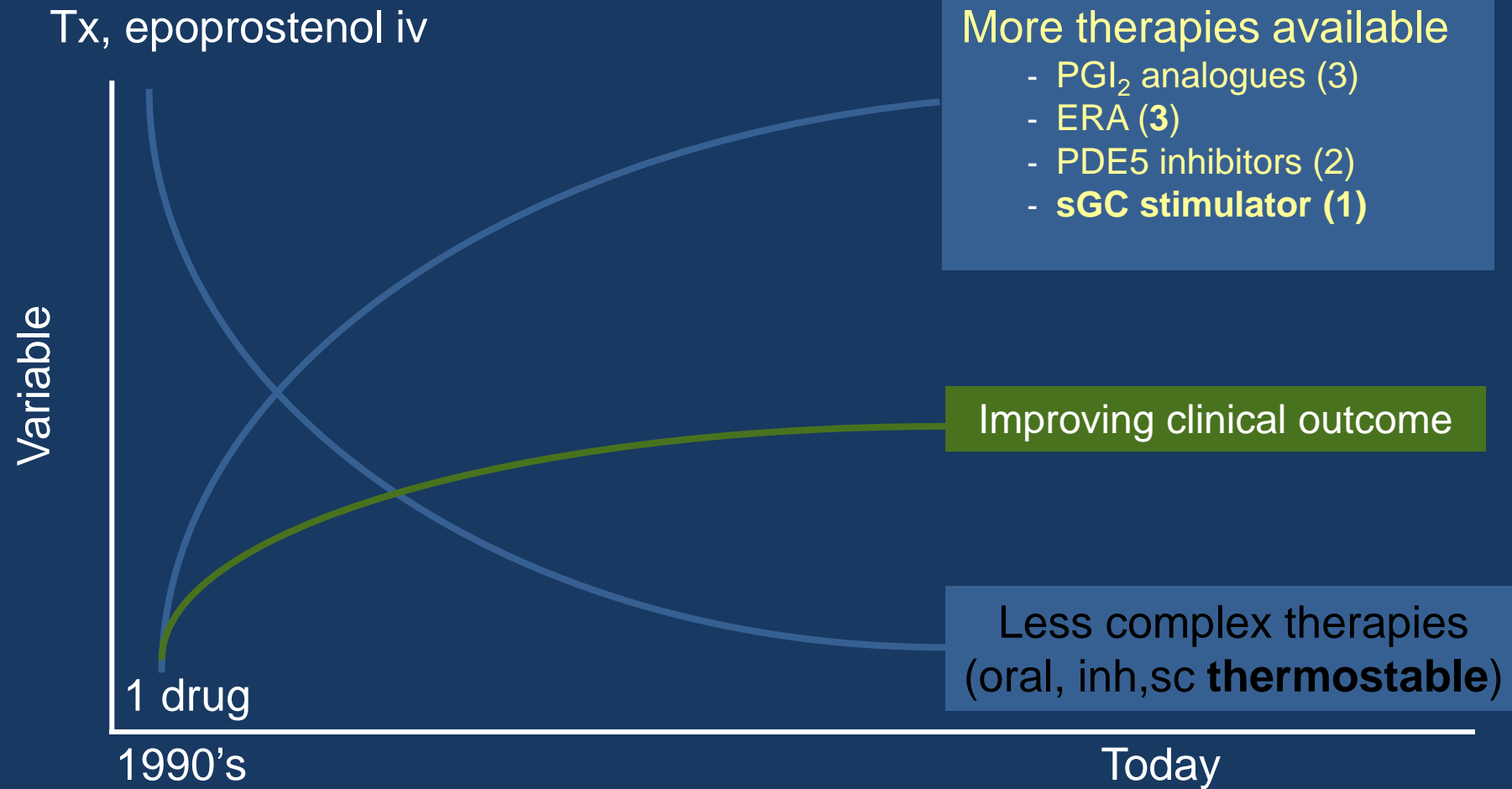


Historical milestones in PAH: Treatment in 2017 – More options and more decisions

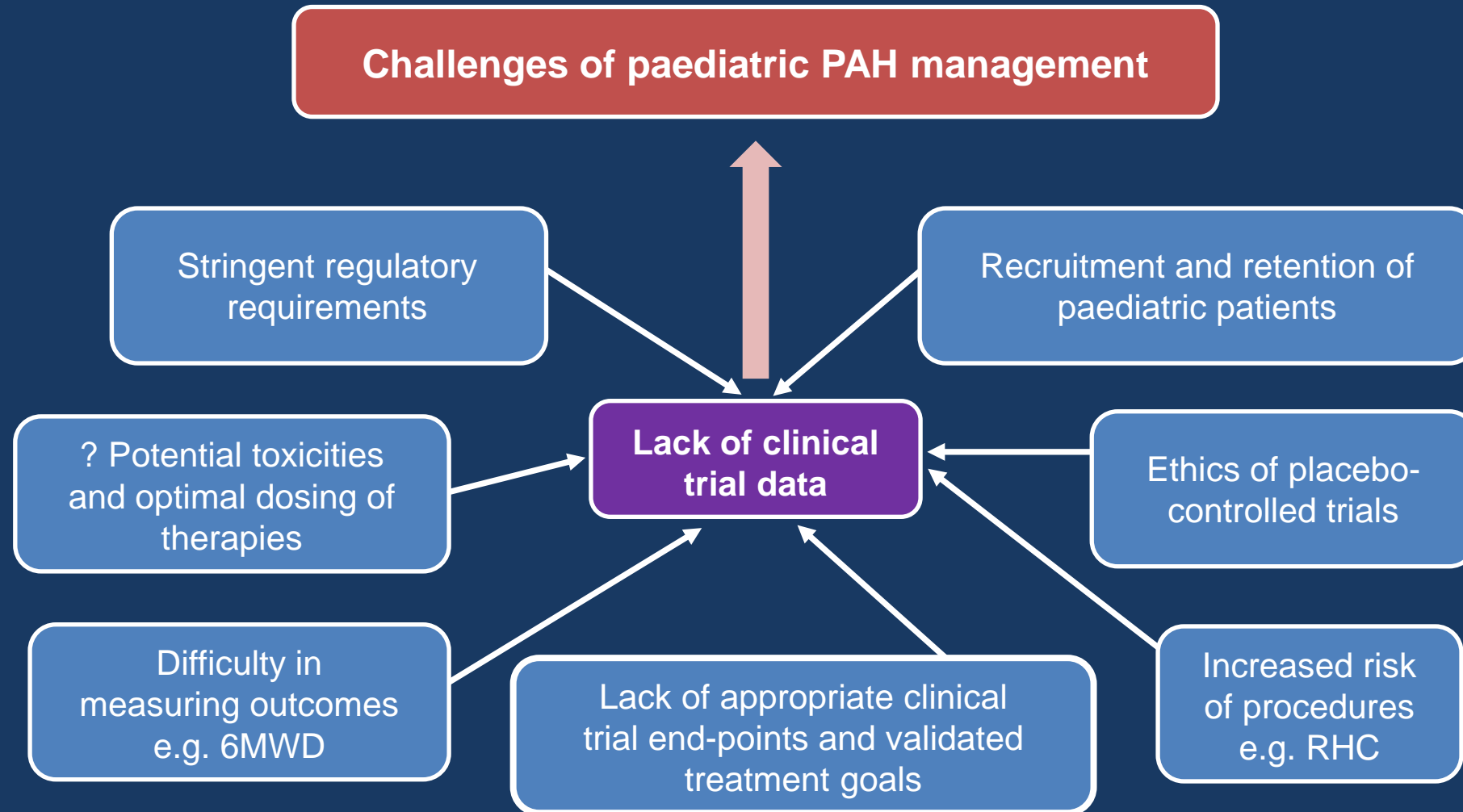


*Date of FDA approval

ADULTS



Challenges of PAH management in children



Treatment of paediatric PAH – Is it too complicated?

No

- Paediatric PAH looks very much like adult PAH
- Treatment should follow the available algorithms
- Efficacy and safety assessments are almost the same

But...

- Children are not “little adults”: PK/PD differences
- Variation not only due to different causes but also age: Infants, toddlers, adolescents
- Study endpoints need to be adapted

PK = pharmacokinetics

PD = pharmacodynamics

Challenges in paediatric PAH study

CHALLENGE

Lack of paediatric data for PAH-specific therapies

Appropriate endpoints for clinical trials in paediatric PAH not defined

Lack of information on symptoms, diagnosis and clinical outcomes in a “real-life” setting

SOLUTION

Prospective clinical trials in paediatric patients

International/national paediatric registries

OUTCOME

Better guidelines for clinical management of paediatric PAH

Overview of completed paediatric PAH trials to date

Clinical trial	Study drug	Study design	Endpoint	Study duration	Results
BREATHE-3 ¹	Bosentan	Open-label, uncontrolled	PK, haemodynamic parameters, 6MWD, CPET	12 weeks	Findings were similar to those observed in adult patients
FUTURE-1 ²	Bosentan [#]	Open-label, uncontrolled	PK, WHO FC, GCI scales	12 weeks	PK profiles were similar between the adult and paediatric formulations
FUTURE-2 ^{*3}	Bosentan [#]	Open-label extension	Safety, time to PAH worsening, survival	Median exposure: 27.7 months	Well tolerated. Efficacy results in line with previous paediatric and adult studies
FUTURE-3 ⁴	Bosentan [#]	Open-label, uncontrolled	PK, safety	24 weeks	To be added after publication
STARTS-1 ⁵	Sildenafil	RCT	Efficacy, safety	16 weeks	Well-tolerated. Efficacy reported with medium and high doses
STARTS-2 ⁶	Sildenafil	Open-label extension	Mortality	Median exposure: 4.1 years	Survival was favourable, although higher doses were associated with increased mortality

*FUTURE-2 is an open-label extension of the FUTURE-1 study

[#]Paediatric formulation. 6MWD: 6-minute walk distance; CPET: Cardiopulmonary exercise testing; GCI: Global Clinical Impression scales; PK: pharmacokinetics; RCT: Randomised controlled trial

1. Barst RJ, *et al. Clin Pharmacol Ther* 2003;73:372-82. 2. Beghetti M *et al. Br J Clin Pharmacol* 2009; 68:948-55. 3. Berger RM *et al. Int J Cardiol* 2016; 202:52-8. 4. www.clinicaltrials.gov; NCT01223352. 5. Barst RJ, *et al. Circulation* 2012;125:324-34. 6. Barst RJ, *et al. Circulation* 2014;129:1914-23.

“Guidelines”: Recommendations for paediatric pulmonary hypertension

Pediatric Pulmonary Hypertension

Ivy DD, et al. *J Am Coll Cardiol* 2013; 62(25 Suppl):D117-26.

Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society

Abman SH, et al. *Circulation* 2015; 132:2037-99.

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

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

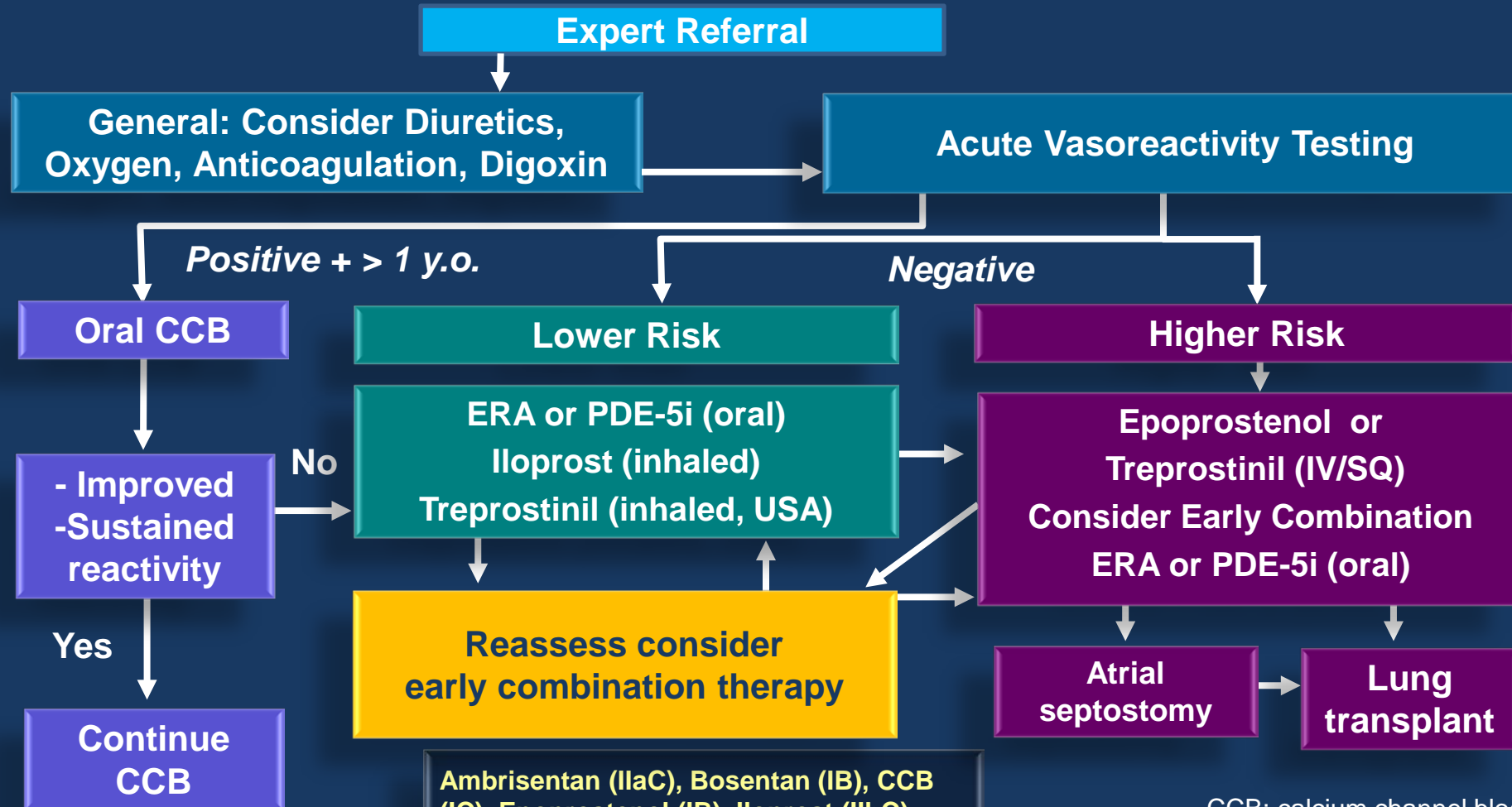
Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK

Hansmann G and Apitz C. *Heart* 2016; 102 Suppl 2:ii67-85.

The lack of RCTs in paediatrics makes it difficult to deliver strong guidelines

Recommendations are based mostly on expert consensus

Paediatric treatment algorithm: World Symposium on PH 2013



*Use of all agents is considered off-label in children aside from sildenafil in Europe
 **Dosing recommendations per European approved dosing for children

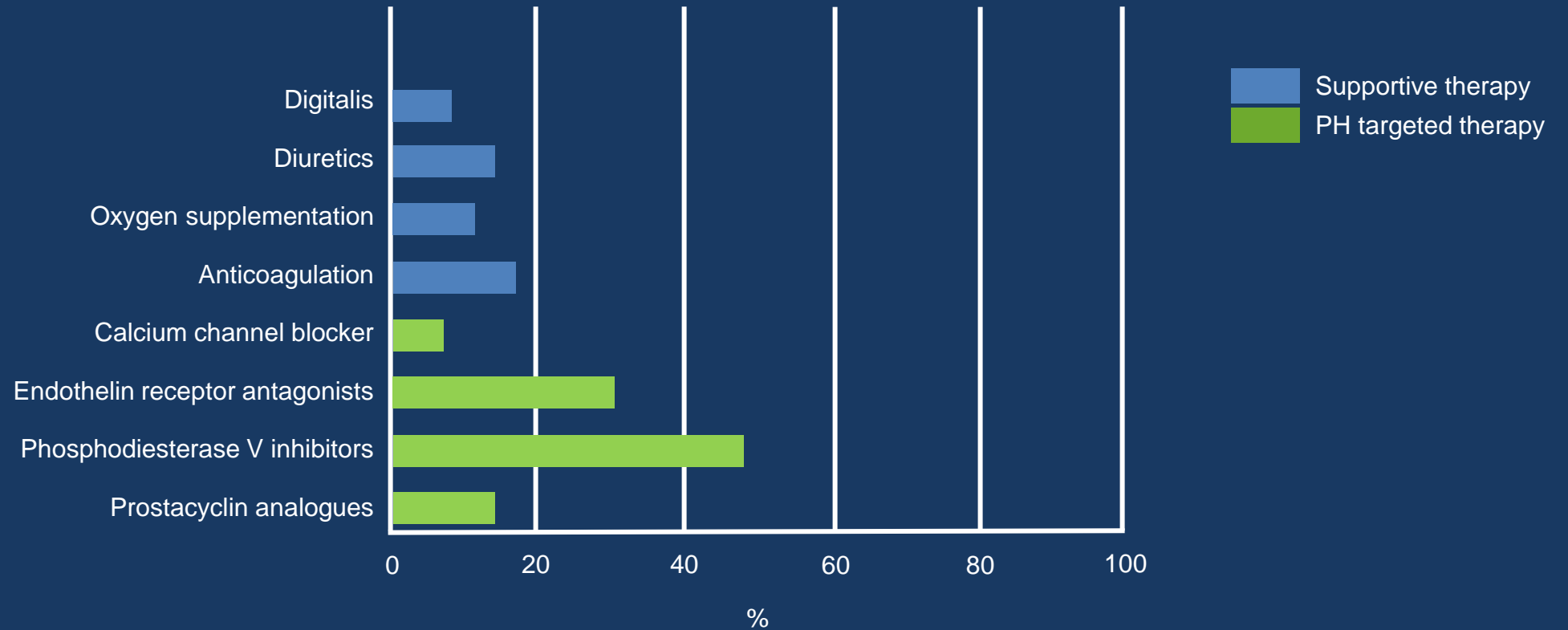
Ambrisentan (IIaC), Bosentan (IB), CCB (IC), Epoprostenol (IB), Iloprost (IIbC), Sildenafil (IB**), Tadalafil (IIaC), Treprostinil SQ/IV (IIbC/IIaC), Treprostinil Inh (IIbC), atrial septostomy (IIaC)

CCB: calcium channel blocker; ERA: endothelin receptor antagonist; IV: intravenous; PDE-5i: phosphodiesterase 5 inhibitor; SQ: subcutaneous

Ivy D, et al. J Am Coll Cardiol 2013; 62:D117-26.

PH treatment: Real life data from TOPP

- Use of supportive and pulmonary hypertension-targeted therapies



Other therapies/studies

- ~~Beraprost~~
- ~~L-Arginine~~
- ~~VIP (vasointestinal peptide)~~
- ~~Adrenomedullin~~
- Bosentan (Future 1-2-3-4)
- Ambrisentan on hold/
- Tadalafil ongoing
- ~~PDGF inhibitors (Imatinib)~~ abandoned
- Treprostinil oral ongoing
- Macitentan RCT to start event driven trial!!!
- Guanylate cyclase stimulator (Riociguat) ongoing
- Oral prostacyclin agonist (selexipag) in preparation

EUROPE

- Approved
 - Sildenafil (pediatric label)
 - Bosentan (pediatric indication)
- However most adult approved drugs are used (data from registries)
- Problems
 - Some approved drugs by EMA not reimbursed in some EU countries and potential problems even to enrol pediatric patients in trials (macitentan in France)

Switzerland

- Access to all adult drugs
- Bosentan formulation available
- Sildenafil approved
- Other drugs reimbursed , sometimes requires direct discussion with insurance (each patient has his own insurance no state insurance)
- Sometimes coverage by state insurance but case by case!!

USA: PAH-specific Treatment Options for Adults with PAH

Oral Therapy				Inhaled Therapy	Continuous Parenteral Therapy
ERAs	PDE5 Inhibitors	sGC Stimulator	Prostacyclin	Prostacyclins	
Ambrisentan	Sildenafil	Riociguat	Treprostinil	Iloprost	Epoprostenol
Bosentan	Tadalafil		Selexipag	Treprostinil	RTS Epoprostenol
Macitentan					Treprostinil (SC or IV)

ALL MEDICATION HAVE BEEN USED IN PEDIATRICS AND REIMBURSED
SOMETIMES INSURANCE REQUIRES CHNAGES TO GENERICS (TADALAFIL TO SILDENAFIL)

Canada: Quebec

- Difference between provinces....
- Physician (expert centre) fill a prerequisite form from government to obtain reimbursement for all approved drugs
- Differences between compounds Bosentan and sildenafil easier than other ones
- But it seems all therapies are available! (except inhaled PGI₂)

Conclusions

- Rare disease
- Expertise difficult to obtain
- Research difficult
- Approval/reimbursement difficult
- Differences between countries and continents
- Use off label
- Not an ideal care for all patients!!!