2014 KSC Joint Scientific Congress

Advanced Pulmonary Vasodilator Therapy on the Horizon

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Diagnostic classification: Dana Point 2008

1 Pulmonary arterial hypertension (PAH) — 1%
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease — 80%
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3 Pulmonary hypertension due to lung diseases and/or hypoxia — 12%
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4 Chronic thromboembolic pulmonary hypertension — 8%

5 PH with unclear and/or multifactorial mechanisms — 1%
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Galiè N et al. Eur Heart J 2009; 30:2493-537
Galiè N et al. Eur Resp J 2009; 34:1219-63

In the past,

1974’ Harrison’s Principles of Internal Medicine 7th Ed.

No definitive treatment is available.

Anticoagulants: Doubtful

Digoxin and Diuretics

O_2

IPA acetylcholine or tolazoline (α-antagonist)

Tp.

In the past,

1983’ Harrison’s Principles of Internal Medicine 10th Ed.

No definitive treatment is available.

Anticoagulants: Doubtful

Digoxin and Diuretics

O_2

Direct sm relaxant/α-agonist/β-blocker/CCBs
Immuosuppressive agent, PG antagonist, PG I_2 (rarely)

Heart-Lung Tp.

Few Year Ago…

2005' Harrison's Principles of Internal Medicine 16th Ed.

Anticoagulants

Digoxin and Diuretics: to treat Right HF

O_2

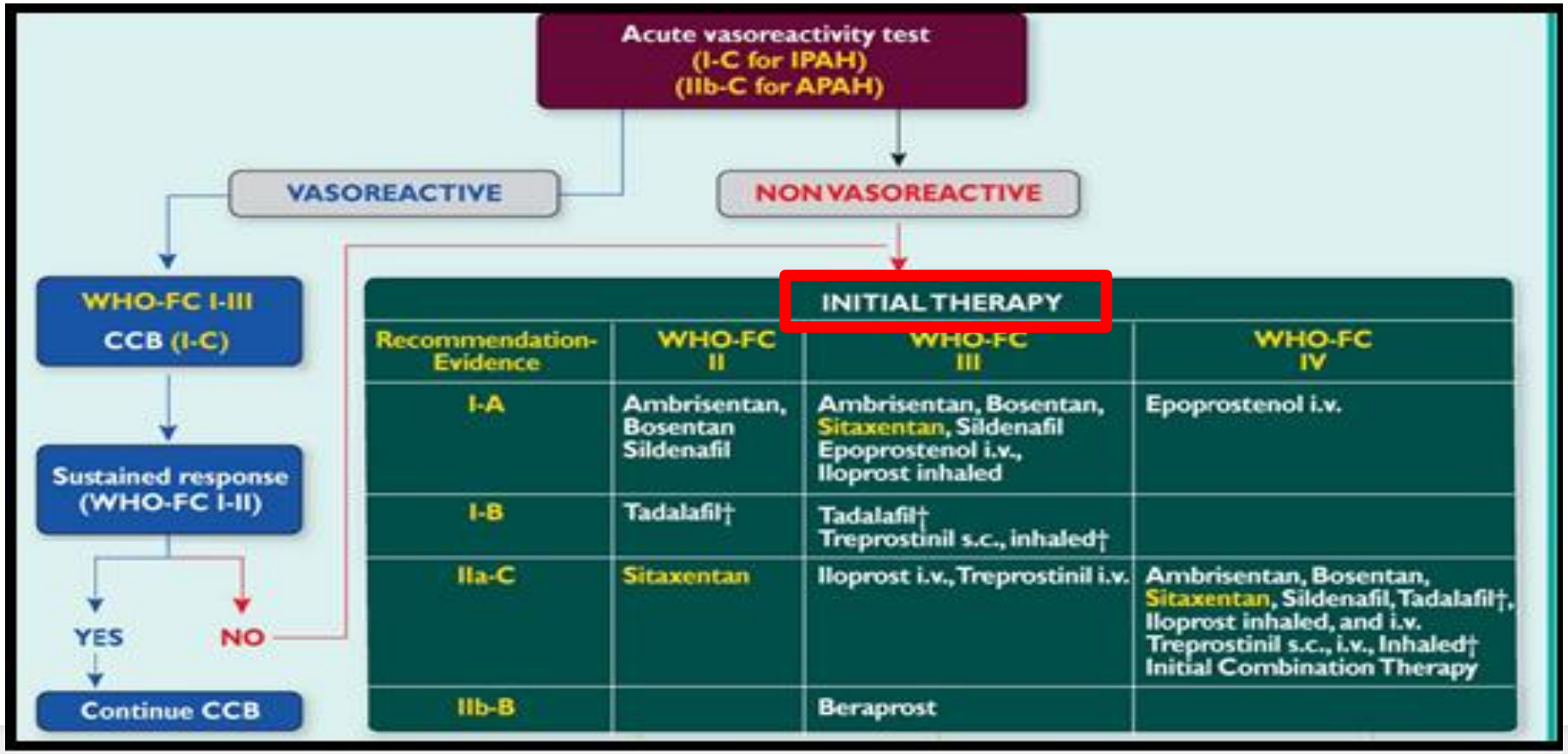
CCBs

PG I_2/ERA/(Sildenafil): **<u>Unresponsive to other therapies</u>**

Heart-Lung Tp.

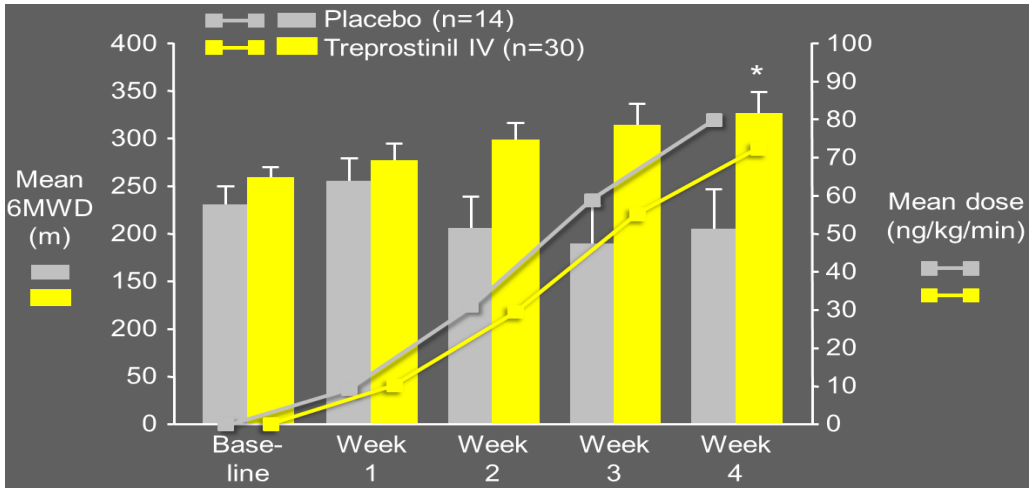
Present…

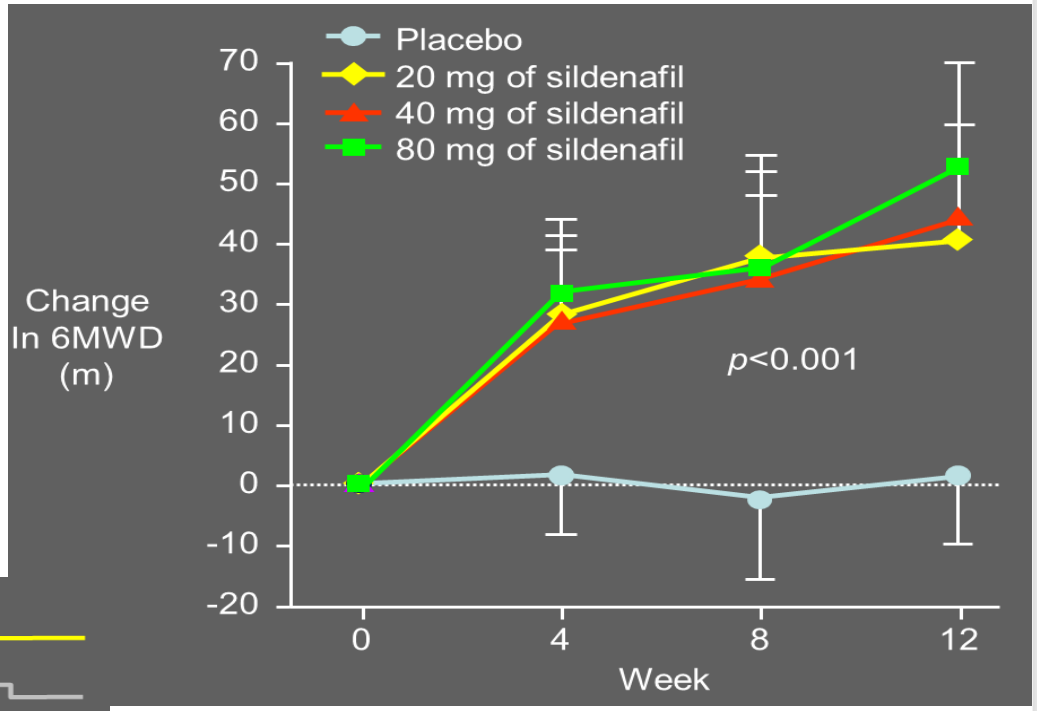
ESC/ERS guidelines for PAH

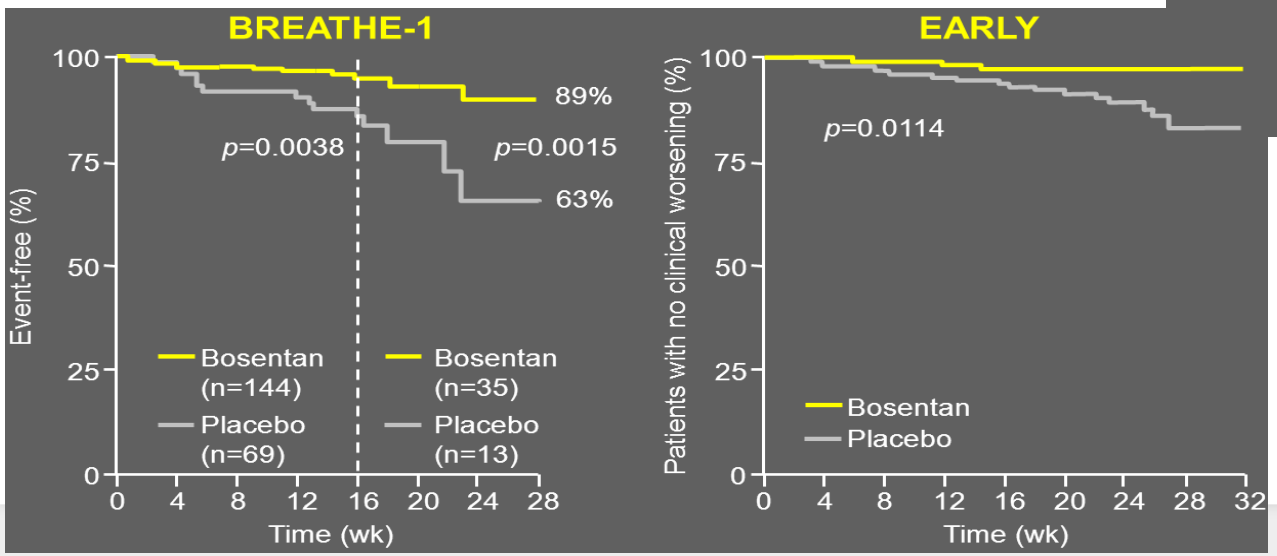


Recommendation-Evidence	WHO-FC II	WHO-FC III	WHO-FC IV
I-A	Ambrisentan, Bosentan Sildenafil	Ambrisentan, Bosentan, Sitaxentan, Sildenafil Epoprostenol i.v., Iloprost inhaled	Epoprostenol i.v.
I-B	Tadalafil†	Tadalafil† Treprostinil s.c., inhaled†	
IIa-C	Sitaxentan	Iloprost i.v., Treprostinil i.v.	Ambrisentan, Bosentan, Sitaxentan, Sildenafil, Tadalafil†, Iloprost inhaled, and i.v. Treprostinil s.c., i.v., Inhaled† Initial Combination Therapy
IIb-B		Beraprost	

PHT is a treatable disease…!







Galiè N et al. N Engl J Med. 2005; 353:2148-2157
Rubin LJ et al. N Engl J Med. 2002; 346:896-903
Galiè N et al. Lancet. 2008; 371:2093-2100
Hiremath J et al. J Heart Lung Transplant. 2010; 29:137-149

Treatment

General measures:

Avoid pregnancy

Immunizations for respiratory illnesses

Influenza & pneumonia vaccinations

Medical

Diuretics, Warfarin (IPAH, Anorexigen), Oxygen

PAH specific therapy

Surgical therapy

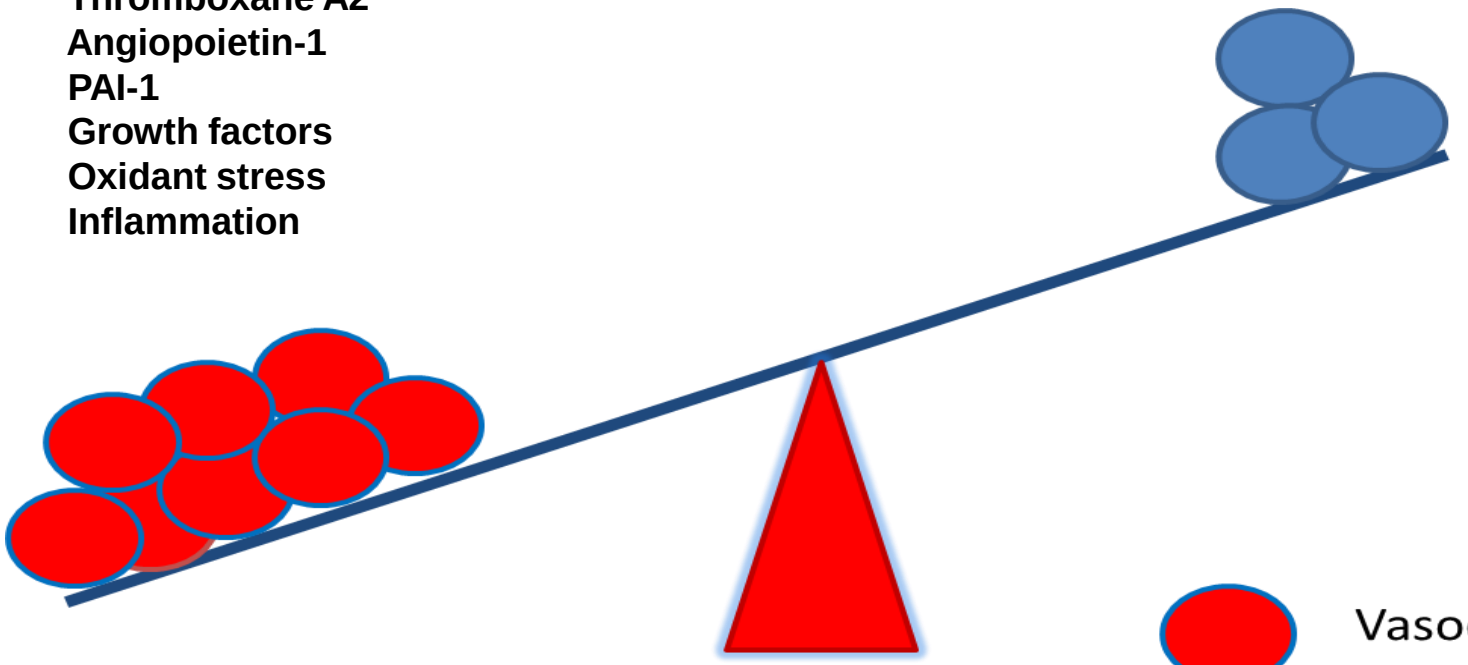
Atrial septostomy

Lung transplantation

An imbalance…

Increased Activity

- Endothelin-1
- Serotonin
- Thromboxane A2
- Angiopoietin-1
- PAI-1
- Growth factors
- Oxidant stress
- Inflammation



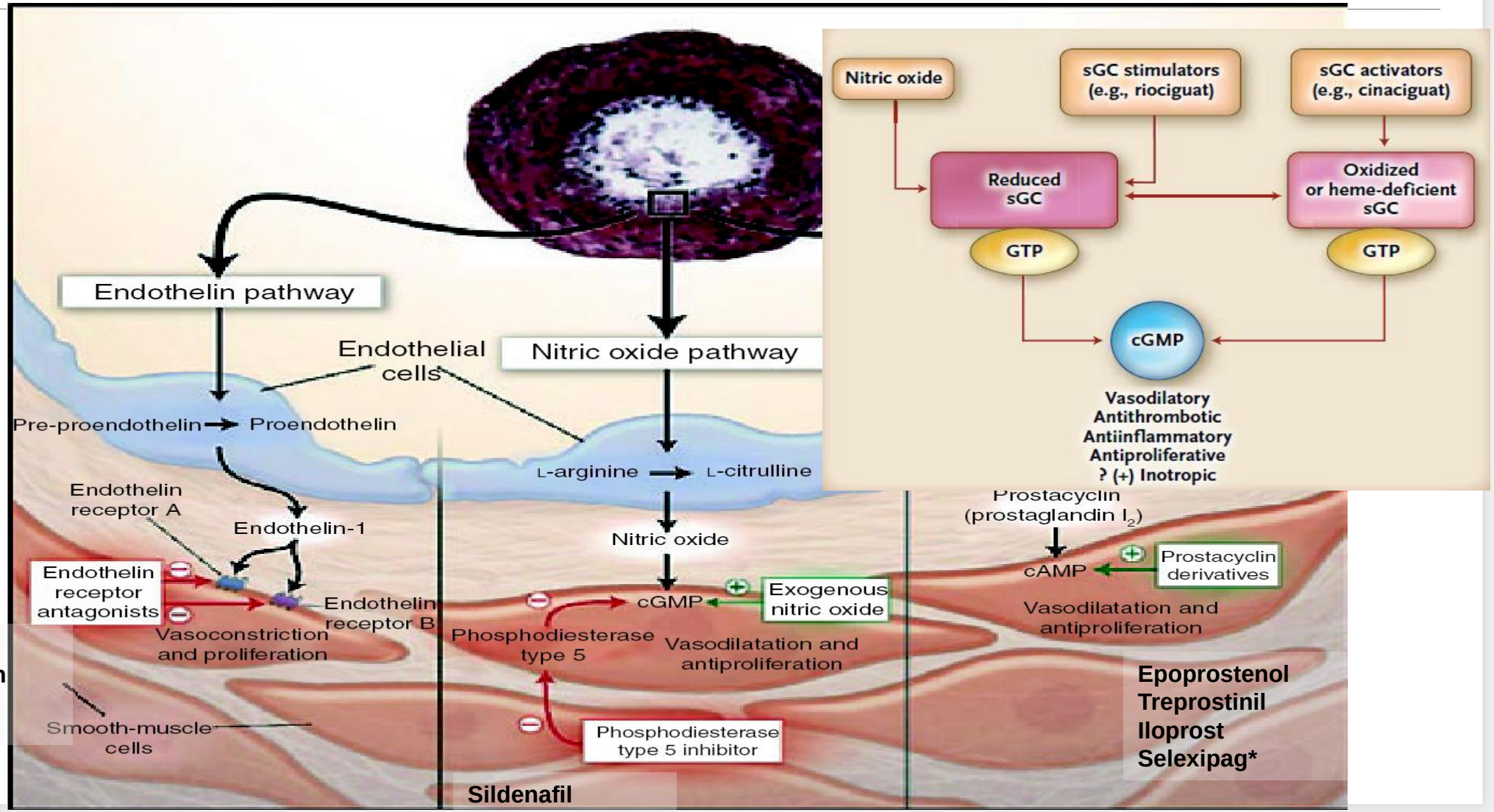
Reduced Activity

- Prostacyclin
- Nitric oxide
- VIP
- Kv channels
- Fibrinolysis

Vasoconstrictors

Vasodilators

Specific Targets for PAH Treatment



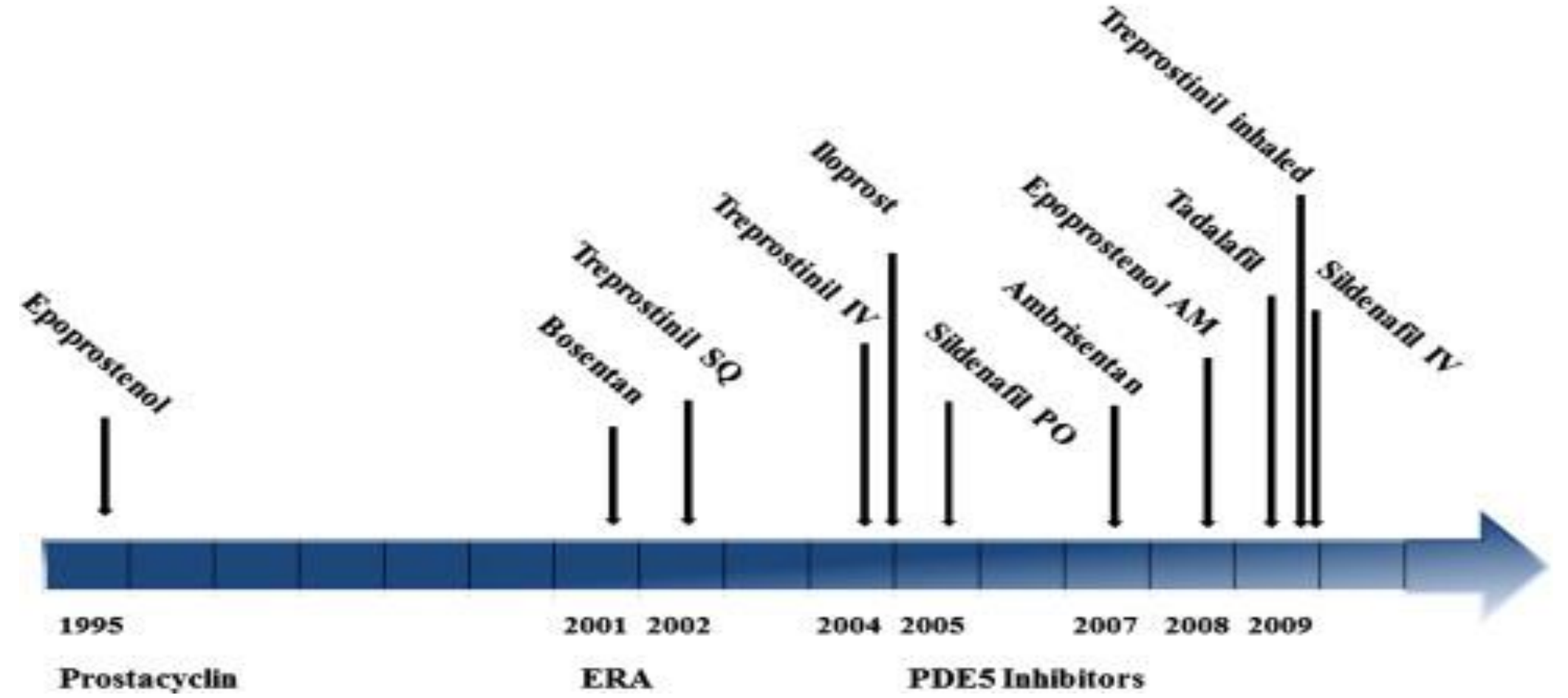
Bosentan
Ambrisentan
Macitentan
Sitaxentan *

Sildenafil
Tadalafil

Epoprostenol
Treprostinil
Iloprost
Selexipag*

Humbert M et al. N Eng J Med. 2004;351:1425-1436

Timeline of drug approval



CE Ventetuolo, JR Klinger. Prog Cardiovasc Dis 2012;55:89-103

Available PAH specific treatments in Korean Market

Sildenafil — Beraprost — Tadalafil — Bosentan — Treprostinil

1990	1999	2000	2001	2002	2003	2004	2005	2006	2009	2010	2011

Iloprost — Ambrisentan

Off-label Use of PDE5s

국내 발기부전 치료제 발매 현황

출시 연도	제조사	제품명
1999년	화이자	비아그라
2003년	릴리	시알리스
2003년	바이엘헬스케어	레비트라
2005년	동아제약	자이데나
2007년	종근당	야일라
2007년	SK케미칼	엠빅스
2010년	한국얀센	브라본토
2011년	바이엘헬스케어	레비트라ODT
2011년 (9월 예정)	JW중외제약	아바나필

Overview of marketed products for PAH

Brand	Molecule	Marketing	Originator	Class	1st approval for PAH
Flolan	epoprostenol	GSK	Glaxo Wellcome	PCA	96' (US)
Ventavis	iloprost	Actelion (US) Bayer (other)	Schering AG	PCA	04' (US)
Careload LA	beraprost	Astellas	Toray	PCA	07' (Japan)
Remodulin	treprostinil	UTC Pharmaceuticals (UK) Ferrer (Taiwan, Korea) Mochida (Japan)	GSK	PCA	02'(US) 05'(EU) Japan PIII
Volibris	ambrisentan	Gilead	BASF/Myogen	ERA(S)	07' (US) 08' (EU) Japan PIII
Tracleer	bosentan	Acetlion	Roche Holding	ERA (NS)	02' (EU)
Thelin	sixtasentan	Encysive	ICOS-Texas Biotechonology	ERA (S)	06' (EU)
Revatio	sildenafil	Pfizer	Pfizer	PDE5	05' (US/EU)
Adcirca	tadalafil	UTC	Eli Lilly	PDE5	09' (US)

Source: Thomson Pharma

Prostacyclin analogs

	Approval	Improve	Route	S/E
Epoprostenol	PAH with FC III/IV	Sx, FC, Ex cap, Hemody, surv in idiopathic PAH Ex cap, Hemody in scleroderma-PAH	Civ via CV cath Reconstitute and dilution, Refrigeration	Cath-related infection, fatal inadvertent discontinuation, headache, jaw pain, flushing, nausea, diarrhea, skin rash, musculoskeletal pain
Treprostinil	PAH with FC II-IV	Sx, Ex cap, Hemody	Civ or SC, inhaled	Iv ; similar to epo Sc ; injec-site pain Inhaled ; Cough, headache, nausea, dizziness, flushing, throat irritation, pharyngolaryngeal pain, diarrhea
Inhaled iloprost	PAH with FC III/IV	Ex cap, FC, Hemody Long-term efficacy established	Inhaled 9/day	Flushing, cough, headache

Endothelin receptor antagonists

block the effects of ET-1 by targeting and inhibiting its receptors (endothelin receptor subtypes A and B, ETA, and ETB, respectively).

Bosentan, ambrisentan

Ambrisentan is more selective for the ETA receptor

	Approval	Improve	Common S/E	S/E
Bosentan	PAH with FC II-IV Twice-daily oral	Ex cap, QOL, Hemody, Time to clinical worsening Long-term use -> 2-year surv rate 87~89% in idiopathic PAH	headache, flushing, peripheral edema, sinus congestion, mild anemia, and rare hypotension teratogenic	Hepatotoxicity 10%
Ambrisentan	PAH with FC II-III Once-daily oral	Sx, Ex cap, FC, QOL, Hemody, Time to clinical worsening Long-term use -> 2 year surv rate 88% in idiopathic PAH and associated PAH as initial Tx		Hepatoxicity 2%

PDE-5 inhibitors

target the nitric oxide pathway

effectively enhancing the effects of nitric oxide by inhibiting the breakdown of cGMP, the intracellular messenger of nitric oxide.

Two oral agents are available

	Approval	Improve	Route	S/E
Sidenafil	PAH with FC II/III	Sx, Ex cap, Hemody No surv benefit	Orally 3/day	Epistaxis, flushing, headaches, GI disturb
Tadalafil	PAH with FC II/III	Ex toler, Hemody, Delay clinical worsening	Once daily	Headache, myalgia, nausea, dyspepsia, flushing, resp tract infection

PAH specific therapies are recommended in FC II patients

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.
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IIb-B		Beraprost	

Combination therapy

- Basic rationale for combination Tx

: pulmonary vascular remodeling in PAH occurs via 3 main pathways

- Several combinations of PAH-specific agents have been evaluated, and although initial results are promising, more controlled trials are needed to confirm the benefit and the combination of agents to use.

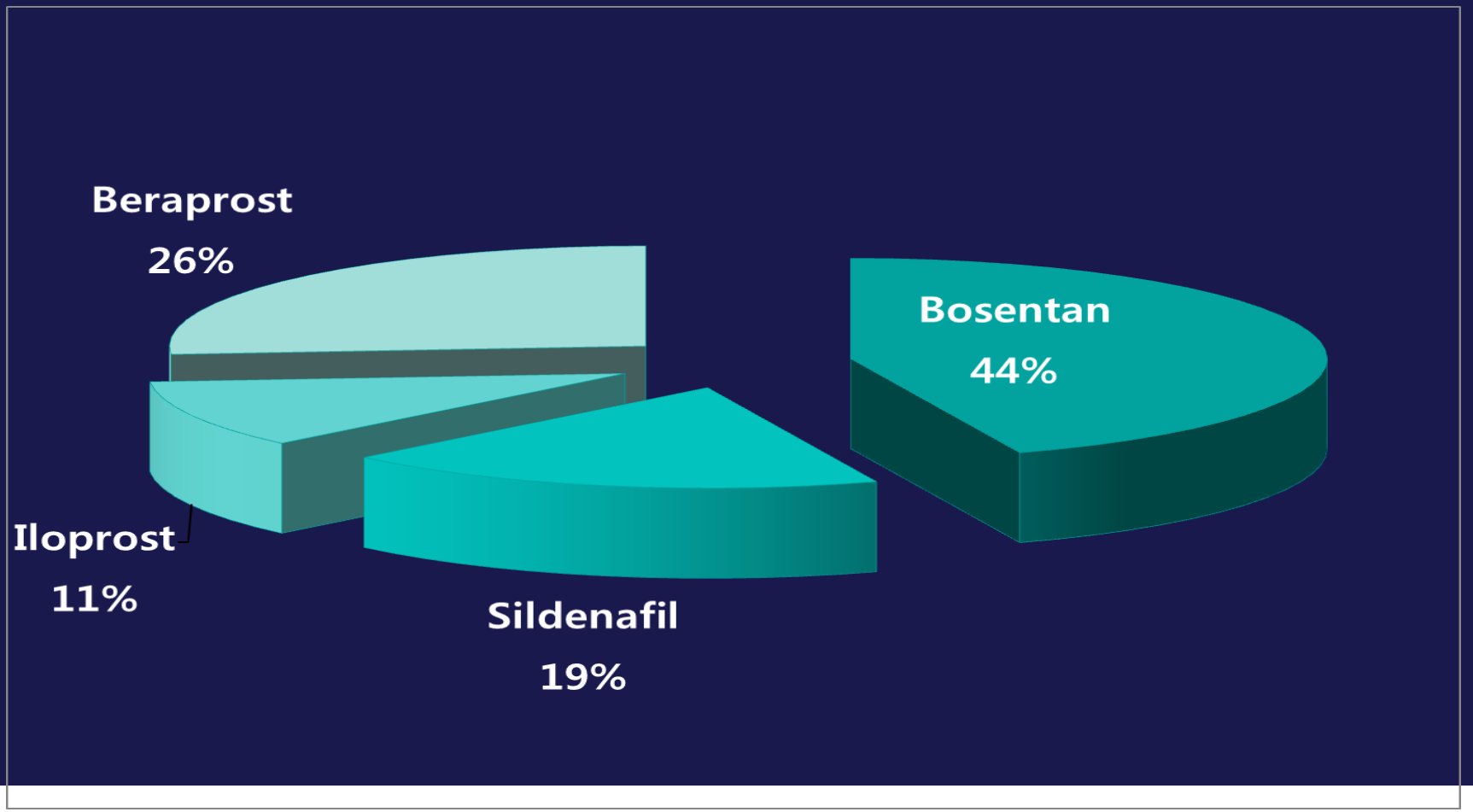
Ex) Bosentan → +sildenafil → + iloprost → LT or iv iloprost

: 6MWD > 380m, peak O2 uptake >10.4mL/min/kg, pSBP during exercise test > 120mmHg

Improvement in 6MWD comparison of trial data

Source: Barst 1996; 2003, 2003; Rubin 2002; Simmonneau 2002; Galie 2003, 2005; Ghofrani 2004

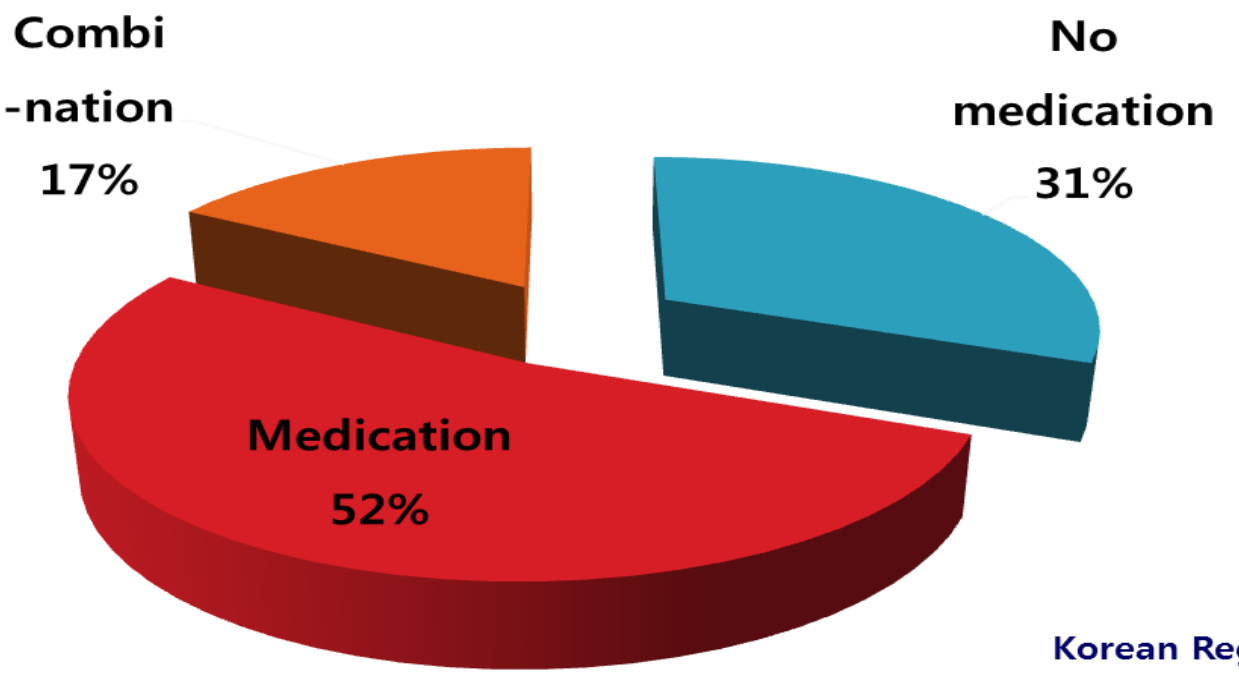
Medication status



Korean Registry of Pulmonary Arterial Hypertension (KORPAH)

Medication status in Korea

- **No PAH-specific treatment 30.9 %**
- **Combination treatment 16.5%**



Korean Registry of Pulmonary Arterial Hypertension (KORPAH)

Endothelin Receptor Antagonists

Bosentan (Tracleer)

(paediatric form available)

62.5 mg

125 mg

1 tablet b.i.d.

Ambrisentan (Volibris)

5 mg

10 mg

1 tablet q.d.

Bosentan – Tracleer (Actelion)

제약

보센탄 제네릭 '대웅 한미 LG' 경합

폐동맥고혈압 치료제... 시장 놓고 경쟁

『의약뉴스』 2013.6.25

제약사들이 보센탄 제네릭 개발에 열을 올리고 있다.

보센탄은 폐동맥고혈압 치료제로 널리 사용되는 약물로 오리지널 제품은 파마수티컬즈코리아의 '트라클리어정'이다.

지난 6월14일 보센탄의 재심사 기간이 만료되면서 제네릭 개발사들도 시장 진출을 노리고 있는 모습이다.

업계에 따르면 대웅제약, 한미약품, LG생명과학, 제일약품, 대원제약이 보센탄 제네릭 개발에 뛰어들었다.

대웅제약이 지난해 7월에 식약처로부터 승인을 받아 시일에 있어 가장 앞서 있으며 한미약품과 제일약품이 지난해 10월에 생동 작업에 착수했다. LG생명과학과 대원제약은 올해 초에 승인을 받았다.

제네릭 개발뿐만 아니라 한올바이오파마는 보센탄 서방정 개발에 착수했다.

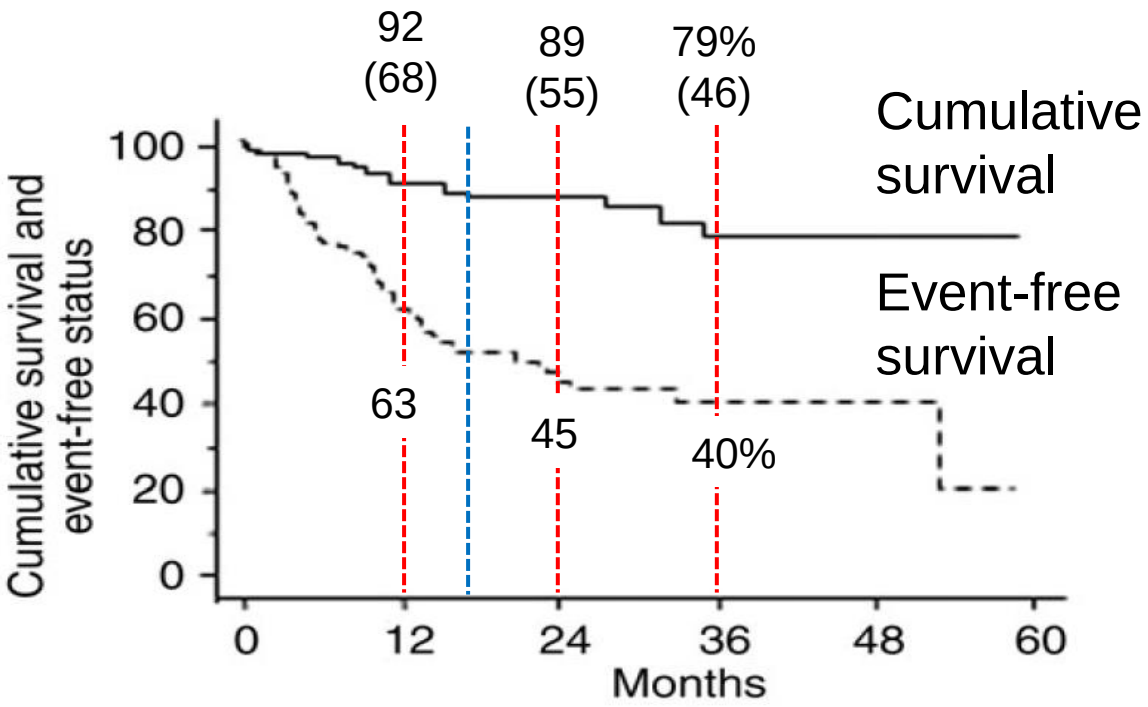
한올바이오파마가 개발 중인 제품은 기존 1일 1회 투여로 복용 편의성을 대폭 개선했다는 평을 받는다.

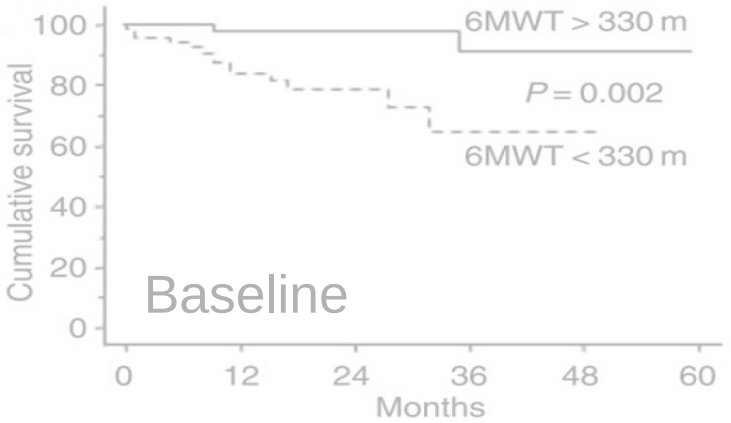
업계 관계자는 "보센탄의 물질이 하이레벨 드럭이라 제네릭을 만들기 까다롭다"며 "간접적으로 제품화력과 기술력을 확인할 수 있는 부분이다"고 말했다.

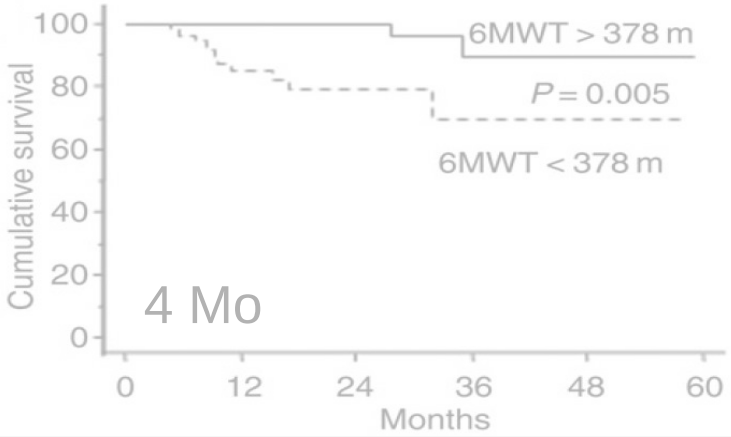
한편, 200억원 정도를 형성하고 있는 국내 폐동맥고혈압 치료제 시장에서 보센탄은 150억원의 실적을 올리며 압도하고 있다. 나머지 50억원을 암브리센탄과 실데나필 제제가 차지한다.

ERAs: Long-term Outcome with bosentan in IPAH

1st line







Provencher S et al. EHJ 2006

Ambrisentan – Letaris (Gilead), Volibris (Glaxo)

FDA and EU Indication

Treatment of patients with Group 1 PAH (FC II–III) to improve exercise capacity. Efficacy has been shown in idiopathic PAH (64%) and in PAH associated with connective tissue disease (32%).

『요양급여의 적용기준 및 방법에 관한 세부사항』 고시2011-134호

구 분	세부인정기준 및 방법(안)
	아래와 같은 기준으로 투여시 요양급여를 인정하며, 허가사항 범위이지만 동 인정기준 이외에 투여한 경우에는 약값 전액을 환자가 부담토록 함 - 아 래 - 가. 대상환자(①과 ②를 동시에 만족해야 함) ① WHO 기능분류 단계 III에 해당하는 폐동맥고혈압(WHO Group Ⅰ) 환자 중 아래 질환으로 진단이 확인된 환자 - Idiopathic pulmonary arterial hypertension 또는 - Familial pulmonary arterial hypertension 또는 - Pulmonary arterial hypertension associated with collagen vascular disease 또는 Pulmonary arterial hypertension associated with HIV infection 또는 - Pulmonary arterial hypertension associated with drug and toxins

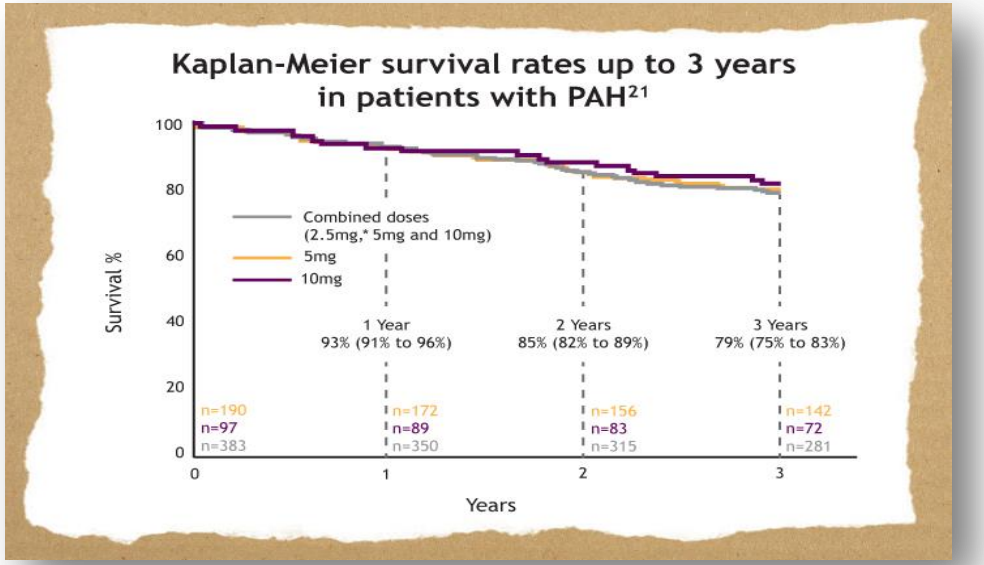
Letairis [package insert]. Glaxo. Inc; 2011.

Ambrisentan survival data

PAH is a debilitating chronic disease with an untreated survival of 2.8 years[22]

With the advent of PAH-specific treatments, survival for PAH patients has improved[23]

3-year survival with Volibris[21]



ARIES-E: A long-term, open-label, uncontrolled extension study of Volibris in subjects with PAH (IPAH or PAH 2º to CTD, HIV or anorexigens). Subjects participated in one of two Phase III, randomised, double-blind, placebo-controlled, 12-week studies (ARIES-1 or -2; n=383). Doses evaluated were 5mg and 10mg in ARIES-1 and 2.5mg* and 5mg in ARIES-2.

Adapted from Oudiz R *et al*. ACCP International Conference 2011.[21]

At 3 years, the Kaplan-Meier survival rate was 79% for PAH patients treated with Volibris[21]

*To comply with regulations, only 5mg and 10mg independent dosage arms are shown.
The 2.5mg dose of Volibris is not licensed or available on the market.

Phosphodiesterase 5-Inhibitors

Sildenafil (Revatio) 

20mg (1 tablet) TID

Tadalafil (Adcirca) 

40mg (2 x 20mg tablets) QD

Sildenafil – Revatio (Pfizer)

EU indication

Oral (adults): Treatment of adult patients with PAH (FC II-III) to improve exercise capacity. Efficacy has been shown in primary PH and PH associated with connective tissue disease

Oral (paediatric): Treatment of paediatric patients aged 1–17 years old with PAH. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary PH and PH associated with congenital heart disease

IV: Treatment of adult patients with PAH who are currently prescribed oral Revatio and who are temporarily unable to take oral medication, but are otherwise clinically and haemodynamically stable

Dosage and administration

Oral Tablets: 20 mg three times a day, approximately 4-6 hours apart, with or without food.

Higher doses not recommended.

Injection: 10 mg (12.5 mL) three times a day administered as an IV bolus injection.

Please consult your physician for additional information or visit www.revatio.com for full Important Safety Information and Prescribing Information

Revatio [package insert]. New York, NY: Pfizer Labs, Inc; 2009.

Sildenafil – Revatio (Pfizer): FDA warning in pediatric use

In Aug 2012, the FDA issued a warning against the use of sildenafil for paediatric PAH between 1 and 17 years of age due to an apparent increase in mortality during long-term therapy in the STARTS-2 study (see Abman et al, 2012; Barst et al, 2012).

[low dose: 10mg tid; medium dose: 10, 20, 40mg tid; high dose: 20, 40, 80mg tid]

Iloprost – Ventavis (Bayer- Shering)

EU indication

Treatment of patients with primary pulmonary hypertension (**FC III**) to improve exercise capacity and symptoms

Dosage and administration

Ventavis is intended to be inhaled using either of 2 pulmonary drug delivery devices: the I-neb® AAD® System or the Prodose® AAD® System. Patients should receive 6 to 9 doses (inhalations) per day (minimum of 2 hours between doses during waking hours) as follows: Starting dose: 2.5 mcg. Up-titrate to 5 mcg if 2.5 mcg is well tolerated. Maintenance dose: 5 mcg. The 20 mcg/mL concentration is for patients who repeatedly experience extended treatment times. Vital signs should be monitored while initiating Ventavis.

Please consult your physician for additional information or visit www.4ventavis.com for full Important Safety Information and Prescribing Information.

NYHA, New York Heart Association; WHO, World Health Organization. I-neb AAD and Prodose AAD are registered trademarks of Philips Respironics.

Ventavis [package insert]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2011.

Iloprost – Ventavis (Bayer- Shering)

- Pros:
  - Non-invasive inhalation route
  - Selective pulmonary effect
  - Stable at room temperature

- Cons:
  - Short-acting
  - Frequent dosing (6-9 a day): continuous interference in daily life
  - Compliance issues
  - Few controlled studies
  - Less efficient than parenteral prostanoids

Treprostinil – Remodulin (United Therapeutics)

EU indication

Remodulin (treprostinil) is a prostacyclin vasodilator indicated for the treatment of PAH (WHO group 1) idiopathic or heritable to diminish symptoms associated with exercise.

Studies establishing effectiveness included patients with NYHA FC II-IV symptoms (In Europe is FCIII) and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%).

It may be administered as a continuous subcutaneous infusion or continuous intravenous infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious bloodstream infections, continuous intravenous infusion should be reserved for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted.

In patients with PAH requiring transition from Flolan® (epoprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

Dosage and administration

Initial dose for patients new to prostacyclin infusion therapy: 1.25 ng/kg/min (or 0.625 ng/kg/min if not tolerated); dose increase based on clinical response (increments of 1.25 ng/kg/min per week for the first 4 weeks of treatment, later 2.5 ng/kg/min per week). Limited experience with doses >40 ng/kg/min. Abrupt cessation of infusion should be avoided.

Mild to moderate hepatic insufficiency: Initial dose should be decreased to 0.625 ng/kg/min ideal body weight; cautious dosage increase. Severe hepatic insufficiency: No studies performed.

Transition from Flolan: Increase the Remodulin dose gradually as the Flolan dose is decreased, based on constant observation of response.

Administration: Continuous subcutaneous infusion (undiluted) is the preferred mode. Use intravenous infusion (dilution required) if subcutaneous infusion is not tolerated.

Please consult your physician for additional information or visit www.remodulin.com for full Important Safety Information and Prescribing Information.

Remodulin [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2011.

Treprostinil

- Tricyclic benzidene analogue of epoprostenol (Flolan®, prostacyclin, PGI_2)
- Chemically stable at room temperature and neutral PH
- Prolonged half-life compared to epoprostenol (approximately 3 hours sc versus 3 minutes iv for epoprostenol)
- FDA approval: SQ (02'), IV (04') Inhale (09')

Prostanoids – Inhaled

Iloprost

I-neb® AAD®

Treprostinil

Tyvaso Inhalation System

I-neb AAD is a registered trademark of Philips Respironics.

Agents and drugs approved or in development for the treatment of PAH

1. Prostacyclin agonists (thermostable epoprostenol)
2. Endothelin receptor antagonists (macitentan)
3. PDE-5 inhibitors (sildenafil, tadalafil)
4. Non-prostanoid IP receptor agonists (selexipag)
5. Tyrosine kinase inhibitors (imatinib, nilotinib, sorafenib, sunitinib)
6. Soluble guanylate cyclase stimulator (riociguat)
7. Rho-kinase inhibitors (azaindole-1)
8. Elastase inhibitors (elafin)
9. Vasoactive intestinal peptide (aviptadil)

1. Prostacyclin agonists (thermostable epoprostenol)
2. Endothelin receptor antagonists (bosentan, ambrisentan, macitentan)
3. PDE-5 inhibitors (sildenafil, tadalafil)
4. Non-prostanoid IP receptor agonists (selexipag)
5. Tyrosine kinase inhibitors (imatinib, nilotinib, sorafenib, sunitinib)
6. Soluble guanylate cyclase stimulator (riociguat)
7. Rho-kinase inhibitors (azaindole-1)
8. Elastase inhibitors (elafin)
9. Vasoactive intestinal peptide (aviptadil)

Thermostable epoprostenol (Veletri)- Actelion

Status

Thermostable epoprostenol available as intravenous formulation for continuous infusion
the first-generation formulation approved in June 2008 in the US and launched in April 2010.
A second-generation formulation with an expanded stability profile and prolonged storage capacity was
Approved in June 2012 in the US; this formulation is replacing the first generation product and it is the one which will be launched in EU. Expected to be launched in EU in 2013 (decentralized procedure concluded)

Marketing company

Actelion

EU indication

Not currently marketed in the EU

US indication

Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity.
Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV symptoms and aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

Generic name	Brand name	Formulation
Epoprostenol	Veletri®	Vials of 0,5 and 1,5 mg lyophilized power to be reconstituted (no solvent provided in the packaging)

Half-life

≤6 min

Thermostable epoprostenol (Veletri)- Actelion

[N.B. None of these trials have looked specifically at the 2nd generation formulation]

Study code	Phase	Treatment	Target population	Duration	Primary endpoints	Estimated completion
NCT01105091; EPITOME-1	IV	Epoprostenol (thermostable Veletri®) vs epoprostenol (standard Flolan®)	N=30 iPAH, hPAH, aPAH (CTD- or drug/toxin-associated); FC III-IV; in need of injectable epoprostenol	28 days	PK, 6MWD, FC, ScV02, BP, HR, BW (open-label with no specific primary endpoint)	Completed Jul 2011
NCT01105117; EPITOME-1 Ext	IV	Epoprostenol (thermostable Veletri®) vs epoprostenol (standard Flolan®)	N=2 PAH patients completing EPITOME-1	Until patients transition to commercially-obtained medication	Safety, tolerability	Completed Dec 2011
NCT01431716; EPITOME-2	III	Epoprostenol (standard Flolan®) → Epoprostenol (thermostable Veletri®)	N=40 IPAH, HPAH, APAH (CTD- or drug/toxin-associated); on Flolan® for ≥12 months (stable dose for ≥3 months)	3 months	Cardiac haemodynamics	Jun 2012 (listed as recruiting; primary completion Feb 2012)
NCT01470144; EPITOME-2 Ext	III	Epoprostenol (thermostable Veletri®)	N=40 PAH patients completing EPITOME-2	3 months	Safety, tolerability	Sep 2013

EPITOME.1 results are available on clinical trials.gov (NCT01105091) and at the online Actelion Results Database (http://trials.actelion.com/asp/Trial_Registry/RStudyInfo.asp?ST=AC-066A401)

Thermostable epoprostenol (Veletri)- Actelion

[N.B. None of these trials have looked specifically at the 2nd generation formulation]

Study code	Phase	Treatment	Target population	Duration	Primary endpoints	Estimated completion
NCT01105091; EPITOME-1	IV	Epoprostenol (thermostable Veletri®) vs epoprostenol (standard Flolan®)	N=30 iPAH, hPAH, aPAH (CTD- or drug/toxin-associated); FC III-IV; in need of	28 days	PK, 6MWD, FC, ScV02, BP, HR, BW (open-label with no specific primary endpoint)	Completed Jul 2011
NCT01105117; EPITOME-1 Ext	IV	Epoprostenol (thermostable Veletri®) vs epoprostenol (standard Flolan®)	N=2 PAH patients completing EPITOME-1	Until patients transition to commercially-obtained medication	Safety, tolerability	Completed Dec 2011
NCT01431716; EPITOME-2	III	Epoprostenol (standard Flolan®) → Epoprostenol (thermostable Veletri®)	N=40 IPAH, HPAH, APAH (CTD-	3 months	Cardiac haemodynamics	Jun 2012 (listed as recruiting;
NCT01470144; EPITOME-2 Ext	III		EPITOME-2			

Endpoints were similar between Veletri and Flolan

Preliminary data (based on the first 10 patients who have completed the study) presented at the 2012 ATS Congress have thus far found no unexpected safety, tolerability, efficacy or dosing issues arising from the switch (Sitbon et al, 2012a,b).

EPITOME-1 results are available on clinical trials.gov (NCT01105091) and at the online Actelion Results Database (http://trials.actelion.com/asp/Trial_Registry/RStudyInfo.asp?ST=AC-066A401)

Thermostable epoprostenol (Veletri)- Actelion

Pros:

Epoprostenol perceived as the “Gold standard”and more efficient
Improves convenience vs Flolan (less reservoir changes)

Cons:

Short half-life (safety problems)
Reconstitution is needed
Refrigeration is needed once reconstituted
Stability depends on concentration
No data for temperatures >30ºC
Only IV route
In general, more frequent reservoir changes than with Remodulin sc

Thermostable epoprostenol (Flolan)- Glaxo

Clinical trial (registered in clinicaltrials.gov) is currently underway to investigate the impact on lifestyle of a new thermostable formulation of Flolan

Study code	Phase	Treatment	Target population	Duration	Primary endpoints	Estimated completion
NCT01462565	IV	Thermostable Flolan (switched from standard Flolan)	**N=16** PAH patients already on Flolan (6MWD ≥150m)	4 weeks + extension	QoL (SF-36); medication preparation time and effect on daily activities; change in dose	Oct 2013 (primary completion May 2012)

1. Prostacyclin agonists
2. Endothelin receptor antagonists (bosentan, ambrisentan, macitentan)
3. PDE-5 inhibitors (sildenafil, tadalafil , SLx 2101)
4. Non-prostanoid IP receptor agonists (selexipag)
5. Tyrosine kinase inhibitors (imatinib, nilotinib, sorafenib, sunitinib)
6. Soluble guanylate cyclase stimulator (riociguat)
7. Rho-kinase inhibitors (azaindole-1)
8. Elastase inhibitors (elafin)
9. Vasoactive intestinal peptide (aviptadil)

Macitentan- Opsumit (Actelion)

Status
Filed in the US in October 2012 and in the EU in November 2012
Not currently marketed in the EU
Not currently marketed in the US

Marketing company
Actelion.

Generic names
Macitentan

Brand names
Opsumit (proposed)

Molecular class
Tissue-targeting dual endothelin receptor (ET_A/ET_B) antagonist

Macitentan- Opsumit (Actelion)

MoA

Macitentan blocks the effects of endogenous endothelin-1 (ET-1) at the receptors ET_A and ET_B (with high affinity and a greater selectivity for ET_A vs ET_B).

ET-1 is a powerful vasoconstrictor produced primarily in the vascular endothelium that is elevated in PAH and appears to play a pathogenic role in the disease).

ET-1 also induces proliferation of vascular smooth muscle cells.

Selectivity of macitentan for ET_A may help to retain vasodilator and clearance functions specific to ETB receptors on the endothelial cells, while preventing the vasoconstriction and cellular proliferation mediated by ETA receptors.

Macitentan- Opsumit (Actelion)

Investigated in 742 symptomatic PAH patients in the Phase III study **SERAPHIN** (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome), completed in April 2012.

Designed to evaluate safety and efficacy of macitentan : primary endpoint time to clinical worsening (TTCW) (morbidity and all-cause mortality.)

Results from SERAPHIN :

Mean duration of study treatment was 85.3 weeks for patients on placebo (n=249), 99.5 weeks for patients on 3 mg (n=250) and 103.9 weeks for patients on 10 mg (n=242).

The total treatment duration with macitentan in SERAPHIN amounts to ~82,000 weeks of exposure, which represents nearly double that of all other PAH registration RCTs combined (~47,230 weeks) and eight times that for bosentan (10,040 weeks).

The study met its primary endpoint, with a statistically significant 45% reduction in morbidity/mortality with the 10 mg dose (p<0.0001). For the 3 mg dose group, the observed risk reduction was 30% (p=0.0108)
This effect was observed irrespective of background PAH treatment (mainly PDE-5)

Macitentan- Opsumit (Actelion)

- **Eisenmenger's Syndrome patients with PAH appear to be a key target population for macitentan, as a large (n=220) placebo-controlled clinical trial called MAESTRO (with 3-year open-label extension; MAESTRO-OL) in this patient group was initiated in Dec 2012 (NCT01743001; NCT01739400).**
- **Results from the main trial are expected in the middle of 2014.**

Macitentan- Opsumit (Actelion)

Pros:

- Actelion has large PAH product portfolio
- Oral route
- Once-daily dosing
- Included in new Nize treatment algorithm
- Significant morbidity/mortality benefit demonstrated in a large RCT
- Appears to have good overall tolerability profile
- Good candidate for combination therapy (eg, with sildenafil)
- Extensive exposure in registration trials (relative to other PAH therapies)
- Low potential for drug-drug interactions
- Being studied in a large number of Eisenmenger's patients, potential for greater efficacy versus other ERSs

Cons:

- Potential issue of anaemia
- Limited scope for uptiration (compared with prostacyclins)
- Development in IPF (idiopathic pulmonary fibrosis) cancelled due to lack of efficacy

1. Prostacyclin agonists
2. Endothelin receptor antagonists (bosentan, ambrisentan, macitentan)
3. PDE-5 inhibitors (sildenafil, tadalafil, SLx 2101)
4. Non-prostanoid IP receptor agonists (selexipag)
5. Tyrosine kinase inhibitors (imatinib, nilotinib, sorafenib, sunitinib)
6. Soluble guanylate cyclase stimulator (riociguat)
7. Rho-kinase inhibitors (azaindole-1)
8. Elastase inhibitors (elafin)
9. Vasoactive intestinal peptide (aviptadil)

SLx-2101

Status
Phase IIb?

Marketing company
Kadmon Pharmaceuticals / NT Life Sciences

Not currently marketed in the EU
Not currently marketed in the US

Generic names
Slx-2101, KD027?

Brand names
None yet

Molecular class
Potent, selective PDE-5 inhibitor

SLx-2101

MoA

The induction of vasodilation through smooth muscle relaxation and the prevention and reversal of deleterious cardiac remodelling that results from sustained pressure overload in hypertension

Formulation

Oral tablet q.d.

Half-life

48 hours

Pros:

Novel chemistry technology,
oral, 48-hour half-life

Cons:

Low company profile,
little information disseminated despite Phase II status

1. Prostacyclin agonists
2. Endothelin receptor antagonists (bosentan, ambrisentan, macitentan)
3. PDE-5 inhibitors (sildenafil, tadalafil, SLx 2101)
4. Non-prostanoid IP receptor agonists (selexipag)
5. Tyrosine kinase inhibitors (imatinib, nilotinib, sorafenib, sunitinib)
6. Soluble guanylate cyclase stimulator (riociguat)
7. Rho-kinase inhibitors (azaindole-1)
8. Elastase inhibitors (elafin)
9. Vasoactive intestinal peptide (aviptadil)

Selexipag (ACT-293987/NS-304) - (Actelion / Nippon Shinyaku)

Status
Phase III (expected results mid-2014)

Marketing company
In April 2008, Actelion and Nippon Shinyaku signed a licensing agreement, under which Actelion will be responsible for the global development and commercialization of selexipag outside Japan.

Not currently marketed in the EU
Not currently marketed in the US

Generic names
Selexipag

Brand names
Not known

Molecular class
Non Prostacyclin IP receptor agonist

Selexipag (ACT-293987/NS-304) - (Actelion / Nippon Shinyaku)

MoA

Selexipag is a prodrug with a low affinity for the IP receptor, which is converted in the liver to a highly selective IP receptor agonist.
By this metabolic step, the drug avoids causing gastrointestinal side effects when given orally, and leads to sustained release of MRE-269 with a longer half-life. MRE-269 is chemically distinct from prostanoids and has a 130-fold higher affinity for the IP receptor than for the other human prostanoid receptors.

Formulation

Oral tablet b.i.d.

Half-life

1.7 hours (prodrug); 7.9 hours (active form)

Bioavailability

80-102% (animal models); not reported in humans

Side effects

Common (in PAH, n=33): headache (67%), jaw pain (36%), extremity pain (30%), nausea (27%), nasopharyngitis (24%), diarrhoea (18%), flushing (18%), dizziness (18%), cough (12%), myalgia (12%).

Selexipag (ACT-293987/NS-304) - (Actelion / Nippon Shinyaku)

Pros:

Oral route (oral alternative to parenteral prostanoids),
Phase III,
prodrug = potential for better GI tolerability vs oral prostanoids,
reasonable half-life,
high selectivity for IP receptor (potential for better efficacy and/or tolerability vs prostanoids), novel MoA,
Actelion has large PAH product portfolio,
good KOL support,
very large-scale (n=1150) and long-term Phase III morbidity/mortality study underway

Cons:

High selectivity for IP receptor (potential for fewer off-target benefits
Potential contraindication in HF due to hepatic methabolism

1. Prostacyclin agonists
2. Endothelin receptor antagonists (bosentan, ambrisentan, macitentan)
3. PDE-5 inhibitors (sildenafil, tadalafil)
4. Non-prostanoid IP receptor agonists (selexipag)
5. Tyrosine kinase inhibitors (imatinib, nilotinib, sorafenib)
6. Soluble guanylate cyclase stimulator (riociguat)
7. Rho-kinase inhibitors (azaindole-1)
8. Elastase inhibitors (elafin)
9. Vasoactive intestinal peptide (aviptadil)

Tyrosine kinase inhibitors

- New group of oral drugs in PAH
- Novel MoA: inhibition of tyrosine kinase enzymes
- They are currently approved for the treatment of certain types of cancer
- It seems that they could be a new good option to combine with current treatments
- For most of them their adverse events in PAH have to be determined
- Potential tolerability issues: liver dysfunction, pancreatitis, cardiotoxicity, subdural haematoma…

Imatinib (Glivec/Gleevec) - Novartis

Status
Filed in the EU, US and Japan in April 2012. In August 2012, Novartis withdrew the NDA for imatinib in PAH after the US FDA told the company that additional data would be needed to support approval. The applications in the EU and Japan appear to be proceeding.

Marketing company
Novartis

EU indication Marketed for the treatment of certain types of cancer. Not yet approved in the EU for PAH
US indication Marketed for the treatment of certain types of cancer. Not yet approved in the USA for PAH

Generic names
Imatinib

Brand names
Glivec (EU/Australia), Gleevec (USA)

Molecular class
Tyrosine kinase inhibitor

Imatinib (Glivec/Gleevec) - Novartis

MoA

Imatinib is a 2-phenylaminopyrimidine derivative that functions as a specific inhibitor of a number of tyrosine kinase enzymes. It occupies the *TK* active site, leading to a decrease in activity.
Suppresses platelet-derived growth factor (PDGF) by inhibiting its receptor (PDGF-Rβ)
The antiproliferative effects of this agent are thought to contribute to its therapeutic effect in PAH, although it may also have vasodilatory activity

Formulation

Oral tablet q.d.

Half-life

18 hours (imatinib) 40 hours (active metabolite)

Bioavailability

98%

Side effects

In PAH (Phase II): Common: nausea (50%), headache (36%) and peripheral oedema (25%), rash/pruritis, mild anaemia, other gastrointestinal disturbances. Less common liver dysfunction, pancreatitis.
*In PAH (Phase III):*Nausea, peripheral oedema, facial oedema, diarrhoea vomiting, fatigue. No increase in thrombocytopenia *vs* placebo and no signs of myocardial toxicity on echocardiography.
Potential cardiotoxicity (but not reported in PAH)
Less common: subdural haemotoma

Imatinib (Glivec/Gleevec) - Novartis

Pros:

Oral, Filing
novel MoA (first in class),
good KOL support, product exposure at congresses,
long-term extension studies underway,
attractive combination therapy concept when used with vasodilators,
effective when used in quadruple therapy with PDE5 inhibitors, ERAs and prostanoids

Cons:

May only be effective in patients with more severe haemodynamic impairment,
novel MoA, potential tolerability issues (liver dysfunction, pancreatitis),
lack of impact on TTCW remains unexplained,
potential cardiotoxicity.
Risk of subdural haematoma

Nilotinib (Tasigna) - Novartis

Status
Phase II for PAH

Marketing company
Novartis

EU indication Marketed for the treatment of Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in the chronic and accelerated phase in patients resistant or intolerant to prior therapy including imatinib. Not yet approved in the EU for PAH.
US indication Marketed for the treatment of newly diagnosed Ph+ CML in chronic phase (and in both the chronic and accelerated phase in patients resistant or intolerant to prior therapy including imatinib). Not yet approved in the USA for PAH

Generic names
Nilotinib

Brand names
Tasigna

Molecular class
Tyrosine kinase inhibitor

Nilotinib (Tasigna) - Novartis

MoA

Nilotinib is a small molecule selective inhibitor of Bcr-Abl kinase and its mutations. It also inhibits other kinases, including PDGF-R, c-Kit, CSF-1R and the collagen receptor DDR.

Formulation

Oral tablet

Half-life

~17 hours

Side effects

Unknown in PAH patients

Common (in CML patients): myelosuppression (thrombocytopenia, neutropenia, anaemia), rash/pruritus, gastrointestinal disturbances, headache, fatigue, myalgia

Less common (in CML patients): QTc prolongation, impaired liver function, pancreatitis, electrolyte abnormalities, intracranial haemorrhage.

Nilotinib (Tasigna) - Novartis

Pros: *Oral route, Phase II, novel MoA, Novartis experience developing imatinib in PAH, potential for improved efficacy vs imatinib (based on observations in PAH animal models)*

Cons: *No clinical data at present, potential safety issues (QTc prolongation, liver dysfunction, pancreatitis, electrolyte abnormalities, etc), potential cardiotoxicity, potential for TKIs to induce PH (c.f. dasatinib)*

Sorafenib (Nexavar) - Bayer

Status
Phase I for PAH

Marketing company
Bayer

EU indication Marketed for the treatment of primary kidney cancer and advanced primary liver cancer. Not approved by NICE in the UK for liver cancer (due to cost). Not yet approved in the EU for PAH
US indication Marketed for the treatment of primary kidney cancer and advanced primary liver cancer. Not yet approved in the USA for PAH

Generic names
Sorafenib,

Brand names
Nexavar

Molecular class
Tyrosine kinase inhibitor

Sorafenib (Nexavar) - Bayer

MoA
Sorafenib is a small molecular inhibitor of several tyrosine protein kinases, including Raf kinase, PDGF, VEGF-2 and -3 kinases and c Kit the receptor for stem cell factor

Formulation
Oral tablet

Half-life
25–48 hours

Bioavailability
29–49%

Side effects
Common (based on 12 PAH patients): rash, hand-foot skin reaction, alopecia, hypophosphataemia, diarrhoea, anorexia

Common (≥10% in cancer patients): lymphopenia, hypophosphataemia, haemorrhage, hypertension, diarrhoea, nausea, anorexia, vomiting, rash, alopecia, 'hand foot syndrome', erythema, pruritus, fatigue, pain, and increased pancreatic enzymes. Less common (in cancer patients): cardiac ischaemia, cardiac infarction

Sorafenib (Nexavar) - Bayer

Pros:

Oral route,
Bayer has large PAH product portfolio,
long half-life,
potential beneficial interactions with prostacyclins

Cons:

Phase I,
limited information,
potential cardiotoxicity,
potential for TKIs to induce PH (c.f. dasatinib)

1. Prostacyclin agonists
2. Endothelin receptor antagonists (bosentan, ambrisentan, macitentan)
3. PDE-5 inhibitors (sildenafil, tadalafil)
4. Non-prostanoid IP receptor agonists (selexipag)
5. Tyrosine kinase inhibitors (imatinib, nilotinib, sorafenib, sunitinib)
6. Soluble guanylate cyclase stimulator (riociguat)
7. Rho-kinase inhibitors (azaindole-1)
8. Elastase inhibitors (elafin)
9. Vasoactive intestinal peptide (aviptadil)

Riociguat (Bayer)

Status
Phase III (in CTEPH and WHO group I PAH)
Bayer appears to be aiming for the entire PH market.
Filing in the US, EU and Japan is expected in 2013 with a market launch possible in mid-2014

Marketing company
BayerSchering

EU indication Not yet approved in the EU for PAH
US indication Not yet approved in the USA for PAH

Generic names
Riociguat, BAY63-2521

Brand names
None yet

Molecular class
Potent oral pyarazolopyridine-based sGC stimulator

Riociguat (Bayer)

MoA
Riociguat has a dual mechanism of action — it sensitizes soluble guanylate cyclase (sGC) to the body's own nitric oxide (a vasodilator), while also directly stimulating sGC independently of NO

Formulation
Oral tablet

Half-life
5–10 hours

Bioavailability
94%

Side effects
Common (in PAH; more frequent vs placebo): headache (27% vs 20%), dyspepsia (19% vs 8%), peripheral oedema (17% vs 11%), nausea (16% vs 13%), dizziness (16% vs 12%), diarrhoea (14% vs 10%), vomiting (10% vs 9%)
Common (in CTEPH; more frequent vs placebo): headache (25% vs 14%), dizziness (23% vs 13%), dyspepsia (18% vs 8%), nasopharyngitis (15% vs 9%), nausea (11% vs 8%), diarrhea (10% vs 5%), vomiting (10% vs 3%)
Less common (in PAH/CTEPH): syncope

Riociguat (Bayer)

Pros:

Oral route
good Phase III data available (expect filing in first half of 2013)
Included in new Nize treatment algorithm
Long-term open-label extensions
novel dual MoA,
BayerSchering has large PAH product portfolio
good KOL support
product exposure at congresses
good tolerability profile

Cons:

short half-life so tid dosing
Not suitable for combination with PDE-5

1. Prostacyclin agonists
2. Endothelin receptor antagonists (bosentan, ambrisentan, macitentan)
3. PDE-5 inhibitors (sildenafil, tadalafil)
4. Non-prostanoid IP receptor agonists (selexipag)
5. Tyrosine kinase inhibitors (imatinib, nilotinib, sorafenib, sunitinib)
6. Soluble guanylate cyclase stimulator (riociguat)
7. Rho-kinase inhibitors (azaindole-1)
8. Elastase inhibitors (elafin)
9. Vasoactive intestinal peptide (aviptadil)

Azaindole-1- Bayer Schering

Status
Phase I or II development for PAH

Marketing company
Bayer Schering

EU indication Not yet approved in the EU for PAH
US indication Not yet approved in the USA for PAH

Generic names
Azaindole-1

Brand names
None yet

Molecular class
Azaindole-1 is a Rho-kinase inhibitor

Azaindole-1- Bayer Schering

MoA

Rho kinase is a downstream mediator of RhoA that leads to stress fibre formation, membrane ruffling, smooth muscle contraction and cell motility.
Increased Rho-kinase activity is associated with vasoconstriction and elevated blood pressure

Formulation

Oral?

Bioavailability

~50% in animal models

Side effects

Unknown

1. Prostacyclin agonists
2. Endothelin receptor antagonists (bosentan, ambrisentan, macitentan)
3. PDE-5 inhibitors (sildenafil, tadalafil)
4. Non-prostanoid IP receptor agonists (selexipag)
5. Tyrosine kinase inhibitors (imatinib, nilotinib, sorafenib, sunitinib)
6. Soluble guanylate cyclase stimulator (riociguat)
7. Rho-kinase inhibitors (azaindole-1)
8. Elastase inhibitors (elafin)
9. Vasoactive intestinal peptide (aviptadil)

Elafin – Proteo Biotech

Elastase inhibitors

Increased serine elastase activity has been implicated in the vascular remodelling associated with pulmonary hypertension.

Elafin is a soluble 57 amino acid endogenous protein produced by the human body and is a natural inhibitor of the two tissue-destroying enzymes, neutrophil elastase and proteinase-3. Both of these enzymes are known to be involved in the inflammatory response occurring in a variety of diseases.

Elafin inactivates an additional enzyme (endogenous vascular elastase), which is involved in inflammatory damage to blood vessels.

A recombinant version of elafin for IV administration is being developed by Proteo Biotech.

A positive opinion for orphan drug status for the treatment of PAH and CTEPH was granted by the EMEA in March 2007 (it has also been granted ophan drug status for oesophagus carcinoma).

On 10 January 2013, Proteo Biotech announced that the FDA has also granted orphan drug designation to elafin for the treatment of PAH.

Elafin

No clinical reports of elafin in PAH are currently listed

Pros:

Novel MoA

Cons:

Preclinical,
limited information,
no known ongoing clinical trials in PAH

1. Prostacyclin agonists
2. Endothelin receptor antagonists (bosentan, ambrisentan, macitentan)
3. PDE-5 inhibitors (sildenafil, tadalafil)
4. Non-prostanoid IP receptor agonists (selexipag)
5. Tyrosine kinase inhibitors (imatinib, nilotinib, sorafenib, sunitinib)
6. Soluble guanylate cyclase stimulator (riociguat)
7. Rho-kinase inhibitors (azaindole-1)
8. Elastase inhibitors (elafin)
9. Vasoactive intestinal peptide (aviptadil)

Aviptadil

Status
Phase II-III
Aviptadil received Orphan status for PAH, acute Lung Injury and sarcoidosis in the EU in December 2003 and for PAH and acute respiratory distress syndrome in the US

Marketing company
mondoBIOTECH/United Therapeutics.

EU indication Not currently marketed in the EU. The combination of aviptadil and phentolamine (an injectable medication known as Invacorp) was approved for erectile dysfunction in the UK and Denmark, but is currently not available.
US indication Not currently marketed in the US. Invacorp is in Phase III development for erectile dysfunction in the US.

Generic names
Aviptadil, vasoactive intestinal peptide (VIP)

Brand names
Not known

Molecular class
Synthetically produced version of the endogenous human peptide VIP

Aviptadil

MoA

VIP is a peptide hormone containing 28 amino acid residues and is produced in many areas of the human body including the gut, pancreas and suprachiasmatic nuclei of the hypothalamus in the brain. It is also found in the heart and has significant effects on the cardiovascular system. It causes coronary vasodilation as well as having a positive inotropic and chronotropic effect.

Formulation

Inhalation

Half-life

??

Bioavailability

??

Side effects

Tolerability appears to be similar to placebo. Anti-VIP antibodies have been reported, but the clinical relevance of this is unknown.

Aviptadil

Pros:

Inhaled route,
good KOL support,
well-respected biologic company,
very good safety/tolerability profile

Cons:

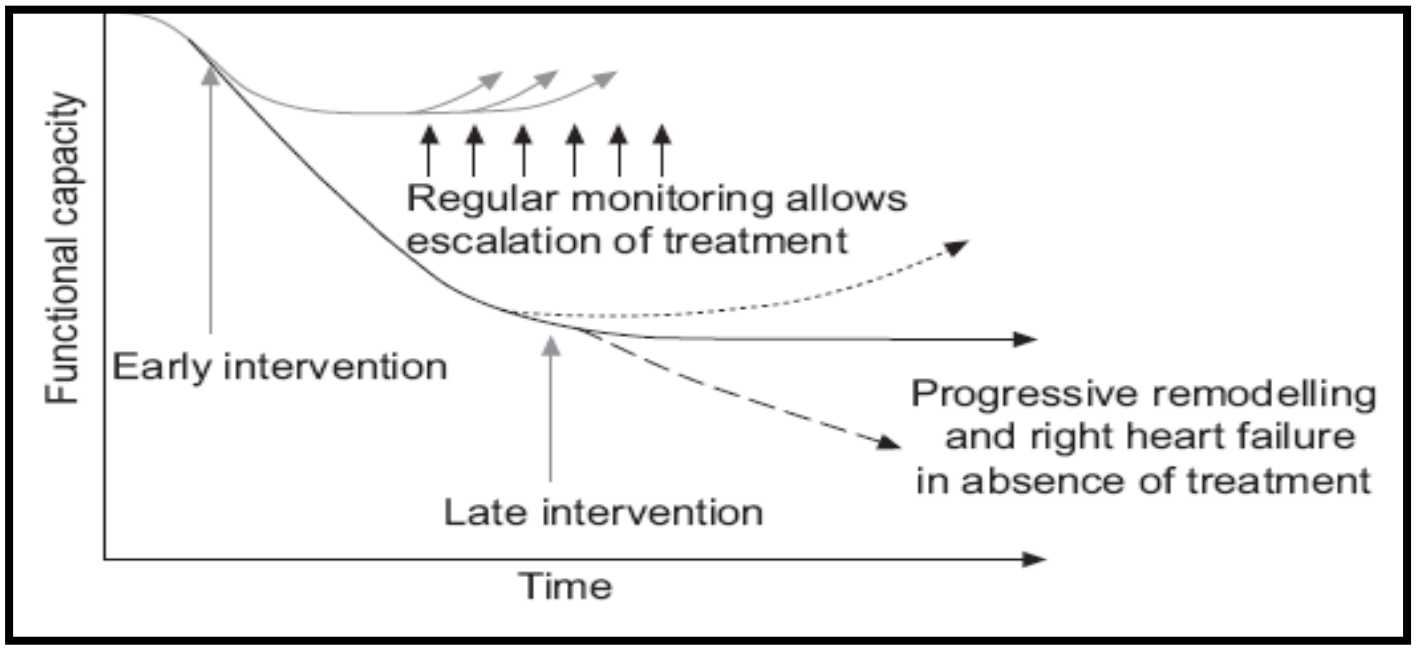
Phase II results negative,
potential issues with dosing via inhaled route

Horizon Scan

		2012	2013	2014	2015
	Registries	TOPP (baseline) VOLT, CTEPH, COMPERA-XL SITAR, ABS-LT, EPITOME-2	RESPIRE PROSPECT		EFORT
	ERA RCTs	COMPASS-2 ATHENA-1	FUTURE-3 AMBITION		
	PDE5 RCTs		AMBITION		
	Prost RCTs	EPITOME-1			
	NCE RCTs	SERAPHIN, PATENT-1 & CHEST-1 DILATE	GRIPHON (interim)	GRIPHON (final)	

Ultimate goals

- No functional impairment
- Prolongation of life



O. Sitbon, et al. Eur Respir Rev 2010

Thank you for your attention