PAH related to congenital heart disease in the adult

ΠΝΕΥΜΟΝΙΚΉ ΥΠΈΡΤΑΣΗ ΣΤΙΣ ΣΥΓΓΕΝΕΊΣ ΚΑΡΔΙΟΠΆΘΕΙΕΣ: UPDATE 2018

Kostas Dimopoulos MD MSc PhD FESC

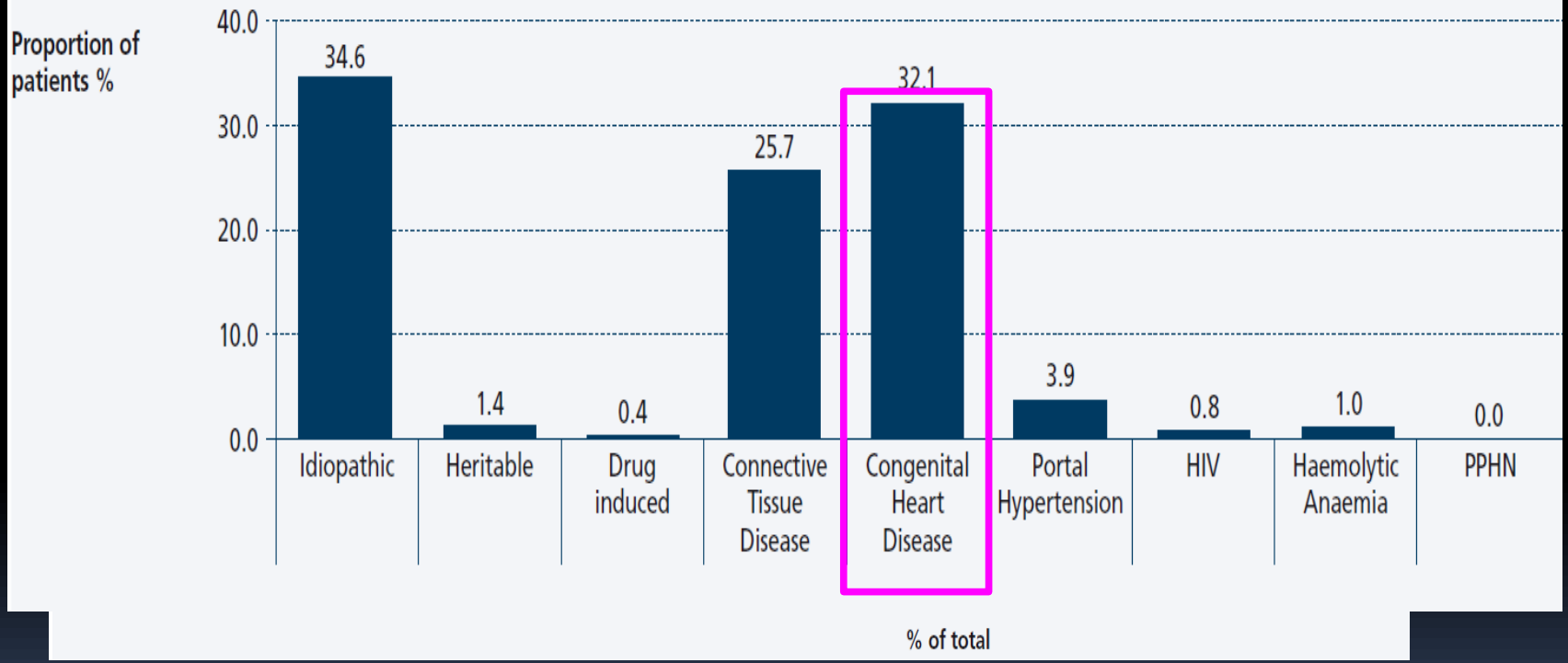
Adult Congenital Heart Centre & Centre for Pulmonary Hypertension

Royal Brompton Hospital & Imperial College London

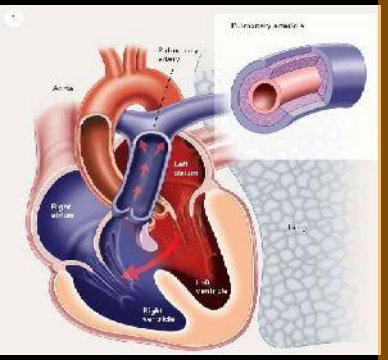
London, UK

PAH-CHD: the most common type or PAH

Figure 4
Proportion of patients in different subcategories of pulmonary arterial hypertension

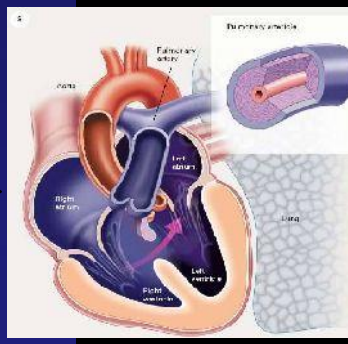


National Audit of Pulmonary Hypertension 2013



PAH associated with L-R shunt

Eisenmenger syndrome



Shunt

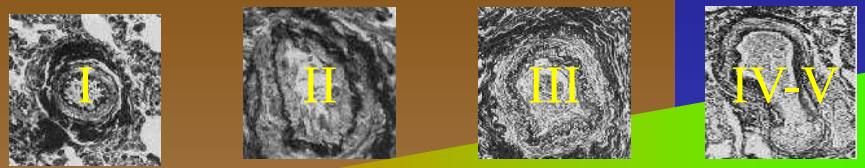
L-R

Bidirectional or RL shunt

Endothelial dysfunction

Shear stress & stretch Vascular Remodeling

Histology



PVR

PVR

Lanigan MJ, Chaney MA, Tissot C, Beghetti M, Dimopoulos K. J Cardiothorac Vasc Anesth. 2013

Clinical classification of PAH-CHD

Four different classes of PAH-CHD …plus a few more!

Table 2 **Types of pulmonary arterial hypertension related to congenital heart disease**

A. Eisenmenger syndrome	Includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis, and multiple organ involvement are present
B. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts	Patients with moderate to large defects, in which the increase in PVR is mild to moderate, left–right shunt is still largely present, and no cyanosis is present at rest
C. Pulmonary arterial hypertension with small defects	Patients with a clinical picture very similar to idiopathic PAH, who have (coincidental?) small defects
Additional types of pulmonary vascular disease related to CHD	
- Segmental pulmonary arterial hypertension	In these cases, part of the lung vasculature develops pulmonary vascular disease, while other areas may be normally perfused or hypoperfused
- Raised PVR in Fontan patients	Patients with a previous Fontan-type operation can develop a rise in PVR, despite low pulmonary arterial pressures

European Heart Journal
doi:10.1093/eurheartj/eht437

REVIEW

Clinical update

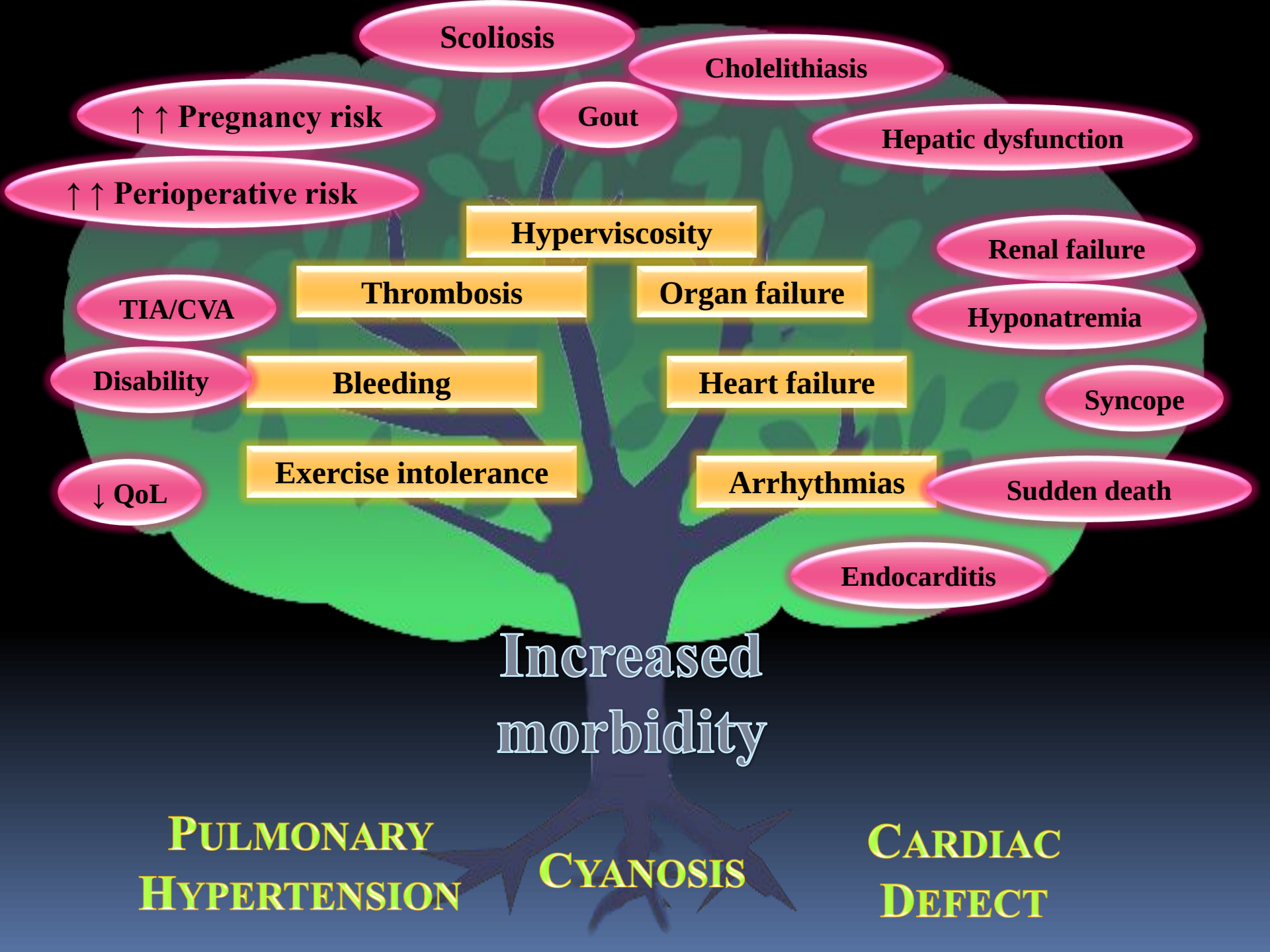
Pulmonary hypertension related to congenital heart disease: a call for action

Konstantinos Dimopoulos, Stephen John Wort, and Michael A. Gatzoulis*

Journal of the American College of Cardiology
Vol. 62, No. 25, Suppl D, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.10.029

Updated Clinical Classification of Pulmonary Hypertension

Gerald Simonneau, MD,* Michael A. Gatzoulis, MD, PhD,† Ian Adatia, MD,‡
David Celermajer, MD, PhD,§ Chris Denton, MD, PhD,‖ Ardeschir Ghofrani, MD,¶
Miguel Angel Gomez Sanchez, MD,# R. Krishna Kumar, MD,** Michael Landzberg, MD,††
Roberto F. Machado, MD,‡‡ Horst Olschewski, MD,§§ Ivan M. Robbins, MD,‖‖
Rogiero Souza, MD, PhD¶¶


Scoliosis
Cholelithiasis
↑↑ Pregnancy risk
Gout
Hepatic dysfunction
↑↑ Perioperative risk
Hyperviscosity
Renal failure
Thrombosis
Organ failure
TIA/CVA
Hyponatremia
Disability
Bleeding
Heart failure
Syncope
Exercise intolerance
↓ QoL
Arrhythmias
Sudden death
Endocarditis
Increased morbidity
Pulmonary Hypertension
Cyanosis
Cardiac Defect

International Journal of Cardiology 249 (2017) 140–144

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Non-invasive assessment of liver changes in Eisenmenger patients

Siegrun Mebus [a,1], Nicole Nagdyman [a,1], Johanna Kügel [a], Reinhart Zachoval [b], Siegmund Lorenz Braun [c], Guido Haverkämper [d], Bernd Opgen-Rhein [d], Felix Berger [d,e], Sophia Horster [b], Jörg Schoetzau [a], Claudia Pujol Salvador [a], Ulrike Bauer [f], John Hess [a], Peter Ewert [a], Harald Kaemmerer [a,*]

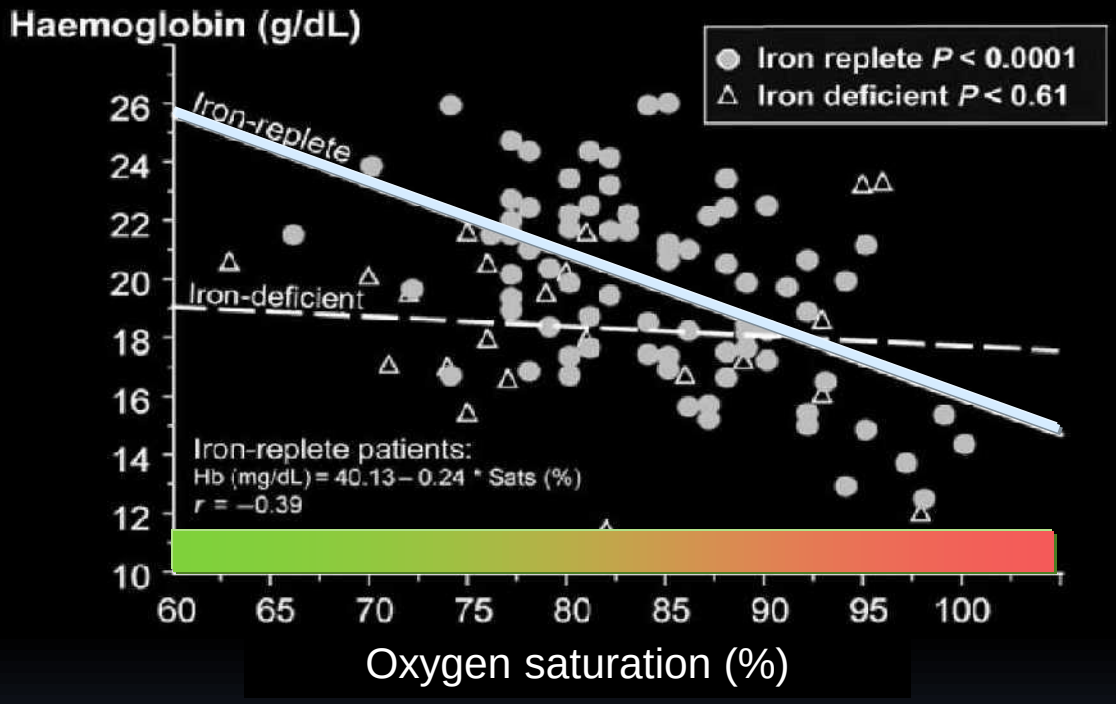
Global assessment of hepatic alterations (n.a. = not available).

Patient	Functional class (Perloff)	Body mass index (kg/m^2 body surface area)	Abdominal sonography (normal/abnormal)	Transient elastography	ARFI	Pathological laboratory findings	Elevated specific fibrosis marker	Global hepatic assessment	
				staging of fibrosis	staging of fibrosis			hepatic alteration	kind of damage
AB	3	19.0	abnormal	**0–1**	**0**			no	
ES	3	21.0	abnormal	**0–1**	**2**			yes	**fibrosis**
SL	2	25.4	abnormal	**0–1**	**0**	total bilirubin		no	
JR	3	19.3	abnormal	**0–1**	**2**	total bilirubin	FIB-4 index	yes	**fibrosis**
SN	3	23.5	abnormal	**0–1**	**0**	total bilirubin	FIB-4 index	no	
KL	2	21.1	abnormal	**0–1**	**2**	GGT		yes	**fibrosis**
AG	3	30.5	normal	**0–1**	**3**	GGT, total bilirubin		yes	**fibrosis**
KH	3	25.3	abnormal	n.a.	**0**	total bilirubin		no	
JK	3	24.4	abnormal	n.a.	**4**			yes	**cirrhosis**
MN	3	20.0	n.a.	**0–1**	**2**	albumin	n.a.	yes	**fibrosis**

Bold: staging of liver fibrosis by transient elastography, ARFI and global hepatic assessment.

The haematologic effect of cyanosis

Prevalence of iron deficiency and relation to saturations



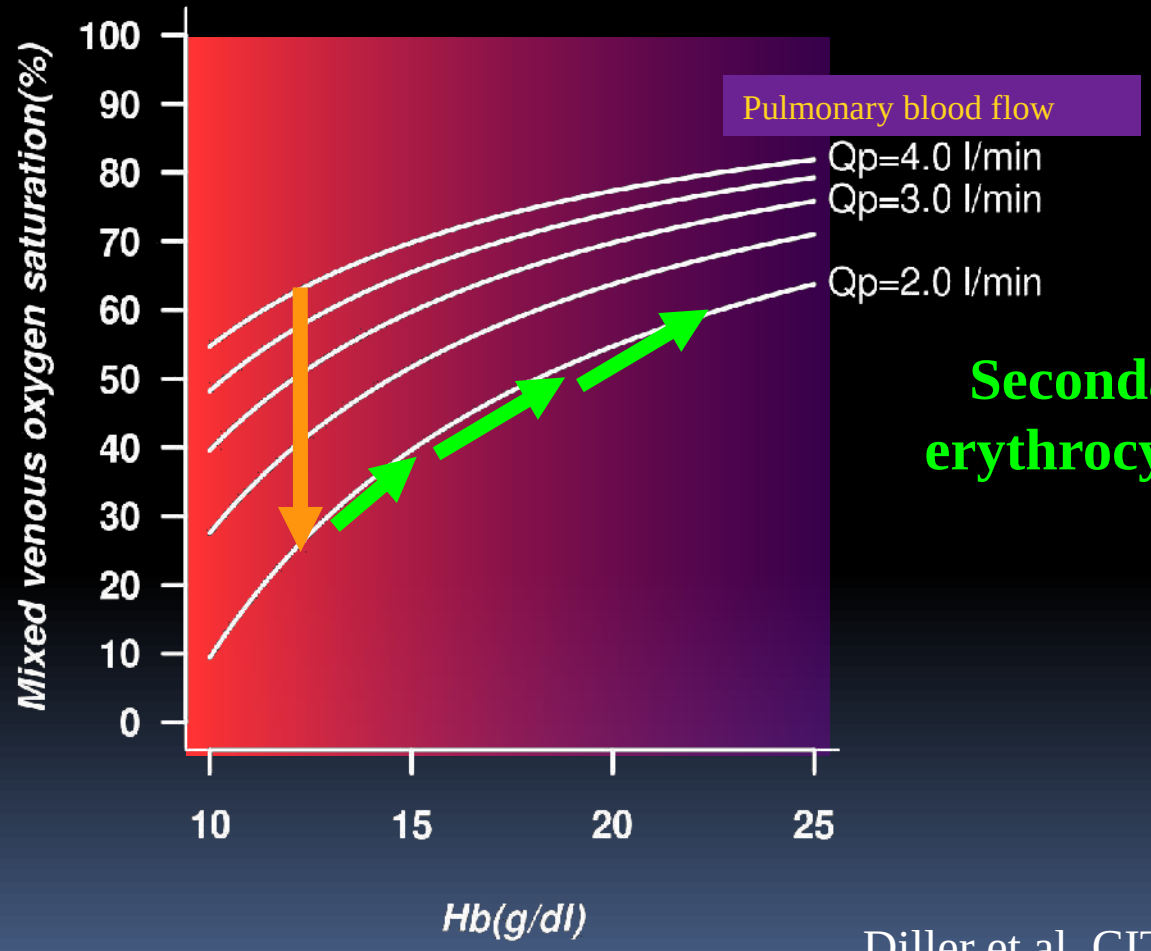
Prevalence of iron deficiency:

- 20-37% of patients with cyanotic CHD
- Easily overlooked as standard laboratory methods (Hb, MCV) do not apply

Diller, Dimopoulos et al. EHJ 2010

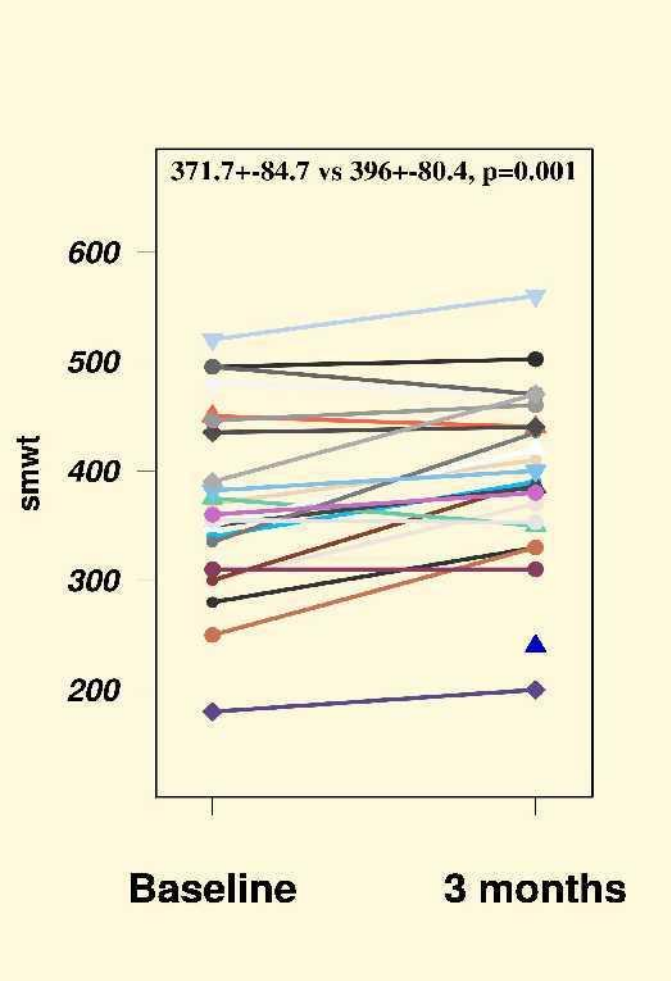
Why do cyanotic patients need a higher hemoglobin

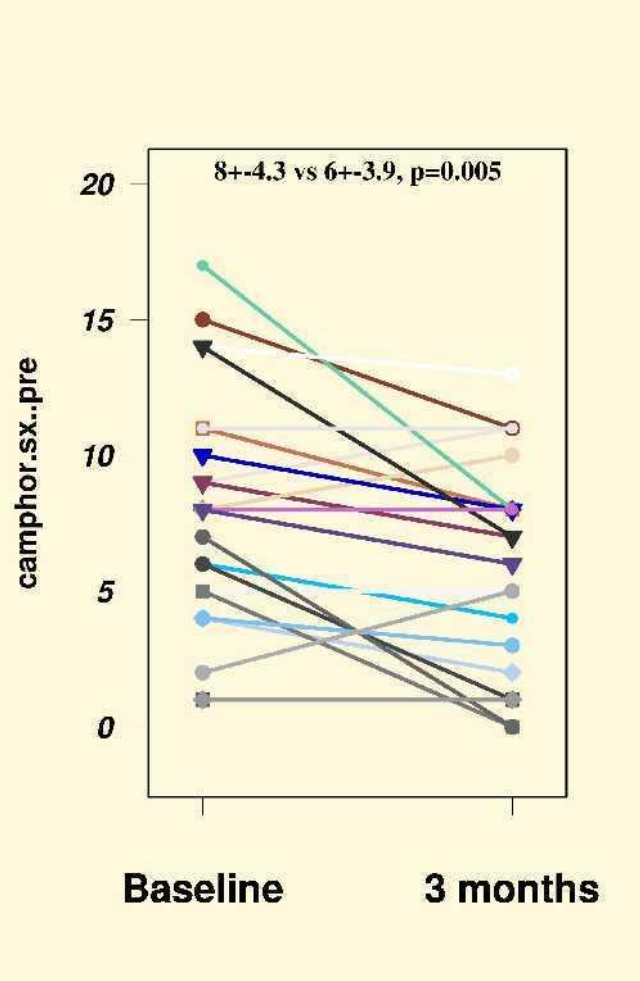
Erythrocytosis maintains adequate oxygen delivery to peripheral tissues



Diller et al, CITY 2010

Iron supplementation in cyanotic ACHD:
Exercise capacity and QoL





Tay E, et al. IJC 2010

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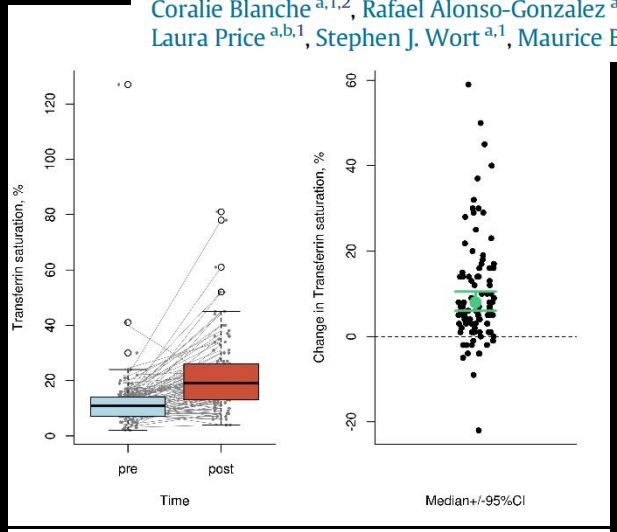
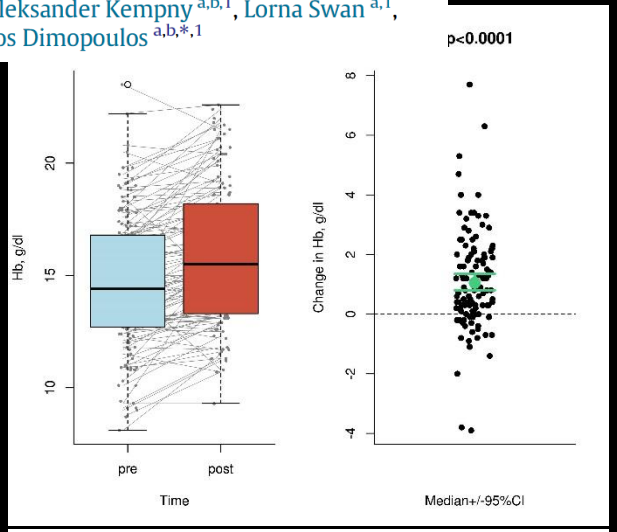
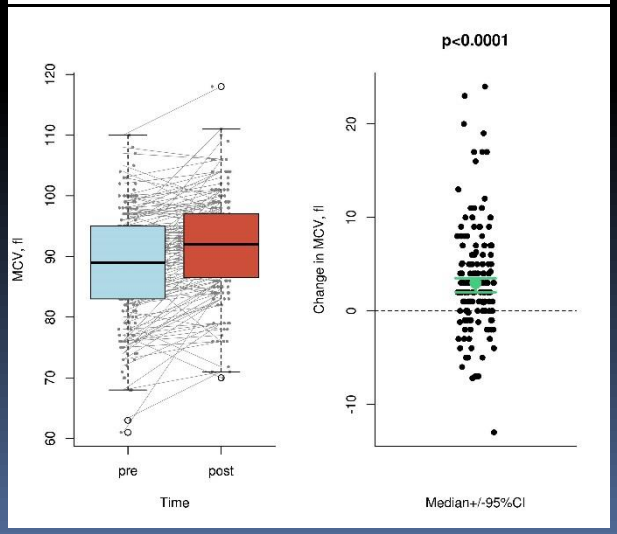
journal homepage: www.elsevier.com/locate/ijcard

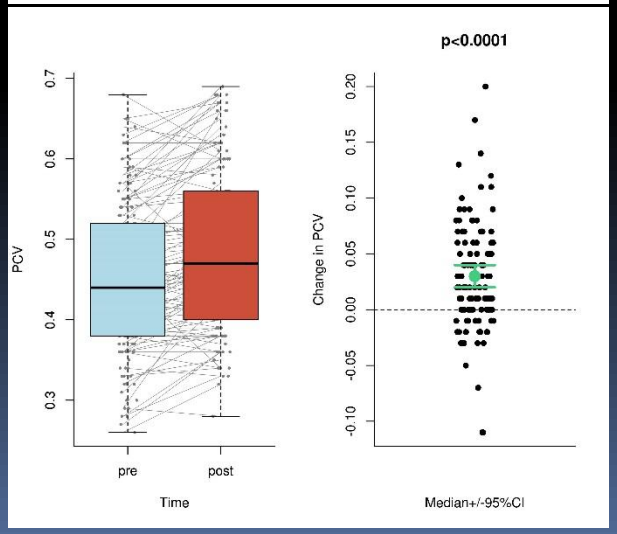
Use of intravenous iron in cyanotic patients with congenital heart disease and/or pulmonary hypertension

Coralie Blanche [a,1,2], Rafael Alonso-Gonzalez [a,1,2], Aitor Uribarri [a,1], Aleksander Kempny [a,b,1], Lorna Swan [a,1], Laura Price [a,b,1], Stephen J. Wort [a,1], Maurice Beghetti [c,1], Konstantinos Dimopoulos [a,b,*,1]

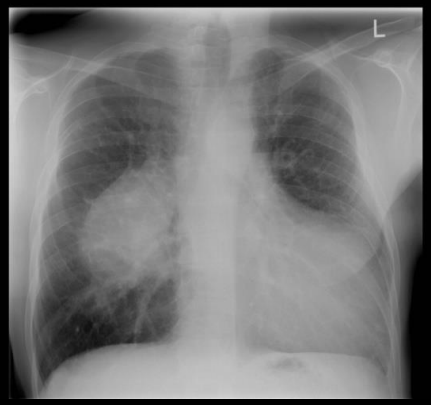


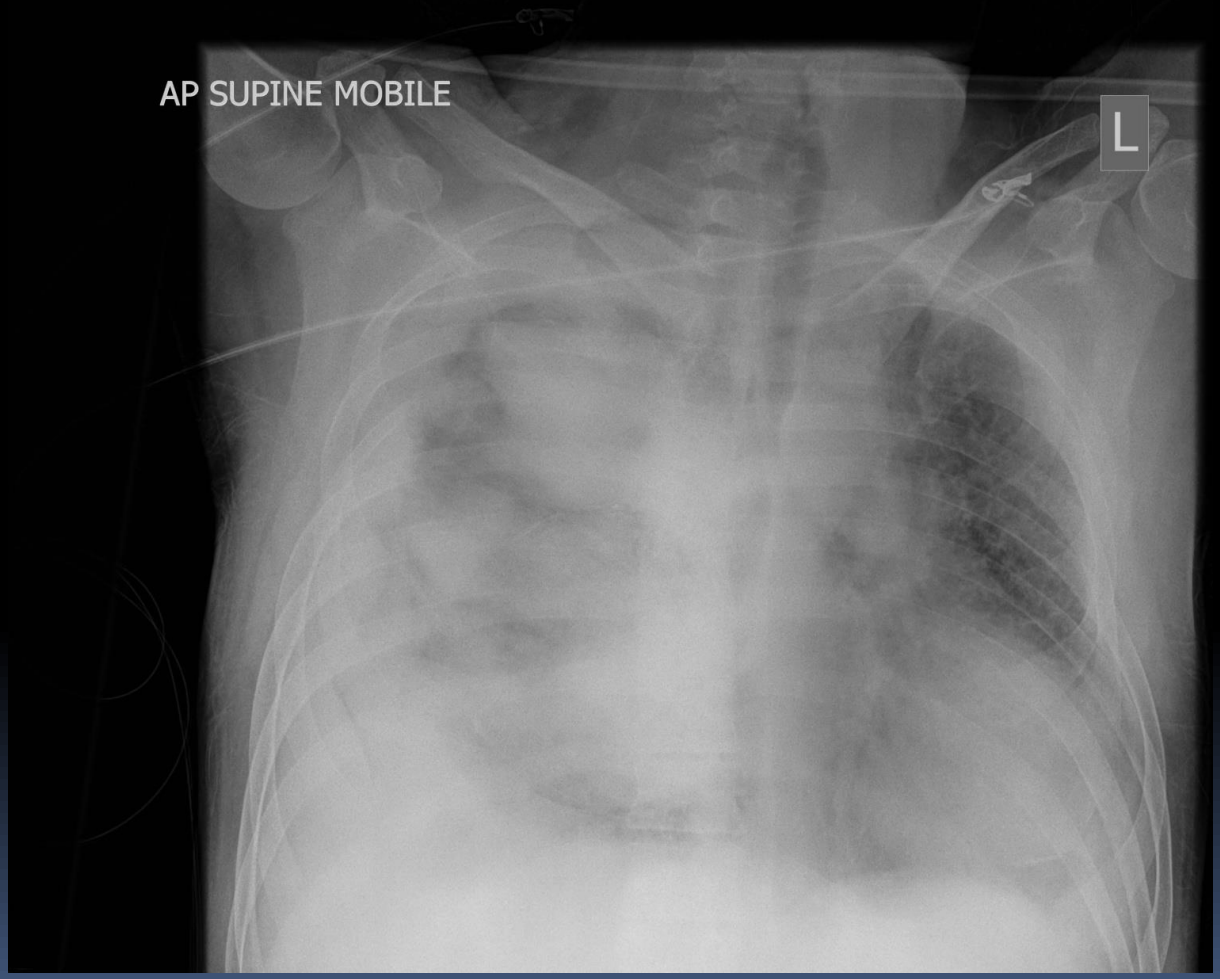






Haemodynamic collapse

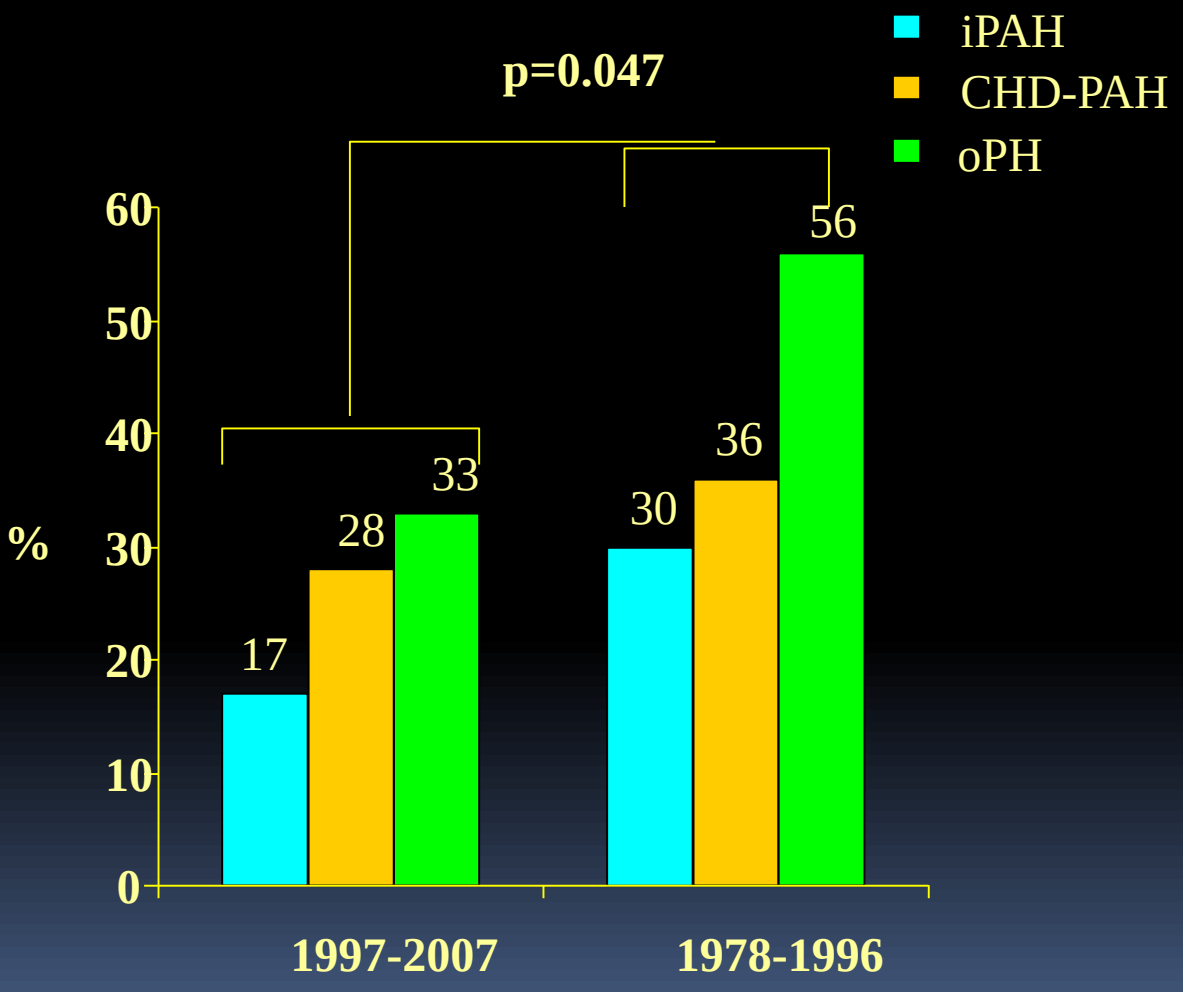




Mortality risk of pregnancy in PAH related to CHD

- Maternal mortality risk 30%
- Baby growth retardation risk 80%: premature
- Risk of spontaneous abortions

- Also interruption of pregnancy carries significant risks



Bedard, Dimopoulos, Gatzoulis, EHJ 2009

Eisenmenger Syndrome in Pregnancy: When Is It Time for ECMO?: A Case Report

Marie-Louise Meng, MD,* Annie Fu, MD,† Carolyn Westhoff, MD,† Matthew Bacchetta, MD,‡ Erika B. Rosenzweig, MD,§ Ruth Landau, MD,* and Richard Smiley, MD, PhD*

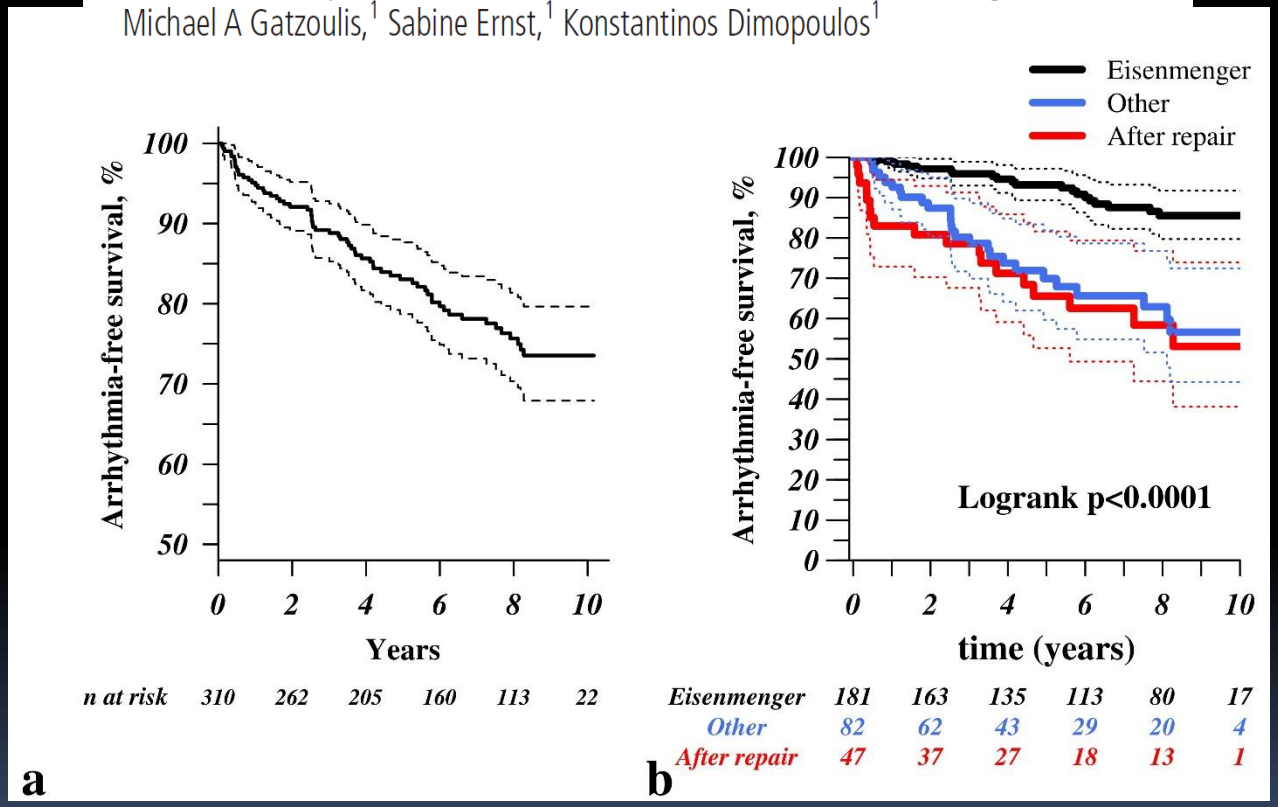
We report the case of a 21-year-old primiparous woman at 22 weeks gestation who presented with a large uncorrected ventricular septal defect, severe pulmonary hypertension, and Eisenmenger syndrome. The patient elected for termination of pregnancy, which was performed under regional anesthesia. Hemodynamic changes apparently associated with uterine contraction immediately after termination resulted in increased right to left shunting across the ventricular septal defect requiring urgent venovenous extracorporeal membrane oxygenation. Thrombocytopenia and systemic anticoagulation for extracorporeal membrane oxygenation presented a challenge for removal of the epidural catheter. Pulmonary hypertension was managed and she was discharged on postoperative day 35. (A&A Practice. XXX;XXX:00–00.)

ORIGINAL RESEARCH ARTICLE

Arrhythmias in adult patients with congenital heart disease and pulmonary arterial hypertension

Heart 2018;**0**:1–7

Maria Drakopoulou,[1,2] Heba Nashat,[1] Aleksander Kempny,[1] Rafael Alonso-Gonzalez,[1] Lorna Swan,[1] Stephen J Wort,[1] Laura C Price,[1] Colm McCabe,[1] Tom Wong,[1] Michael A Gatzoulis,[1] Sabine Ernst,[1] Konstantinos Dimopoulos[1]



Arrhythmia, used as a time-varying covariate in the Cox model, was a strong **predictor of death**

HR 3.41, 95%CI: 2.10-5.53, p<0.0001

Predictors of new arrhythmia in PAH-CHD and relation to mortality

Congenital heart disease

ORIGINAL RESEARCH ARTICLE

Arrhythmias in adult patients with congenital heart disease and pulmonary arterial hypertension

Heart 2018;**0**:1–7

Maria Drakopoulou,[1,2] Heba Nashat,[1] Aleksander Kempny,[1] Rafael Alonso-Gonzalez,[1] Lorna Swan,[1] Stephen J Wort,[1] Laura C Price,[1] Colm McCabe,[1] Tom Wong,[1] Michael A Gatzoulis,[1] Sabine Ernst,[1] Konstantinos Dimopoulos[1]

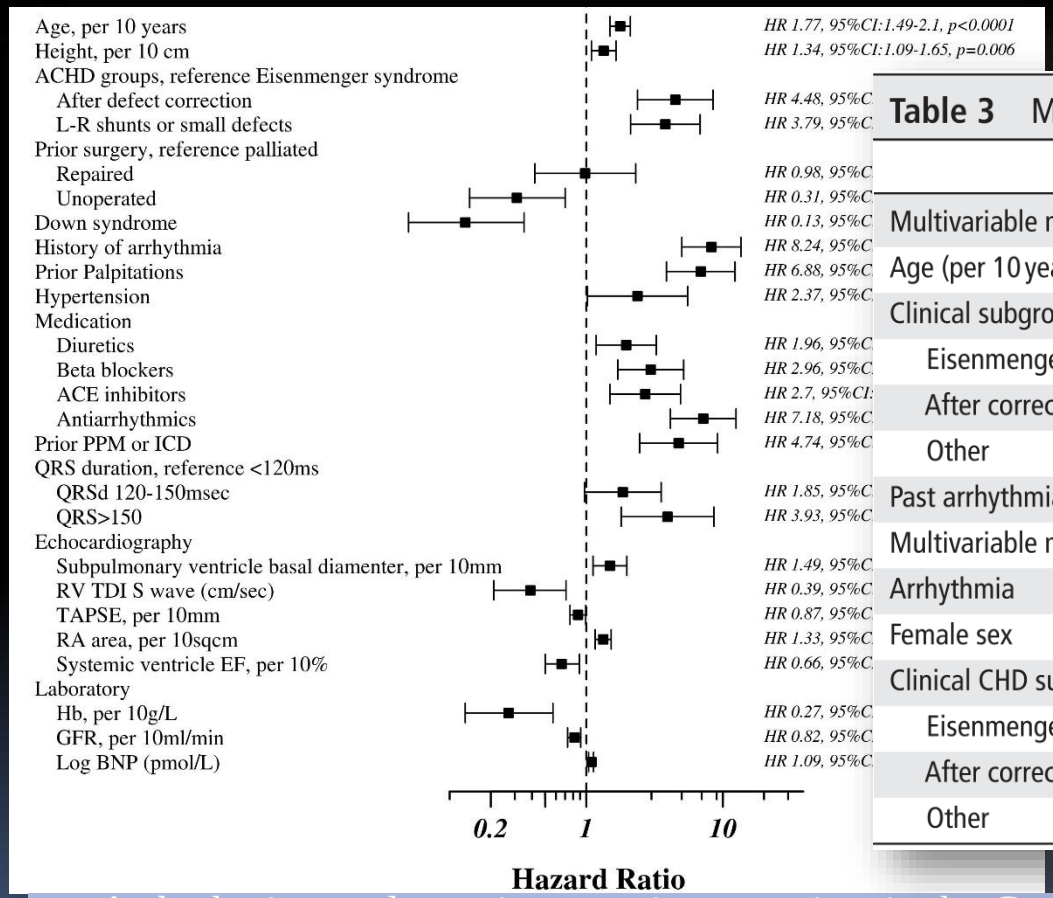


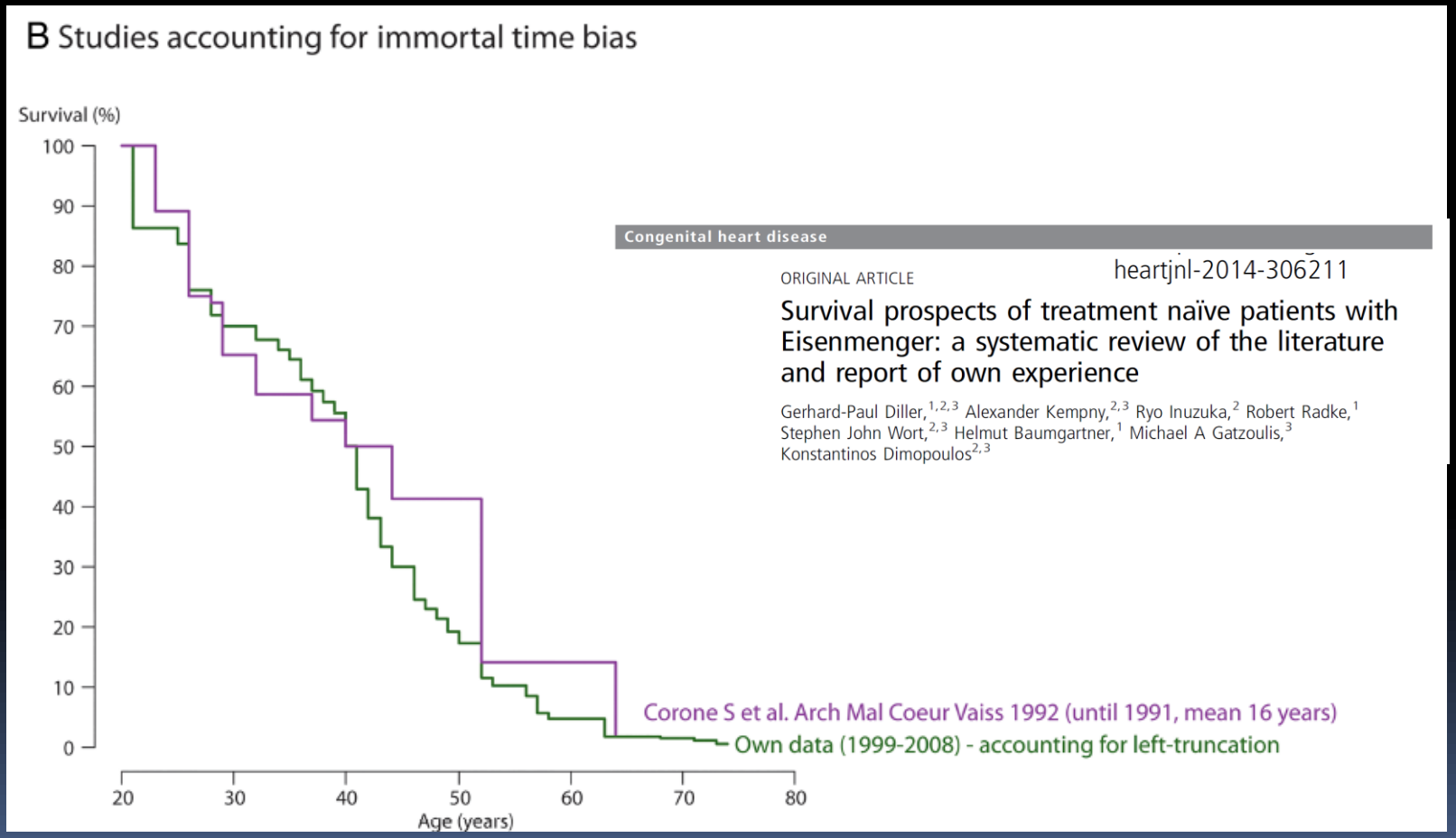
Table 3 Multivariable models for arrhythmia and death

	HR	95% CI	P values
Multivariable model, end point arrhythmia			
Age (per 10 years)	1.51	1.24 to 1.83	<0.0001
Clinical subgroup			
Eisenmenger syndrome	Ref		
After correction	3.18	1.65 to 6.13	0.0006
Other	3.50	1.92 to 6.38	<0.0001
Past arrhythmia	3.87	2.23 to 6.72	<0.0001
Multivariable model, end point death			
Arrhythmia	3.29	1.96 to 5.54	<0.0001
Female sex	1.69	1.04 to 2.73	0.03
Clinical CHD subgroup			
Eisenmenger syndrome	Ref		
After correction	0.76	0.35 to 1.65	0.49
Other	1.76	1.03 to 3.01	0.04

Arrhythmia, used as a time-varying covariate in the Cox model, was a strong **predictor of death**

HR 3.41, 95%CI: 2.10-5.53, p<0.0001

The true survival of Eisenmenger patients



Congenital heart disease

heartjnl-2014-306211

ORIGINAL ARTICLE

Survival prospects of treatment naïve patients with Eisenmenger: a systematic review of the literature and report of own experience

Gerhard-Paul Diller,[1,2,3] Alexander Kempny,[2,3] Ryo Inuzuka,[2] Robert Radke,[1] Stephen John Wort,[2,3] Helmut Baumgartner,[1] Michael A Gatzoulis,[3] Konstantinos Dimopoulos[2,3]

International Journal of Cardiology 254 (2018) 101–106

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Incidence and clinical characteristics of sudden cardiac death in adult congenital heart disease

Benjamin Moore [a,1], Christopher Yu [

[a] University of Sydney Medical School and Department of Cardi
[b] Department of Cardiology, Concord Hospital, Sydney, Australi
[c] Department of Cardiology, Royal Prince Alfred Hospital, Sydne

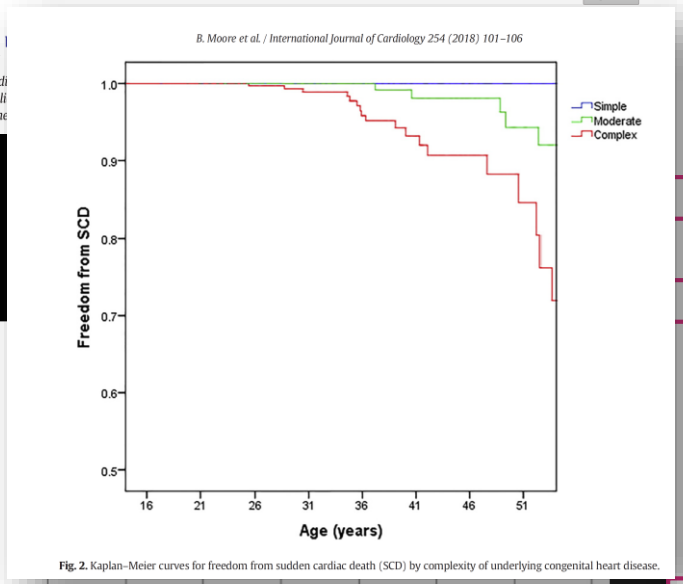


Fig. 2. Kaplan–Meier curves for freedom from sudden cardiac death (SCD) by complexity of underlying congenital heart disease.

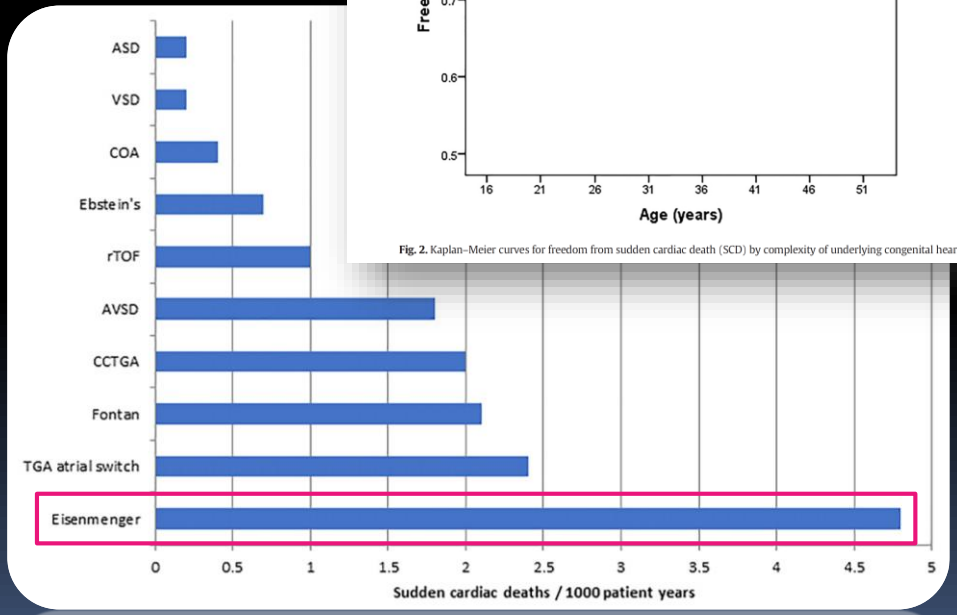
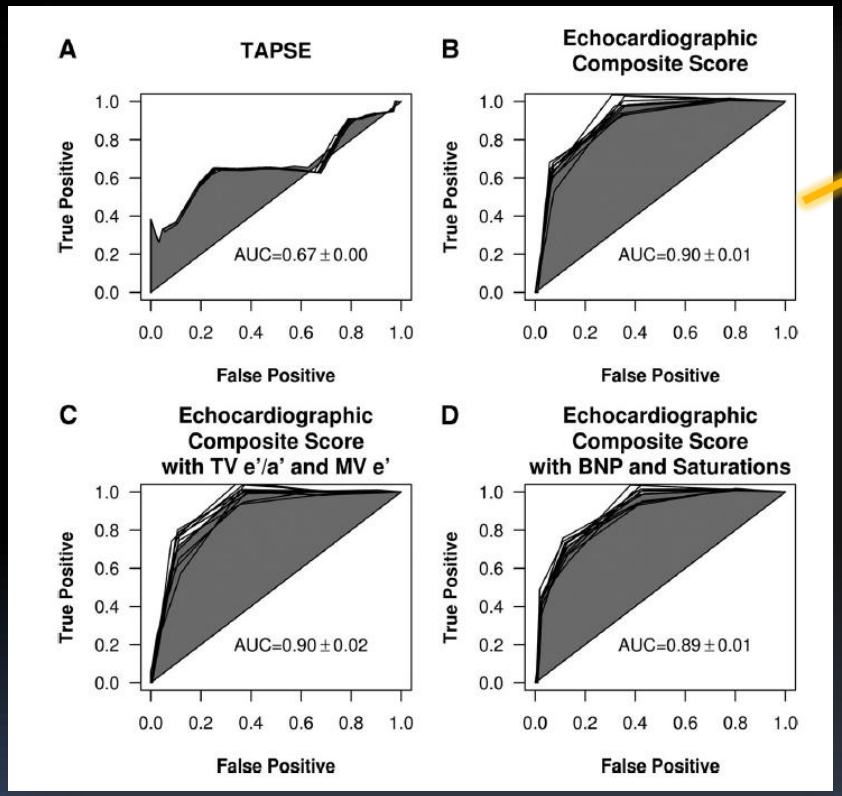


Table 2
Clinical characteristics of sudden cardiac death cases.

Characteristic	n (%)
Complexity	
Simple	2 (6)
Moderate	13 (37)
Severe	20 (57)
Syndrome as cause of defect	7 (20)
Previous cerebrovascular event	4 (12)
Chronic kidney disease[a]	5 (14)
Atrial arrhythmia	15 (43)
Pacemaker	2 (6)
NYHA III–IV symptoms	11 (31)
Heart failure symptoms	13 (37)
Heart failure admission[b]	10 (29)
Palpitations	12 (34)
Syncope	5 (14)
Anti-arrhythmic medication	4 (11)
Digoxin	4 (11)
Heart failure medication	15 (43)
Anticoagulation	8 (23)
Advanced pulmonary hypertension therapy	4 (11)
Systemic ventricle moderate-severely impaired	4 (11)
Systemic ventricle moderate-severely dilated	7 (20)
Subpulmonary ventricle moderate-severely impaired	3 (9)
Subpulmonary ventricle moderate-severely dilated	10 (29)
Moderate-severe systemic AV valve regurgitation	8 (23)
Systemic venous atrium moderate-severely dilated	8 (23)
Rhythm on ECG at last follow up	
Sinus	21 (60)
Atrial arrhythmia	5 (14)
Paced	1 (3)
QRS width (ms, ±SD)	132 ± 33
QTc (ms, ±SD)	452 ± 37

[a] Chronic kidney disease defined as glomerular filtration rate < 60 mL/min. on multiple sequential tests.
[b] Within the 2 years preceding sudden cardiac death. NYHA = New York Heart Association, AV = atrio-ventricular.

Echocardiographic Composite score



Composite score

- TAPSE<15mm
- Systole/diastole time on TR ≥1.5
- RA area ≥25cm^2
- RA area/LA area ratio ≥1.5

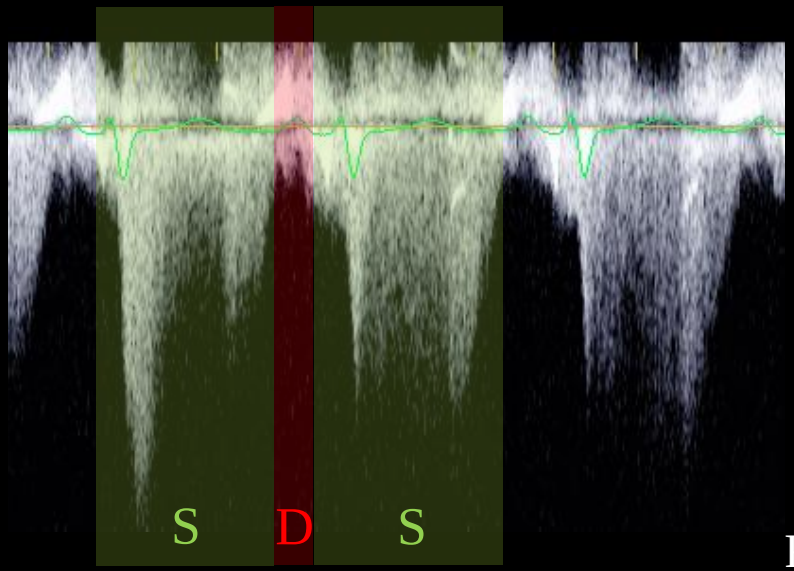
Echocardiographic Predictors of Outcome in Eisenmenger Syndrome

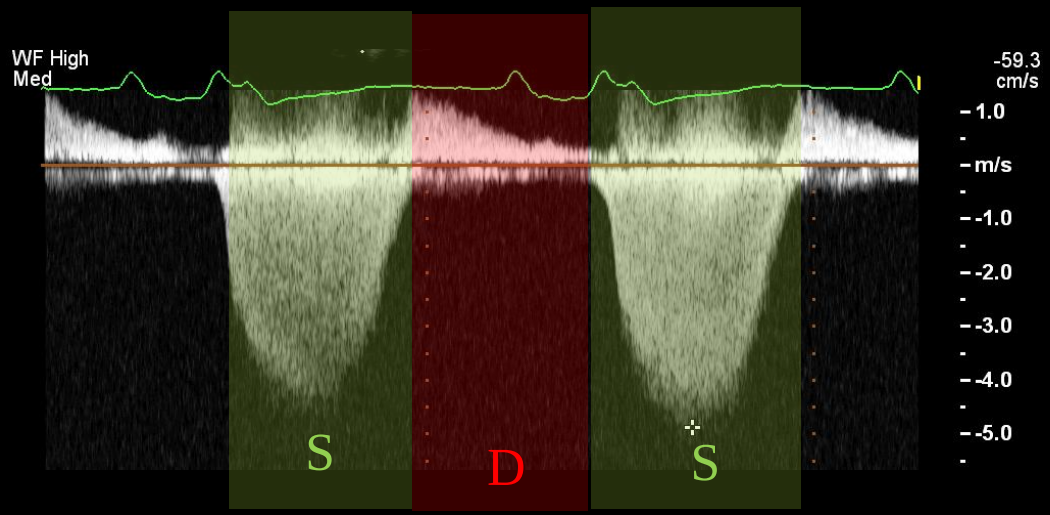
(*Circulation*. 2012;126:1461-1468.)

Pamela Moceri, MD; Konstantinos Dimopoulos, MD, MSc, PhD, FESC; Emmanouil Liodakis, MD; Ioannis Germanakis, MD; Aleksander Kempny, MD; Gerhard-Paul Diller, MD, PhD; Lorna Swan, MB, ChB, MD, FRCP; Stephen J. Wort, MA, MBBS, FRCP, PhD; Philip S. Marino, MD; Michael A. Gatzoulis, MD, PhD, FESC; Wei Li, MD, PhD, FESC

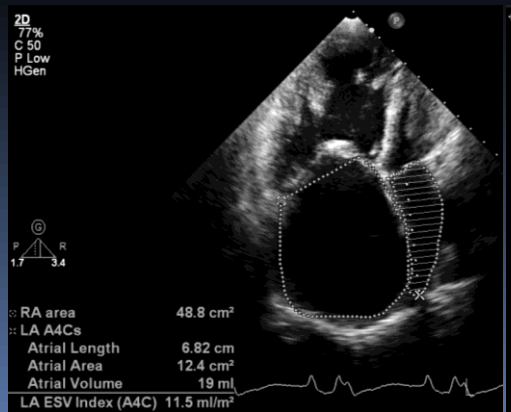
Example of composite score

Systole/Diastole duration

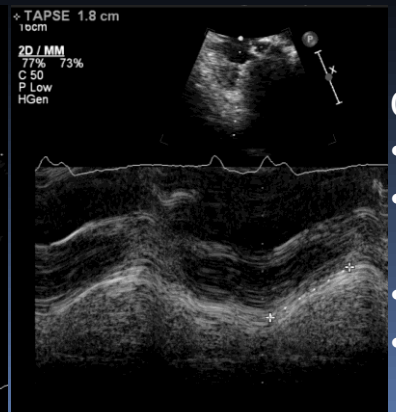




RA area
RA/LA area



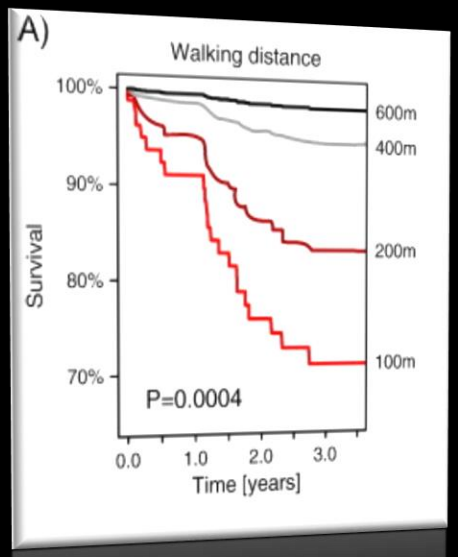
TAPSE

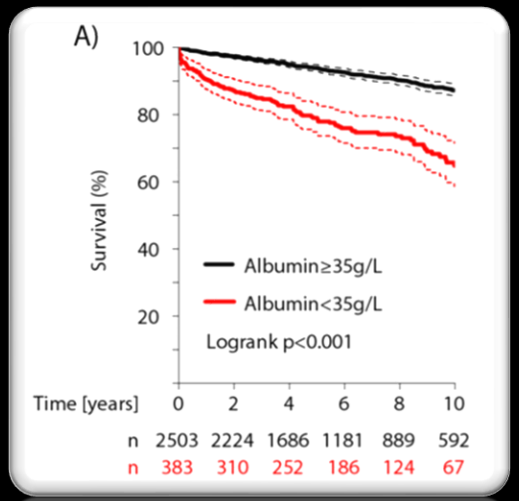


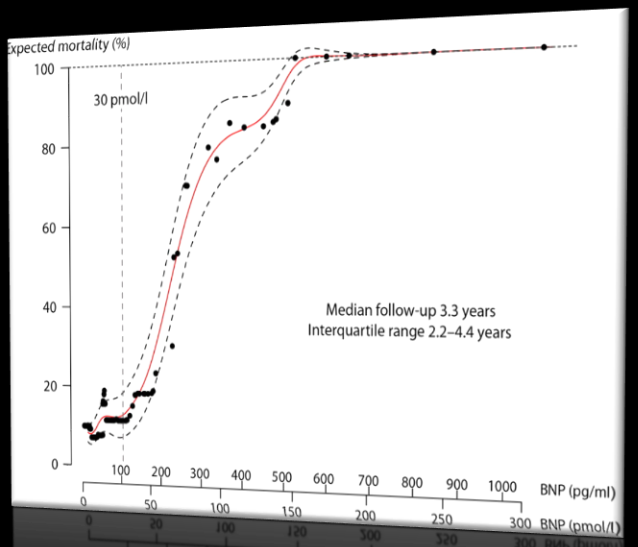
Composite score

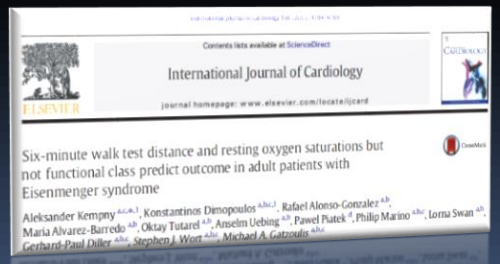
- TAPSE<15mm
- Systole/diastole time on TR ≥1.5
- RA area ≥25cm^2
- RA area/LA area ratio ≥1.5

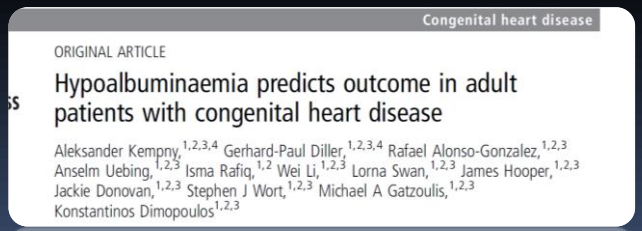
6MWD, Albumin and BNP in Eisenmenger syndrome





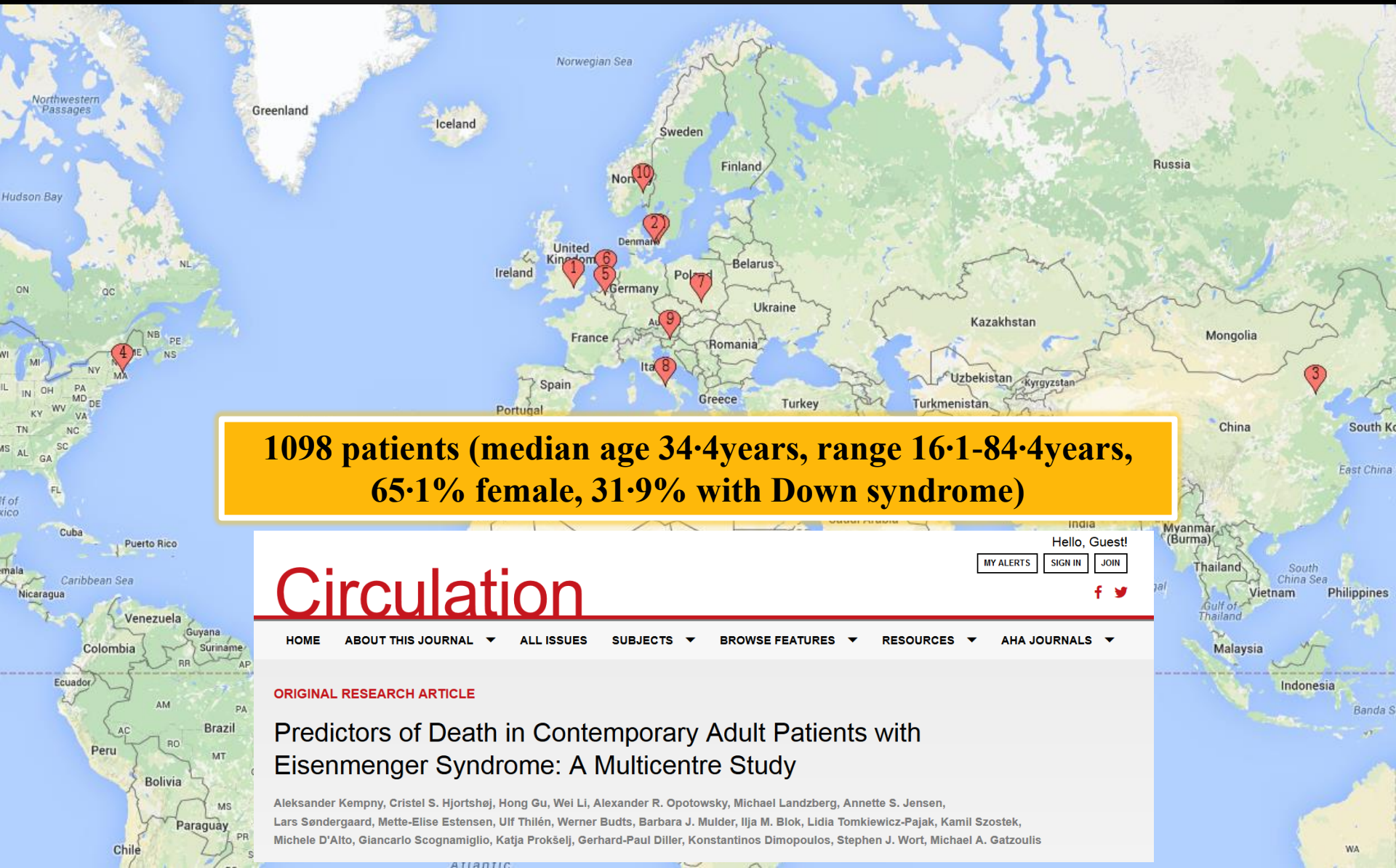






The MUSES study

MUlti-centre Study on Eisenmenger Syndrome



1098 patients (median age 34·4years, range 16·1-84·4years, 65·1% female, 31·9% with Down syndrome)

Circulation

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ORIGINAL RESEARCH ARTICLE

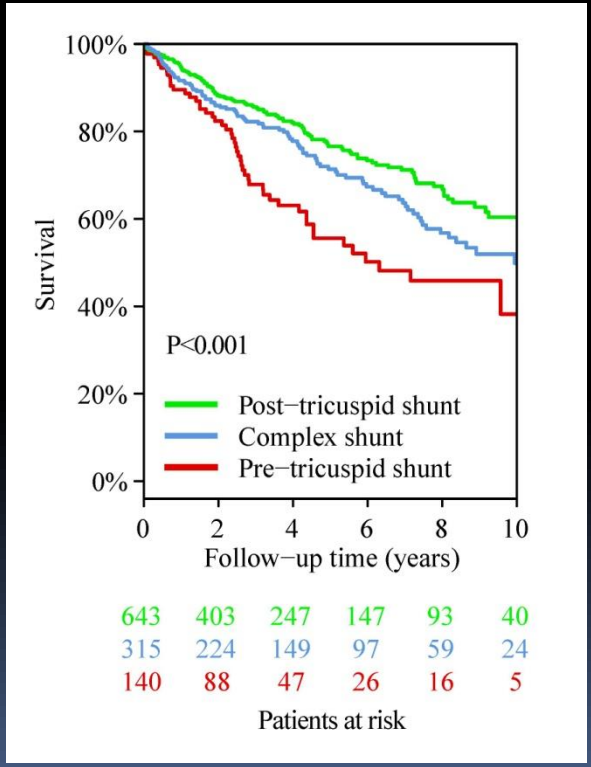
Predictors of Death in Contemporary Adult Patients with Eisenmenger Syndrome: A Multicentre Study

Aleksander Kempny, Cristel S. Hjortshøj, Hong Gu, Wei Li, Alexander R. Opotowsky, Michael Landzberg, Annette S. Jensen, Lars Søndergaard, Mette-Elise Estensen, Ulf Thilén, Werner Budts, Barbara J. Mulder, Ilja M. Blok, Lidia Tomkiewicz-Pajak, Kamil Szostek, Michele D'Alto, Giancarlo Scognamiglio, Katja Prokšelj, Gerhard-Paul Diller, Konstantinos Dimopoulos, Stephen J. Wort, Michael A. Gatzoulis

The MUSES study

MUlti-centre Study on Eisenmenger Syndrome

Parameter	Unit	HR	95% CI	P-value
Age	10years	1·35	1·14 - 1·61	<0·001
Pre-tricuspid shunt	-	1·97	1·12 - 3·46	0·019
Oxygen saturation at rest	10%	0·61	0·46 - 0·82	<0·001
Six minute walking distance	100m	0·67	0·54 - 0·82	<0·001
Presence of pericardial effusion	-	2·35	1·33 - 4·13	0·003



Kempny et al, Circulation 2017

The MUSES study

MUlti-centre Study on Eisenmenger Syndrome

Age	6MWT distance	Pre-tricuspid shunt, PE absent					Pre-tricuspid shunt, PE present					Post-tricuspid or complex shunt, PE absent					Post-tricuspid or complex shunt, PE present				
		70	75	80	85	90	70	75	80	85	90	70	75	80	85	90	70	75	80	85	90
50	600	23	19	15	12	9	48	40	33	27	21	12	10	8	6	5	28	22	18	14	11
	500	33	26	21	17	14	62	53	44	36	30	18	14	11	9	7	38	31	25	20	16
	400	44	36	30	24	19	75	67	57	49	40	25	20	16	13	10	50	42	35	28	23
	300	57	48	40	33	27	87	80	71	62	53	34	28	23	18	14	64	55	46	38	31
	200	71	62	53	44	37	95	91	84	76	67	46	38	31	25	20	78	69	60	51	43
40	600	18	14	11	9	7	38	31	25	20	16	9	7	6	4	3	21	17	13	10	8
	500	25	20	16	13	10	50	42	34	28	23	13	10	8	6	5	29	24	19	15	12
	400	34	28	22	18	14	64	55	46	38	31	19	15	12	9	7	40	33	26	21	17
	300	46	38	31	25	20	78	69	60	51	42	26	21	17	13	11	52	44	36	30	24
	200	59	50	42	35	28	89	82	74	65	55	36	29	24	19	15	66	57	48	40	33
30	600	13	10	8	6	5	29	23	19	15	12	7	5	4	3	3	16	12	10	8	6
	500	19	15	12	9	7	39	32	26	21	17	10	8	6	5	4	22	18	14	11	9
	400	26	21	17	13	11	52	44	36	29	24	14	11	9	7	5	31	25	20	16	13
	300	36	29	24	19	15	66	57	48	40	33	20	16	13	10	8	41	34	28	22	18
	200	48	40	33	27	21	80	71	62	53	44	28	22	18	14	11	54	46	38	31	25
20	600	10	8	6	5	4	22	18	14	11	9	5	4	3	2	2	12	9	7	6	4
	500	14	11	9	7	5	30	25	20	16	13	7	6	4	3	3	16	13	10	8	6
	400	20	16	12	10	8	41	34	28	22	18	10	8	6	5	4	23	19	15	12	9
	300	27	22	18	14	11	54	46	38	31	25	15	12	9	7	6	32	26	21	17	13
	200	38	31	25	20	16	68	59	50	42	35	21	17	13	10	8	43	36	29	24	19

SO_2 at rest (%)

Color scale for 5-years mortality:

≤10% (10%-20%] (20%-30%] (30%-40%] (40%-50%] (50%-60%] >60%

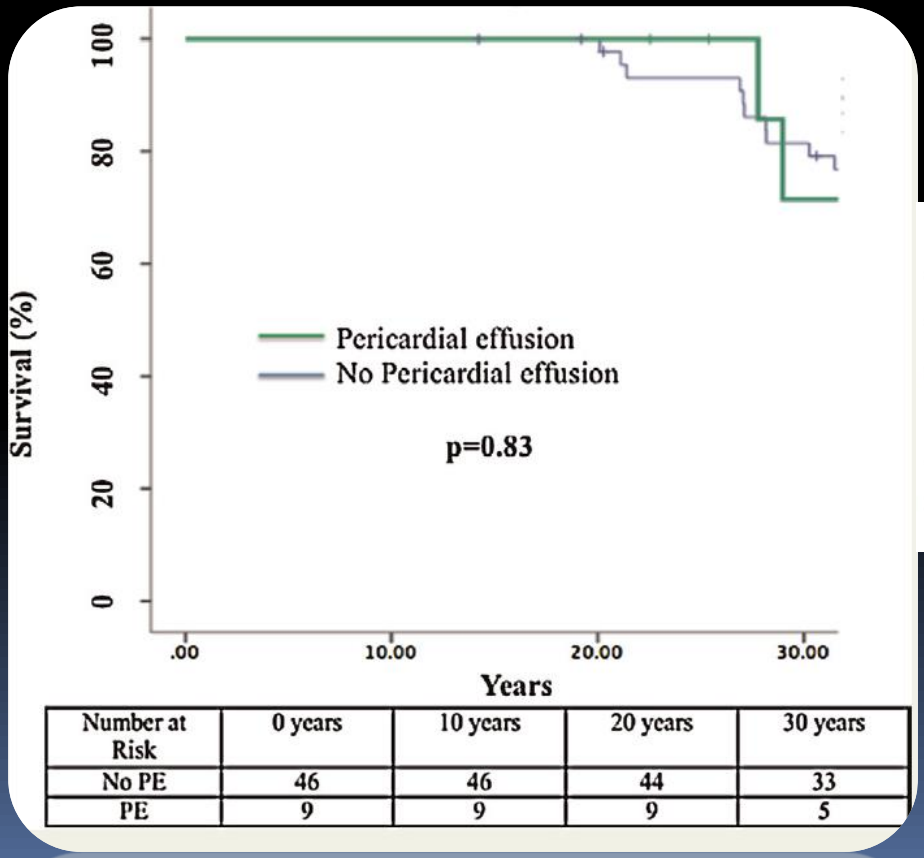
Data from Kempny et al, Circulation 2017

Heart, Lung and Circulation (2018) **27**, 394–396
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2017.05.141

BRIEF COMMUNICATION

The Echocardiographic Characteristics and Prognostic Significance of Pericardial Effusions in Eisenmenger Syndrome

Clare Arnott, MBBS [a,b], Rachael Cordina, PhD [a,b], David S. Celermajer, DSc [a,b*]



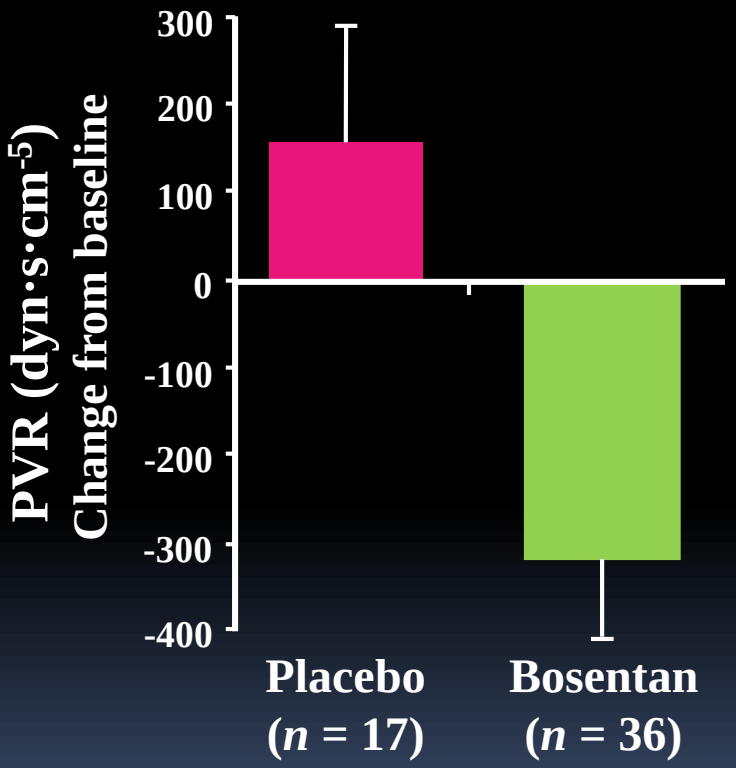
Number at Risk	0 years	10 years	20 years	30 years
No PE	46	46	44	33
PE	9	9	9	5

Statistical Analysis

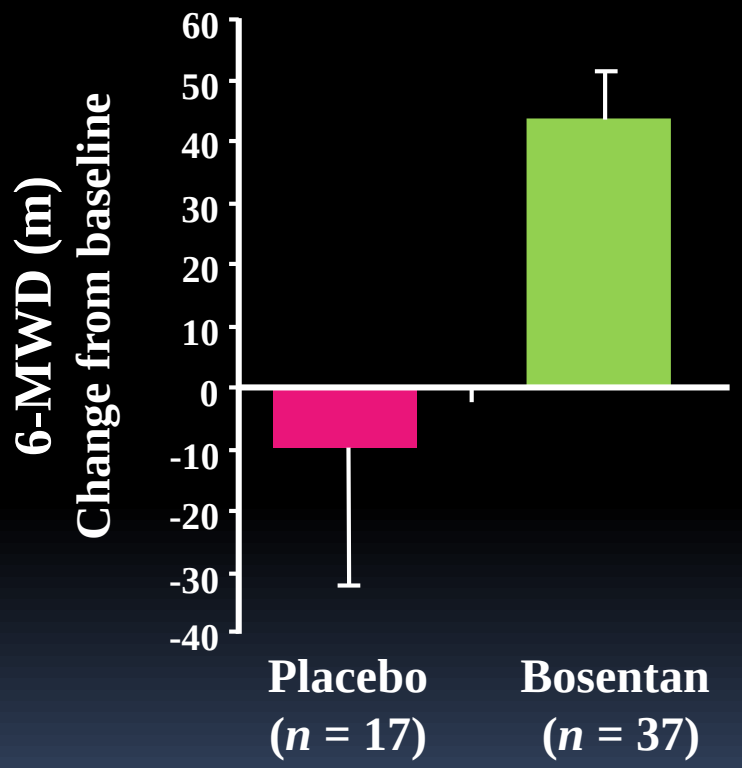
Data was analysed using SPSS version 22.0 (IBM, New York, USA). Comparisons between groups were undertaken using Chi^2 for categorical data. A two-tailed p-value of <0.05 was considered statistically significant. Survival analysis for mortality was estimated using Kaplan-Meier survival curves and Cox proportional hazard models [7].

BREATHE-5: Reduced PVR and increased 6-MWD

TE = -472 dyn·s·cm^{-5}, p = 0.038

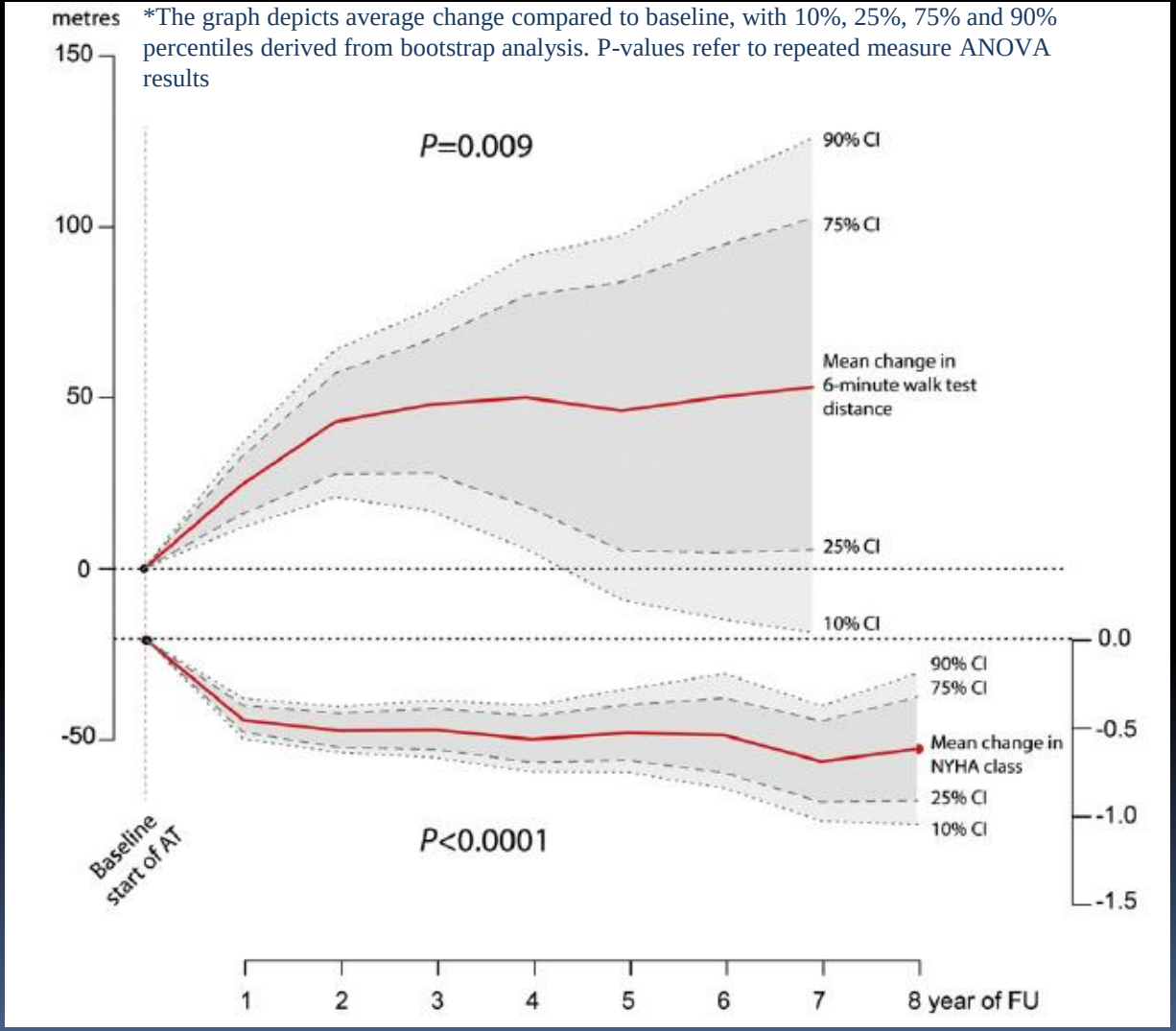


TE = 53.1 m, p = 0.008



Galiè N, *et al. Circulation* 2006; 114:48-54.

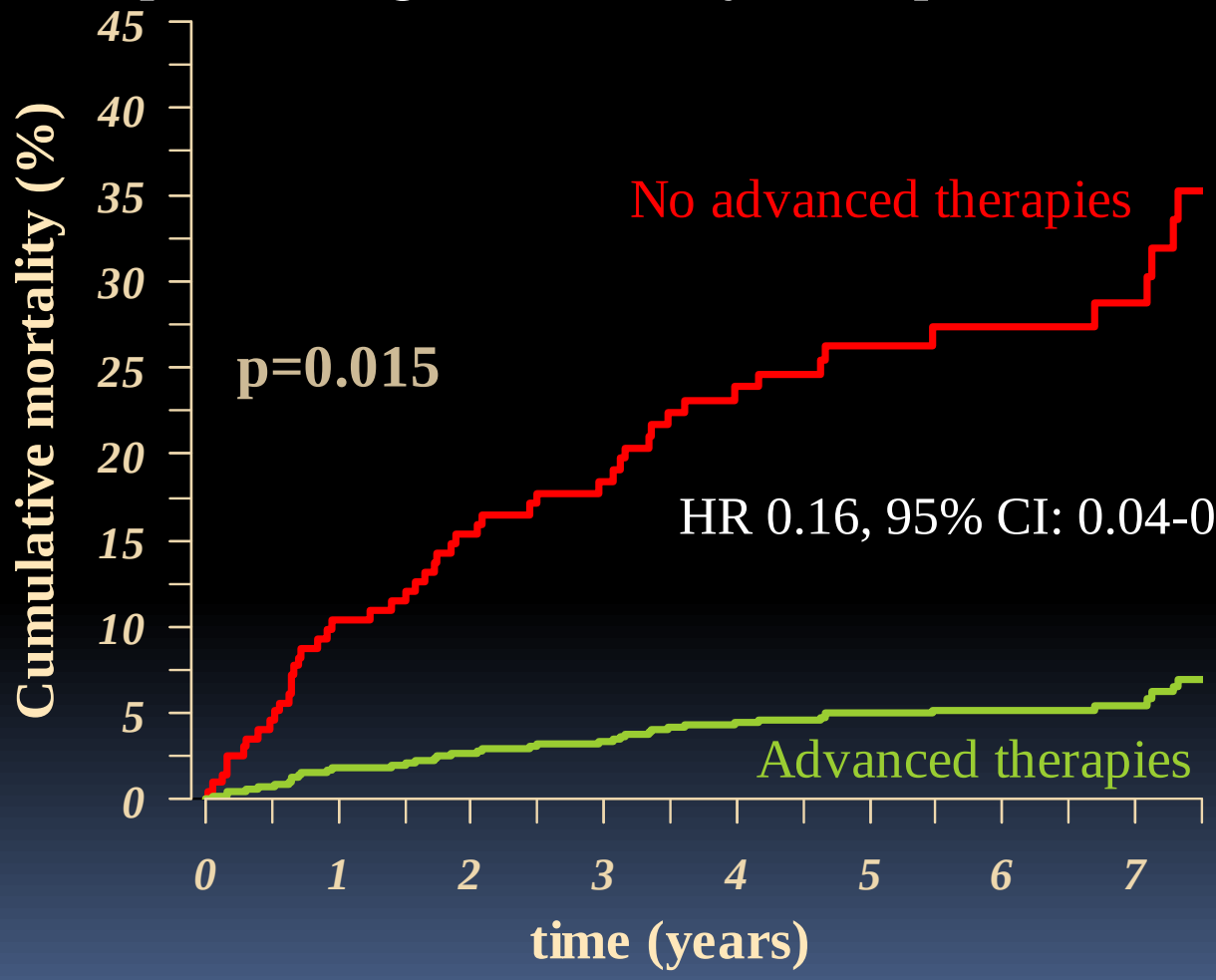
Long-term effect of PAH-advanced therapies in Eisenmenger patients



Diller GP, *et al. Int J Cardiol* 2012.

PAH advanced therapies are associated with an improved outcome in Eisenmenger patients

A retrospective, single-centre study in 229 patients with ES

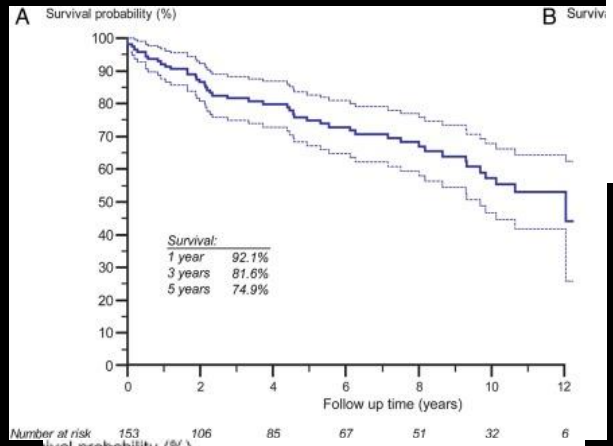


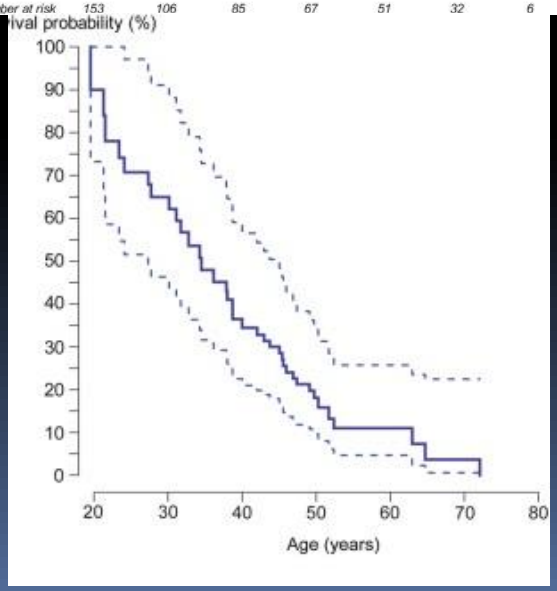
Dimopoulos K, Inuzuka R, *et al. Circulation* 2010; 121:20-5.

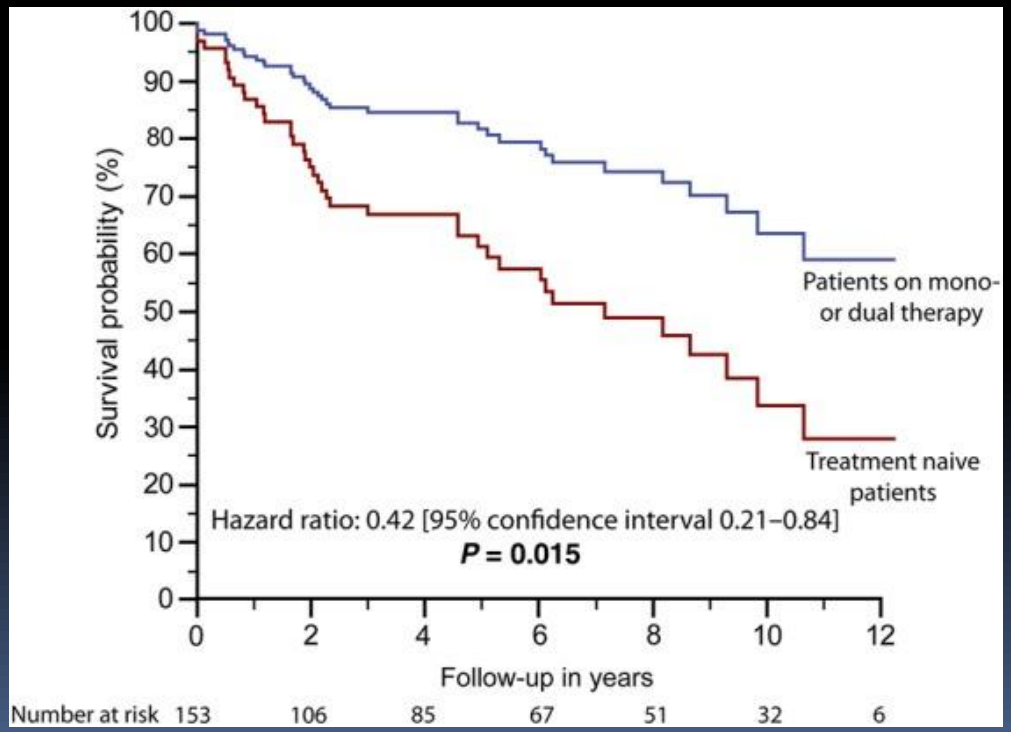
European Heart Journal (2016) **37**, 1449–1455
doi:10.1093/eurheartj/ehv743

Current therapy and outcome of Eisenmenger syndrome: data of the German National Register for congenital heart defects

Gerhard-Paul Diller[1,2]*, Marc-André Körten[3], Ulrike M.M. Bauer[2,3], Oliver Miera[4], Oktay Tutarel[2,5], Harald Kaemmerer[2,6], Felix Berger[2,4], Helmut Baumgartner[1,2], and German Competence Network for Congenital Heart Defects Investigators







Archives of Cardiovascular Disease (2017) 110, 303–316

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

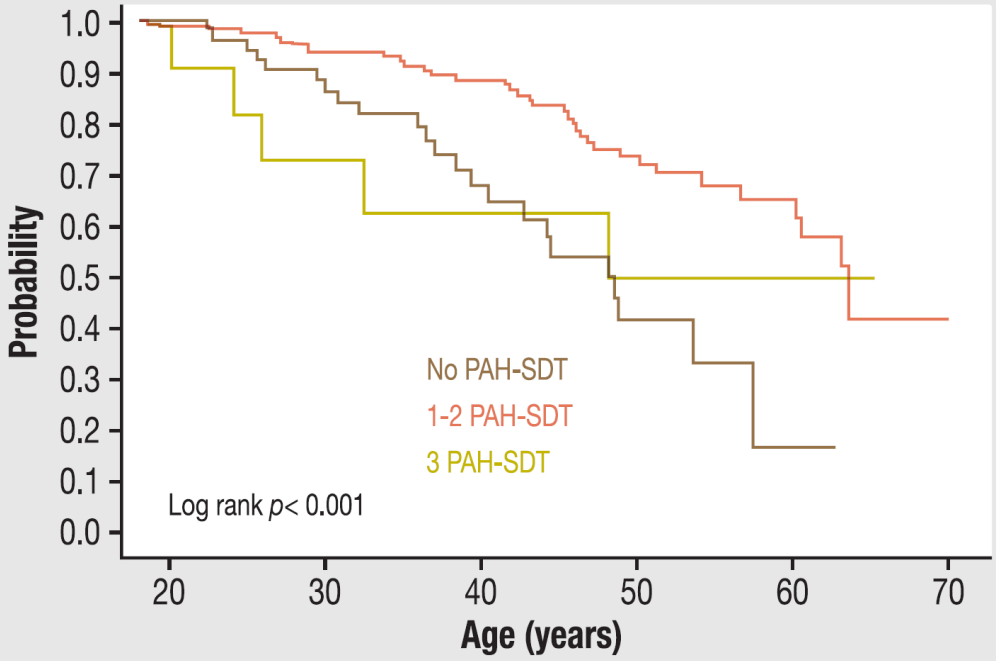
CLINICAL RESEARCH

Outcome of adults with Eisenmenger syndrome treated with drugs specific to pulmonary arterial hypertension: A French multicentre study

Devenir des adultes avec syndrome d'Eisenmenger traités par médicaments spécifiques anti-hypertenseur pulmonaire : données d'une étude multicentrique française

Sebastien Hascoet[a,b,*], Emmanuelle Fournier[a,b,c], Xavier Jaïs[d,e], Lauriane Le Gloan[f], Claire Dauphin[g], Ali Houeijeh[h], Francois Godart[h], Xavier Iriart[c], Adelaïde Richard[i], Jelena Radojevic[j], Pascal Amedro[k], Gilles Bosser[l], Nathalie Souletie[m], Yvette Bernard[n], Pamela Moceri[o], Hélène Bouvaist[p], Pierre Mauran[q], Elise Barre[r], Adeline Basquin[s], Clement Karsenty[m,t,u], Damien Bonnet[v], Laurence Iserin[t,u], Olivier Sitbon[d,e], Jérôme Petit[a,b], Elie Fadel[e,w,x], Marc Humbert[d,e], Magalie Ladouceur[t,u,v]

D



Number at risk

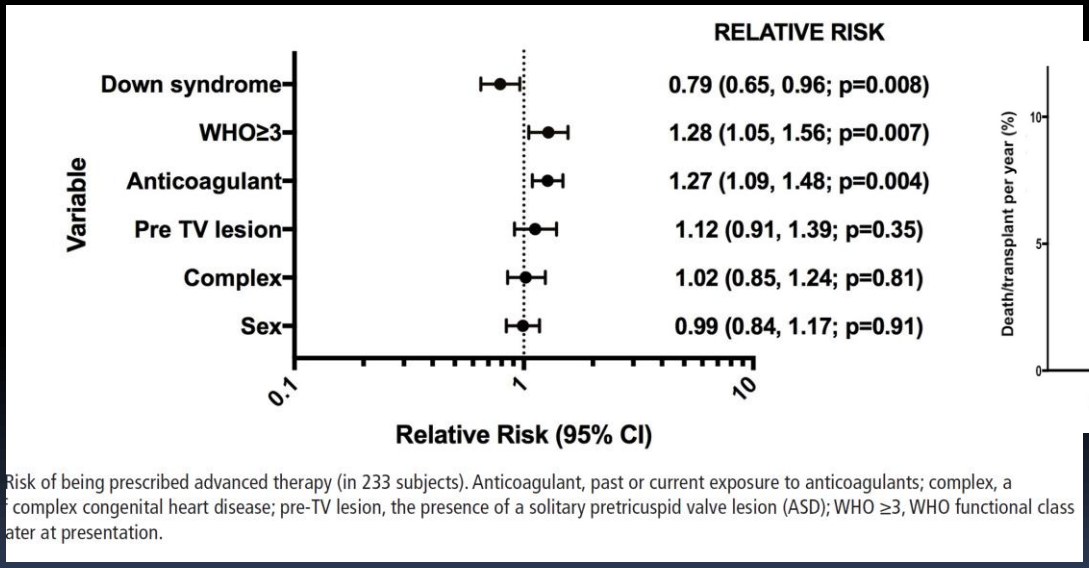
57	42	22	9	1	0
182	146	98	50	18	1
11	7	6	3	1	0

ORIGINAL RESEARCH ARTICLE

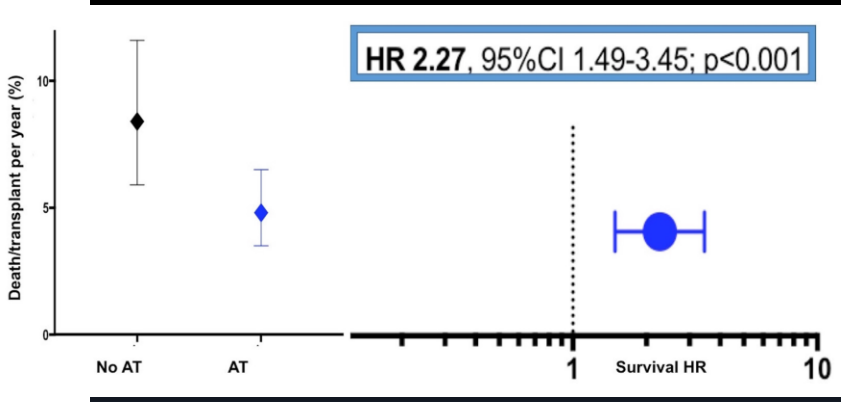
Heart 2018;**104**:732–737

Pulmonary vasodilator therapy is associated with greater survival in Eisenmenger syndrome

Clare Arnott,[1,2] Geoff Strange,[3,4] Andrew Bullock,[5,6] Adrienne C Kirby,[7] Clare O'Donnell,[8,9] Dorothy J Radford,[10,11] Leeanne E Grigg,[12,13] David S Celermajer[1,2]



Risk of being prescribed advanced therapy (in 233 subjects). Anticoagulant, past or current exposure to anticoagulants; complex, a complex congenital heart disease; pre-TV lesion, the presence of a solitary pretricuspid valve lesion (ASD); WHO ≥3, WHO functional class later at presentation.



On multivariable analysis, exposure to AT was independently associated with greater survival (survival HR 2.27, 95% CI 1.49 to 3.45; p<0.001).

MAESTRO

European Heart Journal

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Volume 38, Issue suppl_1
August 2017

Comments (0)

P5462
Evaluation c
Eisenmenge
randomised

N. Galie, M. Landzbe
M.A. Gatzoulis

European Heart Jour
https://doi.org/10.1
Published: 29 Augu

	Placebo	Macitentan	Treatment effect*
	Mean change from baseline to Week 16 (SD)		Least-square mean difference (95% CL)
6MWD, m (main study: n=226)	19.7 (53.0)	18.3 (84.4)	-4.7 (-22.8, 13.5), p=0.6120
6MWD, m (substudy: n=39)	3.5 (51.6)	34.1 (57.4)	24.9 (-9.1, 59.0)
	% of baseline at Week 16 (Geometric mean, gCV)		Geometric mean ratio (95% CL)
NT-proBNP, pg/mL (main study: n=210)	109.2 (70.5)	88.7 (57.7)	0.80 (0.68, 0.94)
PVRi, dyn·sec/cm^5/m^2 (substudy: n=39)	101.1 (21.2)	85.3 (36.1)	0.87 (0.73, 1.03)

*From ANCOVA model adjusted for treatment and baseline variables. CL, confidence limit; gCV, geometric coefficient of variation; PVRi: pulmonary vascular resistance index; SD, standard deviation.

- The primary endpoint evaluating change in 6MWD was not met.
- NT-proBNP improved
- PVRi in the haemodynamic substudy favoured macitentan.
- Macitentan was well tolerated in this patient population.

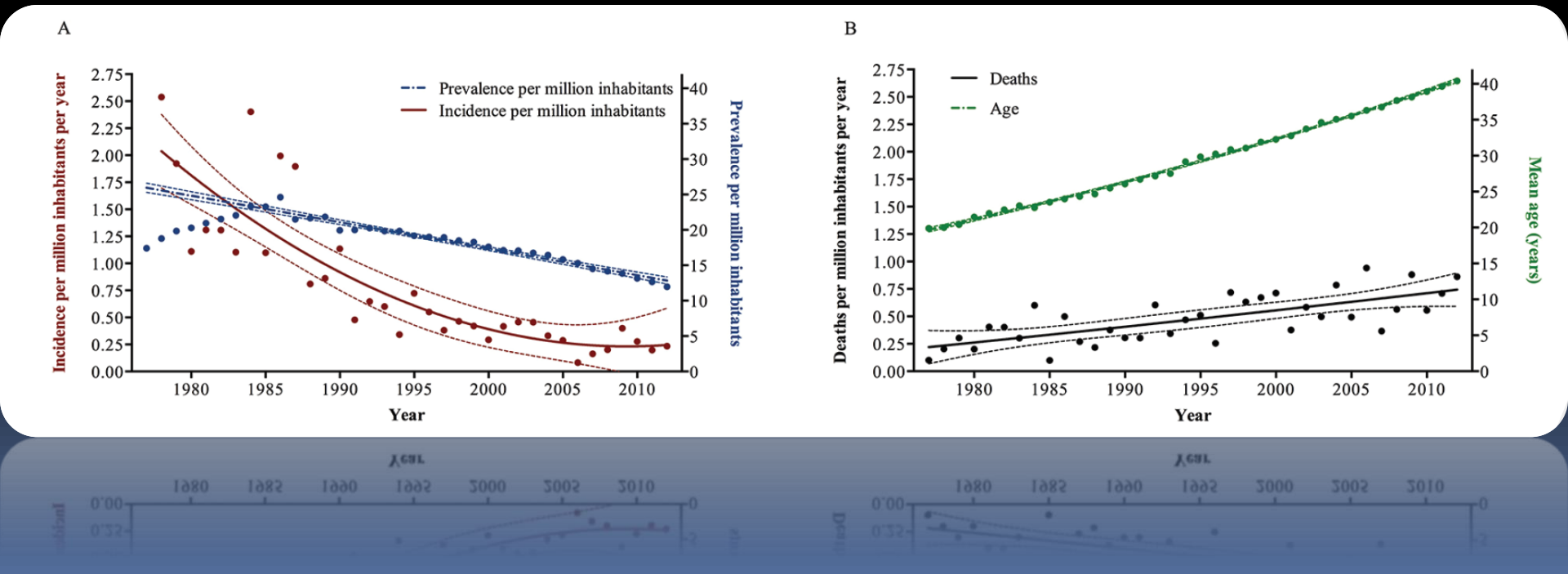
Congenital heart disease

ORIGINAL RESEARCH ARTICLE

Heart 2017;**103**:1353–1358

Epidemiological changes in Eisenmenger syndrome in the Nordic region in 1977–2012

Cristel Sørensen Hjortshøj,[1] Annette Schophuus Jensen,[1] Keld Sørensen,[2] Edit Nagy,[3] Bengt Johansson,[4] Thomas Kronvall,[5] Mikael Dellborg,[6] Mette-Elise Estensen,[7] Henrik Holmstrøm,[8] Maila Turanlahti,[9] Ulf Thilén,[10] Lars Søndergaard[1]



ORIGINAL ARTICLE

Eisenmenger syndrome and long-term survival in patients with Down syndrome and congenital heart disease

Körten M-A, *et al*. *Heart* 2016;**102**:1552–1557

Marc-André Körten,[1,2,3] Paul C Helm,[1,2,3] Hashim Abdul-Khaliq,[2,4] Helmut Baumgartner,[1,2,3,5] Deniz Kececioglu,[1,3,6] Christian Schlensak,[2,3,7] Ulrike M M Bauer,[1,2,3] Gerhard-Paul Diller,[2,3,5] Competence Network for Congenital Heart Defects Investigators

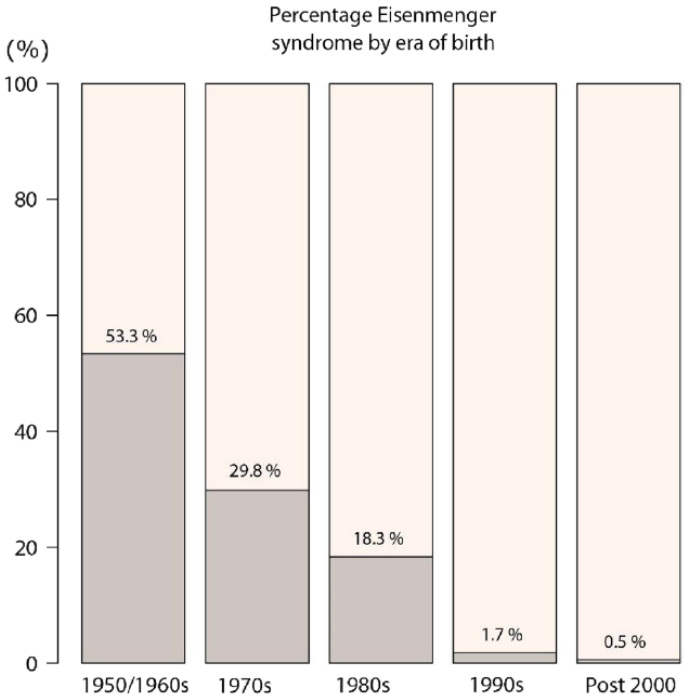
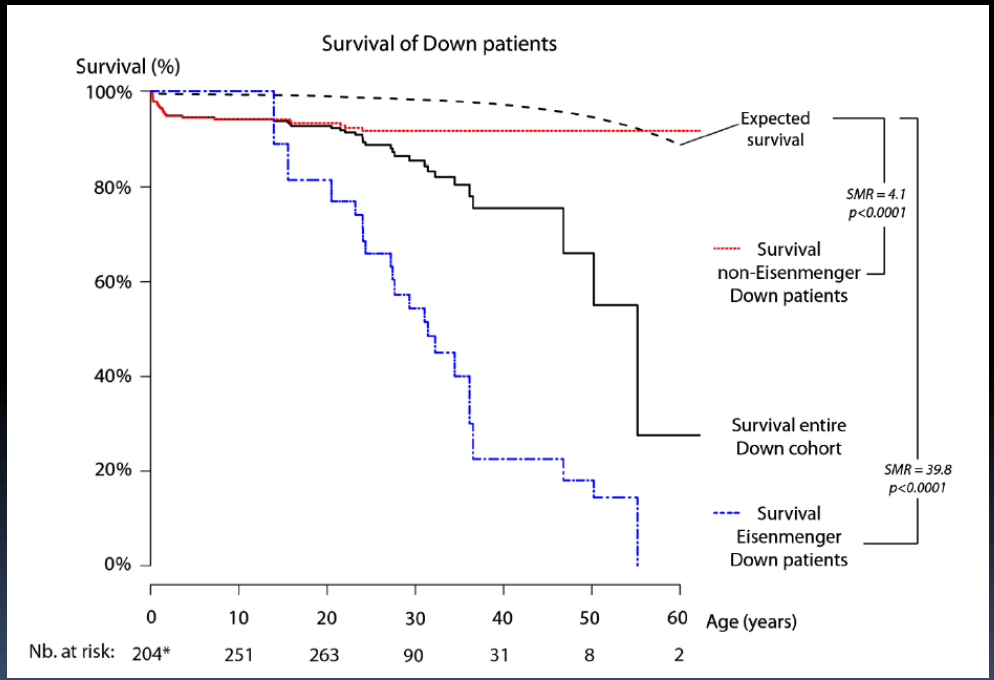
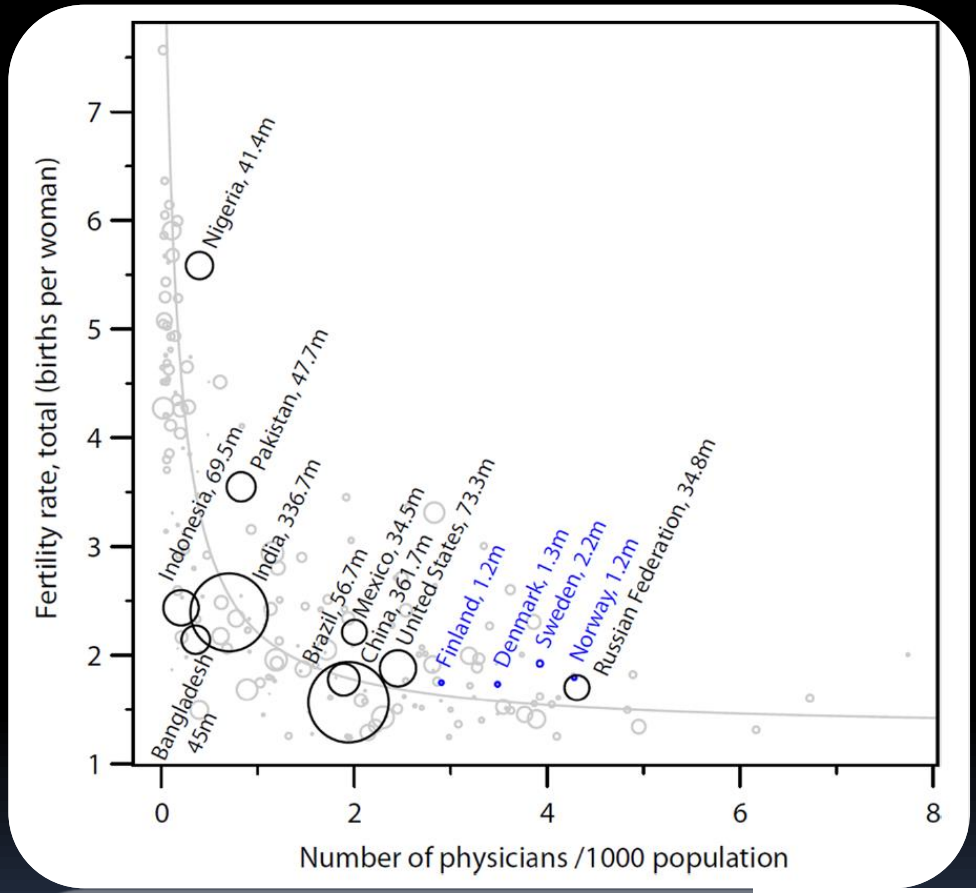


Figure 2 Percentage of patients developing Eisenmenger syndrome by era of birth.



Eisenmenger syndrome in developing countries



Declining incidence and prevalence of Eisenmenger syndrome in the developed world: a triumph of modern medicine

Kempny A, *et al*. *Heart* September 2017 Vol 103 No 17

Aleksander Kempny,[1,2] Konstantinos Dimopoulos,[1,2] Michael A Gatzoulis[1,2]

What about other types of PAH-CHD?

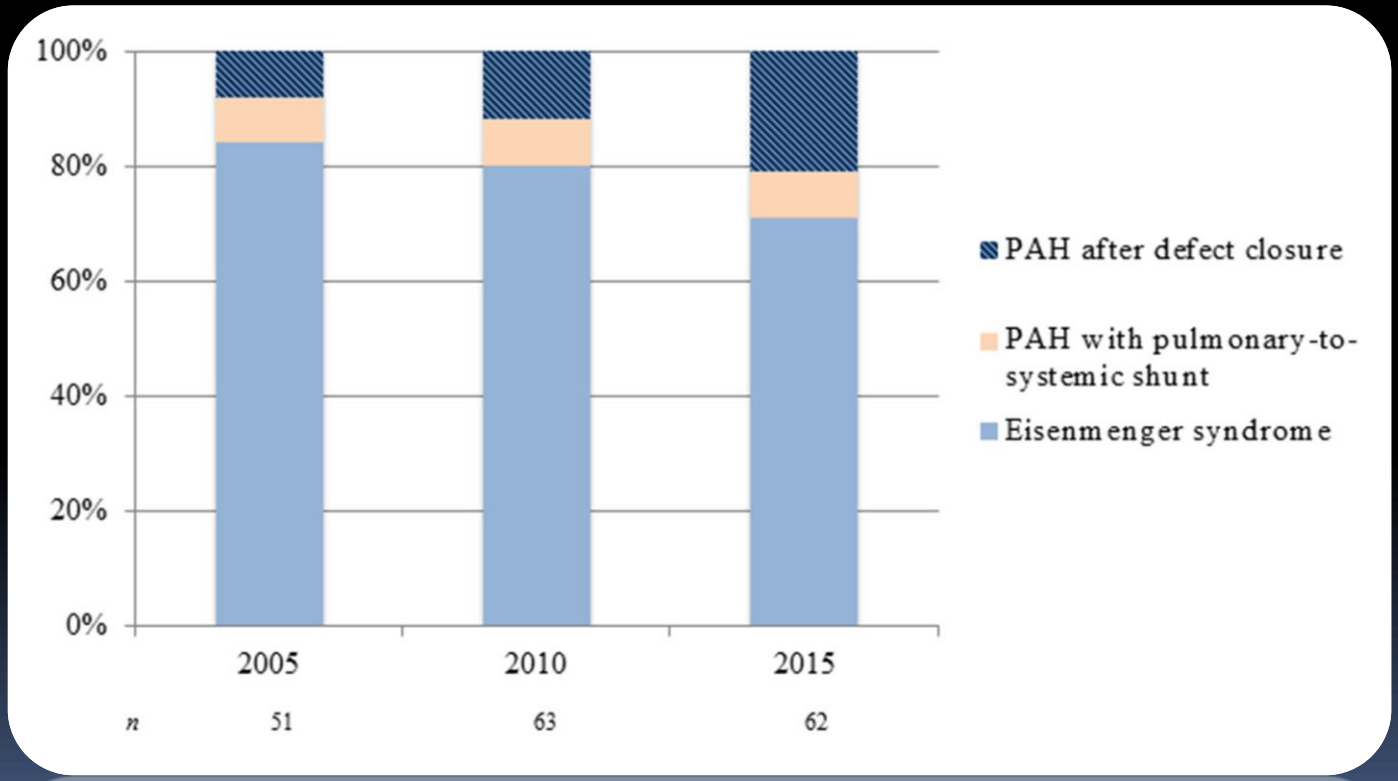
Journal of
Clinical Medicine

MDPI

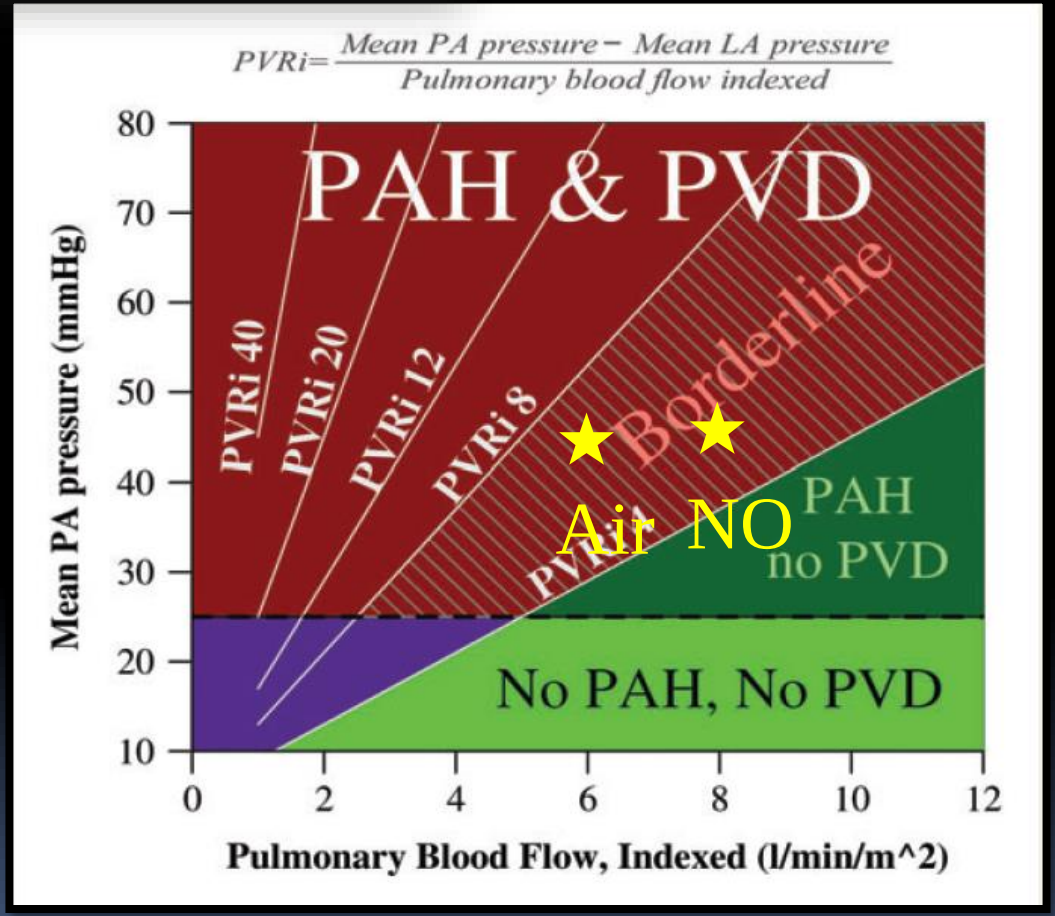
Review

The Changing Landscape of Pulmonary Arterial Hypertension in the Adult with Congenital Heart Disease

Alexandra C. van Dissel [1,2], Barbara J. M. Mulder [1,2] and Berto J. Bouma [1,*]



Age 12 years
VSD, PFO



AIR

Qp/Qs = 2
QPi 6 L/min/m^2
mPAP 44 mmHg
PVRi 6.5 WU x m^2

NO

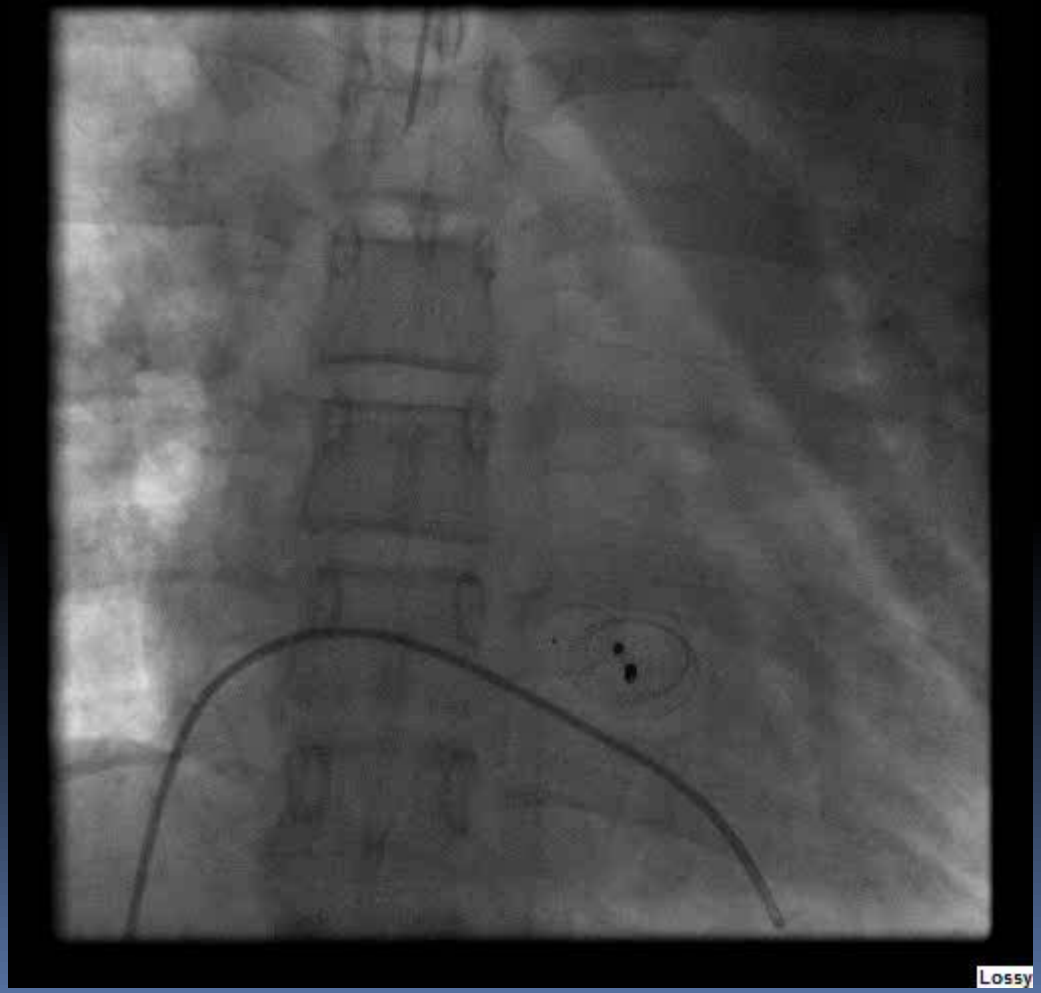
Qp/Qs = 3
Qpi 8 L/min/m^2
mPAP 44 mmHg

PVRi dropped from 6.5 to 4.8 WU x m^2

K. Dimopoulos, S.J. Wort, M.A. Gatzoulis, European Heart Journal (2014) 35, 691–700

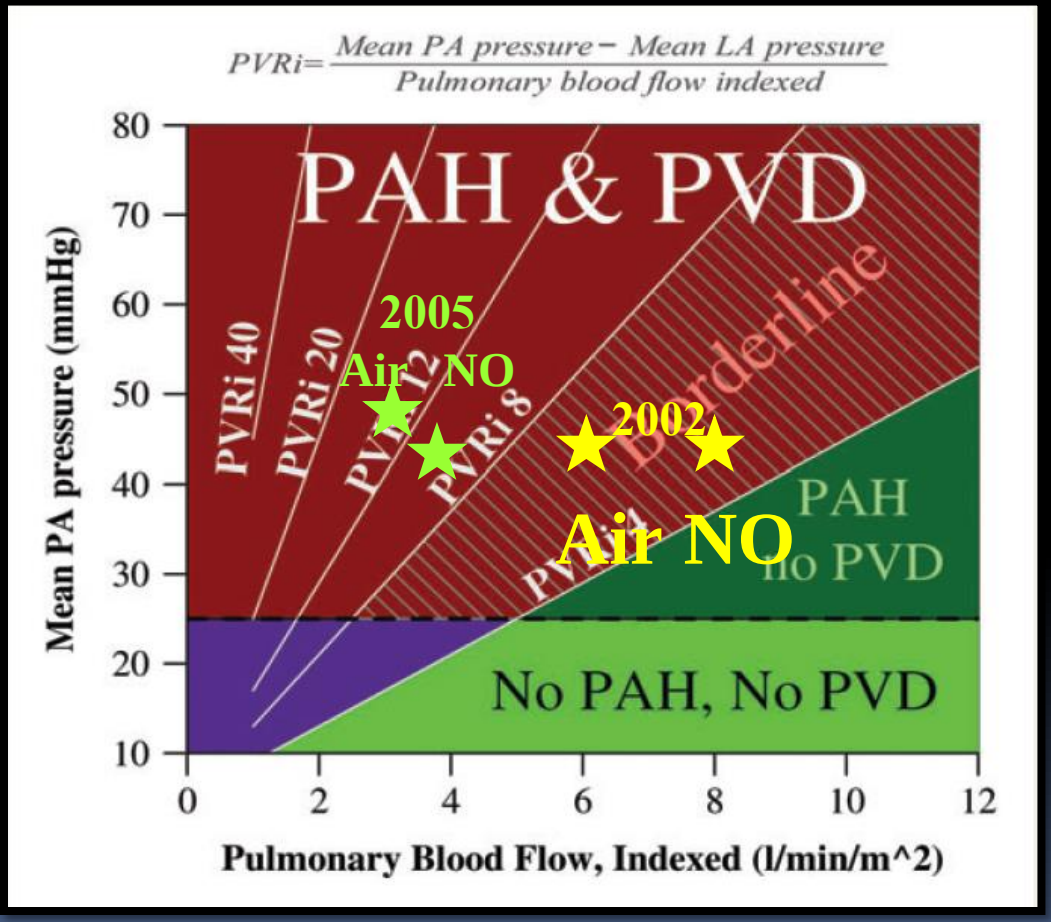
VSD closure (13 years)

14mm Amplatzer perimembranous VSD occluder



The RV pressure post-deployment
48/8 mmHg

Cardiac catheterization (15 years)



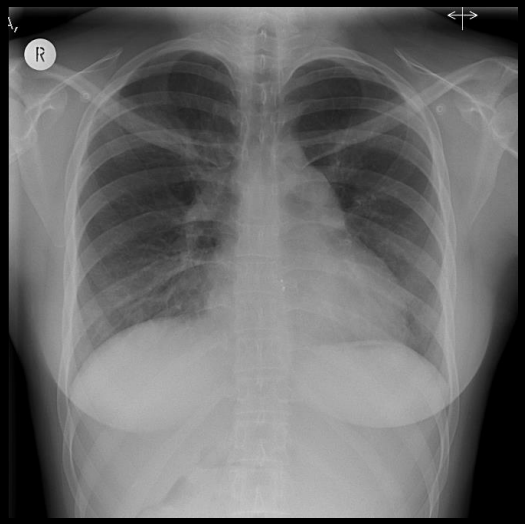
Qp/Qs = 1
Qp 3.2 L/min/m2
PVRi 13.4 WU x m2

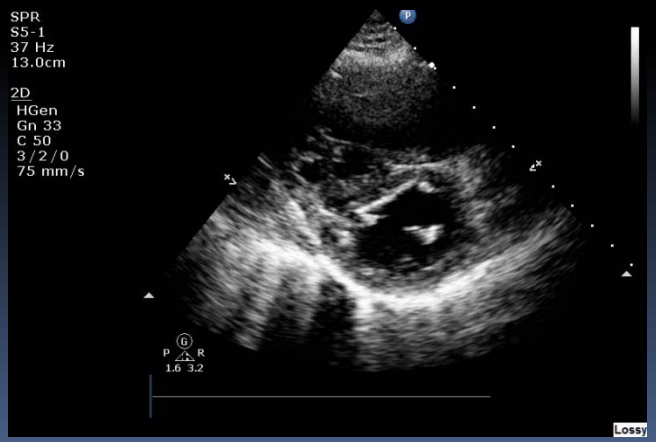
***PVRi increased from 6.5 (12y) to* 13.4 (15y) WU x m2**

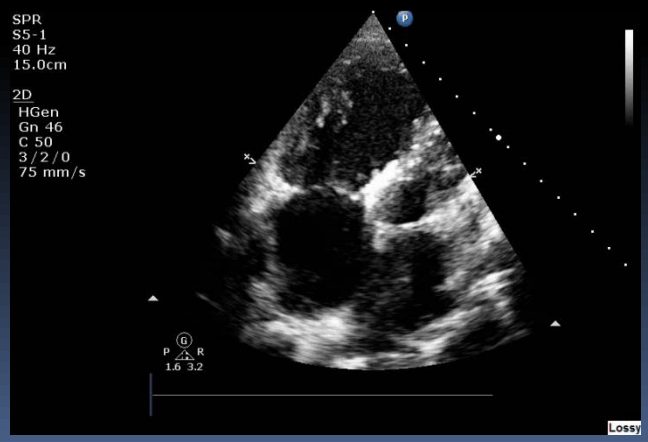
K. Dimopoulos, S.J. Wort, M.A. Gatzoulis, European Heart Journal (2014) 35, 691–700

Admission at 23 weeks of pregnancy (November 2016)

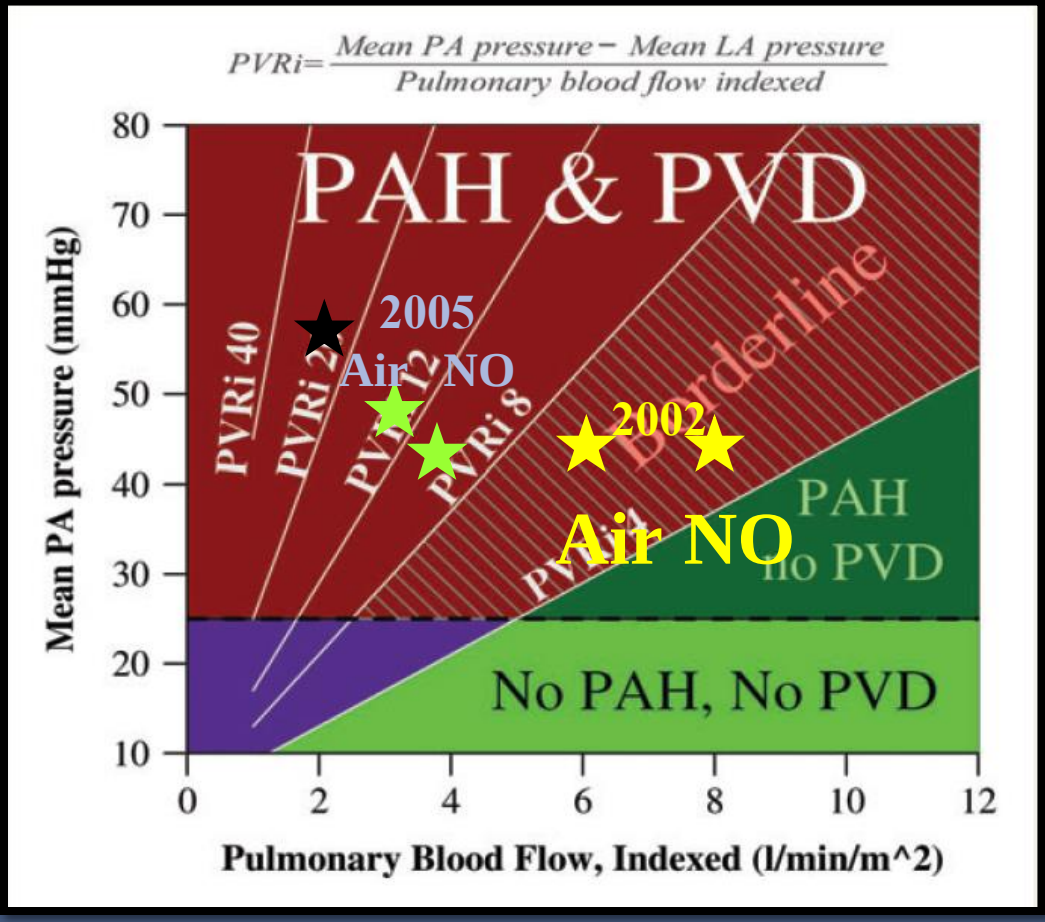
- Haemoptysis related to an **upper respiratory infection**
- Increasing SOB
- Presyncope on effort
- AICU for advanced monitoring
- IV epoprostenol* and escalation of therapy by 1-2ng/kg/min according to tolerance
- Required respiratory support with CPAP and high flow O_2







Cardiac catheter 3 months post partum



Qp/Qs 0.67, PVR 16 WU, **PVRi 26**

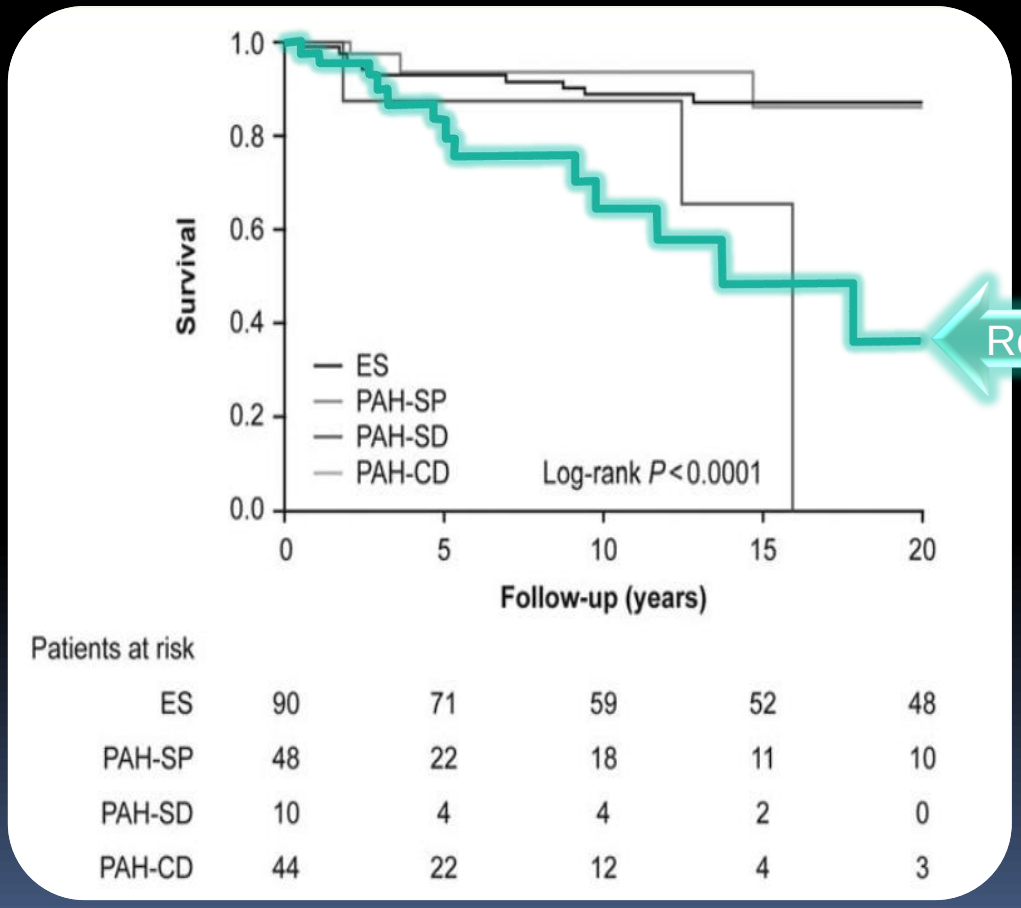
TRIPLE THERAPY

CONTRACEPTION

TRANSPLANTATION

K. Dimopoulos, S.J. Wort, M.A. Gatzoulis, European Heart Journal (2014) 35, 691–700

DO NOT close defects in established pulmonary vascular disease



Patients at risk					
ES	90	71	59	52	48
PAH-SP	48	22	18	11	10
PAH-SD	10	4	4	2	0
PAH-CD	44	22	12	4	3

Repaired defects

European Heart Journal Advance Access published March 1, 2013

European Heart Journal
doi:10.1093/eurheartj/eht072

CLINICAL RESEARCH

Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups

Alessandra Manes, Massimiliano Palazzini, Enri Leci, Maria L. Bacchi Reggiani, Angelo Branzi, and Nazzareno Galiè*

"Treat and repair"

ELSEVIER

International Journal of Cardiology 129 (2008) 163–171

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Review

Evaluating operability in adults with congenital heart disease and the role of pretreatment with targeted pulmonary arterial hypertension therapy

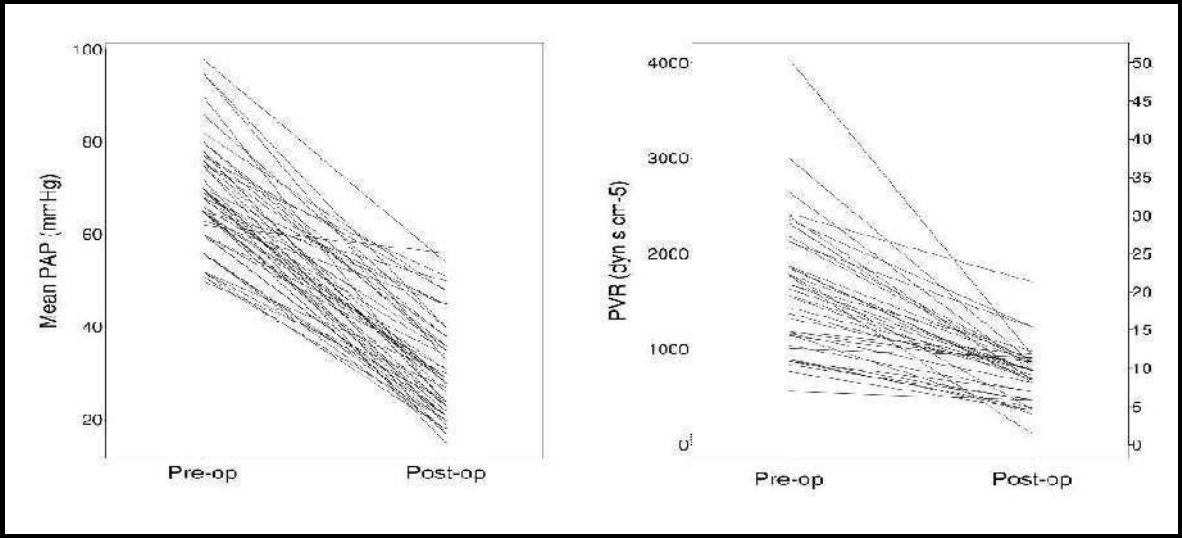
Konstantinos Dimopoulos *, Ana Peset, Michael A. Gatzoulis

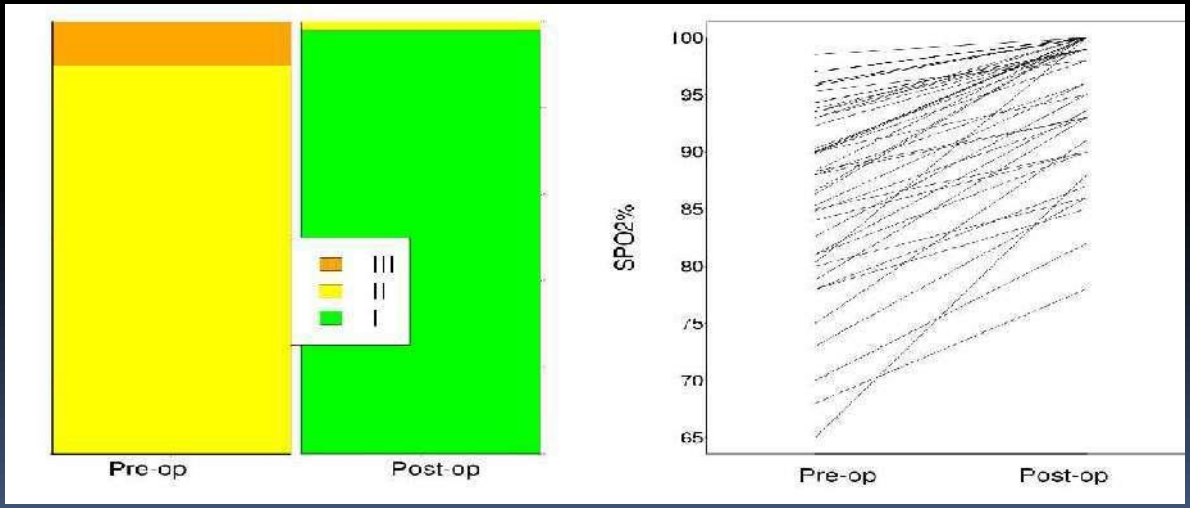
Abstract

Pulmonary arterial hypertension (PAH) associated with congenital heart disease remains a major problem despite advances in cardiac surgery. Recently, advanced therapies for PAH have become available and have been effective in reducing pulmonary vascular resistance and symptoms in patients with near-systemic pulmonary arterial pressures, previously thought to have irreversible pulmonary vascular disease. This has led to a new dilemma, namely could intracardiac communications previously considered inoperable due to severe pulmonary vascular disease become amenable to surgery after successful treatment with advanced therapy? We address, hereby, the potential merits and hazards of a "treat-and-repair" approach using advanced therapies in patients with PAH associated with congenital heart disease.

IN 2017: THERE IS STILL NO EVIDENCE FOR TREATING WITH PAH THERAPIES AND REPAIRING PREVIOUSLY INOPERABLE DEFECTS.

Repair of defects previously considered non-repairable





Huang et al. IJC 2010

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Pediatric Cardiology and Adult Congenital Heart Disease

Treat and Repair Strategy in Patients With Atrial Septal Defect and Significant Pulmonary Arterial Hypertension

Yasufumi Kijima, MD, PhD; Teiji Akagi, MD, PhD; Yoichi Takaya, MD, PhD; Satoshi Akagi, MD, PhD; Koji Nakagawa, MD, PhD; Kengo Kusano, MD, PhD; Shunji Sano, MD, PhD; Hiroshi Ito, MD, PhD

Circ J. 2016;80(1):227-34. doi: 10.1253/circj.CJ-15-0599. Epub 2015 Nov 13.

Treat and Repair Strategy in Patients With Atrial Septal Defect and Significant Pulmonary Arterial Hypertension.

Kijima Y[1], Akagi T, Takaya Y, Akagi S, Nakagawa K, Kusano K, Sano S, Ito H.

Author information

Abstract

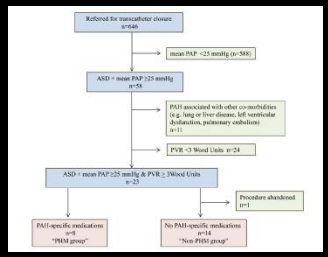
BACKGROUND: A therapeutic strategy in patients with atrial septal defect (ASD) and significant pulmonary arterial hypertension (PAH) remains controversial. This study aimed to assess the effect of PAH-specific medications and subsequent transcatheter shunt closure (ie, a treat and repair strategy) in these patients.

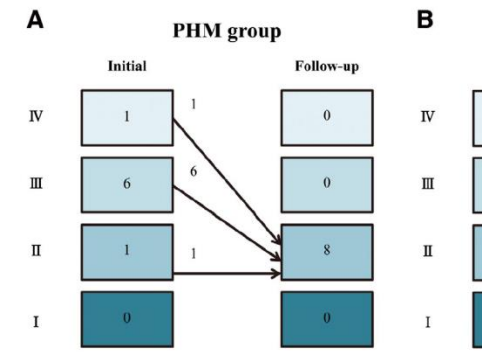
METHODS AND RESULTS: Among 646 patients with ASD, 22 patients (mean age of 56±20 years) who had PAH [mean pulmonary artery pressure ≥25 mmHg and pulmonary vascular resistance (PVR) ≥3 Wood units] underwent successful transcatheter ASD closure. Prior to the procedure, 8 patients received PAH-specific medications (PHM group) and 14 patients did not (non-PHM group). Initially, the PHM group had higher PVR compared with non-PHM group (9.6±3.8 vs. 4.2±1.0 Wood units, P<0.01). After treatment with PAH-specific medications, PVR in this group decreased to 4.0±0.8 Wood units (P<0.01). No adverse events were observed in either the PHM or non-PHM group during or after the transcatheter procedure. In the PHM group, during a treatment period of 52±48 months, the World Health Organization Functional Classification significantly improved (3.0±0.5 to 2.0±0.0, P<0.01), as well as in the non-PHM group (2.1±0.6 to 1.5±0.5, P<0.01).

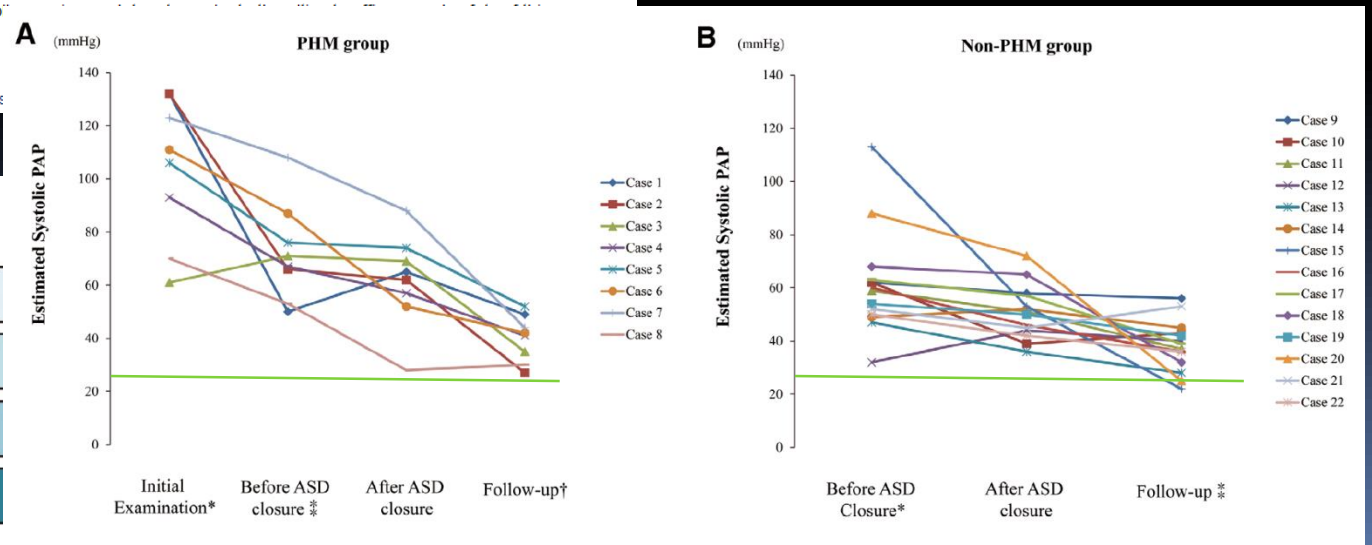
CONCLUSIONS: Treat and repair strategy provided substantial improvement and no worsening of the WHO-FC, even in patients with ASD and significant PAH. Long-term hemodynamic fo… strategy.

Comment in

"Treat-and-Repair" Strategy for Atrial Septal Defect and As…







Case Report

Pulmonary Circulation

Pushing the envelope: a treat and repair strategy for patients with advanced pulmonary hypertension associated with congenital heart disease

Rebecca Johnson Kameny[1], Elizabeth Colglazier[1], Hythem Nawaytou[1], Phillip Moore[1], V. Mohan Reddy[2], David Teitel[1] and Jeffrey R. Fineman[1]

[1]Department of Pediatrics, University of California San Francisco, San Francisco, CA, USA; [2]Department of Surgery, University of California San Francisco, San Francisco, CA, USA

Table 1. Cardiac catheterization data for Patient EJ.

Late diagnosis of theTGA VSD

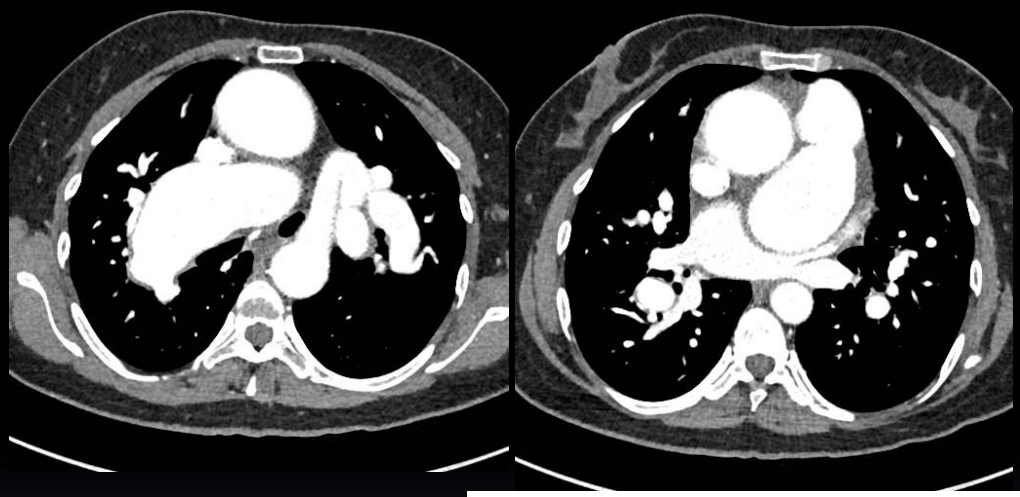
Age	PAH-specific therapies	Condition	PAP (Sys/Dia/Mean, mmHg)	PVRi (WU/m^2)	CI ($mL/min/m^2$)	Qp:Qs	Systemic O2 Sat (%)	PVR:SVR
5 years 1 month	Sildenafil, oxygen	FiO_2 1.0, iNO 20 ppm	55/35/m45	7		0.76:1	60	0.92
5 years 8 months	Sildenafil, bosentan, treprostinil, oxygen	2L NC oxygen	38/13/m24	2.1-2.8	3.8	1.8:1	81	0.2
6 years 3 months	Sildenafil, bosentan,	Room air	26/11/m17	2.2	3.3	1:1	96	0.16

Table 2. Cardiac catheterization data for Patient AT.

Hyploplastiic L Heart+PVD

Age	PAH-specific Tx	Condition	LAP mmHg	Qp $L/min/m^2$	Qp left lung	LPAP mmHg	PVRi left lung (WU/m^2)	Qp right lung	RPAP mmHg	PVRi right lung (WU/m^2)	PVRi total (WU/m^2)
8 months –after atrial stent	None	Intubated FiO_2 0.50	15	3.58	2.18	54	17.86	1.40	40	17.91	8.94
10 months	Bosentan, treprostinil oxygen	Intubated FiO_2 0.21	12	4.00	2.44	35	9.43	1.56	23	7.05	4.03
11 months	Bosentan, treprostinil oxygen	Intubated FiO_2 0.21	12	2.51	1.53	32	13.06	0.98	19	7.15	4.62
		FiO_2 1.0, iNO 40 ppm	12	3.38	2.06	28	7.76	1.32	15	2.28	1.76
15 months – post Glenn	Sildenafil, bosentan, treprostinil oxygen	FiO_2 0.21	14	1.54		19			19		3.25
		Post-coil collaterals, FiO_2 0.21	14	1.68		19			19		2.98

Other types of PAH-CHD



Segmental PH:
ToF Complex
Pulmonary Atresia

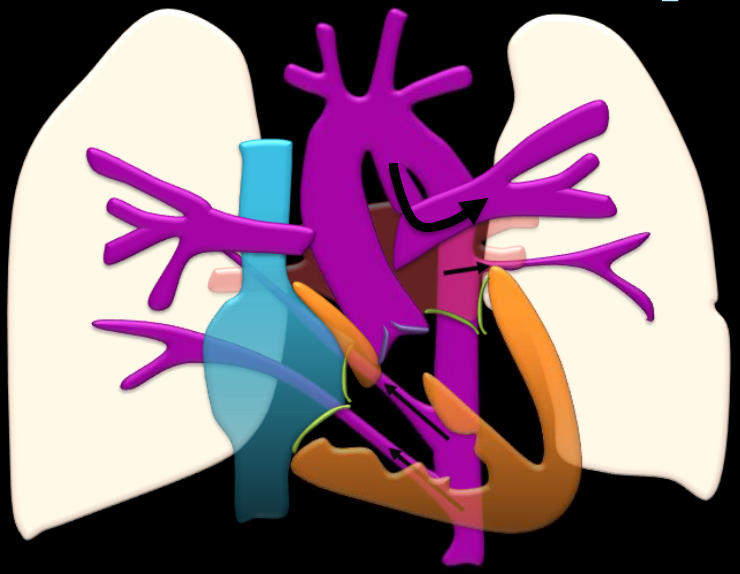
The Definition and Management of Segmental Pulmonary Hypertension

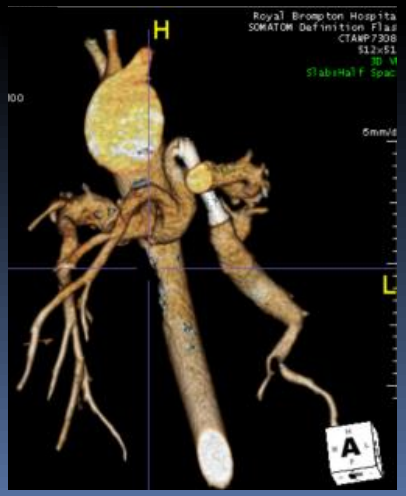
Accepted JAHA 2018

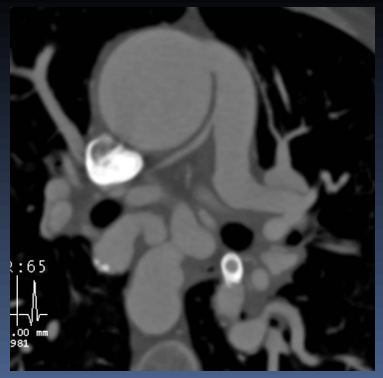
Dimopoulos K MD MSc PhD FESC[1], Diller GP MD PhD FESC [2], Opotowsky AR MD, MPH, MMSc[3], D'Alto M MD PhD FESC [4], Gu H MD PhD [5], Giannakoulas G MD PhD[6], Budts W MD PhD FESC[7], Broberg CS MD[8], Veldtman G FRCP, MBChB [9], Swan L MBChB, FRCP, MD[1], M Beghetti MD FESC [10], Gatzoulis MA MD PhD FESC FACC[1]

Example of segmental PH

Complex pulmonary atresia







- Complex pulmonary atresia
- Large PDA to upper LPA
- Small MAPCA to mid L lung
- MAPCA to R lung
- PH in left upper lung/R lung?
- How do you calculate PVR?
- PAH therapies?

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European Heart Journal
doi:10.1093/eurheartj/eht437

REVIEW

Clinical update

Pulmonary hypertension related to congenital heart disease: a call for action

Konstantinos Dimopoulos, Stephen John Wort, and Michael A. Gatzoulis*

- **Action 1**: identify patients with PAH-CHD lost to follow-up and those followed in non-specialist centres
- **Action 2**: screen all congenital heart disease patients thoroughly for the presence of pulmonary arterial hypertension
- **Action 3**: educate cardiologists and pulmonary hypertension physicians on the distinct features of Eisenmenger syndrome
- **Action 4**: standardize treatment, avoid pitfalls, and challenge old myths in Eisenmenger syndrome
- **Action 5**: do not close defects in Eisenmenger syndrome or other PAH-CHD with established pulmonary vascular disease: ‘I can close it’ does not mean ‘I should close it’


European Heart Journal
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REVIEW

Clinical update

Pulmonary hypertension related to congenital heart disease: a call for action

Konstantinos Dimopoulos, Stephen John Wort, and Michael A. Gatzoulis*

- **Action 6**: use PAH therapies to improve exercise capacity, quality of life, and prognosis in Eisenmenger syndrome
- **Action 7**: be inclusive of other types of PAH-CHD, beyond Eisenmenger syndrome
- **Action 8**: explore the concept of a 'permissive' trait genotype in patients with large ASDs who develop out-of-proportion pulmonary arterial hypertension and Eisenmenger syndrome
- **Action 9**: promote clinical research and collaboration between specialist centres on areas of controversy and lack of evidence
- **Action 10**: support care of pulmonary arterial hypertension related to congenital heart disease patients in the developing world

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Thank you!