How to use pulmonary vasodilators in patients with severe pulmonary hypertension/ Eisenmenger syndrome

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Department of Pediatrics,
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APCASH, Sep 7, 2013

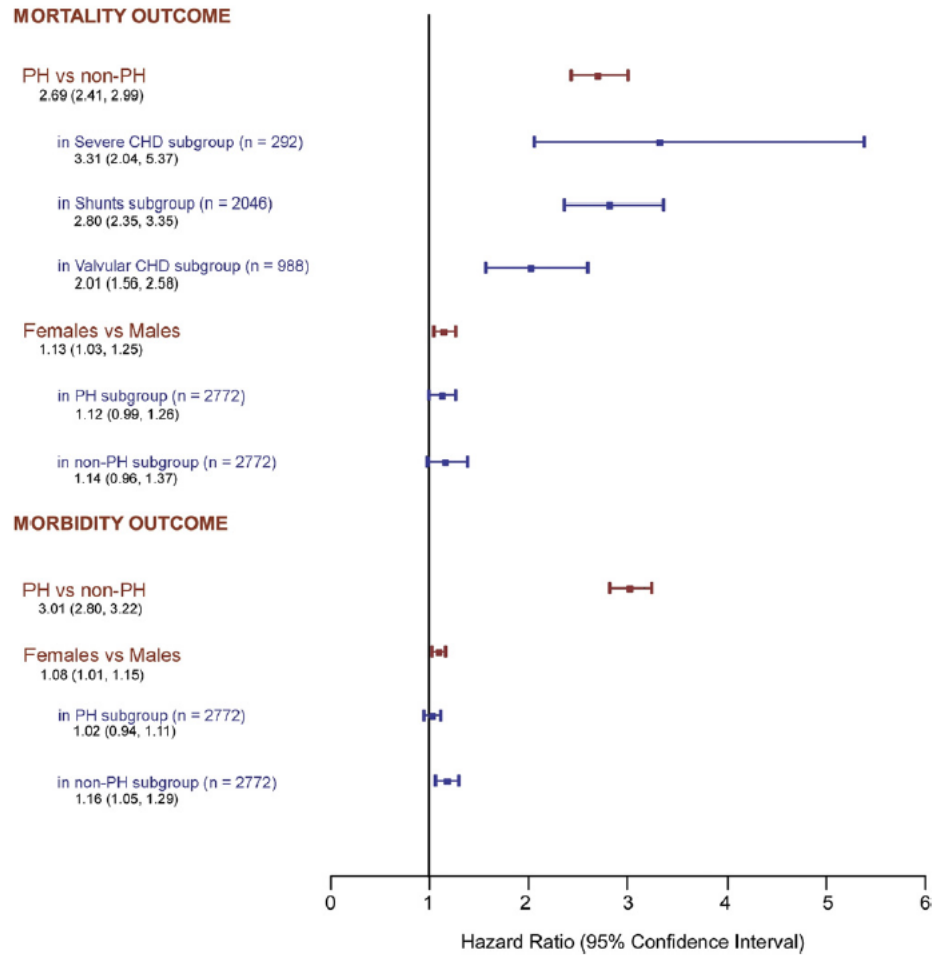


Figure 2 **HRs for Mortality and Morbidity in Adults With CHD With and Without PH**

The pooled effects of PH and sex are from the same model, while sex effects in the PH and no-PH groups are from stratified models. The figure depicts increased risk for all-cause mortality and morbid complications (represented by a hazard ratio [HR] >1) with similar risk to men and women with PH. Abbreviations as in Figure 1.

Left-to-right shunt

↓

Increased pulmonary blood flow
(shear stress/circumferential stretch)

↓

Endothelial dysfunction and vascular remodeling
Smooth muscle cell proliferation, increase in extracellular matrix, intravascular thrombosis

↓

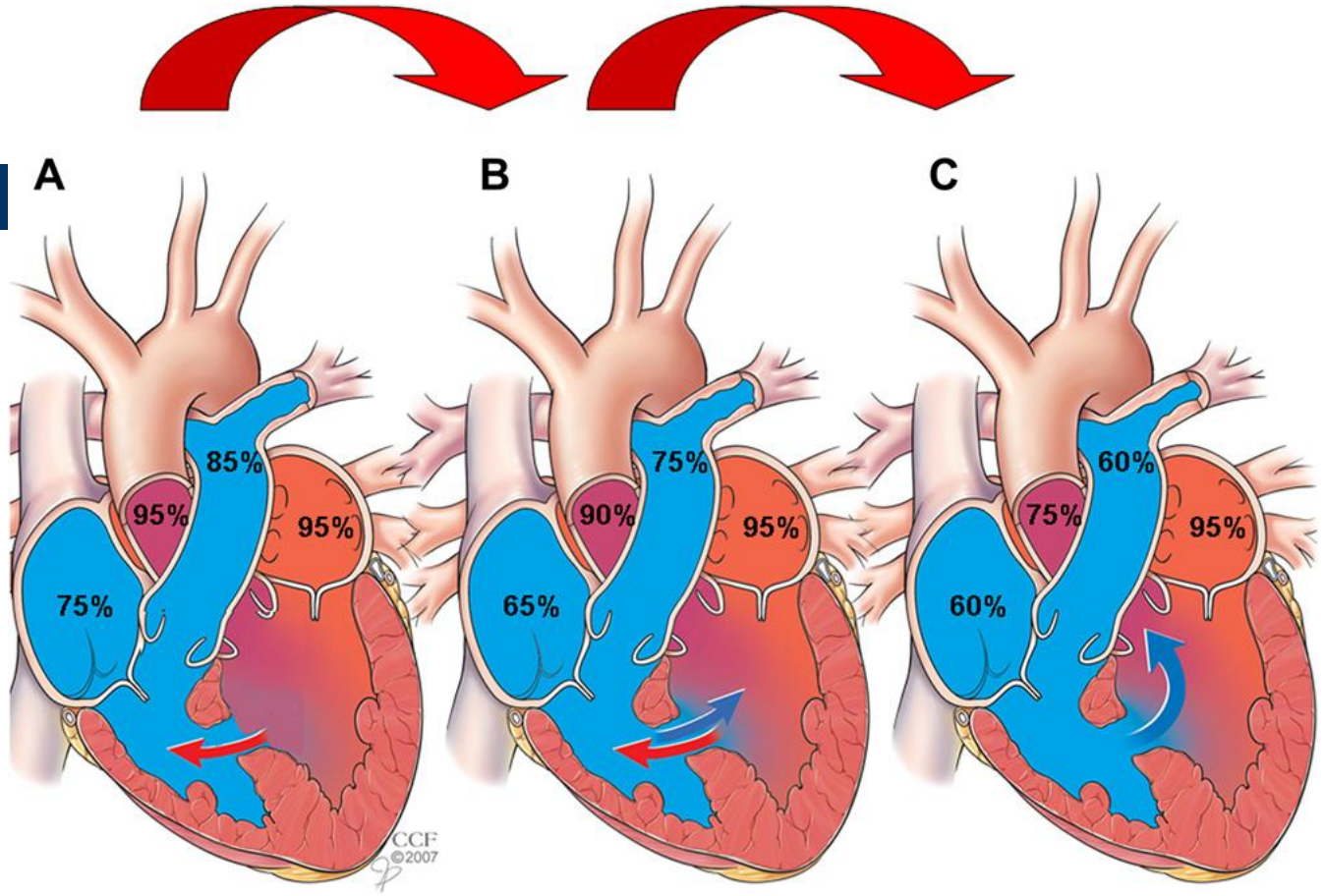
Increase in PVR

↓

Inverted shunt: right-to-left

↓

Cyanosis (Eisenmenger syndrome)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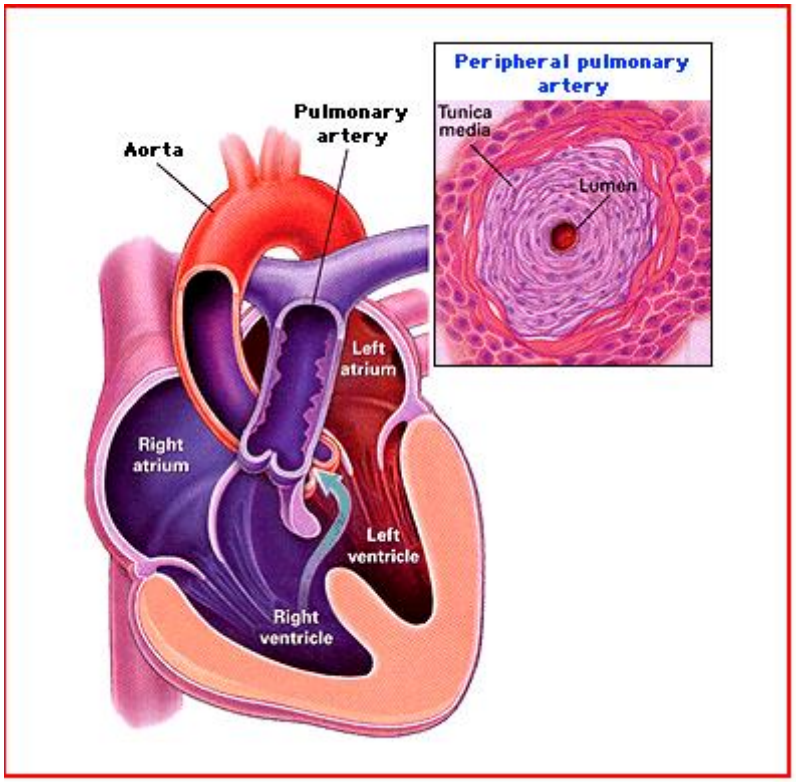
Eisenmenger syndrome



Eisenmenger syndrome

- associated with "L → R shunt"
  congenital heart disease
- most advanced form of pulmonary hypertension

- Inverted shunt R → L

Severe pulmonary hypertension / Eisenmenger syndrome

- Inoperable vs. operable
- Safe upper limit?

  *PVR <6 wood units, PVR/SVR < 2/3,

  Qp/Qs > 1.5

  Grey zone ?

Can "Inoperable" Congenital Heart Defects Become Operable in Patients with Pulmonary Arterial Hypertension? Dream or Reality?

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Review

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

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Received 19 February 2008; accepted 22 February 2008
Available online 26 March 2008

Table 1

Evaluating operability of cardiac defects in adults with CHD and PAH

For	Against
– Abort right-to-left shunting	– Potential conversion of Eisenmenger physiology to iPAH physiology (and thus worse long-term outcome)
– ↓ Cerebrovascular events (stroke /abscess)	
– Prevent cyanosis	
↑ Exercise capacity	– High perioperative risk
↓ Erythrocytosis	
↓ Hemostatic problems	– Very limited experience and no long-term data available
↓ Systemic organ failure	
– Protect pulmonary circulation	

CHD = Congenital heart disease, PAH = pulmonary arterial hypertension, iPAH = idiopathic pulmonary arterial hypertension.

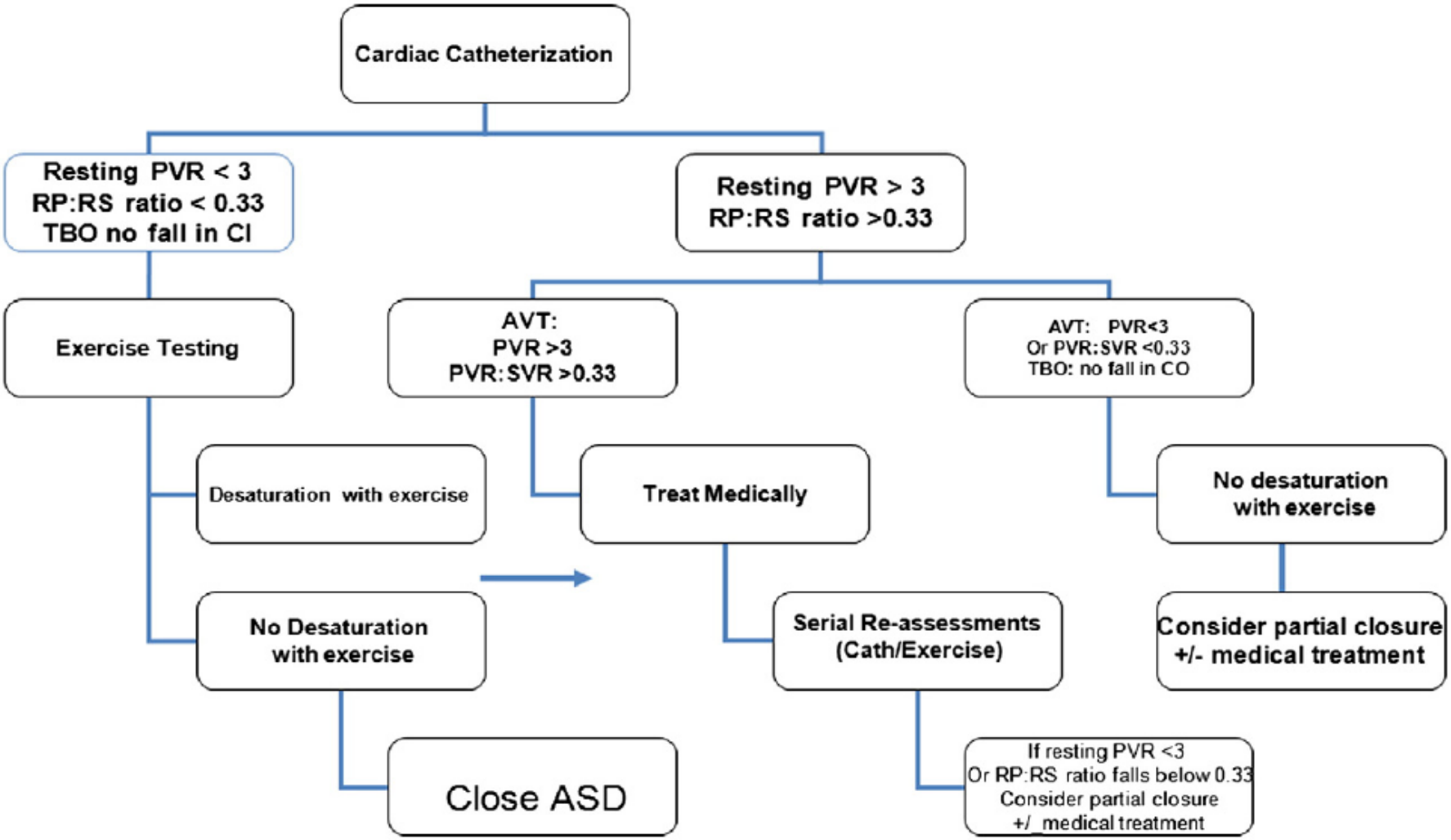
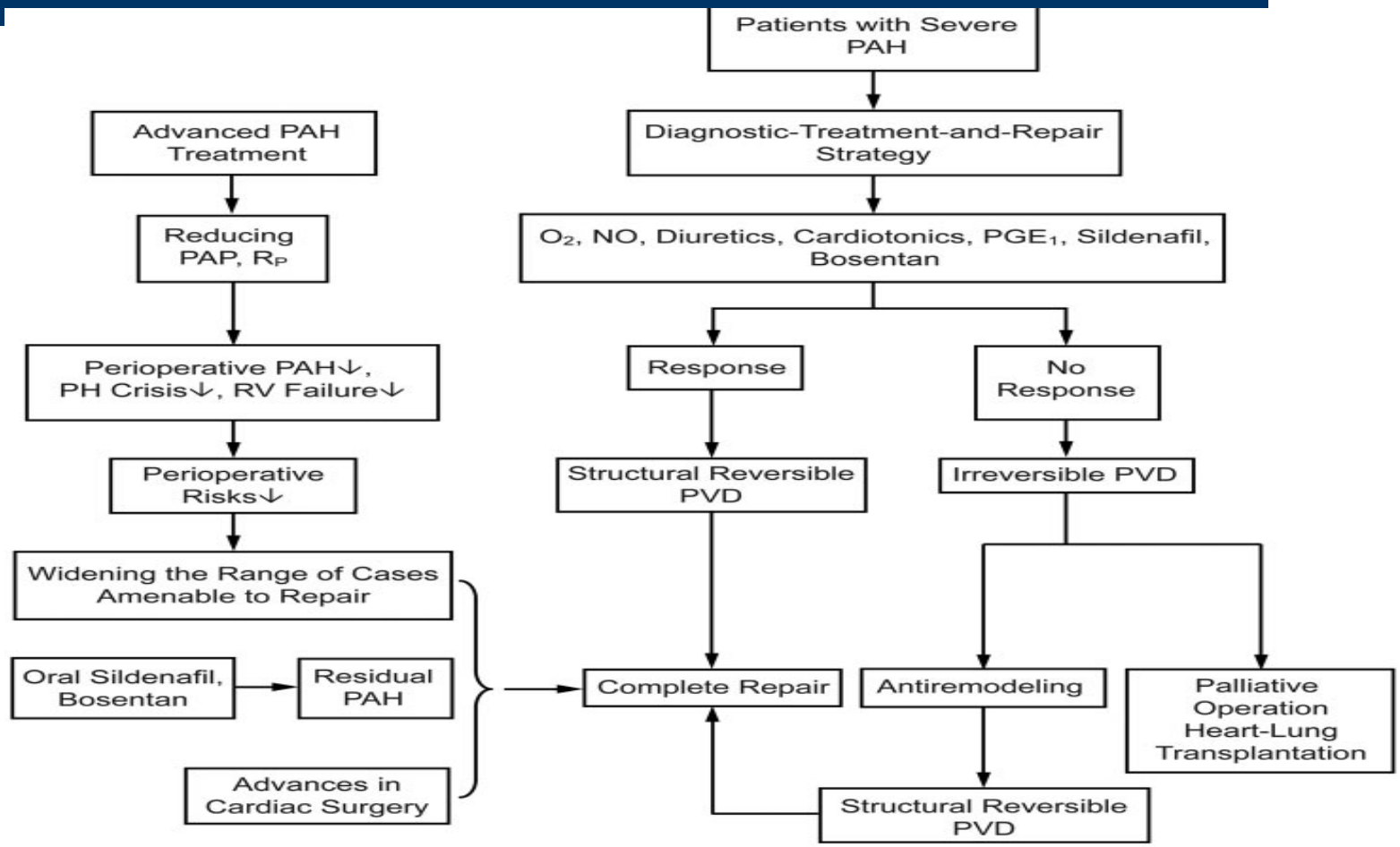


Fig. 1. CHD/PH (ASD) Clinical management algorithm: Individualized case approach.

- Progress in Cardiovascular Diseases 55 (2012) 128–133

Eisenmenger Syndrome: Not Always Inoperable

Jing-Bin Huang , et al. Respir care 2012

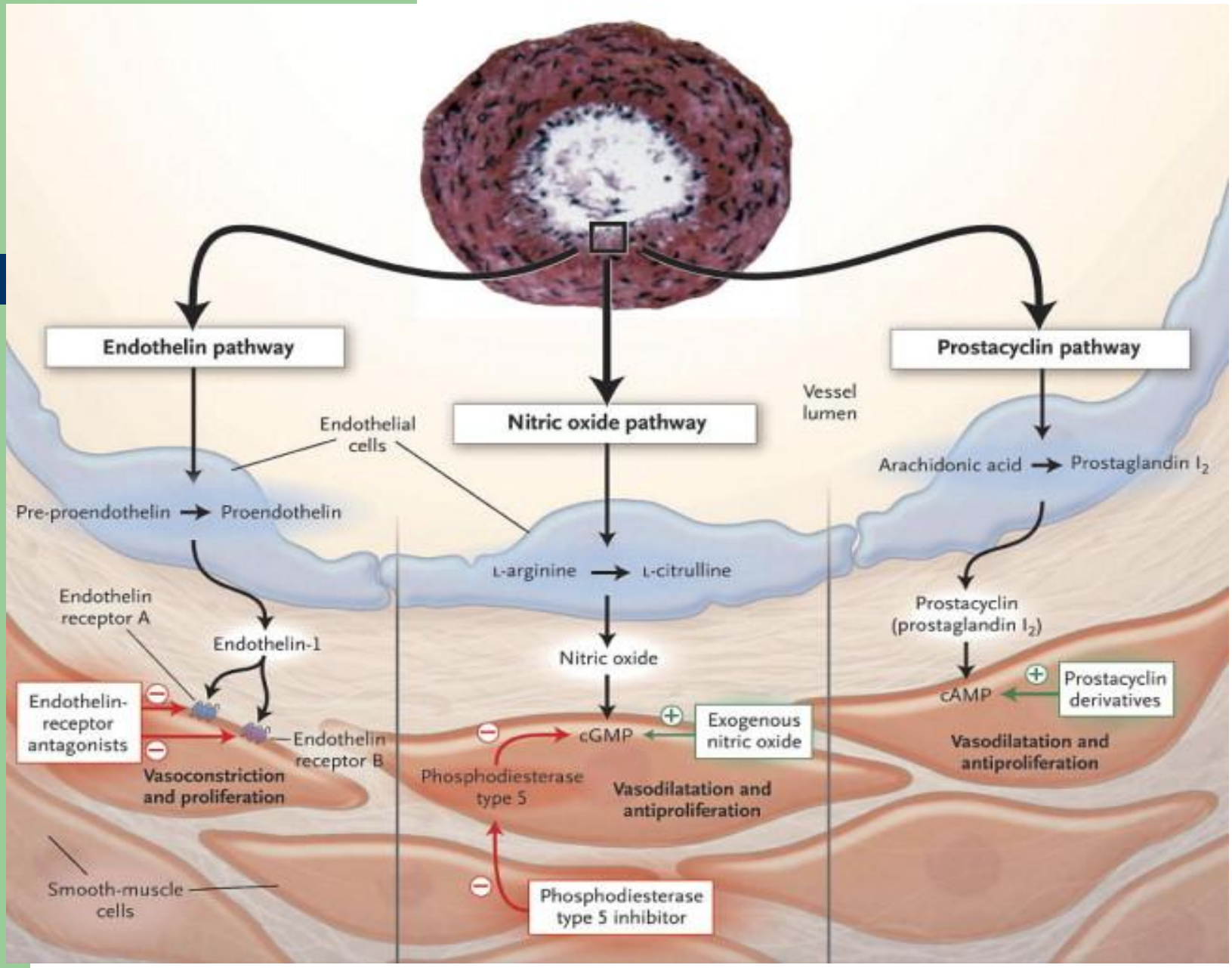


Traditional Treatment of Eisenmenger syndrome

- heart-lung transplantation
- pallative surgery: PA banding, flap valve closure
- supportive treatment
  * oxygen
  * Digoxin, diaretics, ACE, ARB etc
  * anticoagulants
  * calcium channel blocker

3 major pathophysiological pathway in PAH

- Endothelin pathway
- nitric oxide pathway
- prostacyclin pathway


Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Vessel lumen
Endothelial cells
Arachidonic acid
Prostaglandin I_2
Pre-proendothelin
Proendothelin
L-arginine
L-citrulline
Endothelin receptor A
Endothelin-1
Nitric oxide
Prostacyclin (prostaglandin I_2)
Endothelin-receptor antagonists
Endothelin receptor B
Vasoconstriction and proliferation
cGMP
Exogenous nitric oxide
cAMP
Prostacyclin derivatives
Vasodilatation and antiproliferation
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Smooth-muscle cells
Phosphodiesterase type 5 inhibitor

Targeted therapies for ES

- Endothelin receptor antagonists
  * Bosentan, clinical improvements for at least 2 years
  * Sitaxsentan, improvement in PVR/ SVR ratio

- Phosphodiesterase Type-5 inhibitor
  * Sildenafil

- Prostacyclin & prostacyclin analogs

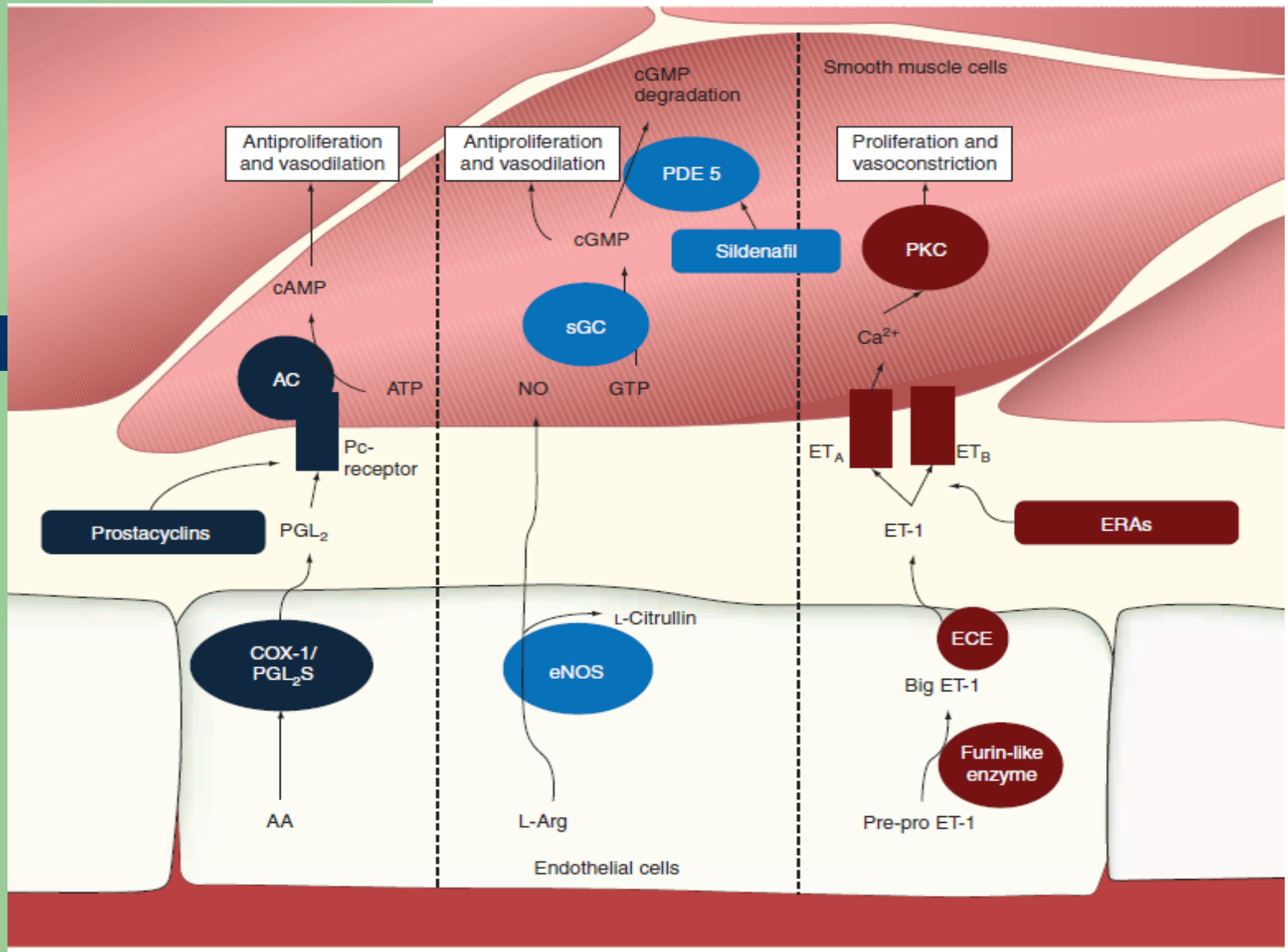


Figure 1. The prostacyclin, nitric oxide and endothelin pathways. Prostacyclin (PGI_2) is synthesized from arachidonic acid by COX-1 and PGI_2 synthase. PGI_2 activates the receptor of smooth muscle cells and in turn activates adenylate cyclase. This leads to increased production of cAMP from ATP with the effect of vasodilation and antiproliferation. Endothelial nitric oxide (NO) synthase produces NO from L-arginine. NO stimulates soluble guanylate cyclase resulting in increased production of cyclic guanylate monophosphate and thus antiproliferation and vasodilation. Preproendothelin is converted to big-endothelin (ET)-1 and subsequently ET-1 by furin-like enzyme and ET-converting enzymes, respectively. ET-1 activates ET-A and ET-B receptors, leading to calcium release and activation of protein kinase C, which leads to vasoconstriction and proliferation of smooth muscle cells.

BREATHE-5 (Bosentan62.5-125 mg bid)

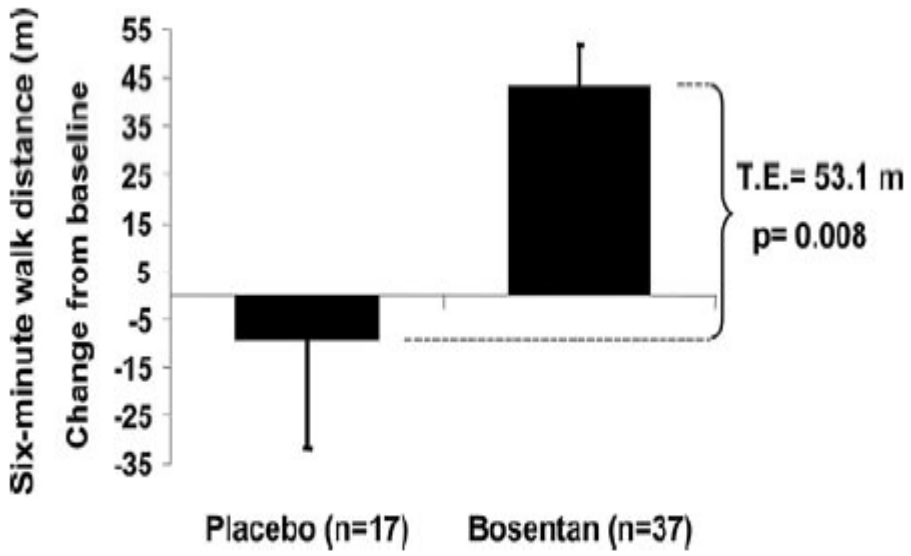


Figure 2. Change from baseline of 6-minute walk distance in placebo and bosentan groups. TE indicates treatment effect.

Breathe-5

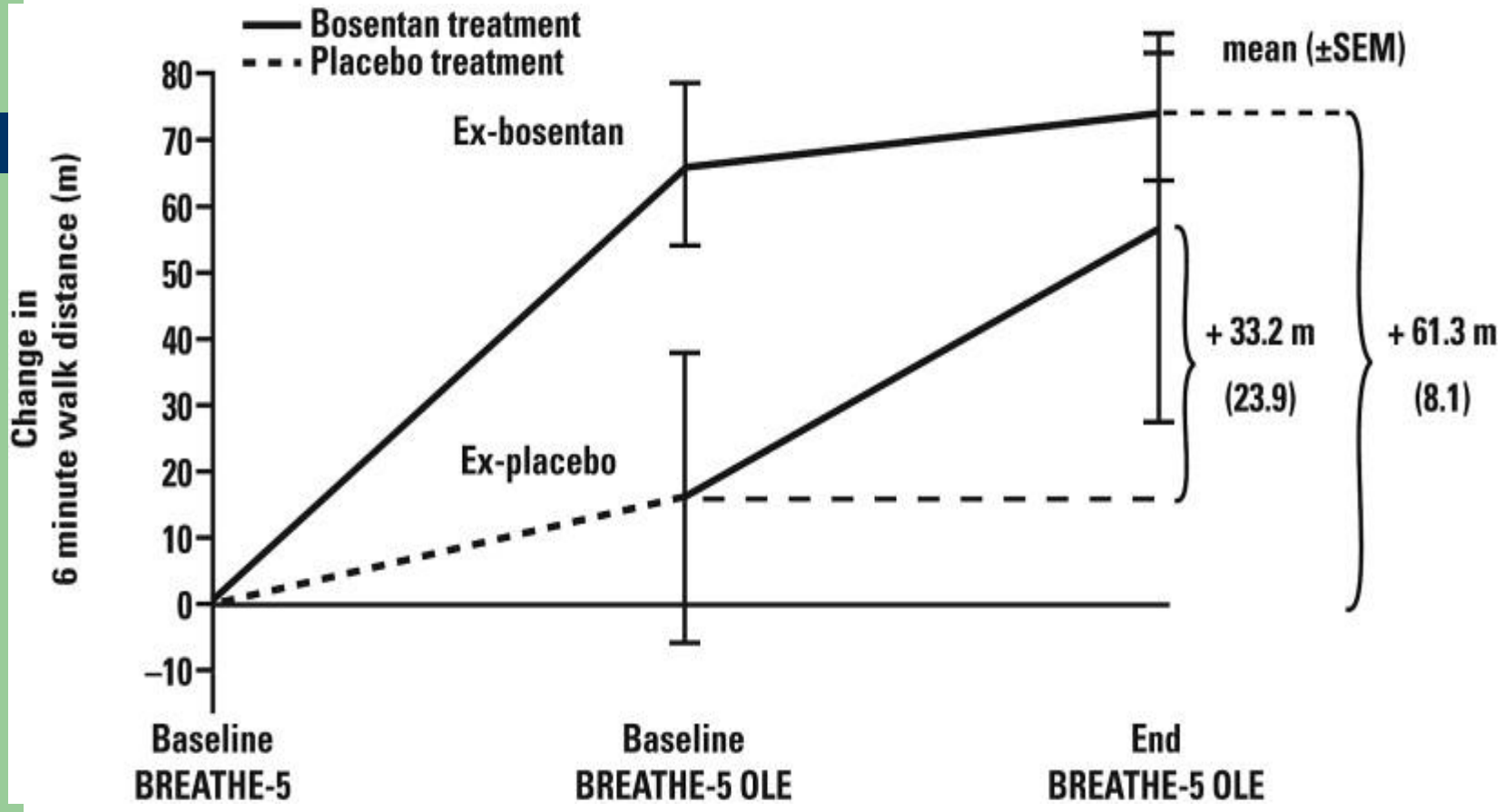
TABLE 2. Hemodynamic Effects of Placebo and Bosentan at Week 16

Parameter	Change From Baseline		Treatment Effect	
	Placebo (n=17)*	Bosentan (n=37)*	(Bosentan−Placebo)	*P*
Heart rate, bpm	−0.8 (2.7)	−2.0 (1.9)	−1.2 (3.4)	0.7329
Mean pulmonary arterial pressure, mm Hg	0.5 (1.4)	−5.0 (1.6)	−5.5 (2.5)	0.0363
Mean left atrial pressure,† mm Hg	0.5 (1.2)	0.4 (0.6)	−0.2 (1.3)	0.8862
Pulmonary flow index, $L \cdot min^{-1} \cdot m^{-2}$	0.0 (0.1)	0.1 (0.1)	0.1 (0.1)	0.4675
Pulmonary vascular resistance index, $dyne \cdot s \cdot cm^{-5}$	155.1 (134.0)	−316.9 (138.3)	−472.0 (221.9)	0.0383
Mean systemic arterial pressure, mm Hg	2.5 (2.2)	−3.8 (1.6)	−6.3 (2.8)	0.0282
Mean right atrial pressure, mm Hg	0.4 (0.9)	0.3 (0.5)	−0.1 (1.0)	0.9448
Systemic flow index, $L \cdot min^{-1} \cdot m^{-2}$	−0.2 (0.1)	0.9 (0.8)	1.1 (1.1)	0.2981
Systemic vascular resistance index, $dyne \cdot s \cdot cm^{-5}$	378.9 (246.8)	−372.9 (244.6)	−751.8 (388.4)	0.0595

Values are expressed as means (SE).

*The number of patients per treatment group varied slightly for each parameter because of missing assessments.

†Directly assessed in the presence of an atrial septal defect or patent foramen ovale, substituted with end-diastolic left ventricular pressure or pulmonary capillary wedge pressure in other cases.


Bosentan treatment
Placebo treatment
mean (±SEM)
Change in
6 minute walk distance (m)
80
70
60
50
40
30
20
10
0
–10
Ex-bosentan
Ex-placebo
+ 33.2 m
(23.9)
+ 61.3 m
(8.1)
Baseline
BREATHE-5
Baseline
BREATHE-5 OLE
End
BREATHE-5 OLE

Long term benefits of bosentan

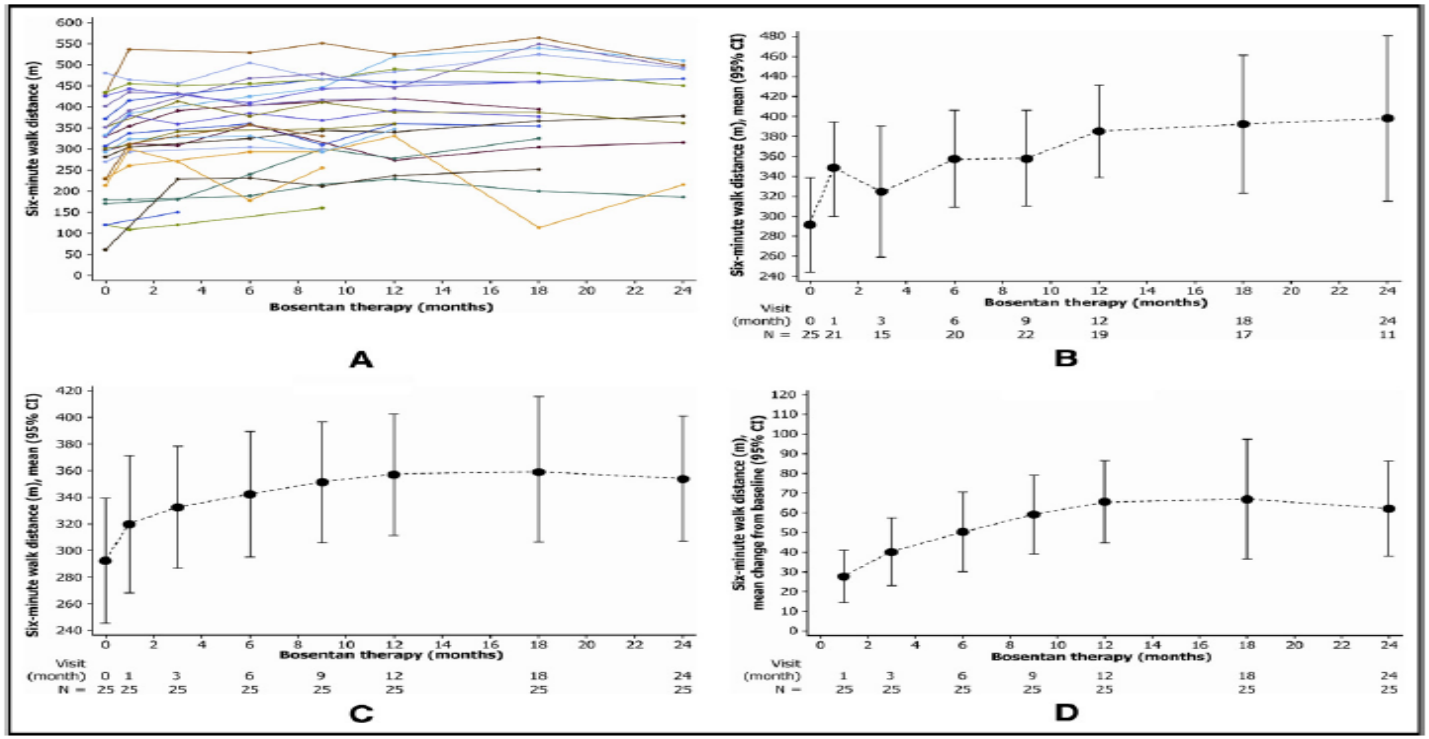


Figure 1. Six-minute walk distance for patients without Down syndrome treated for up to 24 months with bosentan. *(A)* Absolute values for all patients. *(B)* Absolute values (mean ± SD) for all patients with no imputation for missing values. *(C)* Absolute values (mean ± SD) for all patients with last observation carried forward imputation to account for missing values. *(D)* Change from baseline values (mean ± SD) for all patients with last observation carried forward imputation to account for missing values. CI = confidence interval.

Monfredi et al.Am J Cardiol 2011;108:1483

Prolonged beneficial effect of bosentan treatment and 4-year survival rates in adult patients with pulmonary arterial hypertension associated with congenital heart disease

Jeroen C. Vis [a,b], Marielle G. Duffels [a], Pepijn Mulder [a], Rianne H.A.C.M. de Bruin-Bon [a], Berto J. Bouma [a], Rolf M.F. Berger [c], Elke S. Hoendermis [c], Arie P.J. van Dijk [d], Barbara J.M. Mulder [a,b,*]

A B S T R A C T

Pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) due to systemic to pulmonary shunting is associated with a high risk of morbidity and mortality. In this study we evaluated 4 years treatment effect of bosentan on exercise capacity and quality of life and survival rates in 64 adult patients with PAH associated with CHD, including patients with Down syndrome (DS). All patients were evaluated at baseline and during follow-up with laboratory tests, 6-minute walk test, quality of life questionnaires, and Doppler echocardiography. In total, 13 patients (20%) died during 4-years of follow-up; 4 patients with DS and 9 patients without DS. Mean follow-up of all patients treated with bosentan was 3.5 ± 1.2 year. We analyzed treatment efficacy separately within patients without DS (n = 34) and patients with DS (n = 30). Mean 6-minute walking distance (6MWD) in patients without DS significantly increased at 6 months from 417 ± 108 to 458 ± 104 m (+41 m; p = 0.002) and significant improvement continued to exist during at least 2.5 years of follow-up (p = 0.003). Moreover, stroke volume increased significantly (p = 0.02). In the patients with DS, 6-MWD, stroke volume and quality of life remained stable during treatment. In this study we demonstrate a prolonged beneficial effect of bosentan treatment on exercise capacity, stroke volume and quality of life in patients without DS. However the mortality rate of 20% of patients after 4 years of follow-up remains high.

Int J Cardiol 2013;164:64-9

Table 3
Echocardiography parameters during follow-up.

Non Down syndrome	Baseline	Δ 1 year FU	*p*-value	Δ 2 year FU	*p*-value	Δ>3 year FU	*p*-value
Heart rate, bpm	78±11	−0.1	1.0	−3.1	0.3	−5.0	0.1
Stroke volume, ml	72.3±25.9	8.5	0.06	7.8	0.4	13.5	0.02
Cardiac output, L/min	5.5±1.6	0.7	0.2	0.6	0.4	0.6	0.1
TEI index	0.5±0.2	0.03	0.6	0.06	0.6	0.10	0.1
Tricuspid annular plane systolic excursion, cm	1.9±0.6	−0.1	0.9	1.2	0.4	1.0	0.6
Pulmonary arterial pressure, mm Hg	84±23	−3.0	0.6	−6.4	0.2	−4.5	0.3
Down syndrome							
Heart rate, bpm	75±12	1.1	0.7	−2.8	0.4	0.9	0.8
Stroke volume, ml	68.9±37.0	5.4	0.2	7.3	0.1	−1.9	0.8
Cardiac output, L/min	5.1±2.5	0.4	0.3	0.2	0.5	−0.1	0.8
TEI index	0.6±0.2	0	0.9	−0.06	0.3	−0.05	0.4
Tricuspid annular plane systolic excursion, cm	1.9±0.4	0.9	0.4	−0.5	0.7	0.6	0.4
Pulmonary arterial pressure, mm Hg	97±16	−7.3	0.05	−5.2	0.2	−3.7	0.4

Mean values with standard deviation. *p*-values are analyses compared to baseline; FU, follow-up; bpm, beats per minute; FU, follow-up.
TEI index is a combined myocardial performance index (isovolumic contraction time plus isovolumic relaxation time divided by ejection time).

Cardiology in the Young (2011), **21**, 631–638
doi:10.1017/S1047951111000497

Original Article

Comparative efficacy of sildenafil in Eisenmenger's syndrome secondary to atrial septal defect versus ventricular septal defect: a cardiac catheterisation follow-up study

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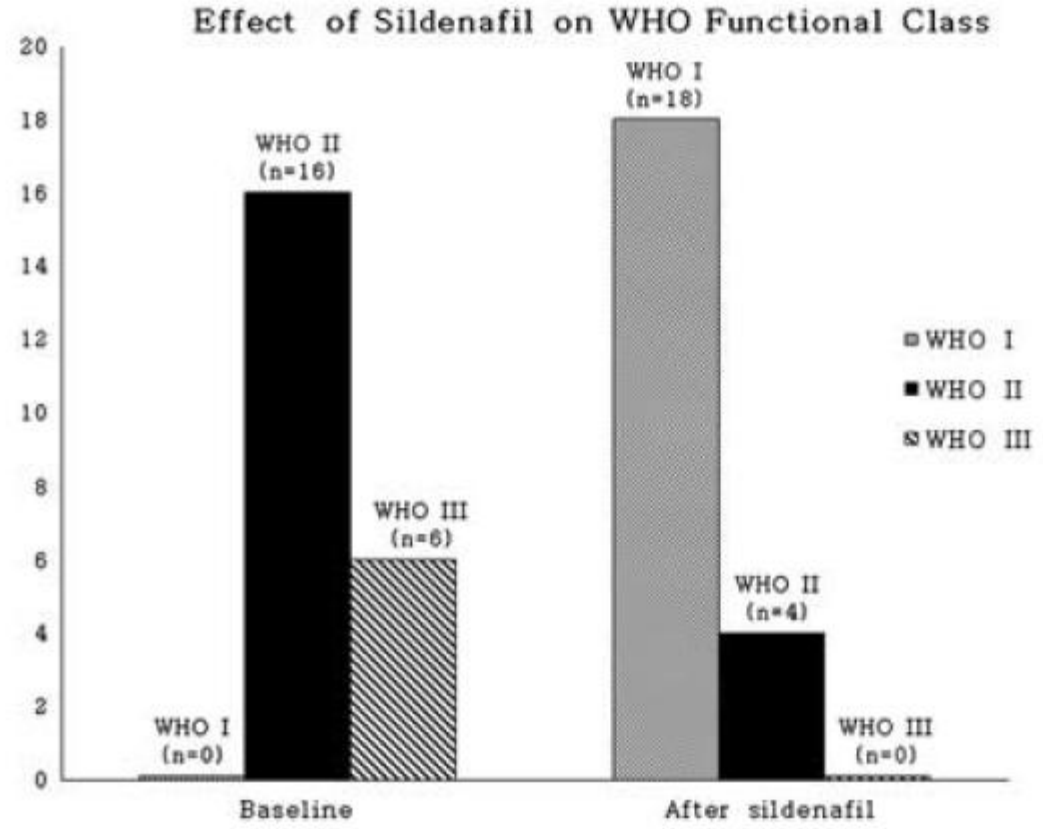
Department of Cardiology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

Table 3. Effects of sildenafil on cardiac catheterisation parameters (n = 22).

Cardiac catheterisation parameters	Pre-treatment	Post-treatment	p-value
Pulmonary arterial pressure (mmHg)			
Systolic	109.4 ± 11.3	101.3 ± 16.0	<0.001
Diastolic	50.5 ± 10.4	42.4 ± 10.2	<0.001
Mean	69.6 ± 10.0	62.2 ± 11.5	<0.001
Mean right atrial pressure (mmHg)	5.0 ± 2.4	4.6 ± 1.9	0.186
Mean PCWP (mmHg)	7.6 ± 2.0	7.4 ± 2.2	0.715
Central aortic pressure (mmHg)			
Systolic	116.4 ± 9.6	113.4 ± 8.2	0.001
Diastolic	70.8 ± 6.8	69.0 ± 7.2	0.001
Mean	85.6 ± 7.6	83.4 ± 6.9	0.003
Systemic arterial oxygen saturation (%)	86.0 ± 2.0	90.6 ± 1.6	0.046
Mixed venous oxygen saturation (%)	60.8 ± 3.5	67.7 ± 3.4	<0.0001
Cardiac output (l/min)	3.9 ± 0.5	4.4 ± 0.6	0.001
Qp/Qs	0.7 ± 0.1	0.8 ± 0.1	0.001
PVR (WU)	21.4 ± 3.9	15.4 ± 3.9	<0.0001
SVR (WU)	21.1 ± 2.7	18.5 ± 2.9	0.001
PVR/SVR ratio	1.0 ± 0.2	0.8 ± 0.2	<0.001

PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; Qp = pulmonary blood flow; Qs = systemic blood flow; SVR = systemic vascular resistance



gure 1.

fect of sildenafil on WHO functional class. WHO = World alth Organization.

Table 2. Clinical efficacy of oral sildenafil therapy (n = 22).

	Baseline	6 months	p-value
WHO class	2.3 ± 0.5	1.2 ± 0.4	<0.0001
SMWT distance (m)	305.3 ± 60.1	476.9 ± 73.6	<0.0001
SpO_2 (%)	86.0 ± 2.01	91.1 ± 1.1	<0.001

SMWT = six-minute walk test; SpO_2 = oxygen saturation by systemic pulse oxymetry; WHO = World Health Organization

Sildenfil ES

- **Sildenafil 22 ES patients**

  - 8 ASD, 14VSD, 6 months sildenafil

  - improvement in the following parameters
    * 6-minute walk test
    * functional class
    * mean PAP, PVR
    * O2 saturation ↑
    * ASD patients better response

Cardiol young 2011;21:631-8

ES Sildenafil mono therapy

- 121 patients (68 vs. 53 on Sildenafil)
- 6-minutes walk test

  WHO functional class

  PVR index p= 0.053
- survival

J Clinical pharma 2013;53:611-8

Inhaled iloprost for ES patients

pediatr cardiol 2012;33:744-8

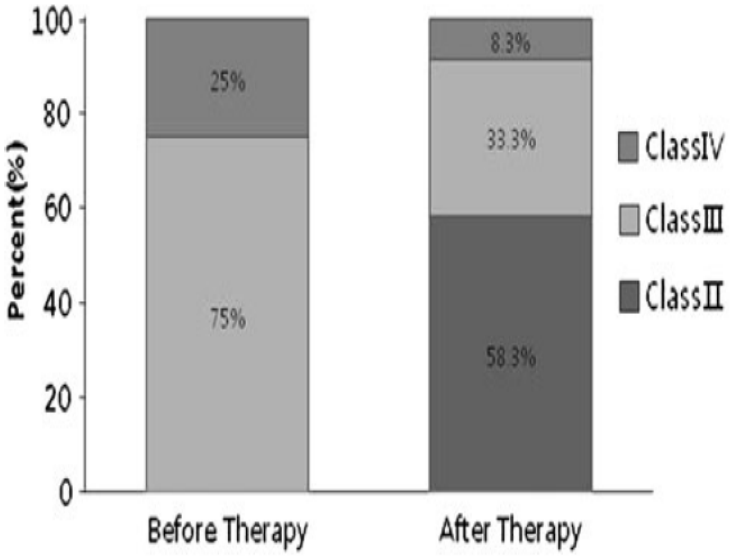


Fig. 2 New York Heart Association (NYHA) functional classification of patients before and after Iloprost inhalation therapy

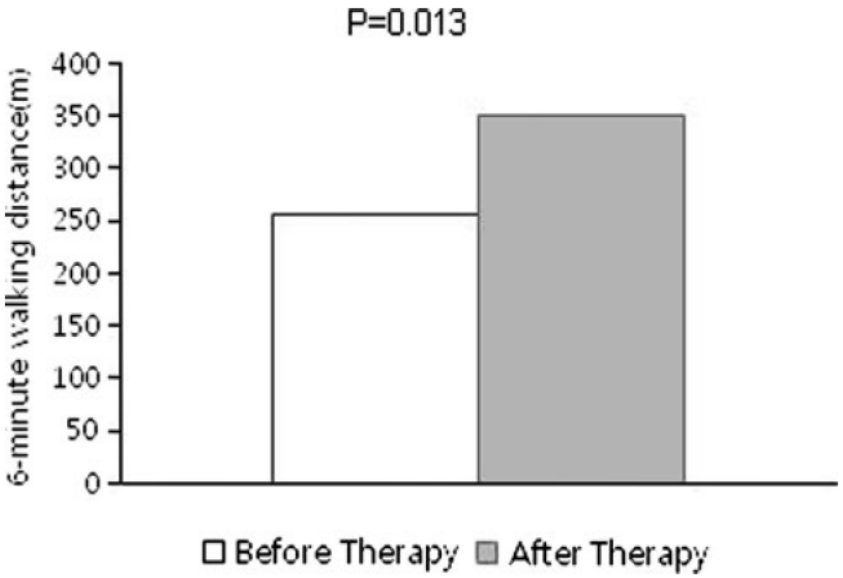


Fig. 1 Improvement in exercise tolerance, as measured by the 6-min walk test

Combination therapy add Sildenafil after clinical worsening

Table 4
Haemodynamic parameters at baseline (bosentan monotherapy) and after 6 months of bosentan–sildenafil combination therapy.

	Basal	End of observation	*P*
RAP (mmHg)	13 ± 4	11 ± 3	0.09
mPAP (mmHg)	73 ± 20	71 ± 17	0.09
PCWP (mmHg)	12 ± 3	11 ± 2	0.18
Qp (l/m/m^2)	3.1 ± 1.2	3.4 ± 1.0	0.0002
Qs (l/m/m^2)	3.6 ± 1.6	3.6 ± 1.5	0.23
Qp/Qs	1.0 ± 0.4	1.1 ± 0.4	0.11
PVRi (WU/m^2)	24 ± 16	19 ± 9	0.003
SVRi (WU/m^2)	28 ± 14	26 ± 9	0.10

RAP, right atrial pressure; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; Qp, pulmonary flow; Qs, systemic flow; PVRi, pulmonary vascular resistance index; SVRi, systemic vascular resistance index.

- D.Alto et al. Int J Cardiol 2012

Combination therapy

Table 3

Clinical status, exercise tolerance and biochemical parameters at baseline (bosentan monotherapy) and after 6 months of bosentan–sildenafil combination therapy.

	Basal	End of observation	*P*
Clinical status			
SpO_2 (%)	80±9	82±8	0,48
HR (bpm)	85±16	84±15	0.87
WHO functional class	2.9±0.3	2.1±0.4	0.042
Exercise tolerance (6MWT)			
Distance (m)	293±68	360±51	0.005
HR post-exercise (bpm)	101±25	105±20	0.87
SpO_2 post-exercise (%)	63±15	72±10	0.047
Borg dyspnoea index	4.4±2.3	2.9±1.5	0.036
Biochemical parameters			
Htc (%)	62±11	60±12	0.69
Hb (mg/dl)	19.8±3.7	18.4±3.8	0.73
RBC (10^6/μl)	6.6±1.3	6.2±1.2	0.41
PLT (1000/μl)	180±77	183±68	0.93
Aspartate aminotransferase (U/l)	19±6	18±7	0.79
Alanine aminotransferase (U/l)	28±9	30±12	0.88
proBNP (pg/ml)	760±943	303±366	0.008

SpO_2, transcutaneous oxygen saturation; HR, heart rate; 6MWT, 6-minute walk test; Htc, haematocrit; Hb, haemoglobin; RBC, red blood cells; PLT, platelets; proBNP, pro-brain natriuretic peptide

Combination therapy in ES patients

- Bosentan + Sildenafil 20 mg twice daily
- 32 patients (4 did not has ES)
- 6 months treatment, improvement in
  - WHO functional class 2.1 0.4 vs. 2.9 0.3
  - 6-min walk distance
  - SPO2
  - pro BNP
  - hemodynamics
  - Borg score
- safe & effective

D'Alto M et al.
Int J Cardiol 2012;155:378-82

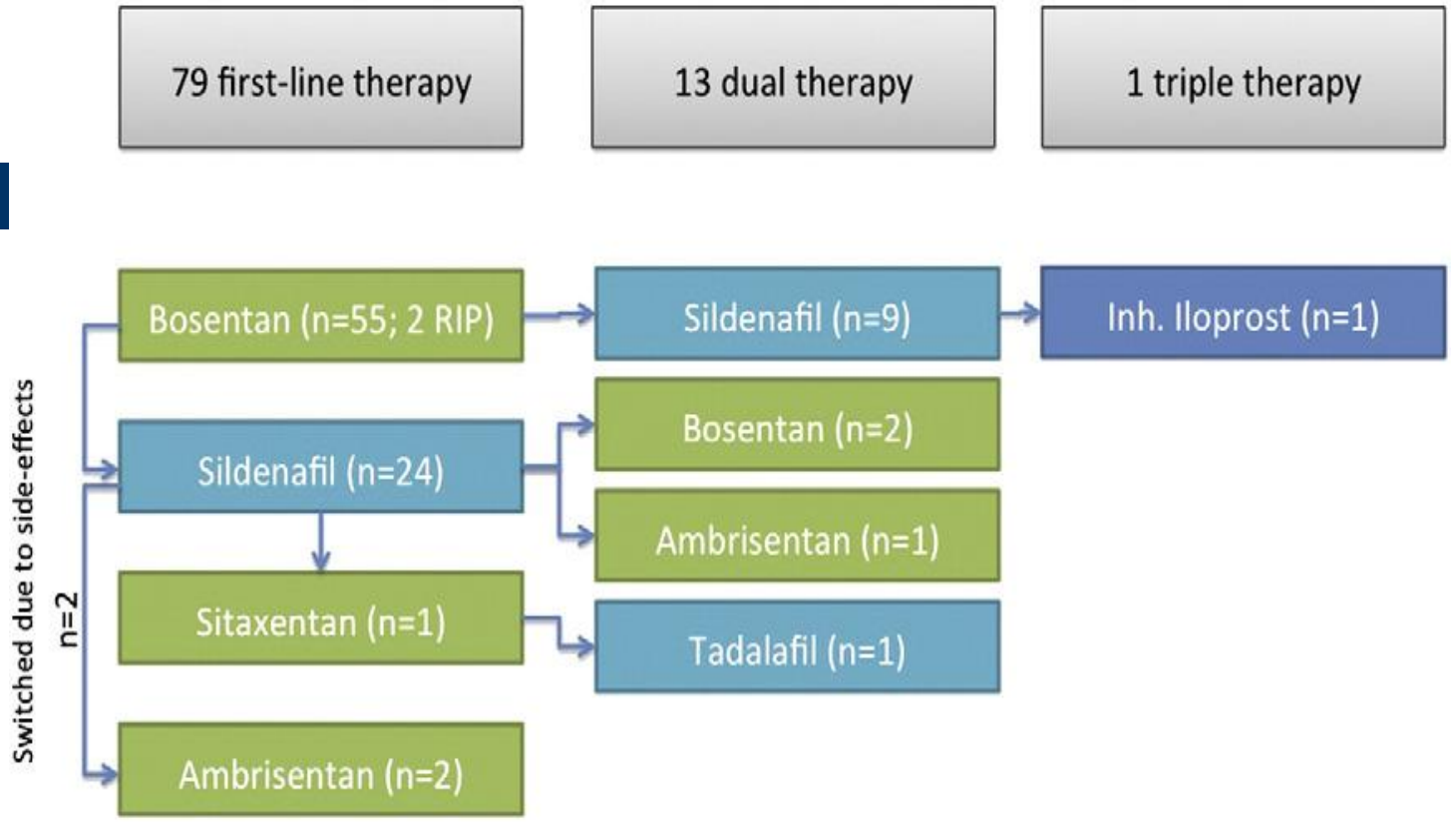
ES combination therapy (Bosentan + Sildenafil)

- 21 patients, Bosentan
  (9months → 3 months → sildenafil/ Placebo)

- improvement in
  - 6- minutes walk distance
  - pro BNP
  - WHO Functional class
  - PVR

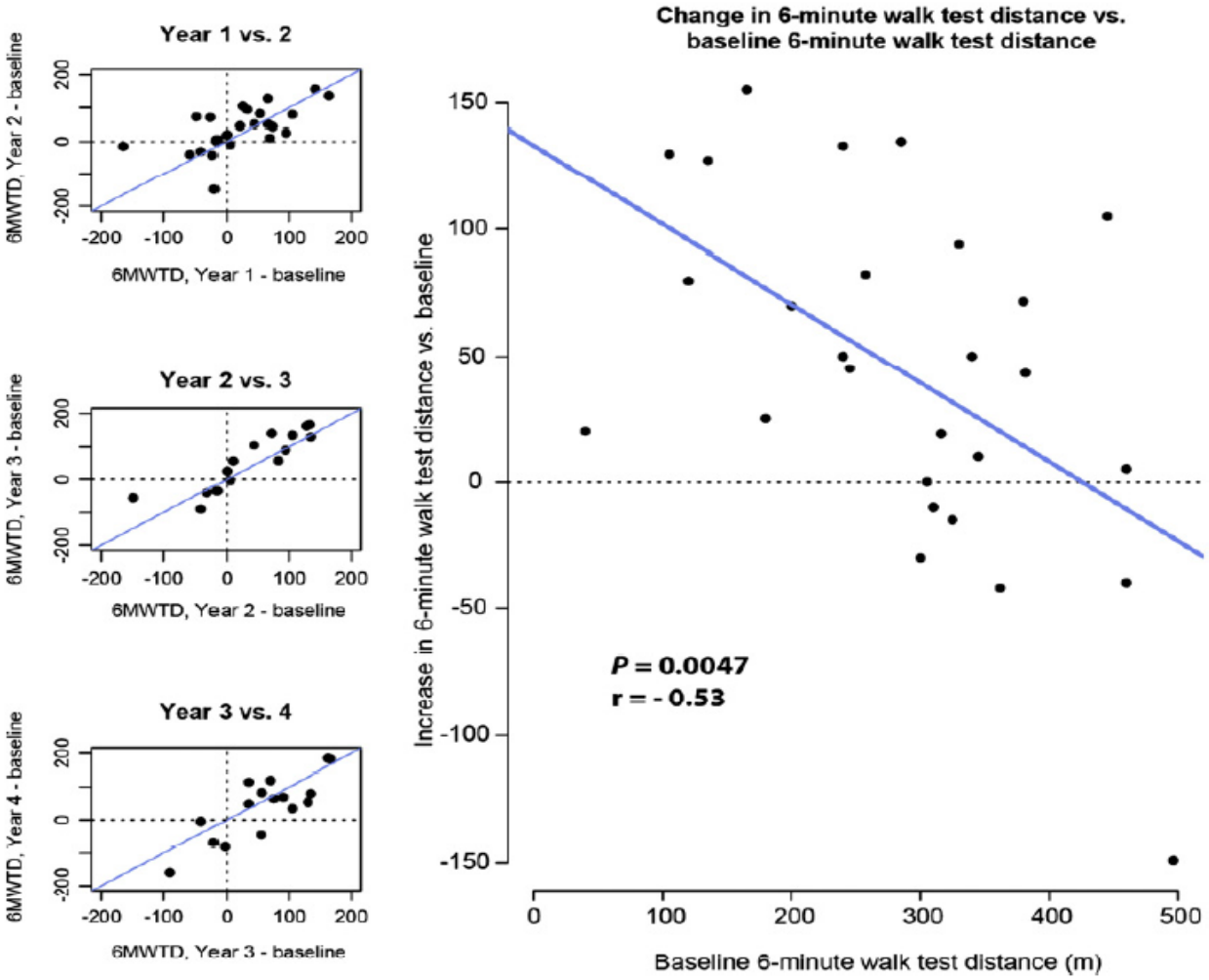
- Add on sildenafil
  - further improvement in O2 saturation

Eur Heart J 2010;31:1124-31



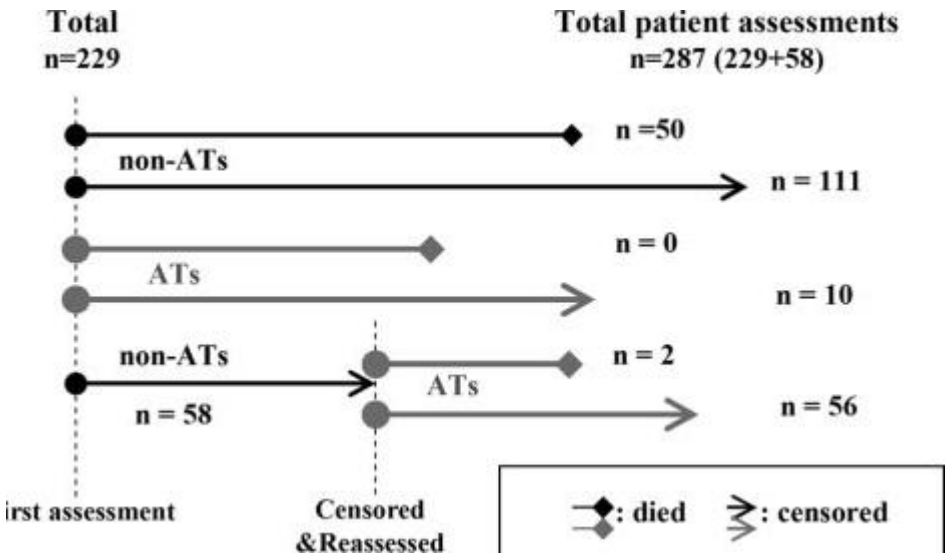
Sildenafil uptitrated from 20 mg b.d. to 50 mg b.d. in 4 patients (1 first-line therapy, 3 on combination therapy)

- Diller GP Int J Cardiol 2013;167:840-7



Scatterplots with superimposed lines of identity of change in 6-minute walk test distance (6MWT) at years 1, 2, 3 and 4 compared to baseline. Right hand ating the association between baseline 6MWTd and increase in 6MWTd at year 3.

- Diller GP Int J Cardiol 2013;167:840-7



- Circulation 2010 Dimopoulous

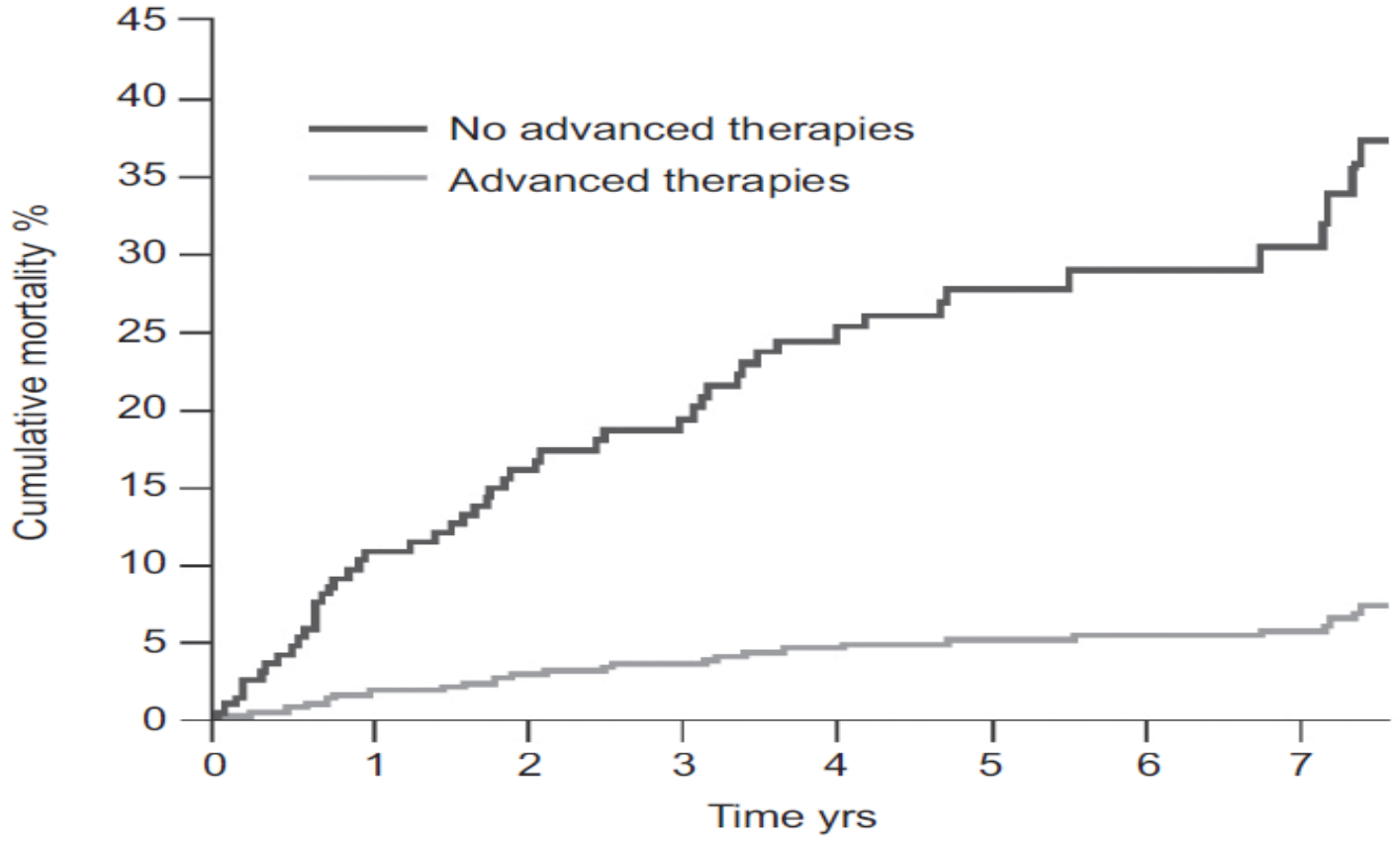
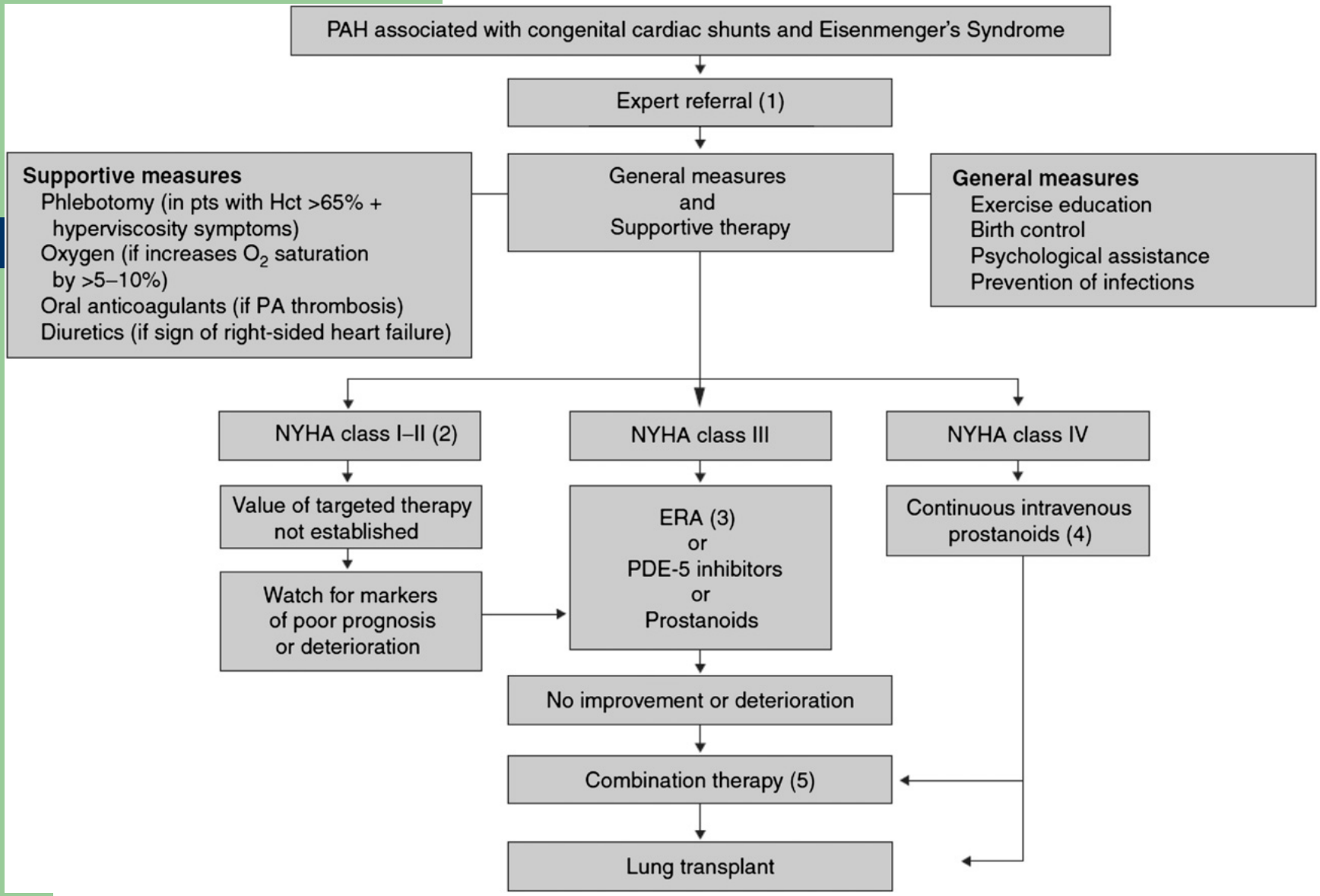


FIGURE 3. Adjusted survival rate curves, based on the propensity score model, of Eisenmenger's syndrome patients with and without advanced therapy (bosentan, sildenafil or epoprostenol). Quartiles of propensity score were based on the average propensity scores from the 10 matched populations. p=0.015. Reproduced from [60] with permission from the publisher.

- Dimopoulos K. Circulation 2010;121:20-5


PAH associated with congenital cardiac shunts and Eisenmenger's Syndrome
Expert referral (1)
General measures and Supportive therapy
Supportive measures
Phlebotomy (in pts with Hct >65% + hyperviscosity symptoms)
Oxygen (if increases O_2 saturation by >5–10%)
Oral anticoagulants (if PA thrombosis)
Diuretics (if sign of right-sided heart failure)
General measures
Exercise education
Birth control
Psychological assistance
Prevention of infections
NYHA class I–II (2)
NYHA class III
NYHA class IV
Value of targeted therapy not established
Watch for markers of poor prognosis or deterioration
ERA (3) or PDE-5 inhibitors or Prostanoids
Continuous intravenous prostanoids (4)
No improvement or deterioration
Combination therapy (5)
Lung transplant

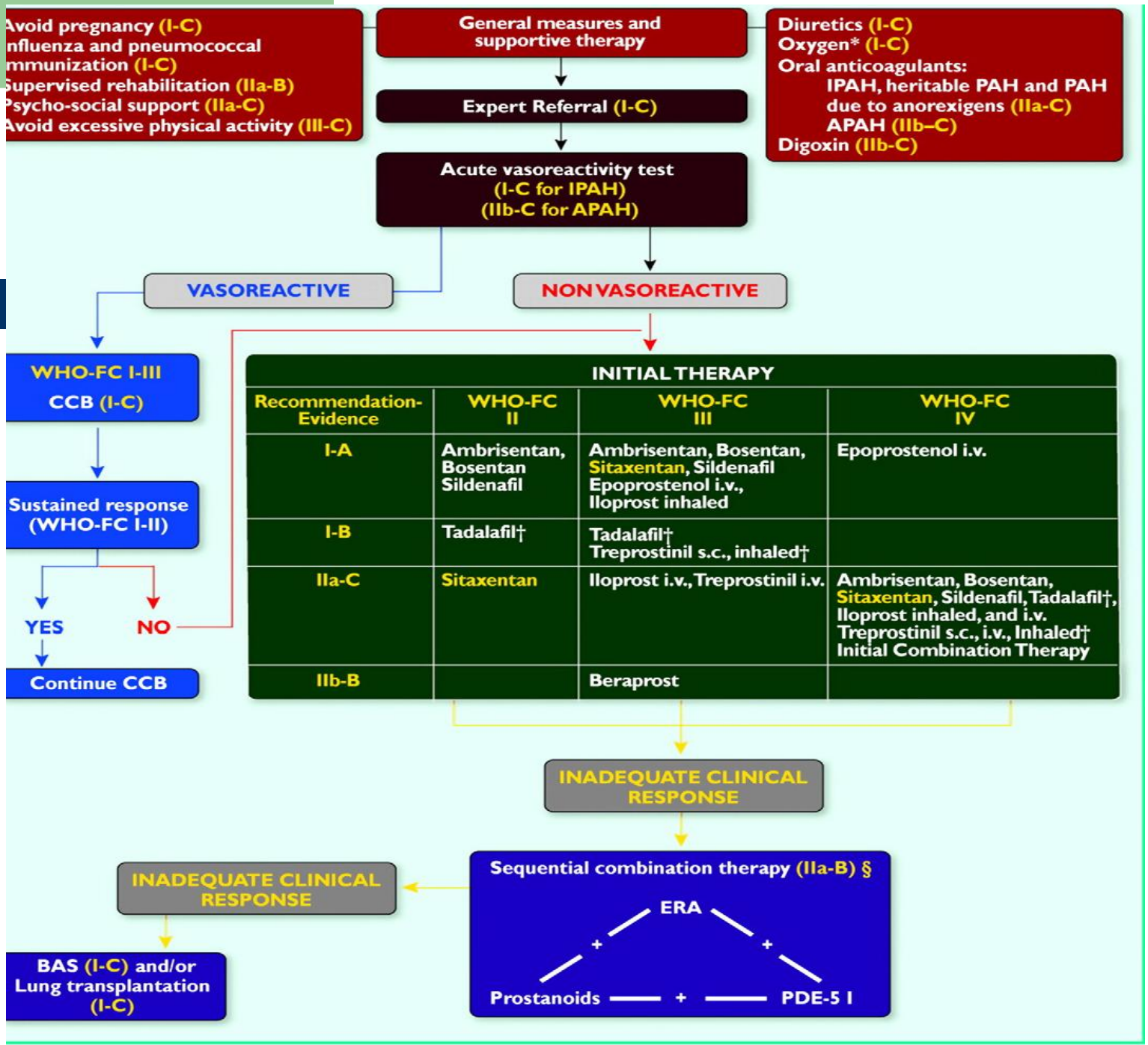

Avoid pregnancy (I-C)
nfluenza and pneumococcal
mmunization (I-C)
Supervised rehabilitation (IIa-B)
Psycho-social support (IIa-C)
Avoid excessive physical activity (III-C)
General measures and supportive therapy
Expert Referral (I-C)
Acute vasoreactivity test
(I-C for IPAH)
(IIb-C for APAH)
Diuretics (I-C)
Oxygen* (I-C)
Oral anticoagulants:
IPAH, heritable PAH and PAH due to anorexigens (IIa-C)
APAH (IIb–C)
Digoxin (IIb-C)
VASOREACTIVE
NON VASOREACTIVE
WHO-FC I-III
CCB (I-C)
Sustained response (WHO-FC I-II)
YES
NO
Continue CCB
INITIAL THERAPY
Recommendation-Evidence
WHO-FC II
WHO-FC III
WHO-FC IV
I-A
Ambrisentan, Bosentan Sildenafil
Ambrisentan, Bosentan, Sitaxentan, Sildenafil Epoprostenol i.v., Iloprost inhaled
Epoprostenol i.v.
I-B
Tadalafil†
Tadalafil† Treprostinil s.c., inhaled†
IIa-C
Sitaxentan
Iloprost i.v., Treprostinil i.v.
Ambrisentan, Bosentan, Sitaxentan, Sildenafil, Tadalafil†, Iloprost inhaled, and i.v. Treprostinil s.c., i.v., Inhaled† Initial Combination Therapy
IIb-B
Beraprost
INADEQUATE CLINICAL RESPONSE
Sequential combination therapy (IIa-B) §
ERA
+
+
Prostanoids
+
PDE-5 I
INADEQUATE CLINICAL RESPONSE
BAS (I-C) and/or Lung transplantation (I-C)

Table 1. Currently available studies assessing disease targeting therapies in pulmonary arterial hypertension associated with congenital heart disease and selected studies of mixed pulmonary arterial hypertension populations.

Study (year)	Study population (n; % with CHD†)	Study design	Outcome (primary outcome in RCTs)	Change in 6MWD	Follow-up period	Medication	Ref.
Rosenzweig *et al.* (1999)	CHD (20)	Retrospective	N/A	+52 m	1 year	Epoprostenol	[49]
Olschewski *et al.* for AIR (2002)	PAH (203; 0)	Randomized, double-blind, placebo-controlled	6MWD	+36 m	16 weeks	Inhaled iloprost	[51]
Rubin *et al.* for BREATHE-1 (2002)	PAH (213; 0)	Randomized, double-blind, placebo-controlled	6MWD	+44 m	16 weeks	Bosentan	[72]
Simonneau *et al.* (2002)	PAH (470; 23)	Randomized, double-blind, placebo-controlled	6MWD	+16 m	12 weeks	Treprostinil	[50]
Fernandes *et al.* (2003)	EES (8)	Retrospective	N/A	+299 m	3 months	Epoprostenol	[48]
Christensen *et al.* (2004)	CHD (9)	Retrospective	N/A	Not reported	9.5 months	Bosentan	[73]
Barst *et al.* for STRIDE-1 (2004)	PAH (178; 24)	Randomized, double-blind, placebo-controlled	Peak VO_2	+35 m (100-mg dose)/ +33 m (300-mg dose)	12 weeks	Sitaxsentan	[74]
Schulze-Neick *et al.* (2005)	CHD (33)	Open label prospective	WHO/6MWD	+72 m	2.1 years	Bosentan	[62]
Gatzoulis *et al.* (2005)	ES (10)	Open label prospective	SpO_2 and 6MWD	+99 m	3 months	Bosentan	[75]
Galie *et al.* for SUPER-1 (2005)	PAH (278; 7)	Randomized, double-blind, placebo-controlled	6MWD	+45 m (20-mg dose)/ +46 m (40-mg dose)/ +50 m (80-mg dose)	12 weeks	Sildenafil	[22]
Galie *et al.* for BREATHE 5 (2006)	ES (54)	Randomized, double-blind, placebo-controlled	SpO_2 and 6MWD	+43 m	16 weeks	Bosentan	[55]
Kotlyar *et al.* (2006)	ES (23)	Retrospective	N/A	No improvement	15 months	Bosentan	[76]
Benza *et al.* (2006)	CHD (24)	Retrospective	N/A	+31 m	1 year	Bosentan	[77]
Sitbon *et al.* (2006)	CHD (27)	Retrospective	N/A	+66 m	15 months	Bosentan	[78]
Mukhopadhyay *et al.* (2006)	ES (16)	Observational prospective	Hemodynamics/SpO_2/ WHO/6MWD	+43 m	12 weeks	Tadalafil	[64]
Singh *et al.* (2006)	ES (10)	Randomized, placebo-controlled, double-blind crossover	6MWD	+98 m	1.5 months	Sildenafil	[79]

†The percentage of patients with CHD included in the study is provided in brackets where applicable.
6MWD: 6-min walking distance; ASD: Atrial septal defects; CHD: Congenital heart disease; DS: Down's syndrome; DTT: Disease-targeting therapies; ES: Eisenmenger syndrome; MPAP: Mean pulmonary arterial pressure; NA: Not applicable; PDA: Patent ductus arteriosus; QoL: Quality of life; RCT: Randomized controlled trial; SpO_2: Arterial oxygen saturation; VSD: Ventricular septal defects.

Table 1. Currently available studies assessing disease targeting therapies in pulmonary arterial hypertension associated with congenital heart disease and selected studies of mixed pulmonary arterial hypertension populations (cont).

Study (year)	Study population (n; % with CHD[f])	Study design	Outcome (primary outcome in RCTs)	Change in 6MWD	Follow-up period	Medication	Ref.
Barst *et al.* for STRIDE-2 (2006)	PAH (245; 11)	Randomized, double-blind, placebo-controlled	6MWD	+24 m (50-mg dose)/ +31 m (100-mg dose)	18 weeks	Sitaxsentan	[80]
D'Alto *et al.* (2007)	CHD (22)	Open label prospective	WHO/hemodynamics/ 6MWD	+67 m	1 year	Bosentan	[81]
Apostolopoulou *et al.* (2007)	CHD (18)	Open label prospective	SpO_2 and 6MWD	No improvement at 2 years	2 years	Bosentan	[82]
Diller *et al.* (2007)	CHD (18)	Retrospective	N/A	+79 m	29 months	Bosentan	[83]
van Loon *et al.* (2007)	CHD (30)	Retrospective	N/A	No improvement	2.7 years	Bosentan	[58]
Chau *et al.* (2007)	ES (7)	Prospective open-label	WHO/SpO_2/ hemodynamics	+28 m (ES)	6 months	Sildenafil	[84]
Gatzoulis *et al.* For BREATHE-5 OLE (2008)	ES (37)	Open label extension of BREATHE 5	6MWD	+61 m	40 weeks	Bosentan	[56]
Galiè *et al.* for ARIES-1 and ARIES (2008)	PAH (394; 0)	Randomized, double-blind, placebo-controlled	6MWD	+51 m (10-mg dose)/ +59 m (5-mg dose)	12 weeks	Ambrisentan	[85]
Galiè *et al.* for PHIRST (2009)	PAH (405; 12)	Randomized, double-blind, placebo-controlled	6MWD	+33 m (40-mg dose)	16 weeks	Tadalafil	[86]
Duffels *et al.* (2009)	CHD (58)	Retrospective	6MWD/QoL	Non-DS patients: +34m at 6 months and stable compared to baseline at 22 months DS patients: no improvement	22 months	Bosentan	[87]
Dimopoulos *et al.* (2010)	ES (68)	Retrospective	Survival	N/A	4 years	Bosentan, sildenafil, epoprostenol	[68]
Kermeen *et al.* (2010)	CHD (53)	Prospective, open-label, uncontrolled	SpO_2/WHO/6MWD	+73 m	24 months	Bosentan, sitaxentan	[88]
Lu *et al.* (2010)	CHD (60)	Prospective, open-label, uncontrolled	6MWD/WHO/ hemodynamics	+51 m	12 weeks	Sildenafil	[89]
Vis *et al.* (2011)	CHD (64)	Prospective, open-label, uncontrolled	6MWD/QoL/WHO/ survival	Non-DS patients: +36 m at 2.5 years. After that, no improvement	4 years	Bosentan	[59]

[f]The percentage of patients with CHD included in the study is provided in brackets where applicable.
6MWD: 6-min walking distance; ASD: Atrial septal defects; CHD: Congenital heart disease; DS: Down's syndrome; DTT: Disease-targeting therapies; ES: Eisenmenger syndrome; MPAP: Mean pulmonary arterial pressure; NA: Not applicable; PDA: Patent ductus arteriosus; QoL: Quality of life; RCT: Randomized controlled trial; SpO_2: Arterial oxygen saturation; VSD: Ventricular septal defects.

Table 1. Currently available studies assessing disease targeting therapies in pulmonary arterial hypertension associated with congenital heart disease and selected studies of mixed pulmonary arterial hypertension populations (cont).

Study (year)	Study population (n; % with CHD†)	Study design	Outcome (primary outcome in RCTs)	Change in 6MWD	Follow-up period	Medication	Ref.
D'Alto *et al.* (2011)	CHD (74)	Prospective, open-label, uncontrolled	WHO/SpO_2/6MWD/ hemodynamics	Non-DS patients: +46 m DS patients: +49 m	12 months	Bosentan	[90]
Zeng *et al.* (2011)	CHD (ASD: 15; VSD: 24; PDA: 16)	Prospective, open-label, uncontrolled	6MWD/ hemodynamics/ WHO/Borg	At least +37 m in all groups; no difference observed	12 weeks	Sildenafil	[91]
Monfredi *et al.* (2011)	CHD (38; ES: 35)	Retrospective	6MWD/SpO_2	Non-DS patients: +54 m	2.1 years	Bosentan	[92]
D'Alto *et al.* (2012)	CHD (32)	Prospective, open-label, uncontrolled	6MWD/WHO/Borg scale/hemodynamics	+33 m	6 months	Sildenafil addition to Bosentan	[66]
Dong *et al.* (2012)	CHD (31)	Prospective, randomized	MPAP/WHO/systolic function	N/A	12 months	Alprostadil	[93]
Diller *et al.* (2012)	ES (79)	Retrospective	6MWD/WHO	+50 m	3.3 years	DTT	[60]

†The percentage of patients with CHD included in the study is provided in brackets where applicable.
6MWD: 6-min walking distance; ASD: Atrial septal defects; CHD: Congenital heart disease; DS: Down's syndrome; DTT: Disease-targeting therapies; ES: Eisenmenger syndrome; MPAP: Mean pulmonary arterial pressure; NA: Not applicable; PDA: Patent ductus arteriosus; QoL: Quality of life; RCT: Randomized controlled trial; SpO_2: Arterial oxygen saturation; VSD: Ventricular septal defects.

Eisenmenger Syndrome

* ES patient with Functional class IIII

	class of recommendation	Evidence level
- Bosentan	I	B
- phosphochiesterase type-5 inhibitor	IIa	C
- prostanoid	IIa	C
- combination therapy	IIb	C

Indications	Class[a]	Level[b]
Patients with significant shunt (signs of RV volume overload) and PVR <5 WU should undergo ASD closure regardless of symptoms	I	B[26]
Device closure is the method of choice for secundum ASD closure when applicable	I	C
All ASDs regardless of size in patients with suspicion of paradoxical embolism (exclusion of other causes) should be considered for intervention	IIa	C
Patients with PVR ≥5 WU but <2/3 SVR or PAP <2/3 systemic pressure (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted PAH therapy) and evidence of net L–R shunt (Qp:Qs >1.5) may be considered for intervention	IIb	C
ASD closure must be avoided in patients with Eisenmenger physiology	III	C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