Hypertension pulmonaire de l'enfant
Avancées minuscules
ou
pas de géant

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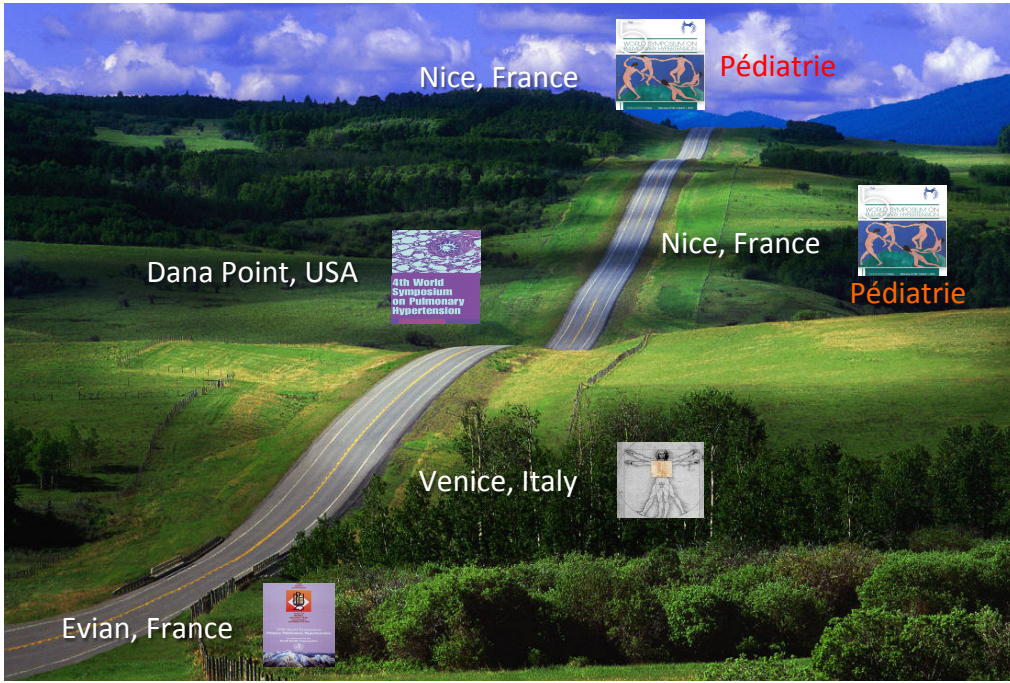
Chemin

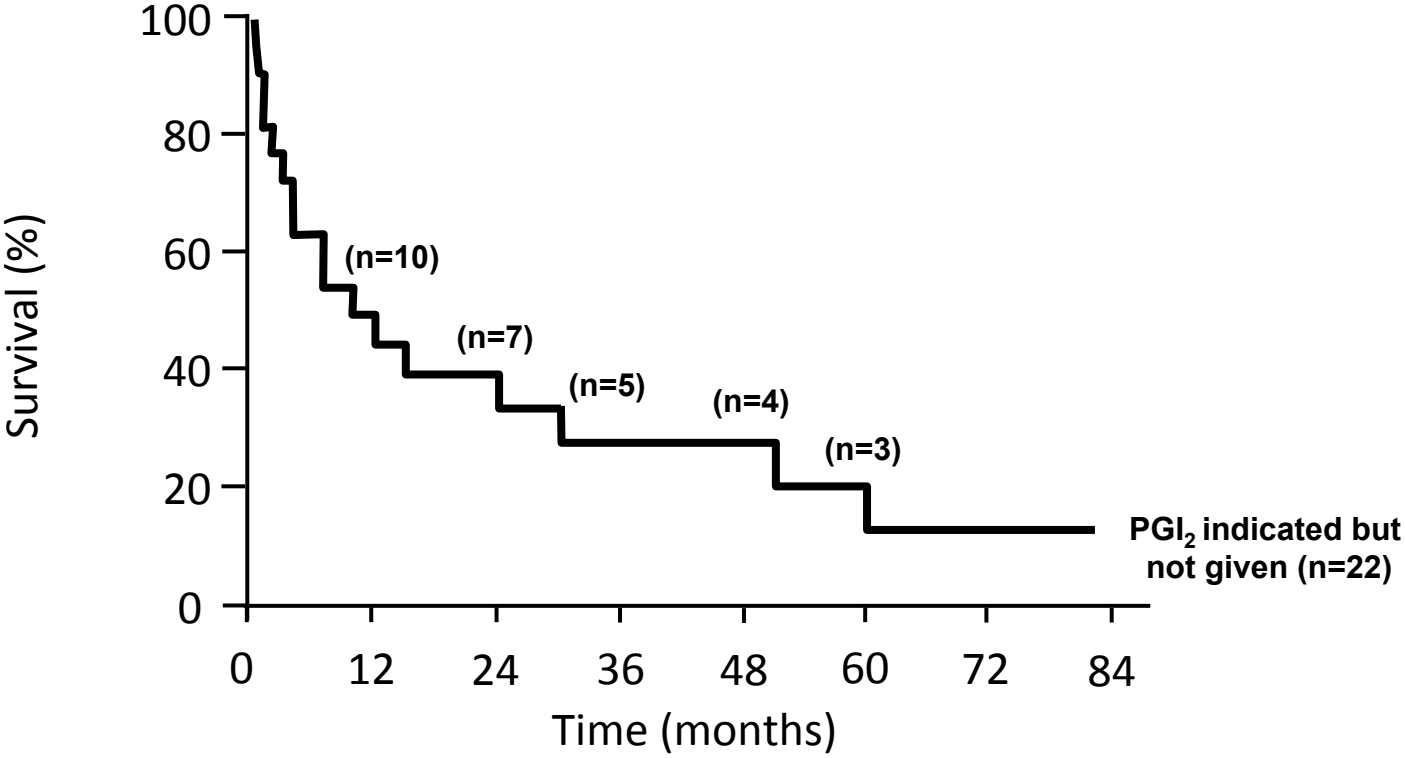
- De nombreux petits pas…
- Quelques grands pas….
- Pas mal d’embuches….



HTAP années 80

- La recherche en HTAP n'a pas d'avenir académique…..
- En clinique tous tes patients vont décéder et tu passeras plus de temps à reconforter les familles…

Courbe de survie
PAH sans traitement

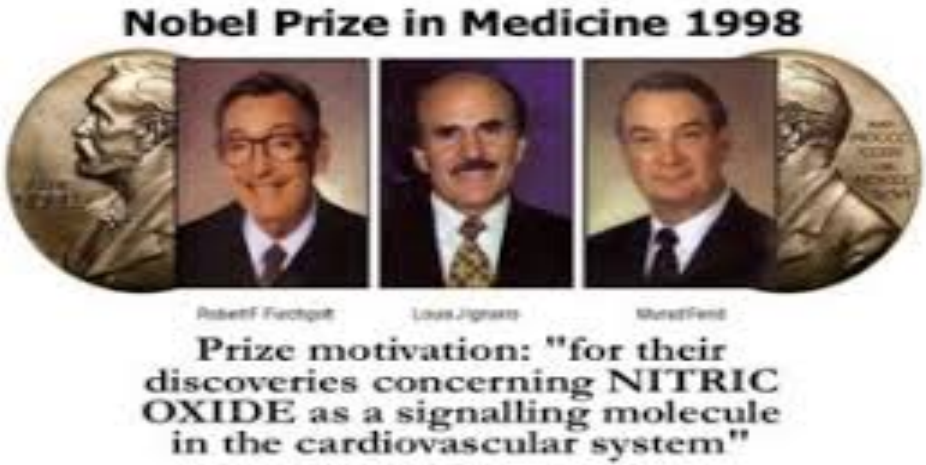


Barst R, *et al. Circulation* 1999:99;1197-208

Petits et grands pas

- Monoxyde d’azoze (Nitric oxide NO)
  - Autres traitements
- Registres
- Diagnostique
- Génétique
- Pediatric task forces and guidelines
- Mais…….

Nitric oxide: The magic bullet!!!???



Circulation. 1991 Jun;83(6):2038-47.

Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction.

Frostell C, Fratacci MD, Wain JC, Jones R, Zapol WM.

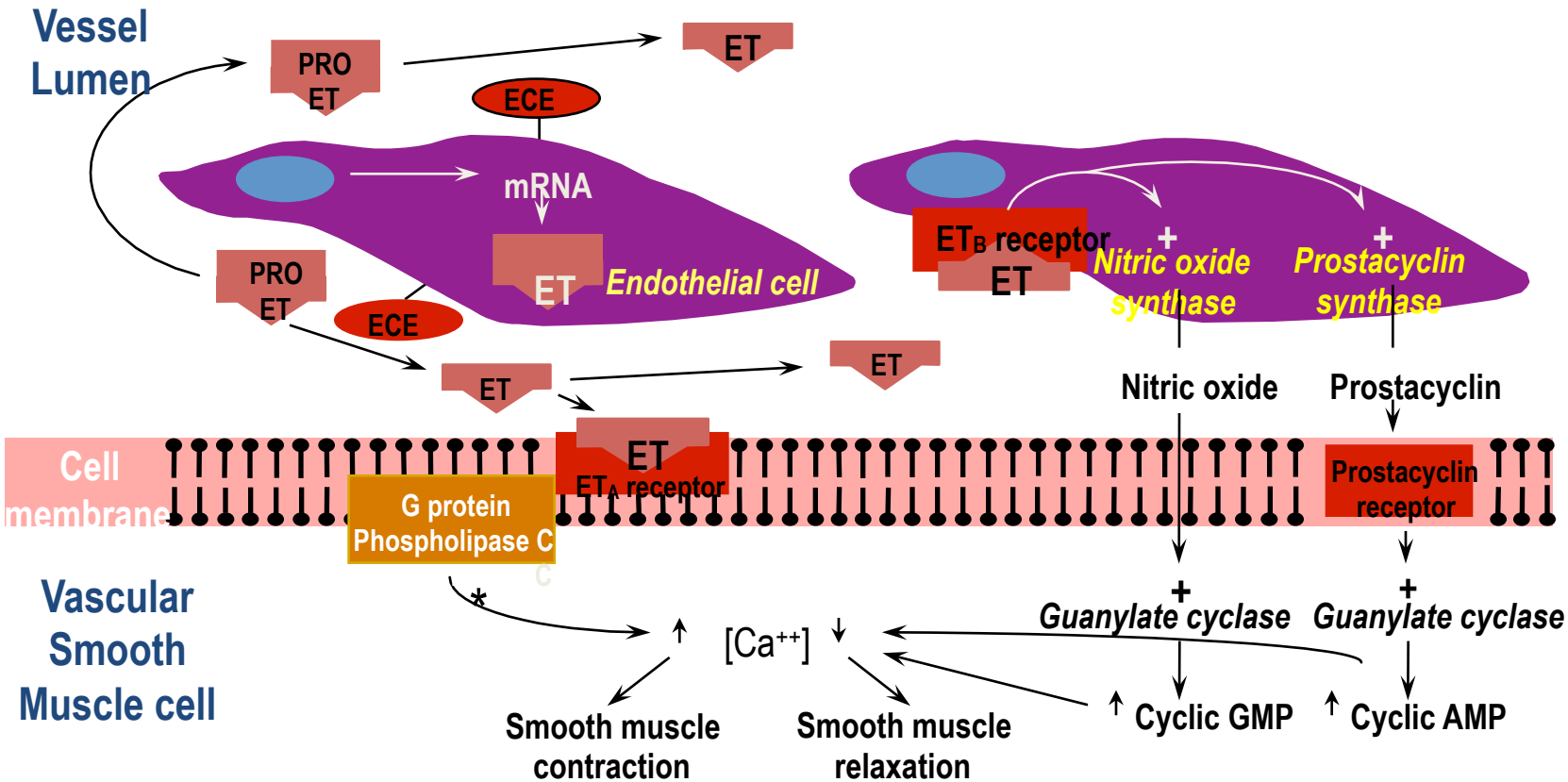
Monoxyde d'azote en inhalation

- Approuvé pour PPHN
- Utilisé pour évaluer la vasoréactivité lit vasculaire pulmonaire
  - Répondeurs
  - « opérabilité » cardiopathie congénitale
- Traitement hypertension pulmonaire post opératoire de cardiopathie congénitale
- A ouvert la voie du traitement de la dysfonction endothéliale dans l'hypertension pulmonaire et en particulier de la voie NO-cGMP……
  - PDE5i (sildenafil)
  - Guanylate stimulators (riociguat)

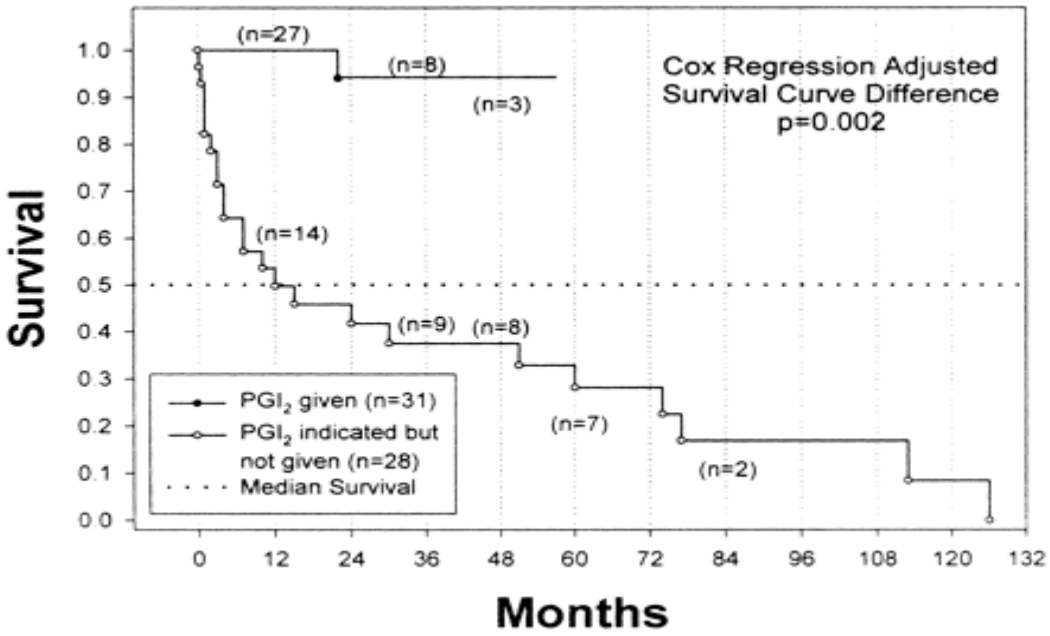
Management option for pulmonary hypertension before 1996

- 1980: Primary pulmonary hypertension: effects of nifedipine. Camerini, F. et al. *Br Heart J,* 44, 352.
- 1983: Sustained beneficial effect of nifedipine in primary pulmonary hypertension. De Feyter, P. J. *Am Heart J,* 105, 333.
- 1987: Nifedipine attenuates acute hypoxic pulmonary vasoconstriction in patients with chronic obstructive pulmonary disease. Burghuber, O. C. *Respiration,* 52, 86.
- 1989: Nifedipine for high altitude pulmonary oedema. Oelz, O. et al. *Lancet,* 2 (8674), 1241.

Dysfonction endothéliale



Chronic PGI_2 infusion

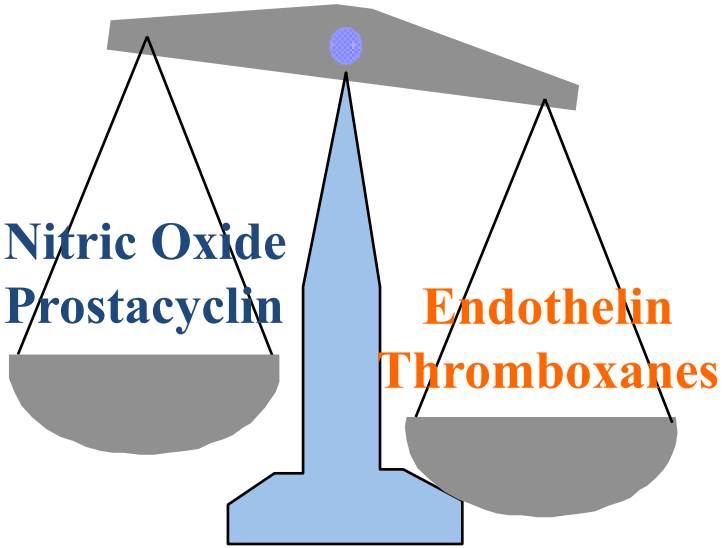


Kaplan-Meier survival curves comparing survival on long-term PGI_2 with survival of patients for whom PGI_2 was indicated but unavailable

Barst et al Circulation 1999;99:1197

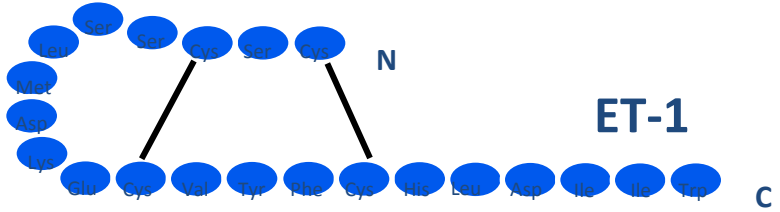
Dysfonction endothéliale

Vasodilatateurs
antiprolifération



Vasoconstricteurs
Prolifération

Endothelin

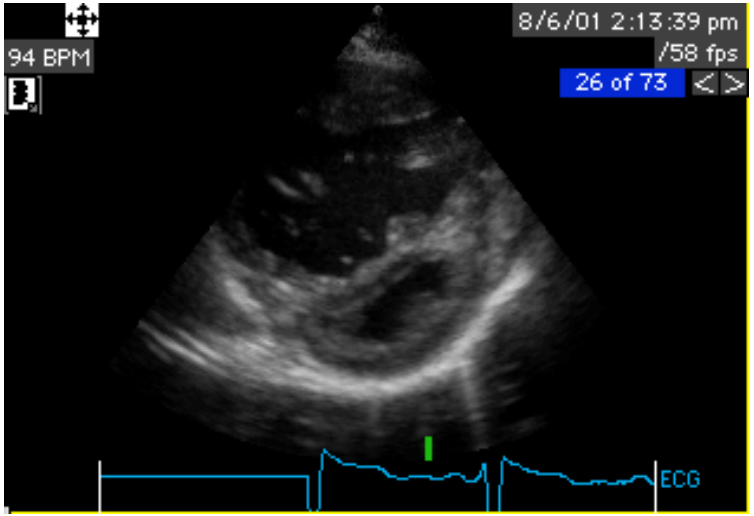


- 21-amino-acid peptide isolated from cultured porcine aortic endothelial cells[1]
- Produced by EC, airway epithelial cells, macrophages, SMC, fibroblasts, cardiomyocytes, brain neurons, …
- Regulates vascular tone, sodium balance, neural crest cell development and neurotransmission

Yanagisawa M, et al. Nature 1988;3 32:411-15.

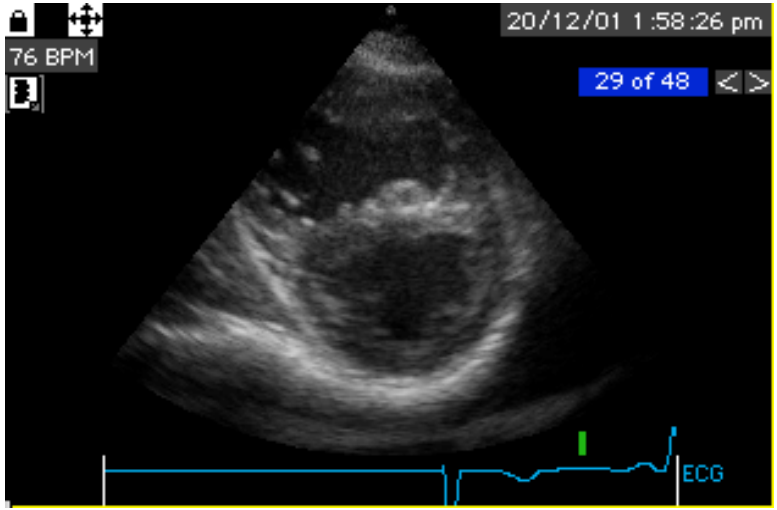
8 year-old boy with idopathic pulmonary hypertension

Iloprost 100 μgr 6 aerosols
Coumadine



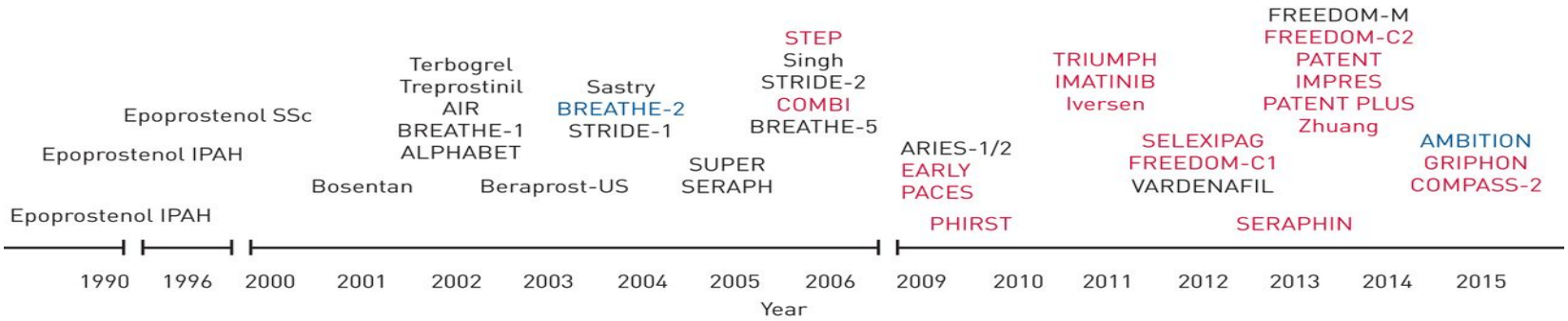
Mean PAP: 66 mmHg
Mean SAP: 57 mmHg
PVR: 23 WU*m2
Area RV: 40 cm2

Same therapy plus
Bosentan 62.5 bid since 3 months

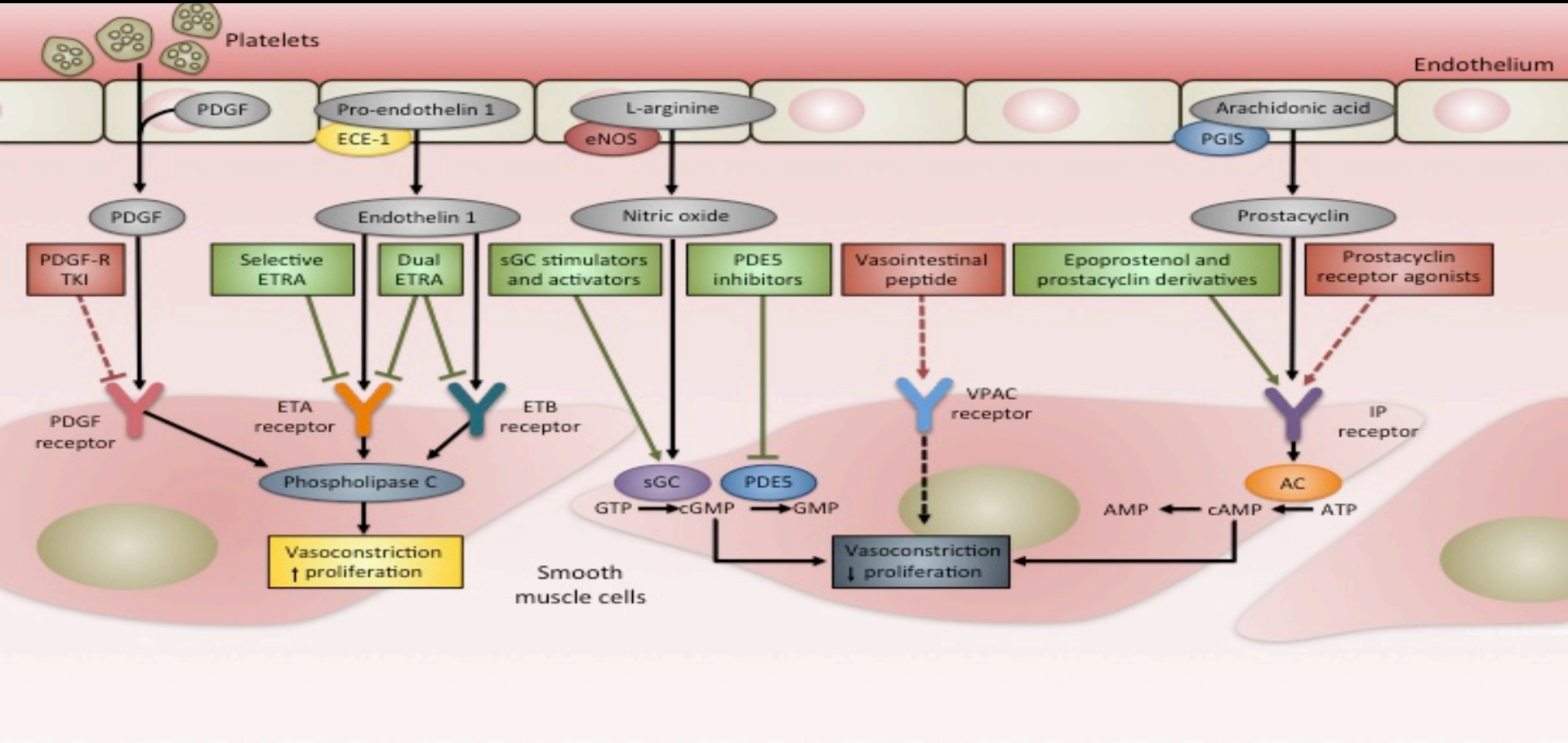


Mean PAP: 53 mmHg
Mean SAP: 75 mmHg
PVR: 16 WU*m2
Area RV: 28 cm2

Time-course of completed randomised controlled trials (RCTs) in pulmonary arterial hypertension (PAH) (n=41) according to treatment strategy.



Nazzareno Galiè et al. Eur Respir J 2019;53:1801889



Lador F. et al, Expert Opin Pharmaco 2015

Overview of completed paediatric PAH trials to date leading to approval!

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	No clinically relevant difference in exposure, and in safety, when increasing the frequency of dosing from b.i.d. to t.i.d.
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

[#]Paediatric formulation. 6MWD: 6-minute walk distance; CPET: Cardiopulmonary exercise testing; GCI: Global Clinical Impression scales

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

Table 1: Overview of medicines available for use in PAH for adults and children

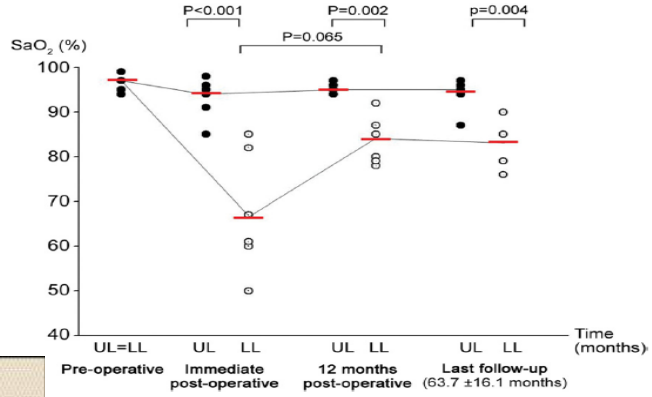
Class of Products	Product	Authorisation for Adults			Authorisation status for Children		
		EU	US	Canada	EU	US	Canada
Prostacyclin Analogue	Treprostinil	**No**	Yes	Yes	No	No	No
	Selexipag	Yes	Yes	Yes	No	No	No
	Treprostinil diethanolamine	No	Yes	No	No	No	No
	Iloprost	Yes	Yes	No	No	No	No
	Epoprostenol	Yes	Yes	Yes	No	No	No
Endothelin Receptors Antagonist	Bosentan	Yes	Yes	Yes	PK data	Yes	PK data
	Ambrisentan	Yes	Yes	Yes	No	No	No
	Macitentan	Yes	Yes	Yes	No	No	No
Phosphodiesterase type 5 inhibitor	Sildenafil	Yes	Yes	Yes	Yes	No	No
	Tadalafil	Yes	Yes	Yes	No	No	No
Guanylate cyclase stimulators	Riociguat	Yes	Yes	Yes	No	No	No

Footnotes: PK=pharmacokinetics, Pharmacokinetic properties of the active substance(s) relevant for a dose, strength and the pharmaceutical formulation

Ollivier..Beghetti et al JAHA in press

Outcome of CHD-PAH may be considered better than IPAH so why not transforming iPAH in CHD-PAH ?

Fig 5. Arterial oxygen saturation (Sao_2) in upper (UL) and lower limbs (LL) at preoperative evaluation and during follow-up. Analysis was performed on the data from the 6 children who survived beyond the first postoperative month. Mean arterial oxygen saturation is symbolized for each scatter plot by a red bar.



- Our experience further suggests that, for a child with suprasystemic right ventricular pressures, a Potts shunt should be considered early on, before ventricular dysfunction ensues. Furthermore, the shunt might even be considered as alternative therapy to prostacyclin infusion. Finally, a Potts shunt should be viewed as a viable step before proceeding to lung transplantation.

Grady et al Ann Thorac surg 2015

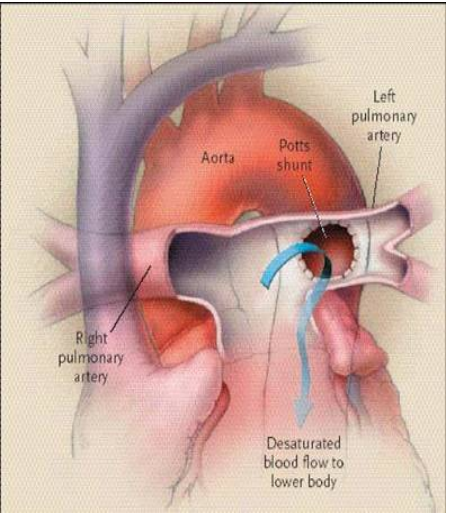


Table 3. Medical Pulmonary Arterial Hypertension Therapy for Each Child Before Potts Shunt, at 12 Months' Follow-Up, and at Last Visit

	Preoperative PAH Therapy			12 Months' Postoperative PAH Therapy			Last Follow-up PAH Therapy			
Patient No.	Bosentan	Sildenafil	Epoprostenol	Bosentan	Sildenafil	Epoprostenol	Follow-up (mo)	Bosentan	Sildenafil	Epoprostenol
1	Yes	Yes	Yes	Deceased			11 days	Deceased		
2	Yes	No	No	Yes	No	No	79	No	No	No
3	Yes	No	Yes	Yes	No	Yes	69	Yes	No	Yes
4	Yes	No	Yes	Yes	No	No	51	Yes	No	No
5	Yes	No	Yes	Yes	No	Yes	49	Yes	No	No
6	Yes	No	No	Deceased			13 days	Deceased		
7	Yes	No	Yes	Yes	Yes	No	43	Yes	Yes	No
8	Yes	Yes	No	yes	Yes	No	37	Yes	Yes	No

PAH = pulmonary arterial hypertension.

Baruteau et al The Annals of Thoracic Surgery, Volume 94, Issue 3, 2012, 817 - 824

Registres

TOPP for Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension

TOPP
Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension

Cardiology in the Young (2017), 27, 1123–1132
doi:10.1017/S1047951116002493

Original Article

Treatment initiation in paediatric pulmonary hypertension: insights from a multinational registry

Haemodynamic characterisation and heart catheterisation complications in children with pulmonary hypertension: Insights from the Global TOPP Registry (tracking outcomes and practice in paediatric pulmonary hypertension)

M. Beghetti [a,*,1], I. Schulze-Neick [b,1], R.M.F. Berger [c,1], D.D. Ivy [d,1], D. Bonnet [e,1], R.G. Weintraub [f,1], T. Saji [g,1], D. Yung [h,1], G.B. Mallory [i,1], R. Geiger [j,1], J.T. Berger [k,1], R.J. Barst [l,1], T. Humpl [m,1], for the, TOPP investigators

Diagnostic evaluation of paediatric pulmonary hypertension in current clinical practice

Maurice Beghetti[1], Rolf M.F. Berger[2], Ingram Schulze-Neick[3], Ronald W. Day[4], Tomás Pulido[5], Jeffrey Feinstein[6], Robyn J. Barst[7]† and Tilman Humpl[8] on behalf of the TOPP registry investigators

Growth in children with pulmonary arterial hypertension: a longitudinal retrospective multiregistry study

Mark-Jan Ploegstra, D Dunbar Ivy, Jeremy G Wheeler, Monika Brand, Maurice Beghetti, Erika B Rosenzweig, Tilman Humpl, Xavier Iriart, Erwan Muros-Le Rouzic, Damien Bonnet, Rolf M F Berger

Acute Vasodilator Response in Pediatric Pulmonary Arterial Hypertension

Current Clinical Practice From the TOPP Registry

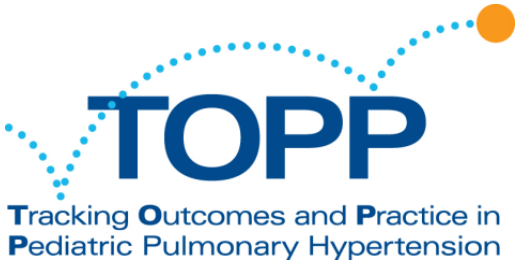
Johannes M. Douwes, MD,[a] Tilman Humpl, MD, PhD,[b] Damien Bonnet, MD, PhD,[c] Maurice Beghetti, MD,[d] D. Dunbar Ivy, MD,[c] Rolf M.F. Berger, MD, PhD,[a] on behalf of the TOPP Investigators

To "Cath" or Not in Pediatric Pulmonary Hypertension?

Clinical features of paediatric pulmonary hypertension: a registry study

Rolf M F Berger, Maurice Beghetti, Tilman Humpl, Gary E Raskob, D Dunbar Ivy, Zhi-Cheng Jing, Damien Bonnet, Ingram Schulze-Neick, Robyn J Barst

From registry to research and clinic



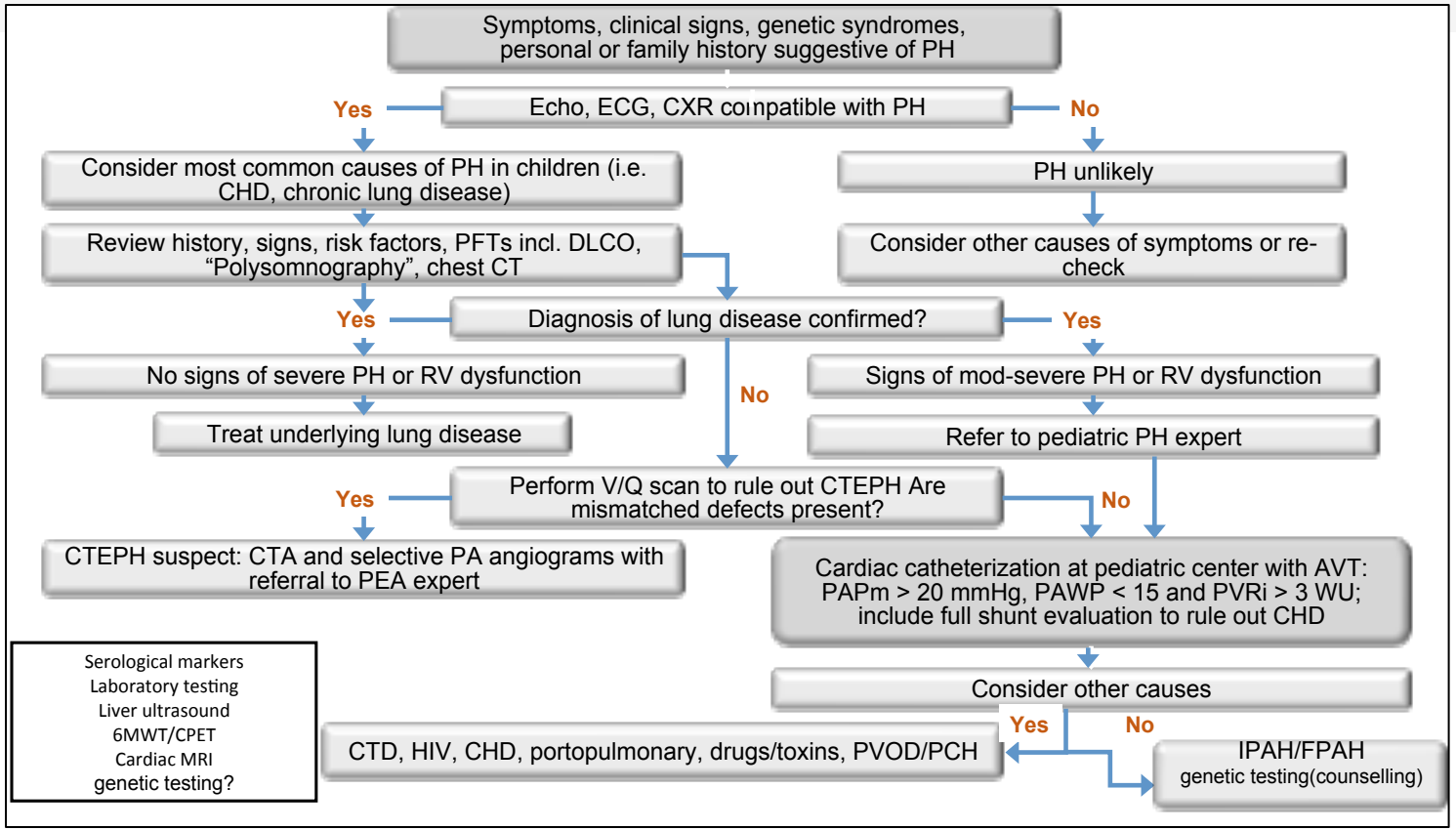
Multi stakeholders meeting

Multistakeholders meeting

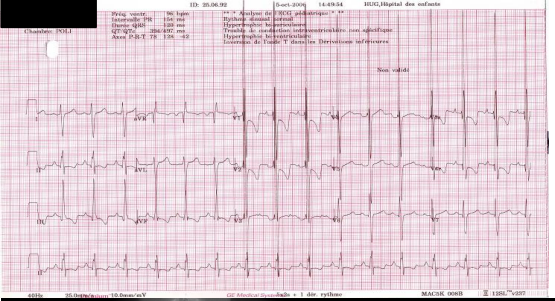
- Develop a plateform to develop research in pediatric pulmonary hypertension (orphan diseases)
  - Authorities (EMA, FDA Japan Canada etc…)
  - Experts
  - Patients association
  - Pharma
- Position paper

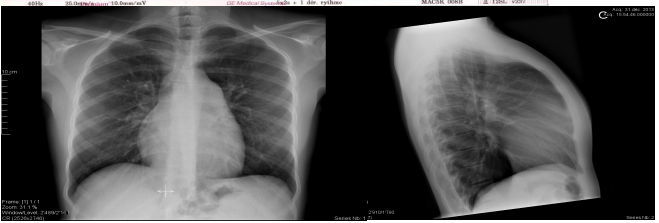
Ollivier et al JAHA 2019

Diagnostic algorythm pediatric Task force WSPH Nice 2018



Rosenzweig et al ERJ 2019



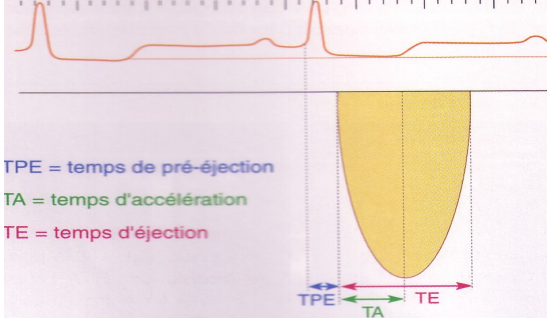


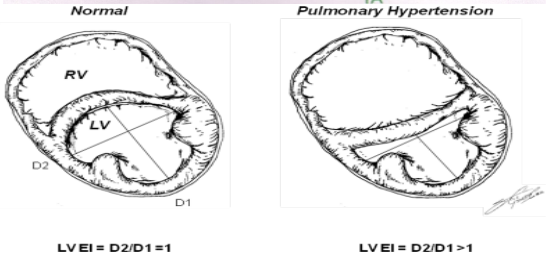
Pulmonary ejection flow

AT < 100ms +++

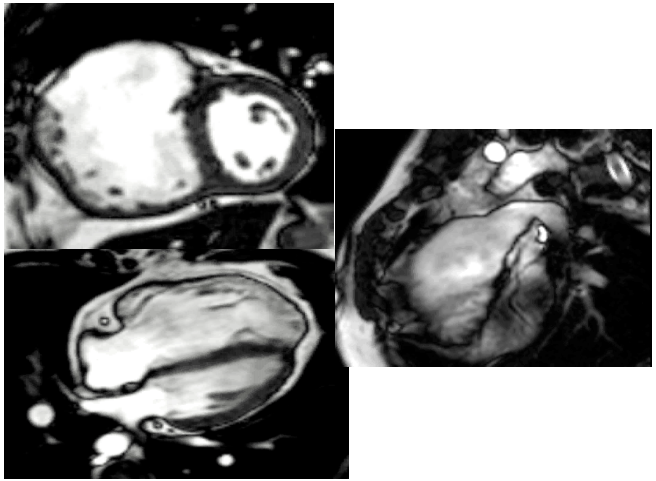
TE < 320 ms

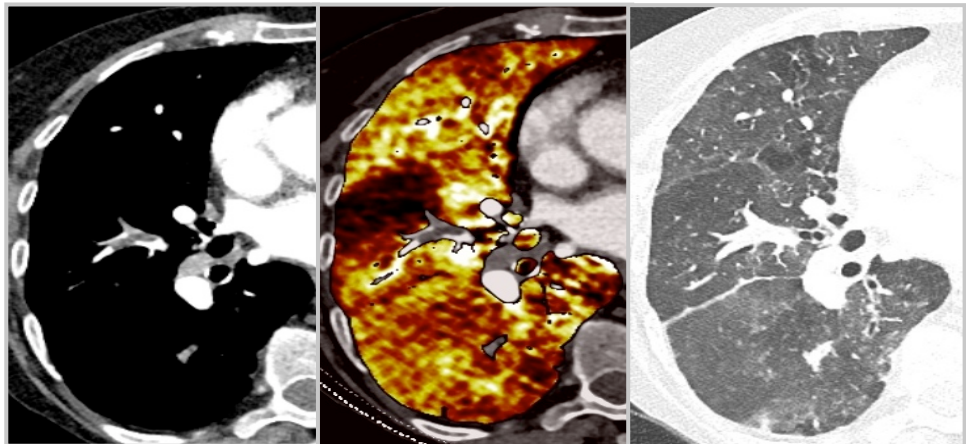
TPE > 100ms





Cardiac catheterization????





Genetics

- *BMPR2* the predominant gene in Peds and Adult PAH
  - Growing data on other genes ALK1, ENG, CAV1, KCNK3, EIF2AK4
- Pediatric PH may have slightly different mutation profile
  - TBX4 (described potential role in pediatric PAH and small patella syndrome, (Kerstjens-Frederikse WS, 2013)
- TBX4 shows us importance to expand beyond ‘pure’ idiopathic
  - E.g., Von Hippel Lindau (JHLTx, 2016)
- Genotype-Phenotype associations needed in Pediatrics

“Guidelines”: Recommendations for pediatric 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.

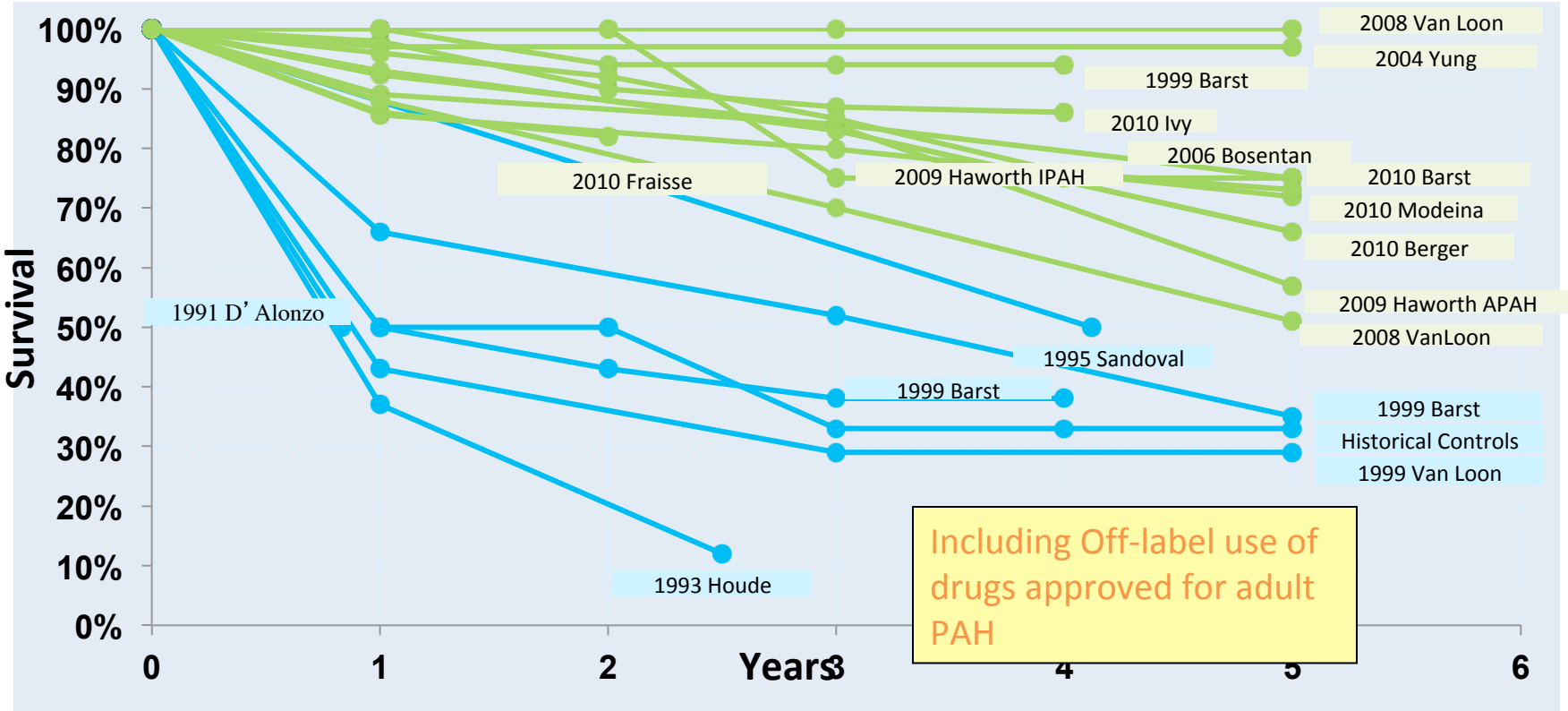
Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK
Hansmann G and Apitz C. *Heart* 2016; 102 Suppl 2:ii67-85.

Paediatric Pulmonary Hypertension: updates on definition, classification, diagnostics and management
Rosenzweig EB, *et al. Eur Respir J* 2018;

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

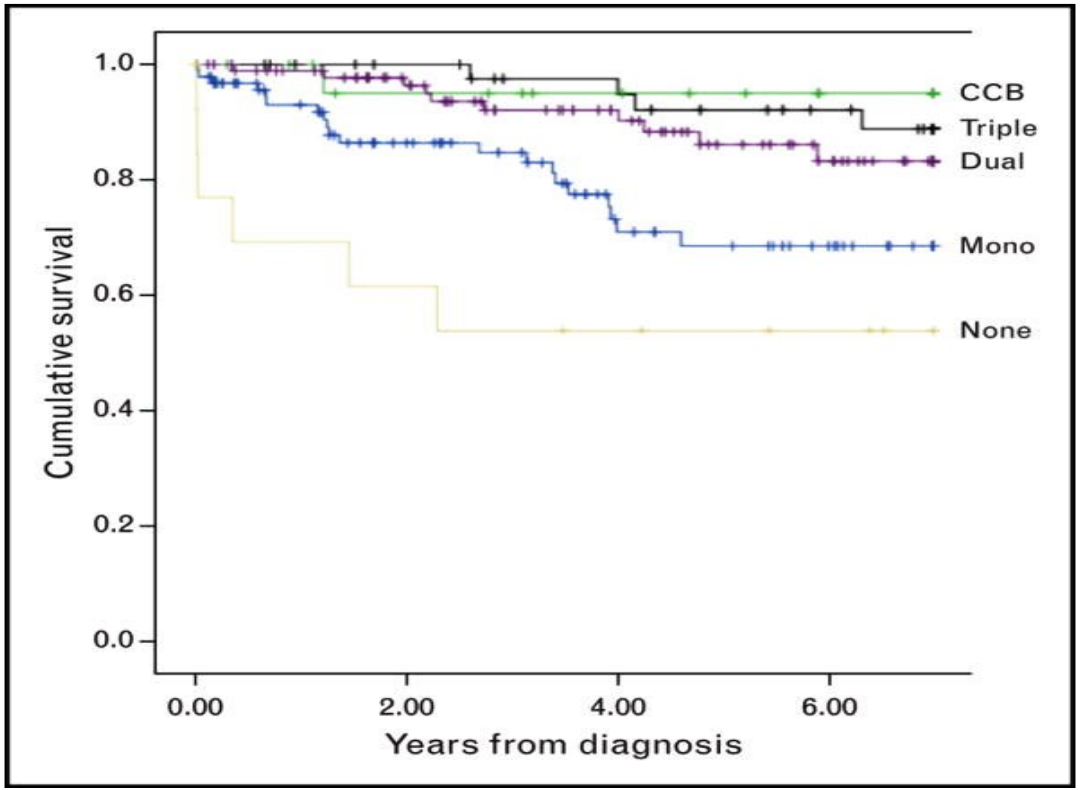
Recommendations are based mostly on expert consensus

Improved Survival in Children



1, 3, 5 year survival: ~ 85 - 95%, ~ 70 - 95%, ~50 - 95%, respectively
vs prior to therapies: ~ 40 - 65%, ~ 45%, ~ 30%, respectively

Current survival in pediatric PAH



Zijlstra WMH, et al. JACC 2014

Futurs traitements

- Mieux utiliser les traitements actuels!
- Nouveaux traitements

  Bcp d'échecs en phase 2 actuellement
- Cellules souches/thérapies génique??
  - Données précliniques positives mais….

Futur

- TT adapté à la pédiatrie
- Diagnostic et suivi non invasif
- Traitement curatif
- IL FAUT TROUVER LA CAUSE ET LA CIBLER ET NON LES SYMPTOMES…..
- Génotype/phénotype
- Génomique

Conclusions

- De nombreux petits pas
- Amélioration de la survie
- Transition chez l'adulte
- Quelques traitements approuvés
- Mais pas de guérison!!!
- Le pas de géant serait le traitment curatif mais on n'en semble pas proche……